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A NEW METHOD FOR STEREOCHEMICAL CONTROL OF MICROBIAL REDUCTION. REDUCTION OF β-KETO ESTERS WITH BAKERS' YEAST IMMOBILIZED BY MAGNESIUM ALGINATE[1)]

Kaoru NAKAMURA,*[†)] Yasushi KAWAI,[††)] Shinzaburo OKA,[††)] and Atsuyoshi OHNO[††)]

[†)] Department of Chemistry, Shiga University of Medical Science, Seta, Ohtsu 520-21 Japan

[††)] Institute for Chemical Research, Kyoto University, Uji, Kyoto 611 Japan

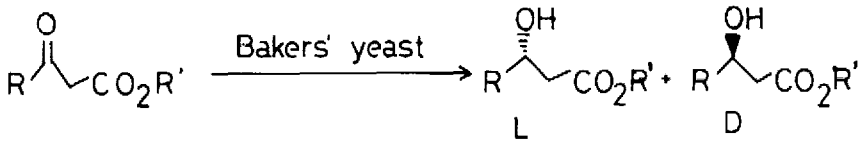
Abstract: Yeast reduction of methyl 3-oxopentanoate gives the L-hydroxy ester when bakers' yeast is immobilized by magnesium alginate and the reaction is run under a high concentration of magnesium ion. The D-hydroxy ester is obtained under normal reaction conditions.

Asymmetric reduction of ketones by yeast has been used widely to obtain chiral alcohols because of simplicity, cheapness, and high enantioselectivity of the reduction. However, this method is not always excellent; *e.g.*, the reduction of methyl 3-oxopentanoate with bakers' yeast yields the D-hydroxy ester only in a low ee.[2)] In the previous reports, we described two methods to improve the ee of D-hydroxy ester by stereochemical control of microbial reduction: immobilization of yeast by polyurethane[3)] and the use of an inhibitor.[4)] At present, therefore, the stereochemical control toward the D-side has been achieved successfully. However, the control toward the L-product has not yet been completed.

Now, we report a new method for stereochemical control of microbial reduction which shifts the direction of stereochemistry toward the L-side. We found that the presence of concentrated metal salt in the reduction system changes the selectivity of the reduction. The reduction of methyl 3-oxopentanoate (1) with bakers' yeast without added salt affords methyl (*R*)-3-hydroxypentanoate (*R*-2) in 12% ee. On the other hand, the addition of 1 M KCl to the reduction system shifts the selectivity toward the L-side and the product is methyl (*S*)-3-hydroxypentanoate (*S*-2) in 8% ee. The reduction in more concentrated KCl solution gives *S*-2 with higher stereoselectivity: 24% and 45% ee at 2 M and 4 M KCl, respectively. The results are summarized in Table 1. It is recognized that chloride ion is more effective than bromide ion as the counter anion of the salt; NaBr and KBr exerted no effect to change the stereochemical course of the reduction toward L. Instead, these salts shift the stereochemistry toward the D-side, although the effect is very small. Chloride of magnesium or calcium ion shifts the stereoselectivity largely toward the L-side and the ee

of *S*-2 increases up to 80% and 75% in 2 M solutions of $MgCl_2$ and $CaCl_2$, respectively. Although the reduction with a higher $MgCl_2$ concentration results in the highest ee (86% at 3 M $MgCl_2$), the chemical yield drops down to 1%. To improve the chemical yield, the yeast was immobilized by magnesium alginate, and it is found that thus immobilized yeast increases the chemical yield up to satisfactory level so that the method is employable to organic synthesis. In the immobilized system, the reduction proceeds even with 4 M $MgCl_2$ concentration and the ee increases to 89%. Other β-keto esters are also reduced with the bakers' yeast immobilized by magnesium alginate and the L-hydroxy esters are afforded in every case. We believe that the present method, combined with the methods reported previously,[3,4] is useful to make the microbial reduction *stereospecific* instead of stereoselective: one can obtain the product of either *S*- or *R*-configuration depending on his purpose in chemistry. The present method might be appricable to other microbes or other substrates. The mechanism of the stereochemical control with the concentrated salt is now investigated in our laboratories.

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



Substrate R	Substrate R'	Additive (Conc., M)	Configuration	ee, %	Chemical Yield, %
Et	Me	none	*R*(D)	12	46
Et	Me	KCl (1.0)	*S*(L)	8	54
Et	Me	KCl (2.0)	*S*(L)	24	47
Et	Me	KCl (4.0)	*S*(L)	45	41
Et	Me	NaCl (2.0)	*S*(L)	43	37
Et	Me	NaCl (4.0)	*S*(L)	47	14
Et	Me	NaBr (2.0)	*R*(D)	10	48
Et	Me	KBr (2.0)	*R*(D)	20	48
Et	Me	$MgCl_2$ (2.0)	*S*(L)	80	20
Et	Me	$MgCl_2$ (3.0)	*S*(L)	86	1
Et	Me	$CaCl_2$ (2.0)	*S*(L)	75	19
Et	Me	$MgCl_2$ (2.0) (IMBY)	*S*(L)	81	58
Et	Me	$MgCl_2$ (4.0) (IMBY)	*S*(L)	89	44
$ClCH_2$	Et	none	*S*(D)	43	62
$ClCH_2$	Et	$MgCl_2$ (3.0) (IMBY)	*R*(L)	64	50
Me	Et	none	*S*(L)	77	66
Me	Et	$MgCl_2$ (3.0) (IMBY)	*S*(L)	99	65

Conditions: [dry bakers' yeast]= 4 g; [substrate] = 1 mmol; Water = 20 mL.
(IMBY): Bakers' yeast immobilized by magnesium alginate.

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