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Chemoenzymatic synthesis of (*S*)- and (*R*)-γ-cyclogeraniols

Naoko Fujiwara, Masako Kinoshita, Hiroyuki Akita*

School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract

For the purpose of the production of expensive perfume such as ambrein, (*S*)- and (*R*)-γ-cyclogeraniols (**2**) seem to be the important chiral synthons for the synthesis of ambrein The lipase QL from *Alcaligenes* sp.-catalyzed enantioselective acetylation of the (±)-(1,2)-*trans*-6,6-dimethyl-2-hydroxyhexane-1-carboxylate (**9**) was carried out and an alcohol (1*S*, 2*S*)-**9** and an acetate (1*R*, 2*R*)-**10** possessing high enantiomeric excess (>99% ee), respectively, were obtained. Both the alcohol (1*S*, 2*S*)-**9** and the acetate (1*R*, 2*R*)-**10** were converted to the (*S*)- and (*R*)-γ-cyclogeraniols (**2**), respectively.

Keywords: Lipase; *Alcaligenes* sp; Enzymatic resolution; Enantioselective acetylation; γ-cyclogeraniol

1. Introduction

The chiral structural unit (A) possessing a cyclohexane ring system attached with two methyl groups and exo-methylene group is an important nucleus found in a variety of natural products such as diterpenes and triterpenes. Among them, ambrein (**1**) is a major constituent of ambergris,[1] which can be obtained as an intestinal concretion of the spermwhale, and is used for the production of expensive perfumes. The key optically active intermediate for the synthesis of (−)-ambrein (**1**) appeared to be (*S*)-γ-cyclogeranol (**2**) [2]. Treatment of the known β-ketoester (±)-**3** with a salt-free Wittig reagent was reported to give methyl (±)-γ-cyclogeranate (**4a**), which was subjected to consecutive mild saponification and optical resolution of the generated (±)-γ-cyclogeranic acid (**4b**) with (*S*)-1-phenylethylamine to afford (+)-**4b**. This compound (+)-**4b** was converted to the enantiomerically pure alcohol (*S*)-γ-cyclogeraniol (**2**) [2]. On the other hand, we reported the synthesis of both enantiomers of (*S*)- and (*R*)-albicanol (**5**) based on an enzymatic resolution of (±)-**5** [3]. Moreover, enzymatic resolution of (±)-allylic(hydroxymethyl)-methylenecyclopentane congener (**6**) was reported to afford (*S*)-alcohol (**6**) [4].

Allylic hydroxymethyl derivatives of the methylenecycloalkane moieties have emerged as highly attractive and versatile blocks for the synthesis of several natural products including (−)-ambrein (**1**) [5,6]. In this paper, we describe the synthesis of both (*S*)- and (*R*)-γ-cyclogeraniols (**2**) based on the enzymatic resolution of (±)-**2** possessing the same moiety as (±)-**5** or (±)-**6**, and an alternative chemoenzymatic synthesis of (*S*)- and (*R*)-γ-cyclogeraniols (**2**). At first, lipase-catalyzed enantioselective acetylation of the reported (±)-γ-cyclogeraniol (**2**) [2] was carried out in the presence of isopropenylacetate to give the optically active alcohol (**2**) and its acetate (**7**), while the results were not satisfactory from the standpoint of yield and enantiomeric excess (ee) as described later in the text. (Table 1.) To overcome this difficulty, an alternative synthesis of (*S*)- and (*R*)-γ-cyclogeraniols (**2**) was carried out. $NaBH_4$ reduction of the β-keto ester (±)-**3** [2] gave (±)-*cis*-β-hydroxy ester (**8**; 72%) and (±)-*trans*–hydroxy ester (**9**; 20%). The structures of (±)-**8** and (±)-**9** were determined by the coupling constants ($J_{1,2}$ = 3.5 Hz and $J_{1,2}$ = 10.5 Hz) due to C(1)–H and C(2)–H, respectively (Schemes 1 and 2).

Enzymatic acetylation of (±)-*cis*-**8** did not occur, while lipase-catalyzed enantioselective acetylation of (±)-*trans*-**9** gave 49% yield of (1*S*, 2*S*)-**9** (97% ee: estimation as (*R*)-MTPA ester (**11**)) and 45% yield of (1*R*, 2*R*)-acetate **10** (>99% ee: estimation as (*R*)-MTPA ester (**12**)) as described later in the text. (Scheme 3, Table 2) In order to determine the absolute structure of (1*S*, 2*S*)-**9**, (1*S*, 2*S*)-**9** was converted to the (*S*)-γ-

* Corresponding author. Tel.: +81 47 472 1805; fax: +81 47 476 6195.
E-mail address: akita@phar.toho-u.ac.jp (H. Akita).

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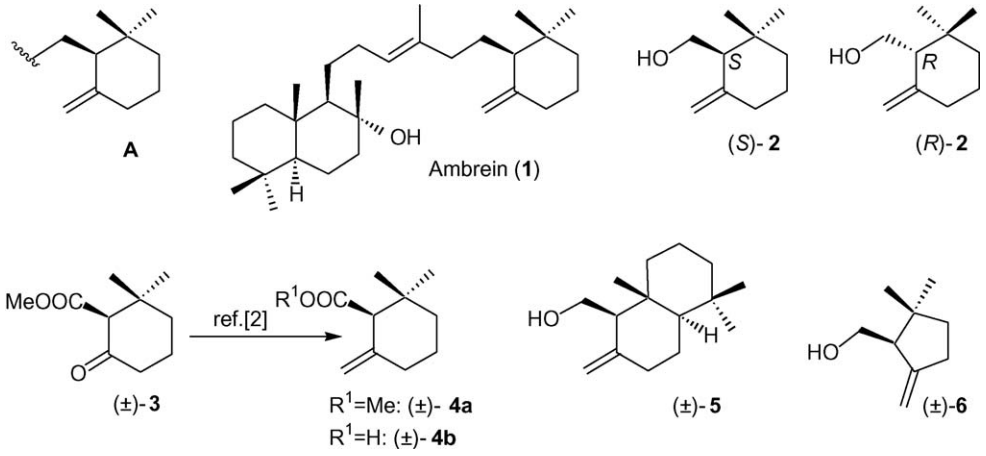
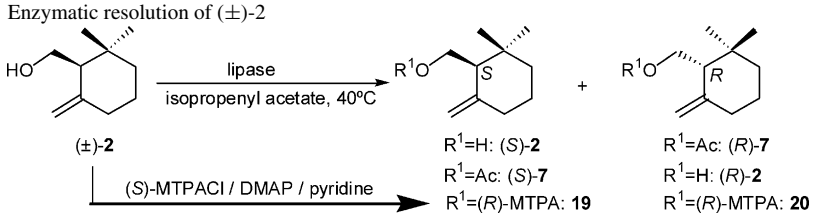


