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# Stereoselective Addition of Organometallic Reagents to β–Hydroxyketones

**José Luis García Ruano,* Amelia Tito,* and Rafael Culebras**

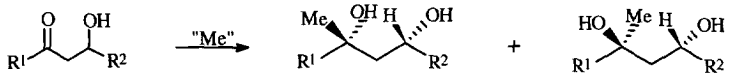
Departamento de Química Orgánica, Universidad Autónoma de Madrid.
Cantoblanco, 28049- Madrid, Spain.

**Abstract**: Reactions of several β–hydroxyketones with different methylation reagents are reported. The *de's* are moderated or good (40-75%) and slightly change with the relative steric size of the R groups at the starting hydroxyketone. The *syn*-diols are predominant in reactions with $Me_3Al/ZnBr_2$ and $MeLi/Me_3Al$, whereas the *anti*-diols are the major ones with $MeLi/ZnBr_2$. The method has been used to synthesize optically pure (+)-(2***R***,4***R***)-2-phenyl-2,4-pentanediol.

Reactions of cyclic and acyclic β-ketosulfoxides with $AlMe_3$ or $AlMe_3/ZnCl_2$[1] as well as those with $Et_2AlCN$ or $Et_2AlCN/ZnCl_2$[2] showed to evolve with very high diastereomeric excesses. In both cases, the results obtained suggested that the observed stereoselectivity could be attributed to the association of the sulfinyl oxygen to some of the acidic centers of the reagents (Al or Zn) as a previous step to the attack (intra or intermolecular) of the aluminum derivative on the carbonyl group. Taking into account that β–hydroxyketones and β–ketosulfoxides have a basic oxygen atom (hydroxylic and sulfinylic respectively) with the same relative position with respect to the carbonyl group, we decided to explore the behavior of the β–hydroxyketones in reactions with $Me_3Al$ and $Et_2AlCN$. The initial studies about hydrocyanation reactions of β–hydroxyketones[3] evidenced that the role of the OH group is not too much different from the one of SO group, but the asymmetric induction was lower in the first case. These results prompted us to study the nucleophilic addition of organometallic reagents to β–hydroxyketones, in order to obtain 1,3-diols, because this method would provide a new entry into the synthesis of polyoxy natural products containing tertiary alcohols.[4]

Concerning the 1,3-asymmetric induction, both the reduction[5,6] and the cyanide addition[3,7] of β–hydroxyketones are well documented. By contrast, only one paper has been reported about their alkylation reactions.[8] Treatment of β–hydroxyketones with $MeTiCl_3$ and $MeTi(O^iPr)_3$ mainly yielded the *anti*-diols (with high *de* when $R^1=R^2=Ph$), whereas reactions of the corresponding β-silyloxyketones with lithium, magnesium and titanium reagents, afforded isomeric mixtures where the *syn*-diols were predominant.[8]

In the present paper we report a convenient method for the stereoselective methylation of the β-hydroxyketones **1a-1f** with aluminum reagents ($AlMe_3$, $Me_3Al/ZnBr_2$) as well as those using MeLi as the methylating agent of the previously chelated substrates ($MeLi/Me_3Al$ and $MeLi/ZnBr_2$) to yield the corresponding *syn*-**2** and *anti*-**3** diols (Scheme 1).




**1 a-f** **2 a-f** **3 a-f**

| $R^1$ | $R^2$ | | | |
|---|---|---|---|---|
| Ph | Me | **1a** | *syn*-**2a** | *anti*-**3a** |
| Tol | Et | **1b** | *syn*-**2b** | *anti*-**3b** |
| *t*-Bu | *i*-Pr | **1c** | *syn*-**2c** | *anti*-**3c** |
| *n*-Pr | *i*-Pr | **1d** | *syn*-**2d** | *anti*-**3d** |
| *i*-Bu | Ph | **1e** | *syn*-**2e** | *anti*-**3e** |
| *i*-Bu | *i*-Pr | **1f** | *syn*-**2f** | *anti*-**3f** |

**Scheme 1**

## Results and discussion

In order to optimize the reactions of hydroxyketones with different reagents, we chose **1c** as the model starting material. The obtained results are collected in Table 1.

Table 1: Alkylation of β-hydroxyketone **1c** with different methylation reagents

| Entry | Method[a] | Reagent(eq)/Lewis acid (eq) | Solvent | t(h) / [b] | *syn*-**2** / *anti*-**3** ratio[c] | Yield (%)[d] |
|---|---|---|---|---|---|---|
| 1 | A | $Me_3Al$(4) | Toluene | 12 h | 65 : 35 | 52 |
| 2 | B | $Me_3Al$(4) / $ZnBr_2$ | $CH_2Cl_2$ | 2h / 1.5h | 79 : 21 | 66 |
| 3 | C | MeLi (1.3) / $Me_3Al$(1.3) | Toluene | 1h / 1h | 79 : 21 | 66 |
| 4 | D | MeLi (4) / $ZnBr_2$(2) | $CH_2Cl_2$ | 2h / 1.5h | 24 : 76 | 72 |

a) For reaction conditions see experimental. b) Chelation time (h) with the second reagent. c) Deduced from the $^1$H-NMR spectra of the reaction mixtures. d) After chromatographic purification of the diols.

