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TETRAHEDRON: *ASYMMETRY*

# Highly enantioselective preparation of $C_2$-symmetrical diols: microbial hydrolysis of cyclic carbonates

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**Abstract**

A new type of microbial enantioselective hydrolysis of $C_2$-symmetrical cyclic carbonates is disclosed. During the screening test of the five-membered substrate (4,5-dimethyl-1,3-dioxolan-2-one **5**), *Pseudomonas diminuta* was selected as the best strain to perform the stereoselective hydrolysis. The reaction of *dl*-**5** with this microorganism in aqueous media containing THF as the co-solvent afforded (*S*,*S*)-**5** and (*R*,*R*)-butanediol **1** in excellent yields. It was found that the ring size did not affect the reactivity and enantioselectivity although the enzyme had a high substrate specificity for the side chain. A six-membered cyclic carbonate, *dl*-4,6-dimethyl-1,3-dioxan-2-one **6**, was smoothly hydrolyzed with higher enantioselectivity to afford the optically active (*S*,*S*)-**6** and (*R*,*R*)-2,4-pentanediol **2**. 

## 1. Introduction

Optically active diols with $C_2$-symmetry, such as 2,3-butanediol **1** and 2,4-pentanediol **2**, are very useful as chiral auxiliaries (Fig. 1).[1] The compounds and their derivatives have also been used as $C_2$-symmetrical chiral catalysts in asymmetric reactions.[2] Much effort has already been devoted to the preparation of such compounds in an optically active form.[3,4] Kinetic resolution of the diol derivatives with hydrolytic enzymes is one of the more attractive methods.[5] These methods, however, are not always satisfactory in terms of their yield, stereoselectivity, and simplicity of operation.


Figure 1.

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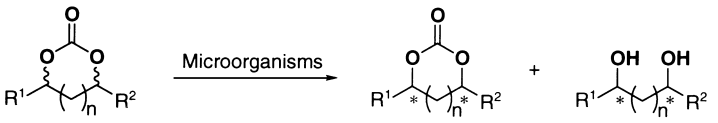
Recently, the enzymatic enantioselective hydrolysis of cyclic carbonates has been disclosed as a useful procedure for the preparation of optically active diols (Scheme 1).[6] We also reported that Porcine Pancreas Lipase (PPL, EC 3.1.1.3, Type II from Sigma) efficiently catalyzed the hydrolysis of various kinds of mono-substituted cyclic carbonates, resulting in the formation of a variety of optically active 1,2- and 1,3-diols.[7] This type of reaction proceeds irreversibly because the acyl moiety of the substrate leaves the reaction system as carbon dioxide. We now present the first example of the preparation of optically active $C_2$-symmetrical diols via the microbial hydrolysis of the corresponding racemic cyclic carbonates ($R^1 = R^2 =$ alkyl).

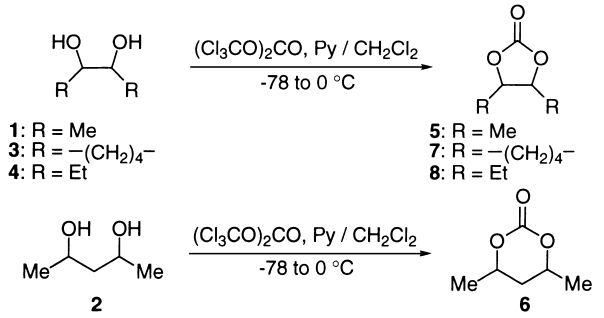



Scheme 1.

