Preparation of Optically Active 1-*O*-Alkyl-3-*O*-arylsulfonyl-*sn*-glycerol Derivatives: Substrate Engineering in Enzyme-Mediated Enantioselective Hydrolysis

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Abstract: Lipase PS catalyzes the enantioselective hydrolysis of various 2-acetyl compounds of the 1-*O*-alkyl-3-*O*-arylsulfonyl-*sn*-glycerol derivatives to afford the corresponding optically active compounds. Changing the structure of the 1-*O*-alkyl and 3-*O*-arylsulfonyl groups affects both the reactivity and enantioselectivity. Finally, the *E* value of the reaction for 2-acetyl-3-*O*-3,5-dimethylbenzenesulfonyl-1-*O*-4-methoxybenzyl-*sn*-glycerol is greater than 200.

Key words: enantioselective hydrolyses, enzymes, kinetic resolution, glycerol derivatives, tosylates

During the synthesis of natural and biologically active compounds, optically active glycerol derivatives play significant roles as useful chiral synthones. Moreover, the 1-*O*-alkyl-*sn*-glycerol derivatives are direct precursors for naturally occurring lipids with a broad spectrum of biological activities. Recently, the enzymatic reaction is one of the practical and attractive methods used for the preparation of such optically active compounds.[1] The hydrolase-mediated kinetic resolutions of the racemic 1,2-diol monotosylate derivatives have also been developed as a representative procedure.[2–4] We have also accomplished the practical preparation of various optically active 1,2-diol monotosylates by enzymatic hydrolysis with lipase PS (*Burkholderia cepacia*) from Amano Enzyme, Inc., and the methodical study of the substrate specificity.[5] We realized that the methodology was applicable to the preparation of the optically active glycerol derivatives, although the reactions did not always satisfactorily work in terms of the enantioselectivity in some cases. In this paper, we disclose the easy preparation of optically active glycerol derivatives by enzymatic hydrolysis of the acetyl compounds of the 1-*O*-alkyl-3-*O*-arylsulfonyl-*sn*-glycerol derivatives. In particular, we focused on engineering the structure of the 1-*O*-alkyl group, which could be easily removed as the protecting group, and the arylsulfonyl part as the leaving group in order to improve the enantioselectivity for obtaining the useful chiral synthon with a high ee, although both groups did not affect the structure of the glycerol backbone.

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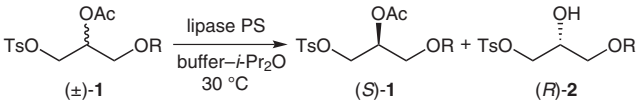
We first examined the lipase-catalyzed hydrolysis of the racemic 2-acetyl-3-*O*-tosyl-*sn*-glycerol derivatives (±)-**1** bearing a suitable protecting group at the *sn*-1 position (Table 1). The substrates were easily prepared from 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane by protection and deprotection processes.[6] In all cases, the enzymatic reactions were performed using 4 mM of the substrates with lipase PS (30 mg per 0.16 mmol of the substrate) in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O for 24 hours at 30 °C. As shown in entry 1, we already found that the *R*-enantiomer of (±)-**1a** with a benzyl group (R = Bn) was selectively hydrolyzed to afford the almost optically pure (*S*)-**1a** as the remaining substrate and the resulting (*R*)-**2a**.[5,7] However, the enantioselectivity was moderate (*E* value = 22)[8] and lower than that in the case of the substrate bearing a methyl group (R = Me), which could not be easily deprotected under mild conditions (*E* value = 292).[5] Interestingly, changing the R group drastically affected both the reactivity and the enantioselectivity. The enzyme catalyzed the hydrolysis of (±)-**1b** bearing a benzyloxymethyl group (R = BOM) with a higher enantioselectivity (conv. = 0.51, *E* value = 127) to afford (*S*)-**1b** with a 98% ee and (*R*)-**2b** with a 93% ee in 46% and 52% yields, respectively (entry 2), although the conversion was lower than that in the case of **1a**. Furthermore, the hydrolysis of the substrate (±)-**1c** bearing a 4-methoxybenzyl group (R = PMB) gave the best result (entry 3). The *E* value was up to 145 (conv. = 0.52), and both enantiomers with high ee were obtained; (*S*)-**1c** with a 99% ee and (*R*)-**2c** with a 93% ee. In these cases, we assumed that the hydrolysis of the *S*-enantiomers could be very slow due to the interaction between the enzyme and the oxygen atom of the R groups, thus this phenomenon could lead to lower conversions and higher enantioselectivities. On the other hand, the substrate (±)-**1d** bearing a *tert*-butyldimethylsilyl group (R = TBS) was also hydrolyzed to give the corresponding (*R*)-**2d** (entry 4). However, the ee of the resulting **2d** was very low (12% ee), and the substrate **1d** was decomposed under the stated reaction conditions.

