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Catalytic asymmetric synthesis of the Colorado potato beetle pheromone and its enantiomer

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ABSTRACT

An efficient catalytic asymmetric synthesis of the CPB pheromone [(*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one] and its enantiomer was accomplished with 99% ee and in gram quantities from geraniol. The key steps in this procedure involve Sharpless asymmetric epoxidation and recrystallization of the 4-bromobenzoate from the CPB pheromone to improve its enantiomeric purity. Furthermore, the absolute configuration of the CPB pheromone enantiomer was confirmed as (*R*) for the first time by the X-ray crystallographic structure of its benzoate.

1. Introduction

The Colorado potato beetle (CPB), *Leptinotarsa decemlineata* (Say), is the most severe defoliator of potatoes worldwide and potatoes are the most important non-grain food crop in the world.[1] The heavy use of synthetic insecticides for controlling CPB has led to insecticide resistance,[2] which prompted us to seek new strategies to combat CPB infestations. The use of insect pheromones is a viable, safe, and environmentally friendly alternative to insecticides. A recent discovery of a male-produced aggregation pheromone of CPB (*S*)-**7** has made it possible for the pest management of CPB.[3]

In 2002, the pheromone was isolated and identified as (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one by Dickens.[4] Meanwhile the formal synthesis of the CPB pheromone and its enantiomer was carried out from (*S*)-linalool and (*R*)-linalool.[5] Preliminary bioassays revealed that (*S*)-**7** was able to attract both sexes of *L. decemlineata*, while (*R*)-**7** was inactive.[5] This result promoted the stereoselective synthesis of the CPB pheromone. Shortly thereafter, the CPB pheromone and its (*R*)-isomer were synthesized by employing a lipase-catalyzed asymmetric acetylation of (±)-2,3-epoxygeraniol as the key step.[6] In 2009, a novel synthetic approach to produce the CPB pheromone was developed, in which the chirality at C3 was introduced by the stereoselective addition of an organometallic reagent to a ketone.[7] The latest example was accomplished from 2-fluoronerol or 2-fluorogeraniol, and involved a 6-endo epoxide ring-opening with ester participation.[8]

A growing awareness of environmentally friendly pest control and some disadvantages in earlier synthetic strategies prompted us to study an efficient asymmetric synthesis of the CPB pheromone in high enantiomeric purity and in gram quantities. Herein, CPB pheromone (99% ee) and its enantiomer were synthesized from known geraniol via Sharpless asymmetric epoxidation as the key step; furthermore, the absolute configuration of its enantiomer was confirmed as (*R*) for the first time by the X-ray crystallographic structure of the benzoate (*R*)-**8**.

2. Results and discussion

The catalytic asymmetric synthesis of the CPB pheromone and its enantiomer is outlined in Scheme 1.

The Sharpless asymmetric epoxidation of geraniol **1**[9] afforded (2*R*,3*R*)-**2** with D-(−)-diethyl tartrate in 95% yield. After acetylation, exposure of the epoxyacetate (2*R*,3*R*)-**3** to aqueous perchloric acid in *N*,*N*-dimethylformamide (DMF), followed by treatment with potassium carbonate in methanol gave triol (2*R*,3*S*)-**4**. The specific rotation measured for (2*R*,3*S*)-**4** {$[\alpha]_D^{25} = +5.0$ (*c* 1.05, $CHCl_3$)} was consistent with the literature value {$[\alpha]_D^{25} = +5.8$ (*c* 0.97, $CHCl_3$)},[10] thereby providing confirmation of its absolute (3*S*)-configuration. The inversion of the configuration at C-3 of the epoxyacetate (2*R*,3*R*)-**3** under these conditions was identical to the study reported by Hanson.[11]

The selective protection of (2*R*,3*S*)-**4** as its mono silyl ether (2*R*,3*S*)-**5** was achieved using *tert*-butyldiphenylsilyl chloride in the presence of a catalytic amount of DMAP, subsequent oxidation

