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Enzyme-mediated enantioselective hydrolysis of cyclic carbonates bearing an unsaturated substituent

Kazutsugu Matsumoto,[a,*] Yasuhide Nakamura,[b] Megumi Shimojo[c] and Minoru Hatanaka[b]

[a]*Department of Chemistry, Meisei University, Hodokubo 2-1-1, Hino, Tokyo 191-8506, Japan*
[b]*Department of Applied Chemistry and Biotechnology, Fukui University, Bunkyo 3-9-1, Fukui 910-8507, Japan*
[c]*Department of Biosciences and Informatics, Keio University, Hiyoshi 3-14-1, Yokohama 223-8522, Japan*

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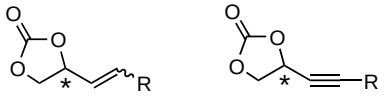
Abstract—A new method for the preparation of optically active five-membered cyclic carbonates bearing an unsaturated substituent via an enzymatic reaction is described. In the examination of the regiospecific recognition of PPL, *dl*-(*E*)-4-(1-octenyl)-1,3-dioxolan-2-one is hydrolyzed with higher enantioselectivity. The reaction is also applicable to the racemic (*E*)-4-[2-(alkoxycarbony)ethenyl]-1,3-dioxolane-2-one, a useful α,β-unsaturated ester in organic syntheses. Introducing the isopropyl group to the ester moiety affords the highest enantioselectivity although the ester group is located at a remote position from the asymmetric carbon.

Optically active 1,2-diols are important intermediates in the synthesis of natural products, and thus many synthetic procedures for such compounds have been developed. Although the asymmetric dihydroxylation of olefins using cinchona alkaloid derived ligands (AD-mix-α and -β) is one of the most popular procedures for the synthesis of chiral 1,2-diols,[1] the method does not always satisfactory work in terms of the enantioselectivity in some cases.

The enzymatic hydrolysis of five-membered cyclic carbonates is one of the attractive methods for the preparation of optically active 1,2-diols.[2–4] We have also accomplished the enzyme-mediated enantioselective hydrolysis of various cyclic carbonates.[5,6] *Pseudomonas diminuta*, a bacterium, hydrolyzes C_2-symmetrical substrates with a dimethyl group, and the reaction of 4,5-dimethyl-1,3-dioxolane-2-one affords the corresponding optically active 2,3-butanediol.[5] On the other hand, porcine pancreas lipase (PPL, EC 3.1.1.3, Type II from Sigma) catalyzes the enantioselective hydrolysis of monosubstituted cyclic carbonates, and then various kinds of optically active unreacted (*R*)-cyclic carbonates and resulting (*S*)-diols are easily obtained.[6] We have already examined the reaction of substrates bearing simple *n*-alkyl groups with or without a benzyloxy group at the terminus. When the reaction could also be applied to the substrates bearing a 1-alkenyl or alkynyl group, more useful optically active compounds, especially as chiral synthons of glyceraldehyde derivatives, would be prepared (Scheme 1). In this paper, we tried to apply the PPL-mediated hydrolysis to the synthesis of the optically active 1,2-diols bearing unsaturated substituents.

We first examined the reactions of three kinds of substrates which have different stereo structures, racemic (*E*)- and (*Z*)-4-(1-octenyl)-1,3-dioxolan-2-one (*dl*-**1a** and **1b**) and 4-(1-octynyl)-1,3-dioxolan-2-one (*dl*-**2**) (Scheme 2, Table 1).[7] In all cases, the reactions were performed using 10 mM of the substrates in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O at 10°C.[6] Unfortunately, the hydrolysis of the (*Z*)-form substrate (*dl*-**1b**) for 24 h slowly proceeded (conv.[8] = 0.17) with low enantioselectivity (*E* value[8] = 3), while the *E* value and conversion were 23 and 0.46, respectively, in the case of the substrate bearing a saturated octyl group under the same reaction conditions.[6b] On the other hand, the substrate with an octynyl group (*dl*-**2**) was smoothly hydrolyzed with moderate enan-



Scheme 1.

Keywords: cyclic carbonates; enzymatic hydrolysis; enzymes; glycerol derivatives; kinetic resolution.

