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Enzyme-Mediated Preparation of Optically Active 1,2-Diols Bearing a Long Chain: Enantioselective Hydrolysis of Cyclic Carbonates

Megumi Shimojo, Kazutsugu Matsumoto* and Minoru Hatanaka

Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Fukui University, Bunkyo 3-9-1, Fukui 910-8507, Japan

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Abstract—A new entry for the efficient preparation of optically active 1,2-diols having a long aliphatic chain via an enzymatic reaction is disclosed. PPL catalyzes the hydrolysis of a racemic five-membered cyclic carbonate, 4-(7-benzyloxy)heptyl-1,3-dioxolan-2-one (**2a**), with high enantioselectivity to produce the optically active (*R*)-**2a** and (*S*)-9-benzyloxynonane-1,2-diol (**3a**) in excellent yields. The reaction is applicable to the substrates with a longer chain (10-benzyloxydecyl (**3b**) and 13-benzyloxytridecyl group (**3c**)). Optically pure (*S*)-(+)-8-hydroxyhexadecanoic acid (**1**), a biologically active natural compound with a chiral long aliphatic part, is effectively synthesized starting from (*R*)-3-(7-benzyloxy)heptyl-2-oxirane (**9**), which is converted from both enantiomers of **3a**.

Introduction

Many biologically active compounds, such as sphingofungins,[1,2] lipid A,[3] coriolic acid,[4,5] and so on, have a long chiral aliphatic part. (*S*)-(+)-8-Hydroxyhexadecanoic acid (**1**) is a hydroxy-fatty acid, which is an endogeneous inhibitor for spore germination in *Lycopodium complanatum* and *Lygodium japonicum*.[6,7] The compound is also known as a component of the resin produced by the insect genus *Laccifer*.[8] In spite of its simple structure, it is difficult to synthesize **1** in an optically pure form because the asymmetric carbon is located at a remote position from the terminus. Such structures have been generally constructed by several tedious steps starting from an optically active C3- or C4-unit (Fig. 1).

The enzymatic reaction is one of the attractive methods for the preparation of optically active compounds.[9] Recently, the enzymatic enantioselective hydrolysis of cyclic carbonates has been disclosed as a useful procedure for the preparation of optically active diols (Scheme 1).[10–13] We also reported that Porcine Pancreas Lipase (PPL, EC 3.1.1.3, Type II from Sigma) efficiently catalyzed the hydrolysis of various kinds of five-membered cyclic carbonates, resulting in the formation of a variety of optically active 1,2-diols.[12] Scheme 1 shows the proposed reaction mechanism. In the first step, the enzyme attacks the carbonyl group of the substrate, and water molecules attack the acyl-enzyme intermediates in the second step. While the first step is reversible, the second step is not reversible because the acyl moiety of the substrate leaves the reaction system as carbon dioxide. When the enzyme recognizes the stereochemistry of the substrate, the unreacted (*R*)-cyclic carbonate and the resulting (*S*)-diol are obtained in optically active forms. These products are easily separated because their physical properties, such as boiling point and polarity, are quite different. Interestingly, the increment in the carbon number of the substituents in the substrates leads to a drastic increase in enantioselectivity. These facts indicate that this enzymatic method can be useful for the preparation of optically active 1,2-diols bearing a long aliphatic chain, the diols of which are important precursors to natural products including part of the chiral secondary alcohol. In this report, we have established the enantioselective enzymatic hydrolysis of the substrates with a long carbon chain, and a new entry for an efficient synthesis of (*S*)-**1** via the enzymatic reaction as the key step.[12d]

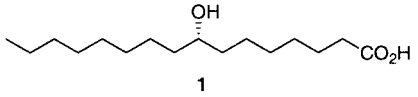

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Figure 1.

Results and Discussion

Enzymatic hydrolysis of cyclic carbonates bearing a long chain *dl*-2

In order to prepare useful chiral building blocks, it is

Keywords: cyclic carbonates; enzymes and enzyme reactions; diols; hydrolysis.

* Corresponding author. Fax: +81-776-27-8747;
e-mail: mkazu@acbio2.acbio.fukui-u.ac.jp

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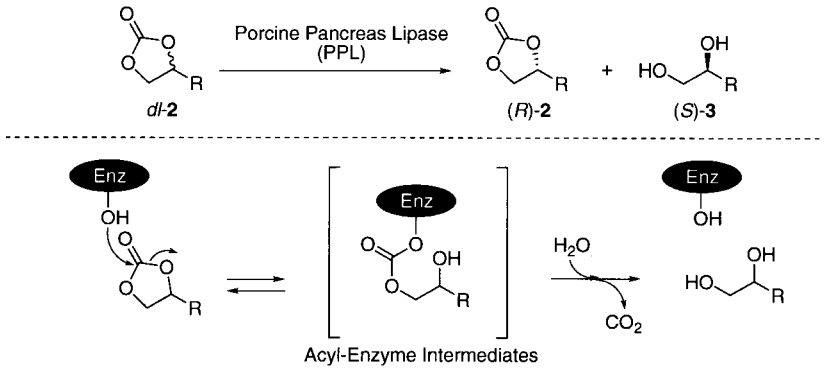
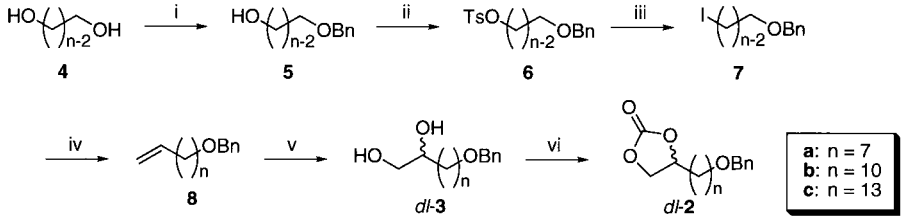
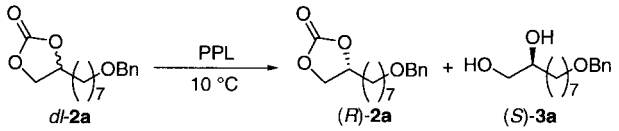


Scheme 1.



