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Greg W. Ebert [a]

[a] Department of Chemistry , State University of New York College at Buffalo , 1300 Elmwood Avenue, Buffalo, New York, 14222

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A TWO-STEP SYNTHESIS OF THE "QUEEN SUBSTANCE" OF THE HONEY BEE

Greg W. Ebert

Department of Chemistry
State University of New York College at Buffalo
1300 Elmwood Avenue, Buffalo, New York 14222

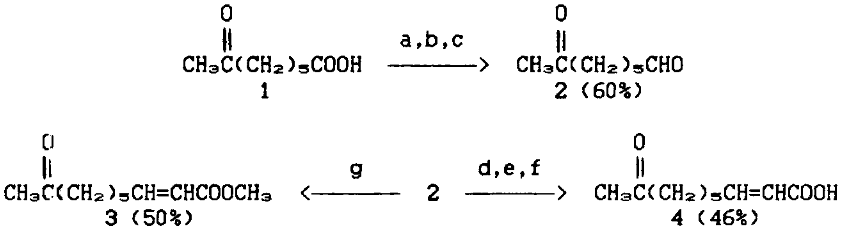
Abstract: A synthesis of the "queen substance" was accomplished in two steps from readily available starting materials. The key step was a novel one-pot reduction of 7-oxooctanoic acid to 7-oxooctanal followed by condensation with malonic acid.

The "queen substance", (E)-9-oxo-2-decenoic acid (4), is a pheromone secreted by the mandibular glands of the queen bee Apis mellifera which inhibits development of the ovaries in worker bees and prevents them from constructing royal cells.[1] The ester, methyl (E)-9-oxo-2-decenoate (3), has also been shown to have considerable biological activity.[2]

In furthering our work on organocopper reagents produced from activated copper[3], we had need of a multigram sample of 3. Several syntheses of 3 and 4 have been published, but most require several steps and suffer from the inaccessibility of starting reagents.[4] We have developed what we believe are two of the most direct, convenient syntheses of 3 and 4 from easily attainable starting materials.

Results and Discussion

Our approach is shown in figure 1. The key to these syntheses is the one-pot reduction of commercially available



$$\underset{1}{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_5COOH} \xrightarrow{a,b,c} \underset{2\ (60\%)}{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_5CHO}$$

$$\underset{3\ (50\%)}{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_5CH{=}CHCOOCH_3} \xleftarrow{g} 2 \xrightarrow{d,e,f} \underset{4\ (46\%)}{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_5CH{=}CHCOOH}$$

Conditions: (a) oxalyl chloride and N,N-dimethylformamide; (b) 10 mol %CuI and $LiAlH(OBu^t)_3$; (c) aqueous 2M HCl; (d) malonic acid in pyridine; (e) cat. amount of piperidine; (f) aqueous H_2SO_4; (g) carbomethoxymethylenetriphenylphosphorane in toluene.

FIGURE 1

7-oxooctanoic acid (1)[5] to 7-oxooctanal (2). This was accomplished by treating the acid (1) with N,N-dimethyleniminium chloride (oxalyl chloride and DMF) to form the carboxylmethyleniminium chloride which upon the addition of lithium tri-t-butoxyaluminum hydride and followed by an aqueous workup produces the aldehyde (2).

This reduction, developed by Fujisawa, Mori, Tsuge, and Sato[6] leaves the ketone functionality intact while efficiently converting the acid to the aldehyde in good yield. The reaction can easily be carried out in a few hours with readily available reagents. This approach bypasses the need to isolate the acid chloride or work with HCl gas as in the commonly employed Rosenmund reduction.

The "queen substance" (4) was conveniently prepared by treating 2 with malonic acid under the conditions of the Doebner reaction. The methyl ester of the "queen substance" (3) was easily formed by employing a Wittig reaction utilizing 2 and commercially available methyl (triphenylphosphoranylidene)acetate.

Summary

In conclusion, we have been able to synthesize gram quantities of the "queen substance" and the related methyl ester in convenient two step procedures from readily available starting materials. In both syntheses the only product isolated was the desired (E)-isomer.

