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Applications of Chiral Sulfoxides in Enantioselective Synthesis of Diols and Total Synthesis of Natural Products

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ABSTRACT: *The sulfoxide mediated enantioselective reduction of carbonyl compounds was extended to the synthesis of enantiomerically pure syn and anti diols, including C_2 symmetric diols. Several applications related to the syntheses of natural products are described. Finally, this sulfoxide mediated enantioselective synthesis was extended to the transformation of ethyl oxalate or other oxalic acid derivatives to enantiomerically pure syn and anti 1,2-diols.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:443–452, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10079

In 1977 we published the first asymmetric aldol-type condensation of α-sulfinyl ester enolates giving β-hydroxy esters with a high enantioselectivity (ee > 85%) [1]. Since that time the use of chiral sulfoxides in asymmetric synthesis has been widely developed [2]. One of the most useful results that we obtained later concerns the reduction of β-ketosulfoxides [3] (Scheme 1). β-Ketosulfoxides are readily prepared from esters and their reduction with diisobutylaluminum (DIBAL) and $ZnCl_2$/DIBAL gives an opposite diastereoselectivity higher than 95%. By desulfurization, it is possible to transform β-hydroxysulfoxides into the corresponding enantiomerically pure carbinols.

Most of the experimental results show that chelated species and intramolecular hydride transfers are important factors for the control of the diastereoselectivity [3,4]. This efficient asymmetric synthesis of methylcarbinols has been used in macrolide synthesis; for example, in the case of Lasiodiplodin [5] (Scheme 2), it was possible to prepare the seco-ester in the very last step of the synthesis in either of the two possible configurations via the corresponding β-ketosulfoxide.

In this short review we cover only the formation of enantiomerically pure diols. Of course, from the preceding results, it follows that C_2 symmetric diols can be prepared in enantiomerically pure form by reduction of diketodisulfoxides [6], obtained for example from methyl succinate and (*R*)-methyl *p*-tolylsulfoxide (Scheme 3). This finding can be extended to the asymmetric synthesis of spiro ketals [7] (Scheme 4). In the case of 6-membered spiro ketals [7a], the configuration of the spiro center was controlled during the cyclization by the anomeric effect. The sulfinyl groups can be easily transformed into the two methyl groups present in natural products by desulfurization with Raney Nickel.

In a sharp contrast to the case of 5-membered spiro-ketals [7b] (Scheme 5), the configuration of the chiral spiro-center was not controlled by the anomeric effect. The cyclization of the corresponding dihydroxy-disulfoxide under classical conditions (PPTS, acetone) afforded indeed a 1:1 mixture of

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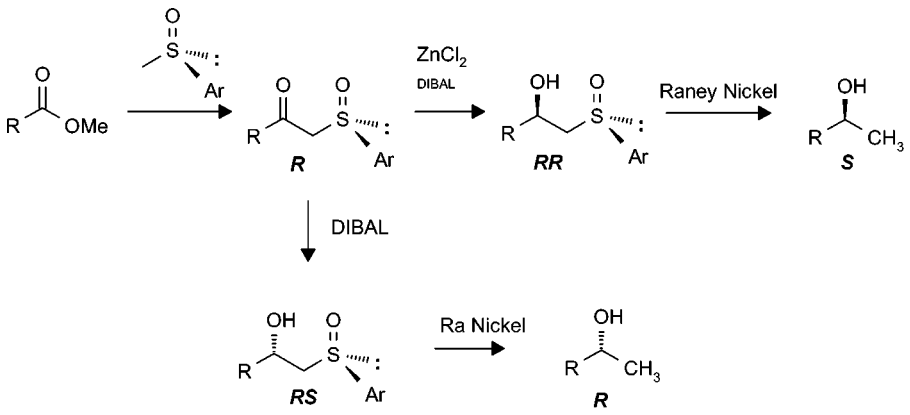

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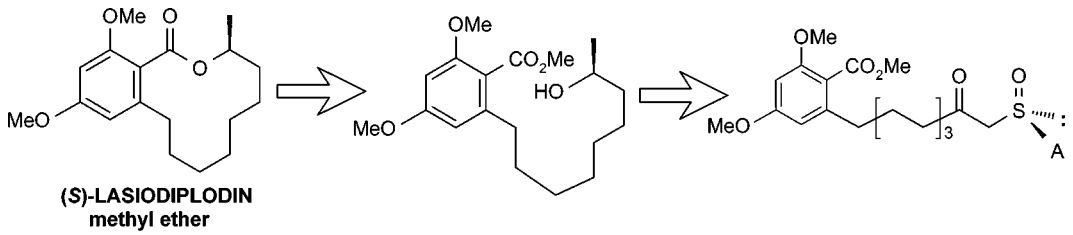

