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ENANTIOSPECIFIC SYNTHESIS OF OPTICALLY PURE (3S)-HYDROXY ESTERS BY THE STEREOCONTROLLED YEAST REDUCTION OF α-SULFENYL-β-KETOESTERS

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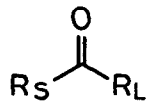
Summary: *Stereocontrol in Baker's yeast reduction of β-ketoesters was successfully achieved by introducing the sulfenyl group at α-position of the esters to afford optically pure (S)-β-hydroxy esters.*

Microbial-mediated reaction of synthetic substrates is one of the useful methods for the preparation of chiral intermediates in synthetic chemistry. The microorganism most popular and frequently used for this purpose is the Baker's yeast *(Saccharomyces cerevisiae)*.[1] Reduction of β-ketoesters with the Baker's yeast produces 3-hydroxy carboxylic acid derivatives, which are especially useful building brocks for the natural product synthesis.[1] Ethyl (*S*)-3-hydroxybutylate (4; R^1 = Me, R^3 = Et) thus obtained from ethyl 3-oxobutanoate has high optical purity in a range of 70 ∿ 97%ee.[2] While ethyl 3-oxobutanoate is reduced to *S* isomer, ethyl 3-oxopentanoate[3] and ethyl 5-benzyloxy-3-oxopentanoate[4] are preferentially converted into *R* isomer of the corresponding alcohols with low optical purities (∿ 40%ee). It is generally assumed that the stereoselectivity of the yeast reduction of acyclic ketones may be predicted by the Prelog's rule.[5] Depending upon the relative size of the groups R_S and R_L, which is recognized by the oxidoreductase in the yeast, reduction may occur from Re-face (see 1 → 2). Consequently, if the carboxylic group of β-ketoesters could be recognized as the R_L group by the reductase, by introducing a certain functional group at α-position of the esters, (*S*)-β-hydroxyesters could be obtained. We now report here that the Baker's yeast reduction of β-ketoesters is strongly influenced by the introduction of



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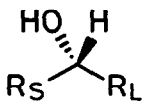

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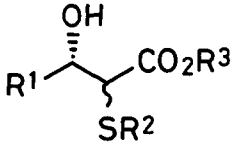

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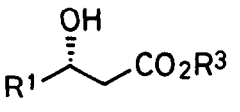

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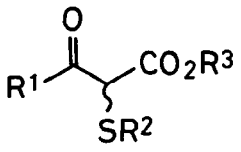
Table I. Results of the Baker's Yeast Reduction of α-Sulfenylated β-Ketoesters (5)

α-Sulfenylated β-Ketoesters R^1	R^2	R^3	Chemical Yield[a](%)	(*threo*:*erythro*)[b]	*threo*-3 $[\alpha]_D$[c]	%ee[d]	*erythro*-3 $[\alpha]_D$[c]	%ee[d]
CH_3	CH_3	CH_3	72	(72:28)	+101°	>96	-77°	>96
CH_3	CH_3	Et	62	(59:41)	+86°	>96	-69°	>96
CH_3	CH_3	*t*-Bu	75	(41:59)	+64°	>96	-72°	>96
CH_3	Ph	CH_3	40	(83:17)	+178°	>96	-133°	>96
CH_3	Ph	Et	49	(73:27)	+179°	>96	-131°	>96
CH_3CH_2	CH_3	Et	44	(47:53)	+69°	>96	-65°	>96
$PhCH_2OCH_2CH_2$	CH_3	Et	30	(32:68)	+24°	>96	-34°	>96

[a] All products were isolated by silica-gel TLC and identified by IR and NMR spectra. [b] Determined by isolated yields. [c] All specific rotations were measured in $CHCl_3$ (C ca. 1). [d] No (*R*)-enantiomer could be detected by NMR. A control experiment established a practical limit for the detection of 4% of diastereo isomer by the ^1H NMR spectrum of JOEL JNM-PMX 60 si spectrometer. All *S* configurations at C_3 were confirmed by the comparison with reported values of the specific rotations of desulfenated 3-hydroxy esters.

sulfenyl substituent[6] at α-position, and that the stereoselectivity is dramatically improved to produce (3*S*)-isomer (3) with high optical purity (>96%ee). α-Sulfenyl-β-hydroxyesters (3) can be then smoothly desulfenylated, and converted to the optically pure *S* isomer of β-hydroxyesters (4).

