Forschung, Wissenschaft

Uses of the Chiral Sulfoxide Group in Asymmetric Synthesis*

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Abstract

The purpose of this article is to show how useful a chiral sulfoxide group can be in asymmetric synthesis. Only two kinds of reactions [1] will be described: aldol type condensation of ester enolates activated by a chiral sulfoxide group and reduction of β-ketosulfoxides. Furthermore several synthetic applications will be described, one of these being the access to optically active α-Tocopherol (vitamine E).

It has been known for decades that suitably substituted tricoordinate sulfur compounds having a pyramidal structure, such as sulfonium salts, sulfoxides and sulfinate esters, contain a chiral sulfur atom and thus in principle, are resolvable into optically active enantiomeric forms.

The sulfoxide group is peculiarly characterized with respect to any other chiral group by the presence of at least three different kinds of ligands from the stereoelectronic point of view: the lone-pair of electrons, the oxygen atom and two alkyl or aryl groups. The activation parameters for pyramidal inversion for several series of dialkyl, diaryl and alkyl aryl sulfoxides have been determined [2].

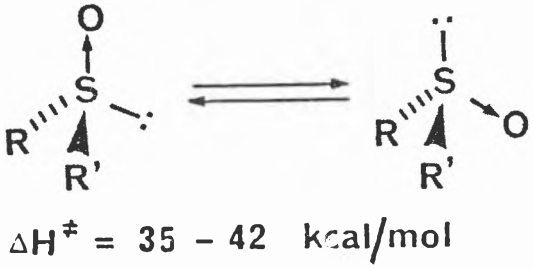
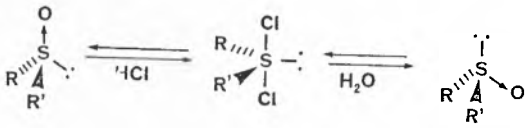


Fig. 1: Thermal stability of sulfoxides

These values show that, in most cases, the thermal stereomutation of sulfoxides occurs at a fairly high rate only at about 200°C. Sulfoxides have therefore a notable optical stability.

However the pyramidal inversion of sulfoxides can be also promoted by acidic catalysis. The first report [3] was the observation that l-menthyl l-p-Toluenesulfinate underwent mutarotation very slowly. It was later shown that indeed this epimerization as well that of sulfoxides was also catalyzed by hydrogen chloride and proceeded through an achiral dichloro-intermediate [1a, 4]:



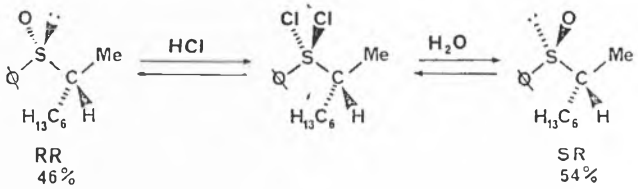


Fig. 2: Acido-catalyzed racemization of sulfoxides

The synthetic utility of sulfoxides arises from the ability of sulfur to stabilize negative charges on an adjacent carbonatom, a property which has been especially important in the development of new ways to form carbon-carbon bonds.

It is well known that the presence of a sulfide, sulfoxide or sulfone group enhances the thermodynamic acidity of an adjacent proton. The results given in the next table show that the acidity of a proton α to a sulfoxide group is just in between those of a benzylic proton and a proton α to a carboxylate function.

Table 1:

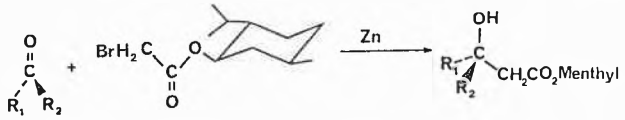
Compound	PK_A
$R\text{-}CH_2NO_2$	10
$R\text{-}CH_2COR$	20
$R\text{-}CH_2CO_2R$	25
$CH_3\text{-}SO_2\text{-}CH_3$	29
$CH_3\text{-}SO\text{-}CH_3$	33
$AR\text{-}CH_3$	41
CH_4	44

*) Lecture given at the University of Basel on March 2, 1984.

I. Aldol Type Condensations

Our first study concerning the use of chiral sulfoxide in asymmetric synthesis was in the field of aldol type condensations of ester enolates.

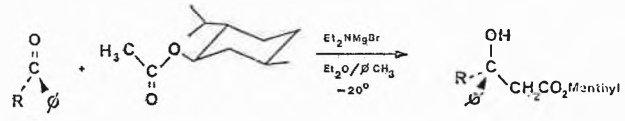
The *Reformatsky* reaction was certainly the first asymmetric synthesis described in this area. However the results [5] reported in fig. 3 show two typical exemples of the condensation of menthylbromoacetate. The enantiomeric excesses are generally poor and chemical yields are good only from aromatic carbonyl compounds.



R_1	R_2	ee%
H	Ø	15
CH_3	Ø	29

Fig. 3: Asymmetric Refortmatsky reaction

More recently we published a complete study [6] concerning the condensation of menthyl acetate at low temperature in presence of diethylamino magnesium bromide. The main advantage of this reaction with respect to the *Reformatsky* reaction is the low reaction temperature which lead to enantiomeric excesses around 50%. But again this reaction gave good chemical yields only from aromatic ketones.



1 2

R	ee%
CH_3	58
Et	58
i-Pr	48
t-Bu	42
CF_3	30

Fig. 4: Asymmetric aldol condensations of methylacetate

For such aldol type condensation of ester enolates, a cyclic transition state is generally admitted. In the case of menthyl acetate or menthyl bromoacetate, the relatively low steric interactions between the prochiral and the chiral centers should explain the low asymmetric induction.

However if we consider this cyclic transition state it can be imagined that an inducing chiral moiety might also be placed around the metal atom (zinc or magnesium) by chelation of a chiral ligand. Alternatively, the methylene carbon might carry a chiral group other

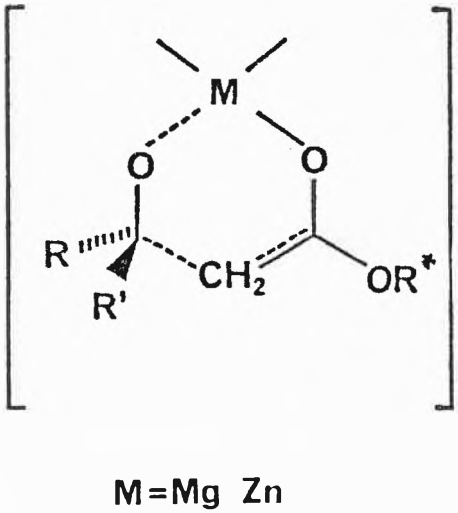


Fig. 5: Aldol type condensation of ester enolates

than a chiral ester group in order to increase the interactions with the prochiral center.