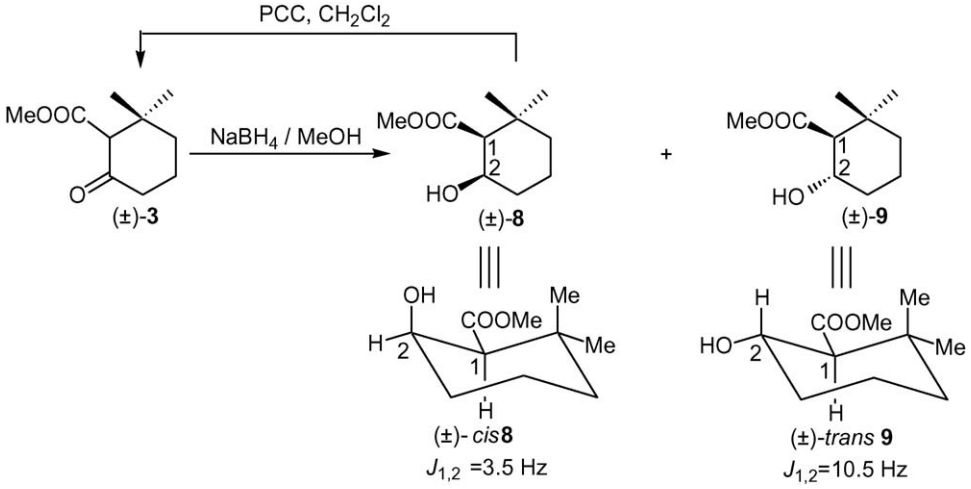
Scheme 1.

Table 1
Enzymatic resolution of (±)-2

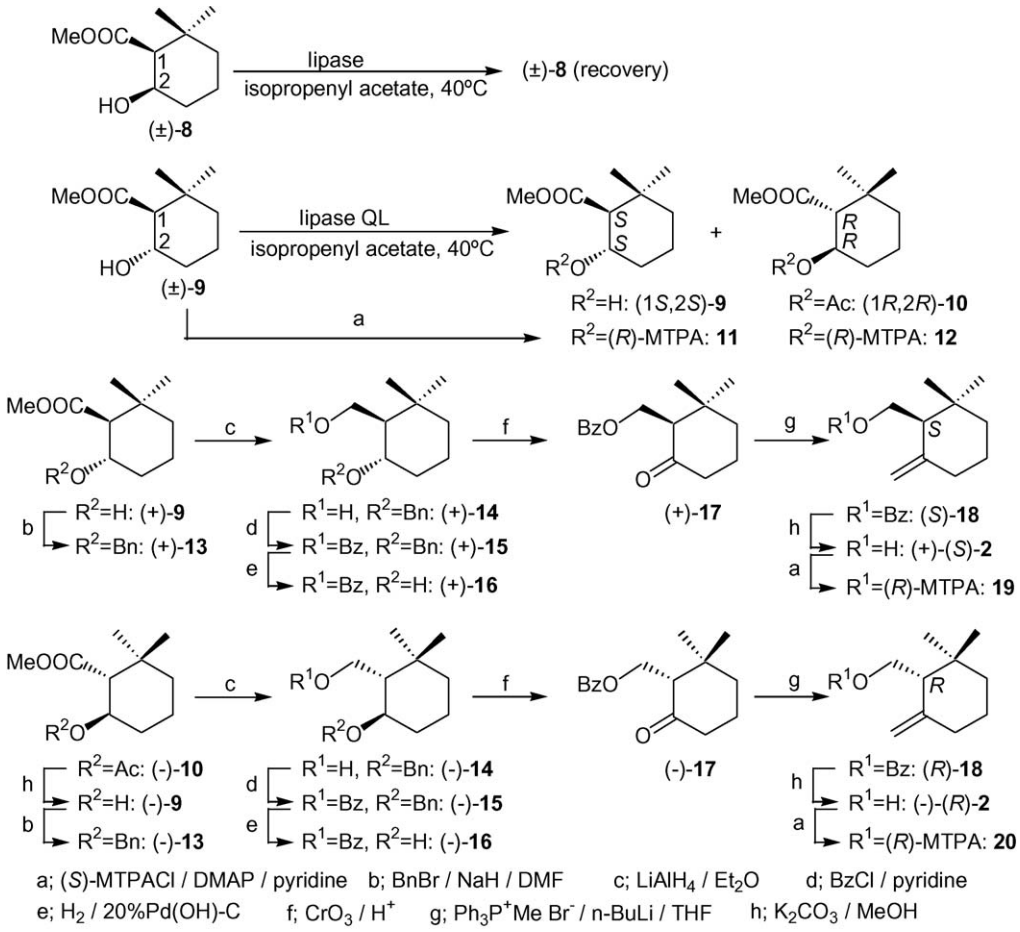


Entry	(±)-2 (g)	Lipase	Time (d)	Products (%, % ee)
1	0.2	Amano P	8	(±)-**2** (72% recovery)
2	0.2	QL	2	(*S*)-(+)-**2** (24, 26) (*R*)-(−)-**7** (30,13)
3	0.2	MY-30	8	(*R*)-(−)-**2** (68, 3) (*S*)-(+)-**7**(12,32)
4	1.08	Amano AK	8	(*S*)-(+)-**2**(60, 14) (*R*)-(−)-**7** (30,30)

cyclogeraniols (**2**) as shown in Scheme 3. Benzylation of (1*S*, 2*S*)-**9** followed by reduction gave a primary alcohol (+)-**14**, which was subjected to benzoylatin to afford a benzoate (+)-**15**. Catalytic hydrogenation of (+)-**15** followed by oxidation gave a ketone (+)-**17**, which was subjected to Wittig reaction to provide an exo-methylene compound (*S*)-**18**. Finally, deprotection of (*S*)-**18** gave the (*S*)-γ-cyclogeraniol (**2**), of which optical purity was found to be 90% ee after conversion to the corresponding (*R*)-MTPA ester (**19**). Synthetic (*S*)-γ-cyclogeraniols (**2**) was identical with the reported (*S*)-γ-cyclogeraniol (**2**) [2].



Scheme 2.



Scheme 3.

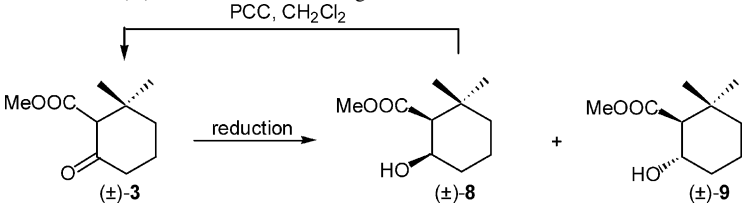
On the other hand, (1*R*, 2*R*)-acetate **10** was also converted to (*R*)-γ-cyclogeraniol (**2**) in the same way as for (1*S*, 2*S*)-**9**. In order to improve the yield of the desired (±)-*trans*-**9**, reduction of (±)-**3** was carried out under various conditions as shown in Table 2. Conversion of the undesired (±)-*cis*-**8** to the desired (±)-*trans*-**9** by oxidation is also mentioned later in the text (Scheme 2).

