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SYNTHESIS OF (*E*)-3,9-DIMETHYL-6-ISOPROPYL-5,8-DECADIEN-1-YL ACETATE, THE SEX PHEROMONE OF THE YELLOW SCALE[1]

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Abstract—Synthesis of a *definable* mixture of the racemic *Z* and *E* isomers of 3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate has been achieved. Comparison of these isomers with the natural pheromone of the yellow scale, *Aonidiella citrina* (Coquillett) resulted in the identification of the pheromone as (*E*)-3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate.

Key Words—Synthesis, sex pheromone, yellow scale, *Aonidiella citrina*, Homoptera, Diaspididae, isomers (*E*)- and (*Z*)-3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate.

INTRODUCTION

The yellow scale, *Aonidiella citrina* (Coquillett), is a pest of citrus and of ornamental plants, and can co-occur with the closely related California red scale, *Aonidiella aurantii* (Maskell). The sex pheromone of the California red scale has been identified as a mixture of two components, 3-methyl-6-isopropenyl-9-decen-1-yl acetate (I) and (*Z*)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate (II) (Roelofs et al., 1977, 1978). More recently, the sex pheromone of the yellow scale was isolated and identified as 3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate (Gieselmann et al., 1979). Since the stereochemistry of the trisubstituted olefin could not be established from the spectral data of the material isolated from the insect, we chose, in a collaborative effort with the Geneva group, to prepare a definable mixture of the racemic *Z* and *E* isomers which could be separated and used

[1] *Aonidiella citrina* (Coquillett) (Homoptera: Diaspididae).
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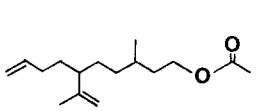
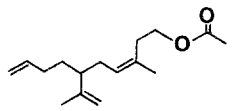
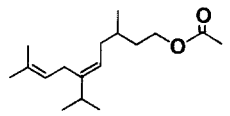


I



II

to confirm the structural assignment and to establish the stereochemistry of the 5-ene double bond in the natural pheromone. We now report the details of the synthetic portion of this collaboration which has resulted in the identification of the pheromone of the yellow scale as (*E*)-3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate (III).



III

METHODS AND MATERIALS

Preparative thin-layer chromatography was, in general, carried out on 1-m × 20-cm glass plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. NMR spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on a Hewlett-Packard model 5984A GC/MS/DS with an all-glass jet separator at 70 eV ionization potential. Gas-liquid chromatographic analyses were performed on model 402 Hewlett-Packard instrument equipped with hydrogen flame ionization detectors. All solvents were dried over activated molecular sieves.

5-(2-Methoxyethoxymethoxy)-3-methyl-1-pentanol (*IV*). To 3.54 g (30 mmol) of 3-methyl-1,5-pentanediol in 60 ml of dry tetrahydrofuran (THF) at 0° under N_2 was added 19.2 ml of 1.56 M *n*-butyllithium (30 mmol). After 30 min, 3.74 g (30 mmol) of 2-methoxyethoxymethyl chloride (MEM-Cl) was added, and the reaction mixture was stirred overnight. The reaction mixture was then poured into a mixture of ether and water. The phases were separated, and the aqueous phase was extracted twice with ether. The combined ether fractions were washed with brine and were dried ($CaSO_4$). After solvent removal *in vacuo*, 6.3 g of crude product was obtained which was applied to seven 1-m × 20-cm preparative silica plates impregnated with Rhodamine 6G (developed with 40% ethyl acetate in hexane). The monoether was isolated in 47% yield (2.9 g, 14 mmol). IR (CCl_4) 3630 and 3500 cm^{-1} (OH); NMR ($CDCl_3$, δ) 4.73 (s, 2H), 3.40 (s, 3H) and 0.92 ppm (d, 3H, $J = 6$ Hz).

5-(2-Methoxyethoxymethoxy)-3-methyl-1-pentanal (*V*). Alcohol IV (1.78 g, 8.65 mmol) was added at room temperature to a suspension of 3.2 g (14.7 mmol) of pyridinium chlorochromate and 246 mg (3 mmol) of sodium acetate in 24 ml of dichloromethane. After 2 hr, the black suspension was diluted with ether and poured onto a 2.5 × 10 cm column of Florisil. The solvent from the eluate was removed *in vacuo* to give 1.44 g (7.1 mmol, 82% yield) of aldehyde V. NMR ($CDCl_3$, δ) 9.63 (t, 1H, $J = 2$ Hz), 4.73 (s, 2H), 3.40 (s, 3H), and 0.98 ppm (d, 3H, $J = 6$ Hz).