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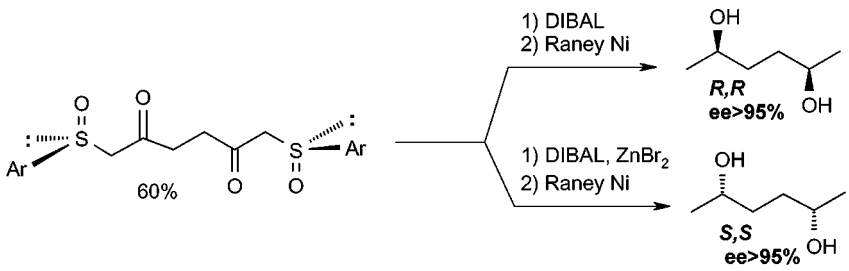
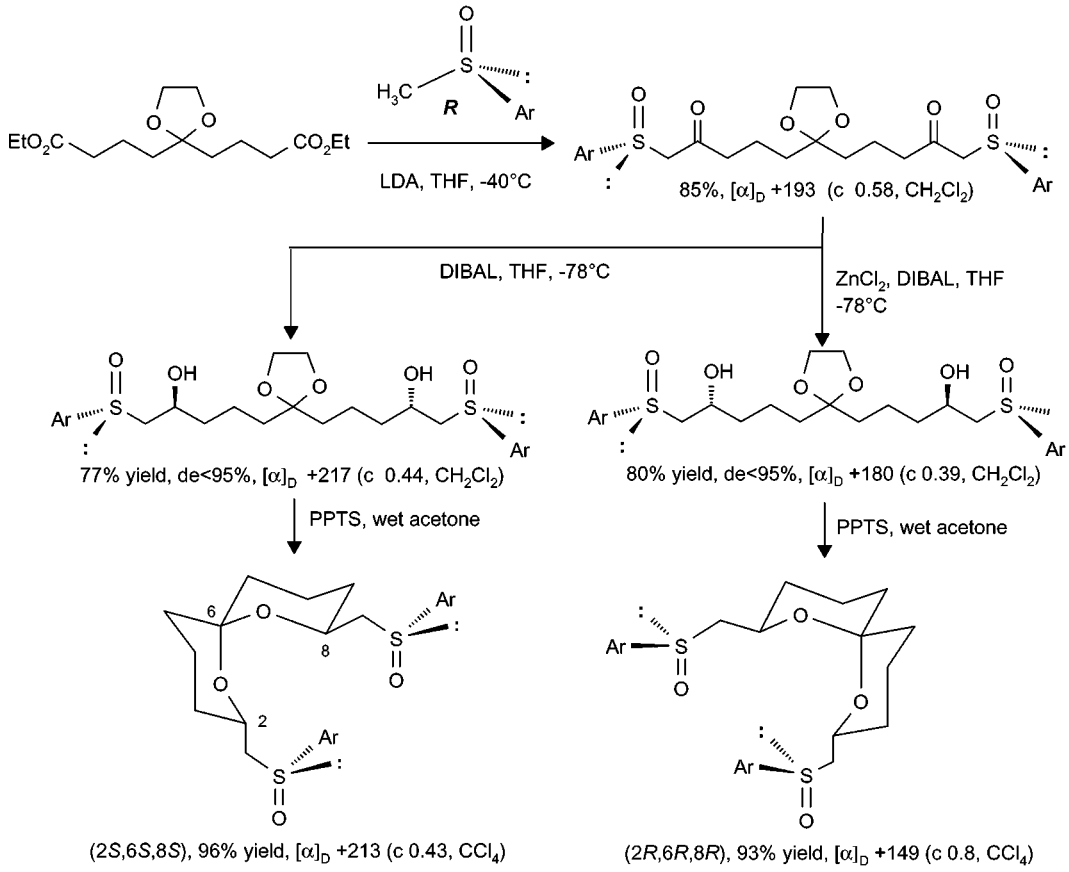


SCHEME 3

the two diastereomeric spiro compounds (5R and 5S). The use of a chelating Lewis acid, such as $ZnBr_2$, allowed us to obtain only the diastereomer 2S, 5S, 7S, *S*R in 75% yield, the cyclization being controlled by the formation of the less hindered bischelate between $ZnBr_2$ and the endocyclic oxygens [7b] (Scheme 6).