2. Methods and results

2.1. Analytical methods

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR

Table 2
Reduction of (±)-3 with five kinds of reagents



Entry	Reagent	Conditions	Yield ((±)-**8** + (±)-**9**), ratio ((±)-**8**:(±)-**9**)
1	$NaBH_4$ (4 equiv.)	MeOH, −78 °C, 30 min	(±)-**8** (72%), (±)-**9** (20%), ((±)-**8**:(±)-**9** = 1:0.27)
2	Me_4NBH_4 (4 equiv.)	MeOH, −78 to 5 °C, 5 h	95% (1:1.7)
3	Bu_4NBH_4(4 equiv.)	MeOH, −78 to −60 °C, 3 h	88% (1:2.7)
4	$Zn(BH_4)_2$(4 equiv.)	Et_2O, −78 °C, 30 min	86% (1:0.02)
5	L-selectride(2 equiv.)	THF, −78 °C, 1 h	89% ((±)-**8**)
6	Bu_4NBH_4(2.5 equiv.)	MeOH, −78 °C, 1 h	(±)-**8**(21%), (±)-**9** (69%), ((±)-**8**:(±)-**9** = 1:3.3)

L-selectride: $LiB[CH(CH_3)C_2H5]_3H$. Ratio ((±)-8:(±)-9) was determined by ^{1}H NMR analysis.

spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

2.2. Materials

2.2.1. (*R*)-MTPA ester formation from (±)-**2**

For the purpose of determining the enantiomeric excess (ee) of the enzymatic reaction products, racemate (±)-**2** was converted to the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*R*)-MTPA esters). To a stirred solution of (±)-**2** (20 mg, 0.13 mmol) in pyridine (0.5 ml) was added (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [7,8] ((*S*)-MTPACl; 53 mg, 0.21 mmol) and DMAP (20 mg), and the whole was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to give a diastereomeric mixture of (*S*)-(*R*)- and (*R*)-(*R*)-MTPA esters (**19** + **20**; 37 mg, 75%). The signals due to the exo-methylene proton appeared in distinctly different fields ((*R*)-MTPA esters from (±)-**2**: δ 4.78 (s) and 4.74 (s)). FAB MS *m*/*z*: 370 (M^+). (*R*)-MTPA esters (**19** + **20**): the detailed NMR data of (*R*)-MTPA esters (**19** and **20**) were shown individually later in the text.

2.2.2. Enantioselective acetylation of (±)-**2**

From a screening experiment using various kinds of lipase, the effective lipases were as follows: Amano P from *Pseudomonas* sp. QL from *Alcaligenes* sp, MY-30 from *Candida rugosa*, Amano AK from *Pseudomonas* sp. Enzymatic acetylation of (±)-**2** was performed under the following condition (entries 1–4). Determination of the enantiomeric excess (ee) of the enzymatic reaction products was carried out by the method mentioned in Section 2.2.1 in this text. A mixture of the unchanged product (**2**; ca. 20 mg) and (*S*)-MTPACl (50 mg) in pyridine (0.5 ml) was stirred at room temperature for 12 h. The reaction mixture was worked up in the same way as for (±)-**2** to give the corresponding (*R*)-MTPA ester, of which ee was calculated by NMR analysis. A mixture of the acetate (**7**; ca. 20 mg) and K_2CO_3 (20 mg) in MeOH (1 ml) was stirred for 12 h. The reaction mixture was diluted with H_2O and extracted with Et_2O, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude **2**, which was treated with (*S*)-MTPACl (50 mg) in pyridine (0.5 ml) with stirring at room temperature for 12h. The reaction mixture was worked up in the same way as (±)-**2** to give the corresponding (*R*)-MTPA ester, of which ee was calculated by NMR analysis. The results were shown in Table 1.

(1) Table 1, entry 1: A suspension of (±)-**2** (200 mg, 1.29 mmol), isopropenyl acetate (30 ml) and lipase Amano P (200 mg) was incubated at 40 °C for 8 d. After the reaction mixture was filtered, the precipitate was washed with *i*-Pr_2O. The combined organic layer was evaporated to give a residue which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to afford (+)-**2** (148 mg 74% recovery).

(2) Table 1, entry 2: A suspension of (±)-**2** (200 mg, 1.29 mmol), isopropenyl acetate (30 ml) and lipase QL (200 mg) was incubated at 40 °C for 2 d. After the reaction mixture was filtered, the precipitate was washed with *i*-Pr_2O. The combined organic layer was evaporated to give a residue which was chromatographed on silica gel (10 g) to afford (*R*)-**7** (77 mg, 30%, 13% ee) from *n*-hexane:AcOEt = 50:1 elution and (*S*)-**2** (48 mg, 24%, 26% ee) from *n*-hexane:AcOEt = 20:1 elution.

(3) Table 1, entry 3: A suspension of (±)-**2** (200 mg, 1.29 mmol), isopropenyl acetate (30 ml) and lipase MY-30 (200 mg) was incubated at 40 °C for 8 d. The reaction mixture was worked up in the same way as entry 2 to give (*R*)-**2** (136 mg, 68%, 3% ee) and (*S*)-**7** (31 mg, 12%, 32% ee). A mixture of the acetate (**7**; 31 mg) and K_2CO_3 (30 mg) in MeOH (1.5 ml) was stirred for 12 h. The reaction mixture was diluted with H_2O and extracted with Et_2O, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude **2**, which was chromatographed on silicagel (5 g, *n*-hexane:AcOEt = 20:1) to provide (+)-**2** (15 mg, $[\alpha]_D^{24}$ + 8.5 (*c* = 0.24, $CHCl_3$)); corresponds to 32% ee). The sign of (+)-**2** was consistent with that ($[\alpha]_D^{21}$ + 23.7 (*c* = 0.31, $CHCl_3$) of the reported (*S*)-**2**,[2] thence the absolute configuration of the acetate (**7**) was determined to be S.

