GLYCALS IN STEREOCHEMICAL SYNTHESIS

SYNTHESIS OF (14R,8Z)-TROGODERMAL AND ITS (14S,8Z)-ENANTIOMER FROM DI-O-BENZOYL-D- AND -L-ARABINALS

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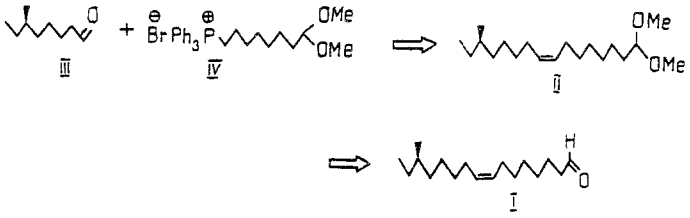
UDC 547.917+547.458+547.313

Enantiomerically pure (14R)-14-methylhexadeca-8Z-enal (cis-trogodermal) – the aggregation pheromone of the khapra beetle (Trogoderma) – and its (14S,8Z)-enantiomer has been effected from di-O-benzoyl-D- and -L-arabinals.

Chiral sources that have been used in stereocontrolled syntheses of the aggregation pheromone of dermestid beetles of the genus Trogoderma, (14R,8Z)-trogodermal [1-3] and its (14S,8Z)-enantiomer [4-6], are R-(+)-citronellol [1], S-(−)-β-methylpropiolactone [2], (R)-1-bromo-4-methylhexane [3], R-(+)-pulegone [4], S-(−)-citronellol [5], and (S)-2-methylbutan-1-ol [6].

We have developed a new approach to the synthesis of optically pure (14R,8Z)-trogodermal (I), according to which the passage to the chiral synthon (III) is made from di-O-benzoyl-D-arabinal (V). The coupling of the aldehyde (III) with the achiral synthon (IV) by the Wittig reaction gave the acetal precursor (II) of the pheromone (I).



The scheme of synthesis of the desired pheromone included the following stages. The glycal (V) was converted into methyl (6S)-6,7-epoxyhepta-2E,4E-dienoate (VI) according to [7].* The opening of the terminal epoxide ring in (VI) with lithium acetylide, performed by the method of [8], took place regiospecifically with attack on the C^6 atom and led to methyl (6S)-6-hydroxymethylocta-2,4-dien-7-ynoate (VII) with a yield of 65%.† An unambiguous confirmation of just this direction of coupling through the epoxide ring is given by the doublet (δ 38.20 ppm) and triplet (δ 65.13 ppm) of carbon atoms linked with ethynyl and hydroxy groups, respectively (see top of following page).

The exhaustive hydrogenation of the double bonds in compound (VII) gave the hydroxy ester (VIII), which was converted into the tosylate (IX) the treatment of which with lithium tetrahydroaluminate led in one stage to (6R)-6-methyloctanol (X). Oxidation of the alcohol (X) by pyridinium chlorochromate gave the chiral synthon (III), the yield of which in the four stages of the transformation of compound (VII) amounted to 38%. The achiral synthon (IV) required for the pheromone (I) was prepared from 8-bromooctanol (XI) [9, 10]. For this, the latter was oxidized and the resulting aldehyde (XII) was converted into the acetal (XIII),

*In [7] the products of the transformation of L-arabinal were assigned to the R series.
†Because the addition of the acetylenic nucleophile at the asymmetric C-6 atom on the opening of the epoxide changes the order of seniority of the substituents, the latter retains the S configuration.

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Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 707-712, September-October, 1991. Original article submitted December 13, 1990.

