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Chiral Building Blocks in Enantiomer Synthesis:
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Syntheses of Enantiomerically Pure Compounds (EPC-Syntheses)

Tartaric Acid, an Ideal Source of Chiral Building Blocks for Syntheses?

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The synthesis of enantiomerically pure target structures rather than of d,l-products has received increasing attention over the past decade. Thus, all the speakers describing natural product syntheses during the 1979 *Bürgenstock* Conference took pride in stating that they were meeting present standards by synthesizing enantiomerically pure compounds. Although elements of fashion and sport are involved, there are two serious reasons for this developement, a pure one, the need for a deeper understanding of the interactions within diastereomeric transition states, and an applied one, the necessity of being able to produce physiologically active natural and unnatural compounds in enantiomerically pure forms[1].

A) INTRODUCTION

The present article is solely concerned with the practical aspects of the synthesis of enantiomerically pure compounds, its main purpose being the description of some recent work aimed at making available synthetically versatile chiral building blocks from readily available hydroxy acids - with emphasis on tartaric acid[2]. Before doing this, however, some general statements and a comparative discussion of the different methods of preparing enantiomerically pure compounds are appropriate.

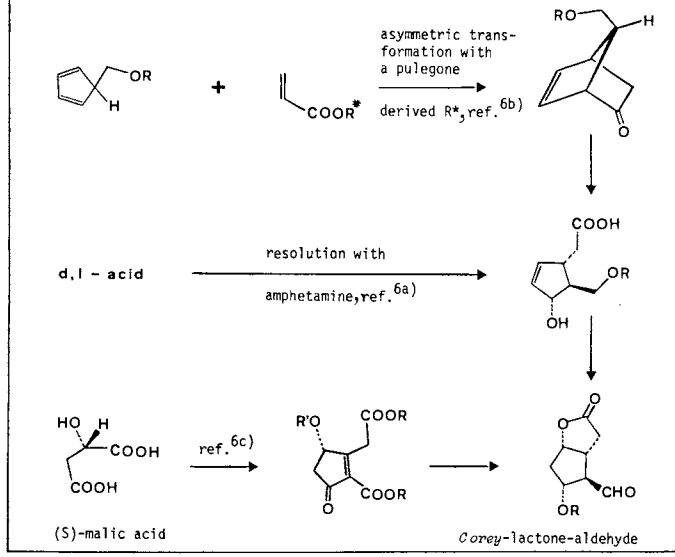
What is an EPC-Synthesis?

Chirality, that most subtle fundamental structural feature molecules can be endowed with, intrigues many chemists to an extent which leads to occasional abuse of the word. Thus, the term "chiral economy"[3] was recently used, and a symposium held during the 1979 fall meeting of the American Chemical Society in Washington was entitled "Chiral Synthesis from Carbohydrate Precursors". An object is chiral if it is not congruent with its mirror image; since neither economy nor synthesis are objects with mirror images, they cannot be chiral. We propose to use the collective name *EPC-synthesis* for all approaches leading to enantiomerically pure compunds. If a target molecule and its immediate precursors are liquid, an enantiomeric excess (e.e.) of at least 98 % (ratio of enantiomers 99:1) must be postulated[4] for an EPC-synthesis; with solid products, a lower value can be satisfactory, because a separation from racemic material is usually possible by crystallization. - Modern analytical methods can determine enantiomeric ratios very accurately[5].

The Minimum Effort to do an EPC-Synthesis

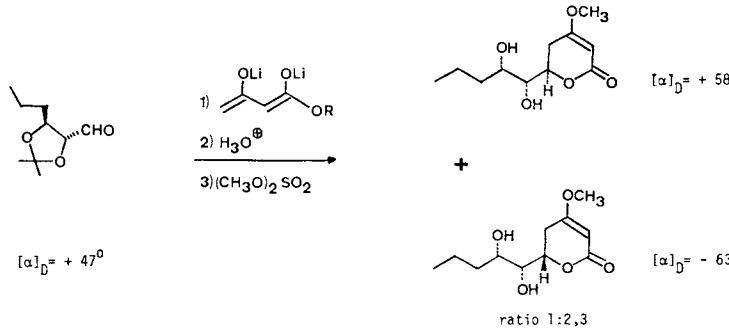
A cautionary note is necessary in order to prevent overemphasis. Important as it may be for practical purposes, for instance the production of a drug, an EPC-synthesis may differ from the synthesis of a d,l-target molecule only by a *single step*. This may be the resolution of a racemate, an asymmetric transformation of an achiral precursor, or the incorporation of *one* enantiomerically pure (e.p.) fragment into an intermediate, see the *Corey*-lactone EPC-syntheses in scheme I and discussion below[6]. Before and/or after this unique event, the synthetic chemist is engaged in a battle to achieve the correct constitution and configuration of the intermediates. Using a recently proposed[7], product structure-oriented nomenclature, the main pursuit during a multistage synthesis has been and will remain to be the attainment of *type selectivity* (e.g. nucleophilic addition to *one* of two or more different carbonyl groups), *regioselectivity* (e.g. direction of elimination, of enolization, or of addition), *ambidoselectivity* (e.g. O- vs. C-alkylation of an enolate or 1.2- vs. 1.4-addition to an enone), and *diastereoselectivity* (e.g. Z-/E-, cis-/trans-, syn-/anti-, endo-/exo-, or R.R,S.S-/R.S,S.R-product). Once an e.p.-intermediate is obtained, in the absence of racemization all products, including those of undesired side reactions, will be enantiomeri-

SCHEME I

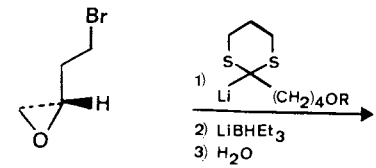


cally pure. This is demonstrated in equation (1) with the preparation of e.p. (+)-LLP-880β along with an e.p. epimer[8a], and in equation (2) which shows the formation of two e.p. diastereomeric spiroacetal pheromones [8b].

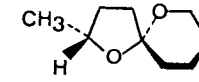
(1)



(2)

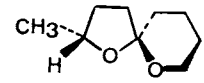


$[\alpha]_D$= -23,5°



$[\alpha]_D$= +88°

+

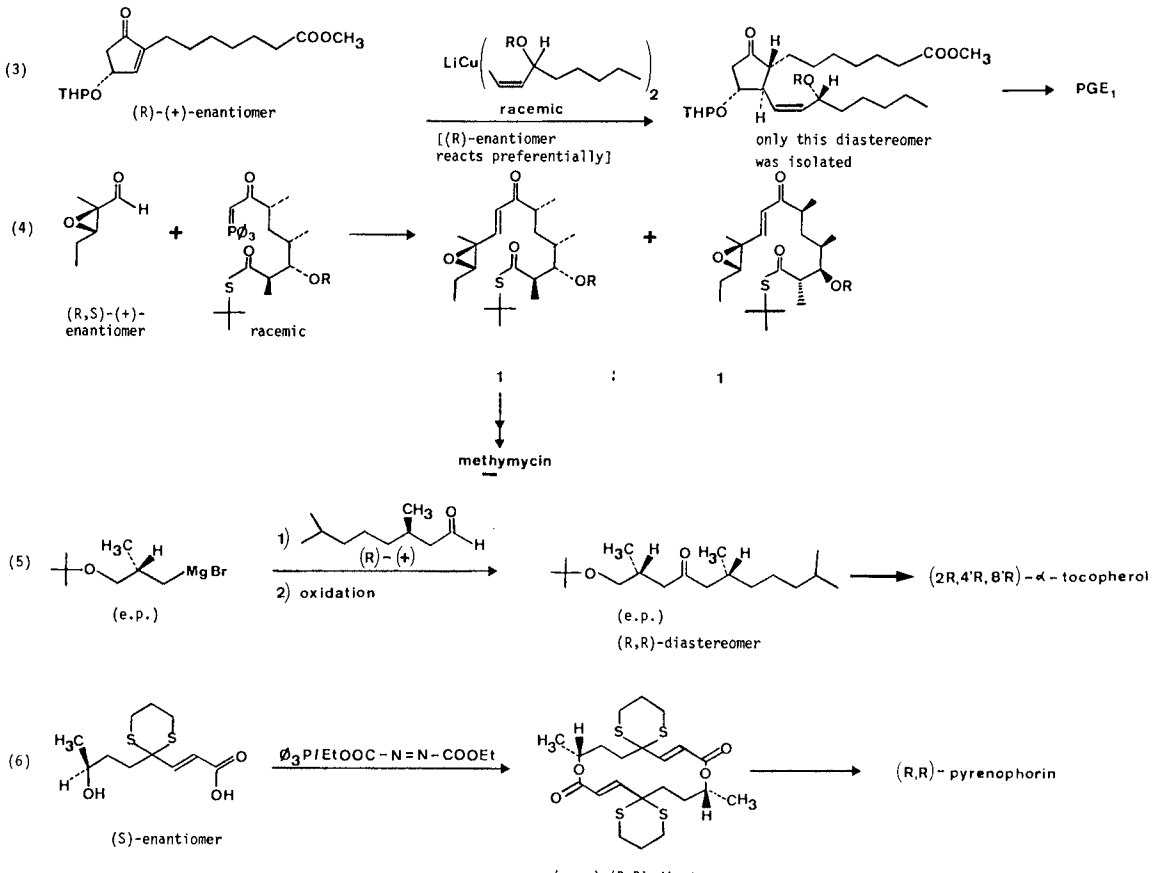


$[\alpha]_D$= -118°

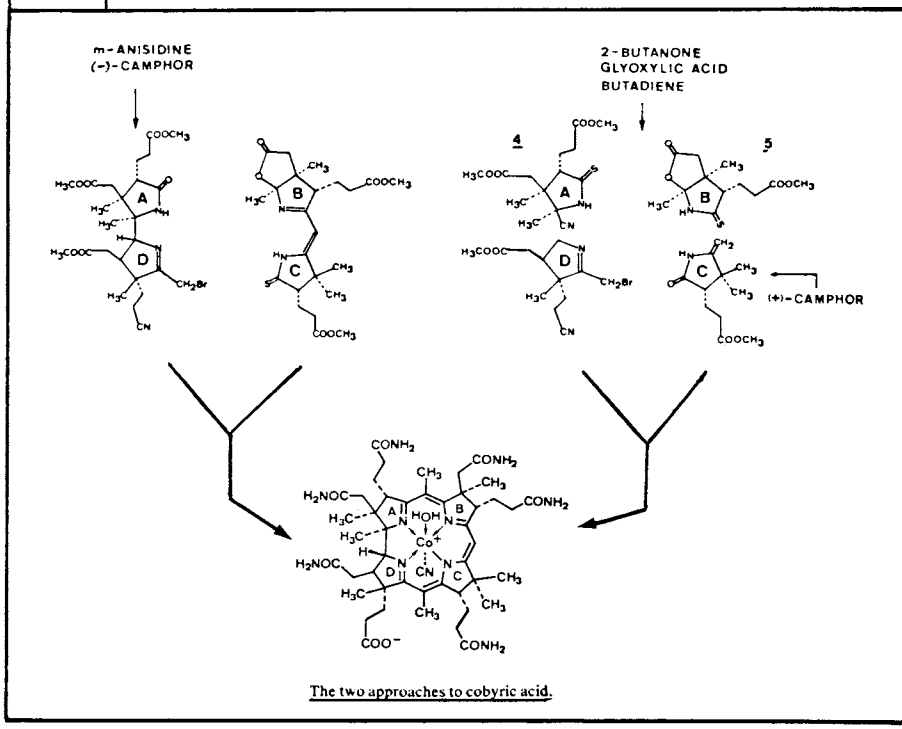
A Bonus from EPC-Synthesis

Diastereomeric mixtures are not only obtained if we generate new asymmetric carbon atoms non-selectively as in equations (1) and (2): remember, that whenever an enantiomerically pure component is combined with a d,l-component without formation of a new center of chirality, a mixture of two enantiomerically pure diastereomeric products results (cf. resolution, below). This leads to loss of half of the material; the virtue of a convergent synthesis gets at least partially lost, as well! Two examples are given in equations (3)[9] and (4)[10]. The loss can be avoided by employing both components in enantiomerically pure form.

As examples of EPC-syntheses employing two or more enantiomerically pure components see the tocopherol synthesis[4] in equation (5), a pyrenophorin synthesis[11] in equation (6) and the EPC-syntheses of cobyric acid[12], of cytochalasin[13] and of monensine[14] in schemes II, III, and IV, respectively.

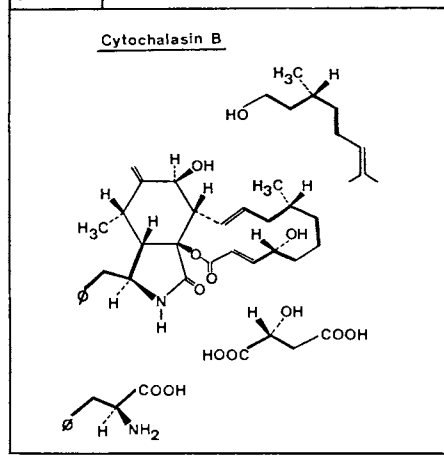

(3)
(R)-(+)-enantiomer
racemic
[(R)-enantiomer reacts preferentially]
only this diastereomer was isolated
PGE1
(4)
(R,S)-(+)-enantiomer
racemic
1 : 1
methymycin
(5)
(e.p.)
1) (R)-(+)
2) oxidation
(e.p.)
(R,R)-diastereomer
(2R,4'R,8'R)-α-tocopherol
(6)
(S)-enantiomer
Ø3P/EtOOC-N=N-COOEt
(e.p.) (R,R)-diastereomer
(R,R)-pyrenophorin

SCHEME II

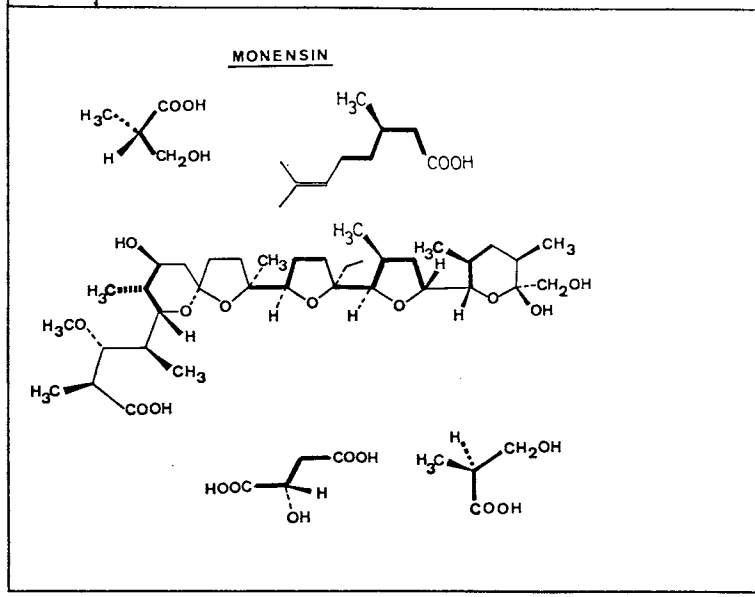


The two approaches to cobyric acid.

SCHEME III



SCHEME IV



B) METHODS OF EPC-SYNTHESIS

Chiral Building Blocks for Syntheses

All we need for EPC-syntheses is readily available enantiomerically pure starting materials having a constitution and a functional group pattern which allow their incorporation into diverse chiral[15] target structures. How do we get hold of such chiral building blocks? Apart from the products of spontaneous crystallization of *one* enantiomer[16], and from the products of absolute asymmetric synthesis[17,18], man-made enantiomerically pure or enriched compounds *originate eventually from living matter*. As a rule, nature converts achiral *natural* substrates containing an element of prochirality[18] to chiral products *enantioselectively*[18]. We have thus a huge supply of e.p. *natural products* at our disposal. The question is, how to utilize them for the preparation of chiral building blocks and thence for EPC-syntheses. Three operationally different methods can be distinguished for practical purposes: the *natural product* or a derivative thereof is used to achieve a *physical separation* or a *chemical differentiation* or it can serve as a *starting material itself*. Detailed elaborations and exemplifications of these three proce-

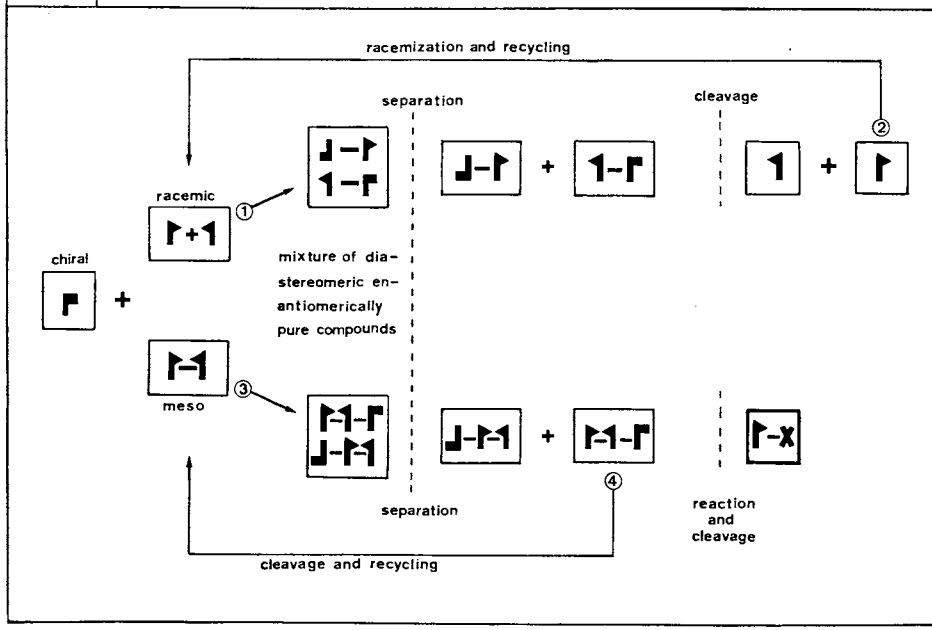
dures are given in the following sections.

For generalizations we will use two-dimensionally chiral symbols[19] for chiral molecules or chiral moieties within molecules. In two-dimensional space  and  are superimposable, while  and  are enantiomeric;  is chiral,  symbolizes a meso-form.