(4) Table 1, entry 4: A suspension of (±)-**2** (1.08 g, 7.03 mmol), isopropenyl acetate (50 ml) and lipase Amano AK (1.0 g) was incubated at 40 °C for 8 d. The reaction mixture was worked up in the same way as entry 2 to give (*S*)-**2** (648 mg, 60%, $[\alpha]_D^{25}$ + 3.7 (*c* = 1.03, $CHCl_3$); corresponds to 14% ee) and (*R*)-**7** (412 mg, 30%, 30% ee). The sign of specific rotation of the enzymatic product (*S*)-**2** was the same as that ($[\alpha]_D^{21}$ + 23.7 (*c* = 0.31, $CHCl_3$) of the reported (*S*)-**2** [2]. (*S*)-**2**: IR(neat): 3391 cm^{-1}; ^1H NMR spectra were identical with those of the reported (*S*)-**2** [2]. FAB MS *m*/*z*: 155 (M^+ + 1). (*R*)-**7**: IR (neat): 1738, 1238 cm^{-1}; ^1H NMR: δ 0.84 (3H, s), 0.96 (3H, s), 1.29 (1H, dt, *J* = 6, 13 Hz), 1.41 (1H, dt, *J* = 6.5, 13 Hz), 1.49–1.56 (2H, m), 1.99 (3H, s), 2.00–2.08 (1H, m), 2.11–2.19 (2H, m), 4.19 (1H, dd, *J* = 9, 11 Hz), 4.23 (1H, dd, *J* = 5, 11 Hz), 4.57 (1H, br.s), 4.79 (1H, br.s). ^{13}C NMR: δ 21.2 (q), 23.5 (t), 25.2 (q), 28.9 (q), 33.5 (t), 34.4 (s), 38.0 (t), 52.2 (d), 62.9 (t), 109.6 (t), 146.9 (s), 170.9 (s). FAB MS *m*/*z*: 197 (M^+ + 1).

2.2.3. Reduction of (±)-**3** using various kinds of reducing reagents

Reduction of (±)-**3** using five kinds of reducing reagents was carried out and results were shown in Table 2.

(1) Table 2, entry 1: To a solution of (±)-**3** (0.506 g, 2.7 mmol) in MeOH (7 ml) was added $NaBH_4$ (0.427 g, 4 equiv.) at −78 °C for 30 min. The reaction mixture was quenched with acetone (2 ml) and diluted with brine, extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 5:1) to give (±)-*cis*-**8** (0.371 g, 72%) as a colorless oil and (±)-*trans*-**9** (0.100 g, 20%) as a colorless oil in elution order. (±)-*cis*-**8**: IR (neat): 3445, 1733 cm^{-1}; ^1H NMR: δ 0.95 (3H, s), 1.01 (3H, s), 1.01 (1H, ddd, J = 4, 8.5, 13 Hz), 1.36–1.52 (2H, m), 1.55–1.62 (1H, m), 1.72–1.82 (1H, m), 1.86–1.95 (1H, m), 2.40 (1H, d, J = 3.5 Hz), 2.84 (1H, br.s, disappeared with D_2O), 3.67 (3H, s), 4.05 (1H, quintette, J = 7 Hz). ^{13}C NMR: δ 18.4(t), 26.5(q), 30.2(q), 30.9(t), 33.8(s), 37.6(t), 51.2(q), 55.7(d), 67.7(d), 174.8(s). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.19; H, 10.02%. FAB MS *m*/*z*: 187 (M^+ + 1). (±)-*trans*-**9**: IR (neat): 3445, 1735 cm^{-1}; ^1H NMR: δ 0.88 (3H, s), 0.97 (3H, s), 1.12–1.24 (2H, m), 1.35 (1H, ddd, J = 1, 4, 13 Hz), 1.46 (1H, ddt, J = 4, 9, 13 Hz), 1.54–1.62 (1H, m), 1.98 (1H, ddd, J = 1, 4, 13 Hz), 2.10 (1H, d, J = 10.5 Hz), 3.68 (3H, s), 3.97 (1H, dt, J = 4, 11 Hz), 4.72 (1H, br.s, disappeared with D_2O). ^{13}C NMR: δ 20.5(t), 21.6(q), 31.4(q) 34.3(t), 35.0(s), 40.5(t), 51.3(q), 61.4(d), 68.5(d), 173.9(s). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.50; H, 9.81%. FAB MS *m*/*z*: 187 (M^+ + 1).

(2) Table 2, entry 2: To a suspension of Me_4NBH_4 (0.980 g, 4 equiv.) in MeOH (7 ml) was added a solution of (±)-**3** (0.506 g, 2.7 mmol) in MeOH (2 ml) at −78 °C to 5 °C for 5.5 h. The reaction mixture was quenched with acetone (1 ml) and diluted with brine, extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 5:1) to give a mixture (0.486 g, 95%) of (±)-*cis*-**8** and (±)-*trans*-**9** as a colorless oil. The ratio of (±)-*cis*-**8**:(±)-*trans*-**9** was determined by a comparison of the integral intensity due to C(1)-protons of (±)-**8** (2.40, d) and (±)-**9** (2.10, d) and found to be 1:1.7 by NMR analysis.

(3) Table 2, entry 3: To a suspension of Bu_4NBH_4 (2.865 g, 4 equiv.) in MeOH (10 ml) was added a solution of (±)-**3** (0.511 g, 2.8 mmol) in MeOH (2 ml) at −78 °C to −60 °C for 3 h. The reaction mixture was quenched with acetone (2 ml) and diluted with brine, extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 5:1) to give a mixture (0.453 g, 88%) of (±)-*cis*-**8** and (±)-*trans*-**9** as a colorless oil. The ratio of (±)-*cis*-**8**:(±)-*trans*-**9** was found to be 1:2.7 by NMR analysis.

(4) Table 2, entry 4: A solution of $Zn(BH_4)_2$ in dry Et_2O (5.2 ml, 4 equiv.) (prepared from 0.69 M solution of $ZnCl_2$ in Et_2O (80 ml) and $NaBH_4$ in Et_2O (300 ml)) [9,10] was added a solution of (±)-**3** (0.509 g, 2.8 mmol) in Et_2O (2 ml) at −78 °C for 30 min. The reaction mixture was quenched with acetone (2 ml) and acidified with 2M aqueous HCl, extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 5:1) to give a mixture (0.443 g, 86%) of (±)-*cis*-**8** and (±)-*trans*-**9** as a colorless oil. The ratio of (±)-*cis*-**8**:(±)-*trans*-**9** was found to be 1:0.02 by NMR analysis.

(5) Table 2, entry 5: To a solution of (±)-**3** (0.501 g, 2.7 mmol) in THF (2 ml) was added 1 M solution of L-selectride in THF (5.4 ml, 2 equiv.) at −78 °C for 1 h. The reaction mixture was quenched with acetone (1 ml) and acidified with 2 M aqueous HCl, extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 5:1) to give (±)-*cis*-**8** (0.450 g, 89%) as a colorless oil.

(6) Table 2, entry 6: To a suspension of Bu_4NBH_4 (34.92 g, 2.5 equiv.) in MeOH (450 ml) was added a solution of (±)-**3** (10.03 g, 54.4 mmol) in MeOH (10 ml) at −78 °C for 1 h. The reaction mixture was quenched with acetone (10 ml) and evaporated under reduced pressure. The resulting residue was diluted with brine, extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (300 g, *n*-hexane:AcOEt = 5:1) to give (±)-*cis*-**8** (2.129 g, 21%) as a colorless oil and (±)-*trans*-**9** (6.996 g, 69%) a colorless oil in elution order.

