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Enantioselective Synthesis of (2S,3S)-2,3-Dihydroxyalkanoates by the Baker's Yeast Reduction of 2-Hydroxy-3-oxoalkanoates

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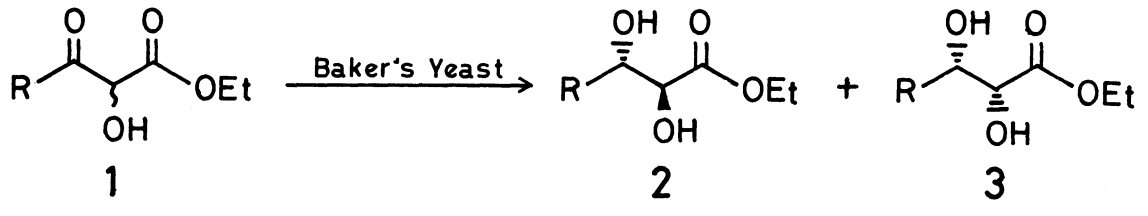
The baker's yeast reduction of ethyl (±)-2-hydroxy-3-oxoalkanoates predominantly gave highly optically pure ethyl (2S,3S)-2,3-dihydroxyalkanoates.

The baker's yeast reduction of β-keto esters or acids has provided a useful method for the asymmetric synthesis of optically active β-hydroxy esters or acids, which have been efficiently employed as chiral building blocks for natural product synthesis.[1,2] Although the stereoselectivity in the baker's yeast reduction is generally predicted by the Prelog rule,[3] the reduction of β-keto esters has a limitation of the substrate specificity of the yeast. For example, ethyl 3-oxobutanoate is reduced by the yeast to give ethyl (S)-3-hydroxybutanoate with >90%ee,[4] while ethyl 3-oxopentanoate gives ethyl (R)-3-hydroxypentanoate with ~40%ee.[2] For controlling the stereoselectivity in the yeast reduction several methods have been devised such as manipulation of the size of ester group[5,6] and immobilization of the yeast.[7] Recently we have reported that the introduction of sulfenyl group into α-position of β-keto esters controls the stereoselectivity of the yeast reduction to give optically pure (S)-3-hydroxy esters.[8] It is well documented that electronegative groups such as sulfur, oxygen, and halogen functional groups at α-position of ketone affect the stereochemistry of the reduction products.[9] In this communication we report that the stereocontrolled yeast reduction of ethyl (±)-2-hydroxy-3-oxoalkanoates predominantly affords ethyl (2S,3S)-2,3-dihydroxyalkanoates with high enantiomeric excess.

Ethyl 2-hydroxy-3-oxoalkanoates (1) are easily prepared in 54 ~ 62% yields by the reaction of ethyl acyloxyacetate with lithium hexamethyldisilazide according to a modified procedure of Lee *et al.*[10] A typical procedure of the baker's yeast reduction is described as follows: A suspension of baker's yeast (40 g) and glucose (40 g) in water (330 ml) was stirred at 23 °C for 30 min. Ethyl 2-hydroxy-3-oxoalkanoate (1) (8 mmol) in ethanol (15 ml) was added to the suspension. After



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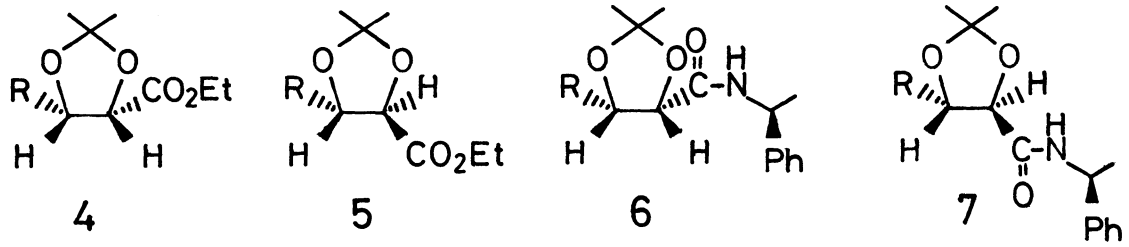
a, R = CH_3, b, R = C_2H_5, c, R = n-C_4H_9,



