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SYNTHESIS OF HOMOFARNESENES: TRAIL PHEROMONE COMPONENTS OF THE FIRE ANT, SOLENOPSIS INVICTA

FRANCISCO M. ALVAREZ[+], ROBERT K. VANDER MEER*, and CLIFFORD S. LOFGREN*

[+]Department of Entomology and Nematology,
University of Florida, Gainesville, FL 32611
*Agricultural Research Service, United States Department of Agriculture,
P.O. Box 14565, Gainesville, FL 32604

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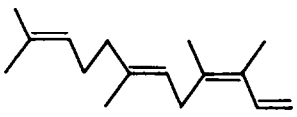
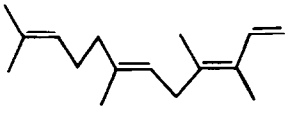
Abstract: The synthesis of four isomeric homofarnesenes, 3,4,7,11-tetramethyl-1,3,6,10-dodecatetraenes, is reported. The major synthetic step was the indirect formation of a tetra-substituted double bond through the acid catalyzed oxidative rearrangement of an appropriate vinyl carbinol. Two of these compounds, the Z,E- and E,E- isomers were identical to two naturally occuring homofarnesene components of the trail pheromone of the fire ant, Solenopsis invicta.

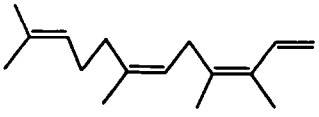
The trail pheromone of the fire ant, Solenopsis invicta Buren, was shown in 1959 to be produced in the Dufour's gland and released through the sting apparatus.[1] The molecular weight of one of the pheromone components was deduced from gas chromatographic data.[2] However, it was not until 1981 that partial chemical elucidation was reported.[3,4] The structures of two a-farnesenes[3] and an allofarnesene[4] were confirmed by synthesis and direct comparison with the natural products. In addition, two homofarnesenes were isolated.[3] The homofarnesene, (Z,E) 3,11-dimethyl-7-ethyldodeca-1,3,6,10-tetraene (Ie) has been synthesized[5] and shown to be identical to the homofarnesene isolated from several Myrmica ant species.[6-9] In contrast, the spectral evidence presented for the homofarnesenes isolated from S. invicta clearly demonstrated that a methyl group was added to the basic a-farnesene structure at the 4-position to give 3,4,7,11-tetramethyl-dodeca-1,3,6,10-tetraene (Ia-d).[3] The Z,E and Z,Z configurations were assigned to the two isolated products based on spectral analogies with the four a-farnesene isomers. We present here the synthesis of the four homofarnesene isomers and the absolute identification of the two naturally occurring homofarnesene trail pheromones.



