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Synthesis of the Female Sex Pheromone of the Citrus Mealybug, *Planococcus citri*

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The citrus mealybug, *Planococcus citri* (Risso) is a common pest in the Southern U. S. and the Mediterranean. Two alternative syntheses of the female sex pheromone, (1*R*)-(+)-*cis*-2,2-dimethyl-3-isopropenyl-cyclobutane methanol acetate, have been developed. Key transformations include an allylic oxidation of (1*R*)-(+)-α-pinene to (+)-*R*-verbenone, oxidative decarboxylation using $RuCl_3$−$NaIO_4$, and methylenation with $Zn/CH_2Br_2/TiCl_4$.

KEYWORDS: (+)-*cis*-Planococcyl acetate; synthesis; pheromones; olefination; oxidation

INTRODUCTION

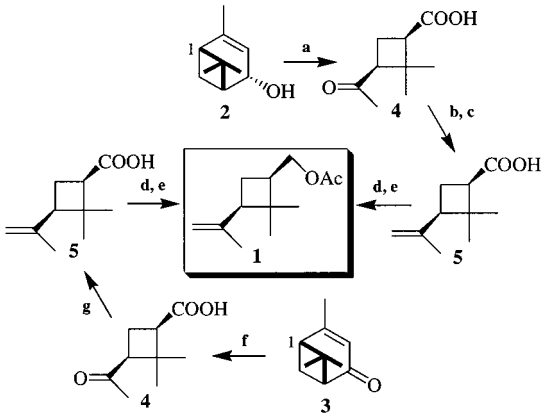
The citrus mealybug, *Planococcus citri* (Risso), is a major pest to coffee, citrus, and cocoa in both the southern U. S. and the Mediterranean. Citrus mealybugs inflict damage by sucking out plant sap and then excreting honeydew, which allows mold to grow. Their toxic saliva can cause further growth distortions and early leaf droppage. Without control, infested plants usually die (*1*, *2*).

Citrus mealybugs often congregate in crevices and cracks. As a result, pesticide treatment is often ineffective in controlling the citrus mealybug. Interest in alternative pest control strategies resulted in the identification of the female-produced sex pheromone as (1*R*)-(+)-*cis*-2,2-dimethyl-3-isopropenyl-cyclobutane methanol acetate ((+)-*cis*-planococcyl acetate, (**1**) by Bierl-Leonhardt et al. in 1981 (*3*). Field tests indicated that the optically pure (+)-*cis*-isomer (**1**, $[\alpha]_{3130}^{25}$ +168°) was 10-fold more attractive to males than either the (+)-*trans*-isomer or the (−)-*cis*-isomer ($[\alpha]_{3130}^{25}$ − 130°) (*3*). Since its identification, there have been numerous syntheses of **1** (*4*−*8*). Previous methods involved either photolytic rearrangement or oxidative decarboxylation as the key step. We have developed two alternative pathways for the synthesis of **1** starting from either (+)-*trans*-verbenol (**2**) or (+)-*R*-verbenone (**3**) (**Scheme 1**).

METHODS AND MATERIALS

General. All bps are uncorrected. NMR (^1H and ^{13}C) were obtained using a Bruker Avance 300 MHz with $CDCl_3$. GC/FID sample analysis was carried out on an HP 6890 instrument equipped with a 30-m DB-5 column. Samples were heated from 50 °C (1 min) to 280 °C (10 min) at a rate of 8°/min. Optical rotations were measured using a Jasco DIP-1000 digital polarimeter. All synthetic procedures were carried out with oven-dried glassware under a N_2(g) atmosphere. Solvents were evaporated using a Büchi R-124 rotary evaporator unless otherwise indicated. All starting materials and reagents were obtained from Aldrich Chemical Co.

Scheme 1



(a) $RuCl_3$-$NaIO_4$, $CH_3CN/CCl_4/H_2O$; (b) $(CH_3)_3SiCH_2MgCl$; (c) Ac_2O; (d) $LiAlH_4$, Et_2O; (e) Ac_2O, pyr; (f) $RuCl_3$-$NaIO_4$, *t*-BuOH/H_2O; (g) $Zn/CH_2Br_2/TiCl_4$.

