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Kinetic Resolution of Racemic α-Hydroxy Ketones by Lipase-catalyzed Irreversible Transesterification

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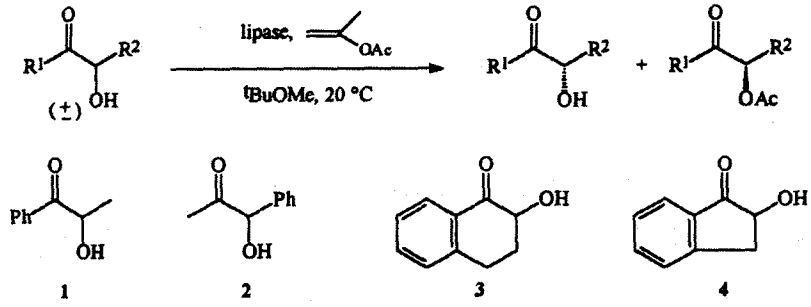
Abstract: Asymmetric acetylation of racemic α-hydroxy ketones with isopropenyl acetate catalyzed by lipases afforded the optically active keto alcohols and acetates in high enantiomeric excess (up to 99%); an enzymatic kinetic resolution which may be performed on preparative scale. Copyright © 1996 Elsevier Science Ltd

The synthesis of optically active α-hydroxy carbonyl compounds, in particular ketones, is of significant importance since they are convenient building blocks in the asymmetric synthesis of biologically active compounds.[1] Recently several methods have been developed for their preparation. For example, the stereoselective oxidation of optically active enolates has been reported[2] as an attractive route. On the other hand, prochiral enolates have been oxidized enantioselectively by optically active oxaziridines as electrophilic oxidants.[3] Recently, we have reported[4] the synthesis of optically active α-hydroxy ketones by stereoselective oxidation of chiral titanium enolate complexes with dimethyldioxirane.

Alternative to the chemical methods, optically active α-hydroxy ketones can be prepared enzymatically by reduction of the α-diketones with yeast as the biocatalyst.[5] However, this enzymatic method possesses the following disadvantages[5b]: further reduction of diketone to the *vic*-diol, formation of both regioisomeric α-hydroxy ketones and moderate chemical yields. Lipases have been frequently used as convenient and efficient biocatalysts for the asymmetric synthesis of a wide range of organic compounds.[6] Although numerous α-hydroxy acids[6,7] and esters[6] have been resolved by lipases, reports on the kinetic resolution of structurally simple α-hydroxy ketones by these readily accessible enzymes are scarce. Very recently, Gala *et al.* have described[1c] the resolution of α-hydroxy aryl ketones (precursors of chiral azole antifungal reagents) by lipase-catalyzed hydrolysis of the corresponding acetates in phosphate buffer; nevertheless, the irreversible transesterification route of this enzymic reaction appears not to be known. Herein we present the results of the kinetic resolution of racemic α-hydroxy ketones **1-4** by lipase-catalyzed irreversible transesterification with isopropenyl acetate in organic media (Scheme 1).



Scheme 1. Kinetic resolution of α-hydroxy ketones **1-4.**

First the efficiency of different lipases in catalyzing the transesterification of α-hydroxy ketones was examined. For this purpose, the racemic substrates **1-4** were prepared from the commercially available ketones by osmium tetroxide oxidation of their corresponding trimethylsilyl enol ethers[8] and subsequently acetylated with isopropenyl acetate in the organic solvent by the catalytic action of the lipase.

Among the lipases tested, Amano PS and Amano AK exhibited the best results, when *tert*-butyl methyl ether was used as solvent. For all subsequent enzymatic kinetic resolutions, the racemic mixture of the particular α-hydroxy ketone **1-4** was then treated at room temperature (ca. 20 °C) with ten equivalents of isopropenyl acetate in *tert*-butyl methyl ether in the presence of the PS or AK lipase. The results are summarized in Table 1, wherein the configurations of the keto alcohols were assessed by comparison of their specific rotations with literature data[3b,9] and the corresponding keto acetates were assigned accordingly. Use of vinyl instead of isopropenyl acetate or exchange of the *tert*-butyl methyl ether solvent for THF, dichloromethane, hexane or toluene did not improve the results.

