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HIGHLY EFFICIENT LIPASE-CATALYZED ASYMMETRIC SYNTHESIS OF CHIRAL GLYCEROL DERIVATIVES LEADING TO PRACTICAL SYNTHESIS OF (*S*)-PROPRANOLOL

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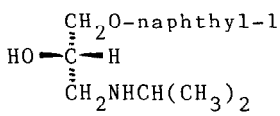
Abstract: Efficient asymmetric synthesis of chiral glycerol derivatives was realized by lipase-catalyzed reaction in organic medium and its application for synthesis of (*S*)-propranolol was demonstrated.

Chiral glycerol derivatives are versatile chiral building blocks for the syntheses of several types of chiral medicines including (*S*)-propranolol (**1**) and the related compounds[1], PAF (**2**) and PAF antagonists[2], and GABOB (**3**)[1b,3] as its simple derivatives.



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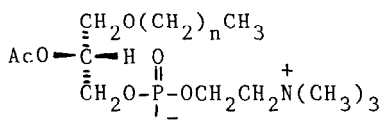
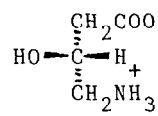


2 (n= 15 or 17)



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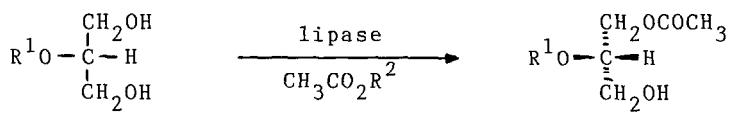
We now wish to report the extremely stereoselective and efficient lipase-catalyzed asymmetric synthesis of (*S*)-2-*O*-substituted glycerol-1 acetates (**4a, b**) from the corresponding 1,3-diols (**5a, b**) and acetates.



5a, b (*S*)-**4a, b**

a: $R^1 = PhCH_2$ **b:** $R^1 = C_2H_5$

R^2 = alkyl, $PhCH_2$, Ph, CH_2=CH

Table 1 Asymmetric Synthesis of (*S*)-2-*O*-Substituted Glycerol-1 Acetates by Lipase-catalyzed Reaction[a)]

Entry	R^1	R^2	Conversion (%)	Isolated yield(%)	Optical yield(%ee)[b)]
1	$PhCH_2$	C_2H_5[c)]	26	20	90 (*S*)
2	$PhCH_2$	n-C_4H_9[c)]	29	23	90 (*S*)
3	$PhCH_2$	i-C_4H_9[c)]	5	4	92 (*S*)
4	$PhCH_2$	$PhCH_2$	32	28	88 (*S*)
5	$PhCH_2$	Ph	92	88	90 (*S*)
6	$PhCH_2$	CH_2=CH	100	92	90 (*S*)
7	$PhCH_2$	CH_2=CH[d)]	100	92	94 (*S*)
8	$PhCH_2$	CH_2=CH[e)]	100	92	92 (*S*)
9	C_2H_5	Ph	100	90	90[f)] (*S*)

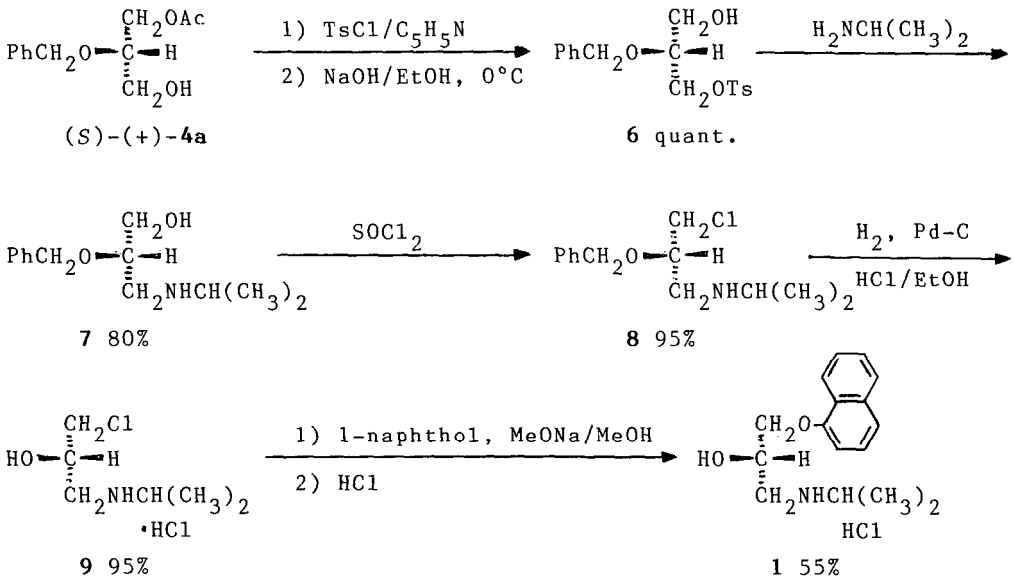
a) All reactions were carried out with substrate (50 mmol), acetate (100 mmol), and Lipase P (0.5 g, 7,500 unit) at 25°C for 3 hr except otherwise cited. *b)* Optical yields were determined by HPLC analysis using a column packed with LKB Enantio Pack (8 mM phosphate buffer cont. 0.1 M NaCl). *c)* Lipase P (7.5 g 112,500 unit). *d)* at 8°C for 4 hr. *e)* at 17°C for 3.5 hr. *f)* determined by using a HPLC column packed with Chiralcel OB (*i*-PrOH/hexane = 1/30) after benzoylation of the hydroxy group.

