Chiral α-substituted α-hydroxy acids

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CHAPTER I

INTRODUCTION

1.1 *CHIRALITY*

The synthesis of optically active compounds is a subject that has occupied chemists for already more than a hundred years. In fact, since the pioneering work of the legendary Louis Pasteur,[1] who recognized that optically activity is a result of molecular asymmetry and who was the first to separate a racemate[2] (sodium ammonium tartrate) into its enantiomers (in 1848), the area of stereochemistry began to evolve into the major field of intensive research that it is nowadays.

In recent years the synthesis of optically active compounds in enantiomerically pure form has gained new impetus due to the recognition that biological systems, such as enzymes, which are themselves chiral, nonracemic compounds, interact with enantiomers in different ways (as a result of a diastereomeric relationship). Thus, for applications of chiral molecules as biologically active compounds, such as pharmaceuticals and pesticides, it is essential to have access to either of the two enantiomers. In general, only one of the enantiomers of a racemate exhibits the desired biological activity whereas the other enantiomer is at best ballast. However, often, this enantiomer inhibits the desired effect or may even cause severe side effects.[3]

A notorious example of the dramatic difference in biological activity of enantiomers is thalidomide, commercially known as Softenon (**100**, Figure 1.1).

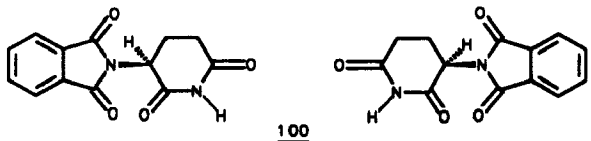

Figure 1.1

Softenon was originally administered as a racemate, but later it turned out, when this drug was associated with fetal abnormalities, that only the (R) enantiomer is responsible for the desired (sedative) therapeutic effect whereas the (S) enantiomer causes teratogenic effects.[4]

An example like this (and there are many more)[3c] underscores the justification of the increasingly restrictive guidelines for registration of chiral biologically active substances.[5] As a consequence much pressure is being exerted on industry to market chiral compounds as single enantiomers.[6] But also for academic purposes study of stereoselective reactions provides many opportunities to learn more about the very subtle interactions between molecules. Thus, the search for syntheses of enantiomerically pure compounds (EPC syntheses)[7] is going on unabated, as clearly reflected by the increasing number of publications in this field of chemistry.[8,9]

1.2 *ROUTES TO ENANTIOMERICALLY PURE COMPOUNDS*

The main routes to obtain pure enantiomers can be divided into three categories: separation of a racemic mixture (resolution), isolation of chiral material from natural sources and stereoselective synthesis.

Racemate resolution, closely connected with the beginning of stereochemistry, is still the main method for industrial synthesis of pure enantiomers.[10] The separation of enantiomers can be accomplished via preferential crystallization[11] and chromatographic techniques.[12] More often resolution is based on preferential crystallization of diastereomeric salts, which in general involves the reaction of the racemate with an enantiomerically pure acid or base.[13] Another way of resolving a racemate is kinetic resolution, which can be defined as a process in which one of the enantiomers of a racemic mixture is more readily converted into a product than is the other.[14] The maximum yield of the desired enantiomer in resolution is no more than 50%. On the other hand, resolution gives in general access to both enantiomers, which is an important consideration in, for example, studies of biological activity.

As most chiral compounds occur in nature mainly as single stereoisomers, isolation of this material provides a second important route to enantiomerically pure compounds. These compounds, such as α-amino acids, carbohydrates, alkaloids,

steroids, carboxylic acids, are often employed as chiral auxiliary (catalytically or stoichiometrically) in the synthesis of new chiral molecules. The use of naturally occurring enantiomerically pure compounds as starting materials for synthesis is also a well established methodology.[7,15]

Last, but not least, is the route to enantiomerically pure compounds via stereoselective synthesis. This method allows, ideally, a 100% conversion of achiral (prochiral) substrates into a single stereoisomer of a chiral product. Stereoselective synthesis can be defined as a process which converts a substrate with a stereogenic and/or a prostereogenic center into a chiral product in such a manner that unequal amounts of stereoisomers are formed.[16,17] Stereoselective synthesis can be divided into diastereoselective and enantioselective synthesis, which terms are more specific.

All stereoselective syntheses are based on the principle that stereoisomeric products are formed via diastereomeric transition states that differ mutually in Gibbs activation energy ($\Delta\Delta G^{\#}$).

In a diastereoselective synthesis a reactant with a prostereogenic center, as well as a stereogenic center, is converted into a product with two stereogenic centers. Thus, diastereomeric products are formed. The Gibbs energy profile for a diastereoselective synthesis is shown in Figure 1.2.

