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INSECT PHEROMONES AND THEIR ANALOGS.

XXIII. SYNTHESIS OF (7R,8S)-(+)-cis-2-METHYL-7,8-EPOXYOCTADECANE – THE SEX PHEROMONE OF Porthetria dispar

V. N. Odinokov, V. R. Akhmetova, Kh. D. Khasanov,
A. A. Abduvakhabov, A. V. Kuchin, N. I. Andreeva,
and G. A. Tolstikov

UDC 632.936.2

A four-stage asymmetric synthesis of (+)-disparlure [(7R,8S)-(+)-cis-methyl-7,8-epoxyoctadecane (V)] has been effected from 8-methylnon-2Z-en-1-ol (I), obtained by the carboalumination of acetylene with tris(5-methylhexyl)aluminum using the Sharpless reaction. The asymmetric epoxidation of (I), (Ar, mol. sieve A, (+)-DET, $(iOPr)_4Ti$, t-BuOOH, −15°C, 20 h; H_2O, 1 h, NaOH, −7°C, 30 min) gave 8-methyl-2S,3R-epoxynonan-1-ol (II), which was oxidized (kieselguhr–CrO_3–Py, 0°C, 2 h; 25°C, 2 h) to 8-methyl-2S,3R-epoxynonan-1-al (III). The coupling of (III) with $n\text{-}C_8H_{17}CH{=}PPh_3$ (−78°C, 1 h; 25°C, 15 h) gave 2-methyl-7R,8S-epoxy-octadec-9Z-ene (IV), the hydrogenation (H_2/5% Pd-C, 25°C, 5 days) of which led to (V) in admixture with an isomerization product. Compound (V) was isolated by HPLC. Substance, yield, $[\alpha]_D^{25}$: (II), 73, −2.75°; (III), 80, [80.8°; (IV), 50, +37.25°; (V), 50, +0.8°. The IR and PMR spectra of (II-IV), the ^{13}C NMR spectra of (II) and (III), and the mass spectrum of (IV) are given.

Of the known methods of synthesizing (+)-disparlure [(7R,8S)-(+)-cis-2-methyl-7,8-epoxyoctadecane] [10-13], the most effective is a route based on the asymmetric epoxidation of the corresponding allyl alcohols [10-13]. The route to (+)-cis-disparlure through an unsaturated precursor – (7R,8S)-2-methyl-7,8-epoxyoctadec-5-ene, which enables a deuterium-labeled product to be obtained [14], requires the use at the stage of epoxidation of an ester of the poorly accessible (−)-D-tartaric acid.

We chose the route for the synthesis of (+)-disparlure (IV) through (7R,8S)-2-methyl-7,8-epoxyoctadec-9-ene (V), as the chiral synthon for which we used (2S,3R)-8-methyl-2,3-epoxynonan-1-ol (III) which is more readily accessible because of the use of an ester of (+)-L-tartaric acid at the stage of epoxidating 6-methylnon-2-Z-en-1-ol (II). The allyl alcohol (II) was obtained by the stereospecific carboalumination of acetylene with tris(5-methylhexyl)aluminum [15] and the subsequent interaction of the organoaluminum intermediate (I) with formaldehyde. The asymmetric epoxidation of the (Z)-allyl alcohol (II) was performed by a modified Sharpless method [16]. Oxidation of the epoxy alcohol (III) to the epoxy aldehyde (IV) and subsequent olefinization with the aid of n-nonylidenetriphenylphosphorane led to the unsaturated epoxide (V), the hydrogenation of which over 5% Pd/C gave the desired (+)-disparlure (VI) containing as impurity (~25%) the ketone (VII), obviously formed

