INSECT PHEROMONES AND THEIR ANALOGUES

XXIV. SYNTHESIS OF LONG-CHAIN 1,5-DIMETHYL-BRANCHED PHEROMONES FROM GERANYL ACETATE

V. N. Odinokov, G. Yu. Ishmuratov,
I. M. Ladenkova, and G. A. Tolstikov

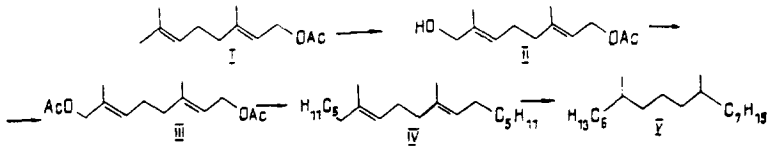
UDC 547.3+632.78

Schemes for the synthesis of long-chain 1,5-dimethyl-branched pheromones (7,11-dimethyloctadecane, 15,19-dimethyltritriacontane, and 2-acetoxy-3,7-dimethylpentadecane) from the product of the allyl oxidation of geranyl acetate (8-acetoxy-2,6-dimethylocta-2E,6E-dien-1-ol) have been developed.

The synthesis of 1,5-dimethyl-branched alkanes, among which pheromones of a number of insect species have been found [1, 2], has been carried out in 5-6 stages starting from octan-2-one [1], 2-methyloctadecanoic acid [2], or 1,5-dimethylcycloocta-1,5-diene [3-5]. Syntheses of racemic 3,7-dimethylpentadec-2-yl acetate, exhibiting the property of a sex attractant of pine sawflies have been multistage operations [6-15].

In the present paper we propose a rational approach to the synthesis of pheromones with a 1,5-dimethyl-branched structure from the bifunctional product of the allyl oxidation of geranyl acetate, which has been used previously to obtain monoterpenoid α,ω-bifunctional insect pheromones [16, 17]. Geranyl acetate (I) is converted according to [18] into 8-acetoxy-1-hydroxy-2,6-dimethylocta-2E,6E-ene (II), for which we have developed selective transformations into 7,11-dimethyloctadecane (V), 15,19-dimethyltritriacontane (X), and 3,7-dimethylpentadec-2-yl acetate (XVI) – the pheromones of the yellow-fever mosquito (Aedes aegypti), the stable fly Stomoxys calcitrans, and Diprion and Neodiprion pine sawflies, respectively.

In the synthesis of the pheromone (V), the hydroxy acetate (II) was converted into the diacetate (III), both acetoxy groups of which are allyl and are capable of nucleophilic substitution with Grignard reagents. The reaction of 1,8-diacetoxy-2,6-dimethylocta-2E,6E-diene (III) with a sixfold molar excess of n-amylmagnesium bromide in the present of CuI led with a 64% yield to the product of cross-coupling at both acetoxy groups – 7,11-dimethyloctadeca-7E,11E-diene (IV), the hydrogenation of which gave the pheromone (V) with an overall yield of 55% calculated on the compound (II).

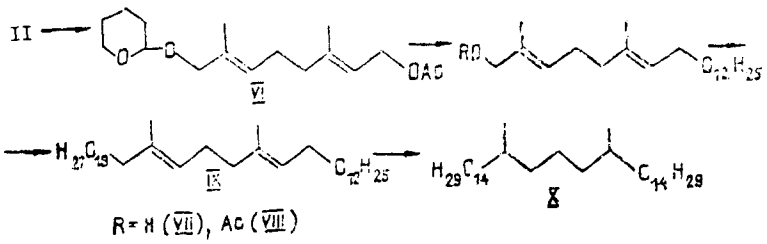


In the synthesis of pheromone (X), selective growth of the chain of synthon (II) was required. Therefore the hydroxy group in the latter was protected by reaction with dihydropyran, and the compound obtained (VI) was coupled with n-dodecylmagnesium bromide. In the coupling product so obtained (VII), the hydroxy group was transformed into an acetate group, and subsequent coupling of the allyl acetate (VIII) with n-tridecylmagnesium bromide gave the dienic precursor (IX) of the pheromone (X). The yield of the latter calculated on the key synthon (II) was 40%. (see scheme on next page)

