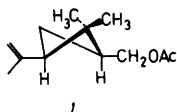


Synthesis of the Female Sex Pheromone of the Citrus Mealybug, *Planoccus citri* (Risso)

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The synthesis of (1*R*-*cis*)-(+)-2,2-dimethyl-3-isopropenylcyclobutanemethanol acetate, *1*, a female sex pheromone of the Citrus Mealybug, *Planoccus citri* (Risso), is described. Ruthenium



catalyzed oxidative decarboxylation of (+)-verbenone or (+)-verbenol yields (+)-pinononic acid, *4*, which was further elaborated in a Wittig step, reduced with lithium aluminium hydride and subsequently acylated to yield *1*.

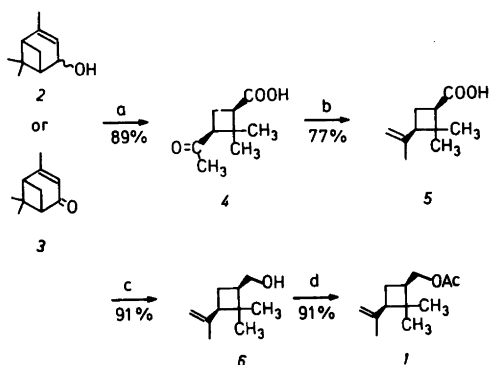
The Citrus Mealybug, *Planoccus citri* (Risso), is a pest widely distributed through the tropics and subtropics, and has been reported in greenhouses in temperate climates as well. This insect is found on numerous hosts, including coffee, citrus and cocoa, and generally aggregates in compact groups.¹ Multiple application of broad spectrum organophosphate insecticides has not been found to provide adequate control.² However, since the females are wingless, while the adult males are winged, a female pheromone may be useful for mass trapping.

Recently Bierl-Leonhardt and co-workers reported the isolation and identification of the female sex pheromone.³ The compound was shown to have the structure (1*R*-*cis*)-(+)-2,2-dimethyl-3-isopropenyl-cyclobutanemethanol acetate, *1*. A synthesis of *1* was published in the

same paper. The synthesis has also been described in a Japanese patent.⁴ The key step in both these syntheses was a photolytic rearrangement of (+)-verbanone.

In this paper we report a non-photochemical synthesis of the pheromone, convenient for large scale preparations. The approach towards the pheromone, *1*, is illustrated in the reaction Scheme 1.

Commercial (+)-verbenone, *3*, or a mixture of *cis* and *trans*-(+)-verbenol, *2*, was converted to (+)-pinononic acid, *4*, in 89 and 79% yields, respectively, when subjected to oxidative decarboxylation conditions with catalytic amounts of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ and sodium metaperiodate as the stoichiometric oxidant. In this reaction we make use of the recently published acetonitrile assisted ruthenium catalyzed oxidation reaction.⁵ The mixed solvent system consisted of carbon tetrachloride, acetonitrile and water in a 2:1:4-ratio. In



Scheme 1. a, $\text{RuCl}_3 \cdot 3 \text{H}_2\text{O} - \text{NaIO}_4$ in $\text{CCl}_4 - \text{CH}_3\text{CN} - \text{H}_2\text{O}$; b, $\text{Ph}_3\text{P} - \text{CH}_3\text{Br} - \text{NaH} - \text{DMF}$; c, $\text{LAH} - \text{THF}$; d, $\text{Ac}_2\text{O} - \text{Et}_3\text{N} - \text{CH}_2\text{Cl}_2$.

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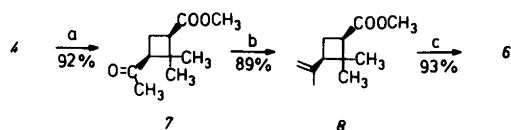
general, $\alpha\beta$ -unsaturated ketones, α -hydroxy or keto carboxylic acids with $\text{RuO}_4/\text{NaIO}_4$ undergo catalytic decarboxylation reactions. A report dealing with this type of reactivity will be published shortly.⁶ This reaction was compared to alternative and previously reported procedures for this type of transformation, and was found to perform better than these. Potassium permanganate, neither in water⁷ nor in benzene in the presence of 18-crown-6,⁸ gave products of satisfactory quality or yield. The ruthenium catalyzed reaction without acetonitrile as a component of the solvent system gave the same product, 4, but less efficiently.

