SYNTHESIS OF (±)-cis-TETRADEC-5-EN-4-OLIDE — THE RACEMATE OF THE SEX PHEROMONE OF THE JAPANESE BEETLE

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A three-stage method has been developed for the stereoselective synthesis of (±)-cis-tetradec-5-en-4-olide — the racemate of the sex pheromone of the Japanese beetle *Popillia japonica* C. The key reactions used were the stereoselective cis reduction of a triple bond with the aid of heterogeneous hydrogenation catalysts (zinc—copper couple, nickel boride, Lindlar catalyst) and the radical lactonization of conjugated systems by the action of acetic acid in the presence of manganese acetate.

The Japanese beetle *Popillia japonica* C, is a polyphage attacking more than 275 species of plants [1, 2]. It is distributed in Japan, Northern India, the USA, Canada, and the Kurile Islands. In the USSR it is classified as an object of external quarantine [1]. The sex pheromone was isolated from female Japanese beetles by Tumlinson in 1977 and was identified as R-(—)-cis-tetradec-5-en-4-olide [3]. Recently, various approaches to the synthesis of the desired compound have been developed which consist in the use of the corresponding optically active starting material [3], the separation of chiral intermediate compounds in the form of diastereomers [4, 5], and the asymmetric synthesis of the precursors of the sex hormone with the aid of chiral reducing agents [6–8]. An alternative approach may be the synthesis of racemic (±)-cis-tetradec-5-en-4-olide with the subsequent isolation of the individual enantiomers by the reaction of the racemate with suitable optically active amines [9]. However, only multistage methods for obtaining the desired racemate have been described in the literature [3, 4]. The aim of the present work was to develop a suitable method of synthesizing racemic (±)-cis-tetradec-5-en-4-olide.

We have investigated two alternative routes for the synthesis of the desired products from dodec-1-en-4-yne, which was selected as the starting compound. The first route includes the stages of the stereoselective cis-reduction of the triple bond with the aid of heterogeneous hydrogenation catalysts and radical lactonization by the action of carbonyl compounds in the presence of manganese(III) acetate. The second route consists of the same two stages performed in the reverse order.

The reduction of dodec-1-en-3-yne (I) to cis-dodeca-1,3-diene (II) was carried out by the action of zinc—copper couple by a modified procedure [10]. The stereochemical assignment was made by comparing the ^{13}C NMR spectrum of compound (II) with the corresponding spectrum of model compounds — cis- and trans-dodeca-9,11-dienyl acetates [11]. It was found that the chemical shifts of the C_2 and C_3 atoms had the greatest diagnostic value. The signals of the corresponding C_{11} and C_{10} atoms in cis-dodeca-9,11-dienyl acetate appear at 132.6 and 129.1 ppm, and in trans-dodeca-9,11-dienyl acetate, at 137.1 and 135.2 ppm [11]. The chemical shifts of the C_2 and C_3 atoms of compound (II) were 133.06 and 129.24 ppm, which permits the unambiguous assignment of the cis configuration to this compound. It must be mentioned that the signals corresponding to the trans isomer, expected in the 135-137 ppm region, were not detected in the spectrum of compound (II), which indicates a high stereoselectivity of this method of hydrogenation. (See scheme on following page.)

The lactonization of compound (II) was carried out by the action of acetic acid in the presence of manganese(III) acetate by a procedure described in the literature [12, 13]. The

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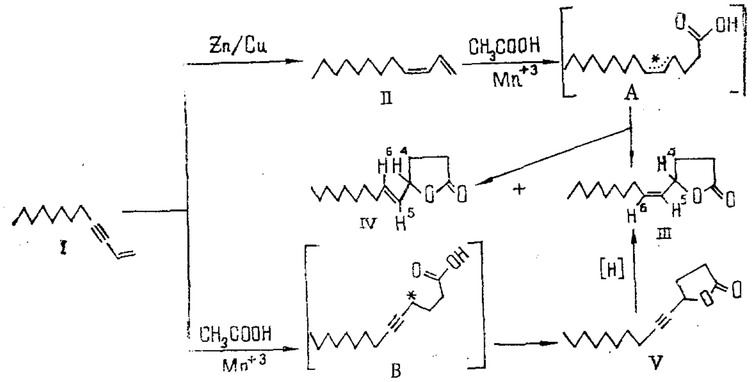

reaction gave tetradec-5-en-4-olide as a mixture of the geometric isomers (III) and (IV) in a ratio of 56:44. The formation of the latter can be explained by the assumption that in the allyl intermediate (A) formed as the result of the addition of the carboxymethyl radical to the terminal double bond, rotation takes place around the C_5—C_6 bond preceding cyclization at the carboxy group. It must be particularly noted that by this reaction the possibility of the inversion of a cis double bond in the reaction of an alka-1,3-diene with a carbon compound in the presence of trivalent manganese acetate has been shown for the first time [14, 15]. We have marked the allyl intermediate (A) with an asterisk in view of the fact, which is not obvious, that either the formation of the lactone ring takes place as the result of the cyclization of an allyl radical or the latter is first oxidized by the manganese (III) acetate to the allyl carbocation [16].