Scheme 2. (i) BnBr, NaH/THF, reflux (**5a**: 54% (recovery of **4a**, 35%); **5b**: 51% (recovery of **4b**, 35%);**5c**: 48% (recovery of **4c**, 33%)); (ii) TsCl, py/CH_2Cl_2, rt; (iii) NaI/acetone, rt (**7a**: 86% from **5a**; **7b**: 79% from **5b**; **7c**: 60% from **5c**); (iv) CH_2=$CHCH_2MgBr$, cat. Li_2CuCl_4/THF, 0°C (**8a**: 83%; **8b**: 76%; **8c**: 98%); (v) cat. OsO_4, NMO/acetone–H_2O, rt (**3a**: 88%; **3b**: 79%; **3c**: 60%); (vi) triphosgene, py/CH_2Cl_2, −78→0°C (**2a**: 84%; **2b**: 91%; **2c**: 97%).

desirable that the substrate has a functional group protected by an appropriate group at the terminus. We have already tried the PPL-mediated reaction for the substrates having benzyloxymethyl, (2-benzyloxy)ethyl, and (3-benzyloxy)-propyl group.[12a,b] Herein, we focused on the compounds bearing longer substituents. The racemic 4-(7-benzyloxy)-heptyl-(*dl*-**2a**, *n*=7), 4-(10-benzyloxy)decyl-(*dl*-**2b**, *n*=10), and 4-(13-benzyloxy)tridecyl-1,3-dioxolan-2-one (*dl*-**2c**, *n*=13) were then selected as the substrates. The substrates *dl*-**2** were readily prepared according to Scheme 2. Monohydroxyl groups of commercially available 1,6-hexane-(**4a**), 1,9-nonane-(**4b**), and 1,12-dodecanediol (**4c**) were protected with benzyl groups using benzyl bromide and sodium hydride, and the following by tosylations and iodinations gave the corresponding **7a**, **7b**, and **7c**, respectively. The iodides **7** were transformed into olefins **8** by coupling with allylmagnesium bromide in the presence of Li_2CuCl_4.[14] The osmium tetraoxide oxidations of **8** gave racemic 9-benzyloxynonane-(**3a**), 12-benzyloxydodecane-(**3b**), and 15-benzyloxypentadecane-1,2-diol (**3c**), respectively. Cyclic carbonates **2** were readily synthesized by the treatments of the corresponding **3** with pyridine and bis(trichloromethyl)carbonate (triphosgene).[15]



Scheme 3.

First, we examined the PPL-catalyzed reactions of *dl*-**2a** (Scheme 3 and Table 1). In all cases, *i*-Pr_2O was used as the co-solvent of the reaction medium (0.1 M phosphate buffer (pH 6.5)) because the hydrolyses without *i*-Pr_2O were very slow.[12] As expected, the hydrolysis of *dl*-**2a** smoothly proceeded with high enantioselectivity. Under the conditions of 10°C for 6 h (Entry 1), the reaction proceeded to afford optically active (*R*)-**2a** (46% ee) and (*S*)-**3a** (87% ee) in 61 and 32% yields, respectively (conv.[16]=0.35, E value[16]=23). The ee of (*R*)-**2a** was determined by HPLC analysis with CHIRALCEL OB-H (Daicel Chemical Industries, Ltd.) and a similar analysis of (*S*)-**2a** derived from (*S*)-**3a** was also performed. When the reaction was continued to 24 h, the enantiomerically pure (*R*)-**2a**, $[\alpha]_D^{22}$=+11.3 (c 1.01, $CHCl_3$), was produced (Entry 2).

Table 1. Enantioselective hydrolysis of cyclic carbonate DL-**2a** with PPL (incubation was performed using 10 mM of DL-**2a** with PPL in 0.1 M phosphate buffer (pH 6.5) at 10°C containing *i*-Pr_2O as the co-solvent)

Entry	Time (h)	Conc. of *i*-Pr_2O (% v/v)	Carbonate (*R*)-**2a**		Diol (*S*)-**3a**		Conv.[a]	E[b]
			Yield (%)	Ee (%)	Yield (%)	Ee (%)		
1	6	10	61	46	32	87	0.35	23
2	24	10	40	>99	52	66	0.60	24
3	24	50	51	66	41	85	0.44	24

[a] Calculated by ee(**2**)/[ee(**2**)+ee(**3**)].
[b] Calculated by ln[(1−Conv.)(1−ee(**2**))]/ln[(1−Conv.)(1+ee(**2**))].

Table 2. Enantioselective hydrolysis of cyclic carbonate DL-**2b** and **2c** with PPL (incubation was performed using 10 mM of DL-**2** with PPL in 0.1 M phosphate buffer (pH 6.5) at 10°C containing 10% *i*-Pr_2O as the co-solvent)

Entry	Substrate	Time (h)	Carbonate (*R*)-**2**		Diol (*S*)-**3**		Conv.	E
			Yield (%)	Ee[a] (%)	Yield (%)	Ee[b] (%)		
1	**2b**	6	72	28	23	91	0.24	28
2	**2b**	24	38	>99	55	68	0.59	27
3	**2c**	6	66	9	17	78	0.10	9
4	**2c**	24	49	50	39	71	0.41	10

[a] Determined by HPLC analysis with CHIRALCEL OJ (**2b**) and OB-H (**2c**).
[b] Determined by HPLC analysis after the transformation into the corresponding cyclic carbonate **2**.

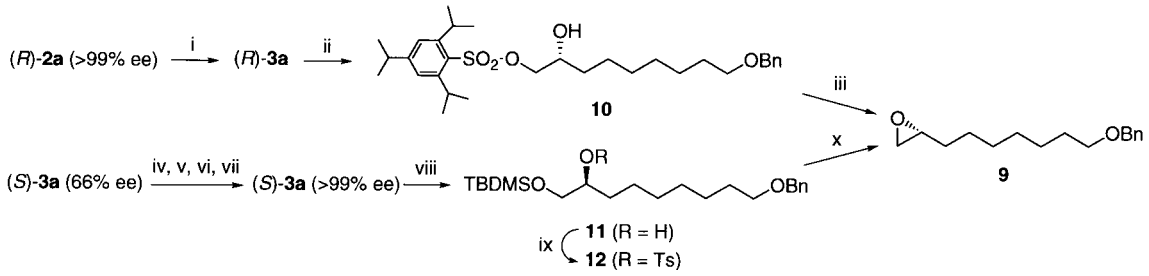
Although the amount of the co-solvent could improve the enantioselectivity in our previous case,[12c] the addition of more *i*-Pr_2O (50% in the reaction medium, Entry 3) did not change the enantioselectivity (E value=24) but decreased the reactivity.

