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PHEROMONE CHIRALITY OF AFRICAN PALM WEEVIL, *Rhynchophorus phoenicis* (F.) AND PALMETTO WEEVIL, *Rhynchophorus cruentatus* (F.) (COLEOPTERA: CURCULIONIDAE)

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Abstract—There are four stereoisomers of both 3-methyl-octan-4-ol, the aggregation pheromone of the African palm weevil, *Rhynchophorus phoenicis* (F.) and 5-methyl-octan-4-ol, the aggregation pheromone of the palmetto weevil, *Rhynchophorus cruentatus* (F.). Synthetic stereoisomers of 3-methyl-octan-4-ol and 5-methyl-octan-4-ol were baseline-separated on a Cyclodex-B fused silica column. Use of this column in gas chromatographic–electroantennographic detection (GC-EAD) and GC–mass spectrometric (GC-MS) analyses revealed that only one stereoisomer, (3*S*,4*S*)-3-methyl-octan-4-ol and (4*S*,5*S*)-5-methyl-octan-4-ol, is produced by male *R. phoenicis* and male *R. cruentatus*, respectively, and elicits good antennal responses by conspecific male and female weevils. In field trapping experiments, with *R. phoenicis* in Côte d'Ivoire and *R. cruentatus* in Florida, (3*S*,4*S*)-3-methyl-octan-4-ol and (4*S*,5*S*)-5-methyl-octan-4-ol strongly enhanced attraction of fresh palm tissue, whereas other stereoisomers were behaviorally benign. Stereoisomeric 3-methyl-octan-4-ol and 5-methyl-octan-4-ol may be utilized to monitor and/or manage populations of these two palm weevils.

Key Words—Coleoptera, Curculionidae, *Rhynchophorus phoenicis*, *Rhynchophorus cruentatus*, aggregation pheromone, pheromone chirality, (3*S*,4*S*)-3-methyl-octan-4-ol, (3*R*,4*R*)-3-methyl-octan-4-ol, (3*S*,4*R*)-3-methyl-octan-4-

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ol, (3*R*,4*S*)-3-methyl-octan-4-ol, (4*S*,5*S*)-5-methyl-octan-4-ol, (4*R*,5*R*)-5-methyl-octan-4-ol, (4*S*,5*R*)-5-methyl-octan-4-ol, (4*R*,5*S*)-5-methyl-octan-4-ol.

INTRODUCTION

Palm weevils in the Rhynchophorinae produce methyl-branched, secondary alcohols as aggregation pheromones: (2*E*)-6-methyl-hepten-4-ol (rhynchophorol) [American palm weevil, *Rhynchophorus palmarum* (L.) (Rochat et al., 1991)]; 3-methyl-octan-4-ol (phoenicol) [African palm weevil, *R. phoenicis* (F.) (Gries et al., 1993, 1994; Rochat et al., 1993]; 4-methyl-nonan-5-ol (ferrugineol) [Asian palm weevils, *R. ferrugineus* (Oliv.), *R. vulneratus* (Panz) Hallett et al., 1993; Rochat et al., 1993) and *R. bilineatus* (Montr.) (Oehlschlager et al., 1994)], and 5-methyl-octan-4-ol (cruentol) [Palmetto weevil, *R. cruentatus* (F.) (Weissling et al., 1994)]. Racemic (rhynchophorol) and stereoisomeric mixtures (phoenicol, ferrugineol, cruentol) of synthetic aggregation pheromones in combination with host material strongly attracted weevils in field experiments. Stereoselective production of and response to pheromone has been demonstrated in *R. palmarum* (Oehlschlager et al., 1992) and recently in the other *Rhynchorphorus* palm weevils (Perez et al., 1993). Male *R. palmarum* stereoselectively produce and both sexes respond to (*S*)-rhynchophorol, while the antipode is behaviorally benign (Oehlschlager et al., 1992). Male *R. phoenicis* produce one stereoisomer of phoenicol but electrophysiological and behavioral activity have not been investigated (Mori et al., 1993). In this study we report that *R. phoenicis* and *R. cruentatus* stereoselectively produce and respond to only one of the four possible stereoisomers of 3-methyl-octan-4-ol and 5-methyl-octan-4-ol, respectively.

METHODS AND MATERIALS

Laboratory Analysis

Male and female *R. phoenicis* were collected in oil palm plantations 40–50 km northeast of Abidjan, Côte d'Ivoire. Male and female *R. cruentatus* were collected in a 300-ha pasture interspersed with *Sabal palmetto* (Walter) and saw palmetto, *Serrenoa repens* (Bartr.), 12 km south of La Belle, Florida. Male-produced phoenicol and cruentol were captured (Gries et al., 1993; Weissling et al., 1994) and subjected to both gas chromatographic–electroantennographic detection (GC-EAD) (Arn et al., 1975) (Hewlett Packard 5890A) and GC–mass spectrometry (GC-MS) (Hewlett Packard 5985 B) on a fused silica, Cyclodex-B-coated column (30 m × 0.25 mm ID, J&W Scientific), which separates all four stereoisomers of phoenicol and cruentol. For GC-EAD recordings, a weevil antenna was removed from the rostrum and suspended between

two glass capillary electrodes with the antennal base being inserted into one and the olfactory club impaled by the other electrode. Chemical ionization (CI, isobutane) GC-MS analysis was conducted in both full-scan and selected-ion monitoring mode (SIM). A full-scan mass spectrum of synthetic phoenicol or cruentol was obtained to select diagnostic ions. For GC-MSCI-SIM, synthetic phoenicol and cruentol, hexane, and concentrated weevil-produced pheromone were injected in split mode and analyzed by scanning for diagnostic ions.

