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Enzymatic Preparation of Glycerol-related Chiral Pool Possessing *tert*-Alkoxy Group[1)]†

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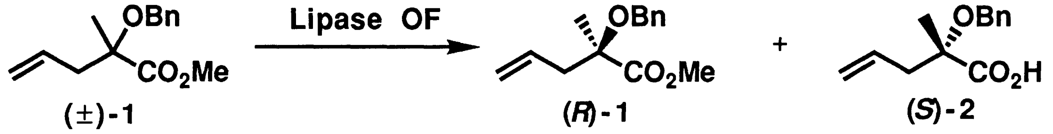
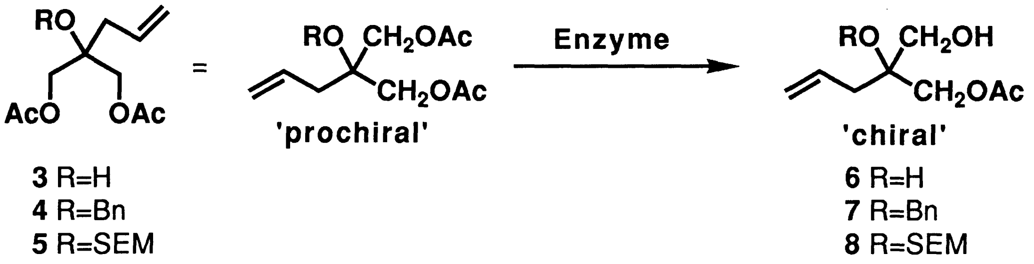
Several kinds of enzymes catalyzed the enantioselective hydrolysis of 2-substituted glycerol 1,3-diacetates to afford optically active monoacetates of 50-73%e.e. under ordinary conditions (phosphate buffer, pH 7, 30 °C). After examining the effect of co-solvents, the hydrolysis of 2-trimethylsilylethoxymethoxyglycerol 1,3-diacetate using lipase LP was improved to afford the monoacetate of 87%e.e. with definite absolute configuration in 50% aqueous DMF at 3 °C.

Optically active tertiary alcohol derivatives are widespread in physiologically important compounds. Recently, we have developed a preparative-scale synthesis of the versatile starting material (*R*)-**1** and (*S*)-**2** in a highly enantiomerically pure state by the enzymatic hydrolysis of (±)-**1**.[2)] While the application of **1** and **2** in natural product syntheses[3)] have been accomplished, a novel glycerol-related optically active starting material **6**-**8** have been disigned. These monoesters obviously have an advantage that the methyl group in **1** and **2** is replaced to hydroxymethyl group which makes the carbon-carbon chain elongation in all three ways possible. Moreover, these compounds can possibly be obtained by the enzymatic asymmetrization of prochiral substrates **3**-**5** theoretically in 100% yield, which in turn is intrinsically impossible in the case of the kinetic resolution of (±)-**1**.





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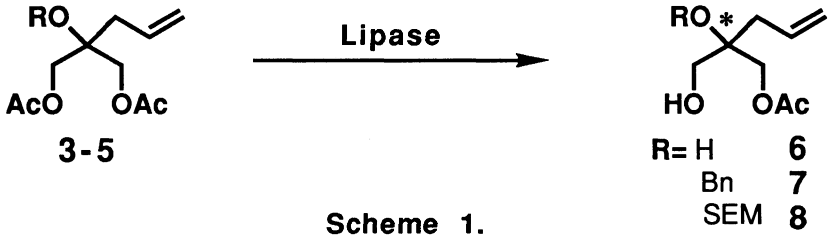
†Dedicated to Professor Emeritus Osamu Simamura of The University of Tokyo on the occasion of his 80th birthday.

Among a number of enzymatic processes for transformation of prochiral compounds,[4] few examples involving the substrate which possesses alkyl chain at C-2 position of glycerol have been reported so far.[5] The substrates (**3**-**5**) are readily prepared from commercially available dihydroxyacetone dimer[6] via Sakurai reaction[7] as a key-step.

At the outset, enantioselective hydrolysis of diacetates **3**-**5** were studied with commercially available enzymes (Scheme 1). The results summarized in Table 1 show that the e.e.[8] and the yields of monoacetates **6**-**8** depend on the protecting groups of tertiary hydroxy group.



Scheme 1.

Table 1. Enantioselective hydrolysis of diacetates (**3**-**5**)[a]

Substrate	R	Enzyme	Yield of monoacetate/%	e.e./%
3	H	PLE	54	50
4	Bn	AP	15	70
5	SEM	LP	37	70
5	SEM	PLE	6	73

a) All reaction were performed in 0.2 M phosphate buffer.