Next, we examined the substrates bearing a much longer chain (*dl*-**2b** and **2c**, Table 2). Changing the substituent from the 7-benzyloxyheptyl group (**2a**) to the 10-benzyloxydecyl group (**2b**) apparently increased the E value up to 28 and 27 (Entries 1 and 2), and optically active (*R*)-**2b** and (*S*)-**3b** were obtained. The reaction for 24 h gave optically pure (*R*)-**2b** in 38% yield. These optically active products can be potentially useful for preparing optically active 11-hydroxyhexadecanoic acid, which is an important intermediate for the synthesis of biologically active macrocyclic glycolipids, such as calonyctin A[17,18] and tricolorin A.[19,20] On the other hand, the reaction of *dl*-**2c** also proceeded to afford the corresponding optically active compounds (Entries 3 and 4). However, the elongation of the side chain to the 13-benzyloxytridecyl group caused a drastic decrease in the reactivity and enantioselectivity. In the reaction of *dl*-**2c** for even 24 h, the conversion and E values were only 0.41 and 10, respectively. These results suggest that the length of substituents of the cyclic carbonate **2b** is most suitable for the active site of PPL and longer chains than that of **2b** do not favorably fit.

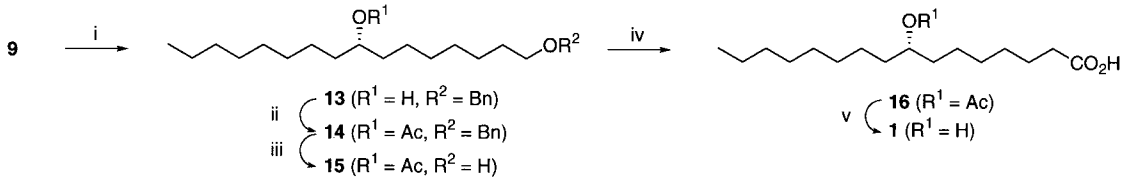
Synthesis of (*S*)-(+)-8-hydroxyhexadecanoic acid (1)

As an example of demonstrating the validity of this enzymatic reaction, we planned the efficient synthesis of the naturally occurring (*S*)-**1** in the optically pure form (Schemes 4 and 5). First, we examined the optically active epoxide **9** as an important intermediate for the target molecule. Optically pure (*R*)-**2a** obtained by the enzymatic hydrolysis as mentioned above was hydrolyzed with K_2CO_3 to afford (*R*)-**3a**, $[\alpha]_D^{22}=+7.8$ (c 0.97, MeOH). The treatment of (*R*)-**3a** with *p*-toluenesulfonyl chloride produced considerable amounts of the bis-tosylated product, which was useless for the synthesis. After several trials, selective protection of the primary hydroxyl group of (*R*)-**3a** was achieved using 2,4,6-triisopropylbenzenesulfonyl chloride and pyridine to afford the alcohol **10**. Successive treatment of the product **10** with K_2CO_3 in MeOH resulted in the intermediate (*R*)-epoxide **9**, $[\alpha]_D^{22}=+4.5$ (c 0.92, $CHCl_3$), in 67% yield (2 steps) and the starting material (*R*)-**3a** in 26% yield.

An alternative route to **9** was also examined starting from



Scheme 4. (i) K_2CO_3/MeOH, rt (94%); (ii) 2,4,6-triisopropylbenzenesulfonyl chloride/py, rt; (iii) K_2CO_3/MeOH, rt (67% from (*R*)-**3a**; recovery of (*R*)-**3a**, 26%); (iv) triphosgene, py/CH_2Cl_2, −78→0°C ((*S*)-**2a**, 90%, 66% ee); (v) PPL, 10% *i*-Pr_2O in buffer, 10°C, 24h ((*S*)-**3a**, 72%, 89% ee; recovery of (*R*)-**2a**, 13%, >99% ee); (vi) triphosgene, py/CH_2Cl_2, −78→0°C ((*S*)-**2a**, 97%, 89% ee); (vii) PPL, 10% *i*-Pr_2O in buffer, 10°C, 6 h (73%); (viii) TBDMSCl, Et_3N, cat. DMAP/CH_2Cl_2, rt; (ix) TsCl, cat. DMAP/py, rt; (x) TBAF/THF, rt (55% from (*S*)-**3a**).



Scheme 5. (i) $CH_3(CH_2)_6MgBr$/THF, −10°C; (ii) Ac_2O, cat. DMAP/py, rt; (iii) H_2, 5% Pd-C/EtOH, rt (67% from **9**); (iv) Jones reagent/acetone, rt; (v) KOH/MeOH–H_2O, rt (68% from **15**).

(*S*)-**3a** obtained by the enzymatic reaction. In order to improve the ee of (*S*)-**3a** (66% ee), we tried repeating enzymatic reaction in the following manner. First, (*S*)-**3a** was converted to (*S*)-**2a**, which was hydrolyzed again with PPL to afford (*S*)-**3a** of 89% ee. In this step, optically pure (*R*)-**2a** was also obtained in 13% yield. Second, re-conversion to the carbonate **2a** and the enzymatic hydrolysis for 6 h gave the optically pure (*S*)-**3a**, $[\alpha]_D^{24}=-8.4$ (c 0.97, MeOH). In total, an optically pure (*R*)-**2a** of 46% and (*S*)-**3a** of 24% were obtained from racemic **2a**. The primary hydroxyl group of the resulting optically pure (*S*)-**3a** was efficiently protected with *t*-butyldimethylsilyl group to afford the alcohol **11**. Inversion of the stereochemistry was accomplished by tosylation and deprotection to give the desired (*R*)-epoxide **9**, $[\alpha]_D^{16}=+5.5$ (c 1.21, $CHCl_3$). Finally, optically pure **10** was synthesized in 41% yield based on racemic **2a**.

