Chemistry of Natural Compounds, Vol. 42, No. 2, 2006

NOVEL SYNTHESIS OF *Planococcus citri* PHEROMONE

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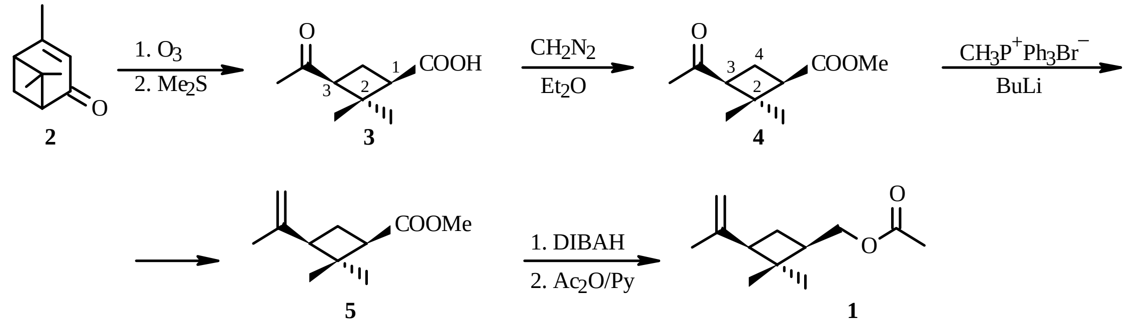
UDC 632.936.2+547.573

*An effective method was proposed for synthesizing (+)-cis-1*R*-acetoxymethyl-3-isopropenyl-2,2-dimethylcyclobutane, a pheromone of the citrus mealybug, based on ozonolysis of verbenone that led in one step to the key synthon 1*R*,3*S*-3-acetyl-2,2-dimethylcyclobutanecarboxylic acid.*

Key words: pheromone, citrus mealybug, olefination, ozonolysis.

Populations of the dangerous grape and citrus pest *Planococcus citri* Risso (citrus mealybug) can be reliably controlled by using traps containing a pheromone of this pest identified as (+)-*cis*-1*R*-acetoxymethyl-3-isopropenyl-2,2-dimethylcyclobutane (**1**) [1]. Several synthetic pathways to it have been described [1-6], the most efficient of which is a method based on selective transformations of α-pinene [3]. Chain shortening steps at the first C atom that conclude with transformation of the ozonolysis product of β-pinene (ketoaldehyde) into the enolacetate and its subsequent ozonolytic cleavage substantially decrease the yield of the sex pheromone **1**.

We propose a novel method for synthesizing **1** that is based on ozonolysis of verbenone (**2**) in CH_3CN or CH_2Cl_2.



1*R*,3*S*-3-Acetyl-2,2-dimethylcyclobutanecarboxylic acid (**3**) was produced from verbenone **2** in 83% yield by reacting it with an excess of ozone (~2 mmol) in CH_3CN at -40°C. Simultaneously with cleavage of the double bond of **2**, the side chain undergoes oxidative dehydration, which we noted for ozonolysis of other α,β-unsaturated ketones [7]. Formation of **3** by ozonolysis of verbenone was proved by the presence in the IR spectrum of the isolated crystalline product of bands at 1715 cm^{-1} (C=O) and 1695 and 2400-3600 (COOH). The PMR spectrum of **3** contained three singlets for methyls (0.95 and 1.45 ppm, *gem*-dimethyl; 2.05, acetyl) and an AB system of protons on C^1 and C^3 of the ring, each of which was split by magnetically nonequivalent H atoms of the methylene. The methylene protons resonated as a doublet of doublets at 1.90 and 2.60 ppm.

The methyl ester of **4** was prepared by treatment of **3** with diazomethane in diethylether. Compound **4** was converted by methylidenetriphenylphosphorane to the olefinic methyl ester (1*R*,3*S*)-3-isopropenyl-2,2-dimethylcyclobutanecarboxylic acid (**5**), hydride reduction of which and subsequent acetylation of the resulting alcohol gave **1**.

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0009-3130/06/4202-0216

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers or in mineral oil. PMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (working frequencies 300.13 and 75.25 MHz, respectively) in $CDCl_3$ with TMS internal standard. GC was performed on a Chrom-5 chromatograph using a column (1200 × 3 mm), stationary phase Chromaton N-AW-DNICS (0.16-0.20 mm) + SE-30 (5%), working temperature 50-300°C (12 deg/min), and He carrier gas.

Verbenone (2) was prepared by liquid-phase oxidation of α-pinene as before [8].

(+)-1*R*,3*S*-3-Acetyl-2,2-dimethylcyclobutanecarboxylic Acid (3). An O_3/O_2 mixture was passed through a solution of **2** (0.5 g, 3.3 mmol) in absolute CH_3CN (5 mL) at -40°C until the starting ketone was completely consumed (TLC monitoring). The reaction mixture was purged with argon, treated with Me_2S (0.5 mL), stirred for 2 h, treated with $CHCl_3$ (30 mL), washed with saturated NaCl solution, dried over $MgSO_4$, and filtered. Solvent was evaporated to produce **3** (0.46 g, 83%), mp 98-100°C, $[\alpha]_D^{25}$ +28.5° (*c* 0.0106 g/mL, $CHCl_3$), $C_9H_{14}O_3$.