Physical Separation Methods

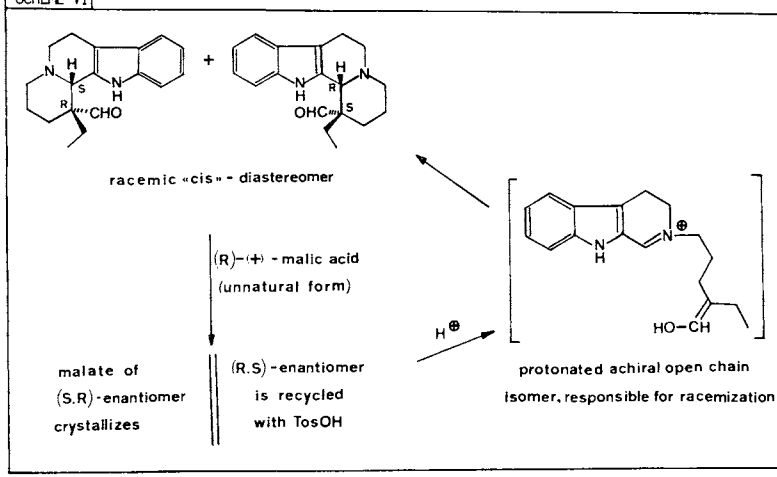
The classical method of resolution[20] of racemic mixtures is demonstrated in scheme V, route ①. Temporary diastereomeric relationships are established between an enantiomerically pure natural product and the components of the racemic mixture. The relationship can be as close as a covalent bond (carboxylic ester[21], amide[22]) or an ionic bond (ammonium salts[20,23]) or it may be as loose as an adsorption on a chiral surface (chromatographic resolution[24]), it must generate different physical properties which are used for the separation. After the separation, the temporary bond is cleaved, which

SCHEME V



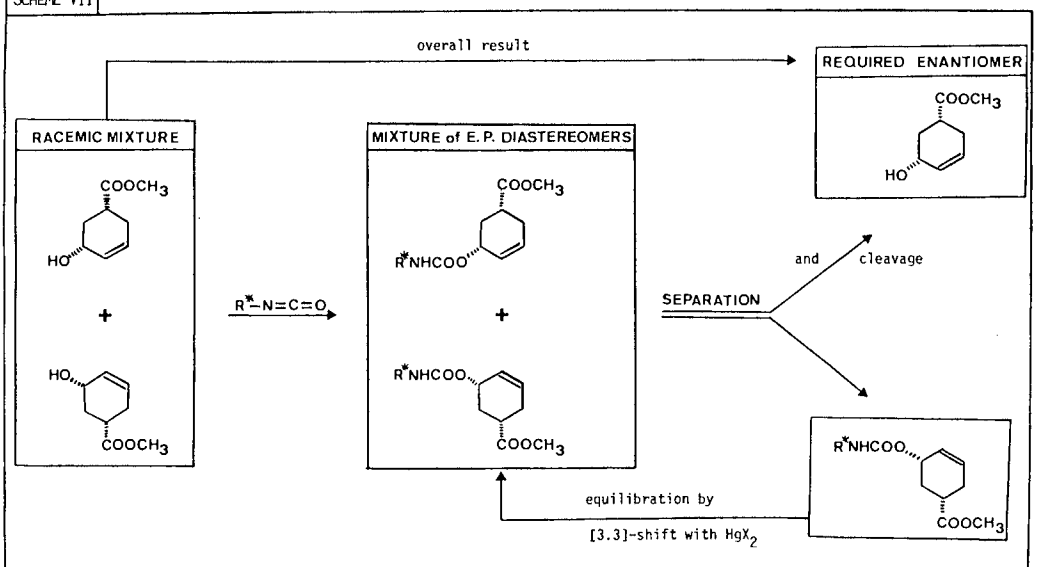
leads to the isolation of the enantiomerically pure components of the original racemic mixture and to the recovery of the auxiliary. With enantiomerically pure compounds thus obtained we can of course do other resolutions. If we need only one particular enantiomer, the theoretical yield of 50 % in such a process is not satisfactory. As indicated in scheme V , route ②, racemizing and recycling the "wrong" enantiomer can give a theoretical yield of 100 %. In EPC-syntheses of emetine[1a,3], of vincamine[25], see scheme VI, and of a prostaglandin precursor, see scheme VII, this principle of resolution with recycling is realized[26]. Using *Izumi's* nomenclature, the *overall result* of a resolution with recycling is an enantiomer differentiating conversion of *one* enantiomer of a racemic mixture into its mirror image.

SCHEME VI

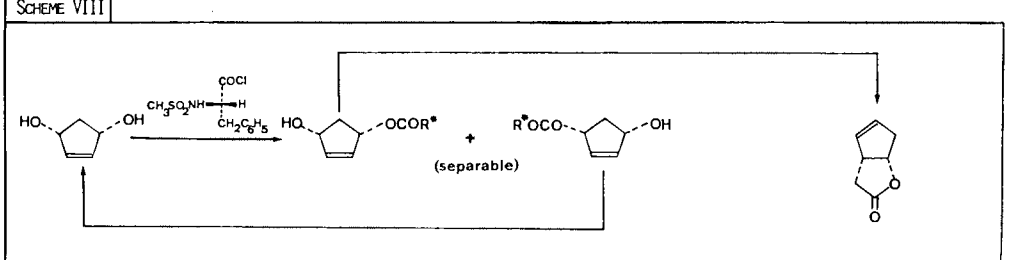


meso-Compounds are achiral molecules which contain one or more pairs of constitutionally identical elements of opposite chirality; they might be regarded as "internal racemates". Step ③ of scheme V shows the conversion of a meso-compound into a mixture of diastereomeric enantiomerically pure compounds by reaction with an auxiliary. Separation by a physical method, for instance crystallization or chromatography, a suitable chemical conversion of the desired diastereomer, and removal of the auxiliary lead to an enantiome-

SCHEME VII

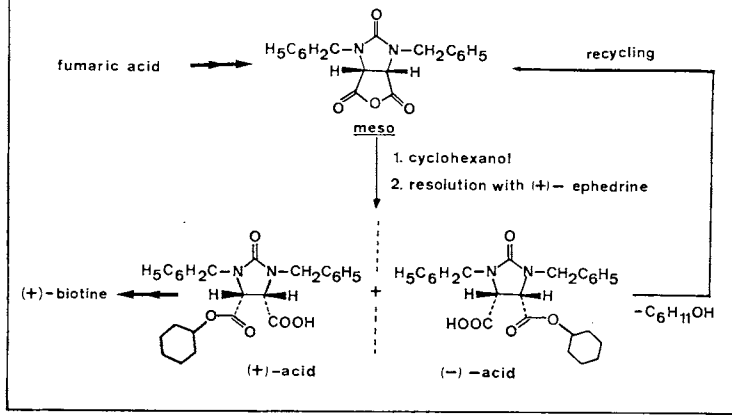


SCHEME VIII



rically pure product. In this case, the recycling is particularly easy because it *does not* require a racemization, i. e. equilibration between molecules of opposite chirality. The auxiliary is just removed from the undesired diastereomer to regenerate the meso-compound; chemically, step ④ in scheme V is the reverse of step ③. Applications of this meso-trick in EPC-syntheses of prostanoids[27] and of biotine[28] are evident from scheme VIII and scheme IX, respectively[29]. - Overall, these processes are enantiotopos differentiating[18] chemical conversions (cf. next section). The enantiomeric purity of the final product does, however, not rely upon the enantiotopos differentiating[18] quality of a chemical reaction, but entirely upon the quality of the diastereomer separation by a physical method - just like the above mentioned resolutions.

SCHEME IX

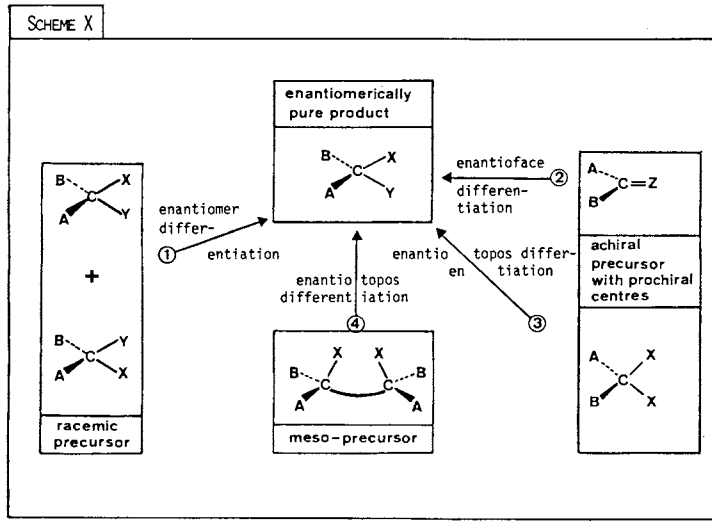


Stereodifferentiating Reactions - The $\Delta\Delta G^{\neq}$-Approach

This mode of preparing enantiomerically pure products utilizes the much more fascinating and intriguing stereoselectivity of chemical reactions. The degree of selectivity determines the enantiomeric purity of the product. The approach is commonly referred to an asymmetric synthesis[30]. This term is controversial[18], there are different definitions and a confusing multitude of subgroups, such as external, eliminative, catalytic, noncatalytic, internal, conservative, immolative, absolute asymmetric synthesis, kinetic resolu-

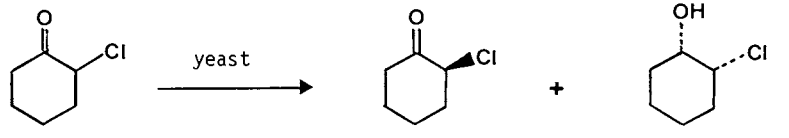
tion and so forth. For the following discussion, we will use the terminology proposed by *Izumi*[18].

In the *overall transformation,* leading to the enantiomerically pure product, enantiomers, enantiotopic faces, or enantiotopic groups have to be differentiated. This is shown in scheme X ① - ④ for the preparation of a molecule with one center of chirality[31]. In route ①, the starting material is a racemic mixture. In routes ② and ③ the precursors are achiral molecules with prochiral centers. Route ④ starts with a meso-compound. We can actually carry out the overall transformations in two different ways: *enantioselectively* or *diastereoselectively.*

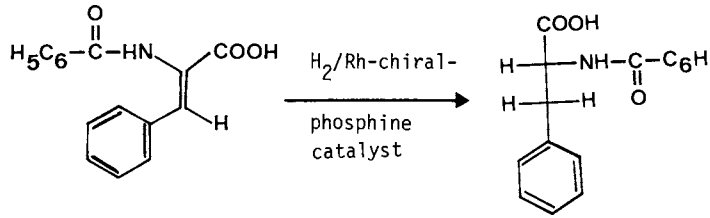


In the first case, we use *enantiomerically pure reagents,* which are capable of recognizing and differentiating enantiomers or enantiotopic faces or groups. Examples of highly enantioselective transformations with different types of precursors, as outlined in scheme X, are given in equations (7)[32], (8)[33], (9)[34], (10)[35], (11)[36], and (12)[37]. Obviously, such reactions are the domain of living organisms such as bacteria and fungi. They use enzymes as chiral reagents with high degree of enantioselectivity.

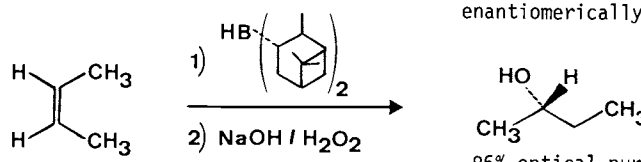
(7)


yeast
racemic
(+)
(-)
both compounds enantiomerically pure

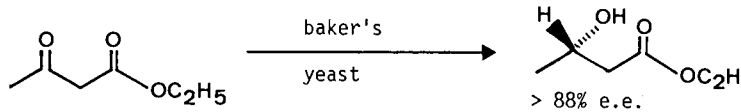
(8)


H2/Rh-chiral-
phosphine
catalyst
enantiomerically pure

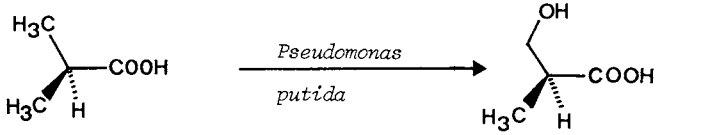
(9)


1)
2) NaOH / H2O2
86% optical purity

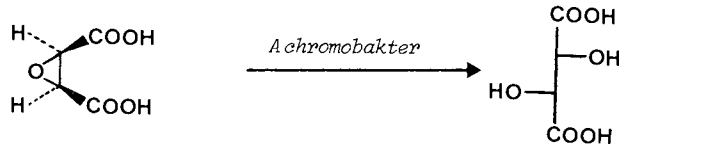
(10)


baker's
yeast
> 88% e.e.

(11)


Pseudomonas
putida
enantiomerically pure

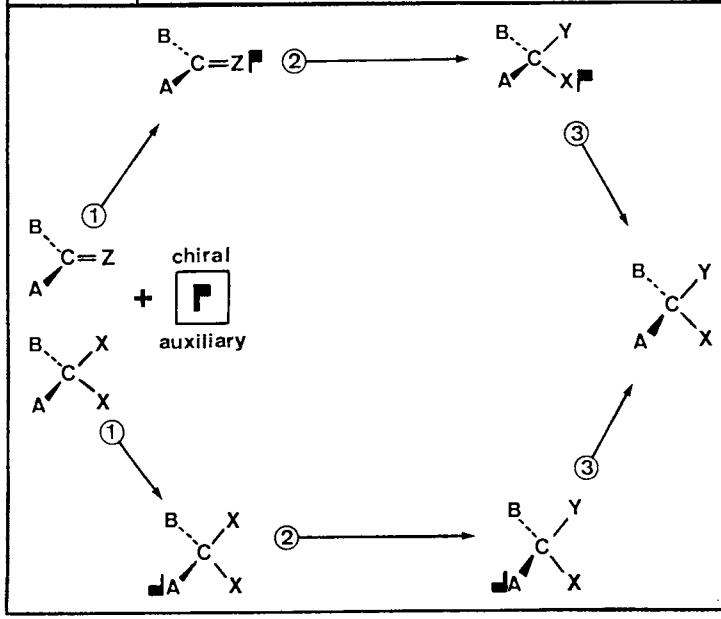
(12)


Achromobakter
enantiomerically pure

Enzymatic and microbiological methods can be used to do such reaction with natural or unnatural substrates, see equations (7)[32], (10)[35], (11)[36] and (12)[37]. An entire chapter of the present book is devoted to this particular subject[38].

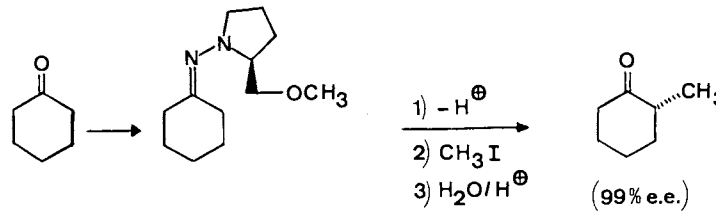
The second way of performing the overall transformations of scheme X is outlined in scheme XI for the achiral precursors with prochiral centers. In step ① of scheme XI, an enantiomerically pure auxiliary is attached to the

SCHEME XI



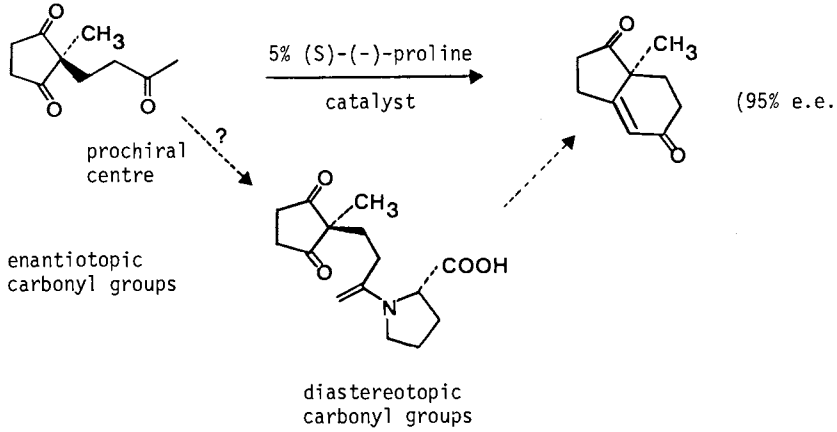
achiral precursors. This converts the enantiotopic faces and groups into diastereotopic faces and groups. In step ②, an *achiral reagent* attacks one of the diastereotopic faces or groups selectively, with formation of a new center of chirality. In step ③, the auxiliary is removed to furnish the desired product, the maximum enantiomeric purity of which depends entirely upon the degree of diastereoselectivity of the chemical reaction ②. An example is given in equation (13)[39,40]: conversion of cyclohexanone into an isolated

proline-derived hydrazone renders the two α-CH_2-groups as well as the hydro-

(13) 

gens within them diastereotopic, so that achiral reagents can create a new center of chirality diastereoselectively, furnishing after cleavage of the hydrazone enantiomerically pure 2-methyl cyclohexanone.

There are cases, such as many enzyme reactions or the process described in equation (14)[41,42], where an assignment to enantio- or diastereoselectivity can become arbitrary or at least unsatisfactory. This is true of so called[18] double differentiating reactions, when the substrate *and* the reagent or catalyst are *both* chiral, but also if we have to follow the rule[18], that the assignment is to be made by simply comparing reactant and product, without considering mechanisms. In the proline catalyzed last step of the *Robinson*-annelation of equation (14)[41,42], a very high preference of the enantiotopic re-carbonyl group to undergo the aldol condensation is observed, overall a catalytic enantioselective synthesis; the decision about the enantiomeric

(14) 

purity of the product, might however very well be made at the stage of an intermediate enamine in which the two carbonyl groups of the five membered ring have become diastereotopic.

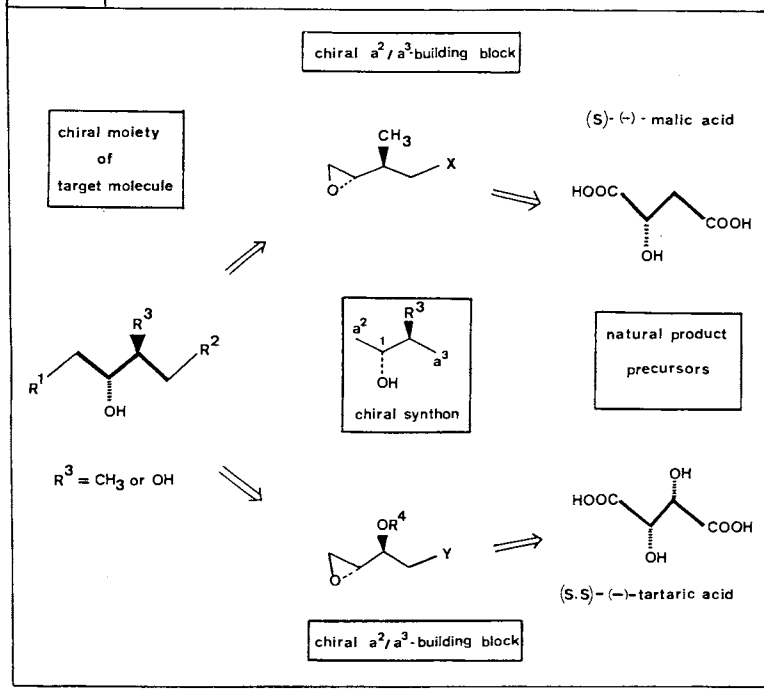
In any event, free energy of activation differences ($\Delta\Delta G^{\neq}$) *between diastereomeric transition states are responsible for the enantiomeric purity of the product* in this approach.

Incorporation of Natural Products - A Pool of Chiral Building Blocks for EPC-Syntheses.

The two preceding chapters described methods of obtaining enantiomerically pure starting materials, intermediates, or target molecules by utilizing an e.p. auxiliary either to perform a physical separation or to effect a stereodifferentiating reaction. The auxiliary molecule was not incorporated into the desired product, and it was a natural product, a derivative of a natural product or a compound which was eventually obtained with the help of a natural product.

There is a third, most direct route of utilizing natural products to obtain chiral building blocks for syntheses: The natural product or parts of it are eventually built into the target molecule. Scheme XII shows, how a chiral moiety within the target structure can be correlated through a chiral building block with the natural products malic acid or tartaric acid[35b,43,44]. The advantages of doing this have become evident in the past decade. All sorts of readily available terpenes, aminoacids, hydroxyacids, and carbohydrates are now converted - by more or less elaborate chemical modifications[45] - to provide a *pool*[1b] *of versatile chiral building blocks* for EPC-syntheses. Although with a different goal, much fundamental work in this area has been done in the first 50 years of this century, when the absolute configuration (sense of chirality) of many natural and unnatural compounds was determined by chemical correlations[45]. Especially rich sources of chiral building blocks for the pool are carbohydrates[46], which have been incorporated into products with such diverse structures[47,48] and activities as have alkaloids, prostanoids, antibiotic macrolides and pyrrolidines, pheromones, pesticidal terpenes, and ß-blockers - see chapter 3 of this volume[2].