Instruments and General Procedures

Nuclear magnetic resonance (NMR) spectroscopy was conducted on a Bruker AMX-400 spectrometer at 400.13 and 100.62 MHz for ^{1}H and ^{13}CNMR spectra, respectively. ^{1}H chemical shifts are reported in parts per million (ppm, δ) and relative to TMS (0.00 ppm). ^{13}C spectra are referred to $CDCI_3$ (77.0 ppm). Gas chromatographic analyses were performed on Hewlett-Packard 5880A and 5890 instruments equipped with a flame ionization detector and a fused silica, DB-1 coated column (15 m $\times$ 0.25 mm ID; 0.25 μm film) (J&W Scientific). Elemental analyses were performed using a Carbo Erba model-1106 Elemental Analyzer. Diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and pentane were freshly distilled from sodium-benzophenone-ketyl, CaH, and P_2O_5, respectively. Chemicals obtained from commercial sources were used without further purification unless otherwise indicated. All moisture and air sensitive reactions were conducted under argon. Column chromatography refers to flash chromatography using Silica Gel 60 (230–400 mesh E Merck, Darmstadt) (Still et al., 1978). Thin-layer chromatography (TLC) was conducted on aluminum-backed plates precoated with Merck Silica Gel 60F-254 as the adsorbent, and visualized by treatment with an acidic solution of 1% $Ce(SO_4)_2$ and 1.5% molybdic acid followed by gentle heating.

Synthesis of Phoenicol Stereoisomers

(3*R*,4*R*)-, (3*S*,4*S*)-, (3*R*,4*S*)-, and (3*S*,4*R*)-3-methyl-octan-4-ol [(*R*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*S*,*R*)-phoenicol] were synthesized according to a method modified from Nakagawa and Mori (1984), which involved: (1) asymmetric epoxidation of (2*Z*-) or (2*E*)-2-penten-1-ol (Gao et al., 1987; Hill et al., 1985); (2) regioselective epoxide opening with trimethylaluminun (Pfaltz and Mattenberger, 1982; Suzuki et al., 1982; Takano et al., 1989; Vaccaro et al., 1992); (3) selective monotosylation; and (4) alkylation reaction using an organomagnesium cuprate reagent. Synthesis of (3*S*,4*S*)-3-methyl-octan-4-ol exemplifies the synthetic procedure (Figure 1):

(2S,3R)-2,3-Epoxy-pentan-1-ol ***(2a).*** Titanium(IV) isopropoxide (11.4 ml, 10.87 g, 38 mmol) in 250 ml of dry CH_2Cl_2 was mixed under argon with 1 g of 4A powdered, activated molecular sieves. After cooling to $-78°C$, diethyl

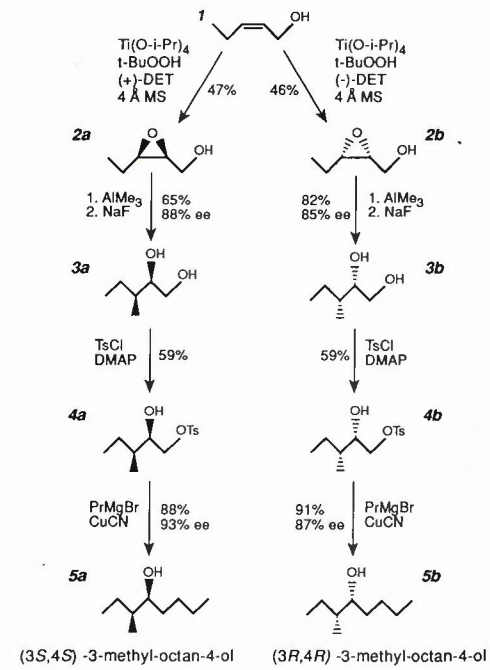

FIG. 1. Scheme for the synthesis of (3*S*,4*S*)-3-methyl-octan-4-ol, **5a,** and (3*R*,4*R*)-3-methyl-octan-4-ol, **5b.**

(2*R*,3*R*)-tartrate [L-(+)-DET, 7.8 ml, 9.9 g, 0.05 mol] was added *via* syringe followed by addition of (2*Z*)-2-penten-1-ol (8.21 ml, 7.0 g, 80 mmol, Aldrich Chemical Co., Milwaukee, Wisconsin). The mixture was stirred 15 min prior to dropwise addition of 25 ml (0.15 mol) of 5.7 M anhyd. *tert*-butyl hydroperoxide in CH_2Cl_2 (prepared as described by Gao et al., 1987) (precooled to −20°C). After the reaction had warmed up to −20°C it was stirred at this temperature for 48 hr. The reaction was monitored by TLC (2:8, pentane–Et_2O; R_f = 0.39). Nonaqueous work-up (Gao et al., 1987) followed by column chromatography (2:8, pentane–Et_2O) gave **2a** (3.79 g, 46% yield, 90% ee) as a colorless liquid [**2a:** ^1H ($CDCl_3$): δ 1.02 (3 H, t, J = 8.6 Hz), 1.52 (2 H, m), 2.04 (1 H, brs, D_2O exchangeable), 2.41 (2 H, t, J = 10 Hz), 3.15 (1 H, dd, J = 5, 10 Hz), 3.68 (1 H, dd, J = 4, 10 Hz); ^{13}C ($CDCl_3$) δ 61.82, 57.10, 56.98, 26.22, 13.91 ppm).] **2b** (3.93 g, 47% yield, 87% ee) was synthesized following the same procedure using diethyl (2*S*,3*S*)-tartrate [D-(−)-DET] as the epoxidation catalyst.

(2R,3S)-3-Methyl-pentane-1,2-diol ***(3a).*** A pentane (200 ml solution of **2a** (3.78 g, 37 mmol) was cooled to −50°C. Then 10.5 ml (0.11 mol) of

neat $AlMe_3$ (Aldrich Chemical Co.) was added dropwise followed by 8 ml of 2.49 M *n*-butyllithium (20 mmol). After stirring at −50°C for 20 min., the cooling bath was removed and the flask allowed to warm to room temperature. Monitoring the reaction by GC and TLC (1:9, pentane–Et_2O; R_f = 0.19) indicated reaction completion after 30 min. The reaction was quenched with NaF–H_2O (1:1) (Suzuki et al., 1982) at 0°C. The white precipitate was filtered and the obtained solid was washed with Et_2O. The ethereal layer was dried over anhyd. $MgSO_4$ and concentrated in vacuo to give a pale yellow liquid. Purification by column chromatography (1:9, pentane–Et_2O) afforded **3a** (2.93 g, 64.4% yield, 88% ee) as a colorless liquid [**3a**: ^1H ($CDCl_3$); δ 0.88 (3 H, t, J = 8 Hz), 0.90 (3 H, d, J = 8 Hz), 1.20 (1 H, m), 1.42 (2 H, m), 2.15 (2 H, brs, D_2O exchangeable), 3.45 (2 H, m), 3.62 (1 H, m); ^{13}C ($CDCl_3$) δ 75.52, 65.21, 37.40, 25.71, 14.11, 11.53 ppm; CI-MS *m/z* (isobutane, relative intensity): 119 (M^++1, 40).] **3b:** 3.59 g, 82% yield, 85% ee.

