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Synthesis of versatile chiral intermediate for drimane sesquiterpenes and labdane diterpenes based on enzymatic resolution

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Abstract

The lipase PL-266 from *Alcaligenes* sp. catalyzed enantioselective acetylation of the decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-ethylene acetal (±)-**6** was carried out and an acetate (8a*S*)-**7** and an alcohol (8a*R*)-**6** possessing high enantiomeric excess (>98% ee), respectively, were obtained. Both (8a*S*)-**7** and (8a*R*)-**6** were converted to the (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylates (**4**), respectively. The (8a*R*)-β-keto ester (**4**) was converted to the important intermediate (8a*R*)-**16** for the synthesis of natural hyatellaquinone (**3**).

Keywords: Lipase; *Alcaligenes* sp.; Enzymatic resolution; Enantioselective acetylation; Formal synthesis

1. Introduction

The chiral structural unit (**1**) possessing decaline ring system attached with three methyl groups is the important nuclei found in a variety of natural products such as drimane sesquiterpenes and labdane diterpenes. Among them, widendiol A (**2**) [1] was reported to inhibit the cholesteryl ester transferprotein (CETP) and hyatellaquinone (**3**) was reported to inhibit the reverse transcriptase of human immunodeficiency virus (HIV) [2]. The key optically active intermediate for the synthesis of the above mentioned natural products appeared to be (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylate (**4**), [3] or (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol (**5**) [3] (Scheme 1).

Enzymatic syntheses of the same type chiral synthons as **4** were reported [4,5]. The synthesis of (8a*S*)- and (8a*R*)-**5** was reported based on the enantioselective acetylation of (±)-**5** in the presence of vinyl acetate using lipase, however, enantiomeric excess (ee) of (8a*S*)-**5** is 53% [6]. In order to overcome this low enantioselectivity, alternative substrate (±)-**6** possessing ethylene acetal moiety at C(2)-position was selected for the enantioselective acylation based on enzymatic function (Scheme 2). In this paper, we describe the synthesis of the versatile chiral synthons, β-keto esters (8a*S*)- and (8a*R*)-**4** based on the kinetic resolution of the decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-ethylene acetal (±)-**6** using lipase and their application to the formal synthesis of hyatellaquinone (**3**) from (8a*R*)-**4**. The summary of the determinations of both absolute structure of enzymatic reaction products and an ee of enzymatic reaction products is shown in Scheme 2 below in the text. The formal synthesis of hyatellaquinone (**3**) from the versatile chiral synthon (8a*R*)-**4** derived from the enzymatic reaction product (8a*R*)-**6** is shown in Scheme 3.