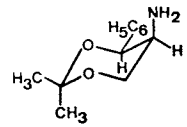
SCHEME XII



A Comparison - The Access to Either Enantiomer

Which of the operationally distinct routes of utilizing enantiomerically pure natural products for EPC-syntheses is the best one? This depends crucially upon the purpose for which such a synthesis is undertaken. Cleary, the separation and the stereodifferentiation can be realized with recovery of the auxiliary and thus with preservation of the resources of the chiral natural product, while incorporation uses it irreversibly. For a large scale industrial production of a particular compound, a catalytic or microbiological route would appear to be ideal, for the discovery and optimization of which great efforts are justified. On the other hand, a diversifying production on smaller scale or preparations in research laboratories require a *versatile, safe approach to a multitude of chiral structures*. Both, the separation and

the stereodifferentiation approach require a strong investment and involve a high degree of adventure, uncertainty and risk with ever new substrates. A resolution with recycling or a second order asymmetric transformation[18], which depend upon crystallization, may capriciously react to apparently minor structural changes. The preparation of e.p. aminoacids outlined in equation (15a)[49] relies upon the crystallization of an intermediate and furni-

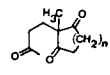
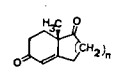
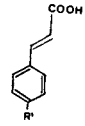
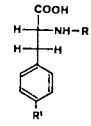
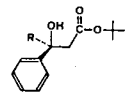
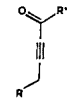
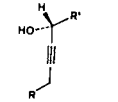
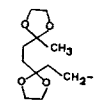
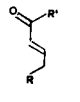
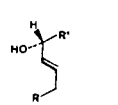
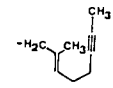
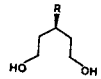
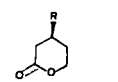
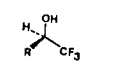
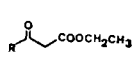
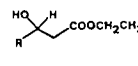
(15a)  + $H_3C-(CH_2)_n-\overset{O}{\overset{\|}{C}}-CH_3$ + HCN ⟶ $H_3C-(CH_2)_n-\underset{NH_2}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-COOH$

n = 1,3 : (S)-configuration

n = 2,4 : (R)-configuration

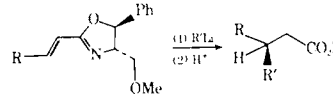
shes S- and R-products if the alkyl chain length is even or odd, respectively. Also, microbiological asymmetric syntheses with unnatural substrates and other asymmetric syntheses are very often subject to the key-lock principle: the enantiomeric purity of the product can drop below the requisite limit for reasons which are not at all understood, see the examples in table 1. There are some recent notable exceptions to the key lock principle such as the *Michael*-additions (table 2) and the enzymatic oxidation of meso-diols in table 3. Generally, the "man made" processes, which occur with very high selectivity and lead to enantiomerically pure products, are *still* unique and exceptional. This is, why the EPC-syntheses incorporating an enantiomerically pure, readily available natural product into the target structure, are so attractive: we do not have to be concerned with enantiomeric purity from the very beginning. One could quote that there is not enough pool material available to meet the various demands - quantitatively and qualitatively. Considering the progress in biotechnology, the aspects opened up by genetic engineering, the prediction that plant material might be one of our final, main sources of energy and - besides CO_2 - the *only* source of carbon compounds after having used up natural gas, oil, and coal, and considering the wealth of useful chiral building blocks which have so far been made from carbohydrates alone, we need not worry about that. Of course, the "safe" enantiomeric purity has to be paid for by additional chemical steps carrying the natural product to the stage of a synthetically useful building

Table 1 Sensitivity of enantiomeric yields in asymmetric transformation with variation of the substrate structure.

achiral starting material	enantiomerically enriched product (sense of chirality)		% e.e.	references
		n=1 n=2	95 70	41 42
		R= C-Ø, R'=H R= C-CH_3, R'=H R= C-CH_3, R'= OCCH_3	99 89 88	33
		R= H R= CH_3	91 68	50
		R= 	84	51
		R'= 	25	
		R= CH_3 R= CH $(CH_3)_2$ R= C_6H_5	90 25 21	52
		R=  R= 	>99 44	53
		R= CH_3 R= CH_2CH_3 R= $(CH_2)_3$ CH_3	88 (S) 40 (S) >90 (R)	35

block. This is especially true of the carbohydrate approach: in certain situations[55], the carbon chain of glucose, the cheapest monosaccharide and - including all of its derivatives - probably the most ubiquitous and abundant natural product, is too long and overfunctionalized with centres of chirality.

Table 2 Diastereoselective *Michael*-additions to chiral oxazolines for the preparation of > 91 % enantiomerically pure 3-substituted alkanoic acid derivatives.

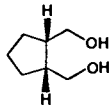
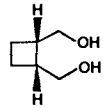
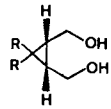
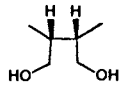
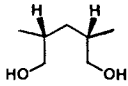
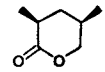
ref.[54]  Chem. yield 40 - 70 %

R	R'Li	config.
Me	Et	*R*
Me	*n*-Bu	*R*
Me	*n*-hexyl	*R*
Me	Ph	*S*
Et	*n*-Bu	*R*
Et	Ph	*S*
i-Pr	*n*-Bu	*R*
t-Bu	*n*-Bu	*R*
cyclohexyl	Et	*R*
cyclohexyl	*n*-Bu	*R*
$MeOCH_2CH_2$	Et	*S*
$MeOCH_2CH_2$	*n*-Pr	*S*
$MeOCH_2CH_2$	*n*-Bu	*S*
$MeOCH_2CH_2$	Ph	*S*
Ph	Et	*R*
Ph	*n*-Bu	*R*
o-MeOPh	Et	*R*
o-MeOPh	*n*-Bu	*R*
o-MeOPh	Ph	*S*

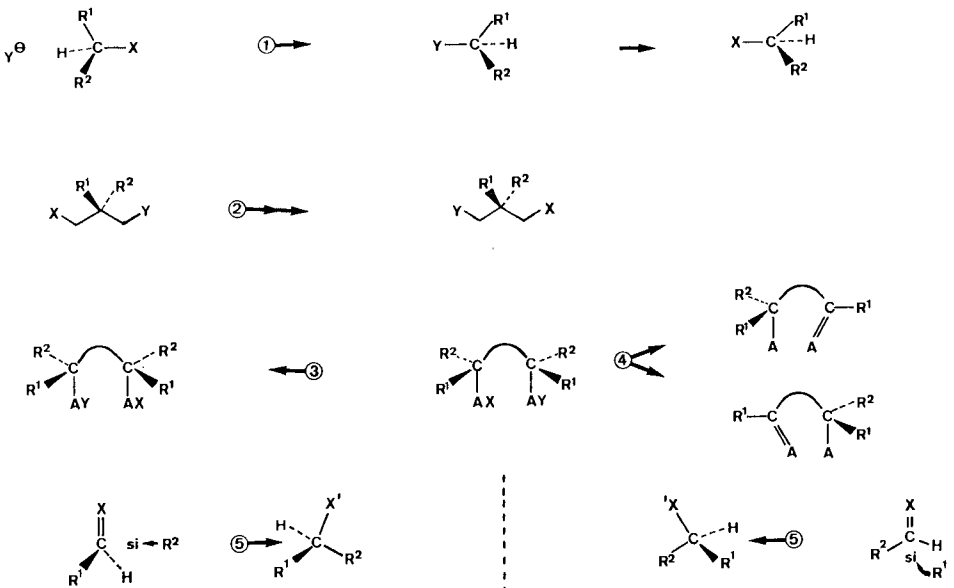
In many EPC-syntheses, for instance of pheromones [46b], of physiologically active synthetic samples for testing, and of complicated natural products, the absolute configuration of the final product is unknown to begin with, or image *and* mirror image moieties are both part of the target structure[56]. In these cases, the synthetic chemist must have access to *both* or - eventually - *either one* of the enantiomeric starting materials. With modern, chromatographic resolutions[5,21,22,24] this aggravating requirement is fulfilled.

Generally, resolutions are more likely to be able to furnish both enantiomers than stereodifferentiating reactions - unless we have both enantiomeric auxiliaries available from a resolution. Natural products, and thus the e.p. auxiliary compounds, reagents and building blocks derived from them, usually come in *one* enantiomeric form only. Some tricks, by which this disadvantage can be overcome, at least when rather simple molecules are concerned, are listed with relevant references in scheme XIII.

Table 3 Horse liver alcohol dehydrogenase (HLADH) catalysed oxidations of meso-diols to 100 % e.p. lactones

Educt	Product (absol. configuration)	Chemical % yield	e.e.
	 (S,R)	72 %	100 %
	 (S,R)	88 %	100 %
	 R = H (S,R) R = Me (R,S)	68 % 71 %	100 % 100 %
	 (S,R)	64 %	100 %
	 (S,R)	65 %	100 %

SCHEME XIII



① inversion by substitution, only possible at heterosubstituted centers[11, 57].

② exchange of groups which are symmetrically disposed with respect to a center of chirality[36, 56, 58, 59].

③ ④ functionality transformations in chiral derivatives of meso-forms (cf. schemes IV, VIII)[27, 28, 29].

⑤ interchange of groups between substrate and reagent in asymmetric syntheses (cf. table 2)[18, 54].

C) TARTARIC ACID AS A SOURCE OF CHIRAL BUILDING BLOCKS FOR SYNTHESES

General Remarks - From Wine to an African Bush Plant

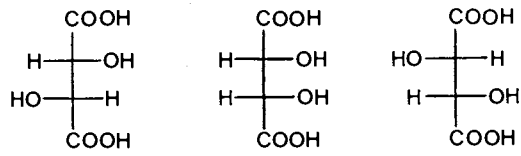
In our own work on EPC-syntheses[1b,8a,8b,11,35b,35d,43,44,57,60-65], we concentrate on two aspects. (a) We try to supply versatile and generally useful chiral building blocks containing structural elements which occur in *many* potential target molecules. (b) We use a unique precursor, a simple *natural product which is readily available in both enantiomeric forms* – namely *tartaric acid*. This compound was involved in the most important events which led to the classical structural and stereochemical theory of organic chemistry in the 19th century, see the delightful description of the history of tartaric acid in *Fieser*'s text book[66], and a recent article[67] entitled "Studies of the structure of tartaric acid before 1874".

(R,R)-(+)-Tartaric acid, the *so called natural form*, is obtained in large quantities from potassium hydrogen tartrate (tartar or cream of tartar), a waste product of wineries, which crystallize it from wine before bottling. The d,l-form, called racemic acid, is synthesized[68] on large industrial scale from maleic anhydride and hydrogen peroxide, to supplement the unrelyable natural source, which depends upon the vintage - like the quality and quantity of the wine. Resolution is possible either by crystallization[69] or by enzymatic or microbiological enantiodifferentiating conversions of racemic acid or of the epoxide of maleic acid anhydride[37,70]. Ten thousands of tons of tartaric acid is used *per annum* in industry and as a food acidulant[68]. The current price is ca.$ 4.--/kg of (R,R)-(+)-tartaric acid (100 kg quantities)[69], which makes it one of the least expensive enantiomerically pure compounds. It is widely unknown, that the enantiomeric (S,S)-(-)-tartaric acid is also a natural product. The frenchmen *Lafitte, Rabaté,* and *Gourévitch* discovered in 1936-38, that the dry leaves of the bush plant *Bauhinia,* a main vegetational form in central Africa (Tschad, Sudan, Guinea) contain ca. 5 % by weight of (-)-tartaric acid, which can be isolated simply by hot water extraction[71]. Thus, tartaric acid is one of the few compounds, of which both enantiomers occur abundantly and in a readily isolable form in nature. This is rather exceptional, other examples being lactic acid, camphor, and citronellol.

Both, (S)-(+)- and (R)-(-)-lactic acids[72] are obtained from fermentations, the (+)-form is being produced on large scale and used as food acidulant[68], the (-)-form is the so called muscle lactic acid, which is, however, not commercially available. More and more D-aminoacids are found to occur naturally in small amounts. Due to industrial production from synthetic racemic mixtures, the prices of some D-aminoacids, such as phenyl alanine, leucine, serine, have become comparable to those of the "natural" L-forms.

The occurrence of the (-)-tartaric acid in the *Bauhinia* plants was recently commented as follows[71]:"Bauhinia reticulata D. C. war die bis dahin einzige Ausnahme von der Regel, nach der es sich bei natürlichen Weinsäure- und Tartratvorkommen stets um L(+)-Weinsäure und L-Tartrate handelt, wie das ja z.B. auch für Weintrauben gilt. Der Fachwelt fiel der Glaube an die Existenz einer solchen Ausnahme der Natur zunächst schwer, denn auch in anderen Bereichen der Natur ist es so, dass stets nur eine von zwei an sich möglichen optisch antipoden Formen einer Verbindung auftritt. So ist z. B. bekannt, dass alle aus natürlichen Eiweisskörpern isolierten optisch aktiven Aminosäuren L-Konfiguration haben. Das ist zwar höchst merkwürdig, denn es ist nicht bekannt, warum die Natur trotz gleichen Energieinhalts und gleicher Bildungswahrscheinlichkeit beider optischer Antipoden die Produktion eines davon vorgezogen hat, aber es ist wichtig für das Leben auf der Erde, denn wären die Organismen der Erde aus D- und L-Aminosäuren aufgebaut, so könnte ein "D-Mann" stets nur "D-Speisen" verdauen, nur mit einer "D-Frau" Kinder zeugen usw. Es hätte also durchaus die Möglichkeit bestanden, die Welt mit zwei voneinander unabhängigen Lebensformen - Pflanzen, Tiere, Menschen - zu bevölkern. Warum das nicht geschehen ist, sondern nur L-Formen gebildet wurden, ist unbekannt. Im Falle der Weinsäure ist die Sachlage ähnlich, und so ist die anfängliche Verblüffung über die hier beobachtete grosse Ausnahme der Natur verständlich. Die Ergebnisse von *Rabaté* und *Gourévitch* sind richtig. Sie wurden später von *Peynaud* bestätigt, und auch in diesem Laboratorium konnten sie voll und ganz bestätigt werden."

The commercial (S,S)-(-)-tartaric acid is not yet produced from its natural source, but rather by the above mentioned resolution methods; its current price is ca. $ 100.--/kg (100 kg quantities)[69].



(R,R)-(+)- (R,S)- or meso- (S,S)-(-)-

1 tartaric acid *1*

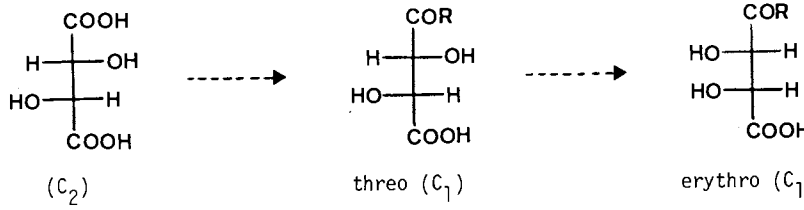
(R,R)- and (S,S)-tartaric acids can be considered as carbohydrates, the "threaric acids". At least on a laboratory scale, they are both cheap starting materials. Most of the work in the following sections was done with (R,R)-(+)-tartaric acid, but we should be aware throughout, that the enantiomers of all chiral structures drawn are accessible from the (S,S)-(-)-form by exactly the same procedures. If a route leading to a particular chiral building block or target molecule has been worked out from the still less expensive (1/25) (+)-acid, *the enantiomeric compound is also available without any synthetic modification!* At the end of their description of the synthesis of L-apiose from (+)-tartaric acid, *Weygand* and *Schmiechen*[73] comment on this fact by saying: "Da bei der Synthese der D-Apiose aus (-)-Weinsäure keine neuen Gesichtspunkte auftreten, haben wir sie nicht vorgenommen." With tartaric acid as starting material, the synthetic chemist has the *choice of synthesizing either one of the enantiomers* of a chiral target structure.

Both Enantiomers and both Configurations

Switching from chirality (absolute configuration) to configuration (relative configuration) and constitution, we note that the C_2-axis in the tartaric acid molecule makes it a very practical starting material: its four functionalized carbon atoms are pairwise homotopic, so that we actually deal with only two functional groups to begin with. Any transformation, by which only one of the groups of such a pair reacts, creates four constitutionally dif-

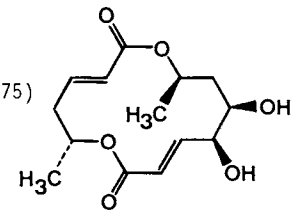
ferent functional groups. Furthermore, after a "mono-reaction" of this type, we can invert the configuration, i. e. epimerize at one of the centers of chirality and passover to the erythro series. This is schematically shown in

(15b)



(C_2) threo (C_1) erythro (C_1)

colletodiol[74,75]

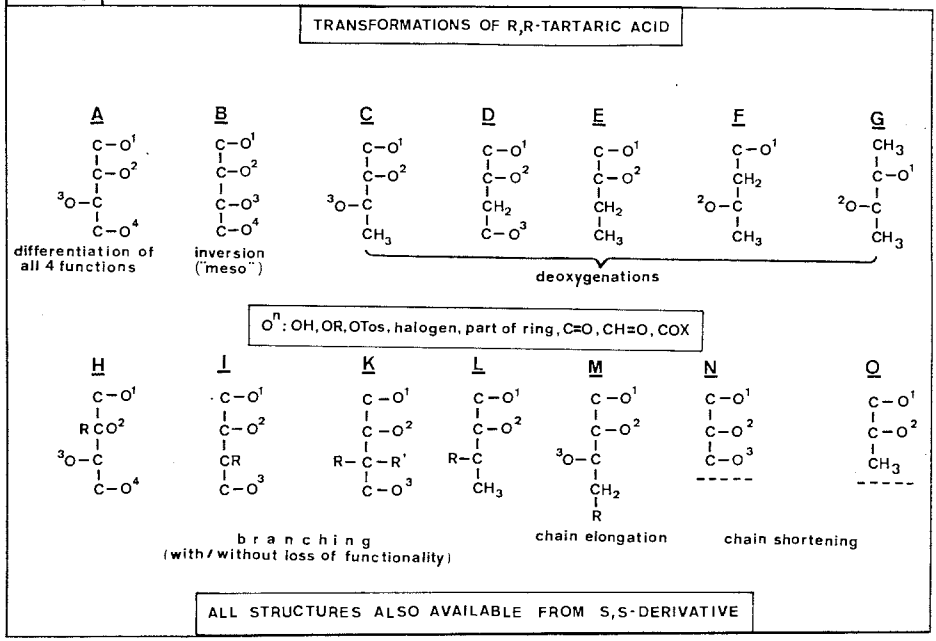


erythro configuration

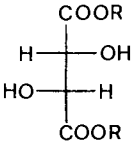
equation (15b) and should enable us to also carry out EPC-syntheses of compounds which are formally derived from meso-tartaric acid("erythraric acid"), see the formula of colletodiol underneath equation (15b). Once we have suitable derivatives with four different functional groups, see *A* and *B* in scheme XIV, we should be able to also arrive at molecules with the structures generalized by *C* to *O*. In *C* and *D* one deoxygenation has been undertaken, the functionality of D corresponds to malic acid. In *E* to *G*, two carbon atoms are reduced, the functionality of *F* corresponds to β-hydroxy butanoic acid [cf. equation (10)[35]]. In *H* to *L*, the original carbon skeleton of tartaric acid has been extended with branching, in *M* with chain elongation. Finally, the

symbols *N* and *O* represent chain shortened structures, *N* corresponds to glyceric acid or aldehyde, *O* to lactic acid. It should be kept in mind that both enantiomers of a chiral building block are accessible from the two tartaric acids; the (R,R)-acid will give derivatives *D* of the unnatural (R)-(+)-malic acid, which is very expensive; the (S,S)-acid will lead to derivatives of (R)-(+)-β-hydroxy butanoic acid, the enantiomer of the compound available by yeast reduction of acetoacetic ester [see equation (10)[35]; large quantities of the (R)-acid are found in the urine of diabetic patients[76]]. Finally, the (R,R)-tartaric acid derived structural moiety *O* corresponds to (R)-(+)-lactic acid, the commercially not available muscle lactic acid. Examples of transformations leading to structural changes as indicated in scheme XIV will be described in the following sections. The symbolized structures *A* to *O* will be referred to without specifically mentioning scheme XIV, from now onwards.

