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TWO APPROACHES TO THE SYNTHESIS OF 9-OXO- AND 10-HYDROXY-2*E*-DECENOIC ACIDS, IMPORTANT COMPONENTS OF QUEEN SUBSTANCE AND ROYAL JELLY OF HONEYBEES *Apis mellifera*

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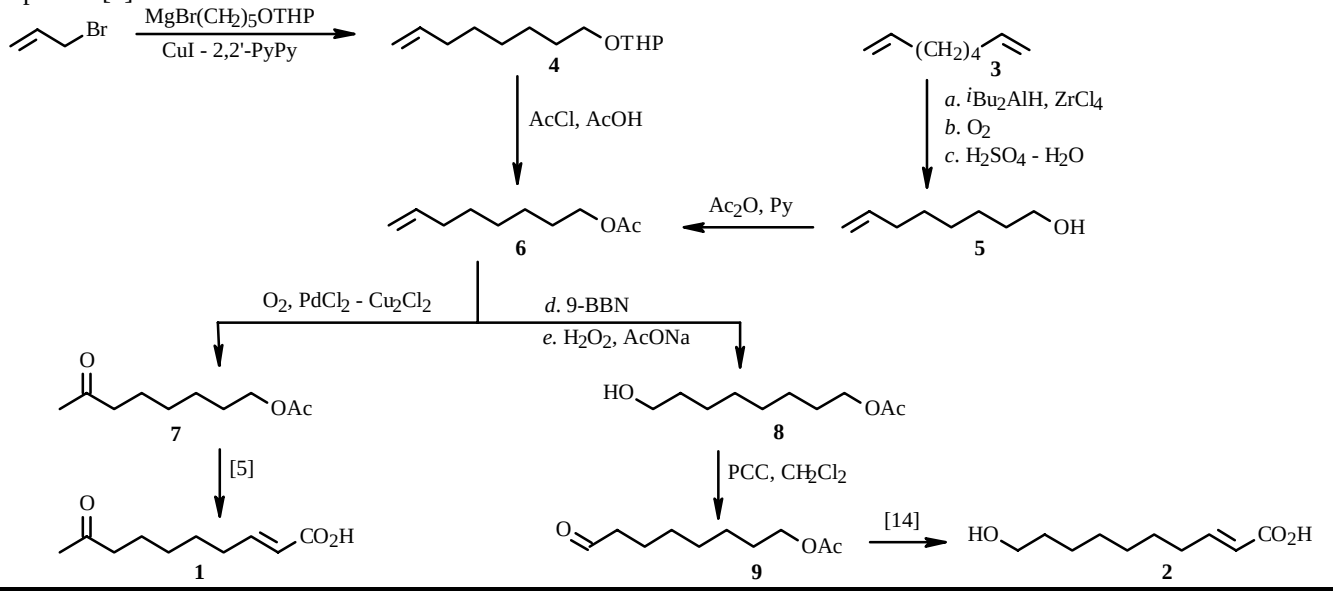
*Two approaches to the synthesis of 9-oxo- and 10-hydroxy-2*E*-decenoic acids, biologically active components of queen substance and royal jelly of honeybees, respectively, were proposed starting with allyl bromide and 1,7-octadiene and using chemo- and regioselective transformations of the common intermediate building block 7-octen-1-ylacetate.*

Key words: allyl bromide, 1,7-octadiene, 7-octen-1-ylacetate, 7-oxooct-1-ylacetate, 8-hydroxyoct-1-ylacetate, 9-oxo-2*E*-decenoic acid, 10-hydroxy-2*E*-decenoic acid, synthesis.

9-Oxo- (**1**) and 10-hydroxy-2*E*-decenoic (**2**) acids have been identified as the most important components of queen substance and royal jelly, respectively, of the honeybee *Apis mellifera* L.

Oxoacid **1** is a polyfunctional pheromone of honeybees, plays the exclusive role of regulating their behavior and activity [1], and possesses significant pharmacological properties (antibacterial, anti-inflammatory, accelerator of graft wound and thermal burn healing, immunomodulator) [2] and antidote activity [3]. Compound **2** has bactericidal, fungicidal, and antitumor properties [4].