* Corresponding author. Tel./fax: +81-42-591-7360; e-mail: mkazu@chem.meisei-u.ac.jp

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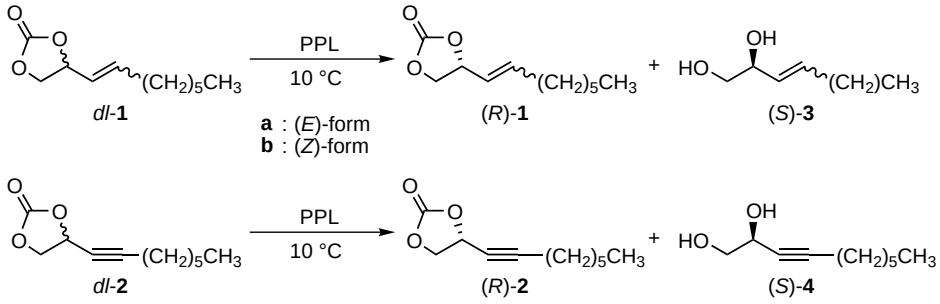


Scheme 2.

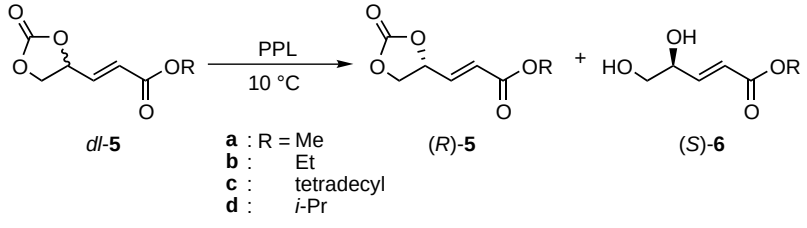
Table 1. Enantioselective hydrolysis of the cyclic carbonates of **1** and **2** with PPL[a]

Substrate	Time (h)	Carbonate		Diol		Conv.[b]	E[c]
		Yield (%)	Ee (%)	Yield (%)	Ee (%)		
1a	24	59	44	33	81[d]	0.36	15
1a	96	27	>99[e]	46	58	0.63	18
1b	24	79	9[f]	17	46[g]	0.17	3
2	24	29	96[h]	58	43[i]	0.69	9

[a] Incubation was performed using 10 mM of *dl*-**1** or **2** with PPL in 0.1 M phosphate buffer (pH 6.5) at 10°C containing 10% *i*-Pr_2O as the co-solvent.
[b] Calculated by ee(carbonate)/[ee(carbonate)+ee(diol)].
[c] Calculated by ln[(1−conv.)(1−ee(carbonate))/ln[(1−conv.)(1+ee(carbonate))].
[d] $[\alpha]_D^{24}=+9.1$ (*c* 1.15, MeOH).
[e] $[\alpha]_D^{24}=+20.8$ (*c* 0.81, $CHCl_3$).
[f] $[\alpha]_D^{26}=+6.1$ (*c* 0.99, $CHCl_3$).
[g] $[\alpha]_D^{26}=+3.3$ (*c* 0.72, MeOH).
[h] $[\alpha]_D^{26}=+3.5$ (*c* 1.34, $CHCl_3$).
[i] $[\alpha]_D^{24}=+5.3$ (*c* 0.81, MeOH).

tioselectivity (conv. = 0.69, E value = 9) to afford (*R*)-**4** with 96% ee. Interestingly, the (*E*)-alkenyl substituent for *dl*-**1a** apparently increased the E value although the reaction rate was slower than that of *dl*-**2**. When the reaction was performed for 96 h using *dl*-**1a** (E value = 18),[9–13] the optical purities of (*R*)-**1a** (27% yield) and (*S*)-(*E*)-3-decen-1,2-diol (**3a**, 46% yield) were greater than 99 and 58% ee, respectively. These results suggest that the (*E*)-alkenyl structure is more suitable for the active site of PPL while the other substrates do not favorably fit. This is a unique example for showing the regio specific recognition of the enzyme.

We then planned the preparation of the optically active (*E*)-5,6-dihydroxy-2-pentenoate derivatives **5**, which belong to the α,β-unsaturated esters bearing a chiral center at the γ-position (Scheme 3). These compounds are of special interest as useful Michael acceptors for conjugate additions[14] and important chiral building blocks for natural product syntheses.[15] We examined the PPL-catalyzed reactions of cyclic carbonates *dl*-**5** bearing a different ester group, and these results are summarized in Table 2. In the case of methyl ester, (*E*)-4-[2-(methoxycarbony)ethenyl]-1,3-dioxolane-2-one (*dl*-**5a**), the hydrolysis smoothly proceeded with enantioselectivity, but the yields of the diol **6a** was lower than the theoretical one. For the reaction of *dl*-**5a** for 24 h, the resulting (*S*)-**6a** (46% ee) was recovered in only 13% yield although (*R*)-**5a** (96% ee) was obtained in 40% isolated yield and the conversion and E value were calculated to be 0.62 and 15, respectively. The reaction of the ethyl ester *dl*-**5b** gave similar results. Although the details are not yet clear, the enzymatic hydrolysis of the ester part could also occur under the reaction conditions to give the corresponding dihydroxylcarboxylic acids, which were difficult to extract from



Scheme 3.

