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

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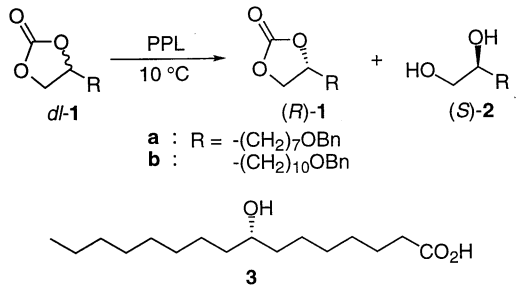
PPL catalyzes the hydrolysis of racemic five-membered cyclic carbonates bearing a long chain with high enantioselectivity. Optically pure (*S*)-(+)-8-hydroxyhexadecanoic acid is effectively synthesized starting from (*R*)-4-(7-benzyloxy)heptyl-1,3-dioxolan-2-one and (*S*)-9-benzyloxynonane-1,2-diol,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

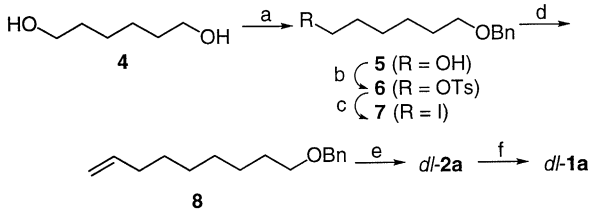
Many biologically active compounds, such as sphingofungins,[1] lipid A,[2] and so on, have a long chiral aliphatic part substituted with a hydroxyl group at a position remote from the terminus. Such structures have been generally constructed by several tedious steps starting from an optically active C_3- or C_4-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- (*dl*-**1a**, R = -$(CH_2)_7$OBn) and 4-(10-benzyloxy)decyl-1,3-dioxolan-2-one (*dl*-**1b**, R = -$(CH_2)_{10}$OBn) 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 / CH_2Cl_2, r.t. (89%), c) NaI / acetone, r.t. (97%), d) CH_2=$CHCH_2MgBr$, cat. Li_2CuCl_4 / THF, 0 °C (83%), e) cat. OsO_4, NMO / acetone-H_2O, r.t. (88%), f) triphosgene, py / CH_2Cl_2, -78→0 °C (84%).

Scheme 2.

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

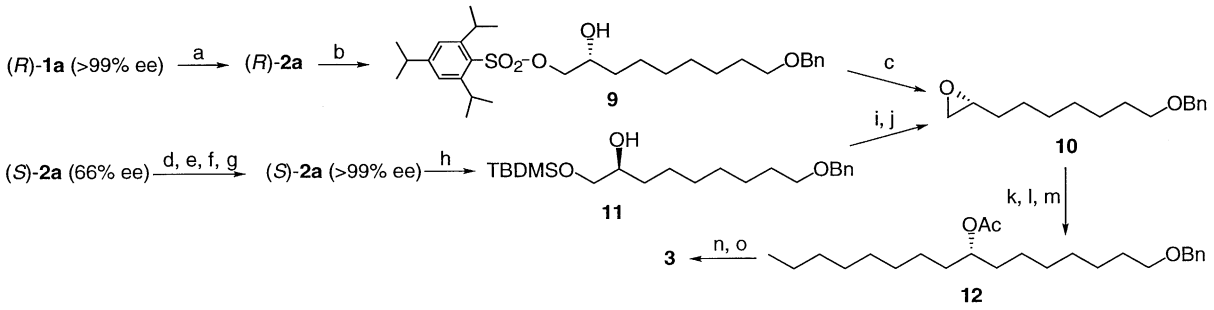
substrate	time/h	(*R*)-**1** yield/%	(*R*)-**1** ee/%	(*S*)-**2** yield/%	(*S*)-**2** ee/%	conv.	E value
1a	6	61	46	32	87[d]	0.35	23
1a	24	40	>99[b]	52	66[d]	0.60	24
1b	24	38	>99[c]	55	68[e]	0.59	27

a) Incubation was performed using 10 mM of *dl*-**1** with PPL in 0.1 M phosphate buffer (pH 6.5) containing 10% *i*-Pr_2O. b) $[\alpha]_D^{22}$ +11.3 ° (c 1.01, $CHCl_3$). c) $[\alpha]_D^{21}$ +13.2 ° (c 1.37, $CHCl_3$). d) $[\alpha]_D^{24}$ -8.4 ° (c 0.97, MeOH) (>99% ee). e) $[\alpha]_D^{21}$ -4.8 ° (c 1.06, MeOH).

transformed into **8** by coupling with allylmagnesium bromide in the presence of Li_2CuCl_4.[6] Osmium tetraoxide 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*-Pr_2O 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*-Pr_2O 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 = -$(CH_2)_{10}$OBn), 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→0 °C ((*S*)-**1a**, 90%, 66% ee), e) PPL, 10% *i*-Pr_2O in buffer, 10 °C, 24h ((*S*)-**2a**, 72%, 89% ee; recovery of (*R*)-**1a**, 13%, >99% ee), f) triphosgene, py / CH_2Cl_2, -78→0 °C ((*S*)-**1a**, 97%, 89% ee), g) PPL, 10% *i*-Pr_2O in buffer, 10 °C, 6 h (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) $CH_3(CH_2)_6MgBr$ / 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 **10**[15] 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 °C (lit.[5a] 77 - 79.5 °C), $[\alpha]_D^{22}$ +0.15 ° (c 1.73, $CHCl_3$) (lit.[5a] $[\alpha]_D^{22}$ +0.34 ° (c 2.2, $CHCl_3$)) The spectral data[16] 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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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 *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 Et_2O and purified using flash column chromatography on silica gel (eluent, hexane / AcOEt = 3 / 1 → hexane / AcOEt = 2 / 1 → 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 $[\alpha]_D^{22}$ +7.8 ° (c 0.97, MeOH).

12 In this reaction, diol (*R*)-**2a** was recovered in 26% yield.

13 $[\alpha]_D^{22}$ +4.5 ° (c 0.92, $CHCl_3$).

14 In this second enzymatic reaction, optically pure (*R*)-**1a** was also obtained in 13% yield.

15 $[\alpha]_D^{16}$ +5.5 ° (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); ^{13}C 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}.