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Highly Enantio- and Diastereoselective Reduction of 2-Methyl-3-oxoalkanoic Acids by Use of Fermenting Bakers' Yeast

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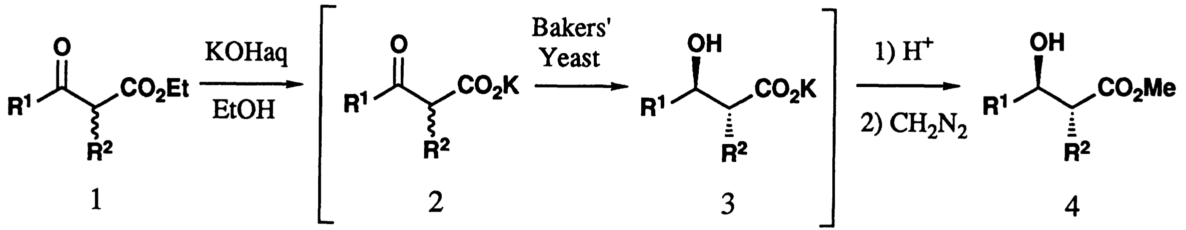
Reduction of 2-methyl-3-oxoalkanoic acids, $RC(=O)CH(CH_3)CO_2H$ ($R=n\text{-}C_4H_9$ - $n\text{-}C_8H_{17}$), gave the corresponding (2R,3R)-anti-3-hydroxy-2-methylalkanoic acids by use of bakers' yeast with >98% ee and >98% de.

Highly enantio- and diastereoselective preparation of α-alkyl β-hydroxy esters by the microbial reduction of the corresponding α-alkyl β-oxo esters have attracted interest because of the usefulness for the chiral building blocks and the efficiency to produce two chiral centers in one step.[1-5] However, the diastereoselectivities of the reduced products were generally not high, although the optical purities were sometimes satisfactorily very high. Recently Ohno and co-workers[1] have reported that the syn/anti ratio was increased to 96/4 by use of 2,2-dimethylpropyl 2-methyl-3-oxobutanoate as substrate.

Herein we wish to report that 2-methyl-3-oxoalkanoic acids (**2**) as substrates have been reduced by bakers' yeast to optically pure (2R,3R)-anti-3-hydroxy-2-methylalkanoic acids as sole diastereomers.



Ethyl 2-methyl-3-oxoalkanoate[6](**1**, 2 mmol) was stirred in a mixture of EtOH (2 mL) and 1 M KOH (4 mL) overnight at room temperature. After the ethanol was evaporated, the residue was diluted with water (36 mL) and then added to a briskly fermenting bakers' yeast suspension[7] at 28-29 °C. After stirring for 24 h, fresh bakers' yeast (12 g) and water (36 mL) were added to the suspension. After additional 24 h, the mixture was adjusted to pH 2 and extracted by the usual method. The product was treated with CH_2N_2 to afford the methyl ester (**4**). The recovery of methyl 2-methyl-3-oxoalkanoate was detected by GLC. The results are shown in Table 1.

In order to determine the absolute configuration, **4c** was transformed to the MTPA ester, which was analyzed by use of ^{1}H NMR spectra[8] in comparison with anti-**4c** which was prepared from authentic methyl (R)-3-hydroxyoctanoate.[9,10]

Table 1. Bakers' Yeast Reduction of $R^1C(=O)CH(R^2)CO_2K$ (**2**)

	2		**4**					
	R^1	R^2	Yield/%[a)]	$[\alpha]_D^{23}$(c,$CHCl_3$)		% ee[b)]	% de[b)]	Confign
a	n-C_3H_7	CH_3	0 (60)	—	—	—	—	—
b	n-C_4H_9	CH_3	32 (8)	-6.0	(1.04)	>98	>98	2R,3R
c	n-C_5H_{11}	CH_3	63 (3)	-3.7	(2.03)	>98	>98	2R,3R
d	n-C_5H_{11}	C_2H_5	trace(50)	—	—	—	—	—
e	n-C_5H_{11}	n-C_3H_7	0 (31)	—	—	—	—	—
f	n-C_6H_{13}	CH_3	68 (0)	-2.9	(1.18)	>98	>98	2R,3R
g	n-C_8H_{17}	CH_3	28 (39)	-2.3	(1.28)	>98	>98	2R,3R
h	n-C_9H_{19}	CH_3	0 (79)	—	—	—	—	—

a) Isolated yields as methyl ester (**4**). Recoveries of methyl 2-alkyl-3-oxoalkanoates are given in parentheses. b) Determined by 100 MHz ^{1}H NMR with $Eu(hfc)_3$. See Ref.11.

Configurations of **4b**, **f**, and **g** were also assigned to be (2R,3R) by comparison of the optical rotation with that of **4c**.

To explain the highly enantio- and diastereoselective reduction, we assume that the carboxylate anion of the substrate (**2**) would be specifically bound to the catalytic site of the enzyme, and the reduction would occur only on the substrate having the (R)-2-methyl group which is compensated from (S)-2-methyl-substituted substrate through the keto-enol tautomerism.

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7) Fresh bakers' Yeast (Oriental Yeast Co.; 12 g), glucose (6 g), $MgSO_4$ (15 mg) in water (36 ml). The pH was adjusted to 5 by addition of KH_2PO_4. As the glucose was consumed, 48 g of glucose was added in eight 6 g portions.

8) δ3.53 (methoxy group) and δ3.64 (methyl ester) for (2R,3R)-anti-**4c**, and δ3.55 (methoxy group) and δ3.67 (methyl ester) for (2S,3R)-syn-**4c** in 500MHz ^{1}H NMR spectra.

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11) A diastereomeric mixture of racemic **4** has four singlets due to the ester methyl groups in the presence of 100 mol% (+)-$Eu(hfc)_3$.

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