Journal of Molecular Catalysis B: Enzymatic 67 (2010) 135–142

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

journal homepage: www.elsevier.com/locate/molcatb

# Lipase-mediated preparation of optically active isomers of Rosaphen®

Masashi Kawasaki[a,*], Naoki Toyooka[b], Tomoki Saka[c], Michimasa Goto[d], Yuji Matsuya[c], Tadashi Kometani[d]

[a] Department of Liberal Arts and Sciences, Faculty of Engineering, Toyama Prefectural University, 5180 Kurokawa, Imizu, Toyama-Ken 939-0398, Japan
[b] Graduate School of Science and Technology, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan
[c] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan
[d] Department of Chemical and Biochemical Engineering, Toyama National College of Technology, 13 Hongo, Toyama 939-8630, Japan

ARTICLE INFO

*Article history:*
Received 1 June 2010
Received in revised form 6 July 2010
Accepted 27 July 2010
Available online 6 August 2010

*Keywords:*
Asymmetric synthesis
Fragrance
Lipase

ABSTRACT

The optically active isomers of Rosaphen® (RS)-**1** were synthesized from the chiral intermediate prepared by lipase-catalyzed desymmetrization of prochiral diol. The results of an olfactory evaluation of the prepared isomers are reported.



## 1. Introduction

Many organic compounds with odor occur in nature as a specific enantiomer, and the odor of the specific enantiomer is distinctive and characteristic [1]. Examples of the differences in odor description and in strength between enantiomers have been reported [1–3]. For example, (*R*)-limonene has an orange odor, while (*S*)-limonene has a harsh odor [1]. Accordingly, the synthesis of fragrance ingredients in highly enantiomerically pure form and the evaluation of their odor properties are of great interest, and many reports on the asymmetric synthesis of fragrance ingredients have been published [2–5].

Among many fragrances, floral notes are very much appreciated and widely used [3b]. Recently, Matteoli et al. reported the enantioselective synthesis of three fragrances displaying floral notes, Phenoxanol® **2a**, Citralis® **2b** and Citralis Nitrile® **2c** (Fig. 1) [3b]. Enantiopure samples of **2a**, **2b** and **2c** were evaluated for the odor profiles. Rosaphen® (*RS*)-**1** {(*RS*)-2-methyl-5-phenyl-1-pentanol}, an analogue of **2a**, is valuable for adding floral note in soaps and domestic fragrances [6,7]. (*RS*)-**1** is used in racemic form, so the odor profiles of the single enantiomers have not been reported.

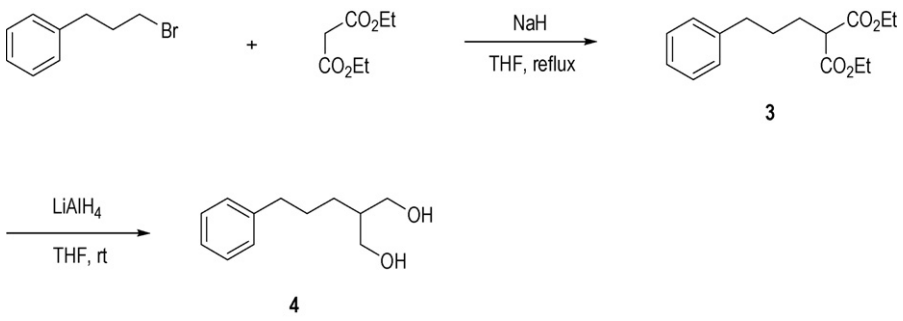
While asymmetric synthesis of (*S*)-**1** has not been reported, there are four reports on the synthesis of (*R*)-**1**. Santini et al. synthesized (*R*)-**1** from an optically active oxazolidinone derivative and used the (*R*)-**1** for determining the absolute configuration of the side chain of zarazonic acid C [8]. Abiko reported the synthesis of a new chiral auxiliary and evaluated the utility of the auxiliary by applying it to the synthesis of (*R*)-**1** [9]. Other reports presented the syntheses of (*R*)-**1**, which was used for the synthesis of zarazonic acid C, with chiral auxiliary methods [10,11]. However, those methods required stoichiometric optically pure compounds to synthesize (*R*)-**1**, so we became interested in developing an enantioselective catalytic route to (*R*)-**1** and (*S*)-**1**.

We have been studying lipase-catalyzed reactions in aqueous or organic media and succeeded in the asymmetric synthesis of chromanones [12,13], flavanones [12–15], and a norsesquiterpene [16]. It is a characteristic of our method to obtain the chiral intermediates for the synthesis of the target compounds by the lipase-catalyzed reactions. Lipase-catalyzed reactions play an important role in the optical resolutions of the racemates and in desymmetrizations of prochiral substrates, and the obtained enantiopure substrates are used for the further synthesis [17]. Many lipase-catalyzed preparations of enantiomerically enriched odorants have been reported [2e–g,3c–f,5a–d].

Herein we report the asymmetric synthesis of (*R*)-**1** and (*S*)-**1** from a chiral primary alcohol prepared by lipase-catalyzed desymmetrization of a prochiral diol and the evaluation of the odor profiles of the optically active isomers.

* Corresponding author. Tel.: +81 766 56 7500; fax: +81 766 56 6117.
*E-mail address:* kawasaki@pu-toyama.ac.jp (M. Kawasaki).

1381-1177/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcatb.2010.07.019




**Scheme 1.** Synthesis of 2-hydroxymethyl-5-phenyl-1-pentanol **4.**

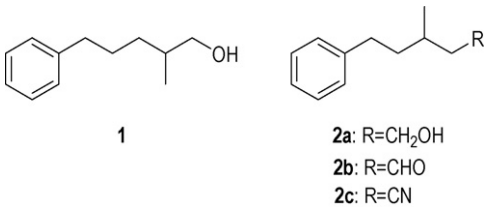



**Fig. 1.** Compounds with floral fragrance.

## 2. Results and discussion

### 2.1. Asymmetric synthesis of (S)-*1*

The first step in the sequence leading to (*S*)-**1** is the alkylation of diethyl malonate with 1-bromo-3-phenylpropane (Scheme 1). The deprotonation of diethyl malonate with NaH and the addition of 1-bromo-3-phenylpropane provided ethyl 2-ethoxycarbonyl-5-phenylpentanoate **3** in 78% yield. The treatment of **3** with $LiAlH_4$ produced the diol, 2-hydroxymethyl-5-phenyl-1-pentanol **4**, in 83% yield.

The most important point of the present synthesis is to prepare a monoester of **4** in an optically active form. We successfully achieved the preparation using lipase-catalyzed desymmetrization of **4** (Scheme 2). Initially, we tested the enantioselectivity of 13 lipases (Amano AK, AY, PS, Meito ALC, MY, OF, PLC, QLM, ST, TL, Novozym 435, Sigma CRL, PPL) in the acetylation of **4** with vinyl acetate in 1,4-dioxane. Among the lipases investigated, lipase PS proved to be the most enantioselective.

Next, diol **4** was subjected to reaction solvent screening experiments (Table 1). The substrate specificity, enantioselectivity, prochiral selectivity, regioselectivity, and chemoselectivity of enzymes have been found to depend on the nature of the solvent [18]. It was observed in our present study that polar solvent systems are more efficient for the prochiral selectivity than nonpolar solvent systems. Because the highest prochiral selectivity and rapid reaction were achieved with 1,4-dioxane (Entry 1), the solvent was chosen for further study. The absolute configuration of the produced monoester was thought to be the (*R*)-configuration on the basis of the empirical rule for the enantiopreference of the lipase [19].

We then investigated the effects of the acyl donors on the prochiral selectivity of the lipase (Table 2), because the enantioselectivity of lipases has been found to depend on the nature of the acyl donors [20]. As a result of the screening of the vinyl esters, we found that vinyl butanoate (Entry 3) was the most suitable regarding the prochiral selectivity (97% *ee*).

