Synthesis of the Sex Pheromone of the Mediterranean Fruit Fly (*Ceratitis capitata* Wiedmann) from Cyclohexanone.1

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Uma nova metodologia para a síntese do 6-nonenoato de metila (**16**) e do 6-nonenol (17), dois componentes do feromônio sexual de machos da mosca *Ceratitis capitata* Wiedmann (mediterranean fruit fly), foi desenvolvida a partir da cicloexanona.

Methyl 6-nonenoate (**16**) and 6-nonenol (**17**), two components of the title pheromone, have been prepared from cyclohexanone by a novel methodology.

Key words: *sex pheromone; methyl 6-nonenoate; 6-nonenol; mediterranean fruit fly*

Introduction

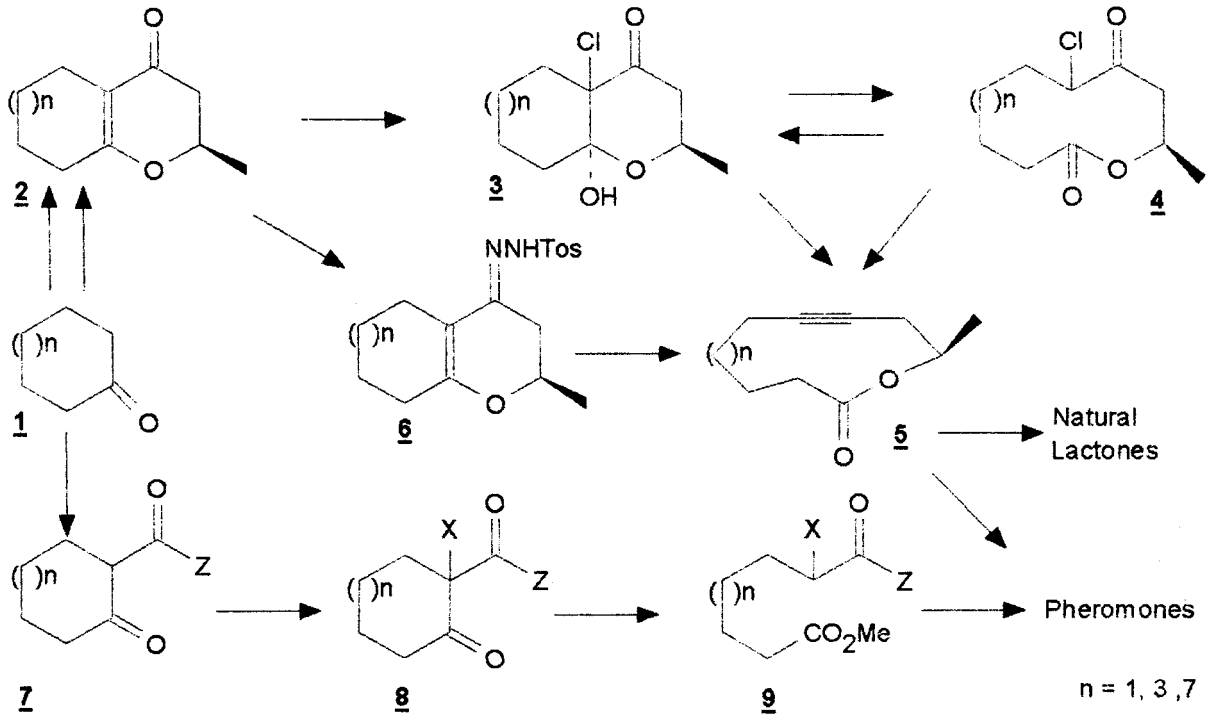
A large number of acyclic pheromones have been isolated from various insects and synthesized by several routes.[2-4] While the earlier synthesis employed mainly the acetylenic chemistry and Wittig or related reactions,[2,3] recently there has been an increasing emphasis on special methods, including ones leading to the optically active pheromones.[4,5]