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

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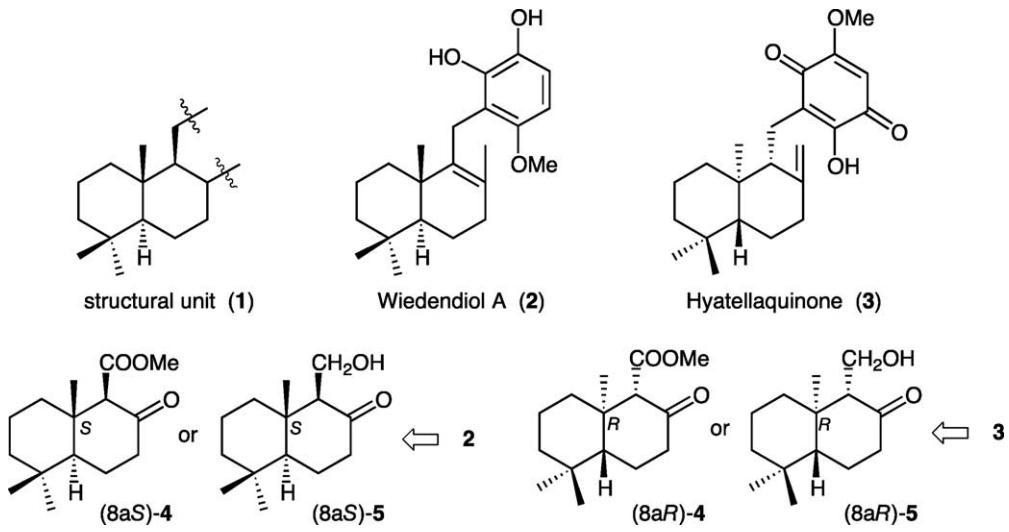
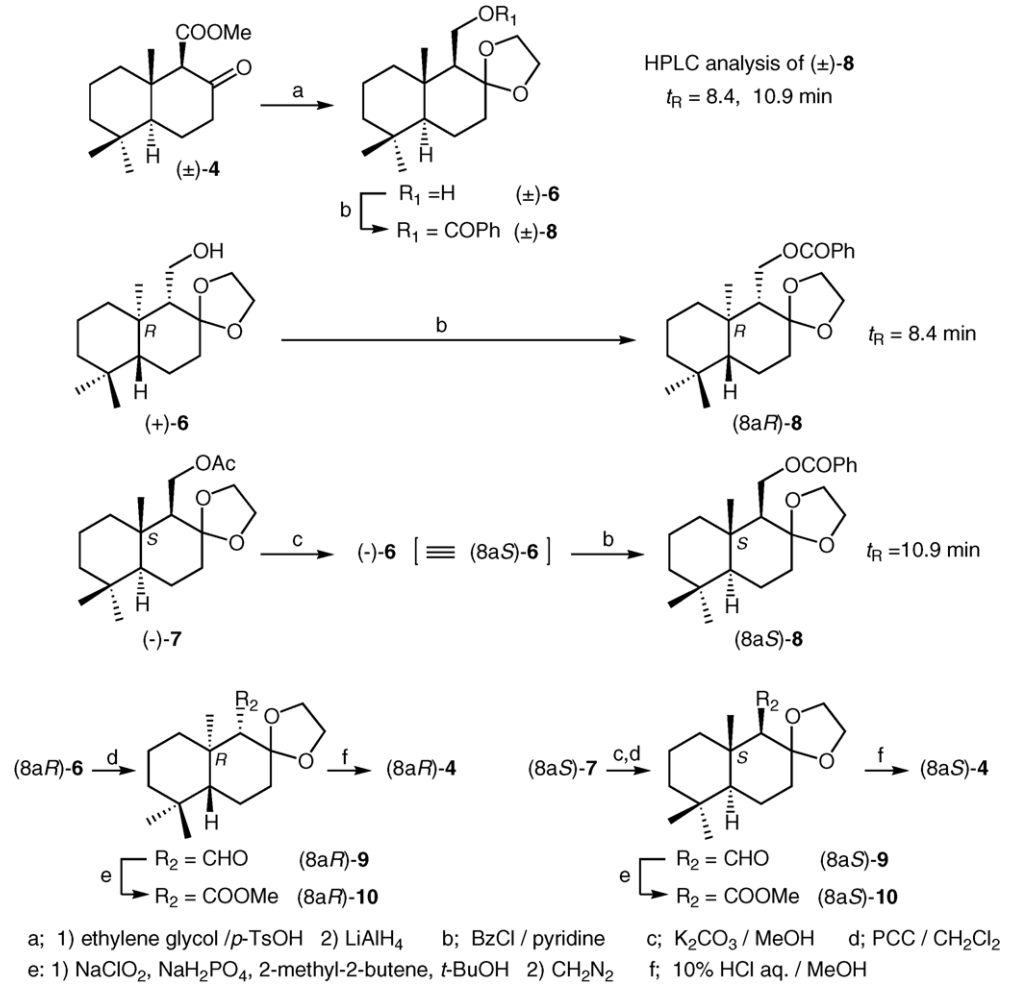
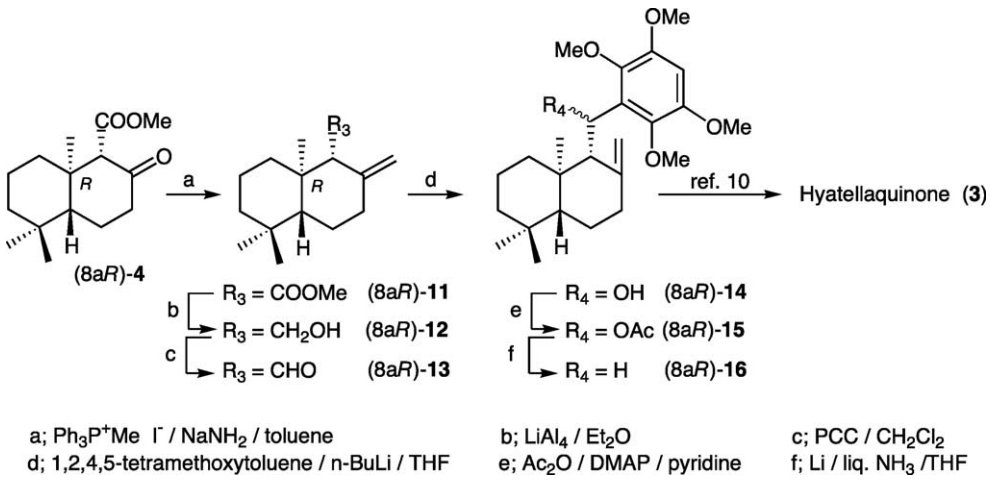


Scheme 1.



Scheme 2.



