INSECT PHEROMONES AND THEIR ANALOGUES.

XLVI. SYNTHESIS OF 13RS-HYDROOXYTETRADEC-5z-ENOIC ACID — THE ACYCLIC PRECURSOR OF THE MACROLIDE COMPONENT OF THE PHEROMONE OF Cryptolestes pusillus

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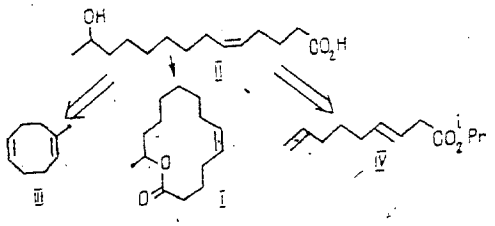
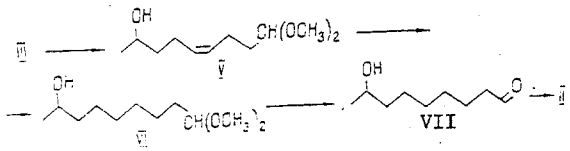
New routes for the synthesis of 13RS-hydroxytetradec-5Z-enoic acid — the acyclic precursor of the macrolide component of the pheromone of Cryptolestes pusillus have been developed on the basis of the readily accessible 1-methylcycloocta-1Z, 5Z-diene or isopropyl nona-3E,8-dienoate.

The macrolide component of the natural aggregation pheromone of the flat grain beetle Cryptolestes pusillus has been identified as 13S-methyltridec-5Z-enolide (I) [1]. Since the racemic analogue of (I) [2] is also biologically active, its synthesis is realistic. The 13RS-hydroxytetradec-5Z-enoic acid (II) required for cyclization to the racemic macrolide (I) has been obtained previously via the corresponding C_{14} acetylenic diol [1].

We have developed a new routes for the synthesis of the hydroxyacid (II), based on the transformation of the readily accessible 1-methylcycloocta-1Z,5Z-diene (III) or isopropyl nona-3E,8-dienoate (IV).



The diene (III) has been used previously for the synthesis of acyclic alk-Z-en-1-ols [3]. The ozonolysis of (III) under the conditions described in [3], followed by sodium tetrahydroborate reduction, gave us 8-hydroxy-1,1-dimethoxynon-4Z-ene (V). Hydrogenation over Raney nickel [4] and hydrolysis of the resulting acetal (VI) led to the 8RS-hydroxynonanal (VII), the olefination of which with 4-carboxybutylidenetriphenylphosphorans yielded the desired hydroxyacid (II) containing not less than 95% of the Z- isomer.



The synthesis of the hydroxyacid (II) from the accessible [5] dienoate (IV) began with its reduction, which we have described in the preceding paper [6] and which leads to nona-3E,8-dien-1-yl acetate (VIII). The oxidation of the latterwith molecular oxygen in the presence of $PdCl_2$—CuCl gave 9-acetoxynon-6E-en-2-one (IX), which was converted into the corresponding ethylenedioxy derivative (X), the alkaline hydrolysis of which liberated the hydroxy group.

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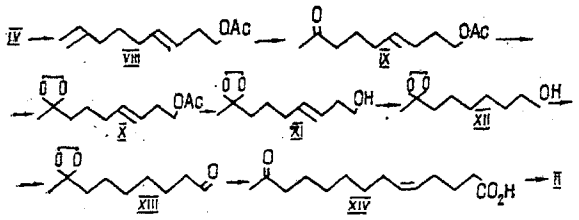
The acetal (XI) of an unsaturated hydroxyketone so obtained was converted by hydrogenation into the corresponding saturated analogue (XII), which was then oxidized to 8-ethylenedioxynonanal (XIII). Its olefination was carried out in a similar way to that of the hydroxyaldehyde (VII), but here the yield of product – 13-oxotetradec-5Z-enoic acid (XIV) – was considerably higher. The hydride reduction of the ketoacid (XIV) took place smoothly, leading to the desired hydroxyacid (II), the overall yield of which, calculated on the initial dienoate (IV), was 17.8%. The stereochemical purity of the Z-unsaturated hydroxy acid obtained in this synthesis was not inferior to that established for the product obtained from the diene (III)



EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer (in a film). PMR spectra for compounds (V) and (VI) were recorded on a Tesla BS-467 instrument (working frequency 60 MHz), with CCl_4 as the solvent. PMR spectra for compounds (II) and (IX)-(XII) were recorded on a Tesla BS-567 instrument)100 MHz), and PMR and ^{13}C NMR spectra for compound (XIV) on an AM-300 instrument (working frequencies 300 and 75.47 MHz, respectively) with $CDCl_3$ as solvent; chemical shifts are given on the δ scale relative to the signal of TMS (internal standard). GLC analysis was conducted on a Chrom-5 instrument with the silicone liquid SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm) as the stationary phase at a working temperature of 50-300°C, except for that on the methyl ester of the hydroxyacid (II), which was conducted on a Shimadzu instrument with PEG-20M as the stationary phase in a 0.2 mm × 25 m glass capillary column at a working temperature of 170°C; helium was the carrier gas. TLC was performed on Silufol plates with a fixed layer of SiO_2. The elementary analyses of the compounds synthesized corresponded to the calculated figures.

1,1-Dimethoxynon-4Z-en-8-ol (V). At 5°C, a mixture of ozone and oxygen (the output of the ozonizer being $50.0\text{-}0.10^{-3}$ mole of O_3 per hour) was passed at the rate of 30 liters/h through a solution of 12.2 g (0.1 mole) of the diene (III) in 100 ml of abs. cyclohexane containing 10 ml of abs. methanol until 4.32 g ($90.0\cdot10^{-3}$ mole) of ozone had been absorbed. The reaction mixture was purged with Ar, and the solvent was decanted off from the peroxide ozonolysis product that had separated out. The latter was dissolved in 100 ml of abs. methanol, 0.3 g of Lindlar catalyst [7] was added, and the mixture was stirred at room temperature in an atmosphere of hydrogen until the peroxide compounds had been reduced completely, as shown by the test with starch-iodide paper ($\sim$ 30 h).

The reaction mixture was filtered, the filtrate was evaporated, the residue was dissolved in 100 ml of hexane, and the solution was dried with $MgSO_4$, and evaporated. The residue was dissolved in 100 ml of abs. methanol, 1.0 g of NH_4Cl was added, and the mixture was stirred at 20°C for 36 h and was then treated with 2 g of solid $NaHCO_3$ and evaporated. The residue was dissolved in 200 ml of diethyl ether, and the solution was washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried with Na_2SO_4, and evaporated. The residue was dissolved in 100 ml of methanol and then, with stirring (15°C, Ar), 1.9 g ($50.0\cdot10^{-3}$ mole) of sodium tetrahydroborate was added in portions, and the reaction mixture was stirred at 20°C for 12 h, after which, at 0°C, 22 ml of a 10:1 mixture of water and AcOH was added and, after another 0.25 h stirring, 3 g of solid $NaHCO_3$ was added and the whole was evaporated.

The residue was dissolved in 200 ml of diethyl ether, and the solution was washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried with Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (1:1)), and 11.3 g (62%) of compound (V) was obtained, n_D^{22} 1.4508. IR spectrum (ν, cm^{-1}): 740 and 1655 (Z-CH=CH), 1065, 1080, 1095 and 1140 (C-O), 3450 (OH), PMR spectrum (60 MHz, CCl_4): 1.05 (d, 3H, J=6 Hz, H-9), 1.2-1.7 (m, 4H, H-2, H-7), 1.8-2.25 (m, 5H, H-3, H-6, OH), 3.17 (s, 6H, OCH_3) 3.6 (q, 1H, J = 6 Hz, H-8), 4.22 (t, 1H, J = 5.5 Hz, H-1), 5.25 (t, 2H, J = 5 Hz, H-4, H-5).

