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Enzyme-Mediated Enantioselective Hydrolysis of Cyclic Carbonates

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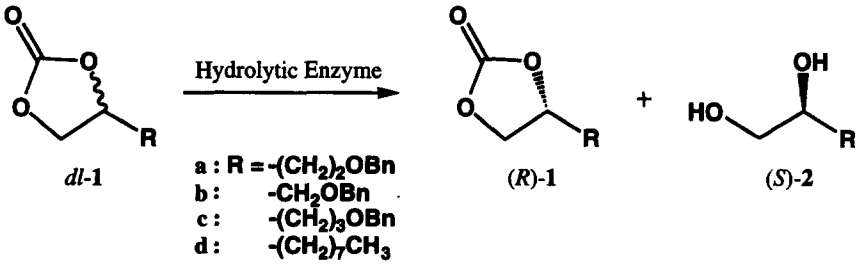
Abstract: The enzyme-mediated enantioselective hydrolysis of cyclic carbonates is disclosed. Racemic 4-(2-benzyloxy)ethyl-1,3-dioxolan-2-one (**1a**) was enantioselectively hydrolyzed by porcine pancreas lipase (PPL) to give optically active (*R*)-**1a** and (*S*)-4-benzyloxybutane-1,2-diol (**2a**). PPL also catalyzed the hydrolysis of seveal five-membered cyclic carbonates with high enatioselectivity.

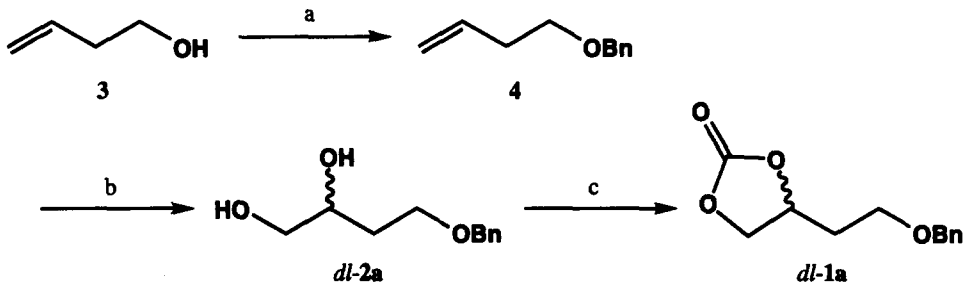
Optically active diols are versatile intermediates of natural products and biologically active compounds, and many synthetic methods for chiral diols have been established. Enzymatic reactions have also been utilized to prepare such compounds.[1] Enzymatic hydrolysis is especially advantageous because it requires no co-factors. Representative biochemical methods include the hydrolysis of diacetates in water[2] and the esterification of diols in organic solvent.[3] These hitherto known reactions produce four compounds (diol, diacetate, and two monoacetates) which are not easily separated, and hence the product yields are low. On the other hand, optically active cyclic carbonates also attracted our attention as target molecules because cyclic carbonates are very useful compounds as masked diols in organic synthesis.[4] We have noticed that hydrolytic enzymes can enantioselectively catalyze the conversion of cyclic carbonates to the corresponding diols. In this report, we present a simple method for obtaining optically active cyclic carbonates and diols using a new type of enzymatic reaction, *i.e.*, the enzyme-mediated enantioselective hydrolysis of cyclic carbonates (Scheme 1).

First, racemic 4-(2-benzyloxy)ethyl-1,3-dioxolan-2-one (*dl*-**1a**, R = -$(CH_2)_2$OBn) was used as the substrate of the screening test. The substrate *dl*-**1a** was readily prepared as shown in Scheme 2. In the



dl-**1** (*R*)-**1** (*S*)-**2**

Scheme 1.



(a) BnBr, NaH / THF, r.t. (82%); (b) $KMnO_4$ / acetone-H_2O, 0 °C (74%); (c) $(Cl_3CO)_2CO$ (triphosgene)[5], py / CH_2Cl_2, -78 → 0 °C (90%).

Scheme 2.