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Several syntheses of **1** and **2** have been reported. They differ in the methods of introducing oxo-, hydroxy-, and α,β-unsaturated carboxylic acid groups [5].

We propose two approaches to preparing acids **1** and **2** that are based on previously described transformations [6, 7] of keto-**7**- and aldehydo-**9**-acetates using the Doebner reaction for constructing the conjugated carboxylic acid. Intermediates **7** and **9**, in turn, were synthesized from available allyl bromide and 1,7-octadiene (**3**) [8] using their common key synthon 7-octen-1-ylacetate (**6**). For this, the former of these was first converted by a catalyzed (CuI:2,2′-bipyridyl) cross-conjugation reaction into the tetrahydropyran ether of 7-octen-1-ol (**4**) and then into the required acetate (**6**). The other approach was based on selective monohydroalumination of **3** by diisobutylaluminum hydride at room temperature in the presence of $ZrCl_4$ catalyst (in contrast with the previously reported [8] thermal version using triisobutylaluminum at 100°C) and oxidation of the resulting organaluminum compound to 7-octen-1-ol (**5**), which was then converted to acetate **6** as usual.

Further transformations of **6** in the direction of **1** consisted of its one-step Walker—Tsuji transformation into ketoacetate **7**. The building block of **9** was constructed for hydroxyacid **2** through a two-step synthesis using the intermediate monoester of 1,8-octanediol **8** based on chemo- and regioselective hydroboration—oxidation reactions.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers. PMR spectra in $CDCl_3$ were recorded on a Tesla BS-567 spectrometer (operating frequency 100 MHz) with TMS internal standard. GC was performed 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 Chrom-41 [column length 2.4 m, stationary phase PEG-6000, operating temperature 50-200°C] instruments with He carrier gas. Column chromatography used SiO_2 (70-230, Lancaster, England). TLC monitoring used SiO_2 (Sorbfil, Russia). Elemental analyses of all compounds agreed with those calculated.

1-(2-Tetrahydropyranyloxy)-7-octene (4). A suspension of CuI (2.85 g, 15.0 mmol) in absolute THF (58 mL) was treated with 2,2′-bipyridine (2.34 g, 15.0 mmol), stirred for 0.5 h (20°C, Ar), cooled to 2°C, treated with allylbromide (10.41 g, 86.0 mmol) in absolute THF (17 mL), stirred for 10 min, treated with Grignard reagent prepared from Mg (1.11 g, 46.0 mg-at) and 1-(2-tetrahydropyranyloxy)-5-bromopentane (**2**) as before [9] in THF (40.5 mL), stirred for 1 h at 10°C, and treated with Et_2O (500 mL). The organic layer was separated, washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, hexane:Et_2O, 15:1) to afford **4** (5.82 g, 69%). IR spectrum (ν, cm^{-1}): 3080, 1650, 920 ($CH=CH_2$), 1150, 1090, 1045 (C–O–C).

7-Octen-1-ol (5). A solution of 1,7-octadiene (**3**, 5.00 g, 45.5 mmol) prepared as before [8] in absolute hexane (45 mL) was stirred (20°C, Ar), treated with $ZrCl_4$ (0.29 g, 1.25 mmol) and diisobutylaluminum hydride (73% solution, 11.5 mL, 45.9 mmol) in toluene, stirred for 7 h at 20°C, purged successively with dry air (0-20°C, 1 h) and oxygen (20°C, 1 h, 30-40°C, 3 h), cooled to 0°C, treated dropwise with H_2SO_4 (38 mL, 10%), stirred for 1 h at room temperature, and extracted with Et_2O (3 × 100 mL). The combined extracts were washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated, and distilled to afford **5** (4.30 g, 74%), bp 64-66°C (7 mm). IR spectrum (ν, cm^{-1}): 3550 (OH), 3090, 1640, 920 ($CH=CH_2$). PMR spectrum (δ, ppm): 1.20-1.70 (8H, m, H-2—H-5), 2.15-2.30 (2H, m, H-6), 3.66 (2H, t, J = 7 Hz, H-1), 5.0-5.4 (2H, m, H-8), 5.6-5.9 (1H, m, H-7), similar to the literature data [10].