Substantial amount of the starting material was recovered in the reactions with $Me_3Al$ (entry 1) despite the excess of the reagent (4 eq) and the long reaction times (12 h) required to achieve significant conversion. By contrast, the reactions conducted on the substrates previously chelated with $ZnBr_2$ (entries 2 and 4) or $Me_3Al$ (entry 3) were accomplished with complete conversion of the starting product.[9] The optimal conditions to achieve the highest stereoselectivity and chemical yields for the different reagents used are those indicated in table 1. As we can see, the less satisfactory results (lower yield and stereoselectivity and longer reaction time) were obtained by Method A and therefore the methods B, C, and D were selected for β-hydroxyketones **1a-1f**.

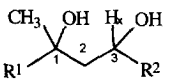
The starting materials were obtained by aldolic reactions following the previously described procedures,[6] and the results obtained in their methylation reactions are shown in Table 2. As we can see, the stereochemical course observed for the reactions with MeLi in the presence of $ZnBr_2$ (*anti*-stereoselectivity) is different to those with $Me_3Al/ZnBr_2$ or $MeLi/Me_3Al$ (*syn*-stereoselectivity). The *syn*-diol **2c** also was predominant in reactions of **1c** with $Me_3Al$ (entry 1, Table 1). Additionally, the relative size of $R^1$ and $R^2$ has only a moderate influence on the stereoselectivity and thus, when $R^1$ is larger than $R^2$ (**1a-1c**) *de's* ranged between 40 and 75%, whereas in the opposite case (**1d-1f**) *de's* were lower than 40%.

Table 2. Results obtained in the addition of organometallic reagents to β-hydroxyketones **1a-f**

| Starting material | Nucleophile(eq)/Lewis acid(eq) | *Syn*-**2** : *Anti*-**3** | Yield % |
|---|---|---|---|
| **1a** | $Me_3Al(4) / ZnBr_2(2)$ | 88 : 12 | 75 |
| **1b** | " | 75 : 25 | 72 |
| **1c** | " | 79 : 21 | 66 |
| **1d** | " | 66 : 34 | 78 |
| **1e** | " | 65 : 35 | 65 |
| **1f** | " | 60 : 40 | 66 |
| **1a** | $MeLi (1.3) / Me_3Al(1.3)$ | 82 : 18 | 75 |
| **1b** | " | 86 : 14 | 76 |
| **1c** | " | 76 : 24 | 75 |
| **1d** | " | 73 : 27 | 72 |
| **1e** | " | 68 : 32 | 70 |
| **1f** | " | 65 : 35 | 70 |
| **1a** | $MeLi (4) / ZnBr_2(2)$ | 21 : 79 | 78 |
| **1b** | " | 26 : 74 | 74 |
| **1c** | " | 24 : 76 | 72 |
| **1d** | " | 39 : 61 | 73 |
| **1e** | " | 35 : 65 | 75 |
| **1f** | " | 30 : 70 | 72 |

