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SYNTHESIS OF 10-HYDROXY- AND 9-OXO-2E-DECENOIC ACIDS FROM OLEIC ACID

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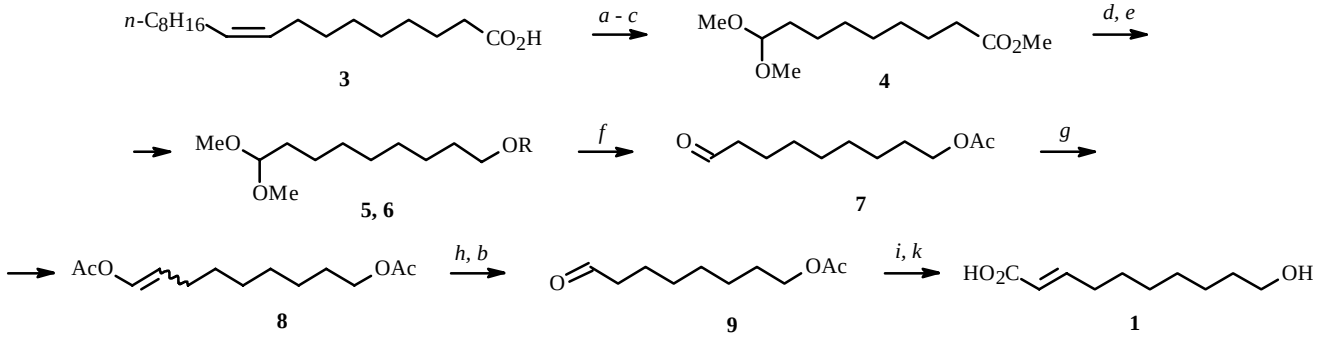
*A practical synthesis of biologically active 10-hydroxy- and 9-oxo-2E-decenoic acids, components of mandibular gland secretion of honeybee (*Apis mellifera *L.), is developed using ozonolysis—reduction of oleic acid and 1,9-diacetoxynon-1-ene in the key steps.*

Key words: 8-acetoxyoctanal, 10-hydroxy-2E-decenoic acid, 1,9-diacetoxynon-1-ene, ozonolysis, 9-oxo-2E-decenoic acid, oleic acid, honeybee, Doebner reaction, mandibular gland secretion, synthesis.

Honeybee (*Apis mellifera* L.) queen substance and royal jelly are known to contain 10-hydroxy- (**1**) and 9-oxo- (**2**) 2E-decenoic acid. Whereas the first of these exhibits bactericidal, fungicidal, and antitumor properties [1], oxoacid **2** regulates the metabolism and behavior of the bee family [2]. Several syntheses of these compounds are known [1, 3]. Many of them are laborious and require expensive starting materials.

We developed a practical synthesis of acids **1** and **2** from readily available oleic acid (**3**). The method is based on selective transformations of the methyl ester of 9,9-dimethoxynonanoic acid (**4**), the product of ozonolysis—reduction of **3** with subsequent acidic methanolysis.



3 **4** **5, 6** **7** **8** **9** **1**

R = H (**5**), Ac (**6**)

a. O_3/CH_2Cl_2-MeOH; *b*. Me_2S; *c*. MeOH/TsOH; *d*. Bu_2AlH; *e*. Ac_2O/Py/DMAP; *f*. PPTS-H_2O; *g*. Ac_2O/AcOK; *h*. O_3/CH_2Cl_2-MeOH-$NaHCO_3$; *i*. $H_2C(CO_2H)_2$/Py-Pyp; *k*.K_2CO_3-MeOH

The initial transformations in the synthesis of unsaturated hydroxyacid **1** are the reduction of the carboxylic group in **4** to the alcohol and transformation of the resulting hydroxyacetal (**5**) to the acetate (**6**). We used the previously described Doebner condensation [4] of malonic acid and 8-acetoxyoctanal (**9**) to introduce the 2E-double bond. Compound **9**, the nor-analog of aldehydoacetate **7**, which was prepared by selective hydrolysis of acetalacetate **6**, was synthesized by ozonolytic cleavage of the double bond of the corresponding enolacetate **8** with subsequent reduction of the peroxide ozonolysis products. It should be noted that enolacetate **8** was formed as an equimolar mixture of the Z- and E-isomers (according to GC and PMR).