We have initiated a different approach starting with cycloalkanones (Scheme 1) and their elaboration to the medium ring and macrocyclic acetylenic lactones[6,7] (**5**) or to the acyclic ketoesters (**9**: Z = R, ϕ) and diesters (9: Z = OMe),[8] containing a suitably placed hetero-atom (X = Cl, Br, Sϕ, Seϕ) to generate a regiospecific olefinic system, possibly a stereoselective formation of the more stable *E*- bond. Moreover, we are studying the conversion of the α-chloroketo function (-ClCHCO-) into an acetylenic linkage,[7] thus leading to both the *Z*- and *E*- olefins. Hereby we report the synthesis of the title pheromone by our new strategy (Scheme 2) as well as by the known base-promoted pyrolysis of tosylhydrazones[9] (Scheme 3).

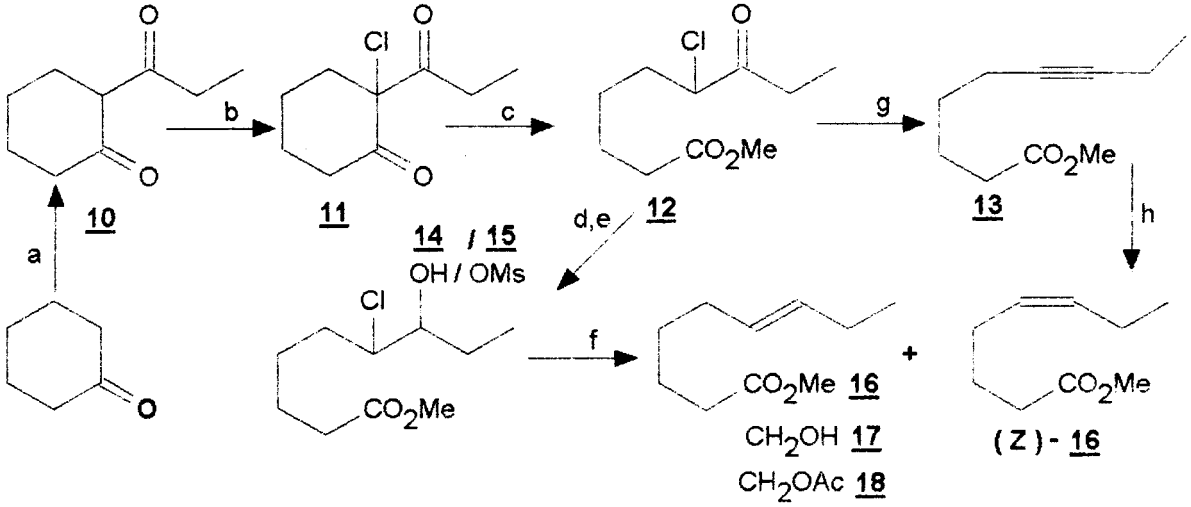
Materials and Methods

2-Propionylcyclohexanone (**10**), easily available from cyclohexanone,[10] was chlorinated with sulphuryl chloride or , more economically, with the house-hold sodium hypochlorite solution, under slightly acidic conditions (pH ~5) to avoid undesired side reactions. The crude chlorinated product **11** was obtained in 90 to 96% yield and was subjected to methanolysis under carefully controlled conditions to supress Favorskii rearrangement. Thus, several attempts to open the chlorodiketone **11** with methanol, containing NaOMe or a tertiary amine (Dabco), or under acidic conditions using, for example, BF_3.MeOH, were either unsuccessful or produced a complex mixture (TLC, ^{1}H NMR). Finally, a gentle reflux in acetone and methanol (6:1), containing anhydrous K_2CO_3, was found satisfactory and furnished the pure product (**12**) in 60% yield after chromatographic purification. As our initial attempts to convert this chloroketoester into the acetylenic product (**13**) or the olefinic ester **16** , using tosylhydrazine,[11] were unpromising, producing only complex mixture of products,[8] we turned our attention to the conventional method of alkene formation by the reductive elimination of halohydrins. The keto group was readily reduced with $NaBH_4$ to afford the chlorohydrin **14**, but attempted elimination with zinc powder (activated or amalgamated), gave only traces of the desired alkene (IR, ^{1}H NMR). Consequently, we replaced the OH by a better-leaving mesyloxy (OMs) group. Attempts to convert the chloro-mesylate **15** into the alkene ester **16**, using KI, proved in vain in acetone, even after several hours' reflux , and were only partly successful in DMSO or DMF (80 - 90 °C, 30 h). However, treatment with anhydrous sodium iodide (NaI)[12] in DMSO, gave the desired ester (**16**) in a modest yield of 45%, after chromatographic purifcation.The spectral (IR, ^{1}H NMR) data of this compound are practically identical with those published for methyl (*E*)-6-nonenoate.[13] However, a careful analysis of the olefinic carbon atoms in the ^{13}C spectrum indicated the presence of ~20% *Z*- isomer. The conversion into 6-nonenol (**17**) and 6-nonenyl acetate (**18**) was carried out according to the described methods;[13,14] the latter (**18**) is a powerful synthetic attractant (parapheromone) for the females of melon fruit fly (*Dacus cucurbitae* Coquillet).[14]