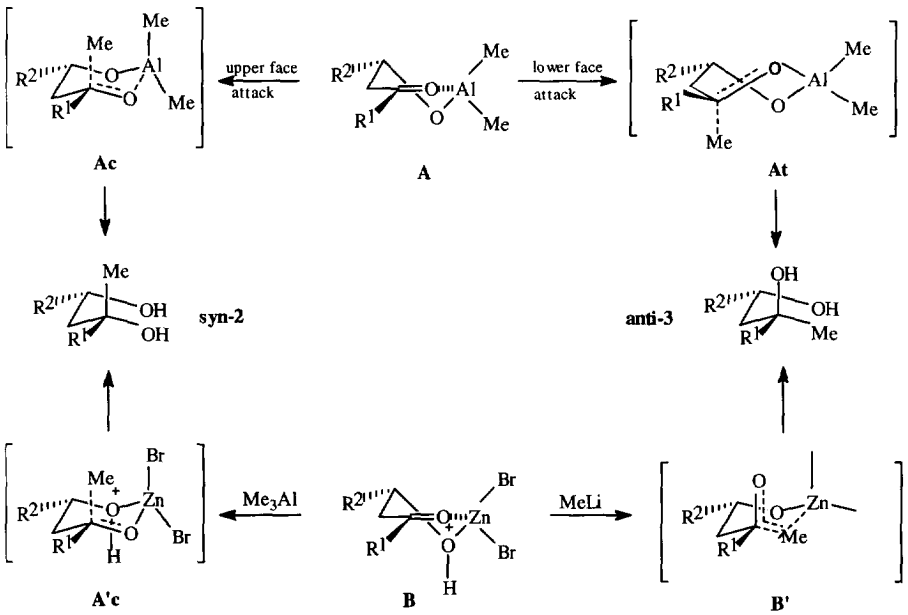
The formation of the acetonides derived from diastereoisomers **2** and **3** was not possible in our hands precluding their unequivocal configurational assignment. Nevertheless, the relative configuration (*syn* or *anti*) of the diols **2** and **3** was reasonably assigned on the basis of their $^1$H-NMR parameters, according to the rule that the methine protons (**CHOH**) of the *syn* diols appeared at lower fields than those of the *anti* isomers. This rule was established by Fujisawa et al. on diols of a similar structures to those of our substrates and confirmed by X-ray diffraction studies.[8] When we studied the chemical shifts of diols **2** and **3**, we found that the methyl group of compounds *syn*-**2** exhibited higher $^1$H-δ values but lower $^{13}$C-δ values[10] (Table 5) than those of their corresponding *anti* isomers. As a consequence, in those cases where one of the three mentioned signals is coincident for both isomers, the configurational assignment is still possible with the aid of the two other parameters.

Table 3. Relevant NMR parameters for the configurational assignment of diols **2** and **3**.




| $R^1$ | $R^2$ | Compounds | δ-**Hx** | δ-$CH_3$ | δ-$CH_3$ |
|---|---|---|---|---|---|
| Ph | Me | *syn*-**2a** / *anti*-**3a** | 4.35 / 3.65 | 1.67 / 1.52 | 27.9 / 32.5 |
| Tol | Et | *syn*-**2b** / *anti*-**3b** | 4.05 / 3.40 | 1.67 / 1.51 | 27.8 / 29.6 |
| *t*-Bu | *i*-Pr | *syn*-**2c** / *anti*-**3c** | 3.78 / 3.78 | 1.25 / 1.23 | 20.8 / 25.2 |
| *n*-Pr | *i*-Pr | *syn*-**2d** / *anti*-**3d** | 3.68 / 3.62 | 1.30 / 1.20 | 25.3 / 28.7 |
| *i*-Bu | Ph | *syn*-**2e** / *anti*-**3e** | 5.20 / 5.10 | 1.42 / 1.25 | 28.0 / 26.0 |
| *i*-Bu | *i*-Pr | *syn*-**2f** / *anti*-**3f** | 3.70 / 3.65 | 1.30 / 1.26 | 25.9 / 29.2 |

The stereochemical results observed in reactions using $Me_3Al$ (method A, Table 1) as the reagent can be explained by assuming the attack of the methylating reagent on the chelated species **A**, resulting from the initial coordination of aluminum with the hydroxylic oxygen, further elimination of $CH_4$ and final coordination of the obtained alkoxydimethylalane with the carbonyl oxygen. The Scheme 2 shows that the approach of the reagent from the upper face of the presumably most stable half-chair conformation of the species **A** (that displaying $R^2$ in pseudoequatorial arrangement) would yield the *syn*-diols **2** through a chair-like TS ($\mathbf{A_c}$), whereas a twist-like TS ($\mathbf{A_t}$) would be involved in the approach from the lower face resulting in the formation of the *anti*-**3** diols. The larger stability of $\mathbf{A_c}$ with respect to $\mathbf{A_t}$ justifies that *syn*-diols were obtained as the major products. A similar explanation could be used to explain the results obtained with both $MeLi/Me_3Al$ (MeLi would act as the nucleophile on the species **A**) and $Me_3Al/ZnBr_2$ ($Me_3Al$ would attack on the chelated species **B**[11] ). A similar stereochemical course has been proposed to explain the results obtained in the alkylation of β-ketosulfoxides[1] and the reduction of β-hydroxyketones.[5,6]