(2R,3S)-3-Methyl-1-tosyloxy-pentan-2-ol ***(4a).*** This was prepared from 2.92 g (25 mmol) of **3a** in dry pyridine, to which 0.73 g (6 mmol) of dimethyl aminopyridine (DMAP) was added. The flask was cooled to −20°C (ethylene glycol–water–Dry Ice) and 5.73 g (0.03 mol) of *p*-toluensulfonyl chloride added in one portion. After stirring 7 hr at −20 to −10°C and monitoring the reaction by GC and TLC (6:4, pentane–Et_2O, R_f = 0.27), the mixture was poured into ice-cooled NaCl solution and extracted (2 × 30 ml) with Et_2O. The organic layer was washed with 3 M HCl, saturated $NaHCO_3$, saturated NaCl, and dried over anhyd. $MgSO_4$. After concentration and column chromatography (6:4, pentane–Et_2O), solvent residues were removed under vacuum to give **4a** (4.0 g, 59 %) as a pale yellow oil. [**4a:** ^1H ($CDCl_3$); δ 0.85 (3 H, d, J = 8 Hz), 0.86 (3 H, t, J = 8 Hz), 1.20 (1 H, m), 1.45 (2 H, m), 1.90 (1 H, brs, D_2O exchangeable), 3.72 (1 H, dt, J = 8, 4 Hz), 3.98 (1 H, dd, J = 8, 2.5 Hz), 4.04 (1 H, dd, J = 8, 1.5 Hz); 7.34 (2 H, d, J = 8 Hz); 7.80 (2 H, d, J = 8 Hz); ^{13}C ($CDCl_3$); δ 144.95, 133.0, 129.89, 127.90, 72.93, 72.75, 36.97, 25.62, 21.57, 13.57, 11.41 ppm; CI-MS *m/z* (relative intensity): 273 (M^+ + 1, 100).] **4b:** 4 g, 59% yield.

(3S,4S)-3-Methyl-octan-4-ol ***(5a).*** This was prepared from propyl magnesium bromide (0.17 mol) in dry Et_2O [prepared by Grignard reaction between *n*-propyl bromide (Aldrich Chemical Co.) and magnesium turnings], which was cooled to −40°C and 1.58 g (17 mmol) of CuCN were added. After stirring the mixture for 30 min, the flask was cooled to −78°C and 4.89 g (17 mmol) of **4a** in 25 ml of dry Et_2O added *via* cannula. After 30 min of stirring, the cold bath was removed and the reaction allowed to warm to room temperature. The course of the reaction was followed by GC and TLC (9:1, pentane–Et_2O, R_f = 0.58). Upon completion, the reaction was quenched with 3 M HCl at 0°C. The aqueous layer was extracted with Et_2O (3 × 25 ml), washed with both saturated $NaHCO_3$ and NaCl, and then dried over anhyd. $MgSO_4$. Column

chromatography (9:1, pentane–Et_2O) afforded 1.97 g (91 %) of **5a** as a colorless liquid. [**5a:** ^1H ($CDCl_3$); δ 0.82 (3 H, d, J = 8Hz), 0.85-0.98 (6 H, m), 1.19 (2 H, m), 1.2–1.58 (7 H, m), 1.68 (1 H, s. D_2O exchangeable), 3.41 (1 H, m); ^{13}C ($CDCl_3$) δ 74.83, 39.94, 34.17, 28.42, 25.98, 22.76, 14.02, 13.11, 11.65 ppm. Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98; found: C, 74.77; H, 13.88.] The use of D-(−)-DET in the asymmetric epoxidation followed by the same synthetic procedure renders the antipode, **5b** (1.97 g, 91% yield, 87% ee. Anal. calcd. $C_2H_{20}O$: C, 74.92;. H, 13.98; found: C, 74.89; H, 13.75).

The corresponding *anti*-alcohols, **5c** and **5d,** were synthesized according to the same synthetic scheme except (2*E*)-2-pentenol **6** was used as starting material (Figure 2). The alkenol **6** was prepared by hydride reduction of 3-pentynol (Aldrich Chemical Co.) in 83% yield (Brandsma, 1988) [**6:** ^1H ($CDCl_3$): δ 1.0 (3 H, t, J = 7 Hz), 1.8 (1 H, brs, D_2O exchangeable), 2.05 (2 H, m, J = 8, 1.2 Hz), 4.05 (2 H, d, J = 8 Hz), 5.60 (1 H, dt, J = 13.8, 1.3 Hz), 5.75 (1 H, dt, J = 13.8, 1.3 Hz); ^{13}C ($CDCl_3$) δ 134.83, 127.94, 63.68, 25.14, 13.30 ppm].

(2S,3S)-2,3-Epoxy-pentan-1-ol ***(7a).*** This was prepared according to the procedure used for **2a.** Thus, 0.5 g of 4A powdered, activated molecular sieves and 5.7 ml (5.42 g, 19 mmol) of titanium(IV) isopropoxide in 150 ml of dry CH_2Cl_2 were cooled to −78°C in an acetone–Dry Ice bath. To this was added *via* syringe 3.9 ml (4.69 g, 23 mmol) of diethyl (2*R*,3*R*)-tartrate [L-(+)-DET] and 3.4 g (39 mmol) of (2*E*)-2-penten-1-ol. After stirring the mixture 15 min., 12 ml (68 mmol) of 5.7 M anhydrous *tert*-butyl hydroperoxide in CH_2Cl_2 (precooled to −20°C) was added dropwise. After the reaction had warmed up to −20°C, it was stirred at this at this temperature for 4 hr and monitored by TLC (2:8, pentane:ether; R_f = 0.39). Nonaqueous work-up followed by column chromatography gave **7a** (1.70 g, 43% yield, 96% ee) as a colorless liquid [**7a:** ^1H ($CDCl_3$): δ 0.96 (3 H, t, J = 8 Hz), 1.52 (2 H, m), 2.80 (2 H, t, J = 8 Hz), 3.02 (1 H, brs, D_2O exchangeable), 3.45 (1 H, dd, J = 4, 8 Hz), 3.70 (1 H, dd, J = 8, 2 Hz); ^{13}C ($CDCl_3$) δ 62.05, 58.32, 57.10, 24.41, 13.91 ppm.] **7b** (1.64 g, 41% yield, 96% ee) was prepared following the same procedure using diethyl (2*S*,3*S*)-tartrate [D-(−)-DET].