7-Octen-1-ylacetate (6), a: ether **4** (5.75 g, 27.1 mmol) was treated with a mixture of AcOH and AcCl (10:1, 27 mL), stored for 48 h at 30-40°C, diluted with Et_2O (250 mL), washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated to afford **6** (3.41 g, 74%). IR spectrum (ν, cm^{-1}): 3090, 1645, 920 ($CH=CH_2$), 1745, 1250 (OAc). PMR spectrum (δ, ppm): 1.30-1.75 (8H, m, H-2—H-5), 2.05 (3H, s, CH_3CO), 2.15-2.30 (2H, m, H-6), 4.06 (2H, t, J = 6.5 Hz, H-1), 5.00-5.40 (2H, m, H-8), 5.60-5.90 (1H, m, H-7).

b: a mixture of **5** (4.00 g, 31.3 mmol), dry Py (63.7 mL), and Ac_2O (27.3 mL) was stored for 24 h at room temperature and evaporated. The residue was dissolved in Et_2O (250 mL), washed with HCl (10%) and saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated. The residue was chromatographed (SiO_2, hexane:Et_2O, 9:1) to afford **6** (4.30 g, 81%), spectral properties identical to those for the compound in **a**.

7-Oxooct-1-ylacetate (7). A mixture of $PdCl_2$ (0.38 g, 2.1 mmol), Cu_2Cl_2 (2.19 g, 11.0 mmol), DMF (11.4 mL), and H_2O (1.4 mL) was stirred for 1 h under O_2, treated with **6** (3.40 g, 20.0 mmol), stirred for 6 h to absorb O_2 (270 mL), diluted

with $CHCl_3$ (250 mL), washed successively with HCl (5%) and saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **7** (2.42 g, 65%). The IR and PMR spectra were identical to those reported earlier [11, 12].

8-Hydroxyoct-1-ylacetate (8). A suspension of 9-BBN (3.55 g, 29.1 mmol) in absolute THF (36 mL) at 10°C was treated with a solution of **7** (3.50 g, 20.6 mmol) in absolute THF (12 mL), stored for 2 h, cooled to 0°C, treated with a solution of NaOAc (5.92 g, 72.2 mmol) in H_2O (14 mL) and dropwise with H_2O_2 (30%, 21.3 mL), stirred for 2 h at room temperature, diluted with Et_2O (300 mL), washed successively with saturated NaCl solution, $Na_2S_2O_3$ solution (0.1 N), again with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, hexane:ether, 10:1) to afford **8** (2.75 g, 71%). The IR and PMR spectra were identical to those reported earlier [13].

8-Acetoxyoctanal (9). A suspension of PCC (5.32 g, 24.7 mmol) in dry CH_2Cl_2 (28 mL, Ar, 20°C) was treated in one portion with a solution of **8** (2.70 g, 14.4 mmol) in dry CH_2Cl_2 (3 mL), diluted after 1.5 h with Et_2O (35 mL), and filtered through a layer of SiO_2 (15 cm). The solid was washed with Et_2O. The combined filtrate was evaporated to afford **9** (2.38 g, 89%). The IR and PMR spectra were identical to those reported earlier [7].

10-Hydroxy-2*E*-decenoic acid (2) was prepared from **9** in two steps in overall yield 49% as before [14], mp 64-65°C [15]. The IR and PMR spectra were identical to those reported earlier [14].

9-Oxo-2*E*-decenoic acid (1) was prepared from 7-oxooct-1-ylacetate (**7**) in three steps in overall yield 34% as before [15], mp 52-54°C [16]. The IR and PMR spectra were identical to those reported earlier [17].

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