## 2. Results and discussion

### 2.1. Enzymatic hydrolysis of 4,5-dimethyl-1,3-dioxolan-2-one 5 containing dl- and meso-isomers

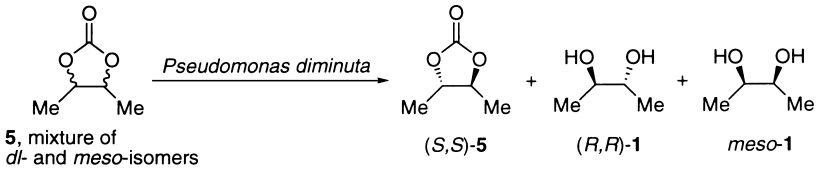
Cyclic carbonates **5**–**8** were readily synthesized by the treatment of the corresponding diols **1**–**4** with pyridine and bis(trichloromethyl)carbonate (triphosgene) as shown in Scheme 2.




Scheme 2.

We selected the mixture of stereoisomers of 4,5-dimethyl-1,3-dioxolan-2-one **5** (*dl*-form:*meso*-form = 42:58) (Scheme 3) as the screening substrate and the selection of the enzyme system focused on not only the enantioselectivity but also the diastereoselectivity of the enzymatic hydrolysis. In the beginning, the enzymatic hydrolysis of **5** was carried out with PPL using the same procedure as that previously reported.[7] Unfortunately, PPL did not catalyze the hydrolysis of **5** at all in regardless of the reaction conditions used. Thus, we started screening microorganisms in terms of their hydrolytic ability of **5**.

First, the screening test was carried out by GLC analysis with tetralone as the internal standard. In the screening test of 109 strains of stock cultures, 25 strains were selected for further screening because they smoothly produced **1** with the remaining **5** in a relatively high diastereomeric ratio.



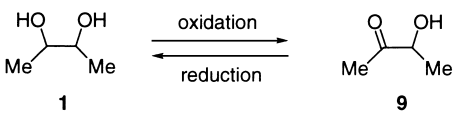

Scheme 3.

In the second screening, the enantioselectivity of the products were measured by GLC analysis using a capillary column coated with CP-Cyclodextrin-B-236-M19 (Chromopack). Finally, *Pseudomonas diminuta* (FU0090), which was a bacteria isolated from the soil and classified by NCIMB Japan Co., Ltd., gave the best result (Table 1). After the reaction of **5** (100 μl, ca. 17 mM) with *P. diminuta* in 50 mL of medium for 6 h at 30°C, **5** was completely consumed and highly optically active (*S*,*S*)-**5** (92% ee) was recovered in 22% yield. Changing the reaction time to 24 h promoted the kinetic resolution to give enantiomerically pure (*S*,*S*)-**5** in 15% yield. The absolute configuration of the resulting (*S*,*S*)-**5**, $[\alpha]_D^{20} = -27.7$ (*c* 1.01, $CHCl_3$), was determined by comparing its specific rotation sign with that of the authentic sample (*R*,*R*)-**5**, $[\alpha]_D^{24} = +27.6$ (*c* 1.09, $CHCl_3$), derived from commercially available (*R*,*R*)-**1**. These results indicate that the enzymatic hydrolysis proceeds with very high enantio- and diastereoselectivities to get (*S*,*S*)-**5** from the mixture of *dl*- and *meso*-isomers. On the other hand, the yield of the resulting diol **1** was lower than the theoretical one and the ratio of the *dl*- to *meso*-isomers and the ee of (*R*,*R*)-**1** was inconsistent with the rule of kinetic resolution. The further analysis of the reaction products detected considerable amounts of acetoin **9** which was produced by the enzymatic oxidation of the resulting **1** in the cells (Scheme 4).[8] Thus, the decrease in the yield, de, and ee of **1** could be explained by the enzymatic oxidation–reduction process occurring between **1** and **9**. The formation of acetoin **9** was also observed in the case of *dl*-**5** as the substrate.

