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A NOVEL METHOD TO SYNTHESIZE (L)-β-HYDROXYL ESTERS BY THE REDUCTION WITH BAKERS' YEAST[1]

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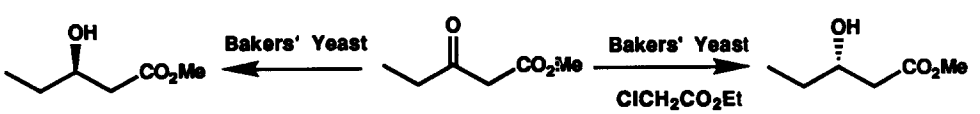
Abstract: β-Keto esters are reduced stereoselectively into the corresponding (L)-β-hydroxyl esters in the presence of ethyl chloroacetate.

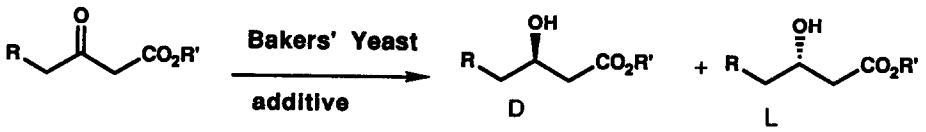
The use of microbial reduction systems to prepare chiral alcohols is widespread and very efficient in many cases.[2] Namely, β-keto esters appear to be general substrates for the reduction mediated by bakers' yeast. However, the optical purities of thus produced β-hydroxyl esters are oftenly variable and the configuration of product cannot be controlled. Since the yeast reduction of β-keto esters is undertaken by a complex of dehydrogenases that individually afford (L)- or (D)-hydroxyl esters enantioselectively,[3,4] inhibition of the "L-enzyme" (the enzyme which affords (L)-hydroxyl esters) will result in the formation of (D)-hydroxyl esters exclusively or *vice versa*. In fact, in the previous papers, we reported that bakers' yeast treated with allyl alcohol[5] or with an α,β-unsaturated carbonyl compound[6] reduces β-keto esters into the correspoding (D)-hydroxyl esters stereoselectively. Since the "L-enzyme" is inhibited selectively by these inhibitors, there may exist other reagents that inhibit the "D-enzyme" selectively. Based on the concept described above, we looked for a new inhibitor which shifts the stereochemistry of the reduction of β-keto esters by bakers' yeast toward the L-side and found that α-haloacetate exerts the desired effect.

For example, the reduction of methyl 3-oxopentanoate with bakers' yeast affords methyl (D)-3-hydroxypentanoate in 12% enantiomer excess (ee), whereas the corresponding (L)-isomer is obtained in 69% ee when the reducing system is treated with ethyl chloroacetate.



Other haloacetates or halopropionates were tested for their ability to shift the stereochemistry of the reduction and the results are summarized in Table 1. Several characteristics of the additives are noteworthy. First of

Table 1. Effect of Halo Esters on Asymmetric Reduction of β-Keto Esters



Substrate R	Substrate R'	Additive,	mM	Reaction Conditions[a]	Configuration	ee, %	Chemical Yield, %
Me	Me	None	--	A	D (*R*)	12	46
		None	--	B	L (*S*)	15	67
		$ClCH_2CO_2Et$	25	A	L (*S*)	69	20
			33	B	L (*S*)	81	67
			50	B	L (*S*)	81	68
			67	B	L (*S*)	91	51
			83	B	L (*S*)	78	43
			100	B	L (*S*)	71	32
		$ClCH_2CO_2Bu$	25	A	L (*S*)	69	25
		$ClCH_2CO_2CHCH{=}CH_2$	25	A	L (*S*)	5	4
		Cl_2CHCO_2Me	25	A	D (*R*)	8	57
		Cl_3CCO_2Et	25	A	D (*R*)	14	45
		$BrCH_2CO_2Me$	25	A	L (*S*)	62	11
		$BrCH_2CO_2Et$	25	A	L (*S*)	65	8
		$BrCH(Me)CO_2Me$	25	A	D (*R*)	20	73
		$BrCH_2CH_2CO_2Et$	25	A	L (*S*)	19	55
		CH_3CO_2Et	25	A	D (*R*)	12	61
		ICH_2CONH_2	25	A	D (*R*)	4	24
Cl	Et	None	--	A	D (*S*)	43	62
		$ClCH_2CO_2Et$	67	B	L (*R*)	80	70
H	Et	None	--	A	L (*S*)	77	66
		$ClCH_2CO_2Et$	67	B	L (*S*)	99	75
Me	Et	None	--	A	D (*R*)	4	61
		$ClCH_2CO_2Et$	67	B	L (*S*)	94	63
CF_3	Et	None	--	A	L (*R*)	69	77
		$ClCH_2CO_2Et$	67	B	L (*R*)	84	60

