INSECT PHEROMONES AND THEIR ANALOGUES.

XXXV. SYNTHESIS OF (R)-(−)-10-METHYLTRIDECAN-2-ONE – THE PHEROMONE OF Diabrotica undecimpunctata

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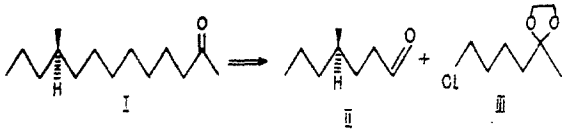
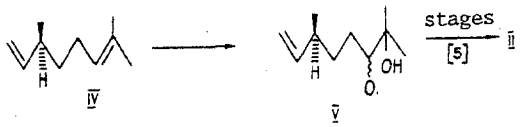
A scheme has been developed for the synthesis of (R)-(−)-10-methyltridecan-2-one, the sex pheromone of the southern corn rootworm (Diabrotica undecimpunctata) using as the chiral synthon (R)-(+)-methylheptenal obtained by the hydroperoxide oxidation of the readily available (S)-(+)-dihydromyrcene.

Pathways for the synthesis of the pheromone of a pest of cereal crops, the southern corn rootworm (Diabrotica undecimpunctata), which has been identified as (R)-(−)-10-methyltridecan-2-one (I) [1], are known that start from undecenoic acid [2], R-(+)-citronellol [3], (R)-(−)-3-methylglutarate [4], and (S)-(+)-dihydromyrcene [5].

In the present communication we describe the synthesis of the pheromone (I) from C_8-chiral (II) and C_6-achiral (III) synthons:



For the synthesis of (R)-4-methylheptanal (II), the readily available [5] (S)-(+)-dihydromyrcene (IV) was oxidized with the aid of tert-butyl hydroperoxide in the presence of a catalyst – molybdenum hexacarbonyl. The reaction took place selectively at the trisubstituted double bond, giving the (3R,6S)-2,6-dimethyloct-7-ene-2,3-diol (V). The subsequent six-stage transformation described in [5] led to the desired chiral synthon, the yield of which, calculated on the initial diene (IV), was 46%.



The achiral synthon 2,2-ethylenedioxy-6-chlorohexane (III) was obtained by a one-pot synthesis in three operations from cyclopentanone (VI) with an overall yield of 54.5%. The chloroaldehyde was introduced into coupling with the aldehyde (II) in the form of the Grignard reagent. This reaction gave a high yield of the secondary alcohol (VII) the deoxygenation of which via the corresponding tosylate (VIII) with the aid of lithium tetrahydroaluminate led to a mixture of compounds (I), (IX), and (X). It followed from the relative intensities of the singlet at δ 1.93 ppm [CH_3CO in ketone (I)], of the sum of the triplets at δ 3.55 and 3.78 ppm [OCH_2CH_2O in acetal (IX)], and of the doublet at 1.24 ppm [H_3C–C–OH in alcohol (X)] in the PMR spectrum of the deoxygenation product that compounds (I), (IX) and (X) were present in a ratio of 1:1:2. With the aid of HPLC it was possible to obtain from this mixture compounds (IX) and (X) in the individual state, and compound (I) contaminated with (IX). The mixture of (I), (IX), and (X) was readily and wholly converted into the pheromone (I) by a two-stage operation having the aim of hydrolyzing the acetal (IX) and oxidizing the

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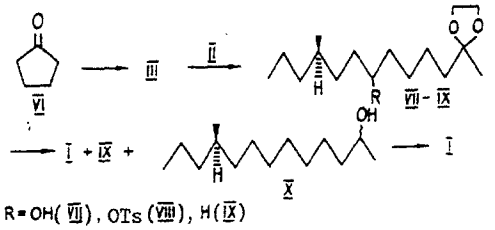
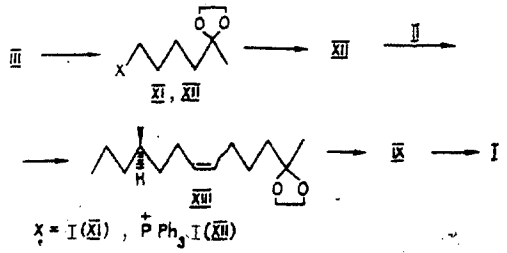
alcohol (X), with the formation of the same compound, (I), in both cases. The overall yield of the pheromone (I), calculated on the chiral synthon (II), was ~60%.