Ethyl 2-isopropyl-7-(2-methoxyethoxymethoxy)-5-methyl-2-heptenoate (*VI*). Sodium hydride (380 mg of 57% NaH in oil dispersion) was washed free of oil with pentane under a N_2 atmosphere (theoretical yield, 9 mmol) and was then suspended in 20 ml of THF. To this suspension was added 2.4 g (9 mmol) of diethyl 1-ethoxycarbonyl-2-methylpropylphosphonate [prepared from commercially available diethyl ethoxycarbonylmethylphosphonate by treatment with 1 equiv of NaH and then with 1 equiv of isopropyl iodide in 10% hexamethylphosphoramide (HMPA)-dimethylformamide]. After 45 min, 1.5 g (7.35 mmol) of aldehyde V was added, and the reaction was stirred for 1.25 hr. Water was added to the reaction, and it was poured into ether. The organic phase was washed with brine and was dried ($CaSO_4$). The residue obtained after solvent removal *in vacuo* was purified on three 1-m × 20-cm preparative silica plates (developed with 30% ethyl acetate in hexane) to give 1.34 g (4.25 mmol, 58% yield) of the *Z* and *E* esters VI in a 4:1 ratio, respectively. IR (CCl_4) 1715 cm^{-1} (C=O); NMR ($CDCl_3$, δ) 6.57 (t, $J = 7$ Hz, C=CH *E* isomer), 5.70 (t, $J = 7$ Hz, C=CH *Z* isomer), 4.72 (s, 2H), 4.22 (q, 2H, $J = 7$ Hz), 3.40 (s, 3H), 1.28 (t, 3H, $J = 7$ Hz), 1.05 (d, 6H, $J = 6.5$ Hz), and 0.88 ppm (d, 3H, $J = 6$ Hz). MS (70eV) *m/e* (relative intensity) for each isomer 240 (10), 89 (100).

2-Isopropyl-7-(2-methoxyethoxymethoxy)-5-methyl-2-hepten-1-ol (*VII*). To 1.68 g (5.3 mmol) of esters VI in 20 ml of dry benzene under a N_2 atmosphere was added 6.7 ml (12 mmol) of 1.8 M diisobutylaluminum hydride in heptane. An additional 1.5 ml of reducing agent was added after 1.5 hr. Saturated ammonium chloride was carefully added to the solution after another hour, and then the mixture was poured into ether and water. To facilitate solution of aluminum salts, the pH of the aqueous layer was adjusted to pH 4 with 2% aqueous HCl. The aqueous layer was extracted twice more with ether, and the combined ether fractions were washed with brine and were dried ($CaSO_4$). Removal of solvent *in vacuo* gave 1.28 g (4.7 mmol, 90% yield) of allylic alcohols VII. IR (CCl_4) 3600 cm^{-1} (OH); NMR ($CDCl_3$, δ) 5.33 (br t, 1H, $J = 7$ Hz), 4.72 (s, 2H), 4.12 (br s, 2H), 3.40 (s, 3H), 1.05 (d, 6H, $J = 7$ Hz), and 0.88 ppm (d, 3H, $J = 6$ Hz).

2-Isopropyl-7-(2-methoxyethoxymethoxy)-5-methyl-2-hepten-1-yl acetate (*VIII*). Allylic alcohols VII (100 mg, 0.36 mmol) in 0.15 ml of acetic anhydride and 0.25 ml of pyridine were stirred overnight at room temperature under N_2 atmosphere. Ice was added to the mixture, and after 30 min the

reaction was poured into ether and 5% aqueous HCl. The organic layer was washed with 2 M Na_2CO_3 and brine and was dried (Na_2SO_4). Removal of solvent *in vacuo* gave 114 mg (0.36 mmol, 100% yield) of allylic acetates VIII. IR (CCl_4) 1740 cm^{-1} (C=O); NMR ($CDCl_3$, δ) 5.43 (br t, 1H, J = 7Hz), 4.70 (s, 2H), 4.60 (br s, 2H), 3.40 (s, 3H), 2.05 (s, 3H), 1.02 (d, 6H, J = 7 Hz), and 0.87 ppm (d, 3H, J = 6 Hz).

