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Enantiospecific Synthesis of Both Enantiomers of the Longtailed Mealybug Pheromone and Their Evaluation in a New Zealand Vineyard

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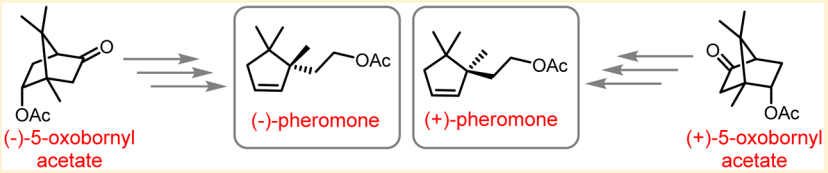
Supporting Information



ABSTRACT: The irregular monoterpenoid sex pheromone of *Pseudococcus longispinus* and its enantiomer were prepared from the corresponding bornyl acetates. The use of readily accessible chiral starting materials and lactone−lactone rearrangement are the highlights of the present synthesis. The biological activities of the two enantiomers and racemic mixture were tested in a New Zealand vineyard. The (*S*)-(+)-enantiomer was significantly more attractive to *P. longispinus* males than the racemic mixture or the (*R*)-(−)-enantiomer.

Pheromones are chemicals released by organisms and serve as a means of communication between individuals of the same species. Among these, sex pheromones are of particular interest and find application in insect pest management. These pheromones are secreted by an individual so as to attract a potential mate. They can be very powerful, attracting conspecifics of the opposite sex from long distances.[1] The female-produced sex pheromone of *Pseudococcus longispinus*, the longtailed mealybug, a widely distributed pest of agricultural crops and ornamental plants, was identified by Millar et al.[2] In field trials, the racemic pheromone was very attractive to male longtailed mealybugs at low doses (25 μg) for more than three months. Because of this interesting biological activity and its utility in pest management strategies, to date five syntheses have been reported for the racemic compound.[2,3] Recently, in collaboration with the Millar group, we showed that the (*S*)-(+)-enantiomer was highly attractive and that the (*R*)-(−)-enantiomer was inactive, suggesting that female longtailed mealybugs produce the (*S*)-enantiomer.[4]

In our previous synthesis, racemic 3,4,4-trimethyl-3-vinylhept-6-en-1-ol was converted to its diastereomeric derivatives using Harada's camphorsultam phthalic acid (CSP acid), then both the diastereomers were separated by chiral HPLC (Scheme 1). Although we were able to synthesize both the enantiomers and determine the likely absolute configuration of the natural pheromone, this method was not suitable for making large quantities of the pure enantiomers. Here, we report enantiospecific routes to both the enantiomers of the pheromone starting from readily accessible chiral synthons and the results of field trials in New Zealand.

Choosing the appropriate starting material and reagents was crucial, as we were looking for a scalable and cheap synthesis. We reasoned that bicyclic terpenes, such as camphor, would be suitable starting materials. Initially, the commercially available (−)-bornyl acetate was chosen as starting material for optimization toward (−)-pheromone. The keto acetate (−)-**2**, prepared from (−)-bornyl acetate following literature procedures,[5] was subjected to Baeyer−Villiger oxidation using H_2O_2−H_2SO_4 conditions in acetic acid (Scheme 2).[6] We settled on these conditions after a few initial optimizations (*m*-CPBA along with additives such as $NaHCO_3$, PTSA, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$). The reaction with *m*-CPBA was very sluggish and gave a mixture of products, and we could not isolate the desired compound in pure form. The present condition using H_2O_2/H_2SO_4 in acetic acid followed by acetate hydrolysis gave the trans-lactonized product (−)-**3** along with a minor amount of the bicyclic lactone (−)-**3a**. The structure of (−)-**3** was unambiguously confirmed by X- ray crystal structure analysis. This translactonization (lactone to lactone rearrangement) might have occurred under the reaction conditions to relieve the extra ring strain of the [3.2.1] bicyclic lactone.[7] The lactone (−)-**3** was subjected to PDC oxidation to provide (−)-**4** in 89% yield. Compound (−)-**4** was refluxed in methanol in the presence of PTSA to obtain cyclopentenone derivative (−)-**5**, whose transesterification followed by dehydration took place in a single-pot operation.[8] The allylic alcohol **6** prepared by Luche reduction of (−)-**5** was then subjected to deoxygenation using $BF_3{\cdot}Et_2O$ and sodium cyanoborohydride.[9]

