

Synthesis of Optically Active Diols Bearing a Long Chain via Enzymatic Hydrolysis of Cyclic Carbonates

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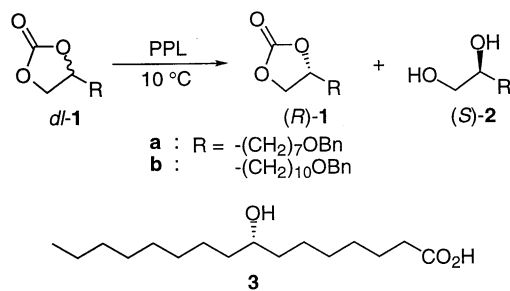
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PPL catalyzes the hydrolysis of racemic five-membered cyclic carbonates bearing a long chain with high enantioselectivity. Optically pure (*S*)-(+)-8-hydroxyhexadecanoic acid is effectively synthesized starting from (*R*)-4-(7-benzyloxy)heptyl-1,3-dioxolan-2-one and (*S*)-9-benzyloxynonane-1,2-diol, which are prepared *via* an enzymatic reaction.

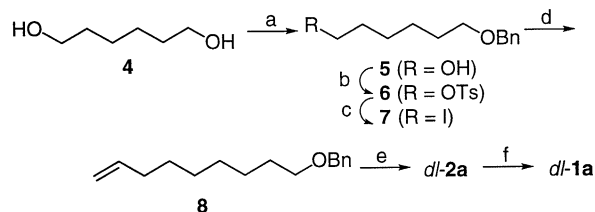
Many biologically active compounds, such as sphingofungins,¹ lipid A,² and so on, have a long chiral aliphatic part substituted with a hydroxyl group at a position remote from the terminus. Such structures have been generally constructed by several tedious steps starting from an optically active C₃- or C₄-unit.

In our previous studies, we have developed a lipase (porcine pancreas, PPL, EC 3.1.1.3, Type II, Sigma)-catalyzed enantioselective hydrolysis of cyclic carbonates.³ For example, optically active 1,2-diol derivatives are easily prepared using five-membered cyclic carbonates as the substrate. In this reaction, the increment in the carbon number of the substituents in the substrates leads to a drastic increase in enantioselectivity. This fact indicates that this method can be potentially useful for the preparation of optically active secondary alcohols bearing long carbon chains. We report herein a useful procedure for the preparation of optically active 1,2-diol derivatives bearing a long chain by a PPL-catalyzed hydrolysis of the corresponding cyclic carbonates (Scheme 1), and an application of the reaction to the synthesis of (*S*)-(+)-8-hydroxyhexadecanoic acid (**3**),^{4,5} an endogenous inhibitor for spore germination in *Lycopodium complanatum* and *Lygodium japonicum*.



Scheme 1.

It is desirable that the substrate has a functional group protected by an appropriate group at the terminus so the compounds obtained by the enzymatic reaction can be useful as chiral synthons. Racemic 4-(7-benzyloxy)heptyl-1,3-dioxolan-2-one (*dl*-**1a**, R = -(CH₂)₇OBn) and 4-(10-benzyloxy)decyl-1,3-dioxolan-2-one (*dl*-**1b**, R = -(CH₂)₁₀OBn) were used as the substrates. The substrate *dl*-**1a** was readily prepared according to Scheme 2. Monobenzylation of commercially available 1,6-hexanediol (**4**), followed by tosylation and iodination gave **7**, which was



a) BnBr, NaH / THF, reflux (54%; recovery of **4**, 35%), b) TsCl, py / CH₂Cl₂, r.t. (89%), c) NaI / acetone, r.t. (97%), d) CH₂=CHCH₂MgBr, cat. Li₂CuCl₄ / THF, 0 °C (83%), e) cat. OsO₄, NMO / acetone-H₂O, r.t. (88%), f) triphosgene, py / CH₂Cl₂, -78→0 °C (84%).

Scheme 2.