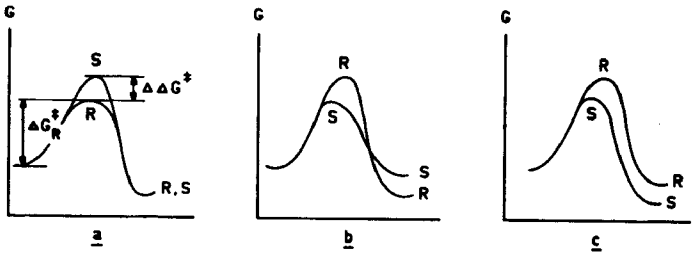

Figure 1.2: Gibbs energy profile for enantioselective (a) and diastereoselective syntheses (b, c).

Enantioselective synthesis refers to a conversion of a reactant with a prostereogenic center into products which are enantiomers of each other. Figure 1.2 depicts also the Gibbs energy profile for an enantioselective process. As these reactions must proceed via diastereomeric transition states, a chiral auxiliary has to participate in the transition state. The chirality can be introduced using either a stoichiometric or a catalytic amount of a chiral auxiliary. If a catalytic amount (a chiral catalyst or chiral ligand) is sufficient in order to obtain the products in high enantiomeric excess, the term catalytic stereoselective synthesis is used. These reactions belong to the most promising and attractive forms of stereoselective synthesis.

Throughout this thesis, examples of the above discussed stereoselective synthesis will be encountered. Chapter II describes the research towards a catalytic stereoselective synthesis. In Chapter III an enantiomerically pure compound which occurs in nature (an α-amino acid) is used as starting material for the synthesis of another enantiomerically pure compound, whereas in Chapter IV kinetic resolution is employed as a route to enantiomerically pure compounds.

1.3 *α-HYDROXY ACIDS*[a]

Among the class of molecules which have proven to be of great value in stereoselective synthesis, chiral α-hydroxy acids take a prominent position. Enantiomerically pure α-hydroxy acids ($R_1R_2C(OH)CO_2H$) are not only important biological compounds[18] but they are also valuable starting materials for the stereoselective synthesis of natural products[19] whereas their use as chiral reagents has also been reported.[20] As a selected example, Scheme 1.1 depicts the use of (S)-methyl lactate (**101**) in the synthesis of the redox coenzyme Factor 420 (F_{420}, **102**).[21]

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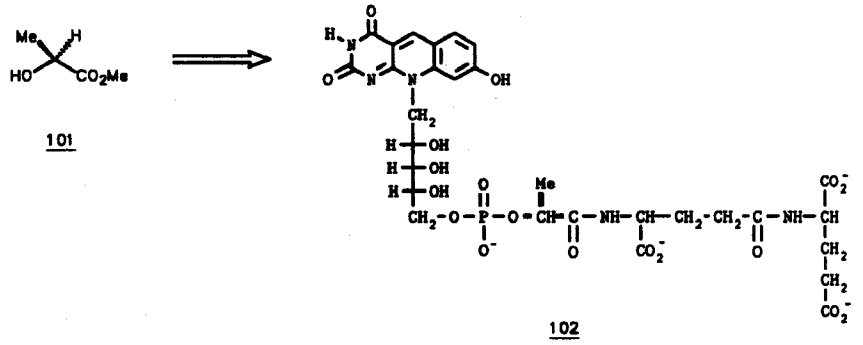
[a] Officially the compounds discussed here are 2-hydroxy carboxylic acids. We prefer, and will use, the term "α-hydroxy acids" in direct analogy to the usage "α-amino acids".



101

102

Scheme 1.1

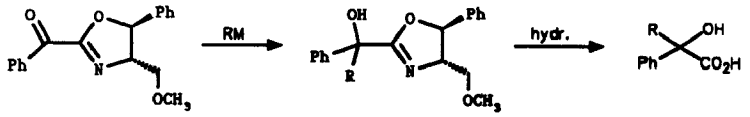
A number of methods for the synthesis of chiral unsubstituted α-hydroxy acids ($R_1C(H)(OH)CO_2H$) and derivatives thereof have been described in the literature. These methods, which give access to the acids in high enantiomeric excess (90-100 % e.e.), include stereoselective reduction of α-keto acids[22] or esters,[23] deaminative hydroxylation of α-amino acids[24] acetoxylation of chiral carboxylic esters,[25] alkylation of chiral glycolate enolates,[26] ene reactions of chiral glyoxylate esters,[27] ring opening of chiral glycidic esters[28] and oxidation of chiral ester,[29] amide,[30] and imide enolates.[31] As some α-hydroxy acids such as lactic acid, mandelic acid, malic acid and tartaric acid, are now readily available in both enantiomeric forms, it is not surprising that these compounds are frequently employed as chiral intermediates.

