BIOCATALYTIC PREPARATION OF CHIRAL β-HYDROXY ESTERS SUBSTITUTED WITH HETERORING AT γ-POSITION

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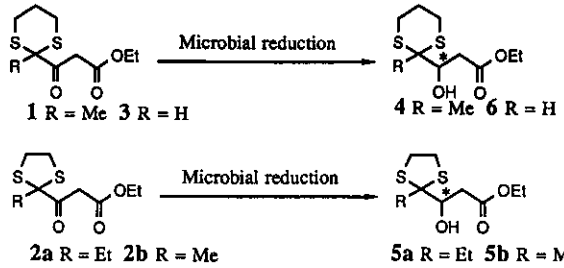
Abstract- Asymmetric reduction were examined of β-keto esters substituted with dithiane ring at γ-position with microorganism and gave the alcohol with high optical purity. Also the chiral carbinol with furan ring was obtained by the hydrolysis of the corresponding acetate with lipase or baker's yeast.

Recently, we have demonstrated that chiral glycine[1] and β-lactam ring moieties[2] can be introduced asymmetrically by using reduction with baker's yeast (Saccharomyces cerevisiae). Enzymes and microbial cells have recently attracted considerable attention as chiral catalysts in organic synthesis.[3]
It has been reported that β-keto esters are readily reduced with baker's yeast with high optical purity,[4] and the optical purity increased when they were substituted with hetero atom at α- or γ- position.[5] Also, there are some reports that the keto dithianes were readily reduced by microorganisms.[6] So we tried to examine the effect of the substituent of heteroring at γ- position on β- keto esters.
We synthesized the β-keto esters (**1**, **2a**, **2b**, **3**), substituted with dithiane ring at γ-position[7]. After screening with 14 kinds of yeast, we selected some microbial cells, and made reduction on those substrates. The results were summarized in Scheme 1. The esters **1**, **2a**, **2b** were reduced to give (R)-alcohol with high optical purity, but the ester **3**, which has no methyl group at γ-position, gave (S)-alcohol with 95 % ee both with Torulaspora delbrueckii and Saccharomyces cerevisiae. Optical purity of **5a**, **5b**, **6** was determined by 400 MHz ^{1}H-nmr analysis as their MTPA esters. In the case of **4**, it was

deprotected to **7**, and esterified with (-)-MTPACl (Scheme 2).

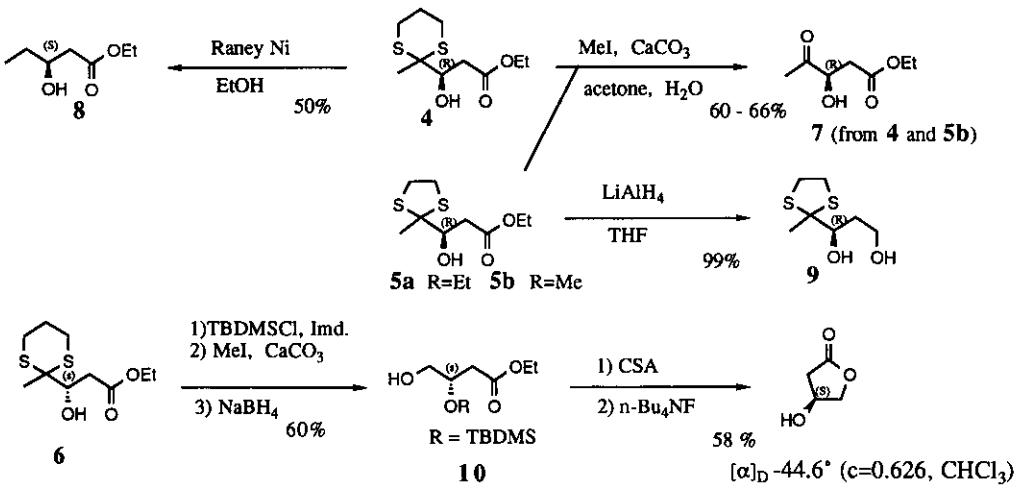


Substrate	Microorganism	Reaction time	Product Yield	$[\alpha]_D$ ($CHCl_3$)	% ee
1	*C. albicans*	6 d	38 %	+19.1° (c=1.159)	85 (R)
	T'spora. delbrueckii	7 d	50 %	–	61 (R)
2a	*T'spora. delbrueckii*	6 d	100 %	+29.6° (c=1.066)	92 (R)
2b	*T'spora. delbrueckii*	3 d	95 %	+24.4° (c=1.021)	85 (R)
3	*T'spora. delbrueckii*	3 d	58 %	–	95 (S)
	S. serevisiae	3 d	78 %	-21.4° (c=1.260)	95 (S)

Scheme 1

Absolute configuration of **4** was determined as (R) by measuring the optical rotation of its reducing derivrertive (**8**).[8] In **5a** and **5b**, they were converted to ketone (**7**) or diol (**9**) and both configurations were determined as (R), comparing those derived from **4**. Also **6** was converted to known ketone (**11**)[9] after 5 steps and determined as (S).