8-Hydroxy-1,1-dimethoxynonane (VI). A solution of 10.1 g ($50.0 \cdot 10^{-3}$ mole) of compound (V)) in 50 ml of abs. methanol was treated with 3 g of Raney nickel [4], and the mixture was stirred in a 100-ml autoclave in an atmosphere of hydrogen (25°C, 80 atm.) until absorption ceased (3 h), and it was then filtered, and the filtrate was evaporated, to give 9.7 g (95%) of the hydroxyacetal (VI), n_D^{22} 1.4423. IR spectrum (ν, cm^{-1}): 1070, 1085 and 1140 (C-O), 3420 (OH). PMR spectrum (60 MHz, CCl_4): 1.05 (d, 3H, J = 6 Hz, H-9), 1.18-1.65 (br.s, 13H, CH_2), 2.95 (m, 1H, OH), 3.17 (s, 6H, OCH_3), 3.55 (m, 1H, H-8), 4.21 (t, 1H, J = 5.5 Hz, H-1).

8RS-Hydroxynonanal (VII). A solution of 2.04 g ($10.0 \cdot 10^{-3}$ mole) of the acetate (VI) in 120 ml of acetone was treated with 3 ml of water and 0.8 g of pyridinium tosylate and was boiled for 2.5 h (Ar). The reaction mixture was evaporated, the residue was dissolved in 100 ml of diethyl ether, and the solution was washed successively with saturated solutions of NH_4Cl, $NaHCO_3$ and NaCl, dried with Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (1:1), to give 1.33 g (84%) of the aldehyde (VII). IR spectrum (ν, cm^{-1}): 1080 (C–O), 1725 and 2735 (CHO), 3420 (OH).

9-Acetoxynon-6E-en-2-one (IX). A mixture of 0.53 g ($3 \cdot 10^{-3}$ mole) of $PdCl_2$, 2.97 g ($30 \cdot 10^{-3}$ mole) of CuCl, 14 ml of DMFA, and 2 ml of water was stirred in an atmosphere of O_2 for 1 h, and then a mixture of 5.46 g ($30 \cdot 10^{-3}$ mole) of the acetate (VIII) (obtained with a yield of 87.4% from the dienoate (IV) according to [6]), 7 ml of DMFA, and 1 ml of water was added. The reaction mixture was stirred in an atmosphere of O_2 for 24 h and then 100 ml of 3 N HCl was added and it was extracted with diethyl ether (5 × 150 ml), and the extract was washed successively with saturated solutions of $NaHCO_3$ and NaCl, and was dried with $MgSO_4$ and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (1:1)), giving 4.4 g (74%) of the acetoxyketone (IX), n_D^{22} 1.4499. IR spectrum (ν, cm^{-1}): 985 and 1660 (E-CH=CH), 1715 (C=O), 1255, 1740 (OAc). PMR spectrum (100 MHz, $CDCl_3$): 1.5-1.85 (m, 2H, H-4), 2.04 (s, 3H, CH_3CO_2), 2.13 (s, 3H, H-1), 1.88-2.55 (m, 6H, H-3, H-5, H-8), 4.07 (t, 2H, J = 6.8 Hz, H-9), 5.35-5.55 (m, 2H, H-6, H-7).

9-Acetoxy-2,2-ethylenedioxynon-6E-ene (X). A mixture of 3.96 g ($20 \cdot 10^{-3}$ mole) of the acetoxyketone (IX), 1.5 g of ethylene glycol, 0.1 g of pyridinium tosylate, and 15 ml of abs. benzene was boiled in a flask fitted with a Dean–Stark trap until the evolution of water ceased (~ 30 h), and then it was diluted with 100 ml of diethyl ether and was washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried with $MgSO_4$, and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (4:1)), and 3.87 g (80%) of the acetoxyacetal (X) was obtained, with n_D^{22} 1.4583. IR spectrum (ν, cm^{-1}): 985 and 1660 (E-CH=CH), 1060, 1075 and 1130 (C–O), 1250 and 1740 (OAc). PMR spectrum (100 MHz, $CDCl_3$): 1.31 (s, 3H, H-1), 1.4-1.8 (m, 4H, H-3, H-4), 2.04 (s, 3H, CH_3CO_2), 1.9-2.5 (m, 4H, H-5, H-8), 3.93 (s, 4H, OCH_2CH_2O), 4.06 (t, 2H, J = 6.8 Hz, H-9), 5.3-5.5 (m, 2H, H-6, H-7).

