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Stereochemical Control in Baker's Yeast Reduction 1.: Diastereoselective Reduction of Alkyl β-Keto-α-methylpentanoates with Three Different Forms of Baker's Yeasts

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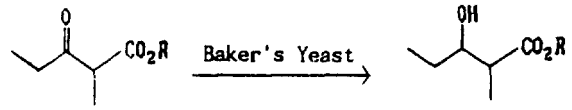
The stereoselective synthesis of α-substituted β-hydroxy ester has been studied in recent years because of its widespread applicability to biologically active substrate synthesis. A variety of chemical methods such as stereoaldol condensation[1] and reduction [$Zn(BH_4)_2$][2] have produced *syn* α-substituted β-hydroxy ester while the α-alkylation[3] of β-hydroxy ester has afforded *anti* ester. However, these methods require an optically active starting material in order to obtain the enantioselective product. Therefore, in order to directly prepare the chiral α-substituted β-hydroxy ester from an achiral starting material, α-substituted β-keto esters were chemically prepared and then reduced by means of certain microbes. Especially, baker's yeast (*Saccharomyces cerevisiae*) which is an inexpensive and facile microbe has frequently been used in the synthesis of valuable chiral building blocks.[4] But the baker's yeast reduction of alkyl β-keto-α-methylpentanoates (**1**) has not much been studied[5] compared with that of alkyl β-keto-α-methylbutanoates.[6] In this paper, we describe the results from the baker's yeasts reduction of **1a-h** using three different forms of baker's yeast, raw baker's yeast (RBY), dry baker's yeast (DBY), and immobilized baker's yeast (IMBY).[7]

In a typical procedure, to the suspension of RBY (30 g) and water (50 m*l*) was added sugar (4 g). The suspension was activated for 30 min, then substrate[8] (1 mmol in EtOH) was added. The reaction mixture was allowed to be stirred (180 rpm) at rt. Sugar (4 g) was added every 12 hrs. After 48 hrs, the mixture was stirred vigorously with Celite and EtOAc, then filtered. Filtrate and the Celite layer were extracted with EtOAc(×3). Combined organic layer was washed with water, sat. $NaHCO_3$ sol'n, and brine, dried (anhyd. $MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed with silica gel (cyclohexane : ether = 4 : 1) to yield β-hydroxy-α-methylpentanoates (**2**). The stereochemistry of **2a-h** were deduced by comparisons of their ^{13}C-NMR[9] and ^1H-NMR[10] data with those of racemic alkyl β-hydroxy-α-methylpentanoates (**3**) obtained by reduction with $NaBH_4$.[11] The stereochemical composition (*syn/anti* ratio) of the compound **2** were determined by GLC (HP-1, capillary column).[12]

Table 1. Reduction of Alkyl β-Keto-α-Methylpentanoates by Baker's Yeast

Substrate	Yeast	*syn/anti*[a]	Reduction ratio[d]
1a	RBY	2/97	24
	DBY[b]	7/93	12
	IMBY[c]	8/92	9
1b	RBY	5/95	32
	DBY	7/93	27
	IMBY	9/91	44
1c	RBY	3/97	50
	DBY	6/94	58
	IMBY	6/94	72
1d	RBY	2/98	444
	DBY	3/97	68
	IMBY	6/94	536
1e	RBY	4/96	220
	DBY	5/95	30
	IMBY	8/92	13
1f	RBY	9/91	32
	DBY	7/93	20
	IMBY	–	–
1g	RBY	11/89	22
	DBY	9/91	12
	IMBY	–	–
1h	RBY	12/88	17
	DBY	10/90	8
	IMBY	–	–

[a] Determined by GLC (HP-1, capillary column), the structures of *syn* and *anti* isomer were identified with ^{13}C-NMR[8] and ^1H-NMR (270 MHz).[9] [b] Substrate 1 mmol; DBY 15 g; H_2O 50 m*l*; sucrose 4 g per 12 hrs. [c] Substrate 1 mmol; IMBY made up of RBY 30 g, 1.5% sodium alginate sol'n (500 m*l*), 2% $CaCl_2$ sol'n. [d] Reduction ratio = $\frac{(\text{product} \times 100)}{\text{unreduced substrate}}$



1 *anti*-**2**

1a R = Methyl **1e** R = n-Pentyl
1b R = Ethyl **1f** R = n-Hexyl
1c R = n-Propyl **1g** R = n-Heptyl
1d R = n-Butyl **1h** R = n-Octyl

In the DBY reduction of alkyl β-keto-α-methylbutanoates, it was reported that octyl ester showed the highest diastereoselectivity of 95 : 5 *syn* predominance.[6a] However, as noted in Table 1, the RBY, DBY, and IMBY reduction of **1** showed the reverse diastereoselectivity of 2 : 98 *anti* predominance [compound **2d**, with 40% enantiomeric excess of (2R, 3R)-**2d**[13]]. Compounds **2a** and **2c** were also found to be reduced with high stereoselectivity but the reduction ratio was relatively poor and **2f-2h** were not reduced by IMBY.

