Tetrahedron Letters, Vol.31, No.25, pp 3631-3632, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOCHEMICAL CONTROL IN DIASTEREOSELECTIVE REDUCTION WITH BAKER'S YEAST[1)]

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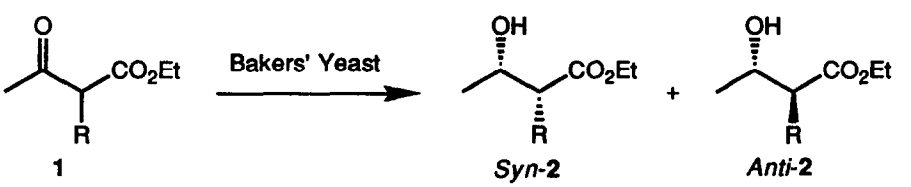
Abstract: Reduction of ethyl 2-alkyl-3-oxobutanoates with bakers' yeast treated with methyl vinyl ketone gave the corresponding (2*R*,3*S*)-*syn*-2-alkyl-3-hydroxybutanoates in excellent enantio- and diastereoselectivities.

Optically active 2-alkyl-3-hydroxybutanoates are versatile chiral building blocks for the syntheses of natural products.[3)] It was reported from our laboratory that the reduction of various esters of 2-alkyl-3-oxobutanoic acids by bakers' yeast yields the corresponding L-(*S*)-hydroxy esters with exclusive enantioselectivity, while the diastereoselectivity, *syn/anti* ratio,[4)] depends on the structure of the alkoxy moiety.[5)] To enhance the diastereoselectivity, we have looked for a novel method to obtain alkyl (2*R*,3*S*)-*syn*-2-alkyl-3-hydroxybutanoate and now would like to report our finding.

Shieh *et al.* reported that three dehydrogenases are responsible for the reduction of β-keto esters in bakers' yeast .[6)] Furuichi *et al.* found that benzyl 2-methyl-3-oxobutanoate is reduced by a purified enzyme from bakers' yeast into the corresponding β-hydroxy ester with a *syn/anti* ratio of 8/1, whereas the reduction of the same substrate with yeast cell provides the *syn/anti* ratio to be 7/3.[7)] Recently, we reported that the reduction of ethyl 2-allyl-3-oxobutanoate with a β-hydroxy ester oxidoreductase isolated from bakers' yeast affords ethyl (2*R*,3*S*)-*syn*-2-allyl-3-hydroxybutanoate in an excellent stereoselectivity.[8)] These results suggest that the low diastereoselectivity observed in the reduction of 2-alkyl-3-oxobutanoates (**1**) is due to the operation of plural dehydrogenases, *i.e.* some dehydrogenases produce the *syn*-product while the others contribute to produce the *anti*-product. Therefore, we may be able to control the diastereoselectivity by inhibiting or activating an appropriate dehydrogenase. We reported in a previous paper that a dehydrogenase is inhibited selectively by certain α,β-unsaturated carbonyl compounds.[9)] Based on the concept mentioned above, the effect of the addition of an α,β-unsaturated carbonyl compound on the diastereoselectivity of the reduction with bakers' yeast was studied. We believe that the method employing a microbe is superior to the use of an isolated enzyme, if the enantio- or diastereoselectivity is satisfactory, because the former does no require the supply of the coenzyme.



1 *Syn*-**2** *Anti*-**2**

The bakers' yeast was preincubated for one hour in the presence of an appropriate concentration of methyl vinyl ketone, then a substrate was added to the reduction system. The diastereomer ratio was determined by gas chromatography.[10] The results are shown in Table 1. It is obvious that the reduction with the procedure mentioned above provides the corresponding ethyl (2*R*,3*S*)-*syn*-2-alkyl-3-hydroxybutanoates (**2**) in a satisfactory stereoselectivity. It is obvious that the present method is quite useful in obtaining the L-*syn*-hydroxy ester.

The reaction is retarded by increased concentrations of methyl vinyl ketone, though the diastereoselectivity increases. This phenomenon indicates that methyl vinyl ketone acts as an inhibitor of the dehydrogenase which affords the L-*anti*-hydroxy ester. Detailed mechanism for the stereochemical control is now investigated in our laboratories.

Acknowledgment. This work was supported by the Ministry of Education, Japan under the Grants Nos. 01470022 and 01303007.

Table 1. Reduction of Ethyl 2-Alkyl-3-oxobutanoate **1** with Bakers' Yeast

Substrate **1** R	Additive	mM	**2** *Syn/Anti*	Conversion %
Me	None		87 / 13	99
	MVK	83	96 / 4	96
Et	None		66 / 34	99
	MVK	50	70 / 30	99
		67	81 / 19	96
		83	86 / 14	95
		100	84 / 16	93
Pr	None		74 / 26	99
	MVK	83	85 / 15	98
Propargyl	None		66 / 34	97
	MVK	83	91 / 9	92
Allyl	None		30 / 70	99
	MVK	83	84 / 16	97

Conditions: Dry Bakers' Yeast 20 g, Water 60 ml, Substrate 1 mmol

References and Footnotes

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(Received in Japan 12 April 1990)