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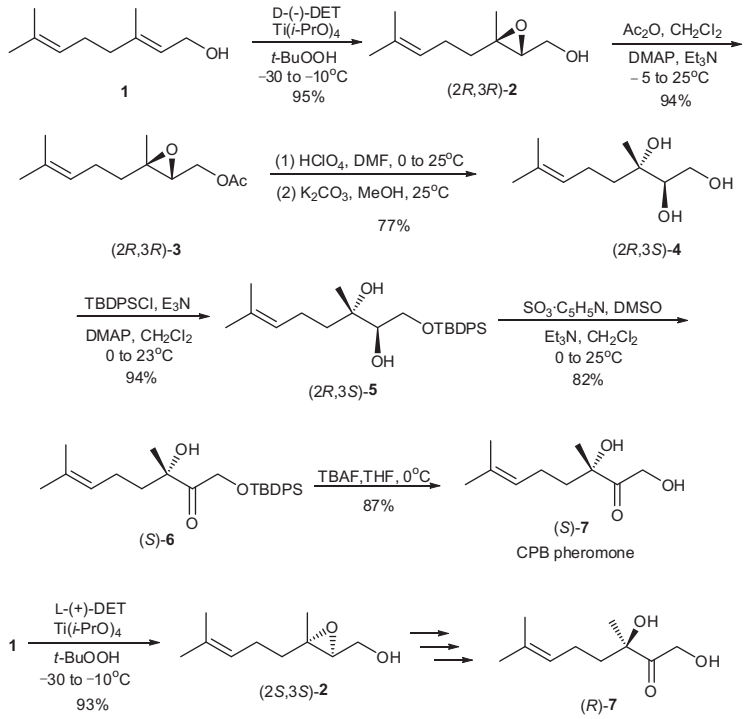
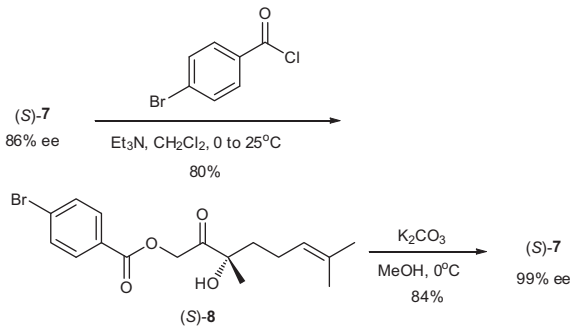


Scheme 1. Synthesis of the CPB pheromone and its enantiomer.

of (2*R*,3*S*)-**5** with dimethyl sulfoxide (DMSO), and the sulfur trioxide-pyridine complex gave (*S*)-**6** in 82% yield.[12] Desilylation with tetra-*n*-butylammonium fluoride (TBAF) provided the desired (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one (*S*)-**7** whose spectroscopic properties matched with the reported values of the natural product.[4] A similar procedure for the synthesis of (*R*)-**7** was developed from the Sharpless asymmetric epoxidation of geraniol **1** with L-(+)-diethyl tartrate. The racemic material was obtained by repeating the sequence described above and gave (±)-**7** from (±)-**2**, being achieved with *tert*-butyl hydroperoxide and vanadium acetylacetonate as described by Sharpless.[13]

Recrystallization of the 4-nitrobenzoates or 3,5-dinitrobenzoates from chiral alcohols can improve the enantiomeric purity,[14] unfortunately those benzoates of CPB pheromone were oils. After careful experimentation, crystalline 4-bromobenzoate from CPB pheromone (*S*)-**8** was obtained with 86% ee determined by chiral HPLC on an AD-H column. Slow recrystallization of benzoate (*S*)-**8** from hexanes–ether improved the enantiomeric purity to 99% ee, and then hydrolysis of it with potassium carbonate and methanol offered nearly enantiomerically pure CPB pheromone (*S*)-**7** (Scheme 2). The specific rotation of (*S*)-**7** {$[\alpha]_D^{25} = +3.3$ (*c* 1.05, $CHCl_3$)} was consistent with the literature value {$[\alpha]_D^{25} = +3.2$ (*c* 0.4, $CHCl_3$)}.[8] A 4-bromobenzoate from the enantiomer of CPB pheromone (*R*)-**8** was obtained, and the enantiomeric purity of (*R*)-**7** was improved to 99% ee with the same method.