Table 1. Enantioselective Hydrolysis of Cyclic Carbonate *dl*-**1** with PPL^a

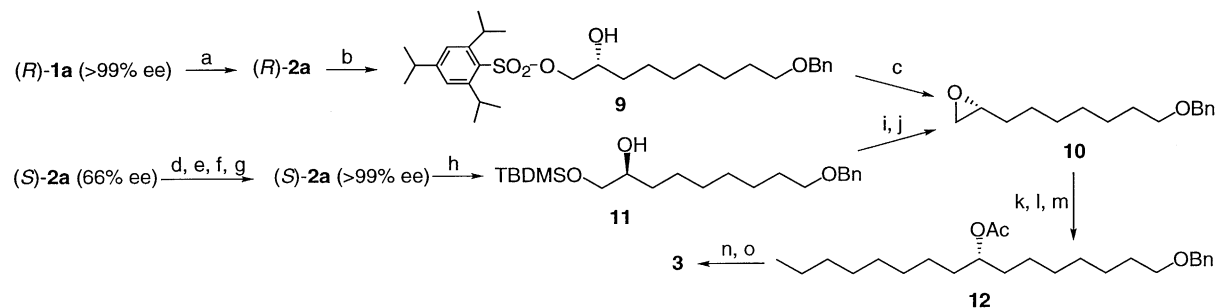
substrate	time/h	(R)-1		(S)-2		conv.	E value
		yield/%	ee/%	yield/%	ee/%		
1a	6	61	46	32	87 ^d	0.35	23
1a	24	40	>99 ^b	52	66 ^d	0.60	24
1b	24	38	>99 ^c	55	68 ^e	0.59	27

a) Incubation was performed using 10 mM of *dl*-**1** with PPL in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr₂O. b) [α]_D²² +11.3 ° (c 1.01, CHCl₃). c) [α]_D²¹ +13.2 ° (c 1.37, CHCl₃). d) [α]_D²⁴ -8.4 ° (c 0.97, MeOH) (>99% ee). e) [α]_D²¹ -4.8 ° (c 1.06, MeOH).

transformed into **8** by coupling with allylmagnesium bromide in the presence of Li₂CuCl₄.⁶ Osmium tetroxide oxidation of **8** gave the racemic 9-(benzyloxy)nonane-1,2-diol (*dl*-**2a**). Successive treatment of *dl*-**2a** with pyridine and triphosgene (bis(trichloromethyl)-carbonate)⁷ gave *dl*-**1a**. Another substrate *dl*-**1b** was synthesized in a similar manner.

Results of the PPL-catalyzed reactions are summarized in Table 1. In all cases, *i*-Pr₂O was used as the co-solvent (10% v/v) of the reaction medium (0.1 M phosphate buffer (pH 6.5)) because the hydrolyses without *i*-Pr₂O were very slow.³ As expected, the hydrolysis of *dl*-**1a** smoothly proceeded with high enantioselectivity. When the reaction was performed for 24 h using 10 mM of *dl*-**1a** (E value = 23 or 24),^{8,9} the optical purities of (*R*)-**1a** (40% yield) and (*S*)-**2a** (52% yield) were greater than 99% ee and 66% ee, respectively. It is noteworthy that this reaction is also applicable to the substrate having a longer chain (*dl*-**1b**, R = -(CH₂)₁₀OBn), which was also executed with higher enantioselectivity (E value = 27) to afford the corresponding chiral compounds.¹⁰

Next, we tried to synthesize naturally occurring (*S*)-(+)-8-hydroxyhexadecanoic acid (**3**) from (*R*)-**1a** and (*S*)-**2a** obtained by the enzymatic hydrolysis. Optically pure (*R*)-**1a** was



a) K_2CO_3 / MeOH, r.t. (94%), b) 2,4,6-triisopropylbenzenesulfonyl chloride / py, r.t., c) K_2CO_3 / MeOH, r.t. (67% from (R)-2a; recovery of (R)-2a, 26%), d) triphosgene, py / CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$ ((S)-1a, 90%, 66% ee), e) PPL, 10% *i*-Pr₂O in buffer, 10°C , 24h ((S)-2a, 72%, 89% ee; recovery of (R)-1a, 13%, >99% ee), f) triphosgene, py / CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$ ((S)-1a, 97%, 89% ee), g) PPL, 10% *i*-Pr₂O in buffer, 10°C , 6h (73%), h) TBDMSCl, cat. DMAP / CH_2Cl_2 , r.t. (94%), i) TsCl / py, r.t., j) TBAF / THF, r.t. (55% from 11), k) $\text{CH}_3(\text{CH}_2)_6\text{MgBr}$ / THF, -10°C , l) Ac_2O , cat. DMAP / py, r.t., m) H_2 , 5% Pd-C / EtOH, r.t. (67% from 10), n) Jones reagent / acetone, r.t., o) KOH / MeOH- H_2O , r.t. (68% from 12).

Scheme 3.

hydrolyzed with K_2CO_3 to afford (R)-2a (Scheme 3).¹¹ Selective protection of the primary hydroxyl group of (R)-2a was achieved using 2,4,6-triisopropylbenzenesulfonyl chloride and pyridine.¹² The product 9 was treated with K_2CO_3 to give (R)-epoxide 10,¹³ which is an important intermediate for the target molecule. On the other hand, (S)-2a of 66% ee was converted to (S)-1a, which was hydrolyzed again with PPL to afford (S)-2a of 89% ee.¹⁴ Reconversion to the carbonate 1a and the enzymatic hydrolysis for 6 h gave optically pure (S)-2a. Inversion of the stereochemistry of (S)-2a was efficiently achieved to the desired (R)-epoxide 10¹⁵ as shown in Scheme 3. Finally, optically pure 10 was synthesized in 41% yield based on racemic 1a.

