Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8109-8112, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10121-6

Enzymatic Hydrolysis of Acylals. A Promising Route to Chiral Aldehydes

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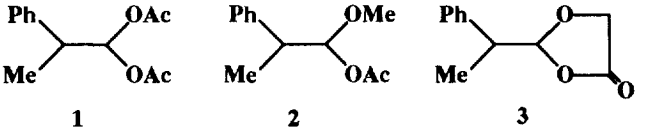
Abstract: A new and convenient method for the optical resolution of aldehydes through lipase-catalyzed resolution of the corresponding acylals has been developed. *Candida rugosa Lipase* (CRL) showed the best stereoselectivity.

Hydrolytic enzymes, especially esterases and lipases, are among the most broadly used classes of enzymes in organic synthesis[1]. Their great catalytic abilities, their broad substrate specificity, their stability and low cost make them attractive for chemical transformations. A great number of natural and non natural substrates involving many alcohols and carboxylic acids have been resolved with these enzymes. The asymmetric synthetic capabilities of lipases-esterases prompted us to investigate the hydrolytic resolution of racemic carbonyl compounds.

In 1990 Ohta and coworkers reported[2] the enzymatic hydrolysis of enol esters which give α-chiral ketones with good to excellent enantiomeric excesses (ee). The stereoselectivity is based on the esterase ability to differentiate enantiotopic faces of the C=C double bond with subsequent selective protonation on the liberated enols. However, the best results concerning stereoselectivity were taken by incubation with the non commercially available microbial culture of *P. miso*.

We report here a new method which involves the optical resolution of aldehydes- precursors of carboxylic acids-, which bear an asymmetric carbon next to the carbonyl carbon. This can be achieved by the use of protected carbonyl compounds[3], for example acylals, whose optical resolution and deprotection can be effected enzymatically in one step. The major advantage of this asymmetric hydrolysis is the recovery of both enantiomers of a racemic carbonyl compound.

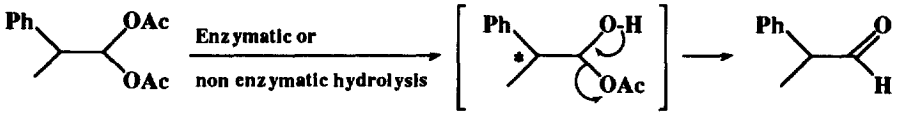


1 **2** **3**

Acylals are acetals with acyloxy substituted alcoholic moieties. Their synthesis is well known[4], as they have been used as selective protective groups of aldehydes[5] in the presence of a ketone functionality.

The nucleophilic hydrolysis of acylals leads to a "hemiacylal" which loses a carboxylate group to liberate the starting aldehyde. If the deprotection step is accomplished enzymatically then the liberated aldehyde is expected to be enantiomerically enriched.

To test this possibility substrates **1-3** were synthesized in high purity[6], starting from racemic 2-



phenyl-propanal. These substrates are proper for this purpose because they bear an asymmetric carbon next to the reactive carbonyl center. In a control experiment, hydrolysis of compound **1** under the reaction conditions (phosphate buffer 10mM, pH 7) was not observed for a period of 18 hours. In contrast, the structurally related compounds **2** and **3** were hydrolyzed in a few hours. Therefore, substrate **1** was chosen to test the enzymatic hydrolysis with the following commercially available (Sigma Co) hydrolytic enzymes: Pig Liver Esterase (PLE), Pig Pancreatic Lipase (PPL), P. *fluorescens* Lipase (PFL) and *Candida rugosa* Lipase (CRL). Lipase catalyzed hydrolyses proceed smoothly by addition of 100mg of substrate to 100mg of crude protein in 0.01M phosphate buffer pH 7, which was maintained stable during the course of the reaction, by addition of 0.2N NaOH solution.

These results are summarized in Table 1.

Table 1. Asymmetric Enzymatic Hydrolysis of Substrate **1** with PLE, PPL, PFL and CRL and **4** and **5** with CRL.

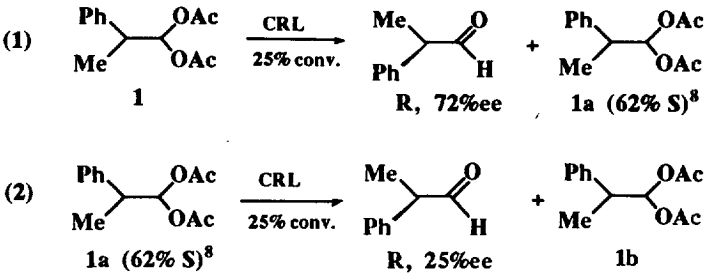
Substrate	Enzyme[a]	Time/min	Conversion%	ee %	Configuration[b]
1	PLE	30	30	2[c]	R
1	PPL	40	18	14[c]	R
1	CRL	70	25	72[c,d]	R
1	PFL	360	5	-	-
4	CRL	90	23	40[d]	R
5	CRL	90	20	35[d]	R

[a] Enzymes used: Pig Liver Esterase (PLE), Pig Pancreatic Lipase (PPL), P. *fluorescens* Lipase (PFL) and *Candida rugosa* Lipase (CRL). [b]Based on $[\alpha]^{25}$=- 238° of the optically pure (R)-(-)-PhCHMeCHO[7]. [c] By optical rotation. [d] By ^{1}H NMR in the presence of Eu(hfc)$_3$ shift reagent. The error was ± 5%.