When the benzyl group is fixed as the R substituent, we can operate by changing the acyl and arylsulfonyl parts in order to improve the enantioselectivity. Because triglycerides of the higher fatty acids are the original substrates of the lipase, the longer-chain acyl group could be better for the enzymatic hydrolysis. However, using a longer-chain

Table 1 Enantioselective Hydrolysis of 2-*O*-Acetyl-1-*O*-alkyl-3-*O*-tosyl-*sn*-glycerol [(±)-**1**][a]



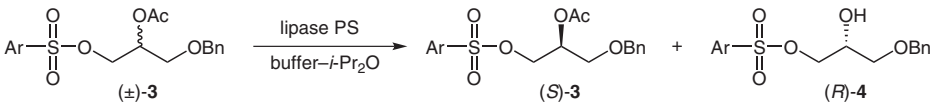
Entry		R	(*S*)-**1**		(*R*)-**2**		Conv.[b]	*E* value[c]
			Yield (%)	ee (%)	Yield (%)	ee (%)		
1[d]	**a**	Bn	29	99.6	58	59	0.63	22
2	**b**	BOM	46	98	52	93	0.51	127
3	**c**	PMB	45	99	52	93	0.52	145
4	**d**	TBS	0	–	27	12	–	–

[a] Unless otherwise noted, the reaction was performed using (±)-**1** (4 mM) with lipase PS in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O for 48 h at 30 °C.
[b] Calculated using ee(**1**)/[ee(**1**) + ee(**2**)].
[c] Calculated using ln{[1 – conv.][1 – ee(**1**)]}/ln{[1 – conv.][1 + ee(**1**)]}.
[d] We already reported these results in ref. 5.

acyl group leads to an increase in the molecular weight of the substrates. We then decided that this method was not good for the practical synthesis, and next became interested in the structure of the arylsulfonyl group. In previous reports, little attention has been paid to the structure of the arylsulfonyl group because this was merely a kind of leaving group. However, we expected that the substitution pattern on the aryl group could affect the reactivity in a similar manner as in the case of the alkyl part, although the aryl group could be remote from the active center of the enzyme. We then carried out the enzymatic hydrolyses of the substrates with various arylsulfonyl groups, and these results are summarized in Table 2.[9]

Changing Ar to a phenyl group [(±)-**3a**], which has no substitution on the ring, slightly improved the enantioselectivity (*E* value = 30), and the conversion was lower than that in the case of **1a** (Table 2, entry 1). Interestingly, the substrate bearing a methyl group at the *meta* position [(±)-**3c**, Ar = 3-MeC_6H_4] was hydrolyzed with a higher enantioselectivity (*E* value = 60) to afford the almost optically pure (*S*)-**3c**, while a methyl substitution at the *ortho* position [(±)-**3b**, Ar = 2-MeC_6H_4] did not improve the enantioselectivity (entries 2 and 3). Based on these observations, we assumed that a methyl group at the *meta* position on the benzene ring could play an important role in the enzymatic distinction of the stereochemistry. As expected, the highest enantioselective hydrolysis of the (±)-**3d** with a 3,5-dimethylphenyl group (Ar = 3,5-$Me_2C_6H_3$), which had two methyl groups at the *meta* positions, for 24 hours at 30 °C smoothly proceeded (conv. = 0.49) to af-

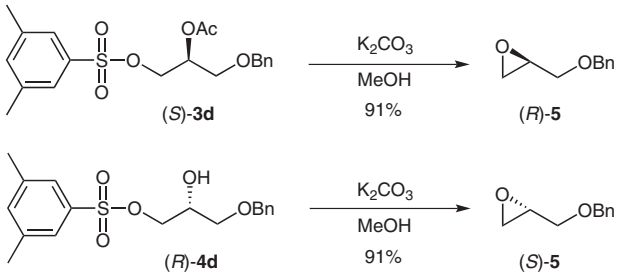
Table 2 Enantioselective Hydrolysis of 2-*O*-Acetyl-1-*O*-benzyl-3-*O*-arylsulfonyl-*sn*-glycerol [(±)-**3**][a]



Entry		Ar	Time (h)	Temp (°C)	(*S*)-**3**		(*R*)-**4**		Conv.	*E* value
					Yield (%)	ee (%)	Yield (%)	ee (%)		
1	**a**	Ph	24	30	28	82	40	89	0.52	30
2	**b**	2-MeC_6H_4	24	30	47	74	43	80	0.48	20
3	**c**	3-MeC_6H_4	24	30	39	99.7	58	81	0.55	60
4	**d**	3,5-$Me_2C_6H_3$	24	30	42	93	48	96	0.49	168
5			48	30	44	>99.8	53	88	0.53	>106
6			24	10	69	26	25	93	0.22	33
7			24	20	46	87	50	87	0.51	42
8			24	40	39	88	40	82	0.52	29
9	**e**	2,4,6-$Me_3C_6H_2$	48	30	52	73	43	82	0.47	22

[a] Unless otherwise noted, the reaction was performed using (±)-**3** (4 mM) with lipase PS in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O.

