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Ethyl (*R*)-3-Hydroxy-4-phenylthiobutyrate: Synthesis by the Bakers' Yeast Reduction and Use as a Precursor of Enantiomerically Pure β-Lactam

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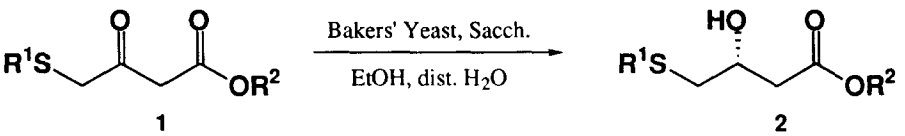
Abstract: The bakers' yeast reduction of ethyl 3-oxo-4-phenylthiobutanoate gave ethyl (*R*)-3-hydroxy-4-phenylthiobutanoate with >99%ee. The resultant enantiomerically pure alcohol was easily transformed into β-lactam without loss of its enatiomeric purity *via* the oxamate derivative.

The esters of homochiral 3-hydroxybutyric acid have been reported to be important building-blocks in the synthesis of antibiotics and natural products.[1] Among the strategies developed for the preparation of the ester derivatives, the bakers' yeast reduction of the corresponding β-ketoesters is one of the most useful methods, because bakers' yeast is an inexpensive and readily available reducing agent.[2] However, the bakers' yeast reduction has two major drawbacks; substrate specificity and stereospecificity. We have already reported that the introduction of a sulfur atom into the substrate improved the enantioselectivity in the bakers' yeast reduction of carbonyl compounds.[3] Moreover, it gave dramatic effects on the stereospecificity and the reaction rate in the bakers' yeast reduction. For example, it has been reported that the bakers' yeast reduction of ethyl 3-oxobutanoate gave ethyl (*S*)-3-hydroxybutanoate with ca. 90%ee,[4] while that of the 2-sulfenyl derivatives improved the enantioselectivity up to >96%ee.[3a] The bakers' yeast reduction of methyl 4-phenylsulfonyl-3-oxobutanoate effected the formation of the stereoisomer possessing the opposite absolute configuration with 98%ee.[5] On the other hand, reduction of methyl ester of 3-oxo-4-sulfenylbutanoic acid using bakers' yeast has been reported to give the reduced product with 50 - 73%ee.[6] Now we wish to report the preparation of (*R*)-3-hydroxy-4-sulfenyl substituted butyric ester derivatives **2** by the bakers' yeast reduction for the synthesis of enantiomerically pure β-lactam.



1 **2**

R^1 = Me, Bn, Ph, *m*-Tol, *o*-Tol, *p*-MeOPh
R^2 = Et, *n*Bu

Table1. Reduction of 4-sulfenylacetoacetate 1 with bakers' yeast.

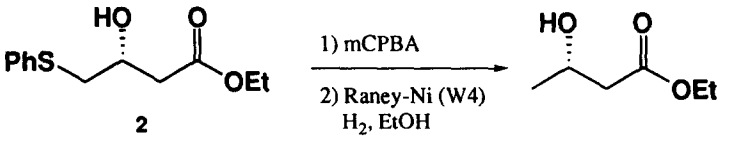
Entry	R^1	R^2	Reaction Time(h)	Yield(%)[a]	%ee [b]
1	Me	Et	11	47	26
2	Bn	Et	4.5	85	45
3	Bn	*n*Bu	26	70	72
4	Ph	Et	13	63	>99[c]
5	*m*-Tol	Et	2.5	72	63
6	*o*-Tol	Et	5	68	5
7	*p*-MeOPh	Et	13	64	56

[a]Isolated yield. [b]Determined by HPLC (Hibar column, Merck) analysis of the corresponding (-)-MTPA ester derivative. [c]Determined by GLC (Chiraldex G-TA, 20m, 140°C).

