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Asymmetric Reduction of α-Methylene Ketones by Using Fermenting Baker's Yeast. Preparation of Optically Active β-Hydroxy α-Methyl Ketones

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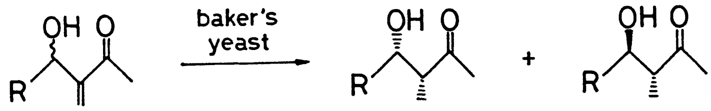
Asymmetric reduction of 4-hydroxy-3-methylenealkan-2-ones with baker's yeast afforded (3*R*,4*S*)-4-hydroxy-3-methylalkan-2-ones in >98% ee and the (3*R*,4*R*) isomers in 67—>98% ee in ratios of 1:1—2.

The use of baker's yeast as chiral reducing agent has shown its versatility by reducing the C=O bond of a variety of ketones with high optical purities.[1)] The reduction of the C=C bond has also been achieved as well, although it is mostly conjugated with a carbonyl group.[1)] To the best of our knowlege, however, the $C=CH_2$ bond has never been subjected to the yeast reduction. This may be mainly due to the difficulty of preparation of methylene compounds or α-methylene carbonyl compounds. Recently, a facile one step synthetic method for α-methylene carbonyl compounds has been reported,[2)] which involves the reaction of aldehydes with methyl vinyl ketone with the aid of 1,4-diazabicyclo[2.2.2]octane (DABCO).

Herein we wish to report results of the baker's yeast reduction of β-hydroxy α-methylene ketones (**1**) that demonstrate a novel approach to *syn* and *anti* β-hydroxy α-methyl ketones (**2**) with moderate to high optical purities (Table 1). Such a class of ketones has been prepared by using the directed aldol reaction, in which much effort has recently been focused on the preparation of optically active aldols.[3)]



1 syn-2 anti-2

Table 1. Reduction of β-Hydroxy α-Methylene Ketones (**1**) to β-Hydroxy α-Methyl Ketones (**2**) by Using Fermenting Baker's Yeast

2	R	Time	Yield	*syn/anti*	$[\alpha]_D^{25}$ a)		% ee		Config	
		h	%		*syn*	*anti*	*syn*	*anti*	*syn*	*anti*
2a	C_2H_5	24	61	53/47	+44.0	+27.2	>98	>98	3*R*,4*S*	3*R*,4*R*
2b	$n-C_3H_7$	27	64	42/58	+37.6	+26.5	>98	72	3*R*,4*S*	3*R*,4*R*
2c	$n-C_4H_9$	69	56[b)]	33/67	+31.5	+22.5	>98	67	3*R*,4*S*	3*R*,4*R*
2d	$n-C_5H_{11}$	114	72	36/64	+26.7	+17.8	>98	69	3*R*,4*S*	3*R*,4*R*

a) In $CHCl_3$, c 1.0—1.2. b) Recovery of **1c** was 8%.

A mixture of 10 g of glucose and 4 g of dry baker's yeast (from Oriental Yeast Co., immobilized with 1 g of sodium alginate[4]) in 500 mL of water was stirred for 1 h at 30 °C. To this mixture 297 mg (2.09 mmol) of **1b** was added and stirring was continued for 27 h. As the glucose was consumed, 20 g of glucose was added in four portions. The mixture was filtered and the filtrate was extracted with EtOAc. The crude oil obtained was passed through a silica gel column (hexane–EtOAc 10:1) to give 194 mg (64%) of **2b**. *Syn*- and *anti*-**2b** were separated by HPLC (Yanapak SA-I, hexane–EtOAc 30:1) in a ratio of 42:58.[5] Their optical purities were determined to be >98 and 72% ee, respectively, by measuring ^{1}H NMR spectra in the presence of Eu(hfc)$_3$.[6]

As observed in the reaction time and yield, the substrates **1a**,**b** having a smaller group R are reduced much faster than **1c**,**d** having a large group. The stereochemical course is found to be also highly dependent on the alkyl group R. Quite interesting is the fact that the optical purity is very high (>98% ee) for both *syn*- and *anti*-**1a** while lowered (67–69% ee) for *anti*-**1c**,**d**, although a high value of >98% ee is still retained by *syn*-**1c**,**d**.

In order to determine the absolute configuration, *syn*- and *anti*-**2a** were converted to *syn*- and *anti*-2,4-dihydroxy-2,3-dimethylhexane with MeLi[7] and these diols were compared with the authentic diols prepared from octyl (*S*)-3-hydroxypentanoate.[8] Thus, *syn*-**2a** was determined as 3*R*,4*S* and *anti*-**2a** as 3*R*,4*R*. The same configuration was assigned to **2b**–**d** on the basis of the optical rotation measured. It can be concluded that the methylene group in **1a**–**d** was reduced to give **2a**–**d** with the *R* configuration in favor of the Prelog rule, irrespective of the stereochemistry of the adjacent hydroxy group.

References

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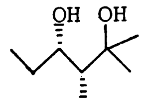
5) δ(C$_4$-H) 3.86, $J_{3,4}$=3.0 Hz for *syn*-**2b**; δ(C$_4$-H) 3.59, $J_{3,4}$=7.0 Hz for *anti*-**2b**.

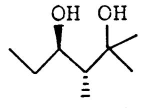
6) Determined by using the signal for the acetyl methyl group.

7)



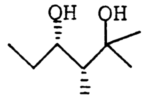
[α]$_D$ +5.53°

and



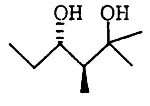
[α]$_D$ +28.1°

from **2a**.



[α]$_D$ +4.95°

and



[α]$_D$ -29.1°

authentic

8) K. Mori, H. Mori, and T. Sugai, Tetrahedron, 41, 919 (1985).

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