LOW-MOLECULAR-MASS BIOREGULATORS.
III. SYNTHESIS OF TRIDEC-4E-ENYL ACETATE - THE SEX PHEROMONE OF *Keiferia lycopersicella*

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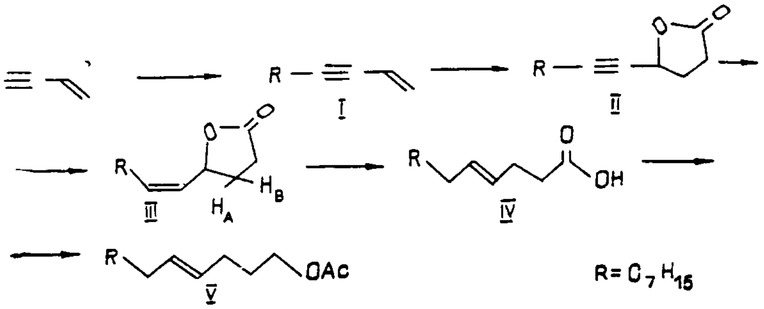
A new method has been developed for the synthesis of tridec-4E-enyl acetate — the sex pheromone of the tomato pinworm Keiferia lycopersicella.

The tomato pinworm is the main pest of tomatoes, damaging both the fruit and the leaves [1, 2]. In the absence of protective measures the losses caused by this pest may reach considerable dimensions. The sex pheromone of the tomato pinworm moth is tridec-E-enyl acetate [3, 4], the use of which in an integrated system of protecting tomatoes is extremely effective under field conditions [2]. We have developed a new method for the synthesis of the sex pheromone of this species by a $C_4 + C_7 + C_2$ scheme, the key stage of which is the one-stage transformation of an alk-5Z-en-4-olide into an alk-4E-enoic acid (hydrogenolysis—migration reaction). The scheme also includes the stages of the radical lactonization of alk-1-en-3-ynes and the stereoselective reduction of alk-5-yn-4-olides, which have been used previously in the synthesis of the sex pheromone of the Japanese beetle [5].

Undec-3-en-3-yne (I), obtained by the alkylation of but-1-en-3-yne with heptyl bromide ($C_4 + C_7$) [6] was brought into reaction with acetic acid (C_2) in the presence of manganese(III) acetate, which played the role of an initiator [7]. The product of the lactonization reaction — tridec-5-yn-4-olide (II) — was reduced with molecular hydrogen in the presence of the tetrahydroborate-reduced P-2 nickel catalyst [8] with the formation of tridec-5Z-en-4-olide (III). The structure of the latter was established on the basis of the results of PMR spectroscopy obtained with the aid of the technique of homonuclear double resonance under the conditions of the successive suppression of all the groups of signals present in the spectrum under review. The Z-configuration of the C_5—C_6 double bond was established on the basis of the SSCC of the vinyl protons (10.86 Hz) and the chemical shift of the H^4 proton (5.19 ppm [5]). We must mention the considerable difference in the chemical shifts of the ring protons 3-H_A and 3-H_B, equal to 0.44 ppm, while the 3-H_A—H^4 and H^4—H^5 spin-spin splitting constants proved to be identical, as was shown by the selective suppression of the 3-H_B signal at 2.32 ppm.



The following stage of the synthesis consisted in the reduction of the lactone (III) with molecular hydrogen in the presence of palladium deposited on barium sulfate [9]. It was found that the reaction took place by the route of the 1,4-addition of a molecule of the reagent to the substrate, accompanied by the hydrogenolysis of the C_4—O bond of the lactone ring and the regio- and sterioselective migration of the double bond into position 4 of the hydrocarbon chain. The reduction product was tridec-4E-enoic acid (IV), the configuration of the double bond of which was established on the basis of SSCC of the vicinal protons, which amounted to 15.9 Hz. The H^4 and H^5 protons, forming an M_2ABX_2 system, were assigned with the aid of the technique of homonuclear double resonance by the selective suppression of the signals at 1.92 ppm (6-CH_2) and 2.26 ppm (3-CH_2).

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The transformation of the lactone (III) into the acid (IV) was effected in the presence of pyridine in a molar ratio of substrate to catalyst of 100:1. In order to select the optimum reaction conditions, a series of experiments was performed which included variations of the temperature of the process and of the amount of pyridine used. In the analysis of the carboxylic acid by the GLC method, the efficacy of separation was insufficiently high because of the asymmetric nature of the peaks and, therefore, for each individual experiment the reduction products were first converted into the corresponding acetates, and these were analyzed by the methods of capillary GLC and GLC-MS. It was shown that:

a) at a molar ratio substrate:catalyst:pyridine of 100:1:60 and a temperature of 20°C the acid (IV) and the product of its complete reduction — tridecanoic acid — were formed in a ratio of 80:20;

b) at the best ratio found of 100:1:80 and a temperature of 20°C, the ratio of (IV) to dihydro(IV) was 96:4;

c) the reaction stopped almost completely when the amount of pyridine was increased further (100:1:100, 20°C); and

d) raising the temperature to 40°C at a ratio of 100:1:60 led to the formation of 28% of the saturated product and 9% of two compounds isomeric with the acid (IV).

