

## Recent results in the field of asymmetric synthesis using chiral sulfoxides

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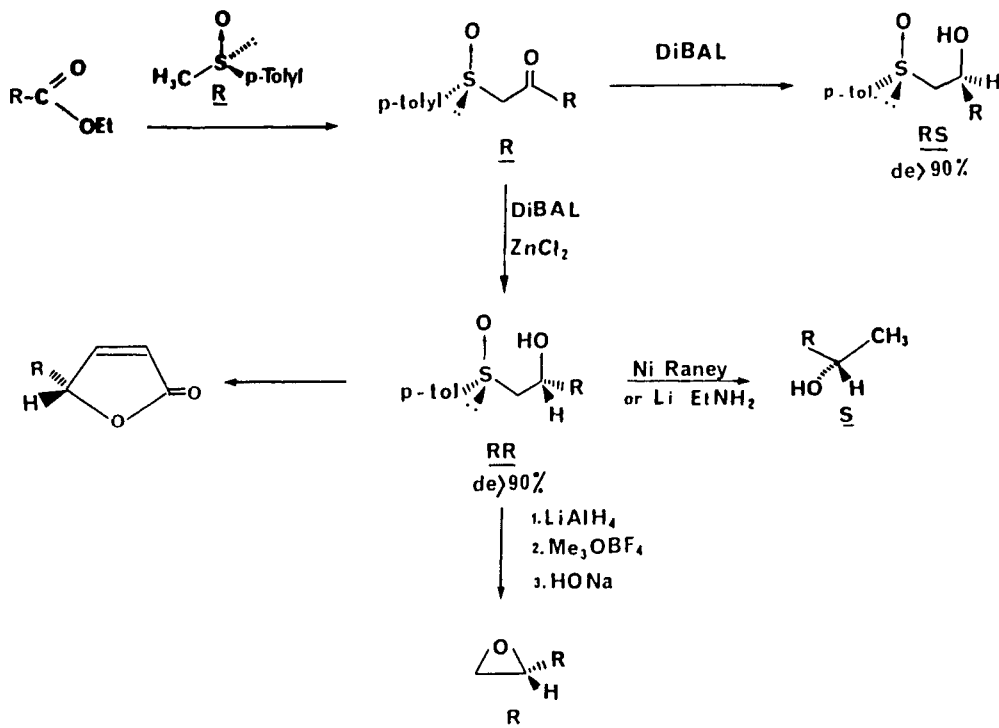
**Abstract** : Chiral sulfoxides are very useful groups in asymmetric synthesis. We have recently concentrated our efforts towards the asymmetric synthesis of optically active poly-hydroxylated chains which are present in many important natural products. Our method is based on the combination of reduction of  $\beta$ -ketosulfoxides and hydroxylation of the double bond, reactions which have been shown to be extremely stereoselective. This method was improved in order to obtain different stereochemistry in the resulting polyol. Several applications will be described to illustrate this methodology.

$\beta$ -ketosulfoxides are readily available from esters and methyl *p*-tolylsulfoxides. We investigated recently the reduction of these  $\beta$ -ketosulfoxides with metal hydrides (1,2). We have shown that the reduction of (*R*)- $\beta$ -ketosulfoxide with DIBAL gave the corresponding (*RS*)- $\beta$ -hydroxysulfoxide (d.e. > 90%), while by adding one equivalent of the complexing agent  $ZnCl_2$  to the (*R*)- $\beta$ -ketosulfoxide and then DIBAL, the (*RR*)- $\beta$ -hydroxysulfoxide was only formed (d.e. > 90%).

These results can be clearly understood in terms of a chelated conformation for the  $\beta$ -ketosulfoxide in presence of  $ZnCl_2$  and a non-chelated conformation in absence of  $ZnCl_2$  (1,2).

This very efficient method to prepare both diastereoisomers of  $\beta$ -hydroxysulfoxides was applied to the synthesis of optically active epoxides and butenolides (2,3,4) (scheme 1).