Next, the sequential steps consisting of alkylation with heptylmagnesium bromide, protection with acetic anhydride, and deprotection of the benzyl group converted from the epoxide **9** into the primary alcohol **15** in 67% yield (3 steps), which was the same precursor of **1** as already reported (Scheme 5).[7] Lastly, Jones oxidation and hydrolysis of the acetyl group gave the desired **1** in 46% yield based on **15**; mp 76–77°C (lit.[7a] 77–79.5°C), $[\alpha]_D^{22}=+0.15$ (c 1.73, $CHCl_3$) (lit.[7a] $[\alpha]_D^{22}=+0.34$ (c 2.2, $CHCl_3$)). The spectral data of **1** are identical with those reported in the literature.[6,7†]

Conclusion

In this paper, we established a facile chemoenzymatic procedure for the preparation of optically active 1,2-diols bearing a long aliphatic chain, which are useful intermediates in the synthesis of natural products. The PPL-mediated enzymatic hydrolysis of *dl*-**2a** followed by several steps afforded both enantiomers of 1,2-diol **3a**.The diols were successfully transformed into (*S*)-(+)-8-hydroxyhexadecanoic acid (**1**). Further investigations for the application of the enzymatic reaction are now in progress.

Experimental

General

^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were measured on a JEOL Lambda 500 with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Hitachi 270-30 spectrometer. Mass spectra were obtained with a JEOL JMS-700T by the EI method. Optical rotations were measured with a Jasco DIP-181 and DIP-1030 polarimeter. HPLC data were obtained on a Jasco TRI ROTAR-VI and UVIDEC-100-VI. Merck Kieselgel 60 F_{254} Art.5715 was used for analytical TLC. Preparative TLC was performed on Merck Kieselgel 60 F_{254} Art.5744. Column chromatography was performed with Merck Kieselgel 60 Art.7734. Melting points were obtained on a Yanako melting point apparatus and were not corrected. Porcine Pancreas Lipase (PPL, EC 3.1.1.3, Type II) was purchased from Sigma Chemical Co. All other chemicals were also obtained from commercial sources.

Preparation of racemic diols *dl*-3

6-Benzyloxy-1-hexanol (5a). Under an argon atmosphere, to a suspension of NaH (60% in oil, 2.03 g, 50.8 mmol) in THF (30 mL) were added a solution of 1,6-hexanediol (**4a**, 5.00 g, 42.4 mmol) in THF (30 mL) and benzyl bromide (3.5 g, 50.8 mmol) at 0°C. The mixture was stirred for 2 h under reflux and the reaction was quenched with 0.2 M phosphate buffer (pH 6.5). The products were extracted with AcOEt (×4), and the organic layer was washed with brine and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=5/1→2/1) to give **5a** as a colorless oil (4.75 g, 54%). Diol **4a** was recovered in 35%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.31–1.74 (m, 8H), 3.47 (t, J=6.5 Hz, 2H), 3.62 (t, J=6.5 Hz, 2H), 4.50 (s, 2H), 7.24–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.0, 29.7, 32.7, 62.9, 70.3, 72.9, 127.5, 127.6, 128.3, 138.6; IR (neat) 3392, 2932, 2856, 1454, 1364, 1100, 1078, 1065, 1028, 736 cm^{-1}; MS *m/z* (rel. intensities) 208 (M^+, 26), 117 (32), 107 (85), 91 (100); HRMS *m/z* 208.1459 (208.1463 calcd for $C_{13}H_{20}O_2$, M^+).

6-Benzyloxy-1-iodohexane (7a). Under an argon atmosphere, to a solution of alcohol (**5a**, 4.00 g, 19.3 mmol) in CH_2Cl_2 (80 mL) was added pyridine (5.50 g, 39.0 mmol) and *p*-TsCl (2.3 ml, 29.0 mmol) at 0°C. The mixture was stirred for 3 days at room temperature. The reaction was stopped with sat. NH_4Cl aqueous solution and the products were extracted with AcOEt (×4). The organic layer was washed with 1 M HCl (×2), brine, sat. $NaHCO_3$ aqueous solution, and brine and dried over Na_2SO_4. After evaporation, the residue **6a** was used the following reaction without purification. To a solution of **6a** in acetone (120 mL) were added NaI (5.78 g, 38.6 mmol) and $NaHCO_3$ (2.43 g, 29.0 mmol) at 0°C. The mixture was stirred for 3 days at room temperature, and the reaction was stopped with sat. $Na_2S_2O_5$ aqueous solution. The products were extracted with AcOEt (×5), and the organic layer was washed with sat. $Na_2S_2O_5$ aqueous solution and brine, and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1) to give **7a** as a colorless oil (5.10 g, 86% from **5a**). ^1H NMR (500 MHz, $CDCl_3$) δ 1.36–1.45 (m, 4H), 1.58–1.65 (m, 2H), 1.79–1.86 (m, 2H), 3.18 (t, J=7.0 Hz, 2H), 3.47 (t, J=6.5 Hz, 2H), 4.50 (s, 2H), 7.26–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.03, 25.5, 30.3, 33.5, 70.2, 72.9, 127.5, 127.6, 128.3, 138.6; IR (neat) 3020, 2928, 2852, 1454, 1366, 1206, 1168, 1104, 734, 698 cm^{-1}; MS *m/z* (rel. intensities) 318 (M^+, 19), 173 (100), 155 (43), 131 (59), 107 (69); HRMS *m/z* 318.0467 (318.0481 calcd for $C_{13}H_{19}OI$, M^+).

8-Benzyloxy-1-nonene (8a). Under an argon atmosphere, allylmagnesium bromide (1.0 M in Et_2O, 47.2 mL) was

† The optical rotations of the intermediates including **1** showed low values. However, the compound **1** must be obtained in an optically pure form because the preparation of the epoxide **9** from the diols (*R*)- and (*S*)-**3a** and the following sequential steps to **1** are the chemically established methods.

added to a solution of **7a** (5.01 g, 0.016 mol) in THF (30 mL) at 0°C, followed by addition of a solution of Li_2CuCl_4 (1.74 g, 7.9 mmol)[14] in THF (10 mL) at 0°C. The mixture was stirred for 2 h. The reaction was quenched with sat. NH_4Cl aqueous solution and the products were extracted with Et_2O (×4). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=50/1) to give **8a** as a colorless oil (3.03 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.40 (m, 8H), 1.61 (tt, *J*=7.5, 7.0 Hz, 2H), 2.03 (td, *J*=7.5, 7.0 Hz, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 4.92 (dd, *J*=10.0, 1.0 Hz, 1H), 4.99 (dd, *J*=17.0, 1.5 Hz, 1H), 5.80 (tdd, *J*=17.0, 10.5, 5.0 Hz, 1H), 7.25–7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 28.9, 29.0, 29.3, 29.8, 33.8, 70.5, 72.9, 114.1, 127.4, 127.6, 128.3, 138.7, 139.2; IR (neat) 3524, 3064, 3020, 2924, 2848, 1640, 1454, 1360, 1102, 910, 734, 698 cm^{-1}; MS *m/z* (rel. intensities) 232 (M^+, 59), 161 (24), 141 (28), 107 (100); HRMS *m/z* 232.1770 (232.1827 calcd for $C_{16}H_{24}O$, M^+).

