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REDUCTION OF β-HYDROXYSULFOXIDES: APPLICATION TO THE SYNTHESIS OF OPTICALLY ACTIVE EPOXIDES

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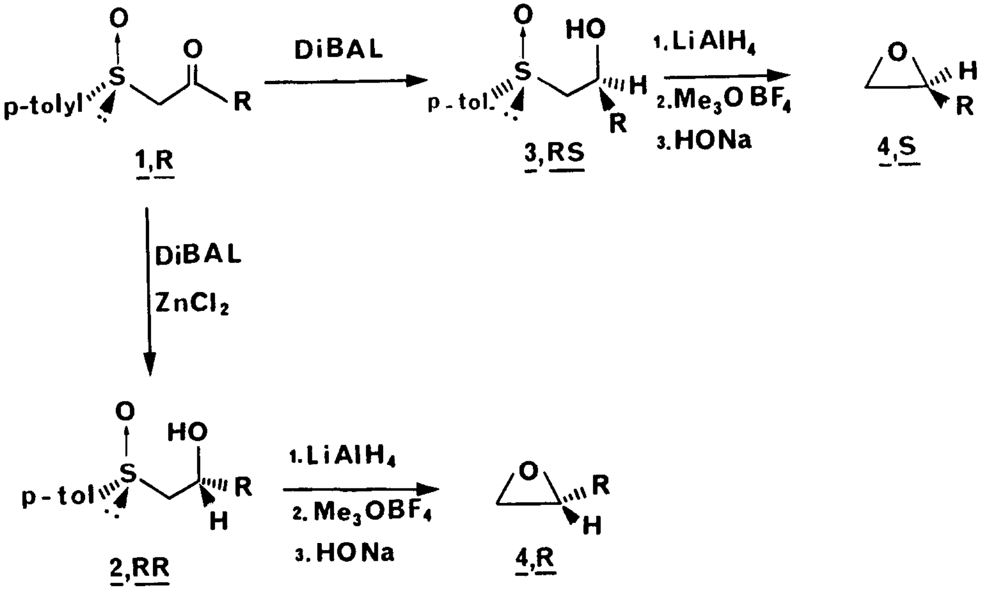
Abstract. *β-hydroxysulfoxides of opposite stereochemistry can be prepared in very high diastereoisomeric excesses (90 to 95%) by reduction of β-ketosulfoxides with DIBAL or DIBAL/$ZnCl_2$. A very efficient method to transform these reduction products into optically active epoxides is also described.*

Recently we have shown that optically active β-ketosulfoxides are convenient intermediates for the synthesis of both enantiomers of methylcarbinols in high ee, through reduction with $LiAlH_4$ or DIBAL[1]. The same methodology was also applied to prepare optically active allylic alcohols[2].

We now report an improvment of this reduction process giving higher asymmetric induction (90 to 95%) and also a very efficient method to transform the resulting β-hydroxysulfoxides into optically active epoxides which are useful chiral synthons.



Scheme 1

As shown in Table I, reduction of β-ketosulfoxides 1a,R and 1b,R with DIBAL according to procedure A (addition at -78°C of 1 in THF to a solution of DIBAL) afforded diastereoisomers 3a,RS and 3b,RS in respectively 60 and 74% d.e. The new procedure B (addition of DIBAL to 1 in THF at -78°C) increased significantly the d.e. to 90 and 86%.

In sharp contrast, $LiAlH_4$ reduction of 1a and 1b lead mainly to the other diastereoisomers 2a,RR and 2b,RR in 60 and 78% d.e. More interesting is the fact that the addition of DIBAL to a solution of 1a and 1b in THF containing one equivalent of anhydrous zinc chloride at -78°C gave still the diastereoisomers 2a,RR and 2b,RR but with more than 90% d.e.

Similar results were obtained from the β-ketosulfoxides 1c,R and 1d,R.