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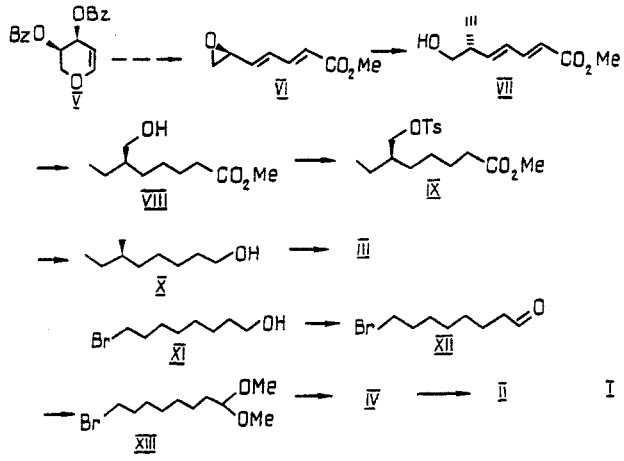
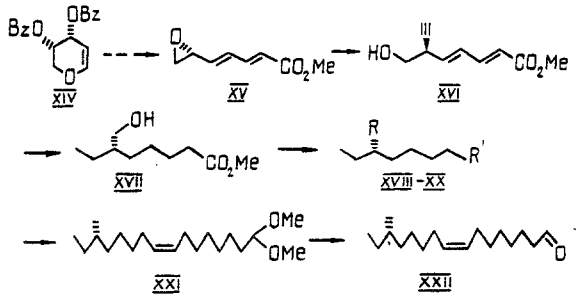


the heating of which with triphenylphosphine in acetonitrile gave the synthon (IV). The coupling of the ylide generated from the phosphonium bromide (IV) with the chiral aldehyde (III) and the subsequent mild hydrolysis of the acetal (II) completed the synthesis of the desired pheromone. According to HPLC and capillary GLC, the amount of the 8E-isomer present did not exceed 5%. The individual (14R,8Z)-trogodermal (I) was isolated by the HPLC method.

The (14S,8Z)-enantiomer (XXII) was synthesized from di-O-benzoyl-L-arabinal by the scheme developed, via the intermediate compounds (XV-XXI). The overall yields of the pheromone (I) and its enantiomer (XXII) calculated on the initial arabinals (V) and (XIV) were 0.8 and 0.7%, respectively.



R = CH_2OTs (XVIII), CH_3 (XIX, XX); R' = CO_2Me (XVIII), CH_2OH (XIX), CHO (XX).

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 instrument with working frequencies of 300 and 75 MHz, respectively, the solvent being $CDCl_3$ and the internal standard TMS. Specific angles of rotation were measured on a Perkin–Elmer 241 MC polarimeter. GLC analysis was conducted on a Shimadzu-9A chromatograph (Japan) in a glass capillary column (0.2 mm × 25 m) with the liquid phase PEG-20M. The HPLC of the desired pheromones (I) and (XXII) was performed on a Du Pont instrument (USA) with an R-401 refractometer, using a Zorbax-Sil 4 mm × 250 mm column for analysis and a 21.2 mm × 250 mm column for separation, with hexane–acetone (0-0.4%). Silica gel L 40/100 μm (Chemapol, Czechoslovakia) was used for column chromatography. The results of the analysis of all the compounds agreed with the calculated figures.

Methyl (6S)-6-Hydroxymethylocta-2E,4E-dien-7-ynoate (VII). A current of dry acetylene was passed at the rate of 7 ml/min for 15 min through a mixture of 2.8 ml ($4.8 \cdot 10^{-3}$ mole) of a 1.78 N solution of n-C_4H_9Li in hexane and 10 ml of anhydrous THF cooled to −78°C. Then 0.63 ml ($5.1 \cdot 10^{-3}$ mole) of freshly prepared $BF_3 \cdot (C_2H_5)_2O$ was added, the mixture was stirred for 10 min, and 0.5 g ($3.2 \cdot 10^{-3}$ mole) of the epoxide (VI) was added and stirring was continued at −78°C for 30 min. The temperature of the reaction mixture was raised to 0°C and it was diluted with 5 ml of saturated NH_4Cl solution, and then the organic layer was separated off, and the aqueous layer was extracted with ether (4 × 10 ml). The combined extracts were dried with Na_2SO_4 and evaporated, and the residue was chromatographed [SiO_2, hexane–ethyl acetate (7:3)]. This gave 0.37 g (65%) of compound (VII) in the form of a yel-