On the basis of the results, we conducted the large scale desymmetrization of **4** with **7c** as the acyl donor in 1,4-dioxane and could obtain (*R*)-**5c** with 96% *ee* in 85% yield.

The optically active (*R*)-**5c** (96% *ee*) obtained above was converted to the corresponding methanesufonate (*S*)-**8** with methanesufonyl chloride (MsCl) and pyridine in 92% yield (Scheme 3). The synthesis of (*S*)-**1** was finally accomplished by the reduction of (*S*)-**8** with $LiAlH_4$ in 57% yield and 95% *ee* $\{[\alpha]_D^{24}$ −13.6° (*c* 1.1, EtOH); Lit. [8] $[\alpha]_D$ +11.2° (*c* 6.4, EtOH), (*R*)$\}$. Because the enantiomeric excess of (*S*)-**1** could not be determined by either GC or HPLC, (*S*)-**1** was converted to the corresponding acetate (*S*)-**12** with acetyl chloride and after that the *ee* was determined.

### 2.2. Asymmetric synthesis of (R)-*1*

We also synthesized (*R*)-**1** from (*R*)-**5c** (97% *ee*) according to Scheme 4. At first, the hydroxyl group of (*R*)-**5c** was protected with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and pyridine to obtain 2-*tert*-butyldimethylsiloxymethyl-5-phenylpentyl butanoate (*S*)-**9** in 97% yield. The ester moiety of (*S*)-**9** was hydrolyzed with NaOH to obtain 2-*tert*-butyldimethylsiloxymethyl-5-phenyl-1-pentanl (*S*)-**10** in 52% yield. Deprotection slightly occurred during the hydrolysis, which resulted in the formation of the diol, confirmed with TLC. The chiral alcohol (*S*)-**10** was converted to the corresponding methanesufonate (*R*)-**11** with methanesufonyl chloride (MsCl) and pyridine in 93% yield (Scheme 3). The synthesis of (*S*)-**1** was finally accomplished by the reaction of (*R*)-**11** with $LiAlH_4$ in 54% yield and 96% *ee* $\{[\alpha]_D^{24}$ +12.6° (*c* 1.1, EtOH), Lit. [8] $[\alpha]_D$ +11.2° (*c* 6.4, EtOH), (*R*)$\}$. Reduction and deprotection took place at the same time. The *ee* of (*R*)-**1** was determined after it was converted to the corresponding acetate (*R*)-**12** with acetyl chloride.

**Table 1**
Effect of organic solvents on desymmetrization of **4** using lipase PS.

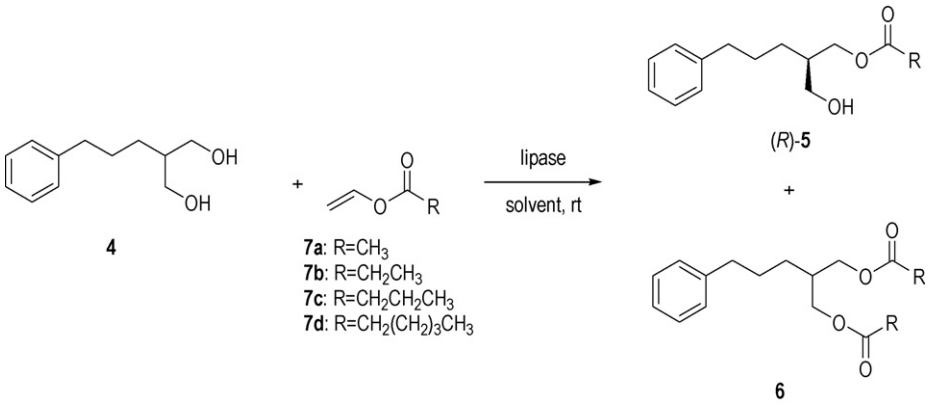
| Entry | Solvent | Time (h) | **4**:(*R*)-**5a**:**6**[a] | *ee* of (*R*)-**5a** (%) |
|---|---|---|---|---|
| 1 | 1,4-Dioxane | 2.8 | 5:92:3 | 95 |
| 2 | Acetone | 6.4 | 2:93:5 | 94 |
| 3 | THF | 5.2 | 2:94:4 | 94 |
| 4 | Diisopropyl ether | 2.1 | 1:88:11 | 91 |
| 5 | Dichloromethane | 20.5 | 3:96:1 | 90 |
| 6 | Toluene | 1.8 | 2:86:12 | 83 |

Conditions: lipase PS (20 mg/mL), **4** (100 mmol/L), **7a** (1 mol/L), rt.
[a] Ratio of the peak areas of **4**, (*R*)-**5a** and **6** in gas chromatogram.

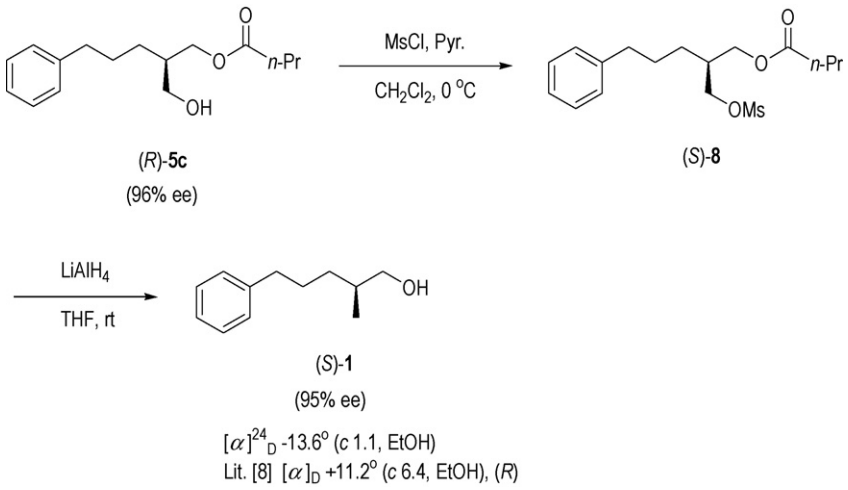
**Table 2**
Effect of vinyl esters **7** on desymmetrization of **4** using lipase PS.

| Entry | Vinyl ester **7** (R) | Time (h) | **4**: (*R*)-**5**: **6**[a] | *ee* of (*R*)-**5** (%) |
|---|---|---|---|---|
| 1 | $CH_3$ | 2.8 | 5:92:3 | 95 |
| 2 | $CH_2CH_3$ | 2.7 | 3:93:4 | 96 |
| 3 | $CH_2CH_2CH_3$ | 3.0 | 1:90:9 | 97 |
| 4 | $CH_2(CH_2)_3CH_3$ | 3.1 | 1:90:9 | 84 |