2,2-Ethylenedioxy-9-hydroxynon-6E-ene (XI). A solution of 1.54 g ($6.4 \cdot 10^{-3}$ mole) of the acetoxyacetal (X) in 7 ml of methanol was treated with 0.4 g of KOH and was boiled for 2 h, and it was then evaporated; the residue was dissolved in 100 ml of diethyl ether, and the solution was washed with saturated NaCl solution, dried with Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (3:7)), giving 1.12 g (88%) of the hydroxyacetal (XI), n_D^{22} 1.4674. IR spectrum (ν, cm^{-1}): 985 and 1660 (E-CH=CH), 1050, 1070 and 1130 (C–O), 3420 (OH). PMR spectrum (100 MHz, $CDCl_3$): 1.31 (s, 3H, H-1), 1.35-1.75 (m, 4H, H-3, H-4), 1.9-2.45 (m, 5H, H-5, H-8, OH), 3.61 (t, 2H, J = 6.3 Hz, H-9), 3.93 (s, 4H, OCH_2CH_2O), 5.3-5.55 (m, 2H, H-6, H-7).

2,2-Ethylenedioxy-9-hydroxynonane (XII). A mixture of 1.0 g ($5.0 \cdot 10^{-3}$ mole) of compound (XI), 15 ml of abs. ethyl acetate, and 0.2 g of Pd–C (5%) was stirred in an atmosphere of hydrogen until the absorption of the gas ceased (~ 10 h), and it was then filtered, and the filtrate was evaporated. This gave 0.92 g (92%) of the hydroxyacetal (XII), n_D^{22} 1.4592. IR spectrum (ν, cm^{-1}): 1050, 1070 and 1130 (C–O), 3420 (OH). PMR spectrum (100 MHz, $CDCl_3$): 1.31 (s, 3H, H-1), 1.2-1.7 (m, 12H, CH_2), 3.2 (s, 1H, OH), 3.62 (t, 2H, J = 6.4 Hz, H-9), 3.93 (s, 4H, OCH_2CH_2O).

8,8-Ethylenedioxynonanal (XIII). At room temperature (Ar) a solution of 0.65 g ($3.22 \cdot 10^{-3}$ mole) of the hydroxyacetal (XII) in 3 ml of CH_2Cl_2 was added to a suspension of 1.03 g ($4.82 \cdot 10^{-3}$ mole) of pyridinium chlorochromate in 10 ml of anhydrous CH_2Cl_2, and the mixture was stirred for 2 h, after which 50 ml of diethyl ether was added, and the solution was decanted off and was filtered through a layer of SiO_2 (5 g) on a porous glass filter. The filtrate was evaporated, giving 0.5 g (78%) of compound (XIII). IR spectrum (ν, cm^{-1}): 1060, 1100, and 1135 (C–O), 1725 and 2735 (CHO).

13-Oxotetradec-57-enoic Acid (XIV). With stirring (Ar, room temperature) a solution of 4.58 g ($25.0 \cdot 10^{-3}$ mole) of sodium hexamethyldisilazide in 10 ml of abs. THF was added to a suspension of 3.33 g ($7.5 \cdot 10^{-3}$ mole) of 4-carboxybutyltriphenylphosphonium bromide in 5 ml of abs. THF, and after 0.5 h the mixture was cooled to −40°C and a solution of 0.5 g ($2.5 \cdot 10^{-3}$ mole) of the aldehyde (XIII) in 3 ml of abs. THF was added; the reaction mixture was stirred for 1 h and then the temperature was raised over 1 h to −10°C, and after 6 hours' standing, 15 ml of water was added (the temperature not being allowed to rise above 10°C). The THF was evaporated off, and the residual aqueous solution was washed with diethyl ether (3 × 10 ml), acidified with 1 N HCl to pH 4, and extracted with diethyl ether (4 × 50 ml). The combined organic extracts were washed with saturated NaCl solution (3 × 20 ml), and evaporated. The residue was dissolved in a mixture of 15 ml of acetone and 0.5 ml of 10% HCl, and after being stirred at 20°C for 6 h, the solution was evaporated.