The first approach was developped by Guette [7], who used, in a Reformatsky reaction, the bidentate ligand sparteine. Condensation of benzaldehyde with ethyl bromoacetate under such conditions yielded 21% of the corresponding β-hydroxyester with 94% ee. From acetophenone the ee was only 38% and the chemical yield was 16%. In the favored transition state there is a minimization of interactions between hydrogens attached to C-15 of the sparteine and the phenyl ring of the carbonyl compound. Although in the case of benzaldehyde the stereoselectivity was remarkable, the low chemical yield makes this reaction of little synthetic utility.

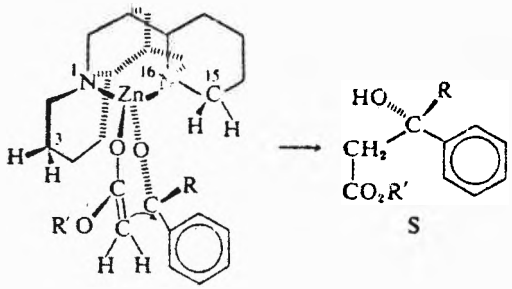


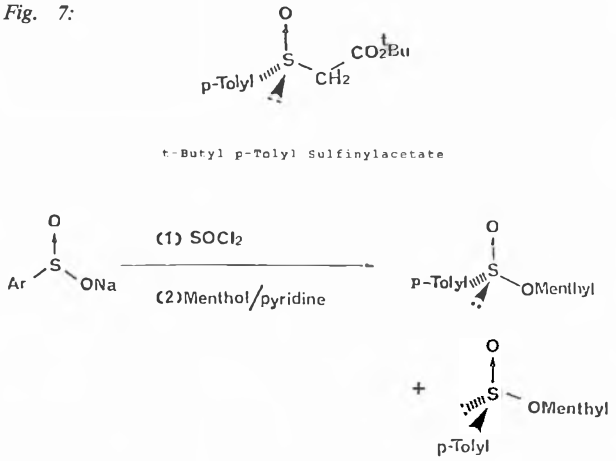
Fig. 6: Asymmetric Reformatsky reaction in presence of (-) sparteine

We developped the second approach by introducing a chiral sulfoxide group on the methylene carbon atom α to the ester function.

The question was: how to prepare optically active t-butyl p-Tolylsulfinyl acetate?

The usual way to obtain optically active sulfoxides is from menthylsulfinate which is obtained as a mixture of two diastereoisomers by esterification of sulfinic acid with l-menthol followed by separation of the 2 diastereoisomers by crystallization.

Fig. 7:



In order to avoid this diastereoisomers separation we choosed to use the acidic epimerization of sulfur to isomerize one diastereoisomer into the other. As shown on fig. 8, in acetone-hydrochloric acid the two diastereoisomers are equilibrated and the equilibrium is readily displaced towards the diastereoisomer (-) *S* which precipitates from the solution: in 2 days a 90% yield was obtained through this second order asymmetric transformation [8].

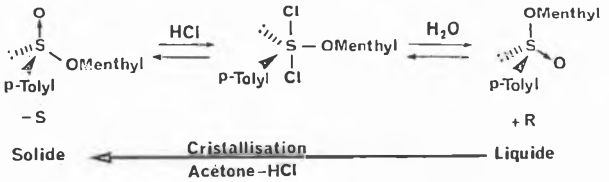


Fig. 8: Sulfur epimerization of menthyl sulfinate

As shown by *Andersen* [9] optically active sulfoxides are readily obtained by displacement of the O-menthyl group of the menthylsulfinate by a Grignard reagent through a SN_2-process. In order to get the corresponding sulfinyl ester we displaced the menthyloxy moiety by the magnesium enolate of t-butylacetate with a 90% yield [9, 10]. The *R* absolute configuration at sulfur was determined by ORD from a positive Cotton effect at 250 nm [11].

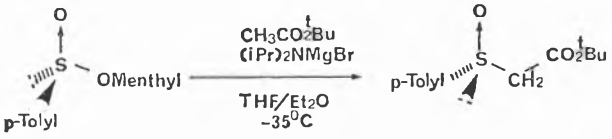


Fig. 9: Synthesis of chiral t-butyl p-tolyl sulfinyl acetate

The enantiomeric purity of sulfinyl ester was easily determined by NMR in presence of a chiral europium complex [10].

The next figure reports the general synthetic scheme to prepare optically pure t-butyl p-tolyl sulfinyl acetate (+) *R*, with a 90% yield in each step.

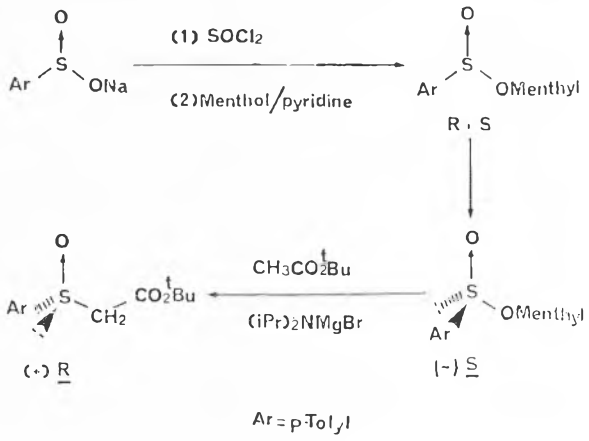


Fig. 10: Synthesis of optically active t-butyl p-tolyl sulfinyl acetate

Aldol type condensations of the enolate anion of racemic ethyl phenylsulfinyl acetate on carbonyl compounds had already been reported by *Kunieda* and coworkers [12] who showed that such condensations could occur only if the enolate anion was prepared using a Grignard reagent as a base. However the product diastereoisomeric ratios were not determined.

We have thoroughly investigated the condensation of *R* (+) t-butyl p-tolylsulfinyl acetate with aldehydes and ketones in the presence of t-butylmagnesium bromide and have demonstrated the high stereoselectivity of this aldol type condensation [13].

