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Enzyme-assisted synthesis of (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one, the male-produced aggregation pheromone of the Colorado potato beetle, and its (*R*)-enantiomer☆

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Abstract—(*S*)-1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one, the male-produced aggregation pheromone of the Colorado potato beetle (*Leptinotarsa decemlineata*), and its (*R*)-isomer were synthesized by employing lipase-catalyzed asymmetric acetylation of (±)-2,3-epoxynerol as the key step.

1. Introduction

The Colorado potato beetle, *Leptinotarsa decemlineata*, is a major pest of potatoes and related solanaceous plants, such as tomatoes and eggplants throughout the world. Heavy use of pesticides for control has led to the development of insecticide resistance in this insect. It is therefore important to study the attractants and pheromones of *L. decemlineata* to make its biorational control possible.

In 1926, McIndoo was the first to study the attractancy of volatiles emitted by mature potato plants against *L. decemlineata*.[2] Subsequently, Dickens identified five volatile components of potatoes, which caused antennal response of the potato beetle.[3] More importantly, in 2002, Dickens isolated about 1 mg of its male-produced aggregation pheromone.[4]

The pheromone was identified as (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one **1** (Scheme 1) by Oliver et al. on the basis of MS and NMR analysis of the isolated material coupled with the synthesis and bioassay of the racemate and enantiomers of this highly oxygenated monoterpene **1**.[5] Bioassay of the synthetic samples revealed that (*S*)-**1** was attractive for both male and female *L. decemlineata*, while (*R*)-**1** was inactive, and its presence in (±)-**1** abolished the response to (*S*)-**1**.[5]

This kind of inhibitory action of the incorrect enantiomer is well known in pheromone science.[6] Pheromones belonging to this category must be prepared in enantiomerically pure or highly enriched form prior to its biological test.

At this stage, Dickens of the US Department of Agriculture requested one of us (K.M.) to synthesize gram quantities of (*S*)-**1** required for its field test. Because Oliver et al. started their synthesis of (*S*)-**1** from scarcely available (*S*)-linalool, they were unable to prepare (*S*)-**1** in a sufficient amount.[5] Their synthesis of (±)-**1**, however, employed readily available (±)-2,3-epoxygeraniol (**2′**, *trans*-epoxide, Table 1) as the starting material, and well-designed to give (±)-**1** smoothly. Accordingly, development of a practical method for the preparation of enantiomerically highly enriched **2** [2,3-epoxynerol (*cis*-epoxide) or **2′** (2,3-epoxygeraniol)] enables us to obtain (*S*)-**1** in gram quantities.

Optically active 2,3-epoxygeraniol or 2,3-epoxynerol is usually prepared by the Sharpless asymmetric epoxidation of geraniol or nerol.[7–9] Their enantiomeric purities, however, are not perfect: 94–95% ee,[7] 86–91% ee,[8] or

☆ Pheromone synthesis, Part 231. For Part 230, see: Ref. 1.

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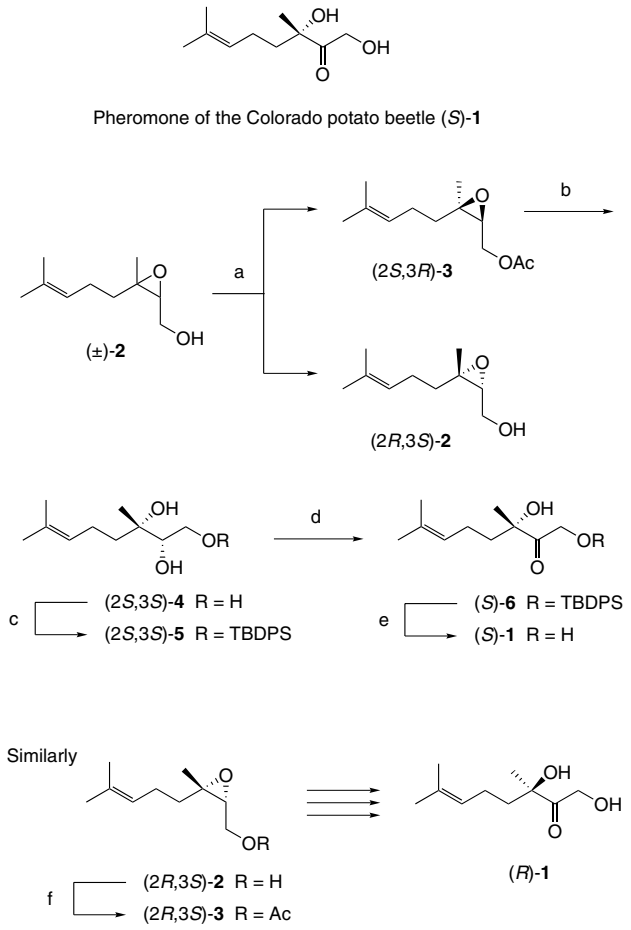