3,9-Dimethyl-6-isopropyl-5,8-decadien-1-yl 2-methoxyethoxymethyl ether (IX). To 190 mg (1 mmol) of cuprous iodide suspended in 4 ml of dry ether at −25° under a N_2 atmosphere was added 3.3 ml (1.98 mmol) of 0.60 M 2-methylpropenyllithium (prepared from 2-methyl-1-bromo-1-propene and lithium—1% sodium wire in ether). After 20 min, an aliquot gave a negative Gilman test (Gilman and Schulze, 1925), and 105 mg (0.33 mol) of allylic acetates VIII in 1 ml of ether was added. After 4 hr, saturated $(NH_4)_2SO_4$ was added, and then the reaction was poured into ether and additional $(NH_4)_2SO_4$ solution. The ether layer was washed with water and was dried (Na_2SO_4). Solvent was removed *in vacuo* and the residue was purified on one 1-m × 20-cm preparative silica plate impregnated with Rhodamine 6G to give 62 mg (0.20 mmol, 60% yield) of diene ethers IX. NMR ($CDCl_3$, δ) 5.27–4.90 (m, 2H), 4.73 (s, 2H), 3.40 (s, 3H), 2.72 (br d, 2H, J = 7 Hz), 1.67 (br s, 6H), and 1.00 ppm (d, 6H, J = 7 Hz). MS (70 eV) m/e (relative intensity) 312 (M^+, 0.2), 69 (100).

3,9-Dimethyl-6-isopropyl-5,8-decadien-1-yl acetate (III and X). A solution of 56 mg (0.18 mmol) of diene ethers IX in 5 ml of ethanol and 1 ml of water containing 75 mg of trichloroacetic acid was heated at 70° for 72 hr under a N_2 atmosphere. The reaction was cooled and poured into a mixture of ether and 2 M Na_2CO_3. The organic layer was washed with brine and was dried (Na_2SO_4). After solvent removal, the desired alcohols were purified by preparative thin-layer chromatography (developed with 30% ether in hexane) to give 27 mg of product. NMR ($CDCl_3$, δ) 5.30–4.90 (m, 2H), 3.70 (t, 2H, J = 6 Hz), 2.73 (br d, 2H, J = 6 Hz), 1.70 (br s, 6H), and 1.00 ppm (d, 6H, J = 7 Hz).

The alcohol isomers were stirred in 0.10 ml of acetic anhydride and 0.15 ml of pyridine for several days. Ice was added to the mixture, and after 30 min the reaction was poured into ether and 5% aqueous HCl. The organic fraction was washed with 2 M Na_2CO_3 and brine, and was dried (Na_2SO_4). After solvent removal *in vacuo*, the product was filtered through a small column of Florisil with ether-pentane (1:4) to give 30 mg (0.12 mmol, 65% yield) of the acetates III and X in a 4:1 ratio, respectively. IR (CCl_4) 1740 cm^{-1} (C=O); NMR (C_6D_6, δ) 5.33–5.03 (m, 2H), 4.07 (t, 2H, J = 6 Hz), 2.78 (br d, 2H, J = 6 Hz), 1.72 (s, 3H), 1.62 (br s, 6H), 1.05 (d, J = 7 Hz, $(CH_3)_2CH$ for major E isomer), 0.98 (d, J = 7 Hz, $(CH_3)_2CH$ for minor Z isomer) and 0.82 ppm (br d, 3H, J = 6 Hz). MS (70eV) m/e (relative intensity) for both isomers 266 (M^+, 14), 43 (100). The diene acetate isomers III and X were

analyzed and resolved by gas-liquid chromatography (4m 3% PDEAS, 145°). The faster eluting *E* isomer had a retention time of 14.6 min, while the minor *Z* isomer was retained on the column for 15.4 min. The isomers were preparatively separated on an XF-1150 column (Gieselmann et al., 1979).

RESULTS AND DISCUSSION

The synthetic scheme outlined in Figure 1 was designed to give a definable mixture of (*Z*)- and (*E*)-3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetates. The stereochemistry of the olefin in the natural pheromone could then be assigned by comparison with the synthetic mixture. Thus, the monomethoxyethoxymethyl (MEM) ether IV of 3-methyl-1,5-pentanediol, obtained by treating the diol with 1 equiv each of *n*-butyllithium and MEM chloride (Corey et al., 1976) followed by chromatography, was oxidized to the aldehyde V in 82% yield with 1.7 equiv of pyridinium chlorochromate and 0.35 equiv of sodium acetate in dichloromethane (Corey et al., 1975). Treatment of aldehyde V with the anion of diethyl 1-ethoxycarbonyl-2-methylpropyl phosphonate (prepared by isopropylation of diethyl ethoxycarbonylmethylphosphonate) in THF gave, in 58% yield, a mixture of isomeric esters in a 4:1 ratio. Inspection of the olefinic hydrogen region of the PMR spectrum of the esters VI allowed the following assignment of stereochemistry (Jackman and Wiley, 1960). For the major isomer (*Z*), the olefinic hydrogen resonance occurred at δ ($CDCl_3$) 5.70 ppm, while for the minor isomer (*E*), this same resonance occurred at δ ($CDCl_3$) 6.57 ppm. This mixture of esters was then reduced with 2.8 equiv of diisobutylaluminum hydride in benzene to give allylic alcohols VII in 90% yield, which were quantitatively converted to their acetates VIII with excess acetic anhydride and pyridine. Reaction of the allylic acetates VIII in ether with 3 equiv of lithium bis(2-methyl-1-propenyl)cuprate (Anderson et al., 1970, 1972) (prepared from isobutenyl bromide; Farrell and Bachman, 1935) at −10° for 4 hr gave the desired diene ethers IX in 60% yield. Cleavage of the ethers IX (trichloroacetic acid in refluxing ethanol, 12 hr) to their corresponding alcohols followed by acetylation with excess acetic anhydride and pyridine gave, in 65% yield, the diene acetates III and X in a ratio of 4:1, respectively. In the PMR spectrum of this mixture in deuterobenzene the isopropylmethyl resonances were resolved, i.e., δ 1.05 ppm (d, $J = 7$ Hz) for the major isomer (*E*) and δ 0.98 ppm (d, $J = 7$ Hz) for the minor isomer (*Z*). Since the isopropylmethyls in the natural pheromone absorb at δ 1.08 ppm, the stereochemistry of this pheromone was established as *E*.