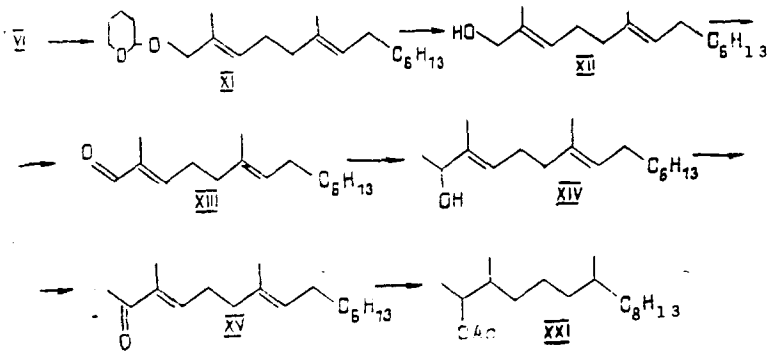
Compound (VI) served as the starting synthon for pheromone (XVI); its coupling with n-hexylmagnesium bromide gave compound (XI), which was converted into the aldehyde (XIII) via the alcohol (XII). Condensation of the aldehyde (XIII) with methylmagnesium iodide led to the dienic analogue (XIV) of the desired pheromone. However, the catalytic hydrogenation of this secondary allyl alcohol was complicated by a hydrogenolysis reaction. Because of this,

Institute of Chemistry, Bashkir Scientific Center, Urals Branch, Academy of Sciences of the USSR, Ufa. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 818-823, November-December, 1990. Original article submitted January 26, 1990.

0009-3130/90/2606-0697$12.50



it was necessary to oxidize the alcohol (XIV) to the ketone (XV), the hydrogenation of the double bonds of which over a palladium catalyst took place selectively and, after reduction of the ketone group with the aid of sodium tetrahydroborate followed by acetylation of the alcohol formed, the desired pheromone (XVI) was obtained with an overall yield of 22% calculated on the compound (II).



EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer (in a film), and PMR spectra on a Tesla BS-567 instrument (working frequency 100 MHz), the solvent being $CDCl_3$ or $(CD_3)_2CO$, and the internal standard TMS. The mass spectra of compounds (V) and (XVI) were measured on a MKh-1306 instrument at a temperature of the ionization chamber of 140-150°C and an energy of the ionizing electrons of 70 eV, and those of compounds (IX) and (X) on a MKh-1320 instrument with the aid of a direct-introduction system at a temperature of the ionization chamber of 100°C and an ionizing energy of 70 eV. GLC analysis was performed on a Chrom-5 instrument with, as stationary phase, the silicone liquid SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm) at a working temperature of 50-300°C, the carrier gas being helium. The results of the analysis of all the compounds corresponded to the calculated figures.

1,8-Diacetoxy-2,6-dimethylocta-2E,6E-diene (III). To 2.12 g (0.01 mole) of the alcohol (II) obtained as in [18], was added 8 ml of a mixture (2:3) of acetic acid and pyridine: the resulting mixture was kept at room temperature for 24 h and was diluted with 150 ml of methylene chloride, and it was then washed successively with 10% HCl and with saturated solutions of $NaHCO_3$ and NaCl, and it was dried with $MgSO_4$ and evaporated. The residue was chromatographed [SiO_2; hexane–diethyl ether (8:2)]. This gave 2.26 g (89%) of the diacetate (III), n_D^{20} 1.4664/ The IR and PMR spectra were identical with those described in [19].

7,11-Dimethyloctadeca-7E,11E-diene (IV). At −20°C in Ar, 1.14 g (0.006 mole) of CuI was added to a solution of the Grignard reagent prepared from 0.91 g (0.006 mole) of n-amyl bromide and 0.19 g (0.008 g-atom) of magnesium in 10 ml of absolute THF, and the mixture was stirred for 0.5 h. Then 0.26 g (0.001 mole) of the diacetate (III) was added and stirring was continued at −15°C for 3 h and at room temperature for 4 h, after which the mixture was cooled to 10°C and 10 ml of saturated NH_4Cl solution was added. The resulting mixture was stirred for 1 h and was extracted with diethyl ether (3 × 100 ml), the extract was dried with $MgSO_4$ and evaporated, and the residue was chromatographed (Al_2O_3, hexane). This gave 0.18 g (64%) of the diene (IV), n_D^{20} 1.4624, PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 6H, J = 6 Hz, H-1, H-18), 1.26 (br.s, 16H, CH_2), 1.59 (s, 6H, CH_3-7, CH_3-11), 1.87-2.10 (m, 8H, H-6, H-9, H-10, H-13), 5.20 (m, 2H, H-8, H-12).