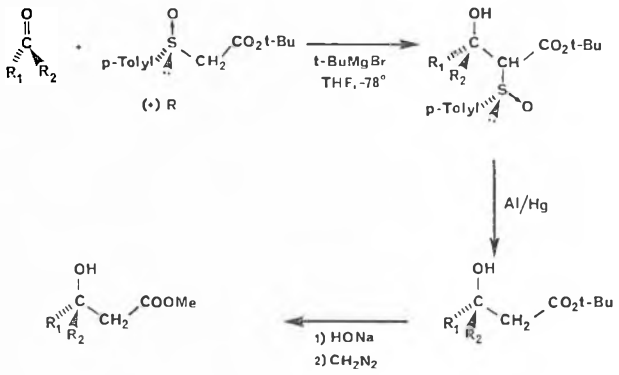
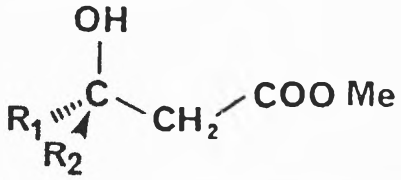


Fig. 11: Asymmetric aldol type condensation of (+) *R* t-butyl p-tolylsulfinyl acetate

The results listed in table 2 show that chemical yields are generally higher than for most aldol-type condensations of ester enolates, mainly because of the chemical activation of the methylene group by the sulfoxide which makes this reaction suitable for any aldehyde or ketone. This is in contrast to the Reformatsky reaction or the condensation of menthylacetate, either of which gave good yield only with aromatic ketones. The results also show that high asymmetric induction is generally observed. Two exceptions are α-ketoesters (ethyl pyruvate) and trifluoro-methylphenyl ketone.

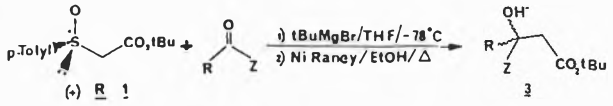
Table 2: Asymmetric syntheses of β-hydroxyesters from chiral t-butyl α-sulfinylacetate



R_1	R_2	Chemical yield	Enantiomeric excess %	Absolute configuration
H	Ph	85%	91%	(−) *S*
CH_3	Ph	75%	68%	(−) *S*
Ph	CF_3	75%	20%	(+) *R*
H	n-C_7H_{15}	80%	86%	(−) *R*
H	C_3H_7	65%	70%	*S*
H	n-$C_{11}H_{23}$	74%	80%	*R*
H	n-C_8H_{17}	80%	83%	*R*
CH_3	cyclohexyl	88%	95%	(−) *S*
CH_3	CO_2Et	80%	8,5%	(+) *S*
CH_3	$(CH_2)_2OAc$	90%	40%	

The presence of oxygen atoms in β, δ or α with respect to the prochiral carbonyl decreases drastically the asymmetric induction [14] and a β-aminoketone does not react anymore with sulfinyl-ester probably because of chelating effects (table 3).

Table 3:

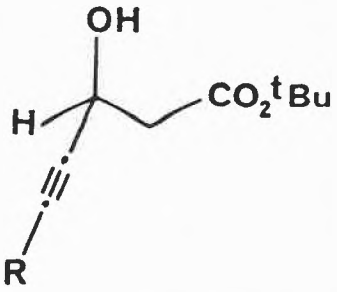


R	Z	Yield %	ee %
CH_3	$-CO_2Et$	80%	8%
CH_3	$-CH(OMe)_2$	60%	10%
CH_3	$-CH_2-CH_2-CH(OMe)_2$	57%	8%
CH_3	$-CH_2-CH_2-OAc$	90%	40%
CH_3	$-CH_2-CH_2CO_2Me$	63%	50%
H	$-(CH_2)_3-CO_2Me$	76%	60%
CH_3	$-CH_2-NMe_2$	–	–

α-β unsaturated aldehydes as well as propargylic aldehydes [15] gave also very high enantiomeric excesses (table 4).

In defining the role of the base in such a condensation we confirmed that no condensation product is obtained from reactions using t-butyl lithium or sodium hydride as a base.
Furthermore when the adduct, the β-hydroxy β sulfinyl ester is treated by t-BuLi, we observed two competitive processes: a retroaldolisation reaction and a ligand exchange on sulfur [8]. The retroaldol process in the t-butyllithium case is due mainly to the more ionic nature of an O-Li bond than an O-Mg bond.

Table 4:



R	Chemical Yield %	enantiomeric excess %
Ph	75%	> 90
n-Pr	73%	90
n-C_6H_{13}	53	90
t-Bu	60	84

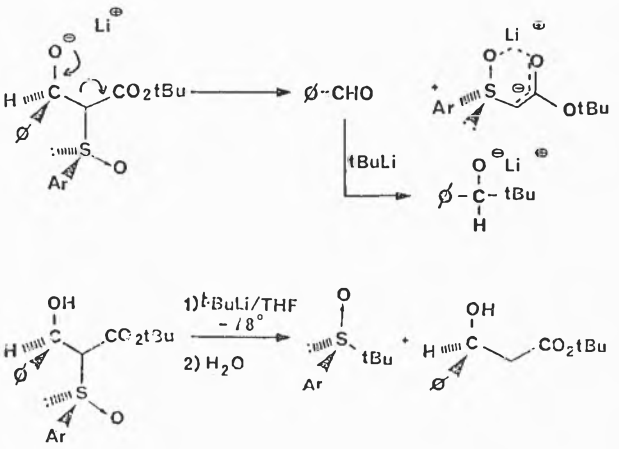
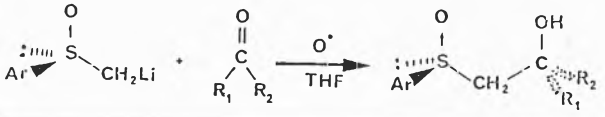


Fig. 12: Stability of β-hydroxy β-sulfinyl acetates in presence of t-BuLi

Some literature results [12] showed also that the condensation of carbanions α to a chiral sulfoxide to car-

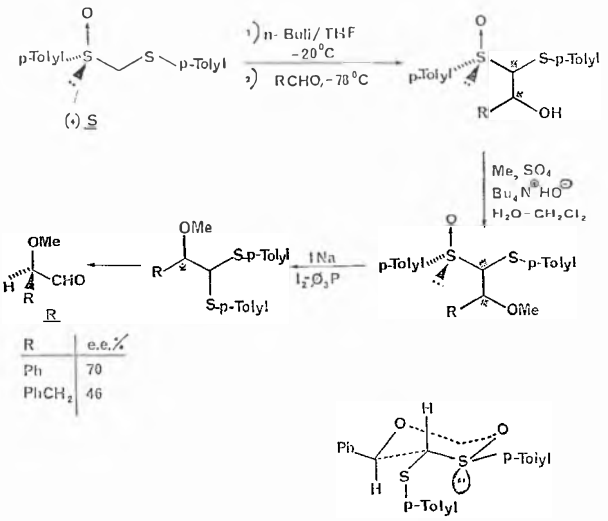
Table 5:



R_1	R_2	% diastéréoisomères
Me	Et	50/50
	iPr	51/49
	tBu	53/47
∅	CH_3	67/33
	tBu	70/30
	C_6H_{11}	59/41

bonyl compounds gave poor asymmetric induction (table 5) results showing that the ester function is also an important factor in the stereo-chemical recognition.