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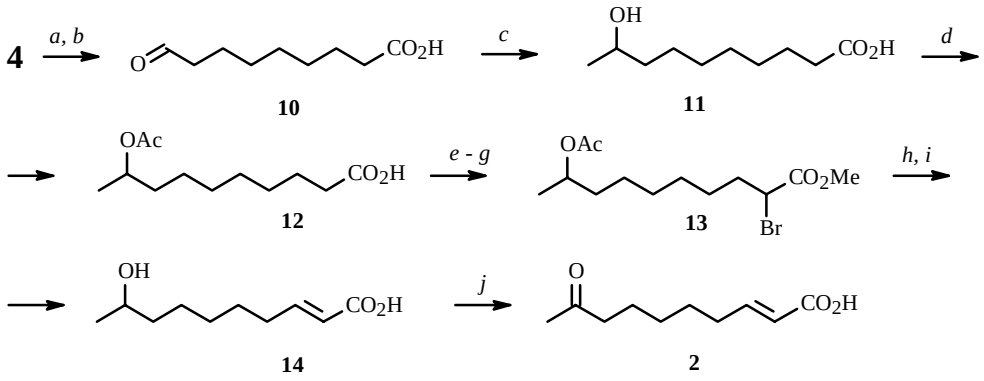
The overall yield of compound **1** according to the proposed scheme was 15% based on starting acid **3**.

Pheromone **2** was constructed using the following sequence of regio- and stereoselective transformations. Successive basic and acidic treatment of acetalester **4** gave aldehydoacid **10**. The carbon chain was lengthened as needed by cross-conjugation of **10** with Grignard reagent from methyl iodide. The reaction was chemically selective for the oxo group with formation of 9-hydroxydecanoic acid (**11**). The 2E-double bond was introduced by α-bromination with subsequent dehydrobromination. Thus, saturated hydroxyacid **11** was transformed into acetoxy derivative **12** in one step, converted to the corresponding acylchloride, and treated successively with bromine and methanol. The resulting bromoester **13** was first mildly dehydrobrominated by calcium carbonate and then totally hydrolyzed with base to give 9-hydroxy-2E-decenoic acid (**14**). Oxidation of this acid by Jones reagent produced the desired product **2** in 16% overall yield based on starting compound **3**.



a. KOH/EtOH; *b*. HCl; *c*. MeMgI; *d*. Ac_2O/Py; *e*. $SOCl_2$; *f*. Br_2; *g*. MeOH; *h*. $CaCO_3$; *i*. KOH/MeOH-H_2O; *j*. CrO_3/H_2SO_4

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in thin layers. NMR spectra were obtained on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for ^1H and 75.47 for ^{13}C) in $CDCl_3$ using chloroform signals as an internal standard (PMR, proton impurity in $CDCl_3$ with δ 7.27 ppm; ^{13}C NMR, average signal with δ 77.00 ppm). Chromatography was performed in a Chrom-5 instrument [column length 1.2 m, stationary phase silicon SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C] with He carrier gas. The ozonator output was 33 mmole O_3/h. Analytical data agreed with those calculated.