β,δ-Diketosulfoxides, which are easily prepared from esters, β-ketoesters or β-diketones, are excellent intermediates for the enantio- and diastereoselective syntheses of syn and anti 1,3-diols [8]. It was shown that the β-carbonyl group could be reduced, as in any β-ketosulfoxide in high stereoselectivity without any protection of the δ-carbonyl group [9] (which is enolized), and then the δ-carbonyl group in the resulting β-hydroxysulfoxide could be reduced following literature procedures to prepare syn and anti 1,3 diols (Scheme 7). In these cases, the



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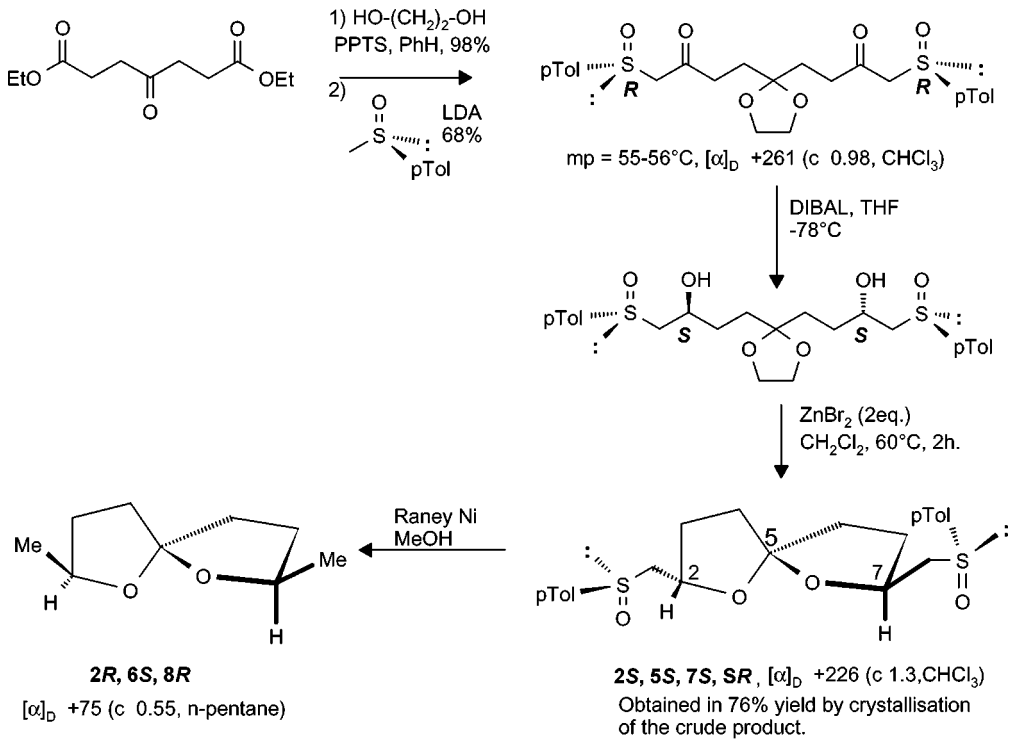

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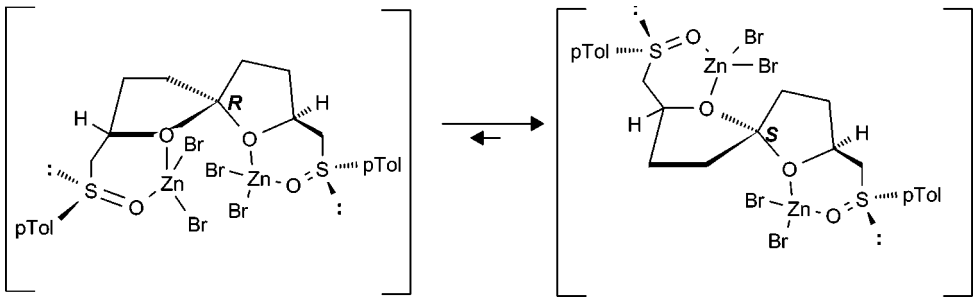

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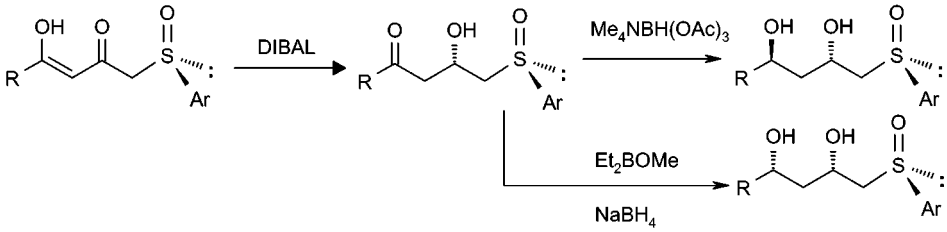
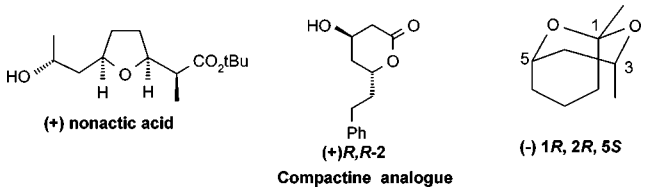


