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Stereoselective Sulfoxide Directed Reduction of 1,2-Diketo-Derivatives to Enantiomerically Pure *Syn* and *Anti* 1,2-Diols.

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Abstract: A new route to enantiopure *syn* and *anti* 1,2-diols is described from oxalyl-di-(N-methyl-N-methoxyamide) *via* the corresponding β-ketosulfoxide. This is the first report of the stereoselective reduction of a γ-keto-β-hydroxysulfoxide. © 1997 Elsevier Science Ltd.

In the course of our studies concerning sulfoxide-directed reduction of carbonyl groups, we have shown that enantiomerically pure *syn* and *anti* 1,2-diols could be obtained by reduction of β-keto-γ-hydroxysulfoxides easily made from α-hydroxyesters.[1]

We report now the synthesis of enantiomerically pure *syn* and *anti* 1,2-diols **6** from the oxalic acid derivative **1** using a new highly diastereoselective reduction of a carbonyl (>95/5 to >97/3) directed by a sulfoxide in γ-position (scheme 1).

The di-N-methyl-N-methoxyamide of oxalic acid **1**[2], reacted smoothly with (+)*R* p-tolylmethyl sulfoxide anion[3] to give in 78% isolated yield the β-ketosulfoxide (*R*)-**2**.[4] The DIBAL reduction of the β–ketosulfoxide **2** provided then the β-hydroxysulfoxide **3**[5] with high *S*-diastereoselectivity (>97/3) and 81% isolated yield, thus showing that there was no significant effect of the vicinal amide function.[6]

The protected β-hydroxysulfoxide (*R,S*)-**4** was transformed, by Grignard addition to the Weinreb amide[7], into the β-hydroxy-γ-ketosulfoxide **5(a-d)** in good to excellent yields (78 to 92%). The *S* absolute configuration at the C-2 chiral center in compound **5**, deduced from our previous results and model of approach[8] for the reduction step, was confirmed by chemical correlation of **5b** to the known (+)(*R*) 1-phenyl-2-hydroxypropanone **7**[9] by desulfurization and deprotection.

DIBAL reduction of the β-silyloxy γ-ketosulfoxide **5a** happened to be a slow process requiring 12h to afford a moderate yield (60%) of the desired *syn* diol **6a** with a low diastereoselectivity (75%), Table I. We discovered that addition of a Lewis acid, having no tendency to chelate, allowed to carry out the reaction in a

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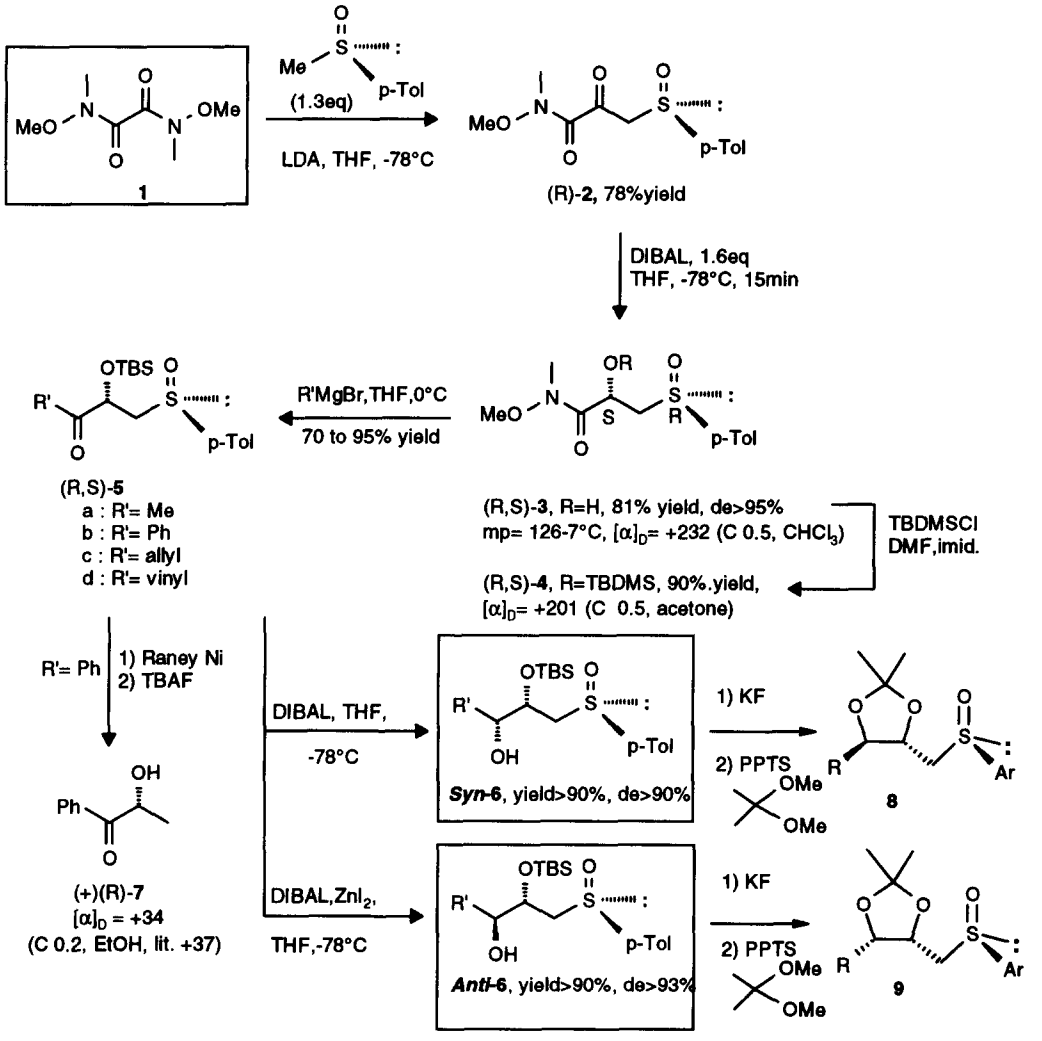
few hours at -78°C and with high and not inverted diastereoselectivities. Ytterbium Triflate in catalytic amount (0.6eq) was found to be the best Lewis acid giving a 96% yield and a stereoselectivity up to 91%.