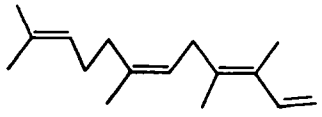
Ia Z,E-HOMOFARNESENE



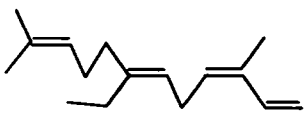
Ib E,E-HOMOFARNESENE



Ic Z,Z-HOMOFARNESENE

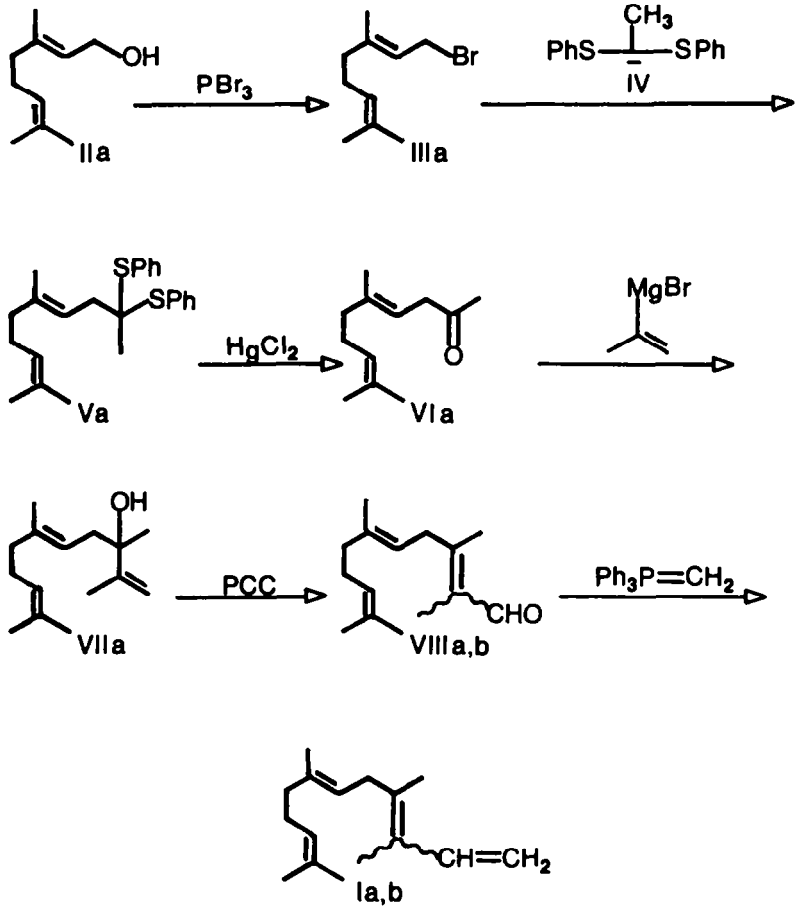


Id Z,E-HOMOFARNESENE



Ie

The key element in the synthesis of the homofarnesenes (Ia-d) is the formation of the tetra-substituted double bond at C-3. Although there are several reports of methods that will produce tri-substituted double bonds,[10,11] and in the case of resonance stabilized precursors, tetra-substituted double bonds,[12] these methods have not been successful in producing the desired tetra-substitution found in the homofarnesenes (Ia-d). Consequently, our approach to the problem turned toward the indirect formation of the tetra-substituted double bond. Scheme 1 illustrates the reaction sequence utilized in taking geraniol to homofarnesenes Ia and b. The other two homofarnesene isomers (Ic,d) were made by a similar scheme starting with nerol (IIb).



SCHEME 1

The commercial availability of geraniol (IIa) and its Z-counterpart nerol (IIb) made them logical starting materials, thus ultimately fixing the stereochemistry of the C-6 double bond in the final homofarnesenes. Geraniol (IIa) was reacted with phosphorous tribromide in hexane-pyridine to give geranylbromide (IIIa), 87% isolated yield (no double bond isomerization was observed). Reaction of bromide (IIIa) with the anion of acetaldehyde thioacetal (IV) resulted in a thioketal (Va). Hydrolysis of (Va) with aqueous mercuric chloride in the presence of calcium carbonate and acetonitrile as cosolvent[13] gave the ketone (VIa, 70% isolated yield). 2-Bromopropene was converted to the corresponding Grignard reagent in ethyl ether and reacted with ketone (VIa) to yield an a,b-unsaturated tertiary alcohol (VIIa, 80%), analogous to the synthesis of nerolidol.[14]

This alcohol contains the proper substituents required for the homofarnesene (Ia-b) tetra-substituted double bond. The double bond was shifted and the terminal carbon functionalized by the acid catalyzed oxidative rearrangement of the vinyl carbinol (VIIa) with pyridinium chlorochromate (PCC).[15,16] The product a,b-unsaturated aldehyde (VIIIa,b) was obtained as a mixture of Z,E and E,E isomers (1:2) in 30% yield. However, the major product of the oxidative rearrangement was the undesired ketone (VIa), 60% yield. A similar major by-product was reported during the oxidation of 2-phenyl-3-butene-2-ol with PCC. This reaction

gave a 60:40 mixture of acetophenone and the expected a,b-unsaturated aldehyde (2-phenyl-2-buten-4-al).[17]

The Z,E- and E,E-homofarnesenes (Ia,b) were obtained from the corresponding aldehydes (VIIIa,b) on reaction with the methylene Wittig reagent (70% yield). The corresponding Z,Z- and E,Z-homofarnesenes could be made by the same reaction sequence from neryl chloride (IIIb), prepared from nerol (IIb) without double bond isomerization.[18] Spectral and gas chromatographic analysis of synthetic and the naturally occurring S. invicta homofarnesenes demonstrated that the homofarnesene components of the ant trail pheromone are Z,E- and E,E-3,4,7,11-tetramethyl-dodeca-1,3,6,10-tetraene. In addition, the synthetic homofarnesenes had trail bioassay activity comparable to that of the natural isomers (ca. 40 pg/cm).