It was deduced that the one extra methylene unit of alkyl β-keto-α-methylpentanoates as compared with the corresponding butanoates caused the reversal of diastereoselectivity from *syn* to *anti* predominance. And the increased bulkiness of the pentanoates made butyl ester **1d** the most favorable substrate in terms of diastereoselectivity and reduction ratio while in case of butanoates the octyl ester was reported to be the best.[6a]

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8. Alkyl β-keto-α-methylpentanoate (**1**) was prepared by self-condensation and transesterification. Esters of methyl (**1a**), ethyl (**1b**), propyl (**1c**), and butyl (**1d**) β-keto-α-methylpentanoate were prepared (63-80% yield) from the corresponding propionate by self-condensation (NaH). Pentyl to octyl β-keto-α-methylpentanoate (**1e-h**) were obtained by transesterification of **1b** and corresponding alcohols under acid catalysis with yield of 60-80%.
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11. The ^{13}C-NMR and ^{1}H-NMR data of **3b** and **2b** are described as representive examples. **2b** (major): ^{13}C-NMR δ 74.8 (carbinol), 45.2 (methine), 14.3 (methyl) ppm; ^{1}H-NMR δ 3.6 (m, C-3 H), 4.0 (dp, methylene of alkoxy) ppm. **3b** (*anti*): ^{13}C-NMR δ 74.7, 45.4, 14.3 ppm; ^{1}H-NMR δ 3.6 (m), 4.0 (dq) ppm. **3b** (*syn*): ^{13}C-NMR δ 73.6, 44.8, 10.3 ppm; ^{1}H-NMR δ 3.8 (m), 4.0 (dq) ppm.
12. The GLC conditions: HP-1, 25 m×0.2 mmI.D.×0.11 μm, N_2 0.55 ml/min, injector 280℃, FID 300℃, split 30 : 1, 60℃ (2 min), to 280℃ (5℃/min).
13. To determine the absolute configuration and enantiomeric excess of **2d**, 5-hydroxy-4-methyl-3-heptanone was synthesized form **2d**. The enantiomeric excess of the **2d** was determined by measuring the optical rotation of 5-hydroxy-4-methyl-3-heptanone and the subsequent GLC (DB1701, capillary column) analysis of the corresponding MTPA ester.

Fourier Transform Raman Spectroscopic Investigation of Silver ion-Flavin Mononucleotide Complexation

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The excitation using near-infrared laser, CW Nd : YAG 1064 nm has been of great interest recently for photolabile and highly fluorescent compounds in Fourier transform Raman spectroscopy.[1] Resonance Raman, surface enhanced Raman, coherent Raman and infrared spectroscopy have been applied to study fluorescent free flavins and flavoproteins.[2] Metal ion bound flavins, such Ag(I) and Ru(II), were studied by resonance Raman spectroscopy as possible models for metal-flavin interactions in biological environments.[3] These metal ions are known to form 1 : 1 complex with flavin chromophores.[3b] Resonance Raman spectroscopic studies of free flavins, flavins embedded in flavoproteins, and metal ion bound flavins bear rather limited molecular informations partly because of the resonance phenomena of exciting light source with flavin chromophores. However, near-infrared laser excitation far from absorption region generates well-defined vibrational Raman spectra under non-resonant conditions.[4] The photodecomposition of sample compounds sensitive to visible light can be almost avoided using near-infrared light source. These conditions have been applied to free flavins and adsorbed flavins on the silver metal surface sucessfully.[1b]

Metal ion interactions with flavin chromophores have been extensively investigated for the electron transfer mechanism of flavoproteins through various redox and ionization states of flavins. Ag^+ ion compelx with flavins show a new band at 530 nm in the electronic absorption spectrum. The structure of 1 : 1 Ag^+-flavin complex was proposed that Ag^+ ion binds through coordinations at N_5 and the carbonyl oxygen of C_4=O to form the inner sphere complex.[3b] The secondary binding site at N_1 and the carbonyl oxygen of C_2=O was implied through X-ray structure study.[5]

In this paper we report Fourier transform Raman spectra by CW 1064 nm excitation of flavin mononucleotide (FMN) (Figure 1a), and 1 : 1 Ag^+-FMN complex (Figure 1b) in each powder form. FT-Raman spectrum of FMN is quite similar to that of riboflavin[1b] except the stretching region of C_2=O and C_4=O in flavin ring III. In that of FMN there are a broad band at 1655 cm^{-1} and a band at 1704 cm^{-1} due to carbonyl stretching modes. Lumiflavin are well studied th-