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INSECT PHEROMONES AND THEIR ANALOGUES

XLIII. CHIRAL PHEROMONES FROM (S)-(+)-3,7-DIMETHYLOCTA-1,6-DIENE

3. SYNTHESIS OF (4R)-4-METHYLNONAN-1-OL — SEX PHEROMONE OF Tenebrio molitor AND ITS RACEMIC ANALOGUE

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UDC 547.381+542.91+632.936.2

Starting from the readily available enantiomerically enriched (S)-(+)-3,7-dimethylocta-1,6-diene (ee ≈ 50%), we have synthesized (4R)-4-methylnonan-1-ol — the sex pheromone of the yellow mealworm bettle *Tenebrio molitor* L. A scheme for synthesizing the racemic analogue of the pheromone from 4-methyltetrahydropyran has been developed.

The sex pheromone of the yellow mealworm beetle *Tenebrio molitor* L, which has been identified as 4-methylnon-1-ol with the (R)-configuration (R-1) [1], has been synthesized previously from (R)-(+)-pulegone [1] and from monomethyl (3R)-3-methylglutarate [2]. Since the racemic alcohol (I) is also biologically active [3], its synthesis is of practical interest and has been performed from methyl oct-2-ynoate [2] and from 2-oxopentan-5-ol [3].

We have developed a new pathway to the synthesis of the pheromone R-1, starting from the readily accessible [4] (S)-(+)-3,7-dimethylocta-1,6-diene (dihydromyrcene, ee ≈ 50%) (II), which, as we have shown, is smoothly converted into β-(−)-citronellol (III) with the aid of the hydroalumination reaction [5]. Alcohol (III) was oxidized to the corresponding aldehyde (IV), the interaction of which with propylmagnesium bromide led to a high yield of (6S)-6,10-diemthylundec-9-en-4-ol (V); this was converted into the corresponding tosylate (VI), which, on reduction with zinc in the presence of NaI, gave the alkene (VII). Ozonolysis of the latter led to the desired pheromone R-1 with an overall yield of 21%, calculated on the initial (II).

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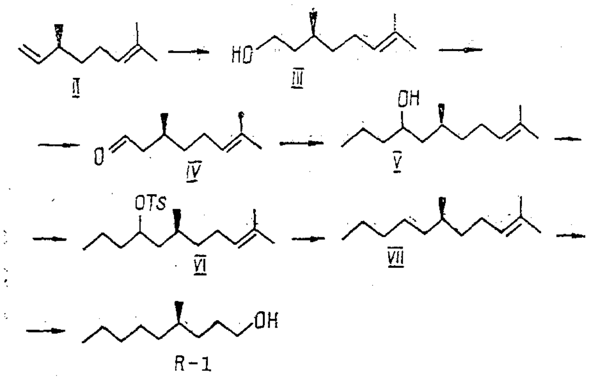
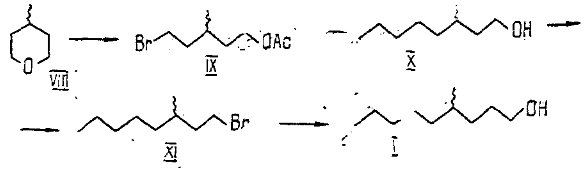


We synthesized the racemate (I) from a readily accessible [6] petrochemical product — 4-methyltetrahydropyran (VIII), which was converted as described in [7] into 1-acetoxy-5-bromo-3-methylpentane (IX). The coupling of the latter with n-propylmagnesium bromide in the presence of the catalyst Li_2CuCl_4 [8] took place selectively and led, after alkaline hydrolysis, to 3-methyloctan-1-ol (X), which was converted into the corresponding bromide (XI). The interaction of the Grignard reagent generated from (XI) with formaldehyde gave the racemate (I) with an overall yield of 32%, calculated on the initial (VIII).



EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer (in a film), and PMR spectra were recorded on a Tesla BS-567 instrument (working frequency 100 MHz, solvent $CDCl_3$); chemical shifts are given on the δ-scale relative to the signal of TMS (internal standard). GLC analysis was conducted on a Chrom-41 instrument with the stationary phase Carbowax-6000 (5%) on the support Inerton Super (0.125-0.160 mm), at a working temperature of 50-200°C, the carrier gas being helium. $[\alpha]_D$ values were determined in $CHCl_3$ and EtOH on a Perkin—Elmer 241 MC polarimeter. The elementary analyses of the compounds synthesized corresponded to the calculated figures.

(3S)-3,7-Dimethyloct-6-enal (IV). With stirring (20°C, Ar) a solution of 4.5 g ($28.8 \cdot 10^{-3}$ mole) of the alcohol (III) (obtained from the diene (II) according to [5]) in 21 ml of abs. CH_2Cl_2 was added to a suspension of 9.27 g ($43.0 \cdot 10^{-3}$ mole) of pyridinium chlorochromate in 100 ml of abs. CH_2Cl_2, and the mixture was stirred for 2 h, diluted with 280 ml of diethyl ether, and filtered through a layer (10 cm) of SiO_2, after which the precipitate on the filter was washed with 300 ml of diethyl ether, and the combined filtrate was evaporated. The residue was chromatographed (SiO_2, CH_2Cl_2) and yielded 3.77 g (85%) of the aldehyde (IV) (with a purity according to GLC of not less than 93%), R_f 0.32 (CH_2Cl_2), $[\alpha]_D^{20}$-6.47° (c 7.1; EtOH), compare [9]. Its IR and PMR spectra were identical with those given in [10].

(6S)-6,10-Dimethylundec-9-en-4-ol (V). With stirring (0°C, Ar), a solution of the Grignard reagent prepared from 2.03 g ($16.5 \cdot 10^{-3}$ mole) of n-propyl bromide and 0.59 g ($24.7 \cdot 10^{-3}$ g-atom) of magnesium in 15 ml of abs. diethyl ether was added to a solution of 0.84 g ($5.5 \cdot 10^{-3}$ mole) of the aldehyde (IV) in 7 ml of abs. diethyl ether, the mixture was stirred at the same temperature for 2 h, and then 5 ml of a saturated solution of NH_4Cl cooled to 5°C was added, extraction was carried out with diethyl ether (3 × 50 ml), and the extract was washed with saturated NaCl solution, dried with Na_2SO_4, and evaporated. Chromatography of the residue (SiO_2; hexane—diethyl ether (87:3)) yielded 0.86 g (80%) of the alcohol (V) (with a purity of not less than 93%, according to GLC), n_D^{22} 1.4635, $[\alpha]_D^{22}$-1.75° (c 0.8; $CHCl_3$). IR spectrum (ν, cm^{-1}): 860 (C=C—H), 1385 (CH_3), 1660 (C=C), 3400 (OH). PMR spectrum (100 MHz, $CDCl_3$): 0.8-1.05 (m, 6H, CH_3-6, H-1), 1.1-1.55 (m, 9H, CH_2, CH), 1.60 and 1.68 (s, 6H, H-11, CH_3-10), 1.8-2.15 (m, 3H, OH, H-8), 3.55-3.8 (m, 1H; H-4), 5.16 (t, 1H, J = 7 Hz, H-9).