low oil, R_f 0.28, $[\alpha]_D^{23}$ +75.6° (c 0.58; $CHCl_3$). PMR spectrum (δ, ppm): 2.01 (1H, br.s, OH), 2.38 (1H, d, J = 2.3 Hz, CH-8), 3.48 (1H, m, CH-6), 3.69 (1H, dd, J_{gem} = −10.7 Hz, J_{vic} = 5.5 Hz, CH_2OH), 3.75 (1H, dd, J_{gem} = −10.7 Hz, J_{vic} = 5.9 Hz, CH_2OH), 5.92 (1H, d, $J_{2,3}$ = 15.4 Hz, CH-2), 6.06 (1H, dd, $J_{5,4}$ = 15.2 Hz, $J_{5,6}$ = 6.05 Hz, CH-5), 6.55 (1H, dd, $J_{3,2}$ = 15.2 Hz, $J_{3,4}$ = 11.0 Hz, CH-3), 7.28 (1H, dd, $J_{4,3}$ = 11.0 Hz, $J_{4,5}$ = 15.2 Hz, CH-4). ^{13}C NMR spectrum (δ, ppm): 38.20 d (C-6), 51.40 q (OCH_3), 65.13 t (CH_2OH), 73.41 d (C-8), 81.16 s (C-7), 121.96 d (C-2), 130.79 d (C-4), 137.08 d (C-5), 143.14 d (C-3), 166.05 s (C-1).

Methyl (6R)-6-Hydroxymethylocta-2E,4E-dien-7-ynoate (XVI). From 0.5 g ($3.2 \cdot 10^{-3}$ mole) of the epoxide (XV) was obtained 0.42 g (72%) of compound (XVI) in the form of a yellow oil, $[\alpha]_D^{20}$ −75.2° (c 0.62; $CHCl_3$). Its PMR and ^{13}C NMR spectra were identical with those of (VII).

Methyl (6R)-6-Hydroxymethyloctanoate (VIII). A mixture of 0.3 g ($1.6 \cdot 10^{-3}$ mole) of compound (VII), 0.05 g of 10% Pd/C, and 10 ml of anhydrous MeOH was hydrogenated at 25°C for 12 h. Then it was filtered, the filtrate was evaporated, and the residue was chromatographed [SiO_2, hexane–ethyl acetate (7:3)]. This gave 0.29 g (95%) of compound (VIII) in the form of a light yellow oil, R_f 0.25, $[\alpha]_D^{20}$ +2.2° (c 0.65; $CHCl_3$). PMR spectrum (δ, ppm): 0.91 (3H, t, J = 7.3 Hz, CH_3-8), 1.29-1.52 (6H, m, CH_2-3–CH_2-5), 1.58-1.72 (4H, m, CH-6, CH_2-7, OH), 2.32 (2H, t, J = 7.4 Hz, CH_2-2), 3.35 (2H, d, J = 5.0 Hz, CH_2O), 3.69 (3H, s, OCH_3).

Methyl (6S)-6-Hydroxymethyloctanoate (XVII). From 0.3 g ($1.6 \cdot 10^{-3}$ mole) of compound (XVI) was obtained 0.28 g (93%) of the hydroxy ester (XVII) in the form of a light yellow oil, $[\alpha]_D^{20}$ −2.0° (c 0.6; $CHCl_3$). Its PMR spectrum was identical with that of (VIII).