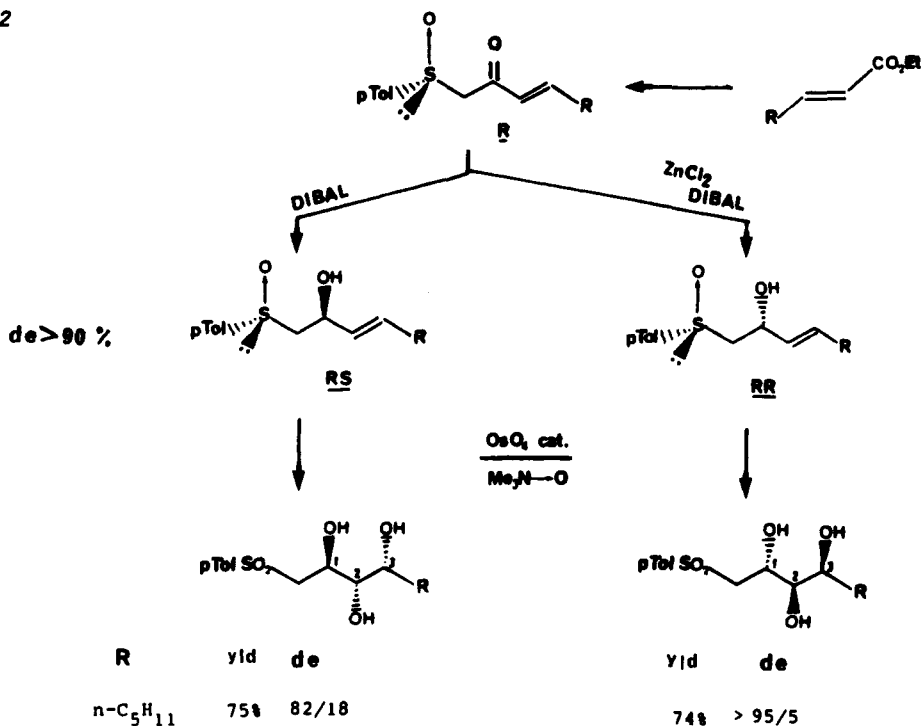
Scheme 1



Allylic and propargylic  $\beta$ -ketosulfoxides could be reduced as well as saturated compounds.

Optically active allylic  $\beta$ -hydroxysulfoxides present some specific interest because of the possible hydroxylation of the double bond leading to vicinal triols. We found that the osmium tetroxide catalyzed hydroxylation reaction of the double bond in presence of trimethylamino N-oxide was highly stereoselective. We showed a strong cooperative effect of the chiral hydroxylic center and of the sulfoxide to the asymmetric induction. The (RR)- $\beta$ -hydroxysulfoxide gave only one diastereoisomeric triol as a result of a cis hydroxylation of the double bond while the (RR)- $\beta$ -hydroxysulfoxide afforded a mixture of the 2 diastereoisomers in the ratio 82/18 (5) (scheme 2).