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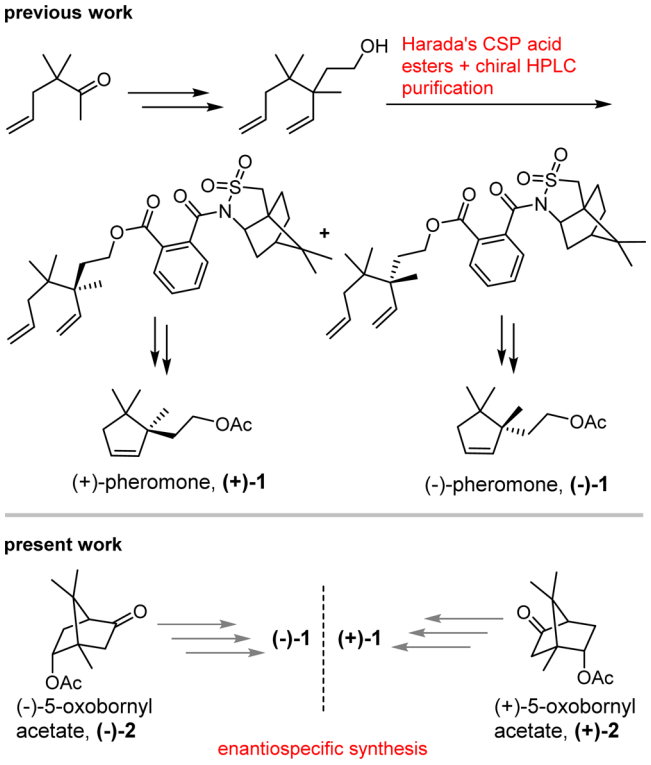
Scheme 1. Access to Enantiopure Pheromones



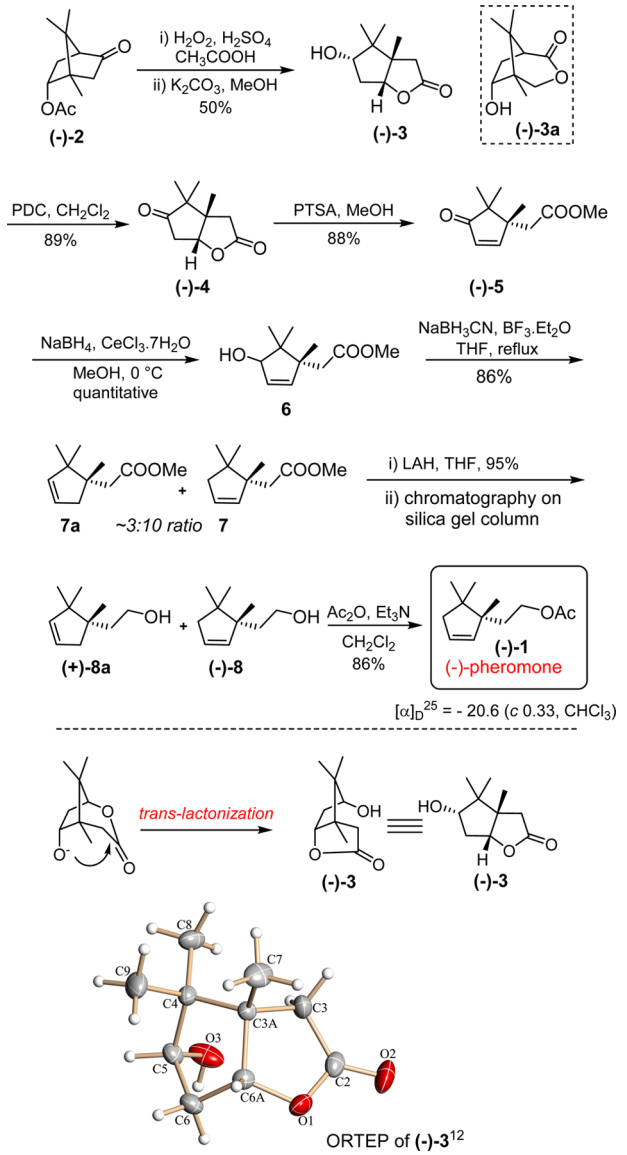
This reaction gave a mixture of both the olefin regioisomers **7** and **7a** in a 10:3 ratio, which on reduction with $LiAlH_4$ resulted in (−)-**8** and (+)-**8a**, with a combined yield of 82%.[10] Although alcohols were inseparable by TLC, we were able to separate them by careful column chromatography. The pure alcohol (−)-**8** was acylated to give the unnatural enantiomer of the pheromone (−)-**1**. The NMR data and optical rotation were in good agreement with the previously reported data.[4,11]