(2R,3R)-3-Methyl-pentane-1,2-diol ***(8a).*** 1.18 g, 59% yield, 96% ee. ^1H

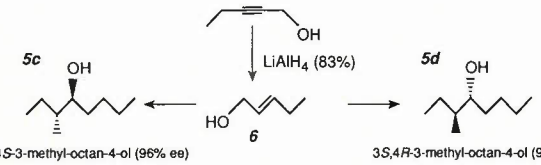

FIG. 2. Scheme for the synthesis of (3*S*,4*R*)- and (3*R*,4*S*)-3-methyl-octan-4-ol.

($CDCl_3$): δ 0.86 (3 H, t, J = 8 Hz), 0.91 (3 H, d, J = 8 Hz), 1.18 (1 H, m), 1.40 (2 H, m), 3.12 (2 H, brs, D_2O exchangeable), 3.40 (2 H, m), 3.55 (1 H, m); CI-MS m/z (relative intensity): 119 (M^++1, 45). **8b:** 1.28 g, 67% yield, 95% ee.

(2R,3R)-3-Methyl-1-tosyloxy-pentan-2-ol ***(9a).*** 1.52 g, 60% yield, ^1H ($CDCl_3$): δ 0.84 (3 H, d, J = 8 Hz), 0.86 (3 H, t, J = 8 Hz), 1.22 (1 H, m), 1.45 (2 H, m), 2.0 (1 H, brs, D_2O exchangeable), 3.64 (1 H, dt, J = 8, 4 Hz), 3.94 (1 H, dd, J = 8, 2.5 Hz), 4.01 (1 H, dd, J = 8, 1.5 Hz); 7.30 (2 H, d, J = 8 Hz); 7.75 (2 H, d, J = 8 Hz); CI-MS m/z (relative intensity): 273 (M^++1, 100). **9b:** 1.71 g, 62% yield.

(3S,4R)-3-Methyl-octan-4-ol ***(5d).*** 0.68 g, 85% yield, 96% ee. ^1H ($CDCl_3$): δ 0.81 (3H, d, J = 8.1 Hz), 0.84–1.0 (6H, m), 1.20 (2H, m), 1.22–1.60 (7H, m), 1.70 (1H, brs, D_2O exchangeable), 3.45 (1H, m); ^{13}C ($CDCl_3$) δ 75.71, 40.50, 33.07, 28.25, 24.55, 22.76, 14.70, 13.11, 11.82 ppm. Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98, found: C, 74.76; H, 14.07. **5d:** 0.76 g, 84% yield, 95% ee. Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98, found: C, 75.06; H, 14.01, Figure 2.

Synthesis of Cruentol Stereoisomers

(4*R*,5*R*)-, (4*S*,5*S*)-, (4*R*,5*S*)-, and (4*S*,5*R*)-5-methyl-octan-4-ol (*R*,*R*-, *S*,*S*-, *R*,*S*-, and *S*,*R*-cruentol) were synthesized according to a method modified from Nakagawa and Mori (1984), followed by Mitsunobu reaction (Mitsunobu, 1981) of the corresponding *anti*-isomers (Figure 3).

(2S,3S)-2,3-Epoxy-hexan-1-ol ***(11a).*** This was prepared according to the procedure employed for **2a.** Thus, 1g of 4A powdered, activated molecular sieves and 8.4 ml (8.79 g, 31 mmol) of titanium(IV) isopropoxide in 250 ml of dry CH_2Cl_2 were cooled to −78°C in an acetone–Dry Ice bath. Then *via* syringe was added 6.3 ml (5.23 g, 25 mmol) of diethyl (2*R*,3*R*)-tartrate [L-(+)-DET] and 6.1 ml (5.2 g, 52 mmol) of (2*E*)-2-hexen-1-ol **10** (Aldrich Chemical Co.). Stirring of the mixture was followed by dropwise addition of 18 ml (0.11 mol) of 6.2 M anhydrous *tert*-butyl hydroperoxide in CH_2Cl_2 (precooled to −20°C). The reaction was allowed to warm to −20°C with stirring and was stirred at this temperature for 3 hr while it was monitored by TLC (4:6, hexane–ether; R_f = 0.19). Ferrous sulfate/tartaric acid work-up (Gao et al., 1987) followed by column chromatography gave **11a** (4.82 g, 80% yield, 95% ee) as a colorless liquid, which crystallized as white needles at −20°C. [**11a:** ^1H ($CDCl_3$): δ 0.96 (3 H, t, J = 7.6 Hz), 1.48 (2 H, m), 1.54 (2 H, m), 1.80 (1 H, brs, D_2O exchangeable), 2.92 (2 H, m), 3.60 (1 H, dd, J = 5, 10 Hz), 3.90 (1H, dd, J = 10, 2.5 Hz); ^{13}C ($CDCl_3$) δ 61.76, 58.34, 55.81, 33.57, 19.23, 13.84 ppm.] **11b** (4.94 g, 82% yield, 95% ee) was prepared following the same procedure but employing diethyl (2*S*,3*S*)-tartrate [D-(−)-DET].

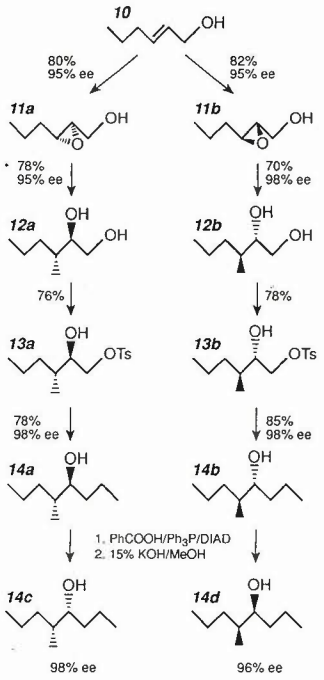

FIG. 3. Scheme for the synthesis of all four stereoisomers of 5-methyl-octan-4-ol.