Scheme 3.

and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and 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. The HPLC system was composed of a detector (UV detector SSC-5200, Senshu), pump (SSC-3210, Senshu) and integrator (chromatocorder SIC 21). HPLC analysis conditions were as follows; column: CHIRALPAC AD, UV at 254 nm, flow rate; 1 ml/min. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

2.2. Synthesis of substrate (±)-6 for enzymatic acetylation

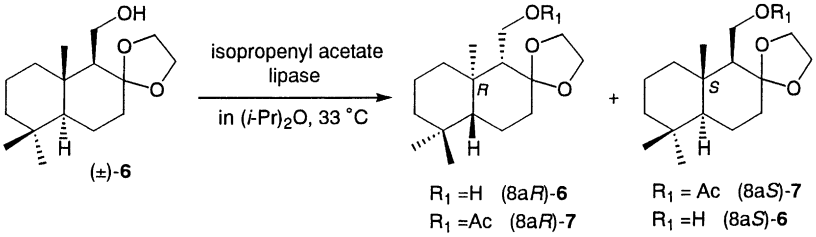
(1) To a solution of (±)-β-keto ester (**4**) [7] (2.00 g, 7.93 mmol) in benzene (40 ml) was added ethylene glycol (1.97 g, 31.7 mmol) and *p*-toluenesulfonic acid (0.151 g, 0.794 mmol) and the whole mixture was stirred for 12 h at reflux. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude acetal, which was used without further purification.

(2) To a suspension of $LiAlH_4$ (0.902 g, 23.8 mmol) in dry ether (15 ml) was added dropwise a solution of the crude acetal in dry ether (30 ml) at 0 °C. After the reaction mixture was stirred at room temperature for 5 h, acetone (5 ml) and water were added to the reaction mixture. The precipitate was filtered with the aid of Celite and the filtrate was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt (30:1)) to give colorless crystals (±)-**6** (1.93 g, 91%). Recrystallization of (±)-**6** from *n*-hexane to afford colorless needles. (±)-**6**: m.p., 109.5–110.5 °C; IR (KBr): 3526 cm^{-1}; ^{1}H NMR: δ 0.82 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.94–0.98 (1H, m), 1.10–1.22 (2H, m), 1.36–1.48 (4H, m), 1.54–1.65 (3H, m), 1.82–1.85 (1H, m), 1.93–1.96 (1H, m), 2.99 (1H, br. s), 3.61 (1H, d, J = 10.5 Hz), 3.84 (1H, dd, J = 11.0, 8 Hz), 3.89–3.94 (2H, m), and 4.02–4.11 (2H, m). ^{13}C NMR: δ 15.6 (q), 18.6 (t), 19.7 (t), 21.7 (q), 33.3 (s), 33.7 (q), 35.6 (t), 38.4 (s), 39.5 (t), 41.9 (t), 55.0 (d), 58.9 (d), 59.0 (t), 62.8 (t), 65.1 (t), and 112.4 (s). Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.36; H, 10.61%. FAB MS *m/z*: 269 (M^++1).

2.3. Benzoylation of (±)-6 for the determination of ee (synthesis of (±)-8)

A solution of (±)-**6** (0.055 g, 0.2 mmol) and benzoyl chloride (0.035 g, 0.25 mmol) in pyridine (2 ml), was stirred for 1 h at room temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with ether. The ether layer was washed with 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 = 40:1) to give a colorless oil (±)-**8** (0.075 g, 97%). (±)-**8**: IR (neat): 1719 cm^{-1} (OCOPh); ^{1}H NMR: δ 0.86 (3H, s), 0.91 (3H, s), 1.02 (3H, s), 1.03–1.04 (1H, m), 1.16–1.26 (2H, m), 1.40–1.48 (4H, m), 1.54–1.64 (2H, m), 1.79–1.82 (1H, m), 1.91–1.97 (2H, m), 3.80–3.86 (1H, m), 3.91–3.98 (2H, m), 4.03–4.08 (1H, m), 4.36 (1H, dd, J = 11.5, 5 Hz), 4.40 (1H, dd, J = 12, 3.5 Hz), 7.40–7.46 (2H, m), 7.51–7.58 (1H, m), and 8.02–8.07 (2H, m). FAB MS *m/z*: 372 (M^+), 373 (M^++1). HPLC (column; CHIRALPAC AD (4.6 × 250 mm), eluent; *n*-hexane:EtOH = 200:1, flow rate; 1 ml/min, detection; UV at 254 nm): t_R = 8.4, 10.9 min.

Table 1
Lipase catalyzed enantioselective acetylation of (±)-**6**



Entry	Substrate (g)	Lipase	Time (d)	Product	
1	(±)-**6** (0.268)	PL-266	1	(8a*R*)-**6** (48%, 98% ee)	(8a*S*)-**7** (47%, 94% ee)
2	(±)-**6** (0.268)	Amano P	7	(8a*R*)-**6** (57%, 53% ee)	(8a*S*)-**7** (36%, 99% ee)
3	(±)-**6** (0.268)	MY-30	7	(8a*S*)-**6** (60%, 8% ee)	(8a*R*)-**7** (34%, 17% ee)
4	(±)-**6** (5.40)	PL-266	1	(8a*R*)-**6** (49%, 98% ee)	(8a*S*)-**7** (49%, 99% ee)

*2.4. Enantioselective acetylation of (±)-***6**

From a screening experiment using various kinds of lipase, the effective lipases were as follows: MY-30 from *Candida rugosa*, PL-266 from *Alcaligenes* sp., Amano P from *Pseudomonas* sp. Enzymatic acetylation of (±)-**6** 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 below in this text. The results were shown in Table 1.

