Preparation of Optically Active 1,2-Diol Monotosylates by Enzymatic Hydrolysis

Yasutaka Shimada, Hiroshi Sato, Shinji Minowa, Kazutsugu Matsumoto*

Department of Chemistry, Meisei University, Hodokubo 2-1-1, Hino, Tokyo 191-8506, Japan
Fax +81(42)5917360; E-mail: mkazu@chem.meisei-u.ac.jp

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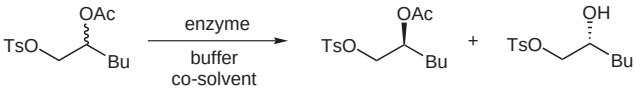
Abstract: An easy preparation of optically active 1,2-diol monotosylate derivatives by enzymatic hydrolysis is disclosed. Lipase PS (*Burkholderia cepacia*) catalyzes the hydrolysis of racemic 2-acetoxyhexyl tosylate with excellent enantioselectivity to afford the corresponding optically active compounds. In this reaction, a unique temperature effect is observed. After optimizing the reaction conditions, this procedure is widely applicable to the practical preparation of both enantiomers of various optically active compounds with high ee.

Key words: enantioselective hydrolyses, enzymes, kinetic resolution, solvent effects, tosylates

During the synthesis of natural and biologically active compounds, optically active 1,2-diol monotosylates play significant roles as useful precursors for chiral nonracemic epoxides,[1] amino alcohols,[2] alkyl carbinols,[3] etc. Many synthetic procedures for optically active 1,2-diols have been developed, and the following monotosylation of the 1,2-diols could give the corresponding 1,2-diol monotosylates. Recently, the enzymatic reaction has been one of the practical and attractive methods used for the preparation of optically active compounds, and the enzyme-mediated kinetic resolutions of the racemic 1,2-diol monotosylate derivatives have also been reported.[4–6] In these papers, several enzymes catalyzed the enantioselective reactions to afford optically active compounds. However, little attention has been paid to the methodical study of the substrate specificity, and the reactions were not useful tools for the preparation of various chiral synthons. Furthermore, the methods reported did not always satisfactorily work in terms of the enantioselectivity. In this report, we disclose the enzyme-mediated kinetic resolution of 2-acetoxyalkyl tosylates, and this procedure is widely applicable for the easy and practical preparation of both enantiomers of various optically active compounds after optimizing the reaction conditions.

We selected the racemic 2-acetoxyhexyl tosylate [(±)-**1**] as the representative substrate, which has a substituent with a moderate carbon number.[7] First, we individually screened the enzyme system to hydrolyze (±)-**1** with sufficient recognition of the stereochemistry. In the screening test, we focused on checking the ee of the substrate and product. Spontaneous hydrolysis of the substrate was not observed under the reaction conditions. Among the 12 commercially available hydrolytic enzymes,[8] lipase PS (*Burkholderia cepacia*) and lipase AK (*Pseudomonas fluorescens*) from Amano Enzyme, Inc., gave the best results (Table 1, entries 1 and 4). The reactions for 24 hours at 30 °C proceeded with moderate enantioselectivity to afford the optically active (*S*)-**1** and (*R*)-**2**,[9,10] and the reactivities and the enantioselectivities were almost same in the both cases (PS, conv. = 0.54, *E* value = 48; AK, conv. = 0.47, *E* value = 52).[11] Second, we tried to examine the reaction using a co-solvent (toluene, DMSO, or *i*-Pr_2O) in order to improve the enantioselectivity. Although both enzymes did not catalyze the hydrolysis of (±)-**1** in the medium containing 10% toluene, the addition of DMSO and *i*-Pr_2O significantly improved the enantioselectivities (entries 2, 3, 5, and 6). In particular, the reaction with lipase PS in buffer–*i*-Pr_2O (9:1) proceeded smoothly (conv. = 0.45) with the highest enantioselectivity (*E* value = 244) to afford the optically active (*S*)-**1** with 80% ee {$[\alpha]_D^{25}$ –13.3 (*c* 0.96, $CHCl_3$) and (*R*)-**2** with 98% ee {$[\alpha]_D^{29}$ –7.9 (*c* 0.71, $CHCl_3$}} in 58% and 39% yields, respectively.[12,13] The addition of *i*-Pr_2O did not make a biphasic system because *i*-Pr_2O was slightly soluble in the

Table 1 Enantioselective Hydrolysis of 2-Acetoxyhexyl Tosylate [(±)-**1**][a]



(±)-**1** (*S*)-**1** (*R*)-**2**

Entry	Lipase	Co-solvent	ee of (*S*)-**1** (%)	ee of (*R*)-**2** (%)	Conv.[b]	*E* value[c]
1	PS	–	97	84	0.54	48
2		DMSO	90	91	0.50	65
3		*i*-Pr_2O	80	98	0.45	244
4	AK	–	80	91	0.47	52
5		DMSO	98	93	0.51	127
6		*i*-Pr_2O	27	96	0.22	64

[a] Unless otherwise noted, the reaction was performed using (±)-**1** (ca. 25 mg, 4 mM) with the enzyme (10 mg) in 0.1 M sodium phosphate buffer (pH 6.5) containing 10% co-solvent.
[b] Calculated using ee (**1**)/[ee (**1**) +ee (**2**)].
[c] Calculated using ln{[1 – conv.][1 – ee (**1**)]}/ln{[1 – conv.][1 + ee (**1**)]}.