The sharp contrast between the extent of asymmetric induction for carbanions α to a chiral sulfoxide and enolate anions of α-sulfinyl esters can be attributed to the capacity of the ester function to chelate. The presence of magnesium permits the formation of highly chelated transition states or intermediates, in addition to providing electrophilic assistance to the carbonyl approach. A result reported later by *Scolastico* [16] for the condensation of the chiral thioacetal monosulfoxide with aldehydes has confirmed the importance of a chelating function: in this case the sulfide cannot be chelated on the metal and the extent of asymmetric induction is lower.



A spectroscopic study of metallated α-sulfinylesters by ^{13}-C-NMR did not show any significant difference between lithium and magnesium species which could be responsible for disparate behavior [17].

The determination of the absolute configuration of the second chiral center formed during the condensation (that of the hydroxylic center was determined by desulfuration leading to known β-hydroxy esters) was performed by stereospecific pyrolytic elimination of the sulfoxide group giving an enol acetate. The relative stereochemistry of this enol was determined by Nuclear Overhauser Effect in ^{1}H-NMR [8].

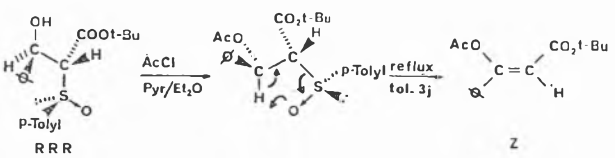


Fig. 14: Determination of the relative configuration of the two chiral centers created by asymmetric addition of *R* t-butyl sulfinyl acetate to benzaldehyde

From these results it is now possible to propose a model that can be useful for predicting the absolute configuration of the major diastereoisomer.

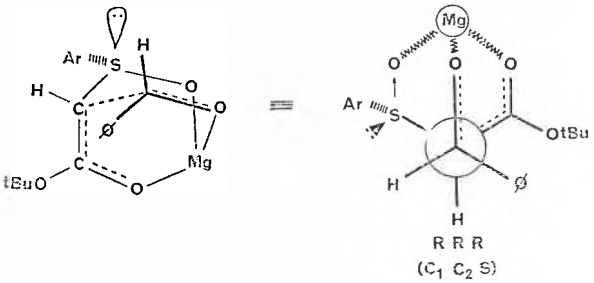


Fig. 15: Model for predicting the absolute configuration in the asymmetric additions of *R* t-butyl p-tolyl sulfinyl acetate to carbonyl compounds

Starting from the O-metallated and chelated structure fro the enolate anion and assuming electrophilic assistance of magnesium to the carbonyl approach, the model results from the following considerations:

1. The carbonyl compound approaches the anion from the side where the sulfur lone pair is located, not on the side where the aromatic ring is located.
2. That face of the carbonyl is preferred for which the steric and electronic interactions between the carbonyl substituents and the sulfoxide group are minimized.

An application of this aldol-type asymmetric synthesis was reported by Corey during the later stages of the total synthesis of maytansine [18]. The asymmetric induction was 86%.

