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Asymmetric Reduction of Ketopantolactone by Baker's Yeast[1]

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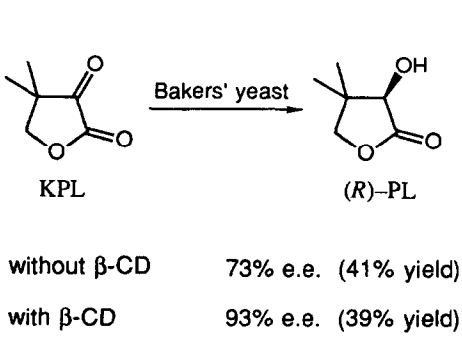
Abstract: *Enantioselectivity in the yeast reduction of ketopantolactone has been improved by addition of β-cyclodextrin to the reaction mixture.*

(*R*)-Pantolactone ((*R*)-PL) is a significant intermediate in the synthesis of coenzyme A. For this purpose, chemical[2-4] and biological methods have been applied to the asymmetric reduction of ketopantolactone (KPL) into PL. Namely, Yamada and his co-workers have contributed to a leading role in enantioselective reduction of KPL by selected microbes.[5,6] Unfortunately, it is difficult for organic chemists to follow this biological method, because they are not familiar with microorganisms except for the popular bakers' yeast. Bakers' yeast has widely been employed for the asymmetric reduction of ketones in organic chemistry.[7,8] Although the reduction of KPL by bakers' yeast has also been reported,[9,10] the enantioselectivity associated with the reduction is poor and the method has not been useful. In this paper, we report a novel method to reduce KPL with bakers' yeast into PL with an excellent enantioselectivity.

When KPL was reduced by bakers' yeast with the substrate concentration of 20 mM, (*R*)-PL was obtained in 41% chemical yield with 73% e.e.[11] In order to improve this unsatisfactory selectivity in the yeast reduction, several methods have been explored and reported by us.[12,13] As one of tricks to improve the selectivity, we employed β-cyclodextrin (β-CD) as an additive to the present reduction system, and found that the e.e. of (*R*)-PL was improved to 93%, a practically satisfactory level.



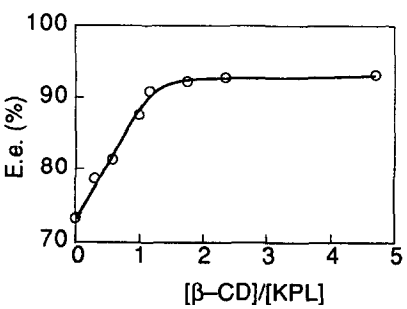


Fig. 1 Effect of β-cyclodextrin on the enantioselectivity of reduction. [KPL] = 20 mM.

Fig. 1 illustrates the effect of β-CD/KPL molar ratio on e.e. in (*R*)-PL. Apparently, the enantioselectivity of the reduction increases with increased amounts of β-CD up to 1.5 equivalent moles relative to KPL, then, the e.e.

stays constant. In contrast, α–CD did not affect the enantioselectivity of the reduction. This fact reveals that β–CD includes KPL into its cavity thus keeping the true concentration of the substrate in the bulk of solution low. There is no doubt that multiple dehydrogenases are responsible to the reduction of KPL, and since these enzymes may have different K_m against KPL, it is conceivable that the enzyme which has smaller K_m becomes more effective for the reduction than the others when the concentration of KPL in the solution is kept low.

This suggestion is supported by the fact that a high e.e. was also achieved at high dilution (3 mM) of KPL in the absence of β–CD. It has been reported that dilution of the substrate results in a high e.e. in the product β–hydroxy ester in the reduction of acetoacetate, a typical β–keto ester, mediated by bakers' yeast.[14] The role of multiple dehydrogenases in changing the selectivity has been demonstrated by Shieh *et al.*[15] and by us.[12]

Several techniques are available to keep the concentration of a substrate low: the substrate may be added in small portions repeatedly,[16] or the use of an organic-water biphasic system will also be effective.[17] In the former system, the reaction with the low substrate concentration of 5 mM or 2 mM indeed gave (*R*)–PL in 91 or 97% e.e., respectively, although the work was troublesome. Contrary, the latter method could not enhance the selectivity, and the e.e. was only 69% in hexane-water system. The observation stems from the fact that KPL is less soluble in hexane than in water, and the substrate concentration is not decreased by the addition of the organic solvent. We propose that the use of an appropriate cyclodextrin is another novel technique applicable to organic syntheses with a biocatalyst. The present method is also effective in protecting a delicate biological system from harmful organic materials.

In a typical run, 38.4 mg (0.3 mmol) KPL was added to 15 ml of water containing 600 mg (0.53 mmol) β–CD and the mixture was stirred vigorously for 10 min. Then, 3.0 g dry bakers' yeast (Oriental Co. Ltd.) was added to the mixture. After 10 h, 20 ml acetone was added to the reaction mixture and the mixture was filtered. The filtrate was evaporated under reduced pressure, then organic materials in the residue were extracted with chloroform (3 × 20 ml). After evaporation of the solvent, residual oil was subjected to column chromatography on silica gel (ethyl acetate : hexane = 1 : 2) to give 15.1 mg (*R*)–PL (39% yield, 93% e.e.).

Applications of the present system to other biological systems and the isolation of KPL reductase from bakers' yeast are now under investigation in our laboratory.

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