Methyl Ester of 9,9-Dimethoxynonanoic Acid (4). An ozone—oxygen mixture was bubbled through a solution of acid **3** (20.00 g, 70.8 mmole) and absolute MeOH (5.7 mL, 4.53 g, 141.6 mmole) in CH_2Cl_2 (200 mL) with stirring (2°C) until 1 equivalent of O_3 was absorbed. The reaction mixture was purged with Ar, stirred (0°C), treated with Me_2S (21 mL, 283.0 mmole), and stirred at room temperature for 16 h. The solvent was evaporated in vacuo. The solid (18.84 g) was dissolved in absolute MeOH (180 mL), stirred at 20°C for 16 h in the presence of TsOH (1.80 g), treated with $NaHCO_3$ (12.0 g), and evaporated. The solid was dissolved in Et_2O (250 mL). The solution was washed successively with $NaHCO_3$ solution (10%) and saturated NaCl solution until the pH was ~7 and dried over Na_2SO_4. The product obtained after evaporating the solvent was vacuum distilled to give acetalester **4** (11.13 g, 67.8%), bp 90-94°C (1 mm). IR and PMR spectra are practically identical to those published previously [5].

9,9-Dimethoxynonan-1-ol (5). A stirred solution of acetalester **4** (4.42 g, 19.05 mmole) in *t*-butylmethyl ether (63 mL, Ar, 3°C) was treated dropwise with a solution of *i*-Bu_2AlH (73%, 9.2 mL, 38.1 mmole). After all *i*-Bu_2AlH was added, the temperature was raised to root temperature (1 h). The mixture was stirred for 1.5 h, cooled to 0°C, treated dropwise with water (9.6 mL), stirred for another hour, left overnight, and treated with KOH (~10 g) until a white precipitate formed. The organic layer was decanted, washed with H_2SO_4 solution (5%) and saturated NaCl solution until the pH was ~7, dried over Na_2SO_4, and evaporated to give **5** (3.53 g, 90.8%).

IR spectrum (KBr, ν, cm^{-1}): 1060, 1080, 1130 (C–O), 3400 (O–H). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.21-1.30 (m, H-3—H-7, 10H), 1.35-1.85 (m, H-2, H-8, 4H), 3.31 (s, CH_3O, 6H), 3.44 (t, J = 6.6, CH_2O, 2H), 4.25 (t, J = 5.6, HCO, 1H).

1-Acetoxy-9,9-dimethoxynonane (6). A reaction mixture containing **5** (2.97 g, 14.58 mmole), dry pyridine (36 mL), Ac_2O (24.5 mL), and a catalytic amount of DMAP (4-dimethylaminopyridine) was stirred at room temperature for 24 h and evaporated in vacuo. The solid was dissolved in *t*-butylmethyl ether (100 mL), washed successively with cold H_2SO_4 solution (5%) and saturated $NaHCO_3$ and NaCl solutions until the pH was ~7, dried over Na_2SO_4, and evaporated to give acetate **6** (3.58 g, 98%).

IR spectrum (KBr, ν, cm^{-1}): 1060, 1080, 1130, 1255 (C–O), 1753 (C=O). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.21-1.39 (m, H-3—H-7, 10H), 1.46-1.65 (m, H-2, H-8, 4H), 2.03 (s, CH_3CO, 3H), 3.30 (s, CH_3O, 6H), 4.05 (t, ^3J = 6.7, H_2CO, 2H), 4.34 (t, ^3J = 5.7, HCO, 1H). ^{13}C NMR spectrum ($CDCl_3$): 20.92 (q, $\underline{C}H_3CO_2$), 24.47 (t, C-7), 25.80 (t, C-3), 28.49 (t, C-2), 29.06 (t, C-6), 29.31 (t, C-4, C-5), 32.36 (t, C-8), 52.49 (q, CH_3O), 64.56 (t, C-9), 104.45 (d, C-1), 171.23 (s, $CH_3\underline{C}O_2$).

9-Acetoxynonal (7). A solution of **6** (3.43 g, 13.93 mmole), PPTS (pyridinium tosylate, 1.02 g), and water (4.18 mL) in acetone (140 mL) was boiled for 9 h and evaporated. The solid was dissolved in Et_2O (100 mL), washed successively with saturated NaCl, $NaHCO_3$, and NaCl solutions, dried over $MgSO_4$, and evaporated to give aldehydoester **7** (2.55 g, 91.7%).

