Tetrahedron Letters,Vol.23,No.48,pp 5047-5050,1982 0040-4039/82/485047-04$03.00/0
Printed in Great Britain

REDUCTION OF β-KETOSULFOXIDES : A HIGHLY EFFICIENT ASYMMETRIC SYNTHESIS OF BOTH ENANTIOMERS OF METHYL CARBINOLS FROM THE CORRESPONDING ESTERS

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Summary *It is shown that reductions of β-ketosulfoxides of identical chirality (R) at sulfur , lead to reduction products of opposite stereochemistry according to the reducing agent used The high enantiomeric excesses obtained (80 to 100%) provide a general route to both enantiomers of methylcarbinols from the corresponding esters*

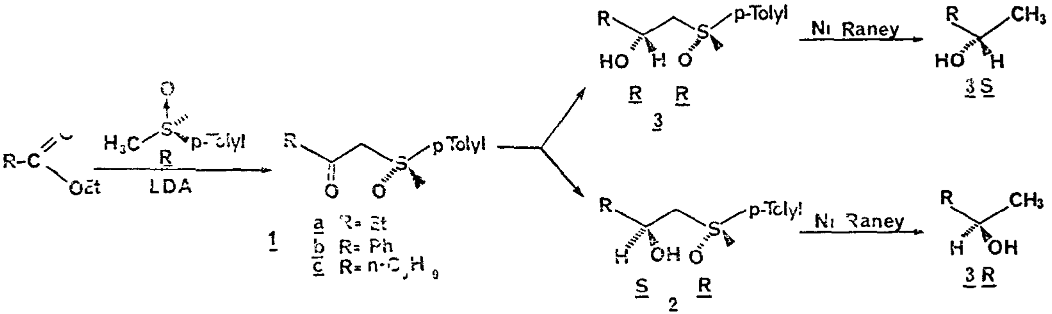
Several studies during the last few years emphasized the versatility of the chiral sulfoxide group in asymmetric synthesis[1] The moderate extent of asymmetric induction in the addition of a carbanion α to a sulfoxide[2] to a carbonyl in comparison to the high enantiomeric excesses obtained[3a,b] during aldol type condensation of α-sulfinylenolate anions suggested the importance of chelating factors

In this context, β-ketosulfoxides seem to be interesting models to study 1,3-asymmetric induction Steric and chelation control of the asymmetric induction in a way similar to that occuring with α-alkoxyketones[4] could be anticipated

However the litterature results showed that Grignard additions to β-ketosulfoxides[5] and metal hydrides reductions[6] were not as stereospecific as expected (40% ee and 68% ee respectively) Reduction of β-ketosulfoximines[7,8] reported recently gave also relatively poor e e

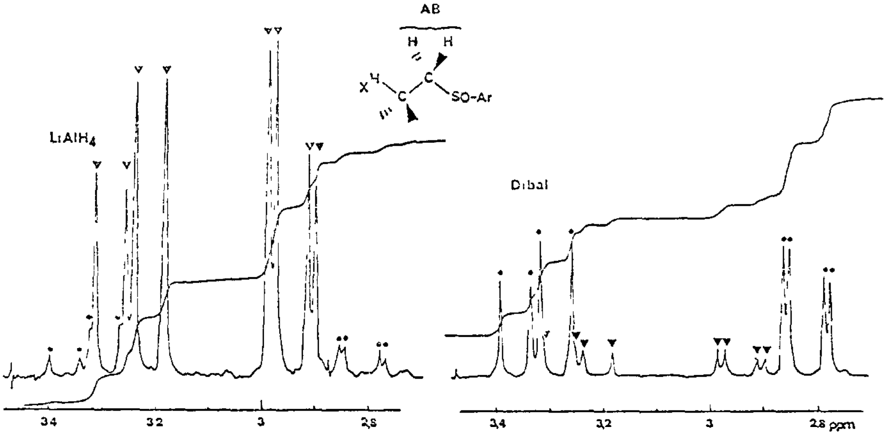
We report in this communication a more complete study of the reduction of β-ketosulfoxides, which provides a general route to both enantiomers of methylcarbinols

β-ketosulfoxides are readily available from esters (sheme 1) Diastereoisomeric ratios of the resulting β-hydroxysulfoxides were determined on crude products by 200 MHz ^{1}H-NMR The AB parts of the ABX systems in the two diastereomers 2 and 3 are (in every case a,b,c) noticeably non-equivalent allowing determination of their ratios One example is shown on scheme 2