2.2.4. *Synthesis of (±)-β-keto ester (**3**) from cis-**8***

To a solution of (±)-*cis*-**8** (8.16 g, 44 mmol) in CH_2Cl_2 (250 ml) was added pyridinium chlorochromate (PCC; 24.24 g, 2.5 equiv.) and Florisil (30 g) at room temperature for 4 h. The reaction mixture was filtered with the aid of celite to afford the filtrate. The filtrate was evaporated to a residue, which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 10:1) to give (±)-**3** (7.66 g, 95%) as a colorless oil. The NMR spectrum of (±)-**3** was identical with that of the reported (±)-**3** [2].

2.2.5. *(R)-MTPA Ester formation from (±)-**9***

For the purpose of determining the enantiomeric excess (ee) of the enzymatic reaction products, racemate (±)-**9** was converted to the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*R*)-MTPA esters. To a stirred solution of (±)-**9** (22 mg, 0.12 mmol) in pyridine (0.5 ml) was added (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [7,8] ((*S*)-MTPACl; 46 mg, 0.18 mmol) and DMAP (20 mg), and the whole was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to give a diastereomeric mixture of (*S*)-(*R*)- and (*R*)-(*R*)-MTPA esters (**11** + **12**; 36 mg, 77%). The signals due to the ester methyl protons appeared in distinctly different fields ((*R*)-MTPA esters from (±)-**9**: δ 4.78 (s) and 4.74 (s)). The detailed NMR data

of (*R*)-MTPA esters (**11** and **12**) were shown individually at rate in the text. FAB MS *m/z*: 403 ($M^+ + 1$). (*R*)-MTPA esters (**11** and **12**): ^{1}H NMR: δ 0.94 (3H, s), 0.95 (3H, s), 0.98 (3H, s), 1.00 (3H, s), 1.12–1.37 (4H, m), 1.39–1.45 (2H, m), 1.51–1.69 (4H, m), 2.21–2.32 (2H, m), 2.38 (1H, d, J = 11.5 Hz), 2.39 (1H, d, J = 11.5 Hz), 3.42 (3H, s), 3.45 (3H, d, J = 3 Hz), 3.48 (3H, d, J = 3 Hz), 3.58 (3H, s), 5.33–5.41 (2H, m), 7.34–7.39 (6H, m), 7.42–7.49 (4H, m).

2.2.6. Enantioselective acetylation of (±)-9

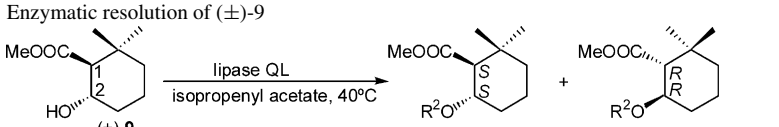
From a screening experiment using various kinds of lipase, the effective lipases were found to be PL-266 from *Alcaligenes* sp. Enzymatic acetylation of (±)-**9** was performed under the following condition (Table 2, entries 1–3). Determination of the enantiomeric excess (ee) of the enzymatic reaction products was carried out by the method mentioned in Section 2.2.1 in this text. A mixture of the unchanged product (**9**; ca. 20 mg) and (*S*)-MTPACl (50 mg) in pyridine (0.5 ml) was stirred at room temperature for 12 h. The reaction mixture was worked up in the same way as (±)-**9** to give the corresponding (*R*)-MTPA ester, of which ee was calculated by NMR analysis. A mixture of the acetate (**10**; ca. 20 mg) and K_2CO_3 (20 mg) in MeOH (1 ml) was stirred for 12 h. The reaction mixture was diluted with H_2O and extracted with Et_2O, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude **9**, which was treated with (*S*)-MTPACl (50 mg) in pyridine (0.5 ml) with stirring at room temperature for 12h. The reaction mixture was worked up in the same way as (±)-**9** to give the corresponding (*R*)-MTPA ester, of which ee was calculated by NMR analysis. The results were shown in Table 3.

(1) Table 3, entry 1: A suspension of (±)-**9** (2.0 g, 11 mmol), isopropenyl acetate (50 ml) and lipase QL (2.0 g) was stirred at 40 °C for 2 d. After the reaction mixture was filtered, the precipitate was washed with *i*-Pr_2O. The combined organic layer was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane:AcOEt = 20:1) to afford an acetate (1*R*, 2*R*)-**10** (1.099 g, 45%, >99% ee) from *n*-hexane:AcOEt = 20:1 elution and unchanged (+)-(1*S*, 2*S*)-**9** (0.990 g, 49%, $[\alpha]_D^{28}$ + 23.4 (c = 0.98, $CHCl_3$); corresponds to 97% ee) from *n*-hexane:AcOEt = 5:1 elution. The 20 mg of (+)-**9** was converted to the corresponding (*R*)-MTPA ester (**11**) in the same way as (±)-**9**. Enantiomeric excess (ee) was determined by a comparison of the integral intensity due to ester methyl groups of (*S*)-(*S*)-(*R*)-MTPA ester (**11**) (3.42, s) and (*R*)-(*R*)-(*R*)-MTPA ester **12** (3.58, s). (*R*)-MTPA ester (**11**): ^{1}H NMR: δ 0.94 (3H, s), 0.98 (3H, s), 1.20–1.37 (2H, m), 1.43 (1H, ddt, J = 1, 3, 13 Hz), 1.52–1.70 (2H, m), 2.29 (1H, dq, J = 4, 12 Hz), 2.38 (1H, d, J = 11.5 Hz), 3.42 (3H, s), 3.48 (3H, d, J = 3 Hz), 5.37 (1H, dt, J = 5, 11.5 Hz), 7.33–7.40 (3H, m), 7.43–7.56 (2H, m). A mixture of the acetate (**10**; 1.099 g) and K_2CO_3 (10 g) in MeOH (10 ml) was stirred for 12 h. The reaction mixture was diluted with H_2O and extracted with Et_2O, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude **9**, which was chromatographed on silicagel (30 g, *n*-hexane:AcOEt = 5:1) to provide (−)-**9** (0.991 g, $[\alpha]_D^{28}$ − 23.5 (c = 0.98, $CHCl_3$); corresponds to >99% ee). The 20 mg of (−)-**9** was converted to the corresponding (*R*)-MTPA ester (**12**) in the same way as (±)-**9**. (*R*)-MTPA ester (**12**): ^{1}H NMR: δ 0.95 (3H, s), 1.00 (3H, s), 1.11–1.25 (2H, m), 1.42 (1H, ddt, J = 1, 3, 13 Hz), 1.51–1.69 (2H, m), 2.24 (1H, dq, J = 4, 12 Hz), 2.39 (1H, d, J = 11.5 Hz), 3.45 (3H, d, J = 3Hz), 3.58 (3H, s), 5.37 (1H, dt, J = 4.5, 11.5 Hz), 7.33–7.40 (3H, m), 7.41–7.43 (2H, m). (+)-(1*S*, 2*S*)-**9** and (−)-**9**; ^{1}H NMR spectra were identical with those of the above-mentioned (±)-**9**. (1*R*, 2*R*)-**10**: IR(neat): 1739, 1240 cm^{-1}; ^{1}H NMR: δ 0.92 (3H, s), 0.98 (3H, s), 1.06–1.24 (2H, m), 1.38 (1H, ddt, J = 1, 3, 13 Hz), 1.46–1.62 (2H, m), 1.93 (3H, s), 2.09–2.15 (1H, m), 2.29 (1H, d, J = 11.5 Hz), 3.63 (3H, s), 5.07 (1H, dd, J = 5, 11.5 Hz). ^{13}C NMR: δ 20.0(t), 21.2(q), 21.6(q), 31.1(t), 31.1(q), 35.1(s), 40.2(t), 51.2(q), 58.0(d), 71.6(d), 169.8(s), 172.2(s). FAB MS *m/z*: 229 ($M^+ + 1$).