Table 1
Stereoselective hydrolysis of **5** (mixture of *dl*- and *meso*-form) with *Pseudomonas diminuta*

| | carbonate **5** | | | diol **1** | | |
|---|---|---|---|---|---|---|
| time/h | yield/%[a] | *dl*:*meso*[b] | ee of (*S*,*S*)-**5**/% | yield/%[a] | *dl*:*meso*[b] | ee of (*R*,*R*)-**1**/% |
| 6 | 22 | >99:<1 | 92 | 25 | 16:84 | 45 |
| 12 | 21 | >99:<1 | 97 | 20 | 18:82 | 64 |
| 24 | 15 | >99:<1 | >99 | 19 | 48:52 | 29 |

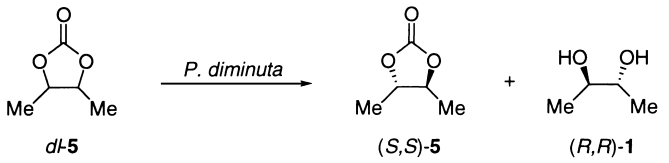
[a] Determined by GLC analysis with tetralone as the internal standard. [b] Determined by $^1$H NMR analysis.




Scheme 4.

### 2.2. Enantioselective hydrolysis of dl-4,5-dimethyl-1,3-dioxolan-2-one **5a**

In order to prepare (*R*,*R*)-**1** with a high ee, we examined the suppression of the oxidation–reduction process mentioned above by the addition of organic solvents as an inhibitor against oxidoreductase because the method was the simplest way to control the enzymatic reaction system. The *dl*-**5** substrate was separated from the mixture of diastereoisomers by column chromatography on silica gel (Scheme 5). The addition of a water-miscible organic solvent, such as acetone, DMF, DMSO, and dioxane, to the reaction broth of *P. diminuta* did not improve the yield of the diol **1**, and did not suppress the production of **9**. However, the addition of THF was found to give the best results, and *i*-$Pr_2O$ and AcOEt also reduced the side reaction. These results are shown in Table 2. Under the conditions of 30°C for 12 h in aqueous media containing 8% THF, the reaction proceeded with high stereoselectivity to afford both enantiomers, (*S*,*S*)-**5** (35% ee) in 81% and (*R*,*R*)-**1** (95% ee), $[\alpha]_D^{26} = -13.2$ (*c* 0.80, $CHCl_3$), in 18% yields (conv.[9] = 0.27, *E* value[9] = 55). Although the hydrolysis was apparently slower than that under the conditions without THF, changing the reaction time from 12 to 48 h improved the ee of (*S*,*S*)-**5** (95% ee, conv.[9] = 0.51, *E* value[9] = 70). In all cases, acetoin **9** was not detected by capillary GLC analysis.




Scheme 5.

Table 2
Enantioselective hydrolysis of *dl*-**5** with *Pseudomonas diminuta*[a]

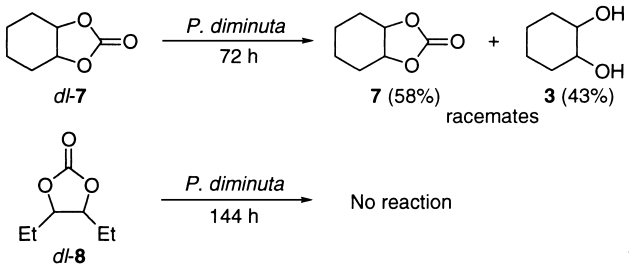
| | carbonate **5** | | diol **1** | | | |
|---|---|---|---|---|---|---|
| time/h | yield/%[b] | ee/%[c] | yield/%[b] | ee/%[c] | conv.[d] | E[e] |
| 12 | 81 | 35 | 18 | 95 | 0.27 | 55 |
| 24 | 42 | 81 | 42 | 93 | 0.47 | 69 |
| 48 | 43 | 95 | 50 | 90 | 0.51 | 70 |

[a] The reaction was performed in aqueous media containing 8% THF as the co-solvent. [b] Determined by GLC analysis with tetralone as the internal standard. [c] Determined by capillary GLC analysis with CP-Cyclodextrin-B-236-M19 column. [d] Calculated by ee(**5**)/[ee(**5**)+ee(**1**)]. [e] Calculated by ln[(1-conv)(1-ee(**5**))/ln[(1-conv)(1+ee(**5**))].