(1) Table 1, entry 1: A suspension of (±)-**6** (0.268 g, 1.0 mmol), isopropenyl acetate (0.5 g, 5 mmol) and lipase PL-266 (0.3 g) in diisopropyl ether (30 ml) was incubated at 33 °C for 1 d. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give **7** (0.146 g, 47%, 94% ee) from *n*-hexane:AcOEt = 20:1 eluate and **6** (0.129 g, 48%, 98% ee) from *n*-hexane/EtOAc = 10:1 eluate, respectively.

(2) Table 1, entry 2: A suspension of (±)-**6** (0.268 g, 1.0 mmol), isopropenyl acetate (0.5 g, 5 mmol) and lipase Amano P (0.3 g) in diisopropyl ether (30 ml) was incubated at 33 °C for 7 d. The reaction mixture was worked up in the same way as entry 1 to give **7** (0.112 g, 36%, 99% ee) and **6** (0.153 g, 57%, 53% ee).

(3) Table 1, entry 3: A suspension of (±)-**6** (0.268 g, 1.0 mmol), isopropenyl acetate (0.5 g, 5 mmol) and lipase MY-30 (0.3 g) in diisopropyl ether (30 ml) was incubated at 33 °C for 7 d. The reaction mixture was worked up in the same way as entry 1 to give **7** (0.106 g, 34%, 17% ee) and **6** (0.161 g, 60%, 8% ee).

(4) Table 1, entry 4: A suspension of (±)-**6** (5.40 g, 20.1 mmol), isopropenyl acetate (10 g, 100 mmol) and lipase PL-266 (6 g) in diisopropyl ether (500 ml) was incubated at 33 °C for 1 d. The reaction mixture was worked up in the same way as entry 1 to give (−)-**7** (3.06 g, 49%, $[\alpha]_D^{26}$ − 2.2 (c = 0.98, $CHCl_3$); corresponds to 99% ee) as a colorless oil and (+)-**6** (2.64 g, 49%, $[\alpha]_D^{25}$ + 7.8 (c = 1.0, $CHCl_3$); corresponds to 98% ee). (−)-**7**; IR (neat): 1737 cm^{-1}; ^1H NMR: δ 0.83 (3H, s), 0.89 (3H, s), 0.94 (3H, s), 0.95–0.98 (1H, m), 1.06–1.21 (2H, m), 1.37–1.47 (4H, m), 1.52–1.64 (2H, m), 1.66–1.71 (1H, m), 1.75 (1H, t, J = 4 Hz), 1.90–1.94 (1H, m), 2.02 (3H, s), 3.77–3.83 (1H, m), 3.90–3.96 (2H, m), 3.99–4.05 (1H, m), 4.08 (1H, dd, J = 11.5, 4.5 Hz), and 4.18 (1H, dd, J = 12.0, 4 Hz). ^{13}C NMR: δ 15.0 (q), 18.5 (t), 19.8 (t), 21.3 (q), 21.8 (q), 33.2 (s), 33.7 (q), 35.8 (t), 38.6 (s), 39.4 (t), 41.8 (t), 54.8 (d), 56.4 (d), 60.9 (t), 63.6 (t), 64.9 (t), 110.4 (s), and 171.3 (s). Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.74; H, 9.77%. FAB MS m/z: 310 (M^+), 311 (M^++1). (+)-**6**; m.p., 110 °C (colorless needles from *n*-hexane). The spectral data (IR (KBr), ^1H and ^{13}C NMR, FAB MS) were identical with those of (±)-**6**.

*2.5. Determination of both absolute structure and ee of the enzymatic reaction products (−)-***7** *and (+)-***6**

(1) To a solution of (+)-**6** (Table 1, entry 4; 0.051 g, 0.19 mmol) in MeOH (2 ml) was added 10% aqueous HCl (1 ml) and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with saturated 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 residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt (10:1)) to give (+)-**5** (0.039 g, 92%). (+)-**5**: $[\alpha]_D^{22}$ + 33.6 (c = 0.99, $CHCl_3$); spectral data (^1H and ^{13}C NMR, $[\alpha]_D$) of (+)-**5** were identical with those ($[\alpha]_D^{24}$ + 38.5 (c = 1.00, $CHCl_3$) of the reported (8a*R*)-**5** [8]. It means that the configuration of C(8a)-position of (+)-**6** was found to be *R*.