The access to α-substituted α-hydroxy acids ($R_1R_2C(OH)CO_2H$) is much more limited; hence these compounds have been less frequently used in stereoselective synthesis than the unsubstituted α-hydroxy acids. The availibility of these compounds in enantiomerically pure form will, however, certainly strengthen the usefulness of α-hydroxy acids as chiral building blocks. Furthermore, some α-alkylated α-hydroxy acids have been reported to exhibit interesting biological activity such as suicide inhibition of flavine dependent oxidoreductases.[32]

As an important route to α-alkylated α-hydroxy acids much research has concentrated on the stereoselective formation of a carbon-carbon bond. Thus far all known methods, with to the best of our knowledge only one exception, to α-substituted α-hydroxy acids or esters rely on the use of chiral auxiliaries (in stoichiometric

quantities) to bring about stereoselectivity in the carbon-carbon bond forming step (diastereoselective syntheses). Some of these methods require elaborate synthesis whereas the observed diastereoselectivities in many cases are only moderate. Stereoselectivities up to 50% have been reported, for example, in the alkylation of menthyl mandelate[33] and additions to menthyl α-keto esters.[34] Higher selectivities (up to 98% d.e.) have been found in nucleophilic addition to chiral α-keto amides,[35] chiral α-keto esters[36] or chiral benzoyl- or acetyl benzoxazines.[37] Enantiomerically pure α-methyl α-hydroxy acids (employed in the synthesis of biologically active compounds) have been prepared via a stereoselective bromolactonization reaction.[38] Very recently a report on the alkylation of THP ethers derived from enantiomerically pure α-hydroxy esters with diastereoselectivities ranging from 20-84% appeared.[39] Kabalka and coworkers reported, recently, on a highly diastereoselective allyl and crotyl boration of α-oxo carboxylic acids, leading to α-allylated α-hydroxy acids.[40]

As a characteristic example of a diastereoselective synthesis, leading to α-substituted α-hydroxy acids, Scheme 1.2 depicts the strategy developed in the group of Meyers.[41] Chiral α-ketooxazoline **103**, which could be prepared starting from (1S,2S)-1-phenyl-2-amino-1,3-propanediol, was allowed to react with a variety of organometallic reagents to afford α-substituted α-hydroxy oxazolines **104** as diastereomeric mixtures. After removal of the chiral auxiliary group, α-substituted α-hydroxy acids **105** were isolated in 30-87% e.e. Although the diastereoselectivity in the addition step was usually only moderate, enantiomerically pure α-substituted α-hydroxy acids **105** could be obtained via liquid chromatrographic separation of the diastereomeric intermediates.[42]

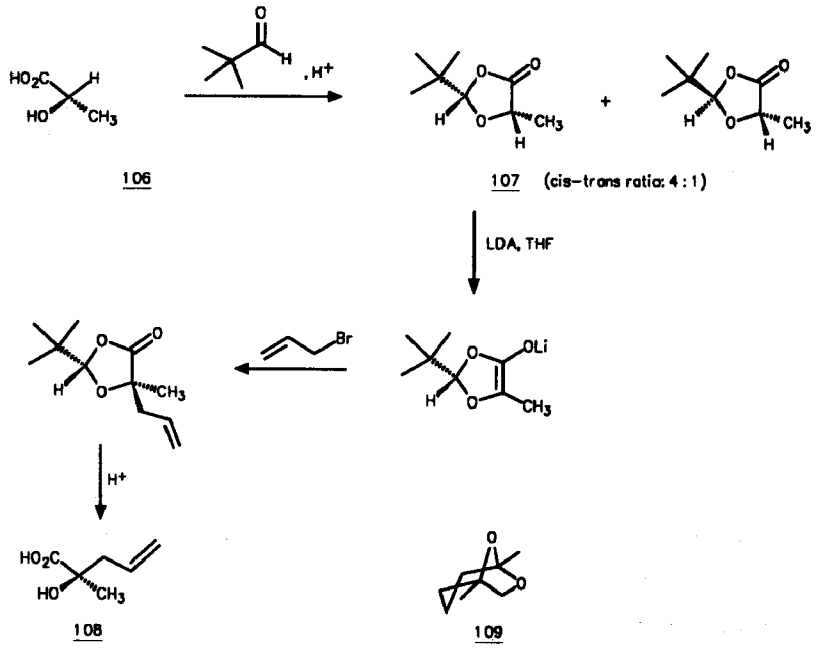


103 104 105

Scheme 1.2

The Seebach group reported on the α-alkylation of α-hydroxy acids with high diastereoselectivity in a process which was called "self reproduction of chirality".[43] In this methodology α-hydroxy acids are condensed with pivaldehyde to give initially cis

