

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 knowledge, however, the C=CH₂ 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⁾

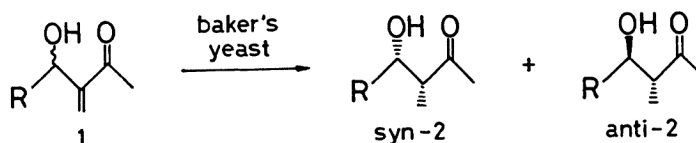


Table 1. Reduction of β -Hydroxy α -Methylene Ketones (**1**) to β -Hydroxy α -Methyl Ketones (**2**) by Using Fermenting Baker's Yeast

2	R	Time h	Yield %	<i>syn/anti</i>	[α] _D ²⁵ a)		% ee		Config	
					<i>syn</i>	<i>anti</i>	<i>syn</i>	<i>anti</i>	<i>syn</i>	<i>anti</i>
2a	C ₂ H ₅	24	61	53/47	+44.0	+27.2	>98	>98	3 <i>R</i> ,4 <i>S</i>	3 <i>R</i> ,4 <i>R</i>
2b	n-C ₃ H ₇	27	64	42/58	+37.6	+26.5	>98	72	3 <i>R</i> ,4 <i>S</i>	3 <i>R</i> ,4 <i>R</i>
2c	n-C ₄ H ₉	69	56 ^{b)}	33/67	+31.5	+22.5	>98	67	3 <i>R</i> ,4 <i>S</i>	3 <i>R</i> ,4 <i>R</i>
2d	n-C ₅ H ₁₁	114	72	36/64	+26.7	+17.8	>98	69	3 <i>R</i> ,4 <i>S</i>	3 <i>R</i> ,4 <i>R</i>

a) In CHCl₃, c 1.0-1.2. b) Recovery of **1c** was 8%.

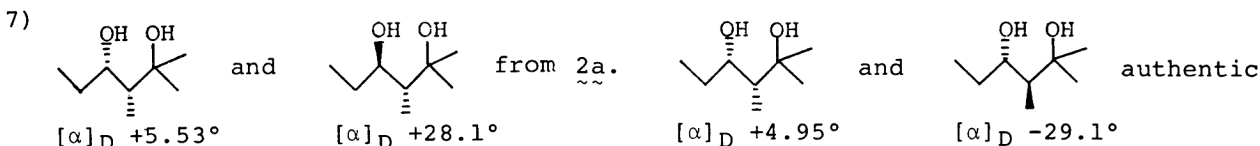
A mixture of 10 g of glucose and 4 g of dry baker's yeast (from Oriental Yeast Co., immobilized with 1 g of sodium alginate⁴⁾) in 500 mL of water was stirred for 1 h at 30 °C. To this mixture 297 mg (2.09 mmol) of 1b was added and stirring was continued for 27 h. As the glucose was consumed, 20 g of 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 ¹H 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 MeLi⁷⁾ and these diols were compared with the authentic diols prepared from octyl (*S*)-3-hydroxyphen-tanoate.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) $\delta(\text{C}_4\text{-H})$ 3.86, $J_{3,4}=3.0$ Hz for *syn*-2b; $\delta(\text{C}_4\text{-H})$ 3.59, $J_{3,4}=7.0$ Hz for *anti*-2b.
- 6) Determined by using the signal for the acetyl methyl group.



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

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