(2) A solution of (+)-**6** (Table 1, entry 4; 0.030 g, 0.11 mmol) and benzoyl chloride (0.047 g, 0.34 mmol) in pyridine (1 ml) was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**8** (2.3.) to give (8a*R*)-**8** (0.041 g, 96%) as colorless oil. The spectral data (IR (neat), ^1H NMR, FAB MS)

were identical with those of (±)-**8**. HPLC analysis (column; CHIRALPAC AD (4.6 × 250 mm), eluent; *n*-hexane:EtOH = 200:1, flow rate; 1 ml/min, detection; UV at 254 nm) of the present benzoate **8** indicated the retention time (t_R = 8.4 min), which is attributed to that of (8a*R*)-**8** derived from (+)-**6** (Scheme 2).

(3) A mixture of (−)-**7** (Table 1, entry 4; 0.033 g, 0.11 mmol) and K_2CO_3 (0.029 g, 0.21 mmol) in MeOH (2 ml) 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 brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue ((8a*S*)-**6**), which was used for the next benzoylation without further purification. A solution of the crude (8a*S*)-**6** and benzoyl chloride (0.045 g, 0.32 mmol) in pyridine (1 ml) was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**8** to give (8a*S*)-**8** (0.037 g, 93% from (−)-**7**) as a colorless oil. The spectral data (IR (neat), ^{1}H NMR, FAB MS) were identical with those of (±)-**8**. HPLC analysis (column; CHIRALPAC AD (4.6 × 250 mm), eluent; *n*-hexane:EtOH = 200:1, flow rate; 1 ml/min, detection; UV at 254 nm) of the present benzoate **8** indicated the retention time (t_R = 10.9 min), which is attributed to that of (8a*S*)-**8** derived from (−)-**7**. Thence, the absolute configuration of C(8a)-position of (−)-**7** was found to be *S* (Scheme 2).

2.6. Determination of both the absolute structure and ee of the enzymatic reaction products

In Section 2.5, the relationship between the absolute configuration of C(8a)-position of the enzymatic reaction product and the retention time of benzoate **8** derived from enzymatic reaction product was found to be apparent. The remainder of three enzymatic reaction products (Table 1, entries 1–3) was converted to the corresponding benzoate **8**.

(1) The alcohol **6** (Table 1, entries 1–3; ca. 0.03 g) corresponding to the starting material was converted to the corresponding benzoate **8** in the same way as for (±)-**8**. Thus obtained benzoate was subjected to HPLC analysis and both the absolute structure and ee of the alcohol **6** (Table 1, entries 1–3) was confirmed as shown in Table.

(2) Alkaline treatment of the acetate **7** (Table 1, entries 1–3; ca. 0.03 g) followed by benzolylation to afford the corresponding benzoate **8**. Thus obtained benzoate was subjected to HPLC analysis and both the absolute structure and ee of the alcohol **6** (Table 1, entries 1–3) was confirmed as shown in Table 1.

2.7. Synthesis of β*-keto ester (8aR)-***4** *from enzymatic reaction product (8aR)-***6**

(1) To a solution of (8a*R*)-**6** (0.160 g, 0.59 mmol) in CH_2Cl_2 (5 ml) was added PCC (0.257 g, 1.19 mmol) and Florisil (0.26 g), and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was filtered with the aid of Celite and the filtrate was evaporated to give a crude residue. It was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 80:1) to give colorless crystals (8a*R*)-**9** (0.136 g, 86%), which was recrystallized from *n*-hexane to afford colorless prisms. (8a*R*)-**9**: m.p., 103 °C; IR (KBr): 1717 cm^{-1}; $[\alpha]_D^{24}$ + 13.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ 0.84–0.95 (1H, m), 0.86 (3H, s), 0.89 (3H, s), 1.14–1.22 (2H, m), 1.25 (3H, s), 1.35 (1H, dd, *J* = 13.5, 5 Hz), 1.39–1.46 (2H, m), 1.51–1.69 (4H, m), 1.95 (1H, t, *J* = 13.3 Hz), 2.09 (1H, d, *J* = 4.5 Hz), 3.76–3.81 (1H, m), 3.90–3.95 (1H, m), 4.01–4.05 (2H, m), and 9.83 (1H, d, *J* = 4.5 Hz). ^{13}C NMR: δ 16.2 (q), 18.1 (t), 19.7 (t), 21.8 (q), 33.2 (s), 33.6 (q), 36.1 (t), 39.4 (s), 39.8 (t), 41.6 (t), 54.3 (d), 63.4 (t), 65.1 (t), 67.6 (d), 109.7 (s), and 205.1 (d). Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.09; H, 9.94%. FAB MS *m*/*z*: 267 (M^++1).