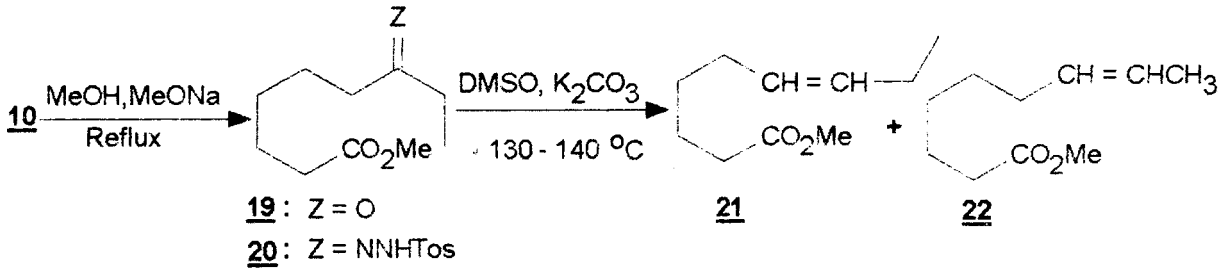
Returning to our original goal of converting the chloroketo compound **12** into the acetylenic ester **13**, we found out that step-wise treament of **12** with tosylhydrazine, in dichloromethane and acetic acid, at 0 °C for several hours, followed



Scheme 1



Scheme 2: ***Reagents & Conditions***: a) Acylation, Ref. 10; b) NaClO, H^+, EtOAc or SO_2Cl_2, CCl_4; c) Acetone, MeOH, K_2CO_3, reflux; d) MeOH, $NaBH_4$; e) MsCl, Et_3N, CH_2Cl_2;f) NaI, DMSO,Δ; g) $TosNHNH_2$, AcOH, CH_2Cl_2, KOAc; h) Pd -C (Lindlar), H_2, Quinoline.



Scheme 3

by reaction with KOAc at room temperature, eventually furnished the pure alkyne **13** in 20% yield (this reaction is being improved and extended to other systems).[15] This compound did not absorb for the triple bond in the IR spectrum, but its Raman spectrum (Ar laser; 514.5 nm) showed the desired bands at 2227 (medium) and 2280 cm^{-1} (weak), while the ^{13}C spectrum proved the presence of sp carbon atoms. Moreover, semihydrogenation gave the desired *Z*-**17**, distinguishable from the *E*- isomer by the direct comparison of its spectra (IR, ^1H NMR).

The synthesis of methyl **6/7**-nonenoate mixture shown in Scheme 3, though neither regio nor stereospecific, can be useful for the preparation of the corresponding **6/7**-nonenyl acetate mixture, an attractant for the melon fruit fly, because this insect responds to both **6**- and **7**-nonenyl acetates.[14] A noteworthy feature of this route is the one-step preparation of 7-oxononanoate (**19**) by the methanolysis of 2-propionylcyclohexanone (**10**). In contrast to the well-explored alcoholysis of 2,2-disubstituted 1,3-diketones,[16] the alcoholysis of the monosubstituted derivatives has been rarely employed, as exemplified by the methanolysis of 2-benzoylcyclohexanone.[17] The decomposition of tosylhydrazone **20** was carried out according to our unpublished procedure developed for the convertion of some 16-membered ketolactones into the corresponding olefinic lactones. Although the crude product was obtained in 85 to 90% yield, chromatographic purification lead to only 42% of methyl 6/7-nonenoates (**21/22**). A similar mixture has been obtained earlier by the dehydration of methyl 7-hydroxynonanoate.[18]