On this basis, it was concluded that the optimum parameters of the reaction are a molar ratio of components of 100:1:80 and a temperature of the process of 20°C.

The hydrogenolysis—migration reaction taking place on a palladium catalyst under the action of molecular hydrogen that has been found has a certain analogy in the literature which consists in the reduction of deoxysantonin over palladium deposited on strontium carbonate [10] and that of 2,5-diacetoxy-2,5-dimethylhex-3-yne on the same catalyst deposited on carbon [11].

The concluding stages of the synthesis included the reduction of the acid (IV) with lithium tetrahydroaluminate and subsequent acetylation with acetyl chloride, leading to the desired pheromone — tridec-4-E-enyl acetate (V). The configuration of the double bond of the desired product (V) was established with the aid of homonuclear double resonance by the selective suppression of the 6-CH_2 and 3-CH_2 signals. The spin-spin splitting constant of the vinyl protons was 15.3 Hz and, as with the acid (IV), the signal of the H^5 proton was shifted downfield in relation to the signal of H^4 by 0.09 ppm.

EXPERIMENTAL

PMR spectra were obtained on Perkin—Elmer P-12B (60.0 MHz) and Varian VXR-400 (400 MHz) spectrometers. Chemical shifts are given in ppm (δ scale) relative to TMS, and SSCCs in Hertz. IR spectra were obtained in thin layers on a UR-20 instrument. GLC-MS analysis was performed on an LKB-2091 chromato-mass spectrometer at an energy of the ionizing electrons of 70 eV, and GLC analysis on a Khrom-12 chromatograph with an FID detector. TLC analysis was carried out on Silufol UV-254 plates with $KMnO_4$ as revealing agent. Column chromatography was conducted on silica gel of the type Silicagel L (40-100 μm).

The elementary analyses of the compounds synthesized corresponded to the calculated figures.

Undec-1-en-3-yne (I) was obtained from but-1-en-3-yne and heptyl bromide [6].

Tridec-5-en-4-olide (II). To a solution of 150 g of KOAc in 500 ml of acetic acid were added 26.8 g (0.1 mole) of $Mn(OAc)_3 \cdot 2H_2O$ and 7.5 g (0.05 mole) of (I). The reaction mixture was heated in an atmosphere of N_2 at 115°C until the solution had lost its color (4 h) and was then cooled to 20°C, diluted with H_2O, and extracted with ether, and the extract was dried ($MgSO_4$). The ether was evaporated off in vacuum and the residue was distilled. This gave 3.5 g (33.6%) of (II), bp 118°C (1 mm), n_D^{20} 1.4710.

TLC analysis: R_f 0.58 (hexane—ether 1:1). PMR spectrum (60 Hz, CCl_4): 0.88 (3H, distorted triplet, CH_3), 1.04-1.64 (10H, br.s, $5CH_2$), 1.88-2.26 (6H, m, 2-CH_2, 3-CH_2, 7-CH_2), 4.88-5.22 (1H, m, 4-H). IR spectrum (ν_{max}, cm^{-1}): 2250 (C≡C), 1780 (C=O).

Tridec-5Z-en-4-olide (III). A hydrogenation vessel previously flushed with hydrogen was charged with a suspension of 30 mg (0.12 mmole) of $Ni(OAc)_2 \cdot 4H_2O$ in 2 ml of methanol, a solution of 4.6 mg (0.12 mmole) of $NaBH_4$ in 1 ml of ethanol was added, and the mixture was stirred until the absorption of hydrogen ceased (10 min). Then 0.012 ml of ethylenediamine was added to the reaction mixture and it was stirred for 5 min, 208 mg (1 mmole) of (II) was added, and stirring was continued until the absorption band of the acetylene bond in the UV spectrum had disappeared (5 h). The reaction mixture was filtered through a layer of activated carbon and absorbent cotton, and the filtrate was diluted with ether, washed with H_2O, and dried (Na_2SO_4). The ether was evaporated off in vacuum and the residue was chromatographed on silica gel (4 g, chloroform). This gave 154 mg (73.3%) of (III), n_D^{20} 1.4740.

TLC analysis: R_f 0.70 (chloroform—ether 5:1). PMR spectrum (400 MHz, $CDCl_3$): 0.82 (3H, tr, CH_3, $J_{CH_3\text{-}CH_2}$ = 6.8), 1.21 (8H, br.s, $4CH_2$), 1.33 (2H, m, 8-CH_2), 1.88 (1H, d.tr.d, 3-H_A, $J_{H_AH_B}$ = 13.5), 2.04 (2H, m, 7-CH_2), 2.32 (1H, d.tr.d, 3-

H_B), 2.49 (2H, m, 2-CH_2), 5.19 (1H, tr.d.d, H4, $J_{H^4\text{-}H^5(3\text{-}H_A)}$ = 8.50, $J_{H^4\text{-}3\text{-}H_B}$ = 6.55, $J_{H^4\text{-}H^6}$ = 1.10), 5.39 (1H, d.d.tr, H^5, $J_{H^5\text{-}H^6}$ = 10.86, $J_{H^5\text{-}7\text{-}CH_2}$ = 1.56), 5.61 (1H d.tr.d, H^6, $J_{H^6\text{-}7\text{-}CH_2}$ = 7.63). IR spectrum (ν_{max}, cm^{-1}): 1780 (C=O), 1660 (C=C).

