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STEREOCONTROL BY INTRODUCTION OF A SULFUR FUNCTIONAL GROUP IN THE ASYMMETRIC REDUCTION OF β-KETOESTERS WITH BAKER'S YEAST: PREPARATION OF OPTICALLY PURE 3S-HYDROXYDITHIOESTERS AS A NEW CHIRAL SYNTHON OF NATURAL PRODUCT SYNTHESIS

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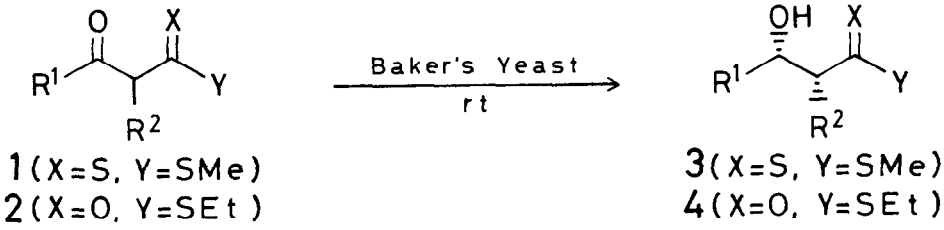
Summary: *Asymmetric reduction of β-ketothioester derivatives with baker's yeast produced the corresponding optically pure 3S-hydroxythioesters, which are useful chiral building blocks in organic synthesis. The utility of the present method was demonstrated in the stereoselective synthesis of sex attractant of pine saw-fly, (2S,3S,7S)-3,7-dimethylpentadec-2-yl acetate from the 3S-hydroxy esters.*

Reactions using yeast cultures have been applied to effect asymmetric reduction of a variety of unnatural functionalized ketones: For example, reduction of β-ketoesters with baker's yeast (*Saccharomyces cerevisiae*) produces β-hydroxy esters, which are especially useful building blocks for the natural product synthesis.[1] The ability of an enzyme to make a prochiral distinction by the selective reduction of one enantiotopic face of a carbonyl group requires the formation of a preferred enzyme-substrate complex.[2] In the previous paper,[3] we have reported that introduction of the sulfenyl group to α-position of the β-ketoesters successfully controls this selectivity in baker's yeast reduction of those to afford optically pure 3*S*-hydroxy esters. Consequently, if the sulfenyl functional group of the ketoesters could be effective for the improvement of the ability of the yeast to make a prochiral distinction, β-ketothioester derivatives, such as dithioester 1 and thiolester 2 could become an effecient substrate of the enantioselective reduction with baker's yeast.[4] We now wish to report the baker's yeast mediated reduction of β-ketothioester derivatives to afford *S*-type asymmetric reduction products (3 and 4) with both high enantio- and diastereoselectivity.

A typical procedure for the microbial reduction is as follows: To a stirred solution of 55 g of D-glucose in 400 ml of water was added 51 g of baker's yeast (Oriental Yeast Co.) and the suspension was stirred for 30 min, then, 10 ml of an ethanol solution of methyl 2-methyl-3-oxodithiobutanoate[5]



1(X=S, Y=SMe)
2(X=O, Y=SEt)
3(X=S, Y=SMe)
4(X=O, Y=SEt)

Table 1. Results of the Baker's Yeast Reduction of β-ketothioester Derivatives

Entry	X	Y	R^1	R^2	Chemical Yield[a] % (*syn* : *anti*)	*syn*-3,4[b] $[\alpha]_D^{23}$	%ee	*anti*-3,4[b] $[\alpha]_D^{23}$	%ee
1	S	SMe	Me	H	50	+31.3°	>96(*S*)		
2	S	SEt	Me	H	30	+19.8°	>96(*S*)		
3	S	SMe	Me	Me	65 (94 : 6)[c]	-345°	>96(*S*)	+231°	>96(*S*)
4	S	SMe	$-(CH_2)_3-$		27 (100 : 0)[c]	+196°	>96(*S*)		
5	O	SEt	Me	H	69	+47.1°	>96(*S*)		
6	O	SEt	Me	Me	77 (81 : 19)[d]	+17.6°	>96(*S*)	———	[e]

a) All products were isolated by TLC on silica-gel and identified by IR and NMR spectra. b) All specific rotations were measured in $CHCl_3$ (c ca. 1.). No (*R*)-enantiomer could be detected by ^1H NMR of the corresponding MTPA ester. c) The ratio was determined after separation of the product. d) Determined by HPLC. e) *anti*-Isomer could not be isolated in diastereomeric pure state.

