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ENANTIOSELECTIVE SYNTHESIS OF A SEX ATTRACTANT
PHEROMONE OF THE PINE SCALE *MATSUCOCCUS FEYTAUDI*

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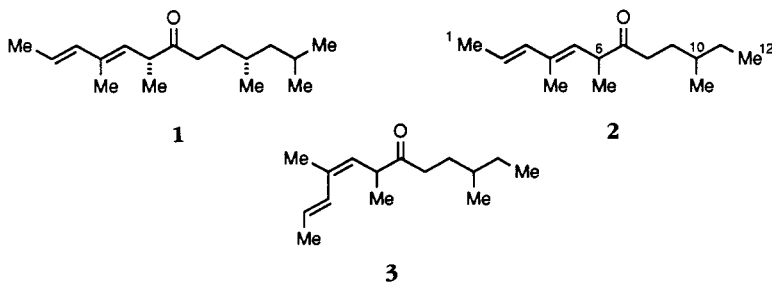
ABSTRACT.—The enantioselective synthesis of $(-)$ -(2*E*,4*E*,6*R*,10*S*)-4,6,10-trimethyl-2,4-dodecadien-7-one [2], a primary sex attractant pheromone of the pine scale *Matsucoccus feytaudi*, is described.

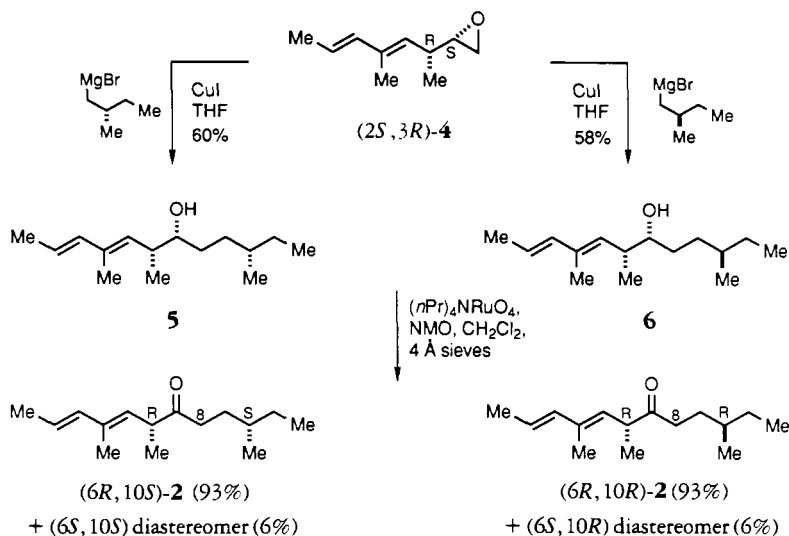
The critical need for effective strategies to control forestland predation by scale insects has fostered efforts to identify the active pheromones of *Matsucoccus* pine scales. Matsuone [1] has been identified as the primary sex attractant pheromone of the red pine scale *Matsucoccus resinosa* (United States) and two related species indigenous to Asia, *Matsucoccus matsumurae* and *Matsucoccus thunbergiana* (1). The gross structure and relative stereochemistry of 1 have recently been confirmed by total synthesis (2). In 1990, a French group reported the isolation and characterization of the structurally related dienes 2 and 3 from collections of *Matsucoccus feytaudi*, a scale species endemic to Europe (3). We now report the convergent, enantioselective synthesis of both diastereomeric forms of the *M. feytaudi* pheromone 2, confirming the assigned structure and establishing the relative stereochemistry of the natural pheromone as priority reflective (4).

Our approach to diene 2 was based on a convergent scheme in which the coupling of an optically active halide and epoxide (+)-4 would establish the carbon framework and remote stereochemi-

cal relationship of the individual pheromone diastereomers. Thus, treatment of the previously prepared (2) epoxide (2*S*,3*R*)-4 with the Grignard reagent derived from (*S*)-1-bromo-2-methylbutane (5) afforded alcohol 5, accompanied by small amounts (ca. 6%) of an inseparable minor diastereomer, an observation consistent with the optical purity of the starting epoxide [ee 88% (2)]. All compounds reported herein were fully characterized by ir, ¹H nmr and hrcims analysis. Oxidation of 5 with tetrapropylammonium perruthenate (6) in the presence of *N*-methylmorpholine *N*-oxide afforded a 93% yield of ketone (6*R*,10*S*)-2, accompanied by the diastereomeric (6*S*,10*S*) ketone (6%). Similarly, addition of (*R*)-1-bromo-2-methylbutane to (2*S*,3*R*)-4 afforded alcohol 6, which upon oxidation yielded (6*R*,10*R*)-2 and the minor (6*S*,10*R*) ketone product (Scheme 1).