Methyl (6R)-6-Tosyloxymethyloctanoate (IX). A mixture of 0.2 g ($1.1 \cdot 10^{-3}$ mole) of compound (VIII), 0.3 g ($1.5 \cdot 10^{-3}$ mole) of TsCl, and 10 ml of anhydrous pyridine was stirred at room temperature for 24 h. Then it was diluted with 10 ml of ethyl acetate and was washed with 10% HCl (2 × 10 ml) and with H_2O (2 × 5 ml), the organic layer was dried with $MgSO_4$ and evaporated, and the residue was chromatographed [SiO_2, hexane–ethyl acetate (1:1)]. This gave 0.28 g (76%) of the tosylate (IX) in the form of a colorless oil, R_f 0.62, $[\alpha]_D^{20}$ −2.65° (c 1.63; $CHCl_3$). PMR spectrum (δ, ppm): 0.82 (3H, t, J = 7.4 Hz, CH_3-8), 1.15-1.39 (6H, m, CH_2-3–CH_2-5), 1.48-1.60 (3H, m, CH-6, CH_2-7), 2.25 (2H, t, J = 6.8 Hz, CH_2-2), 2.45 (3H, s, CH_3Ph), 3.69 (3H, s, OCH_3), 3.92 (2H, d, J = 5.3 Hz, CH_2-O), 7.32 (2H, d, J = 8 Hz, Ph), 7.79 (2H, d, J = 8 Hz, Ph). ^{13}C PMR spectrum (δ, ppm): 10.78 q (C^8), 21.64 q (CH_3Ph), 23.25 t (C-5), 25.07 t (C-4), 26.06 t (C-7), 29.91 t (C-3), 33.92 d (C-6), 39.01 (C-2), 51.49 (OCH_3), 72.33 t (CH_2O), 127.73 d, 129.72 d, 133.25 s, 144.69 s (6C, Ph), 174.01 s (C-1).

Methyl (6S)-6-Tosyloxymethyloctanoate (XVIII). From 0.15 g ($7.9 \cdot 10^{-4}$ mole) of the hydroxy ester (XVII) was obtained 0.19 g (72%) of compound (XVIII) in the form of a colorless oil, $[\alpha]_D^{21}$ +2.6° (c 1.6; $CHCl_3$). Its PMR and ^{13}C NMR spectra were identical with those of (IX).

(6R)-6-Methyloctan-1-ol (X). A solution of 0.2 g ($5.8 \cdot 10^{-4}$ mole) of the tosylate (IX) in 5 ml of anhydrous diethyl ether was treated with 0.08 g ($2.3 \cdot 10^{-3}$ mole) of $LiAlH_4$. The mixture was stirred at room temperature for 2 h and was diluted with 10 ml of diethyl ether, and, after the careful dropwise addition of 5 ml of water, it was filtered. The organic phase was separated off, and the aqueous phase was extracted with ether (3 × 5 ml). The combined extracts were dried with Na_2SO_4 and evaporated, and the residue was chromatographed [SiO_2, hexane–ethyl acetate (1:1)]. This gave 0.07 g (79%) of compound (X) in the form of a colorless oil, R_f 0.52, $[\alpha]_D^{25}$ −7.95° (c 1.9; $CHCl_3$). PMR spectrum (δ, ppm): 0.84 (3H, d, J = 6.4 Hz, CH_3–C-6), 0.87 (3H, t, J = 6.4 Hz, CH_3-8), 1.02-1.42 (8H, m, CH_2-2–CH_2-5), 1.52-1.65 (3H, m, CH-6, CH_2-7), 1.87 (1H, br.s, OH), 3.62 (2H, t, J = 6.8 Hz, CH_2-1). ^{13}C NMR spectrum (δ, ppm): 11.39 q (C-8), 19.24 q (CH_3), 26.17 t (C-3), 26.96 t (C-7), 29.53 t (C-4), 32.91 t (C-2), 34.51 t (C-5), 36.63 (C-6), 63.03 t (C-1).

(6S)-6-Methyloctan-1-ol (XIX). From 0.2 g ($5.8 \cdot 10^{-4}$ mole) of the tosylate (XVIII) was obtained 0.059 g (70%) of compound (XIX) in the form of a colorless oil, $[\alpha]_D^{25}$ +8.1° (c 1.9; $CHCl_3$). Its PMR and ^{13}C NMR spectra were identical with those of (X).