(2R,3R)-3-Methyl-hexane-1,3-diol ***(12a).*** This was prepared according to the procedure employed for **3a.** Thus, to 4.80 g (0.04 mol) of **11a** in 250 ml of dry pentane cooled to −50°C was added dropwise 11.9 ml (8.64, 0.11 mol) of neat $AlMe_3$. This was followed by 16 ml of 2.49 M *n*-butyllithium (0.04 mol). After stirring 20 min, the cooling bath was removed and the flask allowed to warm to room temperature. The reaction was monitored by GC and TLC (2:8, hexane–ethyl acetate, $R_f = 0.33$) and was complete after 30 min. After quenching with 3 M HCl at 0°C and separation of the two phases, the aqueous layer was extracted with ether (3 × 40 ml), dried over anhyd. $MgSO_4$, and concentrated in vacuo. Purification by column chromatography afforded **12a** (4.26 g, 78% yield, 95% ee) as a colorless liquid, which crystallized as a white solid at −20°C. [**12a:** ^{1}H ($CDCl_3$): δ 0.88 (3 H, t, $J = 10$ Hz), 0.90 (3 H, d, $J = 10$ Hz), 1.14 (1 H, m), 1.25 (1 H, m), 1.46 (1 H, m), 1.60 (1 H, m), 2.10 (1 H, brs, D_2O exchangeable), 2.24 (1 H, brs, D_2O exchangeable), 3.50 (2 H, m), 3.70 (1 H, m); ^{13}C ($CDCl_3$) δ 76.28, 64.66, 35.94, 34.68, 20.06, 15.14, 14.26); CI-MS *m/z* (relative intensity): 119 ($M^+ + 1$, 40.] **12b:** 3.91 g, 70% yield, 98% ee.

(2R,3R)-3-Methyl-1-tosyloxy-hexan-2-ol ***(13a).*** After purification by col-

umn chromatography (6:4, pentane–ether, $R_f = 0.45$), **13a** (6.54 g, 76% yield) was obtained as a pale yellow oil, ^{1}H ($CDCl_3$): δ 0.86 (6 H, m), 1.18 (2H, m), 1.40 (2H, m), 1.60 (1H, m), 1.90 (1H, brs D_2O exchangeable), 2.48 (3H, s), 3.64 (1H, m), 3.98 (1H, dd, J = 12, 8 Hz), 4.10 (1H, dd, J = 12, 4 Hz), 7.38 (2H, d, J = 8 Hz), 7.80 (2H, d, J = 8 Hz); ^{13}C ($CDCl_3$) δ 144.99, 132.5, 129.92, 127.93, 73.43, 72.66, 35.54, 34.15, 21.26, 19.96, 15.10, 14.16 ppm. **13b:** 6.09 g, 78% yield.

(4S,5R)-5-Methyl-octan-4-ol ***(14a).*** This was prepared by the route used for **5a** except that ethyl magnesium bromide (Aldrich Chemical Co.) (3 M solution in Et_2O) was used. After purification by column chromatography (9:1, pentane–ether, $R_f = 0.08$), **14a** (2.74 g, 78% yield, 98% ee), was obtained as a colorless liquid, which crystallized as a white solid at −20°C, ^{1}H ($CDCl_3$): δ 0.90 (3 H, t, J = 8 Hz), 0.92 (3 H, d, J = 8 Hz), 0.94 (3 H, t, J = 8 Hz), 1.10 (1 H, m), 1.24 (1 H, m), 1.32 (1 H, m), 1.40 (4 H, m), 1.50 (1 H, m), 1.70 (1 H, brs, D_2O exchangeable), 3.48 (1 H, m); ^{13}C ($CDCl_3$) δ 75.82, 38.61, 35.64, 34.17, 20.42, 19.28, 15.24, 14.34, 14.13 ppm; CI-MS *m/z* (relative intensity): 127 (100) ($M^+ - H_2O$): Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98, found: C, 75.16; H, 14.11. **14b:** 2.73 g, 85% yield, 98% ee; Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98, found: C, 73.87; H, 14.08.

[(4R,5R)-5-Methyl-4-octyl)]benzoate ***(15a).*** Triphenylphosphine (9.97 g, 38 mmol) and **14a** (2.74 g, 19 mmol) in 30 ml of dry benzene were added *via* cannula to diisopropyl azodicarboxyate (7.68 g, 7.5 ml, 38 mmol) (Aldrich Chemical Co.) and benzoic acid (4.64 g, 38 mmol) in 45 ml dry benzene. After stirring overnight at room temperature, pentane was added, at which point a white precipitate formed. The reaction mixture was filtered through a Florisil pad and concentrated under pressure. Purification by column chromatography (9:1, pentane–ether, $R_f = 0.61$) afforded **15a** (2.35 g, 50% yield) as a pale yellow liquid. Unreacted alcohol was recovered. [**15a:** ^{1}H ($CDCl_3$): δ 0.88 (3 H, t, J = 9 Hz), 0.98 (3 H, t, J = 9 Hz), 1.00 (3 H, d, J = 9 Hz), 1.10 (1 H, m), 1.38, (5 H, m), 1.58 (1 H, m), 1.70 (1 H, m), 1.80 (1 H, m), 5.10 (1 H, m), 7.40 (2 H, dd, J = 9, 2 Hz), 7.54 (1 H, ddd, J = 9, 2 Hz), 8.04 (2 H, dd, J = 9, 2 Hz); ^{13}C ($CDCl_3$) δ 166.37, 132.62, 130.98, 129.56, 128.29, 77.74, 36.27, 35.41, 33.77, 20.34, 19.07, 14.48, 14.22, 14.01 ppm; CI-MS *m/z* (relative intensity): 127 ($M^+ - C_6H_5$-CO, 100).] **15b:** 2.70 g, 57.3% yield.