In analogous fashion, the synthesis of the natural enantiomer, (+)-**1** was accomplished from (+)-5-oxo-bornylacetate, (+)-**2**, which in turn was prepared from (+)-camphor using a published procedure (Scheme 3).[5,11,13]

Previously, both the enantiomers and the racemate had been tested in California (USA) vineyards, demonstrating that both the (+)-enantiomer and the racemate were active. We wanted to test all three forms in a completely different geographical location (a New Zealand vineyard infested with the longtailed mealybug) because during initial testing of the racemate in New Zealand, results did not appear as promising as they did in California. Accordingly, a field trial was established in a Hawke's Bay vineyard (39°33′0.93″ S, 176°53′34.13″ E) containing sauvignon blanc vines known to be infested with *Pseudococcus longispinus*. Thus, in March 2014, we tested delta sticky traps baited with red rubber septa dosed with one of the following: 10 μg of (+)-**1**, 10 μg of (−)-**1**, 20 μg of racemic pheromone, or a solvent blank.

The results from the New Zealand trials show that the (+)-enantiomer (+)-**1** was significantly more attractive than the racemate, or the (−)-enantiomer (−)-**1** (Figure 1). Previous work[4] also had shown the highest catches in trap baited with (+)-**1** but not significantly different from the racemate. Here, we report the highest catches again with (+)-**1**, but this time, statistical analysis does show a significant difference from the racemate. The minimal catch of the (−)-**1** treatment is likely a result of contamination with trace amounts of (+)-**1**.[14]

Scheme 2. Synthesis of (−)-(*R*)-Pheromone



In summary, we have developed a new route for the enantiospecific synthesis of both the natural and unnatural enantiomers of the sex pheromone of the longtailed mealybug. Significantly, the route does not rely on the difficult separation of diasteromeric derivatives but on use of readily available enantiopure starting materials from the chiral pool. Trapping trials with the enantiomers in New Zealand further confirmed that the (+)-enantiomer is highly attractive to male longtailed mealybugs.

EXPERIMENTAL SECTION

General. All reagents, starting materials, and solvents (including dry solvents) were obtained from commercial suppliers and used as such without further purification. Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or $KMnO_4$ followed by heating with a heat gun for ∼15 s. Column

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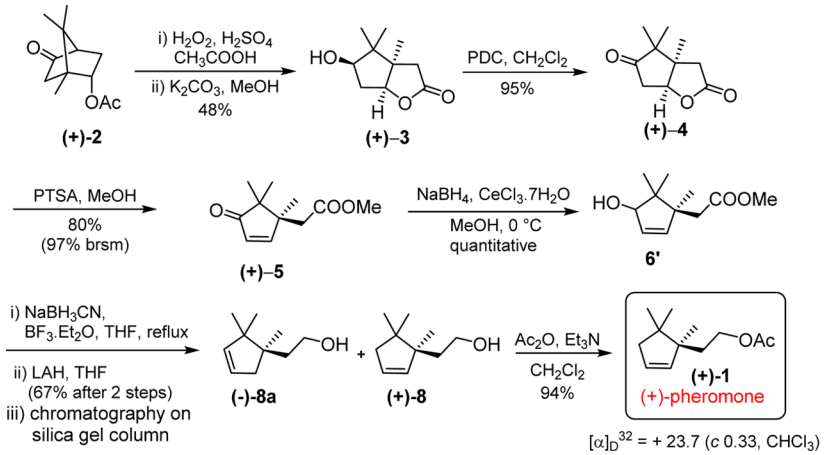
Scheme 3. Synthesis of (+)-(*S*)-Pheromone