SCHEME XIV

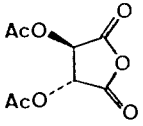


Let us first turn to the problem of annuling the C_2-axis of tartaric acid and of achieving an inversion, see *A* and *B*.



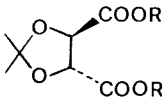
2a : R = CH_3
2b : R = C_2H_5

(90-95% from *1*)[65,77]

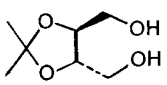


3

(77% from *1*)[78]

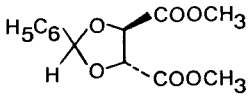


4a : R = CH_3
(80% from *1*)[65,79]
4b : R = C_2H_5
(92% from *2b*)[65,79]



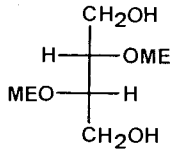
5

(85% from *4a*)[65,80]



6

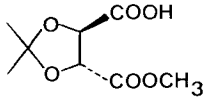
(85% from *2a*)[81,82]



7

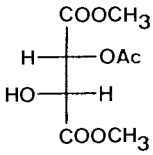
(90% from *2a*)[43]
[ME=CH(OCH_3)CH_3]

The C_2-symmetrical precursors *2* - *5*, the benzaldehyde acetal *6*, and the doubly methoxyethoxy (ME) protected threitol *7* [mixture of diastereomers due to the asymmetric carbons, O-CH(OCH_3)CH_3, in the protecting group] can be used to synthesize C_1-"mono-derivatives". Thus, one equivalent of aqueous base furnishes the half-ester *8* from *4a*; monoacetylation of *2a* yields the acetate *9*, which is converted to the chloride *10* with inversion of configuration by thionyl chloride/pyridine. Direct monobenzylation of tartaric ester *2a* to give *11* has so far been achieved in only moderate yield, but instead of *11*, the readily available acetal *6* can be used as precursor for the monobenzyl ether *14* of threitol (reduction with lithium aluminium hydride/$AlCl_3$). The anhydride *3* serves as starting material, for the preparation of the acid chloride *12* (CH_3OH, then $SOCl_2$) and of the monoamide *13* (HNR_2). Monobenzylation of *7* and monotosylation of *5* give the unsymmetrical derivatives *15* and *16*, respectively, in surprisingly high yields. Relevant references are given with the formulae, together with the yields obtained. All of these transformations have been carried out on large scales, some, up to many kilograms, the products are distillable or recrystallisable, and isolation does not require



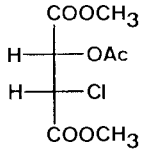
8

(80% from *4b*)[82,83]



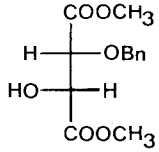
9

(61% from *2a*)[43,84]



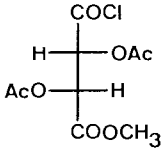
10

(79% from *9*)[43,84]



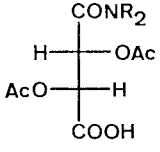
11

(37% from *2a*)[82]
[Bn=$CH_2C_6H_5$]



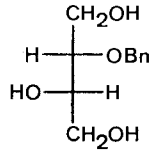
12

(70% from *3*)[73,85]



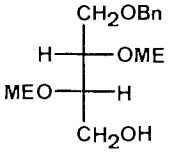
13

(56% from *3*, R=C_2H_5)[86]



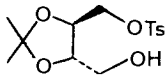
14

(92% from *11*
(91% from *6*)[82]



15

(84% from *7*)[43]



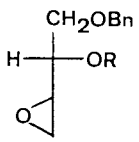
16

(75% from *5*)[8a]

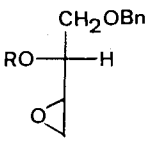
chromatographic purification. Some procedures are described in chapter D.

The four functional groups in the derivatives *8* - *16* are chemically or constituionally different. Except for the anhydride *3*, the acid chloride *12*, and the tosylate *16*, which contain highly electrophilic centers, the compounds mentioned so far cannot be called chiral building blocks, key intermediates or reagents, because they lack such centers.

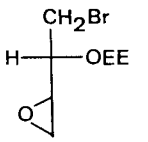
From the threitol derivatives *14* and *15* halides or epoxides or holoepoxides are accessible, which are promising chiral alkylating reagents. The compound *15*, on tosylation, hydrolysis of the ME-protecting groups and treatment with base, furnishes the benzyloxy hydroxy epoxide *17a*, which can be stored as a nicely crystalline p-nitrobenzoate *17c*. Inversion of configuration at the



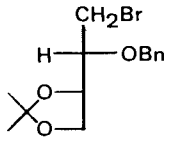
17



18



19[87]



20[82]

a : R = H
b : R = ME
c : R = p-NO_2-C_6H_4CO

[EE = $CH(OC_2H_5)CH_3$]

(*17a* : 59 % from *15*)[43]
(*18c* : 69 % from *17a*)[43,87]

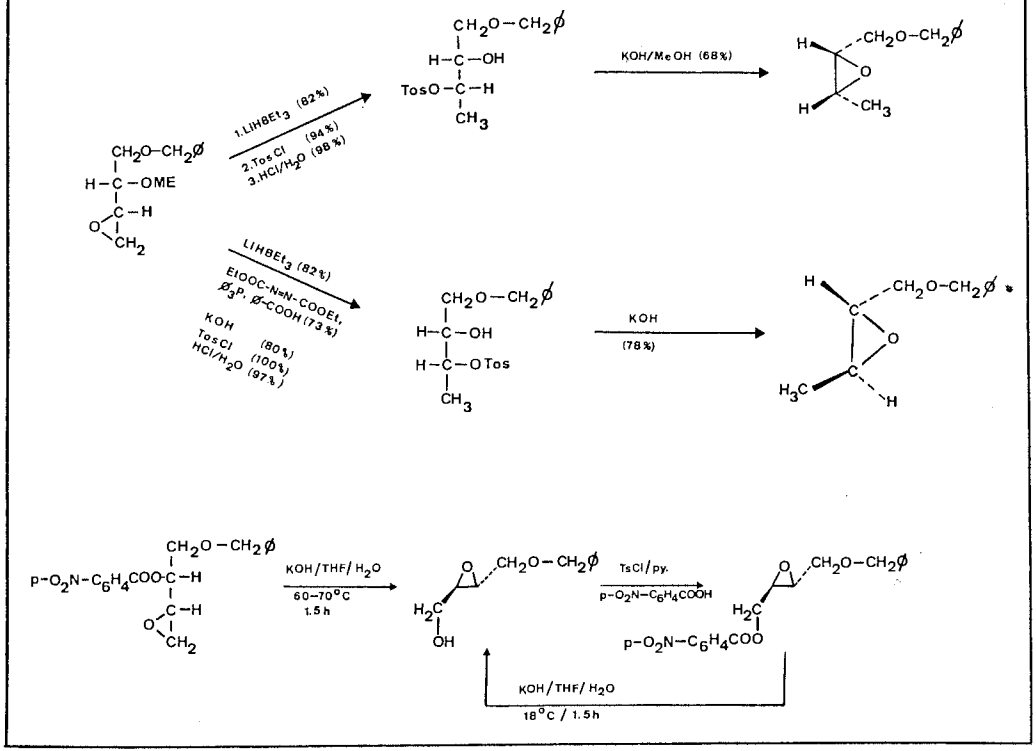
carbinol center of *17* using *Mitsunobu*'s method[88], i.e. reaction with azodicarboxylate/triphenylphosphine/p-nitrobenzoic acid, gives the solid erythritol ester *18c*, from which the alcohol *18a* and its ME-protected derivatives *18b* are obtained (see *B*). The bromoepoxide *19* can be made from *17a* by sequential EE-protection, hydrogenolytic debenzylation, and treatment with triphenylphosphine/CBr_4. Likewise, the dioxolane of *14*, is transformed into the bromide *20*, by the same method.

Apart from the rather trivial deoxygenation in 1- *and* 4-position, see *G* and the procedure for the preparation of enantiomerically pure trans-dimethyl oxirane, the other structural changes which we would like to describe and which are indicated by *C* to *F* and *H* to *O*, can be organized in two groups. One uses the epoxides *17* - *19* as starting materials, and the other one, malic acid.

As shown in scheme XV[43], reductive epoxide opening with lithium triethylborohydride and closure of an oxirane ring between the 2- and the 3-position constitutes an easy access to the cis/trans-isomeric 1-benzyloxy-2-butene epoxides (cf.C). A differently protected derivative of the enantiomeric trans-epoxide in scheme XV[43] has been employed as a chiral building block in an erythronolide synthesis[89] and was shown to be opened by a lithium acetylide, regioselectively at the methyl bearing carbon atom, see equation (16) and compare with *L*.

A 2.3-epoxide in which all four carbons are still functionalized can be ob-

SCHEME XV

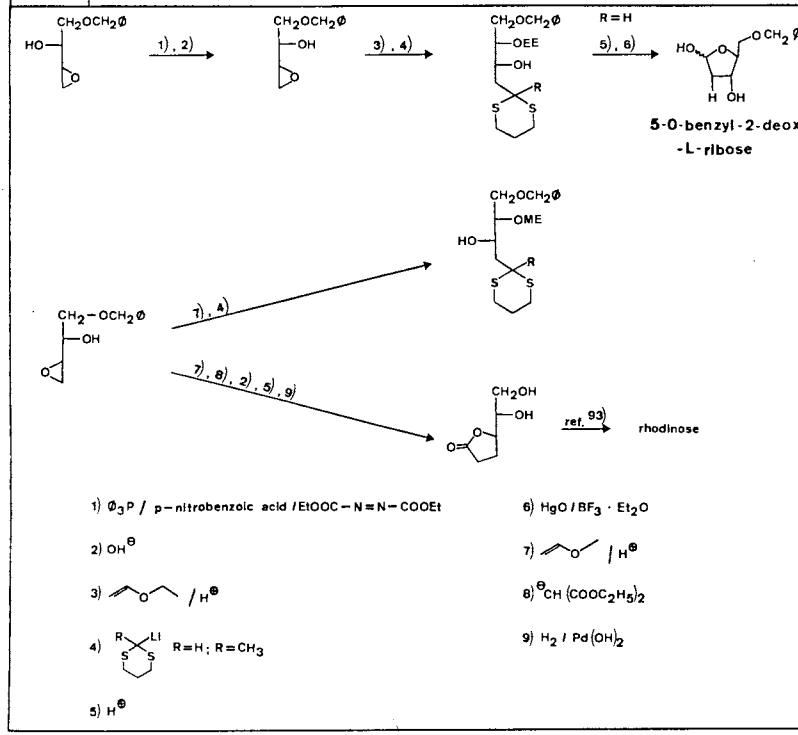

1.LiHBEt3 (82%)
2.TosCl (94%)
3.HCl/H2O (98%)
KOH/MeOH (68%)
LiHBEt3 (82%)
EtOOC-N=N-COOEt, Ø3P, Ø-COOH (73%)
KOH (80%)
TosCl (100%)
HCl/H2O (97%)
KOH
(78%)
KOH/THF/H2O
60-70°C
1.5h
TsCl/py.
p-O2N-C6H4COOH
KOH/THF/H2O
18°C / 1.5h

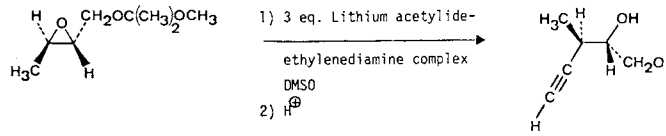
tained as shown in the bottom line equation of scheme XV: alkaline hydrolysis of the inverted benzoate *18c* under equilibrating conditions causes the epoxide ring to shift [91a] without loss of configurational and enantiomeric purity into the 2.3-position[87].

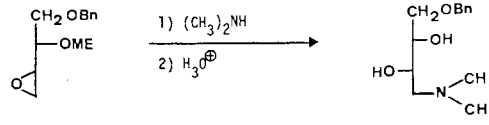
An example for ring opening with a heteronucleophile is the preparation of an aminotriol derivative in equation (17)[43].

Chain elongations with lithio-dithianes and with sodium malonate lead from the epoxide *17a* and its mirror image to the carbohydrates[90,91b], given in scheme XVI[43,92] (cf. *M*).

SCHEME XVI



(16) 

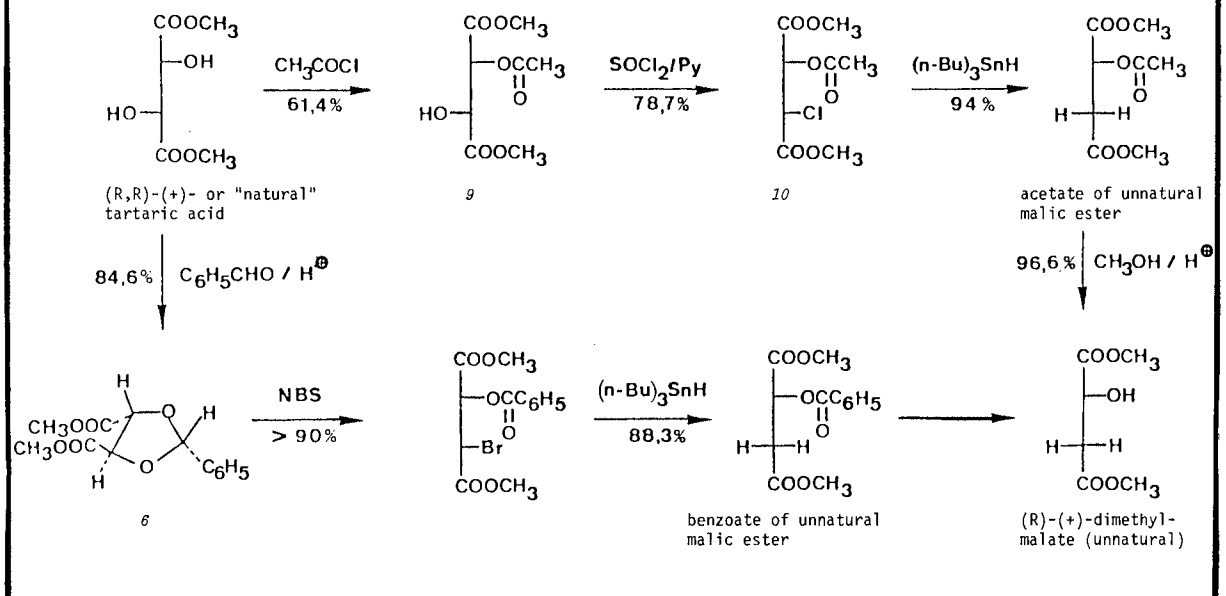
(17) 

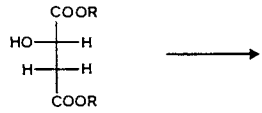
From Tartaric Acid via Malic Acid to Enantiomerically Pure Acetaldol

All the structures indicated by the symbols *D, E, F, H, I, K, N* and *O* are available from malic acid by deoxygenations (*E, F*), branchings (*H, I, K*), or degradations by one carbon atom (*N, O*). The absolute configurations indicated in the symbols of scheme XIV, refer to (R)-(+)-malic acid, the very expensive unnatural enantiomer [94]. We have worked out two efficient routes from the cheap (R,R)-(+)-tartaric ester to malic ester, see scheme XVII[43,95]. Both routes require three steps and involve a halide reduction with tri-*n*-butyl-stannane, one is a modification of *Freudenberg*'s correlation between tartaric and malic acid[84] through the monoacetate *9* and the chloro acetate *10*; the overall yield of the acetate of unnatural malic ester from tartaric ester is 45 %. The other method uses the benzaldehyde acetal *6* as an intermediate and produces the benzoate of malic ester in 67 % yield from dimethyl tartrate. Thus, the chiral synthetic building blocks from malic acid are also available in *both* enantiomeric forms. Those structures indicated in scheme XIV are eventually derived from (+)-tartaric acid, their mirror images from natural malic acid. Although several of the transformations mentioned in the following sections have been carried out with the unnatural malic acid[13,96], we will describe the reactions with the absolute configurations derived from (S)-(-)-malic acid.

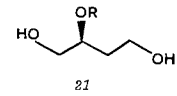
Key products of the conversions without branching, originating from malic acid, are the acetals *21b* and *c* of the triol *21a* (cf. *D*). These are obtained by lithium alanate reductions of the correspondingly protected malic esters, see the references given in the *formulae* diagram.

SCHEME XVII


COOCH3
OH
HO
COOCH3
(R,R)-(+)- or "natural" tartaric acid
CH3COCl
61,4%
OCCH3
O
9
SOCl2/Py
78,7%
Cl
10
(n-Bu)3SnH
94 %
H
acetate of unnatural malic ester
84,6%
C6H5CHO / H⊕
96,6 %
CH3OH / H⊕
CH3OOC
6
NBS
> 90%
Br
OCC6H5
88,3%
benzoate of unnatural malic ester
(R)-(+)-dimethyl-malate (unnatural)

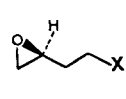


(S)-(-)-malic acid,
R = H, or esters,
R = CH_3, C_2H_5

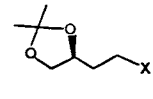


21

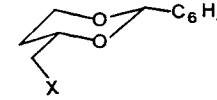
a : R = H[43)]
b : R = THP[35b)]
c : R = EE [$CH(OC_2H_5)CH_3$][8b)]



22



23



24

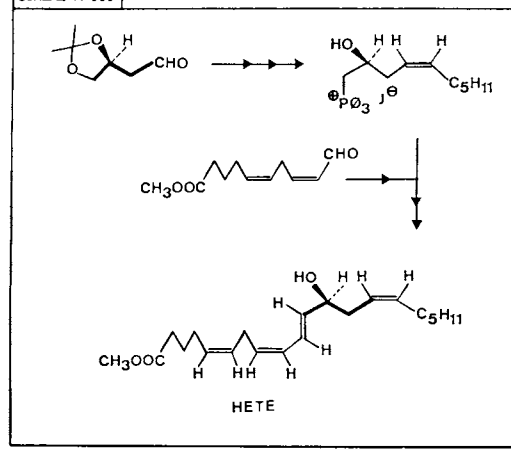
a : X = OH
b : X = OTos
c : X = J
d : X = Br

e : X = H
f : CH_2X = CHO
g : X = P(O)(OR)$_2$
h : X = $\emptyset_3P^{\oplus}\,J^{\ominus}$

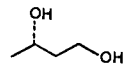
A few simple steps furnish useful four carbon building blocks with electrophilic center, see *22d* (57 % from malate)[8b,35b)], *23b*[97,98)], *23c*[98)], *23f*[96,99)], *24b*[43)], which can be used for chain elongations, for the introduction of other heteroatoms (*22g*[100)], *23g*[100)] and *23h*[98)]) as well as for reductions to intermediates with only two functional groups, see *22e*[35b)], *23e*[97)], and *24e* (32 % from malate)[43,97)] and compare with *E* and *F*. The incorporation of the four carbon atoms of malic acid into HETE[99)] through the aldehyde *23f* is outlined in scheme XVIII. The employment of (R)- or (S)-malic acid as starting materials for the syntheses of prostaglandins[6c)] (scheme I), spiroacetal pheromenes[86)] [from *22d*, equation (2)], pyrenophorin [11)] [from *22d*, equation (6)], cytochalasin[13)] (scheme III), and monensine[14)] (scheme IV) have been mentioned in previous sections of this article.