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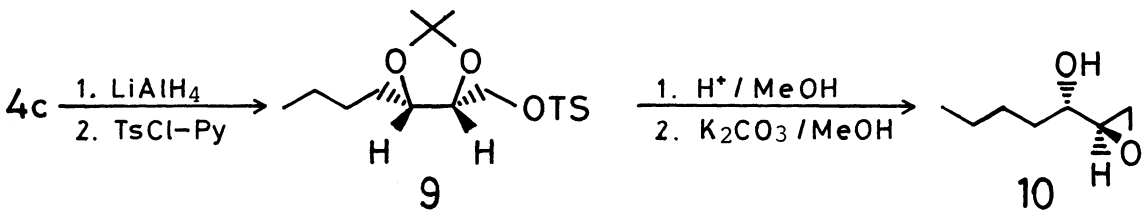
two days ethyl acetate (300 ml) was added. The mixture was stirred for 30 min, and filtered through a celite pad. The filtrate was saturated with NaCl, and extracted with ethyl acetate. The extracts were concentrated *in vacuo* and the residue was subjected to silica-gel TLC or flash column chromatography to give two diastereomers of ethyl 2,3-dihydroxyalkanoates (2 and 3).[11]

The yeast reduction of ethyl 2-hydroxy-3-oxobutanoate (1a) gave the *anti*- and *syn*-2,3-dihydroxy esters (2a and 3a) in 55% and 13% yields, respectively. The relative stereochemistry of *anti* and *syn* was easily confirmed by converting the dihydroxy esters into acetonides 4a and 5a. The ^{1}H NMR chemical shift of the α-proton of 4a or of 5a is easily distinguishable for 4a at δ4.38 (d) or for 5a at δ3.95 (d).[12,13] The *cis* stereochemistry of 4a is obvious from the isomerization of 4a by treatment with lithium diisopropylamide (LDA) at -80 °C to give a mixture of 4a and 5a in a ratio of 16 : 84.[14] The absolute configuration of 2a and 3a was assigned to 2S,3S and 2R,3S, respectively, by comparison of the specific rotation of 2,3-dihydroxybutanoic acids obtained by the hydrolysis of 2a and 3a with the reported values.[15] The enantiomeric excess of 2a and 3a was determined by converting them into the diastereomeric amides of 6a and 7a, which were prepared in over 95% yields by hydrolysis of 4a and 5a, followed by treatment with 1-chloro-2-methyl-N,N-tetramethylenepropenylamine[16] and (-)-1-phenylethylamine. HPLC analysis of 6a and 7a showed the isomeric ratio of 99.8 : 0.2 and 95.1 : 4.9, respectively. Thus, the optical purity of 2a and 3a is >99% and 90%, respectively.

The reduction of ethyl 2-hydroxy-3-oxopentanoate (1b) gave 2b (97%ee) and 3b (69%ee) in 62% and 11% yields, respectively. The relative stereochemistry and enantiomeric excess of the products were determined by converting into 4b, 5b, 6b, and 7b. Diol ester 2b was converted into methyl *cis*-5-ethyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (8) with the specific rotation of $[\alpha]_D^{23}$ +11.5° (c 0.34, $CHCl_3$) *via* 4b. Comparing the specific rotation with $[\alpha]_D^{23}$ -12.4° (c 6.05, $CDCl_3$) of (2R,3R)-8,[12] the configuration of the yeast reduction product was assigned to (2S,3S)-2b. The absolute configuration of 3b was established to be 2R,3S by comparison with the specific rotation of 5b derived from the isomerization of 4b with LDA.

Ethyl 2-hydroxy-3-oxoheptanoate (1c) was similarly reduced by the yeast to give 2c (97%ee) and 3c (70%ee) in 48% and 12% yields, respectively. The 2S,3S-