Experimental Section

General Information. Melting points were determined on a Laboratory Devices' Mel-Temp melting point apparatus and were uncorrected. Boiling points were uncorrected. Infrared spectra were recorded on a Beckman Acculab 4 IR spectrophotometer, neat, between NaCl plates or as KBr disks. ^{1}H NMR spectra were recorded on a JEOL FX-90Q (90 MHz) spectrometer. Chemical shifts are reported in ppm (δ) with Me_4Si used as an internal shift reference.

Air sensitive reactions were carried out on an argon/vacuum dual manifold system. The Airco prepurified argon was further purified by passing it through a catalyst column (Chemical Dynamics Corp. R3-11) and then through a column of anhydrous $CaSO_4$ followed by a column of granular potassium hydroxide. THF was freshly distilled under argon from potassium/sodium alloy.

Chemicals. All chemicals were commercially available and were purchased in a reagent grade or better and used as received.

7-Oxooctanal (2). This synthesis was based upon a procedure reported by Fujisawa, Mori, Tsuge, and Sato.[6] Under an atmosphere of argon at 0°C, N,N-dimethylformamide (2.2 mL) was added to dichloromethane (45 mL) followed by the addition of oxalyl chloride (7.1 mL). The solution was stirred for 1 h followed by the removal of solvent under reduced pressure. Acetonitrile (45 mL) and THF (70 mL) were added to the residual white powder and the solution cooled to -30°C. In another flask, 7-oxooctanoic acid[5] (5.0 g) and anhydrous pyridine (2.3 mL) were added to THF (45 mL) and the mixture cooled to -30°C. The latter solution was transferred into the former solution via cannula and the combined mixture stirred for 1 h at -30°C. The temperature was then lowered to -78°C and a slurry of copper(I) iodide (10 mol %, 0.54 g) in THF (10 mL) was added followed by a solution of $LiAlH(OBu^t)_3$ (1.0 M in THF, 57 mL). After stirring for 10 min at -78°C, an aqueous 2M HCl solution (10 mL) was added to quench the reaction. The organic layer was extracted with ether, washed with a saturated aqueous solution of sodium bicarbonate, and dried over $MgSO_4$. After filtration, the solvent was removed by rotary evaporation to yield the crude 7-oxooctanal (2.49 g, 60%). The product was 90% pure by GC analysis and could be used in subsequent reactions without further purification. For analysis, a portion of the product was further purified by fractional distillation under reduced pressure: bp 170-175°C (20 Torr), lit[4c] bp 62-64°C (0.3 Torr); IR (neat) 2937, 2863, 2725, 1716, 1364, 1166, 914 cm^{-1}, Lit[4c,f] IR 2725, 1715 cm^{-1}.

(*E*)-9-Oxo-2-decenoic Acid (4). Malonic acid (1.61g) and 7-oxooctanal (2.0g) were allowed to react under the conditions of the Doebner reaction. Our procedure was similar to that of Jaeger and Robinson[4c] and yielded a crystalline product (1.22g, 46%): mp 49-51°C, lit[4c] mp 53-54°C; IR (KBr) 3500-2500, 1685, 1640, 1420, 1310, 1280, 1160, 990 cm^{-1}, lit[4f] IR matches sample; ^1H NMR ($CDCl_3$) δ 10.2 (broad s, 1 H), 7.1 (dt, J=15.75, 1 H), 5.8 (d, J=15.75, 1 H), 2.3 (m, 4 H), 2.1 (s, 3 H), 1.45 (m, 6 H), lit[4f] ^1H NMR matches sample.

Methyl (*E*)-9-Oxo-2-decenoate (3). A mixture of 7-oxooctanal (2.0g, 14.06mmol) and carbomethoxymethylenetriphenylphosphorane (4.68 g, 14.06 mmol) were combined in a Wittig reaction. Our procedure was similar to that of Bestmann, Schmidt, and Schobert[4f] and yielded the product as an oil (1.39g, 50%): bp 156-160°C (20 Torr), lit[4f] 86-91 °C (0.0133 mbar); IR (neat) 3005, 2935, 2860, 1720, 1655, 1435, 1280, 1205, 1185 cm^{-1}, lit[4f] IR (neat) similar to sample; ^1H NMR ($CDCl_3$) δ 6.95 (dt, J=15.6, 1 H), 5.8 (d, J=15.6, 1 H), 3.7 (s, 3 H), 2.4 (m, 4 H), 2.1 (s, 3 H), 1.4 (m, 6 H), lit[4f] ^1H NMR matches sample.

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