FACILE PROCESS FOR ENZYMIC RESOLUTION OF RACEMIC ALCOHOLS

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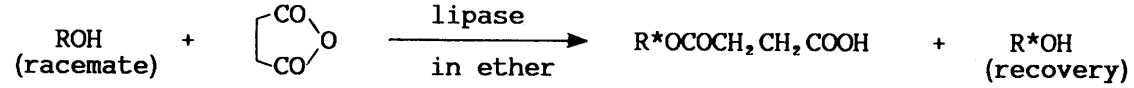
Lipase-catalyzed esterification of a racemic alcohol with succinic anhydride has been found to proceed enantioselectively to afford succinic acid monoester, which was easily separated from non-reacting alcohol by washing with alkaline solution. This procedure provides a facile method for the optical resolution of racemic alcohols.

KEYWORDS optical resolution; racemic alcohol; lipase; succinic anhydride; 1,3-dioxolane-4-methanol

The optical resolution of racemic alcohols is usually carried out by recrystallization of the diastereomeric salt of their phthalic acid or succinic acid monoester with an optically active amine.[1] On the other hand, enzymatic resolution of racemates has been recently developed as an economical process for the large scale production of some optically pure amino acids.[2]

The enzyme-catalyzed reactions are becoming accepted as routine procedures in organic syntheses. Especially, a lipase has been widely used for asymmetric hydrolysis and esterification because It is commercially available and inexpensive, and has a relatively broad substrate specificity.[3] Although the asymmetric syntheses by enzymatic reactions have been recently documented,[3a,b,4] the kinetic resolution of racemates by enzyme-catalyst is still one of the useful methods for the synthesis of optically active compounds. However, it is a major disadvantage to have to separate an unwanted enantiomer for reuse.

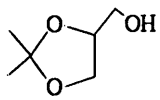
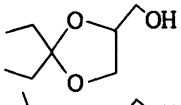
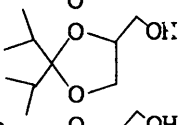
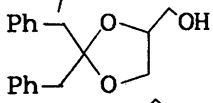
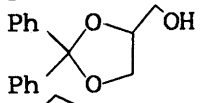
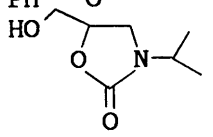
We now wish to report a facile process for the kinetic resolution of racemic alcohols by lipase-catalyzed esterification with acid anhydride in an organic solvent.[5]



ROH: glycerol derivative, secondary alcohol

Racemic alcohols have been found to be enantioselectively acylated with acid anhydride by lipase-catalyst in an ethereal solution leading to the formation of monoester of dibasic acid, which is easily separable with an alkaline solution. We

Table I. Enzymic Resolution of Racemic Alcohols[a)]

Entry	Substrate	Lipase	Time (h)	Reacted alcohol CY (%)[b)]	Reacted alcohol OY (% ee)[c,d)]	Recovered alcohol CY (%)	Recovered alcohol OY (% ee)[c,d)]
1		lipase P	3	42	60 (S)	40	61 (R)
		lipase B	1	40	30 (S)	35	38 (R)
2		lipase P	5	40	61 (S)	47	37 (R)
3		lipase P	12	47	81 (S)	46	80 (R)
4		lipase P	20	45	67 (S)	42	60 (R)
		lipase B	4	45	45 (S)	43	46 (R)
5		lipase P	40	55	30 (S)	40	41 (R)
		lipase B	2	41	92 (S)	50	70 (R)
6		lipase P	1.5	46	75 (R)	38	98 (S)
7	Ph-CH(OH)-CH_3	lipase P	9	45	99 (R)	41	97 (S)
		lipase B	4	46	95 (R)	42	92 (S)
8	$CH_3(CH_2)_5CH(OH)CH_3$	lipase P	9	45	82 (R)	43	78 (S)
		lipase B	4	46	57 (R)	42	61 (S)

a) All reactions were carried out with substrate (5 mmol), succinic anhydride (5 mmol), and lipase (1600 unit) at 25°C. b) Isolated yield of the alcohol obtained by hydrolysis of the produced monoester. c) Optical yields were determined by HPLC analyses using a column packed with Chiralcel OB or OD (2-propanol/hexane system) after benzoylation of the hydroxy group, except entries 4 and 5. d) Absolute configuration (R, S) in parentheses is for the corresponding alcohol, and it was determined by conversion to the authentic specimen.

employed a glycerol derivative as a racemic alcohol because chiral glycerol derivatives are very useful for syntheses of chiral drugs.[6)] The reaction was carried out by incubating at 25°C a mixture of 1,3-dioxolane-4-methanols[7)] (5 mmol), succinic anhydride (5 mmol), and lipase P from Pseudomonas fluorescens[8)] or lipase B from Pseudomonas fragi[9)] (1600 unit) in ether (50 ml). After removal of the lipase by filtration, the ethereal layer was shaken with 1 M sodium carbonate (10 ml). One enantiomer (the recovered substrate) was obtained from the ethereal layer and the other by treatment of the aqueous layer with 10% sodium hydroxide.

Entries 1-5 in Table I show that substituents at the 2-position of 1,3-dioxolane-4-methanols affect the enantioselectivity. The diisopropyl group gave a good result with the use of lipase P (entry 3), and it is of interest that only the phenyl group gave a better result with lipase B than with lipase P (entry 5).

5-Hydroxymethyl-3-isopropyloxazolidin-2-one[10)] is the intermediate for synthesis of 1-alkylamino-3-aryloxy-2-propanols (β-blockers), the S-isomers of which are biologically

more active than the R-isomers.[11] The lipase P-catalyzed esterification with succinic anhydride proceeded smoothly to afford R-isomer, and the S-isomer was recovered in good optical yield (entry 6).

Further research was undertaken for the kinetic resolution of ordinary alcohols. (R)-1-Phenethylalcohol was found to be more rapidly esterified with succinic anhydride than the S-isomer and the racemate was resolved very easily in a similar way (entry 7). It was also possible to obtain two enantiomers of (±)-1-octanol in high chemical and optical yields (entry 8).

The present procedure summarized in Chart 1 seems to rule out the disadvantages of the usual enzymatic resolution or fractional precipitation of the diastereomeric salts in the optical resolutions of racemic alcohols.

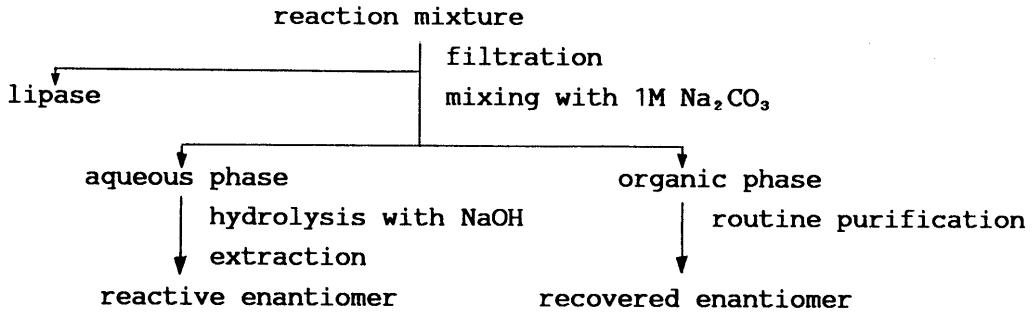


Chart 1

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