7,11-Dimethyloctadecane (V). With a magnetic stirrer, 0.14 g (0.0005 mole) of compound (IV), 10 ml of ethanol, and 0.05 g of 5% Pd/C were stirred in an atmosphere of hydrogen until

the absorption of hydrogen had ceased (30 h), and then the mixture was filtered and evaporated. This gave 0.136 g (97%) of the alkane (V). Its IR and mass spectra were identical with those described in [3].

8-Acetoxy-2,6-dimethyl-1-(2-tetrahydropyranyloxy)octa-2E,6E-diene (VI). At 10-15°C, 11 ml (9.25 g; 0.11 mole) of 2,3-dihydropyran was added to a solution of 5.0 g (0.0236 mole) of the alcohol (II) and 0.05 g of TsOH in 70 ml of absolute diethyl ether, and the mixture was heated to room temperature and stirred for 20 h, and, after the addition of 20 ml of diethyl ether, it was washed successively with saturated solutions of $NaHCO_3$ and NaCl and was dried with Na_2SO_4 and evaporated. Chromatography of the residue [SiO_2; hexane–diethyl ether (8:2)], yielded 6.1 g (87%) of compound (VI) with n_D^{20} 1.4784. The IR and PMR spectra were identical with those described in [20].

2,6-Dimethyleicosa-2E,6E-dien-1-ol (VII). At −15°C in an atmosphere of argon, 0.76 g (0.004 mole) of CuI was added to a solution of the Grignard reagent prepared from 3.0 g (0.015 mole) of n-dodecyl bromide and 0.29 g (0.012 g-atom) of magnesium in 15 ml of absolute THF, and the mixture was stirred for 0.5 h, after which 1.19 g (0.004 mole) of the acetate (VI) was added and stirring was continued at −10°C for 4 h and at room temperature for 4 h; then 15 ml of saturated NH_4Cl solution was added and the resulting mixture was stirred at 10°C for 1 h and was extracted with diethyl ether (3 × 100 ml), and the extract was evaporated. The residue was dissolved in 15 ml of methanol, 1 ml of water and 0.1 g of TsOH were added, and the mixture was stirred at room temperature for 15 h and was then evaporated. The residue was dissolved in 150 ml of diethyl ether and the solution was washed successively with saturated solutions of $NaHCO_3$ and NaCl and was dried with Na_2SO_4 and evaporated. After chromatography of the residue [SiO_2; hexane–diethyl ether (7:3)], 0.93 g (72%) of the alcohol (VII) was obtained. IR spectrum, (ν, cm^{-1}): 865 (C=C–H), 1385 (CH_3), 1665 (C=C), 3350 (OH). PMR spectrum (700 MHz), ($CD_3)_2CO$): 0.88 (t, 3H, J = 5 Hz, H-20), 1.29 (br, s, 22H, CH_2), 1.61 (s, 6H, CH_3-2, CH_3-6), 2.05 (m, 7H, H-4, H-5, H-8, OH), 3.90 (s, 2H, H-1), 5.17 (t, 1H, J = 7 Hz, H-7), 5.38 (t, 1H, J = 7 Hz, H-3).