Although in enzymic reaction an organic solvent generally causes significant inactivation or inhibition of catalytic process[4], the transesterification has been found to be catalyzed even in the organic medium such as 2-*O*-substituted glycerol and acetate. After preliminary screening tests for searching the desirable lipases, we employed Lipase P from *Pseudomonas fluorecens*[5], and examined the esterification of 2-*O*-benzylglycerol with various acetates. The reactions proceeded stereoselectively to afford (*S*)-(+)-2-*O*-benzylglycerol-1 acetate[6] as shown in Table 1. Furthermore, vinyl and phenyl acetates promoted this reaction with high stereoselectivity (entries 5-8). 2-*O*-Ethylglycerol gave also (*S*)-(+)-2-*O*-ethylglycerol-1 acetate[7] in high chemical and optical yields (entry 9).

It is a great advantage of this method that routine filtration to remove the enzyme and concentration of the filtrate give the product without extrac-

tion procedure[8]. Therefore, it makes possible to apply for a large scale production by employing a column technique.

The utility of (*S*)-(+)-2-*O*-benzylglycerol-1 acetate as a chiral building block was demonstrated by the synthesis of (*S*)-propranolol hydrochloride (**1**) which is one of the aryloxypropylamine-type β-blockers[1].



(*S*)-(+)-**4a** → **6** quant. → **7** 80% → **8** 95% → **9** 95% → **1** 55%

Scheme 1

Treatment of **4a** with *p*-toluenesulfonyl chloride in pyridine followed by hydrolysis with sodium hydroxide in ethanol gave **6** quantitatively. The compound **6** was heated at 60°C with excess isopropylamine in a sealed tube to afford (*S*)-2-benzyloxy-3-isopropylamino-1-propanol (**7**) in 80% yield. After chlorination of **7** with thionyl chloride, hydrogenolysis of **8** over 5% Pd-C in ethanol including an equimolar amount of hydrogen chloride gave (*S*)-(-)-1-chloro-3-isopropylamino-2-propanol hydrochloride (**9**). Synthesis of (*S*)-propranolol from **9** was realized by treatment with 1-naphthol in MeONa/MeOH at refluxing temperature in 55% yield. Recrystallization of its hydrochloride from EtOH-ether gave optically pure (*S*)-propranolol hydrochloride (**1**)[9]. According to this process the other β-blockers can be synthesized from **6**, **8**, or **9** by the change of amine or aryl alcohol.

Thus, we have provided an efficient method for syntheses of chiral glycerol derivatives utilized for the practical productions of optically active medicines.

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5. supplied by Amano Pharmaceutical Co.
6. $[\alpha]_D^{21}$ 13.4° (c=2.0, EtOH)(obtained in entry 7)
7. $[\alpha]_D^{21}$ 10.6° (c=1.0, EtOH): The absolute configuration was determined by conversion into (*R*)-2-ethoxy-3-methoxy-1-propanol, which was also derived from (*S*)-**4a**.
8. Recently, the enzymic hydrolysis of 2-*O*-benzylglycerol diacetate in buffer solution has been reported to give (*R*)-(-)-**4a**; D. Breitgoff, K. Lawman, and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, **1986**, 1523.
9. mp 191-192°C, $[\alpha]_D^{21}$ -25.1° (c=0.9, EtOH) [lit.[1c], mp 192-193.5°C, $[\alpha]_D^{21}$ -25.7° (c=1.23, EtOH)], Anal. Calcd. for $C_{16}H_{22}ClNO_2$:C, 64.96; H, 7.50; N, 4.74. Found: C, 64.69; H, 7.47; N, 4.72. The other compounds described here gave also satisfactory spectral (IR, ^{1}H- and ^{13}C-NMR) and analytical data.

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