In all the other cases, **5b-d**, where the carbonyl substituant is an aromatic group, a vinyl or an allyl group, the Lewis acid catalysis was not necessary and DIBAL reduction gave the *syn* diol **6**[10] in high yield (93-95%) and high stereoselectivity (92->95%),Table I.



Scheme 1

In sharp contrast, reduction of the β-silyloxy γ-ketosulfoxide **5** with DIBAL in presence of chelating Lewis acid ZnI_2 afforded in high yield only the *anti*-diol **6**[10], Table I.

Table I. : Reduction of β-silyloxy γ-ketosulfoxide 5 to *syn* and/or *anti* β-silyloxy γ-hydroxysulfoxide 6.

[S(R),2(S)] 5		Reduction Conditions			[S(R),2(S),3(R)]-*Syn* 6,[S(R),2(S),3(S)]-*anti* 6		
	R	Lewis Acid	reaction time	reaction temp.	isolated yield	de%	*Syn*-6 / *Anti*-6
a	Me		12h	-78°C-rt	60%	75%	87 / 13
a	Me	SnCl4	2h	-78°C	88%	80%	90 / 10
a	Me	LiBr	3h	-78°C	90%	70%	85 / 15
a	**Me**	**$Yb(OTf)_3$**	**1h**	**-78°C**	**96%[a]**	**92%**	**96 / 4**
a	**Me**	**ZnI_2**	**3h**	**-78°C**	**96%[a]**	**94%**	**3 / 97**
b	Ph		30 min	-78°C	95%[b,c]	92%	96 / 4
b	Ph	ZnI_2	30 min	-78°C	92%[b]	>95%	2 / 98
c	allyl		30 min	-78°C	93%[b]	>95%	98 / 2
c	allyl	ZnI_2	30 min	-78°C	90%[b]	94%	3 / 97
d	vinyl		30 min	-78°C	97%[a]	>95%	98 / 2
d	vinyl	ZnI_2	30 min	-78°C	91%[a]	>95%	2 / 98

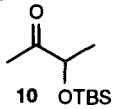
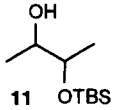
a) isolated by crystallisation; b) isolated by chromatography; c) 2.5eq of DIBAL.

The relative configurations of carbons C-2 and C-3 in diols **6** were assigned by ^{13}C NMR of the corresponding acetonides **8** and **9**[11]: a smaller non-equivalence between the *gem*-dimethyl groups was observed for the *syn* diol than for the *anti* diol (0.8ppm and 3ppm). [12]

Compounds **5** contain two chiral centers(C-2 or S). The reduction of the easily accessible α-silyloxy-ketone **10** has been studied in the same experimental conditions: DIBAL, DIBAL-$Yb(OTf)_3$ and DIBAL-ZnI_2. The results in Table II, compared to those listed in Table I, showed clearly that the chiral sulfoxide group participated to the high stereoselectivity observed in the reduction of compounds **5**.

This is, thus, the first report of high asymmetric induction induced by a sulfoxide located in γ position with respect to the carbonyl.

Table II. Reduction of α-silyloxiketone 10 with DIBAL.

Reagent	Product	Reduction conditions	*Syn* / *Anti* **11**
 **10** OTBS	 **11** OTBS	DIBAL, THF, -78°C	65 / 35
		DIBAL, $Yb(OTf)_3$, THF, -78°C	75 / 25
		DIBAL, ZnI_2, THF, -78°C	50 / 50

References and notes.

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2). Sibi, M.P., Marwin, M., Sharma, R., *J. Org. Chem.* **1995**, *60*, 5016-5023.