1-Acetoxy-2,6-dimethyleicosa-2E,6E-diene (VIII). As described above for compound (III), 0.18 g (0.00056 mole) of the alcohol (VII) and 0.6 ml of a mixture (2:3) of acetic anhydride and pyridine yielded 0.18 g (87%) of the acetate (VIII), n_D^{20} 1.4635. IR spectrum (ν, cm^{-1}): 855 (C=C–H), 1380 (CH_3), 1240 (C–O–C), 1735 (C=O). PMR spectrum (100 MHz, ($CD_3)_2CO$): 0.88 (t, 3H, J = 7 Hz, H-20), 1.29 (br, s, 22H, CH_2), 1.61 (br, s, 6H, CH_3-2, CH_3-6), 1.87-2.11 (m, 9H, CH_3CO, H-4, H-5, H-8), 4.41 (s, 2H, H-1), 5.08 (t, 1H, J = 7 Hz, H-7), 5.38 (m, 1H, H-3).

15,19-Dimethyltritriaconta-15E,19E-diene (IX). At −15°C in an atmosphere of argon, 0.76 g (0.0004 mole) of CuI was added to a solution of the Grignard reagent prepared from 0.79 g (0.003 mole) of n-tridecyl bromide and 0.073 g (0.003 g-atom) of magnesium in 3 ml of absolute THF, the mixture was stirred for 0.5 h, and then 0.15 g (0.0004 mole) of the acetate (VIII) was added and the resulting mixture was stirred at −10°C for 4 h and at room temperature for 4 h, after which 10 ml of a saturated solution of NH_4Cl was added and stirring was continued at 10°C for 1 h; then the mixture was extracted with ether (3 × 50 ml), and the extract was dried with $MgSO_4$ and evaporated. The residue was chromatographed (Al_2O_3, n-heptane). This gave 0.15 g (78%) of the diene (IX) [21]. PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 6H, J = 6 Hz, H-1, H-33), 1.29 (br, s, 46H, CH_2), 1.58 (s, 6H, CH_3-15, CH_3-19), 1.89-2.11 (m, 8H, H-13, H-16, H-17, H-20), 5.18 (m, 2H, H-14, H-18). Mass spectrum, m/z (%); 488 (27.77), 305 (29.62), 250 (10.64), 236 (3.47), 138 (2.77), 69 (100.00).

15,19-Dimethyltritriacontane (X). As described above for compound (V), 0.1 g (0.0002 mole) of the diene (IX) was hydrogenated in 8 ml of ethanol with 0.03 g of 5% Pd/C. This gave 0.095 g (95%) of the alkane (X) with IR and mass spectra identical with those described in [4].

1-(Tetrahydropyran-2-yloxy)tetradec-2E,6E-diene (XI). As described above for compound (IX), 1.78 g (0.006 mole) of compound (VI), 2.48 g (0.015 mole) of n-hexyl bromide, 0.36 g (0.015 g-atom) of magnesium, and 1.14 (0.006 mole) CuI in 15 ml of absolute THF gave 1.53 g (79%) of compound (XI) (after chromatography on SiO_2; hexane–diethyl ether (9:1). IR spectrum (ν, cm^{-1}): 830 (C=CH), 1040, 1070, 1090, 1132 (acetal), 1390 (CH_3), 1670 (C=C). PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 3H, J = 6 Hz, H-14), 1.27 (br, s, 16H, CH_2), 1.59 (s, 3H, CH_3-6), 1.66 (s, 3H, CH_3-2), 1.85-2.16 (m, 6H, H-4, H-5, H-8), 3.32-3.90 (m, 2H, CH_2O), 3.85 (d, 1H, J_{AB} = 11.4 Hz, H-1), 4.10 (d, 1H, J_{BA} = 11.4 Hz, H-1), 4.60 (m, 1H, OCHO), 5.14 (t, 1H, J = 7 Hz, H-7), 5.42 (t, 1H, J = 7 Ha, H-3).

2,6-Dimethyltetradeca-2E,6E-dien-1-ol (XII). A solution of 1.5 g (0.0046 mole) of compound (XI) in 35 ml of methanol was treated with 1 ml of water and 0.15 g of TsOH, and the mixture was stirred at room temperature for 15 h, after which it was evaporated, the residue was dissolved in 150 ml of diethyl ether, this solution was washed successively with saturated solutions of $NaHCO_3$ and NaCl and was dried with Na_2SO_4 and evaporated, and the residue was chromatographed [SiO_2; hexane–diethyl ether (7:3)]. This gave 1.0 g (91%) of the alcohol (XII). IR spectrum (ν, cm^{-1}): 870 (C=CH), 1385 (CH_3), 1670 (C=C), 3350 (OH). PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 3H, M = 6 Hz, H-14), 1.27 (br, s, 10H, CH_2), 1.60 (s, 3H, CH_3-6), 1.66 (s, 3H, CH_3-2), 1.85-2.15 (m, 6H, H-4, H-5, H-8), 3.98 (s, 2H, H-1), 5.10 (t, 1H, J = 7 Hz, H-7), 5.35 (t, 1H, J = 7 Hz, H-3).