The reduction product of the tosylate *24b*, the benzaldehyde acetal *24e*, is easily converted (see procedure below) into the diol *25*[43,97)], yet another highly versatile starting material (see *F*), available in both enantiomeric

SCHEME XVIII

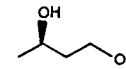


forms. It has already been used for EPC-syntheses of a variety of target structures. For this purpose, derivatives *26* with suitable protection of the secondary carbinol center are necessary. These are prepared directly by lithium alanate reduction of the corresponding protected β-hydroxy butyric ester or through the monobenzoate *28*, which is protected and converted to *26a*, by alkaline ester hydrolysis. The alkylating reagents *26b* and *c*, the



(S)-*25*

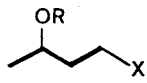
ca. 90 % e.e. from yeast reduction of acetoacetate, eq. (10), or 100 % e.e. from unnatural or (R)-(+) malic acid which is available from (R,R)-(+)-tartaric acid



(R)-*25*

100 % e.e. from natural or (S)-(-) malic acid through the intermediates *21* and *24*

aldehyde *27a*, the *Grignard*-(*26d*) and the *Wittig*-reagents (*27b*) are then obtained from *26a* by standard methods. With these a^3- and d^3-reagents[7], the natural products, given underneath the formulae *26* and *27* with relevant ref-



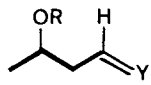
26

a : R = ME, EE, THP, $Si(CH_3)_2(t\text{-}C_4H_9)$, X = OH

b : R = THP, X = I, ⟶ (R,R)-(-)-pyrenophorin[11]

c : R = H, , X = I, ⟶ (R)-(+)-recifeiolide[101]

d :  X = MgBr ⟶ pyrenophorin[102]

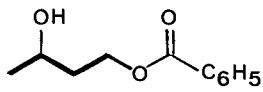


27

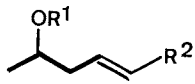
a : R = CH_2OCH_3 Y = O griseoviridin precursor[103]

R =  Y = O pyrenophorin[104]

b : R = H Y = $P(C_6H_5)_3$ (R)-(+)-recifeiolide[101]



28 (82 % from *25*)[97]



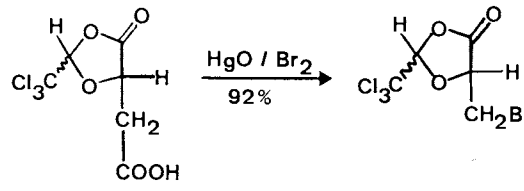
29

R^1 = H, EE, $Si(CH_3)_2(t\text{-}C_4H_9)$

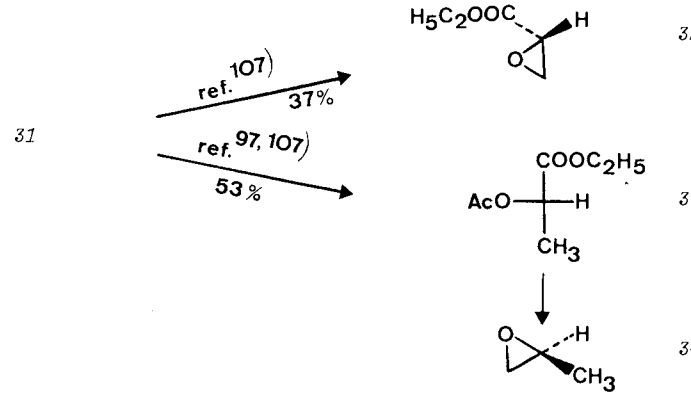
R^2 = COOH, $COOCH_3$, $COOCH_2CCl_3$, CH_2OH, CHO, $CH=CH\text{-}COOR^3$ (t)

erences, were synthesized in enantiomerically pure forms. Also, the derivtives *29* of 5-hydroxy-2-hexenoic and of 7-hydroxy-2.4-octadienoic acids, potential building blocks of macrodiolides[11,74,75,103,105,106], are accessible[97] through the OH-protected, enantiomerically pure acetaldol *27*, R=EE, Y=O.

For the chain shortening leading to chiral C_3-building blocks with three or two functional groups (cf. *N* and *O*), we chose[97,107] the *Hunsdiecker* degradation of malic acid. As shown for the natural, (S)-malic acid, the chloral



30 *31*

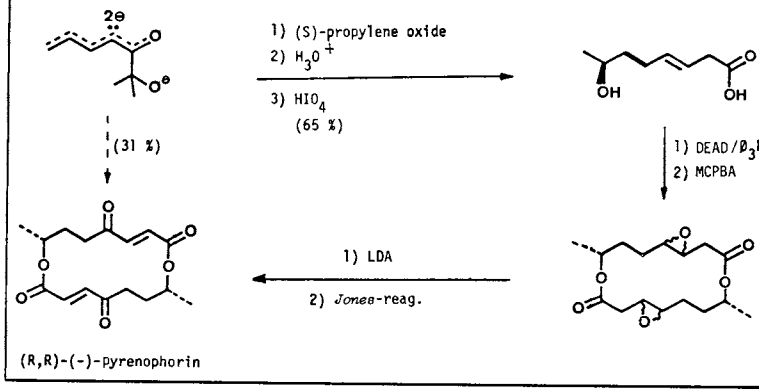


31 *32* *33* *34*

derivative *30* is a readily available substrate for the degradation to the bromide *31*, which is taken to glycidic ester *32* or to acetylated lactic ester *33* in the yields given in the flow sheet. From (R)-malic acid, the enantiomers of *32* and *33* are obtained, and thus, the lactic acid derived, useful (see scheme XIX)[108] chiral C_3-building block *propylene oxide 34* can also be prepared by the present route in both enantiomeric forms.

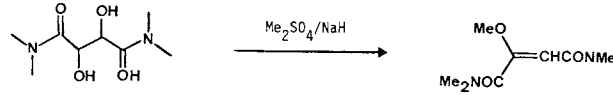
SCHEME XIX

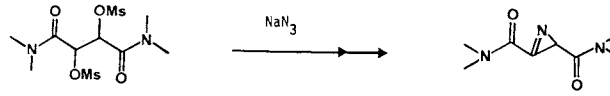
Pyrenophorin synthesis with a d^5-reagent

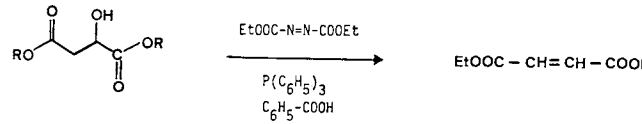


Branching of the C_4-Chain - From Chirality to Dianions

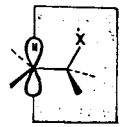
This group of transformations in scheme XIV, *H* to *L* was the most difficult one, from the very beginning of our studies in this area. Of the structures in the previous sections, only the benzyl ether of 2.3-epoxy-1-butanol, see scheme XV[43] and equation (16)[89], was used to prepare a product, in which a non-terminal carbon atom of tartaric acid has been involved in a carbon-carbon bond formation. A direct alkylation of tartaric or malic acid derivatives through enolates does not look promising, because both contain the β-hydroxy carbonyl moiety, which is known to readily undergo elimination to an α.β-unsaturated carbonyl structure, cf. the aldol, *Knoevenagel*, and *Stobbe* condensations, the dehydration of *Reformatzky* products, and the eliminative desamination of *Mannich* bases. In fact, we encountered such eliminations as undesired processes in some of our work, see equations (18)[65], (19)[109], and (20)[97].

(18) 

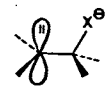
(19) 

(20) 

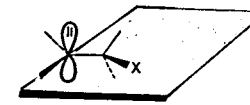
There are examples for three tricks which can be used to prevent elimination from species in which a carbanionoid center is located in the β-position of a leaving group X, see *35*. One is to work at very low temperatures[110], the second one is to make X a poor enough leaving group, see for instance *36*, X = $O^{\ominus}$ or $\overset{\oplus}{N}R$[111], the third one is to place the system into a structural situation in which the carbanionoid bond and the C-X leaving group bond are rigidly held perpendicular to each other, see *37*. This last case is examplified by



35

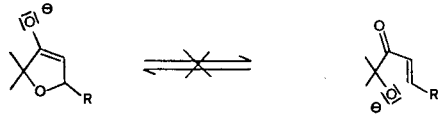


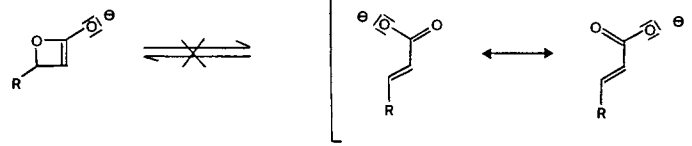
36



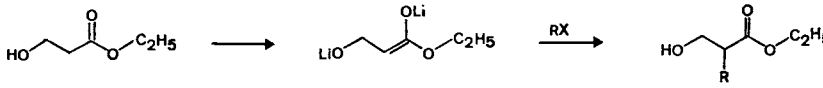
37

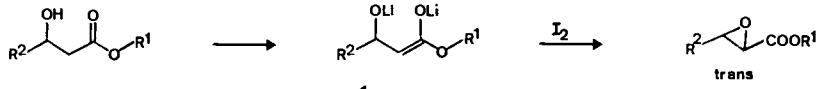
the surprisingly large stabilities of the enolates shown in (21)[112] and (22)[115]; the ring openings could be called the reversals of ring closures, which are *forbidden* (4- and 5-endo-trig.) by what is now commonly referred to as the *Baldwin*-rules. On the other hand, sticking to rules, we could treat the ring opening (22) as a *Woodward-Hoffmann allowed* conrotatory electrocyclic process, which releases considerable strain *and* generates a highly sta-

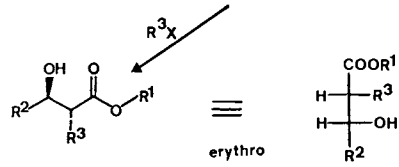
(21) 

(22) 

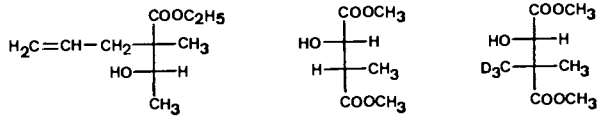
bilized carboxylate anion..... *Baldwin* wins!? At any rate, β-hydroxycarboxylic acids can be α-alkylated through the enolates of their lactones[113]. The poor leaving group ability of Li_2O was probably first exploited in enolate chemistry deliberately by *Hermann* and *Schlesinger*[114]. When they showed, that methyl β-hydroxypropionate can be alkylated by sequential treatment with two equivalents of base and with alkyl halides, see equation (23). *Kraus* and *Taschner*[115] have then used doubly deprotonated β-hydroxyesters to prepare *trans*-glycidic esters, see equation (24). The dilithioderivatives involved in

(23) 

(24) 

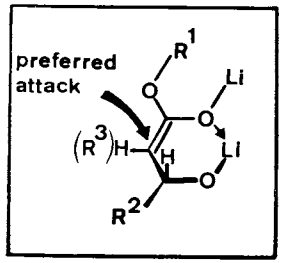


38 *38*



39 *40* *41*

these cyclizations have finally been demonstrated by *Fráter*[35c] [with $R^1=C_2H_5$, R^2= alkyl in equation (24)] and by our own group[35d,44,116] [with $R^1=CH_3$ or C_2H_5, R^2 = COOR in equation (24)] to undergo up to 98 % diastereoselective alkylation with formation of erythro-products *38* and without loss of optical activity. In the *Fischer*-projection, the newly introduced substituent is on the same side as the OH-group. If we assume that iodine attacks the enolate in the same way as the alkyl halides do, the erythro iodide *38*, $R^3=I$, is formed and gives rise to the actually observed trans-epoxides. Double deprotonation of the alkylated products of type *38* and reaction with electrophiles is diastereoselective in the same sense as the first reaction: the entering group winds up on the same side as the OH-group in the *Fischer*-projection: allylation of the dilithio derivative of 3-hydroxy-2-methyl butanoate furnishes *39*[35c]; the enolate-alkoxide from erythro-2-hydroxy-3-methyl succinate gives *40* (2 : 1 threo/erythro) and *41* (8 : 1 erythro/threo) upon protonation and methylation with CD_3I, respectively. The simplistic, strictly operational



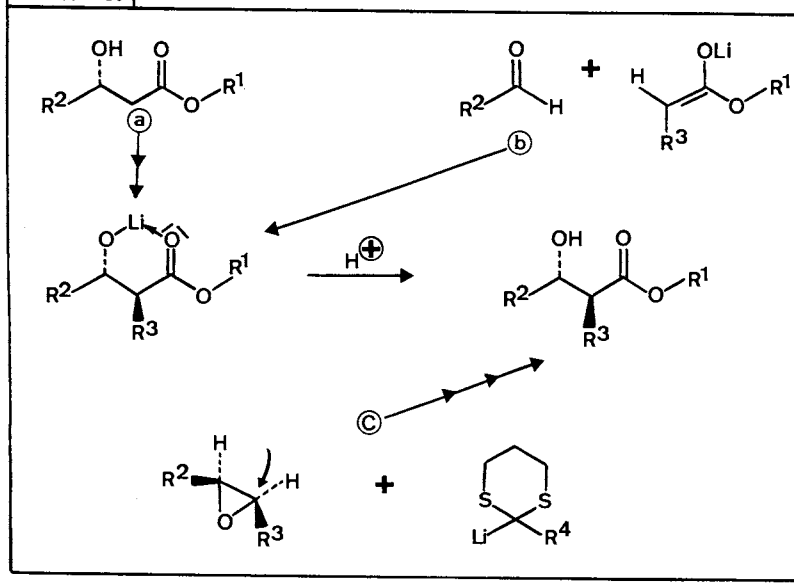
42a : $R^1 = C_2H_5$, $R^2 = CH_3$
[from ethyl (R)-(-)-3-hydroxy-butyrate]

42b : $R^1 = CH_3$, $R^2 = COOCH_3$
[from dimethyl (S)-(-)-malate]

mechanistic picture *42* "rationalizes" the strereochemical outcome: the electrophiles tested so far (proton, alkyl halides, carbonyl compounds, nitro olefins) attack from the diostereotopic face of the enolate which is marked with a fat arrow in *42*, no matter whether the reacting enolate carbon atom bears a proton or a substituent R^3. Furthermore, in the arrangement *42* the C-O-σ-bond of the potential leaving group oxygen is perpendicular to the π-system of the enolate so that the stability of these dianion derivatives might be due to a combination of the effects indicated in *36* and *37*.

Alkylation of the doubly deprotonated β-hydroxyesters leads primarily, see ⓐ in scheme XX, to a lithioalkoxide of an aldol type structure, the same one, which is formed in the experimentally quite tricky diastereoselective aldol additions[117a], see ⓑ in scheme XX. It is surprising, that this alkoxide is chemically and configurationally stable during some of the rather slow alkylation reactions; the importance of the metal in *Reformatzky* and aldol additions employing preformed enolates is well known[117a,b]. - The present method offers an alternative route to diastereoisomeric aldols, with the added advantage of being applicable to the synthesis of enantiomerically pure products. In a way, route ⓐ in scheme XX does in two steps what is accomplished in one step on route ⓑ : the starting material of ⓐ is a compound with only one center of chirality, it is alkylated diastereoselectively, while in ⓑ *two* prochiral centers are combined during the aldol-type bond forming process. It is interesting to note, that alkylation of the β-lactone enolate [see equation (22)] furnishes the same diastereomeric product as the dianion-route. - Another practical method of preparing enantiomerically pure

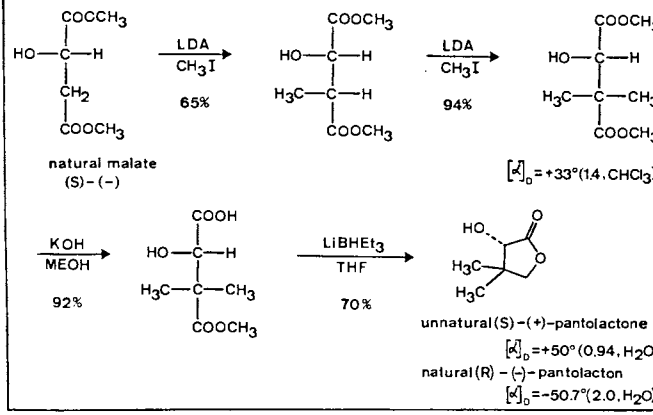
SCHEME XX

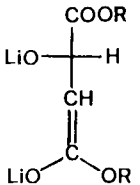


β-hydroxy-carbonyl derivatives, route Ⓒ in scheme XX, uses a different synthon combination (a^2/d^1 instead of a^1/d^2, aldol with umpolung)[7], for example see the vermiculine synthesis[11]; in this case, the relative and absolute configuration of the product is determined by the epoxide structure.

Some of the products which we obtained from the doubly deprotonated malates *43* and *44* are shown in the accompanying formulae *45* - *48* and in scheme XXI. While the cyclization of *44* with iodine, which produced a 1 : 1 mixture of the epoxides *47a* and *b*, and the reaction of *43a* with the carbonyl compound acetone, which gave a 3 : 1 mixture of two lactones with structure *46*, were not or poorly diastereoselective, the first (→ *45*) and the second alkylation (→ *48*) of malate were at least 90 % diastereoselective. The synthesis of pantolactone[44,116a], described in scheme XXI proves that no racemization occurs: the lactone obtained from malic ester and the natural product have the same value of specific rotation within experimental error. The chemical yields of these transformations are not optimized as yet, but it appears that the parent enolate-alkoxide *43* is less reactive in alkylation reactions than the methylated analogue *44*. It is also possible to add doubly deprotonated β-hydroxy-esters to nitro olefins[116b]. This *Michael*-addition is again > 85 % diastereoselective with respect to the newly formed center of chirality in the 2-position of the 3-hydroxyester, see *49*, while new centers of chirality

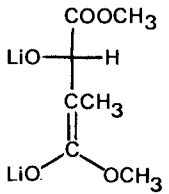
SCHEME XXI



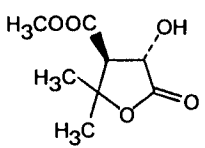


43a : R = CH_3

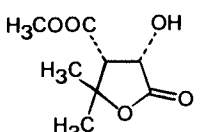
b : R = C_2H_5



44

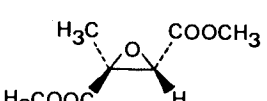


46a

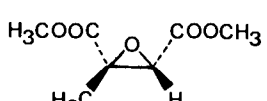


46b

(total yield 55 % from *43a*)



47a

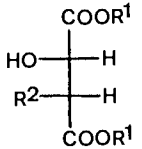


47b

(total yield 64 % from *44*)

$[\alpha]_D$ = +99 ^{o}(1.7,$CHCl_3$)

$[\alpha]_D$ = +27 ^{o}(1.7,$CHCl_3$)



45a : R^1 = C_2H_5

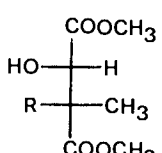
R^2 = $CH_2CH = CH_2$

(>20:1,51% from *43b*)

45b : R^1 = C_2H_5

R^2 = $CH_2C_6H_5$

(10:1, 48 % from *43b*)



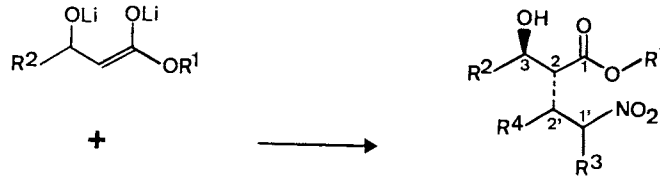
48a : R = C_2H_5(>10:1,36 % from *44*)

$[\alpha]_D$ = +22 ^{o}(1.0,$CHCl_3$)

48b : R = CH_2-CH = CH_2(>20:1, 74 % from *44*)

$[\alpha]_D$ = +29 ^{o}(1.4,$CHCl_3$)

at the 1'- and 2'-positions give rise to diastereomer formation. Hydrogenation of the nitro group in *49* and lactam formation furnishes compounds *50* and *51* (*a* and *b* are the two diastereomers of as yet unassigned configuration) from (S)-(+)-3-hydroxybutanoate, while the six membered ring structure *52* is tentatively assigned to the product obtained from (S)-(-)-malate.