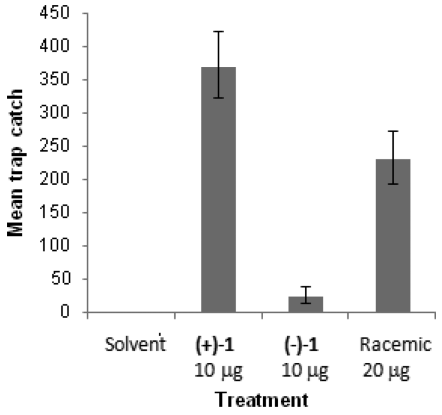


Figure 1. Mean numbers of male *Pseudococcus longispinus* caught per trap in a New Zealand vineyard using pheromone enantiomers, racemate, or solvent controls (n = 5 for each treatment). Error bars are 95% confidence limits for the means. Trap catches varied significantly between all treatments ($P < 0.001$).

chromatography was performed on silica gel (100–200 or 230–400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200, 400, or 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. HRMS (ESI) were recorded on an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as thin films using NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

Synthesis of (*R*)-(−)-Pheromone. *(3aS,5S,6aR)-5-Hydroxy-3a,4,4-trimethylhexahydro-2H-cyclopenta[b]furan-2-one ((−)-3).* Acetic acid (6 mL) and H_2O_2 (35 wt % in water, 5 mL) were taken in a single neck round-bottomed flask and cooled to 0 °C, and H_2SO_4 (1 mL) was added. Then a solution of (−)-**2**[5] (1.9 g, 9.03 mmol) in acetic acid (3 mL) was added and stirred at RT for 24 h. Ethyl acetate was added, and the aqueous layer was extracted thrice (30 mL × 3). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude thus obtained was dissolved in methanol (20 mL), K_2CO_3 (3.74 g, 27.09 mmol) was added, and stirred at RT for 3 h. The reaction mixture was passed through Celite, and the filtrate was concentrated and purified by column chromatography (230–400 silica gel) using 25–30% ethyl acetate/pet ether to afford the product (−)-**3** as a colorless crystalline solid (832 mg, 50%) along with minor amount of (−)-**3a** (5:2 ratio in this experiment). Mp = 224–226 °C; $[\alpha]_D^{29}$ −9.2 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.55 (dd, J = 8.6, 2.0 Hz, 1H), 3.92 (dd, J = 5.6, 1.7 Hz, 1H), 3.35 (d, J = 18.1 Hz, 1H), 2.51 (ddd, J = 15.9, 8.6, 5.9 Hz, 1H), 2.07 (d, J = 18.1 Hz, 1H), 1.88 (dt, J = 16.1, 2.0 Hz, 1H), 1.73 (brs, 1H), 1.14 (s, 3H), 1.04 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.9, 90.5, 81.4, 50.7, 46.5, 40.2, 39.8, 24.2, 22.1, 18.2; IR ν_{max} (thin film applied as $CHCl_3$ solution) 3470 (broad peak), 2969, 1764, 1069 cm^{-1}. HRMS (ESI): m/z calculated for $C_{10}H_{16}O_3Na$ [M + Na]$^+$ 207.0992; found, 207.0985.

X-ray Crystal Structure Details of (−)-3. Single crystals of compound (−)-**3** was obtained from chloroform. X-ray intensity data were collected on a APEX II CCD diffractometer with graphite-monochromatized (Mo Kα = 0.71073 Å) radiation at room temperature 296(2) K. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with a ω scan width of 0.5° and at different settings of φ and 2θ. The sample-to-detector distance was fixed at 5.00 cm. The X-ray data acquisition was monitored by an APEX II program suite.[15] All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in the APEX II program package.[15] The structures were solved by a direct method and refined by full matrix least-squares, based on F^2, using SHELX-97.[16] ORTEP diagrams were generated using the XSHELL program integrated in the SHELXTL package[16] with 30% probability displacement ellipsoids, and H atoms are shown as small spheres of arbitrary radii. All of the H atoms were placed in geometrically idealized position (C–H = 0.97 Å for the methylene H atom, C–H = 0.96 Å for the methyl H atom, C–H = 0.98 Å for the methine H atom, and O–H = 0.82 Å for the hydroxyl H atom) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C) for the methylene and methine group, U_{iso}(H) = 1.5 U_{eq}(C) for the methyl group and U_{iso}(H) = 1.5U_{eq}(O) for the hydroxyl group].