Fig. 16 see next page

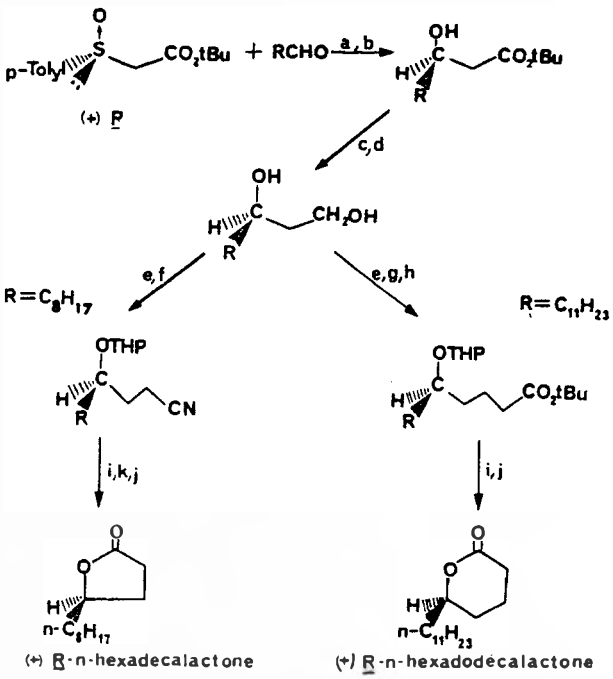


Fig. 17: Asymmetric synthesis of lactones

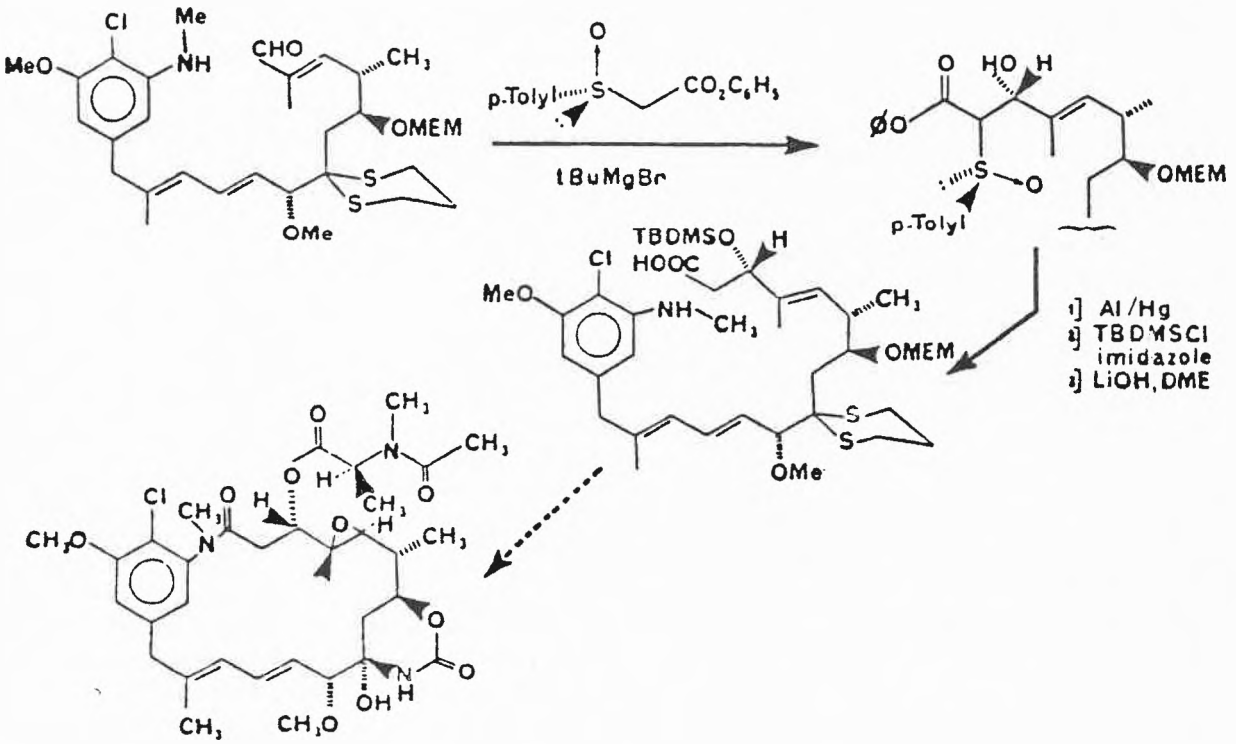


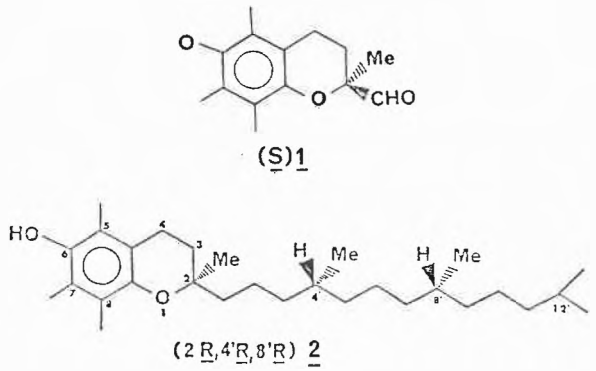
Fig. 16: Asymmetric synthesis of Maytansine

We applied this asymmetric addition to the synthesis of optically active five and six-membered lactones, molecules of importance as insect pheromones [19].

II. Enantiospectific Synthesis of the Chromane Ring of α-Tocopherol [30]

Our synthetic target was the *S* chroman-2 carboxaldehyde **1**, a key intermediate in the total synthesis of naturally occuring (2R.4'R.8'R) α-Tocopherol **2**.

Fig. 18:



The optically active aldehyde **1** was till now mainly prepared through optical resolution of the corresponding carboxylic acid [20, 21] or synthetized from an optically active precursor [22, 23, 24]. Only one report mentioned an attempt of asymmetric synthesis with a poor ee.

Our first approach was to cyclize the vinylic sulfoxide **3** in a precursor of the aldehyde **1**.

Fig. 19:

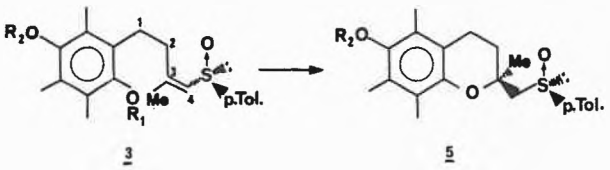
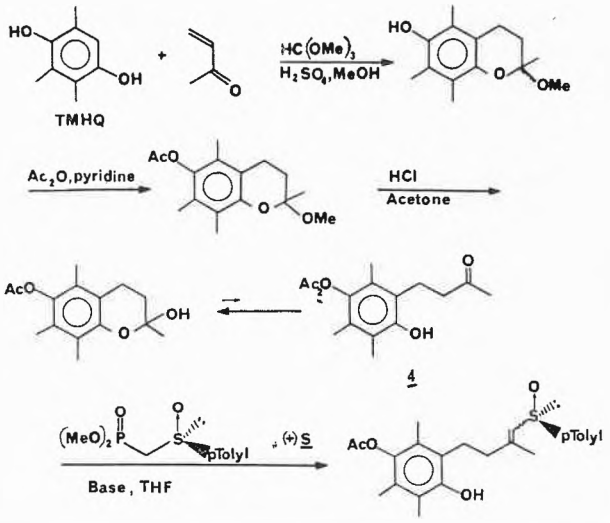


Fig. 20:



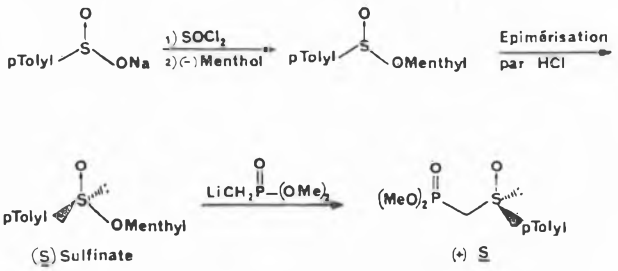
It is known from literature that nucleophiles react with vinylic sulfoxides [26, 27, 28] and that it is not always necessary to activate the double bond by a carboxylic function as shown by *Posner* [29].

The synthesis of the vinylic sulfoxide **3** derived from a work of Isler [20] who showed that the hydroxyketone **4**, which mainly exists as an hemi-ketal, was able to react in a *Wittig* reaction through the open form. Therefore we prepared this ketone by the standard procedure from trimethylhydroquinone allowed to react with methylvinyl ketone in presence of methyl ortho formiate, followed by acetylation of the phenol group and acidic hydrolysis to the hemi-ketal.

Then we intended to use the *Mikolajcryk* [31] reagent, a β-sulfinylphosphonate, to introduce the vinylic sulfoxide by a *Wittig* reaction.

The chiral β-sulfinylphosphonate was prepared from menthyl-sulfinate and lithium dimethyl methylphosphonate according *Mikolajczyk's* procedure.