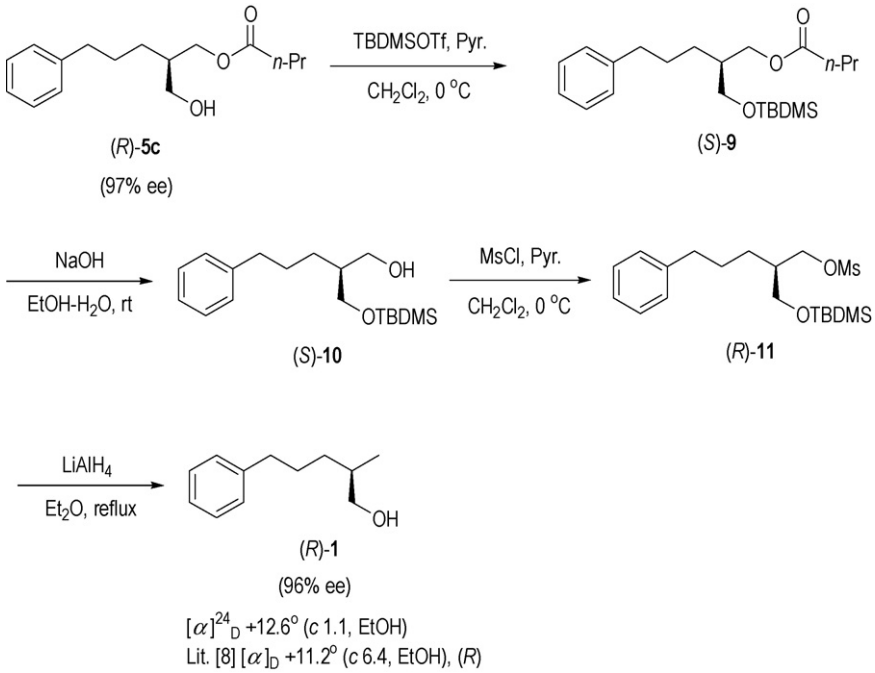
Conditions: lipase PS (20 mg/mL), **4** (100 mmol/L), **7** (1 mol/L), rt.
[a] Ratio of the peak areas of **4**, (*R*)-**5** and **6** in gas chromatogram.




**Scheme 2.** Enantioselective esterification of 2-hydroxymethyl-5-phenyl-1-pentanol **4.**




**Scheme 3.** Synthesis of (*S*)-2-methyl-5-phenyl-1-pentanol (*S*)-**1.**




**Scheme 4.** Synthesis of (*R*)-2-methyl-5-phenyl-1-pentanol (*R*)-**1.**

The obtained optically active alcohols {(*R*)-**1** and (*S*)-**1**} and the corresponding racemate (*RS*)-**1** which was synthesized according to the procedure in Section 4.8 were submitted to the evaluation of the odor profiles by skilled perfumers. The following descriptions were obtained. (*R*)-**1**: green tea-like, fatty, slightly fruity, heavy, green and citrus-like; (*S*)-**1**: slightly citrus-like, fruity, aldehydic, citrus peel-like, pine terpene-like, powdery plum-like; (*RS*)-**1**: fruity, brilliant, rosy, wine-like, honey, tea-like, geranyl acetate-like, sweet grapefruit-like.

## 3. Conclusion

We synthesized optically active Rosaphen® **1** (2-methyl-5-phenyl-1-pentanol) from the chiral intermediates obtained via the lipase-catalyzed desymmetrization of prochiral diol. We are now synthesizing other optically active fragrance ingredients according to the method described here.

## 4. Experimental

### 4.1. Materials and methods

All commercially available reagent chemicals were obtained from Aldrich, Kanto Kagaku, Nacalai Tesque, Tokyo Kasei and Wako Chemicals, and generally used without further purification. Ether and THF were distilled from Na/benzophenone under Ar. Dichloromethane, diisopropyl ether, 1,4-dioxane, toluene, diisopropylamine and pyridine were distilled from $CaH_2$ under Ar. Acetone was distilled from molecular sieves 3A under Ar. HMPA was distilled from $CaH_2$ under reduced pressure (70.1–72.1 °C/0.5 mm Hg). Vinyl acetate was distilled from molecular sieves 4A under Ar. Amano AK, PS, Sigma CRL, PPL were purchased from Amano Enzyme, Inc., and Sigma–Aldrich, Inc. Amano AY, Meito ALC, MY, OF, PLC, QLM, ST, TL, Novozym 435 were provided by Amano Enzyme Inc., Meito Sangyo Co., Ltd., and Novozymes Japan, Inc. All the lipases except Novozym 435 were dried over $P_2O_5$. The NMR spectra were recorded using a Bruker Advance II 400 (400 MHz $^1$H, 100 MHz $^{13}$C) spectrometer for solution in $CDCl_3$ with TMS as the internal standard, and the *J* values are given in hertz. The IR spectra were obtained using a Jasco FT/IR-410 spectrometer. The MS spectra were obtained using a Jeol JMS-GCmate II spectrometer. The HRMS spectra were obtained using a Jeol JMS-AX505HAD spectrometer and the electron ionization method. The optical rotations were measured with a Horiba SEPA-300 polarimeter. The melting point was measured by a Yanaco MP-S3 micro-melting point apparatus. The gas chromatograms were recorded on a Shimadzu GC-14B with INTERCAP 1 capillary column (GL Sciences, 30 m × 0.25 mm). The HPLC analyses were carried out on a Hitachi L-6250 intelligent pump with a Hitachi L-4000 UV detector and CHIRALCEL OJ, CHIRALCEL OB-H and CHIRALCEL OJ-H (all the columns from Daicel, 250 mm × 4.6 mm).

### 4.2. Ethyl 2-ethoxycarbonyl-5-phenylpentanoate **3**

A solution of diethyl malonate (6.010 g, 37.52 mmol) in dry THF (9 mL) was added dropwise to a suspension of 60% sodium hydride (1.282 g, 32 mmol) in dry THF (9 mL). After stirring for 20 min, a solution of 1-bromo-3-phenylpropane (5.015 g, 25.19 mmol) in dry THF (9 mL) added dropwise to the suspension. The reaction mixture was refluxed for 16 h. After cooling to 0 °C, the mixture was added acidified with 1 mol/L HCl (50 mL) and extracted three times with ether. The organic layer was washed with a saturated sodium chloride solution, then dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 5/1 (v/v)} to give **3** as a colorless oil (5.455 g, 78%); $^1$H NMR: 7.26–7.29 (2H, m), 7.16–7.20 (3H, m), 4.19 (4H, q, *J* = 7.1), 3.34 (1H, t, *J* = 7.6), 2.64 (2H, t, *J* = 7.8), 1.94 (2H, q, *J* = 7.7), 1.66 (2H, quintet, *J* = 7.8), 1.25 (6H, t, *J* = 7.0); $^{13}$C NMR: 169.43, 141.71, 128.36, 128.35, 125.87, 61.31, 51.92, 35.48, 29.10, 28.36, 14.07; IR (neat): 1732 cm$^{-1}$; MS (*m*/*z*) 278 ($M^+$, base peak), 232, 186, 173, 158, 131, 117, 104, 91; HRMS calcd for $C_{16}H_{22}O_4$ ($M^+$), 278.1518. Found: 278.1490.

### 4.3. 2-Hydroxymethyl-5-phenyl-1-pentanol **4**

A solution of **3** (5.347 g, 19.21 mmol) in dry THF (12 mL) was slowly added to a suspension of 80% $LiAlH_4$ (2.013 g, 42 mmol) in dry THF (10 mL) at 0 °C under an Ar atmosphere. The reaction mixture was stirred for 21 h at room temperature and quenched at 0 °C with 3 mol/L HCl (60 mL). The resulting mixture was extracted three times with ether. The organic phase was washed with a saturated sodium chloride solution and dried over $Na_2SO_4$. After removal of the solvents, the residue was chromatographed (silica gel, ethyl acetate) to give **4** as a colorless viscous oil, which turned to a white solid a few days later (3.061 g, 83%); mp: 38.7–40.2 °C (lit. [21] 43–44 °C); $^1$H NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 3.81 (2H, dd, *J* = 3.8, *J* = 10.6), 3.65 (2H, dd, *J* = 7.4, *J* = 10.6), 2.62 (2H, t, *J* = 7.8), 1.74–1.84 (1H, m), 1.67 (2H, quintet, *J* = 7.8), 1.27–1.33 (3H, m); $^{13}$C NMR: 142.20, 128.37, 128.33, 125.79, 66.48, 41.87, 36.09, 29.05, 27.30; IR ($CCl_4$): 3349 cm$^{-1}$; MS (*m*/*z*) 194 ($M^+$), 177 (base peak), 176, 157, 145, 130, 115, 103, 91, 80, 71, 63, 51; HRMS calcd for $C_{12}H_{18}O_2$ ($M^+$), 194.1307. Found: 194.1336.

