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Regio- and Enantioselective Synthesis of (*S*)-1-Acetoxy-2-hydroxy-4-alkanones by Use of Bakers' Yeast Reduction of 1-Acetoxy-2,4-alkanediones

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Abstract: Using bakers' yeast, 1-acetoxy-2,4-alkanediones were regio- and enantioselectivly reduced to trifunctional optically active (*S*)-1-acetoxy-2-hydroxy-4-alkanones with 82~97% ee in 42~57% yield.

In previous papers, we have reported highly enantioselective reductions of 1-acetoxy-2-alkanones by use of bakers' yeast whole cells[1] or its cell-free extract,[2] in which the reduction of the ketones proceeded to give the (*S*)-alcohol with 95~ >99% ee (eq.1). The role of the α-acetoxy group seems to direct the stereochemistry of reduction toward the *S* configuration, as compared with the *R*-directing α-hydroxy group in the bakers' yeast reduction of 1-hydroxy-2-alkanones[3] (eq.2).

Herein we report a novel and convenient asymmetric reduction of 1-acetoxy-2,4-alkanediones (**1**) by use of bakers' yeast, demonstrating the *S*-directing effect of the α-acetoxy group and the regioselectivity in the reduction of 2,4-dione leading to useful trifunctional chiral γ-acetoxy β-hydroxy ketones (**2**)[4] with high enantioselectivity.

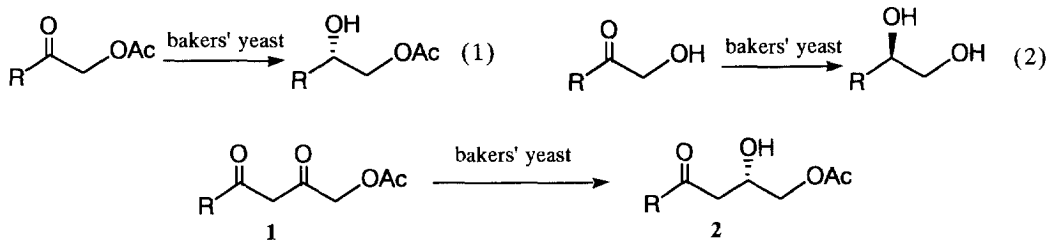


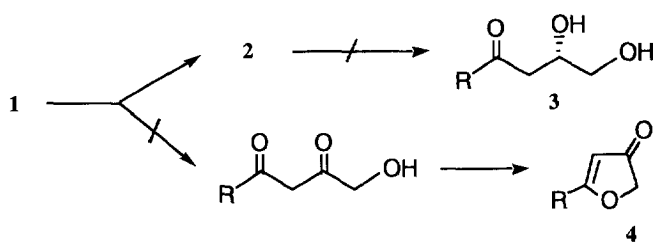
Table 1. Asymmetric Reduction of **1** to **2** with Bakers' Yeast

R	time (h)	% yield	% ee	$[\alpha]_D$(c,$CHCl_3$)		*R* / *S*
CH_3	4	42	82		-8.86 (2.19,THF)	*S*
C_2H_5	4	57	90	-8.06 (2.03)	-2.54 (2.12,THF)	*S*
n-C_3H_7	4	48	89	-21.1 (2.23)		*S*
n-C_4H_9	4	49 (16)[a]	97	-14.7 (2.15)		*S*
n-C_5H_{11}	4	43 (16)[a]	95	-10.4 (2.45)		*S*

[a] % recovery for **1**.

Typically, the substrate **1** (1 mmol)[5] was added to a mixture of dry bakers' yeast (3.5 g) and glucose (5 g) in water (75 mL) at 30 °C with stirring. After 2 h, glucose (3 g) was added and the stirring was continued further for 2 h. The mixture was stirred with Hyflo supercel (7 g) and filtered. The filtrate was extracted with ethyl acetate. The crude product **2** was purified through a silica gel column. The % ee was determined by using 500-MHz ^{1}H NMR spectra of MTPA ester of **2**. To establish the configuration, the acetate **2** was hydrolyzed with aqueous KOH-THF solution to 1,2-diol and converted to acetonide. The $[\alpha]_D$ value was compared with that of the authentic sample derived from (*S*)-malic acid.[4a]

Results are shown in Table 1. Few features of the reaction are worthy of remark in comparison with the results for 1-acetoxy-2-alkanones as substrate.[1] (1) Owing to the presence of the oxo substituent at C(4), the enantioselectivity or the effect of the *S*-directing acetoxy group is somewhat diminished depending upon the carbon chain length. (2) Hydrolysis of the acetoxy group, observed for 1-acetoxy-2-alkanones as substrates to the extent of 26~34%, disappeared fortunately, otherwise which would produce byproducts 1,2-diol **3** and/or furanone **4**.



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References and Notes

1. Utaka, M.; Sakai, T.; Tsuboi, S. *J. Synth. Org. Chem., Jpn.* **1991**, *7*, 647~656. For $RCOCH_2OAc \rightarrow$ (*S*)-$RCHOHCH_2OAc$ + (*S*)-$RCHOHCH_2OH$, the % yield and % ee for the α-acetoxy alcohols were as follows: R=n-C_3H_7, 55, 98; R=n-C_4H_9, 49, 95; R=n-C_5H_{11}, 51, 99; R=n-C_6H_{13}, 65, >99; R=n-C_7H_{15}, 53, >99, For the diols: R=n-C_3H_7, 26, 72; R=n-C_4H_9, 34, 73; R=n-C_5H_{11}, 31, 87; R=n-C_6H_{13}, 23, 89; R=n-C_7H_{15}, 26, 82.
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3. Levene, P. A.; Walti, A. *Org. Synth., Coll. Vol. II* **1943**, 545~547. Barry, J.; Kagan, H. S. *Synthesis* **1981**, 453~454.
4. a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419~5422. b) Kim. B.H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557~2560.
5. Prepared by reduction of 5-acetoxymethyl-3-alkylisoxazoles and hydrolysis of the resulting imino group. The isoxazoles were obtained by 1,3-dipolar cycloaddition of nitrile oxides to propargyl acetate.

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