Fig. 21:



However when we allowed the β-sulfinyl phosphonate lithium salt to react with the hemi-ketal in basic medium, we obtained, whatever was the base used to obtain the corresponding phenolate, a mixture of 3 products. The results shown, in fig. 22, obtained with 2 equivalents of β-sulfinylphosphonate lithium salt, are the following:

- 45% of vinylic sulfoxide **3** as a 1 to 1 mixture of E and Z isomers as shown by ^{13}C NMR
- 40% of chromane **5** as a mixture of diastereoisomers (68/32) as shown by ^{1}H NMR from the 2 non-equivalent singlets of the methyl group on C_2.
- 10% of allylic sulfoxide **6** resulting from isomerisation of the double bond.

The moderate diastereoselectivity (36%) is probably the result of the low stereoselectivity of the Wittig reaction leading to a 1/1 mixture of E and Z isomers. It was not possible to separate these 2 geometric isomers even by HPLC. The direct cyclization of this mixture with NaOH gave a 25% de.

We could slightly modify the E/Z ratio of this vinylic sulfoxide **3** by making the corresponding lithium salt (LDA-THF, -78°) giving after protonation a ratio E:Z = 2/1. The cyclization of this novel mixture with sodium hydroxide gave a 12% d.e., confirming the importance of the double bond stereochemistry in the cyclization reaction.

The absolute configuration of the main diastereoisomer was determined by using a Pummerer reaction which yields the known aldehyde **1**.

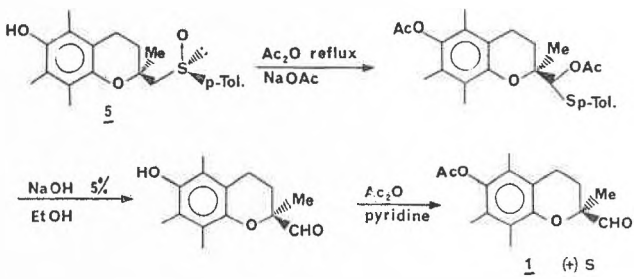


Fig. 23: Determination of the absolute configuration of *5*

Our next approach which appears to be the good one was to cyclize the vinylic sulfoxide B having a pure stereochemistry on the double bond.

The synthetic strategy was to prepare first the vinylic sulfoxide **7**, stereochemically pure and then to obtain molecule *B* from this metallated vinylic sulfoxide and the corresponding benzylic bromide. The R group

Fig. 22:

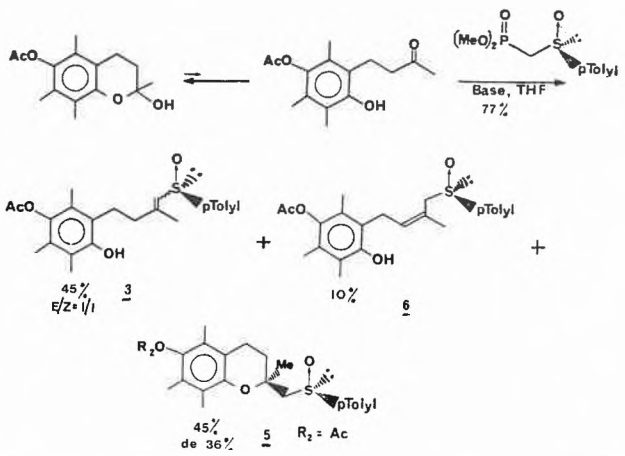
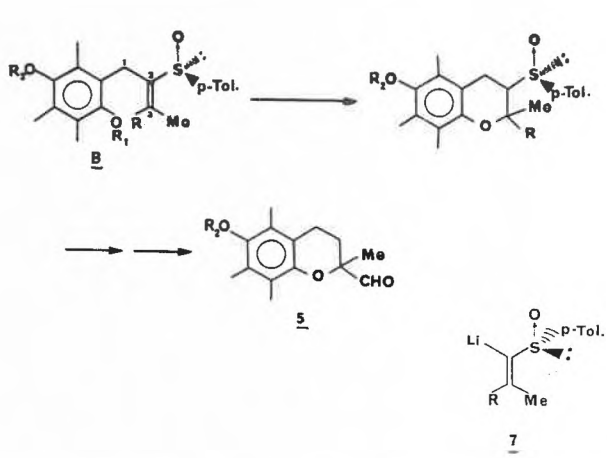
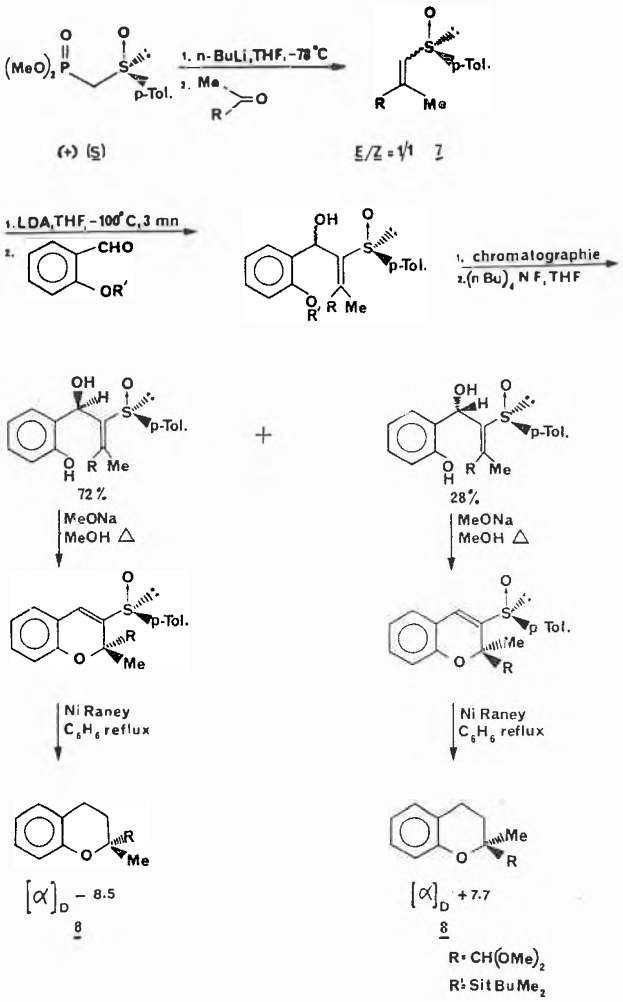


Fig. 24:



must be a ketal in order to have a precursor of the aldehyde function.
Unfortunately it was not possible to displace the benzylic bromide by such a reagent and we had to replace the benzylic bromide by a benzylic carboxaldehyde.
This synthetic strategy was first applied to a model molecule, salicylaldehyde.