(4R,5R)-5-Methyl-octan-4-ol ***(14c).*** To a 15% KOH solution of methanol was added **15a** (1.30 g, 52 mmol). After stirring the mixture overnight, it was quenched with water and extracted with Et_2O (3 × 30 ml). The ether extracts were washed with dilute HCl and saturated NaCl and then dried over anhyd. $MgSO_4$. Concentration *in vacuo* and column chromatography (9:1, pentane–ether, $R_f = 0.13$) gave **14c** (0.71 g, 95% yield, 98% ee) as a colorless liquid. [**14c:** ^{1}H ($CDCl_3$): δ 0.89 (3 H, d, J = 8 Hz), 0.92 (3 H, t, J = 8 Hz), 0.95 (3 H, t, J = 8 Hz), 1.12 (1 H, m), 1.24 (1 H, m), 1.33 (1 H, m), 1.39 (5 H,

m), 1.48 (1 H, m), 3.40 (1 H, m); ^{13}C ($CDCl_3$) δ 75.04, 38.70 36.73, 35.73, 20.51, 19.51, 15.33, 14.38, 13.65 ppm; Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98, found: C, 74.74; H, 13.84.] **14d:** 0.75 g, 89% yield, 96% ee; Anal. calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98; found: C, 74.69; H, 13.81.

The enantiomeric excesses of **5a** (93%), **5b** (87%), **5c** (96%), **5d** (95%), **14a** (98%), **14b** (98%), **14c** (98%), and **14d** (96%) and their corresponding intermediates except epoxides were determined by GC analyses on the Cyclodex-B column and by formation of the *O*-acetyllactyl methyl esters (Slessor et al., 1985). Enantiomeric excesses of epoxides **2a** (85%), **2b** (88%), **7a** (96%), **7b** (96%), **11a** (95%), and **11b** (95%) were determined by GC analysis of corresponding *O*-acetyllactyl methyl esters (Slessor et al., 1985) on a DB-23 column. Racemic 3-methyl-octan-4-ol and 5-methyl-octan-4-ol were synthesized as previously described (Gries et al., 1993; Weissling et al., 1994).

Field Experiments

African Palm Weevil. A six-replicate, five-treatment field experiment in a 10-year-old oil palm stand (La Me Research Station, Côte d'Ivoire) tested attraction of palm tissue (250 g) alone or in combination with either stereoisomeric, (*S*,*S*)-, (*R*,*R*)-, or (*S*,*S*)- plus (*R*,*R*)-phoenicol. Traps (Oehlschlager et al., 1993) were attached at breast height to oil palms in randomized blocks with traps at 27-m intervals and blocks 81 m apart. (*S*,*S*)- and (*R*,*R*)-phoenicol were released at 0.5 mg/day (at 25°C) from a 1.5-ml polyethylene centrifuge tube with two 2-mm holes below the top. Racemic phoenicol was dispensed at 2 mg/day (at 25°C) from four 1.5-ml polyethylene centrifuge tubes. Fresh palm tissue in each trap was treated with insecticidal (biodegradable) Evisect "S" (0.3% thiocyclamhydrogenoxalate in water) to retain captured weevils (Gries et al., 1993, 1994).

Trap catch data were subjected to analysis of variance followed by Scheffé test for comparisons of means (Zar, 1984).

Palmetto Weevil. A 12-replicate, four-treatment experiment in the same location as for weevil collection tested attraction of *Sabal palmetto* tissue (1.5 kg) alone or in combination with either stereoisomeric, (*S*,*S*)- or (*R*,*R*)-cruentol. Traps (Weissling et al., 1994) were secured on the ground in randomized complete blocks with traps at 20-m intervals and blocks at least 50 m apart. Unlike Weissling's trap, a tapered, inverted white plastic container (4.9 liter) with a screened lid was suspended in the mouth of the bucket by a capped PVC pipe (1.3 cm diameter) from which pheromone release devices were hung. (*S*,*S*)- or (*R*,*R*)-cruentol were released at 0.06 mg/day (at 25°C) from one and stereoisomeric cruentol from four bottom-sealed 1-μl microcapillary tubes (Drummond Scientific Co., Broomall, Pennsylvania) placed in bottom-sealed microhematocrit tubes (length 75 mm, ID 1.1–1.2 mm; Fisher Scientific, Pittsburgh, Penn-

sylvania). Hematocrit tubes were placed into polypropylene centrifuge tubes (Corning Glass Works, Corning, New York, with 6-mm holes drilled 1.8 cm from the top). Trap catch data were subjected to square root ($x + 0.5$) transformation and ANOVA (SAS Institute, 1990) followed by Waller-Duncan k-ratio t test to test differences between means ($P \leq 0.05$).

RESULTS AND DISCUSSION

Many coleopteran pheromones are optically active (Seybold, 1993; Leal and Mochizuki, 1993; Bestmann and Vostrowsky, 1988; Evershed, 1988; Borden, 1985, and literature cited therein). Enantioselective production of and response to pheromones contribute to species specificity of semiochemical communication (Borden et al., 1976, 1980; Brand et al., 1979; Birch et al., 1980; Payne et al., 1982; Oehlschlager et al., 1987; Pierce et al., 1987; Birch, 1984; Byers, 1989). The presence of nonnatural (non-beetle-produced) enantiomers in synthetic pheromones has been demonstrated to interfere with optimal attraction. For instance, the male-produced aggregation pheromone in the southern pine beetle, *Dendroctonus frontalis* Zimm., (1*R*,5*S*,7*S*)-(+)-*endo*-brevicomin, *endo*-7-ethyl-5-methyl-6,8-dioxa-[3.2.1]octane, markedly enhances the response by both sexes to female-produced frontalin (1,5-dimethyl-6,8-dioxa-[3.2.1]octane), whereas the presence of the antipode in racemic *endo*-brevicomin interferes with optimal attraction (Vité et al., 1985). In the Japanese beetle, *Popillia japonica* (N.), female-produced Japonilure, (*R*,*Z*)-(−)-5-(1-decyl)oxacyclopentan-2-one, strongly attracts males, whereas the antipode inhibits responses (Tumlinson et al., 1977). In the scarab beetle, *Anomala cuprea* only the (*R*,*Z*)-5-(−)-(oct-1-enyl)oxacyclopentan-2-one attracts conspecifics, while the presence of the nonnatural enantiomer reduced attraction (Leal and Mochizuki, 1993). Determination of insect-produced pheromone enantiomer(s) and/or stereoisomers is required to fully elucidate the chemical communication system for a target insect and to implement efficient pheromone-based monitoring and/or management. In this study, we confirmed the chirality of weevil-produced phoenicol (Gries et al., 1993; Perez et al., 1993; Mori et al., 1993), determined chirality of weevil-produced cruentol (Weissling et al., 1994), and field tested weevil attraction to natural and nonnatural stereoisomers.