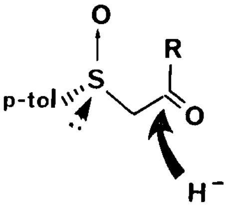
TABLE I

Reduction of β-ketosulfoxides 1,R

R	Reducing Agent	β-hydroxysulfoxides 2,RR / 3,RS	Yields%
1a , C_6H_5	DIBAL,method A	20 / 80	95
	DIBAL,method B	> 5 / 95	95
	$LiAlH_4$	80 / 20	80
	DIBAL,$ZnCl_2$	> 95 / 5	90
1b ,$C_6H_5CH_2CH_2$	DIBAL,method A	13 / 87	98
	DIBAL,method B	7 / 93	95
	$LiAlH_4$	88 / 12	90
	DIBAL,$ZnCl_2$	> 95 / 5	95
1c, n-C_8H_{17}	DIBAL,method B	5 / 95	95
	DIBAL,$ZnCl_2$	> 95 / 5	92
1d, n-$C_{13}H_{27}$	DIBAL,method B	5 / 95	95
	DIBAL,$ZnCl_2$	> 95 / 5	95

The different stereochemistry of these reductions according to the nature of the reducing agent can be understood in terms of different conformations of the β-ketosulfoxide.

In absence of any chelating metal,the reduction is expected to occur in the conformation 5 because of dipolar interactions,the hydride entering the side where the sulfoxide lone pair is located (giving the diastereoisomer RS) while in presence of Li^+ or Zn^{++},the β-ketosulfoxide is expected to adopt the chelated conformation 6 which,the hydride entering again the lone pair side, leads to the diastereoisomer RR.



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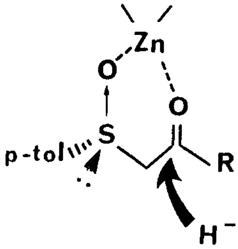

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The diastereoisomeric ratios 2/3 were always determined by ^1H NMR at 200 MHz of the crude product from the diastereotopic protons of the methylene group α to the sulfoxide,giving non equivalent ABX system in each diastereoisomer.

The absolute configuration of 2a,RR was known[3],while that of 2b,RR was determined by desulfurization with Raney nickel to the known 4-phenyl 2-butanol[4]. Finally,those of 2c,RR and 2d,RR were deduced from NMR characteristics in $CDCl_3$: a smaller non equivalence for the CH_2 α to the sulfoxide group was always observed in the diastereoisomer RR[1,2,6];as well as a more deshielded signal for the proton α to the hydroxyle.

The β-hydroxysulfoxides were then reduced to the corresponding sulfides with one equivalent of $LiAlH_4$ at room temperature for 6 hours (80% yield).The crude sulfide was then treated by one equivalent of trimethyloxonium fluoroborate in THF at room temperature and then by a solution of HONa for one hour giving the corresponding epoxide in 80% yield (Scheme 1).All these reactions can be conducted on the crude products.

Epoxides 4a and 4c (Table II) were already prepared by Pirkle[5] through chromatographic resolution of the β-hydroxysulfide.The absolute configurations are consistent with our assignment as well as the optical rotations.

TABLE II

Optically active epoxides 4,R and 4,S

R	Reducing Agent	Epoxide R/S	Yield* %	$\|\alpha\|_D$(solvent)
4a , C_6H_5	DIBAL,method B DIBAL,$ZnCl_2$	5 / 95 95/ 5	60 60	- 44° (ØH)[a] + 45° (ØH)
4c , n-C_8H_{17}	DIBAL,method B DIBAL,$ZnCl_2$	>5/95 >95/ 5	63 67	+ 9° ($CHCl_3$)[b] - 9.2° ($CHCl_3$)
4d , n-$C_{13}H_{27}$	DIBAL,method B DIBAL,$ZnCl_2$	>5/95[c] >95/ 5	65 70	+ 3° ($CHCl_3$) - 3° ($CHCl_3$)

**Yield calculated from the starting β-ketosulfoxide.*
a) $|\alpha|_{max.}$ =- 47°(ref.5). b) $|\alpha|_{max.}$ =- 8.8°(ref.5). c) From the d.e. of 3.

The 60 to 70% overall yields, calculated from the starting β-ketosulfoxides and the extremely high asymmetric induction step make this synthesis very attractive to prepare optically active epoxides.

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