An alternative method for coupling synthons (II) and (III) made use of the Wittig reaction. For this, the chloroacetal (III) was converted into the phosphonium iodide (XII) via the intermediate iodide (XI). However, the coupling of the aldehyde (II) with the phosphorane generated from the salt (XII) gave the required alkene (XIII) in the form of a mixture of Z- and E- isomers in fairly low yield. And although the subsequent stages of hydrogenating the unsaturated acetal (XIII) and hydrolyzing the saturated acetal (IX) proceeded with high yields, the overall yield of pheromone (I) in this case was substantially lower than in the scheme given above, amounting to 26%.



EXPERIMENTAL

The IR spectra of the substances were taken on a UR-20 instrument in a thin layer, while PMR spectra were obtained on a Tesla BS-576 (100 MHz) spectrometer in $CDCl_3$ solution relative to TMS. Analysis by the GLC method was carried out on a Chrom-5 chromatograph with a column 1200 mm long, the stationary phase SE-30, the carrier gas helium, and a working temperature 50-300°C (12°C/min). The results of elementary analysis corresponded to the calculated figures. Preparative separation was achieved on a Du Pont-Zorbax instrument [21.5 × 250 mm column; eluent hexane–ethyl acetate (7:3), rate of flow 1 ml/min].

(3RS,6S)-2,6-Dimethyloct-7-ene-2,3-diol (V). At 0°C, 12.2 ml of a 35% solution of tert-butyl hydroperoxide in methylene chloride was added dropwise to a solution of 13.3 g of dihydromyrcene [containing, according to capillary chromatography, ~60% of (S)-(+)-3,7-dimethylocta-1,6-diene (IV)] and 0.08 g of molybdenum hexacarbonyl in 60 ml of benzene. The mixture was left to stand for 20 min, and 30 ml of a mixture of benzene and methylene chloride was distilled off. Then the reaction mixture was heated at 50°C for 5 h, cooled to room temperature, washed with 10% $NaHCO_3$, and evaporated under reduced pressure (30 mm Hg). The residue was treated at 0°C with a mixture of 38.9 ml of 0.1 N $HClO_4$ and 77 ml of THF, and the resulting mixture was stirred at 0°C for 1 h and at 20°C for 5 h; it was then extracted with ether, and the organic layer was washed successively with 10% $NaHCO_3$, water, and saturated NaCl solution, and was dried with $MgSO_4$ and evaporated, and the residue was distilled. This gave 9.5 g (95%) of compound (V), bp 89-90°C (1.5 mm Hg), n_D^{20} 1.4602, $[\alpha]_D^{20}$ 1.93° (c 8.5; ether). Its IR and PMR spectra were identical with those given in [6].

6-Chloro-2,2-ethylenedioxyhexane (III). At 0°C, with stirring, 75.5 ml of ketone (VI) was added to the Grignard reagent obtained from 24.3 g of magnesium and 64 ml of methyl iodide in 150 ml of ether, and then the temperature was raised to the boil over 1 h and the mixture was boiled for 1 h. After 12 h, 500 ml of saturated NH_4Cl was added to the reaction mixture at 0°C. The organic layer was separated off, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated NaCl, dried, and evaporated. The residue (75 g) was treated with a solution of 60 g of NaOH in 1400 ml of water, and, with ice-salt cooling, chlorine was bubbled through the reaction mixture for 2 h. The yellow oil that separated out was taken off, and the solution was extracted with methylene chloride.

the combined organic layer was washed with saturated $NaHCO_3$ and with water, and was dried with $MgSO_4$ and evaporated. This gave 73.13 g of 6-chlorohexan-2-one [bp 80-81°C (10 mm Hg), see [7]; IR spectrum (ν, cm^{-1}): 580, 1720 (C=O); PMR spectrum (100 MHz, $CDCl_3$): 1.67 (m, 4H, CH_2), 2.06 (s, 3H, H-1), 2.4 (t, 2H, H-3, J = 7 Hz), 3.49 (t, 2H, H-6, J = 6.5 Hz)], which was dissolved in 150 ml of benzene; then 30 g of ethylene glycol and 2.23 g of TsOH were added and the mixture was boiled with a Dean–Stark trap until the evolution of water ceased. The benzene layer was evaporated under reduced pressure (30 mm Hg), the residue was dissolved in 150 ml of ether, and the solution was washed with saturated NaCl, dried with $MgSO_4$, and evaporated. This gave 72.8 g (54.5%) of compound (III), bp 105-106°C (10 mm Hg), n_D^{24} 1.4594. IR spectrum (ν, cm^{-1}): 530, 580, 650, 840, 1070. PMR spectrum (100 MHz, $CDCl_3$): 1.32 (s, 3H, H-1), 1.63 (m, 6H, H-3, H-4, H-5), 3.54 (t, 2H, H-6, J = 6.5 Hz), 3.94 (br.s, 4H, OCH_2CH_2O).