Scheme 1. Synthesis of the male-produced aggregation pheromone of the Colorado potato beetle (*S*)-**1** and its (*R*)-isomer. Reagents and conditions: (a) lipase PS (Amano), CH_2=CHOAc, Et_2O, 0 °C, 4 h, three times, 10–16% for (2*S*,3*R*)-**3** and 11–22% for (2*R*,3*S*)-**2** based on (±)-**2**; (b) 60% $HClO_4$, DMF, 0 °C–room temp, 12 h; then K_2CO_3, MeOH, room temp, 20 h, 77–92%; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, room temp, 24 h, 93–97%; (d) $SO_3{\cdot}C_5H_5N$, DMSO, Et_3N, CH_2Cl_2, 0 °C–room temp, 24 h, 78–91%; (e) TBAF, THF, 0 °C, 5 min, 65%-quant.; (f) Ac_2O, DMAP, C_5H_5N, 30 min, 86–92%.

62–81% ee.[9] Although recrystallization of their *p*-nitrobenzoates can afford enantiomerically pure materials, this purification is cumbersome and inefficient.[7,8] We therefore envisaged to employ enzymatic and asymmetric acetylation of (±)-**2** as the key step to prepare enantiomerically highly enriched acetate **3**. Herein we report the lipase-catalyzed asymmetric acetylation of (±)-**2** to give (2*S*,3*R*)-**3**, as well as its conversion to (*S*)-**1** via (2*S*,3*S*)-**4**. The synthesis of (*R*)-**1** is also reported.

2. Results and discussion

2.1. Lipase-catalyzed asymmetric acetylation of 2,3-epoxynerol and 2,3-epoxygeraniol

Lipase-catalyzed asymmetric acetylation of racemic alcohols with vinyl acetate is one of the most established methods for kinetic resolution of racemic alcohols.[10] In the present case, enantiomer discrimination only at the C-3 of 2,3-epoxynerol **2** or 2,3-epoxygeraniol **2′** was required, because the stereogenic center at C-2 would later be destroyed to give the target 2-ketone (*S*)-**1**. We therefore decided to examine both **2** and **2′** concerning their suitabilities as the substrate for asymmetric acetylation. These two epoxy alcohols **2** and **2′** could readily be prepared from nerol and geraniol, respectively, by their oxidation with *tert*-butyl hydroperoxide in refluxing benzene in the presence of vanadyl acetylacetonate [$VO(acac)_2$] according to Sharpless and Michaelson.[11]

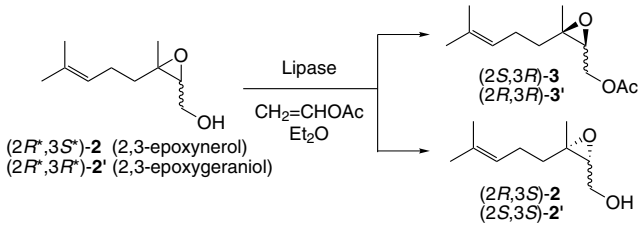
Esterases and lipases are known to catalyze asymmetric hydrolysis of 2,3-epoxyalkyl acetates[12] and also asymmetric acetylation of 2,3-epoxy alcohols.[13] We therefore screened various lipases for the asymmetric acetylation of 2,3-epoxy alcohols **2** and **2′** as shown in Table 1. All the lipases tested showed enantioselectivity in the acetylation reaction with vinyl acetate in diethyl ether: (±)-2,3-Epoxynerol **2** yielded (2*S*,3*R*)-2,3-epoxyneryl acetate **3**, and (±)-2,3-epoxygeraniol **2′** afforded (2*R*,3*R*)-2,3-epoxygeranyl acetate **3′**. Assignment of the above absolute configuration was made possible by comparing the sign of the specific rotation of these products with those reported previously.[7–9] Thus, lipases do not discriminate the stereoisomers at C-2, which is adjacent to the hydroxy group, but recognize the absolute configuration at C-3. Both **2** and **2′** were good substrates for acetylation, and lipase PS (Amano) was selected as the enzyme of choice. Since lipase PS did not work efficiently at −18 °C, the reaction temperature was set at 0 °C. Under these conditions, both **2** and **2′** were half-acetylated within 3 h to give the products in 72–74% ee. It was therefore evident that the repetition of the above lipase-catalyzed acetylation would give epoxy acetate **3** or **3′** and epoxy alcohol **2** or **2′** in satisfactory enantiomeric purity.