(2) Table 3, entry 2: A suspension of (±)-**9** (20 g, 108 mmol), isopropenyl acetate (15 g, 153 mmol) and lipase QL (15 g) in isopropyl ether (500 ml) was stirred at 40 °C for 2 d. After the reaction mixture was filtered, the precipitate was washed with *i*-Pr_2O. The combined organic layer was evaporated to give a residue, which was chromatographed on silica gel (500 g) to give (1*R*, 2*R*)-**10** (11.277 g, 46%, >99% ee) from *n*-hexane:AcOEt = 20:1 elution and (1*S*, 2*S*)-**9** (9.687 g, 48%, 96% ee) from *n*-hexane:AcOEt = 5:1 elution.

(3) Table 3, entry 3: A suspension of (1*S*, 2*S*)-**9** (96% ee, 9.687 g), isopropenyl acetate (6.7 g, 68 mmol) and lipase QL (2 g) in isopropyl ether (300 ml) was incubated at 40 °C for

Table 3
Enzymatic resolution of (±)-9



R^2=H: (1*S*,2*S*)-**9** R^2=Ac: (1*R*,2*R*)-**10**
R^2=Ac: (1*S*,2*S*)-**10** R^2=H: (1*R*,2*R*)-**9**
R^2=(*R*)-MTPA: **11** R^2=(*R*)-MTPA: **12**

Entry	(±)-9 (g)	Time (d)	Products (%, % ee)
1	2.0	2	(1*S*, 2*S*)-**9** (49,97), (1*R*,2*R*)-**10** (45, >99)
2	20	2	(1*S*, 2*S*)-**9** (48, 96), (1*R*,2*R*)-**10** (46, >99)
3	(1*S*, 2*S*)-**9** 9.7 (96% ee)	2	(1*S*, 2*S*)-**9** (87, >99), (1*R*,2*R*)-**10** (2, 78)

2 d. After the reaction mixture was filtered, the precipitate was washed with *i*-Pr_2O. The combined organic layer was evaporated to give a residue, which was chromatographed on silica gel (300 g) to give (1*R*, 2*R*)-**10** (0.237 g, 2%, 78% ee) from *n*-hexane:AcOEt = 20:1 elution and (1*S*, 2*S*)-**9** (8.428 g, 87%, >99% ee) from *n*-hexane:AcOEt = 5:1 elution.

*2.2.7. Synthesis of (S)-γ-cyclogeraniol (**2**) from (+)-(1S, 2S)-**9***

(1) After NaH (0.234 g 9.8 mmol) was washed with *n*-hexane, (+)-(1*S*, 2*S*)-**9** (>99% ee, 0.497 g, 2.7 mmol) and benzyl bromide (0.575 g, 3.3 mmol) were added to a suspension of NaH in DMF (5 ml). The reaction mixture was stirred for 6.5 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (+)-**13** (0.789 g) as a colorless oil. (+)-**13**; $[\alpha]_D^{25}$ + 27.6 (c = 0.84, $CHCl_3$), IR(neat): 1734 cm^{-1}; ^{1}H NMR: δ 0.94 (3H, s), 0.96 (3H, s), 1.10–1.23 (2H, m), 1.33–1.40 (1H, m), 1.44 (1H, tq, J = 4, 14 Hz), 1.56–1.64 (1H, m), 2.13–2.20 (1H, m), 2.66 (1H, d, J = 11 Hz), 3.66 (3H, s), 3.77 (1H, dt, J = 5, 11 Hz), 4.45 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 7.19–7.31 (5H, m). ^{13}C NMR: δ 20.3(t), 21.7(q), 31.2(q), 31.3(t), 34.8(s), 40.5(t), 51.1(q), 59.7(d), 71.6(t), 76.6(d), 127.2(d), 127.4(d), 127.4(d), 128.0(d), 128.0(d), 138.7(s), 173.6(s). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.17; H, 9.03%. FAB MS *m/z*: 277 (M^+ + 1). To a suspension of $LiAlH_4$ (0.209 g, 5.5 mmol) in Et_2O (7 ml) was added a solution of (+)-**13** (0.789 g) in Et_2O (5 ml) and the reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with ice water and 2 M aqueous NaOH, and filtered with the aid of celite to give the filtrate. The filtrate was extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to afford (+)-**14** (0.537 g, 81% from (+)-**9**) as a colorless oil. (+)-**14**; $[\alpha]_D^{25}$ + 80.4 (c = 0.52, $CHCl_3$), IR(neat): 3514 cm^{-1}; ^{1}H NMR: δ 0.72 (3H, s), 1.01 (3H, s), 1.16–1.32 (3H, m), 1.32–1.46 (2H, m), 1.62 (1H, diquintette, J = 3, 13 Hz), 2.23 (1H, dq, J = 4, 6 Hz), 3.45 (1H, br.s, disappeared with D_2O), 3.55 (1H, dt, J = 4, 11 Hz), 3.58 (1H, dd, J = 8, 6 Hz), 3.77 (1H, d, J = 11 Hz), 4.43 (1H, d, J = 11 Hz), 4.69 (1H, d, J = 11 Hz), 7.25–7.69 (5H, m). ^{13}C NMR: δ 20.5(t), 20.9(q), 30.7(q), 31.4(t), 34.2(s), 41.5(t), 54.1(d), 64.5(t), 70.5(t), 82.4(d), 127.67(d), 127.71(d), 127.71(d), 128.4 (d), 128.4 (d), 137.9(s). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.10; H, 9.97%. FAB MS *m/z*: 249 (M^+ + 1).