Experimental

IR spectra (ν cm^{-1}) were obtained on a Nicolet 5ZDX - FT spectrometer as neat films or KBr discs (solids). ^1H NMR spectra (^1H-δ) were recorded for solution in CCl_4, at 90 MHz, unless noted otherwise. The coupling constants (6.5 to 7.5 Hz), being nondiagnostic, are ommitted, as are also the obvious assignments. Na_2SO_4 was used for drying organic extracts and solvents were removed on a rotary evaporator. Silica gel (60, E. Merck) was used for column chromatography, using hexane-EtOAc (9:1) as eluant. 2-Propionylcyclohexanone (10) was prepared by the described procedure.[10]

2-Chloro-2- propionylcyclohexanone (**11**): a) To a solution of **10** (0.92 g, 6 mmol) in EtOAc (90 ml) was added house-hold sodium hypochlorite solution (24 ml), followed by dil. HCl (1.2 N; 6 ml) and the mixture stirred vigorously for 45 min , when the organic layer was separated and washed successively with distilled water, satd. solution of Na_2CO_3 and brine to remove excess of chlorine. Drying and evaporation furnished an agreeable smelling, pale-yellow liquid (1.09 g; 96% yield), which was used in the next step without further purification; cm^{-1}: 1720; ^1H-δ : 1.07 (3 H, t, CH_3), 1.6 - 2.3 (6 H, m, CH_2) and 2.3 - 3.1 (4 H, m, H_2CCO).

b) Sulphuryl chloride (0.90 g, 6.6 mmol) dissolved in CCl_4 (7 ml) was added dropwise to a stirred solution of **10** (0.92 g, 6 mmol) in CCl_4 (9 ml) and stirring continued at room temperature for 2 h, after which the reaction mixture was washed and worked up, as described above, affording a pale-yellow liquid (1.03 g; 91%), identical (TLC, IR, ^1H NMR) with the sample obtained by method (a).

6-Chloro-7-oxononanoate (**12**): A mixture of the chloro-compound **11** (3.06 g, 16.2 mmol), acetone (50 ml), MeOH (8.5 ml) and K_2CO_3 (0.65 g, 4.7 mmol) was refluxed (N_2) gently for 6 - 8 h. After evaporating excess of solvents, addition of water (15 ml) and extraction with EtOAc (3 x 50 ml), followed by the usual work-up gave a yellow liquid (3.38 g; 94%), showing four spots on TLC. Chromatography over silica gel (54 g) furnished the pure sample as a pale-yellow liquid (2.16 g; 60%); cm^{-1}:1737, 1206 and 1175; $^1H\delta$-: 1.03 (3 H, t), 1.2 - 2.1(6 H, m,), 2.27 (2 H, t, H_2CCO_2), 2.67 (2 H, q), 3.60 (3 H, s) and 4.1 - 4.3 (1 H, dd, HCCl).

Reduction of ketoester **12** (1.80 g, 8.1 mmol), in MeOH (40 ml), with $NaBH_4$ (0.15 g, 4 mmol), at room temperature for 1.5 h, followed by evaporation of solvent, extraction with EtOAc (3 x 50 ml) and usual wok-up gave *6-chloro-7-hydroxynonanoate* (**14**), a colorless liquid (1.71 g; 95%); cm^{-1}:3456, 1737, 1235, 1200 and 1170; $^1H\delta$-: 0.95 (3 H, t), 1.2 - 2.1 (8 H, m), 2.3 (2 H, t, H_2CCO_2), 2.97 (1 H, broad s, OH), 3.4 - 4.0 (2 H, m, HCCl and HC-O) and 3.62 (3 H, s). It was converted into the corresponding mesylate 15, under the usual conditions (MsCl, Et_3N, CH_2Cl_2, 0 °C) (93% yield); cm^{-1}: 1736, 1357, 1341, 1176 and 932; $^1H\delta$-: 1.03 (3 H, t), 1.2 - 2.1 (8 H, m), 2.1 - 2.4 (2 H, ~t, H_2CCO_2), 3.07 (3 H, s, H_3CSO_3), 3.63 (3 H, s), 3.9 - 4.2 (1 H, m, HCCl) and 4.5 - 4.8 (1 H, m, $HCOSO_2$).