The residue was extracted with diethyl ether (3 × 50 ml), and the extract was washed with saturated NaCl solution, dried with $MgSO_4$, and evaporated. The new residue was chromatographed (SiO_2, petroleum ether−diethyl ether (2:3)), and gave 0.39 g (65%) of the ketoacid (XIV) in the form of a colorless oil, R_f 0.30 (petroleum ether−diethyl ether (2:3)). IR spectrum (ν, cm^{-1}): 725 (Z-CH=CH), 1710 and 2400-3600 CO_2H, C=O). PMR spectrum (300 MHz, $CDCl_3$): 1.2-1.75 (m, 10H, CH_2), 2.02-2.2 (m, 4H, H-4, H-7), 2.14 (s, 3H, H-14), 2.32-2.47) (m, 4H, H-2, H-12), 5.35-5.48 (m, 2H, H-5, H-6). ^{13}C NMR spectrum (75.45 MHz, $CDCl_3$): (s, C-1), 33.97 (t, C-2), 24.37 (t, C-3), 24.50 (t, C-4), 129.66 (d, C-5, C-6), 26.46 (t, C-7), 33.88 (t, C-8), 24.54 (t, C-9), 28.80 (t, C-10), 23.60 (t, C-11), 43.64 (t, C-12), 209.41 (s, C-13), 28.78 (q, C-14).

13RS-Hydroxytetradec-5Z-enoic Acid (II). a. With stirring (Ar, room temperature) a solution of 3.66 g ($20.0 \cdot 10^{-3}$ mole) of sodium hexamethyldisilazide in 8 ml of abs. THF was added to a suspension of 2.66 g ($76.0 \cdot 10^{-3}$ mole) of 4-carboxybutyltriphenylphosphonium bromide in 4 ml of abs. THF, and the mixture was kept for 0.5 h and was then cooled to −40°C, and a solution of 0.32 g ($2.0 \cdot 10^{-3}$ mole) of the aldehyde (VII) in ∿ 2 ml of abs. THF was added; the resulting reaction mixture was stirred for 1 h and was then heated to −10°C over 1 h and was stirred for 6 h. Then 12 ml of water was added to it (without the temperature being allowed to rise above 10°C). The THF was evaporated off, and the residual aqueous solution was washed with diethyl ether (3 × 10 ml), acidified with 1 N HCl to pH 4, and extracted with diethyl ether (4 × 50 ml).

The combined organic extracts were washed with saturated NaCl solution (3 × 20 ml), dried with $MgSO_4$, and evaporated. The residue was chromatographed (SiO_2, hexane−diethyl ether (1:4)), and 0.116 g (24%) of the hydroxyacid (II) was obtained in the form of a colorless oil, R_f 0.36 (hexane−diethyl ether (1:4)). The purity of the product (according to the results of the capillary GLC of its methyl ester, obtained by treating 0.01 g of (II) with an ethereal solution of CH_2N_2) was not less than 95%. Its IR and PMR spectra were identical with th ose described in the literature [1].

b. At 0°C, 0.125 g ($3.25 \cdot 10^{-3}$ mole) of sodium tetrahydroborate was added to a solution of 0.30 g ($1.25 \cdot 10^{-3}$ mole)) of the ketoacid (XIV) in 5 ml of abs. ethanol and the reaction mixture was stirred for 10 min and was then heated to room temperature, treated with 5% HCl that had been cooled to 0°C, and extracted with diethyl ether (3 × 35 ml). The extract was washed with saturated NaCl solution and was dried with $MgSO_4$, and evaporated. This gave 0.25 g (84%) of the hydroxyacid (II), identical with that obtained in experiment a.

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