(6R)-6-Methyloctanal (III). A solution of 0.05 g ($3.5 \cdot 10^{-4}$ mole) of the alcohol (X) in 2 ml of anhydrous CH_2Cl_2 cooled to 0°C was treated with 0.11 g ($5.2 \cdot 10^{-4}$ mole) of the complex $PyHCrO_3Cl$ and 0.022 g ($5.2 \cdot 10^{-4}$ mole) of AcONa and was stirred at 0°C for 0.5 h and then at room temperature for 0.5 h and was filtered; the filtrate was evaporated, and the residue was chromatographed [SiO_2, hexane–ether (7:2)]. This gave 0.03 g (68%) of the aldehyde (III) in the form of a light yellow oil, R_f 0.43, $[\alpha]_D^{23}$ −2.87° (c 0.7; $CHCl_3$). PMR spectrum (δ, ppm): 0.84 (3H, d, J = 6.4 Hz, CH_3C-6), 0.87 (3H, t, J = 6.4 Hz, CH_3-8), 1.05-1.41 (6H, m, CH_2-3–CH_2-5), 1.49-1.71 (3H, m, CH-6, CH_2-7), 2.42 (2H, m, CH_2-2), 9.75 (1H, t, J = 1.7 Hz, CH-1).

(6S)-6-Methyloctanal (XX). From 0.05 g ($3.5 \cdot 10^{-4}$ mole) of compound (XIX) was obtained 0.035 g (72%) of the aldehyde (XX) in the form of a light yellow oil, $[\alpha]_D^{21}$ +2.85° (c 0.7; $CHCl_3$). Its PMR spectrum was identical with that of (III).

8-Bromooctanal (XII). A solution of 5 g ($2.4 \cdot 10^{-2}$ mole) of the bromooctanol (XI) in 50 ml of anhydrous CH_2Cl_2 was treated with 7.7 g ($3.5 \cdot 10^{-2}$ mole) of the complex $PyHCrO_3Cl$ and 1.9 g ($2.4 \cdot 10^{-2}$ mole) of AcONa, and the mixture was stirred at room temperature for 4 h. Then it was diluted with 25 ml of diethyl ether and filtered, the filtrate was evaporated, and the residue was chromatographed [SiO_2, ethyl acetate–hexane (2:7)]. This gave 3.6 g (73%) of compound (XII). R_f 0.54. PMR spectrum (δ, ppm): 1.20-1.67 (8H, m, CH_2-3–CH_2-6), 1.80 (2H, quintet, $J_{7,8}$ = 6.75 Hz, $J_{7,6}$ = 7.25 Hz, CH_2-7), 2.40 (2H, dt, $J_{2,3}$ = 7.3 Hz, $J_{2,1}$ = 1.7 Hz, CH_2-2), 3.38 (2H, t, J = 6.75 Hz, CH_2-8), 9.51 (1H, t, J = 1.7 Hz, CH-1).

8-Bromo-1,1-dimethoxyoctane (XIII). A mixture of 3 g ($1.4 \cdot 10^{-2}$ mole) of the aldehyde (XII), 20 ml of anhydrous MeOH, and 0.8 g ($1.4 \cdot 10^{-2}$ mole) of dry NH_4Cl was stirred at room temperature for 72 h. Then it was alkalinized with MeONa to pH 8, and was evaporated; the residue was diluted with 20 ml of ether and was washed with a saturated solution of NaCl (2 × 10 ml), dried with $MgSO_4$, and evaporated, and the new residue was chromatographed [SiO_2, ethyl acetate–hexane (1:9)]. This gave 3.4 g (92%) of the acetal (XIII), R_f 0.48. PMR spectrum (δ, ppm): 1.52-1.82 (10H, m, CH_2-3–CH_2-7), 2.52 (2H, m, CH_2-2), 3.02 (6H, s, $2CH_3O$), 3.42 (2H, t, J = 6.7 Hz, CH_2-8), 4.32 (1H, t, J = 6.5 Hz, CH-1).

1,1-Dimethoxyoctyltriphenylphosphonium Bromide (IV). A mixture of 3 g ($1.2 \cdot 10^{-2}$ mole) of the bromide (XIII), 4.6 g ($1.7 \cdot 10^{-2}$ mole) of Ph_3P, and 10 ml of anhydrous MeCN was heated in a sealed glass tube (65°C, 12 h). Then it was evaporated and the viscous residue was washed with hexane (5 × 10 ml) to eliminate traces of Ph_3P and was reevaporated. This gave 4.8 g (80%) of compound (IV) in the form of white crystals, mp 48-50°C (diethyl ether).