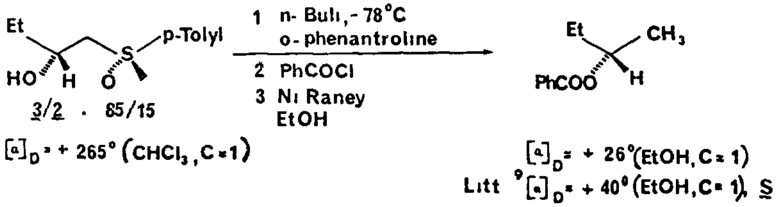


Scheme 1

We investigated a variety of reducing agents, and table I reports the corresponding results in the case of the β-ketosulfoxide 1a at -78°C The absolute configuration 2a or 3a of the major stereoisomer was assigned by chemical correlation with the known benzoate of (+) S 2-butanol (scheme 3)



Scheme 2. ^{1}HNMR (CDCl$_3$/TMS, Bruker WP-200) of the AB parts of diastereomeric mixtures (2a + 3a) obtained from LiAlH$_4$ or DIBAL reductions.



Scheme 3

These results show that it is actually possible to obtain, from the same chirality (*R*) at sulfur, reduction products of opposite stereochemistry according to the reducing agent used Sodium, lithium, tetrabutylammonium borohydride as well as lithium aluminium hydride gave mainly the diastereoisomer *3a* *R* *R* (about 60% e e) which indicated that the cation is not playing an important role in the control of the stereochemistry On the other hand diborane and diisobutylaluminium hydride (DIBAL) gave a completely reverse result with the main formation of the diastereoisomer *2a* *S* *R* (60% e e with DIBAL) Other reducing agents such as lithium tri-sec-butyl borohydride, zinc borohydride and borane-methylsulfide complex, showed a lower stereospecificity

TABLE I

Reduction of β-ketosulfoxide *1a* at -78°C

reducing agent	Solvant	% diastereoisomeric ratio *3*(*RR*)/*2* (*SR*)
$NaBH_4$	Et_2O/THF	69/31
$NaBH_4$	EtOH	80/20
$LiBH_4$	Et_2O/THF	81/19
$(n\text{-}Bu)_4NBH_4$	Et_2O/THF	85/15
$LiAlH_4$	Et_2O/THF	84/16
$LiEt_3BH$	THF	80/20
$Li(sec\text{-}Bu)_3BH$	THF	66/34
$Zn(BH_4)_2$	Et_2O/THF	66/34
$Zn(BH_4)_2$	EtOH	60/40
Me_2S, BH_3	THF	53/47
B_2H_6, THF	THF	30/70
$(i\text{-}Bu)_2AlH$	THF	22/78

Finally as shown in Table II the enantiomeric excesses can be significantly increased by lowering temperature to -100°C Compound *1a* was reduced to the diastereoisomer *3a* *R* *R* (86% e e) with lithium aluminium hydride while DIBAL lead to the other diastereoisomer *2a* *S* *R* (76% e e) In the same conditions *1b* having a phenyl ring α to the ketone was reduced with a slightly lower asymmetric induction It is important to note that the longchain β-ketosulfoxide *1c* gave at -78°C, with both reagents, the highest enantiomeric excesses 80 and 100% e e

TABLE II

Reduction of β-ketosulfoxides 1

Reducing Agent	Diastereoisomeric ratio 3(RR)/2(SR)		
	1a R = Et $-100°C^{\alpha}$	1b R = Ph $-100°C^{\alpha}$	1c $R{=}n\text{-}C_9H_{19}{}^{\delta}$ $-78°C^{\alpha}$
$LiAlH_4/Et_2O/THF$	$93/7^{\beta}$	$90/10^{\beta}$	$90/10^{\beta}$
DIBAL/THF	12/88	18/82	0/100

$^{\alpha}$reduction temperature $^{\beta}$diastereoisomeric ratios were determined by proton NMR at 200 MHz. $^{\gamma}$absolute configuration was determined from the known optical rotations[10] of 2b and 3b. $^{\delta}$absolute configuration was determined by chemical correlation to the known[11] alcohol 4c, (-) R

Synthetic applications of this asymmetric reduction are under progress

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(Received in France 13 July 1982)