3). Solladié, G., Hutt,J., Girardin, A., *Synthesis* **1987**, 173.

4). After 3h at -78°C, only the compound **2** was obtained in the reaction. The symmetrical diketodisulfoxide was never detected by ^{1}H NMR of the crude product.

5). Compound **3** : ^{1}H NMR (200 MHz, $CDCl_3$): 2,41 (s, 3H, ptol); 2,91 (ddd, 2H, ABX, J_{AB}=13Hz J_{AX}=15Hz, $\Delta\nu$ = 55Hz); 3,2 (s, 3H, N-Me); 3,7 (s, 3H, OMe); 3,78 (d, 1H, OH, J = 7Hz); 4,97 (m, 1H, X from ABX); 7,32 and 7,55 (4H, AA'BB', J = 8Hz CH arom).^{13}C NMR (50MHz, $CDCl_3$): 21,50 (CH_3 , pTol); 32,72 (N-Me); 61,84 (OMe); 62,59 (CH_2); 64,09 (CH); 124,05 (CH arom); 130,13 (CH arom) 140,92 and 141,71 (C arom); 174,03 (C = O).

6) A drastic effect of the vicinal amide was shown when we tried to get with Zn chelation[8] the reverse stereoselectivity for the carbonyl reduction : by reduction with DIBAL in presence of zinc bromide, chloride or iodide the diastereomer (*R,S*)-**3** was still obtained as the main product but with a lower diastereoselectivity, probably due to the Zn chelation on the vicinal amide and not on the sulfoxide.

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10). Other zinc Lewis acids gave a lower diastereoselectivity :.

Lewis acid	$Zn(OTf)_2$	$ZnCl_2$	$ZnBr_2$
Syn / Anti	1 / 1	35 / 65	20 / 80

***Syn* 6a** : ^{1}H NMR (200MHz, $CDCl_3$): 0,21 (s, 3H, CH_3Si); 0,32 (s, 3H, CH_3Si); 1,01 (s, 9H, tBuSi); 1,08 (d, 3H, J=7Hz); 2,38 (d, 1H, J=9Hz, OH); 2,42 (s, 3H, pTol); 2,83 (m, 2H, CH_2); 3,92 (m, 1H, CHOSi); 4,16 (m, 1H, CHOH); 7,31 and 7,53 (d, 4H, J=8Hz, H arom).^{13}C NMR (50MHz, $CDCl_3$): -4,62 and -4,3 (CH_3Si); 18,25 (C, tBuSi); 21,47 (CH_3, pTol); 25,35 (tBuSi); 61,34 (CH_2); 70,01 and 71,83 (CH); 123,42 and 130,83 (CH arom); 141,1 and 141, 97 (C-arom).

***Anti* 6a** : ^{1}H NMR (200Mhz, $CDCl_3$): 0,18 (s, 3H, CH_3Si); 0,28 (s, 3H, CH_3Si); 0,98 (s, 9H, tBuSi); 1,16 (d, 3H, J=9Hz, Me); 2,3 (d, 1H, J=10Hz, OH); 2,43 (s, 3H, ptol); 2,91 (ddd, 2H, J_{AB}=11Hz, J_{AX}=13Hz; $\Delta\nu$=35Hz); 3,65 (m, 1H, CHOSi); 4,18 (m, 1H, CHOH); 7,3 and 7,51 (d, 4H, AA'BB', Harom, J=8Hz). ^{13}C NMR (50MHz, $CDCl_3$): -4,25 and -4,20 (CH_3-Si); 18,30 (C, tBuSi); 18,75 (CH_3); 21,60 (CH_3, pTol); 26,03 (tBuSi); 63,29 (CH_2); 70,21 and 70,64 (CH); 123,90 and 130,14 ((CH arom); 141,22 and 141,62 (C arom).

11) acetonide **8a** : ^{13}C NMR (50MHz, $CDCl_3$): 15.42 ($\underline{C}H_3$-CH), 21.49 ($\underline{C}H_3$-Ph), 25.66 ($\underline{C}H_3$-C), 28.45 ($\underline{C}H_3$-C), 60.94 ($\underline{C}H_2$-SO), 72.16 ($\underline{C}$H-O), 73.23 ($\underline{C}$H-O), 108.80 (C-0), 123.65 (arom.CH), 130.17 (arom. CH), 141.42 (arom.C), 141.71 (arom.C).

acetonide **9a** : ^{13}C NMR (50MHz, $CDCl_3$): 16.04 ($\underline{C}H_3$-CH), 20.76 ($\underline{C}H_3$-Ph), 26.46 ($\underline{C}H_3$-C), 26.74 ($\underline{C}H_3$-C), 61.13 ($\underline{C}H_2$-SO), 75.36 ($\underline{C}$H-O), 75.86. ($\underline{C}$H-O), 108.60 (C-0), 123.14 (arom.CH), 129.29 (arom. CH), 140.50 (arom.C), 141.07 (arom.C).

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