### 4.4. (RS)-2-hydroxymethyl-5-phenylpentyl acetate (RS)-***5a*** and 2-acetoxymethyl-5-phenylpentyl acetate ***6a***

(*RS*)-2-Hydroxymethyl-5-phenylpentyl acetate (*RS*)-**5a** and 2-acetoxymethyl-5-phenylpentyl acetate **6a** were prepared as authentic samples. Acetyl chloride (0.06 g, 0.8 mmol) was slowly added to a solution of **4** (0.100 g, 0.515 mmol) and dry pyridine (0.109 g, 1.38 mmol) in dry $CH_2Cl_2$ (4 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and quenched at 0 °C with 1 mol/L HCl (2 mL). The resulting mixture was extracted with ether. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution in this order, and then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 1:1 (v/v)} to give (*RS*)-**5a** (0.059 g, 49%) and **6a** (0.018 g, 13%) as colorless oils.

(*RS*)-**5a**: $^1$H NMR: 7.26–7.29 (2H, m), 7.16–7.20 (3H, m), 4.18 (1H, dd, *J* = 4.8, *J* = 11.2), 4.08 (1H, dd, *J* = 6.4, *J* = 11.2), 3.59 (1H, dd, *J* = 4.6, *J* = 11.4), 3.51 (1H, dd, *J* = 6.6, *J* = 11.4), 2.62 (2H, t, *J* = 7.6), 2.05 (3H, s), 1.78–1.87 (1H, m), 1.68 (2H, quintet, *J* = 7.9), 1.29–1.45 (2H, m); $^{13}$C NMR: 171.71, 142.14, 128.37, 128.34, 125.81, 64.56, 62.57, 40.35, 36.01, 28.78, 27.41, 20.92; IR (neat): 3448, 1738 cm$^{-1}$; MS (*m*/*z*) 236 ($M^+$, base peak), 176, 157, 145, 130, 115, 103, 91, 80, 71, 61, 51; HRMS calcd for $C_{14}H_{20}O_3$ ($M^+$), 236.1413. Found: 236.1423.

**6a**: $^1$H NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 4.08 (2H, dd, *J* = 5.2, *J* = 11.2), 4.02 (2H, dd, *J* = 6.4, *J* = 11.2), 2.62 (2H, t, *J* = 7.6), 2.04 (6H, s), 1.97–2.04 (1H, m), 1.68 (2H, quintet, *J* = 7.8), 1.37–1.43 (2H, m); $^{13}$C NMR: 169.54, 140.40, 126.84, 126.82, 124.32, 62.63, 35.56, 34.32, 26.94, 26.13, 19.35; IR (neat): 1739 cm$^{-1}$; MS (*m*/*z*) 278 ($M^+$), 219 (base peak), 218, 176, 157, 145, 130, 115, 103, 91, 80, 71, 61, 51; HRMS calcd for $C_{16}H_{22}O_4$ ($M^+$), 278.1518. Found: 278.1554

### 4.5. (RS)-2-hydroxymethyl-5-phenylpentyl propanoate (RS)-***5b*** and 5-phenyl-2-propanoyloxymethylpentyl propanoate ***6b***

(*RS*)-2-Hydroxymethyl-5-phenylpentyl propanoate (*RS*)-**5b** and 5-phenyl-2-propanoyloxymethylpentyl propanoate **6b** as authentic samples were prepared from **4** (0.101 g, 0.520 mmol), propionyl

chloride (0.07 g, 0.8 mmol), dry pyridine (0.108 g, 1.37 mmol) and dry $CH_2Cl_2$ (3 mL) as a solvent according to the procedure described in Section 4.4. Chromatography {silica gel, hexane/ethyl acetate = 2:1 (v/v)} of the crude product afforded (*RS*)-**5b** (0.066 g, 51%) and **6b** (0.028 g, 18%) as colorless oils.

(*RS*)-**5b**: $^1$H NMR: 7.26–7.29 (2H, m), 7.16–7.20 (3H, m), 4.20 (1H, dd, *J* = 4.4, *J* = 11.2), 4.09 (1H, dd, *J* = 6.6, *J* = 11.0), 3.58 (1H, dd, *J* = 4.4, *J* = 11.2), 3.50 (1H, dd, *J* = 6.6, *J* = 11.4), 2.62 (2H, t, *J* = 7.6), 2.33 (2H, q, *J* = 7.6), 1.78–1.87 (1H, m), 1.69 (2H, quintet, *J* = 7.8), 1.29–1.45 (2H, m), 1.12 (3H, t, *J* = 7.6); $^{13}$C NMR: 175.10, 142.13, 128.37, 128.33, 125.80, 64.35, 62.63, 40.45, 36.01, 28.79, 27.58, 27.40, 9.17; IR (neat): 3446, 1737 cm$^{-1}$; MS (*m*/*z*) 250 ($M^+$), 232, 177 (base peak), 175, 157, 145, 130, 115, 103, 91, 80, 71, 65, 51; HRMS calcd for $C_{15}H_{22}O_3$ ($M^+$), 250.1569. Found: 250.1603.

**6b**: $^1$H NMR: 7.26–7.29 (2H, m), 7.15–7.20 (3H, m), 4.08 (2H, dd, *J* = 5.2, *J* = 11.2), 4.03 (2H, dd, *J* = 6.2, *J* = 11.0), 2.62 (2H, t, *J* = 7.6), 2.31 (4H, q, *J* = 7.5), 1.98–2.07 (1H, m), 1.69 (2H, quintet, *J* = 7.8), 1.37–1.43 (2H, m), 1.12 (6H, t, *J* = 7.4); $^{13}$C NMR: 174.43, 141.94, 128.36, 128.33, 125.83, 64.00, 37.22, 35.86, 28.47, 27.68, 27.52, 9.11; IR (neat): cm$^{-1}$; MS (*m*/*z*) 306 ($M^+$), 232 (base peak), 175, 159, 144, 129, 117, 104, 92, 65, 57; HRMS calcd for $C_{18}H_{26}O_4$ ($M^+$), 306.1831. Found: 306.1839

### 4.6. 2-Hydroxymethyl-5-phenylpentyl butanoate (RS)-**5c** and 2-butanoyloxymethyl-5-phenylpentyl butanoate **6c**

(*RS*)-2-Hydroxymethyl-5-phenylpentyl butanoate (*RS*)-**5c** and 2-butanoyloxymethyl-5-phenylpentyl butanoate **6c** as authentic samples were prepared from **4** (0.102 g, 0.525 mmol), butyryl chloride (0.09 g, 0.8 mmol), dry pyridine (0.135 g, 1.71 mmol) and dry $CH_2Cl_2$ (3 mL) as a solvent according to the procedure described in Section 4.4. Chromatography {silica gel, hexane/ethyl acetate = 2:1–1:1 (v/v)} of the crude product afforded (*RS*)-**5c** (0.072 g, 52%) and **6c** (0.030 g, 17%) as colorless oils.

