Note

Simple Synthesis of 5,9-Dimethylated Long-Chain Alkanes, the Sex Pheromones of Leaf Miner Moths

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Each stereoisomeric mixture of 5,9-dimethylpentadecane and 5,9-dimethylhexadecane, the major and the minor sex pheromone components of Perileucoptera coffeella, respectively, was synthesized in about 25% overall yield through 6 steps from β-citronellol. 5,9-Dimethylheptadecane, the major sex pheromone component of Leucoptera malifoliiella, was also synthesized analogously as a stereoisomeric mixture in a 22% overall yield.

Key words: sex pheromone; Perileucoptera coffeella; 5,9-dimethylpentadecane; 5,9-dimethylheptadecane; 5,9-dimethylhexadecane

The leaf miner moths, Leucoptera malifoliiella and Perileucoptera coffeella are important pests of apple and pear trees in many temperate regions of Europe and coffee trees in Brazil, respectively. The isolation of the sex pheromone of L. malifoliiella as a mixture of 5,9-dimethylpentadecane (3, the main component), 5,9-dimethylhexadecane (2), and 5,9-dimethyloctadecane prompted the synthesis of these compounds either as stereoisomeric mixtures or as optically active forms, aiming the pest management by the pheromones. These efforts brought about the findings that (S,S,9S)-3 has the substantial pheromonal activity and 5,9-dimethyloctadecane is synergistic, while 5,9-dimethylhexadecane and the other stereoisomers of 3 have virtually no effect on the activity. On the other hand, the female-produced sex pheromone of P. coffeella was proposed to consist of 5,9-dimethylpentadecane (1) and 5,9-dimethylhexadecane (2) as the major and the minor components, respectively, and the syntheses of these compounds as stereoisomeric mixtures were also reported. Since a stereoisomeric mixture of 3, which was prepared by the Kolbe coupling of (±)-4-methyldecanoic acid and (±)-3-methylheptanoic acid followed by purification by GLC, is known, in a field trapping test to L. malifoliiella, to have nearly the same pheromonal activity as its pure (S,S,9S)-


Scheme. Synthesis of the Pheromones of Leaf Miner Moths.
Reagents: a) TsCl, Py; b) EtMgBr, Li₂CuCl₂, THF (77%), 2 steps; c) SeO₂, t-BuOOH, salicylic acid, CH₃Cl; d) H₂, PtO₂, EtOH (49%, 2 steps); e) TsCl, Py; f) CH₃(CH₂)₃MgBr, CH₃(CH₂)₃MgBr, or CH₃(CH₂)₃MgBr, Li₂CuCl₂, THF (59-67%, 2 steps).

5a X=OH, Y=Z=H
5b X=Y, Z=H
5c X=OH, Y=H, Z=OH
6a R=C₆H₅
6b R=C₆H₄Ts
5a X=OH, Y=Z=H
5b X=Y, Z=H
5c X=OH, Y=H, Z=OH
6a R=C₆H₅
6b R=C₆H₄Ts

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the two steps after chromatographic removal of a diol derived from 5c. The diastereomeric ratio of 6a was ca. 1:1 by its 500 MHz 1H-NMR analysis (see Experimental). Finally, the alcohol (6a) was converted to tosylate 6b, which was then coupled with pentylmagnesium bromide, hexylmagnesium bromide or heptylmagnesium bromide in the presence of dilithium tetrachloroplatinate to give the desired hydrocarbons 1, 2 or 3 in yields of 67%, 66%, or 59%, respectively.

This synthesis of 1, 2, and 3 accomplished through 6 steps in about 22–25% overall yields from a commercially available and cheap starting material, (±)-β-citronellol, is considered to be operationally easier than the previous syntheses, and could be practically useful for large-scale production of these pheromones. Field trapping tests with 1 are now well underway in Brazil (Prof. Villela, Universidade Federal de Vicsa) and the results will be published elsewhere.

**Experimental**

IR spectra were measured with a Jasco FT/IR-5000 spectrometer. 1H-NMR spectra (500 MHz) were recorded with TMS as an internal standard in CDCl3 by a Jeol JNM-A500 spectrometer. High-resolution mass spectra (70 eV) were measured with a Shimadzu GCMS 9020-DF spectrometer. Merck silica gel 60 Art 7734 was used for silica gel column chromatography.