Scheme 2. Improvement of the enantiomeric purity of (*S*)-**7**.

To further confirm the absolute configuration of the CPB pheromone, the structural X-ray investigation of 4-bromobenzoate of (*R*)-**7** was carried out. Benzoate (*R*)-**8** with 99% ee was carefully crystallized from hexane–ether to give good crystals, and the X-ray crystallographic structure of it (Fig. 1) indicating that the absolute configuration was (*R*).

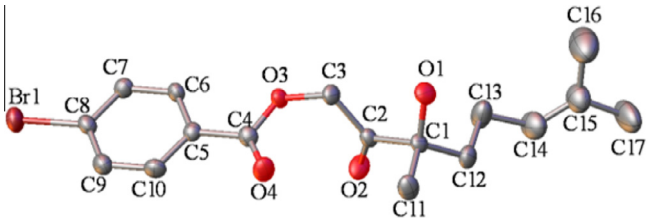


Figure 1. X-Ray crystallographic structure of (*R*)-**8** (CCDC 958550).

3. Conclusion

Herein the pheromone secreted by the male Colorado potato beetle and its enantiomer was prepared with high enantiomeric purity (99% ee) and in gram quantities from Sharpless asymmetric epoxidation of geraniol. Moreover, the absolute configuration of the CPB pheromone enantiomer was confirmed as (*R*) for the first time by the X-ray crystallographic structure of its benzoate.

4. Experimental

4.1. General

All reactions were performed under an argon atmosphere. Solvents were dried according to standard procedures and distilled

before use. All reagents were purchased commercially and used without further purification, unless stated otherwise. Melting points were recorded using a STUART-SMP3 Melt-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. High-resolution mass spectra were recorded on an Agilent instrument by the TOF MS technique. Enantiomeric excesses (ee) were determined by chiral HPLC analyses using a chiral column (Chiralpak AD-H), and elution with isopropanol–hexanes. The optical rotations were measured on a PERKIN ELMER 341 Polarimeter. Crystallographic data were obtained using a Rigaku MM007HF Saturn724+ X-ray diffractometer.

4.2. Synthesis of the CPB pheromone and its enantiomer

4.2.1. Synthesis of (2*R*,3*R*)-3-methyl-3-(4-methylpent-3-en-1-yl)-oxiran-2-yl)methanol (2*R*,3*R*)-2

A solution of 4 Å molecular sieves (2.12 g) and CH_2Cl_2 (60 mL) was cooled to −10 °C, D-(−)-diethyl tartrate (0.56 g, 2.7 mmol) and Ti(*i*-PrO)$_4$ (0.54 g, 1.9 mmol) were added sequentially. The mixture was stirred and a solution of *tert*-butyl hydroperoxide (11.6 mL, 5.5 M in heptane, 64 mmol) was added via a syringe at a slow rate. The solution was cooled to −30 °C and stirred for 30 min, after which geraniol (5.0 g, 32 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for an additional 5 h at −30 to −10 °C, and the reaction was quenched with water (24 mL). The mixture was allowed to warm to 23 °C, and a 30% aqueous solution of NaOH (3 mL) was added. The mixture was stirred for 1 h, and filtered through a Celite pad. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to give (2*R*, 3*R*)-**2** (5.16 g, 95%) as a colorless oil. $[\alpha]_D^{25} = +4.5$ (*c* 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (s, 3H), 1.40–1.50 (m, 1H), 1.61 (s, 3H), 1.61–1.76 (m, 1H), 1.66 (s, 3H), 1.96 (br s, 1H), 2.05–2.13 (m, 2H), 2.98 (dd, *J* = 4.2, 6.7 Hz, 1H), 3.64–3.71 (m, 1H), 3.80–3.87 (m, 1H), 5.09 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ: 16.68, 17.56, 23.61, 25.58, 38.43, 61.12, 61.38, 62.93, 123.29, 132.07; HRMS (TOF) *m*/*z* calcd for $C_{10}H_{19}O_2$ $[M+H]^+$ 171.1385, found 171.1385.