IR spectrum (KBr, ν, cm^{-1}): 1040, 1244 (C–O), 1727 (HC=O), 1750 (OC=O), 2720 (H–CO). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.21-1.45 (m, H-4—H-7, 8H), 1.50-1.63 (m, H-3, H-8, 4H), 2.02 (s, CH_3CO_2, 3H), 2.40 (td, ^3J = 7.3, ^3J = 1.9, H-2, 2H), 4.02 (t, ^3J = 6.6, H-9, 2H), 9.74 (s, J = 5.5, H-1, 1H).

1,9-Diacetoxynon-1-ene (8). A reaction mixture consisting of **7** (2.86 g, 14.3 mmole), Ac_2O (3.32 mL, 35.7 mmole), and fused AcOK (0.21 g) was boiled for 4 h and evaporated. The solid was treated with Et_2O (50 mL), washed successively with H_2O, Na_2CO_3 (5%), and H_2O until the pH was ~7, dried over $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, hexane—CH_2Cl_2, 5:2) to give enolacetate **8** (2.19 g, 63.4%).

IR spectrum (KBr, ν, cm^{-1}): 765, 920, 950 (C=C), 1040, 1070, 1120, 1250, 1270 (C–O), 1645 (C=C), 1690, 1760 (OC=O), 3040, 3075 (=C–H). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.20-1.44 (m, H-4—H-7, 8H), 1.51-1.67 (m, H-8, 2H), 2.01 and 2.05 (both s, Z- and E-CH_3CO_2C-9, 3H), 2.09 and 2.11 (both s, Z- and E-CH_3CO_2C-1, 3H), 1.95-2.10 (m, H-3, 2H), 4.04 (t, ^3J = 6.8, H-9, 2H), 4.86 (dt, ^3J = 6.4, ^3J = 7.4, Z-H-2, 0.5H), 5.37 (dt, ^3J = 7.4, ^3J = 12.5, E-H-2, 0.5H), 6.98 (dt, ^3J = 5.9, ^4J = 1.4, Z-H-1, 0.5H), 7.05 (dt, ^4J = 1.5, ^3J = 12.5, E-H-1, 0.5H).

^{13}C NMR spectrum ($CDCl_3$): 20.42 (q, E-$\underline{C}H_3CO_2$C-1), 20.54 (q, Z-$\underline{C}H_3CO_2$C-1), 20.70 (q, $\underline{C}H_3CO_2$C-9), 24.41 (t, Z-C-3), 25.65 (t, C-7), 26.99 (t, E-C-3), 28.40 (t, C-8), 28.81 (t, C-6), 28.92 (t, C-4, C-5), 64.30 (t, C-9), 113.82 (d, E-C-2), 114.62 (d, Z-C-2), 133.92 (d, Z-C-1), 135.32 (d, E-C-1), 167.90 (s, Z-$\underline{C}O_2$C-1), 168.72 (s, E-$\underline{C}O_2$C-1), 170.83 (s, $\underline{C}O_2$C-9).

8-Acetoxyoctanal (9). An ozone—oxygen mixture was bubbled through a stirred solution of **8** (1.40 g, 5.79 mmole) in a 1:1 mixture (12.5 mL) of CH_2Cl_2 and absolute MeOH in the presence of $NaHCO_3$ (0.22 g) at -70°C to give one mole O_3 per mole of **8**. The reaction mixture was purged with Ar, treated with Me_2S (1.12 mL, -40°C), stirred at room temperature for 3 h, and evaporated in vacuo. The solid was dissolved in water (40 mL) and extracted with Et_2O (3×50 mL). The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to give acetoxyaldehyde **9** (0.78 g, 72.4%). IR and PMR spectra are practically identical to those previously reported [6].

