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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/$ZnBr_2$ 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/$ZnCl_2$,[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 carboxylic[7] 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/$ZnBr_2$,[10] 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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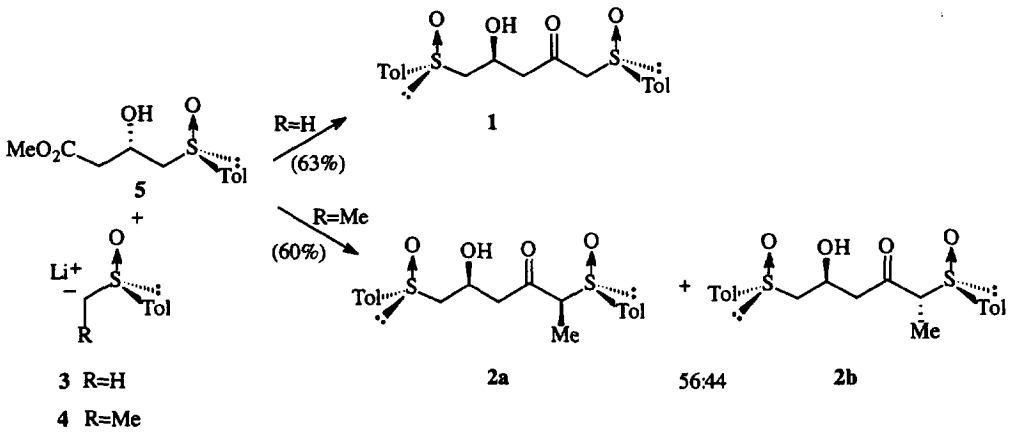
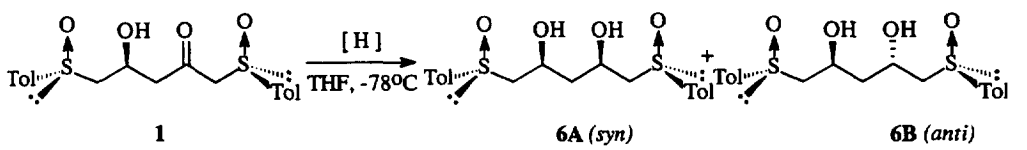
Compound **2** was obtained as a 56:44 mixture of epimers **2a** and **2b** at the new stereogenic center, which was used without prior separation in the subsequent reduction reactions. Configurations of **2a** and **2b** were tentatively assigned as indicated in Scheme 1, from the relative values of 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 $ZnBr_2$ (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.

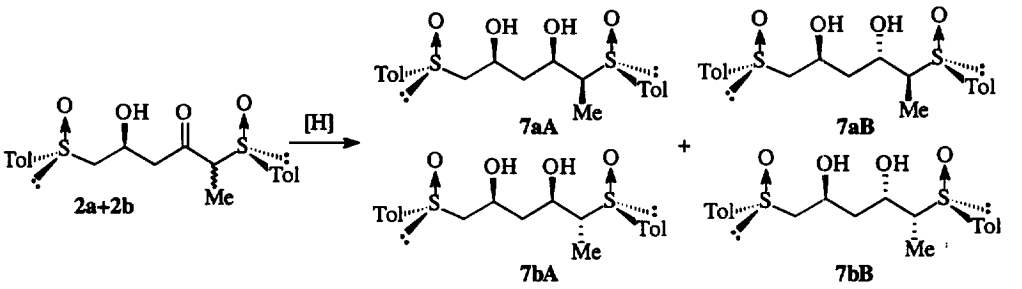


Scheme 2.

The DIBALH reduction of a 56:44 epimeric mixture of compounds **2a** and **2b**, previously chelated with $ZnBr_2$ (2.4 eq) yielded a 57:43 mixture (by ^{1}H-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 C*H*–OH and C*H*–Me



Scheme 3.