### 2.3. Microbial hydrolysis of other substrates

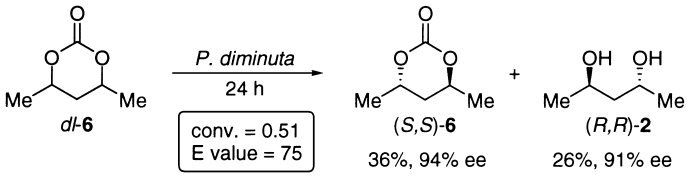
We examined this microbial reaction of other $C_2$-symmetrical cyclic carbonates (Scheme 6). First, we tried the reaction using the cyclohexanediol derivative *dl*-**7**. The procedure was the same when using *dl*-**5** as the substrate. After the reaction for 72 h, the remaining substrate **7** and the hydrolyzed product **3** were isolated in 58% and 43% isolated yields, respectively, but both compounds were racemates. On the other hand, the substrate having diethyl groups, *dl*-4,5-diethyl-

1,3-dioxolan-2-one **8**, was not hydrolyzed under the same conditions. Thus, the enzyme has a high substrate specificity for the side chain.




Scheme 6.

Next, we tried the hydrolysis of a six-membered cyclic carbonate, *dl*-4,6-dimethyl-1,3-dioxan-2-one **6**, having dimethyl groups similar to those of **5** (Scheme 7). In the case of **6**, THF was not used as the co-solvent because the oxidation of the resulting 2,4-pentanediol **2** did not occur even without THF. The substrate *dl*-**6** was smoothly hydrolyzed with higher enantioselectivity (conv. = 0.51 and *E* value = 75 for 24 (h) to afford the optically active (*S*,*S*)-**6** (94% ee; $[\alpha]_D^{28} = -74.5$ (*c* 1.10, $CHCl_3$)) and (*R*,*R*)-**2** (91% ee; $[\alpha]_D^{28} = -31.2$ (*c* 1.55, $CHCl_3$), lit.[10] $[\alpha]_D = -41.3$ ($CHCl_3$)) in 36 and 26% isolated yields, respectively. The reaction could be continued to over 50% conversion leading to the enantiomerically pure (*S*,*S*)-**6**. As a result, the ring size does not affect the reactivity and enantioselectivity




Scheme 7.

## 3. Conclusion

We have demonstrated a new procedure for the preparation of optically active $C_2$-symmetrical diols, five-membered **5** and six-membered **6** substrates, via the microbial enantioselective hydrolysis of the corresponding cyclic carbonates. In both cases, the hydrolytic enzyme catalyzed the hydrolysis of the (*R*,*R*)-isomers of the cyclic carbonates faster than the (*S*,*S*)-isomers. Further investigations into this reaction are now in progress.

## 4. Experimental

### 4.1. General

$^1H$ (400 or 500 MHz) and $^{13}C$ (100 or 125 MHz) NMR spectra were measured on a JEOL JNM FX-400 or 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. GLC data were taken on a Hitachi 163, and capillary GLC on a Hitachi C-3000. 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. Kugelrohr distillation was performed with a Shibata GTO-250RS. 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.

### 4.2. Preparation of cyclic carbonates **5**–**8**

#### 4.2.1. 4,5-Dimethyl-1,3-dioxolan-2-one **5**

Under an argon atmosphere, pyridine (13.2 g, 168 mmol) was added to a solution of commercially available 2,3-butanediol (**1**, mixture of *dl*- and *meso*-isomers; 3.00 g, 33.6 mmol) in $CH_2Cl_2$ (70 mL) at 0°C, followed by addition of a solution of triphosgene (8.08 g, 27.1 mmol) in $CH_2Cl_2$ at –78°C. The mixture was then slowly warmed to 0°C and stirred for 1 h. The reaction was stopped with a 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, sat. $NaHCO_3$ aqueous solution, and brine, and dried over $Na_2SO_4$. After evaporation, the residue was purified by column chromatography on silica gel, followed by Kugelrohr distillation (bath temperature, 190°C (33 mmHg)) to give the mixture of diastereoisomers of **5** (*dl*-form:*meso*-form = 42:58) as a colorless oil (3.58 g, 92%). The isomers could be separated by column chromatography on silica gel (hexane:AcOEt = 7:1).