2.2. Synthesis of the pheromone (*S*)-1 and its (*R*)-isomer

The synthesis of pheromone (*S*)-**1** is summarized in Scheme 1. The synthesis started from nerol, which we had in quantity. (±)-2,3-Epoxynerol **2**[14] was subjected to the enzymatic kinetic resolution three times with lipase PS and vinyl acetate to give, in 16% yield based on (±)-**2**, (2*S*,3*R*)-2,3-epoxyneryl acetate **3**. It was enantiomerically almost pure (98.8% ee) as determined by its HPLC analysis on Chiralcel-OD®. Unreacted alcohol (2*R*,3*S*)-**2** (98.6% ee) was obtained in 22% yield. Through this enzyme reaction, a sufficient amount (about 5 g) of both (2*S*,3*R*)-**3** and (2*R*,3*S*)-**2** could be secured, and the former was further processed to give the pheromone (*S*)-**1** essentially according to Oliver et al.[5]

Inversion of the (3*R*)-configuration of (2*S*,3*R*)-**3** was achieved by treating epoxide **3** with aqueous perchloric acid in *N*,*N*-dimethylformamide (DMF) at 0 °C, followed by treatment of the resulting 1,2,3-triol-1-acetate-2-formate with potassium carbonate in methanol to give triol (2*S*,3*S*)-**4** in 86% yield.[5,15] Inversion of configuration at C-3 of epoxide **3** under these conditions had been studied conclusively by Hanson.[15] The enantiomeric purity of (2*S*,3*S*)-**4**, as determined at the stage of (*S*)-**6** (vide infra), was 93.2% ee. When the ring

Table 1. Lipase-catalyzed asymmetric acetylation of (±)-2,3-epoxynerol **2** and (±)-2,3-epoxygeraniol **2′**[a]



Lipase	Temperature	2,3-Epoxyneryl acetate[b]			2,3-Epoxygeranyl acetate[b]		
		Time (min)[c]	Yield (%)[d]	ee (%)[e]	Time (min)[c]	Yield (%)[d]	ee (%)[e]
AK	Rt	70	23	24	60	20	50
AH	Rt	25	25	50	20	26	46
PS	Rt	125	30	59	120	31	60
PS	0 °C	165	21	72	160	23	74
PS-C	Rt	15	26	42	15	21	26

[a] Conditions: To a solution of 2,3-epoxy alcohol (100 mg) in diethyl ether (2 mL) and vinyl acetate (0.5 mL) was added lipase (50 mg) at the shown temperature. The enzymes were a generous gift of Amano Enzyme, Inc. (Lipase AK from *Pseudomonas fluorescens*; Lipase AH from *Burkholderia cepacia*; Lipase PS from *B. cepacia*; PS-C = PS on Celite).

[b] The absolute configuration of the resulting 2,3-epoxyneryl acetate **3** was 2*S*,3*R*, while that of 2,3-epoxygeranyl acetate (**3′**) was 2*R*,3*R*.[7–9]

[c] The acetylation was monitored by TLC.

[d] Yields were based on the starting racemates **2** or **2′**.

[e] Determined by HPLC analysis of **3** and **3′**.

opening of epoxide **3** was performed at room temperature (about 20 °C), partial racemization at C-3 took place to give (2*S*,3*S*)-**4** of only 83% ee. The epoxide cleavage did not occur at −18 °C.

Prior to the oxidation of the secondary hydroxy group at C-2 of (2*S*,3*S*)-**4**, the terminal hydroxy group at C-1 was selectively protected by treatment with 1.1 equiv of *tert*-butyldiphenylsilyl chloride (TBDPSCl) and triethylamine in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) to give (2*S*,3*S*)-**5** in 97% yield. Subsequent oxidation of (2*S*,3*S*)-**5** with dimethyl sulfoxide (DMSO) and sulfur trioxide-pyridine complex in the presence of triethylamine[16] yielded (*S*)-**6** in 85% yield. HPLC analysis of (*S*)-**6** on Chiralcel-OD® revealed its enantiomeric purity as 93.2% ee.