As seen from Table 1, PLE, PPL and CRL hydrolyzed acylal **1** relatively fast , with R stereoselectivity, whereas PFL unexpectedly did not hydrolyze **1**. CRL gave the best results among the four enzymes with good enantiomeric excess.

In an effort to understand the stereoselectivity trend of the CRL-induced hydrolysis, we examined the four possible diastereomeric transition states between enzyme- substrate, by analysing the products as a function of the extent of reaction. The conversion % was controlled by titrating the liberated acetic acid with 0.2N NaOH solution.

The R enantiomer[7] of the aldehyde was resolved preferentially up to 72%ee starting from racemic substrate (eq. 1). The stereoselectivity for the R enantiomer is persistent, even in the case where the starting acylal **1a** is 62% enriched in S enantiomer[8] (eq. 2). This result indicates that among the four possible transition states between CRL- substrate, two of them with lower activation energy lead to the major R aldehyde. From the stereoselectivities mentioned above it seems that *Candida rugosa* lipase

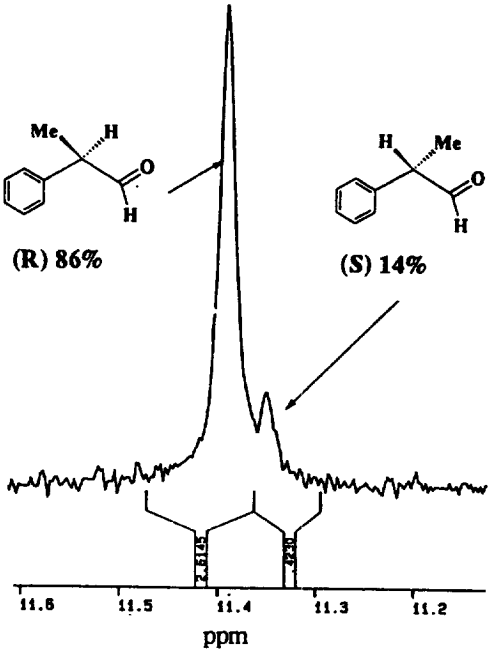


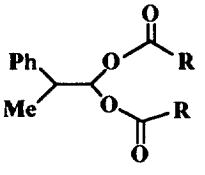
reacts preferentially with R- proR and R- proS conformations. This is consistent with the R enantioselectivity of lipases recently reported[9] for other systems. It is important to note that the stereocenter which dictates the reaction selectivity is remote by four bonds from the reaction center. Kazlauskas and coworkers have reported[10] a simple rule which predicts the enantiopreference of *Candida rugosa* lipase toward secondary alcohols[10a] and *Pseudomonas cepacia* lipase (PCL) enantiopreference toward primary alcohols[10b].

However, in this stage of investigation the obtained results do not allow us to provide mechachanistic details concerning the nature of the transition states and subsequently a rational of the observed enantioselectivity.

Furthermore, in order to optimize the enantiomeric excess of the product, we varied the reaction solvent by the addition of 15% of DMSO or acetone.[11] However this experiment did not show any significant change in stereoselectivity. Transesterification of the above substrate with n-BuOH in hexane or diisopropyl ether, with the use of 1,6 lutidine as an acid scavenger gave similar results.

Figure 1. ^{1}H NMR determination of ee% by integration of the resolved carbonyl hydrogens in the presence of Eu(hfc)3 shift reagent.





1. R=Me
4. R=Et
5. R=Pr

In order to investigate the effect of the size of the acyloxy group on the enzyme stereoselectivity, acylals **4** and **5** were prepared[6] and hydrolyzed by CRL. As shown in Table 1, the enantiomeric excess decreases from 72 to 35% ee, as the alkyl chain of the acyl moiety increases from methyl to propyl respectively.

In conclusion, our results on the asymmetric lipase-catalyzed hydrolysis of protected aldehydes provide a promising new method for the optical resolution of certain aldehydes with the advantage of recovering both enantiomers.

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(*Received in UK* 13 *August* 1997; *revised* 11 *September* 1997; *accepted* 12 *September* 1997)