Methyl 6-nonenoate (**16**): Anhydrous NaI (4.87 g, 32.5 mmol) was added to a solution of mesylate **15** (1.95 g, 6.5 mmol) in dry DMSO (16.5 ml) and the mixture stirred in a preheated oil bath (130 - 135 °C) for 6 h. After cooling, the reaction mixture was shaken with a satd. solution of $NaHSO_3$ (10 ml) and extracted with EtOAc (3 x 30 ml), the extract being washed with sodium carbonate solution and brine. Drying and evaporation gave a brown liquid (0.93 g), showing several spots on TLC. The crude product (2.2 g) obtained from two experiments was chromatographed over silica gel (50 g), affording a pleasant smelling, colorless liquid (1.1 g; 45%); cm^{-1}: 1742, 1232, 1203, 1168 and 969; ^1H-δ: 0.92 (3δ H, t), 1.1 - 1.8 (4 H, m), 1.8 - 2.2 (4 H, m, allylic H), 2.22 (2 H,t, H_2CCO_2), 3.58 (3 H, s) and 5.2 - 5.5 (2 H, m, olefinic H); ^1H-δ ($CDCl_3$) (300 MHz): 0.91 (3 H, t), 1.33 (2 H, quintet), 1.58 (2 H, quintet), 1.95 (4 H, m, allylic H), 2.25 (2 H, t), 3.61 (3 H, s) and 5.23 - 5.45 (2 H, m); ^{13}C-δ ($CDCl_3$) (75 MHz): 174.16 (C-1), 33.72 (C-2), 25.35 (C-3), 28.86 (C-4), 31.93 (C-5), 132.38(C-6), 128.52 (C-7), 24.21 (C-8), 13.66 (C-9) and 51.18 (OCH_3); 131.98 and 128.45 (*Z*- isomer, ~20% , estimated by the relative intensities of the olefinic signals).

Reduction of this ester with $LiAlH_4$ in ether gave the corresponding *6-nonenol* (**17**) in 85 - 95% yield; an agreeable smelling colorless liquid; cm^{-1}: 3341, 1056 and 968; $^1H\delta$-: 1.0 (3 H, t), 1.2 - 1.8 (6 H, m), 1.8 - 2.3 (4 H, m), 3.53 (2 H, t, H_2C-O), 3.9 (1 H, s, variable, OH) and 5.2 - 5.6 (2 H, m). It was smoothly converted (Ac_2O, py, 85 - 90 °C, 3 h) into the corresponding acetate (18); cm^{-1}: 1743, 1239, 968; $^1H\delta$-: 0.96 (3 H, t), 1.1 - 1.8 (6 H, m), 1.8 - 2.2 (m) and 1.96 (s) (7 H, Ac and allylic H), 3.98 (2 H, t, H_2C-OAc) and 5.4 (2 H, m).

Methyl 6-nonynoate (**13**): Tosylhydrazine (0.22 g, 1.2 mmol) was added to a stirred and cooled (ice bath) solution of the chloroketoester **12** (0.22 g, 1 mmol) in CH_2Cl_2 (5 ml), containing AcOH (0.5 ml). The mixture was stirred for 3 h under these conditions and then kept in the ice-chest overnight. Next the reaction mixture was surrounded by tap water

