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DIASTEREO- AND ENANTIO-SELECTIVE REDUCTION OF 2-METHYL-3-OXOBUTANOATE BY BAKERS' YEAST[1)]

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Reduction of octyl 2-methyl-3-oxobutanoate by bakers' yeast gave the corresponding (2*R*,3*S*)-*syn*-hydroxy ester diastereo- and enantio-selectively.

We wish to report here that (2*R*,3*S*)-*syn*-hydroxybutanoate can be prepared diastereo- and enantio-selectively by using bakers' yeast. The esters of optically active 3-hydroxy-2-methylbutanoic acid (1) have become important building blocks in the synthesis of antibiotics and natural products.[2)] Among many methods for preparing 1, reduction of 2-methyl-3-oxobutanoates (2) into the corresponding hydroxy esters with the help of bakers' yeast is expected to be a good method because bakers' yeast is an unexpensive and readily available "reagent".[3)]

Since the C-2 position of 2 is a chiral center, selection of configuration on this position may also be exerted during the microbial reduction and it is expected that the reduction will afford only one particular diastereo-isomer out of four possible stereo-isomers of the 3-hydroxy ester, if the complete selection is attained.[4)]

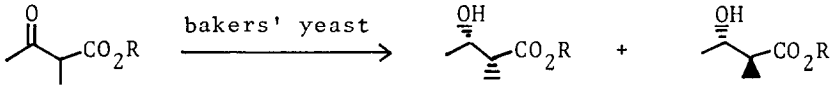
Various alkyl 2-methyl-3-oxobutanoates (2a-f) were subjected to the reduction by bakers' yeast.[5)] The reaction was run to 100% conversion in every case and the results are summarized in Table 1. In contrast to moderate ratios from the methyl, ethyl, and other esters, a high *syn/anti* ratio (95/5) was obtained in the reduction of the octyl ester (2f). That is, the reduction proceeds diastereo-selectively. To determin the diastereomeric composition of 1f, the produced octyl 3-hydroxy-2-methylbutanoate was converted into the corresponding methyl ester[6)] and the NMR spectrum of its MTPA ester[7)] was compared with those of the authentic samples prepared by methylation of racemic and (*S*)-methyl 3-hydroxybutanoates.[3b)] The ratio of (2*R*,3*S*):(2*S*,3*R*):(2*S*,3*S*):(2*R*,3*R*) was found to be 95: <1: 5: <1. One enantiomer was obtained selectively as expected. Although the precise mechenism of the stereochemical control observed in this reduction is not clear now, it is obvious that the present method is useful to the synthesis of chiral *syn*-3-hydroxy-2-methylbutanoate which is an important chiral synthon in organic synthesis.

The reduction of octyl 2-methyl-3-oxobutanoate (2f) is as follows; to a suspension of bakers' yeast (100 g) in 125 ml of water, 1.14 g (5 mmol) of the substrate was added and the suspension was stirred at 30 °C. Glucose (2.5 g

x 6 portions) was added at each 6 h. After 2 days, ethyl acetate and then Celite (Hyflo Super-Cel) were added to the suspension and the mixture was filtered. The Celite layer was washed with ethyl acetate for 3 times. The combined ethyl acetate layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The *syn/anti* ratio was measured by NMR spectroscopy. The residue was subjected to a column chromatography on silica gel using hexane-ethyl acetate (9:1) as an eluent, giving 0.93 g (82%) of octyl 3-hydroxy-2-methylbutanoate, $[\alpha]_D^{24}$ +3.33 (c 3.00, $CHCl_3$). Other esters were reacted and analyzed similarly.

The improvement of diastereoselectivity via structual modification of ester group in a β-keto ester is documented here for the first time, while that of enantioselectivity has been documented.[8)]

Table 1. Reduction of 2 by bakers' yeast.



2 *syn*-1 *anti*-1

	R	Yield	*syn/anti*		R	Yield	*syn/anti*
a	CH_3	71	81/19	b	C_2H_5	75	83/17
c	$C(CH_3)_3$	40	55/45	d	n-C_5H_{11}	70	84/16
e	$CH_2CH(CH_3)_2$	56	83/17	f	n-C_8H_{17}	82	95/ 5

References

1. Stereochemical control in microbial reduction. part 3.
2. (a) T. Oishi and T. Nakata, *Acc. Chem. Res.*, 17, 338 (1984); (b) S. Masamune and W. Choy, *Aldrichimica Acta*, 15, 47 (1982).
3. Reduction of 2 by bakers' yeast: (a) benzyl ester; H. Akita, A. Furuichi, H. Koshiji, K. Horikoshi, and T. Oishi, *Chem. Pherm. Bull.*, 31, 4376 (1983): (b) ethyl ester; G. Fräter, U. Muller, and W. Gunther, *Tetrahedron*, 40, 1269 (1984): (c) ethyl ester; R.W. Hoffman, W. Ladner, K. Steinback, W. Massa, R. Schmidt, and G. Snatzke, *Chem. Ber.*, 114, 2786 (1981).
4. B. S. Doel, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, 29,2459 (1976).
5. Bakers' yeast was purchased from Oriental Yeast Co., Ltd.
6. Octyl ester was converted into the corresponding acid and then to the methyl ester; see ref. 3b.
7. J.A. Dale, D.L. Dull, and H.S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).
8 M. Hirama, M. Shimizu, and M. Iwashita, *J. Chem. Soc., Chem. Commun.*, 599 (1983): (b) B. Zhou, A.G. Gopalan, F. VanMiddlesworth, W. Shieh, and C.J. Sih, *J. Am. Chem. Soc.*, 105, 5929 (1983).

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