***trans*-(*R*)-Verbenol (2).** (1*R*)-(+)-α-Pinene (91% + ee/GLC, 7.42 g, 54.5 mmol) was dissolved in benzene and heated to 65−70 °C. Lead (IV) tetraacetate (26.5 g, 59.8 mmol, 1.1 eq) was added over 15 min, and the mixture was allowed to stir 1.5 h further. The reaction mixture was filtered and the filtrate was washed with H_2O (2×), brine, dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in glacial AcOH (35 mL, 0.609 mol, 11 eq) and allowed to stand (35 min). The solution was diluted with H_2O and extracted with hexane (2×). The combined extracts were washed with H_2O, 5% aq $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and evaporated to yield crude acetate. The residue was distilled under high vacuum (0.05 mmHg) to afford verbenol acetate (bp 65−67 °C).

The acetate collected was dissolved in MeOH (10 mL) with 20% aq KOH (10 mL) and placed in the refrigerator (2 days). The mixture was diluted with H_2O and extracted with Et_2O (2×). The combined

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organics were washed with H_2O and brine, dried (Na_2SO_4), filtered, and evaporated to give *trans*-(*R*)-verbenol **2** (4.54 g, 29.9 mmol, yield 55% for both steps), whose ^1H NMR spectrum was in accordance with literature data collected at a lower field strength (*9*). $[\alpha]^{22}_D$ +110.3° ($CHCl_3$, $c = 12.9$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.86$ [s, 3H, C(6)−CH_3], 1.32 [s, 3H, C(6)−CH_3], 1.71 [s, 3H, C(2)−CH_3], 1.94−2.29 [m, 4H], 4.25 [s, 1H, C(4)−H], 5.33 [s, 1H, C(3)−H]. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 20.8$, 23.0, 27.0, 29.1, 47.5, 48.2, 48.5, 70.8, 119.2, 149.2.

(+)-*R*-Verbenone (3). (1*R*)-(+)-α-Pinene (91% + ee/GLC, 25.0 g, 183.7 mmol) was dissolved in acetone (590 mL) with H_2O (80 mL). *N*-Hydroxyphthalimide (33.0 g, 202 mmol, 1.1 eq.) was added and allowed to dissolve. Chromium trioxide was added every 3 h (3 portions of 18.7 g, 561.3 mmol, 3.1 equiv) and allowed to stir overnight. The mixture was partitioned between hexane and 1 N HCl then separated. The aqueous layer was extracted with hexane (3 × 110 mL), and the combined organics were washed with saturated aqueous $NaHCO_3$ (2×), brine, dried (Na_2SO_4), filtered, and evaporated to yield crude **3**. The residue was distilled under vacuum (1.4 mmHg) with a dry ice/acetone cooled collection flask to afford pure **3** (9.90 g, bp 78−82 °C, 66.0 mmol, yield 36%) whose NMR spectra (^1H and ^{13}C) were in accordance with literature data collected at a lower field strength (*10*). $[\alpha]^{22}_D$ +180.1° ($CHCl_3$, $c = 78.7$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.95$ [s, 3H, C(6)−CH_3], 1.44 (s, 3H, C(6)−CH_3], 1.96 [d, 3H, $^4J_{H,H} = 1.6$ Hz, C(2)−CH_3], 2.02 [d, 1H, $^3J_{H,H} = 9.1$ Hz, C(7)−H], 2.37 [td, 1H, $^3J_{H,H} = 5.8$ Hz, $^2J_{H,H} = 1.4$ Hz, C(7)−H], 2.58 [dt, 1H, $^3J_{H,H} = 6.0$ Hz, $^3J_{H,H}$ 1.7 Hz, C(5)−H], 2.75 [dt, 1H, $^3J_{H,H} = 9.1$ Hz, $^3J_{H,H} = 5.5$ Hz, C(1)−H], 5.67 [m, 1H, C(3)−H]. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 21.9$, 23.4, 26.4, 40.7, 49.5, 53.9, 57.4, 121.0, 170.0, 203.8.