4c → 1. $LiAlH_4$ 2. TsCl-Py → 9 → 1. H^+/MeOH 2. K_2CO_3/MeOH → 10

Table 1. The Baker's Yeast Reduction of Ethyl 2-Hydroxy-3-oxoalkanoate 1

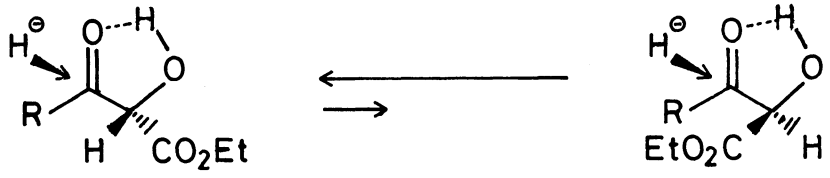
Ester	Yield / % (2 : 3)[a]	Optical Purity / %ee (2S,3S)-2	(2R,3S)-3
1a	68 (72 : 28)	>99	90
1b	72 (90 : 10)	97	69
1c	60 (80 : 20)	97	70[b]

a) Isolated yield. The ratio was determined after separation of the product.
b) The absolute configuration is 2S,3R.

configuration of 2c is elucidated by converting into the known epoxide 10 as follows: Reduction of 4c with lithium aluminum hydride and tosylation with *p*-toluenesulfonyl chloride in pyridine gave 9 in 93% yield. Deprotection of 9 and epoxidation with potassium carbonate in methanol gave 10 in 37% yield, $[\alpha]_D^{23}$ +17.9° (c 0.22, $CHCl_3$), lit[17] $[\alpha]_D^{20}$ -24.5° (c 1.22, $CHCl_3$) for (2S,3R)-10, which is a key intermediate of pestalotin synthesis. Isomerization of 4c with LDA gave (2R,3S)-5c, $[\alpha]_D^{23}$ -14.3° (c 0.70, $CHCl_3$), while 5c derived from the yeast reduction product 3c showed the opposite sign of the specific rotation of $[\alpha]_D^{23}$ +10.7° (c 1.35, $CHCl_3$). Thus the configuration of the minor product 3c from 1c should be 2S,3R, different from the cases of the reduction of 1a and 1b.

The above results are summarized in Table 1. Although the starting materials 1 are racemic, the major reduction products 2 are the (2S,3S)-isomers with over 97% optical purity. It is noteworthy that the yeast reduction of 1b exclusively gave the 3S isomers, while ethyl 3-oxopentanoate without 2-hydroxy group is known to give (R)-3-hydroxy ester with 40%ee.[2]

Although the mechanism of the yeast reduction has not been clear yet, the following speculation seems to be plausible for the explanation of the predominant formation of the (2S,3S)-isomers 2. If the yeast prefers the *re*-face reduction by the Prelog rule, the reduction of (2S)-11, forming a five membered chelate in terms of hydrogen bond between 2-hydroxy and carbonyl oxygen at C-3 with less hindered *re*-face site, to give (2S,3S)-2 is more favorable than that of (2R)-12 to give (2R, 3S)-2, and the equilibrium from 12 to 11 is possible. Degradation of the (2R)-isomers by the yeast may also cause the predominant formation of the (2S,3S)-isomers.



11 12

In conclusion, the yeast reduction of 2-hydroxy-3-oxoalkanoates gave highly optically pure (2S,3S)-2,3-dihydroxyalkanoates which are easily converted into the (2R,3S)-isomers as mentioned above. These 2,3-dihydroxy esters and their derivatives have been useful key intermediates in a variety of optically active natural product synthesis.[12,18,19]

References

1) For examples, K. Mori and M. Katsurada, *Justus Liebigs Ann. Chem.*, 1984, 157; A. Kramer and H. Pfander, *Helv. Chim. Acta*, 65, 293 (1982); M. Hirama and M. Uei, *J. Am. Chem. Soc.*, 104, 4251 (1982); R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt, and G. Snatzke, *Chem. Ber.*, 114, 2786 (1981).

2) G. Fráter, *Helv. Chim. Acta*, 62, 2825, 2829 (1979).

3) C. J. Sih and C. -S. Chen, *Angew. Chem., Int. Ed. Engl.*, 23, 570 (1984).

4) D. Seebach, F. Giovannini, and B. Lamatsch, *Helv. Chim. Acta*, 68, 958 (1985); T. Sugai, M. Fujita, and K. Mori, *Nippon Kagaku Kaishi*, 1983, 1315.

5) W. -R. Shieh, A. S. Gopalan, and C. J. Sih, *J. Am. Chem. Soc.*, 107, 2993 (1985).

6) M. Hirama, M. Shimizu, and M. Iwashita, *J. Chem. Soc., Chem. Commun.*, 1983, 599.

