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COLEOPTERAN PHEROMONES. COMMUNICATION 10.\* SYNTHESIS OF THE CHIRAL PHEROMONE OF THE ELEVEN-SPOTTED LEAF BEETLE (COLEOPTERA: CHRYSAMELIDAE)

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Starting compounds utilized for the synthesis of (R)-(-)-10-methyl-2-tridecanone (I) - the sex pheromone of the eleven-spotted leaf beetle Diabrotica undecimpunctata howardi - and related grain species [2] are (R)-(+)-citronellol [3, 4], (R)-(-)-3-methylglutarate [5], and the racemic 2-propyl-10-undecenoic acid [6, 7].

We previously showed that the utilization of the available (S)-(+)-3,7-dimethyl-1,6-octadiene (II) provides a short and effective approach to different coelopteran pheromones [8-10]. The present work studies the synthesis of the (R)-enantiomer of the diolefin (II) via the previously [9] synthesized tosylate (III) having the required (R)-configuration.



The lengthening of the chain by one atom is readily achieved by the condensation of (III) with MeMgI, catalyzed by  $Li_2CuCl_4$ . The acetonide (IV) is also hydrolyzed after the oxidation of the diol (V); the aldehyde (VI) is reduced to the alcohol (VII). The total yield of the tosylate (VIII) by this route comprises 65.0% based on (III).



 $\mathrm{R}^1+\mathrm{R}^2=\mathrm{C(CH_3)_2}$  (IV);  $\mathrm{R}^1=\mathrm{R}^2=\mathrm{H}$  (V);  $\mathrm{R}=\mathrm{CHO}$  (VI),  $\mathrm{CH_2OH}$  (VII),  $\mathrm{CH_2OTs}$  (VIII), COOH (IV).

Another route for the synthesis of this fragment from the tosylate (III) is also based on the utilization of the acetonide (IV). The Jones oxidation of (IV) led (with the simultaneous deblocking of the glycol group) to the formation of the acid (IX), from which the tosylate (VIII) is obtained by standard reactions. The yield of the

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## tosylate (VIII) by this method comprised 61% in the four stages.

To complete the synthesis, the compound (VIII) is combined with the Grignard reagent obtained from the bromoketal (X) (THF,  $Li_2CuCl_4$ , -70 to +20°C) with the subsequent deblocking of the carbonyl group of (XI) in a yield of ~80% (in two stages). The total yield of (R)-(-)-(I), obtained by this method in 13-14 stages, comprises 24-26% based on the initial diolefin (II).

The spectral characteristics (IR, PMR) fully correspond to those published for the pheromone [3, 5]. The chemical purity of 96.5 % follows from the data of capillary GLC and the PMR spectrum; the  $[\alpha]_D$  -0.86° by comparison with the  $[\alpha]_D$  -1.64° for the pheromone (I) [5] corresponds to the 52% optical purity.

## Experimental

The capillary GLC was performed on a "Biokhrom-1" instrument with a flame-ionization detector and a glass column with OV-101 (1 = 52 m, d = 0.27 mm) having the temperature of the vaporizer and the thermostat set at 180-220°C and 70-150°C, correspondingly (flow rate of He 19 ml/min, division of flow 1:10). The IR spectra were taken on a UR-20 instrument. The PMR spectra were taken in CDCl<sub>3</sub> solutions using the "Bruker WM-250" instrument (250 MHz). The rotation angles were determined on the AI-EPO polarimeter using CHCl<sub>3</sub>. The initial (6S, 3 RS)-2,3-isopropylidenedioxy-7-tosyloxy-2,6-dimethylheptane (III) was identical to the sample described in [7]. The 1-bromo-5,5-ethylenedioxyhexane (X) was obtained by the treatment of hex-5-en-2-one with dry HBr, with the subsequent ketalization by ethylene glycol [11]; it had the boiling point 82° (6 mm) and  $n_D^{2°}$  1.4742. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 1.27 s (3H, CH<sub>3</sub>), 1.40-1.7 m (4H, CH<sub>2</sub>), 1.83 quintet (2H, J = 6, 2-CH<sub>2</sub>), 3.6 (2H, J = 6, CH<sub>2</sub>Pr), and 3.88 m (4 H, OCH<sub>2</sub>CH<sub>2</sub>) (it does not contain the signals of the isomeric bromoketal).