Fig. 25:



The *Mikolajczyck* phosphonate allowed to react in a *Wittig-Horner* reaction with the dimethylketal of pyruvic aldehyde afforded the optically vinylic sulfoxide **7** in 98% yield as a 1/1 mixture of E/Z isomers.
The E,Z mixture of sulfoxide **7** was readily isomerized with LDA in THF to the E isomer. This result is fully consistent with that of *Okamura* [32]: the exclusive formation of the E isomer might be due to a substantial lowering of the inversion barrier of the vinylic anions [33], the driving force for the isomerisation being the chelation of lithium with the two oxygens of the ketal. The equilibration in the same experimental conditions of the vinylic sulfoxide R = phytyl did not allow to prepare the corresponding pure E isomer but only a 1/1 mixture of the two isomers.

Addition of the lithium salt of the E isomer of sulfoxide **7** to salicylaldehyde gave in 76% yield a mixture of diastereoisomers in the ratio 72/28 which could be easily separated by chromatography.
After removing the phenol protecting group it was possible to cyclize quantitatively each diastereoisomer with sodium methoxide in methanol. This cyclization was shown to be completely stereo-specific, the desulfurization with Raney Nickel giving the two enantiomers of the chromane **8**.
The mechanism of the cyclization could be a SN'_2 mechanism with elimination of the hydroxyl group activated by the sulfoxide. We observed actually that no cyclization occurs in absence of the sulfoxide group.
After these results we decided to apply the synthetic methodology to the synthesis of the chromane carboxaldehyde **1**, precursor of vitamine E. In order to get the natural isomer it was necessary to prepare vinylic sulfoxide **7** having a *S* configuration.

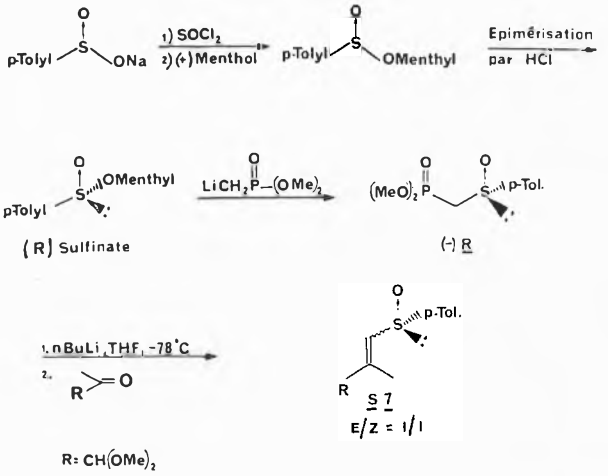


Fig. 26: Synthesis of *S* vinylic sulfoxide *7*

(+)*R*(+) Menthyl p-tolylsulfinate readily prepared in 70% overall yield from (+) Menthol followed by epimerization of the *S*-sulfinate towards the *R*, was treated with 2 moles of dimethyl-phosphoryl-methyllithium at -70° in THF to give the (-*R*) *β*-sulfinylphosphonate in about 50% yield. *Witting-Horner* reaction of its lithio derivative with the dimethyl ketal of pyruvic aldehyde afforded the optically active vinylic sulfoxide **7** *S* in 98% yield as a mixture of isomers (E/Z = 55/45).
This E,Z mixture was readily isomerized with LDA in THF to the E isomer of the metallated species of **7**. Addition of the lithio reagent **7** to TMHQ aldehyde at -78° provided the allylic alcohol **9a** in 75% yield as a sole diastereoisomer as shown by ^{1}H- and ^{13}C-NMR. Removal of the silyl protecting group was smoothly achieved with tetrabutyl ammonium fluoride in THF at room temperature to give the air sensitive hydroquinone **9b** in 60% yield.

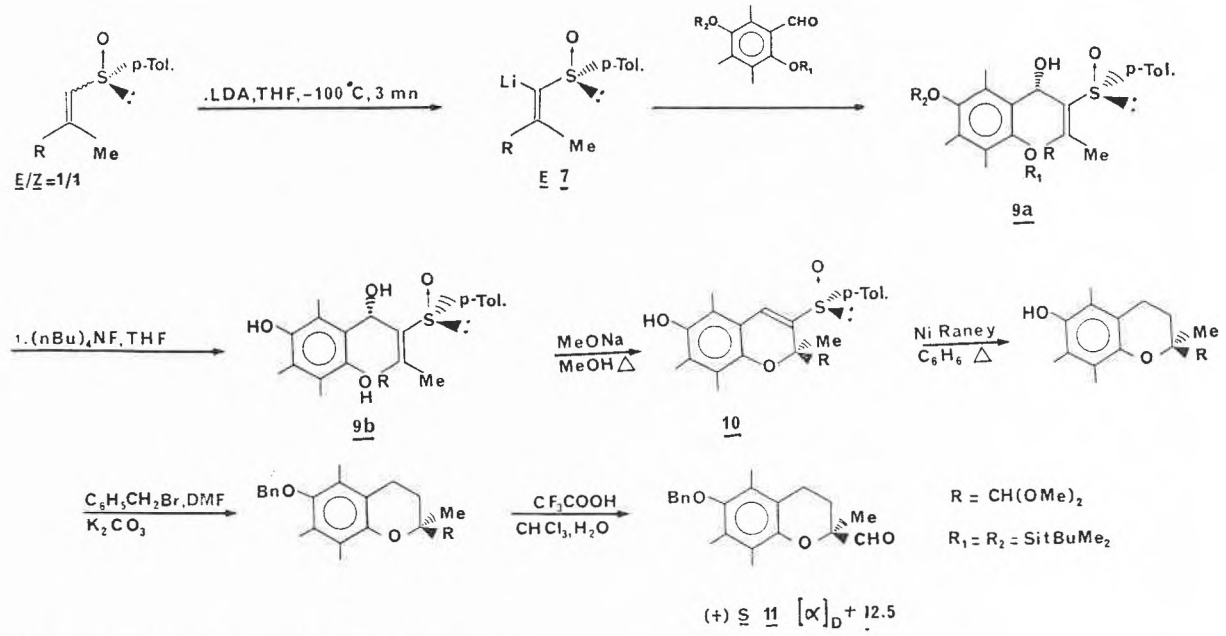


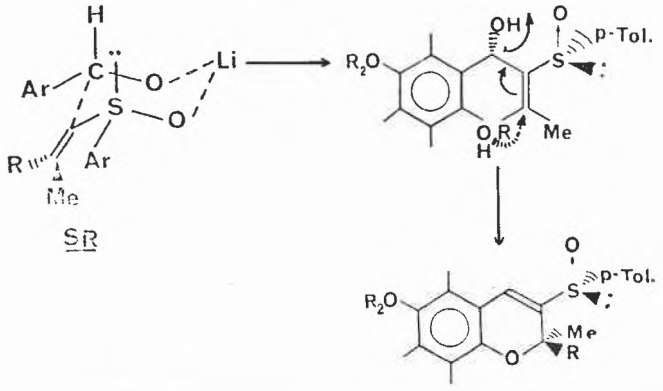
Fig. 27: Asymmetric synthesis of the formylchromane *11*

The cyclization was achieved in refluxing methanol in presence of a three fold excess of sodium methoxide leading to the stereospecific formation of chromene **10** in 96% yield.

