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Enzymatic Preparation of Chiral 1-Phenylglycidols and 1-Phenyl-1,2-propanediols

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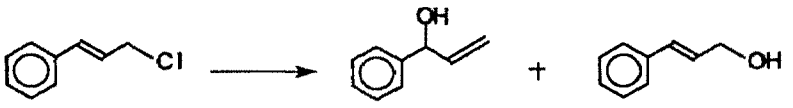
Abstract: Asymmetric synthesis of chiral 1-phenylglycidols and the *O*-acetates, which were expected to be useful intermediates for the synthesis of β-blockers, has been achieved effectively by use of baker's yeast and lipase PS. These chiral epoxides could be reduced regioselectively with lithium aluminium hydride to give chiral 1-phenyl-1,2-propanediols.

Asymmetric synthesis catalyzed by enzymes has been recognized as a potentially useful tool for the synthesis of chiral building blocks. Lipase-catalyzed esterifications of racemic compounds based on their abilities to discriminate between enantiotopic hydroxy groups have been proven valuable in this regard.[1,2] Encouraged with the reports of highly stereoselective syntheses using lipase,[2] we have investigated the synthesis of optically active 1-phenylglycidols, which are expected to be chiral intermediates for the synthesis of biologically active compounds such as β-blockers.[3] We now report the enantioselective syntheses of 1-phenylglycidols (**4a-b**) and the acetates (**5a-b**) by use of lipase PS (*Pseudomonas sp.*)(Amano),[2] and the regioselective syntheses of 1-phenyl-1,2-propanediols (**6a-d**), which could be important chiral building blocks in asymmetric organic synthesis, by reduction of **4a-b** and **5a-b**.

First of all, a facile synthesis of 1-phenyl allylalcohol **2**[4] as starting material has been investigated. As shown in Table 1, when cinnamyl chloride **1** was treated with water (without baker's yeast) for 17 h at 30°C, 1-phenyl allylalcohol **2** and cinnamyl alcohol **3** were obtained in the yield of 7:66%. In this reaction, some hydrolysis with rearrangement had taken place to give **2** as the minor product. On the other hand, very interestingly, when **1** was treated with baker's yeast, rearrangement preferentially occurred to give **2** as the main product [the yield ratio(%), **2**:**3** = (48~58) : (0~15). However, the optical activity of **2** was low (<5% ee).