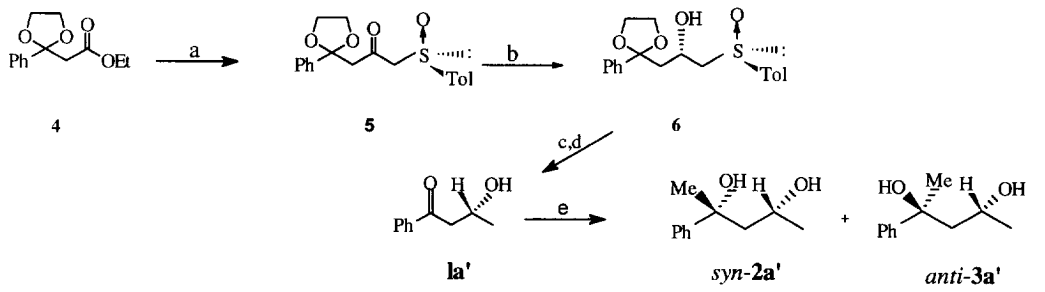



**Scheme 2**

The reaction with $MeLi/ZnBr_2$ displays the opposite diastereofacial preference. This can be justified by assuming that the chelated species **B** evolves into **B'** by attack of the MeLi, which gives rise to the Me-Zn bonds as it has been previously suggested.[12] The intramolecular methylation from **B'** would be easier through the conformation exhibiting the carbonyl oxygen in pseudoaxial arrangement and thus, the obtention of the *anti*-diols as the major ones is not unexpected. Similar intramolecular transfer has been proposed by Evans[5a] to justify the obtention of the *anti* diastereoisomers in the reduction of β-hydroxyketones.

Finally we have checked the usefulness of the present alkylation reaction in the asymmetric synthesis of (+)-(2***R***,4***R***) and (-)-(2***S***,4***R***)-2-phenyl-2,4-pentanediol, according to the sequence depicted in Scheme 3.

The reaction of the protected β-ketoester **4**[13] with the carbanion of (***R***)-methyl-*p*-tolylsulfoxide yielded the α-sulfinyl ketone **5**, which was reduced with DIBAL affording the β-hydroxysulfoxide **6** in 66% yield and *de* higher than 96% by $^1$H-NMR. The ***S*** configuration of compound **6** was assigned according to the expected stereochemical course for DIBAL reduction of β-ketosulfoxides.[14] Desulfurization with Raney nickel yielded hydroxyketal **7** with $^1$H-NMR spectrum identical to that reported for racemic (±)-**7**.[15] Hydrolysis of the ketal group with camphorsulfonic acid yielded optically pure β-hydroxyketone **1a'**.[16] The reaction of **1a'** with $Me_3Al/ZnBr_2$ yielded a 88:12 mixture of *syn*-**2a'**:*anti*-**3a'**, separated by flash chromatography. The high optical purity (*ee* > 96%) of the major diol, established by $^1$H-NMR analysis of both *syn*-**2a'** and its racemic *syn*-**2a** in the presence of $Eu(hfc)_3$, indicates that the conditions used do not affect the configurational stability of the chiral carbon present in the starting β-hydroxyketone **1a'**.




a) $LiCH_2SOTol$, THF, -78°C; b) DIBAL; c) Raney nickel; d) $CH_3COCH_3$ , CSA; e) $Me_3Al/ZnBr_2$

**Scheme 3**

## Experimental

Melting points were determined on a Gallenkamp apparatus in open capillaries and are uncorrected. $^1$H-NMR and $^{13}$C-NMR were recorded in the FT mode on a Bruker AC-200 instrument coupled to an ASPECT 2000 computer, transforming 16K data points. Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constant (Hz) were obtained by first order analysis of spin patterns. Mass spectra were recorder on a VG Autospec spectrometer. The HRGCMS were obtained in the SIR-voltage mode on a Carlo Erba MFC500. Elemental analyses were performed in a Perkin-Elmer 2400-CHN Elemental analyzer. Infrared (IR) spectra were recorded on a Philips PU-9716 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Analytical thin-layer chromatography was performed on DC-Alufolien 0.2 mm silica gel 60-F plates (MERCK) and flash chromatography by use of silica gel (MN-Kieselgel 60, 230-400 mesh).

***General Methods for alkylation of β-hydroxyketones.***

***Method A*** : *$Me_3Al$*. To a 2M solution of $Me_3Al$ (4 mmol) in hexane was added dropwise a solution of the β-hydroxyketone **1c** (1 mmol) in 5 mL of toluene at 0° C. The mixture was allowed to reach room temperature and then stirred for 12h. The reaction was monitored by TLC (ethyl acetate/hexane 1:4). The mixture was decomposed with 2 mL of 10% aqueous hydrochloric acid. The aqueous layer was extracted with diethyl ether (3x10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo to give a mixture of **2c** and **3c** as a ellow oil.

***Method B***: *$Me_3Al/ZnBr_2$*. To a suspension of $ZnBr_2$ (2 mmol) in 5 mL of $CH_2Cl_2$ was added at room temperature a solution of β-hydroxyketone (1 mmol) in 5 mL of $CH_2Cl_2$. The resulting mixture was stirred for 1h and then added into a 2M solution of $Me_3Al$ (4 mmol) in hexane at 0°C. The reaction mixture was allowed to warm to room temperature and then stirred for 2h. The reaction was worked up as in method A.