This work represents the first reported synthesis of the homofarnesenes, 3,4,7,11-tetramethyl-1,3,6,10-dodecatetraene. A structural isomer of (I) has been reported from Myrmica ant species and identified spectroscopically as 7-ethyl-3,11-dimethyl-1,3,6,10-dodecatetraene.[19] However, no behavioral function has been associated with this homofarnesene. The availability of the physiologically active fire ant homofarnesenes will provide valuable tools for future insect behavior studies and may lead to a more environmentally acceptable method for the control of S. invicta.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded in deuterochloroform ($CDCl_3$) using a 300 MHz, Nicolet NT300 spectrometer. Mass spectra were obtained on a Finnigan Model 1015 SL/3200 GC-MS. Methane was the ionizing gas for the chemical ionization mass spectra. Gas chromatography (GC) was carried out on a Varian 3700 gas chromatograph with either a flame ionization or thermal conductivity detector. Analytical analyses were performed using a J&W Scientific DB-1 fused silica capillary column (0.32mm I.D. X 15m, 0.25um film thickness). A Varian Vista 54 HPLC was used with a Perkin Elmer LC 75 variable wavelength uv/vis detector and the columns specified below. GC data was processed with a Varian Vista 401.

Geranylbromide (IIIa): A solution of 35.1 g (0.130 mol.) phosphorous tribromide in 12 ml of hexane was added with stirring over a period of 1.5 hours to a cold, -10°, solution of 40.0 g (0.260 mol.) geraniol in 200 ml of anhydrous hexane containing 6.2 g of freshly distilled pyridine. The reaction mixture was then partitioned with ice-cold saturated sodium bicarbonate. The hexane layer was washed with water and dried over anhydrous sodium sulfate. The oil remaining after removal of solvent was distilled to give geranyl bromide (IIIa) (42.2 g, 0.194 mol., 87%), b.p. 78-80° at 1 mm (lit.[20] 47-48° at 0.005 mm), homogeneous by TLC and GC.

Nerylchloride (IIIb): Nerol (0.35 mol.), hexamethyl phosphoramide (130 ml, anhydrous), ethyl ether (360 ml, anhydrous) and triphenylmethane (180 mg) were added to a dry, 2000 ml, three necked round bottom flask equipped with an overhead mechanical stirrer. The solution was stirred, cooled to 0° and methyllithium (360.5 ml) added via a dropping funnel, at which time the solution turned red in color. p-Toluene sulfonyl chloride (72.1 g) in ethyl ether (360 ml, dry) was slowly added to the red solution at 0°, followed by 15.1 g of solid LiCl. The above mixture was warmed to room temperature and stirred for 15 hours. The reaction mixture was then washed four times with water and once with saturated aqueous sodium chloride. The organic phase so obtained was dried over anhydrous $MgSO_4$ and the solvent removed under pressure. The oil remaining was distilled to give nerylchloride (IIIb) 90% isolated yield (96% pure by GC), b.p. 45° at 0.125 mm. The product had PMR and IR spectra identical to literature values[21].

(E)-5,9-dimethyl-4,8-decadiene-2-one diphenylmercaptal (Va): Acetaldehyde diphenylmercaptal (15.0 g, 0.061 mol.) was dissolved in dry THF (100 ml) and stirred at -20° under anhydrous conditions. n-Butyl lithium solution was added slowly (1.6M in hexane, 41.0 ml, 0.066 mol.) and stirred for one hour. The reaction was cooled to -78° and 12.8 g (0.058 mol.) of geranylbromide (IIIa) added slowly. After stirring overnight at room temperature, the reaction mixture was diluted with hexane and partitioned with 5% sodium hydroxide. The hexane layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the crude thioacetal (Va) was used for hydrolysis without further purification (22.8 g, 0.060 mol.).