The racemic *Z* and *E* isomers were separated by preparative GLC on an XF-1150 column. The faster eluting *E* isomer had the same retention

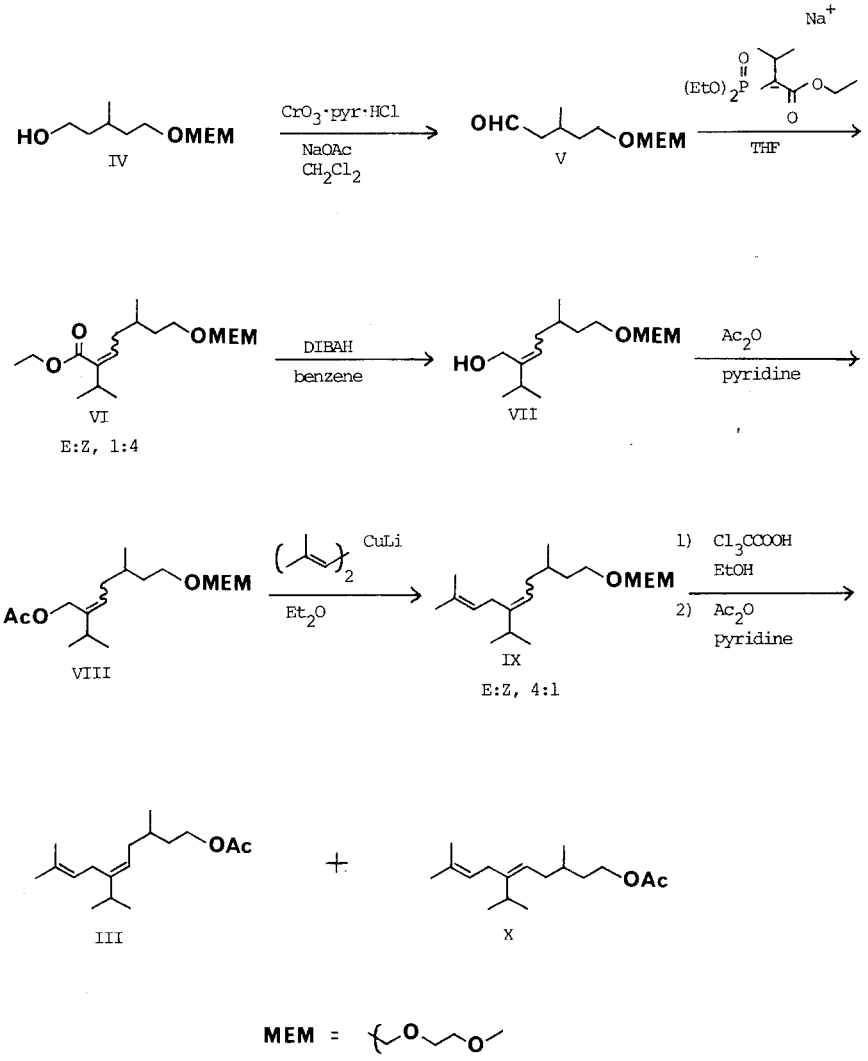


FIG. 1. Synthesis of (*E*)- and (*Z*)-3,9-dimethyl-6-isopropyl-5,8-decadien-1-yl acetate.

time as the natural pheromone and had an identical PMR spectrum. In greenhouse bioassays the *E* isomer was found to be attractive to the male yellow scale, whereas the *Z* isomer was inactive. The absolute configuration of the naturally occurring pheromone has not been determined, and the effect of enantiomeric purity on the attraction of males to synthetic (*E*)-III also has as yet not been established.

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