(2) To a solution of (8a*R*)-**9** (0.136 g, 0.51 mmol) and 2-methyl-2-butene (1.0 ml, 9.4 mmol) in *tert*-BuOH (15 ml) was added $NaClO_2$ (80%, 0.58 g, 6.72 mmol) and NaH_2PO_4 (0.43 g, 3.6 mmol) in H_2O (4 ml) at room temperature, the whole was stirred for 15 h at room temperature. The reaction mixture was acidified with aqueous 2 M HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was treated with CH_2N_2–ether solution. The reaction mixture was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane:AcOEt = 100:1) to give colorless crystals (8a*R*)-**10** (0.125 g, 83%), which was recrystallized from *n*-hexane to afford colorless needles. (8a*R*)-**10**: m.p., 111.5–112.5 °C; $[\alpha]_D^{25}$ − 31.7 (*c* = 0.98, $CHCl_3$); IR (KBr): 1732 cm^{-1}; ^{1}H NMR: δ 0.85 (3H, s), 0.89 (3H, s), 0.90–0.97 (1H, m), 1.15–1.28 (2H, m), 1.23 (3H, s), 1.33–1.68 (7H, m), 1.85 (1H, dt, *J* = 12.5, 3 Hz), 2.51 (1H, s), 3.63 (3H, s), 3.71–3.76 (1H, m), 3.82–3.87 (1H, m), 3.91–3.96 (1H, m), and 4.06–4.10 (1H, m). ^{13}C NMR: δ 14.7 (q), 18.4 (t), 20.0 (t), 21.5 (q), 33.1 (s), 33.5 (q), 37.6 (t), 39.0 (s), 39.7 (t), 41.8 (t), 50.8 (q), 54.7 (d), 62.6 (d), 63.8 (t), 65.4 (t), 109.0 (s), and 170.9 (s). Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.48; H, 9.42%. FAB MS *m*/*z*: 297 (M^++1).

(3) To a solution of (8a*R*)-**10** (0.117 g, 0.39 mmol) in MeOH (10 ml) was added 10% aqueous HCl (2 ml) and the whole mixture 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 residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt (20:1)) to give (8a*R*)-**4** (0.09 g, 90%). (8a*R*)-**4**: $[\alpha]_D^{23}$ + 57.0 (*c* = 0.90, $CHCl_3$); spectral data (^{1}H and ^{13}C NMR, $[\alpha]_D$) were identical with those ($[\alpha]_D^{22}$ + 55.0 (*c* = 1.05, $CHCl_3$)) of the reported (8a*R*)-**4** [8] (Scheme 2).

2.8. Synthesis of β-keto ester (8aS)-**4** from enzymatic reaction product (8aS)-**7**

(1) To a solution of (8a*S*)-**6** (0.254 g, 0.94 mmol) derived from (8a*S*)-**7** in CH_2Cl_2 (10 ml) was added PCC (0.408 g, 1.89 mmol) and Florisil (0.715 g), and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was worked up in the same way as for (8a*R*)-**6** to afford (8a*S*)-**9** (0.217 g, 86%). (8a*S*)-**9**: $[\alpha]_D^{24}$ − 12.0 (c = 1.0, $CHCl_3$); Spectral data (^{1}H and ^{13}C NMR, FAB MS) were identical with those of the reported (8a*S*)-**9**.

(2) To a solution of (8a*S*)-**9** (0.217 g, 0.81 mmol) and 2-methyl-2-butene (1.5 ml, 14.1 mmol) in *tert*-BuOH (15 ml) was added $NaClO_2$ (80%, 0.92 g, 8.14 mmol) and NaH_2PO_4 (0.683 g, 5.7 mmol) in H_2O (3 ml) at room temperature, the whole was stirred for 15 h at room temperature. The reaction mixture was worked up in the same way as for (8a*R*)-**9** to afford (8a*S*)-**10** (0.207 g, 86%). (8a*S*)-**10**: $[\alpha]_D^{24}$ + 30.9 (c = 0.96, $CHCl_3$); Spectral data (^{1}H and ^{13}C NMR, FAB MS) were identical with those of the reported (8a*R*)-**10**.

(3) To a solution of (8a*S*)-**10** (0.193 g, 0.65 mmol) in MeOH (10 ml) was added 10% aqueous HCl (2 ml) and the whole mixture was stirred for 12 h at room temperature. The reaction mixture was worked up in the same way as for (8a*R*)-**10** to afford (8a*S*)-**4** (0.152 g, 93%). (8a*S*)-**4**: $[\alpha]_D^{23}$ − 57.4 (c = 0.99, $CHCl_3$); spectral data (^{1}H and ^{13}C NMR, $[\alpha]_D$) were identical with those ($[\alpha]_D^{22}$ − 54.3 (c = 0.82, $CHCl_3$)) of the reported (8a*S*)-**4** [8] (Scheme 2).

2.9. Synthesis of (8aR)-albicanol (**12**)

(1) A solution of $Ph_3P^+Me\ Br^-$ (10.5 g, 29.4 mmol) and $NaNH_2$ (1.08 g, 27.7 mmol) in toluene (100 ml) was heated under reflux for 6 h under argon. After the suspension had settled, the decanted yellow solution ($Ph_3P{=}CH_2$) was poured into (8a*R*)-**4** (1.46 g, 5.79 mmol) at 0 °C. The whole was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (60 g, *n*-hexane:AcOEt = 50:1) to give a crude (8a*R*)-**11** (1.42 g).