Table 1. Reduction of ketosulfoxide **2a** and **2b** with DIBALH and DIBALH/$ZnBr_2$

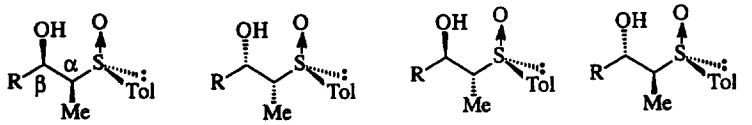
Ketosulfoxide	H^-	Yield (%)	7aA	7bA	7aB	7bB	C*-OH *(R/S)*
2a (56) +**2b** (44)	DIBALH/$ZnBr_2$	90	57	43	0	0	100/0
2a (56) +**2b** (44)	DIBALH	72	15	0	40	45	15/85

protons.[14] Unfortunately, diastereomers **7** exhibit a very complex spectra precluding the measure of such constants. However, from the study of the ^{1}H-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, δ(C*H*–OH) values are higher and δ(C*H*–Me) are lower than those of their corresponding **aB** and **bA** ones; (b) δ(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/ZnX_2 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 ^{13}C 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 Evans[16] 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 ^{13}C-δ values observed for acetonides **8A**, **9aA**, and **9bA**, respectively derived from **6A**, **7aA** and **7bA** (those obtained as major diastereomers in DIBALH/$ZnBr_2$ 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).

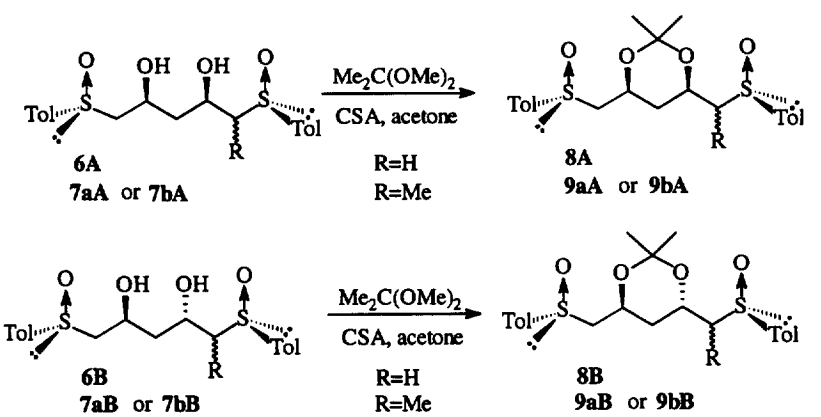
This result indicated that the presence of the stereogenic hydroxylic center in the starting β-ketosulfoxide has a scarce influence in the stereoselectivities of DIBALH reductions. The sulfur configuration completely controls the stereochemical course of these reductions on the non methylated substrates, 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. ^{1}H-NMR significant parameters of α-methyl-β-hydroxysulfoxides $RCH_\beta(OH)CH_\alpha(CH_3)SOTol$



aA **bB** **bA** **aB**

R	δ H_β				δ H_α				$J_{\alpha,\beta}$ (Hz)				δ CH_3				*Ref.*
Compound	**aA**	**bB**	**bA**	**aB**	**aA**	**bB**	**bA**	**aB**	**aA**	**bB**	**bA**	**aB**	**aA**	**bB**	**bA**	**aB**	
Me	4.56	4.34	4.22	4.07	2.54	2.54	2.87	2.83	2.5	1.8	9.1	8.2	1.34	1.37	1.28	1.29	*2a*
nPr	4.33	4.17	4.05	3.90	2.56	2.56	2.90	2.79	2.5	1.8	8.6	8.0	1.05	1.30	0.93	0.89	*2a*
iPr	3.87	3.73	3.79	3.72	2.73	2.71	2.96	2.96	2.2	1.8	9.3	8.9	0.86	1.3	0.88	0.9	*2a*
tBu	4.65	3.76	4.43	3.53	2.89	2.76	3.07	2.85	1.2	0.9	7.5	4.6	1.08	1.52	1.03	1.11	*2a*
Ph	5.53	5.32	4.86		2.78	2.69	3.05		2.7	1.7	9.1		0.94	1.27	0.68		*2a*
p-MeOPh	5.37	5.30	4.86		2.74	2.68	3.10		3.4	1.8	9.2		0.97	1.18	0.63		*2a*
$CH_2CH(OMe)_2$	4.30	4.40	4.01	4.10	2.62	2.56	3.00	2.62	3.3	1.9	7.8	7.1	1.07	1.21	0.94	0.94	*4c*
(7)	4.37	4.68	4.50	4.30	2.66	2.70	3.05	2.70	3.5				1.03	1.10	0.87	0.89	