***dl*-9-Benzyloxy-1,2-nonandiol (3a).** To a solution of **8a** (2.84 g, 12.0 mmol) in acetone (150 mL) and H_2O (105 mL) were added 4-methylmorpholine *N*-oxide (6.0 g, 48.0 mmol), *tert*-butanol (10 mL), and a catalytic amount of OsO_4, and the mixture was stirred for 2 h at room temperature. After addition of $Na_2S_2O_4$ and stirring for 30 min, the mixture was filtrated through a celite pad, and the products were extracted with AcOEt (×3) from the filtrate, washed with brine, and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give *dl*-**3a** as a colorless oil (2.86 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26–1.42 (m, 10H), 1.61 (dt, *J*=13.5, 7.0 Hz, 2H), 2.33 (br.s, 2H), 3.41 (dd, *J*=10.5, 7.0 Hz, 1H), 3.46 (t, *J*=6.5 Hz, 2H), 3.63 (dd, *J*=11.0, 2.5 Hz, 1H), 3.63–3.73 (m, 1H), 4.50 (s, 2H), 7.25–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 26.1, 29.3, 29.5, 29.7, 33.1, 66.7, 70.4, 72.3, 72.8, 127.5, 127.6, 128.3, 138.6; IR (neat) 3368, 2928, 2852, 1542, 1545, 1366, 1096, 1076, 736, 700 cm^{-1}; MS *m/z* (rel. intensities) 266 (M^+, 23), 249 (100), 141 (15), 91 (100); HRMS *m/z* 266.1826 (266.1882 calcd for $C_{16}H_{26}O_3$, M^+). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%. Found: C, 71.55; H, 9.72%.

9-Benzyloxy-1-nonanol (5b). According to the procedure for the preparation of **5a** described above, **4b** (5.0 g, 31.3 mmol) was converted to **5b** (4.0 g, 51%) as a colorless oil. Diol **4b** was recovered in 35%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21–1.45 (m, 10H), 1.45–1.68 (m, 4H), 2.78 (brs, 1H), 3.46 (t, *J*=6.5 Hz, 2H), 3.61 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 7.22–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 26.1, 29.29, 29.32, 29.5, 29.7, 32.6, 62.9, 70.4, 72.8, 127.4, 127.6, 128.3, 138.6; IR (neat) 3426, 2924, 2848, 1718, 1454, 1368, 1102 cm^{-1}; MS *m/z* (rel. intensities) 250 (M^+, 42), 232(0.9), 107 (79), 91, (100); HRMS *m/z* 250.1915 (250.933 calcd for $C_{16}H_{26}O_2$, M^+).

1-Benzyloxy-9-iodononane (7b). According to the sequential procedure for the preparation of **7a** described above, **5b** (3.86 g, 15.4 mmol) was converted to **7b** (4.2 g, 79% from **5b**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.45 (m, 10H), 1.56–1.65 (m, 2H), 1.76–1.86 (m, 2H), 3.18 (t, *J*=7.0 Hz, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 7.18–7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 26.1, 28.4, 29.3, 29.7, 30.4, 33.5, 70.4, 72.8, 127.4, 127.6, 128.3, 138,6; IR (neat) 2924, 2848, 1738, 1454, 1368, 1240, 1102, cm^{-1}; MS *m/z* (rel. intensities) 360 (M^+, 12), 269 (14), 155 (24), 141 (4.0), 123 (24), 107 (15), 91 (100); HRMS *m/z* 360.0954 (360.0951 calcd for $C_{16}H_{25}OI$, M^+).

1-Benzyloxy-11-dodecene (8b). According to the procedure for the preparation of **8a** described above, **7b** (4.2 g, 11.6 mmol) was converted to **8b** (2.4 g, 76%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.43 (m, 14H), 1.61 (tt, *J*=7.0 Hz, 2H), 2.04 (dt, *J*=7.0 Hz, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 4.93 (dd, *J*=1.0, 10.0 Hz, 1H), 4.99 (dd, *J*=1.0, 17.0 Hz, 1H), 5.81 (tdd, *J*=4.5, 10.0, 17.0 Hz, 1H), 7.24–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 28.9, 29.1, 29.3, 29.46, 29.53, 29.56, 29.8, 33.8, 70.5, 72.8, 114.1, 127.4, 127.6, 128.3, 138.8, 139.2; IR (neat) 3060, 3024, 2924, 2852, 1454, 1362, 1104, 1026, 994, 910, 734, 698 cm^{-1}.

***dl*-12-Benzyloxy-1,2-dodecandiol (3b).** According to the procedure for the preparation of **3a** described above, **8b** (1.5 g, 5.4 mmol) was converted to **3b** (728.5 mg, 79%) as a white crystal. This was further recrystallized from hexane–Et_2O. Mp 56–58°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.47 (m, 16H), 1.61 (tdd, *J*=6.5, 7.0 Hz, 2H), 2.78 (brs, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 3.61–3.66 (m, 1H), 3.66–3.73 (m, 1H), 4.50 (s, 2H), 7.18–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.1, 29.42, 29.51, 29.58, 29.7, 33.1, 66.7, 70.5, 72.3, 72.8, 127.4, 127.6, 128.3, 138.6; IR (KBr) 3500, 3224, 2912, 2844, 1468, 1126, 872, 734 cm^{-1}; MS *m/z* (rel. intensities) 256 (M^+-H_2O, 2.7), 149 (3.5), 107 (8.6), 91 (100); HRMS *m/z* 274.2321 (274.2296 calcd for $C_{19}H_{30}O_3$, M^+).