2,6-Dimethyl-2-decene (4c). To a stirred solution of (±)-β-citronellol (4a) (10.0 g, 64.0 mmol) in pyridine (36 ml) was added portionwise p-toluensulfonyl chloride (16.4 g, 82.3 mmol) at 0°C. After 1 h, the mixture was allowed to warm gradually to room temperature, and stirred overnight. To the mixture was added water (5 ml), and the resulting mixture was stirred for 20 min. The mixture was poured into water and extracted with ether. The etheral solution was successively washed with 2 M HCl aq., sat. NaHCO3 aq. and brine, dried (MgSO4) and concentrated in vacuo to give 19.4 g of crude 4b. The tosylate (4b) (19.4 g, 62.5 mmol) was dissolved in THF (250 ml) and cooled to –78°C. To the solution was added successively a solution of ethylmagnesium bromide in THF (1.00 m, 89.0 ml, 89.0 mmol) and a solution of dilithium tetrachloroplatinate in THF (0.1 m, 5.92 ml, 0.592 mmol). After 30 min the mixture was warmed gradually to room temperature and stirred for 14 h. The mixture was poured into sat. NH4Cl aq. and extracted with ether. The etheral solution was successively washed with water and brine, dried (MgSO4) and concentrated in vacuo. The residue was chromatographed over silica gel (100 g, hexane) and distilled to give 8.03 g (77%) of 4c, b.p. 82–84°C (20 Torr). IR νmax cm⁻¹: 2960 (s), 2930 (s), 29860 (s), 1460 (m), 1380 (m), 1090 (w), 1020 (w), 825 (w); 1H-NMR δ: 0.86 (3H, d, J = 6.5 Hz, 6-CH3), 0.89 (3H, t, J = 6.9 Hz, 10-CH3), 1.07–1.16 (2H, m, 9-H2), 1.19–1.34 (6H, m, 5-H2, 7-H2, and 8-H2), 1.35–1.42 (1H, m, 6-H), 1.60 (3H, br s, C=CH2), 1.68 (3H, br s, C=CH2), 1.90–2.03 (2H, m, 4-H2), 5.10 (1H, m, J = 7.1 Hz, 3-H). HRMS m/z (M⁺): calcd. for C12H24, 186.1877; found, 168.1901.

A mixture of (E)-2,6-dimethyl-2-decen-1-ol (5a), (E)-2,6-dimethyl-2-decenoate (5b), and 2-(4-methylcydilene)-1,3-propanediol (5c). To a mixture of selenium dioxide (0.40 g, 3.63 mmol) and salicylic acid (0.63 g, 4.54 mmol) in dichloromethane (15 ml) was added successively a solution of t-BuOOH in dichloromethane [about 3 M, 60 ml, ca. 180 mmol; prepared by drying a mixture of 70% t-BuOOH aq. (50 ml) and dichloromethane (100 ml) with MgSO4] and a solution of 4c (8.03 g, 48.6 mmol) in dichloromethane (15 ml) at 0°C. After the mixture was stirred at room temperature for 9 h, selenium dioxide (0.10 g, 0.91 mmol) was added again, and the mixture was stirred for an additional 9 h. The mixture was diluted with ether and water, and cooled to 0°C. To the mixture was added ferrous sulfate heptahydrate (80 g) and the resulting mixture was stirred for 10 min. The ether layer was separated and the water layer was extracted with ether. The combined extracts were successively washed with water, sat. NaHCO3 aq. and brine, dried (MgSO4) and concentrated in vacuo to give a mixture (9.8 g) containing 5a, 5b, and 5c, the 1H-NMR analysis of which revealed the ratio of the components to be 5.5:1:0:1.7. Each component isolated by silica gel column chromatography showed the following physical properties: 5a: IR νmax cm⁻¹: 3340 (m), 2960 (s), 2925 (s), 2860 (s), 1460 (m), 1380 (m), 1010 (m); 1H-NMR δ: 0.87 (3H, d, J = 6.5 Hz, 6-CH3), 0.89 (3H, t, J = 7.0 Hz, 10-CH3), 1.08–1.18 (2H, m, 9-H2), 1.18–1.34 (6H, m, 6-H, 7-H2, 8-H2 and OH), 1.34–1.44 (2H, m, 5-H2), 1.67 (3H, br s, C=CH2), 1.93–2.10 (2H, m, 4-H2), 4.00 (2H, br s, 1-H2), 5.40 (1H, m, J = 7.1 Hz, 3-H). HRMS m/z (M⁺): calcd. for C12H17O3, 184.1826; found, 184.1819. 5b: IR νmax cm⁻¹: 2960 (s), 2930 (s), 2860 (m), 2710 (w), 1690 (vs), 1645 (m), 1460 (m), 1380 (m), 1240 (w), 1080 (w), 1000 (w); 1H-NMR δ: 0.88 (3H, t, J = 6.5 Hz, 6-CH3), 0.91 (3H, d, J = 6.8 Hz, 10-CH3), 1.10–1.35 (6H, m, 7-H2, 8-H2 and 9-H2), 1.40–1.55 (3H, m, 5-H2 and 6-H), 2.28–2.42 (2H, m, 4-H2, 6-H), 4.69 (1H, m, J = 7.4 Hz, 3-H), 9.39 (1H, s, 1-H). HRMS m/z (M⁺): calcd. for C12H17O2, 182.1670; found, 182.1684.