Comparison of the 500 MHz ¹H-nmr spectra of the synthetic diastereomers of 2 to the spectrum of *M. feytaudi* pheromone kindly provided by Dr. J. Einhorn revealed that synthetic (6*R*,10*S*)-2 was identical to the natural pheromone, while the ¹H-nmr spectrum of (6*R*,10*R*)-





SCHEME 1

2 was clearly distinct from that of authentic **2**. Individual diastereomers of **2** are easily distinguished by the ^1H -nmr chemical shifts of signals assigned to the diastereotopic C-8 protons. For authentic **2** and (6*R*,10*S*)-**2**, the H-8 signals appear at 2.19 (ddd, $J = 16.8, 9.3, 5.5$ Hz) and 2.29 ppm (ddd, $J = 16.8, 8.6, 6.4$ Hz), while for (6*R*,10*R*)-**2** the H-8 signals are observed at 2.13 (ddd, $J = 16.8, 8.7, 6.1$ Hz) and 2.32 ppm (ddd, $J = 16.8, 9.3, 5.5$ Hz). A similar chemical shift pattern is observed for diastereomers of matsuone [**1**].

In summary, we have completed the first asymmetric synthesis of the major component of the *M. feytaudi* pheromone complex. Our observations serve to confirm the assigned structure of **2** and establish the relative stereochemistry of the natural product as priority reflective. We note that the syn relative configuration of the *M. feytaudi* pheromone corresponds to that of matsuone [**1**] (2). Efforts to define the absolute configuration of **2** and extend our scheme to the preparation of other *Matsucoccus* pheromones will be the subject of future reports.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Nmr spectra were recorded on General Electric

QE-300 or GN-500 nmr spectrometers. All spectra were recorded using CDCl_3 or C_6D_6 solutions. ^1H -nmr spectra were acquired at 300 MHz and 500 MHz, and peak positions are reported in parts per million (ppm) with CHCl_3 or C_6H_6 (7.26 ppm or 7.15 ppm respectively) as internal standards. ^{13}C -nmr spectra were acquired at 75 MHz, and peak positions are reported in ppm with CDCl_3 as internal standard (center peak of triplet at 77 ppm). Ir spectra were recorded on an IBM instruments IR/32 Ft-ir. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Low resolution mass spectra were acquired at SUNY College of Environmental Science and Forestry. High resolution mass spectra were performed at the University of Illinois, Urbana-Champaign.

Solvents were distilled prior to use except as noted. Preparative chromatography columns and reactions were monitored by tlc utilizing Merck Si gel 60 F₂₅₄ precoated 0.25 mm plates, developed in hexane-Et₂O (4:1); R_f values are reported for this solvent mixture unless otherwise noted. All reactions were run under an inert atmosphere of argon unless otherwise noted.

(2*E*,4*E*,6*R*,7*R*,10*S*)-4,6,10-TRIMETHYL-2,4-DODECADIEN-7-OL [**5**].—(2*E*,4*E*,6*R*)-4-methyl-6-[(1*S*)-oxiranyl]-2,4-heptadiene [**4**] (7.0 mg, 46.0 μmol) was dissolved in THF (0.5 ml) and treated with CuI (1.4 mg, 7.4 μmol). To this solution was added (2*S*)-2-methylbutylmagnesium bromide (1.00 ml, 0.66 M in THF, 660 μmol). After 4 h the reaction was quenched with NH_4Cl (1 ml, aqueous saturated), extracted with Et₂O (3 \times 2 ml), dried, and concentrated (75° at atmospheric pressure) to a volume of 1 ml. The resulting solution was subjected to cc [pentane,