(+)-(1*R*)-*cis*-2,2-Dimethyl-3-acetyl-cyclobutanecarboxylic Acid (4) using $CH_3CN/CCl_4/H_2O$. Verbenol **2** (4.54 g, 29.9 mmol) was dissolved in a mixture of CH_3CN (30 mL), CCl_4 (60 mL), and H_2O (90 mL) and then cooled to 0 °C. Ruthenium chloride (0.148 g, 0.714 mmol, 0.024 equiv) was added, followed by portion-wise addition of $NaIO_4$ (55.0 g, 257.2 mmol, 8.60 equiv) over 0.5 h. The mixture was stirred (5 h) and then vacuum filtered. The filtrate was separated, and the aqueous layer was extracted with CCl_4 (5×). Ethyl alcohol (95%, 2 mL) was added to the combined organics, dried (Na_2SO_4), filtered, and decolorized with carbon. The solution was refiltered, evaporated, and dissolved in Et_2O. The ether solution was filtered through Celite and evaporated to yield ketoacid **4** (1.79 g, 10.53 mmol, yield 35%) whose NMR spectra (^1H and ^{13}C) were in accordance with literature data collected at a lower field strength (*11*). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.95$ [s, 3H, C(2)−CH_3], 1.43 [s, 3H, C(2)−CH_3], 1.89 [dt, 1H, $^3J_{H,H} = 11.7$ Hz, $^3J_{H,H} = 7.8$ Hz, C(4)−H], 2.05 [s, 3H, CH_3-COO], 2.61 [m, 1H, C(4)−H], 2.81 [dd, 1H, $^3J_{H,H} = 10.7$ Hz, $^3J_{H,H} = 8.0$ Hz, C(3)−H], 2.89 [dd, 1H, $^3J_{H,H} = 10.6$ Hz, $^3J_{H,H} = 7.7$ Hz, C(1)−H], 8.25−8.60 [bs, 1H, COOH]. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 17.9$, 18.7, 29.8, 30.2, 44.8, 44.9, 52.9, 177.7, 206.9.

(+)−(1*R*)-*cis*-2,2-Dimethyl-3-acetyl-cyclobutanecarboxylic Acid (4) using Aqueous *t*-Butanol: Sodium metaperiodate (90.4 g, 422 mmol, 9 equiv) was suspended in aqueous *t*-BuOH (42%, 217 mL), and (+)-*R*-verbenone (**3**, 7.04 g, 46.9 mmol) was added. The reaction mixture was heated to 32 °C, and $RuCl_3 \cdot 3H_2O$ was added (0.215 g, 1.04 mmol, 0.022 equiv). The mixture was stirred 2 h further, cooled to 0 °C, diluted with Et_2O (100 mL), and acidified using 6 N HCl (pH 2). After stirring (20 min), the milky mixture was vacuum filtered, and the solids were washed with Et_2O (2×). The combined organics were washed with H_2O and brine, dried (Na_2SO_4), and allowed to stand in the refrigerator overnight. The solution was filtered and evaporated to afford ketoacid **4** (7.50 g, 44.1 mmol, yield 94%) whose NMR spectra (^1H and ^{13}C) were identical with those collected for the ketoacid **4** prepared using the alternative $CH_3CN/CCl_4/H_2O$ solvent system described above.

(+)-(1*R*)-*cis*-2,2-Dimethyl-3-isopropenyl-cyclobutanecarboxylic Acid (5) using $(CH_3)_3SiCH_2SiCl$. A trimethylsilylmethylmagnesium chloride solution (30 mL, 1 M/Et_2O, 30 mmol) was cooled to 0 °C, and the ketoacid (**4**) solution (1.79 g, 10.53 mmol in 15 mL THF) was added dropwise over 15 min. The reaction mixture was warmed to room temperature for 1 h then cooled again to 0 °C, and acetic anhydride was added dropwise (3.5 mL, 37.1 mL, 3.5 equiv). Once a precipitate formed, the mixture was warmed to room temperature (1.5 h). The reaction was quenched with H_2O (20 mL) and then separated. The aqueous layer was extracted with Et_2O (2×), and the combined organics were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was taken up in Et_2O and washed with aq Na_2CO_3 (3×). The combined aqueous layers were acidified with 1 N HCl (pH 2) and extracted with Et_2O (2×). The extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to yield isopropenyl acid **5** (0.532 g, 3.17 mmol, yield 30%). The residue was immediately reduced with $LiAlH_4$ to prevent epimerization (see below).