IR spectrum (ν, cm^{-1}): 3600-2400 (COOH), 1715 (C=O), 1695.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 and 1.45 (6H, s, CH_3-2), 1.90 (1H, ddd, $J_{4\text{-}1cis} = J_{4\text{-}3cis} = 8.0$, $J_{gem} = 11.0$, *Z*-CH-4), 2.05 (3H, s, CH_3CO), 2.60 (1H, ddd, $J_{4\text{-}1trans} = J_{4\text{-}3trans} = J_{gem} = 11.0$, *E*-HC-4), 2.70 and 2.90 (2H, dd, $J_{1\text{-}4cis} = J_{3\text{-}4cis} = 8.0$, $J_{1\text{-}4trans} = J_{3\text{-}4trans} = 11.0$, HC-1 and HC-3), 11.30 (1H, s, COOH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 17.80 (CH_3CO, q), 18.59 and 29.78 (CH_3, q), 30.04 (CH_2, t), 44.77 (C-2, s), 45.18 (C-1, d), 52.75 (C-3, d), 177.45 (COOH, s), 207.33 (C=O, s).

Methyl Ester of (1*R*,3*S*)-*cis*-3-Acetyl-2,2-dimethyl-1-(methoxycarbonyl)cyclobutane (4). A solution of **3** (1 g, 5.88 mmol) in diethylether (20 mL) was treated over 40 min in portions with diazomethane in ether [prepared from KOH solution (6 mL, 40%) and nitrosomethylurea (2 g, 19.42 mmol)] and stirred for 2 h on an ice bath. Solvent was evaporated to produce **4** (1.06 g, 98%), $[\alpha]_D^{20}$ +37.88° (*c* 0.00924 g/mL, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 1710 (C=O), 1735 ($COOCH_3$), 1190.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.98 and 1.40 (6H, s, CH_3-2), 2.03 (3H, s, CH_3CO), 2.11 (1H, ddd, $J_{4\text{-}1} = J_{4\text{-}3} = J_{gem} = 11.0$, *Z*-CH-4), 2.53 (1H, ddd, $J_{4\text{-}1} = J_{4\text{-}3} = 8.0$, $J_{gem} = 110$, *E*-CH-4), 2.66 and 3.06 (2H, ddd, J = 7.0, 8.0, 11.0, H-1 and H-3), 3.63 (3H, s, OCH_3).

Methyl Ester of (1*R*,3*S*)-3-Isopropenyl-2,2-dimethylcyclobutanecarboxylic Acid (5). Triphenylphosphonium bromide (0.87 g, 2.46 mmol) in THF (13 mL) was treated dropwise with *n*-BuLi (3 mL, 1.3 M, 2.47 mmol) in hexane over 30 min at -75°C. The temperature was raised to -30°C. Ester **4** (1 g, 5.81 mmol) was added over 6 min. The reaction mixture was held at -30°C for 1 h, at 25°C for 15 h, diluted with heptane, and filtered through a thin layer of silica gel. Solvent was evporated to produce **5** (0.81 g) that was purified by chromatography (SiO_2, eluent petroleum ether:ethylacetate, 85:15, with increasing content of the latter). Yield 88%, $C_{11}H_{18}O_2$.

IR spectrum (ν, cm^{-1}): 3080 ($C{=}CH_2$), 1740 ($COCH_3$), 1650, 915.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.86 and 1.08 (6H, s, CH_3), 1.42 (1H, m, H-1), 1.57 (3H, s, $CH_3C{=}$), 2.15 (1H, m, H-3), 2.45 (2H, m, CH_2), 4.85 (2H, br.s, $=CH_2$), 3.65 (3H, s, OCH_3).

(+)-*cis*-1*R*-Acetoxymethyl-3-isopropenyl-2,2-dimethylcyclobutane (1). A solution of **5** (0.25 g, 1.09 mmol) in diethylether (10 mL) was treated at 0°C with a solution of diisobutylaluminum hydride (DIBAH, 0.5 mL, 70%) in toluene. The reaction mixture was stirred for 1 h at 0°C, 15 h at 25°C, cooled to 5°C, and treated with water (0.5 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated to produce a compound (0.19 g) to which was added at 0-5°C Ac_2O (1.72 g, 16.88 mmol) and dry pyridine (1.58 mL). The mixture was stirred for 2.5 h at 0°C, held for 12 h at 10°C, diluted with CH_2Cl_2, washed successively with HCl (1 N) and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. Solvent was evaporated to produce **1** (0.2 g, 85%), the constants and spectral properties of which were identical to those in the literature [1], $[\alpha]_D^{20}$ +7.11° (*c* 1.7101, $CHCl_3$).

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