For the alcohols **1** and **2**, the lipase AK was shown to be a more suitable biocatalyst than PS (entries 1-3). For substrate **1**, 50% conversion could not be achieved within a reasonable time for the lipase PS (entry 3). Thus, while the enantiomeric excess was high for the resulting keto acetate, as expected it was low for the remaining alcohol. For the alcohols **3** and **4**, both lipases AK and PS showed higher rates of acylation (entries 7-11); however, the corresponding acetates were obtained, even at ca. 50% conversion, in lower ee values (entries 7, 8, 10 and 11). The control experiments with authentic optically active acetates under the conditions of enzymatic reaction proved them to be configurationally stable and racemization is not responsible for their lower enantiomeric purities. The reduced selectivity of the enzymes is more pronounced in the case of the lipase PS with the α-hydroxy ketone **3** (entry 8). Apparently, the enzymes lipase PS and AK accept both enantiomers of the keto alcohols **3** and **4**, however, with higher preference for the *R* configurations.

Pseudomonas lipases belong to the group of the most useful enzymes for biocatalytic transformations and it is gratifiying that they catalyze efficiently also the transesterification of racemic α-hydroxy ketones, carbonyl substrates which have previously not been employed for this purpose. The *R* enantiomer of the keto alcohol is recognized selectively resulting in enantiomerically enriched *R* keto acetate and *S* keto alcohol.

Table 1. Lipase-catalyzed kinetic resolution of the racemic keto alcohols **1-4**.

Entry	Substrate	Lipase	Time (h)	Conv.[b] (%)	Keto alcohols ee[c] (%)	Keto alcohols config.	Keto acetates ee[d] (%)	Keto acetates config.	E[e]
1	**1**	AK	92	48	89	*S* (-)	95	*R* (+)	113
2	**1**	AK	138	52	99	*S* (-)	90	*R* (+)	82
3	**1**	PS	210	19	23	*S* (-)	99	*R* (+)	249
4	**2**	AK	87	48	92	*R* (-)	98	*S* (+)	311
5	**2**	AK	138	51	99	*R* (-)	95	*S* (+)	201
6	**2**	PS	87	46	83	*R* (-)	98	*S* (+)	261
7	**3**	AK	40	57	99	*S* (-)	79	*R* (+)	35
8	**3**	PS	25	49	77	*S* (-)	79	*R* (+)	19
9	**3**	PS	39	60	95	*S* (-)	63	*R* (+)	16
10	**4**	AK	20	58	99	*S* (+)	72	*R* (-)	34
11	**4**	PS	14	52	95	*S* (+)	86	*R* (-)	45

[a]From Amano Pharmaceutical Co. [b]Calculated (Ref. 10) from c = ee (alc)/ee (alc) + ee (acet), ca. 5% error. [c]HPLC analysis on a Chiralcel OD column for substrates **1-2** and Chiralcel OB-H for substrates **3-4** (9:1 hexane/isopropyl alcohol as eluent). [d]HPLC analysis on a Chiralcel OD column with 9:1 hexane/isopropyl alcohol as eluent.[e] Enantiomeric ratio (Ref. 10).

An exception is keto alcohol **2**, for which the *S* enantiomer is preferentially selected by the enzyme. This may be rationalized in terms of the established empirical rules based on relative sizes of the substituents[11] (Fig. 1). Moreover, the preferred orientation is also in accord with the proposed π-π interaction of the phenyl group in the substrate with an aromatic moiety in the enzyme, which efficiently controls the enantioselectivity of the reaction.[12] This rationale may also account for the fact that higher conversion rates were observed for the more rigid substrates **3** and **4**.

Figure 1. Preferred enantiomer in the lipase-catalyzed transesterification.

The results presented here demonstrate that lipases catalyze the enantioselective transesterification of α-hydroxy ketones with isopropenyl acetate in organic media, to provide enantiomerically pure keto alcohols and enantiomerically enriched keto acetates in good chemical yields.

General procedure for the lipase-catalyzed irreversible transesterification. Isopropenyl acetate (10 equiv.) and lipase powder (100-200 mg/mmol of substrate) were added to the solution (0.1 M) of the racemic α-hydroxy ketone (up to 0.1 mol) in *tert*-butyl methyl ether. The mixture was vigorously stirred at room temperature (ca. 20 °C) and after the appropriate time (12-210 h), the enzyme was removed by filtration and the solvent evaporated under reduced pressure (40 °C/40 Torr). Column chromatography on silica gel afforded the optically active alcohol and acetate in good yields (78-91% based on substrate conversion).

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