***Method C***: *MeLi/$Me_3Al$*. To a 2M solution of $Me_3Al$ (1.3 mmol) in hexane was added a solution of β-hydroxyketone (1 mmol) in 10 mL of toluene at 0° under argon atmosphere. The resulting mixture was stirred for 1h at room temperature, cooled at -78°C and then 1.3 mmol of MeLi (1.5 M in ethyl ether) were added. The mixture was allowed to warm to ambient temperature, stirred for 1h and worked up as in method A.

***Method D***: *MeLi/$ZnBr_2$* To a suspension of $ZnBr_2$ (2 mmol) in 5 ml of $CH_2Cl_2$ was added at room temperature a solution of β-hydroxyketone (1 mmol) in 5 mL of $CH_2Cl_2$. The resulting mixture was stirred for 1h and then added to a solution of MeLi (4 mmol) 1.5 M in ethyl ether at 0°C. After the addition, the mixture was stirred at room temperature for 2h and worked up as in method A.

$^1$H- and $^{13}$C-NMR of the *syn*- and *anti*-diols are collected in Table 4 and 5, respectively.

Table 4- **$^1$H-NMR** data of 1,3-diols.

| $R^1$ | $R^2$ | Compounds | δ-$CH_3$ | δ-$CH_2$ | δ-Hx | δ-$R^1$ | δ-$R^2$ |
|---|---|---|---|---|---|---|---|
| Ph | Me | *syn*-**2a** | 1.67 (s) | 1.81 (m) | 4.35 (m) | 7.20-7.60 (m, 5H, Ar) | 1.21 (d, 3H, J=7) |
| | | *anti*-**3a** | 1.52 (s) | 1.97 (m) | 3.65 (m) | 7.20-7.60 (m, 5H, Ar) | 1.12 (d, 3H, J=7) |
| Tol | Et | syn-**2b** | 1.67 (s) | 1.81 (m) | 4.05 (m) | 2.35 (s, 3H),<br>7.10-7.50 (m, 4H, Ar) | 0.95 (t, 3H, J=7)<br>1.50 (m, 2H) |
| | | *anti*-**3b** | 1.51 (s) | 2.01 (m) | 3.40 (m) | 2.35 (s, 3H)<br>7.10-7.50 (m, 4H, Ar) | 0.82 (t, 3H, J=7)<br>1.40 (m, 2H) |
| *t*-Bu | *i*-Pr | syn-**2c** | 1.25 (s) | 1.3-1.5 (m) | 3.78 (m) | 0.92 (s, 9H) | 0.91 (d, 6H, J=6.9)<br>1.30-1.60 (m, 1H) |
| | | *anti*-**3c** | 1.23 (s) | 1.70-1.90 (m) | 3.78 (m) | 0.92 (s, 9H) | 0.91 (d, 6H, J=6.9)<br>1.30-1.60 (m, 1H) |
| *n*-Pr | *i*-Pr | syn-**2d** | 1.30 (s) | 1.50 (m) | 3.68 (m) | 0.92 (t, 3H, J=6.8)<br>1.40 (m, 2H), 1.60 (m, 2H) | 0.91 (d, 6H, J=6.5)<br>1.33-1.60 (m, 1H) |
| | | *anti*-**3d** | 1.20 (s) | 1.50 (m) | 3.62 (m) | 0.92 (t, 3H, J=6.8)<br>1.40 (m,2H), 160 (m, 2H) | 0.91 (d, 6H, J=6.5)<br>1.33-1.60 (m, 1H) |
| *i*-Bu | Ph | syn-**2e** | 1.42 (s) | 1.60-2.00 (m) | 5.20 (m) | 0.92 (d, 6H, J=6.9)<br>1.60-170 (m, 1H), 1.80-2.00 (m, 2H) | 7.20-7.40 (m, 5H, Ar) |
| | | *anti*-**3e** | 1.25 (s) | 1.60-2.00 (m) | 5.10 (m) | 0.92 (d, 6H, J=6.9)<br>1.60-170 (m,1H), 1.80-2-00 (m, 2H) | 7.20-7.40 (m, 5H, Ar) |
| *i*-Bu | *i*-Pr | syn-**2f** | 1,30 (s) | 1.52 (m) | 3.70 (m) | 0.92 (d, 6H, J=7.1)<br>1.50 (m, 1H), 1.55 (m, 2H) | 0.92 (d, 6H, J=7)<br>1.80 (m, 1H) |
| | | *anti*-**3f** | 1.26 (s) | 1.52 (m) | 3.65 (m) | 0.92 (d, 6H, J=7.1)<br>1.50 (m, 1H), 1.55 (m, 2H) | 0.92 (d, 6H, J=7)<br>1.80 (m, 1H) |