Crystallographic Data for (−)-3. ($C_{10}H_{16}O_3$): M = 184.23. Crystal dimensions 0.64 × 0.60 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$, a = 6.9872(7), b = 11.6575(12), c = 11.8586(12) Å, V = 965.92(17) Å^3, Z = 4, ρ_{calcd} = 1.267 gcm^{-3}, μ (Mo–K$_\alpha$) = 0.092 mm^{-1}, $F(000)$ = 400, 2θ_{max} = 50.00°, T = 296(2) K, 5178 reflections collected, 1648 unique, 1532 observed ($I > 2\sigma$ (I)) reflections, 122 refined parameters, R value 0.0329, $wR2$ = 0.0806, (all data R = 0.0356, $wR2$ = 0.0824), S = 1.091, minimum and maximum transmission 0.943 and 0.982; maximum and minimum residual electron densities +0.09 and −0.11 e Å^{-3}.

(1S,5R,6R)-6-Hydroxy-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one ((−)-3a). In the above experiment, compound (−)-**3a** was also isolated as a colorless solid (330 mg, 20%). Mp = 264–267 °C; $[\alpha]_D^{28}$ −10.8 (c 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.54 (d, J = 12.7 Hz, 1H), 4.23 (dd, J = 9.6, 2.9 Hz, 1H), 3.84 (d, J = 12.5 Hz, 1H), 2.63–2.55 (m, 1H), 2.46 (d, J = 7.6 Hz, 1H), 1.81 (brs, 1H), 1.64 (dd, J = 14.9, 3.9 Hz, 1H), 1.08 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.9, 76.3, 70.4, 51.7, 46.3, 42.0, 36.0, 21.5, 20.2, 13.2; IR ν_{max} (thin film applied as $CHCl_3$ solution) 3480 (broad peak), 2965, 1716, 1461, 1246, 1057 cm^{-1}. HRMS (ESI): m/z calculated for $C_{10}H_{16}O_3Na$ [M + Na]$^+$ 207.0992; found, 207.0992.

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(3aS,6aR)-3a,4,4-Trimethyltetrahydro-2H-cyclopenta[b]furan-2,5(3H)-dione ((−)-4). To a solution of (−)-**3** (1.2 g, 6.5 mmol) in dry DCM (20 mL), 4 Å molecular sieves was added followed by PDC (3.7 g, 9.8 mmol) and stirred at RT overnight. The reaction mass was filtered through Celite. The filtrate was washed with 1 N HCl, dried over Na_2SO_4, and concentrated. The crude mass was purified by column chromatography (100−200 silica gel) using 15% ethyl acetate/pet ether to give the compound as a white crystalline solid (1.05 g, 89% yield). Mp = 169−171 °C; $[\alpha]_D^{29}$ −98.3 (c 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.79 (dd, J = 9.0, 4.2 Hz, 1H), 3.02 (dd, J = 20.3, 8.8 Hz, 1H), 2.44 (dd, J = 20.3, 4.2 Hz, 1H), 2.32 (AB quartet, 2H), 1.27 (s, 3 H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.3, 175.3, 82.7, 52.4, 50.1, 41.1, 39.0, 21.2, 19.3, 18.8; IR ν_{max} (thin film applied as $CHCl_3$ solution) 2973, 2884, 1783, 1747, 1460, 1288, 1177, 1050 cm^{-1}. HRMS (ESI): m/z calculated for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1016; found, 183.1011.

Methyl (R)-2-(1,5,5-Trimethyl-4-oxocyclopent-2-en-1-yl)acetate ((−)-5). The compound (−)-**4** (900 mg, 4.95 mmol) was dissolved in dry methanol (20 mL), and PTSA monohydrate (3.8 g, 19.8 mmol) was added and refluxed for 24 h. The reaction mass was cooled to RT, and solvent was removed under reduced pressure. Water (10 mL) and DCM (25 mL) were added, and the organic layer was separated, the aqueous layer was extracted with DCM (20 mL × 2), and the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The pure product was obtained by column chromatography (silica gel 100−200) using 10% ethyl acetate/pet ether to afford the product as a colorless liquid (850 mg, 88% yield) along with the recovery of starting material (60 mg, 94% brsm). $[\alpha]_D^{29}$ −4.4 (c 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.71 (d, J = 5.8 Hz, 1H), 6.08 (d, J = 5.8 Hz, 1H), 3.71 (s, 3H), 2.51 (d, J = 14.9 Hz, 1H), 2.39 (d, J = 14.9 Hz, 1H), 1.18 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 213.5, 171.9, 168.5, 129.0, 51.6, 51.3, 48.5, 41.5, 23.0, 22.7, 20.9; IR ν_{max} (thin film applied as $CHCl_3$ solution) 2969, 2883, 1715, 1594, 1203 cm^{-1}. HRMS (ESI): m/z calculated for $C_{11}H_{17}O_3$ $[M + H]^+$ 197.1172; found, 197.1173.

