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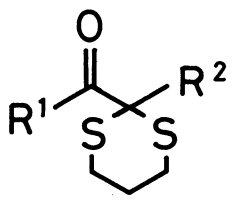
ENANTIOSELECTIVE SYNTHESIS OF α-HYDROXYTHIOACETALS BY THE BAKER'S YEAST REDUCTION OF α-KETOTHIOACETALS

Tamotsu FUJISAWA,* Eiji KOJIMA, Toshiyuki ITOH, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

Asymmetric reduction of α-ketothioacetals was achieved by fermenting baker's yeast to afford optically pure α-hydroxythioacetals which play as equivalents of valuable α-hydroxy aldehydes. The utility of the present method was demonstrated in the stereoselective syntheses of (4S,5S)- and (4S,5R)-4,5-dihydroxydecanoic acid γ-lactones from (S)-(-)-1-(1,3-dithian-2-yl)-1,4-butanediol.

Microbial-mediated reaction of synthetic substrates has provided an effective tool of preparing chiral building blocks for natural product synthesis.[1,2] Baker's yeast (*Saccharomyces cerevisiae*) is one of the microorganisms most frequently used in asymmetric reduction of carbonyl compounds because of its easy availablity and operation, and broader substrate specificity.[3] Recently introduction of α-sulfenyl group to ketones has been found to improve the chemical and optical yields of the baker's yeast reduction to afford optically active alcohols which are useful chiral synthons for the further manipulation of the sulfenyl group.[4] We now wish to report here that the baker's yeast reduction of α-ketothioacetals 1 gave optically pure α-hydroxythioacetals 2 which are equivalent of chiral α-hydroxy aldehydes or ketones 3.

A typical procedure for the baker's yeast reduction is as follows: A mixture of 12 g of D-glucose, 10 mg of $MgSO_4$, and 10 g of baker's yeast (Oriental Yeast Co.) in 80 ml of water was stirred for 1 h at room temperature, then 10 ml of an ethanol solution of 1-(1,3-dithian-2-yl)-1-ethanone[5] (1; $R^1 = CH_3$, $R^2 = H$) (2.0 mmol) was added to the yeast suspension. The reaction was monitored by silica-gel TLC analysis until the disappearance of the starting ketone. After the ketone faded (ca. one day), celite and ethyl acetate were added, and the mixture was stirred for 6 h, and then filtered through a celite pad. The filtrate was extracted with ethyl acetate and the solvent was evaporated in vacuo. 1-(1,3-Dithian-2-yl)-1-ethanol (2; $R^1 = CH_3$, $R^2 = H$) was obtained after the purification by TLC on silica-gel.



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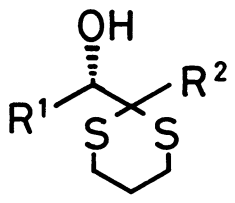

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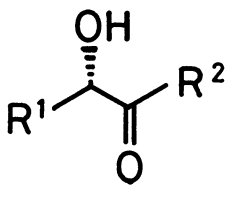

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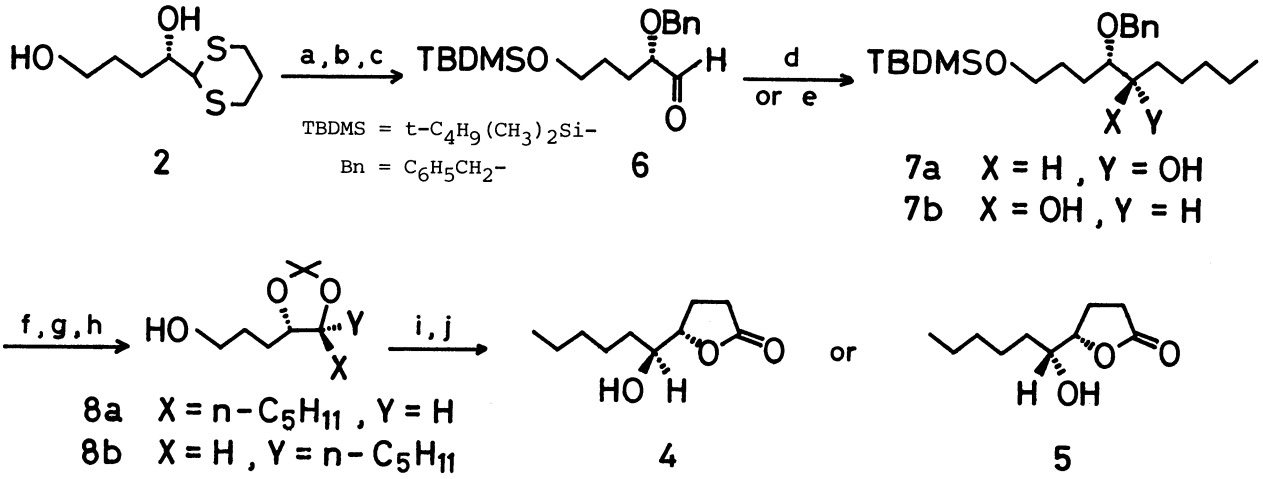
Table 1. The Baker's Yeast Reduction of α-Ketothioacetals 1 to α-Hydroxythioacetals 2