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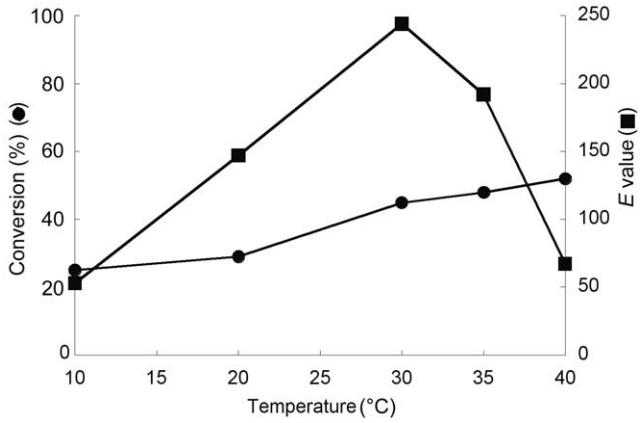


Figure 1 Temperature effect on conversion and *E* value for the reaction of (±)-**1** with lipase PS. The reaction was carried out for 24 h.

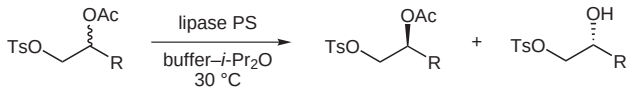
buffer and the shaking of the mixed solvent during the reaction would form a fine-particle emulsion. On the other hand, we also examined the enzymatic esterification of (±)-**2** with lipase PS-C Amano II, vinyl acetate and Et_3N in MTBE for 48 hours at 30 °C according to the procedure reported by Boaz et al.[5d] Although the esterification proceeded, the reactivity (conv. = 0.12) and the enantioselectivity (*E* value = 75) were lower than those obtained by our hydrolysis version.

For the enzymatic kinetic resolution as well as the nonenzymatic reactions, the dependence of the enantioselectivity on the reaction temperature has been evaluated. In many cases, lowering the temperature could increase the enantioselectivity, although the conversion could decrease. We then tried to examine the temperature effect (10–40 °C) on the reaction of (±)-**1** with lipase PS using *i*-Pr_2O as the co-solvent (Figure 1). As expected, the conversion decreased by lowering the reaction temperature. On the other hand, the *E* value was out of proportion to the temperature based on our expectation. While the *E* value decreased above 30 °C as the standard temperature, lowering the temperature to 10 °C also decreased the *E* value. Overall, an effect on the enantioselectivity by temperature was observed at 30 °C. To the best of our knowledge, there have been only a few reports on the presence of this temperature inversion on the enantioselectivity for enzymatic reactions,[14,15] and this is a rare case which reveals the phenomenon apparently.

To achieve efficient preparative-scale experiments, the substrate concentration was increased to 64 mM (16 times higher than the former value). In this case, the reaction of (±)-**1** (ca. 800 mg) was carried out with lipase PS (ca. 30 mg) in a mixed solvent (buffer, 36 mL; *i*-Pr_2O, 4 mL) for 72 hours at 30 °C. Fortunately, the enzyme catalyzed the hydrolysis without any inhibition to afford both enantiomers with high ee; (*S*)-**1** with 96% ee (38%) and (*R*)-**2** with 99% ee (38%) (conv. = 0.49), and the *E* value was up to 790. Furthermore, we succeeded in the enantioselective hydrolysis using ca. 1.6 g of (±)-**1** (128 mM) under the same conditions (*E* value = 311), although the conversion decreased to 0.31.

We next applied the reaction to various acetates, and these results are summarized in Table 2. In all cases except for entry 7, the hydrolyses proceeded with excellent enantioselectivities to afford the corresponding optically active compounds.[16,17] In particular, almost complete optical resolution of (±)-**3b** bearing the chloromethyl group (entries 2 and 3) was accomplished after only one hour. It is noteworthy that the length of the substituent R group did not affect both the reactivity and the enantioselectivity, and the enzyme preferred *R*-enantiomers in all the sub-

Table 2 Enantioselective Hydrolysis of 2-Acetoxyalkyl Tosylates (±)-**3**[a]