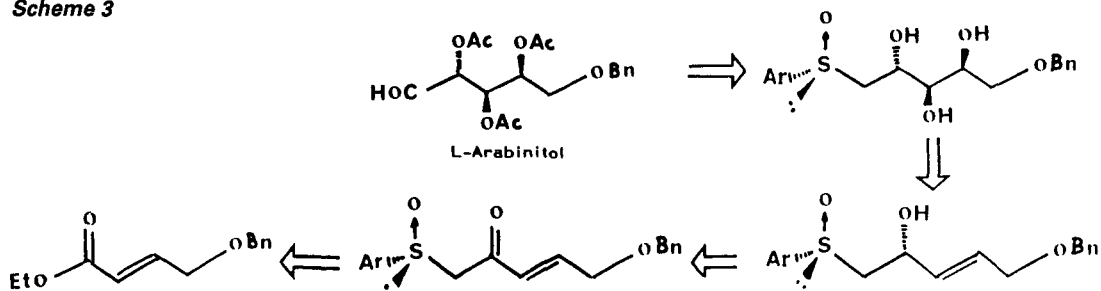
Scheme 2



The sulfoxide group can be also oxidized to a sulfone after the double bond hydroxylation depending on the amount of oxidant used for the reaction. With only one equivalent of trimethylamino N-oxide, the sulfoxide group was recovered unchanged. The nature of the chain R played also a role in the asymmetric induction. The presence of a ramified chain R  $\alpha$  to the double bond decreased significantly the diastereoselectivity.

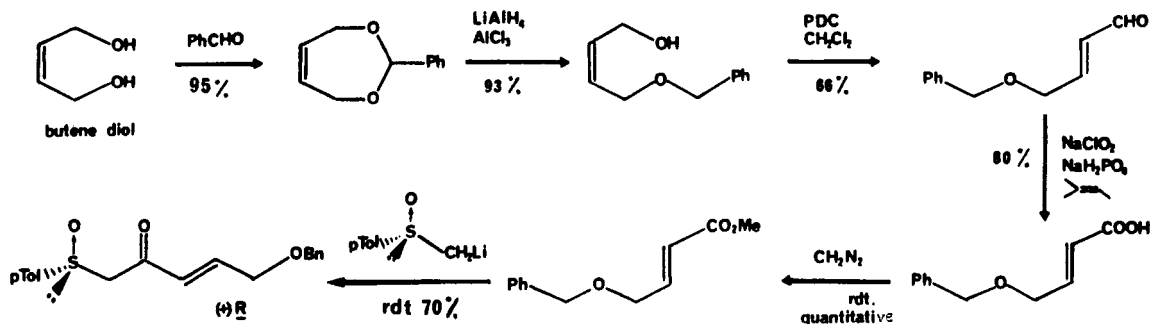
The first application of these results was the asymmetric synthesis of carbohydrates in the unnatural configuration. L-Arabinitol was readily prepared by application of this methodology (5,6). According to the retrosynthetic scheme (scheme 3) the aldehyde function of L-Arabinitol can be obtained by a Pummerer rearrangement of a sulfoxide group and the corresponding sulfoxide triol can be readily prepared from an appropriate allylic  $\beta$ -ketosulfoxide via reduction of the ketone and hydroxylation of the double bond.

Scheme 3



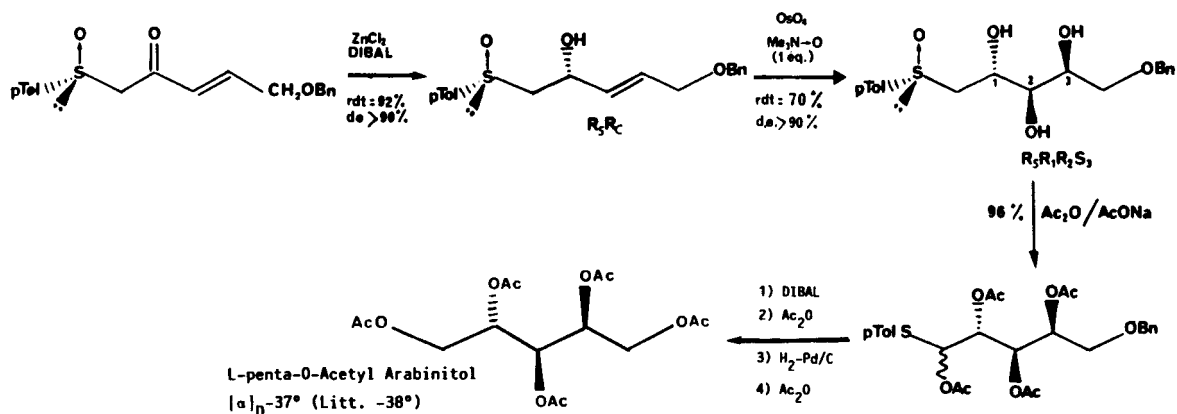
The unsaturated  $\beta$ -ketosulfoxide was readily prepared from butene diol by the following reactions: acetalisation with benzaldehyde, opening of the acetal with LiAlH<sub>4</sub> and AlCl<sub>3</sub>, oxidation of the allylic alcohol to the trans aldehyde, oxidation to the corresponding carboxylic acid, esterification and reaction with the carbanion of (+)(R)-p-tolylmethylsulfoxide (scheme 4).