7) K. Nakamura, M. Higaki, K. Ushio, S. Oka, and A. Ohno, *Tetrahedron Lett.*, 26, 4213 (1985).

8) T. Fujisawa, T. Itoh, and T. Sato, *Tetrahedron Lett.*, 25, 5083 (1984).

9) T. Fujisawa, T. Itoh, M. Nakai, and T. Sato, *Tetrahedron Lett.*, 26, 771 (1985); T. Itoh, A. Yoshinaka, T. Sato, and T. Fujisawa, *Chem. Lett.*, 1985, 1679; T. Fujisawa, E. Kojima, T. Itoh, and T. Sato, *ibid.*, 1985, 1751; S. Iriuchijima and N. Kojima, *Agric. Biol. Chem.*, 42, 451 (1978); T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1984, 587; J. -P. Guetté, N. Spassky, and D. Bougherot, *Bull. Soc. Chim. Fr.*, 1972, 4217; R. L. Crumbie, D. D. Ridley, and G. W. Simpson, *J. Chem. Soc., Chem. Commun.*, 1977, 315.

10) S. D. Lee, T. H. Chan, and K. S. Kwon, *Tetrahedron Lett.*, 25, 3399 (1984).

11) The specific rotation of 2, 3, 4, and 5 is as follows:
2a, $[\alpha]_D^{23}$ +10.44° (c 1.05, EtOH); 2b, $[\alpha]_D^{23}$ +2.84° (c 1.06, EtOH);
2c, $[\alpha]_D^{23}$ +4.0° (c 1.28, EtOH); 3a, $[\alpha]_D^{23}$ +7.19° (c 1.20, EtOH);
3b, $[\alpha]_D^{23}$ +2.49° (c 0.80, EtOH); 3c, $[\alpha]_D^{23}$ -7.55° (c 0.21, EtOH);
4a, $[\alpha]_D^{23}$ +23.8° (c 2.78, $CHCl_3$); 4b, $[\alpha]_D^{23}$ +11.5° (c 0.94, $CHCl_3$);
4c, $[\alpha]_D^{23}$ +15.5° (c 1.06, $CHCl_3$); 5a, $[\alpha]_D^{23}$ +12.3° (c 0.59, $CHCl_3$);
5b, $[\alpha]_D^{23}$ -13.28° (c 0.26, $CHCl_3$); 5c, $[\alpha]_D^{23}$ +10.7° (c 1.35, $CHCl_3$).

12) R. W. Hoffmann and W. Ladner, *Chem. Ber.*, 116, 1631 (1983).

13) M. Viscontini and W. F. Frei, *Helv. Chim. Acta*, 55, 574 (1972).

14) A. W. M. Lee, V. S. Martin, S. Masamune, K. B. Sharpless, and F. J. Walker, *J. Am. Chem. Soc.*, 104, 3515 (1982).

15) The specific rotation of the *anti*-acid from 2a and the *syn*-acid from 3a is $[\alpha]_D^{23}$ +6.8° (c 4.0, H_2O) and $[\alpha]_D^{23}$ +10.3° (c 0.9, H_2O), respectively. The reported values for the (2R,3R)- acid and the (2S,3R)- acid are $[\alpha]_D^{25}$ -9.5° (c 1.0, H_2O) and $[\alpha]_D^{25}$ -17.75° (c 1.0, H_2O), respectively (F. W. Bachelor and G. A. Miana, *Can. J. Chem.*, 47, 4089 (1964)).

16) A. Devos, J. Remion, A. -M. Frisque-Hesbain, A. Colens, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1979, 1180.

17) K. Mori, T. Otsuka, and M. Oda, *Tetrahedron*, 40, 2929 (1984).

18) S. Servi, *J. Org. Chem.*, 50, 5865 (1985) and references cited therein.

19) T. Fujisawa, E. Kojima, T. Itoh, and T. Sato, *Tetrahedron Lett.*, 26, 6089 (1985); H. Meyer and D. Seebach, *Justus Liebigs Ann. Chem.*, 1975, 2261; P. DeShong and J. M. Leginus, *J. Am. Chem. Soc.*, 105, 1686 (1983); W. Ladner, *Chem. Ber.*, 116, 3413 (1983); K. C. Nicolau and S. E. Webber, *J. Chem. Soc., Chem. Commun.*, 1985, 297.

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