(6R)-2,6-Dimethylundec-2-ene (VII). At −5 to 0°C, 0.93 g ($4.9 \cdot 10^{-3}$ mole) of TsCl was added in portions to a solution of 0.8 g ($4{,}04 \cdot 10^{3}$ mole) of the alcohol (V) in 1.5 ml of dry pyridine, and the mixture was stirred at −5°C for 6 h, kept at 0°C for 12 h, and then poured onto ice (~2 g) and extracted with diethyl ether (3 × 50 ml). The extract was washed successively with 10% HCl and with saturated solutions of $NaHCO_3$ and of NaCl, and was dried with $MgSO_4$ and evaporated. The residue consisted of 1.32 g of the tosylate (VI) [IR spectrum (ν, cm^{-1}: 855 (C=C–H); 1385 (CH_3); 1185, 1370, 1600 (OTs); 1660 (C=C)], and to this was added 2.6 g ($39.8 \cdot 10^{-3}$ g-atom) of Zn dust, dried by azeotropic distillation with abs. benzene, and 3.07 g ($20.5 \cdot 10^{-3}$ mole) of dry sodium iodide in 10 ml of abs. THF, and the mixture was boiled with stirring for 3 h and was then cooled, diluted with 100 ml of diethyl ether, and filtered; the precipitate was washed with 100 ml of diethyl ether, and the combined filtrate was washed with saturated NaCl solution, dried with $MgSO_4$, and evaporated. The residue was chromatographed (SiO_2; pentane), to give 0.45 g (66%) of the alkene (VII) (with a purity of not less than 95%, n_D^{22} 1.4398, $[\alpha]_D^{22}$ + 0.53° (c 2.45; $CHCl_3$), see [1]. PMR spectrum (100 MHz, $CDCL_3$): 0.75-1.05 (m, 6H, CH_3-6, H-11), 1.1-1.5 (m, 11H, CH_2, CH), 1.61 and 1.69 (s, 6H, CH_3-2, H-1), 1.85-2.12 (m, 2H, H-4), 5.16 (t, 1H, J = 7 Hz, H-3).

(4R)-4-Methylnonan-1-ol (R-1). At 5°C, a mixture of ozone and oxygen (2% by wt. of O_3) was passed at the rate of 2 liters/h through a solution of 0.16 g ($0.88 \cdot 10^{-3}$ mole) of the alkene (VII) in 3 ml of of abs. cyclohexane containing 0.2 ml of MeOH until 0.048 g ($1.0 \cdot 10^{-3}$ mole) of ozone had been absorbed. The reaction mixture was purged with argon and was diluted with 1 ml of MeOH, and, after the addition, at 15°C, of 0.19 g ($5.0 \cdot 10^{-3}$ mole) of $NaBH_4$, it was stirred at room temperature for 12 h; then 2.2 ml of a 10:1 mixture of water and AcOH was added and, after being stirred for 1 h, the whole was evaporated. The residue was extracted with diethyl ether (3 × 30 ml), and the extract was washed with a saturated solution of $NaHCO_3$, dried with Na_2SO_4, and evaporated. The new residue was chromatographed (SiO_2; pentane–diethyl ether (7:3)), to give 0.11 g (82%) of the alcohol R-1 (with a purity of not less than 95%, according to GLC), n_D^{29} 1.4322, $[\alpha]_D^{20}$+0.63° (c 2.6; $CHCl_3$), its IR and PMR spectra being identical with those given in [2].

3-Methyloctan-1-ol (X). A solution of 5.0 g ($22.4 \cdot 10^{-3}$ mole) of 1-acetoxy-5-bromo-3-methylpentane (IX) (obtained from (VIII) according to [7]) in 10 ml of abs. THF was treated (Ar, −10°) with 1.04 ml of a 0.1 M solution of Li_2CuCl_4 [8], and the mixture was stirred for 10 min, after which, at −15 to −10°C, a solution of the Grignard reagent obtained from 4.13 g ($33.6 \cdot 10^{-3}$ mole) of n-propyl bromide and 0.88 g ($36.6 \cdot 10^{-3}$ g-atom) of magnesium in 68 ml of abs. THF was added dropwise, the reaction mixture was stirred at −10°C, for 6 h, and then 30 ml of saturated NH_4Cl solution was added, extraction was carried out with diethyl ether (4 × 100 ml), and the extract was washed with saturated NaCl solution, and evaporated. The residue was dissolved in 23 ml of MeOH, and, after the addition of 1.31 g of KOH, the solution was boiled for 4 h and was then evaporated; the residue was extracted with diethyl ether (3 × 130 ml), and the extract was washed with saturated NaCl solution, dried with Na_2SO_4 and evaporated. The residue was chromatographed (SiO_2; hexane–diethyl ether (8:2)), to give 2.83 g (88%) of the alcohol (X), n_D^{20} 1.4297, its IR and PMR spectra being identical with those given in [2].

