Chiral α-substituted α-hydroxy acids

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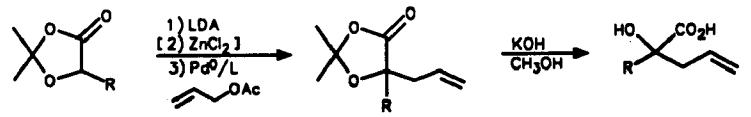
SUMMARY

This thesis deals with new synthetic routes to enantiomerically pure α-substituted α-hydroxy acids. These compounds are valuable synthetic intermediates in stereoselective synthesis. α-Substituted α-hydroxy acids in optically active form have thus far been synthesized by rather elaborate stoichiometric syntheses. The access to α-substituted α-hydroxy acids in enantiomerically pure form is limited owing to the lack of general stereoselective routes. The aim of the research described in this thesis is to develop a general catalytic stereoselective synthesis of chiral α-substituted α-hydroxy acids. This will allow further exploration of the synthetic opportunities provided by these chiral building blocks.

In Chapter I a short introduction to stereoselective synthesis in general is given. A literature survey of recent achievements in the synthesis of chiral α-substituted α-hydroxy acids reveals that most syntheses rely on the use of chiral auxiliaries (in stoichiometric quantities) and that the observed stereoselectivities are in many cases only moderate.

A straightforward synthesis of α-alkylated α-hydroxy acids would be an alkylation of unsubstituted α-hydroxy acids. Chapter II focusses on a palladium catalyzed allylic alkylation of α-hydroxy acids, protected as 1,3-dioxolan-4-ones. The enolates of the dioxolanones **206** and **207** afforded after reaction with allyl acetate in the presence of a catalytic (1 mol%) amount of a palladium catalyst, the allylated dioxolanones **209** and **222**, which could be hydrolyzed to the corresponding α-allyl α-hydroxy acids **223** and **224**. A variety of substituted allylic acetates could be coupled with the enolate of **206** using this catalytic reaction. The regioselectivity in these allylation reactions was excellent.



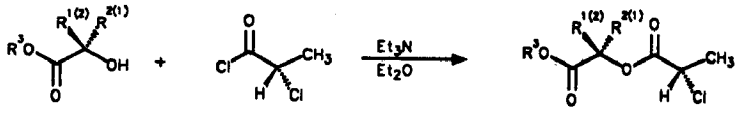
206: R = C_6H_5
207: R = CH_3

209: R = C_6H_5
222: R = CH_3

223: R = C_6H_5
224: R = CH_3

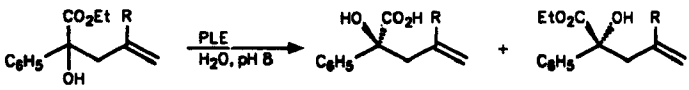
Various attempts were made to achieve enantioselectivity in the allylation step using chiral ligands on the palladium catalyst. The use of the zinc enolate of **206** was found to improve the enantioselectivity which remained, however, only modest, about 30% e.e. being the best result obtained. (2S,3S)-(-)-Bis(diphenylphosphino)butane ((S,S)-chiraphos) proved to be the best optically active ligand of a variety that were tested.

As no direct methods for establishing the enantiomeric excess of chiral α-substituted α-hydroxy acids were available, a new chiral derivatizing agent suitable for e.e. determination of these compounds using ^{1}H NMR spectroscopy is presented in Chapter III. (S)-2-Chloropropanoyl chloride (**304**), readily obtained from L-alanine, is coupled with α-substituted α-hydroxy acids (or esters) to afford O-acylated products **308**, the methyl group of which can be used as a probe for determining the enantiomeric composition of the original α-hydroxy compound.



304 308

A route to optically active α-substituted α-hydroxy acids in which an enzyme, pig liver esterase (PLE), is employed as a chiral catalyst in the hydrolysis of racemic α-substituted α-hydroxy esters is described in Chapter IV. Although sterically hindered esters possessing a quaternary stereogenic carbon center were long believed to be difficult to hydrolyze enzymatically, it could be shown that PLE accepts and hydrolyses many substituted mandelates and lactates. Very high enantioselectivity of PLE was observed in the hydrolysis of α-allyl ethyl mandelate (**414a**) and α-methallyl ethyl mandelate (**414b**).



414a: R = H
414b: R = CH3

416a: R = H
416b: R = CH3

A single crystallization of the acidic products led to the α-allylated α-hydroxy acids in enantiomerically pure form. An important advantage of the employed kinetic resolution procedure is that both enantiomers of the α-substituted α-hydroxy compounds are accessible. Although some other substituted mandelates could be obtained in optically enriched form (up to 75% ee), PLE catalyzed hydrolysis of substituted lactates proceeded almost without enantioselectivity.

As PLE seemed to be quite aselective as far as hydrolysis of these esters concerns, it was thought to be worthwile to concentrate more on the factors that determine the enantioselectivity in hydrolysis. Chapter V, therefore, describes a study of these factors using a model for the catalytic active site of PLE. A recently proposed model that reflects the topography of the enzyme pocket proved to be of value in rationalizing the stereochemical outcome of the enzymatic ester hydrolysis. A significant interaction of a three carbon atom moiety with a hydrophobic region in the active site may partially account for the preferred fit of one of the enantiomers of **414a** and **414b** in the catalytic active site, resulting in highly enantioselective hydrolysis. However, owing mainly to the conformational flexibility of the α-substituted α-hydroxy esters, it is diffcult to specify a well defined fit of these compounds in the active site of the enzyme. For compounds that fail to interact well with the active site, many enzyme-substrate complexes, which differ mutually in conformation, may be formed and as a result low enantioselectivity in hydrolysis will result.