Table I. Synthesis of 1-phenyl allylalcohol

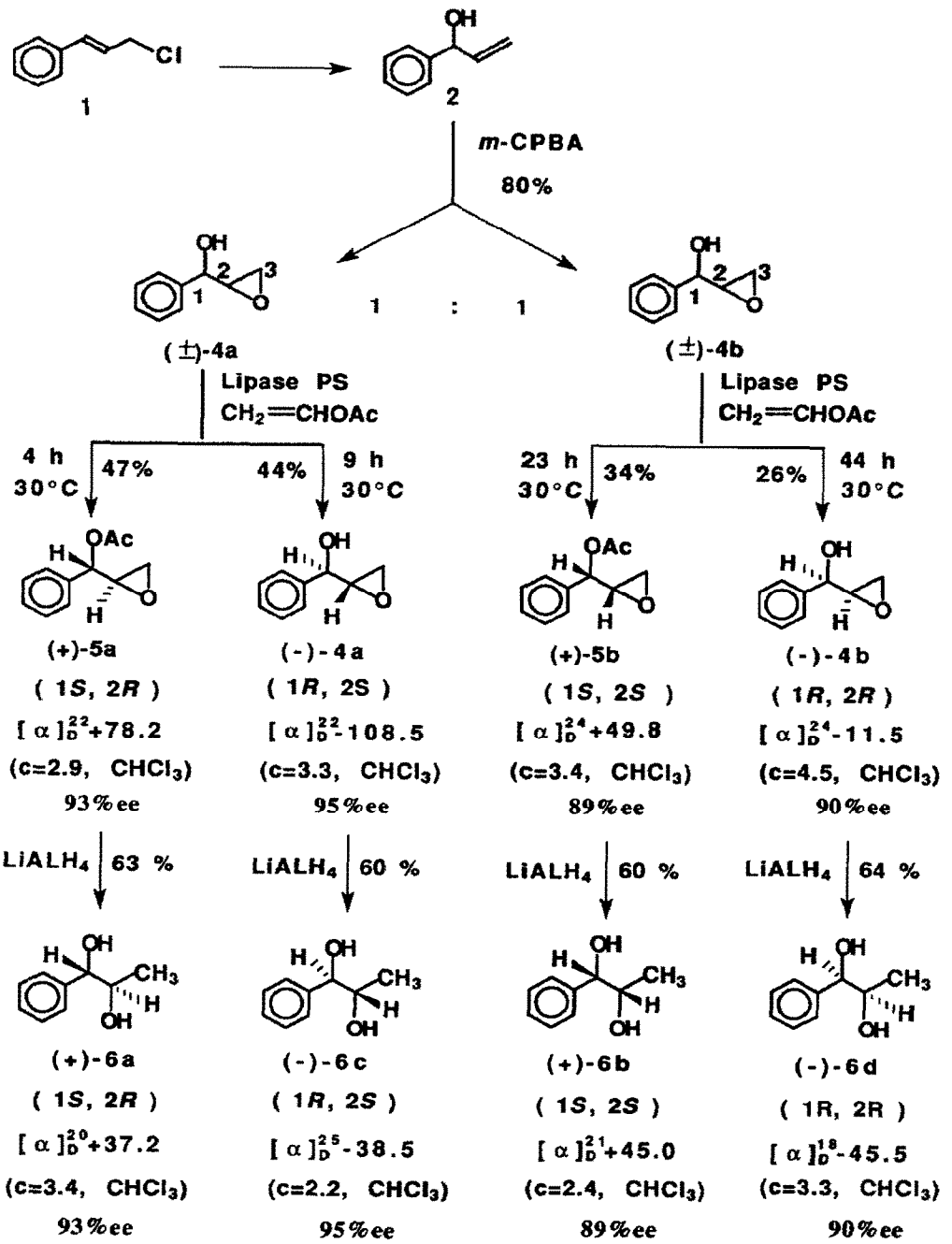


1 2 3

Reaction	Temp. °C	Time h	Yield of2(%)	Yield of3(%)
H_2O only	30	17	7	66
Baker's yeast no buffer	30	45	58	15
Baker's yeast pH 6.90	30	24	48	7
Baker's yeast pH 7.48	30	40	53	2
Baker's yeast pH 8.03	25	44	50	0

Secondly, when each of the two pairs of the racemic 1-phenylglycidols (±)-(**4a**) and (±)-(**4b**), which were prepared by epoxidation of 1-phenyl allylalcohol **2** with *m*-chloroperbenzoic acid (total yield 80%), were treated with vinyl acetate in *t*-butyl methylether in the presence of lipase PS[2d] for 4~44 h at 30°C, as summarized in Scheme 1, the optically active acetates (1*S*,2*R*)-(+)-**5a** and (1*S*, 2*S*)-(+)-**5b** and the optically active alcohols (1*R*,2*S*)-(-)-**4a** and (1*R*,2*R*)-(-)-**4b** were obtained in the yields of 47, 34, 44 and 26% respectively, The absolute configuration and the optical purities (%ee) of epoxides **4a-b** and **5a-b** were determined by converting them into the phenyl-1,2-propanediols (**6a-d**).[5,6] The reduction of **4a-b** and **5a-b** with lithium aluminium hydride proceeded regioselectivley at C-3 to give only products (**6a-d**).[7] Thus, (1*S*,2*R*)- and (1*S*,2*S*)-1-phenyl-1,2-propanediol (+)-**6a**[6] and (+)-**6b** were obtained from (+)-**5a** and (+)-**5b** in 93 and 89%ee, while (1*R*,2*S*)- and (1*R*,2*R*)-1-phenyl-1,2-propanediol (-)-**6c** and (-)-**6d** were obtained from (-)-**4a** and (-)-**4b** in 95 and 90%ee, respectively.

Thus it has been found that baker's yeast is an efficient catalyst for the synthesis of 1-phenyl allylalcohol **2**. Asymmetric synthesis of glycidol derivatives by enantioselective esterification using lipase PS and the new synthesis of chiral 1-phenyl-1,2-propanediols (**6a-d**) by regioselective ring opening of epoxides


Cl
1
OH
2
m-CPBA
80%
1 : 1
(±)-4a
(±)-4b
Lipase PS
CH2=CHOAc
4 h
30°C
47%
44%
9 h
30°C
23 h
30°C
34%
26%
44 h
30°C
OAc
OH
(+)-5a
(1S, 2R)
[α]D22+78.2
(c=2.9, CHCl3)
93%ee
(-)-4a
(1R, 2S)
[α]D22-108.5
(c=3.3, CHCl3)
95%ee
(+)-5b
(1S, 2S)
[α]D24+49.8
(c=3.4, CHCl3)
89%ee
(-)-4b
(1R, 2R)
[α]D24-11.5
(c=4.5, CHCl3)
90%ee
LiALH4
63 %
60 %
60 %
64 %
CH3
(+)-6a
(1S, 2R)
[α]D20+37.2
(c=3.4, CHCl3)
93%ee
(-)-6c
(1R, 2S)
[α]D25-38.5
(c=2.2, CHCl3)
95%ee
(+)-6b
(1S, 2S)
[α]D21+45.0
(c=2.4, CHCl3)
89%ee
(-)-6d
(1R, 2R)
[α]D18-45.5
(c=3.3, CHCl3)
90%ee

4a-b and **5a-b** with lithium aluminium hydride could be expected to provide a versatile and synthetically useful method for the preparation of biologically active compounds.

References and Notes

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6. See ref. 5a. As we previously reported the synthesis of the three diastereoisomers (+)-**6b**, (-)-**6c**, and (-)-**6d**, the absolute configuration of the remaining (+)-**6a** was easily deduced to 1*S*, 2*R* and the optical yield of (+)-**6a** was evaluated by Mosher's method. see; Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.*, 1969, **34**, 2543.
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