4-Sulfenyl substituted acetoacetic ester derivatives **1** as substrate were prepared from ethyl 3-oxo-4-chlorobutanoate and the thiol, and *n*-butyl ester was synthesized by ester exchange reaction from the corresponding ethyl ester. In a typical procedure of the bakers' yeast reduction, a suspension of 42 g of dry bakers' yeast (S. I. Lesaffre) and 50.4 g of saccharose in 420 ml of dist. H_2O was stirred for 0.5 h at 30 °C for prefermentation. To the resulting suspension was added an ethanol (42 ml) solution of ethyl 3-oxo-4-phenylthiobutanoate (8.4 mmol). After 13 h, Celite and ethyl acetate were added to the reaction mixture, and the whole mixture was stirred for 0.5 h. The resulting mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (100 ml x 5). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (a 4:1 mixture of hexane and ethyl acetate was used as the eluent) followed by distillation (140 °C/2mmHg, bulb to bulb) to give pure ethyl (*R*)-3-hydroxy-4-phenylthiobutanoate as an oil (63% yield, >99%ee).[7]

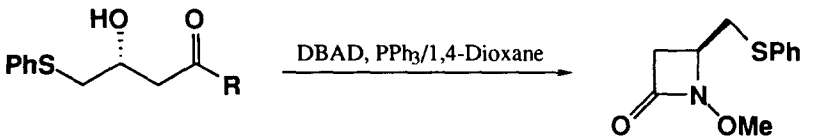
The results of bakers' yeast reduction of various 4-sulfenylacetoacetic ester derivatives **1** are summarized in Table 1. Ethyl 4-methylthio-3-oxobutanoate was reduced with low enantioselectivity (entry 1), although the reduction of ethyl 2-methylthio-3-oxobutanoate gave the corresponding alcohol with high enantioselectivity.[3] The reduction of ethyl 4-benzylthio-3-oxobutanoate afforded ethyl (*R*)-4-benzylthio-3-hydroxybutanoate in 85% yield with 45%ee (entry 2). Replacement of the alcohol part of the ester with an *n*-butyl group enhanced the enantiomeric excess up to 72%ee (entry 3). The use of ethyl ester derivative of 3-oxo-4-phenylthiobutanoic acid as substrate gave the best result, in which the reduction proceeded smoothly to give enantiomerically pure ethyl (*R*)-3-hydroxy-4-phenylthiobutanoate in 63% yield (entry 4). On the other hand, substitution of the aromatic ring with a methyl group accelerated the reaction. Especially, a substituent at the *meta*-position enhanced the reactivity, and the starting material was completely consumed after 2.5 h, albeit the enantioselectivity was moderate (entry 5). Although at present the effect of the substituent with a sulfenyl group is not clear, the sulfur atom or aromatic ring would interact with the active site of reductase. Even a substitution with an *o*-tolylthio group, a sterically bulky substituent, accelerated the reduction.

The absolute configuration of ethyl 3-hydroxy-4-phenylthiobutanoate **2** thus obtained was established to be *R* by its derivatization to the known ethyl 3-hydroxybutanoate[4] in the following manner; oxidation to the corresponding sulfoxide with mCPBA in 85% yield, followed by desulfinylation in the presence of Raney-Ni (W4) under a hydrogen atmosphere in 68% yield.



$[\alpha]_D^{23}$+40 (c 0.9, $CHCl_3$)