***(+)-(Rs)-4,4-(Ethylenedioxy)-4-phenyl-1-p-tolylsulfinylbutan-2-one 5.*** To a solution of *i*-$Pr_2NH$ (2.4 mL, 17 mmol, 2 eq) in THF (25 mL) was added at -78°C a 2.5 M solution of *n*-BuLi in hexane (6.8 mL, 17

mmol, 2 eq). The mixture was stirred for 45 min before adding (+)-(***R***)-methyl *p*-tolylsulfoxide[17] (2.62 g, 17 mmol, 2 eq) in THF (20 mL). After stirring between -78°C to -30°C for 30 min, the ester **4**[18] (2 g, 8.47 mmol, 1 eq) in THF (15 ml ) was cooled to -78°C prior to the dropwise addition. The reaction mixture was stirred for 1.5 h and the reaction was monitored by TLC (ethyl acetate/hexane 3:2). Saturated aqueous $NH_4Cl$ (5 ml) was added and the aqueous layer extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were washed with saturated NaCl, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography (ethyl acetate/ hexane 3:2) to yield pure β-ketosulfoxide **5** (1.62g, 66% yield) $[\alpha]_D$= +114.5 (c=2, $CHCl_3$). IR ($CHCl_3$): 2990,1720, 1620, 1220 and 1060 $cm^{-1}$. $^1$H-NMR 7.2-7.6 (m, 4H, AA'BB', Ar), 7.2-7.6 (m, 5H, Ar), 3.95 (m, 2H, $CH_2$-SO), 3.7-4.1 (m, 4H, $CH_2$-$CH_2$), 2.99 and 3.04 (AB, 2H, $J_{AB}$=17.3 Hz, $CH_2$-CO), 2.41 (s, 3H, $CH_3$-Ar). $^{13}$C-NMR 198.2, 142.0, 140.9, 140.0 (3 C), 130.0, 128.5, 125.4, 124.3 (9 CH), 108.0, 69.4, 64.5, 54.2 and 21.5. MS (EI): 344 (0.05) $M^+$, 328 (0.7), 149 (100), 139 (20), 105 (40), 91 (23) and 77 (24).

Table 5. $^{13}$**C-NMR** data of 1,3-diols.

| $R^1$ | $R^2$ | Compounds | δ-$CH_3$ | δ-$C_2$ | δ-$C_3$ | δ-$C_1$ | δ-$R^1$ | δ-$R^2$ |
|---|---|---|---|---|---|---|---|---|
| Ph | Me | *syn*-**2a** | 27.9 | 50.9 | 65.8 | 75.1 | 124.3, 126.8, 128.3 (CH)<br>149.2 (C) | 24.3 ($CH_3$) |
| | | *anti*-**3a** | 32. 5 | 50.1 | 66.4 | 75.1 | 124.3, 124.8, 126.4 (CH)<br>149.2 (C) | 24.4 ($CH_3$) |
| Tol | Et | *syn*-**2b** | 27.8 | 48.8 | 70.9 | 74.8 | 20.9 ($CH_3$)<br>128.9, 124.4 (CH); 136.3, 146.4 (C) | 9.7 ($CH_3$)<br>30.8 ($CH_2$) |
| | | *anti*-**3b** | 29.6 | 47.7 | 71.5 | 75.4 | 20.9 ($CH_3$)<br>128.9, 124.7 (CH); 135.8, 144.4 (C) | 9.3 ($CH_3$)<br>32.7 ($CH_2$) |
| *t*-Bu | *i*-Pr | *syn*-**2c** | 20.8 | 36.6 | 73.7 | 76.1 | 24.7 ($CH_3$)<br>37.8 (C ) | 7.1, 18.4 ($CH_3$)<br>34.0 (C) |
| | | *anti*-**3c** | 25.2 | 39.7 | 72.1 | 75.9 | 24.7 ($CH_3$)<br>37.9 (C) | 17.0, 18.2 ($CH_3$)<br>34.3 (CH) |
| *n*-Pr | *i*-Pr | *syn*-**2d** | 25.3 | 47.2 | 73.8 | 73.9 | 14.5 ($CH_3$)<br>16.8, 41.9 ($CH_2$) | 17.6, 18.1 ($CH_3$)<br>34.1 (CH) |
| | | *anti*-**3d** | 28.7 | 47.1 | 73.7 | 74.0 | 14.6 ($CH_3$)<br>17.7, 41.9 ($CH_2$) | 17.6, 18.3 ($CH_3$)<br>34.1 (CH) |
| *i*-Bu | Ph | *syn*-**2e** | 28.0 | 49.7 | 71.7 | 73.9 | 25.2 ($CH_3$)<br>24.4 (CH), 48.5 ($CH_2$) | 128.8, 125.5, 127.2 (CH)<br>144.8 (C) |
| | | *anti*-**3e** | 26.0 | 52.9 | 71.6 | 73.9 | 24.7 ($CH_3$)<br>23.7 (CH), 48.6 ($CH_2$) | 128.8, 125.5, 127.2 (CH)<br>144.8 (C) |
| *i*-Bu | *i*-Pr | *syn*-**2f** | 25.9 | 53.4 | --- | 74.0 | 18.2 ($CH_3$)<br>24.4 (CH), 42.6 (CH) | 24.8 ($CH_3$)<br>34.2 (CH) |
| | | *anti*-**3f** | 29.2 | 48.5 | --- | 73.9 | 17.7 ($CH_3$)<br>23.8 (CH), 43.7 ($CH_2$) | 24.8 ($CH_3$)<br>34.2 (CH) |