4.2.2. Synthesis of (2*S*,3*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)-oxiran-2-yl)methanol (2*S*,3*S*)-2

According to the similar procedure described above, geraniol (5.0 g, 32 mmol) was converted into (2*S*,3*S*)-**2** (5.06 g, 93%) as a colorless oil with L-(+)-diethyl tartrate. $[\alpha]_D^{25} = -4.2$ (*c* 3.0, $CHCl_3$), lit[9c] $[\alpha]_D^{24} = -5.3$ (*c* 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (s, 3H), 1.42–1.52 (1H, m), 1.61 (s, 3H), 1.63–1.73 (m, 1H), 1.66 (s, 3H), 2.02–2.12 (m, 3H), 2.98 (dd, *J* = 4.2, 6.8 Hz, 1H), 3.64–3.72 (m, 1H), 3.80–3.87 (m, 1H), 5.06–5.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.68, 17.56, 23.61, 25.58, 38.44. 61.14, 61.36, 63.02, 123.30, 132.07; HRMS (TOF) *m*/*z* calcd for $C_{10}H_{19}O_2$ $[M+H]^+$ 171.1385, found 171.1381.

4.2.3. Synthesis of (2*R*,3*R*)-(3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl) methyl acetate (2*R*,3*R*)-3

Triethylamine (5.40 mL, 38.4 mmol) and DMAP (0.39 g, 3.2 mmol) were added to a stirred solution of (2*R*,3*R*)-**2** (5.45 g, 32 mmol) in CH_2Cl_2 (60 mL) at −5 °C. Acetic anhydride (3.63 mL, 38.4 mmol) was added via a syringe and the mixture was stirred for 20 min. Water was poured into the mixture after an additional stirring for 3 h at room temperature. The aqueous phase was extracted with EtOAc, and combined organic phases were washed with saturated $NaHCO_3$ solution and brine, successively, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give (2*R*,3*R*)-**3** (6.40 g, 94%) as a colorless oil. $[\alpha]_D^{25} = +25.0$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 3H), 1.43–1.53 (m, 1H), 1.61–1.74 (m, 1H), 1.64 (s, 3H), 1.71 (s, 3H), 2.05–2.11 (m, 2H), 2.12 (s, 3H), 2.99 (dd, *J* = 4.2, 6.9 Hz, 1H), 4.03 (dd, *J* = 6.9, 12.1 Hz, 1H), 4.32 (dd, *J* = 4.2, 12.1 Hz, 1H), 5.06–5.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.77, 17.55, 20.70, 23.54, 25.57, 38.20, 59.57, 60.45, 63.34, 123.17, 132.10, 170.73; HRMS (TOF) *m*/*z* calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1491, found 213.1494.

4.2.4. Synthesis of ((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-en-1-yl) oxiran-2-yl)methyl acetate (2*S*,3*S*)-3

According to the similar procedure described above, (2*S*,3*S*)-**2** (5.45 g, 32 mmol) was converted into (2*S*,3*S*)-**3** (6.31 g, 93%) as a colorless oil. $[\alpha]_D^{25} = -20.2$ (*c* 1.7, $CHCl_3$), lit[11] $[\alpha]_D^{20} = -24$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 3H), 1.43–1.53 (m, 1H), 1.61 (s, 3H), 1.63–1.73 (m, 1H), 1.71 (s, 3H), 2.05–2.11 (m, 2H), 2.12 (s, 3H), 2.99 (dd, *J* = 4.3, 6.9 Hz, 1H), 4.03 (dd, *J* = 6.9, 12.1 Hz, 1H), 4.31 (dd, *J* = 4.2, 12.1 Hz, 1H), 5.06–5.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.77, 17.55, 20.70, 23.54, 25.57, 38.20, 59.57, 60.45, 63.34, 123.17, 132.10, 170.73; HRMS (TOF) *m*/*z* calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1491, found 213.1494.