(2) A mixture of (+)-**14** (0.207 g, 0.83 mmol) and benzoyl chloride (0.133 g, 0.95 mmol) in pyridine (3 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (+)-**15** (0.257 g) as a colorless oil. (+)-**15**; $[\alpha]_D^{32}$ + 65.8 (c = 0.89, $CHCl_3$), IR(neat): 1712 cm^{-1}; ^{1}H NMR: δ 1.00 (3H, s), 1.01 (3H, s), 1.26–1.44 (3H, m), 1.52 (1H, dq, J = 3.5, 13 Hz), 1.63–1.74 (2H, m), 2.30–2.36 (1H, m), 3.65 (1H, dt, J = 4.5, 11 Hz), 4.44 (1H, d, J = 11 Hz), 4.58 (1H, dd, J = 2.5, 11.5 Hz), 4.66 (1H, d, J = 11 Hz), 4.70 (1H, dd, J = 5, 11.5 Hz), 7.16–7.27 (3H, m), 7.27–7.32 (2H, m), 7.42–7.47 (2H, m), 7.54–7.60 (1H, m), 8.01–8.05 (2H, m). ^{13}C NMR: δ 20.4(t), 22.3(q), 31.2(q), 31.9(t), 34.7(s), 41.8(t), 51.3(d), 62.5(t), 71.0(t), 75.4(d), 127.2(d), 127.6(d), 127.6(d), 128.09(d), 128.09(d), 128.14(d), 128.14(d), 129.3(d), 129.3(d), 130.5(s), 132.5(d), 138.4(s), 166.3(s). FAB MS *m/z*: 353 (M^+ + 1). A suspension of (+)-**15** (0.257 g) and 20% Pd(OH)–C (56 mg) in AcOEt (3 ml) was subjected to a catalytic hydrogenation under hydrogen atmosphere for 9 h and the reaction mixture was filtered with the aid of celite to give the filtrate. The filtrate was evaporated to give a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 10:1) to afford (+)-**16** (0.188 g, 86% from (+)-**14**) as a colorless oil. (+)-**16**; $[\alpha]_D^{32}$ + 12.7 (c = 0.26, $CHCl_3$), IR(neat): 3429, 1716 cm^{-1}; ^{1}H NMR: δ 0.92 (3H, s), 1.07 (3H, s), 1.20–1.50 (5H, m), 1.52–1.59 (1H, m), 1.99–2.07 (1H, m), 2.84 (1H, br.s, disappeared with D_2O), 3.67 (1H, dt, J = 4.5, 11 Hz), 4.43 (1H, dd, J = 3.5, 12 Hz), 4.79 (1H, dd, J = 4, 12 Hz), 7.40 (2H, t, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 8.00 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 20.5(t), 22.0(q), 31.0(q), 34.6(s), 35.5(t), 41.9(t), 53.6(d), 63.2(t), 68.2(d), 128.2(d), 128.2(d), 129.4(d), 129.4(d), 129.8(s), 132.9(d), 166.8(s). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.99; H, 8.59%. FAB MS *m/z*: 263 (M^+ + 1).

(3) To a solution of (+)-**16** (0.241 g, 0.92 mmol) in acetone (5 ml) was added Jones reagent (2 ml) at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was treated with *iso*-PrOH and diluted with H_2O, extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (+)-**17** (0.184 g, 77%) as a colorless oil. (+)-**17**; $[\alpha]_D^{32}$ + 6.9 (c = 0.95, $CHCl_3$), IR(neat): 1710 cm^{-1}; ^{1}H NMR: δ 0.86 (3H, s), 1.18 (3H, s), 1.60 (1H, ddt, J = 1, 4, 13 Hz), 1.73 (1H, dt, J = 4, 13 Hz), 1.78–1.99 (2H, m), 2.28–2.44 (2H, m), 2.66 (1H, dd, J = 4, 8 Hz), 4.44 (1H, dd, J = 4, 11 Hz), 4.63 (1H, dd, J = 8, 11 Hz), 7.38 (2H, t, J = 8 Hz), 7.51 (1H, t, J = 8 Hz), 7.96 (2H, d, J = 8 Hz). ^{13}C NMR: δ 22.1(q), 23.0(t), 29.7(q), 39.1(s), 39.9(t), 41.3(t), 59.3(d), 60.6(t), 128.1(d), 128.1(d), 129.4(d), 129.4(d), 130.0(s), 132.7(d), 166.3(s), 209.2(s). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.83; H, 8.15%. FAB MS *m/z*: 261 (M^+ + 1).

(4) To a suspension of methyltriphenylphosphonium bromide (0.554 g, 1.5 mmol) in THF (3 ml) was added 1.6 M *n*-butyllithium in hexane solution (0.46 ml, 0.73 mmol) under argon atmosphere at −78 °C and the reaction mixture was

stirred for 30 min. A solution of (+)-**17** (0.158 g, 0.61 mmol) in THF (2.5 ml) was added to the above-mentioned reaction mixture and the reaction mixture was stirred for 30 min at −78 °C, for 20 min at −20 °C, for 30 min at 0 °C, and for 1 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (*S*)-**18** (0.076 g, 48%) as a colorless oil. (*S*)-**18**; IR(neat): 1719 cm^{-1}; ^1H NMR: δ 0.93 (3H, s), 1.02 (3H, s), 1.31–1.37 (1H, m), 1.45–1.53 (1H, m), 1.53–1.62 (2H, m), 2.08 (1H, dt, *J* = 6, 11 Hz), 2.21 (1H, dt, *J* = 6, 13 Hz), 2.31 (1H, dd, *J* = 5, 10 Hz), 4.42 (1H, dd, *J* = 10, 11 Hz), 4.52 (1H, dd, *J* = 5, 11 Hz), 4.68 (1H, s), 4.83 (1H, s), 7.40 (2H, t, *J* = 8 Hz), 7.52 (1H, t, *J* = 8 Hz), 7.79 (2H, d, *J* = 8 Hz). ^{13}C NMR: δ 23.5(t), 25.5(q), 28.9(q), 33.4(t), 34.5(s) 37.9(t), 52.4(d), 63.4(t), 109.9(t), 128.1(d), 128.1(d), 129.4(d), 129.4(d), 130.4(s), 132.6(d), 146.9(s), 166.4(s). FAB MS *m/z*: 259 ($M^+ + 1$).

(5) To a suspension of $LiAlH_4$ (0.013 g, 0.35 mmol) in Et_2O (2 ml) was added a solution of (*S*)-**18** (0.054 g, 0.21 mmol) in Et_2O (2.5 ml) and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with ice-water and 2 M aqueous NaOH, and filtered with the aid of celite to give the filtrate. The filtrate was extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to afford (+)-**2** (0.024 g, 74%) as a colorless oil. (+)-**2**; $[\alpha]_D^{25}$ + 21.3 (*c* = 0.97, $CHCl_3$), ^1H NMR spectrum of (+)-**2** was identical with that of the reported (+)-**2**. [2] The 10 mg of (+)-2 was converted to the corresponding (*R*)-MTPA ester (**19**) in the same way as for (±)-**2**. (*R*)-MTPA ester (**19**): ^1H NMR: the optical purity of the synthesized (+)-**2** was estimated to be 90% ee after conversion of the corresponding (*R*)-MTPA ester (**19**). (*R*)-MTPA ester (**19**): ^1H NMR δ 0.85 (3H, s), 0.95 (3H, s), 1.27–1.33 (1H, m), 1.38–1.45 (1H, m), 1.47–1.59 (2H, m), 1.99–2.06 (1H, m), 2.09–2.17 (1H, m), 2.22 (1H, dd, *J* = 4.5, 9.5 Hz), 3.51 (3H, br.s), 4.43 (1H, dd, *J* = 4.5, 11 Hz), 4.49 (1H, d, *J* = 11 Hz), 4.55 (1H, br.s), 4.78 (1H, br.s), 7.33–7.40 (3H, m), 7.49–7.52 (2H, m).