49

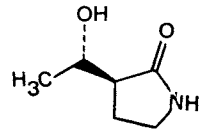
(the absolute configuration shown in *49* refers to products from (S)-(-)-malate)

R^1 = CH_3, C_2H_5

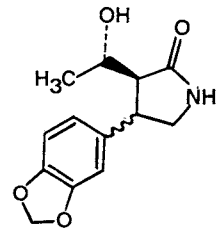
R^2 = CH_3, $COOCH_3$, $COOC_2H_5$

R^3 = H, CH_3

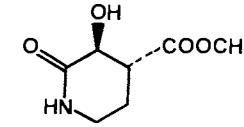
R^4 = H, CH_3, CH_2Br, C_6H_5, 3.4-methylendioxy-C_6H_3



50



51

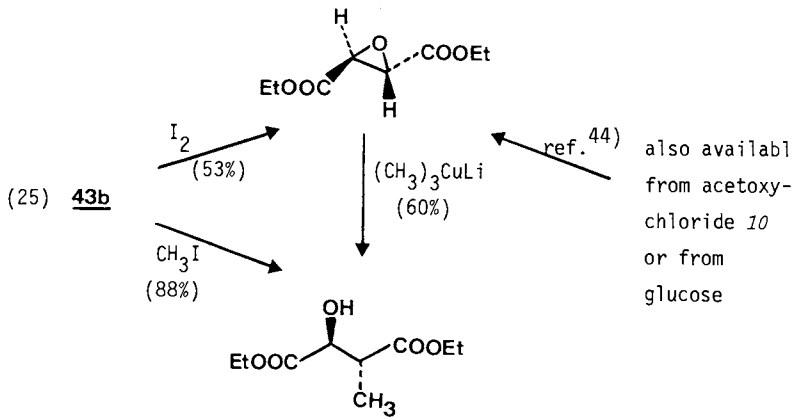


52

$[\alpha]_D$ = +40 ^{o}(C=1,$CHCl_3$) *51a* : $[\alpha]_D$ = +47^o(C=1,$CHCl_3$) $[\alpha]_D$ = -56 ^{o}(C=1,$CHCl_3$)

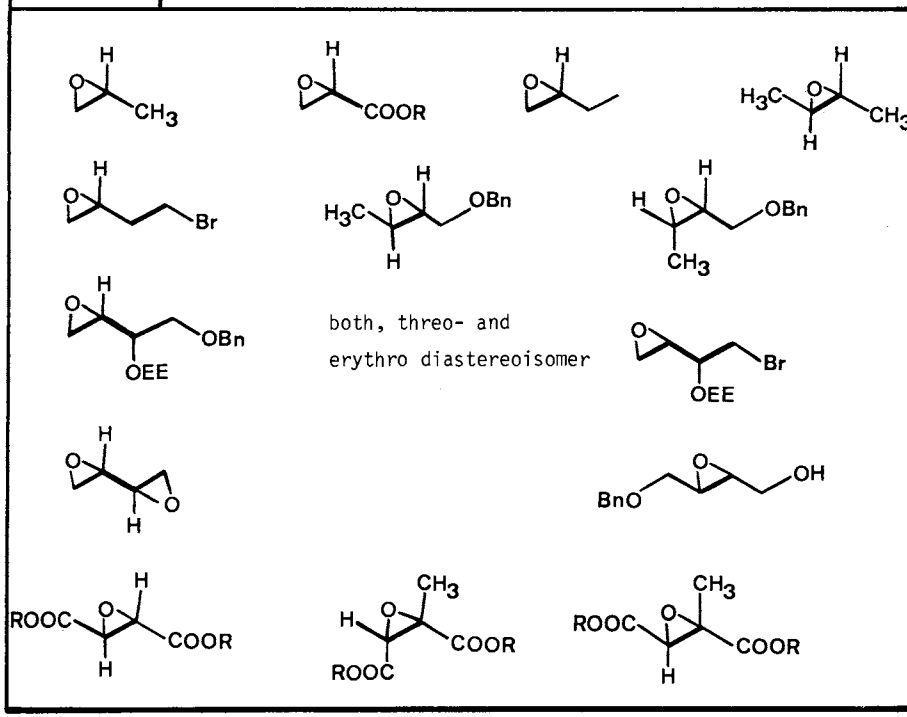
51b : $[\alpha]_D$ = -38^o(C=1,$CHCl_3$)

The reactions of malic ester enolate-alkoxides with *electrophiles* lead to structural changes as generalized by the symbols *H* (see *47*), *I* (see *40*, *45*, *46*, *52*), and *K* (see *41*, *48*, and scheme XXI). Branching with *nucleophilic* alkylating reagents is exemplified by the epoxide ring opening in equation (25)[44,118].



With the branching reactions we have completed the description of the various transformations *A* to *O* depicted in scheme XIV. On the way, we have obtained a large number of chiral synthetic building blocks. They are all derived from simple natural hydroxy acids such as lactic, β-hydroxy butyric, malic, and tartaric acids which are readily available. Through the enantiomeric tartaric acids, all the building blocks have been made accessible in both image and mirror image form using the same chemical transformations, and avoiding the risks involved in developing resolutions with recycling or highly efficient asymmetric syntheses. As was emphasized in the introduction, all we really need for EPC-syntheses, is a few versatile chiral building blocks which are not too highly functionalized; once these are incorporated into a synthesis, diastereoselective steps will be of utmost importance and will create further centers or elements of chirality all along the way to the target molecule. The arsenal of methods for stereocontrol in the synthesis of acyclic[119] and cyclic systems is huge and rapidly increasing. A pool of chiral synthetic building blocks from which we can scoop out the necessary components ought to be a welcome addition to the pool of synthetic methods for the organic chemist - just have a look at scheme XXII containing the epoxides mentioned in the present article!

SCHEME XXII

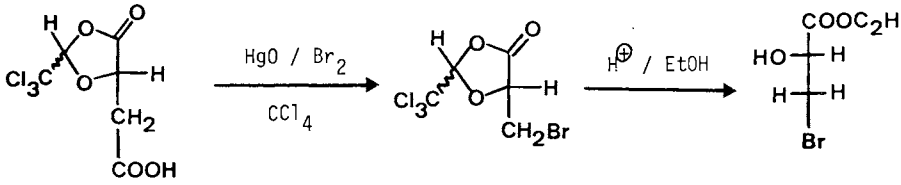


Acknowledgements

First of all, *D. S.* would like to thank the undergraduate and graduate students and the postdoctoral research fellows, whose names are given in the list of references, for their enthusiastic collaboration. General financial support of our investigations by the *Sandoz AG*, Basel, and especially *Dr. H. Braunschweiger's* generous supplies of starting materials and intermediates from tartaric acid are gratefully acknowledged. We thank the *Benkiser AG*, Ludwigshafen, *Boehringer*, Ingelheim, and *Chemische Fabrik Uetikon* for gifts of lactic, malic and tartaric acid and ester. Last not least, we are greatly obliged to *Dr. R. S. Mali*, *Frau A. Hungerbühler* and *Frl. S. Sigrist* for their invaluable help and dedication in preparing this manuscript.

D) PROCEDURES - LAST NOT LEAST

Ethyl (R)-3-bromo-2-hydroxy propionate:[97,107)]

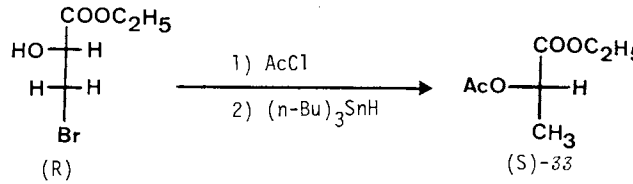


(2S)-*30* (2R)-*31* (R)

To a stirred mixture of 26 g (98.5 mmol) (S)-(-)-malic acid, protected as chloral acetal[120)], and 21.7 g (100 mmol) red HgO in 250 ml CCl_4, 1.7 g (7.35 mmol) Ag_2O is added and the temperature of the reaction mixture is increased to 65-70°C with an oil bath. The reaction mixture is irradiated with a normal 100 W lamp, and 1/5 of a solution of 16,0 g (100 mmol) bromine in 50 ml CCl_4 is added dropwise over a period of 10 minutes. After 15 min. an intensive controlled evolution of CO_2 begins. The rest of the bromine solution is added over a period of about 30 min., ensuring that an excess of bromine is never observed in the reaction mixture. After refluxing for another 30 min. and cooling to room temperature, the mixture is filtered through celite. The filtrate is washed once with $KHCO_3$ and once with H_2O, dried over $MgSO_4$ and the solvent evaporated in vacuo to yield 27.3 g (92.5 %) (R)-*31*, m.p. ~80°C. Recrystallisation from hexane gives an analytically pure sample, m.p. 98-99°C.

A mixture of 16.0 g (60.5 mmol) (R)-*31* and 42 g Dowex 50 W (strongly acidic ion exchange resin) is refluxed in 450 ml ethanol for about 60 hours. After filtering and washing the residue with chloroform, the solvent is evaporated at 30°C in vacuo. After removing the chloral-ethyl hemiacetal by distillation (45°C / 5 Torr), the product is distilled off. 8.5 g (71.5 %) of the bromo-hydroxy-ester (b.p. 53-55°C/0.3 Torr) is obtained as a colourless viscous liquid. Crystallization from 10 ml ether and 70 ml hexane at -20°C gives 7.35 g (61.5 %) of the analytically pure compound, m.p. 31-32°C, $[\alpha]_D^{25} = -11.9^\circ$ (c = 1.09 in $CHCl_3$).

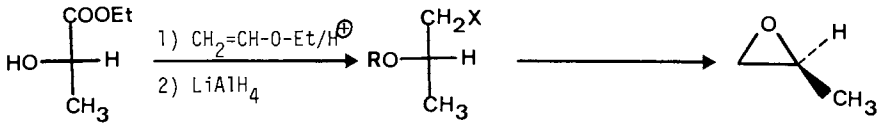
Ethyl (S)-(-)-O-acetyl-lactate [(S)-*33*]:[97]



To a solution of 1.97 g (10 mmol) (R)-bromo-hydroxy-ester in 2 ml ethyl acetate, is added at room temperature 1.0g (12.7 mmol) acetyl chloride. After stirring at 80°C for 3 hours the reaction mixture is concentrated in vacuo and distilled in a Kugelrohr at 75°C / 0.3 Torr to give 2.33 g (97.5 %) of the acetylated product as a colourless liquid; $[\alpha]_D^{25}$ = -15.7° (c=1,37,$CHCl_3$).

A solution of 1.2 g (5 mmol) acetylated product and 100 mg 2,2'-azo-bis-(2-methylpropionitrile) in 50 ml benzene is refluxed with 1.74 g (5.95 mmol) tri-n-butyltin hydride for about 3 hours. After concentration in vacuo, the residue is distilled in a Kugelrohr at 110°C / 15 Torr to give 600 mg (74 %) (S)-*33* as a colourless liquid. $[\alpha]_D^{25}$ = -48.8° (neat).

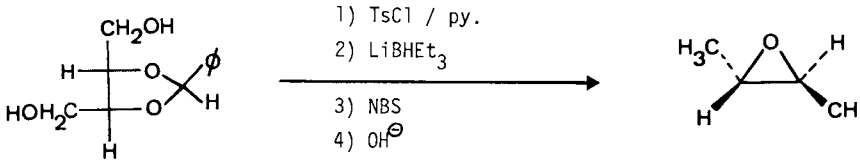
(S)-(-)-1,2-Epoxypropane [(S)-*34*]:[8b,35b]



88.5 g (0.75 mol) (S)-(-)-ethyl lactate (Fluka AG; $[\alpha]_D$ = -10,0° (neat)) is mixed with 250 ml of freshly distilled ethyl vinyl ether at 0°C. CF_3COOH (1.6 ml) is added dropwise and the clear solution is stirred for 20 hours at 0°C and an additional 0.5 hour at room temperature. 8.2 ml triethylamine is added and the mixture is stirred for 30 min. The excess of ethyl vinyl ether is re-

moved in vacuo. To the crude EE protected ethyl lactate is added, 350 ml ether and 170 ml H_2O and the organic layer is washed neutral with a small amount of H_2O and saturated NaCl solution. After drying over $MgSO_4$ and evaporating the solvent, 143 g (100 %) of protected lactic ester is obtained, which is dissolved in 100 ml ether and added dropwise to a stirred suspension of 18 g LAH in 1 l ether. After refluxing for 15 hours the reaction mixture is hydrolyzed cautiously by adding, first 18 ml H_2O, then 18 ml 15 % KOH and finally 30 ml H_2O. After filtering the filter cake is refluxed in 300 ml ether, and filtered again. The combined filtrates are dried over $MgSO_4$ / K_2CO_3 and the solvent is evaporated below 40°C in vacuo. 106 g (95 %) of the crude EE protected diol is obtained which is dissolved in 130 ml pyridine at 0°C. To this stirred solution is added dropwise a solution of 143 g (0,75 mol) tosyl chloride in 350 ml of $CHCl_3$ at 0°C. After 2 hours at 0°C the mixture is stirred for further 12 hours at room temperature. Then the reaction mixture is poured on to 800 g ice and 70 ml conc. HCl, and extracted twice with 400 ml CH_2Cl_2. The organic layer is washed once with cold 0.5 N HCl , once with saturated $NaHCO_3$ - and once with $NaHSO_3$ - solution, decolourised with charcoal and dried over $MgSO_4$. After evaporation of the solvent in vacuo at room temperature, 200 g of a yellow oil is obtained. For complete deprotection the oil is dissolved in 500 ml THF, and water is added to the vigorously stirred solution until it turns cloudy, then 2 ml conc. HCl is added. 100 ml of H_2O is added under vacuo to remove the volatile acetaldehyde continuously and keep the reaction mixture homogeneous. After 2 hours at room temperature the solvent is evaporated in vacuo (max. 25°C), the residue is neutralized with $NaHCO_3$ and extracted 3 times with $CHCl_3$. The organic layer is dried over $MgSO_4$ and the solvent evaporated in vacuo at 30°C. 144 g (87 %) of crude hydroxy tosylate is obtained as a yellow oil, which crystallizes in the refrigerator. The crude hydroxy tosylate is added as a warm oil (40 - 50°C) to 150 ml 50 % KOH at 50 - 60°C. Over a distillation bridge, the crude (S)-*34* is collected in a cooled flask, finally under low vacuo (200 Torr). Immediate redistillation over KOH over a 20 cm Vigreux column gives ca. 20 g (46 % from lactate)(S)-*34*, b.p. 34°C / 760 Torr. $[\alpha]_D$ = - 7.1° (c = 2.66 in $CHCl_3$), $[\alpha]_D$ = - 12.5° (neat).

trans-(S,S)-Epoxybutane:[121,122]



(S,S) (S,S)

A mixture of 50 ml pyridine and 50,46 g (240 mmol) of the (S,S)-diol[123] in 200 ml CH_2Cl_2 is cooled to 0°C. 92 g (484 mmol) p-toluenesulfonyl chloride is added in small portions. The solution is stirred for 4 hours at room temperature. After cooling to 0°C, 80 ml H_2O is added dropwise and the mixture is stirred for 0.5 hour. The aqueous layer is separated and extracted twice with CH_2Cl_2. The combined organic phases are washed with saturated solutions of $NaHCO_3$, $CuSO_4$ and with H_2O. After drying over $MgSO_4$ and evaporating the solvent in vacuo, 120.7 g (97 %) of ditosylate is obtained as a white powder, m.p. 128-129°C.

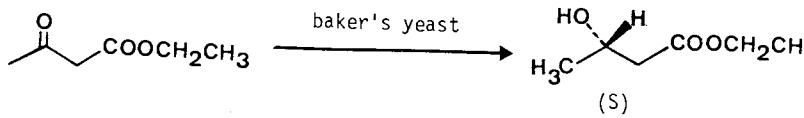
A stirred solution of 100 g of the ditosylate in 500 ml dry THF is cooled to -20°C under argon. 500 ml of 1 M lithium trietylborohydride in THF is slowly added. After stirring the reaction mixture for 48 hours at 0°C the following solutions are added at 0°C: 1) 250 ml H_2O, 2) 600 ml 3N NaOH and 3) 600 ml 30 % hydrogen peroxide. The mixture is then stirred for a further period of 0.5 hour at 0°C and is extracted twice with CH_2Cl_2. The combined organic layers are washed with a dilute solution of NH_4Cl (pH~8) and dried over $MgSO_4$. After evaporating the solvent in vacuo, the residue is distilled in a Kugelrohr. 24.8 g (72 %) of dimethyldioxolane is obtained as a colourless oil, b.p. 140°C/ 15 Torr.

A stirred suspension of 21 g (118 mmol) N-bromosuccinimide in 250 ml CCl_4 is cooled to 0°C under argon. A solution of 21 g (118 mmol) of the dimethyldioxolane in 100 ml CCl_4 is added slowly. The suspension is stirred for 45 hours at room temperature. The white precipitate disappears and is replaced by succinimide floating on the yellow solution. The solid is filtered off, the filtrate washed twice with 15 ml saturated $NaHCO_3$ solution and dried over $MgSO_4$. The

solvent is evaporated in vacuo. 30.2 g (99.5 %) of the bromo-benzoate is obtained as a yellow oil. ^{1}H-NMR. ($CDCl_3$): 1.47 (d, J = 6Hz, 3H); 1.77 (d, J = 6Hz, 3H); 4.35 (qxd, J_q = 6Hz, J_d = 4.5Hz, 1H); 5.2 (qxd, J_q = 6 Hz, J_d = 4.5Hz, 1H); 7.3 - 8.1 (m, 5H).

A mixture of 5.8 g (23 mmol) of the bromoester and 1.9 g (47 mmol) NaOH in 15 ml of diethyleneglycol is gradually heated to 120°C, while the product is distilled through a microdistillation apparatus. The receiver is cooled to about -70°C. 1.65 g (98 %) trans-(S,S)-epoxybutane, b.p. 58°C / 760 Torr, is obtained after careful redistillation. $[\alpha]_D^{25}$ = -58.2 (c = 2.52 in Et_2O).

Ethyl (S)-(+)-3-hydroxy butyrate:[35]



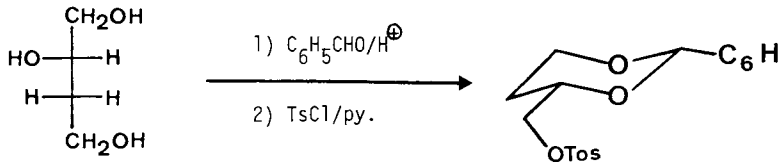
(S)

300 g of sucrose (Migros) is dissolved in 1.6 liter of fresh water in a 4 liter three-necked round-bottomed flask, equipped with bubble counter, thermometer and mechanical stirrer. Baker's yeast (200 g, Klipfel & Co. S.A., Rheinfelden, Switzerland) is added and the resulting mixture stirred at 25 - 30°C for one hour.Ethyl acetoacetate (20 g, 0.154 mol) is added to the fermenting suspen-

sion (2 bubbles/sec.) and the mixture is shaken vigorously. Stirring is continued at room temperature for one day, whereupon another part of sucrose (200 g) in 1.0 liter of water (ca. 40°C) is added in portions. After one hour further ethyl acetoacetate (20 g, 0,154 mol) is added and the reaction mixture stirred for another two days at room temperature. The reaction is monitored by gas-chromatography (Capillary glass column "Carbowax 20M", 20 m, Ø = 0,3 mm; oven temperature: 220°C. Carrier gas: hydrogen (0,4 atm). Retention time: ethyl acetoacetate 450 sec., (S)-(+)-ethyl-3-hydroxy butyrate 609 sec.), until all starting material is consumed.