4.2.5. Synthesis of (2*R*,3*S*)-3,7-dimethyl-6-octene-1,2,3-triol (2*R*,3*S*)-4

An aqueous solution of $HClO_4$ (4.45 mL, 60%) was added slowly to a stirred solution of (2*R*,3*R*)-**3** (5.75 g, 27 mmol) in DMF (60 mL) at 0 °C. After stirring for 12 h at room temperature, the mixture was diluted with EtOAc (150 mL). The resulting mixture was washed with saturated $NaHCO_3$ solution, water and brine sequentially, dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in MeOH (50 mL), and K_2CO_3 (0.42 g, 4.25 mmol) was added. After an additional stirring for 20 h, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 3:1) to yield (2*S*,3*S*)-**4** (3.91 g, 77%) as a colorless oil. $[\alpha]_D^{25} = +5.0$ (*c* 1.05, $CHCl_3$), lit[10] $[\alpha]_D^{25} = +5.8$ (*c* 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (s, 3H), 1.31–1.42 (m, 1H), 1.55–1.68 (m,1H), 1.61 (s, 3H), 1.68 (s, 3H), 1.97–2.15 (m, 2H), 3.29 (br s, 1H), 3.49 (br s, 1H), 3.67–3.73 (m, 2H), 3.95 (br s, 1H), 4.13–4.14 (m, 1H), 5.10 (t, *J* = 6.9 Hz 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.62, 22.10, 23.17, 25.61, 37.69, 63.10, 74.50, 76.86, 124.12, 131.89. HRMS (TOF) *m*/*z* calcd for $C_{10}H_{19}O_3$ $[M-H]^+$ 187.1334, found 187.1333.

4.2.6. Synthesis of (2*S*,3*R*)-3,7-dimethyl-6-octene-1,2,3-triol (2*S*,3*R*)-4

According to the similar procedure described above, (2*S*,3*S*)-**3** (5.75 g, 27 mmol) was converted into (2*S*,3*R*)-**4** (3.87 g, 76%) as a colorless oil. $[\alpha]_D^{25} = -6.7$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H), 1.25–1.43 (m, 1H), 1.55–1.68 (m, 1H), 1.62 (s, 3H), 1.68 (s, 3H), 2.00–2.13 (m, 2H), 3.13 (br s, 1H), 3.48 (br s, 1H), 3.73–3.74 (m, 3H), 3.92–3.93 (m, 1H), 5.10 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.63, 22.13, 23.23, 25.63, 37.74, 63.14, 74.60, 76.73, 124.11, 131.97. HRMS (TOF) *m*/*z* calcd for $C_{10}H_{19}O_3$ $[M-H]^+$ 187.1334, found 187.1334.

4.2.7. Synthesis of (2*R*,3*S*)-1-*tert*-butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (2*R*,3*S*)-5

To a stirred solution of (2*R*,3*S*)-**4** (5.6 g, 30 mmol) in CH_2Cl_2 (100 mL), triethylamine (9.3 mL, 66.1 mmol), *tert*-butylchlorodiphenylsilane (8.5 mL, 34 mmol) and DMAP (47 mg, 0.38 mmol) were added sequentially at 0 °C. The reaction mixture was maintained for 12 h at 23 °C, and quenched with water. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, water, and brine consecutively, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to furnish (2*S*,3*S*)-**5** (12.01 g, 94%) as

a colorless oil. $[\alpha]_D^{25} = -1.92$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 9H), 1.09 (s, 3H), 1.19–1.39 (m, 1H), 1.32–1.61 (m, 2H), 1.50–1.62 (m, 2H), 1.56 (s, 3H), 1.66 (s, 3H), 1.94–1.95 (m, 1H), 2.07–2.09 (m, 1H), 2.70 (s, 1H), 2.91 (d, *J* = 5.0 Hz, 1H), 3.47–3.52 (m, 1H), 3.76–3.84 (m, 2H), 5.03–5.07 (m, 1H), 7.37–7.48 (m, 6H), 7.65–7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.54, 19.09, 22.07, 23.12, 25.60, 26.80, 38.05, 64.84, 73.80, 75.80, 124.23, 127.81, 129.91, 131.65, 132.53, 132.67, 135.47, 135.50; HRMS (TOF) *m*/*z* calcd for $C_{26}H_{35}O_3Si$ $[M-H]^+$ 425.2512, found 425.2504.