Table 1. Enantioselective Hydrolysis of cyclic carbonate *dl*-**1a** with PPL.[a]

				(*R*)-**1a**		(*S*)-**2a**			
co-solv.	PPL/mg	temp./°C	time/h	yield/%	ee/%	yield/%	ee/%	conv.[b]	E value[b]
-	200	30	24	64	44	34	82	0.35	15
-	500	30	12	49	54	36	80	0.40	15
-	500	30	48	38	79	53	64	0.55	11
t-BuOH	500	30	12	46	68	41	71	0.49	12
DMSO	500	30	12	55	41	40	80	0.34	13
acetone	500	30	12	63	40	31	75	0.35	10
toluene	500	30	12	91	12	9	80	0.13	10
i-Pr_2O	500	30	12	31	>95	65	52	>0.65	12[c]
i-Pr_2O	500	10	12	37	94	51	64	0.59	15

(a) Incubation was performed using 10 mM of *dl*-**1a** with PPL in 0.1 M phosphate buffer (pH 6.5) containing 10% co-solvent. (a) Conv. was calculated by ee(S)/(ee(P)+ee(S)), E value = ln[(1-conv.)(1-ee(S))]/ln[(1-conv.)(1+ee(S))]. See, ref 8. (b) Calculated at conv. = 0.45 - 0.59.

first screening test using 23 commercially available hydrolytic enzymes, the selection of enzymes was carried out on the basis of hydrolytic activity without taking enantioselectivity into account. The assay was performed by checking the production of diol **2a** using thin-layer chromatography. As a result, only porcine pancreas lipase (EC 3.1.1.3, PPL Type II, Sigma) hydrolyzed **1a** to give **2a** while other enzymes could not. A typical experimental procedure of the reaction using PPL is as follows. Thus, 90mg (10 mM) of *dl*-**1a** and 200 mg of the enzyme were added to 40 ml of 0.1 M sodium phosphate buffer (pH 6.5) and incubated at 30 °C for 24 hr. The products were extracted with Et_2O and purified using flash column

Table 2. Enantioselective Hydrolysis of Cyclic Carbonates *dl*-**1**.[a]

	R	time/h	(*R*)-**1** yield/%	(*R*)-**1** $[\alpha]_D$/°[c]	(*R*)-**1** ee/%[b]	(*S*)-**2** yield/%	(*S*)-**2** $[\alpha]_D$/°[c]	(*S*)-**2** ee/%[b]	conv.	E value
b	CH_2OBn	12	34		80	49	-1.9	58	0.58	9
		24	28	+14[d]	98	61		39	0.72	9
c	$(CH_2)_3OBn$	12	40		78	40	-10	81	0.49	22
		18	35	+18[d]	96	51		72	0.57	23
d	$(CH_2)_7CH_3$	12	31[e]	+8.7[c,e]	70[e]	38	-10	84	0.46	23

(a) Incubation was performed using 10 mM of *dl*-**1** with 500 mg of PPL in 0.1 M phosphate buffer (pH 6.5) containing of 10% *i*-Pr_2O at 10 °C. (b) Determined by HPLC analysis of the corresponding bis-(*R*)-MTPA esters with Zorbax SIL (DuPont Instruments). (c) Measured in MeOH at r.t. (c 0.84 - 1.22). (d) Measured in $CHCl_3$ at r.t. (c 0.65 - 1.10). (e) Based on (*R*)-**2d** after hydrolysis of (*R*)-**1d**.

chromatography on silica gel. The reaction of *dl*-**1a** proceeded with high enantioselectivity to afford optically active (*R*)-**1a**[6] (44% ee) and (*S*)-**2a**[7] (82% ee; $[\alpha]^{23}_D$ -17.9 ° (c 0.78, MeOH)) in 64% and 34% yield, respectively (conv.[8] = 0.35, E value[8] = 15). The absolute configurations of the products were determined by comparing the optical rotation of **2a** with that of an authentic sample derived from L-malic acid; (*S*)-form, $[\alpha]^{19}_D$ -21.0 ° (c 0.72, MeOH).[9] The ee of diol (*S*)-**2a** was determined by the ^{1}H-NMR measurement of the bis-(*R*)-MTPA ester which was converted from **2a**.[10] A similar analysis of (*R*)-**2a** derived from (*R*)-**1a** with K_2CO_3 determined the ee of (*R*)-**1a**.