Table 2. Enantioselective hydrolysis of cyclic carbonate *dl*-**5** with PPL[a]

Substrate	Time (h)	Carbonate		Diol		Conv.	*E*
		Yield (%)	Ee (%)	Yield (%)	Ee (%)		
5a[b]	24	40	96[c]	13	46[d]	0.68	10
5b	24	30	97[e]	24	59[f]	0.62	15
5c	24	74	10[g]	15	59[h]	0.14	4
5d[i]	6	61	55	28	88[j]	0.38	32
5d[i]	12	51	85	36	84	0.50	33
5d[i]	24	42	>99[k]	39	77	0.56	41

[a] Incubation was performed using 10 mM of *dl*-**5** with PPL in 0.1 M phosphate buffer (pH 6.5) at 10°C containing 10% *i*-Pr_2O as the co-solvent unless otherwise noted.
[b] Incubation in 0.1 M phosphate buffer (pH 6.5) containing 7.5% *i*-Pr_2O and 2.5% DMSO as the co-solvent.
[c] $[\alpha]_D^{22}=-19.7$ (*c* 1.18, $CHCl_3$).
[d] $[\alpha]_D^{24}=-24.3$ (*c* 1.07, MeOH).
[e] $[\alpha]_D^{22}=-16.6$ (*c* 1.13, $CHCl_3$).
[f] $[\alpha]_D^{22}=-19.1$ (*c* 1.07, MeOH).
[g] $[\alpha]_D^{22}=-0.8$ (*c* 0.54, $CHCl_3$).
[h] $[\alpha]_D^{22}=-13.8$ (*c* 0.65, MeOH).
[i] Incubation in 0.1 M phosphate buffer (pH 6.5) containing 6.25% *i*-Pr_2O and 3.75% DMSO as the co-solvent.
[j] $[\alpha]_D^{22}=-32.4$ (*c* 1.02, MeOH).
[k] $[\alpha]_D^{22}=-14.8$ (*c* 0.91, $CHCl_3$).

the water layer and the yields of the diols **6** would finally decrease.

In order to prepare both **5** and **6** with high yield and ee, we focused on the suppression of the hydrolysis process mentioned above by changing the ester group. The elongation of the ester moiety to a tetradecyl group (*dl*-**5c**) caused a drastic decrease in both the reactivity and enantioselectivity (conv. = 0.14, *E* values = 4; reaction time, 24 h). As expected, an isopropyl group, which is a more sterically hindered chain (*dl*-**5d**), improved the yield of the corresponding diol (isopropyl (*E*)-5,6-dihydroxy-2-pentenoate, **6d**), which was isolated without a significant decrease in the yield.[16–19] Surprisingly, the isopropyl ester also affected the enantioselectivity, and the *E* value was apparently twice those of the other substrates although the hydrolysis of the ester part could not be ignored. The reaction of *dl*-**5d** for 24 h proceeded to afford the optically pure (*R*)-**5d** and (*S*)-**6d** (77% ee) in 42 and 39% yields, respectively (conv. = 0.56, *E* value = 41).

In conclusion, we have established a facile enzymatic procedure to prepare optically active diol derivatives bearing an unsaturated substituent. The resulting compounds are important synthons of chiral glyceraldehyde derivatives. Amongst the PPL-catalyzed hydrolyses of cyclic carbonates reported,[2b,6] the highest enantioselectivity was observed in the reaction of *dl*-**5d**. It is noteworthy that introducing the bulky ester group provides such a high enantioselectivity although the ester group is located at a remote position from the asymmetric carbon. Further investigations for application of the enzymatic hydrolysis are now in progress.

