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Asymmetric Synthesis Monitored by Chiral Sulfoxides: Syn and Anti Functionalized 1,2-Diols from α-Hydroxy-Esters.

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Abstract : the reduction of chiral b-keto-g-alkoxy-sulfoxides, readily made from chiral a-hydroxyesters, allowed the preparation of optically pure syn and anti functionalized 1,2-diols. The reduction is completely stereo controlled by the sulfoxide group.

Functionalized optically active 1,2-diols are very important building blocks for total synthesis of natural products. On the other hand, chiral α-hydroxyesters are very often used in enantioselective synthesis and some of them are commercially available. We report in this paper a very efficient transformation of chiral α-hydroxyesters into optically pure syn and anti 1,2-diols via β-keto-γ-alkoxy sulfoxides.

The methodology will be, first of all, described in the case of (-)(S) ethyl lactate **1a** and (+)(S) ethyl mandelate **1b** (scheme I).

(S) Ethyl lactate, protected with a t-butyldimethylsilyl group, **1a**, was allowed to react with (+)(R) methyl p-tolyl sulfoxide [1] anion, made with LDA in THF, to give the [S(R), 3(S)] β-keto γ-alkoxy sulfoxide **2a** in 89% yield. The [S(S), 3(S)] β-keto γ-alkoxy sulfoxide **4a** was prepared in a similar manner in 96% yield by use of (-)(S) methyl p-tolyl sulfoxide [1].
In this way eight different β-keto γ-alkoxy sulfoxides were prepared (Table I).

Table I : Synthesis of β-keto-γ-alkoxy sulfoxides.

1	R	P	2,Yld%	[S(R),3(S)]-2, $[\alpha]_D$	4,Yld%	[S(S),3(S)]-4, $[\alpha]_D$
a	Me	TBS	89	+146 (c=1.4, $CHCl_3$)	96%	-108 (c=1.3,$CHCl_3$)
b	Ph	TBS	95	+74 (c=1.4, $CHCl_3$)	95%	-38 (c=0.8, $CHCl_3$)
c	Me	MEM	90	(1)	90%	(1)
d	Ph	MOM	85	+263 (c=1, $CHCl_3$)	86%	+16 (c=1.1, $CHCl_3$)

1) This product could not be completely purified at this stage because it has the same Rf as methyl p-tolyl-sulfoxide.

Reduction of **2a** with DIBAL [2], gave the corresponding [S(R), 2(S), 3(S)] β-hydroxy γ-alkoxy sulfoxide **anti-3a** in 93% yield as the unique diastereomer [3] as shown by ^1H NMR (only one AB

system was detected for the methylene α to sulfoxide) and by ^{13}C NMR (only one set of signals). The absolute configuration of the new chiral center was deduced from our preceding studies of β-keto sulfoxides reduction [2] and confirmed by chemical correlation with the known acetonide of (3S,2R)-butanetriol [4] **8**: hydrolysis of the TBS group, formation of the acetonide, Pummerer rearrangement and reduction of the resulting intermediate.

Reduction of the β-keto sulfoxide **2a** with $ZnBr_2$/DIBAL [2] afforded the corresponding [S(R), 2(R), 3(S)] β-hydroxy γ-alkoxy sulfoxide **syn-3a** in 91% yield and 95% d.e (determined by ^1H NMR [5]). The absolute configuration of the new chiral center was deduced from our preceding results based on the formation of a chelate with $ZnBr_2$ [2].

(S) Ethyl mandelate, protected with a t-butyldimethylsilyl group, **1b**, was transformed into the [S(R), 3(S)] β-keto γ-alkoxy sulfoxide **2b** which gave by reduction with DIBAL the [S(R), 2(S), 3(S)] β-hydroxy γ-alkoxy sulfoxide **anti-3b** [6] in 91% yield and d.e>95%, and with $ZnBr_2$/DIBAL the [S(R), 2(R), 3(S)] β-hydroxy γ-alkoxy sulfoxide **syn-3b** [7] in 87% yield and 86% d.e.

DIBAL reduction of **4b** afforded the [S(S), 2(R), 3(S)] β-hydroxy γ-alkoxy sulfoxide **syn-5b** [8] in 91% yield and a d.e>95%. A configurational correlation between compounds **syn-3b** and **syn-5b** was carried out by oxidation of the sulfoxide group to sulfone, giving the same dihydroxy sulfone **6b**.

The results from table II showed that in DIBAL reduction the nature of the hydroxyl protecting group has no effect on the diastereoselectivity, which was always higher than 95%.