3,7-Dimethylpentadeca-3E,7E-dien-2-ol (XIV). With stirring (10°C, Ar), a solution of 0.95 g (0.004 mole) of compound (XII) in 2 ml of CH_2Cl_2 was added to a suspension of 1.29 g of pyridinium chlorochromate in 15 ml of dry CH_2Cl_2, and the mixture was stirred at room temperature for 2 h after which it was diluted with 100 ml of diethyl ether and was filtered through a layer of SiO_2. The residue on the filter was washed with 100 ml of diethyl ether, and the solution was dried with $MgSO_4$ and evaporated. The residue (0.71 g) of 2,6-dimethyltetradeca-2E,6E-dienal (XIII) [IR spectrum (ν, cm^{-1}): 870 (C=CH), 1385 (CH_3), 1650 (C=C), 1690 (C=O), 2725 (CHO)] was dissolved in 1 ml of absolute diethyl ether, and the resulting solution was added (0°C, Ar) to a solution of the Grignard reagent prepared from 0.71 g (0.005 mole) of methyl iodide and 0.12 g (0.005 g-atom) of magnesium in 100 ml of absolute diethyl ether. The reaction mixture was stirred at room temperature for 1 h and was then boiled for 0.5 h and was cooled to 0°C, after which 10 ml of saturated NH_4Cl solution was added, and the resulting mixture was stirred at 20°C for 0.5 h and was extracted with diethyl ether (3 × 50 ml); the extract was dried with Na_2SO_4 and evaporated. The residue was chromatographed (SiO_2; hexane–diethyl ether (1:1). This gave 0.61 g [81% calculated on the (XII)] of the alcohol (XIV). IR spectrum (ν, cm^{-1}): 870 (C=CH), 1090 (C–O), 1385 (CH_3), 1660 (C=C), 3380 (OH). PMR spectrum (100 MHz, $(CD_3)_2CO$); 0.88 (t, 3H, J = 5.5 Hz, H-15), 1.16 (d, 3H, J = 6.6 Hz, H-1), 1.30 (br, s, 10H, CH_2), 1.60 (s, 6H, CH_3-3, CH_3-7), 1.85-2.15 (m, 6H, H-5, H-6, H-9), 3.2 (br, s, 1H, OH), 4.11 (q, 1H, J = 6.6 Hz, H-2), 5.16 (t, 1H, J = 6 Hz, H-4).

3,7-Dimethylpentadeca-3E,7E-dien-2-one (XV). As described above for compound (XIII), 0.50 g (0.002 mole) of compound (XIV) and 0.65 g of pyridinium chlorochromate in 8 ml of dry CH_2Cl_2 yielded 0.43 g (85%) of the ketone (XV), n_D^{20} 1.4685, IR spectrum (ν, cm^{-1}): 835 (C=CH), 1370 (CH_3), 1650 (C=C), 1675 (C=O). PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 3H, J = 6 Hz, H-15), 1.26 (m, 10H, CH_2), 1.61 (s, 3H, CH_3-7), 1.77 (s, 3H, CH_3-3), 1.83-2.38 (m, 9H, H-1, H-5, H-6, H-9), 5.18 (t, 1H, J = 6 Hz, H-8), 6.61 (t, 1H, J = 7 Hz, H-4).