SCHEME 7

stereoselectivity of the reduction to syn or anti 1,3-diols was still controlled by the chiral hydroxylic center and there was no effect of the sulfinyl group. Several applications of these results have already been published: a very short enantioselective synthesis of (+)-nonactic acid [10], a stereoselective synthesis of a compactine analogue [11], which is an inhibitor of the biosynthesis of cholesterol, and a closely related stereoselective synthesis of a bicyclic ketal [12], which is an insect pheromone (Scheme 8).

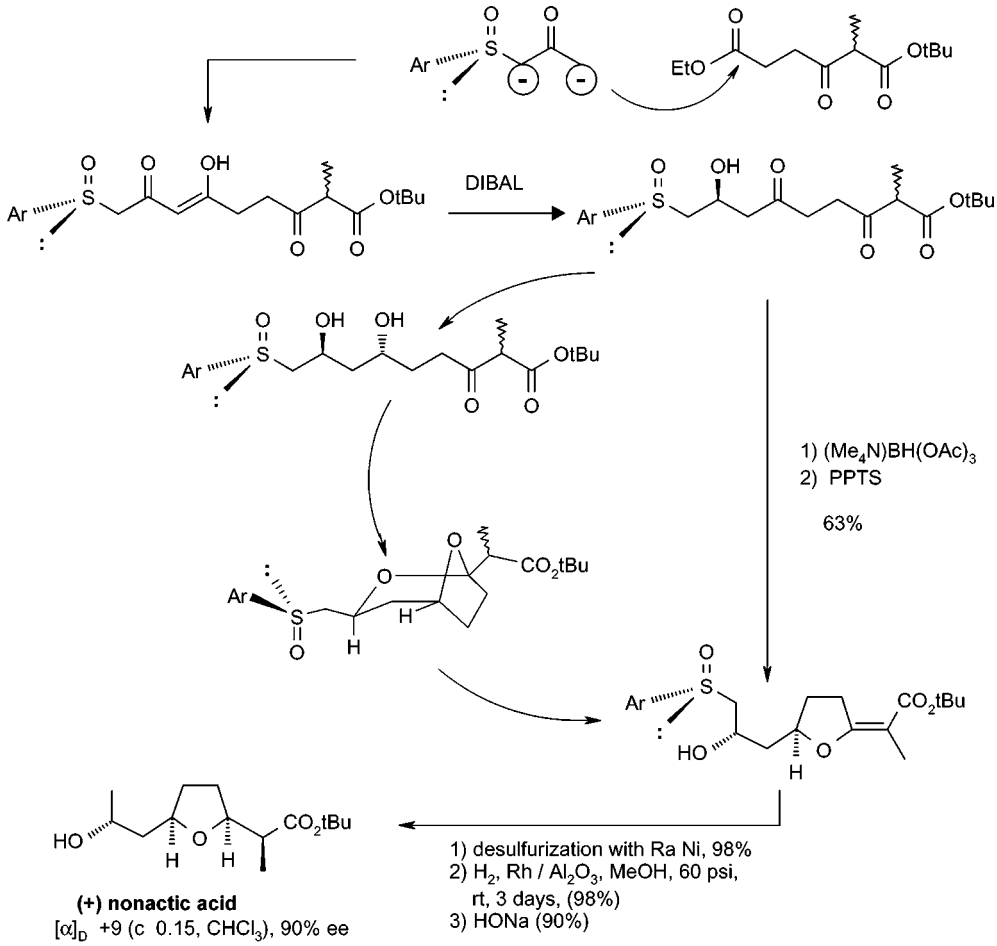
Scheme 9 shows the main features of (+)-nonactic acid synthesis [10]. Mono stereoselective reduction of the diketosulfoxide was effected, followed by reduction to the anti-diol, which was cyclized under the reaction conditions to a bicyclic ketal, which in turn was hydrolyzed to dehydrononactic acid and finally transformed into (+)-nonactic acid by known methods.