A detailed analysis of the PMR spectra of compounds (III) and (IV) showed that the chemical shifts of the H^4, H^5, and H^6 protons depend in different ways on the geometry of the C_5—C_6 double bond. Thus, the signals of the H^5 and H^6 protons shift downfield by 0.05 and 0.15 ppm, respectively, on passing from (III) to (IV). Conversely, the H^4 proton in the cis isomer (III) gives a signal at 5.21 ppm and in the trans isomer (IV) at 4.86 ppm, i.e., an upfield shift by 0.35 ppm takes place. This fact may apparently have diagnostic value for distinguishing geometric isomers of alk-5-en-4-olides.

It must be mentioned that trans-tetradec-5-en-4-olide (IV) is a natural compound which has been isolated together with cis-tetradec-5-en-5-olide (III) from female Japanese beetles [3].

The formation of a mixture of geometric isomers of tetradec-5-en-4-olide in the synthetic route considered above induced us to develop an alternative method including the radical lactonization of dodec-1-ene-3-yne followed by the selective hydrogenation of the triple bond of tetradec-5-yn-4-olide.

The lactonization of dodec-1-ene-3-yne (I) was performed by the action of acetic acid in the presence of trivalent manganese acetate [13]. The reaction gave tetradec-5-yn-4-olide (V), formed by the cyclization of the propargyl intermediate (B) at the carboxy group. Compound (V) has been described previously as a precursor of the sex pheromone of the Japanese beetle [3, 4, 7, 8], the cis-hydrogenation in the concluding stage being performed in the presence of a Lindlar catalyst. The conditions of the reduction reaction are given in only one paper, and in this case palladium on barium sulfate poisoned with quinoline [4] was used and the yield of the sex pheromone amounted to 28%. We have performed the hydrogenation of compound (V) in the presence of the P-2 Ni catalyst [17]. The product — cis-tetradec-5-en-4-olide (III) was isolated by column chromatography on silica gel with a yield of 75%. The cis configuration of the double bond was determined with the aid of PMR spectroscopy, the spin-spin coupling constant of the vinyl protons amounting to 10.8 Hz. It must be mentioned that this reaction indicates the suitability of the P-2 Ni catalyst for the selective cis hydrogenation of alk-5-yn-4-olides.

The reduction of compound (V) was also carried out in the presence of a Lindlar catalyst — palladium on barium sulfate poisoned with pyridine [18]. In this case, (III) was isolated by column chromatography with a yield of 70%.

EXPERIMENTAL

PMR spectra were obtained on Bruker WM-250 (250.0 MHz) and Perkin-Elmer R-12B (60.0 MHz) spectrometers, and ^{13}C NMR spectrum on a Bruker WH-90 spectrometer (22.63 MHz) under conditions of complete suppression of spin-spin coupling. The chemical shifts are given in ppm (δ scale) relative to TMS, and the SSCCs in Hz. The IR spectra of the pure substances were obtained in a thin layer on a UR-20 instrument. GLC analysis was performed on a Tsvet-104 chromatograph under the following conditions: column No. 1, glass, 2 m × 3 mm, containing 3% of PDEAS on Chromaton N Super (0.125-0.160 mm), FID, nitrogen; and column No. 2, steel, 2 m × 3 mm, containing 15% of Apiezon L on Chromaton N-AW-DMCS (0.125-0.160 mm), katharometer, helium. Compound (III) was analyzed on an LKB-2091 chromato-mass spectrometer with a glass capillary column (50 m × 0.3 mm) containing SE-30 (column No. 3) under temperature-programmed conditions. The mass spectrum of compound (III) was obtained on a MKh-1303 spectrometer with an energy of the ionizing electrons of 70 eV.