4-Methylnonan-1-ol (I). Gaseous formaldehyde from the thermal (180°C) decomposition of 2 g ($66.o \cdot 10^{-3}$ mole) of paraformaldehyde was passed through a solution of the Grignard reagent prepared in 16 ml of abs. diethyl ether from 0.18 g ($7.6 \cdot 10^{-3}$ g-atom) of magnesium and 1.42 g ($6.9 \cdot 10^{-3}$ mole) of 1-bromo-3-methyloctane (XI) (obtained in 85% yield from the alcohol (X) according to [2]). Then 10 ml of 5% HCl was added to the reaction mixture, and it was dried with Na_2SO_4 and evaporated. The residue was chromatographed (SiO_2, hexane–diethyl ether (:3)), to give 0.52 g (48%) of the alcohol (I), n^{29} 1.4327, its IR and PMR spectra being identical with those given in [2].

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INSECT PHEROMONES AND THEIR ANALOGUES

XLIV. CHIRAL PHEROMONES BASED ON (S)-(+)-3,7-DIMETHYLOCTA-1,6-DIENE

4. SYNTHESIS OF (S)-14-METHYLOCTADEC-1-ENE — SEX PHEROMONE OF Lyonetia clerkella

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The synthesis has been achieved of optically active (S)-(+)-14-methyloctadec-1-ene — the sex pheromone of the leaf miner peach moth Lyonetia clerkella Linne from the readily accessible enantiomerically enriched (ee ≈ 50%) (S)-(+)-3,7-dimethyloct-1,6-diene.

Syntheses of (S)-14-methyloctadec-1-ene (I) — the sex pheromone of the leaf miner peach moth (Lyonetia clerkella L.) — are known that start from (R)-(+)-pulegone [1] and from methyl (R)-3-hydroxy-2-methylpropionate [2]. A synthesis based on the product of the epoxidation of the trisubstituted double bond in a readily accessible chiral compound (ee ≈ 50%) — (S)-3,7-dimethylocta-1,6-diene (dihydromyrcene) (II) has also been published [3].

We propose a new pathway for the conversion of the diene (II) into the desired pheromone (I). By using the hydroalumination reaction, diene (II) was smoothly converted into β-(−)-citronellol (III) [4]. Ozonolysis of the tetrahydropyranyl ether (IV) of the alcohol (III) in methanol, followed by the sodium tetrahydroborate reduction of the peroxidic ozonolysis product, gave (S)-6-(tetrahydropyan-2-yloxy)-4-methylhexan-1-ol (V), which was converted into the corresponding tosylate (VI). The Li_2CuCl_4-catalyzed methylation of the tosylate (VI) with the aid of methylmagnesium iodide gave (S)-3-methylheptan-1-ol (VII). Bromination of the alcohol (VII) with phosphorus tribromide, followed by the coupling of the resulting bromide (VII) with undecenylmagnesium bromide in the presence of CuI and 2,2'-bipyridyl led to the desired pheromone (I), the overall yield of which, calculated on the initial dihydromyrcene (II), amounted to 17.1%.

From a comparison of the specific angle of rotation found for alkene (I) ($[\alpha]_D^{20}$ + 0.59°) with literature figures [1] for an optically pure specimen ($[\alpha]_D^{20}$ + 1.20°), it followed that the optical purity of the pheromone obtained was ≈50%, which corresponded to the optical purity of the initial dihydromyrcene [5].

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