Final deprotection of the TBDPS group of (*S*)-**6** by short treatment (0 °C, 5 min) with tetra-*n*-butylammonium fluoride (TBAF) in THF furnished oily (*S*)-**1** in a quantitative yield after chromatographic purification, $[\alpha]_D^{25} = +3.8$ (*c* 0.79, $CHCl_3$) {lit.[5] $[\alpha]_D^{25} = +0.7$ ($CHCl_3$)}. Its ^1H NMR spectrum (500 MHz, $CDCl_3$) was identical to that reported for the natural pheromone.[5] A longer reaction time at room temperature over the course of the TBAF treatment resulted in a drastically reduced yield (about 12% after 16 h) due to the isomerization followed by retroaldol reaction caused by the basicity of TBAF. This decomposition is similar to that of D-fructose under basic conditions. Through the present synthesis, about 2.5 g of (*S*)-**1** was synthesized in 71% overall yield based on (2*S*,3*R*)-**3** (four steps). For the synthesis of (*R*)-**1**, (2*R*,3*S*)-**2** was acetylated to give (2*R*,3*S*)-**3** (99.3% ee), which was converted to (*R*)-**1** (2.0 g) in 42% overall yield based on (2*R*,3*S*)-**2** (five steps).

3. Conclusion

Lipase-catalyzed asymmetric acetylation of (±)-2,3-epoxynerol **2** enabled us to prepare (2*S*,3*R*)-2,3-epoxyneryl acetate **3** in a substantial amount, which afforded (*S*)-2,3-dihydroxy-3,7-dimethyl-6-octen-2-one **1**, the male-produced aggregation pheromone of the Colorado potato beetle in an amount sufficient for its field test. The unnatural (*R*)-**1** was also synthesized, and supplied for further biological study. The field trial to catch adult Colorado potato beetles in pitfall traps baited with (*S*)-**1** was successfully conducted in Virginia, USA. However, more research is necessary to optimize the release rate of (*S*)-**1** and incorporate control methods for cohabiting pests. Details of the field test will be reported in due course.[17]

4. Experimental

4.1. General

All boiling points (bp) data are uncorrected. Refractive indices (n_D) were measured by an Atago 1T refractometer. Optical rotation values were measured by a Jasco DIP-1010 instruments. IR spectra were recorded by Jasco FT/IR-460 plus spectrometer. ^1H NMR spectra were recorded by Jeol JNM-90A (90 MHz), JNM-AL300 (300 MHz) and Jeol JNM-LA500 (500 MHz) spectrometers (TMS at $\delta_H = 0.00$, $CHCl_3$ at $\delta_H = 7.26$, or benzene at $\delta_H = 7.15$ as an internal standard). Coupling constants (*J*) were reported in hertz. ^{13}C NMR spectra were recorded by Jeol JNM-LA500 (126 MHz) spectrometer ($CHCl_3$ at $\delta_C = 77.0$, or benzene at 128.0 as an internal standard). Mass spectra were recorded by Jeol JMS-SX102A and Hitachi M-80B instruments. Column chromatography was carried out with Merck Kieselgel

60 Art 1.07734, and TLC was carried out with 0.25 mm Merck silica gel plates (60F-254).

4.2. (2*S*,3*R*)-3,7-Dimethyl-2,3-epoxy-6-octenyl acetate 3, and (2*R*,3*S*)-3,7-dimethyl-2,3-epoxy-6-octen-1-ol 2

To a stirred solution of (±)-**2** (23.6 g, 162 mmol) and vinyl acetate (60 mL) in Et_2O (230 mL) was added lipase-PS (Amano Enzyme, Inc., 4.6 g) at 0 °C. The mixture was stirred at 0 °C for 4 h. It was then filtered through a bed of Celite and the filtrate concentrated in vacuo. The residue was purified by chromatography on silica gel [1.1 kg, hexane/ethyl acetate = 5:1 for (2*S*,3*R*)-**3**, and 2:1 for (2*R*,3*S*)-**2**] to give (2*S*,3*R*)-**3** and (2*R*,3*S*)-**2**.