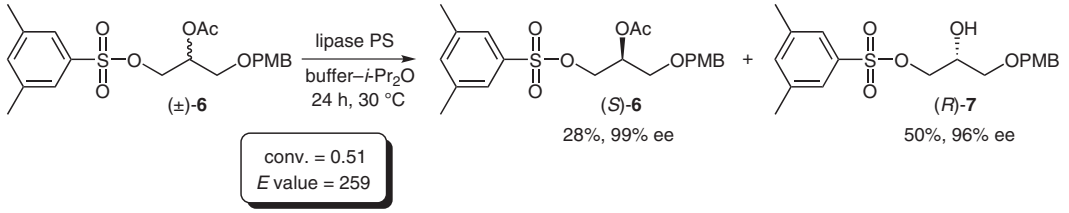
ford (*S*)-**3d** with a 93% ee and (*R*)-**4d** with a 96% ee, and the *E* value was up to 168 (entry 4). Successive treatment of (*S*)-**3d** and (*R*)-**4d** with K_2CO_3 in MeOH resulted in both enantiomers of the useful chiral synthons (*R*)- and (*S*)-benzyloxy-1,2-epoxypropane (**5**), respectively, without any racemization (Scheme 1).[10] A 48-hour reaction gave the optically pure (*S*)-**3d** (entry 5). It is noteworthy that lowering and raising the reaction temperature decreased the enantioselectivities (entries 6–8), and the results were not inconsistent with our previous report.[5] We also examined the enzymatic esterification of (±)-**3d** with lipase PS-C Amano II, vinyl acetate, and Et_3N in *i*-Pr_2O for 24 hours at 30 °C according to the modified procedure reported by Boaz et al.[3d] Although the esterification proceeded, the reactivity (conv. = 0.34) and enantioselectivity (*E* value = 19) were lower than those obtained by our hydrolysis version. On the other hand, the substitution of a 2,4,6-trimethyl group on the benzene ring [(±)-**3e**, Ar = 2,4,6-$Me_3C_6H_2$] did not improve the *E* value, but decreased the reactivity (entry 9).



Scheme 1

Finally, we examined the enzymatic reaction of the racemic 2-acetyl-3-*O*-3,5-dimethylbenzenesulfonyl-1-*O*-4-methoxybenzyl-*sn*-glycerol [(±)-**6**] bearing the substitutions, which produced the excellent result mentioned above (Scheme 2). As expected, the reaction for 24 hours at 30 °C smoothly proceeded with the highest enantioselectivity to afford the corresponding (*S*)-**6** with a 99% ee and (*R*)-**7** with a 96% ee in 37% and 48% isolated yields, respectively (conv. = 0.51, *E* value = 259), and we did not detect any byproducts.[11] We postulated that the structure of the PMB and 3,5-dimethylphenyl groups could precisely fit the enzyme active site.

In summary, we have developed a simple and efficient preparation of optically active 1-*O*-alkyl-3-*O*-arylsulfonyl-*sn*-glycerol derivatives, which are useful chiral synthons, by the enzyme-mediated hydrolysis. In particular, we have successfully shown that engineering the structure of the protecting and leaving groups was a very important technique for the enzymatic reaction in a manner similar to that for typical organic reactions.



Scheme 2

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(6) The racemic alcohols (±)-**2**, except for **2d**, as the precursor of the substrates were prepared in three steps: 1) protection of the hydroxyl group of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane, 2) 2 M aq HCl–THF, 3) TsCl, Bu_2SnO, Et_3N–CH_2Cl_2.[12] In all cases, the resulting (±)-**2** contained the regioisomers, 3-acetyl-2-*O*-tosyl-*sn*-glycerol (±)-**7**, as the minor product. After the enzymatic acylation of the mixture using porcine pancreas lipase (PPL, Sigma), the pure (±)-**2** was obtained. The details will be reported separately. On the other hand, (±)-**2d** was prepared from the coupling of (±)-glycidol with TsOH, followed by selective protection of the primary hydroxyl group with TBS.
(7) The absolute configuration of **2a** {$[\alpha]_D^{25}$ –4.19 (*c* 2.49, C_6H_6) (59% ee)} was confirmed by comparing the obtained optical rotation value with the reported value: lit.[13] $[\alpha]_D^{25}$ –6.70 (*c* 10, C_6H_6; *R* form).
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(9) The substrate with a mesyl group was quite unstable and decomposed under the enzymatic reaction conditions.
(10) Compound (*R*)-**5**: $[\alpha]_D^{30}$ +1.89 (*c* 0.90, $CHCl_3$; 93% ee). Compound (*S*)-**5**: $[\alpha]_D^{21}$ –1.81 (*c* 0.83, $CHCl_3$; 95% ee); lit.[14] $[\alpha]_D^{21}$ +1.79 (*c* 5.02, $CHCl_3$; *R* form).
(11) To a 200 mL Erlenmeyer flask containing (±)-**6** (72.3 mg, 0.17 mmol; sub. concd, ca. 4 mM) were added of *i*-Pr_2O (4 mL), 0.1 M phosphate buffer (40 mL, pH 6.5), and lipase PS (30 mg). After the mixture was incubated for 24 h at 30 °C, the products were extracted with EtOAc and purified by flash column chromatography on SiO_2 (eluent: hexane–EtOAc, 4:1) to afford (*S*)-**6** (26.4 mg, 37%, 99% ee) and (*R*)-**7** (31.5 mg, 48%, 96% ee).
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