4.2.8. Synthesis of (2*S*,3*R*)-1-*tert*-butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (2*S*,3*R*)-5

According to the similar procedure described above, (2*S*,3*R*)-**4** (5.6 g, 30 mmol) was converted into (2*S*,3*R*)-**5** (12.03 g, 94%) as a colorless oil. $[\alpha]_D^{25} = +1.92$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 9H), 1.19 (s, 3H), 1.26–1.39 (m, 2H), 1.50 (s, 3H), 1.50–1.56 (m, 1H), 1.66 (s, 3H), 1.92–1.98 (m, 1H), 2.05–2.09 (m, 1H), 2.71 (s, 1H), 2.92 (d, *J* = 4.8 Hz, 1H), 3.49–3.52 (m, 1H), 3.79–3.81 (m, 2H), 5.03–5.05 (m, 1H), 7.37–7.45 (m, 6H), 7.66–7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.54, 19.09, 22.07, 23.13, 25.60, 26.80, 38.05, 64.84, 73.80, 75.81, 124.24, 127.81, 129.91, 131.64, 132.54, 132.67, 135.47, 135.50; HRMS (TOF) *m*/*z* calcd for $C_{26}H_{37}O_3Si$ $[M-H]^+$ 425.2512 found 425.2497.

4.2.9. Synthesis of (*S*)-1-*tert*-butyldiphenylsilyloxy-3-hydroxy-3,7-dimethyl-6-octen-2-one (*S*)-6

To a solution of (2*R*,3*S*)-**5** (2.63 g, 6.1 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 °C, DMSO (22 mL), triethylamine (6 mL, 42.64 mmol) and sulfur trioxide pyridine complex (4.86 g, 30.6 mmol) were added sequentially. After stirring for 24 h at room temperature, the reaction was quenched with water at 0 °C, and extracted with CH_2Cl_2. The combined organic phases were successively washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to give (*S*)-**6** (2.13 g, 82%) as a colorless oil. $[\alpha]_D^{25} = -0.52$ (*c* 1.46, $CHCl_3$), lit[6] $[\alpha]_D^{21} = -0.5$ (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 9H), 1.09 (s, 3H), 1.51 (s, 3H), 1.54–1.74 (m, 3H), 1.63 (s, 3H), 1.96–2.01 (m, 1H), 3.46 (s, 1H), 4.52 (s, 2H), 4.93–4.99 (m, 1H), 7.36–7.47 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.61, 19.24, 22.08, 25.54, 25.59, 26.71, 39.46, 66.28, 78.31, 123.35, 127.82, 129.98, 132.46, 132.49, 135.51, 135.57, 135.58, 211.15. HRMS (TOF) *m*/*z* calcd for $C_{26}H_{35}O_3Si$ $[M-H]^+$ 423.2355, found 423.2358.

4.2.10. Synthesis of (*R*)-1-*tert*-butyldiphenylsilyloxy-3-hydroxy-3,7-dimethyl-6-octen-2-one (*R*)-6

According to the similar procedure described above, (2*S*,3*R*)-**5** (2.63 g, 6.1 mmol) was converted into (*R*)-**6** (2.15 g, 83%) as a colorless oil. $[\alpha]_D^{25} = +0.5$ (*c* 1.46, $CHCl_3$), lit[6] $[\alpha]_D^{20} = +0.45$ (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 9H), 1.10 (s, 3H), 1.51 (s, 3H), 1.54–1.76 (m, 3H), 1.63 (s, 3H), 1.96–2.01 (m, 1H), 3.46 (s, 1H), 4.52 (s, 2H), 4.93–4.99 (m, 1H), 7.36–7.47 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.63, 19.26, 22.09, 25.55, 25.60, 26.72, 39.47, 66.28, 78.32, 123.36, 127.84, 130.00, 132.46, 132.50, 132.52, 135.59, 135.60, 211.16. HRMS (TOF) *m*/*z* calcd for $C_{26}H_{35}O_3Si$ $[M-H]^+$ 423.2355, found 423.2366.