*Methyl (R)-2-(1,5,5-trimethylcyclopent-2-en-1-yl)acetate (**7**).* A solution of (−)-**5** (70 mg, 0.356 mmol) in dry methanol (3 mL) was cooled to 0 °C, added $CeCl_3{\cdot}7H_2O$ (146 mg, 0.392 mmol), followed by sodium borohydride (27 mg, 0.712 mmol) and stirred at RT for 1 h. The reaction mass was cooled to 0 °C and quenched with sat. NH_4Cl, and methanol was removed in a rotary evaporator. Ethyl acetate (10 mL) was added, and the aqueous layer was extracted (10 mL × 3), dried over Na_2SO_4, and concentrated to give the allyl alcohol **6** as a colorless liquid (70 mg, quantitative).

A solution of **6** (70 mg, 0.353 mmol) in dry THF (3 mL) was cooled to 0 °C, $BF_3{\cdot}Et_2O$ (0.13 mL, 1.059 mmol) was added, followed by sodium cyanoborohydride (66 mg, 1.059 mmol) and refluxed overnight. The reaction was quenched with 2 N NaOH, DCM (10 mL) was added, and the organic layer was separated. It was then dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel 230−400 gel) using 2% ethyl acetate/pet ether to give product **7** as a mixture with its regioisomer **7a** (55 mg, 86% combined yield, 10:3 ratio by NMR). Data for the major isomer **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.80−5.76 (m, 1H), 5.68−5.65 (m, 1H), 3.68 (s, 3H), 2.44−2.07 (m, 4H), 0.99 (s, 6H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.6, 138.7, 127.9, 51.2, 49.8, 46.7, 44.1, 40.6, 24.4, 24.0, 19.8.

(R)-2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethan-1-ol ((−)-8). The regioisomeric mixture (**7** and **7a**) obtained in the above step was used to prepare the title compound. This mixture (50 mg, 0.275 mmol) was dissolved in dry THF (3 mL), cooled to 0 °C, added to LAH (31 mg, 0.824 mmol), and stirred at RT for 2 h. The reaction mixture was quenched with saturated Na_2SO_4 solution, ethyl acetate (10 mL) was added, and the organic layer was separated, the aqueous layer was again extracted (10 mL X 2), dried over Na_2SO_4, concentrated in a rotary evaporator, and purified by column chromatography (silica gel 230−400 mesh) using 5% ethyl acetate/pet ether to give the product as a colorless liquid (40 mg, 95% yield along with its regioisomer (+)-**8a**). Both the regioisomers could be separated by flash column chromatography, although they were inseparable in TLC. $[\alpha]_D^{26}$ −10.4 (c 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.65−5.63 (m, 1H), 5.59−5.57 (m, 1H), 3.81−3.68 (m, 2H), 2.15−2.13 (m, 2H), 1.73−1.65 (m, 1H), 1.59−1.52 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H). HRMS (ESI): m/z calculated for $C_{10}H_{19}O$ $[M + H]^+$ 155.1435; found, 155.1430.

(S)-2-(1,2,2-Trimethylcyclopent-3-en-1-yl)ethan-1-ol ((+)-8a). $[\alpha]_D^{25}$ +14.5 (c 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.54−5.51 (m, 1H), 5.44−5.43 (m, 1H), 3.79−3.64 (m, 2H), 2.32−2.28 (m, 1H), 2.03−2.00 (m, 1H), 1.73−1.60 (m, 2H), 0.92 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