and treated with KOAc (0.14 g), when there was an intense yellow coloration, which slowly faded as a gas (N_2) was evolved. After 1 h, the reaction mixture was taken up in hexane (70 ml) and washed with a satd. solution of Na_2CO_3 and brine. Usual work-up gave a yellow liquid, which upon distillation (110 - 120 °C / 4 torr) furnished a colorless product (0.078 g; 46%), having pleasant smell and showing 3 spots on TLC. The combined product (0.26 g) from three such experiments was purified over silica gel (12 g), affording the pure acetylenic ester 13 (0.10 g; ~20%); cm^{-1}: 1741, 1205, 1173 and 1166; ^{1}H-δ: 1.05 (3 H, t), 1.3 - 1.8 (4 H, m), 1.8 - 2.3 (6 H, m) and 3.58 (3 H, s); ^{13}C- ($CDCl_3$) (75 MHz): 173.89 (C-1), 33.50 (C-2), 24.01 (C-3), 28.39 (C-4), 18.33 (C-5), 78.65 (C-6), 81.96 (C-7), 12.28 (C-8), 14.21 (C-9) and 51.36(OCH_3).

Semihydrogenation (Lindlar cat., quinoline, H_2) gave *methyl (Z)-6-nonenoate* (Z-**16**); cm^{-1}: 1742, 1203, 1166, 970 (weak) and 680 (weak); ^{1}H-δ: 0.97 (3 H, t), 1.1 - 1.8 (4 H,m), 1.8 - 2.4 (6 H,m), 3.65 (3 H, s) and5.2 - 5.6 (2 H,m).

Methyl 7-oxononanoate (**19**): 2-Propionylcyclohexanone (10) (1.54 g, 10 mmol) in MeOH (20 ml), containing NaOMe prepared from 60 mg Na, was refluxed for 18 h. Removal of the excess of solvent, extraction with ether (4 x 40 ml) and usual wok-up furnished a pale-yellow liquid (1.13 g), which upon distillation (110 - 120 °C / 4 torr) gave a colorless sample (1.02 g; 56%); cm^{-1}: 1739, 1714, 1200 and 1168; ^{1}H-δ: 0.99 (3 H, t), 1.1 - 1.8 (6 H, m), 2.1 - 2.5 (6 H, m) and 3.61 (3 H, s).

Two-step preparation of this ester by hydrolysing **10** to 7-oxononanoic acid,[10] followed by esterification (MeOH, H^+, reflux) gave the same overall yield (56%).

The tosylhydrazone **20** was obtained as a colorless solid (80 - 85% yield), m.p. 98-101 °C; cm^{-1}: 3218, 1732, 1640, 1600,1448, 1163 and 872; ^{1}H-δ: ($CDCl_3$) 0.99 (3 H,t), 1.1 - 1.8 (6 H, m), 2.0 - 2.4 (6 H, m), 2.44 (3 H,s), 3.68 (3 H,s), 7.3 -7.9 (4 H,dd) and 8.0 - 8.4 (1 H, m, NH).

Methyl 6/7-nonenoate (**21, 22**): A mixture of tosylhydrazone **20** (1.06 g, 3 mmol), dry DMSO (9 ml) and anhydrous K_2CO_3 (1.24 g, 9 mmol) was stirred and kept in an oil bath preheated to 130 - 140 °C. Gas (N_2) evolution was observed after a few min and heating was continued for 1 h, when the reaction mixture was cooled, treated with water (30 ml) and extracted with ether (4 x 30 ml). Usual work-up gave an orange liquid, which upon chromatography over silica gel (15 g) gave a colorless sample (0.215 g; 42%); cm^{-1}: 1744, 1200, 1168 and 968; ^{1}H-δ: 0.96 (t); 1.2 - 1.5 (m), 1.5 - 1.8 (m), 1.8 - 2.2 (m), 2.25 (t), 3.61 (3 H, s), 5.2 - 5.5 (2 H, m); H count for other signals is fractional due to the overlaping signals of isomers.

Conclusion

The new methodology described here for the preparation of methyl 6-nonynoate (**13**) and methyl 6-nonenoate (**16**) may be applied for the synthesis of several other acyclic insect pheromones,[2-4] considering that the size of the cycloalkanone defines the position of the double or the triple bond, while the acyl group (RCO) appropriately extends the desired carbon chain.

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