4.2.11. Synthesis of (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one (CPB pheromone) (*S*)-7

To a stirred solution of (*S*)-**6** (2.23 g, 5.25 mmol) in THF (25 mL) was added tetra-*n*-butylammonium fluoride (7.9 mL, 1.0 M in THF, 7.9 mmol) slowly at 0 °C. After the reaction mixture was maintained for 40 min at 0 °C, it was poured into water and extracted with EtOAc. The combined organic phases were washed with water and brine consecutively, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to give (*S*)-**7** (0.85 g, 87%) as a colorless oil. $[\alpha]_D^{25} = +2.3$ (*c* 0.79, $CHCl_3$), lit[8] $[\alpha]_D^{25} = +3.2$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (s, 3H), 1.58 (s, 3H), 1.71 (s, 3H), 1.58–1.85 (m, 2H), 1.86–1.91 (m, 1H), 2.06–2.08 (m, 1H), 2.92 (s, 1H), 2.94 (t, *J* = 4.9 Hz, 1H), 4.48–4.51 (m, 2H), 5.02–5.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.64, 22.16, 25.60, 26.07, 39.93, 64.66, 78.47, 122.98, 133.25, 214.15. HRMS (TOF) *m*/*z* calcd for $C_{10}H_{17}O_3$ $[M-H]^+$ 185.1178, found 185.1173.

4.2.12. Synthesis of (*R*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one (*R*)-7

According to the similar procedure described above, (*R*)-**6** (2.23 g, 5.25 mmol) was converted into (*R*)-**7** (0.83 g, 85%) as a colorless oil. $[\alpha]_D^{25} = -2.5$ (*c* 0.79, $CHCl_3$), lit[6] $[\alpha]_D^{25} = -4.0$ (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.68–1.81 (m, 2H), 1.82–1.96 (m,1H), 2.03–2.13 (m, 1H), 3.13 (t, *J* = 4.9 Hz, 1H), 3.17 (s, 1H), 4.49–4.58 (m, 2H), 5.04 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.56, 22.07, 25.53, 25.93, 39.89, 64.65, 78.42, 122.96, 133.06, 214.22. HRMS (TOF) *m*/*z* calcd for $C_{10}H_{17}O_3$ $[M-H]^+$ 185.1178, found 185.1177.

4.3. Improvement of the enantiomeric purity of (*S*)-7 and (*R*)-7

4.3.1. Synthesis of (*S*)-3-hydroxy-3,7-dimethyl-2-oxo-6-octenyl 4-bromobenzoate (*S*)-8

To a stirred solution of (*S*)-**7** (1.86 g, 10 mmol) and triethylamine (3.1 mL, 22 mmol) in CH_2Cl_2 (10 mL) at 0 °C, a solution of 4-bromobenzoyl chloride (2.63 g, 12 mmol) in CH_2Cl_2 was added dropwise over 15 min. After stirring overnight at room temperature, the reaction was quenched with water and extracted with CH_2Cl_2. The organic phase was washed sequentially with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to give (*S*)-**8** (3.5 g, 95%, 86% ee) as a white solid. Slow recrystallization of (*S*)-**8** from hexanes-ether improved the enantiomeric purity to 99% ee, and gave nearly enantiomerically pure (*S*)-**8** as colorless crystals. The overall yield of the parabromobenzoylation was 80% (2.95 g, 8 mmol). mp 85.1–85.2 °C; $[\alpha]_D^{25} = +5.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 3H), 1.62 (s, 3H), 1.67 (s, 3H), 1.71–1.84 (m, 1H), 1.85–1.92 (m, 1H), 2.00–2.05 (m, 1H), 2.11–2.16 (m, 1H), 3.06 (s, 1H), 5.07–5.15 (m, 1H), 5.15–5.27 (m, 2H), 7.58–7.63 (m, 2H), 7.93–7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.69, 22.15, 25.65, 25.91, 39.72, 65.69, 79.03, 123.20, 128.20, 128.56, 131.38, 131.81, 133.15, 165.21, 207.05; HRMS (TOF) *m*/*z* calcd for $C_{17}H_{22}BrO_4$ $[M+H]^+$ 369.0701, found 369.0684. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *n*-hexanes/isopropanol, 1.0 mL/min, 230 nm); minor (*R*)-enantiomer t_r = 8.2 min, major (*S*)-enantiomer t_r = 9.0 min.

