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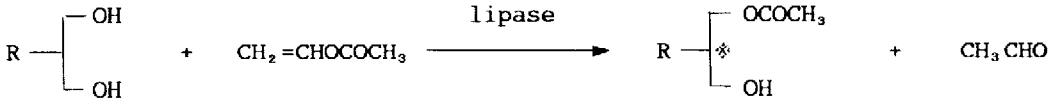
LIPASE-CATALYZED ASYMMETRIC SYNTHESIS OF CHIRAL 1,3-PROPANEDIOLS AND ITS APPLICATION TO THE PREPARATION OF OPTICALLY PURE BUILDING BLOCK FOR RENIN INHIBITORS

Keiichiro Tsuji, Yoshiyasu Terao, and Kazuo Achiwa*
School of Pharmaceutical Sciences, University of Shizuoka
395 Yada, Shizuoka 422, Japan

Abstract: Asymmetric synthesis of chiral 2-substituted-1,3-propanediols was realized by the lipase-catalyzed transesterification in vinyl acetate and it was applied to the synthesis of an optically active sulfone derivative.

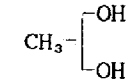
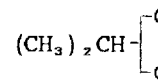
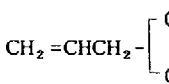
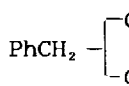
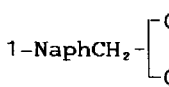
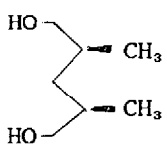
Chiral 1,3-propanediols are useful building blocks for the syntheses of biologically active compounds. Recently, chiral 2-substituted propanediols have been reported to be prepared by diastreoselective reactions.[1] On the other hand, Enzyme-catalyzed asymmetric syntheses have been recognized as a practical method for synthesis of chiral compounds.[2] We have already reported facile synthesis of chiral 2-O-alkylglycerol monoesters by the transesterification catalyzed with lipase in organic medium.[3] We now wish to describe lipase-catalyzed asymmetric synthesis of chiral 1,3-propanediols and its application to synthesis of optically pure (S)-3-isopropylsulfonyl-2-benzylpropionic acid which was a key compound for synthesis of renin inhibitor.[4]



R = CH_3, $(CH_3)_2CH$, $CH_2=CHCH_2$, $C_6H_5CH_2$, $C_{10}H_7CH_2$,

We used lipase P (from pseudomonas fluorescens)[5] and lipase B (from pseudomonas fragi)[5] for these reactions based on our knowledge. The lipase-catalyzed transesterification of 1,3-propanediols proceeded smoothly in 1.5 molar excess of vinyl acetate to afford optically active monoester although the formation of a small amount of diester was observed. The rate of esterification by lipase B was much faster than that by lipase P. However,

Table 1 Lipase-Catalyzed Asymmetric Syntheses of Chiral 1,3-Propanediols[a)]

Entry	Substrate	Lipase	Time (hr)	Monoacetate CY (%)[b)]	Monoacetate OY (% ee)[c)]
1		lipase P	2.5	70	60 (R)
		lipase B	0.5	44	30 (R)
2		lipase P	6	85	61[d)]
		lipase B	1	55	38
3		lipase P	2	89	81[d)]
		lipase B	1	60	65
4		lipase P	1.5	96	97 (R)
		lipase B	0.5	80	77 (R)
5		lipase P	7	95	90[d)]
		lipase B	3.5	86	28
6		lipase P	6	82	98[e)]
		lipase B	1	55	95[e)]

a) All reactions were carried out with substrate (5 mmol), vinylacetate (7.5 mmol), and lipase P (100 mg) or lipase B (50mg) at 25 °C. b) Isolated yield c) Optical yields were determined by HPLC analyses using the column packed with Chiralcel OB or OD (2-propanol/hexane system) after benzoylation of the hydroxy group except entries 4 and 5. d) Absolute configurations of the products are under investigation. e) (2R, 4S)-1-hydroxy-2, 4-dimethylpentyl acetate.

the enantioselectivity of lipase P was better than that of lipase B. It is noteworthy that 2-benzyl- and 2-(1-naphthylmethyl)propanediols gave the corresponding monoester in extremely high chemical and optical yields (entries 4 and 5) compared with the other cases as summarized in Table 1. In addition, It was unexpected that 2-benzyl-1,3-propandiol gave the (R)-monoester[6] (entry 5) because 2-O-benzylglycerol gave the (S)-monoester in high optical yield by the same lipase P-transesterification[3] (Chart 1). This fact seems to offer some suggestions on designing the reaction model[7] from the viewpoint of the enzymic discrimination of an enantiotopic group.