References

1. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771; (b) Kolb, H. C.; VanNieuwhenze, M.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
2. (a) Barton, P.; Page, M. I. *Tetrahedron* **1992**, *48*, 7731–7734; (b) Kawashima, M.; Horikawa, Y. *Biotechnol. Lett.* **1993**, *15*, 1039–1042; (c) Kojima, T.; Ando, T. JP07031497 [*Chem. Abstr.* **1995**, *122*, 263703].
3. For the hydrolysis of non-chiral ethylene carbonate in metabolic system, see: Yang, Y.-L.; Ramaswamy, S. G.; Jakoby, W. B. *J. Biol. Chem.* **1998**, *273*, 7814–7817.
4. Dioxolenone esters, a kind of cyclic carbonates, are used as an important prodrug moiety which can be hydrolyzed by esterases in the blood, liver, and other organs and tissues. See: (a) Alexander, J.; Bindra, D. S.; Glass, J. D.; Holahan, M. A.; Renyer, M. L.; Rork, G. S.; Stiko, G. R.; Stranjeri, M. T.; Stupienski, R. F.; Veerapanane, H.; Cook, J. J. *J. Med. Chem.* **1996**, *39*, 480–486; (b) Sun, C.-Q.; Cheng, P. T. W.; Stevenson, J.; Dejneka, T.; Brown, B.; Wang, T. C.; Robl, J. A.; Poss, M. A. *Tetrahedron Lett.* **2002**, *43*, 1161–1164.
5. Matsumoto, K.; Sato, Y.; Shimojo, M.; Hatanaka, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1965–1973.
6. (a) Matsumoto, K.; Fuwa, S.; Kitajima, H. *Tetrahedron Lett.* **1995**, *36*, 6499–6502; (b) Matsumoto, K.; Fuwa, S.; Shimojo, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2977–2987; (c) Matsumoto, K.; Shimojo, M.; Kitajima, H.; Hatanaka, M. *Synlett* **1996**, 1085–1086; (d) Matsumoto, K.; Shimojo, M.; Hatanaka, M. *Chem. Lett.* **1997**, 1151–1152; (e) Shimojo, M.; Matsumoto, K.; Hatanaka, M. *Tetrahedron* **2000**, *56*, 9281–9288.