Of several methods available to prepare the target chiral α-methyl secondary alcohols, the Sharpless asymmetric epoxidation combined with diastereoselective ring opening was the most appealing (Gao et al., 1987; Hill et al., 1985; for use of trimethylaluminum and organocuprates: Pfaltz and Mattenberger, 1982; Suzuki et al., 1982; Takano et al., 1989; Vaccaro et al., 1992; Miyashita et al., 1993). This strategy allowed the use of inexpensive reagents and the synthesis of all four stereoisomers from the same starting material.

Sharpless asymmetric epoxidation has been previously used for the synthesis of the stereoisomers of the elm bark beetle pheromone, 4-methyl-heptan-3-ol (Nakawaga and Mori, 1984). In contrast to this previous synthesis, preparation of phoenicol and cruentol used 0.5 equivalents of catalyst in the presence of a 4A molecular sieve coupled with addition of the oxidizing agent at −78°C to increase the optical purity of the initial epoxide product. Epoxidations were maintained at −20°C until 97–98% conversion was obtained for **2a** and **2b** (two days) as well as for **7a, 7b, 11a,** and **11b** (3–4 hr). Although reactions are not reported for diisopropropyl tartrate, higher enantioselectivities were achieved with diethyl tartrate. Nonaqueous work-up (Gao et al., 1987) followed by flash chromatography was used in the synthesis of the C-5 epoxides. Separation of the tartrate from the C-5 epoxides required two or more chromatographic cycles, whereas ferrous sulfate/tartaric acid work-up (Gao et al., 1987) followed by a single chromatography cleanly gave the C-6 epoxides. Diasteroselective epoxide ring-opening was conducted with neat $AlMe_3$ instead of a hexane solution of this reagent, as was employed by Nakawaga and Mori. This facilitated completion of the reaction in less than 1 hr compared to two to three days. Work-up *via* addition of saturated NaF at −40°C (Suzuki et al., 1982) for **3a, 3b, 8a,** and **8b,** and 3 M HCl for **12a** and **12b** afforded the corresponding diols after flash chromatography. Quenching with NaF rather than HCl improved isolated yields of 3-methyl-1,2-pentanediols, probably due to the high solubility of the diols in water. Products arising from breakage of the α-bond or retention of configuration during the cleavage of the β-epoxide bond were not detected by GC or ^{1}H NMR analysis. The *syn*-isomers of phoenicol and cruentol were obtained with moderate optical purities from asymmetric epoxidation of the requisite *Z*-alkenols. In contrast, Mori and Brevet (1991) and Mori and Harashima (1993) generated chirally pure epoxides through crystallization of derivatives, a process that leads to yields in the range of 40%. The *p*-nitrobenzoates or 3,5-dinitrobenzoates of **2a** and **2b** were oils at room temperature and below.

The *syn* isomers of 5-methyl-octan-4-ol were obtained in high enantiomeric excess through Mitsunobu (Mitsunobu, 1981; Hughes, 1992, and references cited therein) mediated inversion of configuration of the *anti*-isomers **14a** and **14b.** Use of *p*-nitrobenzoic acid–Ph_3P–diethyl azocarboxylate (DEAD) in THF yielded less than 25% of the corresponding *p*-nitrobenzoates. Successful Mitsunobu conditions (~51% yields) employed benzoic acid–Ph_3P–diisopropyl azocarboxylate (DIAD) and benzene as a solvent (Paquette and Sugimura, 1986; Dai et al., 1988; Dyer and Kishi, 1988). No epimerization or retention of configuration products were observed.

Both stereoisomeric phoenicol and cruentol elute from a polar SP-1000-coated, fused silica column in two resolved components. The shorter eluting component coincided with the male-produced pheromone of each weevil and was hypothesized to be the *syn* diastereoisomer, consisting of coeluting *S,S* and

R,R isomers. This assignment was made by analogy with the aggregation pheromone of the smaller European elm bark beetle, *Scolytus multistriatus* (Marsham), 4-methyl-heptan-3-ol, that also has two stereogenic centers and exists as two diastereoisomeric forms that are separable by GC on a polar Carbowax 20 M column (Pearce et al., 1975). Analysis of stereoselectively prepared *syn* and *anti* stereoisomers of phoenicol and cruentol confirmed the assignments. Synthetic (*R,R*)-, (*S,S*)-, (*R,S*)-, and (*S,R*)-phoenicol and cruentol were separated with baseline resolution on a fused silica, Cyclodex-B column. These analyses revealed that male *R. phoenicis* and male *R. cruentatus* produce the *S,S* stereoisomer of phoenicol (Figure 4) and cruentol (Figure 5), respectively. *S. multistriatus* also produces the *S,S* stereoisomer of 4-methyl-heptan-3-ol (Pearce et al., 1975), whereas the large European elm bark beetle, *Scolytus scolytus* (F.), produces both (3*S*,4*S*)- and (3*R*,4*S*)-4-methyl-heptan-3-ol (Blight et al., 1977, 1978, 1979; Wadhams et al., 1982).