(14R)-1,1-Dimethoxy-14-methylhexadec-8Z-ene (II). A suspension of 0.14 g ($2.8 \cdot 10^{-4}$ mole) of the phosphonium salt (IV) in 2 ml of anhydrous THF was treated with 0.05 g ($4.2 \cdot 10^{-4}$ mole) of dry tert-BuOK, and the mixture was stirred for 15 min; then the temperature was lowered to −60°C and the light yellow solution of the ylide that had formed was treated with a solution of 0.02 g ($1.4 \cdot 10^{-4}$ mole) of the aldehyde (III) in 0.1 ml of anhydrous THF and was stirred for 0.5 h, after which 2 ml of diethyl ether was added, the mixture was filtered, the filtrate was evaporated, and the residue was chromatographed [SiO_2, ether–hexane (1:15)]. This gave 0.026 g (62%) of the acetal (II) in the form of a light yellow oil, R_f 0.25, $[\alpha]_D^{23}$ −4.4° (c 0.88; $CHCl_3$). PMR spectrum (δ, ppm): 0.84 (3H, d, J = 6.45 Hz, CH_3 C-14), 0.87 (3H, t, J = 6.5 Hz, CH_3-16), 1.1-1.74 (17H, m, CH_2-3–CH_2-6, CH_2-11–CH_2-13, CH-14, CH_2-15), 2.05 (4H, m, CH_2-7, CH_2-10), 2.50 (2H, m, CH_2-2), 3.00 (6H, s, $2CH_3O$), 4.30 (1H, t, J = 6.5 Hz, CH-1), 5.32 m (2H, CH-8–CH-9).

(14S)-1,1-Dimethoxy-14-methylhexadec-8Z-ene (XXI). From 0.032 g ($2.2 \cdot 10^{-4}$ mole) of the aldehyde (XX) and 0.23 g ($4.5 \cdot 10^{-4}$ mole) of the phosphonium salt (IV) was obtained 0.046 g (68%) of compound (XXI) as a light yellow oil, $[\alpha]_D^{23}$ +4.36° (c 1.6; $CHCl_3$). Its PMR spectrum was identical with that of (II).

(14R)-14-Methylhexadec-8Z-enal [(14R,8Z)-Trogodermal] (I). A mixture of 0.02 g ($6.7 \cdot 10^{-5}$ mole) of the acetal (II), 2 ml of acetone, and 0.05 ml of 10% HCl was boiled for 1 h, neutralized with 10% $NaHCO_3$ solution (1 ml), and extracted with diethyl ether (5 × 2 ml). The combined extracts were dried with Na_2SO_4 and evaporated, and the residue was chromatographed (HPLC). This gave 0.011 g (62%) of the pheromone (I) in the form of a colorless oil, $[\alpha]_D^{23}$ −5.64° (c 0.37; $CHCl_3$), (compare [2], $[\alpha]_D^{20}$ −5.96° (c 1.06; $CHCl_3$)). PMR spectrum (δ, ppm): 0.84 (3H, d, J = 6.45 Hz, CH_3–C-14), 0.87 (3H, t, J = 6.5 Hz, CH_3-16), 1.02-1.74 (17H, m, CH_2-3–CH_2-6, CH_2-11–CH_2-13, CH-14, CH_2-15), 2.06 (4H, m, CH_2-7, CH_2-10), 2.52 (2H, m, CH_2-2), 5.30 (2H, m, CH-8–CH-9), 8.60 (1H, t, J = 1.75 Hz, CHO-1).

(14S)-14-Methylhexadec-8Z-enal [(14S,8Z)-Trogodermal] (XXII). From 0.02 g of the acetate (XXI) was obtained 0.014 g (87%) of compound (XXII), $[\alpha]_D^{20}$ +5.76° (c 0.33; $CHCl_3$), (compare [4], $[\alpha]_D^{24}$ +6.15° (c 2.89; $CHCl_3$)).

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