The separated (2*S*,3*R*)-**3** (16.8 g, 79.1 mmol) was then methanolyzed with K_2CO_3 (1.09 g, 7.89 mmol) in MeOH (200 mL) at room temperature for 4 h. The resulting mixture was concentrated in vacuo. The residue was diluted with Et_2O, and filtered through a bed of Celite. The filtrate was concentrated in vacuo to give the enantiomerically enriched crude alcohol (2*S*,3*R*)-**2** (ca. 15 g). This procedure, enzymatic resolution followed by methanolysis as described above, was repeated for the resulting alcohol (2*S*,3*R*)-**2** for additional two times to give (2*S*,3*R*)-**3** [first: 10.1 g, 92.9% ee; second: 5.49 g, 98.8% ee; 16% based on (±)-**2**, two steps] as a colorless oil. For (2*R*,3*S*)-**2**, enzymatic acetylation described above was repeated twice more to give unreacted (2*R*,3*S*)-**2** [first: 8.42 g; 92.7% ee; second: 5.19 g, 98.6% ee, 22%, based on (±)-**2**, two steps] as a colorless oil. The enantiomeric purity of (2*R*,3*S*)-**2** was determined by HPLC analysis after acetylation to (2*R*,3*S*)-**3**. (2*S*,3*R*)-**3**: HPLC analysis (Chiralcel-OD®, *n*-hexane/*i*-PrOH 200:1, 0.25 mL/min, detection at 210 nm): t_R 13.3 min [(2*R*,3*S*)-**3**, 0.6%], 16.0 min [(2*S*,3*R*)-**3**, 99.4%]; n_D^{20} 1.4570; $[\alpha]_D^{23} = -25.7$ (*c* 0.58, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = -23.4$ (*c* 1.7, $CHCl_3$)}; ν_{max} (film): 1745 (s, CO), 1675 (w, C=C), 1235 (s, C–O), 1035 (s, C–O), 880 (w); δ_H (90 MHz, $CDCl_3$): 1.34 (3H, s, 3-Me), 1.61 (3H, br s, 7-Me), 1.68 (3H, br s, 7-Me), 1.41–1.76 (2H, m, 4-H_2), 2.10 (3H, s, Ac), 1.88–2.27 (2H, m, 5-H_2), 2.98 (1H, dd, *J* 4.4, 7.1, 2-H), 4.00 (1H, dd, *J* 7.1, 12, 1-H_a), 4.34 (1H, dd, *J* 4.4, 12, 1-H_b), 5.09 (1H, br t, *J* 7.1, 6-H); MS (EI, 70 eV) *m*/*z* (%): 17 (7), 18 (32), 41 (46), 43 (100), 67 (23), 69 (47), 82 (20), 95 (15), 103 (13), 109 (52), 119 (6), 134 (7), 152 (3), 169 (1), 178 (1), 194 (1), 212 (M^+, 1); HRMS calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1408. This was immediately used in the next step without further purification.

(2*R*,3*S*)-**2**: n_D^{28} 1.4702; $[\alpha]_D^{28} = +13.3$ (*c* 1.09, $CHCl_3$); ν_{max} (film): 3420 (s, OH), 1035 (s, C–O), 870 (m); δ_H (90 MHz, $CDCl_3$): 1.34 (3H, s, 3-Me), 1.62 (3H, br s, 7-Me), 1.69 (3H, br s, 7-Me), 1.35–1.93 (2H, m, 4-H_2), 1.93–2.38 (2H, m, 5-H_2), 2.96 (1H, dd, *J* 4.9, 6.4, 2-H), 3.51–3.82 (3H, m, 1-H_2, OH), 5.10 (1H, br t, *J* 7.3, 6-H); MS (EI, 70 eV) *m*/*z* (%): 17 (44), 18 (100), 28 (20), 39 (21), 41 (80), 43 (58), 55 (27), 61 (26), 67 (45), 69 (69), 82 (38), 95 (25), 109 (83), 121 (6), 141 (2), 151 (3), 161 (1), 170 (M^+, 1); HRMS calcd for $C_{10}H_{18}O_2$ (M^+) 170.1307, found 170.1301. This was immediately used in the next step without further purification.