A typical procedure of the Baker's yeast reduction is described as follows: A suspension of 160 ml of water, 11 g of D-glucose and 10 g of Baker's yeast (Oriental yeast Co.), was stirred for 30 min at room temperature (23 °C), then 10 ml of ethanol solution of ethyl 2-methylthio-3-oxobutylate (5; R^1 = R^2 = Me, R^3 = Et) (2.0 mmol) was added to the suspension. The reaction was monitored by silica-gel TLC analysis for the disappearance of the starting ketoester. After the ketoester faded (about 2 days), ca. 15 g of celite and 50 ml of ether was added, and the mixture was stirred for 30 min, then was filtered through a celite pad. The filtrate was extracted with ethyl acetate and was evaporated in vacuo. The product of α-sulfenyl-β-hydroxyester (3) consisted of *threo* and *erythro*[8] isomers, which could be easily separated into each pure isomers by TLC on silica gel. These two isomers were clearly distingished by those ^1H NMR data.[9] The optical purity of each isomer of 3 was determined by ^1H NMR using chiral shift reagent, Eu(hfc)$_3$.



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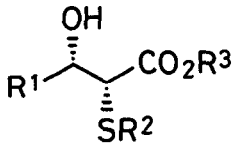
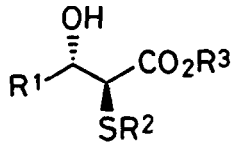


3 (threo)

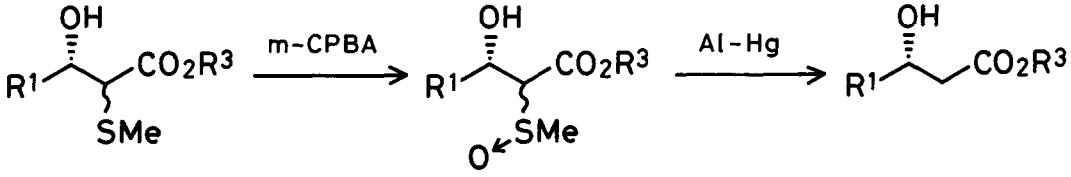


3 (erythro)

Table I summerizes the results obtained by the Baker's yeast reduction of α-sulfenyl β-ketoesters. Although it gives both *threo* and *erythro* isomers, it should be noted that complete *S* configuration in the 3 position with hydroxy group of both *threo* and *erythro* α-sulfenyl-β-hydroxyesters was confirmed in all cases. Even the reduction of 2-methylthio-3-oxopentanoate and 2-methylthio-5-benzyloxy-3-oxopentanoate gave only *S* alcohols with very high optical purity. All these results shows that the sulfenyl functional group at α-position of β-ketoester could control the stereospecificity of reductase in the yeast. 3-Oxobutanoate with the methylthio group at the 2 position was reduced in better yield than the 2-phenylthio-3-oxobutanoate. On the other hand, *t*-butylester of α-phenylthio-3-oxobutanoate could not give the corresponding alcohols, but it slowly decomposed under this fermenting conditions.

The desulfenylation of α-sulfenylated β-hydroxyesters was next examined, which was successfully achieved by the two step procedure. α-Methylthio-β-hydroxyester (3; R^2 = Me) was oxidized to the corresponding sulfoxide 6 with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at -78 °C. The sulfoxide 6, without any purification, was then converted into β-hydroxyester (4) by the reductive removal of α-sulfinyl group using aluminum amalgam according to the method of Corey *et al.*[10] Both *threo* and *erythro* isomers of 3 (R^1 = CH_3, R^3 = *t*-Bu) gave 4 (R^1 = CH_3, R^3 = *t*-Bu) which have entirely same value of the specific rotation.[11] The results of the desulfenylation of α-sulfenylated β-hydroxyesters were shown in Table II. From the value of the specific rotation of the β-hydroxyesters, it can be confirmed that all these β-hydroxyesters have *S* configuration of the hydroxy group of 3-carbon.

Although numerous efforts[2,12,13] have been paid to find useful species of microorganisms, which have the ability to produce useful products, by screening



3 6 4

Table II. Yield and Optical Rotation of β-Hydroxyesters (4) obtained by Desulfenylation of α-Sulfenyl-β-hydroxyesters (3)[a]

R^1	R^3	Yield(%)[b]	$[\alpha]_D$ in $CHCl_3$	
CH_3	Et	44	+43.6° (c 0.990)	lit.[2] $[\alpha]_D^{23}$ +42.7° (100%ee)
CH_3	*t*-Bu	56	+26.3° (c 1.64)	
CH_3CH_2	Et	52	+33.1° (c 0.875)	lit.[13] $[\alpha]_D^{23}$ +28° (84%ee)
$PhCH_2OCH_2CH_2$	Et	39	+13.5° (c 0.960)	

[a] The results were obtained from the mixtures of *threo* and *erythro* isomers. [b] Over all yield (3 → 4). All products were isolated by silica-gel TLC and distillation (Kugelrohr).

them, there have been a few trial[14] to improve the stereochemistry of easily available Baker's yeast reduction by modifing the substrate as described here. Thus we could show that the control of the stereochemistry in enzymatic reduction is effective by the introduction of sulfenyl group to the substrate, and that the sulfenyl substituent plays an important role in enantiospecific reduction with Baker's yeast. Studies on the synthetic application and development of this stereocontrolled reduction with easily available Baker's yeast are in progress.[15]

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