The last synthetic steps were straight forward: reductive desulfurization with Raney Nickel (76% yield), benzylation of the phenol (87% yield), acidic cleavage of the ketal (98% yield) leading to optically pure (+) *S* formylchromane **11.**

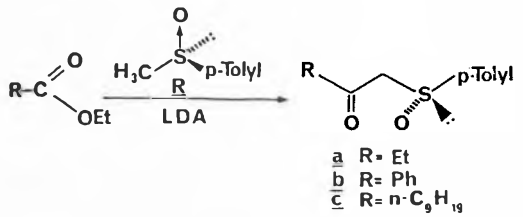
The absolute configurations of compounds **9** and **10** were not established. However from the models generally used to explain the asymmetric induction of chiral sulfoxides it is possible to predict the chirality *S* for the created hydroxylic center. In such a case the observed *S* chirality of the formyl chromane **11** would support a syn SN'2 mechanism for the stereospecific cyclization of molecule **9.**

Fig. 28:



III. Reduction of β-Ketosulfoxides [34]

β-ketosulfoxides are easily prepared in high yields from carboxylic esters (or the corresponding acid chlorides or imidazoles). A stereospecific reduction of the ketone would give after desulfurization optically active methylcarbinols or alkyl carbinols by the way of a substitution on the carbon atom α to the sulfoxide.



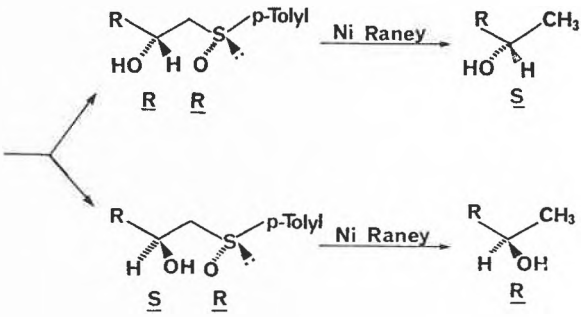


Fig. 29: Reduction of β-ketosulfoxides

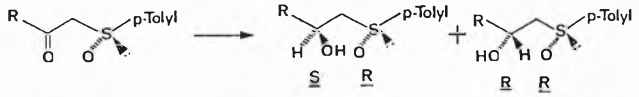
Cinquini [35] already showed that $NaBH_4$ or $LiAlH_4$ reduction of β-ketosulfoxides lead to the corresponding carbinols with 60% diastereoselectivity.

We investigated the reduction of these β-ketosulfoxides with two reagents: $LiAlH_4$ and DIBAL. The results listed in Table VI showed that the stereoselectivity of both reagents was opposite: $LiAlH_4$ gave the *RR* β-hydroxysulfoxide in 80% d.e. while DIBAL lead to the *SR* isomer in 90% d.e.

Therefore according the reagent used for the reduction it is possible to get one or the other diastereoisomer in high e.e. from the same chirality at sulfur.

It is interesting to remark that it is quite possible to apply the reduction to $\alpha\beta$-unsaturated or propargylic β-ketosulfoxides.

Table 6: Reduction de β-ketosulfoxides



R (t°C)	$LiAlH_4$ (Et_2O-THF)		DIBAL (THF)	
	Rdt %	RR/SR	Rdt %	RR/SR
Et (−100°C)	85	93/7	90	12/88
∅ (−100°C)	80	90/10	95	18/82
i-Pr (−78°C)	93	83/17	85	5/95
t-Bu (−78°C)	90	82/18	80	5/95
n-C_9H_{19} (−78°C)	80	90/10	83	0/100
Ph⟍═⟋ (−78°C)	90	80/20	95	5/95
CH_3⟍═⟋ (−78°C)	91	81/19	90	10/90
Ph −·≡·− (−78°C)	80	91/9	82	5/95
nC_3H_7 −·≡·− (−78°C)	92	75/25	97	8/92

The different stereochemical pathway of the reduction according the reducing agent is propably due to a different conformation of the β-keto sulfoxide in the transition state.

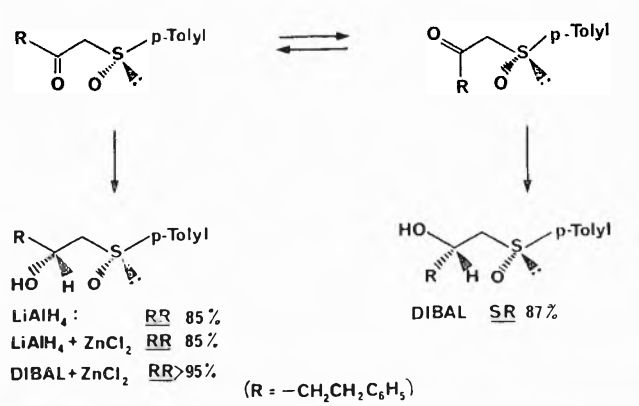
This point was clearly demonstrated by the following experiments:

The reduction of the ketosulfoxide shown in fig. 30 gave with $LiAlH_4$ 85% of the *RR* diastereoisomer and with DIBAL 87% of the *SR* diastereoisomer (the chirality at sulfur being *R* in both cases).

Now if we add to the reaction mixture zinc chloride, a well-known chelating agent, we observed no change in the diastereoselectivity with $LiAlH_4$ but with DIBAL the main diastereoisomer has now the *RR* absolute configuration.

Therefore it is possible now to conclude that the reaction proceeds with $LiAlH_4$ through a chelated transition state with the aluminium chelated between the carbonyloxygen and the sulfoxide oxygen, while with DIBAL the β-ketosulfoxide is in a conformation which does not allow the chelation on the two oxygen atoms. In both conformations the hydride attacks on the less hindered side of the molecule where the sulfur lone-pair is located.

Fig. 30:



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