Compound *dl*-**5**: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.44–1.48 (m, 6H), 4.31–4.38 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 18.3, 79.8, 154.5; IR (neat) 2990, 1800, 1370, 1200, 1080, 780 cm$^{-1}$; MS *m*/*z* (rel. intensities) 116 ($M^+$, 76), 101 (68), 86 (29), 71 (22), 57 (100); HRMS *m*/*z* 116.0467 (116.0473 calcd for $C_5H_8O_3$, $M^+$).

*meso*-**5**: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.35–1.39 (m, 6H), 4.81–4.87 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1, 75.9, 154.4; IR (neat) 2990, 1800, 1370, 1200, 1080, 780 cm$^{-1}$; MS *m*/*z* (rel. intensities) 116 ($M^+$, 8), 101 (68), 86 (0.8), 71 (2), 43 (100); HRMS *m*/*z* 116.0510 (116.0473 calcd for $C_5H_8O_3$, $M^+$).

#### 4.2.2. dl-4,6-Dimethyl-1,3-dioxan-2-one **6**

According to the procedure for the preparation of **5** described above, *dl*-2,4-pentanediol **2** (406 mg, 3.89 mmol) was converted to *dl*-**6** (336 mg, 66%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, $J$ = 6.5 Hz, 6H), 1.94 (dd, $J_1 = J_2$ = 5.5 Hz, 2H), 4.73 (qt, $J_1$ = 5.5 Hz, $J_2$ = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 20.8, 72.5, 149.4; IR (neat) 2990, 1740, 1400, 1200, 1120, 770 cm$^{-1}$; MS *m*/*z* (rel. intensities) 130 ($M^+$, 12), 89 (3), 71 (7), 42 (100); HRMS *m*/*z* 130.0636 (130.0630 calcd for $C_6H_{10}O_3$, $M^+$).

#### 4.2.3. dl-3a,4,5,6,7,7a-Hexahydro-1,3-benzodioxol-2-one **7**

According to the procedure for the preparation of **5** described above, *dl*-1,2-cyclohexanediol **3** (500 mg, 4.30 mmol) was converted to *dl*-**7** (423 mg, 69%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.33–1.52 (m, 2H), 1.52–1.79 (m, 2H), 1.79–2.02 (m, 2H), 2.19–2.36 (m, 2H), 4.02 (td,

$J_1 = 9.5$ Hz, $J_2 = 5.0$ Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 22.8, 27.9, 83.3, 154.9; IR (neat) 2920, 1795, 1105, 1040, 785 cm$^{-1}$; MS *m*/*z* (rel. intensities) 142 ($M^+$, 21), 97 (58), 83 (90), 57 (100); HRMS *m*/*z* 142.0622 (142.0630 calcd for $C_7H_{10}O_3$, $M^+$).

*4.2.4.* dl-*4,5-Diethyl-1,3-dioxolan-2-one* ***8***

To a solution of *trans*-3-hexene **10** (1.00 g, 11.9 mmol) in acetone (60 mL) and $H_2O$ (40 mL) were added 4-methylmorpholine *N*-oxide (5.74 g, 59.4 mmol), *tert*-butanol (5 mL) and a catalytic amount of $OsO_4$, and the mixture was stirred at rt overnight. After addition of $NaS_2O_3$ 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 to give *dl*-3,4-hexanediol **4** as a colorless oil (869 mg, 62%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, $J = 7.5$ Hz, 6H), 1.36–1.53 (m, 2H), 1.53–1.72 (m, 2H), 2.30 (br.s, 1H), 2.35 (s, 1H), 3.26–3.44 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 9.9, 26.2, 75.4; IR (neat) 3390, 2960, 1460, 1070, 970 cm$^{-1}$; MS *m*/*z* (rel. intensities) 118 ($M^+$, 15), 101 (100), 71 (100), 60 (100); HRMS *m*/*z* 118.0979 (118.0994 calcd for $C_6H_{14}O_2$, $M^+$).