5c: IR νmax cm⁻¹: 3350 (s), 2970 (s), 2940 (s), 2880 (s), 1460 (m), 1380 (m), 1010 (s); 1H-NMR δ: 0.87 (3H, d, J = 6.5 Hz, 6-CH3), 0.89 (3H, t, J = 6.9 Hz, 10-CH3), 1.09–1.33 (7H, m, 6-H, 7-H2, 8-H2 and 9-H2), 1.33–1.45 (2H, m, 5-H2),
1.97 (2H, br, OH × 2), 2.02–2.16 (2H, m, 4-H), 4.22 (2H, s, O–CH₂), 4.33 (2H, s, O–CH₂), 5.56 (1H, t, J = 7.5 Hz, 3-H). HRMS m/z (M⁺): calcld. for C₁₈H₂₃O₂, 200.1775; found, 200.1798.

2,6-Dimethyl-1-decanol (6a). The mixture of 5a, 5b, and 5e obtained above (9.8 g) was dissolved in ethanol (100 ml) and stirred vigorously at reflux with platinum dioxide (0.71 g) under a hydrogen atmosphere for 36 h, with more platinum dioxide (2 × 0.23 g) being added after 12 and 24 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was chromatographed over silica gel (100 g, hexane-ether = 30:1) and distilled to give 4.35 g (49% from 4c) of 6a, b.p. 126–130°C (30 Torr). IR νmax cm⁻¹: 3350 (s), 2960 (s), 2930 (s), 2870 (s), 1460 (m), 1380 (m), 1035 (m), 990 (w), 730 (w); ¹H-NMR δ: 0.846 (3 × 0.5H, d, J = 6.7 Hz, 6-CH₃), 0.848 (3 × 0.5H, d, J = 6.7 Hz, 6-CH₃), 0.89 (3H, t, J = 7.0 Hz, 10-H), 0.918 (3 × 0.5H, d, J = 6.8 Hz, 2-CH₃), 0.922 (3 × 0.5H, d, J = 6.8 Hz, 2-CH₃), 1.04–1.14 (3H, m, 1.18–1.34 (8H, m), 1.22 (1H, t, J = 5.8 Hz, OH), 1.34–1.42 (2H, m), 1.58–1.65 (1H, m, 2-H), 3.42 (1H, ddd, J = 10.5, 6.2, 5.8 Hz, 1-H), 3.510 (1 × 0.5H, dt, J = 10.5, 5.8 Hz, 1-H), 3.514 (1 × 0.5H, dt, J = 10.5, 5.8 Hz, 1-H). HRMS m/z (M⁺): calcld. for C₁₈H₃₄O, 186.1982; found, 186.1943.

2,6-Dimethyloctyl tosylate (6b). To a solution of 6a (4.13 g, 22.2 mmol) in pyridine (14 ml) was added portionwise p-toluenesulfonyl chloride (5.67 g, 28.9 mmol) at 0°C. After the mixture was stirred at 0°C for 1 h and then at room temperature overnight, water (5 ml) was added to the mixture. The mixture was stirred for 20 min, poured into water, and then extracted with ether. The etheral solution was successively washed with 2 ml HCl aq. and water, dried (MgSO₄) and concentrated in vacuo to give 7.32 g of crude 6b. IR νmax cm⁻¹: 2960 (s), 2930 (s), 2860 (s), 1600 (w), 1465 (m), 1365 (s), 1190 (s), 1180 (s), 1095 (m), 965 (s), 810 (s), 670 (s), 550 (s). This tosylated product was used for the next step without further purification.