4.3. (2*R*,3*S*)-3,7-Dimethyl-2,3-epoxy-6-octenyl acetate (2*R*,3*S*)-3

To a stirred solution of (2*R*,3*S*)-**2** (5.17 g, 30.4 mmol) in pyridine (50 mL) were added acetic anhydride (8.40 mL, 88.9 mmol) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP, 0.04 g) at 0 °C. The mixture was stirred for 30 min at room temperature. It was then poured into water and extracted with EtOAc (20 mL × 2). The combined organic solution was successively washed with water (50 mL × 2), saturated $CuSO_4$ solution (20 mL × 5), water (20 mL), saturated $NaHCO_3$ solution (30 mL), and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (100 g, hexane/EtOAc 30:1) to give (2*R*,3*S*)-**3** (5.93 g, 92%, 98.6% ee) as a colorless oil; HPLC analysis (Chiralcel-OD®, *n*-hexane/*i*-PrOH = 200:1, 0.5 mL/min, detection at 210 nm): t_R 13.6 min [(2*R*,3*S*)-**3**, 99.3%], 16.7 min [(2*S*,3*R*)-**3**, 0.7%]; n_D^{23} 1.4580; $[\alpha]_D^{23} = +27.0$ (*c* 0.86, $CHCl_3$); Its IR, ^1H NMR, and MS were identical with those of (2*S*,3*R*)-**3**; HRMS calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1409. This was immediately used in the next step without further purification.

4.4. (2*S*,3*S*)-3,7-Dimethyl-6-octene-1,2,3-triol (2*S*,3*S*)-4

To a stirred solution of (2*S*,3*R*)-**3** (8.00 g, 37.7 mmol) in DMF (80 mL) was added slowly an aqueous solution of $HClO_4$ (60%, 6.2 mL) at 0 °C. The mixture was gradually warmed to room temperature with stirring. After stirring for 12 h, the mixture was diluted with EtOAc (150 mL), and the resulting mixture successively washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in MeOH (70 mL). To the mixture was added K_2CO_3 (588 mg, 4.25 mmol) at room temperature. The mixture was stirred for 20 h. It was then concentrated in vacuo, and the residue purified by chromatography on silica gel (150 g, $CHCl_3$/MeOH 20:1) to give (2*S*,3*S*)-**4** (6.08 g, 86%) as a colorless oil; n_D^{25} 1.4815; $[\alpha]_D^{25} = -1.5$ (*c* 1.05, $CHCl_3$); ν_{max} (film): 3390 (s, OH), 1085 (m, C–O), 1015 (m, C–O), 880 (m), 835 (w), 790 (w), 755 (w); δ_H (300 MHz, $CDCl_3$): 1.18 (3H, s, 3-Me), 1.62 (3H, s, 7-Me), 1.68 (3H, s, 7-Me), 1.20–1.78 (2H, m, 4-H_2), 1.78–2.14 (2H, m, 5-H_2), 2.14–2.87 (3H, m, OH × 3), 3.42–3.61 (1H, m, 2-H), 3.76 (2H, br d, *J* 4.6, 1-H_2), 5.12 (1H, br t, *J* 6.8, 6-H). This was immediately used in the next step without further purification.

4.5. (2*R*,3*R*)-3,7-Dimethyl-6-octene-1,2,3-triol (2*R*,3*R*)-4

In the same manner as described above, (2*R*,3*S*)-**3** (9.41 g, 44.3 mmol) was converted to (2*R*,3*R*)-**4** (6.92 g, 83%) as a colorless oil; $n_D^{25} = 1.4822$; $[\alpha]_D^{25} = +1.5$ (*c* 1.37, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (2*S*,3*S*)-**4**. This was immediately used in the next step without further purification.

4.6. (2*S*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (2*S*,3*S*)-5

To a stirred solution of (2*S*,3*S*)-**4** (6.06 g, 32.2 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (10 mL), *tert*-butylchlorodiphenylsilane (9.20 mL, 36.9 mmol), and a catalytic amount of DMAP (0.05 g) at 0 °C. After stirring for 24 h at room temperature, the reaction was quenched by the addition of MeOH (2 mL). After stirring for 30 min at room temperature, the mixture was poured into water and extracted with $CHCl_3$. (30 mL × 2). The combined organic solution was successively washed with saturated $NaHCO_3$ solution (30 mL), water (40 mL), and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (300 g, hexanes/EtOAc 15:1) to give (2*S*,3*S*)-**5** (13.3 g, 97%) as a colorless oil; n_D^{21} 1.5170; $[\alpha]_D^{20} = -10.6$ (*c* 1.01, $CHCl_3$); ν_{max} (film): 3460 (s, OH), 3070 (w, arom. C–H), 3050 (w, arom. C–H), 1590 (w, arom. C=C), 1115 (s, C–O), 825 (s, C=C–H), 740 (s), 705 (s), 615 (s); δ_H (300 MHz, $CDCl_3$): 1.07 (9H, s, *t*-Bu), 1.10 (3H, s, 3-Me), 1.49–1.55 (2H, m, 4-H_2), 1.60 (3H, s, 7-Me), 1.67 (3H, s, 7-Me), 1.96–2.03 (2H, m, 5-H_2), 2.72 (1H, br s, OH), 2.92 (1H, br d, *J* 4.5, OH), 3.52 (1H, ddd, *J* 4.2, 4.5, 6.0, 2-H), 3.77 (1H, dd, *J* 6.0, 11, 1-H_a), 3.81 (1H, dd, *J* 4.5, 11, 1-H_b), 5.09 (1H, br t, *J* 6.9, 6-H), 7.37–7.47 (6H, m, Ph), 7.65–7.69 (4H, m, Ph). Anal. Calcd for $C_{26}H_{38}O_3Si$ (426.66): C, 73.19; H, 8.98. Found: C, 73.29; H, 9.02. HRMS calcd for $C_{26}H_{38}O_3Si$ (M^+) 426.2590, found 426.2594.