12-Benzyloxy-1-dodecanol (5c). According to the procedure for the preparation of **5a** described above, **4c** (2.02 g, 9.9 mmol) was converted to **5c** (1.41 g, 48%) as a colorless oil. Diol **4c** was recovered in 33%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21–1.39 (m, 16H), 1.46–1.50 (brs, 1H), 1.52–1.64 (m, 4H), 3.46 (t, *J*=6.5 Hz, 2H), 3.63 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 7.23–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 26.2, 29.4, 29.5, 29.6, 29.8, 32.8, 63.1, 70.5, 72.8, 127.4, 127.6, 128.3, 138.7; IR (neat) 3412, 2924, 2852, 1454, 1364, 1102, 1076, 1028, 736, 698 cm^{-1}; MS *m/z* (rel. intensities) 292 (M^+, 34), 274 (2.5), 201 (0.5), 185 (0.5), 107 (81), 91 (100); HRMS *m/z* 292.2439 (292.2402 calcd for $C_{19}H_{32}O_2$, M^+).

12-Benzyloxy-1-iodododecane (7c). According to the sequential procedure for the preparation of **7a** described above, **5c** (1.36 g, 4.6 mmol) was converted to **7c** (1.12 g, 60% from **5c**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.41 (m, 16H), 1.61 (tt, *J*=7.0 Hz, 2H), 1.81 (tt, *J*=7.0 Hz, 2H), 3.18 (t, *J*=7.0 Hz, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 4.50 (s, 2H), 7.24–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.31, 26.2, 28.5, 29.37, 29.44, 29.48, 28.49, 29.5, 29.7, 30.5, 33.5, 70.5, 72.8, 127.4, 127.6, 128.3, 138,7; IR (neat) 2924, 2852, 1454, 1362, 1204, 1176, 1104, 1026, 734, 698, 602 cm^{-1}; MS *m/z* (rel. intensities) 402 (M^+, 13), 311 (16), 246 (29), 123 (34), 91 (100); HRMS *m/z* 402.1395 (402.1420 calcd for $C_{19}H_{31}OI$, M^+).

15-Benzyloxy-1-pentadecene (8c). According to the procedure for the preparation of **8a** described above, **7c** (1.04 g, 2.6 mmol) was converted to **8c** (0.80 g, 98%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21–1.40 (m, 20H), 1.60 (tt, J=7.0 Hz, 2H), 2.04 (dt, J=7.0 Hz, 2H), 3.46 (t, J=6.5 Hz, 2H), 4.50 (s, 2H), 4.92 (dd, J=10.0, 1.0 Hz, 1H), 4.99 (dd, J=17.0, 1.5 Hz, 1H), 5.81 (tdd, J=17.0, 10.5, 5.0 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 28.9, 29.2, 29.5, 29.59, 29.63, 29.8, 33.8, 70.5, 72.8, 114.0, 127.4, 127.6, 128.3, 138.7, 139.3; IR (neat) 2924, 2852, 1454, 1362, 1104, 1026, 994, 910, 734, 648 cm^{-1}; MS m/z (rel. intensities) 317 (M^++H, 25), 226 (0.6), 207 (2.0), 107 (34), 91 (100); HRMS m/z 316.2776 (316.2766 calcd for $C_{22}H_{36}O$, M^+).

***dl*-15-Benzyloxy-1,2-pentadecandiol (3c).** According to the procedure for the preparation of *dl*-**3a** described above, **8c** (0.77 g, 2.4 mmol) was converted to *dl*-**3c** (0.50 g, 60%) as a white crystal. Mp 65–66°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.37 (m, 22H), 1.39–1.45 (m, 2H), 1.61 (tt, J=7.0 Hz, 2H), 2.16–2.38 (brs, 2H), 3.38–3.49 (m, 2H), 3.61–3.72 (m, 1H), 4.50 (s, 2H), 7.24–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.2, 29.4, 29.51, 29.56, 29.58, 29.6, 29.7, 33.2, 66.8, 70.5, 72.3, 72.8, 127.4, 127.6, 128.3, 138.7; IR (KBr) 3380, 2916, 2848, 2792, 1470, 1370, 1122, 1094, 1078, 1058, 1044, 1020, 736, 698 cm^{-1}; MS m/z (rel. intensities) 350 (M^+, 33), 333 (9.3), 320 (29), 227 (20), 123 (17), 107 (100), 91 (100); HRMS m/z 350.2803 (350.2821 calcd for $C_{22}H_{38}O_3$, M^+).

Preparation of racemic cyclic carbonates *dl*-2

***dl*-4-(7-Benzyloxy)heptyl-1,3-dioxolan-2-one (2a).** Under an argon atmosphere, pyridine (4.9 g, 62 mmol) was added to a solution of *dl*-**3a** (2.75 g, 0.01 mol) in CH_2Cl_2 (100 mL) at 0°C, followed by addition of a solution of triphosgene (1.85 g, 6.2 mmol) in CH_2Cl_2 (30 mL) at −78°C. The mixture was then slowly warmed to 0°C and stirred for 1 h. The reaction was stopped with sat. NH_4Cl aqueous solution and the products were extracted with CH_2Cl_2 (×3). The organic layer was washed with 1 M HCl (×2), brine and sat. $NaHCO_3$ aqueous solution, and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel to give *dl*-**2a** (2.14 g, 84%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26–1.79 (m, 14H), 3.46 (t, J=6.5 Hz, 2H), 4.05 (dd, J=8.0 Hz, 1H), 4.50 (dd, J=8.0 Hz, 2H), 4.67 (tdd, J=13.5, 8.5, 2.0 Hz, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 25.8, 27.6, 28.9, 29.0, 33.5, 69.2, 70.1, 72.6, 76.9, 127.0, 127.3, 127.4, 128.1, 128.7, 138.5, 155.0; IR (neat) 2928, 2852, 1804, 1454, 1386, 1168, 1102, 1070, 776, 738, 700 cm^{-1}; MS m/z (rel. intensities) 292 (M^+, 18), 274 (8.5), 236 (7.2), 124 (24), 107 (97), 91 (100); HRMS m/z 292.1660 (292.1675 calcd for $C_{17}H_{24}O_4$, M^+).