(±)-**3** (*S*)-**3** (*R*)-**4**

Entry		R	(*S*)-**3**		(*R*)-**4**		Conv.	*E* value
			Yield (%)	ee (%)	Yield (%)	ee (%)		
1	**a**	Me	31	99.7	23	95	0.51	251
2	**b**	CH_2Cl	41	>99.9	41	90	0.53	>141
3[b]	**b**	CH_2Cl	48	>99.9	52	99.2	0.50	>1890
4	**c**	C_7H_{15}	52	78	45	99.0	0.44	474
5	**d**	CH_2CH_2OBn	37	99.9	35	97	0.51	497
6	**e**	CH_2OMe	33	99.7	19	98	0.50	642
7	**f**	CH_2OBn	29	99.6	58	59	0.63	22
8	**g**	$CH_2OC_{14}H_{29}$	45	99.0	54	92	0.52	126

[a] Unless otherwise noted, the reaction was performed using (±)-**3** (4 mM) with the enzyme in 0.1 M sodium phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O for 24 h at 30 °C.
[b] The reaction was carried out for 1 h.

strates. Only the glycerol-type substrate (±)-**3f** bearing the benzyloxymethyl group (entry 7) showed a moderate enantioselectivity. In this case, even the slow reactive enantiomer might be more suitable for the enzyme active site than those of other substrates. Further investigations for applying the method and improving the *E* value for the hydrolysis of **3f** are now in progress.

In summary, a simple and efficient approach to produce optically active 1,2-diol monotosylate derivatives by the enzyme-mediated hydrolysis has been developed. Furthermore, we observed a unique temperature effect on the enantioselectivity. This method is applicable for various compounds, and is expected to be a potentially useful tool for organic synthesis.

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(8) In the screening test, we used the following enzymes: lipase type II, type VII (Sigma), lipase PS, lipase AY, lipase A, PLE-A, lipase D-360, lipase AK, lipase D (Amano Enzyme, Inc.), lipase OF (Meito Sangyo Co., Ltd), lipase (Nagase ChemteX Corp.), Novozym (NovoNordisk A/S). The hydrolysis of (±)-**1** with lipase type II, lipase type VII, PLE-A or lipase OF proceeded with low enantioselectivity. The other enzymes did not catalyze the reaction.

(9) The absolute configurations of **1** and **2** were confirmed by comparing the obtained optical rotation value with the reported value: (*R*)-**1**, lit.[5a] $[\alpha]_D^{25}$ +13.4 ($CHCl_3$), 86% ee; (*S*)-**2**, lit.[5a] $[\alpha]_D^{25}$ +4.2 ($CHCl_3$), 66% ee.

(10) The ee of **1** was determined by HPLC analysis with CHIRALCEL AD-H (Daicel Chemical Industries, Ltd.); eluent: hexane–*i*-PrOH (90:10); flow rate: 0.5 mL min^{-1}; t_R = 18 (*S*) and 19.5 (*R*) min. A similar analysis of **2** was also performed with CHIRALCEL OD-H; eluent: hexane–*i*-PrOH (95:5); flow rate: 0.5 mL min^{-1}; t_R = 32 (*R*) and 35.5 (*S*) min.

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(12) Compound (*S*)-**1**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H) 1.13–1.34 (m, 4 H), 1.46–1.65 (m, 2 H), 1.98 (s, 3 H), 2.46 (s, 3 H), 4.05 (dd, J_1 = 5.5 Hz, J_2 = 10.5 Hz, 1 H), 4.10 (dd, J_1 = 3.5 Hz, J_2 = 10.5 Hz, 1 H), 4.90–5.00 (m, 1 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 20.8, 22.2, 27.0, 30.0, 70.0, 70.9, 127.8, 130.0, 132.7, 145.0, 170.3. IR (neat): 3460, 2957, 2870, 1730, 1597, 1454, 1362, 1177 cm^{-1}. MS (EI): *m/z* (%) = 314 (7.2) [M^+], 254 (27), 228 (38), 198 (16), 172 (16), 143 (36), 129 (17), 91 (100), 82 (16). HRMS: *m/z* [M^+] calcd for $C_{15}H_{22}O_5S$: 314.1188; found: 314.1187.

(13) Compound (*R*)-**2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 1.10–1.53 (m, 6 H), 2.19 (br s, 1 H), 2.45 (s, 3 H), 3.78–3.91 (m, 1 H), 3.84–3.94 (m, 1 H), 4.00–4.08 (m, 1 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.5, 22.4, 27.2, 32.2,

69.2, 73.9, 132.5, 144.9. IR (neat): 3539, 2955, 2872, 1599, 1454, 1360, 1177, 1098, 974 cm^{-1}. MS (EI): *m/z* (%) = 242 (25), 172 (11), 155 (52), 139 (10) 107 (20), 91 (100), 87 (42). HRMS: *m/z* [M^+] calcd for $C_{13}H_{20}O_4S$: 272.1082; found: 272.1085.

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