***(+)-(2S,Rs)-4,4-(Ethylenedioxy)-4-phenyl-1-p-tolylsulfinylbutan-2-ol 6***. To a solution of DIBAL (7.8 mmol, 1 M in hexane) in THF (20 mL) was added 1,92 g (5.6 mmol ) of ketosulfoxide **5** in THF (15 mL) at -78°C. The mixture was stirred for 2 h, hydrolyzed with methanol (5 mL) and water (5 mL) and the aqueous layer extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were washed with sat. NaCl, dried ($Na_2SO_4$) and evaporated. The solid product was recrystallised from hexane to give 1.35g (70%) of pure hydroxysulfoxide **6** as a white solid, mp 125°C. $[\alpha]_D$=+162.7 (c=2, $CHCl_3$). IR($CHCl_3$): 3510, 2985, 1600, 1200, 1040 and 925 $cm^{-1}$. $^1$H-NMR 7.2-7.6 (AA'BB', 4H, Ar), 7.2-7.6 (m, 5H, Ar), 4,52 (m, 1H, CH), 3.15-4.15 (m, 4H, $CH_2$-$CH_2$), 2.85 (m, 2H, $CH_2$-S), 2.41 (s, 3H, $CH_3$) and 2.1 (m, 2H, $CH_2$). $^{13}$C-NMR 141.2, 140.9, 140.3, 129.6, 128.0, 125.0, 123.6, 109.4, 64.0, 63.8, 63.6, 62.5, 45.9 and 21.1. MS (EI) 346 (12) $M^+$,

331 (14), 330 (34), 163 (48), 145 (29), 140 (43), 139 (100), 121 (15), 117 (33), 106 (37) and 77 (46). HRMS calcd for $C_{19}H_{22}O_4S$: 346.12485. Found: 346.12485. Anal calcd for $C_{19}H_{22}O_4S$: C, 65.89; H, 6.35. Found: C, 65.64; H, 6.46.

***(+)-(2R)-4,4-(Ethylenedioxy)-4-phenylbutan-2-ol 7.*** A solution of the β-hydroxysulfoxide **6** (1.35 g, 4 mmol) in methanol (20 mL) was desulfurized with Raney nickel at room temperature for 3h (monitored by TLC). After filtration on celite, the solvent was evaporated and the yellow oil purified by chromatography (ethyl acetate-hexane 1:4) yielding 0.68 g (82%) of pure compound $[\alpha]_D$= +5.3 (c=2, $CHCl_3$). IR ($CHCl_3$) 3300-3600 $cm^{-1}$. $^1$H-NMR: 7.2-7.6 (m, 5H, Ar), 3.6-4.2 (m, 5H, **$CH_2$-$CH_2$** + **CH**-OH ), 1.92 (m, 2H, **$CH_2$**), 1.06 (d, 3H, J=6 Hz, **$CH_3$**-CH). $^{13}$C-NMR 141.8, 128.0, 127.9, 125.5, 110.4, 64.3, 63.7, 63.4, 48.0 and 22.7.

***(-)-(3R)-3-Hydroxy-1-phenylbutan-1-one 1a'.*** To a solution of 0.68g (3.27 mmol) of the hydroxyacetal **7** in acetone (25 mL) was added 75 mg (0.33 mmol) of camphorsulfonic acid. The reaction mixture was stirred for 1h, diluted with $CH_2Cl_2$, washed with $NaHCO_3$ solution and brine, dried ($Na_2SO_4$) and the organic layer evaporated to leave the crude product as a yellow oil which was purified by column chromatography (ethyl acetate-hexane 1:4) to produce **1a'** in 80 % yield (0.43 mg). $[\alpha]_D$= -63 (c = 2, $CHCl_3$), lit [16] $[\alpha]_D$=-67 (c= 0.02, $CHCl_3$). $^1$H-NMR 7.4-8.01 (m, 5H, Ar), 4.45 (m, 1H, **CH**), 3.33 (s, 1H, **OH**), 3.05 and 3.21 (m, 2H, **$CH_2$**), 1,31 (d, 3H, J= 6.4 Hz, **$CH_3$**). $^{13}$C-NMR 200.3, 136.5, 133.2, 46.4 and 22.3.