(6R, 3RS)-2,3-Isopropylidenedioxy-2,6-dimethylnonane (IV). To the stirred solution of MeMgI [28.5 g (0.2 mole) of MeI and 5.2 g (0.216 g-atom) of Mg in 220 ml of absolute ether] were added, at -50°C in an Ar atmosphere, 13.2 g (0.04 mole) of (III) in 120 ml of THF. The mixture was cooled to -70°C; it was treated with 6 ml of 0.25 M Li<sub>2</sub>CuCl<sub>2</sub> in THF dropwise, and was stirred for 1 h at -70°C and for 4 h at 20-25°C. It was decomposed with a saturated solution of NH<sub>4</sub>Cl prior to the extraction with ether. The extract was washed with 10% NaHCO<sub>3</sub>, water, and a saturated solution of NaCl; it was dried with MgSO<sub>4</sub> and concentrated in vacuo. The residue was dissolved in hexane and filtered through a layer of Al<sub>2</sub>O<sub>3</sub>. Distillation in vacuo gave 8.85 g (96%) of (IV) having the bp 63°C (2 mm), np<sup>1\*</sup> 1.4320, and  $[\alpha]_{D}^{2^2}$  -0.7° (c 9). The IR spectrum (v, cm<sup>-1</sup>) was as follows: 2980, 2955, 2930, 2870, 1460, 1380, 1270, 1240, 1220, 1120, 1050, 1005, and 910. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.86 d (3H, J = 6.5, CH<sub>3</sub>-C<sup>6</sup>), 0.87 t (3H, J = 6.5, 10-CH<sub>3</sub>), 1.08 s, 1.14 s (6H, CH<sub>3</sub>), 1.22 and 1.31 s [6H, (CH<sub>3</sub>)<sub>2</sub>CO<sub>2</sub>], and 3.64 m (1H, H-C<sup>3</sup>). Found, %: C 73.48, H 12.35. C<sub>14</sub>H<sub>28</sub>O<sub>2</sub>. Calculated, %: C 73.63, H 12.36. The GLC at 120°C was characterized by  $\tau_{\rm R}$  10.6 min; the purity was >98%.

<u>(6R, 3RS)-2,6-Dimethyl-2,3-dihydroxynonane</u> (V). The solution of 3.4 g (15 mmole) in 25 ml of 50% AcOH was boiled for 3 h prior to the addition of a saturated solution of NaCl and the extraction with ether. The usual treatment of the extract gave 2.6 g (92%) of (V), which was an oil having the  $n_D^{17}$  1.4515 and  $[\alpha]_D^{22}$  -0.4° (c 5). The IR spectrum ( $\nu$ , cm<sup>-1</sup>) was as follows: 3410, 2970, 2930, 2880, 1460, 1380, 1160, 1080, 990, 970, 940, and 915. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.79 d (3H, J = 6.5, CH<sub>3</sub>-C<sup>6</sup>), 0.80 t (3H, J = 6.5, CH<sub>3</sub>), 1.17 s and 1.22 s (6H, CH<sub>3</sub>), 1.0-1.7 m (9H, CH<sub>2</sub> and CH), 3.23 m (1H, H-C<sup>3</sup>), and 4.14 broad s (2H, OH). Found, %: C 70.21, H 12.87. C<sub>11</sub>H<sub>24</sub>O<sub>2</sub>. Calculated, %: C 70.16, H 12.85. The GLC at 120°C was characterized as  $\tau_R$  12.8 min; the purity was >98%.

<u>(R)-4-Methyl-1-heptanal (VI)</u>. To the solution of 3.0 g (15.6 mmole) of (V) in 45 ml of absolute ether was added, dropwise at 20°C, the solution of 4.4 g (19 mmole) of HIO<sub>4</sub>•2H<sub>2</sub>O in 40 ml of THF; the mixture was stirred for 3 h. The filtrate was washed with 10% NaHCO<sub>3</sub>, water, and a saturated solution of NaCl; it was dried with MgSO<sub>4</sub>. The solution was carefully evaporated at 60°C (650-700 mm). We obtained 1.8 g (90%) of (VI) of 88% purity (GLC data at 120°C,  $\tau_{\rm R}$  4.8 min). The yield of (VI) was ~79%. The IR spectrum ( $\nu$ , cm<sup>-1</sup>) was as follows: 2960, 2925, 2700, 1720, 1460, and 1380. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.79 d (3H, J = 6.5, CH<sub>3</sub>-C<sup>4</sup>), 0.8 t (3H, J = 6.5, 7-CH<sub>3</sub>),

0.9-1.7 (7H, CH<sub>2</sub> and CH), 2.35 m (2H, CH<sub>2</sub>CHO), and 9.69 t (1H, J = 1.8, CHO). This product was utilized without further purification in the following stage of the synthesis.