(*RS*)-**5c**: $^1$H NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 4.22 (1H, dd, *J* = 4.4, *J* = 11.2), 4.09 (1H, dd, *J* = 6.4, *J* = 11.2), 3.59 (1H, dd, *J* = 4.6, *J* = 11.4), 3.50 (1H, dd, *J* = 6.6, *J* = 11.4), 2.62 (2H, t, *J* = 7.4), 2.30 (2H, t, *J* = 7.4), 1.78–1.87 (1H, m), 1.60–1.73 (4H, m), 1.29–1.45 (2H, m), 0.94 (3H, t, *J* = 7.4); $^{13}$C NMR: 174.32, 142.12, 128.37, 128.33, 125.80, 64.22, 62.66, 40.47, 36.19, 36.01, 28.79, 27.39, 18.48, 13.68; IR (neat): 3449, 1734 cm$^{-1}$; MS (*m*/*z*) 264 ($M^+$), 176 (base peak), 159, 144, 129, 117, 104, 92, 77, 65, 57; HRMS calcd for $C_{16}H_{24}O_3$ ($M^+$), 264.1726. Found: 264.1720.

**6c**: $^1$H NMR: 7.26–7.29 (2H, m), 7.15–7.20 (3H, m), 4.08 (2H, dd, *J* = 5.2, *J* = 11.2), 4.03 (2H, dd, *J* = 6.4, *J* = 11.2), 2.62 (2H, t, *J* = 7.6), 2.27 (4H, t, *J* = 7.4), 1.97–2.06 (1H, m), 1.58–1.72 (6H, m), 1.37–1.42 (2H, m), 0.94 (3H, t, *J* = 7.4); $^{13}$C NMR: 173.64, 141.94, 128.36, 128.33, 125.82, 63.89, 37.20, 36.15, 35.88, 28.48, 27.70, 18.43, 13.67; IR (neat): 1738 cm$^{-1}$; MS (*m*/*z*) 334 ($M^+$), 246 (base peak), 175, 159, 144, 129, 117, 104, 91, 83, 65, 57; HRMS calcd for $C_{20}H_{30}O_4$ ($M^+$), 334.2144. Found: 334.2142

### 4.7. 2-Hydroxymethyl-5-phenylpentyl hexanoate (RS)-**5d** and 2-hexanoyloxymethyl-5-phenylpentyl hexanoate **6d**

(*RS*)-2-Hydroxymethyl-5-phenylpentyl hexanoate (*RS*)-**5d** and 2-hexanoyloxymethyl-5-phenylpentyl hexanoate **6d** as authentic samples were prepared from **4** (0.104 g, 0.535 mmol), hexanoyl chloride (0.12 g, 0.89 mmol), dry pyridine (0.152 g, 1.92 mmol) and dry $CH_2Cl_2$ (3 mL) as a solvent according to the procedure described in Section 4.4. Chromatography {silica gel, hexane/ethyl acetate = 2:1–1:1 (v/v)} of the crude product afforded (*RS*)-**5d** (0.088 g, 57%) and **6d** (0.066 g, 32%) as colorless oils.

(*RS*)-**5d**: $^1$H NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 4.21 (1H, dd, *J* = 4.4, *J* = 11.2), 4.09 (1H, dd, *J* = 6.8, *J* = 11.2), 3.59 (1H, dd, *J* = 4.6, *J* = 11.4), 3.50 (1H, dd, *J* = 6.6, *J* = 11.4), 2.62 (2H, t, *J* = 7.6), 2.31 (2H, t, *J* = 7.6), 1.78–1.87 (1H, m), 1.69 (2H, quintet, *J* = 7.8), 1.62 (2H, quintet, *J* = 7.3), 1.25–1.45 (6H, m), 0.90 (3H, t, *J* = 6.9); $^{13}$C NMR: 174.50, 142.12, 128.36, 128.33, 125.80, 64.25, 62.66, 40.48, 36.02, 34.28, 31.30, 28.79, 27.42, 24.68, 22.29, 13.90; IR (neat): 3447, 1734 cm$^{-1}$; MS (*m*/*z*) 292 ($M^+$), 176 (base peak), 157, 145, 129, 117, 104, 91, 80, 71, 65, 55; HRMS calcd for $C_{18}H_{28}O_3$ ($M^+$), 292.2039. Found: 292.2028.

**6d**: $^1$H NMR: 7.26–7.29 (2H, m), 7.15–7.20 (3H, m), 4.08 (2H, dd, *J* = 5.2, *J* = 11.2), 4.03 (2H, dd, *J* = 6.2, *J* = 11.0), 2.62 (2H, t, *J* = 7.6), 2.28 (4H, t, *J* = 7.4), 2.02 (1H, septet, *J* = 6.1), 1.68 (2H, quintet, *J* = 7.9), 1.60 (4H, quintet, *J* = 7.5), 1.24–1.42 (10H, m), 0.89 (6H, t, *J* = 6.9); $^{13}$C NMR: 173.97, 142.10, 128.50, 128.47, 125.97, 64.08, 37.35, 36.04, 34.38, 31.44, 28.64, 27.89, 24.77, 22.44, 14.05; IR (neat): 1738 cm$^{-1}$; MS (*m*/*z*) 390 ($M^+$), 275, 192 (base peak), 174, 158, 143, 129, 117, 104, 91, 80, 71, 65, 55; HRMS calcd for $C_{24}H_{38}O_4$ ($M^+$), 390.2770. Found: 390.2771

### 4.8. 2-Methyl-5-phenyl-1-pentanol (Rosaphen®) (RS)-**1**

Racemic 2-methyl-5-phenyl-1-pentanol (Rosaphen®) (*RS*)-**1** was prepared as an authentic sample. Dry THF (20 mL) and dry diisopropylamine (5.125 g, 50.65 mmol) were added to a three-necked, round-bottomed flask and maintained under an argon atmosphere. After cooling the mixture to 0 °C, 2.6 mol/L *n*-butyl lithium in hexane solution (19.5 mL, 51 mmol) was added via a syringe over a period of 10 min. The mixture was stirred for 20 min at 0 °C. A solution of propanoic acid (1.655 g, 22.34 mmol) in dry THF (4.5 mL) was dropwise added over a period of 10 min. After stirring for 10 min, dry HMPA (4.4 mL, 25 mmol) was introduced via a syringe over a period of 10 min, and the mixture was stirred for 40 min at room temperature. 1-Bromo-3-phenylpropane (4.459 g, 22.40 mmol) dissolved in dry THF (4.467 g, 24.93 mmol) was dropwise added over the period of 15 min at 0 °C. After stirring overnight at room temperature, the mixture was treated with 1 mol/L HCl (60 mL) at 0 °C and extracted three times with ether. The ether solution was washed with deionized water, saturated aqueous sodium chloride, and dried with sodium sulfate. The solvent was evaporated and the residue was chromatographed {silica gel, hexane/acetone = 2:1 (v/v)} to give a colorless oil, which was distilled (223–243 °C/0.9 mm Hg) to give 2-methyl-5-phenylpentanoic acid (2.658 g, 62%); $^1$H NMR: 7.25–7.29 (2H, m), 7.16–7.19 (3H, m), 2.62 (2H, t, *J* = 7.6), 2.49 (1H, sextet, *J* = 6.9), 1.63–1.78 (3H, m), 1.44–1.53 (1H, m), 1.18 (3H, t, *J* = 6.8); $^{13}$C NMR: 182.92, 142.08, 128.37, 128.33, 125.80, 39.24, 35.74, 33.09, 28.95, 16.84; IR (neat): 1705 cm$^{-1}$; MS (*m*/*z*) 192 ($M^+$, base peak), 174, 131, 117, 104, 92, 87, 74, 65; HRMS calcd for $C_{12}H_{16}O_2$ ($M^+$), 192.1150. Found: 192.1149.

A solution of 2-methyl-5-phenylpentanoic acid (2.570 g, 13.37 mmol) in dry THF (20 mL) was added to a suspension of 80% $LiAlH_4$ (0.669 g, 14 mmol) in dry THF (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 1 mol/L HCl (60 mL). The resulting mixture was extracted three times with ether. The organic phase was washed with a saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvents, the residue was chromatographed twice {silica gel, first: hexane/acetone = 2:1 (v/v), second: hexane/ethyl acetate = 2:1 (v/v)} to give a colorless oil, which was distilled (187–208 °C/0.8 mm Hg) to give (*RS*)-**1** as a colorless oil (2.088 g, 88%). The $^1$H NMR spectra data were identical to those in the literature [8].