(R)-2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethyl acetate ((−)-1). To a solution of (−)-**8** (10 mg, 0.065 mmol) in dry DCM (2 mL), triethylamine (36 μL, 0.26 mmol) and acetic anhydride (12 μL, 0.13 mmol) were added, followed by a pinch of DMAP, and stirred at RT for 3 h. The reaction mixture was diluted with DCM, water was added, the organic layer was separated, dried over Na_2SO_4, concentrated, and purified by column chromatography (100−200 silica gel) using 20% DCM/pentane to afford the product as a colorless liquid (11 mg, 86%). $[\alpha]_D^{25}$ −20.6 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.66−5.63 (m, 1H), 5.58−5.56 (m, 1H), 4.24−4.07 (m, 2H), 2.14 (t, J = 2.2 Hz, 2H), 2.06 (s, 3H), 1.75−1.68 (m, 1H), 1.63−1.54 (m, 1H, merged with moisture peak), 0.97 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H). HRMS (ESI): m/z calculated for $C_{12}H_{20}O_2Na$ $[M + Na]^+$ 219.1356; found, 219.1355.

Synthesis of (*S*)-(+)-Pheromone. The same route was followed for the synthesis of the other antipode (*S*)-(+)-pheromone starting from (+)-**2**.[5,13] The NMR data of all the compounds in this series were found to be exactly matching with the other enantiomeric series. The optical rotations also showed the same magnitude but with an inverse sign.

(3aR,5R,6aS)-5-Hydroxy-3a,4,4-trimethylhexahydro-2H-cyclopenta[b]furan-2-one (+)-3. Yield: 48%; $[\alpha]_D^{28}$ +6.8 (c 0.34, $CHCl_3$).

(3aR,6aS)-3a,4,4-Trimethyltetrahydro-2H-cyclopenta[b]furan-2,5(3H)-dione (+)-4. Yield: 95%; $[\alpha]_D^{28}$ +98.3 (c 0.27, $CHCl_3$).

Methyl (S)-2-(1,5,5-trimethyl-4-oxocyclopent-2-en-1-yl)acetate (+)-5. Yield: 80%, 97% brsm; $[\alpha]_D^{25}$ +4.5 (c 0.50, $CHCl_3$).

(S)-2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethan-1-ol ((+)-8). $[\alpha]_D^{26}$ +11.3 (c 0.30, $CHCl_3$)

(R)-2-(1,2,2-Trimethylcyclopent-3-en-1-yl)ethan-1-ol ((−)-8a). $[\alpha]_D^{24}$ −13.8 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.54−5.51 (m, 1H), 5.44−5.43 (m, 1H), 3.79−3.64 (m, 2H), 2.32−2.28 (m, 1H), 2.03−1.98 (m, 1H), 1.73−1.60 (m, 2H), 0.91 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.6, 126.2, 61.1, 48.7, 44.9, 44.7, 39.6, 23.8, 22.3, 22.2.

(S)-2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethyl acetate ((+)-1). Yield: 94%; $[\alpha]_D^{32}$ +23.7 (c 0.33, $CHCl_3$).

Methyl (*S*)-2-(1,2,2-Trimethyl-3-oxocyclopentyl)acetate. The compound (−)-**5** (350 mg, 1.79 mmol) was dissolved in methanol (5 mL), and palladium on carbon (35 mg, 10 wt %) was added and was stirred under an atmosphere of hydrogen for 1 h. The reaction mass was then filtered through Celite and washed with DCM and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the product as a colorless liquid (330 mg, 93%). $[\alpha]_D^{27}$ −74.5 (c 1.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.64 (s, 3H), 2.36−2.17 (m, 4H), 2.04−1.96 (m, 1H), 1.87−1.80 (m, 1H), 0.97 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 222.3, 172.4, 52.5, 51.4, 43.1, 41.1, 33.6, 30.9, 21.3, 19.8, 18.2; IR ν_{max} (thin film applied as $CHCl_3$ solution) 2968, 1737, 1450, 1206, 1105 cm^{-1}; HRMS $C_{11}H_{18}O_3Na$ $[M + Na]^+$ 221.1148; found, 221.1147.

Methyl (*S*)-2-(1,2,3-Trimethylcyclopent-2-en-1-yl)acetate (S6). The saturated ketone (50 mg, 0.25 mmol) obtained in the above reaction was dissolved in dry methanol (3 mL) and cooled to 0 °C, and $NaBH_4$ (10 mg, 0.25 mmol) was added cautiously and stirred at RT for 1 h. The reaction mass was cooled to 0 °C and quenched with sat. NH_4Cl, and methanol was removed in a rotary evaporator. Ethyl acetate (10 mL) was added, the organic layer was separated, the aqueous layer was again extracted (20 mL × 3), and the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give **S5** (40 mg). The crude mass was used for the next step without further purification.