(7RS,10R)-2,2-Ethylenedioxy-10-methyltridecan-7-ol (VII). To the Grignard solution obtained from 0.47 g of magnesium, 2.2 g of the chloroketal (III), and 0.5 g of dibromoethane in 1 ml [sic] of THF were added 12 ml of THF and then, at 0°C, dropwise, a solution of 1.1 g of the aldehyde (II) (obtained from the diol (V) as described in [5]) in 5 ml of THF and the mixture was stirred at 20°C for 1 h and then, after the addition of 25 ml of saturated NH_4Cl solution and stirring for another 0.5 h, it was extracted with ether. The ethereal solution was washed with saturated NH_4Cl, dried with $MgSO_4$, and evaporated. The residue was chromatographed on a column of 60 g of silica gel, with elution by hexane–ether (1:1). This gave 3.1 g (92%) of the alcohol (VII), $[\alpha]_D^{20}$ +2.46° (c 0.18; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1080, 3420 (OH). PMR spectrum (100 MHz, $CDCl_3$): 0.89 (t, 3H, H-13, J = 6.0 Hz), 1.18 (d, 3H, CH_3-10, J = 7 Hz), 1.28 (s, 3H, H-1), 1.62-1.7 (m, 17H, CH_2, CH), 3.45 and 3.68 (t, 4H, OCH_2CH_2O, J = 5 Hz), 5.16 (m, 1H, H-7).

(7RS,10R)-2,2-Ethylenedioxy-10-methyl-7-tosyloxytridecane (VIII). A mixture of 1.5 g of the alcohol (VIII) and 1.79 g of TsCl in 12 ml of pyridine was stirred at 0°C for 1 h and was left at 5°C for 12 h, and it was then diluted with ether and was washed successively with 5 N HCl and saturated solutions of $NaHCO_3$ and NaCl and was dried with $MgSO_4$ and evaporated. This gave 1.8 g (85%) of the tosylate (VIII). IR spectrum (ν, cm^{-1}): 950, 1190, 1600, 3080. PMR spectrum (100 MHz, $CDCl_3$): 0.88 (t, 3H, H-13, J = 6 Hz), 1.26 (d, 3H, CH_3-10, J = 7 Hz), 1.27 (s, 3H, H-1), 1.66-1.73 (m, 17H, CH_2, CH), 2.44 (s, 3H, CH_3-Ar), 3.59 and 4.11 (t, 4H, OCH_2CH_2O, J = 5 Hz), 4.15 (m, 1H, H-7), 7.33 and 7.8 (d, 4H, Ar, J = 7.5 Hz).

(10R)-2,2-Ethylenedioxy-10-methyltridecane (IX) and (2RS,10R)-2-Hydroxy-10-methyltridecane (X). At 0°C, 0.19 g of $LiAlH_4$ was added to a solution of 1.5 g of the tosylate (VIII) in 100 ml of ether; the temperature was raised to that of the room over 0.5 h and stirring was continued for another 12 h. Then the reaction mixture was decomposed with 10 ml of water, the ethereal layer was separated off, and the aqueous layer was extracted with ether. The combined organic solution was dried with $MgSO_4$ and evaporated. This gave 0.82 g of a mixture (1:1:2, PMR results) of compounds (I), (X), and (IX) from which by HPLC were obtained, in the order of their elution, 0.12 g (13%) of compound (IX), 0.44 g of a mixture of (IX) and (I), and 0.2 g (26.3%) of the alcohol (X).

For the acetal (IX): n_D^{20} 1.4521, $[\alpha]_D^{20}$ −0.89° (c 3; $CHCl_3$), see [5]: $[\alpha]_D^{23}$ −0.9° (c 6.6; $CHCl_3$); its IR and PMR spectra were identical with those given in [5].