Table II: Reduction of β-keto γ-alkoxy sulfoxides with DIBAL

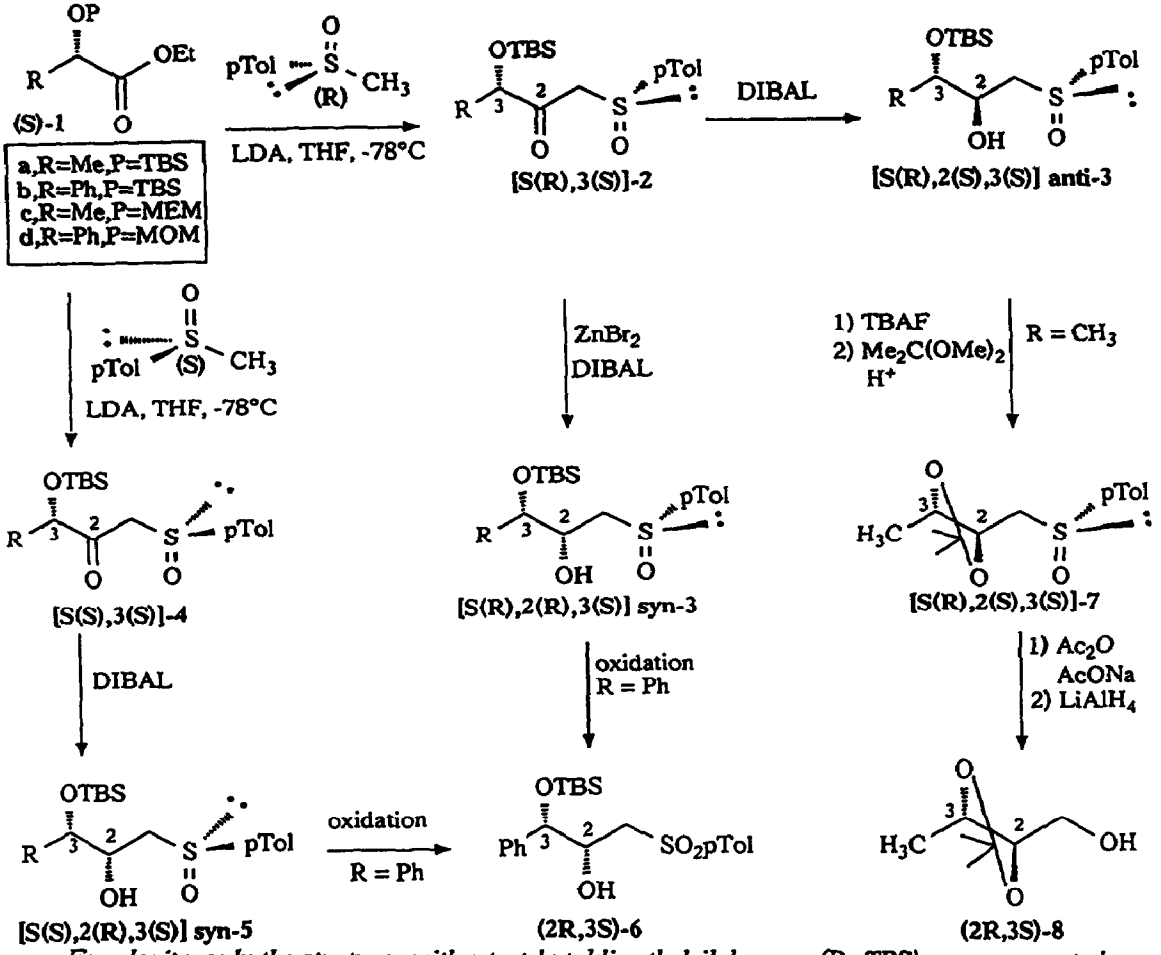
3 or 4			[S(R),2(S),3(S)], Anti-3			[S(S),2(R),3(S)], Syn-5		
	R	P	Yld%	de%	$[\alpha]_D$,($CHCl_3$)	Yld%	de%	$[\alpha]_D$,($CHCl_3$)
a	Me	TBS	93%	>95%	+176,(c=0.7)			
a	Me	TBS				91%	>95%	-159,(c=1.8)
b	Ph	TBS	94%	>95%	+165,(c=1.6)			
b	Ph	TBS				94%	>95%	-135,(c=2)
c	Me	MEM	94%	>95%	+191,(c=1)			
c	Me	MEM				91%	>95%	-161,(c=1.8)
d	Ph	MOM	91%	>95%	+289,(c=0.4)			
d	Ph	MOM				90%	>95%	-112,(c=0.34)

In sharp contrast, $ZnBr_2$/DIBAL reduction, which is based on a zinc chelate formation between the carbonyl and sulfoxide oxygens, gave low d.e. when other oxygen atoms, which can compete in the chelation, are present in the protecting group (Table III). The diastereomers [S(R), 2(R), 3(S)] **syn-3** or [S(S), 2(S), 3(S)] **anti-5** are, as predicted, the major product, according to the absolute configuration of the inducing sulfoxide, except in one case : a MOM protecting group and a large excess of $ZnBr_2$.