(1.66 g, 10.2 mmol) was added. The mixture was stirred at room temperature for 24 h. Extraction of the reaction mixture with ethyl acetate and purification by silica-gel column chromatography gave methyl 3-hydroxy-2-methyldithiobutanoate (1.09 g, 65%). The product consisted of *syn*- and *anti*-isomers, which could be easily separated into each pure isomers by TLC on silica-gel. These two isomers were clearly distinguished by ^1H NMR.[6] The optical purity of each isomer of the hydroxy esters was determined by ^1H NMR according to the method of Mosher *et al.*[7] As shown in Table 1, completely enantioselective reduction was achieved, and highly *syn* selective reduction was observed. Reduction of methyl 3-oxo-2-methyldithiobutanoate yielded an easily separable 94 : 6 mixture of *syn*-3 and *anti*-3 (entry 3), whereas the yeast reduction of ethyl 3-oxo-2-methylbutanoate gave 86 : 14 mixture of the corresponding *syn*- and *anti*-hydroxy esters,[8a] which could not be separated each other by TLC.[8b] Although the reduction of ethyl 2-oxocyclohexanecarboxylate was known to give the corresponding (1*R*,2*S*)-hydroxy ester with 86%ee,[9] the reduction of methyl 2-oxocyclohexanedithiocarboxylate gave an optically pure single product of (1*R*, 2*S*)-2-hydroxycyclohexanedithiocarboxylate (entry 4). This extremely high *syn* diastereoselectivity was probably due to the enhanced enolization[5] of β-keto group by the thiocarbonyl group. These results illustrated that the simple change of oxygen atoms in the ester group of β-ketoester to sulfur atoms can control both of diastereo- and enantioselectivity of the yeast mediated reduction. These 3-hydroxydithioesters can be easily converted into the corresponding 3-hydroxy esters using copper (II) chloride and copper (II) oxide according to the method of Nozaki *et al.*[10] All *S* configurations at C-3 were confirmed by the comparison with reported values of the specific rotations of 3-hydroxy esters. The results are summarized in Table 2.

The utility of the present compounds as a chiral synthon was demonstrated in the synthesis of (2*S*,3*S*,7*S*)-3,7-dimethylpentadec-2-yl acetate (6), a sex attractant of pine saw-fly (*Neodiprion lecontei*).[12] The three asymmetric centers

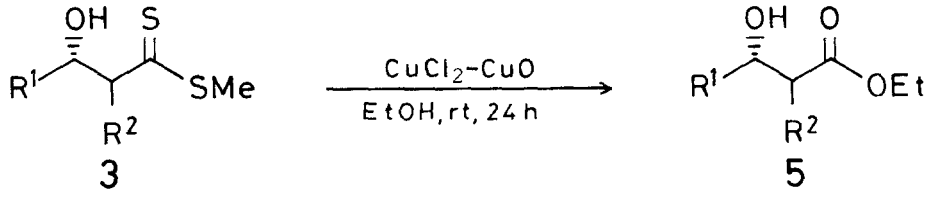
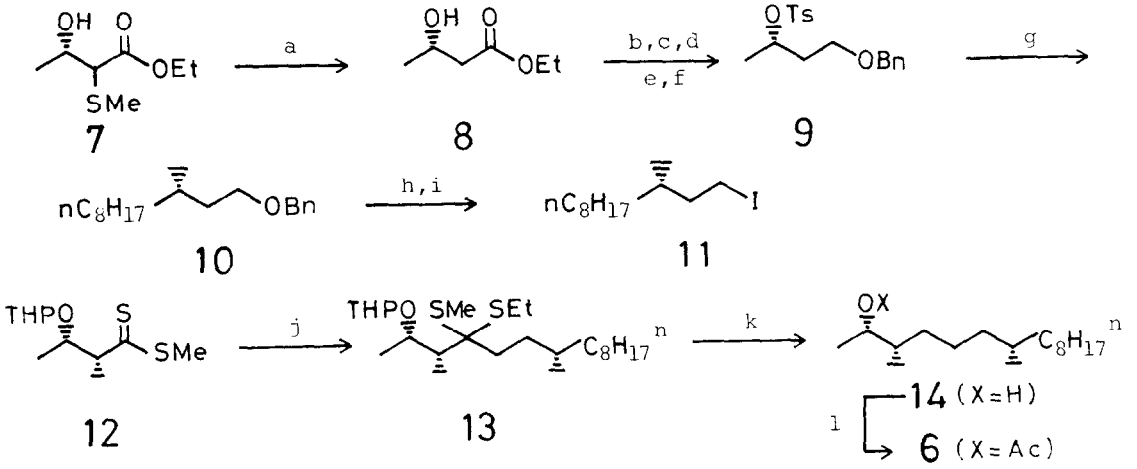


Table 2. Yield and Optical Rotation of 3-Hydroxy Esters 5 Converted from Dithioesters 3.