and trans substituted dioxolanones. By crystallization the isomers may be separated (the cis isomer is formed predominantly) to furnish, after deprotonation with lithium diisopropylamide (LDA) and subsequent reaction with electrophiles, 5-disubstituted dioxolanones. The diastereoselectivity in the alkylation step is high, mostly above 95%: the electrophile attacks the enolate nearly exclusively trans to the *t*-butyl group. In this manner, after hydrolysis the α-substituted α-hydroxy acids are obtained with retention of configuration in the alkylation of the cis dioxolanones, whereas alkylation of the trans isomers affords products with inversion of configuration. A typical example of this strategy is given in Scheme 1.3 where (S)-lactic acid (**106**) is alkylated after formation and separation of dioxolanone **107**[44] stereoselectively to yield (S)-α-allyl lactic acid (**108**). This compound has been employed as chiral building block in the synthesis of frontalin (**109**), a pheromone of the pine bark beetle.[45]

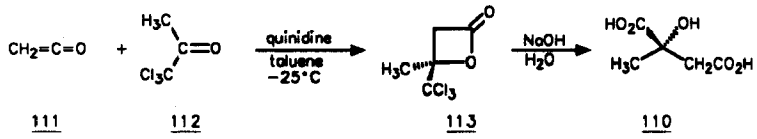


Scheme 1.3

The methodology of "self reproduction of chirality" has also been suitable for the α-alkylation of α-amino[46] and α-mercapto carboxylic acids.[47]

It should be emphasized again, that all the above discussed methods to α-substituted α-hydroxy acids are dependent on the availibility of chiral auxiliaries or (as is the case in Seebach's strategy) enantiomerically pure unsubstituted α-hydroxy acids.

A catalytic enantioselective synthesis of α-hydroxy acids was developed in our laboratory by Wynberg and Staring, using a catalytic stereoselective cycloaddition reaction.[48] This reaction was also useful for the enantioselective synthesis of an α-substituted α-hydroxy acid (citramalic acid, **110**, Scheme 1.4).[49] Thus, the cycloaddition reaction of ketene (**111**) and trichloroacetone (**112**) in the presence of 2 mol% of quinidine, afforded (R)-2-oxetanone **113** in high yield (83%) and high e.e. (95%). After one recrystallization compound **113** was obtained in enantiomerically pure form. Hydrolysis of this 2-oxetanone under basic conditions gave enantiomerically pure (S)-citramalic acid (**110**). Using benzoylquinine as a catalyst in the cycloaddition reaction, the other enantiomer, (R)-**110**, could be obtained. Citramalic acid (**110**) has been employed as chiral starting material in the synthesis of various natural products.[50]



111 112 113 110

Scheme 1.4

This method, however, has its limitations as in addition to a methyl substituent (originating from compound **112**), only strongly polarized substituents (for example, p-nitrophenyl) can be introduced in the 2-oxetanone.

Clearly, a general stereoselective route to α-substituted α-hydroxy acids would be of great value for developing further the synthetic opportunities provided by these compounds as either chiral building blocks in EPC synthesis or as reagents.

1.4 *OBJECTIVE OF THIS THESIS AND SURVEY OF ITS CONTENTS*

From an economic point of view, catalytic enantioselective synthesis belongs to the most attractive tools of building chiral molecules. We started this investigation in order to develop a new catalytic enantioselective synthesis of chiral α-substituted α-hydroxy acids.

As, in principle, the most direct way to these compounds would be an alkylation of unsubstituted α-hydroxy acids, we turned to a catalytic carbon-carbon bond forming reaction as starting point. The results of this approach is described in Chapter II, in which we focus on a catalytic allylation reaction. The possibility to achieve enantioselectivity was investigated by using chiral optically active ligands, which are coordinated to the catalytic active intermediate.

No direct methods were available for establishing the enantiomeric excesses of chiral α-substituted α-hydroxy acids at the initiation of this work. Therefore, Chapter III deals with a new chiral derivatizing agent suitable for e.e. determination of these compounds using ^{1}H NMR spectroscopy.

A different strategy to α-substituted α-hydroxy acids is the basis of the research, described in Chapter IV. As biocatalysis is an area which is receiving much current interest, a study was undertaken to see whether enzymes can be employed as useful chiral catalysts in the resolution of α-substituted α-hydroxy esters.

The observed results in pig liver esterase catalyzed hydrolysis of the above mentioned esters are the basis of Chapter V. Using an active site model we try to gain more insight in the factors that determine PLE enantioselectivity in hydrolysis.

Part of this work has already been published or will be published in the near future.[51]

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