Scheme 4



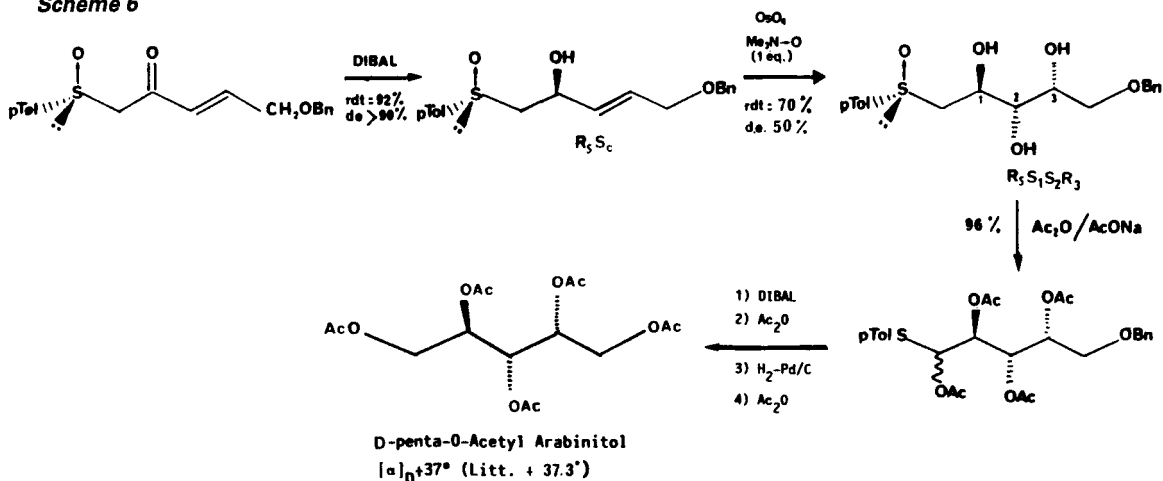
Reduction of this  $\beta$ -ketosulfoxide with DIBAL in presence of zinc chloride afforded the corresponding  $\beta$ -hydroxysulfoxide (it was shown by 200 MHz NMR that only one diastereoisomer was obtained). Hydroxylation of the double bond with one equivalent of trimethylamine N-oxide in presence of a catalytic amount of osmium tetroxide lead to one diastereoisomer of the sulfoxide triol (according to the NMR spectrum). The Pummerer rearrangement was conducted in excellent yield by using acetic anhydride under reflux. Finally, DIBAL reduction, acetylation, debenzoylation and final acetylation gave L-penta-O-acetyl arabinitol in good yield and high enantiomeric purity as shown by the optical rotation (scheme 5).

Scheme 5



The same method can also be used to the asymmetric synthesis of D-carbohydrates. It was already mentioned that the two chiral centers, the sulfoxide and the hydroxylic group, have a symbiotic effect in the asymmetric induction. As a matter of fact, the osmium tetroxide hydroxylation of the *RS*-diastereoisomer gave only 50% d.e. (scheme 6). Therefore, the asymmetric synthesis of D-sugars or related polyols has to be performed from the *SS*<sub>C</sub> diastereoisomer. Chiral sulfoxides in the *S* configuration are easily obtained from (+) menthol by the method already used for the *R*-configuration (7).