The alkylation of **1a'** with $Me_3Al/ZnBr_2$ according to the method B yielded a 88:12 mixture of **2a'** and **3a'** which were separated by column chromatography (ethyl acetate-hexane 1:4).

***(+)-(2R,4R)-2-Phenyl-2,4-pentanediol 2a':*** Rf = 0.26. 75% yield (0.30 g), mp 60°C (white solid by cyclohexane). $[\alpha]_D$ = + 25.4 (c=1.26, $CHCl_3$). Anal. calcd.for $C_{11}H_{16}O_2$: C, 73.33; H, 8.88.Found: C, 73.04; H, 8.75 IR ($CHCl_3$): 3450, 2970, 1600, 1100. $^1$H-NMR (see Table 4.) $^{13}$C-NMR (see Table 5). MS (EI): 180 (0.83) $M^+$, 165 (23) $M^+$-$CH_3$, 147 (8), 121 (100),118 (37), 105 (86), 91 (24), 77 (44).

***(-)-(2S,4R)-2-Phenyl-2,4-pentanediol 3a':*** Rf = 0.27. 13% yield (0.05 g, oil) $[\alpha]_D$=-21.5 (c=1, $CHCl_3$). Anal. calcd.for $C_{11}H_{16}O_2$: C, 73.33 H, 8.88.Found: C, 73.10;H, 8.58. IR (CHCl): 3450, 2970, 1600, 1100. $^1$H-NMR (see Table 4). $^{13}$C-NMR (see Table 5). MS (EI) 180, (0.83) $M^+$, 165 (23,) $M^+$-$CH_3$, 147 (8), 121 (100),118 (37), 105 (86), 91 (24), 77 (44)

Table 6. **HRGCMS** data of 1,3-diols.

| $R^1$ | $R^2$ | Compounds | Calcu. | Found | Assign. |
|---|---|---|---|---|---|
| Ph | Me | *syn*-**2a**/*anti*-**3a** | a | a | $M^+$ |
| | | | | | $M^+$- $CH_3$ |
| Tol | Et | *syn*-**2b**/*anti*-**3b** | 208.1461 | 208.1461 / 208.1461 | $M^+$ |
| | | | 193.1228 | 193.1228 / 193.1228 | $M^+$- $CH_3$ |
| *t*-Bu | *i*-Pr | *syn*-**2c**/*anti*-**3c** | 188.1776 | - | $M^+$ |
| | | | 173.1542 | 173.1542 | $M^+$- $CH_3$ |
| *n*-Pr | *i*-Pr | *syn*-**2d**/*anti*-**3d** | 174.1620 | - | $M^+$ |
| | | | 159.1387 | 159.1387 / 159.1387 | $M^+$- $CH_3$ |
| *i*-Bu | Ph | *syn*- **2e**/*anti*-**3e** | 222.1620 | - | $M^+$ |
| | | | 207.1385 | 207.1385 | $M^+$- $CH_3$ |
| *i*-Bu | *i*-Pr | *syn*-**2f**/*anti*-**3f** | 188.1776 | - | $M^+$ |
| | | | 173.1542 | 173.1542 | $M^+$- $CH_3$ |

a) See experimental part for microanalysis results of *syn* **2a'** and *anti*-**3a'**.

**Dedicatory**. We would like to dedicate this paper to the memory of the late Prof Dr Francisco Fariña.

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9. We have also made the reactions of **1c** with MeLi (1.3 eq) in the presence of methylaluminum *bis* (2,4,6-tri-*tert*-butyl-phenoxide). Nevertheless the use of MAT did not improve the stereoselectivity and the chemical yield was even lower than under other conditions used in Table 1.
10. The criterium of the $^{13}$C-δ values is only valid when $R^2$=Alkyl. Therefore, in the case of **2e** and **3e** the relative configuration has been assigned on basis of the $^{1}$H-δ values as well by assuming a similar stereochemical course for all these reactions.
11. Partial or complete Al-Zn exchange resulting in the formation of **A** from **B** species can not be disregarded.
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13. We used the protected β–ketoester **4** as the starting material to avoid the presumably negative influence of the free carbonyl on the stereoselectivity of the β–ketosulfoxide reduction. Nevertheless, Solladié showed that this protection was not necessary (Solladié, G.; Ghiatou , N. *Tetrahedron Lett.*, **1992**, *33*, 1605).
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