(2) To a solution of the crude (8a*R*)-**11** (1.42 g) in Et_2O (30 ml) at 0 °C was added $LiAlH_4$ (0.293 g, 7.72 mmol) and the whole was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl and extracted with Et_2O. The ether layer was washed brine and dried over $MgSO_4$. Evaporation of the organic layer was evaporated to give a crude residue. It was chromatographed on silica gel (50 g, *n*-hexane:AcOEt = 5:1) to give a colorless oil which was crystallized from *n*-hexane to provide a colorless needles (8a*R*)-**12** (1.10 g, 85% from (8a*R*)-**4**). (8a*R*)-**12**: m.p., 67–68 °C; $[\alpha]_D^{24}$ − 12.7 (c = 0.74, $CHCl_3$); IR (KBr): 3358 cm^{-1} (OH); ^{1}H NMR: δ 0.72 (3H, s), 0.80 (3H, s), 0.88 (3H, s), 1.11–2.45 (12H, m), 3.75 (1H, dd, J = 11, 9.5 Hz), 3.82 (1H, dd, J = 11, 4 Hz), 4.64 (1H, d, J = 1.5 Hz), and 4.93 (1H, d, J = 1.5 Hz). ^{13}C NMR: δ 15.4 (q), 19.4 (t), 21.9 (q), 24.3 (t), 33.6 (s), 33.7 (q), 38.0 (t), 39.0 (s), 39.1 (t), 42.1 (t), 55.2 (d), 58.8 (t), 59.2 (d), 106.2 (t), and 147.7 (s). Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79%. Found: C, 81.19; H, 11.97. EI MS m/z: 222 (M^+).

2.10. Synthesis of (8aR)-**16** (synthetic intermediate for hyatellaquinone (**3**))

(1) To a solution of (8a*R*)-**12** (0.440 g, 1.98 mmol) in CH_2Cl_2 (10 ml) was added PCC (1.28 g, 5.94 mmol) and Florisil (1.3 g), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered with the aid of Celite and the filtrate was evaporated to give a crude residue. It was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 100:1) to give a crude (8a*R*)-**13** (0.337 g).

(2) To a solution of 1,2,4,5-tetramethoxybenzene [9] (0.91 g, 4.59 mmol) in THF (15 ml) was added dropwise *n*-BuLi (1.58 M in *n*-hexane, 2.4 ml, 3.79 mmol) at 0 °C. After the reaction mixture was stirred for 30 min at the same temperature, a solution of the above mentioned (8a*R*)-**13** (0.337 g) in THF (5 ml) was added dropwise. After the reaction mixture was stirred for 1 h at room temperature, a saturated aqueous NH_4Cl solution was added, and then the resulting mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (40 g, *n*-hexane:AcOEt (50:1)) to give a crude oil (1.19 g) including (8a*R*)-**14**. It was used for the next reaction without further purification.

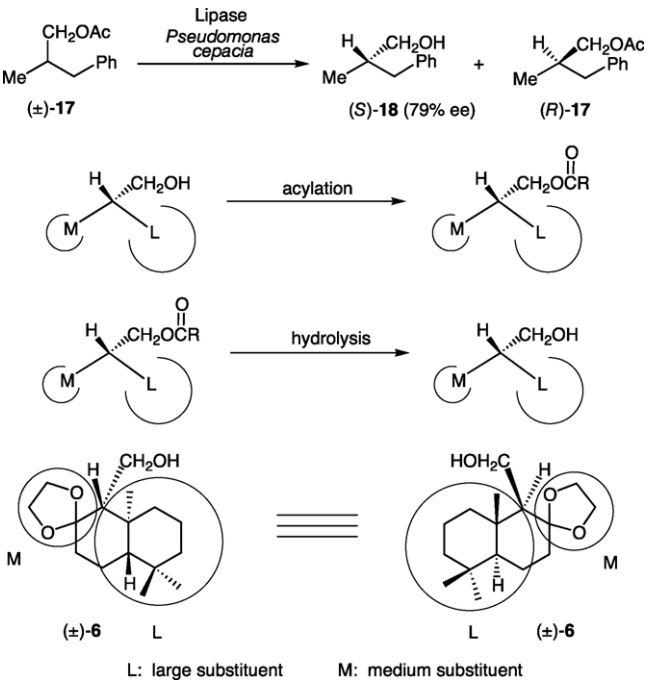
(3) To a solution of the above-mentioned crude oil (1.19 g) in pyridine (15 ml) was added Ac_2O (1.56 g, 15.3 mmol) and 4-dimethylaminopyridine (4-DMAP, 0.037 g, 0.3 mmol), the reaction mixture was stirred for 9 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g *n*-hexane:AcOEt (10:1)) to give a crude oil (0.761 g) including a diastereomeric mixture of acetate (8a*R*)-**15**.