(R)-4-Methylheptanoic Acid (IX). To the solution of 2.3 g of (IV) in 50 ml of Me<sub>2</sub>CO were added, dropwise at 0-4°C, 15 ml of the Jones chromic mixture; the reaction mixture was stirred for 6 h at 20-25°C. After the distillation of the solvent, the mixture was extracted with ether (3 portions of 50 ml). The extract was washed with water and a saturated solution of NaCl; it was dried with MgSO<sub>4</sub>. After the removal of the ether, we obtained 1.1 g (76%) of (IX) having the  $n_D^{22.5}$  1.4302 and  $[\alpha]_D$  -0.8° (c 18). The IR spectrum ( $\nu$ , cm<sup>-1</sup>) was as follows: 2500-3500 (COOH), 2965, 2940, 2880, 1710, 1465, 1417, 1380, 1290, 1240, 1220, 1115, 945, and 765. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.8-1.0 m (6H, CH<sub>3</sub>-C<sup>4</sup> and 7-CH<sub>3</sub>), 1.0-1.8 m (7H, CH<sub>2</sub> and CH), 2.32 m (2H, CH<sub>2</sub>COOH), and 11.66 s (1H, COOH).

(R)-4-Methyl-1-heptanol (VII). a) To the solution of 1.28 g (10 mmole) of (VI) in 15 ml of EtOH was added 0.38 g (10 mmole) of NaBH<sub>4</sub> in portions at 0-5°C; the mixture was stirred for 3 h at 20°C prior to diluting it with water, and extracting it with ether. After the usual treatment of the extract and distillation, 1.2 g (92%) of (VII) were obtained; it had the bp 72-74°C (6 mm),  $n_D^{19}$  1.4307,  $[\alpha]_D^{21}$  -0.35° (c 5), and the GLC characteristic (at 80°C)  $\tau_R$  8.6 min. The IR spectrum (v, cm<sup>-1</sup>) was as follows: 3330, 2950, 2920, 2860, 1455, 1380, and 1050. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.84 d (3H, J = 6.5, CH<sub>3</sub>-C<sup>4</sup>), 0.85 t (3H, J = 6.5, 7-CH<sub>3</sub>), 1.0-1.7 m (9H, CH<sub>2</sub> and CH), 2.05 broad s (1H, OH), and 3.59 t (2H, J = 6, CH<sub>2</sub>O). Found, %: C 73.67, H 13.90. C<sub>8</sub>H<sub>18</sub>O. Calculated, %: C 73.78, H 13.92.

b) To the suspension of 0.43 g (10 mmole) of LiAlH<sub>4</sub> in 20 ml of ether was added the solution of 1 g (7 mmole) of (IX) in 60 ml of ether dropwise; the mixture was boiled for 6 h. The excess of the LiAlH<sub>4</sub> was decomposed. The ether layer was washed with water, 10% NaHCO<sub>3</sub>, and a saturated solution of NaCl; it was dried with MgSO<sub>4</sub>. Distillation yielded 0.76 g (92%) of (VII).

(R)-1-Tosyloxy-4-methylheptane (VIII). The mixture of 1.1 g (8.5 mmole) of (VII) and 1.9 g (10 mmole) of TsCl in 14 ml of pyridine was kept at 0-5°C for 4 h; it was poured into 10% HCl (30 ml, 0°C) and extracted with ether. The extract was washed sequentially with a saturated solution of CuSO<sub>4</sub>, NaHCO<sub>3</sub>, and NaCl; it was dried with MgSO<sub>4</sub>. After the removal of the solvent, the residue was maintained at 100°C (2 mm). The yield of 2.2 g (91%) of (VIII), having the  $n_D^{23}$  1.4945, was obtained. The IR spectrum (v, cm<sup>-1</sup>) was as follows: 2960, 2930, 2875, 1600, 1460, 1380, 1190, 1000, 970, 920, and 815. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.77 d (3H, J = 6.5, CH<sub>3</sub>-C<sup>4</sup>), 0.81 t (3H, J = 6.5, 6-CH<sub>3</sub>), 1.0-1.7 m (9H, CH<sub>2</sub> and CH), 2.4 s (3H, Ar-CH<sub>3</sub>), 3.98 t (2H, J = 6, CH<sub>2</sub>O), and 7.30 and 7.60 (4H, A<sub>2</sub>B<sub>2</sub>-system of Ar-H). The sample obtained was utilized in the subsequent stage without further purification.