According to the procedure for the preparation of **5** described above, *dl*-**4** (498 mg, 4.22 mmol) was converted to *dl*-**8** (561 mg, 92%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.5$ Hz, 6H), 1.62–1.82 (m, 4H), 4.09–4.12 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 8.5, 26.7, 82.5; IR (neat) 2970, 1795, 1185, 1040, 775 cm$^{-1}$; MS *m*/*z* (rel. intensities) 144 ($M^+$, 5), 115 (18), 71 (22), 43 (100); HRMS *m*/*z* 144.0779 (144.0786 calcd for $C_7H_{12}O_3$, $M^+$).

### *4.3. Screening of microorganisms for hydrolysis of* ***5***

The basal medium for screening of microorganisms consists of glucose (10 g), polypeptone (7 g), and yeast extract (5 g) in 1 L of 100 mM phosphate buffer (pH 6.5).

In the first screening, a loopful of each microorganism from a nutrient slant was transferred to a test tube containing 5 mL of the sterilized basal medium. After cultivation for 48 h at 30°C, 10 μL of **5** (the mixture of diastereoisomers) was added to the suspension of grown cells and incubation was continued for an additional 24 h. The products were extracted with ether and analyzed by GLC. The conditions of GLC analysis were as follows: column, butanediol succinate–uniport B (GL Science Inc.); injection, 140°C; oven, 120°C; carrier gas, $N_2$; head pressure, 0.2 kg/cm$^2$; *dl*-**1**: 0.87 min, *meso*-**1**: 0.97 min; *dl*-**5**: 3.7 min, *meso*-**5**: 5.6 min; tetralone 11.0 min (internal standard).

In the second screening, the enantiomeric excesses of the products were analyzed by capillary GLC. The conditions of capillary GLC analysis were as follows: column, CP-Cyclodextrin-B-236-M19 (Chromopack), 0.25 mm×50 m, Inc.; injection, 100°C; detection, 100°C; oven, 80°C; carrier gas, He; head pressure, 2.4 kg/cm$^2$; (*S*,*S*)-**1** 15.7 min, (*R*,*R*)-**1** 16.0 min, (*R*,*R*)-**5** 53.3 min, (*S*,*S*)-**5** 54.2 min.

### *4.4. Typical procedure for hydrolysis of cyclic carbonates with* Pseudomonas diminuta

A 500 mL Erlenmeyer flask each containing 100 mL of sterilized basal medium was inoculated with a loopful of *P. diminuta*, and incubated for 48 h at 30°C. To the broth was added 100 μL (113 mg) of **5** (the mixture of diastereoisomers) and the cultivation was continued. After 50 mL of acetone was added to the mixture following by saturation with NaCl and filtration through a Celite pad, the products were extracted with AcOEt, and the organic layer was dried over

$Na_2SO_4$. Evaporation and purification afforded **1** and **5**. The results are shown in Table 1. The yields were determined by GLC analysis.