The compound **S5** (40 mg, 0.20 mmol) was dissolved in dry benzene (3 mL), and P_2O_5 (170 mg, 0.599 mmol) was added and refluxed

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overnight.[17] The reaction mixture was cooled to RT, diluted with DCM (10 mL), and 2 N NaOH was added. The organic layer was separated, washed with brine, and dried over Na_2SO_4, and the solvent was removed in a rotary evaporator. The reaction mixture was purified by column chromatography (silica gel 100−200) using 2−3% ethyl acetate/pet ether to afford the product as a colorless liquid (28 mg, 78% yield). $[\alpha]_D^{30}$ −6.4 (c 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.61 (s, 3H), 2.26 (AB quartet, 2H), 2.16 (m, 2H), 2.05−1.98 (m, 1H), 1.64−1.55 (m, 1H, merged with methyl singlet), 1.58 (s, 3H), 1.49 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.0, 136.0, 131.3, 51.1, 49.7, 43.4, 35.6, 35.2, 25.0, 14.2, 9.4; IR ν_{max} (thin film applied as $CHCl_3$ solution) 3022, 2926, 2856, 1729, 1446, 1322, 1214, 1017 cm^{-1}; HRMS $C_{11}H_{19}O_2$ $[M + H]^+$ 183.1380; found, 183.1379.

(1*S*,5*R*)-5,8,8-Trimethyl-2-oxabicyclo[3.2.1]oct-6-en-3-one (S7). $[\alpha]_D^{27}$ −207.3 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.85 (d, J = 5.9 Hz, 1H), 5.65 (dd, J = 5.8, 1.3 Hz, 1H), 5.05 (m, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.04 (d, J = 17.1 Hz, 1H), 1.19 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 176.9, 146.3, 125.8, 93.8, 51.7, 47.6, 40.0, 26.4, 22.6, 18.4; IR ν_{max} (thin film applied as $CHCl_3$ solution) 3023, 2967, 2876, 1774, 1611, 1457, 1346, 1215, 1178 cm^{-1}; HRMS $C_{10}H_{15}O_2$ $[M + H]^+$ 167.1067; found, 167.1066.

Field Trial of the Pheromone Enantiomers. A field trial of the pheromone was established in a Hawke's Bay vineyard (39°33′0.93″ S, 176°53′34.13″ E) containing sauvignon blanc vines known to be infested with *Pseudococcus longispinus*. Thus, in March 2014, we tested red delta traps with white sticky base baited with red rubber septa dosed with one of the following: 10 μg of (+)-**1**, 10 μg of (−)-**1**, 20 μg of racemic pheromone, or a solvent blank. Using a complete randomized block design, each of the four treatments was replicated five times. The four treatments per trapping row were separated by 25 m; replicate rows were separated by 40 m. The traps were periodically visited during the study. At each visit, traps were allocated a new position within the replicate row using a random number table, with a new sticky base replacing the old one in each trap. Back in the laboratory, male mealybugs were counted. The trapping trial concluded on May 23, 2014. Pheromone lures were not replaced during the trial. The trap counts from March 28 to May 23, 2014 (the first week of data was omitted due to low catch) were analyzed with a Poisson generalized linear model.[18] The model used a logarithmic link function, with dispersion estimated ("Quasi-Poisson").The analysis of deviance assessed various contrasts between the treatments using F-tests. All analyses were carried out with GenStat (version 14). Trap catches of the four treatments were compared examining the effect of the presence of (+)-**1** and the presence/absence of (−)-**1**. Overall, trap catches varied significantly among all of the treatments (P < 0.001).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Initial synthetic plan toward pheromones, optimization conditions for deoxygenation, CIF file (CCDC 1058183), and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01131.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor D. Basavaiah, University of Hyderabad, on the occasion of his 65th birthday.

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(11) In an attempt to determine enantiopurity, we have tried a few methods to resolve the racemic pheromone and alcohol using chiral GC. It was not satisfactory for us to determine the % ee as the baseline separation was not seen. Professor Millar also mentioned in his original paper (see ref 2a of this paper) that it was difficult to resolve the compounds under various methods. As we are starting from chiral pool material and also at no place during the sequence can it (possibly) racemize, we are confident that they are pure enantiomers.

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