### 4.9. 2-Methyl-5-phenylpentyl acetate (RS)-**12**

2-Methyl-5-phenylpentyl acetate (*RS*)-**12** was prepared as an authentic sample. Acetyl chloride (0.09 g, 1 mmol) was slowly added to a solution of (*RS*)-**1** (0.100 g, 0.561 mmol) and dry pyridine (0.133 g, 1.68 mmol) in dry dichloromethane (5 mL) at 0 °C.

The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 1 mol/L HCl (10 mL). The resulting mixture was extracted with ether. The organic phase was washed with a saturated sodium chloride solution, and then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 5:1 (v/v)} to give (*RS*)-**12** as a colorless oil (0.114 g, 93%); $^1$H NMR: 7.26–7.29 (2H, m), 7.16–7.19 (3H, m), 3.94 (1H, dd, *J* = 6.2, *J* = 10.6), 3.85 (1H, dd, *J* = 6.8, *J* = 10.8), 2.54–2.66 (2H, m), 2.04 (3H, s), 1.81 (1H, sextet, *J* = 6.6), 1.55–1.74 (2H, m), 1.39–1.47 (1H, m), 1.16–1.26 (1H, m), 0.90 (3H, d, *J* = 6.8); $^{13}$C NMR: 171.27, 142.44, 128.37, 128.28, 125.71, 69.34, 36.06, 32.93, 32.40, 28.69, 20.96, 16.79; IR (neat): 1739 cm$^{-1}$; MS (*m*/*z*) 220 ($M^+$), 161 (base peak), 160, 145, 132, 115, 103, 92, 82, 77, 65, 51; HRMS calcd for $C_{14}H_{20}O_2$ ($M^+$), 220.1463. Found: 220.1513.

### 4.10. Lipase-catalyzed desymmetrization of 2-hydroxymethyl-5-phenyl-1-pentanol **4** (screening experiments)

In a typical run, a 1,4-dioxane solution (1 mL) containing diol **4** (0.1 mmol) and vinyl acetate **7a** (1 mmol) was added to a vial in which lipase PS (20 mg) was placed. The resulting suspension was then magnetically stirred at room temperature. Samples were withdrawn from the vial and analyzed by gas chromatography. The reaction was stopped by filtration of the lipase when the peak area of optically active monoester (*R*)-**5a** in gas chromatogram reached about 90% of the total of peak areas of **4**, (*R*)-**5a** and diester **6a**. The filtrate was concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 2:1–1:1 (v/v)} with a short column (10 mm × 80 mm) to give (*R*)-**5a**. The *ee* of (*R*)-**5a** was determined by HPLC.

Conditions for the determination of the ees of (*R*)-**5a**, (*R*)-**5b**, (*R*)-**5c** and (*R*)-**5d** were as follows. (*R*)-**5a**: Chiralcel OJ-H, hexane/2-propanol = 5:1 (v/v); (*R*)-**5b**: Chiralcel OJ-H, hexane/2-propanol = 5:1 (v/v); (*R*)-**5c**: Chiralcel OJ, hexane/2-propanol = 5:1 (v/v); (*R*)-**5d**: Chiralcel OJ, hexane/2-propanol = 5:1 (v/v).

### 4.11. Synthesis of (S)-2-methyl-5-phenyl-1-pentanol (S)-**1**

#### 4.11.1. (R)-2-hydroxymethyl-5-phenylpentyl butanoate (R)-**5c** (preparative desymmetrization of **4**)

Lipase PS (0.653 g) was added to a solution of **4** (0.658 g, 3.39 mmol) and **7c** (3.873 g, 33.93 mmol) in dry 1,4-dioxane (30 mL). The mixture was stirred for 2 h 45 min at room temperature. The reaction was quenched by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 2:1 (v/v)} to give (*R*)-**5c** as colorless oil (0.754 g, 85%, 96% ee). The $^1$H NMR spectra data were identical to those of (*RS*)-**5c**.

#### 4.11.2. (S)-2-methanesulfonyloxymethyl-5-phenylpentyl butanoate (S)-**8**

Methanesulfonyl chloride (0.656 g, 5.73 mmol) was slowly added to a solution of (*R*)-**5c** (0.744 g, 2.81 mmol) and dry pyridine (0.676 g, 8.55 mmol) in dry $CH_2Cl_2$ (10 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 1 mol/L HCl (20 mL). The resulting mixture was then extracted with ether. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution in this order, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 2:1 (v/v)} to give (*S*)-**8** as a colorless oil (0.886 g, 92%): $^1$H NMR: 7.26–7.30 (2H, m), 7.16–7.21 (3H, m), 4.21 (1H, dd, *J* = 5.0, *J* = 9.8), 4.18 (1H, dd, *J* = 5.8, *J* = 9.8), 4.14 (1H, dd, *J* = 4.6, *J* = 11.4), 4.04 (1H, dd, *J* = 6.8, *J* = 11.2), 2.98 (3H, s), 2.63 (2H, t, *J* = 7.4), 2.28 (2H, t, *J* = 7.4), 2.05–2.14 (1H, m), 1.59–1.74 (4H, m), 1.36–1.50 (2H, m), 0.94 (3H, t, *J* = 7.4); $^{13}$C NMR: 171.36, 139.57, 126.29, 126.27, 123.84, 66.92, 60.77, 35.63, 35.16, 33.96, 33.65, 26.27, 25.01, 16.29, 11.57; IR (neat): 1734, 1358, 1175 cm$^{-1}$; MS (*m*/*z*) 342 ($M^+$), 254 (base peak), 246, 175, 157, 145, 130, 115, 103, 91, 80, 71, 65, 55; HRMS calcd for $C_{17}H_{26}O_5S$ ($M^+$), 342.1501. Found: 342.1477.

#### 4.11.3. (S)-2-methyl-5-phenyl-1-pentanol (S)-**1**

A solution of (*S*)-**8** (0.832 g, 2.43 mmol) in dry THF (5 mL) was slowly added to a suspension of 80% $LiAlH_4$ (0.130 g, 2.7 mmol) in dry THF (6 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 0.5 mol/L HCl (40 mL). The resulting mixture was extracted three times with ether. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution in this order, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, first: hexane/acetone = 5:1 (v/v)} to give a colorless oil, which was distilled twice (first time: 170–180 °C/0.7 mm Hg; second time: 160–178 °C/1.0 mm Hg) to give (*S*)-**1** as a colorless oil (0.246 g, 57%); $[\alpha]_D^{24}$ −13.6° (*c* 1.1, EtOH), {Lit. [8] $[\alpha]_D$ +11.2° (*c* 6.4, EtOH), (*R*)}; The $^1$H NMR spectra data were identical to those of (*RS*)-**1**.

#### 4.11.4. Determination of the ee of (S)-**1**

Acetyl chloride (7 drops) was slowly added to a solution of (*S*)-**1** (2 drops) and dry pyridine (9 drops) in $CH_2Cl_2$ (5 mL) at 0 °C. The reaction mixture was stirred 2.5 h at room temperature and quenched at 0 °C with 1 mol/L HCl. The resulting mixture was then extracted with ether. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution in this order, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 10:1 (v/v)} with a short column (80 mm × 10 mm) to give the corresponding acetate (*S*)-**12** as a colorless oil. The $^1$H NMR spectra data were identical to those of the acetate of (*RS*)-**12**. The *ee* of (*S*)-**12** was determined by HPLC {Chiralcel OB-H, hexane:2-propanol = 75:1 (v/v)} and found 95%.