Ruthenium promoted oxidations of olefins, e.g. pinene derivatives, using sodium metaperiodate or sodium hypochlorite as the stoichiometric oxidant can be very efficient. However, problems such as slow and incomplete reactions have often been encountered. As a general procedure, the acetonitrile assisted modification has been found to be far more applicable.

Another commonly observed difficulty on oxidation of α -pinene and its derivatives is the formation of mixtures of diastereomers, evidently the result of epimerization of the very labile α -carbonyl carbon, e.g. in pinonic acid, thus resulting in low yields of the *cis*-compounds.⁸ The *cis*-pinonic acid derivatives in particular are susceptible to epimerization due to the two α -carbonyl positions, resulting in *cis-trans* isomerization and hence racemization of the optically active compounds. Thus, (+)-pinonic acid undergo epimerization and racemization in the presence of catalytic amounts of acid or base. However, during the oxidation of (+)-verbenone or (+)-verbenol using the method described, no epimerization was observed.

Treatment of the acid 4 in a Wittig reaction with methylene triphenylphosphine ($\text{Ph}_3\text{P}^+-\text{CH}_2\text{Br}^-$, NaH, DMF), gave the isopropenyl compound 5 in good yield. Reduction of this compound with lithium aluminum hydride, LAH, yielded the corresponding alcohol, 6, which on subsequent acylation with acetic anhydride (Ac_2O , Et_3N , CH_2Cl_2), afforded the pure pheromone, 1. The combined yield for the last two steps was 82 %.

An alternative route *via* the (+)-pinonic methyl ester, 7, was studied. Esterification of pinonic acid, 4, under a variety of basic and



Scheme 2. a, $\text{CH}_3\text{I}-\text{NaHCO}_3-\text{DMF}$; b, $\text{Ph}_3\text{PCH}_2\text{Br}-n\text{-BuLi}-\text{THF}$; c, $\text{LAH}-\text{THF}$.

acidic conditions all gave the desired product, but was accompanied by epimerization and racemization. However, we found that 7 could be obtained in quantitative yield by reaction with methyl iodide in *N,N*-dimethylformamide, DMF, at room temperature in the presence of sodium bicarbonate.

A GLC and spectroscopic analysis of the reaction mixture gave no indication of any *trans*-7. A Wittig reaction with $\text{Ph}_3\text{P}=\text{CH}_2$ and subsequent reduction with LAH gave 6 in a 71 % overall yield.

EXPERIMENTAL

General. Proton NMR spectra were recorded on a Varian A 60 spectrometer. IR spectra were measured in KBr tablets or as neat films on a Perkin-Elmer Infracord spectrometer. Optical rotation was determined on a Perkin-Elmer 141 instrument.

Synthesis of (1*R*-*cis*)-(+)-2,2-dimethyl-3-acetylcyclobutanecarboxylic acid, (+)-*cis*-Pinonic acid, 4. Ruthenium-catalyzed oxidative decarboxylation of (+)-verbenone, 3. A mixture containing 31 g, 0.2 mol of (+)-verbenone, 3, $[\alpha]_D^{22}=200^\circ$ (CHCl_3 , $c=7$), 1 g of $\text{RuCl}_3 \cdot 3 \text{H}_2\text{O}$ and 370 g of sodium metaperiodate in 200 ml of carbon tetrachloride, 100 ml acetonitrile and 400 ml of water, was stirred at room temperature for 5 h. At this point the reaction mixture had turned bright yellow. The precipitated inorganic material was separated by filtration on a sintered glass funnel, and washed with 2×50 ml of carbon tetrachloride. The organic layer was separated and the aqueous phase extracted with 6×50 ml carbon tetrachloride. To the combined organic phase was added 1 ml of ethanol. This caused an immediate darkening of the solution, and after some time precipitation of ruthenium compounds occurred. After a couple of hours the precipitated, spent ruthenium catalyst was separated by filtration, and re-used without any further purification. The organic solution was dried over anhydrous magnesium sulfate, treated with activated carbon, filtered and the solvent evaporated under