Dodec-1-en-3-yne (I). This was obtained from vinylacetylene and octyl iodide with 73% yield [19].

cis-Dodeca-1,3-diene (II). With vigorous stirring, a solution of 7.5 g of $CuCl_2 \cdot 2H_2O$ in 37.5 ml of water was added to a suspension of 30 g of zinc dust in 10 ml of water heated to the boil. The dark gray precipitate that had formed was washed with water (2 × 50 ml), and then a solution of 42 g of caustic potash in 250 ml of water was added and the mixture was heated at 90°C for 40 min. The catalyst so obtained was washed with water to neutrality, and then 100 ml of a 33% aqueous solution of 2-propanol was added and was heated to the boil (25°C), 11.0 g (0.067 mole) of (I) was added, and heating was then continued at 85°C for 2.5 h. The reaction was monitored by GLC. After the disappearance of the starting material, the reaction mixture was cooled and filtered. The catalyst was washed with 2-propanol (2 × 30 ml) and with pentane (1 × 30 ml). The organic layer was separated off and the aqueous layer was extracted with pentane (2 × 30 ml). The combined extracts were dried ($MgSO_4$), the pentane was evaporated off in vacuum, and the residue was distilled. This gave 10.2 g (91.7%) of (II), $C_{12}H_{22}$, bp 58-59°C (1 mm), n_D^{20} 1.4610. GLC analysis: column No. 1, 113°C, 35 ml/min, t_{ret} 19.3 min. PMR spectrum (60.0 MHz, CCl_4): 0.87 (3H, tr, CH_3, $J_{CH_3-CH_2} = 6.0$), 1.27 (12H, br,s, $6CH_2$), 2.12 (2H, d.tr, 5-CH_2, $J_{5-CH_2-6-CH_2(H^4)} = 7.0$), 4.95-6.94 (5H, m, $CH{=}CHCH{=}CH_2$). ^{13}C NMR spectrum ($CHCl_3$): 14.11 (C_{12}), 22.74 (C_{11}), 27.81, 29.35 (2), 29.56, 29.71, 31.97 (C_5–C_{10}), 116.64 (C_1), 129.24 (C_3), 132.45 (C_4), 133.06 (C_2). IR spectrum, cm^{-1}: 3090 (w), 3015 (w), 2950 (s), 2870 (s), 1795 (w), 1635 (m), 1586 (m), 1465 (s), 1432 (s), 1375 (m), 1002 (s), 965 (m), 910 (s), 792 (m), 730 (m). Mass spectrum: M^+ 166.

cis- and trans-Tetradec-5-en-4-olides (III) and (IV). To a solution of 54.0 g of potassium acetate in 180 ml of acetic acid were added 9.6 g (0.036 mole) of $Mn(OAc)_3 \cdot 2H_2O$ and 3.0 g (0.018 mole) of (II). The reaction mixture was heated in an atmosphere of nitrogen at 115°C until the solution had lightened in color (6 h), and it was then cooled to room temperature, washed with water, and extracted with ether. The ethereal extract was treated with an aqueous solution of Na_2CO_3 and with water and was dried (Na_2SO_4). The ether was evaporated off in vacuum, giving 2.97 g of crude product. Compounds (III) and (IV) were isolated by chromatography on silica gel (30 g, 40/100 μm) with hexane–ether (1:1) as the eluent (250 ml). From 1.0 g was obtained 0.61 g (45%) of (III) and (IV) with n_D^{20} 1.4663. The (III):(IV) ratio determined from the PMR spectrum by integration of the 5.21 and 4.86 ppm signals, respectively, amounted to 56:44. The PMR spectrum of (IV), determined from the spectrum of the mixture of (III) and (IV) (250.0 MHz, $CDCl_3$, ppm) was: 4.86 (1H, q.d, H^4, $J_{H^4-3-CH_2(H^5)} = 7.3$, $J_{H^4-H^6} = 0.9$), 5.46 (1H, d.d.tr, H^5, $J_{H^5-H^6} = 15.3$, $J_{H^5-7-CH_2} = 1.5$), 5.77 (1H, d.tr.d, H^6, $J_{H^6-7-CH_2} = 7.0$). The other signals coincided with the corresponding signals of compound (III).

Tetradec-5-yne-4-olide (V). Similarly, a mixture of 150.0 g of potassium acetate in 500 ml of acetic acid, 26.8 g (0.1 mole) of $Mn(OAc)_3 \cdot 2H_2O$, and 8.2 g (0.05 mole) of (I) was heated at 115°C for 4 h and was worked up. Two distillations gave 5.7 g (51.3%) of (V), $C_{14}H_{22}O_2$, bp 130°C (1 mm), n_D^{20} 1.4710. According to the literature [4]: bp 122-124°C (0.35 mm); n_D^{20} 1.4700. GLC analysis: column No. 2, 220°C, 50 ml/min, t_{ret} 18.0 min. PMR spectrum (250.0 MHz, CCl_4, ppm): 0.89 (3H, tr, CH_3, $J_{CH_3-CH_2} = 6.0$), 1.28 (8H, br.s, $4CH_2$), 1.36 (2H, m, 9-CH_2), 1.52 (2H, quintet, 8-CH_2, $J_{8-CH_2-7(9)-CH_2} = 6.0$), 2.23 (3H, tr.d, 7-$CH_2$, $J_{7-CH_2-H^4} = 1.5$), 2.25, 2.65 (2H, m 3-CH_2), 2.46-2.56 (2H, m; 2-CH_2), 5.13 (1H, tr.tr, H^4, $J_{H^4-3-CH_2} = 6.0$). IR spectrum, cm^{-1}: 1780 (lactone carbonyl), 2250 (C≡C).