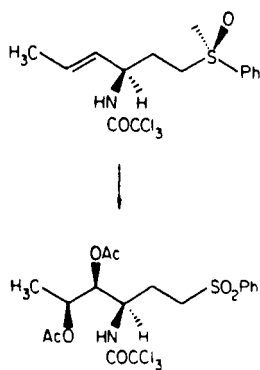
Scheme 6



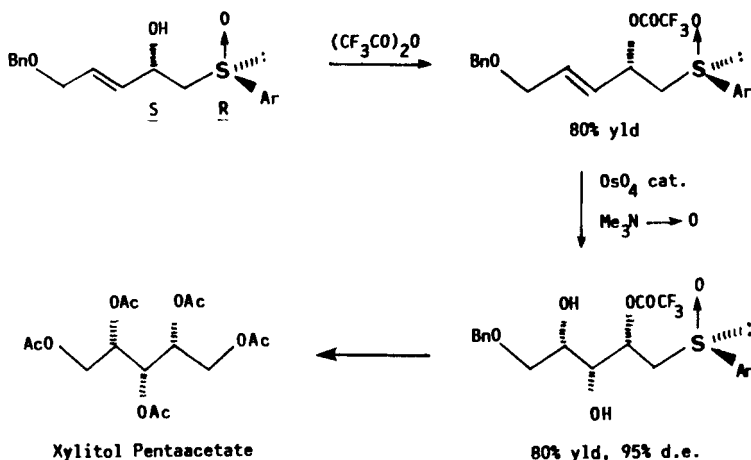
However, a related work of Hauser (8) showed that the osmium tetroxide hydroxylation of allylic *N*-trichloroacetyl  $\gamma$ -sulfoxides was completely mediated by the sulfoxide group which controlled the stereochemistry of the resulting diol (scheme 7).

Following this result, we protected the hydroxylic group, in the (*S*,*R*) allylic  $\beta$ -hydroxysulfoxide, with trifluoroacetic anhydride (at room temperature there is less than 5% of Pummerer rearrangement) and submitted the resulting trifluoroacetate to the hydroxylation reaction which was shown to give only one diastereoisomer, easily identified by transformation into the known xylitol pentaacetate (scheme 8).

Scheme 7



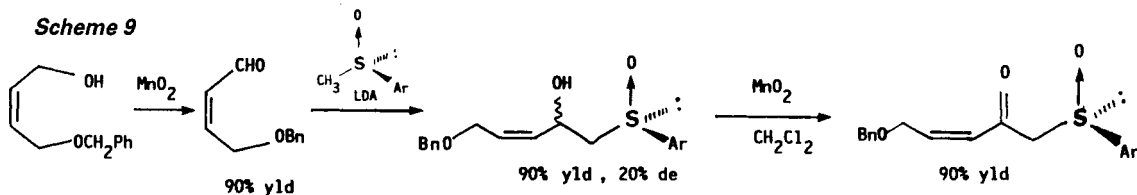
Scheme 8



This result confirms the work of Hauser and strongly supports the initial formation of a complex between the osmium and the sulfoxide group followed by an intramolecular hydroxylation process.