4.7. (2*R*,3*R*)-1-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (2*R*,3*R*)-5

In the same manner as described above, (2*R*,3*R*)-**4** (6.33 g, 33.7 mmol) was converted to (2*R*,3*R*)-**5** (13.3 g, 93%) as a colorless oil; n_D^{20} 1.5171; $[\alpha]_D^{20} = +10.5$ (*c* 1.06, $CHCl_3$); Its IR and ^1H NMR spectra were identical with those of (2*S*,3*S*)-**5**. Anal. Calcd for $C_{26}H_{38}O_3Si$ (426.66): C, 73.19; H, 8.98. Found: C, 73.18; H, 9.02. HRMS calcd for $C_{26}H_{38}O_3Si$ (M^+) 426.2590, found 426.2588.

4.8. (*S*)-1-*tert*-Butyldiphenylsilyloxy-3-hydroxy-3,7-dimethyl-6-octen-2-one (*S*)-6

To a stirred solution of (2*S*,3*S*)-**5** (13.0 g, 30.5 mmol) in dry CH_2Cl_2 (40 mL), dimethyl sulfoxide (DMSO, 110 mL), and Et_3N (30 mL) was added sulfur trioxide pyridine complex (24.3 g, 153 mmol) at 0 °C. After stirring for 24 h at room temperature, the mixture was poured into water and extracted with CH_2Cl_2 (40 mL × 3). The combined organic solution was successively washed with water (30 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (150 g, hexane/EtOAc 30:1) to give (*S*)-**6** (11.0 g, 85%, 93.2% ee) as a colorless oil; HPLC analysis (Chiralcel-OD®, *n*-hexane/*i*-PrOH = 50:1, 0.5 mL/min, detection at 254 nm): t_R 15.8 min (*R*, 3.4%), 18.0 min (*S*, 96.6%); n_D^{23} 1.5176; $[\alpha]_D^{21} = -0.5$ (*c* 1.46, $CHCl_3$); ν_{max} (film): 3485 (s, OH), 3070 (w, arom. C–H), 3050 (w, arom. C–H), 1725 (s, C=O), 1590 (w, arom. C=C), 1115 (s, C–O), 825 (s, C=C–H), 740 (m), 705 (s), 610 (m); δ_H (300 MHz, $CDCl_3$): 1.12 (9H, s, *t*-Bu), 1.21 (3H, s, 3-Me), 1.51 (3H, s, 7-Me), 1.63 (3H, s, 7-Me), 1.45–1.77 (3H, m, 4-H_2, 5-H_a), 1.88–2.12 (1H, m, 5-H_b), 3.47 (1H, s, OH), 4.51 (2H, s, 1-H_2), 4.96 (1H, br t, *J* 6.9, 6-H), 7.38–7.50 (6H, m, Ph), 7.60–7.73 (4H, m, Ph). Anal. Calcd for $C_{26}H_{36}O_3Si$ (424.65): C, 73.54; H, 8.54. Found: C, 73.67; H, 8.46. HRMS calcd for $C_{26}H_{36}O_3Si$ (M^+) 424.2434, found 424.2434.

4.9. (*R*)-1-*tert*-Butyldiphenylsilyloxy-3-hydroxy-3,7-dimethyl-6-octen-2-one (*R*)-6

In the same manner as described above, (2*R*,3*R*)-**5** (12.8 g, 30.0 mmol) was converted to (*R*)-**6** (11.5 g, 91%, 92.0% ee) as a colorless oil; HPLC analysis (Chiralcel-OD®, *n*-hexane/*i*-PrOH = 50:1, 0.5 mL/min, detection at 254 nm): t_R 15.4 min (*R*, 96.0%), 17.5 min (*S*, 4.0%); n_D^{20} 1.5175; $[\alpha]_D^{20} = +0.45$ (*c* 1.17, $CHCl_3$); Its IR and ^1H NMR spectra were identical with those of (*S*)-**6**. Anal. Calcd for $C_{26}H_{36}O_3Si$ (424.65): C, 73.54; H, 8.54. Found: C, 73.40; H, 8.59. HRMS calcd for $C_{26}H_{36}O_3Si$ (M^+) 424.2434, found 424.2445.