(R)-2,2-Ethylenedioxy-10-methyltridecane (XI). We added 1.9 g (5 mmole) in 8 ml of absolute ether at -50°C under Ar to the stirred Grignard reagent obtained from 2.3 g (10 mmole) of (X) and 0.26 g (0.0011 g-atom) of Mg in 8 ml of absolute THF. The mixture was cooled to -70°C. We added to it, dropwise, 1 ml of a 0.5 M solution of Li<sub>2</sub>CuCl<sub>4</sub> in absolute THF; the mixture was stirred at -70°C for 1 h, and at 20°C for 4 h. The mixture was treated with a saturated solution of NH<sub>4</sub>Cl and extracted with ether. The extract was washed with 10% NaHCO<sub>3</sub>, water, and a saturated solution of NaCl; it was dried with MgSO<sub>4</sub> and concentrated. The solution of the residue in hexane was filtered through 50 g of Al<sub>2</sub>O<sub>3</sub> (act. II, neutral); we obtained 1.5 g (84%) of (XI) with the n<sub>D</sub><sup>22</sup> 1.4502 and [ $\alpha$ ]<sub>D</sub><sup>23</sup> -0.9° (c 6.6). The IR spectrum ( $\nu$ , cm<sup>-1</sup>) was as follows: 2970, 2930, 2880, 1470, 1380, 1255, 1220, 1120, 1070, 950, and 860. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.84 d (3H, J = 7, CH<sub>3</sub>-C<sup>1°</sup>), 0.87 t (3H, J = 7, 13-CH<sub>3</sub>), 1.3 s (3H, 1-CH<sub>3</sub>), 1.0-1.7 (19H, CH<sub>2</sub> and CH), and 3.93 m (4H, OCH<sub>2</sub>CH<sub>2</sub>O). The GLC was characterized by  $\tau_R$  26.3 min (at 150°C). Found, %: C 74.87, H 12.51. C<sub>16</sub>H<sub>32</sub>O<sub>2</sub>. Calculated, %: C 74.94, H 12.58.

(R)-10-Methyl-2-tridecanone (I). The mixture of 0.77 g (3 mmole) of (XI) and 0.5 ml of  $10\frac{7}{10}$  HCl in 15 ml of Me<sub>2</sub>CO was stirred for 3 h at 20-25°C; it was treated with a saturated solution of NaHCO<sub>3</sub>, and was extracted with ether. The extract was washed with water and a saturated solution of NaCl; it was dried over MgSO<sub>4</sub>. On distillation, we obtained 0.6 g (94%) of the pure (I) having the bp 100°C (bath, 1.5 mm), nD<sup>23</sup> 1.4335, and [ $\alpha$ ]D<sup>23</sup>

-0.86° (c 6). The literature values are as follows: bp 98-99°C (0.5 mm) and  $[\alpha]_D^{24}$ -1.64°. The GLC (at 150°C) was characterized as  $\tau_R$  11.3 min. The IR spectrum ( $\nu$ , cm<sup>-1</sup>) was as follows: 2960, 2930, 2860, 1720, 1460, 1360, and 1160. The PMR spectrum ( $\delta$ , ppm; J, Hz) was as follows: 0.85 d (3H, J = 6, CH<sub>3</sub>-C<sup>10</sup>), 0.90 t (3H, J = 6, 13-CH<sub>3</sub>), 1.0-1.7 (17H, CH<sub>2</sub> and CH), 2.14 s (3H, 1-CH<sub>3</sub>), and 2.41 t (2H, J = 6, CH<sub>2</sub>CO). Found, %: C 78.95, H 13.18. C<sub>14</sub>H<sub>28</sub>O. Calculated, %: C 79.18, H 13.29.

## Conclusions

The synthesis of (R)-10-methyl-2-tridecanone from the chiral (S)-3,7-dimethyl-1,6octadiene was accomplished with the total yield of 24-26% in the 13-14 stages of the synthesis.

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CONVERSION OF UBIQUINONE-9 TO UBIQUINONE-10

BY USE OF THE WITTIG REACTION

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The coenzyme ubiquinone-10 (I) is widely used in the therapy of cardiovascular diseases and immune system disorders, for lowering the toxicity of anthracyclic antibiotics, and for other purposes [1]. Because of the scarcity of (I) in natural sources, a simple method for obtaining this compound is needed. We have investigated the conversion of the readily available ubiquinone-9 (II) [2] to quinone (I) by attaching the missing  $C_s$ -group of the isoprenoid side chain by means of the Wittig reaction. This approach involved the use of quinone (II) and its 0,0'-dibenzyl ether (III), first obtained by the reduction of quinone (II) with NaBH4 and subsequent 0-alkylation of the bis-Na salt of the hydroquinone intermediate with PhCh<sub>2</sub>Br under the conditions used for the synthesis of the 0,0'-dibenzyl ether of ubiquinone-7 [3].

The attachment of the side chains of molecule (II) was carried out in three stages, the first of which involved obtaining aldehydes (X), (XI). Our earlier attempts to

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