10-Hydroxy-2E-decenoic Acid (1). A solution of **9** (0.70 g, 3.8 mmole), malonic acid (0.55 g, 5.3 mmole), pyridine (2.71 mL), and Pyp (0.13 mL) was held for 17 h at 22°C, 6 h at 30°C, and 1.5 h at 120°C, cooled to room temperature, treated with Et_2O (20 mL), washed successively with HCl (15%, 10 mL) and saturated NaCl solution (15 mL), and treated with saturated $NaHCO_3$ solution (22 mL) until the pH was 8-9. The aqueous layer was separated, acidified with conc. HCl until the pH was ~2, and extracted with Et_2O (3×20 mL). The extract was dried over Na_2SO_4 and evaporated to give 0.46 g of an oily product that was dissolved in absolute MeOH (6 mL) and treated with K_2CO_3 (2.72 g). The reaction mixture was stirred at room temperature for one day, acidified with HCl (10%) until the pH was ≤3, and extracted with Et_2O (3×20 mL). The extract was washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated to give hydroxyacid **1** (0.42 g, 60%), mp 63-65°C (Et_2O—hexane, 2:1). IR and PMR spectra are practically identical to those previously reported [7].

9-Oxononanoic Acid (10). Compound **4** (8.35 g, 36.0 mmole) was dissolved in absolute EtOH (100 mL), treated with KOH (6.62 g, 118.2 mmole), boiled for 2 h, cooled to room temperature, treated with HCl (160 mL, 30%), stirred at 50°C for 45 min, cooled, and extracted with $CHCl_3$ (3×100 mL). The combined extracts were dried over $MgSO_4$ and evaporated to give oxoacid **10** (6.08 g, 98%).

IR spectrum (KBr, ν, cm^{-1}): 1720 (HC=O), 1750 (OC=O), 2720 (H–CO), 3500 (O–H). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.15-1.4 (m, H-4—H-6, 6H), 1.50-1.70 (m, H-3, H-7, 4H), 2.25-2.40 (m, H-2, H-8, 4H), 9.70 (s, H-9, 1H), 11.00 (br.s, COOH, 1H).

9-Hydroxydecanoic Acid (11). A solution of **10** (6.00 g, 34.9 mmole) in absolute Et_2O (117 mL) was treated (0°C,

Ar) with Grignard reagent prepared from Mg (4.22 g, 176.0 mg-at) and methyliodide (17.04 g, 120.0 mmole) in Et_2O (80 mL). The reaction mixture was heated to room tempeature, left overnight, treated with saturated NH_4Cl solution (80 mL), and stirred for 30 min. The organic layer was separated. The aqueous layer was acidified with conc. HCl until the pH was ~2 and extracted with Et_2O (3×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give hydroxyacid **11** (5.63 g, 86%). IR and PMR spectra are practically identical to those previously reported [8].

9-Acetoxydecanoic Acid (12). A mixture of **11** (5.63 g, 29.95 mmole) and Ac_2O (16 mL, 17.31 g, 170 mmole) at 2°C was treated with pyridine (20 mL), heated to room temperature, stirred for 3 d, and evaporated in vacuo. The solid was acidified with H_2SO_4 (5%) until the pH was ~2 and extracted with Et_2O (5×50 mL). The combined extracts were washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated in vacuo to constant mass to give acetoxyacid **12** (6.42 g, 80%).

IR spectrum (KBr, ν, cm^{-1}): 1100, 1265 (C–O), 1745, 1760 (OC=O), 3500 (O–H). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.15 (d, ^3J = 6.2, H-10, 3H), 1.18-1.42 (m, H-4—H-8, 10H), 1.50-1.61 (m, H-3, 2H), 2.02 (s, CH_3CO, 3H), 2.15 (t, ^3J = 7.0, H-2, 2H), 4.82-5.01 (m, H-9, 1H), 11.1 (br.s, CO_2H, 1H).