(Z)-5,9-dimethyl-4,8-decadiene-2-one diphenylmercaptal (Vb): This compound was prepared from neryl chloride and acetaldehyde diphenylmercaptal by the same method described above for Va.

(E)-5,9-dimethyl-4,8-decadiene-2-one (VIa): 22.8 g (0.060 mol.) of crude thioacetal (Va) was dissolved in 80% acetonitrile-water (200 ml) and calcium carbonate (12.0 g, 0.120 mol.) added with stirring. Mercuric chloride (3.3 g, 0.012 mol.) was then added and the reaction refluxed (80°) overnight. The reaction mixture was then filtered and the filtrate diluted with hexane and partitioned with 5 M ammonium acetate, pH 7. The hexane layer was washed with water and dried over anhydrous magnesium sulfate. The oil remaining after removal of solvent was distilled to give 5,9-dimethyl-4,8-decadiene-2-one (VIa) (7.3 g, 0.041 mol., 70% from geranyl bromide), b.p. 64-70° at 0.15 mm Hg, homogeneous by TLC and GC. PMR (d) 1.59, s, 3H (CH_3); 1.64, s, 3H (CH_3); 1.7, s, 3H (CH_3); 2.08, m, 4H ($-CH_2-CH_2-$); 2.16, s, 3H ($O=C-CH_3$); 3.12, d, 2H ($=C-CH_2-C=O$), 5.09, t, 1H (=C-CH); 5.32, t, 1H (=C-CH).

(Z)-5,9-dimethyl-4,8-decadiene-2-one (VIb): This compound was prepared as described above for VIa, substituting Vb for Va. The yield was 65.1% from the neryl chloride (b.p. 63.5° at 0.1 mm Hg, homogeneous by TLC and GC). PMR (d) 1.61, s, 3H (CH_3); 1.68, s, 3H (CH_3); 1.76, s, 3H (CH_3); 2.04, m, 4H ($-CH_2-CH_2-$); 2.14, s, 3H ($O=C-CH_3$); 3.14, d, 2H ($=C-CH_2-C=O$); 5.09, t, 1H (=C-CH); 5.32, t, 1H (=C-CH).

2,3,6,10-Tetramethyl-1,5,9-undecatriene-3-ol (VIIa): The Grignard reagent from 2-bromopropene (3.4 g, 0.028 mol.) was treated at 0° with 5,9-dimethyl-4,8-decadiene-2-one (VIa) (2.7 g, 0.015 mol.) in ether (20 ml) for 12 hours. The product VIIa (2.7 g, 0.012 mol. 80%) was obtained after partition with saturated ammonium chloride followed by column chromatography of the ether fraction (Silica gel, 10% chloroform-hexane). IR (CCl_4,cm^{-1}) :3540 (weak). 2960, 2920, 2860, 1715, 1640, 1440, 1370, 1090, 900. Mass spectrum, (CI) m/z: 222 (M+), 204 (base peak), 148, 137, 117. PMR, (d) 1.34, s, 3H (CH_3); 1.61, s, 3H (CH_3); 1.65, s, 3H (CH_3); 1.69, s, 3H (CH_3); 1.83, s, 3H (CH_3); 2.2, m, 4H (CH_2-CH_2-); 2.37, m, 2H ($=C-CH_2-C-OH$); 4.85, d, 2H ($-C=CH_2$); 5.17, m, 2H (-C=C-H).