***dl*-4-(10-Benzyloxy)decyl-1,3-dioxolan-2-one (2b).** According to the procedure for the preparation of *dl*-**2a** described above, *dl*-**3b** (1.29 g, 4.2 mmol) was converted to *dl*-**2b** (1.27 g, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.40 (m, 13H), 1.54–1.73 (m, 3H), 1.73–1.85 (m, 1H), 3.46 (t, J=6.5 Hz, 2H), 4.05 (dd, J=8.0 Hz, 1H), 4.50 (s, 2H), 4.51 (dd, J=8.0, 8.5 Hz, 1H), 4.68 (tdd, J=5.5, 8.0, 8.5 Hz, 1H), 7.22–7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 26.1, 29.1, 29.26, 29.31, 29.37, 29.42, 29.7, 33.8, 69.3, 70.5, 72.8, 77.0, 127.4, 127.6, 128.3, 138.7, 155.0; IR (neat) 3472, 2924, 2848, 1802, 1168, 1064 cm^{-1}; MS m/z (rel. intensities) 316 (M^+, 4.0), 255 (0.3), 228 (0.6),138 (3.8), 107 (18), 91 (100), 87 (10); HRMS m/z 316.2023 (316.2038 calcd for $C_{20}H_{28}O_3$, M^+).

***dl*-4-(13-Benzyloxy)tridecyl-1,3-dioxolan-2-one (2c).** According to the procedure for the preparation of *dl*-**2a** described above, *dl*-**3c** (476.9 mg, 1.4 mmol) was converted to *dl*-**2c** (497.5 mg, 97%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.41 (m, 18H), 1.53–1.85 (m, 2H), 3.46 (t, J=6.5 Hz, 2H), 4.06 (t, J=7.5 Hz, 1H), 4.50 (s, 2H), 4.53 (dd, J=8.0 Hz, 1H), 4.69 (tt, J=7.0 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 26.1, 29.1, 29.3, 29.40, 29.45, 29.5, 29.8, 33.9, 69.3, 70.5, 72.8, 127.4, 127.6, 128.3, 138.8, 155.0; IR (neat) 2924, 2852, 1802, 1454, 1384, 1366, 1170, 1102, 1068, 1028, 776, 736, 700 cm^{-1}; MS m/z (rel. intensities) 376 (M^+, 17), 285 (4), 107 (58), 91 (100); HRMS m/z 376.2576 (376.2613 calcd for $C_{17}H_{24}O_4$, M^+).

Typical procedure for the hydrolysis of cyclic carbonates *dl*-2 with PPL

To a solution of 114 mg (0.39 mmol, 10 mM) of *dl*-**2a** 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 for 24 h at 10°C. The products were extracted with AcOEt and purified using flash column chromatography on silica gel (hexane/AcOEt=3/1→2/1→AcOEt) to afford (*R*)-**2a** (45.5 mg, 40%, >99% ee) and (*S*)-**3a** (53.4 mg, 52%, 66% ee).

Enantioselective hydrolysis of the other substrates were carried out by means of the same procedure. All the spectral data (^{1}H and ^{13}C NMR, IR, and MS) of cyclic carbonates and diols were in full agreement with those of the racemates. Properties of the products and the determination methods of the ees are as follows.

Compound (*R*)-2a. $[\alpha]_D^{22}$=+11.3 (c 1.01, $CHCl_3$), >99% ee. The ee of (*R*)-**2a** was analyzed by HPLC. The conditions were as follows: column, CHIRALCEL OB-H (Daicel Chemical Industries, Ltd); Eluent, hexane/*i*-PrOH=50/50; flow rate, 0.5 ml/min; retention time, 62 (*R*) and 74 (*S*) min.

Compound (*S*)-3a. $[\alpha]_D^{24}$=−8.4 (c 0.97, MeOH), >99% ee. The ee of (*S*)-**3a** was determined by similar analysis of the corresponding cyclic carbonate.

Compound (*R*)-2b. $[\alpha]_D^{21}$=+13.2 (c 1.37, $CHCl_3$), >99% ee. The products were analyzed by HPLC. The conditions were as follows: column, CHIRALCEL OJ (Daicel Chemical Industries, Ltd); Eluent, hexane/*i*-PrOH=80/20; flow rate, 0.5 ml/min; retention time, 53 (*R*) and 56 (*S*) min.

Compound (*S*)-3b. $[\alpha]_D^{21}$=−4.8 (c 1.06, MeOH), 68% ee. The ee of (*S*)-**3b** was determined by similar analysis of the corresponding cyclic carbonate.

Compound (*R*)-2c. $[\alpha]_D^{28}=+7.6$ (c 0.46, $CHCl_3$), 50% ee. The products were analyzed by HPLC. The conditions were as follows: column, CHIRALCEL OB-H (Daicel Chemical Industries, Ltd); Eluent, hexane/*i*-PrOH=80/20; flow rate, 0.5 ml/min; retention time, 48 (*R*) and 55 (*S*) min.

Compound (*S*)-3c. $[\alpha]_D^{32}=-6.5$ (c 0.77, MeOH), 78% ee. The ee of (*S*)-**3c** was determined by similar analysis of the corresponding cyclic carbonate.

Synthesis of (*S*)-(+)-8-hydroxyhexadecanoic acid (1)

(*R*)-2-(7-Benzyloxy)heptyloxirane (9) from (*R*)-2a. K_2CO_3 was added to a solution of optically pure (*R*)-**2a** in MeOH (3 mL) at 0°C, and stirred for 2 h. The reaction was stopped with brine, and the mixture was saturated with NaCl, the products were extracted with Et_2O (×3), and the organic layer was dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give (*R*)-**3a** as a colorless oil (147.4 mg, 94%), $[\alpha]_D^{22}=+7.8$ (c 0.97, MeOH). 2,4,6-Triisopropylbenzenesulfonyl chloride (210 mg, 0.35 mmol) was added to a solution of optically pure (*R*)-**3a** in pyridine (6 mL) at 0°C, and stirred for 3 days. The reaction was stopped with H_2O, and the mixture was extracted with AcOEt (×4), and washed with 1 M HCl (×2), brine, sat. $NaHCO_3$ aqueous solution and brine. The organic layer was dried over Na_2SO_4. After evaporation, the residue **10** was used in the following reaction without purification. K_2CO_3 was added to a solution of **10** in MeOH (12 mL) at 0°C, and stirred for 2 h. The reaction was stopped with H_2O, and the mixture was extracted with Et_2O (×3), and washed with H_2O (×2), brine, and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=5/1→2/1→1/1→AcOEt) to afford **9** as a colorless oil (58.1 mg, 67%). (*R*)-diol **3a** (23.8 mg) of 26% was recovered. $[\alpha]_D^{22}=+4.5$ (c 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34–1.58 (m, 12H), 2.46 (dd, J=5.0, 2.5 Hz, 1H), 2.74 (dd, J=5.0, 4.0 Hz, 1H), 2.86–2.93 (m, 1H), 3.46 (t, J=6.5 Hz, 2H), 4.50 (s, 2H), 7.25–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 25.9, 26.1, 29.4, 29.7, 32.5, 47.1, 52.4, 70.4, 72.9, 127.5, 127.6, 128.3, 138.7; IR (neat) 3900, 3536, 3024, 2924, 2848, 1454, 1362, 1102, 736, 698 cm^{-1}; MS *m/z* (rel. intensities) 248 (M^+, 5.5), 187 (9.2), 107 (59), 91 (100); HRMS *m/z* 248.1750 (248.1777 calcd for $C_{16}H_{24}O_2$, M^+).