5,9-Dimethylpentadecane (1). To a solution of 6b (2.50 g, 7.47 mmol) in THF (30 ml) was added successively a solution of pentylmagnesium bromide (1.0 mol in THF, 11.2 ml, 11.2 mmol) and a solution of dilithium tetrachlorocuprate (0.1 mol in THF, 0.75 ml, 0.075 mmol) at −78°C. After 30 min, the mixture was allowed to warm gradually to room temperature and stirred at room temperature for 14 h and then at 40°C for 4 h. The mixture was poured into sat. NH₄Cl aq. and extracted with ether. The etheral solution was successively washed with water and brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over silica gel (100 g, hexane) and distilled to give 1.18 g (67%) of 1, b.p. 108–110°C (4 Torr). IR νmax cm⁻¹: 2960 (s), 2930 (s), 2860 (s), 1460 (m), 1380 (m), 1155 (w), 725 (w); ¹H-NMR δ: 0.84 (6H, br d, J = 6.7 Hz, 5-CH₃ and 9-CH₃), 0.883 (6 × 0.75H, t, J = 7.0 Hz, 1-H₃ and 15-H₃), 0.888 (6 × 0.25H, t, J = 7.0 Hz, 1-H₃ or 15-H₃), 1.02–1.14 (4H, m, 2-H₂ and 14-H₂), 1.17–1.32 (18H, m), 1.32–1.41 (2H, m, 5-H and 9-H). HRMS m/z (M⁺): calcld. for C₂₀H₄₀, 240.2815; found, 240.2828.

5,9-Dimethylhexadecane (2). In a similar manner as described for the preparation of 1, the coupling reaction of tosylate 6b (2.13 g, 6.26 mmol) and heptylmagnesium bromide (1.0 mol in THF, 9.4 ml, 9.4 mmol) in the presence of dilithium tetrachlorocuprate (0.1 mol in THF, 0.63 ml, 0.063 mmol) gave 1.05 g (66%) of 2, b. p. 132–138°C (9 Torr). IR νmax cm⁻¹: 2960 (s), 2930 (s), 2860 (s), 1460 (m), 1380 (m), 1155 (w), 725 (w); ¹H-NMR δ: 0.84 (6H, br d, J = 6.7 Hz, 5-CH₃ and 9-CH₃), 0.884 (6 × 0.75H, t, J = 7.0 Hz, 1-H₃ and 16-H₃), 0.889 (6 × 0.25H, t, J = 7.0 Hz, 1-H₃ or 16-H₃), 1.01–1.13 (4H, m, 2-H₂ and 15-H₂), 1.17–1.32 (20H, m), 1.32–1.41 (2H, m, 5-H and 9-H). HRMS m/z (M⁺): calcld. for C₂₁H₄₈, 254.2972; found, 254.2979.

5,9-Dimethylheptadecane (3). In a similar manner as described for the preparation of 1, the coupling reaction of 6b (2.69 g, 7.91 mmol) and heptylmagnesium bromide (1.0 mol in THF, 11.9 ml, 11.9 mmol) in the presence of dilithium tetrachlorocuprate (0.1 mol in THF, 0.79 ml, 0.079 mmol) gave 1.25 g (59%) of 3, b. p. 152–158°C (20 Torr). IR νmax cm⁻¹: 2960 (s), 2930 (s), 2860 (s), 1460 (m), 1380 (m), 1155 (w), 725 (w); ¹H-NMR δ: 0.84 (6H, br d, J = 6.7 Hz, 5-CH₃ and 9-CH₃), 0.882 (6 × 0.75H, t, J = 7.0 Hzm 1-H₃ and 17-H₃), 0.888 (6 × 0.25H, t, J = 7.0 Hz, 1-H₃ or 17-H₃), 1.01–1.14 (4H, m, 2-H₂ and 16-H₂), 1.17–1.32 (22H, m), 1.32–1.41 (2H, m, 5-H and 9-H). HRMS m/z (M⁺): calcld. for C₂₂H₄₄, 268.3128; found, 268.3147.

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