9-Hydroxy-2E-decenoic Acid (14). Compound **12** (6.40 g, 27.8 mmole) was added over 1 h to $SOCl_2$ (9.3 mL, 14.23 g, 119.5 mmole), heated at 65-70°C for 0.5 h, stirred, treated (60°C) over 1 h with Br_2 (1.00 mL, 7.20 g, 45.0 mmole), and stirred another 5 h at the same temperature. The excesses of $SOCl_2$ and Br_2 were vacuum distilled. The solid at room temperature was treated with absolute MeOH (4.3 mL) and boiled for 2 h. The reaction mixture was vacuum distilled to give bromoester **13** (6.79 g, 79%), bp 125-130°C (0.1 mm).

IR spectrum (KBr, ν, cm^{-1}): 570, 650 (C–Br), 1070, 1120, 1250, 1270 (C–O), 1750 (OC=O), 3500 (O–H). A boiling suspension of $CaCO_3$ (9.32 g, 93.2 mmole) in dimethylacetamide (370 mL) was treated with compound **13** (6.75 g, 21.85 mmole) in the same solvent (45 mL) and boiled for 2 h. The solvent was evaporated in vacuo. The solid was dissolved in Et_2O (200 mL) and acidified with HCl (10%) until the pH was 2. The organic layer was separated. The aqueous layer was extracted with Et_2O (3×50 mL). The extract was combined with the organic layer and evaporated. The solid was boiled for 10 h in a mixture of MeOH (23 mL) and H_2O (3.7 mL) in the presence of KOH (3.71 g, 66.25 mmole). The solvent was evaporated. The solid was acidified with H_2SO_4 (10%) until the pH was 2, extracted with Et_2O (4×50 mL), dried over $MgSO_4$, and evaporated to give hydroxyacid **14** (2.47 g, 61%), bp 152-155°C (0.2 mm). IR and PMR spectra are identical to those previously reported [9].

9-Oxo-2E-decenoic Acid (2). Jones reagent prepared from CrO_3 (2.90 g, 26.9 mmole), H_2SO_4 (2.3 mL), and H_2O (14 mL) was treated with stirring with **14** (2.45 g, 13.2 mmole). The reaction mixture was stirred for 1 h at 50°C, cooled, and extracted with Et_2O (4×50 mL). The extract was washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated to give oxoacid **2** (2.06 g, 85%), mp 54-55°C (Et_2O—petroleum ether, 2:1). IR and PMR spectra are identical to those previously reported [10, 11].

REFERENCES

1. Yu. B. Pyatnova, L. L. Ivanov, and A. S. Kyskina, *Usp. Khim.*, **38**, 248 (1969).
2. K. V. Lebedeva, V. A. Minyailo, and Yu. B. Pyatnova, *Insect Pheromones* [in Russian], Nauka, Moscow (1984), p. 268.
3. V. N. Odinokov and E. P. Serebryakov, *Synthesis of Insect Pheromones* [in Russian], Gilem, Ufa (2001), p. 371.
4. J. I. Fray, R. H. Jager, E. D. Morgan, R. Robinson, and A. D. B. Sloan, *Tetrahedron*, **15**, 18 (1961).
5. R. O. Adlof, W. E. Neff, E. A. Emken, and E. H. Pryde, *J. Am. Oil Chem. Soc.*, **54**, 414 (1977).
6. H. J. Bestmann, W. Stransky, and O. Vostrowsky, *Chem. Ber.*, **108**, 3582 (1975).
7. R. Chiron, *J. Chem. Ecol.*, **8**, 709 (1982).
8. Y. Naoshima, H. Hasegawa, T. Nishiyama, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **62**, 608 (1989).
9. A. A. Kandil and K. N. Slessor, *Can. J. Chem.*, **61**, 1166 (1983).
10. L. I. Zakharkin and D. A. Kamernitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 443 (1981).
11. Yu. B. Pyatnova, S. G. Lavrenko, V. Kh. Taksidi, L. A. Shkolina, and N. K. Shaposhnikova, *Novel Chemical Means of Plant Protection* [in Russian], Moscow (1979), p. 37.