[a] A: [Dry bakers' yeast] = 4 g, [Substrate] = 1 mmol, [Total volume] = 20 ml.
B: [Dry bakers' yeast] = 20 g, [Substrate] = 1 mmol, [Total volume] = 60 ml.
At room temperature for 4h.

all, although it is recognized in general that halo esters are effective to shift the stereochemistry of the reduction toward the L-side, the effect of alkoxy moiety on the reaction course is also significant: ethyl or butyl ester of chloroacetic acid is effective, whereas the corresponding allyl ester results in the lowering of both the chemical yield and ee. The allyl ester seems to inhibit both the "L- and D-enzymes" almost equally. This phenomenone is explicable by the idea that a part of the allyl ester is hydrolyzed, either enzymatically or non-enzymatically, during the reaction to release allyl alcohol, which is known to inhibit the "L-enzyme" strongly.[5] Secondly, a polychloroacetate is ineffective to the reduction. The phenomenone indicates that a monochloro ester acts as an electrophile to be attacked by a nucleophilic residue of the dehydrogenase. It is known that an S_N2 reaction is retarded by an α-halo substituent.[7] Thus, a polychloroacetate is a weaker inhibitor than a monochloroacetate. Thirdly, the corresponding α-bromo esters are also effective to shift the stereochemistry. However, the chemical yield drops off with these esters. These α-bromo esters seem to disturb the "L-enzyme" in some extent in addition to the strong inhibition on the "D-enzyme". Fourthly, although a primary bromide is effective even at the β-position, a secondary bromide is ineffective as is exemplified by methyl α-bromopropionate.

The concentration of the additive is also a candidate to affect the stereoselectivity and the best result was obtained with its concentration of 67 mM. Other β-keto esters were reduced under the conditions of 67 mM of ethyl chloroacetate and (L)-hydroxyl ester of high ee was obtained in each case without lowering the chemical yield.

In a typical run, 1 mmol of methyl 3-oxopentanoate was added to a suspension of dry bakers' yeast (20 g) in 67 mM aqueous ethyl chloroacetate and the resulted mixture was stirred for 4 h at room temperature. Ethyl acetate was added to the mixture and organic materials were extracted. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel using hexane-ethyl acetate (10 : 1) as an eluent yielding methyl (L)-3-hydroxypentanoate of 91% ee in 51% chemical yield.

In the previous papers, we reported that stereochemistry of the reduction of β-keto esters is controlled by immobilization method: immobilization of bakers' yeast by hydrophobic polyurethane gives (D)-hydroxyl esters,[8] whereas the reduction with bakers' yeast immobilized by magnesium alginate affords the (L)-hydroxyl esters.[9] Together with these systems, we now have a new system to control the stereochemistry of the yeast reduction. That is, an additive such as allyl alcohol or an α,β-unsaturated carbonyl compound shifts the reduction toward the D-side, whereas the addition of a chloroacetate shifts the reductin toward the L-side.

We believe that the present method, combined with those reported previously is useful to obtain optically active hydroxyl esters of desired configurations.

Application of the present method to other microbes or to other substrates is now investigated in our laboratory.

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