These results lead to the two following conclusions : the asymmetric induction was totally

controlled by the sulfoxide group and the highest d.e was obtained with DIBAL. Therefore syn or anti β-hydroxy γ-alkoxy diols can be obtained with a d.e higher than 95% by DIBAL reduction of respectively the corresponding [3(S), S(S)] or [(3(S), S(R)] β-keto γ-alkoxy sulfoxide.

Application of this method to more complex α-hydroxyesters will be reported very soon.



For clarity, only the stuctures with a tert-butyldimethylsilyl group (P=TBS) are represented.

Scheme I

References and notes.

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3) ^{1}H NMR of [S(R), 2(S), 3(S)] anti-3a: δ: 0.06 and 0.08 (s, 6H, Me_3Si), 0.86 (s, 9H, tBu), 1.08 (d,

3H, J=6Hz, CH_3), 2.43 (s, 3H, Ar-CH_3), 2.85 (AB from ABX, 2H, J_{AB}=13.5Hz, J_{AX}=9Hz, J_{BX}=2Hz, Δν=34Hz, H-1), 3.51 (d, 1H, J=4Hz, OH), 3.82 (qd, 1H, J=6Hz, H-3), 3.95 (m, 1H, H-2), 7.35 and 7.53 (AA'BB', 4H, J=8 Hz, arom.).

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5) ^{1}H NMR of [S(R), 2(R), 3(S)] **syn-3a** : δ : 0.05 (s, 6H, Me_3Si), 0.86 (s, 9H, tBu), 1.08 (d, 3H, J=6Hz, CH_3), 2.40 (s, 3H, Ar-CH_3), 2.94 (AB from ABX, 2H, J_{AB}=13Hz, J_{AX}=8Hz, J_{BX}=3.5Hz, Δν=22Hz, H-1), 3.41 (d, 1H, J=4.5Hz, OH), 3.88 (m, 2H, H-2, H-3), 7.32 and 7.55 (AA'BB', 4H, J=8Hz, arom.).

6) ^{1}H NMR of [S(R), 2(S), 3(S)] **anti-3b** : δ : -0.14 and 0.07 (s, 6H, Me_3Si), 0.89 (s, 9H, tBu), 2.41 (s, 3H, Ar-CH_3), 2.82 (AB from ABX, 2H, J_{AB}=13.5Hz, J_{AX}=9Hz, J_{BX}=2Hz, Δν=34Hz, H-1), 3.45 (d, 1H, J=4Hz, OH), 4.20 (m, 1H, H-2), 4.71 (d, 1H, J=5Hz, H-3), 7.30 and 7.40 (AA'BB', 4H, J=8Hz, arom. p-tolyl), 7.21-7.29 (m, 5H, arom.).

7) ^{1}H NMR of [S(R), 2(R), 3(S)] **syn-3b** : δ : -0.16 and 0.05 (s, 6H, Me_3Si), 0.88 (s, 9H, tBu), 2.40 (s, 3H, Ar-CH_3), 2.80 (AB from ABX, 2H, J_{AB}=13Hz, J_{AX}=5Hz, J_{BX}=1.5Hz, Δν=12Hz, H-1), 3.30 (d, 1H, J=3Hz, OH), 3.95 (m, 1H, H-2), 4.75 (d, 1H, J=6Hz, H-3), 7.27 and 7.47 (AA'BB', 4H, J=8Hz, arom. p-tolyl), 7.26, (m, 5H, arom.)

8) ^{1}H NMR of [S(S), 2(R), 3(S)] **syn-5b** : δ : -0.20 and 0.07 (s, 6H, Me_3Si), 0.81 (s, 9H, tBu), 2.40 (s, 3H, Ar-CH_3), 2.65 (AB from ABX, 2H, J_{AB}=13.5Hz, J_{AX}=10Hz, J_{BX}=2.5Hz, Δν=33Hz, H-1), 3.60 (d, 1H, J=2.5Hz, OH), 4.25 (m, 1H, H-2), 4.56 (d, 1H, J=6Hz, H-3), 7.27 and 7.47 (AA'BB', 4H, J=8Hz, arom. p-tolyl), 7.28 (m, 5H, arom.).

Table III : Reduction of β-keto γ-alkoxysulfoxides with $ZnBr_2$ [1]/DIBAL

3 or 4			[S(R),2(R),3(S)], Syn-3 [2]		[S(S), 2(S), 3(S)], Anti-5 [2]	
	R	P	Yield%	de% [3]	Yield%	de% [4]
a	Me	TBS	91	95		
b	Ph	TBS	87	86		
c	Me	MEM			85	62
c	Me	MEM			83	86[5]
d	Ph	MOM	86	50		
d	Ph	MOM	87	4[5]		
d	Ph	MOM			92	80

1) 1 equiv. of $ZnBr_2$; 2) major diastereomer ; 3) de% = (syn-3 %) - (anti-3 %) ; 4) de% = (anti-5 %) - (syn-5 %) ; 5) 5 eq. of $ZnBr_2$.

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