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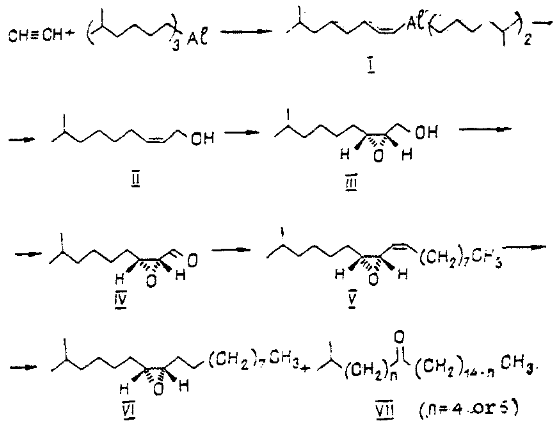
Institute of Chemistry, Bashkir Scientific Center, Urals Branch, Academy of Sciences of the USSR, Ufa. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 715-718, September-October, 1989. Original article submitted December 19, 1988; revision submitted April 11, 1989.

as the result of the isomerization of the epoxide (VI). When 10% Pd/C was used for hydrogenation, the secondary alcohol corresponding to the ketone (VII) (~40%) was detected in the reaction mixture. The ketone or alcohol impurity was eliminated with the aid of HPLC.



EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer (in a film). PMR spectra of solutions of the substances in $CDCl_3$ were measured relative to IMS on a Tesla-487 B instrument (100 MHz). ^{13}C NMR spectra were taken on a JEOL FX-90 Q spectrometer (22.50 MHz in $CDCl_3$). Mass spectra were obtained on a MKh-1320 instrument with the aid of a system for direct introduction at a temperature of the ionization chamber of 100-150°C and an ionizing energy of 70 eV. Specific angles of rotation were determined with the aid of a Perkin-Elmer 141 polarimeter. GLC analysis was performed on a Chrom-4 instrument using a stainless steel column (3 mm × 1.2 m) with the stationary phase SE-30 (5%) on Chromaton NAW-DMCS (0.2-0.25 mm) at working temperatures of 100-300°C, with helium as the carrier gas. The values of R_f are given for a fixed layer of Silufol-type SiO_2, the revealing agent being anisaldehyde. Column chromatography was carried out on silica gel L 100/160 (Czechoslovakia). The (+)-disparlure was purified by the HPLC* method on a Du Pont 8800 instrument with a Zorbax Sil column (21.2 mm × 25 cm) with hexane—ethyl acetate (97:3) as eluent, using a reflectometer as detector.

8-Methyl-2Z-en-1-ol (II). Under Ar, 36.59 g (0.19 mole) of $Bu_3{}^iAl$ was heated at 120°C until 10.85 g of isobutylene had been evolved, and 62.4 g (0.64 mole) of 5-methylhexyl-1-ene was added dropwise at the same temperature and the isobutylene liberated was collected in a trap. The reaction was complete after the evolution of 32.58 g of isobutylene. Then the reaction mixture was heated to 140-150°C and was kept there for 3 h, and the unchanged 5-methylhexene was distilled off. The residue was treated with 80 ml of absolute hexane and the $CaCl_2$-dried acetylene was passed in at 60°C for 6 h, after which the hexane was distilled off. The organoaluminum compound obtained (28.5 g) was treated with 50 ml of absolute THF, the mixture was cooled to 0°C, and 3.66 g of paraformaldehyde was added in portions. The reaction mixture was stirred at 20°C for 5 h and was then diluted with 50 ml of Et_2O, and 20 ml of 15% HCl was added. The resulting mixture was extracted with ether and the organic extracts were washed successively with saturated solutions of $NaHCO_3$ and of NaCl and were dried with $MgSO_4$ and evaporated, and the residue was distilled. This gave 25.8 g (90%) of the alcohol (II) with bp 70-72°C (6 mm), n_D^{20} 1.4450, Z/E ratio 98.5:1.5 (GLC, capillary column [15]). IR spectrum (ν, cm^{-1}): 720, 750, 990, 1010, 1050, 1380, 1395, 1480, 1660, 3025, 3350 br. PMR (δ, ppm): 0.85 (6H, d, J = 6 Hz, CH_3-8 and H-9), 1.23 (7H, br.s, H-5—H-8), 1.83 (1H, br.s, OH-1), 2.05 (2H, m, H-4), 4.09 (2H, m, H-1), 5.40 (2H, m, H-2 and H-3).