6A **7aA** or **7bA** **8A** **9aA** or **9bA**

6B **7aB** or **7bB** **8B** **9aB** or **9bB**

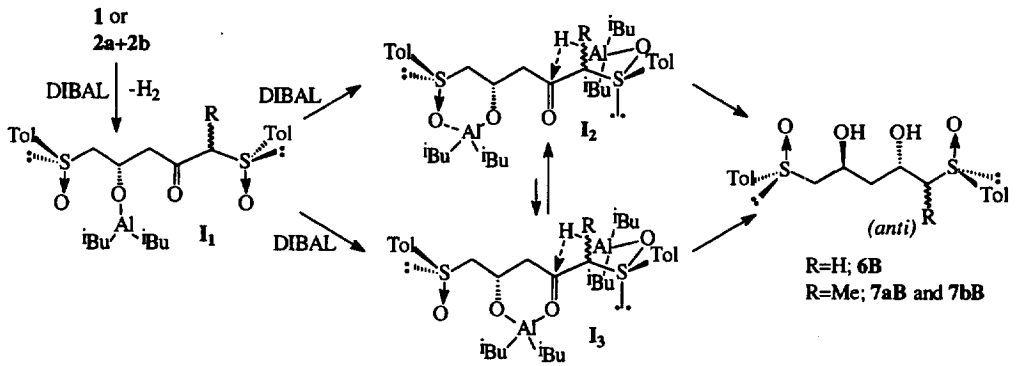
Scheme 4.

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 $\mathbf{I_1}$ (Scheme 5) with hydrogen evolution. These intermediates must be stabilized by association with the sulfinyl oxygen (species $\mathbf{I_2}$) or with the carbonyl one (species $\mathbf{I_3}$), 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 $\mathbf{I_2}$ (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.

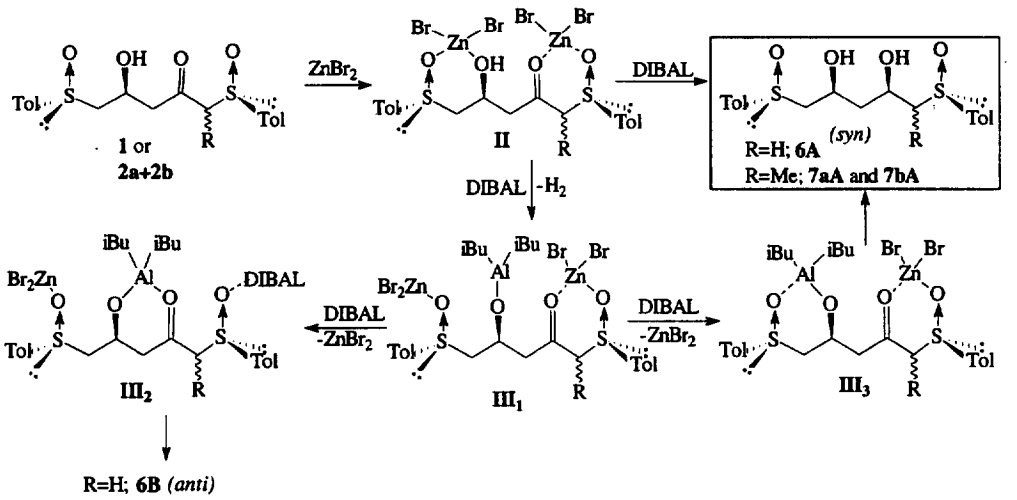
When reactions are carried out in the presence of $ZnBr_2$, the formation of chelated species like **II**, must be expected. The intermolecular DIBALH attack on such a species would yield the *syn*-1,3-diols **6A** (from **1**), **7aA**, and **7bA** (both from the mixture **2a** and **2b**).

