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Enzymes in Organic Synthesis: Lipase Catalyzed Resolution of Secondary α-Ketoalcohols

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Abstract - Resolution of several α-ketoalcohols of synthetic value using lipase as a catalyst is described.

α-Ketoalcohols are versatile synthons in organic synthesis. They can be converted into either erythro or threo 1, 2-diols via reduction with a hydride reagent[1] or a hydrosilane / F^- reagent.[2] They can also be transformed to erythro or threo 1, 2-N-benzyloxy amino alcohols via the reduction of their corresponding (E)-oxime or (Z)-oxime derivatives, respectively.[3] α-Alkyl arylacetic acids, a group of biologically interesting compounds, have been prepared via an aryl 1,2-migration from the corresponding α-ketoalcohol derivatives.[4] Some of them, like α-(6-methoxyl-2-naphthyl)propionic acid show potent anti-inflammatory and analgesic activities[5] and others, like α-isopropyl arylacetic acid, are used as a moiety of synthetic pyrethroids.[6] Because most of the α-alkyl arylacetic acids possess an unique stereogenic center required for biological activity,[7] a synthetic strategy based on enantiomerically pure or enriched α-ketoalcohols is considered to be important for the preparation of many of these molecules.

Previously reported methods for the preparation of chiral α-ketoalcohols involve the use of chiral oxazaborolidine or the use of microbes as catalysts in the enantioselective reduction of α-keto thioacetals following the removal of the dithiane group.[8] In these processes, more procedures for the introduction and removal of the pungent dithiane group are required. Another method for the preparation of chiral α-ketoalcohols is using baker's yeast as catalyst to reduce 1,2-diketones, however, the selectivity of reduction was low.[9] We report here the enzymatic resolution of several α-ketoalcohols of synthetic value using lipase as a catalyst.

Substrates **1a-1d** and **3** were synthesized in high yield (82-90%) from their corresponding α-bromo ketones[10] via the treatment with one equivalent of sodium methoxide in methanol following acidic hydrolysis and then acetylation with acetic anhydride in pyridine. These α-keto esters **1a-d** and **3** were then resolved with lipoprotein lipase from *Pseudomonas sp.* (LPL, from Amano company)[11] as shown in Scheme 1. These results are summarized in Table 1. The E values[12] for the resolution of **1a-1d** were 42, 42, 43 and 34, respectively. The optical purities of 1**a**, **1b**, **1c** and **1d** isolated are 89%, 85%, 83% and 85% when the conversions are of 40 %, 51 %, 53 % and 45%, respectively. Because the rate of hydrolysis of **3** was very slow, the chloroacetate **4** was prepared and resolved. The hydrolysis rate of **4** was improved, however, the ee was low. Lipase AP6 from Asperg illus niger (AP6, from Amano company) has also been examined in the resolution of **4**, again very low E value was obtained.

Scheme 1

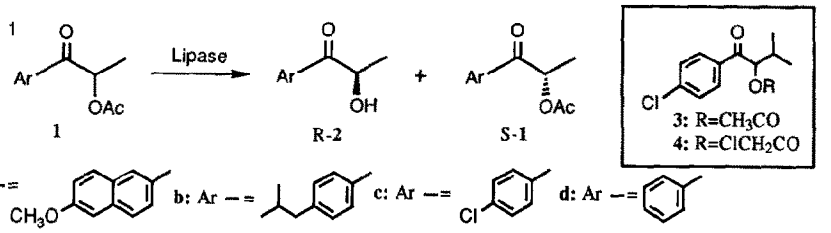

Table 1. Lipase-Catalyzed Enantioselective Hydrolysis of a-Ketoesters **1a** - **1d**, **3**, and **4**

Compound	Enzyme	Extent of Conversion	% ee[a] & $[\alpha]_D^{25c}$ Acetate	Alcohol	Stereochemical preference	E[b]
1a	LPL	40	61 (-9.3)	89 (+69.7)	R	42
1b	LPL	51	90 (-15.0)	85 (+46.0)	R	42
1c	LPL	53	95 (-11.5)	83 (+15.2)	R	43
1d	LPL	45	72 (-72.7)	85 (+104.9)	R	34
3	LPL	very slow				
4	LPL	62	17	10	R	1.5
4	AP6	89	77	9	R	2.5

a : The ee's of acetate and alcohol were determined according ref. 13
b : E is the ratio of the specificity of the two enantiomers.[12]
c : The specific rotation was measured in $CHCl_3$ with the concentration of 1.0-2.0 g/100 mL.

To determine the absolute stereochemistry, **2a** ($[\alpha]_D^{25}$ +69.7, ee = 89 %) was converted to naproxen methyl ester (**7**).[14] The absolute configuration of **7** was determined to be **S** by comparison of its specific rotation value, $[\alpha]_D^{25}$ +88.4 (c 1.02, $CHCl_3$), with the literature value.[15] This indicated that **2a** has the **R** configuration.

In conclusion, the enzymatic resolution as described here enables the preparation of either antipodes of the optically pure α-keto alcohol desired.

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10. α–Bromo ketones were prepared via a known two step procedure see ref. 4.
11. After screening with **1d** as a substrate, the LPL enzyme was chosen because it gave the best enantioselectivity.
12. E is the ratio of the specificity constants of the two enantiomers. see: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J., *J. Am. Chem. Soc.* **1982**, *104*, 7294.
13. The ee of acetates, **1a-1d**, **3** and **4** was determined by ^{1}H-NMR spectroscopy in the presence of Tris[(3-heptafluoropropylhydroxymethyene)-(+)camphorato]-europium(III). The alcohol product was converted to the corresponding acetate and then analyzed with the same method as described.
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