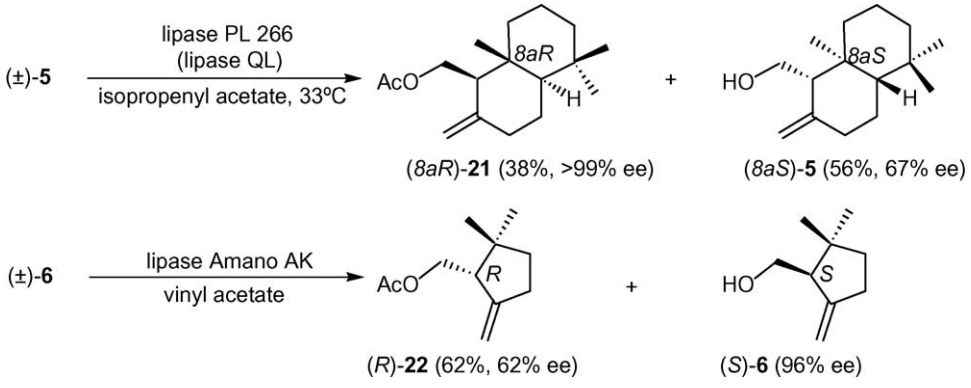
2.2.8. Synthesis of (R)-γ-cyclogeraniol (2) from (−)-(1R, 2R)-9

Synthesis of (*R*)-cyclogeraniol (**2**) from (−)-(1*R*, 2*R*)-**9** was carried out in the same way as for conversion of (+)-(1*S*, 2*S*)-**9** to (*S*)-cyclogeraniol (**2**). Spectral data of (−)-**13**, (−)-**14**, (−)-**15**, (−)-**16**, (−)-**17**, (*R*)-**18**, and (−)-(*R*)-**2** were identical with those of (+)-**13**, (+)-**14**, (+)-**15**, (+)-**16**, (+)-**17**, (*S*)-**18**, and (+)-(*S*)-**2** except for the sign of specific rotation, respectively. The 10 mg of (−)-**2** was converted to the corresponding (*R*)-MTPA ester (**20**) in the same way as for (±)-**2**. (*R*)-MTPA ester (**19**): ^1H NMR: the optical purity of the synthesized (−)-(*R*)-**2** ($[\alpha]_D^{24}$ − 23.0 (*c* = 0.31, $CHCl_3$)) was estimated to be 90% ee after conversion of the corresponding (*R*)-MTPA ester (**20**). (*R*)-MTPA ester (**20**): ^1H NMR δ 0.84 (3H, s), 0.96 (3H, s), 1.26–1.33 (1H, m), 1.36–1.44 (1H, m), 1.49–1.56 (2H, m), 1.97–2.04 (1H, m), 2.10–2.18 (1H, m), 2.23 (1H, t, *J* = 7 Hz), 3.50 (3H, br.s), 4.48 (2H, d, *J* = 7 Hz), 4.55 (1H, br.s), 4.74 (1H, br.s), 7.33–7.40 (3H, m), 7.48–7.52 (2H, m).

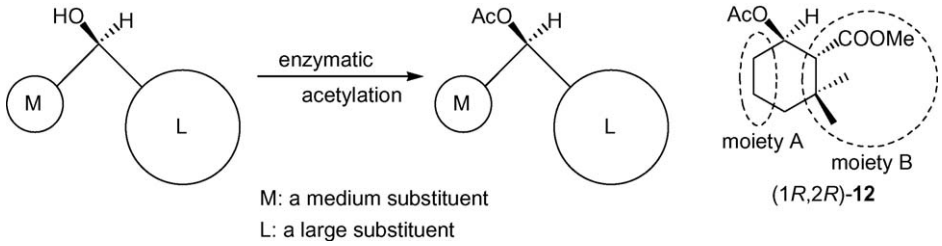
3. Discussion

Previously, we reported that lipase-catalyzed enantioselective acetylation of (±)-(**5**) gave an alcohol (8*aS*)-**5** (56%, 67% ee) and an acetate (8*aR*)-**21** (38%, >99% ee). The 67% ee of (8*aS*)-**5** was again subjected to enzymatic acetylation to afford an optically pure (8*aS*)-**5** (>99% ee).[3] Moreover, lipase-catalyzed enantioselective acetylation of (±)-(**6**) gave an alcohol (*S*)-**6** (96% ee) and an acetate (*R*)-**22** (62%, 62% ee) [4] (Scheme 4).

In the present case, the results were not satisfactory from the standpoint of yield and ee. It was apparent that optical purities of the enzymatic reaction products ((*S*)-**2** and (*R*)-**7**) were dependent upon subtle structural differences between (±)-(**2**) and (±)-(**5**) or between (±)-(**2**) and (±)-(**6**). Surprisingly, enzyme-assisted acetylation of (±)-*cis*-β-hydroxy ester (**8**) did not entirely occur, while lipase-catalyzed acetylation of (±)-*trans*-β-hydroxy ester (**9**) provided satisfactory results (Table 3, entries 1–3) from the standpoint of yield and ee. The result of the enantioselective acetylation of (±)-**9** with the lipase PL-266 from *Alcaligenesis* sp. was explained by applying the reported empirical rules [11] to predict which enantiomer possessing a secondary hydroxyl group reacts faster in lipase-catalyzed reactions by comparing the relative sizes of substituents at the



Scheme 4.



Scheme 5.

stereocenter. The moiety A seems to be a relatively small-sized substituent (M) and the moiety B appears to be a relatively large-sized substituent (L). (Scheme 5.) It is worth noting that the preparation of both an alcohol (1*S*, 2*S*)-**9** and an acetate (1*R*, 2*R*)-**10** possessing high enantiomeric excess was achieved based on lipase-catalyzed acetylation.

4. Conclusion

The lipase QL from *Alcaligenes* sp.-catalyzed enantioselective acetylation of the (±)-(1,2)-*trans*-6,6-dimethyl-2-hydroxyhexane-1-carboxylate (**9**) was carried out and an alcohol (1*S*, 2*S*)-**9** and an acetate (1*R*, 2*R*)-**10** possessing high enantiomeric excess (>99% ee), respectively, were obtained. Both the alcohol (1*S*, 2*S*)-**9** and the acetate (1*R*, 2*R*)-**10** were converted to the (*S*)- and (*R*)-γ-cyclogeraniols (**2**), respectively.

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