This situation could be complicated by the DIBALH reaction with the OH group, forming the species $\mathbf{III_1}$ able to evolve, by shifting of $ZnBr_2$, into $\mathbf{III_2}$ and $\mathbf{III_3}$. The stereochemical course of the DIBALH reduction of the species $\mathbf{III_3}$ must be identical to that of **II**, whereas $\mathbf{III_2}$ 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 $CDCl_3$ 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 $CHCl_3$ 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 H_2SO_4 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,S_4,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, $CHCl_3$). mp 134–135°C. ^{1}H-NMR δ: 2.41 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3Ar), 2.73 (AB of ABX, 2H, J_{AB}=17 Hz, J_{AX}=7.3 Hz, J_{BX}=4.8 Hz, Δν=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, Δν=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). ^{13}C-NMR δ: 21.3 (CH_3Ar), 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 (^{1}H-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** ^{1}H-NMR δ: 1.26 (d, 3H, J=7.0 Hz, H-1), 2.40 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3Ar), 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). ^{13}C-NMR δ: 8.3 (C-1), 21.1 (CH_3Ar), 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)-**2b** ^{1}H-NMR δ: 1.24 (d, 3H, J=7.0 Hz, H-1), 2.40 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3Ar), 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). ^{13}C-NMR δ: 9.5 (C-1), 21.1 (CH_3Ar), 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 H_2SO_4 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/$ZnBr_2$ 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 $ZnBr_2$ (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 H_2SO_4 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,R_2,S_4,R_S)*1,5-Bis(p-tolylsulfinyl)-2,4-pentanediol* **6A**

It was obtained by DIBALH/$ZnBr_2$ reduction starting from β-ketosulfoxide **1** (80%, de 65%). $[\alpha]_D$=+406 (c=1.7, $CHCl_3$). MS (EI): m/z: 380 (0.4), 241 (9), 223 (3), 139 (100), 123 (34), 91 (70). HRMS: Calcd for $C_{19}H_{24}O_4S_2$: 380,1110. Found: 380.1105. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, Δν=45.0 Hz, H-3), 2.39 (s, 3H, CH_3Ar), 2.40 (s, 3H, CH_3Ar), 2.90 (AB of ABX, 2H, J_{AB}=13.4 Hz, J_{AX}=10.5 Hz and J_{BX}=3.8 Hz, Δν=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, Δν=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). ^{13}C-NMR δ: 21.3 (CH_3Ar), 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,S_2,S_4,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%). $[\alpha]_D$=+332 (c=1,

$CHCl_3$). 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. ^{1}H-NMR δ: 1.68–1.62 (m, 2H, H-3), 2.40 (s, 6H, CH_3Ar), 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). ^{13}C-NMR δ: 21.2 (CH_3Ar), 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/$ZnBr_2$, 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** ^{1}H-NMR. δ: 1.10 (d, 3H, J=7.0 Hz, H-1), 1.85–1.40 (m, 2H, H-4), 2.41 (s, 3H, CH_3Ar), 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, Δν=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** ^{1}H-NMR. δ: 0.89 (d, 3H, J=6.8 Hz, H-1), 1.85–1.40 (m, 2H, H-4), 2.41 (s, 3H, CH_3Ar), 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, Δν=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** ν_{max}: 3370, 2920, 1085, 1045, 1010 cm^{-1}.