For the alcohol (X): n_D^{20} 1.4412, $[\alpha]_D^{20}$ −0.69° (c 0.25; $CHCl_3$), see [3]: n_D^{20} 1.4392, $[\alpha]_D^{20}$ −1.1° (c 3.2; $CHCl_3$); its IR and PMR spectra were identical with those given in [3].

(5,5-Ethylenedioxyhexyl)triphenylphosphonium Iodide (XII). A mixture of 8.21 g of the chloride (II), 14.8 g of NaI, 7.45 ml of DMSO, 14.04 g of dicyclohexyl-18-crown-6, and 30 ml of toluene was stirred at 90-100°C for 6 h. The reaction mixture was poured into water, and the organic layer was separated off, washed with saturated NaCl, dried with $MgSO_4$, and evaporated, and the residue was distilled in vacuum. This gave 10.94 g (88%) of 2,2-ethylenedioxy-6-iodohexane (XI) [bp 76°C (0.05 mm Hg)], which was then heated with 13.4 g of recrystallized triphenylphosphine in a sealed tube at 150°C for 10 h. The product was the salt (XII) (10.72 g, 50%), mp 152-154°C [from alcohol–ether (1:9)].

(6E/Z,10R)-2,2-Ethylenedioxy-10-methyltridec-6-ene (XIII). A suspension of 5.52 g of the phosphonium salt (XII) in 70 ml of THF was treated (at −78°C, under argon) with 5.48 ml of a 2.3 N solution of n-butyllithium in hexane, the mixture was stirred until the solid had dissolved completely, 1 g of the aldehyde (II) in 30 ml of THF was added dropwise, and stir-

ring was continued at −78°C for another hour; then the temperature of the mixture was raised to that of the room over 2 h and it was left to stand for 12 h. After the addition of 50 ml of pentane it was filtered through a 30-g layer of silica gel and the filtrate was evaporated under reduced pressure (30 mm Hg). This gave 0.63 g (32%) of compound (XIII), $[\alpha]_D^{20}$ −0.69° (c 0.098; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1660 (C=C). PMR spectrum (100 MHz, $CDCl_3$): 0.86 (d, 3H, CH_3-10, J = 7 Hz), 0.9 (t, 3H, H-13, J = 7 Hz), 1.3 (s, 3H, H-1), 1.35-1.7 (m, 11H, CH_2, CH), 2.13 (m, 4H, H-5, H-8), 5.37 (m, 2H, H-6, H-7).

(R)-10-Methyltridecan-2-one (I). a. A solution of 0.82 g of the mixture of compounds (I), (IX), and (X) in 30 ml of acetone was treated with 0.31 of water and 0.08 g of pyridinium tosylate, and the mixture was boiled for 2 h. Then it was evaporated under reduced pressure (30 mm Hg) and the residue, dissolved in 30 ml of CH_2Cl_2, was added with stirring to a solution of 0.58 g of pyridinium chlorochromate in 20 ml of CH_2Cl_2; stirring was continued for another 2 h at 20°C and the reaction mixture was diluted with 200 ml of ether and was filtered through a 15-g layer of SiO_2, with elution by hexane–ethyl acetate (7:3). This led to 0.56 g of the pheromone (I), $[\alpha]_D^{20}$ −0.93° (c 0.25; $CHCl_3$), see [5]: $[\alpha]_D^{23}$ −0.86° (c 6; $CHCl_3$).

b. A mixture of 0.6 g of compound (XIII), 0.05 g of 10% Pd/C, and 10 ml of EtOH was stirred in an atmosphere of hydrogen until 51.5 ml (0.0046 g) of H_2 had been adsorbed. The catalyst was filtered off and washed on the filter with 10 ml of ethanol, and the filtrate was evaporated. This gave 0.59 g (98%) of the acetal (IX) [identical with that isolated from the mixture of (I), (IX), and (X)], which was dissolved in 20 ml of acetone; then 0.5 ml of water and 0.15 g of pyridinium tosylate were added and the mixture was boiled for 1 h. After evaporation, the residue was diluted with 30 ml of ether, washed with saturated $NaHCO_3$ solution, dried with $MgSO_4$, and evaporated. This gave 0.38 g (82%) of pheromone (I), identical with that obtained in experiment a.

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