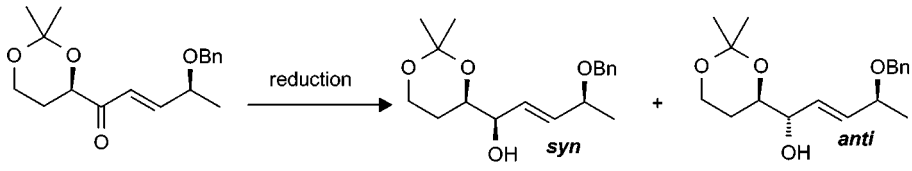
SCHEME 8

All the preceding results show that chiral sulfoxides can control the reduction of a carbonyl group in β position to the corresponding hydroxylic center in the desired configuration and in high stereoselectivity. Application of this method to 1,3-diketones allows to obtain enantiomerically pure 1,3-hydroxyketones, which can then be reduced to enantiomerically pure syn or anti 1,3-diols. C_2 symmetric diols can also be obtained from diketodisulfoxides. We have also looked into the enantioselective reduction of 1,2-dicarbonyl compounds. We were faced with the problem of the reduction of α-hydroxyketones in the total synthesis of descarestrictine (published recently [13]) (Scheme 10).

Although it is possible to get the pure syn diol by stereoselective reduction of a chiral α-hydroxyketone with L-selectride (a result already reported in the literature [14a]), it is, however, not possible to obtain such stereoselectivity in the formation of the anti diol [14b]. In a preliminary report concerning the formation of 1,2-diols, we have shown that enantiomerically pure syn and anti 1,2-diols are readily obtained from α-hydroxyesters that are commercially available in enantiomerically pure form, via the corresponding δ-hydroxy β-ketosulfoxides [14c] (Scheme 11). The stereoselectivity of the reduction was completely controlled by the sulfoxide chirality and not by the vicinal chiral hydroxylic center. We

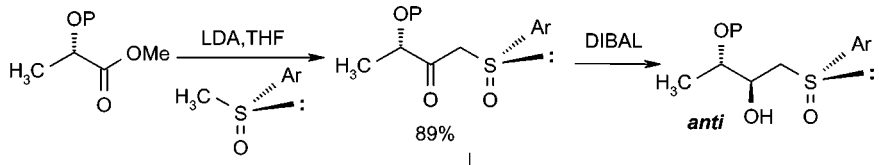


SCHEME 9



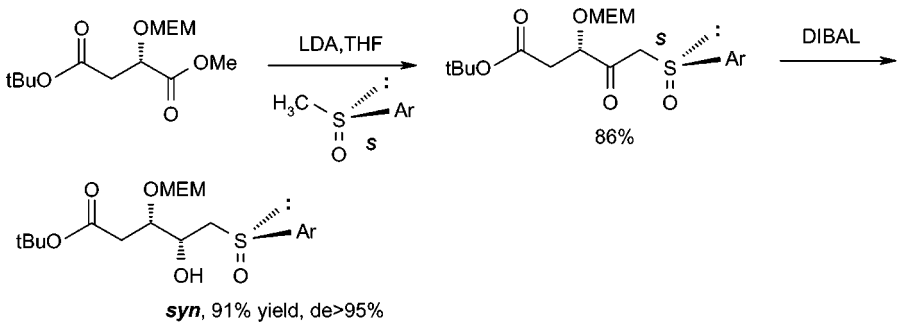
Reducing agent	$LiAlH_4$	DIBAL	$ZnBr_2$, DIBAL	L-Selectride $LiB[-CH(CH_3)-C_2H_5]_3H$
Syn / Anti	30/ 70	45 / 55	23 / 77	05 / 95

SCHEME 10



P	DIBAL, THF	$ZnBr_2$, DIBAL
TBDMS	***anti***, 96%, de>95%	***syn***, 91%, de>95%
MEM	***anti***, 91%, de>95%	***syn***, 85%, de = 84%