(Z)-2,3,6,10-Tetramethyl-1,5,9-undecatriene-3-ol (VIIb): The Grignard reagent from 2-bromopropene (40.3 g, 0.333 mol.) at 0° was treated with (Z)-5,9-dimethyl-4,8- decadiene-2-one (VIb) (30.0 g, 0.167 mol.) in ether (300 ml) for 12 hours. The product VIIb (31.0 g, 0.140 mol., 84%) was obtained after partition with saturated ammonium chloride followed by column chromatography of the ether fraction (Silica gel, 15%

$CHCl_3$-hexane). Mass spectrum, (CI) m/z: 222 (M+), 204 (base peak), 148, 134, 122, 120. PMR, (d) 1.31, s, 3H (CH_3); 1.61, s, 3H (CH_3); 1.69, s, 3H (CH_3); 1.73, s, 3H (CH_3); 1.78, s, 3H (CH_3); 2.07, m, 4H (CH_2-CH_2); 2.31, d, 2H (=C-CH_2-C-OH); 4.91, d, 2H (-C=CH_2); 5.08 m, 2H (-C=C-H).

2,3,6,10-Tetramethyl-2,5,9-undecatriene-1-al (VIIIa-b): To a magnetically stirred slurry of pyridinium chlorochromate (13.9 g, 0.065 mol.) in 40 ml of dichloromethane, was added in one portion a solution of alcohol (VIIa) (2.4 g, 0.010 mol.) in 10 ml of dichloromethane at room temperature. The mixture was allowed to stir for 6 hours under a nitrogen atmosphere and was diluted with an equal volume of ether. The ethereal solution was filtered and the filtrate washed successively with 5% aqueous sodium hydroxide and twice with water. The product (1.6 g) was a mixture of five components (GC) of which the major peak was ketone (VIa), while 30% (0.5 g, 0.021 mol.) corresponded to an isomeric mixture of aldehydes (VIII a-b) (1:2, Z,E: E,E). The isomers were purified on a low pressure liquid chromatography system (silica gel 13-24 um; 0-10% chloroform-hexane gradient solution) and/or HPLC, silica gel in hexane at a flow rate of 1.5 ml/min.

E,E-Aldehyde (VIIIb), Mass Spectrum (CI) m/z: 220 (M+, base peak), 212 (M-H_2O), 160, 150, 126, 108. PMR, (d) :1.56, s, 3H (CH_3); 1.60, s, 3H (CH_3); 1.67, s, 3H (CH_3); 1.69, s, 3H (CH_3); 1.78, s, 3H (CH_3); 2.1, m, 4H (-CH_2-CH_2-); 2.98, d, 2H (=C-CH_2-C=); 5.0, m, 2H (-C=C-H); 10.1, s, 1H (H-C=O).

Z,E-Aldehyde (VIIIa), Mass Spectrum (CI) m/z; 220 (M+, base peak), 212 (M-H_2O), 160, 150, 126, 108. PMR, ( ) : 1.46, s, 3H (CH_3); 1.6, s, 3H (CH_3); 1.67, s, 3H (CH_3); 1.69, s, 3H (CH_3); 1.75, s, 3H (CH_3); 2.15, m, 4H (-CH_2-CH_2-); 3.29, d, 2H (=C-CH_2-C=); 5.06, m, 2H (=C-H); 10.1, s, 1H (H-C=O).

(Z,Z) and (E,Z)-2,3,6,10-Tetramethyl-2,5,9-undecatriene-1-al (VIIIc-d): To a magnetically stirred slurry of pyridinium chlorochromate (244.0 g, 1.132 mol.) in 960 ml of dichloromethane, was added in one portion a solution of alcohol (VIIb) (35.9 g, 0.162 mol.) in 240 ml of dichloromethane at room temperature. The mixture was allowed to stir for 11.5 hours under a nitrogen atmosphere and was diluted with an equal volume of ether. The ethereal solution was filtered and the filtrate washed successively with 5% aqueous sodium hydroxide and twice with water. The product (46.7 g) was a mixture of six components (GC) of which the major band was ketone (VIb), while 32.8% (10.1 g, 0.0359 mol.) corresponded to an isomeric mixture of aldehydes (VIIIc-d) (1:1.3, ZZ: EZ). The isomers were resolved and purified on a low pressure liquid chromatography system (Silica gel 13-24 um; 0-10% chloroform-hexane gradient elution) and/or HPLC (Silica gel, 1.5 ml/min., UV detector at 244 nm).

Z,Z-Aldehyde (VIIIc), Mass Spectrum (CI) m/z; 220 (M+) 203, 202, 150, 127, 126 (base).