The resulting 10 was transformed to 12, which was the same precursor of 3 as that already reported,⁵ via the sequence consisting of alkylation with heptylmagnesium bromide, protection and deprotection steps. Finally, Jones' oxidation and hydrolysis of the acetyl group gave the desired 3 in 46% yield based on 10; mp $76 - 77^\circ\text{C}$ (lit.^{5a} $77 - 79.5^\circ\text{C}$), $[\alpha]_{\text{D}}^{22} +0.15^\circ$ (c 1.73, CHCl_3) (lit.^{5a} $[\alpha]_{\text{D}}^{22} +0.34^\circ$ (c 2.2, CHCl_3)). The spectral data¹⁶ of 3 are identical with those reported in the literature.^{4,5}

In conclusion, we have established a facile chemicoenzymatic procedure to prepare optically active 1,2-diols bearing a long chain, and the synthesis of (S)-(+)-8-hydroxyhexadecanoic acid (3) has been efficiently accomplished via the enzymatic hydrolysis as a key step.

References and Notes

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- 4 For isolations of 1, see: a) A. P. Tulloch, *Can. J. Chem.*, **43**, 415 (1965); b) H. Yamane, Y. Sato, N. Takahashi, K. Takano, and M. Furuya, *Agric. Biol. Chem.*, **44**, 1697 (1980).
- 5 For syntheses of 1, see: a) Y. Masaoka, M. Sakakibara, and K. Mori, *Agric. Biol. Chem.*, **46**, 2319 (1982); b) T. Sugai and K. Mori, *Agric. Biol. Chem.*, **48**, 2155 (1984).
- 6 a) J. Drouin, F. Leyendecker, and J. M. Conia, *Tetrahedron*, **36**, 1195 (1980); b) A. Commercon, J. F. Normant, and J. Villieras, *J. Organomet. Chem.*, **128**, 1 (1977).
- 7 A review for triphosgene in organic synthesis, see: L. Cotarca, P. Delogu, A. Nardelli, and V. Šunjić, *Synthesis*, **1996**, 553.
- 8 The ee of 1a was determined by HPLC analysis with CHIRALCEL OB-H (Daicel Chemical Industries, Ltd); Eluent, hexane / 2-propanol = 50 / 50; flow rate, 0.5 ml / min; retention time, 62 (R) and 74 (S) min. On the other hand, the ee of 2a was determined by HPLC analysis of the corresponding cyclic carbonate 1a.
- 9 Experimental procedure is as follows. To a solution of 114 mg (0.390 mmol, 10 mM) of *d*-1a in *i*-Pr₂O (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 Et₂O and purified using flash column chromatography on silica gel (eluent, hexane / AcOEt = 3 / 1 $\rightarrow$ hexane / AcOEt = 2 / 1 $\rightarrow$ AcOEt) to afford (R)-1a (45.5 mg, 40%, >99% ee) and (S)-2a (53.4 mg, 52%, 66% ee).
- 10 The ee of 1b was determined by HPLC analysis with CHIRALCEL OJ (Daicel Chemical Industries, Ltd); Eluent, hexane / 2-propanol = 80 / 20; flow rate, 0.5 ml / min; retention time, 53 (S) and 56 (R) min. On the other hand, the ee of 2b was determined by HPLC analysis of the corresponding cyclic carbonate 1b.
- 11 $[\alpha]_{\text{D}}^{22} +7.8^\circ$ (c 0.97, MeOH).
- 12 In this reaction, diol (R)-2a was recovered in 26% yield.
- 13 $[\alpha]_{\text{D}}^{22} +4.5^\circ$ (c 0.92, CHCl_3).
- 14 In this second enzymatic reaction, optically pure (R)-1a was also obtained in 13% yield.
- 15 $[\alpha]_{\text{D}}^{16} +5.5^\circ$ (c 1.21, CHCl_3).
- 16 Spectral data of 3: ¹H NMR (400 MHz, CDCl_3) δ 0.88 (t, J = 7.0 Hz, 3H), 1.19 - 1.52 (m, 22H), 1.52 - 1.61 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 3.53 - 3.69 (m, 1H), 5.00 (br, 2H); ¹³C NMR (100 MHz, CDCl_3) δ 57.3, 65.9, 67.8, 68.6, 68.9, 72.2, 72.5, 72.8, 72.9, 80.7, 115.3, 120.0, 120.2, 120.4, 120.5, 222.3; IR (KBr) 3314, 3200, 2924, 2851, 1698, 1470, 1439, 1412, 1343, 1291, 1235, 1130, 1100, 1019, 901, 721 cm^{-1} .