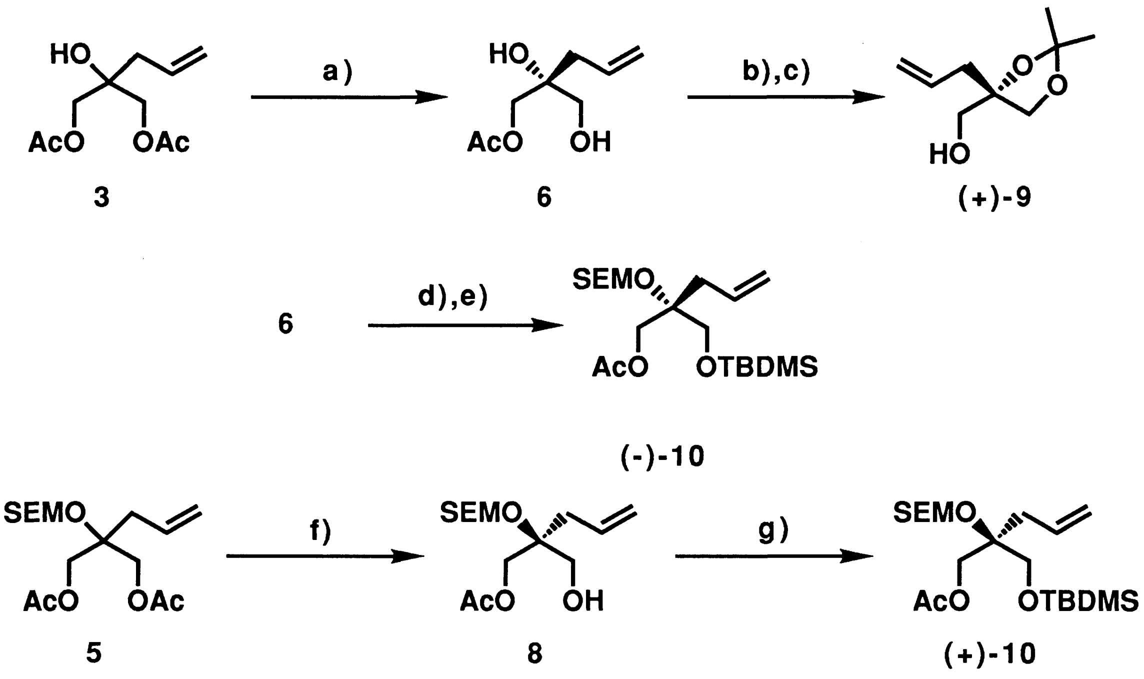
As hydrolysis of SEM (trimethylsilylethoxymethyl)[9] protected substrate **5** by PLE (pig liver esterase) and lipase LP (from *Chromobacterium viscosum*) afforded monoacetate **8** of relatively high e.e., we decided to study the reaction conditions of **5** in more detail, concerning the addition of water miscible organic co-solvent, pH and the concentration of buffer solution[10] (Table 2). In the case of lipase LP, the addition of N,N-dimethylformamide (DMF) gave preferable results (run 3). Lowering the reaction temperature to 3 °C (ice-water bath) raised the e.e. of **8** from 60 to 71% (runs 3, 4) as expected. Moreover, increasing the concentration of DMF in phosphate buffer from 20 to 60% improved the e.e. up to 84% (run 6), while further addition of DMF brought about the decrease in the rate of hydrolysis. The effect of pH was finally examined at 3 °C in the presence of 50% DMF. Surprisingly, both raising (to 8) and lowering (to 6) the pH resulted in improvement of the optical yield of the reaction to 88%. Under acidic conditions (pH below 6.5), the rate of hydrolysis became smaller compared with that under basic conditions (pH above 7.5). In the case of PLE, the effective way to increase the e.e. of resulting monoacetate **8** was to dilute the concentration of phosphate buffer from 0.2 M to 0.06 M.[11] As shown in column 11 and 12, the e.e. of the monoacetate rose to 92% in contrast to 73%, although the yield of the product was not sufficiently high because of overhydrolysis to the corresponding diol.

The absolute configuration of monoacetate (**8**) was determined as shown in Scheme 2. Enzymatic hydrolysis product **6** was derived to acetonide alcohol (+)-**9** of which absolute configuration had been already established to be (*S*).[12] Hence, the configuration of **6** could be confirmed to be (*R*). This (*R*)-monoacetate **6** was converted to silyl derivatives (-)-**10** $[\alpha]_D^{25}$ $-8.5°$ (c 1.4, $CHCl_3$) of which absolute configuration is defined

Table 2. Effects of organic co-solvents, temperature and pH[a)]

Run	Enzyme	pH	Org. co-solvent		Temp/°C	Yield/%	e.e./%
1	LP	7	DMSO	20%	r.t	38	67
2	LP	7	Acetone	10%	r.t	42	62
3	LP	7	DMF	20%	r.t	68	60
4	LP	7	DMF	20%	3	47	71
5	LP	7	DMF	50%	3	38	77
6	LP	7	DMF	60%	3	37	84
7	LP	7.5	DMF	50%	3	74	88
8	LP	8.0	DMF	50%	3	74	87
9	LP	6.5	DMF	50%	3	55	85
10	LP	6.0	DMF	50%	3	58	85
11	PLE[b)]	7	*t*-BuOH	10%	r.t	23	80
12	PLE	7	none		3	40	92
13	PLE	7	DMF	20%	3	51	90

a) Unless otherwise stated, 0.06 M phosphate buffer was used as aqueous component.
b) Phosphate buffer of 0.2 M was used.



a) PLE/phosphate buffer b) 2,2-dimethoxypropane, TsOH/Acetone
c) K_2CO_3/ MeOH d) TBDMSCl, imidazole/DMF e) SEMCl, *i*-Pr_2NEt/CH_2Cl_2
f) lipase LP/phosphate buffer-(50%)DMF g) TBDMSCl, imidazole/DMF

Scheme 2.

to be (*S*). On the other hand, monoacetate **8** obtained via lipase LP-mediated hydrolysis of diacetate **5** was protected by TBDMS to afford (+)-**10** $[\alpha]_D^{22}$ +14.1° (c 1.1, $CHCl_3$). These observations lead to the conclusion that the compound **10** of different origin has the opposite configuration with each other. Thus the absolute configuration of monoacetate **8** was unambiguously determined to be (*S*).

In conclusion, optically active triol derivatives **8** was efficiently prepared by the asymmetric hydrolysis. The synthetic application of **8** is demonstrated in the subsequent paper.

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12) (*S*)-**9** from **3**, $[\alpha]_D^{25}$ +1.4° (c 1.4, $CHCl_3$); lit$^{13)}$ $[\alpha]_D^{20}$ −3° (c 3, $CHCl_3$).

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