4.10. (*S*)-1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one (*S*)-1

To a stirred solution of (*S*)-**6** (5.64 g, 13.3 mmol) in THF (60 mL) was added a solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M, 20 mL, 20 mmol) at 0 °C. After stirring for 5 min, the mixture was poured into water and extracted with EtOAc. The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (100 g, hexane/EtOAc 30:1) to give (*S*)-**1** (2.47 g, quant.) as a colorless oil. An analytical sample was purified by distillation; bp = 103–105 °C/1.2 Torr; n_D^{25} 1.4745; $[\alpha]_D^{25} = +3.8$ (*c* 0.79, $CHCl_3$); ν_{max} (film): 3425 (s, OH), 2970 (s, CH), 2920 (s, CH), 1720 (s, CO), 1450 (m, CH_2), 1375 (m, CH_3), 1265 (w), 1195 (m), 1135 (m, C–O), 1095 (m), 1035 (m, C–O), 1010 (m, C–O), 875 (w), 830 (w, C=C–H), 790 (w), 745 (w), 670 (w); δ_H (500 MHz, $CDCl_3$): 1.37 (3H, s, 3-Me), 1.58 (3H, s, 7-Me), 1.67 (3H, s, 7-Me), 1.71 (1H, br ddd, *J* 5.8, 10, 14, 4-H_a), 1.79 (1H, br ddd, *J* 6.1, 9.8, 14, 4-H_b), 1.90 (1H, br dt, *J* 6.4, 14, 5-H_a), 2.09 (1H, br dt, *J* 6.4, 14, 5-H_b), 2.90–2.95 (2H, m, OH × 2), 4.48 (1H, d, *J* 4.9, 1-H_a), 4.50 (1H, d, *J* 4.9, 1-H_b), 5.04 (1H, br t, *J* 6.4, 6-H); δ_C (126 MHz, $CDCl_3$): 17.6, 22.1, 25.6, 26.0, 39.9, 64.6, 78.4, 122.9, 133.2, 214.2; δ_H (500 MHz, C_6D_6): 0.87 (3H, s, 3-Me), 1.33 (1H, ddd, *J* 5.5, 11, 14, 4-H_a), 1.44 (3H, br s, 7-Me), 1.45 (1H, ddd, *J* 6.0, 11, 14, 4-H_b), 1.59 (3H, d, *J* 0.5, 7-Me), 1.75–1.84 (1H, m, 5-H_a), 1.91–2.00 (1H, m, 5-H_b), 2.20 (1H, s, OH), 2.90 (1H, t, *J* 5.0, OH), 4.15 (1H, dd, *J* 5.0, 20, 1-H_a), 4.21 (1H, dd, *J* 5.0, 20, 1-H_b), 4.94 (1H, tquint. *J* 1.5, 7.0, 6-H); δ_C (126 MHz, C_6D_6): 17.5, 22.4, 25.7, 25.8, 40.2, 64.9, 78.2, 123.8, 132.5, 214.6; MS (EI, 70 eV) *m*/*z* (%): 18 (22), 41 (32), 43 (45), 53 (6), 55 (8), 58 (7), 67 (8), 69 (100), 70 (7), 71 (12), 83 (11), 86 (10), 104 (20), 109 (77), 127 (28), 168 (4), 186 (M^+, 1); HRMS calcd for $C_{10}H_{18}O_3$ (M^+) 186.1256, found 186.1253.

4.11. (*R*)-1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one (*R*)-1

In the same manner as described above, (*R*)-**6** (7.11 g, 16.7 mmol) was converted to (*R*)-**1** (2.02 g, 65%) as a colorless oil; bp = 94–97 °C/ 0.7 Torr; n_D^{25} 1.4742; $[\alpha]_D^{25} = -4.0$ (*c* 1.08, $CHCl_3$); IR, ^1H and ^{13}C NMR and mass spectra were identical with those of (*S*)-**1**; HRMS calcd for $C_{10}H_{18}O_3$ (M^+) 186.1256, found 186.1255.

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