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NEW APPROACH TO THE SYNTHESIS OF 9-OXO-2*E*-DECENOIC ACID, A MULTIFUNCTIONAL PHEROMONE OF QUEEN HONEYBEE, FROM THE TELOMER OF BUTADIENE AND WATER

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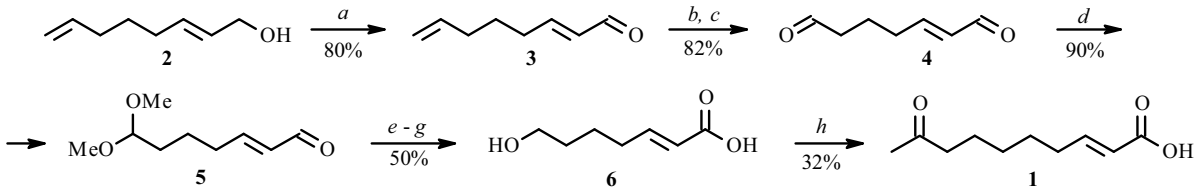
*A new approach was proposed for the synthesis of 9-oxo-2*E*-decenoic acid, a multifunctional pheromone of queen honeybee (*Apis mellifera *L.), starting from the available telomer of butadiene and water (2*E*,7-octadien-1-ol) using in the key steps partial ozonolysis of the corresponding carbonyl compound, selective oxidation of the conjugated aldehyde into a carboxylic acid, and alkylation of acetoacetic ester to introduce the oxo group.*

Keywords: 2*E*,7-octadien-1-ol, 2*E*,7-octadienal, ozonolytic cleavage, 9-oxo-2*E*-decenoic acid, synthesis.

9-Oxo-2*E*-decenoic acid (**1**) was identified as an important component in the honeybee (*Apis mellifera* L.) queen substance. It regulates the behavior and vital activity of the bee family. Furthermore, according to our research [1], it exhibits significant pharmacological properties such as antibacterial (for infections caused by *Staphylococcus aureus*, *Proteus*, *Escherichia coli*, *Pseudomonas aeruginosa*) and anti-inflammatory (for formalin, protein, and lidocaine inflammation models), acts as a wound-healing accelerator for flap wounds and thermal burns, an antidote, and an immunomodulator. Several approaches to the synthesis of **1** exist. They differ by the methods of introducing the oxo- and α,β-unsaturated carboxylic acid [2].

Herein we propose a new approach to the synthesis of the biologically active keto acid **1** starting from the available telomer of butadiene and water (**2**) [3] that involves conversion of the allyl alcohol in the substrate into a conjugated acid and introduction of the oxo group using acetoacetic ester.

The carbon skeleton of the starting diene alcohol **2** had to be shortened by one C atom in order to carry out the synthetic scheme. This was accomplished by partial ozonolysis of the carbonyl compound corresponding to it, 2*E*,7-octadienal (**3**), and selective protection of the intermediate dialdehyde **4**. For this, we were guided by the known reduced reactivity of conjugated aldehydes for ozone [4] and in reactions that form acetals [5].



2 **3** **4** **5** **6** **1**

a. PCC, CH_2Cl_2; *b*. O_3, *c*-C_6H_{12}, MeOH; *c*. PPh_3; *d*. MeOH, NH_4Cl; *e*. H_2O_2–$AgNO_3$ (cat.), MeCN; *f*. HCl, H_2O, MeOH; *g*. NaOH, $NaBH_4$, MeOH, then HCl; *h*. *i*) CH_2NH_2, Et_2O (82%); *ii*) PBr_3, Py, PhH (85%); *iii*) $CH_3C(O)CH_2CO_2Et$, EtONa, EtOH, then NaOH, H_2O, then H_2SO_4 (46%)

Scheme 1

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Further sequential work up of the resulting monosubstituted dialdehyde **5** by a reagent [30% H_2O_2–$AgNO_3$ (cat.)] for selective oxidation of conjugated aldehydes to the corresponding acids [6], dilute HCl (for removal of the acetal protection), and $NaBH_4$ produced the 2*E*-unsaturated hydroxy acid **6** that was converted by the known method [7] using alkylation of acetoacetic ester in the key step into the target pheromone **1** in overall yield 8.8% calculated per starting telomer **2**.

EXPERIMENTAL

IR spectra were recorded in thin layers on a Shimadzu IR Prestige-21 instrument. PMR spectra were obtained in $CDCl_3$ with TMS internal standard on a Bruker AM-100 spectrometer (operating frequency 100.13 MHz). Chromatographic analysis was carried out on Chrom-5 [column length 1.2 m, stationary phase silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–300°C] and Shimadzu GC-9A [quartz capillary column length 25 m, stationary phase OV-101, operating temperature 80–260°C] instruments with He carrier gas. Column chromatography was performed over silica gel L (60–200 μm, Lancaster, England). TLC analysis was carried out on Sorbfil plates (Krasnodar). Solvents were dried by standard methods. Et_2O was distilled before use over diisobutylaluminum hydride.