Enantioselective hydrolysis of the other substrates were carried out by means of the same procedure. In the cases of *dl*-**5**, **6**, and **7**, the substrates were added to the broth with THF (4 mL) as the co-solvent. The results are shown in the text. All the spectral data ($^1H$ and $^{13}C$ NMR, IR, and MS) of cyclic carbonates 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*,*R*)-**1**: 95% ee, $[\alpha]_D^{26} = -13.2$ (*c* 0.80, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.16–1.20 (m, 6H), 2.47 (br.s, 2H), 3.48–3.56 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 19.3, 72.5; IR (neat) 3365, 2970, 1375, 1060, 890 $cm^{-1}$; MS *m*/*z* (rel. intensities) 90 ($M^+$,14), 75 (18), 57 (47), 45 (100); HRMS *m*/*z* 90.0687 (90.0681 calcd for $C_4H_{12}O_2$, $M^+$). The absolute configuration was confirmed by comparing its specific rotation sign with that of the commercially available (*R*,*R*)-**1**; $[\alpha]_D^{26} = -14.1$ (*c* 0.53, $CHCl_3$), lit.[11] $[\alpha]_D^{26} = -12.8$ (neat). The ee was determined by capillary GLC analysis with CP-Cyclodextrin-B-236-M19 under the conditions mentioned above.

Compound (*S*,*S*)-**5**: >99% ee, $[\alpha]_D^{20} = -27.7$ (*c* 1.01, $CHCl_3$). The absolute configuration was confirmed by comparing its specific rotation sign with that of the authentic sample (*R*,*R*)-**5**, $[\alpha]_D^{24} = +27.6$ (*c* 1.09, $CHCl_3$), derived from commercially available (*R*,*R*)-**1** with triphosgene and pyridine in $CH_2Cl_2$. The ee was determined by capillary GLC analysis with CP-Cyclodextrin-B-236-M19 under the conditions mentioned above.

Compound (*R*,*R*)-**2**: 91% ee; $[\alpha]_D^{28} = -31.2$ (*c* 1.55, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.16 (d, $J = 6.5$ Hz, 6H), 1.51 (dd, $J_1 = J_2 = 5.5$ Hz, 2H), 3.55 (br.s, 1H), 4.06 (qt, $J_1 = 5.5$ Hz, $J_2 = 6.5$ Hz, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 23.2, 45.8, 65.0; IR (neat) 3365, 2970, 1660, 1380, 1125 $cm^{-1}$; MS *m*/*z* (rel. intensities) 105 (55, $M^+$+H), 103 (17), 89 (100), 71 (100); HRMS *m*/*z* 105.0924 (105.0915 calcd for $C_5H_{13}O_2$, $M^+$+H). The absolute configuration was confirmed by comparing its specific rotation sign with the reported one; lit.[10] $[\alpha]_D = -41.3$ ($CHCl_3$). The ee was determined by $^1H$ NMR analysis of the corresponding bis-(+)-MTPA ester **12** which was transformed in a conventional manner. Signals at $\delta$ 4.97–5.07 (m, 1H, $CH_3CH$, (*R*,*R*)) and 5.08–5.20 (m, 1H, $CH_3CH$, (*S*,*S*)) were observed in the case of the racemic sample.

Compound (*S*,*S*)-**6**: 94% ee, $[\alpha]_D^{28} = -74.5$ (*c* 1.10, $CHCl_3$). The ee was determined by similar analysis of the corresponding diol **2** derived from **6** with $K_2CO_3$ in MeOH.

Compound **3**: a white solid, mp 98–100°C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.18–1.34 (m, 2H), 1.61–1.77 (m, 2H), 1.89–2.03 (m, 2H), 3.27–3.44 (m, 2H) 4.28 (br.s, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 24.3, 32.8, 75.6; IR ($CHCl_3$ solution) 3405, 2940, 1715, 1060, 930 $cm^{-1}$; MS *m*/*z* (rel. intensities) 116 (27, $M^+$), 98 (36), 83 (30), 70 (100); HRMS *m*/*z* 116.0861 (116.0837 calcd for $C_6H_{12}O_2$, $M^+$). The ee was determined by capillary GLC analysis with CP-Cyclodextrin-B-236-M19 (Chromopack) column; injection, 140°C; detection, 140°C; oven, 120°C; carrier gas, He; head pressure, 2.4 $kg/cm^2$; retention times, 22.9 and 24.1 min (the absolute configurations were not determined).

Compound **7**: The ee was determined by similar analysis of the corresponding diol **3** derived from **7** with $K_2CO_3$ in MeOH.

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