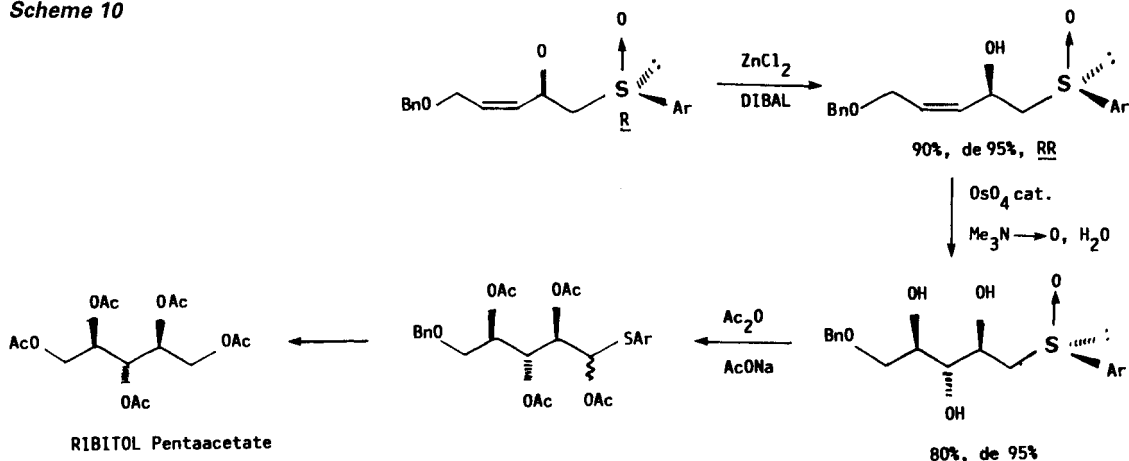
Allylic  $\beta$ -ketosulfoxides having a *Z* geometry on the double bond cannot be prepared from the corresponding esters, the strongly basic medium giving in every case a complete isomerization of the double bond in the resulting  $\beta$ -ketosulfoxide.

*Z* allylic  $\beta$ -ketosulfoxides were finally obtained in two high yield steps by addition of *p*-tolylmethyl sulfoxide to the corresponding aldehyde (a very poor diastereoselectivity was observed as expected) and  $MnO_2$  oxidation (scheme 9).



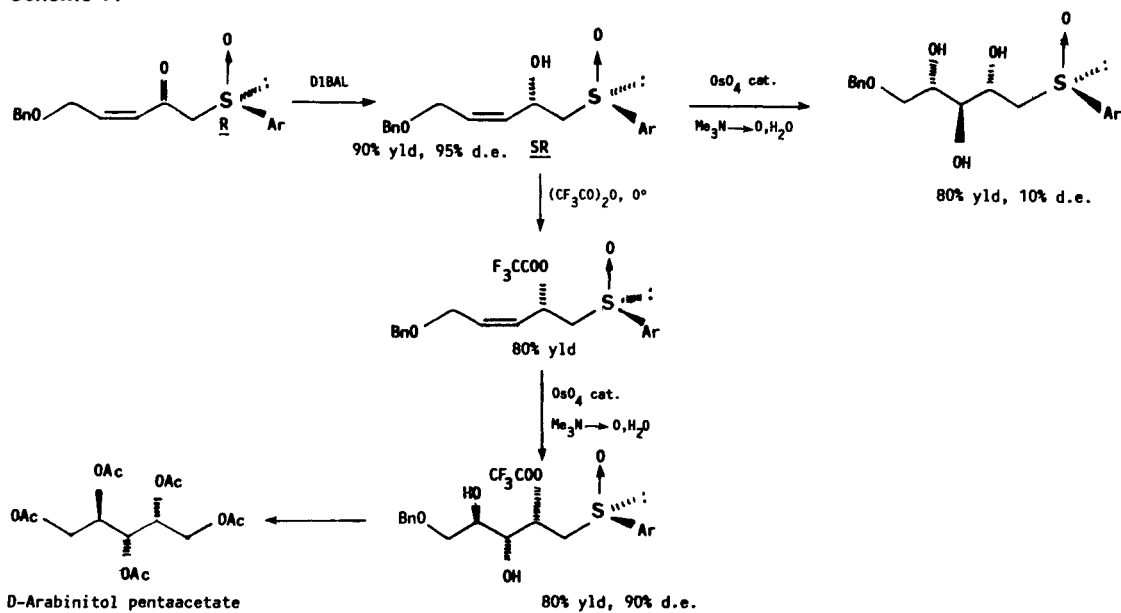
Hydroxylation of the corresponding (*RR*)- $\beta$ -hydroxysulfoxide in the usual conditions gave as expected only one diastereoisomer which was easily identified after Pummerer rearrangement by conversion to the known Ribitol (scheme 10).

