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Note

Convenient Synthesis of Muscalure, the Housefly Sex Pheromone*

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Recently we have synthesized (*E, E*)-8,10-dodecadien-1-ol,[1] 2-methylheptadecane,[2] and (*Z*)-7-eicosen-11-one and (*Z*)-7-nonadecen-11-one,[3] which are the sex pheromones of the codling moth, the tiger moths (*Arctiidae*), and the peach fruit moth, respectively, from readily available diethyl 3-oxoglutarate (**1**) in a few steps by using its regioselective two-step alkylation.

For the purpose of additional demonstration of the synthetic utility of this compound, we have now synthesized muscalure, (*Z*)-9-tricosene (**5**), which is a hydrocarbon sex attractant pheromone isolated from the female housefly (*Musca domestica* L)[4] and which was supplied as the first commercial one to control pest populations[5]; a good result was obtained especially on the application of crown ether to the second alkylation step.[6]

Diethyl 3-oxoglutarate (**1**) was treated with oleyl bromide in ethanol in the presence of magnesium ethoxide to be converted to 2-(9-octadecenyl)-3-oxoglutarate (**2**) only with a yield of 62%, which was subjected to the second alkylation with sodium hydride and ethyl iodide in 1,2-dimethoxyethane (DME). The 2,4-dialkylated diester (**3**) was subjected to hydrolysis and decarboxylation simultaneously by heating with an aqueous solution of sodium hydroxide to give (*Z*)-14-tricosen-4-one (**4**) in a yield of 42% from **2**. When the second alkylation was carried out with the addition of a catalytic amount of 18-crown-6, the yield of **4** could be increased to the high values of 85.6% in toluene and 64% in DME. The keto function in **4** was finally reduced to a methylene group by Huang–Minlon reduction with an 85% yield and the overall yield of the desired muscalure (**5**) was 45%. The IR and ^1H NMR spectra of muscalure (**5**) were superimposable on those reported.[7]

EXPERIMENTAL

All boiling points were uncorrected. IR spectra were obtained on a Hitachi 260-10 spectrometer keeping neat liquids between two salt plates. ^1H NMR spectra were determined in $CDCl_3$ solutions on a Hitachi R-24B spectrometer using Me_4Si as an internal standard. ^{13}C NMR spectra were obtained in $CDCl_3$ solutions. Mass spectra were recorded on a JEOL JMS-D300 spectrometer connected to a GLC inlet system under electron impact (EI, 70 eV) and chemical ionization (CI, 200 eV, isobutane). Column chromatographies were carried out with Merck 230-400 mesh silica gel.

Ethyl 4-ethoxycarbonyl-3-oxo-(Z)-13-docosenoate (**2**). To a solution of the monoanion of the magnesium chelate[8] prepared from diethyl 3-oxoglutarate (**1**, 14 g, 0.07 mol), magnesium turnings (2.52 g, 0.105 mol) and a trace of iodine in absolute ethanol (100 ml) was added oleyl bromide (27.8 g, 0.084 mol), which was prepared with an 83% yield by treating chemically pure oleyl alcohol with triphenylphosphine dibromide in methylene chloride, and the mixture was refluxed for 30 hr with stirring. The reaction mixture was cooled, and concentrated *in vacuo* to give a dark brown residue which was extracted with ether after acidification with 10% HCl. The crude reaction product obtained by concentration of the ethereal solution was eluted on a silica gel column with *n*-hexane and then a *n*-hexane–ether mixture (10 : 1), and monoalkyl diester **2** was obtained from the mixed solvent eluate as a yellow viscous liquid (19.5 g, 62%). IRν_{max} cm^{-1}: 1740, 1720, 1460, 1370, 720. ^1H NMR δ: 0.90 (3H, distorted t, $J=5$ Hz), 1.05~1.45 (30H, broad s at 1.25), 2.00 (6H, m), 3.55 (2H, s), 3.59 (1H, t, $J=7$ Hz), 4.20 (4H, q, $J=7$ Hz), 5.32 (2H, t, $J=4.5$ Hz).