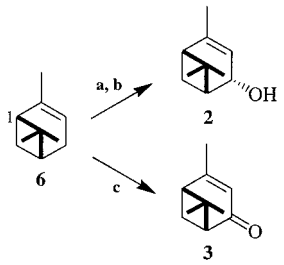
(+)-(1*R*)-*cis*-2,2-Dimethyl-3-isopropenyl-cyclobutanecarboxylic Acid (5) using $Zn/CH_2Br_2/TiCl_4$. Activated zinc (*12*) (24.9 g, 381 mmol, 10.9 equiv) was suspended in anhydrous THF (150 mL) with dibromomethane (10 mL, 142.5 mmol, 4.1 equiv). The reaction mixture was cooled to −45 °C and $TiCl_4$ (12 mL, 109 mmol, 3.1 equiv) was added dropwise. When the formation of yellow smoke had subsided, the mixture was warmed to 0 °C and maintained with good stirring for 2 days. Anhydrous CH_2Cl_2 (40 mL) was added followed by dropwise addition of ketoacid **4** (5.97 g, 35.1 mmol) in CH_2Cl_2 (35 mL). The mixture was stirred (0.5 h) and then warmed to room temperature (3 h). Hexane (100 mL) was added with 1.5 N HCl (slow initially, total 140 mL). The mixture was stirred for 0.5 h and then separated. The aqueous layer was extracted with hexane (2×), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was immediately reduced with $LiAlH_4$ to prevent epimerization (see below).

(+)-(1*R*)-*cis*-2,2-Dimethyl-3-isopropenyl-cyclobutane Methanol Acetate (1). Lithium aluminum hydride (1.04 g, 27.4 mmol, 0.92 equiv) was suspended in anhydrous Et_2O (220 mL) and cooled to 0 °C. Isopropenyl acid **5** (5.0 g, 29.8 mmol) in Et_2O (30 mL) was added dropwise, and the mixture was allowed to stir (1.5 h). Excess $LiAlH_4$ was destroyed (*13*), and the mixture was then warmed to room temperature overnight. The reaction mixture was vacuum filtered and the filtrate was dried (Na_2SO_4), filtered, and evaporated. The residue was added to a solution of Ac_2O (7 mL) and pyridine (32 mL) at 0 °C. The mixture was stirred (15 min) and then warmed to room temperature overnight. The resulting solution was partitioned between H_2O and hexane then separated. The aqueous layer was extracted with hexane (2×) and the combined organics were washed with 1 N HCl (3×), brine, dried (Na_2SO_4), filtered, and evaporated to yield crude isopropenyl acetate **1** (4.20 g, 24.7 mmol, yield 83%). The crude residue was distilled under vacuum (1.4 mmHg) to afford **1** (3.03 g, bp 83−86 °C, yield from **4** 44%) whose NMR spectra (^1H and ^{13}C) were in accordance with literature data (*5*). $[\alpha]^{22}_D$ +17.2° ($CHCl_3$, $c = 49.5$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.80$ [s, 3H, C(2)−CH_3], 1.18 [s, 3H, C(2)−CH_3], 1.62 [m, 1H], 1.64 [s, 3H, isopropenyl CH_3], 1.88 [dt, 1H, $^3J_{H,H} = 10.7$ Hz, $^3J_{H,H} = 7.6$ Hz, C(4)−H], 2.01 [s, 3H, CH_3COO], 2.15 [m, 1H], 2.38 [m, 1H], 3.93 [dd, 1H, $^2J_{H,H} = 11.1$ Hz, $^3J_{H,H} = 8.6$ Hz, CH_2OAc], 4.05 [dd, 1H, $^2J_{H,H} = 11.1$, $^3J_{H,H} = 6.4$ Hz, CH_2OAc), 4.55 [bs, 1H, isopropenyl vinylic], 4.79 [sextet, 1H, $^2J_{H,H} = 1.4$ Hz, isopropenyl vinylic]. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 16.0$, 20.9, 22.8, 23.0, 30.9, 39.8, 41.0, 48.9, 64.9, 109.4, 144.9, 170.9.