SCHEME 11



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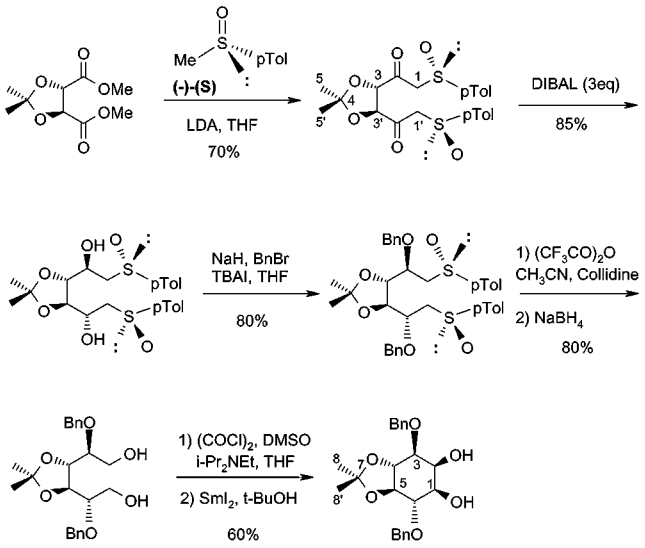
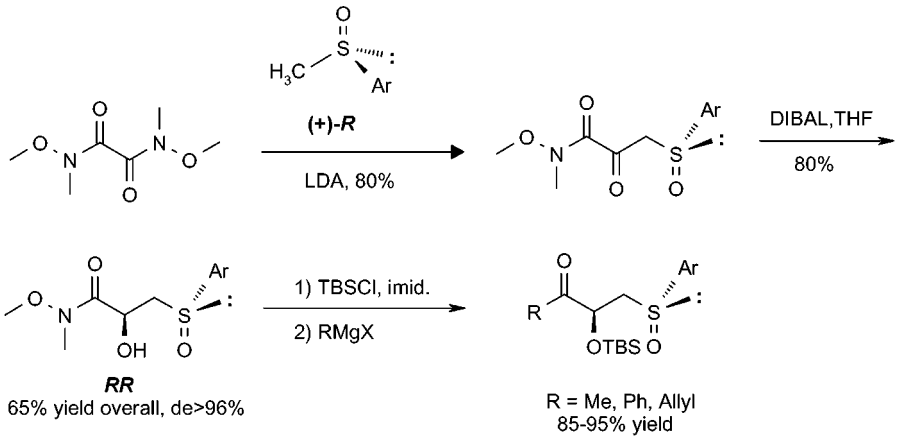


SCHEME 13

noticed the effect of the protecting group on the diastereoselectivity reaction with $ZnBr_2$-DIBAL (a minimum Eagle's essential medium (MEM) group giving a lower diastereomeric excess (de)). If the MEM group had to be used or could not be replaced by TMS, the syn diol could be obtained in 95% de by using the sulfoxide enantiomer, as has been shown for malic acid conversion [15] (Scheme 12). This new method was used in the synthesis of the macrolide (−)(2E, 4R, 5S,11R) cladospolide [16]. Another interesting application is the synthesis of a chiral derivative of myo-inositol from tartaric acid by using the sulfoxide mediated reduction of a β-keto-γ-hydroxysulfoxide [17] (Scheme 13). The reduction of the diketodisulfoxide was totally controlled by the sulfoxides without any effect of the chiral hydroxylic centers.

Finally, it was important for us to try to reduce stereoselectively the two carbonyl groups of an oxalic



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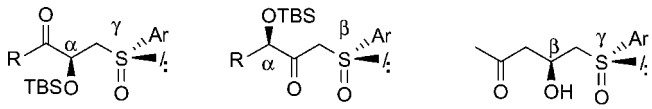
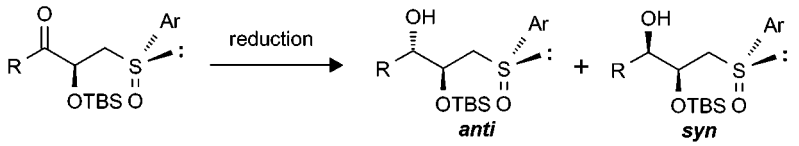


SCHEME 15

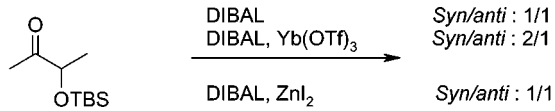
acid derivative into 1,2-diols, using only a chiral sulfoxide as the inducer of chirality [18]. We first started with the known Weinreb diamide of oxalic acid (Scheme 14). The β-ketosulfoxide derived from the Weinreb amide of oxalic acid was stereoselectively



R	DIBAL(1.5eq)	DIBAL(1.5eq)+Yb(OTf)$_3$ (0.6eq), -78°, 1/2h	DIBAL(1.5eq), ZnI$_2$ (1.1eq) -78°C, 1/2h
Me	-78° to rt,1 night 60% 75% *anti* / 25% *syn*	96% 92% *anti* / 8% *syn*	96% 7% *anti* / 93% *syn*[a,b]
Ph	-78°, 1/2h, 94% 91% *anti* / 9% *syn*	95% 96% *anti* / 4% *syn*	quant. 2% *anti* / 98% *syn*
allyl	-78°, 1/2h, 95% 98% *anti* / 2% *syn*		90% 4% *anti* / 96% *syn*
vinyl	-78°, 1/2h, 97% 97% *anti* / 3 *syn*%		91% 2% *anti* / 98% *syn*

a) $ZnBr_2$: 20/80, $ZnCl_2$: 35/65.

b)