R^1	R^2	Yield (%)[a]	Optically Purity (%ee)[b] Configuration	$[\alpha]_D^{23}$ in $CHCl_3$ (c ca. 1.)
Me	H	62	>96 (*S*)	+42.2° lit.[11] +42.7° (100%ee *S*)
Me	Me (*syn*)	74	>96 (*S*)	-6.0°
Me	Me (*anti*)	70	>96 (*S*)	+14.8°
$+CH_2+_4$	(*syn*)	75	>96 (*S*)	+45.2° lit.[9] +24.5° (86%ee *S*)

a) All products were isolated by silica-gel TLC and distillation (Kugelrohr). b) No (*R*)-isomer could be detected by ^1H NMR of their (+)-MTPA esters in the presence of Eu(fod)$_3$ shift reagent.

in 6 were constructed by the utilization of the two yeast mediated reduction products of β-ketoesters, ethyl (3*S*)-2-methylthio-3-hydroxybutanoate (7) and methyl (2*S*,3*R*)-2-methyl-3-hydroxydithiobutanoate. Hydroxy ester 7, prepared by the reduction of ethyl 2-methylthio-3-oxobutanoate with baker's yeast, was converted into optically pure ethyl (3*S*)-3-hydroxybutanoate (8); 76%, $[\alpha]_D^{23}$ +43.3° (c 1.05, $CHCl_3$),[3] The hydroxy ester 8 was converted into the tosylate 9 (76%, $[\alpha]_D^{23}$ +15.0° (c 1.11, $CHCl_3$), lit.[13] +13.2°) in usual manner,[13] then substitution reaction of the tosylate with a octylcuprate derivative gave the coupling product 10; 82%, $[\alpha]_D^{23}$ -2.62° (c 3.92, $CHCl_3$).[14] Deprotection of 10 and iodination[15] afforded (3*S*)-3-methyl-1-iododecane (11); 95%, $[\alpha]_D^{23}$ +5.93°



a) mCPBA, Al/Hg b) DHP, cat PPTS, CH_2Cl_2 c) LAH d) NaH, BnBr, cat. nBu_4NI e) pTsOH, MeOH f) TsCl, Py g) n-$Oct_2CuMgBr$, THF, -25 °C, 7 days h) Li, NH_3, -78 °C i) HI(46% aqueous solution), reflux, 8 h j) EtMgI(2 eq), THF, -10 °C, 6 h, then Iodide 11 (2.5 eq), THF-HMPA (5 : 1), 0 °C, 12 h k) Raney Ni (W-2), EtOH, reflux, 24 h l) Ac_2O, Py

(c 10.59, hexane) with 96% purity.

The thiophilic reaction of Grignard reagent with dithioester to produce dithioacetal anion was applied to the coupling reaction of two chiral building blocks 11 and 12. The tetrahydropyranoxy ether 12 (92% from (3*S*)-hydroxy-dithioester) was treated with ethylmagnesium iodide (2.0 eq) in THF at -10 °C,[16] followed by the alkylation with the optically pure iodide 11 in THF-HMPA (5 : 1) at 0 °C to produce 13 in 67% yield.[17] No epimerization at C-3 could be confirmed in this coupling reaction.[18] The thioacetal derivative 13 was desulfurized by Raney Ni, accompanied with deprotection of tetrahydropyranoxy group to give the optically active alcohol 14 (90%, $[\alpha]_D^{23}$ -9.57° (c 0.648 hexane), lit.[12c] -9.8° (neat)). Acetylation of 14 gave the pheromone 6 (88%, $[\alpha]_D^{23}$ -10.5° (c 0.200 hexane), lit.[12c] -5.76° (neat)).

Thus, stereocontrol by the introduction of a sulfur functional group in the asymmetric reduction of ketones with baker's yeast is a usuful means and the enantioselective reduction of 3-oxothioester derivatives with baker's yeast is the promising method providing the useful chiral building blocks for construction of optically active natural products.

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