RESULTS AND DISCUSSION

Oxidative ring opening of verbenol **2** with loss of CO_2 was carried out with $RuCl_3-NaIO_4$ in a mixed solvent system ($CH_3CN/CCl_4/H_2O$) to yield ketoacid **4** in 35% yield (*11*). In our hands, the reaction was difficult to control on a larger scale (50 g) and resulted in decreased product yields due to the excessive pressure released. In addition, isolation of **4** was challenging, due to the difficulty in removing the residual ruthenium salts. It was found that allowing the particulates to settle out overnight made the workup easier. Methylenation of **4** using trimethylsilylmethylmagnesium chloride and acetic anhydride gave olefinic acid **5** in 30% yield (*14*). An excess amount of Grignard reagent (≥2.8 equiv) was needed to complete the reaction, in part, due to the presence of the acid functionality. Reduction

Scheme 2



(a) $Pb(OAc)_4$, benzene; (b) KOH, MeOH; (c) CrO_3, *N*-hydroxyphthalimide.

of **5** with lithium aluminum hydride followed by acetylation using acetic anhydride in pyridine afforded pheromone **1**. The overall yield of pheromone **1** from **2** was 2%. Due to the poor yields obtained and the impracticality of scale-up, another route to **1** was devised.

An alternative ruthenium catalyzed oxidative ring opening with concomitant decarboxylation using a different solvent system (aqueous *tert*-butyl alcohol) and a different substrate ((+)-*R*-verbenone, **3**) afforded ketoacid **4** in 94% yield (*15*). Compared with the previous conditions above (*1*), the alternative procedure was more easily carried out, and the isolation was less cumbersome. Methylenation of **4** using a $Zn/CH_2Br_2/TiCl_4$ procedure gave olefinic acid **5** (*16*, *17*). It was found that **5** had to be immediately taken on to the next step to avoid epimerization. Although the need to move through to next step quickly might have been inconvenient, the $Zn/CH_2Br_2/TiCl_4$ methylenation procedure was sizably more applicable to larger scale preparations, unlike similar Wittig procedures, which often require extensive chromatographic purification. Olefinic acid **5** that was kept in the refrigerator (2−3 days) epimerized to a 1:1 mixture of diastereomers. Subsequent reduction of **5** with lithium aluminum hydride and acetylation with acetic anhydride in pyridine afforded pheromone **1**. Overall yield for the second sequence was 42% from **3**.

The structure of isopropenyl acetate **1** was verified using ^1H and ^{13}C NMR. Optical rotation of **1** in $CHCl_3$ was determined to be +17.2° ($[\alpha]_D$, c = 49.5, 22 °C) and was in accordance with previously collected data (*4*−*8*). The enantiomeric excess of the synthetic pheromone 1 is most likely ~91%, because the starting α-pinene was 91% + ee R-isomer. No diastereomers were detected by either GC/FID or NMR analyses as a result of epimerization at C-1 or C-3. Epimerization would have to occur at both C-1 or C-3 to have any appreciable amount of the opposite enantiomer. Comparison of our data to the literature data is somewhat challenged by the inconsistency among the sample concentrations. Pheromone **1** was highly attractive to male mealybugs in the field (*18*).

Both (+)-*trans*-verbenol (**2**) and (+)-*R*-verbenone (**3**) are commercially available, but only at steep prices and in small quantities. There are numerous conditions reported in the literature for the oxidation of (1*R*)-(+)-α-pinene (**6**) to either (+)-*trans*-verbenol or *R*-verbenone, and (+)-α-pinene **6** is also reasonably affordable and commercially available in large amounts. We found it convenient to oxidize (1*R*)−(+)-α-pinene (**6**) to *trans*-verbenyl acetate by using lead tetraacetate in benzene (*9*) followed by saponification using aqueous KOH in MeOH to give *trans*-verbenol (**2**) in 55% overall yield (**Scheme 2**). Of the few methods available to oxidize **6** to verbenol **2**, lead tetraacetate affords a single oxidation product, whereas the other methods generate complicated product mixtures. Because the oxidation reaction could not easily be scaled up, involved expensive reagents ($Pb(OAc)_4$), and required the use of benzene as a solvent, the use of verbenol **2** as a substrate was abandoned.

Work by Lardy and Padma indicated that (+)-*R*-verbenone (**3**) could be produced from (+)-α-pinene, using chromium trioxide and *N*-hydroxyphthalimide in aqueous acetone in 51% yield (**Scheme 2**) (*19*). Compared with the oxidation of (+)-α-pinene using $Pb(OAc)_4$ to verbenol **2**, the experimental conditions to produce intermediate **3** were simple, the reagents were cheap, and the procedure could be substantially scaled up. The allylic oxidation of **6**, when carried out using the described conditions (*19*), afforded **3** in 36% yield after distillation.

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