(R_S,S_2,R_3,S_5,R_S)-**7aA** ^{1}H-NMR. δ: 1.03 (d, 3H, J=7.0 Hz, H-1), 1.60–2.00 (m, 2H, H-4), 2.39 (s, 3H, CH_3Ar), 2.41 (s, 3H, CH_3Ar), 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, Δν=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). ^{13}C-NMR δ: 4.6 (C-1), 21.4 (CH_3Ar), 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_S,R_2,R_3,S_5,R_S)-**7bA** ^{1}H-NMR. δ: 0.87 (d, 3H, J=7.1 Hz, H-1), 1.60–2.00 (m, 2H, H-4), 2.39 (s, 3H, CH_3Ar), 2.41 (s, 3H, CH_3Ar), 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). ^{13}C-NMR δ: 8.8 (C-1), 21.4 (CH_3Ar), 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** ($CHCl_3$ 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 $NaHCO_3$ 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,R_2,S_4,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%. ^{1}H-NMR δ: 1.38 (s, 3H, CH_3C), 1.42 (s, 3H, CH_3C), 1.40–1.65 (m, 2H, H-3), 2.41 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3Ar), 2.74 (d, 2H, J=6.3 Hz, CH_2CHO), 2.90 (AB of ABX, 2H, J_{AB}=13.0 Hz, J_{AX}=6.8 Hz, J_{BX}=4.0 Hz, Δν=71.6 Hz, CH_2CHO), 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). ^{13}C-NMR δ: 19.7 (CH_3C), 21.4 (CH_3Ar), 29.7 (CH_3C), 35.6 (C-3), 63.3, 62.7 (C-1, C-5), 64.5, 64.2 (C-2, C-4), 99.7 ($C(CH_3)_2$), 141.5, 130.0, 124.4, 123.7 (arom C). **IR** ($CHCl_3$) ν_{max}: 3390, 2910, 1600, 1490, 1380, 1265, 1160, 1085, 1035, 1015, 810 cm^{-1}.

*(R_S,S_2,S_4,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%. ^{1}H-NMR δ: 1.53 (s, 6H, CH_3C), 1.72 (dd, 2H, J=7.8 Hz and 7.8 Hz, H-3), 2.41 (s, 6H, CH_3Ar), 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). ^{13}C-NMR δ: 21.3 (CH_3Ar), 24.5 ((CH_3)$_2$C), 36.9 (C-3), 61.0 (C-2, C-4), 63.8 (C-1, C-5), 101.9 (C(CH_3)$_2$), 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 ^{1}H-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, CH_3C), 1.49 (s, 3H, CH_3C), 1.70–1.50 (m, 2H, H-4), 2,41 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3Ar), 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_S,S_2,R_3,S_5,R_S)-**9aA** ^{1}H-NMR. δ: 1.13 (d, 3H, J=7.0 Hz, H-1), 1.44 (s, 3H, CH_3C), 1.49 (s, 3H, CH_3C), 1.72–1.51 (m, 2H, H-4), 2.41 (s, 6H, CH_3Ar), 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). ^{13}C-NMR (50 MHz, $CDCl_3$) **9aA** and **9bA** δ: 6.3, 5.8 (C-1), 20.0, 19.8 (CH_3C), 21.6 (CH_3Ar), 29.3, 29.6 (CH_3C), 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(CH_3)$_2$), 141.5, 141.1, 129.9, 129.6, 129.4, 125.7, 124.6, 123.7 (arom C). MS (EI) **9aA** and **9bA**: m/z: 434 (M^+), 419, 404, 295, 203, 139, 123, 91. HRMS: Calcd for $C_{23}H_{30}O_4S_2$: 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 ^{1}H-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** ^{1}H-NMR. δ: 0.83 (d, 3H, J=6.9 Hz, H-1), 1.52 (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C), 1.76 (dd, 2H, J=7.0 Hz and 2.4 Hz, H-4), 2.41 (s, 6H, CH_3Ar), 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_S)-**9bB** ^{1}H-NMR. δ: 0.93 (d, 2H, J=7.0 Hz, H-1), 1.50 (s, 3H, CH_3C), 1.51 (s, 3H, CH_3C), 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, CH_3Ar), 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). ^{13}C-NMR δ: 4.3, 7.2 (C-1), 21.5 (CH_3Ar), 24.6, 24.5, 24.4, 24.2 (CH_3C), 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(CH_3)$_2$), 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/$ZnCl_2$ 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 six-membered 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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