Entry	R^1	R^2	Reaction time/d	Yield of 2/%	$[\alpha]_D^{23}$/°	Optical Purity/%ee a)	Config.
1	CH_3	H	1	84	-5.79 (MeOH)	>96	S b)
2	C_2H_5	H	2 c)	71	-15.5 ($CHCl_3$)	>96	S d)
3	n-C_3H_7	H	4 c)	92	-28.6 ($CHCl_3$)	>96	S d)
4	n-C_4H_9	H	3 c)	71	-31.0 ($CHCl_3$)	>96	S d)
5	HO$(CH_2)_3$	H	10 c)	74	-26.1 ($CHCl_3$)	>96	S e)
6	CH_3	CH_3	2.5 c)	50	-5.77 ($CHCl_3$)	>96	S f)
7	CH_3	$-CH_2CH=CH_2$	4 c)	31	+12.4 ($CHCl_3$)	>96	R e)

a) No other enantiomer could be detected by ^1H NMR using Eu(hfc)$_3$. b) The specific rotation for (R)-(+)-1-(1,3-dithian-2-yl)-1-ethanol is $[\alpha]_D$ +5.8° (MeOH).[6] c) After 1 d, yeast 2.5 g, glucose 3.0 g, water 20 ml, and $MgSO_4$ 2.5 mg per 1.0 mmol of ketone were added every 12 h. d) The configuration was tentatively assigned to be S by the levorotatory power of the specific rotation. e) See the text. f) Methylation of (S)-1-(1,3-dithian-2-yl)-2-ethanol gave the present thioacetal with the same specific rotation.

Table 1 summarizes the results obtained by the baker's yeast reduction of various kinds of α-ketothioacetals 1. It is noteworthy that (S)-α-hydroxythioacetals with complete optical purity (>96% ee) were obtained in good yields from α-ketothioacetals (Entries 1 - 5).[7] These results show the favorable effect of the introduction of sulfenyl group to α-position of ketone as compared with the results of the baker's yeast reduction of β-ketoesters, in which both the enantioselectivity and absolute configuration remarkably depend on the length of alkyl chains of them.[2] The reduction of 1-(2-methyl-1,3-dithian-2-yl)-1-ethanone gave also the corresponding optically pure (S)-α-hydroxythioacetal (Entry 6). Surprisingly, the change of the substituent R^2 in 1 from methyl to allyl group resulted in the formation of the (R)-α-hydroxythioacetal with high enantiomeric excess (Entry 7). The (R)-configuration was determined by converting the α-hydroxythioacetal into (R)-(+)-2-hexanol on treatment with lithium in ethylamine[8] (54%, $[\alpha]_D^{23}$ +12.5° (c 0.966, EtOH), lit[9] $[\alpha]_D^{23}$ +12.7° (EtOH)).

Optically active α-hydroxythioacetal obtained by the above method is an equivalent of optically active α-hydroxy aldehyde which is useful for the syntheses of optically active natural products.[10] The utility of the present method was demonstrated in the synthesis of (4S, 5S)- and (4S,5R)-4,5-dihydroxydecanoic acid γ-lactones, 4 and 5,[11] which are novel natural products from strains of *Streptomyces griseus*. The trifunctional thioacetal derivative, (S)-(-)-1-(1,3-dithian-2-yl)-1,4-butanediol 2 (R^1 = $(CH_2)_3OH$, R^2 = H, Entry 5), was converted to the corresponding optically pure aldehyde 6 (75%, $[\alpha]_D^{23}$ -45.2° (c 0.730, THF)) by the hydrolysis of thioacetal group[12] after the protection of the primary and secondary hydroxy groups. The absolute configuration and optical purity of 6 were verified by converting into (R)-1,4-pentanediol, $[\alpha]_D^{23}$ -14.5° (c 0.760, MeOH), lit[6] $[\alpha]_D^{23}$ -14.5° (c 1.01, MeOH).[13] Treatment of 6 with amylmagnesium bromide in the presence of zinc bromide in ether at 0 °C gave the adduct 7a (66%) with excellent *syn*-diastereoselectivity (*syn* : *anti* = 46 : 1) by HPLC analysis.[10] *anti*-Diastereoselective addition to the aldehyde 6 was achieved by using amyltitanium triisopropoxide in ether, at -78 °C to room temperature, to yield the adduct 7b in 37% yield with the



a) TBDMSCl - Imidazole, b) NaH, BnBr, 10 mol% Bu_4NI, c) MeI - $CaCO_3$, d) $n\text{-}C_5H_{11}MgBr - ZnBr_2$ e) $n\text{-}C_5H_{11}Ti(O\text{-}i\text{-}C_3H_7)_3$, f) Li - NH_3, g) $CH_2{=}C(OCH_3)CH_3$, h) Bu_4NF, i) CrO_3 - Py, j) Ag_2O

diastereoselectivity of *syn* to *anti* in a ratio of 1 : 2.4.[14] These diastereomers, 7a and 7b, could be easily separated by TLC on silica-gel, and the corresponding MTPA-esters of 7a and 7b were shown to be diastereomerically single products by HPLC analysis, respectively. Debenzylation of 7a and 7b, protection of 1,2-diol, and desilylation gave acetonide derivatives 8a (47%, $[\alpha]_D^{23}$ -10.1° (c 0.494, $CHCl_3$)) and 8b (76%, $[\alpha]_D^{23}$ -19.8° (c 1.28, MeOH)), respectively. Oxidation of 8a with chromium oxide in pyridine and silver oxide gave γ-lactone 4 in 41% yield, $[\alpha]_D^{23}$ +15.9° (c 0.565, CCl_4), lit[10] $[\alpha]_D^{23}$ +11° (CCl_4). By the identical reaction sequence, 8b was converted to 5 in 36% yield, $[\alpha]_D^{23}$ +21.3° (c 0.375, $CHCl_3$), lit[14] $[\alpha]_D^{23}$ +24.3° ($CHCl_3$).

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13) Aldehyde 6 was reduced with $LiAlH_4$, and then treated with methanesulfonyl chloride in pyridine to give the corresponding methanesulfonate, which was reduced with $LiAlH_4$ and lithium in liquid ammonia to give (R)-1,4-pentanediol.

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