pentane-Et₂O (16:1)] to afford (2*E*,4*E*,6*R*,7*R*,10*S*)-4,6,10-trimethyl-2,4-dodecadien-7-ol [**5**] (6.2 mg, 60%) containing ca. 6% of the (6*S*,10*S*) diastereomer, as determined by the ¹H-nmr spectrum: *R*_f 0.36 [pentane-Et₂O (4:1)]; [α]²⁴_D 9.4 (*c* = 0.620, CDCl₃) [optical rotation is not corrected for the presence of the (6*S*,10*S*) diastereomer]; ir (neat/NaCl) 3353, 2961, 2930, 2874, 963; ¹³C nmr 136.1, 133.9, 132.3, 122.8, 76.4, 38.8, 34.5, 32.9, 32.1, 29.7, 19.1, 18.1, 16.3, 12.9, 11.4; ¹H nmr (300 MHz, CDCl₃, 7.26), 6.08 (d, *J* = 15.4, 1H, H-3), 5.61 (dq, *J* = 15.4, 6.7, 1H, H-2), 5.20 (d, *J* = 9.7, 1H, H-5), 3.39 (vbr s, 1H, H-7), 2.62–2.50 (m, 1H, H-6), 1.77 (d, *J* = 6.7, 3H, H-1), 1.75 (s, 3H, 4-Me), 1.55–1.02 (m, 7H, H-8, H-9, H-10, H-11), 1.01 (d, *J* = 6.7, 3H, 6-Me), 0.89–0.83 (m, 6H, H-12, 10-Me); eims *m/z* (rel. int.) [M]⁺ 224 (0.56), 110 (49.60), 109 (22.02), 95 (base), 67 (14.49), 55 (18.70); hrcims (CH₄, M + H) calcd for C₁₅H₂₉O, 224.2218, found 224.2213.

(2*E*,4*E*,6*R*,7*R*,10*R*)-4,6,10-TRIMETHYL-2,4-DODECADIEN-7-OL [**6**].—(2*E*,4*E*,6*R*)-4-methyl-6-[(1*S*)-oxiranyl]-2,4-heptadiene [**4**] (7.2 mg, 47.6 μmol) was dissolved in THF (0.5 ml) and treated with CuI (1.3 mg, 6.8 μmol). To the resulting solution was added (2*R*)-2-methylbutylmagnesium bromide (0.50 ml, 0.66 M in THF, 330 μmol). After 3 h the reaction was quenched with NH₄Cl (1 ml, aqueous saturated), extracted with Et₂O (3 × 2 ml), dried, and concentrated (65° at atmospheric pressure) to a volume of 1 ml. The resulting solution was subjected to cc [pentane, pentane-Et₂O (16:1)] to afford (2*E*,4*E*,6*R*,7*R*,10*R*)-4,6,10-trimethyl-2,4-dodecadien-7-ol [**6**] (6.2 mg, 58%) containing ca. 6% of the (6*S*,10*R*) diastereomer as determined by the ¹H-nmr spectrum: *R*_f 0.34 [pentane-Et₂O (4:1)]; [α]²⁴_D 8.8 (*c* = 0.340, CDCl₃) [optical rotation is not corrected for the presence of the (6*S*,10*R*) diastereomer]; ir (neat/NaCl) 3401, 2959, 2928, 2874, 963; ¹³C nmr 136.1, 134.2, 122.8, 38.7, 34.6, 32.9, 32.2, 29.3, 19.3, 18.1, 16.1, 12.9, 11.3; ¹H nmr (300 MHz, CDCl₃, 7.26) 6.08 (d, *J* = 15.5, 1H, H-3), 5.61 (dq, *J* = 15.5, 6.6, 1H, H-2), 5.21 (d, *J* = 9.7, 1H, H-5), 3.42–3.35 (m, 1H, H-7), 2.63–2.51 (m, 1H, H-6), 1.77 (d, *J* = 6.6, 3H, H-1), 1.75 (s, 3H, 4-Me), 1.56–1.05 (m, 7H, H-8, H-9, H-10, H-11), 1.05 (d, *J* = 6.7, 3H, 6-Me), 0.88–0.83 (m, 6H, H-12, C-10 methyl); eims *m/z* (rel. int.) [M]⁺ 224 (1.02), 110 (55.84), 109 (22.69), 95 (base), 67 (12.82), 55 (17.67); hrcims (CH₄, M + H) calcd for C₁₅H₂₉O, 224.2218, found 224.2216.

(2*E*,4*E*,6*R*,10*S*)-4,6,10-TRIMETHYL-2,4-DODECADIEN-7-ONE (6*R*,10*S*)-[**2**].—(2*E*,4*E*,6*R*,7*R*,10*S*)-4,6,10-Trimethyl-2,4-dodecadien-7-ol [**5**] (3.3 mg, 14.7 μmol) was dissolved in CH₂Cl₂ (0.3 ml), and a 1/8" 4 Å sieve was added. The re-