(Z)-14-Tricosen-4-one (**4**). Compound **2** (19 g, 0.042 mol) was dissolved in dry toluene (30 ml) and the mixture added dropwise to a mixed solution of sodium hydride (50% mineral oil dispersion, 2.02 g, 0.042 mol) and 18-crown-6 (1.11 g, 0.0042 mol) in dry toluene (100 ml) at room temperature with stirring and stirring was continued for an additional one hour. To the solution was then added ethyl iodide (7.9 g, 0.0504 mol) and the mixture was refluxed for 24 hr with stirring. The reaction mixture was cooled, the solvent was evaporated off *in vacuo* and the residual substance was heated with a 15% aqueous solution of NaOH (200 ml) under reflux for 40 hr. The resulting solution was acidified with conc. HCl, and saturated with NaCl to be extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The pale yellow viscous substance thus obtained was purified by column chromatography with a *n*-hexane–ether mixture (100 : 1) to give **4** (12.1 g, 85.6%) in a homogeneous state for TLC: $Rf=0.52$ on Merck plastic sheets Silica gel 60 F_{254} (Art 5735) by *n*-hexane–ether (10 : 1), bp 165~168°C (0.3 mmHg). IRν_{max} cm^{-1}: 3005, 2925, 1715, 1460, 720. ^1H NMR δ: 0.87 and 0.90 (6H, both t, $J=5$ Hz and 6 Hz), 1.00~1.70 (28H, broad s at 1.27), 2.00 (4H, m), 2.32 (4H,

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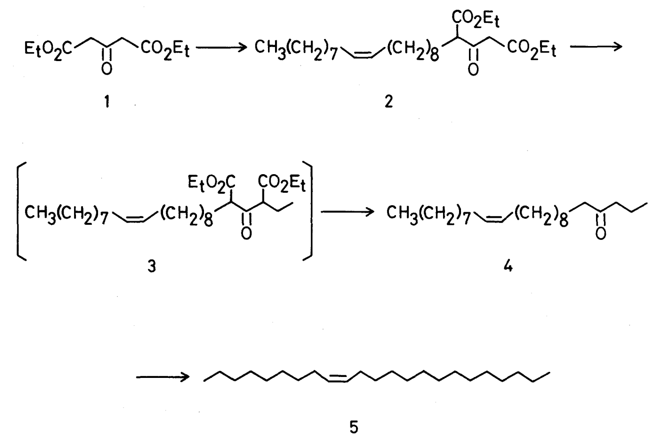
* Selective Alkylation of Diethyl 3-Oxoglutarate. Part VII. For Part VI, see ref. 3.



t, $J=7$ Hz), 5.30 (2H, t, $J=4.5$ Hz). ^{13}C NMR δ: 42.96 (t), 44.76 (t), 129.99 (d), 210.98 (s). EIMS m/z: 336 (M^+, 5), 293 (15), 275 (4), 153 (22), 71 (100), 55 (53), 43 (85). CIMS m/z: 337 [$(M+H)^+$, 100].

(Z)-9-Tricosene (**5**). To a solution of KOH (5 g) in diethylene glycol (50 ml), compound **4** (6.72 g, 0.02 mol) and hydrazine hydrate (85%, 3.8 g) were added and the mixture was heated at 140°C, when the water was distilled off, and then the mixture was heated at 190 ~ 200°C for 5 hr. The reaction mixture was cooled, poured into water and neutralized with dil. HCl to be taken up into ether. The crude product obtained by the usual work-up of the ethereal solution was purified by column chromatography with n-hexane to give the desired hydrocarbon pheromone **5**, 5.65 g, 85%, 89% purity for the GLC analysis (3% OV-1, 2 m glass column, at 230°C, N_2 50 ml/min), main peak at t_R 11.4 min (~89%), impurity peaks at t_R 6.4 min (~4.5%), 6.8 min (~4.5%), 8 min (~0.9%) and 8.5 min (~1.1%), these impurities were assumed to be saturated and/or unsaturated hydrocarbons on the basis of the IR and ^{1}H and ^{13}C NMR spectra, bp 150 ~ 154°C (0.35 mmHg). IR ν_{max} cm^{-1}: 3010, 2930, 2850, 1460, 720. ^{1}H NMR δ: 0.88 (6H, distorted t, $J=5$ Hz), 1.27 (34H, broad s), 2.00 (4H, m), 5.29 (2H, t, $J=5$ Hz). ^{13}C NMR δ: 129.98 (d). EIMS m/z: 322 (M^+, 11), 83 (100). CIMS m/z: 379 [$(M+C_4H_9)^+$, 89], 323 [$(M+H)^+$, 94], 321 [$(M-H)^+$, 100].

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