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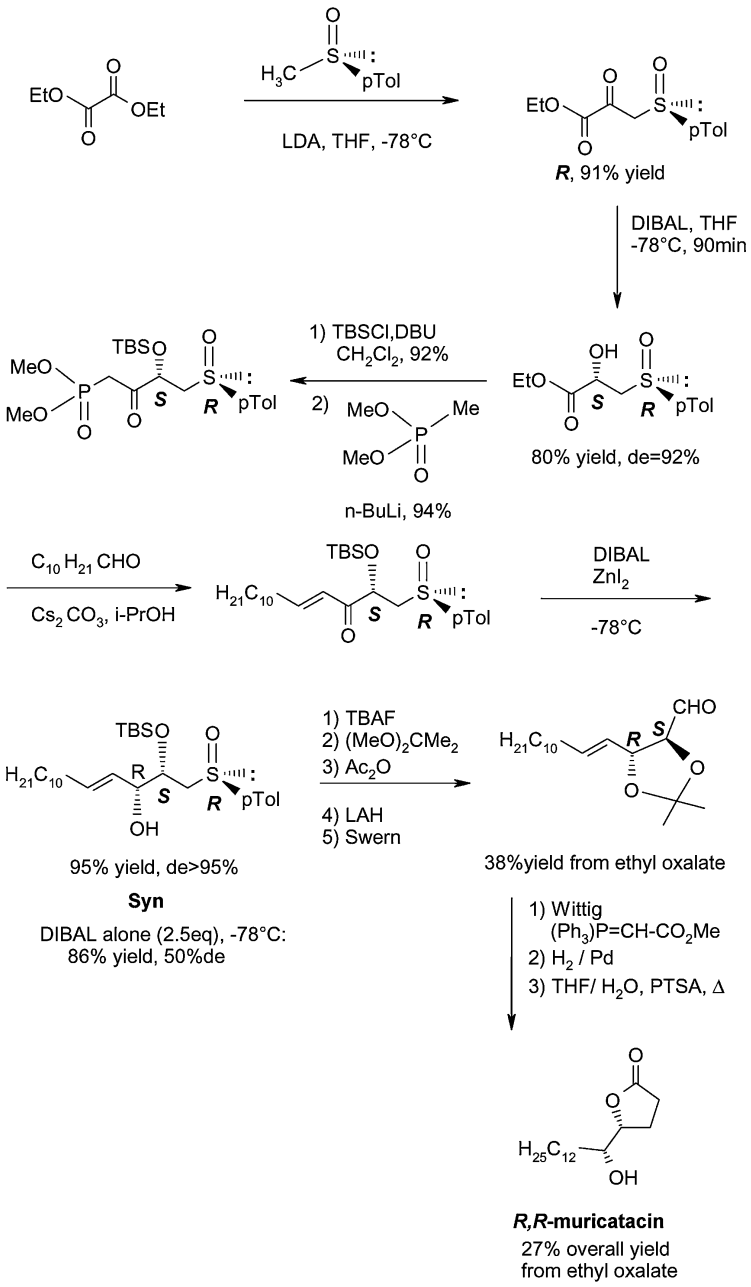
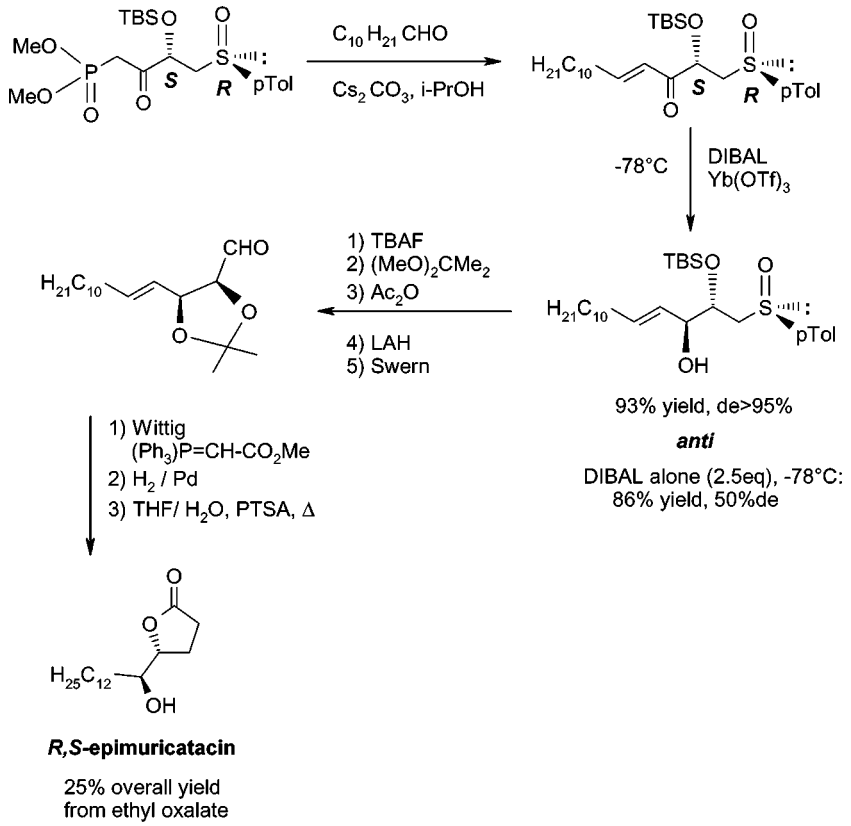