Scheme 10



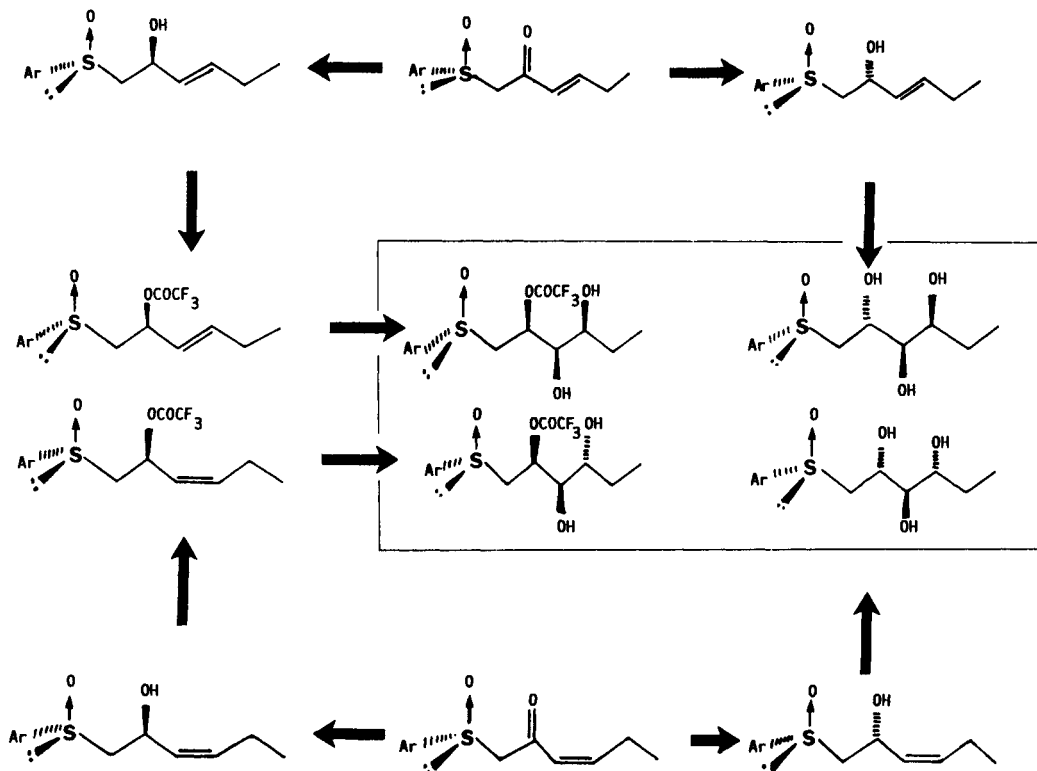
Direct hydroxylation of the (SR)- $\beta$ -hydroxysulfoxide gave a very poor diastereoselectivity (10%). However, after protection of the hydroxylic group as a trifluoroacetate, the osmium tetroxide oxidation gave again one diastereoisomer which was identified by correlation with the known D-Arabinitol (scheme 11).

Scheme 11



All these results have clearly shown that it is possible to obtain vicinal triols in all possible configurations by using the highly powerful asymmetric induction of sulfoxides (scheme 12).