2*E*,7-Octadienal (3). A suspension of pyridinium chlorochromate (18.00 g, 83.5 mmol) in anhydrous CH_2Cl_2 (100 mL) was stirred (20°C, Ar), treated in one portion with a solution of **2** [2] (8.60 g, 68.3 mmol) in CH_2Cl_2 (20 mL), stirred for 1.5 h, diluted with anhydrous Et_2O (100 mL), and filtered through a layer of Al_2O_3 (5 cm). The precipitate was washed with anhydrous Et_2O (100 mL) and evaporated to afford **3** (6.76 g, 80%).

IR spectrum (ν, cm^{-1}): 3085 (*trans*-CH=CH, CH=CH_2), 2740 (CHO), 1700, 1645, 1000, 980, 920 .

PMR spectrum (δ, ppm, J/Hz): 1.40–1.80 (2H, m, H-5), 1.85–2.60 (4H, m, H-4, H-6), 4.75–5.20 (2H, m, H-8), 5.40–5.75 (1H, m, H-7), 6.00 (1H, dd, J = 16.2, 8.3, H-2), 6.8 (1H, dt, J = 16.2, 7.0, H-3), 9.43 (1H, d, J = 8.3, H-1).

2*E*-Heptendial (4). An O_3–O_2 mixture was passed at 30 L/h through a mixture of **3** (6.54 g, 52.7 mmol), anhydrous MeOH (5.2 mL), and distilled cyclohexane (63 mL) at 5°C until 2.4 g (50 mmol) of O_3 was absorbed (ozonator production 2.4 g O_3/h). The reaction mixture was purged with Ar and treated with PPh_3 (14.60 g, 55.6 mmol). The temperature was increased to ambient. The mixture was stored for 10 h and evaporated. The solid was chromatographed (SiO_2, hexane:EtOAc, 1:1) to afford **4** (5.50 g, 82%).

PMR spectrum (δ, ppm, J/Hz): 1.71–2.70 (6H, m, H-4, H-5, H-6), 6.11 (1H, dd, J = 15.8, 7.5, H-2), 6.85 (1H, dt, J = 15.8, 6.0, H-3), 9.53 (1H, d, J = 7.5, H-1), 9.81 (1H, t, J = 5.8, H-7) [8].

7,7-Dimethoxy-2*E*-heptenal (5). A solution of **4** (5.50 g, 43.2 mmol) in anhydrous MeOH (50 mL) was treated with dry NH_4Cl (0.5 g, 9.3 mmol), stirred for 24 h, and evaporated. The solid was treated with Et_2O (150 mL), washed successively with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated to afford **5** (6.73 g, 90%).

IR spectrum (ν, cm^{-1}): 2730 (CHO), 1685, 1160 (C–O), 1130, 1095, 1060, 1645 (*trans*-CH=CH), 980.

PMR spectrum (δ, ppm, J/Hz): 1.55–1.77 (4H, m, H-4, H-5), 2.33–2.42 (2H, m, H-6), 3.33 (6H, s, OCH_3), 4.38 (1H, t, J = 5.2, H-7), 6.13 (1H, dd, J = 15.6, 7.9, H-2), 6.85 (1H, dt, J = 15.6, 6.7, H-3), 9.51 (1H, d, J = 7.9, H-1) [8, 9].

7-Hydroxy-2*E*-heptenoic Acid (6). A solution of $AgNO_3$ (0.64 g, 0.38 mmol) and **5** (6.50 g, 37.8 mmol) in MeCN (75 mL) was stirred, treated dropwise with H_2O_2 (30%, 21.5 mL, 189.0 mmol), heated to 50°C, stored for 10 h, decomposed by $Na_2S_2O_3$ solution (20 mL, 10%) at 5°C, and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was worked up with saturated $NaHCO_3$ solution (to pH 8–9). The aqueous layer was separated, acidified with HCl (conc.) (to pH ~2), and extracted with Et_2O (3 × 150 mL). The extract was dried over Na_2SO_4 and evaporated. The solid (5.30 g) was dissolved in MeOH (100 mL), stirred (Ar, 0°C), treated with HCl (15 mL, 10%), stirred for 5 h at room temperature, and evaporated. The solid was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 150 mL). The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The resulting solid (3.22 g) of aldehyde-acid was diluted with a mixture of MeOH (250 mL) and NaOH solution (38.6 mL, 1N), cooled to 5°C, treated with $NaBH_4$ (2.92 g, 76.8 mmol), stirred for 3 h at room temperature, cooled to 5°C, acidified with HCl (10%, to pH 1), and extracted with EtOAc (3 × 150 mL). The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **6** (2.80 g, 50%). The IR and PMR spectra of **6** were identical to those published [7].

9-Oxo-2*E*-decenoic Acid (1). Hydroxy acid **6** (2.50 g, 17.4 mmol) produced [7] **1** (1.02 g, 32%), the IR and PMR spectra of which were identical to those published [7].

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