sulting solution was treated successively with 4-methylmorpholine 4-oxide (3.0 mg, 2.1 μmol) and tetrapropylammonium perruthenate (1.0 mg, 2.95 μmol) and stirred 30 min. The reaction mixture was subjected to cc [pentane, pentane-Et₂O (16:1)] to afford quantitatively (2*E*,4*E*,6*R*,10*S*)-4,6,10-trimethyl-2,4-dodecadien-7-one [**2**] (3.3 mg) containing ca. 6% of the (6*S*,10*S*) diastereomer, as determined by the ¹H-nmr spectrum: *R*_f 0.80 [pentane-Et₂O (4:1)]; [α]²⁴_D -48.5 (*c* = 0.330, CDCl₃) [optical rotation is not corrected for the presence of the (6*S*,10*S*) diastereomer]; ir (neat/NaCl) 2961, 2928, 2874, 2855, 1717, 963; ¹H nmr (500 MHz, C₆D₆, 7.15), 6.01 (dq, *J* = 15.6, 1.5, 1H, H-3), 5.49 (dq, *J* = 15.6, 6.5, 0.5, 1H, H-2), 5.24 (br d, *J* = 9.9, 1H, H-5), 3.28 (dq, *J* = 9.9, 6.8, 1H, H-6), 2.26 (ddd, *J* = 16.8, 9.3, 6.3, 1H, H-8), 2.15 (ddd, *J* = 16.8, 9.2, 5.7, 1H, H-8'), 1.71–1.58 (m, 1H, H-9), 1.66 (d, *J* = 1.5, 3H, 4-Me), 1.60 (dd, *J* = 6.5, 1.3, 3H, H-1), 1.42–1.14 (m, 3H, H-9', H-10, H-11), 1.13 (d, *J* = 6.8, 3H, 6-Me), 1.06–1.00 (m, 1H, H-11'), 0.80 (t, *J* = 7.3, 3H, H-12), 0.75 (d, *J* = 6.8, 3H, 10-Me); eims *m/z* (rel. int.) [M]⁺ 222 (6.99), 113 (11.53), 109 (base), 95 (21.47), 81 (5.88), 67 (14.98); hrcims (CH₄, M + H) calcd for C₁₅H₂₇O, 223.2062, found 223.2052.

(2*E*,4*E*,6*R*,10*R*)-4,6,10-TRIMETHYL-2,4-DODECADIEN-7-ONE (6*R*,10*R*)-[**2**].—(2*E*,4*E*,6*R*,7*R*,10*R*)-4,6,10-Trimethyl-2,4-dodecadien-7-ol [**6**] (3.1 mg, 13.8 μmol) was dissolved in CH₂Cl₂ (0.3 ml), and a 1/8" 4 Å sieve was added. The resulting solution was treated successively with 4-methylmorpholine 4-oxide (3.0 mg, 22.1 μmol) and tetrapropylammonium perruthenate (1.0 mg, 2.95 μmol) and stirred 30 min. The reaction mixture was subjected to cc [pentane, pentane-Et₂O (16:1)] to afford quantitatively (2*E*,4*E*,6*R*,10*R*)-4,6,10-trimethyl-2,4-dodecadien-7-one [**2**] (3.1 mg) containing ca. 6% of the (6*S*,10*R*) diastereomer as determined by the ¹H nmr spectrum: *R*_f 0.80 [pentane-Et₂O (4:1)]; [α]²⁴_D -44.0 (*c* = 0.150, CDCl₃) [optical rotation is not corrected for the presence of the (6*S*,10*R*) diastereomer]; ir (neat/NaCl) 2961, 2928, 2874, 1717, 963; ¹H nmr (500 MHz, C₆D₆, 7.15) 6.01 (br d, *J* = 15.5, 1H, H-3), 5.48 (dq, *J* = 15.5, 6.6, 1H, H-2), 5.24 (br d, *J* = 9.7, 1H, H-5), 3.28 (dq, *J* = 9.7, 6.7, 1H, H-6), 2.29 (ddd, *J* = 16.8, 9.3, 5.9, 1H, H-8), 2.11 (ddd, *J* = 16.8, 9.4, 6.0, 1H, H-8'), 1.67–1.58 (m, 1H, H-9), 1.65 (br s, 3H, 4-Me), 1.60 (dd, *J* = 6.6, 1.4, 3H, H-1), 1.44–1.15 (m, 3H, H-9', H-10, H-11), 1.13 (d, *J* = 6.7, 3H, 6-Me), 1.06–0.99 (m, 1H, H-11'), 0.80 (t, *J* = 7.4, 3H, H-12), 0.75 (d, *J* = 6.5, 3H, 10-Me); eims *m/z* (rel. int.) [M]⁺ 222 (6.27), 113 (11.21), 109 (base), 95 (22.49), 81 (6.23), 67 (15.68); hrcims (CH₄, M + H) calcd for C₁₅H₂₇O, 223.2062, found 223.2056.

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