cis-Tetradec-5-en-4-olide (III). A. A hydrogenation vessel previously flushed with nitrogen was charged with a suspension of 150 mg (0.0006 mole) of $Ni(OAc)_2 \cdot 4H_2O$ in 5.4 ml of ethanol, and then a solution of 23 mg (0.0006 mole) of $NaBH_4$ in 2 ml of ethanol was added and the mixture was stirred until the evolution of hydrogen ceased (10 min). After this, 0.06 ml of ethylenediamine and 1.1 g (0.005 mole) of (V) were added and the reaction mixture was stirred until the absorption band of an acetylenic bond had disappeared from the IR spectrum (4.5 h). The mixture was filtered through a layer of activated carbon and absorbent cotton, and the filtrate was diluted with ether, washed with water (3 × 10 ml) and dried (Na_2SO_4). The ether was evaporated off in vacuum and the residue (1.06 g) was chromatographed on silica gel (30 g, 40/100 μm) with hexane–ether (2:1) as eluent (250 ml). The separation was monitored by GLC. This gave 0.84 g (75%) of (III), $C_{14}H_{24}O_2$, n_D^{20} 1.4660. According to the literature [4]: n_D^{20} 1.4663. GLC analysis: column No. 3, 100°C (2 min) → 4°C/min → 210°C, t_{ret} 29 min. PMR spectrum (250.0 MHz, $CDCl_3$): 0.84 (3H, tr, CH_3, $J_{CH_3-CH_2}$ = 7.2), 1.23 (10H, br.s, 5 CH_2), 1.32 (2H, m, 8-CH_2), 1.91 (1H, d.d.tr, 3-H_B, $J_{H_A-H_B}$ = 13.3, $J_{H_B-H^4}$ = 8.4, $J_{H_B-2-CH_2}$ = 6.3), 2.34 (1H, d.q, 3-H_A, $J_{H_A-H^4}$ = 8.4, $J_{H_A-2-CH_2}$ = 8.4), 2.07 (2H, m, 7-CH_2), 2.52 (2H, d.d, 2-CH_2), 5.21 (1H, tr.d.d, H^4, $J_{H^4-H^5}$ = 6.5, $J_{H^4-H^6}$ = 1.0), 5.41 (1H, d.d.tr, H^5, $J_{H^5-H^6}$ = 10.8, $J_{H^5-7-CH_2}$ = 1.5), 5.63 (1H, d.tr.d, H^6, $J_{H^6-7-CH_2}$ = 7.5).

Mass spectrum, m/z (%): M^+ 224 (7.3), 126 (28.3), 111 (100.0), 98 (22.5), 85 (24.9), 81 (39.0), 67 (25.7), 55 (34.4), 43 (23.9), 41 (38.8), 29 (24.3).

B. A solution of 1.1 g (0.005 mole) of (V) in 25 ml of methanol containing 0.5 ml of pyridine was stirred at room temperature in an atmosphere of hydrogen in the presence of 175 mg of 5% $Pd/BaSo_4$ [20] until the absorption band of an acetylenic bond disappeared from the IR spectrum (4 h). The reaction mixture was filtered, and the filtrate was diluted with ether (20 ml), washed with water (3 × 15 ml), with 20% H_2SO_4 solution (15 ml), and again with water (2 × 10 ml), and was dried (Na_2SO_4). Ether was evaporated off in vacuum and the residue (1.09 g) was chromatographed on silica gel (50 g, 40/100 μm) with hexane–ether (2:1) as eluent (260 ml). Separation was monitored by GLC. This gave 0.79 g (70.2%) of (III).

SUMMARY

1. A three-stage method for the stereoselective synthesis of (±)-cis-tetradec-5-en-4-olide – the racemate of the sex pheromone of the Japanese beetle – has been developed.

2. Inversion of a cis double bond in the radical lactonization of an alka-1,3-diene has been detected.

3. The applicability of P-2 Ni catalyst for the selective hydrogenation of alk-5-yne-4-olides has been demonstrated.

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