Tridec-4E-enoic Acid (IV). A hydrogenation vessel previously flushed with nitrogen was charged with a solution of 210 mg (1 mmole) of (III) and 63.2 mg (0.8 mmole) of pyridine in 5 ml of methanol; 21.2 mg of 5% $Pd/BaSO_4$ (0.01 mmole of Pd) was added in a current of nitrogen, and the mixture was shaken at 20°C in an atmosphere of hydrogen for 20 h. The end of the reaction was monitored by TLC. The reaction mixture was filtered, and the filtrate was diluted with ether and was washed with H_2O, 15% HCl solution, and H_2O again, and was dried ($MgSO_4$). The ether was evaporated off in vacuum and the residue was filtered through silica gel (4 g, chloroform). This gave 150 mg (70.7%) of (IV), n_D^{25} 1.4520. According to the literature [12]: n_D^{25} 1.4510.

TLC analysis: R_f 0.53 (hexane—ether 1:1). PMR spectrum (400 MHz, $CDCl_3$): 0.83 (3H, tr, CH_3, $J_{CH_3\text{-}CH_2}$ = 7.1), 1.21 (12H, br.s, 6CH_2), 1.92 (2H, q, 6-CH_2, $J_{6\text{-}CH_2\text{-}7\text{-}CH_2(H^5)}$ = 6.8), 2.26 (2H, m, 3-CH_2), 2.35 (2H, m, 2-CH_2), 5.34 (1H, d.tr, H^4, $J_{H^4\text{-}H^5}$ = 15.9, $J_{H^4\text{-}3\text{-}CH_2}$ = 6.6), 5.43 (1H, d.tr, H^5). IR spectrum (ν_{max}, cm^{-1}): 3600-2500 (O—H), 1710 (C=O).

Tridec-4E-enyl Acetate (V). A solution of 110 mg (0.52 mmole) of (IV) in 5 ml of absolute ether was added to a suspension of 22.6 mg (0.78 mmole) of $LiAlH_4$ at such a rate as to ensure the gentle boiling of the ether. After the end of addition, the reaction mixture was boiled for 30 min and was then cooled to 10°C and 0.03 ml of H_2O, 0.3 ml of 15% NaOH solution, and 0.09 ml of H_2O were added dropwise. The ethereal solution was decanted off and dried ($MgSO_4$). The ether was evaporated off and the residue was dissolved in 15 ml of absolute ether; this solution was treated with 105 mg (1.04 mmoles) of triethylamine and cooled to −10°C after which 82 mg (1.04 mmoles) of AcCl was added dropwise. The reaction mixture was warmed to 20°C and was stirred for 1 h (with TLC monitoring) after which it was made weakly acid with dilute HCl and was extracted with ether. The ethereal extract was washed with H_2O and dried ($MgSO_4$). The ether was evaporated off in vacuum and the residue was chromatographed on silica gel (3 g, hexane—ether, 4:1). This gave 94 mg (75.2%) of (V), n_D^{22} 1.4440. TLC analysis: R_f 0.71 (hexane—ether, 1:1).

GLC analysis (capillary, glass, 0.25 mm × 50 m, XE-60, 160°C): 96% of (V) and 4% of tridecyl acetate, GLC-MS analysis (capillary, glass, 0.25 mm × 25 m, SE-30, 125°C): m/z (%): (V) 180 ($M^+ - CH_3COOH$, 2798), 152 (684), 138 (657), 124 (985), 123 (846), 110 (1517), 111 (1713), 97 (1133), 96 (4116), 95 (4085), 83 (2396), 82 (7392), 81 (7101), 70 (679), 69 (2999), 68 (10,000), 67 (7960), 66 (793), 57 (1319), 56 (612), 55 (4698), 54 (4865), 53 (778); triphenyl acetate 182 ($M^+ - CH_3COOH$). PMR spectrum (400 Hz, $CDCl_3$): 0.83 (3H, tr, CH_3, $J_{CH_3\text{-}CH_2}$ = 7.1), 1.21 (14H, br.s, 7CH_2), 1.92 (2H, q, 6-CH_2, $J_{6\text{-}CH_2\text{-}7\text{-}CH_2(H^5)}$ = 6.8), 1.99 (3H, s, CH_3CO), 1.95-2.05 (2H, m, 3-CH_2), 4.0 (2H, t, OCH_2, $J_{CH_2\text{-}2\text{-}CH_2}$ = 7.6), 5.25-5.35 (1H, m, H^4), 5.39 (1H, d.tr, H^5, $J_{H^5H^6}$ = 15.3). IR spectrum (ν_{max}, cm^{-1}): 1740 (C=O).

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