For work up 80 g of celite is added and the mixture is filtered by suction through a sintered glass-funnel (G4, Ø 12 cm). The filtrate is extracted with ether (500 ml). The aqueous layer is saturated with sodium chloride and extracted with ether (3x500 ml). (In the case of emulsions, addition of small amounts of methanol may be helpful.) The combined ether extracts are dried over magnesium sulfate, filtered and concentrated on a rotatory evaporator at 40°C. The residue is distilled through a 20 cm Vigreux column and the fractions boiling at 63-65°C / 11 Torr are collected to give 25.5 g (62 %) ethyl hydroxy butyrate. $[\alpha]_D^{25} = +38.6^\circ$ (C = 1, $CHCl_3$).

(S,S)-4-(Tosyloxymethyl)-2-phenyl-1.3-dioxane [(S,S)-*24b*]:[43]



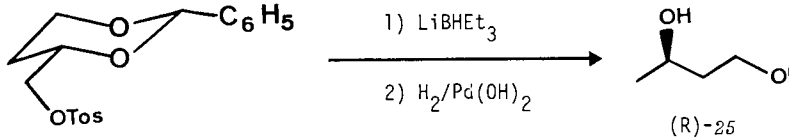
(S)-*21a* (S,S)-*24b*

49.2 g (464 mmol) (S)-*21a*[8b,43] is emulsified in 1650 ml CH_2Cl_2 and 68.8 g (649 mmol) benzaldehyde is added. Then 5 ml CF_3COOH is added cautiously to the stirred reaction mixture. The mixture is refluxed under argon atmosphere for 1 day. The generated H_2O is removed by distillation as an azeotropic mixture (CH_2Cl_2 / H_2O). The amount of CH_2Cl_2 / H_2O which is distilled off (400 ml)

is replaced and the solution refluxed for 5 days. The clear solution is washed with 150 ml saturated $KHCO_3$ and dried over Na_2SO_4. The solvent is removed by distillation in vacuo. After removing the excess of benzaldehyde, by keeping the mixture at 80°C and 0,01 Torr for 4 hours, 73.6 g (379 mmol, 81.7 %) of a mixture of isomeric benzaldehyde acetals is obtained.

The acetal mixture (73.6 g) is dissolved in 2 l CH_2Cl_2, and after cooling to -20°C, 117 ml (1.45 mol) pyridine is added over a period of 30 min. Then, 86 g (452 mmol) p-toluenesulfonyl chloride is added in several portions. The resulting clear solution is stirred overnight (16 hours). 30 ml H_2O is added dropwise to the reaction mixture over a period of 1 hour and worked up by adding 1 l CH_2Cl_2, ice and 55 ml (660 mmol) concentrated HCl. The organic layer is washed with 300 ml saturated $CuSO_4$, 300 ml $KHCO_3$ and finally with 200 ml H_2O. After drying over Na_2SO_4 and removing the solvent in vacuo, the residue is dissolved in 150 ml ether. 100 ml ether/pentane (1:1) is added and the solution cooled to 0°C, whereupon the crystallization starts. After 3 hours at 0°C and 15 hours at -32°C, the white crystals formed are filtered off and dried in vacuo to yield 89.3 g (67.7 %) of (S,S)-*24b*, m.p. 57-59°C, $[\alpha]_D^{25}$ = -2.5° (c = 1.01 in $CHCl_3$). Recrystallization from ether/pentane (1:2) gives an analytically pure sample; m.p. 65°C, $[\alpha]_D^{25}$ = - 2.1° (c = 0.89 in $CHCl_3$).

(R)-1,3-Butanediol [(R)-*25*]:[43,97]



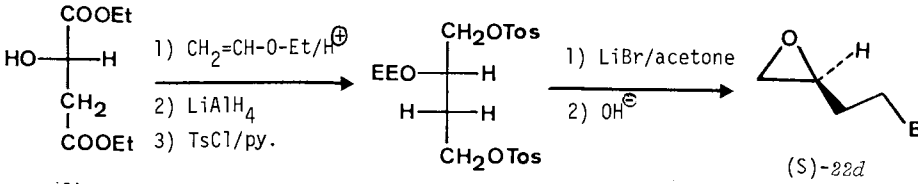
(S,S)-*24b* (R)-*25*

A solution of 4.0 g (11.6 mmol) (S,S)-*24b* (prepared in the previous experiment) in 10 ml THF is cooled to -60°C, and 40 ml of a 1M solution of lithium triethylborhydride in THF is added over a period of 10 hours. The reaction mixture is allowed to warm up to +10°C and stirred for 2 hours at room temperature.

After cooling the reaction mixture to -50°C, 4 ml H_2O is added cautiously to the reaction mixture, followed by 32 ml 3N NaOH, and 32 ml 30 % H_2O_2. After 0.5 hour stirring, the reaction mixture is extracted in 3 portions with, in total, 250 ml CH_2Cl_2. The organic layer is washed with a dilute solution of NH_4Cl and dried over Na_2SO_4. Evaporation of the solvent in vacuo gives 1.95 g (96 %) crude (S,R)-*24e* which is Kugelrohr-distilled at 90°C / 0,3 Torr to give 1.85 g (91 %) as a colourless oil. $[\alpha]_D^{25}$ = -0,1°(c = 1,19 in $CHCl_3$); $[\alpha]_{365}^{25}$ = -2,3° (c = 1,19 in $CHCl_3$).

885 mg (5 mmol) of (S,R)-*24e* is dissolved in 15 ml ethyl acetate. 500 mg $Pd(OH)_2$ on carbon is added at room temperature and 1 atm. The hydrogenation is complete in a few minutes. After filtration through celite and evaporation of the solvent at room temperature in vacuo, the residue is Kugelrohr-distilled. 392 mg (87 %) (R)-*25*, b.p. 135°C / 23 Torr, is obtained as a clear colourless liquid. $[\alpha]_D^{25}$ = -30.5° (c = 1.51 in EtOH).

(S)-(-)-4-Bromo-1,2-epoxy butane [(S)-*22d*]:[8b,35b]



(S) (S)-*22d*

To a solution of 106.4 g (560 mmol) of diethyl (S)-(-)-malate[65] in 1000 ml ethyl vinyl ether is added dropwise at 0°C 2 ml of CF_3COOH. The mixture is stirred for 48 hours at room temperature, whereupon 2g Na_2CO_3 is added. Half an hour later, the excess of ethyl vinyl ether is removed in vacuo, furnishing a residue of 145 g (99%) of the EE protected diethyl malate An analytically pure sample is obtained by Kugelrohr-distillation, b.p. 99°C/ 0.01 Torr, n_D^{20} = 1.4268.

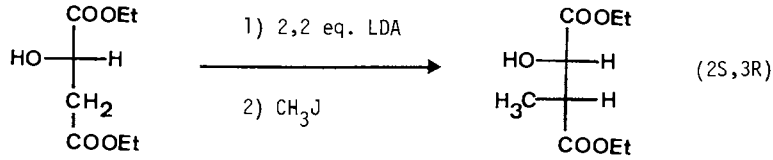
To a stirred suspension of 28.2 g (594 mmol) of 80% $LiAlH_4$ in ether is added dropwise at -10°C a solution of 95.7 g (365 mmol) EE protected malate in 200 ml of the same solvent. After stirring for 20 hours at room temperature, the reaction mixture is carefully hydrolyzed at 0°C by adding first 24 ml H_2O, then 24 ml 15% KOH, and finally again 45 ml H_2O. After filtering, extracting the filter cake with 400 ml of refluxing CH_2Cl_2, filtering again and washing the undissolved material with 200 ml of the same solvent, the combined organic layers are dried over Na_2SO_4 and a small amount Na_2CO_3. The solvent is evaporated in vacuo at room temperature. Distillation at 99°C/0.01 Torr gives 60.2 g (93%) of the 1,2,4-butane-triol EE protected at the 2-position.

60 g (337 mmol) of this material is added to a solution of 204 ml (2.53 mol) pyridine in 390 ml CH_2Cl_2. 170.3 g (893 mmol) tosyl chloride is added at -20°C over a period of 2 hours. The reaction mixture is allowed to warm up to room temperature overnight. After dropwise addition of 60 ml H_2O the reaction mixture is added to 900 ml CH_2Cl_2, 111 ml (1.3 mol) conc. HCl, and 300 g ice. The organic layer is washed once each with 300 ml saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated in vacuo, leaving behind 146.8 g (89.5%) of the ditosylate.

A stirred mixture obtained by adding at 0°C 261 g (3.01 mol) LiBr (Fluka purum), 4.13 g (28.8 mmol) CuBr and 11.6 g (138.1 mmol) $NaHCO_3$ to 1000 ml acetone (p.a.), is combined at room temperature with 145 g (298 mmol) of the ditosylate. After stirring for 48 hours at 25°C and for 18 hours at 50°C under argon atmosphere in the darkness, the mixture is filtered. The filtrate is evaporated at 25°C in vacuo, and the residue is combined with 200 ml H_2O and 800 ml CH_2Cl_2. The aqueous layer is extracted once with 100 ml CH_2Cl_2 and the combined organic layers are washed with a 1:1 mixture of saturated aqueous NaCl and $NaHCO_3$ and then with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated in vacuo at 25°C. 54.7 g (79%) of (S)-1,4-dibromo-2-butanol is obtaind after distillation, b.p. 51°C/0.01 Torr. The colourless oil solidified occasionally, m.p. 27-28°C, $[\alpha]_D^{23} = -38.9^\circ$ (c=4.51 in $CHCl_3$).

46.2 g (200 mmol) (S)-1,4-dibromo-2-butanol is added to a well stirred solution of 13.0 g (232 mmol) KOH in 1.7 l H_2O kept at 40°C. After 1 hour, the solution is saturated with NaCl and extracted several times with a total of 1.8 l ether. The combined ether solutions are washed once with saturated aqueous NaCl, dried over Na_2SO_4 and evaporatively concentrated at 20°C / 30 Torr. The residue is distilled at 75°C / 35 Torr, to give 25.9 g (86 %) (S)-*22d*, as a colourless liquid. [GC > 99.8 %, $[\alpha]_D^{23}$ = -23.5° (c = 4.02 in $CHCl_3$)].

Diethyl (2S,3R)-2-hydroxy-3-methyl-succinate:[44,116]



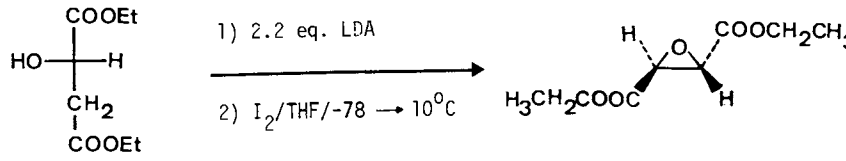
(S) erythro (threo-content < 10 %)

To a stirred cooled (-78°C) solution of lithium diisopropylamide (33 mmol) in anhydrous tetrahydrofuran (40 ml) is added over a period of 1 min. a solution of diethyl (S)-malate (2.85 g, 15 mmol) in tetrahydrofuran (4 ml). The mixture is stirred for 1 hour at -78°C and treated with freshly distilled methyliodide (5 g, 35 mmol).

After stirring for 48 hours at -78°C the heterogeneous reaction mixture is quenched with acetic acid (3 g, 50 mmol in 4 ml tetrahydrofuran). The reaction mixture is distributed between ether and $NaHSO_3$-solution.

After separation, the organic layer is washed successively with H_2O, saturated $NaHCO_3$-solution and NaCl-solution. The organic layer is dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue is dried using high vacuum to give a colourless oil (2,92 g). Chromatography on silica gel with ether/hexane 8:2 gives the pure product (2,69g, 88 %) erythro:threo (>10:1 by GC.), $[\alpha]_D^{20}$ = -9,16° (c = 1,25, ether).

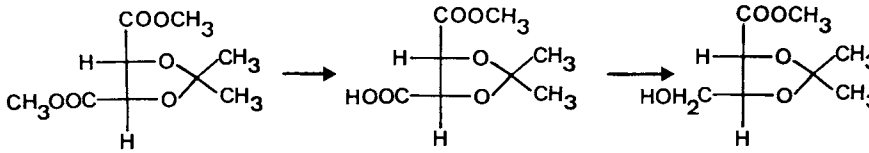
Diethyl (S,S)-2,3-epoxysuccinate:[44,116]



(S) (2S,3S)

To a stirred, cooled (-78°C) solution of lithium diisopropylamide (22 mmol) in anhydrous tetrahydrofuran (20 ml) is added over a period of 1 min. a solution of diethyl (S)-malate (1.9 g, 10 mmol) in tetrahydrofuran (3 ml). The mixture is stirred for one hour at -78°C and then pressed through a teflon tubing into a cooled solution (-78°C) of iodine (2.61 g, 10.3 mmol) in tetrahydrofuran (30 ml). After stirring for half an hour at -78°C the mixture is allowed to warm up to about +10°C (in one hour). The clear homogeneous solution is quenched with acetic acid (1.6 g, 27 mmol). The reaction mixture is distributed between ether (300 ml) / water (30 ml). After separation,the organic layer is washed once with $NaHSO_3$-solution (20 ml) and then dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is dried using high vacuum to give a clear, yellow oil (1.68 g). Chromatography on silica gel with CH_2Cl_2 : CH_3OH (98 : 2) gives the pure product (0.994 g, 53 %). $[\alpha]_D^{20}$ = + 114,7° (C = 0,91, EtOH).

Methyl (2R,3S)-2,3-O-isopropylidene-threonate:[82,83]



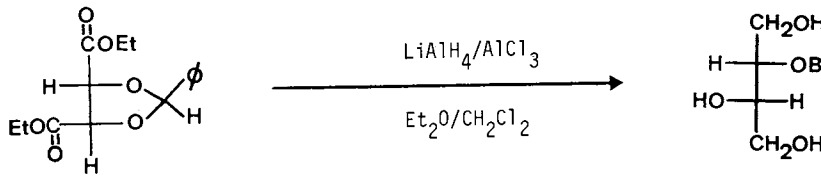
(R,R)-*4a* (2R,3R)-*8* (2R,3S)

To a solution of 2,18 g (10 mmol) (R,R)-*4a*[65,79] in 3 ml CH_3OH, is added a solution of 561 mg (10 mmol) KOH in 5 ml CH_3OH over a period of 1 hour. The re-

action mixture is stirred for an additional hour and evaporated to give a residue which is distributed between H_2O (10 ml) and Et_2O (3x20 ml). The combined Et_2O extracts are dried and evaporated to give 207 mg (9.5 %) of recovered (R.R)-*4a*. The aqueous portion is acidified to pH 3.5 with 2 M HCl, saturated with NaCl, and extracted with 6 x 20 ml Et_2O, readjusting the pH to 3.5 after each extraction. The combined Et_2O extracts are dried and evaporated, and the residue is Kugelrohr-distilled at 75 - 80°C (0.02 Torr) to give 1.18 g (58 %) (2R,3R)-*8*. $[\alpha]_D^{20} = -53^\circ$ (c = 0.52, CH_3OH).

To a solution of 4.5 g (22 mmol) (2R,3R)-*8* in 65 ml THF is added at 0°C over a period of 10 min. 33 ml (33 mmol) of a 1 M solution of BH_3 in THF. The bath is removed, and the reaction mixture is stirred at room temperature for 24 hours, and then evaporated. The residue is distributed between 40 ml H_2O and 4x150 ml Et_2O, with the H_2O portion being saturated with NaCl. The combined Et_2O extracts are washed with 30 ml 0.5 M $NaHCO_3$ and 30 ml saturated NaCl, dried, and evaporated. The residue is Kugelrohr-destilled at 80 - 85°C (0.1 Torr) giving 1.85 g (44 %) of methyl (2R,3S)-2,3-O-isopropylidene-threonate. $[\alpha]_D^{20} = -19.2^\circ$ (c = 0.55, CH_3OH).

(S,S)-2-Benzyloxy-1,3,4-butane-triol [S,S-*14*]:[82]



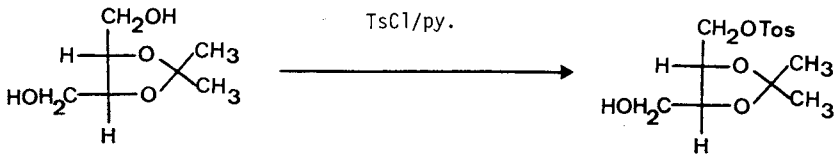
(R,R) (S,S)-*14*

38 g (800 mmol) lithium aluminium hydride (80 %) is suspended in 600 ml ether at -40°C under N_2. To the stirred mixture is added dropwise a solution of 106.7 g (800 mmol) $AlCl_3$ in 360 ml ether at -5 to -10°C. After the addition of 1 l CH_2Cl_2, a solution of 58.8g (0.2 mol) diethyl tartrate-benzaldehydeacetal[81,82] in 600 ml CH_2Cl_2 is added dropwise during 45 min. to the ice cooled reaction mixture. After stirring for 1 hour at room temperature the reaction mix-

ture is refluxed for 3 hours. The reaction mixture is quenched cautiously with 57.5 ml H_2O and a solution of 134.5 g KOH in 224 ml H_2O at -20°C. Then the acetone-dry ice bath is removed and the reaction mixture is stirred overnight at room temperature. After adding 350 ml THF the heterogeneous mixture is stirred for a further period of 2 hours at about 30°C, until the colour of the reaction mixture is white. After filtration over celite, the filter cake is suspended in 500 ml CH_2Cl_2, refluxed for 45 min. and filtered again. The combined filtrates are concentrated in vacuo to give 27 g (64 %) of (S,S)-*14* as white crystals, m.p. 70°C. The filter cake is washed with CH_2Cl_2 in a 2 l Soxhlet over 3 days and from the concentrated CH_2Cl_2 solution another 11.7 g (27 %) (S.S)-*14* is obtained.

Recrystallization from CH_2Cl_2 gives an analytically pure sample. m.p. 75.5 - 76.5°C, $[\alpha]_D^{25}$ = +15.5° (c = 1.14 in EtOH).

(4S,5S) -[5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolane-4-ylmethyl]-p-toluenesulfonate [(4S.5S)-*16*]:[8a)]

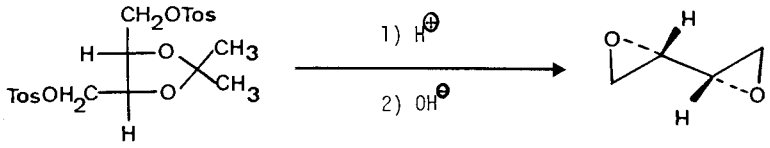


(S,S)-*5* (4S,5S)-*16*

To a stirred solution of 120 g (0.74 mol) (S,S)-*5* {$[\alpha]_D^{25}$= -8.2° (c = 7.8 in CH_3OH)}[79,80,123)] and 69.6 g (0,89 mol) pyridine in 500 ml dry CH_2Cl_2 at 0°C is added dropwise within 36 hours a solution of p-toluenesulfonyl chloride (141 g, 0.74 mol) in 2.5 l CH_2Cl_2. After keeping for 12 hours at room temperature the reaction mixture is washed three times successively with 1 l H_2O, dilute HCl, saturated $NaHCO_3$ and finally with H_2O. The organic layer is dried over Na_2SO_4 and concentrated in vacuo. The crude tosylate (234 g) is dissolved in 250 ml ether and kept at -15°C to crystallize 62 g (18 %) of the ditosylate. After concentration of the filtrate in vacuo, 143 g (61 %) (4S.5S)-*16* is ob-

tained as an oil. The purity determined by ^{1}H-NMR. spectroscopy is > 90 %. An analytically pure sample is obtained by chromatography on SiO_2 with $CHCl_3$ / EtOH (98:2) as an oil, $[\alpha]_D^{25} = -12.2^o$ (c = 21.82 in $CHCl_3$).