4.3.2. Hydrolysis of (*S*)-8 to (*S*)-7

To a solution of (*S*)-**8** (1.92 g, 5 mmol) in methanol (10 mL) at 0 °C was added NaOH (25 mL, 1 mol/L, 25 mmol). After stirring for 3 h, the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to give (*S*)-**7** (0.78 g, 84%) as a colorless oil. $[\alpha]_D^{25} = +3.3$ (*c* 1.7, $CHC1_3$), lit[8] $[\alpha]_D^{25} = +3.2$ (*c* 0.4, $CHCl_3$).

4.3.3. Synthesis of (*R*)-3-hydroxy-3,7-dimethyl-2-oxo-6-octenyl 4-bromobenzoate (*R*)-8

According to the similar procedure described above, (*R*)-**7** (1.86 g, 10 mmol) was converted into (*R*)-**8** (2.92 g, 79%, 99% ee) as colorless crystals. mp 85.1–85.3 °C; $[\alpha]_D^{25} = -5.4$ (*c* 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.71–1.84 (m, 1H), 1.85–1.92 (m, 1H), 2.00–2.05 (m, 1H), 2.11–2.16 (m, 1H), 3.08 (s, 1H), 5.07–5.12 (m, 1H), 5.15–5.28 (m, 1H), 7.58–7.63 (m, 2H), 7.93–7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.69, 22.15, 25.65, 25.91, 39.72, 65.69, 79.03, 123.20, 128.20, 128.56, 131.38, 131.81, 133.15, 165.21, 207.05. HRMS (TOF) m/z calcd for $C_{17}H_{22}BrO_4$ $[M+H]^+$ 369.0701, found 369.0696. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 *n*-hexanes/isopropanol, 1.0 mL/min, 230 nm); major (*R*)-enantiomer t_r = 8.5 min, minor (*S*)-enantiomer t_r = 9.6 min.

4.3.4. Hydrolysis of (*R*)-8 to (*R*)-7

According to the similar procedure described above, (*R*)-**8** (1.92 g, 5 mmol) was converted into (*R*)-**7** (0.75 g, 81%) as a colorless oil. $[\alpha]_D^{25} = -3.7$ (*c* 1.0, $CHCl_3$), lit[6] $[\alpha]_D^{25} = -4.0$ (*c* 1.08, $CHCl_3$).

4.4. X-Ray crystal data of (*R*)-8

$C_{17}H_{21}BrO_4$, crystal system: monoclinic; unit cell dimensions: P_1, a = 5.985 (2), b = 10.491 (4), c = 14.028 (5) Å; α = 90, β = 92.25(6), γ = 90°; volume = 880.2 (5) Å^3; Z = 2; calculated density: 1.393 mg/cm^3; absorption coefficient: 2.349 mm^{-1}; F(000): 380; θ range for data collection: 2.91–27.49°; refinement method: full-matrixleast-squares on F^2; data/parameters: 3930/203; goodness-of-fit on F^2: 1.071; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0414, wR_2 = 0.0868; R indices (all data): R_1 = 0.0445, wR_2 = 0.0890.

The structure was solved by direct methods program SHELXL-97. The chirality of the asymmetric carbon atom $C_3(C_1)$ was determined by a Flack analysis, and absolute structure parameter is 0.008(10). Therefore, the absolute configuration assigns the (*R*)-chirality to the quaternary carbon center.

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