β-Lactam antibiotics have received considerable attention due to their high antibacterial activity and broad therapeutic spectrum.[8] The β-lactam **4** which would be derived from the enantiomerically pure alcohol **2** has no substituent at the 3-position of the β-lactam ring. 3-Unsubstituted β-lactams are useful precursors, because other necessary substituents can be introduced into the 3-position with trans geometry.[8c, 9] Moreover, the conversion of the phenylthiomethyl group of the 4-position of β-lactam **4** into other useful functional groups such as alcohols, aldehydes, and so on would be feasible. Thus derivatization of enantiomerically pure ethyl (*R*)-3-hydroxy-4-phenyltiobutanoate **2** to β-lactam **4** was next investigated. The transformation of β-hydroxy ester to β-lactam has already been extensively studied. For instance, β-hydroxy ester was reported to be transformed into β-lactam *via* oxamate, mesylate, then cyclization.[10] The alcohol **2** was treated with 5 eq of aluminum amide[11] of *O*-methylhydroxylamine hydrochloride in benzene at 0 °C to give the corresponding oxamate **3** in 55% yield.[12] The enantiomeric purity of oxamate **3** was determined to be >99%ee by HPLC analysis (Hibar column, Merck) of the corresponding (-)-MTPA ester. However, transformation of the enantiomerically pure oxamate **3** into the mesylate derivative gave only a dehydration product. Mitsunobu reaction[13] as an alternative method for cyclyzation of oxamate **3** to β-lactam **4** was conducted by the use of diethyl azodicarboxylate and triphenylphosphine. However, a complex mixture including the dehydration product and the amination product with diethoxycarbonylhydrazine was obtained. Fortunately, the use of bulky di-*t*-butyl azodicarboxylate (DBAD) gave the desired cyclyzed product exclusively. Namely, cyclization of the oxamate **3** to the β-lactam compound **4** was carried out with 1.1 eq of DBAD and 1.1 eq of triphenylphosphine in 1,4-dioxane at 0 °C to give the β-lactam **4** in 72% yield without loss of its stereochemical integrity, as determined by GLC analysis (Chiraldex G-TA, 20m, 140°C).[14]



2 : R = OEt
3 : R = NHOMe

Y. 55% $[\alpha]_D^{23}$+18 (c 0.2, $CHCl_3$) Y.72% $[\alpha]_D^{23}$-38 (c 0.2, $CHCl_3$)

In summary, enantiomerically pure ethyl (*R*)-3-hydroxy-4-phenylthiobutanoate **2** was obtained by asymmetric reduction with readily available bakers' yeast. The homochiral alcohol **2** was transformed into β-lactam compound **4** in enantiomerically pure form by a simple method in two steps, demonstrating the synthetic usefulness of the bakers' yeast reduction of 4-sulfenyl substituted 3-oxobutanoate.

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7. ^{1}H NMR ($CDCl_3$, 270MHz) δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.56 (dd, *J* = 7.9, 16.5 Hz, 1H), 2.67 (dd, *J* = 4.5, 16.5 Hz, 1H), 3.01 (bs, 1H), 3.06-3.09 (m, 2H), 4.09-4.20 (m, 3H), 7.18-7.41 (m, 5H). IR (neat) 3400, 2950, 1740, 1500, 1200, 1038, 740, 695 cm^{-1}. $[\alpha]_D^{23}$ +5.7(c 1.0, $CHCl_3$).
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12. ^{1}H NMR ($CDCl_3$, 270MHz) δ 2.25-2.47 (m, 2H), 3.05 (d, *J* = 5.6 Hz, 2H), 3.53-3.76 (br, 2H), 3.71 (s, 3H), 4.10 (br, 1H), 7.18-7.37 (m, 5H). IR ($CHCl_3$) 3350, 3000, 2940, 1680, 1480, 1460, 1090 cm^{-1}. $[\alpha]_D^{23}$ +18 (c 0.20, $CHCl_3$).
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14. ^{1}H NMR ($CDCl_3$, 270MHz) δ 2.42 (dd, *J* = 2.5, 13.9 Hz, 1H), 2.78 (dd, *J* = 5.3, 13.9 Hz, 1H), 3.09 (dd, *J* = 7.4, 13.7 Hz, 1H), 3.34 (dd, *J*= 4.8, 13.7 Hz, 1H), 3.80 (s, 3H), 4.00-4.06 (m, 1H), 7.25-7.44 (m, 5H). IR (neat) 2920,1765, 1580, 1480, 1438, 1440, 740, 690 cm^{-1}. $[\alpha]_D^{23}$ -38 (c 0.2, $CHCl_3$). Chiraldex G-TA, φ 0.25 mm x 20 m, Carrier gas: He 30 ml/min. Temp: 140 °C, Inlet pressure: 0.75 Kg/cm^2, Detection: FID; $Rt_{(S)}$ = 264.0 min., $Rt_{(R)}$ = 276.1 min. Only a single peak was detected at 264.0 min.

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