(S,S)-1,2-3,4-Diepoxybutane:[65)]

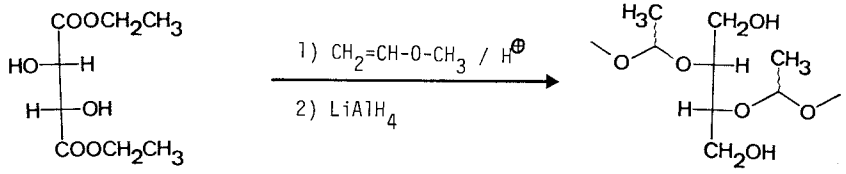


(S,S) (S,S)

4.7 g (10 mmol) of the ditosylate[65,80)] is refluxed in 10 ml 2 N HCl and 20 ml CH_3OH for 4 hours. After cooling at room temperature a white precipitate is formed. The mixture is neutralised with solid KOH and extracted with $CHCl_3$. The organic layer is dried over Na_2SO_4 and after evaporation of the solvent in vacuo and recrystallization of the resulting residue from $CHCl_3$, 3.0g (70 %) dihydroxy-ditosylate, m.p. 73°C, $[\alpha]_D = -5.7^o$ (c = 5 in DMF) is obtained.

To a stirred mixture of 4.3 g (10 mmol) dihydroxy-ditosylate and 40 ml ether is added 1.2 g (21 mmol) pulverized KOH. After refluxing for 2.5 hours, the precipitate is filtered off and washed with ether. The solvent from the filtrate is evaporated and the residue distilled to yield 0.7 g (81 %) of the colourless diepoxide, b.p. 64°C / 50 Torr, $[\alpha]_D^{20} = +23^o$ (c = 4.6 in CCl_4).

(R,R)-2,3-Bis-(1'-methoxyethoxy)-butane-1,4-diol [(R,R)-7] :[43,92]

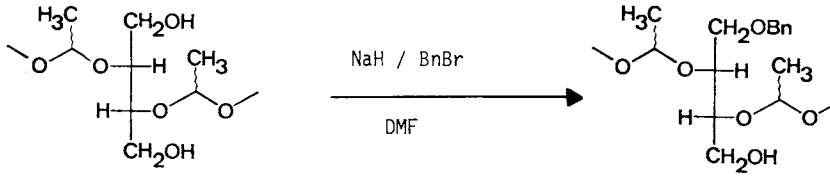


(S,S)-2b (R,R)-7

To a solution of 400 ml (~300 g, ~5 mol) methyl vinyl ether in 400 ml CH_2Cl_2, 88 g (0.426 mol) diethyl (S,S)-tartrate (S,S)-2b is added. To the mixture is added dropwise at 0°C, 10 drops of CF_3COOH. After stirring for 2 days at room temperature the clear solution is cooled at 0°C and 4 g K_2CO_3 is added. The reaction mixture is washed with 400 ml saturated aqueous $KHCO_3$ solution. The aqueous layer is washed twice with, in total, 300 ml CH_2Cl_2. The combined organic layers are dried over Na_2SO_4 and the solvent is evaporated in vacuo. 133.8 g (98 %) of the ME protected diethyl tartrate is obtained as a pale yellow oil. For an analytically pure sample a small amount is distilled in a Kugelrohr, b.p. 140°C/0.03 Torr.

A suspension of 20 g (525 mmol) $LiAlH_4$ in 500 ml ether is formed under argon at -30°C. A solution of 130 g (403 mmol) of the ME protected diethyl tartrate in 500 ml ether is added dropwise over a period of 1 hour at about -10°C. The mixture is stirred at RT. overnight and hydrolyzed at -10°C by careful addition of 100 ml saturated aqueous $MgSO_4$ solution. 2 g K_2CO_3 is added and after stirring 4 hours at room temperature the mixture is filtered through celite. The residue is refluxed in 250 ml of CH_2Cl_2 for 0.5 hour . After filtering and extracting the filter cake with 400 ml of refluxing CH_2Cl_2, filtering again and washing the undissolved material with 200 ml CH_2Cl_2, the combined organic solutions are dried over Na_2SO_4 and a small amount Na_2CO_3 and evaporated in vacuo. 82.1 g (86%) (R,R)-7 is obtained as a colourless oil, which crystallized slowly at -30°C. An analytically pure sample is obtained by Kugelrohr-distillation, b.p. 130°C/0.05 Torr.

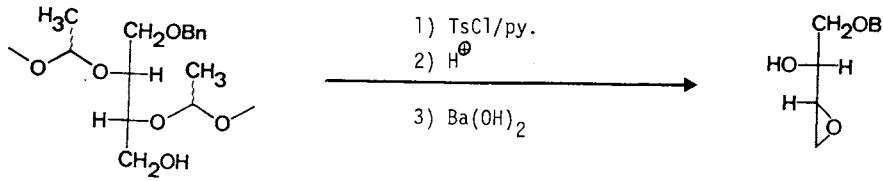
(R,R)-1-Benzyloxy-2,3-bis-(1'-methoxyethoxy)-4-butanol [(R,R)-*15*]:[43,92]



(R,R)-*7* (R,R)-*15*

In 500 ml DMF, 8.5 g (0.354 mol) of NaH in granulated form is suspended, under argon at -20°C. 7.8 g (0.328 mol) of (R,R)-*7* in 400 ml DMF is added at -20°C over a period of 15 minutes. After adding 59 g (0.345 mol) freshly distilled benzyl bromide in 200 ml DMF the solution is warmed up, at 0°C a controlled development of H_2 is observed. After 1 hour stirring at room temperature, the DMF is distilled off at the rotavapor.(Bath temperature about 40°C, 0.1 Torr). To the residue 0.5 l CH_2Cl_2 and 250 ml H_2O is added. The aqueous layer is washed twice with, in total 400 ml CH_2Cl_2 and the combined organic phases are washed with 200 ml H_2O, decolourised with 3 g of activated charcoal, dried over Na_2SO_4, filtered through celite and concentrated in vacuo. The crude product is Kugelrohr-distilled at 150-160°C/0.01 Torr to give 95.4 g (88.5%) of (R,R)-*15* as a pale yellow oil.

(2R,3R)-1-Benzyloxy-3,4-epoxy-2-butanol [(2R,3R)-*17α*]:[43,92]



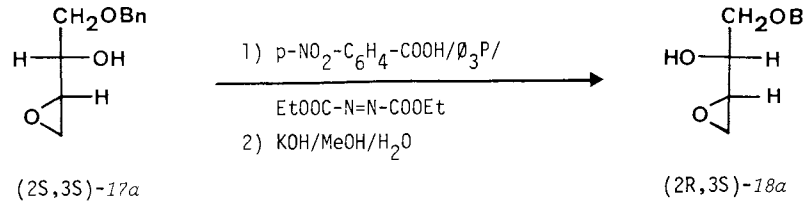
(2R,3R)-*15* (2R,3R)-*17α*

(2R,3R)-*15* (22 g, 68 mmol) is dissolved in THF (15 ml) and the solution is cooled to -18°C (ice/NaCl); 4-N,N-dimethylaminopyridine (1,0 g, 8.2 mmol) in pyridine (10.8 ml, 137 mmol) is added to the above solution. Tosyl chloride (14.2 g, 74.5 mmol) is added in four portions to the well stirred solution over

a period of 1 hour at -18°C. The reaction mixture is stirred for 12 hours at 0°C(ice/water) and for 6 hours at room temperature. It is cooled to 0°C and water (3.0 ml) is added dropwise within 5 min. The resulting clear orange solution is stirred for 1 hour at 0°C and then added dropwise over a period of 30 min. to a stirred solution of 2N HCl (85 ml) in acetone (200 ml) under reduced pressure (about 50 Torr) maintaining the temperature at 20°C. The resulting clear solution is evaporated below 40°C. (Removal of most of the acetone). The residue is extracted with CH_2Cl_2 (400 ml) and the organic layer is washed with a 1:1-mixture of saturated $MgSO_4/KHCO_3$ solution (100 ml). The organic layer is concentrated in vacuo, to a volume of about 150 ml, and added to a suspension of finely powdered $Ba(OH)_2 \cdot 8H_2O$,9.5 g (30 mmol),in water (150 ml). The heterogeneous mixture is stirred overnight at room temperature and then filtered through celite. The organic phase is separated and the water phase extracted twice with CH_2Cl_2. The combined organic phases are washed with 75 ml H_2O, dried over $MgSO_4$, and the solvent is evaporated at max. 40°C, in vacuo, to give an orange oil (10.5 g). This is filtered through 20 g of neutral alox with ether to yield 9.7 g, 75 % (2R,3R)-*17a*.

This material is Kugelrohr-distilled, at 110°C and $3 \cdot 10^{-6}$ Torr to yield 7.0 g (54%) of (2R,3R)-*17a* as a pale yellow oil. The chemical purity is > 90% determined by ^{1}H-NMR. spectroscopy. $[\alpha]_D^{25}$ = -14,0° (c=1.03, $CHCl_3$). An analytically pure sample is obtained by preparing the nicely crystalline p-nitrobenzoate (ether/pentane 1:1, m.p. 49°C, $[\alpha]_D^{25}$ = -11.2° (c= 0.955, $CHCl_3$)), followed by careful hydrolysis (KOH/THF/1.5 hours/15°C). ^{1}H-NMR. (90 MHz, $CDCl_3$): 2.2 ppm (d, broad, J=7Hz, -O*H*); 2.65 (d, J=3Hz, 2H-C(4)); 2.98 (q, J=3, 1H-(3)); 3.3-4.0 (m, 3H, 2H-C(1), 1H-C(2)); 4.51 (s, 2H, O-C*H*$_2$Ø); 7.24 (s, broad, 5 arom. H).

(2R,3S)-1-Benzyloxy-3,4-epoxy-2-butanol [(2R,3S)-*18a*]:[43,92]

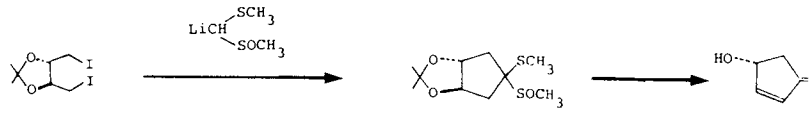


(2S,3S)-*17a* (2R,3S)-*18a*

To a solution of 2.7 g (13.9 mmol) (2S,3S)-*17a* in 90 ml toluene is added 2.8 g (16.7 mmol) p-nitrobenzoic acid and 4.36 g (16.7 mmol) triphenylphosphine at room temperature under argon. After cooling to -3°C a solution of 2.91 g (16.7 mmol) diethyl azodicarboxylate in 20 ml benzene is added over a period of 20 min. The reaction mixture is allowed to warm up to room temperature and stirred for a total period of 6 hours. After concentration in vacuo at 30°C the residue is filtered through 160 g SiO_2 using pentane/ethyl acetate (6:4). From the first fractions is isolated, after concentration and crystallization from CH_2Cl_2 / pentane (2:8) at -30°C, 3.3 g (69 %) p-nitrobenoate *18c*. Recrystallization from CH_2Cl_2 / pentane 2:8 at -30°C gives an analytically pure sample, m.p. 72 - 73°C, $[\alpha]_D^{25}$ = +2.8° (c = 1.20 in $CHCl_3$).

To a solution of 1.57 g (4.56 mmol) *18c* in 30 ml CH_3OH / THF (1:1), is added over a period of 5 minutes, a solution of 5.5 ml 1M KOH in CH_3OH and 7.5 ml H_2O at 15°C. After stirring for 1 hour at 15°C, the reaction mixture is extracted with CH_2Cl_2 (100 ml) , the combined organic layers are washed with 20 ml saturated aqueous solution of $KHCO_3$ and dried over Na_2SO_4. The solvent is evaporated in vacuo, leaving behind 880 mg (99 %) (2R,3S)-*18a* as a clear yellow oil. An analytically pure sample is obtained by Kugelrohr-distillation, b.p. 110°C/ $5 \cdot 10^{-6}$ Torr, $[\alpha]_D^{25}$ = -10.5° (c = 0.93 in $CHCl_3$). ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.34 (d, J = 4 Hz, 1H, -O*H*); 2.73 (d, J = 3 Hz, 2H, 2H-C(4)); 2.95-3.15(m, 1H, 1H-C(3)); 3.4-3.9 (m, 3H, 2H-C(1), 1H-C(2)); 4.55 (s, 2H, -C*H*$_2$-Ø); 7.28 (s, br., 5H, 5 arom. H).

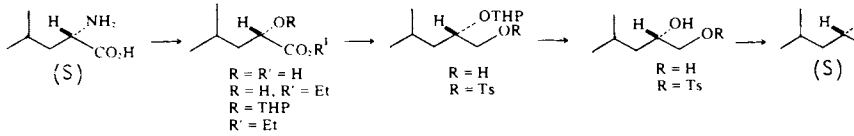
(R)-4-Hydroxy-2-cyclopentenone:[125]



(S,S) (R,R) (R)

(S.S)-1,4-diiodo-2,3-isopropylidene-dioxybutane $[\alpha]_D^{29}$ = +16.6°,(Lit.[79,124a] $[\alpha]_D^{24}$ +17.5°)is prepared from D-tartaric acid in four steps, (total yield: 42 %) by known reactions. A hexane solution (42 ml: 60.5 mmol) of n-butyllithium is added at -70° to a solution containing methyl methylthiomethyl sulfoxide[124b] (7.485 g, 60.4 mmol), which is stirred for 1 hour at -70° and for 1 hour at -10°. After dropwise addition of the diiodocompound (10.086 g, 26.4 mmol), the resulting mixture is further stirred for 1 hour at -70° and for 2 days at room temperature. A usual work up (consisting of addition of water, extraction with methylene chloride, and evaporation) gave an oil which is dissolved in ethyl acetate and washed with water to remove the unreacted sulfoxide. Drying over anhydrous magnesium sulfate and concentration under reduced pressure afforded a dark reddish oil (5.21 g), which is shown by its NMR.spectrum to consist mainly of the cyclization products. This oil is dissolved in diethyl ether (300 ml), and then, 1N sulfuric acid (4 ml) is added under ice-cooling. The resulting mixture is stirred at room temperature for 3 days, followed by neutralization with sodium bicarbonate and drying over anhydrous magnesium sulfate. After the removal of the insoluble materials by filtration, the filtrate is evaporated under reduced pressure. The oily residue is column-chromatographed on silica gel (eluted with diethyl ether) to give (R)-4-hydroxy-2-cyclopentenone as an oil (1.467 g, 52.5 %). This oil is further purified by distillation under reduced pressure, b.p. 63 - 64° / 0.2 Torr; $[\alpha]_D^{28}$ = +68.6° (c = 2.48, in $CHCl_3$). The optical purity is about 85 %, determined by ^{1}H-NMR. spectroscopy with a chiral shift reagent.

(S)-1,2-Epoxy-4-methylpentane:[126]



A soln. of $NaNO_2$ (63 g) in water (200 ml) is added dropwise during 3 hours to an ice-cooled and stirred soln. of (S)-(+)-leucine (75 g) in 1N H_2SO_4. The mixture is stirred for an additional 2 hours after the addition at 0 - 5° and left to stand overnight at room temperature. The resulting clear soln. is concentrated in vacuo. The residual semi-solid is extracted with ether and the ether soln. concentrated in vacuo. The residue is mixed with C_6H_6 and concentrated to remove a trace of water. The above operations are repeated to give 108 g of crude leucic acid from 150 g of leucine. The crude acid crystallised when cooled. This is recrystallised three times from ether-pet. ether to give 85.5 g (57 %) of pure leucic acid, m.p. 80 - 81°, as rods, $[\alpha]_D^{23}$ = -26.9° (c = 1.55 1N NaOH).

A soln. of leucic acid (70 g) in 99 % EtOH (400 ml) is mixed with toluene (200 ml) and conc. HCl (2.5 ml). The mixture is heated on a boiling water bath for 1.5 hours with slow removal of the solvent. The concentrated residue is diluted with 99 % EtOH (200 ml) and toluene (120 ml). The soln. is again heated on a boiling water bath for 1 hour with removal of the solvent. The residue is fractionally distilled to give 74 g (87 %) of ethyl leucate, b.p. 85 - 87°/16 Torr , n_D^{23} = 1.4222; $[\alpha]_D^{23}$ = -10.8° (neat).

Dihydropyran (50 g) and *p*-TsOH (0.1 g) are added to a soln. of ethyl leucate (83 g) in dry ether (200 ml). The mixture is left to stand overnigth at room temperature. Then the soln. is washed with K_2CO_3 aq, dried (K_2CO_3) and concentrated. The residue is distilled to give 123 g (97 %) of ethyl leucate-THP ether, b.p. 99 - 100°/1.3 Torr, n_D^{23} = 1.4403; $[\alpha]_D^{23}$ = 52.8° (c = 1.24 %, acetone).

A soln. of ethyl leucate-THP ether (122 g) in dry ether (200 ml) is added during 30 min. to an ice-cooled and stirred suspension of $LiAlH_4$ (15 g) in dry ether (800 ml). The mixture is stirred for 2 hours at 0 - 5° and left to stand overnight at room temperature. Then the stirred mixture is ice-cooled and decomposed by successive addition of water (15 ml), 20 % NaOH soln. (15 ml) and water (45 ml). The mixture is stirred for 1.5 hours and filtered. The filter cake is washed thoroughly with ether. The combined ether soln. is dried (K_2CO_3) and concentrated. The residue is distilled to give 99 g (99 %) of 4-methylpentane-1,2-diol-2-THP ether, b.p. 97 - 98°/1.2 Torr, n_D^{21} = 1.4521; $[\alpha]_D^{23}$ = -35.4° (c = 2.8 %, acetone).

Powdered p-TsCl (46 g) is added to an ice-cooled and stirred soln. of 4-diethylpentane-1,2-diol-2-THP ether (40 g) in dry C_5H_5N (200 ml). The mixture is stirred for 1 hour at 0 - 5°, then poured into ice-water and extracted with ether. The ether extract is washed with water, $CuSO_4$ soln., water and NaCl soln., dried ($MgSO_4$) and concentrated in vacuo to give 80 g of crude tosylate.

The crude tosylate (80 g) is dissolved in a mixture of AcOH (200 ml), THF (100 ml) and water (100 ml). The soln. is left to stand overnight at room temperature, warmed for 2 hours at 50 - 60°, poured into water and extracted with ether. The ether soln. is washed with water and NaCl soln., dried ($MgSO_4$) and concentrated. The residual crude tosylate alcohol (70 g) is used for the next step without further purification.

A soln. of KOH (100 g) in water (100 ml) is added to a stirred and ice-cooled soln. of crude tosylate alcohol (70 g) in ethylene glycol (100 ml). The mixture soon silidifies. It is diluted with water and shaken vigorously to dissolve the solid. The mixture is extracted with a small amount of ether. The ether soln. is washed with water and NaCl soln., dried (K_2CO_3) and filtered. The ether soln. is fractionated through a Vigreux column. Careful fractional distillation is essential. The epoxide is obtained in 53 % yield, from 4-methylpentane-1,2-diol-2-THP ether (10.7 g), b.p. 64 - 66°/150 Torr, n_D^{23} = 1,4006; $[\alpha]_D^{23}$ = -17.9° (c = 1.42 %, EtOH).

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