Preparation of 9 from (*S*)-3a

Under an argon atmosphere, to a solution of optically pure (*S*)-**3a** (56.8 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (178 μL, 1.28 mmol), 194 μL (0.64 mmol) of TBDMSCl in toluene (3.3 M) and a catalytic amount of DMAP at 0°C. The mixture was then warmed to room temperature, and stirred overnight. The reaction was stopped with 0.2 M phosphate buffer (pH 6.5) and the products were extracted with AcOEt (×3). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1) to give **11** as a colorless oil. This was used in the following reaction without further purification. Under an argon atmosphere, to a solution of **11** (69.4 mg, 0.18 mmol) in pyridine (2 mL) was added *p*-TsCl (115 mg, 0.60 mmol) and a catalytic amount of DMAP at 0°C. The mixture was then warmed to room temperature and stirred overnight. The reaction was stopped with pH 6.5 buffer and the products were extracted with AcOEt (×3). The organic layer was washed with 2 M HCl (×2), brine, sat. $NaHCO_3$ aqueous solution, and brine and dried over Na_2SO_4. After evaporation, the residue was used in the following reaction without purification. To a solution of **12** in THF (4 mL) was added $Bn_4NF{\cdot}xH_2O$ (88 mg, 0.27 mmol) at 0°C. The mixture was then warmed to room temperature and stirred overnight. The reaction was stopped with H_2O and the products were extracted with AcOEt (×3). The organic layer was washed with sat. NH_4Cl aqueous solution, sat. $NaHCO_3$ aqueous solution, and brine and dried over Na_2SO_4. After evaporation, the residue was purified by preparative TLC (hexane/AcOEt=10/1) to afford **9** as a colorless oil (24.9 mg, 0.10 mmol). $[\alpha]_D^{16}=+5.5$ (c 1.21, $CHCl_3$). All the spectral data (^{1}H and ^{13}C NMR, IR, and MS) of the resulting **9** were in full agreement with those of **9** derived from (*R*)-**2a**.

(*S*)-8-Acetoxy-1-hexadecanoic acid (15). Under an argon atmosphere, to a solution of **9** in THF (5 mL) was added a solution of 0.58 M *n*-heptylmagnatium bromide at 0°C, and stirred for 3 h. The reaction was quenched with sat. NH_4Cl aqueous solution, and the products were extracted with Et_2O (×4), washed with brine, and dried over Na_2SO_4. After evaporation, the residue **13** was used in the following reaction without purification. To a solution of **13** in pyridine (2 mL) was added 137 μL of acetic anhydride and a catalytic amount of DMAP at 0°C and stirred overnight. The reaction was stopped with H_2O and the products were extracted with AcOEt (×3), washed with 2 M HCl (×2), brine, sat. $NaHCO_3$ aqueous solution, and brine and dried over Na_2SO_4. After evaporation, the residue **14** was used in the following reaction without purification. To a solution of **14** in EtOH (10 mL) was added 120 mg of 5% Pd-C, and the solution was degassed under reduced pressure. The reaction was carried out in an atmosphere of hydrogen and stirred overnight. After the mixture was filtrated and evaporated in vacuo, the residue was purified by flash column chromatography (hexane/AcOEt=5/1) to give **15** as a colorless oil (63.7 mg, 69%). $[\alpha]_D^{26}=-1.83$ (c 2.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.21–1.34 (m, 19H), 1.48–1.59 (m, 8H), 2.04 (s, 3H), 3.64 (t, J=6.5 Hz, 2H), 4.86 (ttt, J=6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.3, 22.6, 25.2, 25.3, 25.6, 29.2, 29.3, 29.4, 29.47, 29.52, 31.8, 32.7, 34.07, 34.11, 63.0, 74.4, 171.0; IR (neat) 3452, 2924, 2852, 1738, 1464, 1376, 1244, 1052, 1022, 612 cm^{-1}; MS *m/z* (rel. intensities) 257 (M^+−Ac), 239 (16), 222 (58), 187 (32), 127 (46), 109 (100); HRMS *m/z* 301.2739 (301.2743 calcd for $C_{18}H_{37}O_3$, M^++H).

Compound 1. To a solution of **15** (54.2 mg, 0.18 mmol) in acetone (6 mL) was added 3 M Jones reagent (3 mL) and stirred for 10 min at 0°C. The mixture was added MeOH (3 mL) and diluted with H_2O. The products were extracted with Et_2O (×4) and dried over Na_2SO_4. After evaporation, the residue **16** was used in the following reaction without purification. To a solution of **16** in MeOH (5 mL) was added 10% KOH aqueous solution at 0°C and stirred for 2 h. The reaction was stopped with H_2O. The mixture was acidified

by the addition of 2 M HCl, and the products were extracted with Et_2O and washed with brine. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=1/1→AcOEt) to afford **1** as a white crystal (34.1 mg, 69%). Mp 76–77°C; $[\alpha]_D^{22}=+0.15$ (c 1.73, $CHCl_3$); ^1H NMR (500 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 (brs, 2H); ^{13}C NMR (125 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, 2815, 1698, 1470, 1439, 1412, 1343, 1291, 1235, 1130, 1100, 1019, 901, 721 cm^{-1}; MS m/z (rel. intensities) 254 (M^+, 9.4), 236 (39), 192 (9.6), 159 (100), 95 (100); HRMS m/z 254.2192 (254.2246 calcd for $C_{16}H_{32}O_3$, M^+). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84%. Found: C, 70.89; H, 11.74%.

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