(4) A suspension of Li (0.212 g, 30.5 mmol) in liquid NH_3 (50 ml) was stirred for 5 min at −78 °C. A solution of the above-mentioned crude oil (0.761 g) in THF (15 ml) was added to the above reaction mixture, and the whole mixture was stirred for 30 min at −78 °C. After an excess of NH_3 was removed at room temperature, the reaction mixture was diluted with aqueous NH_4Cl solution and extracted with Et_2O. The organic layer was washed with

brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt (80:1)) to give a colorless oil (8a*R*)-**16** (0.449 g, 56% overall yield from (8a*R*)-**12**). Recrystallization of (8a*R*)-**16** from *n*-hexane:AcOEt gave colorless needles. (8a*R*)-**16**; m.p., 170 °C, IR (KBr): 2933, 1647, 1594, 1489, 1080, and 896 cm^{-1}; $[\alpha]_D^{23}$ + 34.6 (c = 0.99, $CHCl_3$); ^{1}H NMR: δ 0.80 (3H, s), 0.81 (3H, s), 0.84 (3H, s), 1.15–1.33 (4H, m), 1.36–1.39 (1H, m), 1.45–1.50 (1H, m), 1.54–1.59 (1H, m), 1.65–1.69 (1H, m), 1.85–1.94 (2H, m), 2.24 (1H, ddd, J = 12.5, 4, 2.5 Hz), 2.55–2.58 (1H, m), 2.70 (1H, dd, J = 13.5, 3.5 Hz), 2.79 (1H, dd, J = 13.5, 10 Hz), 3.74 (6H, s), 3.81 (6H, s), 4.66 (1H. s), 5.00 (1H, s), and 6.38 (1H, s). ^{13}C NMR: δ 14.1 (q), 19.6 (t), 20.2 (t), 21.8 (q), 24.5 (t), 33.6 (s), 33.6 (q), 38.5 (t), 38.5 (t), 40.0 (s), 42.2 (t), 55.4 (d), 55.6 (d), 55.9 (q), 60.6 (q), 96.2 (d), 106.7 (t), 130.3 (s), 140.9 (s), 148.4 (s), and 148.5 (s). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.60; H, 9.48%. FAB MS m/z: 403 (M^++1). The spectral data (^{1}H and ^{13}C NMR, $[\alpha]_D$) of the synthetic (8a*R*)-**16** were identical with those ($[\alpha]_D^{24}$ + 34 (c = 1.0, $CHCl_3$)) of the reported (8a*R*)-**16** [10,11]. Thus, obtained (8a*R*)-**16** was already converted to the natural hyatellaquinone (**3**) [10] (Scheme 3).

3. Discussion

Although lipases are widely used as enantioselective hydrolysis or transesterification catalysts, the structural basis for this enantioselectivity was unknown so far. The specificity of lipase from *Candida rugosa* has established a simple empirical rule that predicts its enantiopreference toward secondary alcohols [12,13]. On the other hand, explanation concerning the molecular recognition of primary alcohols has been more difficult. Most lipases indicate low enantioselectivity toward primary alcohols. Only lipase from *Pseudomonas cepacia* (PCL) and lipase from porcine pancreas (PPL) show moderate to high enantioselectivity toward a wide range of primary alcohols, but even for these the enantioselectivity is usually lower than toward secondary alcohols. Lipase from *Pseudomonas cepacia* (PCL) catalyzes the enantioselective hydrolysis of the (±)-**17** to afford (*S*)-alcohol **18** (79% ee) and unchanged (*R*)-17 (ee; nd) (Scheme 4) [14]. The empirical rule summarize the enantioperference of PCL toward primary alcohol or its acylated derivative as shown in Scheme 4 [14,15]. When the hydroxy methyl (−CH_2OH) or acyloxy methyl (−CH_2OCOR) groups exist back with the plane of the page, the favored enantiomer bears a large substituent (L) on the right, and a medium substituent (M) on the left.



Scheme 4.

In the present case, the recognition of both substituent L and M in the substrate (±)-**6** by lipase is considered to be difficult and thence enantiopreference toward primary alcohol is depended upon the used lipase. It is worth noting that the preparation of both (8a*S*)- and (8a*R*)-**6** possessing high enantiomeric excess was achieved based on lipase-catalyzed esterification.

4. Conclusion

The lipase PL-266 from *Alcaligenes* sp. catalyzed enantioselective acetylation of the decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-ethylene acetal (±)-**6** was carried out and an acetate (8a*S*)-**7** and an alcohol (8a*R*)-**6** possessing high enantiomeric excess (>98% ee), respectively, were obtained. Both (8a*S*)-**7** and (8a*R*)-**6** were converted to the (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylates (**4**), respectively. The (8a*R*)-β-keto ester (**4**) was converted to the important intermediate (8a*R*)-**16** for the synthesis of natural hyatellaquinone (**3**).

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