(2S,3R)-8-Methyl-2,3-epoxynonan-1-ol (III). At −5°C, with stirring (Ar), a solution of 0.24 g of diethyl (+)-tartrate in 1.2 ml of CH_2Cl_2 and 0.22 g of $(i\text{-}OPr)_4Ti$ were added to 0.3 g of 4 Å molecular sieves ground to a powder and 10 ml of absolute CH_2Cl_2, and then the mixture was cooled to −20°C and a solution containing 1.08 g (12 mmoles) of t-BuOOH in 2 ml of CH_2Cl_2 was added, and, after the reaction mixture had been stirred for 20 min, a solution

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*Purification by the HPLC method was carried out by A. A. Berg and V. R. Sultanmuratove of the Institute of Chemistry of the Bashkir Scientific Center, Urals Branch, Academy of Sciences of the USSR.

of 1.25 g (8 mmoles) of the alcohol (II) in 1 ml of CH_2Cl_2 was added dropwise, and after being kept for 15 min at −20°C the resulting mixture was stirred at −15°C for another 20 h. Then the temperature of the reaction mixture was raised to −7°C, and 4.6 ml of H_2O was added and the resulting mixture was stirred at room temperature for 1 h, after which 1.7 ml of 30% NaOH solution saturated with NaCl was added and after 30 min the solid matter was filtered off. The organic layer and methylene extracts from the aqueous layer (3 × 30 ml) were dried with $MgSO_4$ and evaporated. The residue (1.7 g) was chromatographed on SiO_2 [with hexane—ethyl acetate (4:1) as eluent], giving 1.0 g (73%) of the epoxyalcohol (III), R_f 0.1, $[\alpha]_D^{28}$ −2.75° (c 1.89, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 770, 860, 930, 1055, 1250, 1370, 1390, 1470, 3410 br. PMR (δ, ppm): 0.87 (6H, d, J = 7 Hz, CH_3-8 and H-9), 1.24-1.50 (2H, m, CH_2), 2.30 (1H, br.s, OH-1), 2.95-3.19 (2H, m, H-2 and H-3), 3.74-3.82 (2H, m, H-1). ^{13}C NMR (δ, ppm): 22.58 q (CH_3); 26.92 t, 27.87 t, 28.00 t (C-4, C-5, C-6); 27.18 d (C-8); 38.84 t (C-7); 56.91 d (C-3), 57.30 d (C-2); 60.89 t (C-1).

(2S,3R)-8-Methyl-2,3-epoxynonan-1-al (IV). A mixture of 3 g of CrO_3 and 70 ml of absolute CH_2Cl_2 was added to 3 g of kieselguhr that had been calcined for 5-10 min in the flame of an alcohol lamp in an atmosphere of argon and had been cooled to room temperature. With stirring (0°C, Ar), 9 ml of absolute Py was added dropwise to the mixture and it was left for 30 min, and then a solution of 0.6 g (3.5 mmoles) of the epoxyalcohol (III) in 5 ml of CH_2Cl_2 was added in one portion. The reaction mixture was stirred at 0°C for 2 h and then at room temperature for 2 h and was diluted with 70 ml of diethyl ether. The precipitate was filtered off and washed with ether, the filtrates were evaporated, and the residue (1 g) was chromatographed on SiO_2 [with hexane—ethyl acetate (3:2) as eluent]. This gave 0.48 g (8%) of the epoxyaldehyde (IV), R_f 0.6, $[\alpha]_D^{25}$ +80.8° (c 1.75; $CHCl_3$).