reduced pressure. The crude product was recrystallized from ethyl acetate-pentane. The isolated yield of **4** was 89 %; m.p. 131–132 °C; IR (KBr): 3500–2300 (broad), 1729, 1685, 1462, 1444, 1400, 1368, 1310, 1280, 1230, 1191, 1170, 1149, 1131, 1112, 1079, 830, 700 cm^{-1} ; NMR (CDCl_3): δ 1.00 (s, 3H), 1.48 (s, 3H), 2.10 (s, 3H), 1.7–2.2 (m, 1H), 2.5–3.1 (m, 3H), 11.2 (s, 1H, exchanged w. D_2O); $[\alpha]_{\text{D}}^{25} +71^\circ$ (CHCl_3 , $C=2$).

Ruthenium catalyzed oxidation of (+)-verbenol, 2. The same procedure as described above was used for the oxidation of a commercial mixture of *cis* and *trans*-(+)-verbenol, except that 430 g of sodium metaperiodate and 500 ml of water was used. Yield 79 %, m.p. 131–132 °C. The spectroscopic properties were identical to those of the product obtained from **3**.

(1R-cis)-(+)-2,2-dimethyl-3-isopropenyl-cyclobutane carboxylic acid, 5. To a solution containing 50 g, 0.14 mol, of triphenyl methylphosphonium bromide in 220 ml of dry DMF, was added 6.6 g of 50 % sodium hydride in mineral oil, 0.137 mol, and the mixture stirred at room temperature for 2 h. The ylide solution was then added slowly at 0 °C to a stirred solution of 20 g, (0.12 mol), of (+)-pinonic acid, **4**, in 80 ml of dry DMF. The reaction mixture was stirred at room temperature for 5 h, and then poured into 500 ml of ice-water acidified with hydrochloric acid, and then worked up by extraction with chloroform. The crude product could be used directly in the next step, but was distilled under reduced pressure, b.p. 91–93 °C at 0.5 mmHg, resulting in 15.6 g, (0.09 mol), (77 %) of the pure product which exhibited the following spectroscopic properties; IR (neat): 3500–2300 (broad), 3080, 1705, 1645, 1452, 1420, 1385, 1371, 1330, 1284, 1248, 1211, 1155, 1110, 888 cm^{-1} ; NMR (CDCl_3): δ 0.9 (s, 3H), 1.34 (s, 3H), 1.68 (s, 3H), 1.8–3.0 (m, 4H), 4.67 (m, 1H), 4.83 (m, 1H), 11.0 (1H, exchange w. D_2O) p.p.m. $[\alpha]_{\text{D}}^{23} +27^\circ$ (CHCl_3 ; $C=5$).

(1R-cis)-1-hydroxymethyl-2,2-dimethyl-3-isopropenyl-cyclobutane, 6. A solution containing 8 g of **5** or **7** in 10 ml of dry THF was added to a slurry of 2 g, (.05 mol), LAH in 50 ml of THF at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then worked up by adding a solution of sodium fluoride and extracted with ether. From the ether extract was isolated the crude alcohol which after distillation, b.p. 51–54 °C at 0.1 mm Hg, gave 91 % and 93 % respectively of pure **6**. IR (neat): 3380 (broad), 3085, 2965, 1647, 1460, 1385, 1370, 1242, 1160, 1015, 885 cm^{-1} ; NMR (CDCl_3): δ 0.83 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.4–2.5 (m, 4H), 3.58 (d, $J=6.5$ Hz, 2H), 4.55 (m, 1H),

4.78 (m, 1H) p.p.m.; $[\alpha]_{\text{D}}^{25} +15.9^\circ$ (CHCl_3 , $c=2.5$).