7. In the cases of *dl*-**1a** and **1b**, the substrates were prepared from (*E*)- and (*Z*)-2-nonen-1-ol in seven steps, respectively. On the other hand, the coupling of trityloxyacetaldehyde with lithium 1-octylide, followed by protection and deprotection of hydroxyl groups afforded *dl*-**2**. The details will be reported separately.
8. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
9. A typical experimental procedure is as follows. To a solution of 80.0 mg (0.404 mmol, 10 mM) of *dl*-**1a** in *i*-Pr_2O (4 mL) were added 0.1 M sodium phosphate buffer (pH 6.5, 36 mL) and 500 mg of PPL, and the mixture was incubated at 10°C for 24 h. The products were extracted with AcOEt and purified by flash column chromatography on silica gel (eluent, hexane/AcOEt = 6/1) to afford (*R*)-**1a** (21.4 mg, 27%, >99% ee) and (*S*)-**3a** (32.5 mg, 46%, 58% ee). The enantioselective hydrolyses of the other cases were carried out by the same procedure.
10. Compound (*R*)-**1a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3H), 1.22–1.46 (m, 8H), 2.10 (dt, J = 7.0, 7.0 Hz, 2H), 4.12 (dd, J = 8.0, 8.0 Hz, 1H), 4.56 (dd, J = 8.0, 8.0 Hz, 1H), 5.08 (dt, J = 8.0, 8.0 Hz, 1H), 5.51 (dd, J = 8.0, 15.5 Hz, 1H), 5.95 (td, J = 7.0, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 28.4, 28.7, 31.5, 32.1, 69.4, 78.0, 123.8, 140.1, 154.9; IR (neat) 2952, 2924, 2852, 1797, 1166, 1072, 970 cm^{-1}; MS m/z (rel. intensities) 199 (M^++H, 0.9), 136 (36), 129 (94), 111 (7.4), 69 (92), 67 (100), 55 (100); HRMS m/z 199.1374 (199.1334 calcd for $C_{11}H_{19}O_3$, M^++H).
11. Compound (*S*)-**3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.21–1.41 (m, 8H), 1.90–2.19 (m, 4H), 3.49 (dd, J = 7.0, 11.0 Hz, 1H), 3.63 (dd, J = 3.5, 11.0 Hz, 1H), 4.20 (ddt, J = 1.0, 3.5, 7.0 Hz, 1H), 5.40 (tdd, J = 1.5, 6.5, 15.5 Hz, 1H), 5.78 (dtd, J = 1.0, 7.0, 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.8, 29.0, 31.6, 32.3, 66.6, 73.2, 128.1, 134.3; IR (neat) 3368, 2952, 2920, 2848, 1028, 970 cm^{-1}; MS m/z (rel. intensities) 172 (0.5, M^+), 141 (50), 136 (19), 110 (23), 69 (68), 67 (50), 55 (100); HRMS m/z 172.1441 (172.1463 calcd for $C_{10}H_{20}O_2$, M^+).
12. The ee of **3a** was determined by ^{1}H NMR analysis of the corresponding bis-(+)-MTPA ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.29 (dd, J = 8.0, 15.5 Hz, 1H, C<u>H</u>=CH-CH_2 (*R*)), δ = 5.44 (dd, J = 8.0, 15.5 Hz, 1H, C<u>H</u>=CH–CH_2 (*S*)). The ees of other compounds were determined by similar analysis of **3a**.
13. To determine the stereochemistry of **3a**, **3a** was hydrogenated to the corresponding 1,2-decandiol (**7**), and then the sign of the optical rotation of **7** ($[\alpha]_D^{23}$ = −10.6 (*c* 0.98, MeOH)) was compared with that of the authentic sample (*S*)-**7** ($[\alpha]_D^{23}$ = −10.0 (*c* 0.95, MeOH)). Thus, the absolute configuration of the original **3a** was confirmed to be *S*.
14. For representative examples, see: (a) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009–3012; (b) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525–2528; (c) Nomura, M.; Kanemasa, S. *Tetrahedron Lett.* **1994**, *35*, 143–146; (d) Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002–4006.
15. For representative examples, see: (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109–1111; (b) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284–291; (c) Trost, B. M.; Mignani, S. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1988**, *110*, 1602–1608.
16. Compound (*R*)-**5d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.5 Hz, 6H), 4.23 (dd, J = 8.5, 8.5 Hz, 1H), 4.67 (dd, J = 8.5, 8.5 Hz, 1H), 5.09 (septet, J = 6.5 Hz, 1H), 5.31 (dd, J = 5.5, 8.5 Hz, 1H), 6.18 (d, J = 15.5 Hz, 1H), 6.85 (dd, J = 5.5, 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 68.4, 68.8, 74.7, 78.3, 125.6, 139.0, 154.0, 164.4; IR (neat) 2980, 2932, 1806, 1720, 1274, 1170, 1070 cm^{-1}; MS m/z (rel. intensities) 200 (M+, 4.6), 185 (45), 171 (31), 157 (31), 143 (26), 129 (77), 115 (32), 83 (65), 73 (100); HRMS m/z 185.0439 (185.0450 calcd for $C_8H_9O_5$, M^+–CH_3).
17. Compound (*S*)-**6d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.5 Hz, 6H), 2.98 (br.s, 1H), 3.15 (br.s, 1H), 3.55 (dd, J = 7.0, 11.5 Hz, 1H), 3.76 (dd, J = 3.5, 11.5 Hz, 1H), 4.39–4.47 (m, 1H), 5.06 (septet, J = 6.5 Hz, 1H), 6.12 (dd, J = 1.5, 15.5 Hz, 1H), 6.88 (dd, J = 4.5, 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.0, 21.7, 60.4, 65.5, 68.1, 71.6, 122.3, 145.9, 146.0, 166.1; IR (neat) 3428, 2980, 2932, 2872, 1714, 1280, 1180, 1072 cm^{-1}; MS m/z (rel. intensities) 175 (M^++H, 0.9), 143 (36), 115 (81), 102 (100). 87 (12), 84 (100), 73 (92); HRMS m/z 175.0970 (175.0970 calcd for $C_8H_{15}O_4$, M^++H).
18. The ee of diol **6a** was determined by HPLC analysis with CHIRALCEL OJ (Daicel Chemical Industries, Ltd); eluent, hexane/2-propanol = 98/2; flow rate, 0.5 mL/min; λ = 240 nm; retention time, 235 (*S*) and 259 (*R*) min. To determine the ees of the other compounds including **5d** and **6d**, the compounds were transformed into **6a** by refluxing in MeOH with cat. amount of TsOH.
19. To determine the stereochemistry of **6a**, the dihydroxy group of **6a** was protected to give the corresponding methyl (*S*)-(*E*)-3-(2,2-dimethyl-1,3-dioxolane-4-yl)propenoate (**8**), and then the sign of the optical rotation of **8** (73% ee, $[\alpha]_D^{25}$ = +31.1 (*c* 1.18, $CDCl_3$), $[\alpha]_D^{26}$ = +30.8 (*c* 1.18, $CHCl_3$)) was compared with that in the literature; (*S*)-**8** ($[\alpha]_D^{22}$ = +33.6 (*c* 10, $CDCl_3$)).[15b] Thus, the absolute configuration of the original **6a** was confirmed to be *S*.