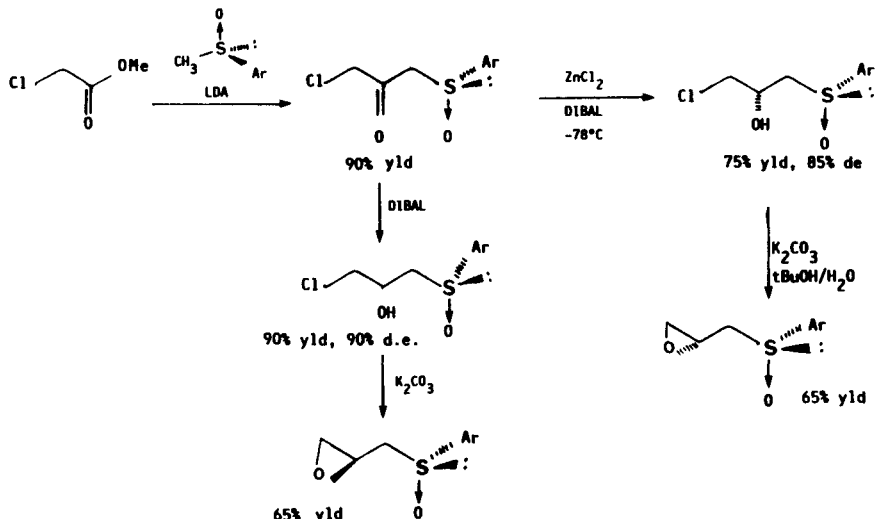
Scheme 12



Homoallylic  $\beta$ -hydroxysulfoxides should also be very interesting molecules which can be considered as precursors of 1,3,4-triols but their synthesis were not very obvious. We have finally been able to make these molecules from  $\beta$ -epoxysulfoxides.

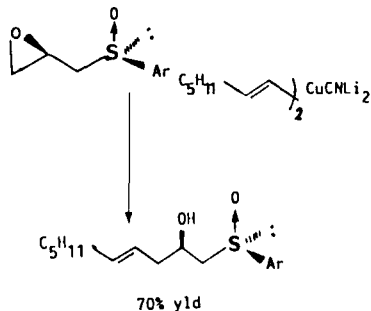
Optically active  $\beta$ -epoxysulfoxides were readily prepared from methyl monochloroacetate which gave the corresponding  $\beta$ -ketosulfoxide in very high yield. Reduction proceeded as usual in a very high diastereoselectivity without any important effect of the vicinal chloro atom. We noticed a slightly lower d.e. during the reduction in presence of  $\text{ZnCl}_2$ . Finally, the two diastereoisomeric epoxides were obtained in basic medium (scheme 13). These 2 epoxides are solid and can be easily purified.

Scheme 13

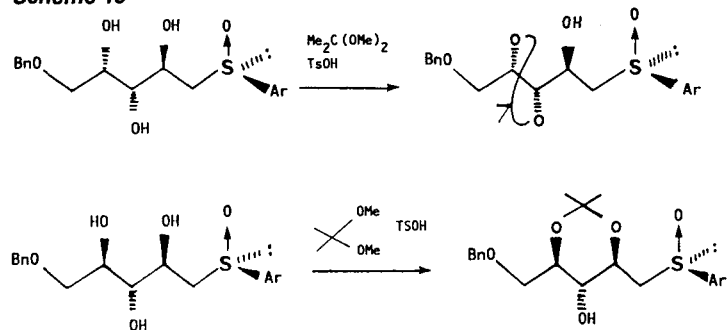


The epoxide opening in these  $\beta$ -epoxysulfoxides is not so easy because of the possible elimination of one acidic hydrogen  $\alpha$  to sulfoxide with concerted epoxide opening. This elimination reaction was indeed observed even with Grignard reagents. We have been able to avoid it by using cuprates which opened cleanly the epoxide ring leading to the expected homolallylic  $\beta$ -hydroxysulfoxide in very high yield (scheme 14).

Scheme 14



Scheme 15



However, the synthetic utility of these triols in organic synthesis would be increased if it was possible to selectively protect the different hydroxylic groups. In the case of allylic  $\beta$ -trifluoroacetylsulfoxides, it will be very easy to protect the resulting triol as an acetonide (scheme 15).

In the other cases, we found that a monoacetonide was obtained in very high yield.

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