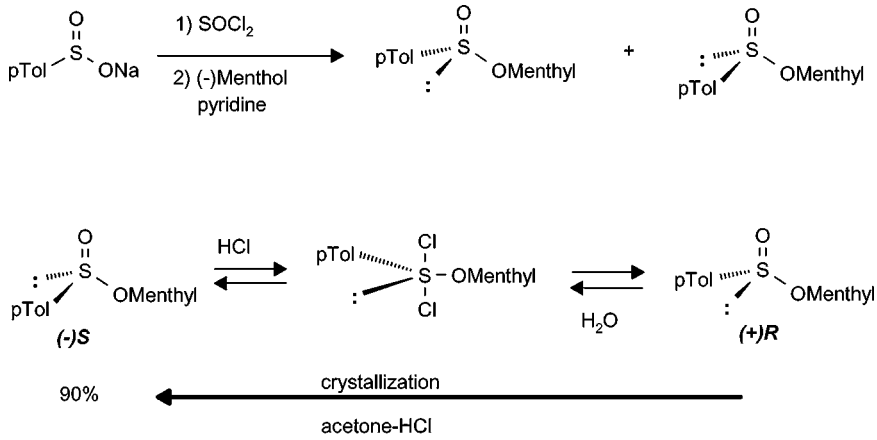
SCHEME 17

reduced to the corresponding β-hydroxysulfoxide as usual. The amide was not reduced but was, after protection of the hydroxyl group, transformed in the next step into a ketone by the action of a Grignard reagent. The reductions of these β-hydroxy-γ-sulfinyl ketones were then studied.

We have previously shown that in the case of α-hydroxy-β-sulfinyl ketones, the stereoselectivity of the reduction is totally controlled by the sulfoxide and not by the chiral hydroxylic center [14b], and also that in the case of β-hydroxy-δ-sulfinyl ketones, the reduction is controlled by the configuration of the hydroxylic center and not by the sulfinyl group [10] (Scheme 15). The results, listed in a tabular form in Scheme 16, were as follows: The anti diol was formed by reduction with DIBAL and in some cases with 0.6 equiv of ytterbium triflate catalyst (which increased the reaction rate and in some cases the diastereoselectivity too). The syn diol was obtained with DIBAL and ZnI_2. Comparison with the hydroxyketone



SCHEME 18



SCHEME 19

reduction showed that the sulfoxide group brought about the main contribution to the stereoselectivity of the reduction.

Ethyl oxalate could also be transformed to the corresponding β-ketosulfoxide, which could be highly strereoselectively reduced with DIBAL (Scheme 17). Then, after protection of the hydroxyl group, the β-hydroxysulfoxide was transformed into a chiral highly functionalized Wittig reagent, a β-keto-γ-(*S*)-hydroxy-δ-(*R*)-*p*-tolylsulfinyl phosphonate. After the Wittig reaction with a long-chain aldehyde, the reduction with DIBAL/ZnI_2 gave the syn diol (de > 95%). In a sharp contrast, the diastereoselectivity was only 50% with DIBAL alone. This new phosphonate can be very useful in many applications related to the syntheses of natural products (Scheme 17). Reduction with DIBAL/$Yb(OTf)_3$ gave the anti diol (de > 95%) as shown in the application to the synthesis of (*S,R*)-epimuricatacin (Scheme 18).

Finally, the method used to obtain optically active sulfoxides (which is based on the synthesis of enantiomerically pure menthyl *p*-tolylsulfinate) also needs to be described. Esterification of the sulfinic acid with natural 1-menthol affords a mixture of the two diastereomeric menthyl *p*-tolylsulfinates, which can be equilibrated and transformed into pure (−)-(*S*)-menthyl *p*-tolylsulfinate in large quantities following our earlier reported procedure [19] (Scheme 19).

ACKNOWLEDGMENTS

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