

Microbial Oxidation of Racemic *vic*-Diols  
Synthesis of (*R*)- and (*S*)- $\alpha$ -Hydroxypropiophenones

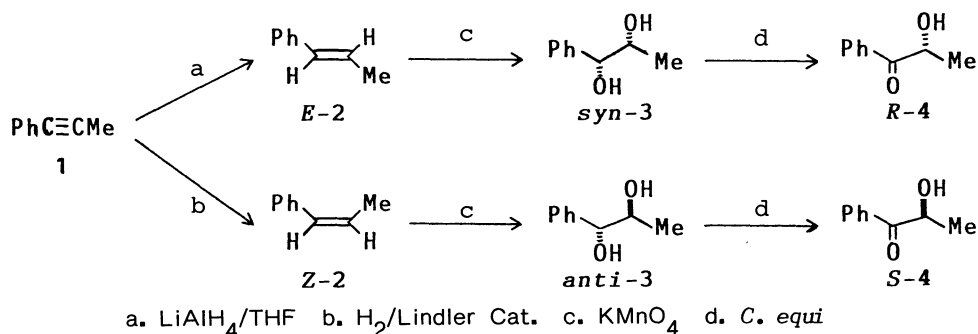
Hiromichi OHTA,\* Hiroshi YAMADA, and Gen-ichi TSUCHIHASHI

Department of Chemistry, Faculty of Science and Technology, Keio University,  
Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223

Both enantiomers of 2-hydroxy-1-phenyl-1-propanone have been synthesized by microbial oxidation of racemic *syn*- and *anti*-1-phenylpropane-1,2-diols, which are available from 1-phenylpropyne.

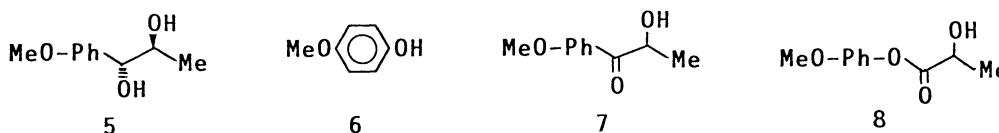
Preparation of both enantiomers starting from a common prochiral compound is a quite useful method in asymmetric synthesis. Utilization of selectivity and *non*-selectivity of enzymes to synthetic substrates sometimes presents elegant methods for asymmetric synthesis.<sup>1)</sup> In this letter, we wish to report microbial oxidation of diastereomeric ( $\pm$ )-*vic*-diols resulting in the formation of either enantiomer of  $\alpha$ -hydroxyketone, which has been demonstrated to be useful in the synthesis of natural products.<sup>2)</sup>

*Corynebacterium equi* IFO 3730 was grown in 50 ml of a medium containing inorganic salts and 1,2-propanediol (0.5%)<sup>3)</sup> as the sole source of carbon. After 2 days, 100 mg of racemic-*syn*-1-phenylpropane-1,2-diol (( $\pm$ )-*syn*-3)<sup>4)</sup> was added to the suspension of grown cells and incubated for 2 days at 30 °C. Extraction and isolation with preparative TLC afforded (*R*)-(+)-2-hydroxy-1-phenyl-1-propanone (*R*-4)<sup>5)</sup> in a yield of 28%, together with 40% of (*S,S*)-1-phenylpropane-1,2-diol. The reaction is highly regioselective, no regioisomeric 1-hydroxy-1-phenyl-2-propanone being detected on <sup>1</sup>H NMR analysis of the products. The resulting hydroxyketone exhibited  $[\alpha]_D^{26} +81^\circ$  (c 1.5, CHCl<sub>3</sub>) indicating the configuration to be (*R*),<sup>6)</sup> with over 99% optical purity as determined by HPLC using a Pirkle column<sup>7)</sup> after derivation to the corresponding acetate. The optical purity of the recovered diol *syn*-3 was estimated to be 80% from its specific rotation  $[\alpha]_D^{25} +49^\circ$  (c 2.2, CHCl<sub>3</sub>).<sup>8)</sup> Thus, the reaction was revealed to be highly regio- and enantioselective. Then, the remaining problem is the effect of relative configuration. When ( $\pm$ )-*anti*-3 (mixture of 1*R*,2*S* and 1*S*,2*R*) was incubated under the same conditions as for *syn*-3, again only the benzylic hydroxy group was oxidized to afford (*S*)-4 in



a yield of 30%,  $[\alpha]_D^{26} -80^\circ$  (c 1.5,  $\text{CHCl}_3$ ). The starting *anti*-diol (3) enriched with (1*S*,2*R*)-isomer was recovered in 62% yield,  $[\alpha]_D^{30} +22^\circ$  (c 3.2,  $\text{CHCl}_3$ ).<sup>9)</sup> These two results show that the enzyme system of *C. equi* oxidizes benzylic hydroxy group of (*R*) configuration, regardless to the relative configuration of the two hydroxy groups, leaving behind the diol with (*S*) configuration on benzylic carbon intact. As a result of present kinetic resolution, both (*R*)- and (*S*)-4 were obtained only by selecting *syn*- or *anti*-diol as the substrate for microbial oxidation. Diastereomeric diols were easily available by  $\text{KMnO}_4$  oxidation of (*E*)- and (*Z*)-olefins 2, which in turn were obtained from a common starting material, phenylpropyne 1, by reduction with  $\text{LiAlH}_4$ <sup>10)</sup> and catalytic hydrogenation, respectively. The diols were confirmed to be diastereomerically pure before subjecting to microbial oxidation by  $^1\text{H}$  NMR and GLC analysis of the corresponding acetone.

The reaction was applied to other diols. While *anti*-(4-chlorophenyl)-1,2-propanediol was recovered intact under the same conditions, 4-methoxy derivative (5) afforded 4-methoxyphenol (6) in a yield of 49%, on consuming the whole diol. The most probable mechanism for the formation of 6 involves oxidation of racemic 5 to afford hydroxyketone 7, followed by further oxidation to 8 and hydrolysis.



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#### References

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- 5) IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3500, 2950, 1690, 1590, 1440, 1260, 1130, 1020, 980, 700.  $^1\text{H}$  NMR  $\delta_{\text{TMS}}$  ( $\text{CCl}_4$ ): 1.37 (d,  $J=7.5$ , 3H,  $\text{CH}_3$ ), 3.50 (bs, 1H, OH), 4.98 (quart,  $J=7.5$ , 1H, CH), 7.38-7.63 (m, 3H, aromatic *m*- and *p*- to C=O), 7.72-7.98 (m, 2H, aromatic *o*- to C=O). MS  $m/e$  (%): 150 ( $\text{M}^+$ , 3), 149 ( $\text{M}-1$ , 21), 122 ( $\text{M}-\text{H}_2\text{O}$ , 20), 108 (22), 107 (42), 105 (PhCO, 100), 79 (26), 77 ( $\text{C}_6\text{H}_5$ , 42).
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