IR spectrum (ν, cm^{-1}): 750, 860, 1040, 1080, 1175, 1255, 1375, 1395, 1435, 1480, 1730, 2740. PMR (δ, ppm): 0.87 (6H, d, J = 6 Hz, CH_3-8 and H-9), 1.23-1.50 (9H, m, H-8, CH_2), 3.17-3.34 (2H, m, H-2 and H-3), 9.47 (1H, d, J = 5.4 Hz, H-1). ^{13}C NMR (δ, ppm): 22.59 q (CH_3); 26.89 t, 27.87 t, 28.19 t (C-4, C-5, C-6); 27.02 d (C-8), 38.77 t (C-7); 57.21 d, 59.96 d (C-2 and C-3), 199.15 d (C-1).

(7R,8S,9Z)-(+)-2-Methyl-7,8-epoxyoctadec-9-ene (V). A suspension of 2.25 g (4.8 mmoles) of nonyltriphenylphosphonium bromide (obtained according to [17]) in 20 ml of absolute THF (−78°C, Ar) was treated with 0.54 g (4.8 mmoles) of t-BuOK. After 15 min, a solution of 0.4 g (2.4 mmoles) of the epoxyaldehyde (IV) in 5 ml of THF was added dropwise to the reaction mixture, and it was stirred at −78°C for 1 h and at room temperature for 1 h and was left for 16 h. Then it was diluted with 20 ml of petroleum ether (bp 40-70°C), separated from the precipitate, and evaporated. The residue (1.1 g) was chromatographed on SiO_2 (with hexane—ether (10:1) as eluent], giving 0.3 g (50%) of the methylepoxyoctadecene (V). R_f 0.66 [hexane—ether (3:1)], $[\alpha]_D^{25}$ +37.25° (c 1.43; $CHCl_3$).

IR spectrum (ν, cm^{-1}): 710, 820, 1100, 1250, 1360, 1380, 1450, 1660. PMR (δ, ppm): 0.86 (9H, m, CH_3-2, H-1 and H-18), 1.27 (21H, br.s, H-1 and CH_2), 2.25 (2H, m, H-11), 3.18-3.45 (1H, m, H-7), 3.50-3.70 (1H, m, H-8), 5.16-5.30 (1H, m, H-10), 5.63-5.82 (1H, m, H-9).

Mass spectrum, m/z (%): 280 (M^+; 1.54), 279 (6.4), 265 ($M^+ - CH_3$, 1.28), 262 ($M^+ - H_2O$, 0.77), 209 ($M^+ - C_5H_{11}$, 1.8), 196 ($M^+ - C_6H_{12}$; 3.1), 181 (6.2), 179 (4.6), 167 (5.6), 153 (2.3), 138 (3.3), 135 (6.4), 127 (51.3), 121 (3.6), 111 (12.8), 110 (12.8), 109 ($C_8H_{13}^+$; 100), 97 (11.03), 85 (53.9), 57 (61.4), 43 (37.5), 42 (6.25).

(7R,8S)-(+)-cis-2-Methyl-7,8-epoxyoctadecane (VI). A mixture of 0.2 g of the epoxyolefin (V), 10 ml of hexane, 5 ml of ethyl acetate, and 0.02 g of 5% Pd—C was stirred at room temperature in an atmosphere of H_2 for 5 days and was then filtered, and the filtrate was evaporated. The residue was chromatographed by HPLC. This gave 0.1 g (50%) of the epoxyoctadecane (VIII), $[\alpha]_D^{25}$ +0.8° (c 2.53; $CHCl_3$); according to the literature [13]: $[\alpha]_D^{20}$ +0.6 ± 0.2° (c 5.6; CCl_4).

SUMMARY

(7R,8S)-(+)-cis-2-Methyl-7,8-epoxyoctadecane — the sex pheromone of Porthetria dispar — has been synthesized by the carboalumination of acetylene with tris(5-methylhexyl)aluminum and asymmetric epoxidation of the (Z)-allyl alcohol obtained.

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