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ENANTIOTOPICALLY SELECTIVE OXIDATION OF 1,3-DIOLS WITH A MICROORGANISM

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Microbial oxidation of 2-methylpropane-1,3-diol (1a) proceeded with distinction of pro-(R) and pro-(S) hydroxymethyl groups resulting in the formation of β-hydroxyisobutyric acid (2a) of high optical purity. 2-Ethyl and 2-isopropyl derivatives (1b, c) were also oxidized to give the corresponding hydroxy acids (2b, c), but the optical yields were low.

Utilization of enzyme systems is one of the favorable methods in asymmetric synthesis.[1] We wish to report the enzymatic oxidation of 2-methylpropane-1,3-diol (1a) with distinction of pro-(R) and pro-(S) hydroxymethyl groups.

A number of bacteria which belong to Acetobacter and Gluconobacter species were examined for the oxidation of diol 1a. Gluconobacter roseus IAM 1841 was found to produce β-hydroxyisobutyric acid (2a) in the highest yield. The following preparative experiment is representative. In a 500 ml Erlenmyer flask was added 50 ml of sterilized acetate buffer (pH 5.0), 50 mg of 1a, resting cells of G. roseus (grown in 50 ml of a nutrient medium and harvested by centrifugation) and the whole was incubated for 48 hr at 30°C on a rotary shaker. The broth was adjusted to pH 3~4 with hydrochloric acid and extracted with ethyl acetate. To the organic layer, an etherial solution of an excess amount of diazomethane was added and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure. GLC analysis revealed that methyl β-hydroxyisobutyrate (3a) was formed in 47% yield based on the fed substrate 1a. The product was isolated by column chromatograpy on silica gel. Elution with ethyl acetate-dichloromethane (1:4 v/v) gave pure β-hydroxyisobutyrate (3a). This was identified by comparing the spectroscopic data[2] with those of an authentic specimen (racemate) prepared according to the literature procedures.[3] The ester 3a showed the specific rotation of $[\alpha]_D^{25}$ -22.5° (c=1.80, MeOH, 83% o.p)[4] and its absolute configuration was decided to be (R) by correlating the sign of the specific rotation to the results of Retey[5] and Sprecher.[6] Thus the oxidation catalyzed by the enzyme system was demonstrated to be enantiotopically selective for the pro-(R) hydroxymethyl group. Optically active β-hydroxyisobutyrate is expected to be an useful intermediate for the synthesis of chiral molecules because it has two different functional groups.[7] Diols 1b and 1c were also oxidized to the corresponding β-hydroxy acid (2b, c).[8] Although the exact optical purities of these compounds are not clear at present, it will be certain that they are almost racemic, judging from the values of the specific rotation of 3a-c as shown in Table 1. The bacterium oxidized 2-phenylpropane-1,3-diol (1d) to give hydroxy acid 2d,[8] but very slowly. These results may be ex-

plained by the effect of the bulkiness of the substituents at 2-positions of the substrates; methyl group is almost just fit the binding site of the enzyme system and so the substrate is fixed as to give a high optical yield, but the substrate with ethyl or larger groups are not. Jones et al. obtained chiral 3-alkyl and 3-phenyl-δ-valerolactones from the corresponding pentane-1,5-diols by the horse liver alcohol dehydrogenase catalyzed oxidation.[9] The effects of the steric bulkiness of C-3 substituents on the optical yields were similar to our results. The key for understanding the characteristics of the enzymatic reactions might be found in these results and the work along this line is now underway.

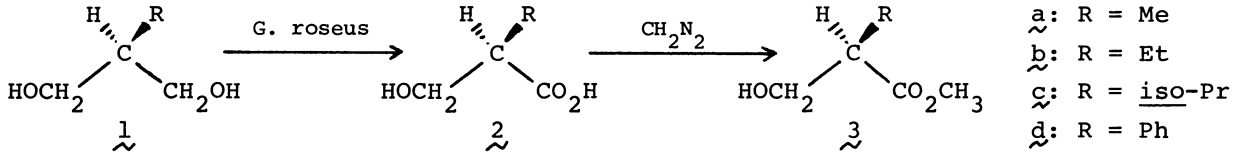

Table 1. Yield of β-Hydroxyisobutyrate

Compd.	R	Incubation (day)	Chem. Yield[a] (%)	$[\alpha]_D^{25}$ MeOH (% e.e.)
a	Me	2	47	-22.5°(83)
b	Et	5	55 (52)	-0.33°
c	iso-Pr	6	(10)	-0.39°
d	Ph	7	(2>)	-

a) The yields were determined by GLC using internal standards. In the parentheses are cited the isolated yields by column chromatography on silica gel with ethyl acetate-dichloromethane (1:4 v/v) as eluent.

References and Notes

1) G. S. Fonken and R. A. Johnson, "Chemical Oxidation with Microorganisms," Marcell Dekker Inc., New York, 1972: J. B. Jones, C. J. Sih, and D. Perlman, ed., "Application of Biological Systems in Organic Chemistry," Part I, John Wiley and Sons, Inc., New York, London, Sidney, Tront, 1976.

2) The yield of the most pure fraction was 8.7%. The purity of this sample was determined to be over 97% from the GLC peak areas. IR (KBr) 3450, 1735, 1200, 1035 cm^{-1}. NMR ($CDCl_3$) δ 1.18 (3H, d, J=7.2 Hz, CH_3CH), 2.4-3.0 (2H, m, CH + OH), 3.70 (5H, s + d, OCH_3 + CH_2OH). Mass (m/e) 15, 29, 31, 57, 59, 88.

3) E. Santaniello and A. Manzocchi, Synthesis, 698 (1977).

4) The optical purity was calculated based on the value of $[\alpha]_D^{25}$ +27.0° (c=4.06, MeOH) reported for L-(+)-methyl β-hydroxyisobutyrate; C. T. Goodhue and J. R. Schaeffer, Biotech. Bioeng., 13, 203 (1971).

5) J. Retey and F. Lynen, Biochem. Biophys. Res. Comm., 16, 358 (1964).

6) M. Sprecher, M. J. Clark, and D. B. Sprinson, Biochem. Biophys. Res. Comm., 15, 581 (1964); M. Sprecher and D. B. Sprinson, J. Biol. Chem., 241, 868 (1966); M. Sprecher, M. J. Clark, and D. B. Sprinson, ibid., 241, 872 (1966).

7) Q. Branca und A. Fischli, Helv. Chem. Acta, 60, 925 (1977).

8) Methyl esters of the products showed the agreeable NMR, IR and MS spectra.

9) A. J. Irwin and J. B. Jones, J. Amer. Chem. Soc., 99, 556 (1977).

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