(1R-cis)-(+)-2,2-dimethyl-3-isopropenyl-cyclobutane methanol acetate, 1. A solution containing 1.54 g, (10 mmol), of **6**, 1.2 g of acetic anhydride and 2 ml of triethyl amine in 20 ml of dry dichloromethane was stirred at room temperature for 24 h. The reaction mixture was then washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was distilled, b.p. 111–113 °C at 13 mmHg, and 1.66 g, (91 %) of pure **1** was obtained. GLC analysis (5 % FFAP) indicated a purity better than 98 %. IR (neat): 3080, 2960, 1745, 1645, 1460, 1384, 1370, 1240, 1160, 1030, 970, 886 cm^{-1} ; NMR (CDCl_3): δ 0.81 (s, 2H), 1.21 (s, 3H), 1.67 (s, 3H), 2.02 (s, 3H), 1.5–2.8 (m, 4H), 4.0 (d, $J=6.5$ Hz, 2H), 4.58 (m, 1H), 4.83 (m, 1H) p.p.m.; $[\alpha]_{\text{D}}^{25} +22^\circ$ (CHCl_3 , $C=2.5$).

Methyl (1R-cis)-(+)-2,2-dimethyl-3-acetyl-cyclobutane-carboxylate, 7. A reaction mixture containing 17 g, (0.1 mol), of **4**, 12 g 0.15 mol of anhydrous sodium bicarbonate and 12 ml, 0.19 mol of methyl iodide in 150 ml of DMF was stirred at room temperature for 24 h. Then 250 ml of water was added and the mixture extracted with 5×50 ml of pentane. The organic phase was washed and dried over anhydrous magnesium sulfate followed by evaporation of the solvent, leaving behind the crude product. Distillation, b.p. 58–59 °C at 0.1 mmHg gave 17.1 g, (92 %) of pure **7**. IR (neat): 2962, 1740, 1712, 1463, 1438, 1372, 1358, 1335, 1236, 1188, 1112, 1088, 1035, 955 cm^{-1} ; NMR (CDCl_3): 0.92 (s, 3H), 1.47 (s, 3H), 2.09 (s, 3H), 1.9 (m, 1H), 2.8 (m, 3H), 3.70 (s, 3H) p.p.m.; $[\alpha]_{\text{D}}^{23} +42^\circ$ (CHCl_3 , $c=3$).

Methyl (1R-cis)-(+)-2,2-dimethyl-3-isopropenyl-cyclobutane carboxylate, 8. A solution of methylene triphenylphosphine in THF (from 17.4 g, 0.05 mol $\text{Ph}_3\text{PCH}_3\text{Br}$ and 24 ml 2.1 M *n*-BuLi solution in 180 ml dry THF at –5 °C) was added to a solution containing 9.3 g, (0.05 mol), of **7** in 30 ml dry THF at –78 °C. The reaction mixture was stirred overnight while allowed to reach room temperature. The solvent was then carefully evaporated under reduced pressure and the residue extracted with pentane. Distillation of the solvent left the product behind as a clear liquid. Distillation of the crude product, b.p. 45 °C at 2 mmHg, gave 8.2 g, 0.045 mol, (89 %) of the pure product, **8**. IR (neat): 3090, 2960, 2880, 1740, 1650, 1460, 1435, 1386, 1374, 1343, 1237, 1200, 1128, 1119, 1087, 1035, 890 cm^{-1} ; NMR (DCCl_3): δ 0.80 (s, 3 H), 1.30 (s, 3H), 1.67 (s, 3H), 1.8–2.7 (m, 4H), 3.67 (s, 3H), 4.66 (m, 1H), 4.81 (m, 1H) p.p.m. $[\alpha]_{\text{D}}^{22} -6.4^\circ$ (CHCl_3 , $c=2.3$).

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Received July 18, 1983.