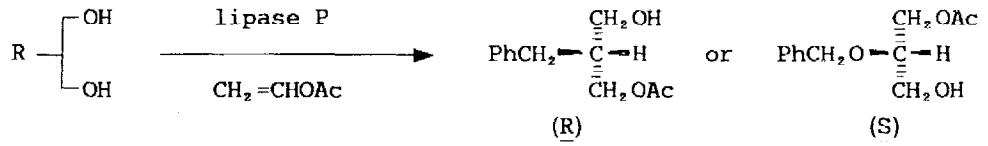


Chart 1

The lipase-catalyzed transesterification in vinyl acetate was undertaken for 1, 5-pentanediols. A similar transesterification of 2, 4-dimethyl-1, 5-pentandiol (meso) afforded (2R, 4S)-1-hydroxy-2, 4-dimethylpentyl acetate[8] in high optical yield (entry 6).

In order to demonstrate the usefulness of optically active 2-substituted-1,3-propanediols for syntheses of biologically active chiral compounds, we prepared optically pure (R)-2-benzyl-3-isopropylsulfonyl-propionic acid which was reported to be a key compound for synthesis of renin inhibitor (7)[4] (Chart 2).

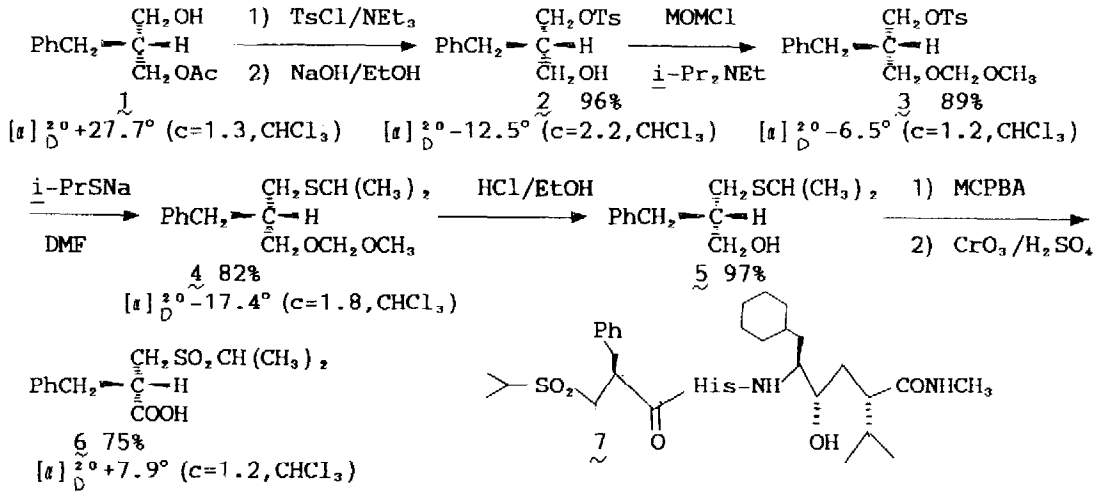


Chart 2

The treatment of (R)-2-benzyl-1-hydroxypropyl acetate (1) with tosyl chloride followed by hydrolysis with sodium hydroxide in ethanol gave the (S)-tosylate (2) in quantitative yield. After protection of the hydroxy group of 2, the compound (3) reacted with sodium isopropylthiolate in DMF at room temperature to afford the sulfide (4) in 82% yield. The oxidation of 5 was first carried out with m-chloroperbenzoic acid, and the usual Jone's oxidation of the isolated sulfone gave (S)-2-benzyl-3-isopropylsulfonyl-propionic acid (6). After treatment of 6 with diazomethane, the optical

purity of the methyl ester[8] was determined to be >97%ee by the HPLC analysis (Chiracel OC, 2-propanol/hexane). The renin inhibitor (7) can be synthesized from 6 according to the reported method.[4]

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5. Lipase P and Lipase B were supplied by Amano Pharmaceutical Co. Ltd. and Sapporo Breweries Ltd., respectively.
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8. $[\alpha]_D^{20}$+11.7 (c=1.9 $CHCl_3$). C. J. Sih and his co-workers obtained (2S, 4R)-2, 3-dimethyl-1-hydroxypentyl acetate, $[\alpha]_D^{25}$-9.5 (89.7%ee), by the lipase-catalyzed hydrolysis of 1,5-diacetoxy-cis-2, 4-dimethylpentane; Y-F Wang, C-S Chen, G. Girdaukas, and C. J. Sih, J. Am. Chem. Soc., 106, 3695 (1984).
9. Structures of the new compounds obtained here were determined by their spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution MS). The (R)-isomer was also prepared from the compound obtained by protection of the hydroxy group of 1 with methyloxymethyl chloride according to a similar synthetic route.

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