Coupled GC-EAD of synthetic phoenicol (Figure 6) and cruentol (Figure 7) revealed strong antennal responses to weevil-produced (*S,S*)-phoenicol and (*S,S*)-cruentol. Lack of or reduced response to later-eluting stereoisomers can hardly be explained by an antennal refractory period. In GC-EAD recordings with the same Cyclodex-B column, antennae of two Asian palm weevils, *R. ferrugineus* (Oliv.) and *R. vulneratus* (Panz.), distinctively responded to both, closely eluting, (4*S*)- and (4*R*)-4-methyl-nonan-5-one (Perez et al., unpublished). Similarly, in GC-EAD analyses of oil palm volatiles, antennae of male

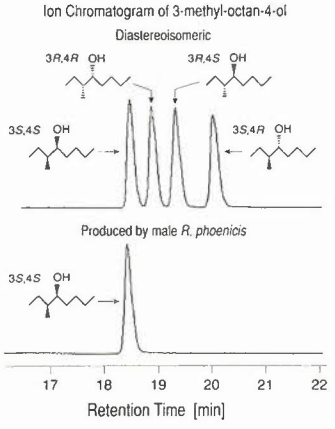

FIG. 4. Selected ion *m/z* 127 chromatogram (Hewlett Packard 5985B) of stereoisomeric and weevil-produced 3-methyl-octan-4-ol. *m/z* 127 was the parent ion [(M^+-H) 143, (M^+-H-OH) 127] of the full-scan mass spectrum in CI mode. (Cyclodex-B column; 90°C isothermal; linear flow velocity of carrier gas: 35 cm/sec; injector temperature: 220°C).

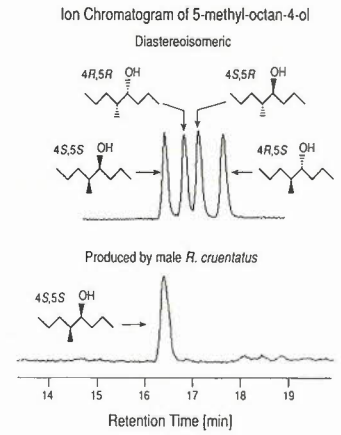

FIG. 5. Selected ion *m/z* 127 chromatogram of stereoisomeric and weevil-produced 5-methyl-octan-4-ol. *m/z* 127 was the parent ion [(M^+-H) 143, (M^+-H-OH) 127] of the full-scan mass spectrum in CI mode (instrument and chromatographic conditions as in Figure 4).

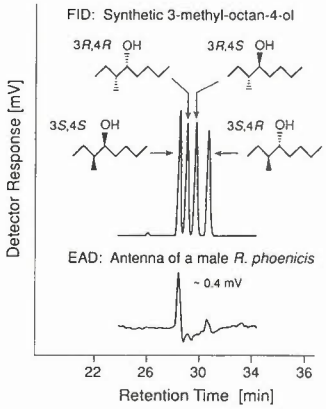

FIG. 6. Representative GC-EAD recording of a female *Rhynchophorus phoenicis* antenna responding to stereoisomers of 3-methyl-octan-4-ol (Hewlett Packard 5890A; split injection; column and chromatographic conditions as in Figure 4).

and female *R. phoenicis* responded within 2.5 min to four esters, two of which were barely baseline separated (Gries et al., 1994). Strong antennal activity of the *S,S*, and weak activity of *S,R* and *R,S* isomers of the pheromones (Figures 6 and 7) suggest that sensory recognition of the natural *S,S* stereoisomer is more dependent on the stereochemistry of the methyl than the hydroxy group.

In field experiments (*S*,*S*)-phoenicol and (*S*,*S*)-cruentol strongly synergized attraction of weevils to palm tissue (Figures 8 and 9). Because racemic, stereoisomeric mixtures were as synergistic as *S*,*S* isomers, the weakly EAD-active *S*,*R* isomers (Figures 6 and 7) neither enhanced nor reduced behavioral activity in the stereoisomeric mixtures (Figures 8 and 9). Lack of strong antennal (Figures 6 and 7) and any behavioral activity (Figures 8 and 9) of nonnatural isomers suggests that sympatric beetles are unlikely to utilize one or more stereoisomers

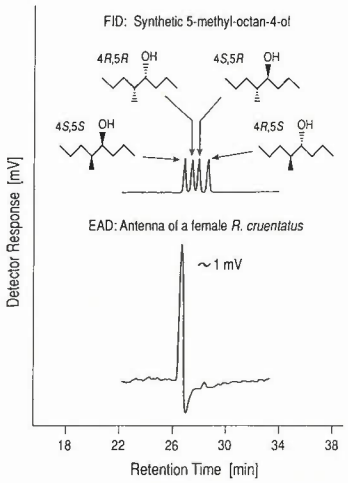

FIG. 7. Representative GC-EAD recording of a female *Rhynchophorus cruentatus* antenna responding to stereoisomers of 5-methyl-octan-4-ol (Hewlett Packard 5890A; split injection; column and chromatographic conditions as in Figure 4).

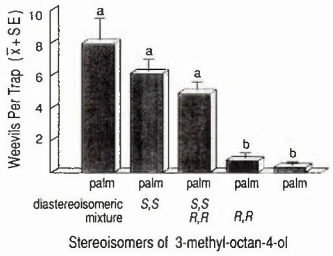

FIG. 8. Mean counts (+ standard error) of male and female *R. phoenicis* in traps baited with 250 g of chopped oil palm tissue alone and in combination with either stereoisomeric, (3*S*,4*S*)-, (3*R*,4*R*)- or (3*S*,4*S*)- plus (3*R*,4*R*)-phoenicol. La Me Research Station, Côte d'Ivoire; May 6–10, 1993; six blocks. Bars superscripted by the same letter are not significantly different. ANOVA followed by Scheffé test, $P < 0.05$.

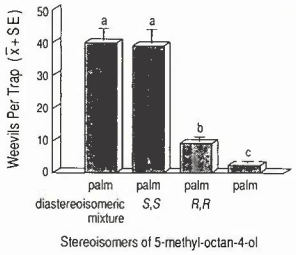

FIG. 9. Mean counts (+ standard error) of male and female *R. cruentatus* in traps baited with 1.5 kg of chopped *Sabal palmetto* palm tissue alone and in combination with either stereoisomeric, (4*S*,5*S*)- or (4*R*,5*R*)-cruentol. La Belle, Florida, USA, June 9–16, 1993; 12 blocks. Bars superscripted by the same letter are not significantly different. ANOVA followed by Waller-Duncan *k*-ratio *t* test on square root transformed data ($x + 0.5$), $P \leq 0.05$.

of phoenicol or cruentol as a pheromone. In practice, mixtures of all four stereoisomers of each pheromone could be used in combination with host materials to monitor and/or mass trap *R. phoenicis* and *R. cruentatus* populations.

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