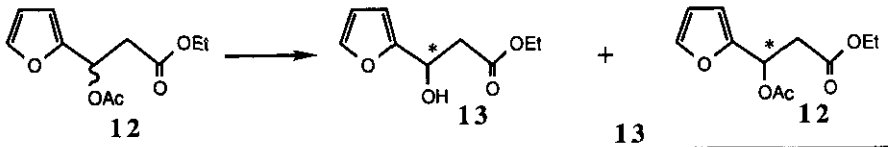
Thus, the stereochemistry of the reduction product could be controlled by choosing the substituent at γ-position of the starting β-keto esters.



Scheme 2

Next, we found the β-acetoxy-γ-furyl ester[10] was biocatalytically hydrolyzed to give chiral β-hydroxy ester. Several conditions were examined (Scheme 3).

Scheme 3



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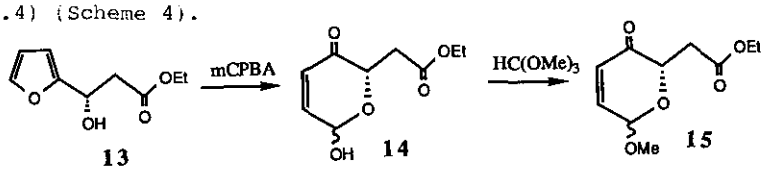
Method	Biocatalyst	Config.	Chemical Yield	Optical Yield	$[\alpha]_D$ (EtOH)
A	baker's yeast	(S)	19 %	~82 % ee	-18.4° (c = 1.08)
B	Immobilized B.Y.	(S)	18	84	-18.5° (c = 1.01)
C	lipase SIGMA	(R)	30 (37)*	85 (67)*	(+16.5° (c = 1.13))*
D	lipase AmanoA-6	(S)	35 (40)*	96 (76)*	- 21.5° (c = 1.18)

A; **12** 1 g, B.Y. 10 g, Na buffer (pH = 7.0), 200 ml, 27 °C, 1 h
B; **12** 1 g, B.Y. 13 g, immobilized on calcium alginate, 27 °C, 2.5 h
C; **12** 100 mg, Enzyme (Candida cylindracea) 50 mg (3400 units), Na buffer (pH = 7.25), 20 ml, 80 min
D; **12** 100 mg, Enzyme (Aspergillus niger) 50 mg (3000 units), Na buffer (pH = 7.25), 20 ml, 105 min
( )* ; values before recycle reactions
Optical yields were determined as their MTPA esters.

Baker's yeast has been generally used as a chiral reducing reagent,[4] but we now detected it is also effective in asymmetric hydrolysis of **12**.[11] When baker's yeast was immobilized,[12] optical purity of the product **13** became invariable and the isolation of it was much more convenient. We examined the use of enzyme for this hydrolysis. A suspension of the reagent with Amano A-6 gave the (S)-β-hydroxy-γ-furyl ester **13** and the (R)-β-acetoxy-γ-furyl ester **12**. The hydrolysis product **13** was acetylated and reacted with AmanoA-6 once more. This recycle product had higher optical yield (Scheme 3). Interestingly the use of different enzyme preparations gave different absolute configurations,[13] and this variation would be valuable for the synthesis of various natural products such as α-L-amicetoside and α-L-mycaminoside.[14]

Chiral **13** was converted with mCPBA to the hydropyranone **14** in 63% yield, which would be an important synthon for the synthesis of the above two compounds.[15] Thus **14** was obtained as an anomeric mixture, and protected with methyl orthoformate in 59 % yield. The anomers were separated each other by hplc (α:β =1:2.4) (Scheme 4).



Scheme 4

ACKNOWLEDGMENT

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7) (a) 2-Metyl-1,3-dithiane was treated with n-BuLi and DMF to afford 2-formyl-2-methyl-1,3-dithiane, which was reacted with LDA and ethyl acetate to provide **4**, which was oxidized with DMSO to give **1** in total 47% yield. (b) Ethyl pyruvate was treated with 1,2-ethanedithiol and $BF_3.Et_2O$ to produce thioacetal, which was hydrolyzed with LiOH to afford 2-methyl-1,3-dithiolane-2-carboxylic acid, then converted to acyl chloride with thionyl chloride. It was reacted with the enolates prepared from ethyl acetate or methyl acetate with LiHMDS to provide **2a** or **2b** in total 82% yield. (c) Compound **3** was prepared from 1,3-dithiane in 34% yield.

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