2-Acetoxy-3,7-dimethylpentadecane (XVI). In an atmosphere of hydrogen, 0.25 g (0.001 mole) of the ketone (XV), 0.1 g of 5% Pd/C, and 5 ml of 2% ethanolic KOH was stirred until the absorption of hydrogen had ceased (5 h), and then the mixture was filtered and the filtrate was evaporated. The residue was dissolved in 50 ml of diethyl ether, and the solution was washed successively with 5% HCl and saturated solutions of $NaHCO_3$ and NaCl and was dried with Na_2SO_4 and evaporated. The residue was dissolved in 5 ml of ethanol and, after the addition of 0.05 g of 5% Pd/C, the solution was stirred in an atmosphere of hydrogen until the absorption of hydrogen had ceased (20 h). Then it was filtered, the filtrate was cooled to 0-5°C and was treated with 0.038 g (0.001 mole) of $NaBH_4$; the mixture was slowly heated to room temperature and was stirred for 8 h, after which 5 ml of 5% HCl was added, stirring was continued for 2 h, the mixture was evaporated and was extracted with diethyl ether (3 × 50 ml), and the extract was dried with Na_2SO_4 and evaporated. The residue was treated with 1.5 ml of a mixture (2:3) of acetic anhydride and pyridine, and the product was worked up as described above for compound (III). This gave 0.18 g (61%) of the acetate (SVI). Its IR, PMR, and mass spectra were identical with those described in [9].

LITERATURE CITED

1. I. Ikeshoji, I. Ishimoto, I. Kopishi, Y. Naoxhima, and H. Ueda, J. Pest. Sci., 4, No. 2, 187 (1979).
2. E. Ade, G. Helmchen, and G. Heiligenmann, Tetrahedron Lett., 21, No. 12, 1137 (1980).
3. V. N. Odinokov, V. R. Akhmetova, and G. A. Tolstikov, Dokl. Akad. Nauk SSSR, 271, No. 5, 1143 (1983).
4. V. N. Odinokov, V. R. Akhmetova, R. G. Savchenko, and G. A. Tolstikov, Khim. Prir. Soedin., No. 4, 595 (1987).
5. V. N. Odinokov, V. R. Akhmetova, R. G. Savchenko, E. M. Vyrypaev, and G. A. Tolstikov, Zh. Org. Khim., 24, No. 1, 84 (1988).

6. P. J. Kocienski and J. M. Ansell, J. Org. Chem., 42, No. 6, 402 (1977).
7. D. Jewett, F. Matsumura, and H. C. Coppel, J. Chem. Ecol., 4, No. 3, 277 (1978).
8. K. Mori, S. Masuda, and M. Matsui, Agric. Biol. Chem., 42, No. 5, 1015 (1978).
9. P. Place, M.-L. Roumestant, and J. Yore, J. Org. Chem., 43, No. 5, 1001 (1978).
10. G. Magnussen, Tetrahedron, 34, No. 9, 1385 (1978).
11. R. Baker, P. M. Winton, and R. W. Turner, Tetrahedron Lett., 21, No. 12, 1175 (1980).
12. V. N. Odinokov, V. R. Akhmetova, G. Yu. Ishmuratov, L. P. Botsman, and G. A. Tolstikov, Zh. Org. Khim., 22, No. 5, 953 (1986).
13. J. Kallmerten and M. Balestra, J. Org. Chem., 51, No. 14, 2855 (1986).
14. É. P. Serebryakov and G. D. Gamalevich, Iav. Akad. Nauk SSSR, Ser. Khim., No. 1, 144 (1987).
15. V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, and G. A. Tolstikov, Khim. Prir. Soedin., No. 4, 573 (1989).
16. S. Teng. R. Vyalimyaé, and K. Leete, Iav. Akad. Nauk ÉSSR, Khimiya, 33, No. 3, 194 (1984).
17. P. Gramatica, G. Giardina, G. Speranza, and P. Manitto, Chem. Lett., No. 9, 1395 (1985).
18. A. C. Oehlschlager, J. W. Wong, V. G. Verigin, and H. D. Pierce, Jr., J. Org. Chem., 48, No. 25, 5009 (1983).
19. K. Sato, S. Inoue, A. Onishi, N. Uchida, and N. Minowa, J. Chem. Soc. Perkin Trans., Part I, No. 3, 761 (1981).
20. J. A. Marshall and R. C. Andrews, J. Org. Chem., 50, No. 10, 1602 (1985).
21. P. E. Sonnet, J. Am. Oil Chem. Soc., 53, No. 2, 57 (1976).