Next, we tried to improve the conversion % of the reaction with the aim of preparing (*R*)-**1a** with higher optical purity, but the conversion % did not remarkably increase by the incremental amount of enzyme and the reaction time (Table 1). We then proceeded with the addition of co-solvents to the reaction mixture. As a result, the use of representative co-solvents was not satisfactory. Thus, the addition of a 10% water-miscible organic solvent (*t*-BuOH, DMSO, or acetone) did not improve the reactivity; the nonpolar solvent, toluene, noticeably reduced the reactivity. However, the reaction containing partially water-miscible *i*-Pr_2O at 30 °C for 12 h (PPL, 500 mg) smoothly proceeded (conv. = *ca.* 0.65) to give optically pure (*R*)-**1a**, $[\alpha]^{19}_D$ +32.0 ° (c 0.90, $CHCl_3$). It was also found that the enantioselectivity was somewhat improved at lower reaction temperature (E value = 12 at 30 °C; E value = 15 at 10 °C).

This reaction was also applicable to several five-membered cyclic carbonates to afford various chiral compounds (Table 2). It is noteworthy that the increment of the carbon number of the substituents reflects the drastic increase in enantioselectivity. While the reaction of **1b** having a benzyloxymethyl group showed moderate enantioselectivity (E value = 9), the change in the substituent to a benzyloxypropyl group (**1c**) which was longer than that of **1a** and **1b** increased the E value to 22 ~ 23. Similarly, the substrate **1d** having a long alkyl chain (R = $-(CH_2)_7CH_3$) was hydrolyzed with higher enantioselectivity (E value = 23). In all cases, PPL hydrolyzed the (*S*)-isomers of cyclic carbonates faster than the (*R*)-isomers.[11,12]

In conclusion, a new type of enzymatic reaction of cyclic carbonates has been established, resulting in the formation of some optically active cyclic carbonates and diols. Our method is expected to be versatile in organic synthesis. Further investigations are now in progress.

Acknowledgements

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5. Burk, R. M.; Roof, M. B., *Tetrahedron Lett.*, **1993**, *34*, 395.
6. (*R*)-**1a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.95 - 2.17 (m, 2H), 3.62 (ddd, J_1 = 5.0 Hz, J_2 = 10 Hz, J_3 = 9.5 Hz, 1H), 3.64 (ddd, J_1 = 5.0 Hz, J_2 = J_3 = 9.5 Hz, , 1H), 4.18 (dd, J_1 = 7.5 Hz, J_2 = 8.5 Hz, 1H), 4.49 (s, 2H), 4.52 (dd, J_1 = 7.5 Hz, J_2 = 8.5 Hz, 1H), 4.88 (dddd, J_1 = J_2 = 7.5 Hz, J_3 = 7.0 Hz, 1H), 7.15 - 7.46 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 33.9, 65.4, 69.8, 73.2, 75.2, 127.6, 127.8, 128.4, 137.9, 155.0; IR (neat) 3570, 3040, 2870, 1800, 1450, 1360, 1170, 1090, 1060, 770, 740, 700 cm^{-1}; MS, m/z (rel. intensity) 222(M^+, 4.7), 160 (39), 131 (6.3), 107 (26), 105 (27), 91 (100).
7. Spectroscopic data of (*S*)-**2a** were in agreement with those reported. See, Tang, K. C.; Tropp, B. E.; Engel, R. *Tetrahedron*, **1978**, *34*, 2873.
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9. Authentic sample was synthesized from L-malic acid in four steps; 1) BH_3·Me_2S, 2) *p*-TsOH, acetone, 3) BnBr, NaH, and 4) *p*-TsOH, MeOH. See also, Mulzer, J.; Lasalle, P. D. *J. Chem. Research (S)*, **1983**, 10.
10. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.66 (dd, J_1 = 2.5 Hz, J_2 = 12.5 Hz, 1H, MTPAOC**H**$_2$, (*S*)-form), δ 4.72 (dd, J_1 = 2.5 Hz, J_2 = 12.5 Hz, 1H, MTPAOC**H**$_2$, (*R*)-form).
11. The absolute configurations of all compounds except **2d** were determined by comparing the optical rotations with those of synthesized authentic samples. Authentic samples: (*S*)-**1b** from D-mannitol, $[\alpha]^{23}_D$ -11.7 ° (c 0.89, $CHCl_3$); (*S*)-**2c** from (*R*)-glycidol, $[\alpha]^{21}_D$ -11.1 ° (c 0.96, MeOH).
12. The ablolute configuration of **2d** was determined by comparing the optical rotation with that already reported; (*S*)-**2d**, $[\alpha]^{22}_D$ -11.9 ° (c 0.43, MeOH). See, Masaoka, Y.; Sakakibara, M.; Mori, K. *Agric. Biol. Chem.*, **1982**, *46*, 2319.

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