E,Z-Aldehyde (VIIId), Mass Spectrum (CI) m/z; 220 (M+, base peak), 202, 195, 136, 126, 124, 122. PMR (d) : 1.54, s, 3H (CH_3); 1.62, s, 3H (CH_3); 1.63, s, 3H (CH_3); 1.66, s, 3H (CH_3); 1.80, s, 3H (CH_3); 2.02, m, 4H (-CH_2-CH_2-); 2.64, d, 2H (=C-CH_2-C=); 5.1, m, 2H (-C=C-H); 10.0, s, 1H (H-C=O).

Homofarnesenes (Ia-d): The formation of E,E-homofarnesene (Ib) is representative of the procedure for the synthesis of homofarnesenes (Ia-d).

n-Butyllithium (0.011 mol.) was added with stirring to a solution of methyltriphenylphosphonium bromide (4.0 g, 0.011 mol.) in 50 ml of dry THF at -15° under N_2. The reaction mixture was stirred for one hour at room temperature. Aldehyde (VIIIa) (0.8 g, 0.004 mol.) was then added and the mixture heated under reflux for 2.5 hours, (ca 55°). The reaction mixture was then partitioned between water and hexane. The hexane layer was dried over anhydrous sodium sulfate, concentrated under vacuum, and passed through a silica gel gravity flow column with hexane as solvent to give the corresponding hydrocarbon fraction (0.6 g, 0.003 mol., 70%). Final purification for spectral analysis was done by preparative GC (OV-101 on 120/140 Gas Chrom Q (Applied Science, Inc.) 4 mm I.D. x 1.8 m) at a column oven setting of 90° isothermally.

Z,E-Homofarnesene (Ia), Mass Spectrum (CI) m/z; 218 (M+, base peak), 204, 162, 148, 132, 122. PMR (d) : 1.629, s, 3H (CH_3); 1.71, s, 3H (CH_3); 1.76, s, 3H (CH_3); 1.81, s, 3H (CH_3); 1.86, s, 3H (CH_3); 2.16, m, 4H (-CH_2-CH_2-); 3.02, d, 2H (=C-CH_2-C=); 5.16, m, 1H (=C-H); 5.27, m, 3H (=C-H); 6.90, q, 1H (=C-H).

E,E-Homofarnesene (Ib), Mass Spectrum (CI) m/z; 218 (M+, base peak), 204, 162, 148, 136, 132, 122. PMR (d) : 1.52, s, 3H (CH_3); 1.59, s, 3H (CH_3); 1.65, s, 3H (CH_3); 1.74, s, 3H (CH_3); 1.81, s, 3H (CH_3); 2.1, m, 4H (-CH_2-CH_2-); 2.82, d, 2H (=C-CH_2-C=), 5.10, dd, 1H (=C-H); 5.21, m, 3H (=C-H); 7.15, q, 1H (=C-H).

Z,Z-Homofarnesene (Ic), Mass Spectrum (CI) m/z; 218 (M+, base peak), 213, 200, 133, 128, 123. PMR (d) : 1.56, s, 3H (CH_3); 1.65, s, 3H (CH_3); 1.68, s, 3H (CH_3); 1.71, s, 3H (CH_3); 1.75, s, 3H (CH_3); 2.13, m, 4H (-CH_2-CH_2); 2.95, d, 2H (=C-CH_2-C=); 5.03, dd, 1H (=C-H); 5.20, m, 3H (=C-H); 6.98, q, 1H (=C-H).

E,Z-Homofarnesene (Id), Mass Spectrum (CI) m/z; 218 (M+, base peak), 204, 162, 148, 136, 134, 122. PMR (d) : 1.56, s, 3H (CH_3); 1.67, s, 6H (CH_3); 1.75, s, 3H (CH_3); 1.82, s, 3H (CH_3); 2.1, s, 4H (-CH_2-CH_2-); 2.85, d, 2H (=C-CH_2-C=); 5.03, dd, 1H (=C-H); 5.20, m, 3H (=C-H); 6.94, q, 1H (=C-H).

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