### 4.12. Synthesis of (R)-2-methyl-5-phenyl-1-pentanol (R)-**1**

#### 4.12.1. (R)-2-hnydroxymethyl-5-phenylpentyl butanoate (R)-**5c** (preparative desymmetrization of **4**)

(*R*)-2-Hydroxymethyl-5-phenylpentyl butanoate (*R*)-**5c** with 97% *ee* for the synthesis of (*R*)-**1** was newly prepared via the preparative desymmetrization of **4** in 89% yield according to the procedure described in Section 4. 11. 1. The $^1$H NMR spectra data of (*R*)-**5c** obtained here were identical to those of (*RS*)-**5c**.

#### 4.12.2. (S)-2-tert-butyldimethylsiloxymethyl-5-phenylpentyl butanoate (S)-**9**

*Tert*-butyldimethylsilyl trifluoromethanesulfonate (3.66 g, 13.8 mmol) was slowly added to a solution of (*R*)-**5c** (1.824 g, 6.900 mmol) and dry pyridine (1.66 g, 21.0 mmol) in dry $CH_2Cl_2$ (15 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with deionized water (50 mL). The resulting mixture was then extracted with ether. The organic phase was washed with deionized water twice and dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 5:1 (v/v)} to give (*S*)-**9** as a colorless oil (2.521 g, 97%); $^1$H NMR: 7.25–7.29 (2H, m), 7.16–7.19 (3H, m), 4.06 (2H, d, *J* = 5.6), 3.52–3.60 (2H, m), 2.60 (2H, t, *J* = 7.6), 2.26 (2H, t, *J* = 7.4), 1.81 (1H, septet, *J* = 6), 1.61–1.70 (4H, m), 1.24–1.45 (2H, m), 0.94 (3H, t, *J* = 7.4), 0.87 (9H, s), 0.02 (6H, s); $^{13}$C NMR: 173.74, 142.35, 128.37, 128.27, 125.70, 64.27,

62.56, 40.16, 36.27, 36.13, 28.77, 27.50, 25.86, 18.48, 18.26, 13.70, −5.54; IR (neat): 1738, 1092 $cm^{-1}$; MS (*m*/*z*) 378 ($M^+$), 322 (base peak), 321, 187, 163, 146, 131, 115, 104, 91, 81, 76, 59; HRMS calcd for $C_{22}H_{38}O_3Si$ ($M^+$), 378.2590. Found: 378.2574

*4.12.3. (S)-2-tert-butyldimethylsiloxymethyl-5-phenyl-1-pentanol (S)-**10***

Six mole per Litre NaOH (4 mL, 24 mmol) was added to a solution of (*S*)-**9** (2.426 g, 6.408 mmol) in EtOH (24 mL). The mixture was stirred overnight at room temperature. After removal of the solvent, the residue was extracted three times with ether. The organic layer was washed with brine, then dried over sodium sulfate and concentrated. The residue was chromatographed {silica gel, hexane/ethyl acetate = 3:1 (v/v)} to give (*S*)-**10** (1.028 g, 52%) as a colorless oil; $^1H$ NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 3.80 (1H, dd, *J* = 4.0, *J* = 9.6), 3.74 (1H, dd, *J* = 3.4, *J* = 10.6), 3.63 (1H, dd, *J* = 7.2, *J* = 10.8), 3.59 (1H, dd, *J* = 7.4, *J* = 9.8), 2.61 (2H, t, *J* = 7.6), 1.71–1.80 (1H, m), 1.57–1.70 (2H, m), 1.21–1.35 (2H, m), 0.89 (9H, s), 0.07 (6H, s); $^{13}C$ NMR: 142.30, 128.37, 128.31, 125.75, 67.35, 66.73, 41.80, 36.17, 29.13, 27.36, 25.84, 18.14, −5.56, −5.63; IR (neat): 3418, 1086 $cm^{-1}$; MS (*m*/*z*) 308 ($M^+$), 252 (base peak), 251, 233, 160, 145, 130, 115, 101, 90, 81, 73, 60, 55; HRMS calcd for $C_{18}H_{32}O_2Si$ ($M^+$), 308.2172. Found: 308.2186.

*4.12.4. (R)-2-tert-butyldimethylsiloxymethyl-5-phenylpentyl methanesulfonate (R)-**11***

Methanesulfonyl chloride (0.75 g, 6.5 mmol) was slowly added to a solution of (*S*)-**10** (0.990 g, 3.21 mmol) and dry pyridine (0.76 g, 9.6 mmol) in dry $CH_2Cl_2$ (10 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with deionized water. The resulting mixture was then extracted with ether. The organic phase was washed with deionized water (twice) and a saturated sodium chloride solution in this order, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 3:1 (v/v)} to give (*R*)-**11** as a colorless oil (1.146 g, 93%): $^1H$ NMR: 7.26–7.30 (2H, m), 7.16–7.20 (3H, m), 4.22 (2H, d, *J* = 5.6), 3.64 (1H, dd, *J* = 4.4, *J* = 10.0), 3.53 (1H, dd, *J* = 6.4, *J* = 10.0), 2.97 (3H, s), 2.62 (2H, t, *J* = 7.5), 1.84–1.92 (1H, m), 1.67 (2H, quintet, *J* = 7.8), 1.36–1.42 (2H, m), 0.88 (9H, s), 0.04 (6H, s); $^{13}C$ NMR: 142.03, 128.38, 128.36, 125.84, 70.04, 61.53, 40.62, 36.93, 36.00, 28.70, 26.88, 25.84, 18.22, −5.50, −5.55; IR (neat): 1359, 1177, 1094 $cm^{-1}$; MS (*m*/*z*) 387 ($M^+ + H$), 233 (base peak), 195, 171, 156, 145, 137, 130, 115, 101, 90, 81, 71, 60, 51; HRMS calcd for $C_{19}H_{34}O_4SSi$ ($M^+$), 386.1947. Found: 386.1915.

*4.12.5. (R)-2-methyl-5-phenyl-1-pentanol (R)-**1***

A solution of (*R*)-**11** (1.049 g, 2.713 mmol) in dry $Et_2O$ (10 mL) was slowly added to a suspension of 80% $LiAlH_4$ (0.148 g, 3.1 mmol) in dry $Et_2O$ (8 mL) at room temperature. The reaction mixture was refluxed for 6.5 h. After cooling to 0 °C, deionized water was added to the mixture and extraction was performed three times with ether. The organic layer was washed with a saturated sodium chloride solution, then dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 2/1 (v/v)} to give a colorless oil, which was distilled (165–180 °C/1.0 mm Hg) to give (*R*)-**1** as a colorless oil (0.246 g, 57%, 96% ee); $[\alpha]_D^{24}$ +12.6° (*c* 1.1, EtOH), {Lit. [8] $[\alpha]_D$ +11.2° (*c* 6.4, EtOH), (*R*)}; The $^1H$ NMR spectra data were identical to those of (*RS*)-**1**; The *ee* was determined after (*R*)-**1** was converted to the corresponding acetate (*R*)-**12** according to the procedure in Section 4.11.4.

## Acknowledgements

We are grateful to the researchers at the Biotechnology Research Center, Toyama Prefectural University, for their generous support with the NMR spectroscopic and optical rotation measurements. We are also grateful to Dr. Yasuo Tanaka, Taiyo Koryo Corporation for the olfactory evaluation. Amano Enzyme Inc., Meito Sangyo Co., Ltd., and Novozymes Japan, Inc provided the lipases.

## References

[1] (a) J. Margetts, in: D.J. Rowe (Ed.), Chemistry and Technology of Flavors and Fragrances, Blackwell Publishing, Oxford, 2005, p. 171;
(b) T. Yamamoto, Koryo 184 (1994) 57–72.
[2] For reviews, see:
(a) A. Ciappa, S. Bovo, M. Bertoldini, A. Scrivanti, U. Matteoli, Chem. Biodivers. 5 (2008) 1058–1069;
(b) T. Tachihara, Koryo 238 (2008) 61–66;
(c) L.A. Saudan, Acc. Chem. Res. 40 (2007) 1309–1319;
(d) Y. Shimotori, T. Miyakoshi, Koryo 236 (2007) 69–82;
(e) A. Abate, E. Brenna, C. Fuganti, F.G. Gatti, S. Serra, Chem. Biodivers. 1 (2004) 1888–1898;
(f) A. Abate, E. Brenna, C. Fuganti, F.G. Gatti, S. Serra, J. Mol. Catal. B: Enzym. 32 (2004) 33–51;
(g) E. Brenna, C. Fuganti, S. Serra, P. Kraft, Eur. J. Org. Chem. (2002) 967–978.
[3] (a) H. Nemoto, W. Zhong, T. Kawamura, M. Kamiya, Y. Nakano, K. Sakamoto, Synlett (2007) 2343–2346;
(b) U. Matteoli, A. Ciappa, S. Bovo, M. Bertoldini, A. Scrivanti, Tetrahedron: Asymmetry 18 (2007) 797–802;
(c) A. Abate, E. Brenna, G. Fronza, C. Fuganti, F.G. Gatti, S. Maroncelli, Chem. Biodivers. 3 (2006) 677–694;
(d) S. Serra, C. Fuganti, E. Brenna, Helv. Chim. Acta 89 (2006) 1110–1122;
(e) A. Abate, M. Allievi, E. Brenna, C. Fuganti, F.G. Gatti, S. Serra, Helv. Chim. Acta 89 (2006) 177–189;
(f) A. Abate, E. Brenna, C. Fuganti, F.G. Gatti, T. Giovenzana, L. Malpezzi, S. Serra, J. Org. Chem. 70 (2005) 1281–1290;
(g) A.Q. Stang, G. Helmchen, Helv. Chim. Acta 88 (2005) 2738–2746;
(h) T. Yamamoto, M. Ogura, A. Amano, K. Adachi, T. Hagiwara, T. Kanisawa, Tetrahedron Lett. 43 (2002) 9081–9084.
[4] For reviews, see:
(a) P. Kraft, J.A. Bajgrowicz, C. Denis, G. Fráter, Angew. Chem. Int. Ed. 39 (2000) 2980–3010;
(b) G. Fráter, J.A. Bajgrowicz, P. Kraft, Tetrahedron 54 (1998) 7633–7703.
[5] (a) B. Čiško-Anić, Z. Hameršak, Chirality 21 (2009) 894–904;
(b) E. Brenna, C. Fuganti, F.G. Gatti, L. Malpezzi, S. Serra, Tetrahedron: Asymmetry 19 (2008) 800–807;
(c) M. Luparia, P. Boschetti, F. Piccinini, A. Porta, G. Zanoni, G. Vidari, Chem. Biodivers. 5 (2008) 1045–1057;
(d) A. Wallner, H. Mang, S.M. Glueck, A. Steinreiber, S.F. Mayer, K. Faber, Tetrahedron: Asymmetry 14 (2003) 2427–2432;
(e) S. Bovo, A. Scrivanti, M. Bertoldini, V. Beghetto, U. Matteoli, Synthesis (2008) 2547–2550;
(f) M. Luparia, L. Legnani, A. Porta, G. Zanoni, L. Toma, G. Vidari, J. Org. Chem. 74 (2009) 7100–7110;
(g) P. Scafato, A. Larocca, C. Rosini, Tetrahedron: Asymmetry 17 (2006) 2511–2515;
(h) M. Kosaka, S. Sekiguchi, J. Naito, M. Uemura, S. Kuwahara, M. Watanabe, N. Harada, K. Hiroi, Chirality 17 (2005) 218–232;
(i) S. Superchi, M. Nardiello, M.I. Donnoli, P. Scafato, R. Menicagli, C. Rosini, C. R. Chimie 8 (2005) 867–874;
(j) A. Porta, G. Vidari, G. Zanoni, J. Org. Chem. 70 (2005) 4876–4878;
(k) P. Kraft, K. Popaj, A. Abate, Synthesis (2005) 2798–2809;
(l) A. Ciappa, A. Scrivanti, U. Matteoli, J. Mol. Cat. A: Chem. 219 (2004) 217–220;
(m) A. Corma, S. Iborra, M. Mifsud, M. Renz, M. Susarte, Adv. Synth. Catal. 346 (2004) 257–262;
(n) M.I. Donnoli, P. Scafato, M. Nardiello, D. Casarini, E. Giorgio, C. Rosini, Tetrahedron 60 (2004) 4975–4981;
(o) E.J. Hicken, E.J. Corey, Org. Lett. 10 (2008) 1135–1138;
(p) A. Ciappa, U. Matteoli, A. Scrivanti, Tetrahedron: Asymmetry 13 (2002) 2193–2195.
[6] H. Surburg, J. Panten, Common Fragrance and Flavor Materials, Wiley-VCH, Weinheim, 2006, p. 110.
[7] D.J. Rowe, in: D.J. Rowe (Ed.), Chemistry and Technology of Flavors and Fragrances, Blackwell Publishing, Oxford, 2005, p. 60.
[8] C. Santini, R.G. Ball, G.D. Berger, J. Org. Chem. 59 (1994) 2261–2266.
[9] A. Abiko, Jpn. Kokai Tokkyo Koho (1997), JP 09241262.
[10] S. Comesse, O. Piva, Tetrahedron: Asymmetry 10 (1999) 1061–1067.
[11] D.A. Nicewicz, A.D. Satterfield, D.C. Schmitt, J.S. Johnson, J. Am. Chem. Soc. 130 (2008) 17281–17283.
[12] M. Kawasaki, Y. Asano, K. Katayama, A. Inoue, C. Hiraoka, H. Kakuda, A. Tanaka, M. Goto, N. Toyooka, T. Kometani, J. Mol. Catal. B: Enzym. 54 (2008) 93–102.
[13] M. Kawasaki, H. Kakuda, M. Goto, S. Kawabata, T. Kometani, Tetrahedron: Asymmetry 14 (2003) 1529–1534.

[14] M. Kawasaki, H. Yoshikai, H. Kakuda, N. Toyooka, A. Tanaka, M. Goto, T. Kometani, Heterocycles 68 (2006) 483–493.
[15] M. Kawasaki, N. Toyooka, Y. Matsui, A. Tanaka, M. Goto, H. Kakuda, S. Kawabata, T. Kometani, Heterocycles 65 (2005) 761–765.
[16] M. Kawasaki, Y. Hayashi, H. Kakuda, N. Toyooka, A. Tanaka, M. Goto, S. Kawabata, T. Kometani, Tetrahedron: Asymmetry 16 (2005) 4065–4072.
[17] For reviews, see:
(a) A. Ghanem, H.Y. Aboul-Enein, Chirality 17 (2005) 1–15; (b) A. Ghanem, H.Y. Aboul-Enein, Tetrahedron: Asymmetry 15 (2004) 3331–3351.
[18] C.R. Wescott, A.M. Klibanov, Biochim. Biophys. Acta 1206 (1994) 1–9.
[19] A.N.E. Weissflock, R.J. Kazulauskas, J. Org. Chem. 60 (1995) 6959–6969.
[20] M. Kawasaki, M. Goto, S. Kawabata, T. Kometani, Tetrahedron: Asymmetry 12 (2001), 585–596 and references cited therein.
[21] B.J. Ludwig, L.S. Powell, F.M. Berger, J. Med. Chem. 12 (1969) 462–472.