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SIMPLE STEREOSPECIFIC SYNTHESIS OF THE INSECT SEX PHEROMONES OF COSSUS COSSUS, EUPOECILIA AMBIGUELLA AND ORGYIA PSEUDOTSUGATA

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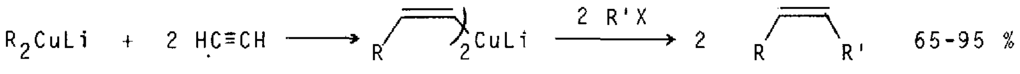
Summary -

Insect sex Pheromones 6, 7 and 15 are prepared in high yield with a very high degree of Z purity (> 99.9 %) by alkylation of Z dialkenyl cuprates.

The growing interest in insect sex pheromones has stimulated a large variety of organic syntheses[1]. The main challenge lies in the high purity which is needed ; the presence of even 1-2 % of the wrong isomer acts often as an inhibitor of their biological activity. Many of the known methods need a chromatographic separation or a low temperature recristallization of the final compound, thus limiting their availability in a large scale preparation[1].

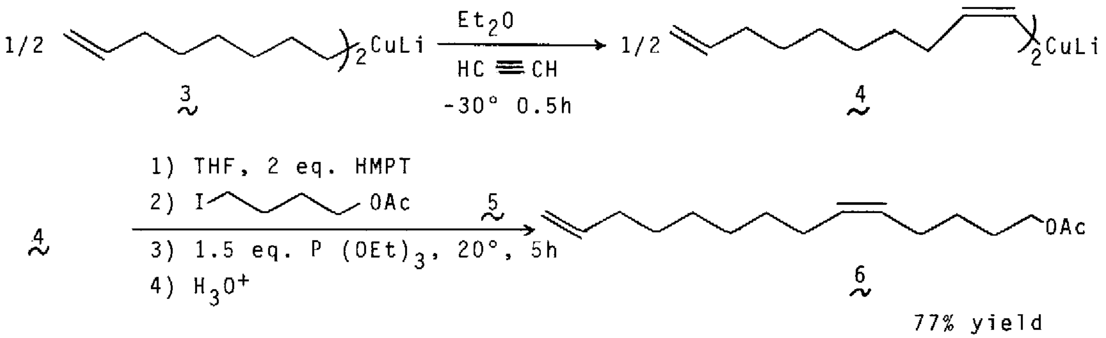
We have recently reported that lithium dialkyl cuprates add quantitatively to acetylene affording Z-dialkenyl cuprates[2]. The latter can be alkylated under conditions where both alkenyl groups are used[3] :



1 2

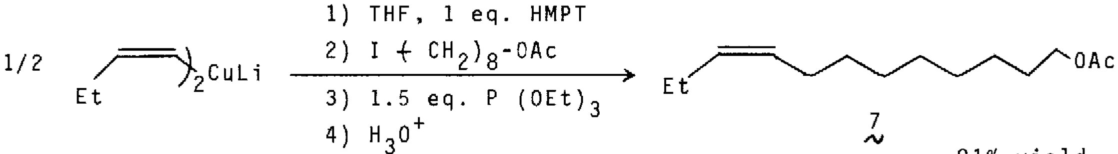
The syn-addition is stereospecific and the Z purity of 2 is > 99.95 % as determined by G.C. analysis. We have used this reaction for the synthesis of some insect sex pheromones, one of which has been performed in a large scale (180 mmol).

The synthesis of the pheromone of Cossus cossus[1d] is depicted below :



The cuprate 3 (prepared from 27 mmol, 5.15 g, of CuI and 50 mmol of the lithium reagent) reacts with 1250 ml (56 mmol) of acetylene, in ether at -30° to afford the vinylic cuprate 4 as a greenish solution. To this solution are added successively 40 ml THF and 20 ml HMPT (100 mmol), then 11.6 g (48 mmol) of the iodide 5 and finally 12.5 g (75 mmol) of $P(OEt)_3$. The mixture is allowed to reach room temperature, stirred 5h and hydrolysed with 80 ml HCl 5N. After standard work-up, the crude mixture is distilled on a 10 cm Vigreux column to afford 9.3 g (77% yield) of pure pheromone 6 : b.p. 93°/0.01 mm. n_D^{20} 1.4554. IR (neat) 3080, 3020, 1740, 1660, 1645, 1240, 990, 910, 730 cm^{-1}. ^1H NMR (CCl_4/TMS) 5.66-6.06 ppm (m, 1H) 5.40 (m, 2H) 4.93-5.12 (m, 2H) 4.08 (t, 2H). ^{13}C NMR ($CDCl_3$/TMS) 170.9 ppm (C=O) 139.2, 130.7, 129.4, 114.5 (C=C) 64.5 (CH_2-O).

The pheromone of *Eupoecilia* (*Clysia*) *ambiguella* Hb[1,4] 7 has to be of the highest Z purity since even 1% of the E isomer has an almost total inhibiting effect on its biological activity[4a]. The synthesis of 7 has been performed on a large scale (180 mmol) using the same synthetic scheme :

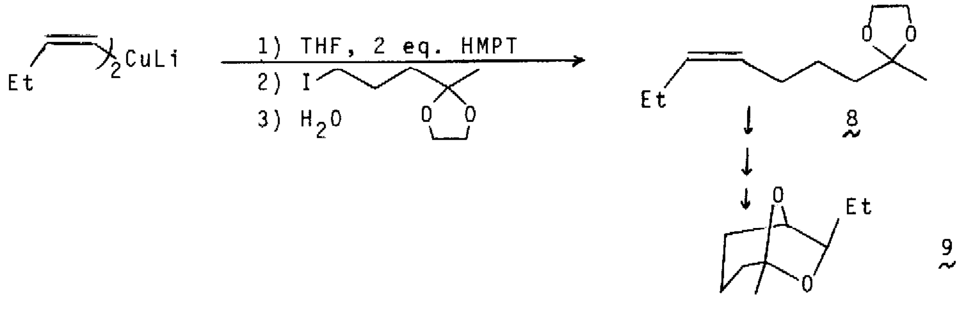


81% yield
99.9% Z purity [5]

b.p. 98°/0.1 mmHg. n_D^{20} 1.4429. IR (neat) 3020, 1745, 1240, 725 cm^{-1} ^1H NMR (CCl_4/TMS) 5.36 ppm (m, 2H) 4.04 (t, 2H). ^{13}C NMR ($CDCl_3$/TMS) 170.6 ppm (C=O) 131.5, 129.1 (C=C) 64.5 (CH_2-O).

Analogously, we have prepared the main intermediate 8 of Kocienski's synthesis of exo-Brevicomin[6], the pheromone of *Dendroctonus Brevicomis*[1,7] 9.

The yield is 65% under the standard conditions ; it may be improved using only one equivalent of electrophile and no P(OEt)$_3$[3].



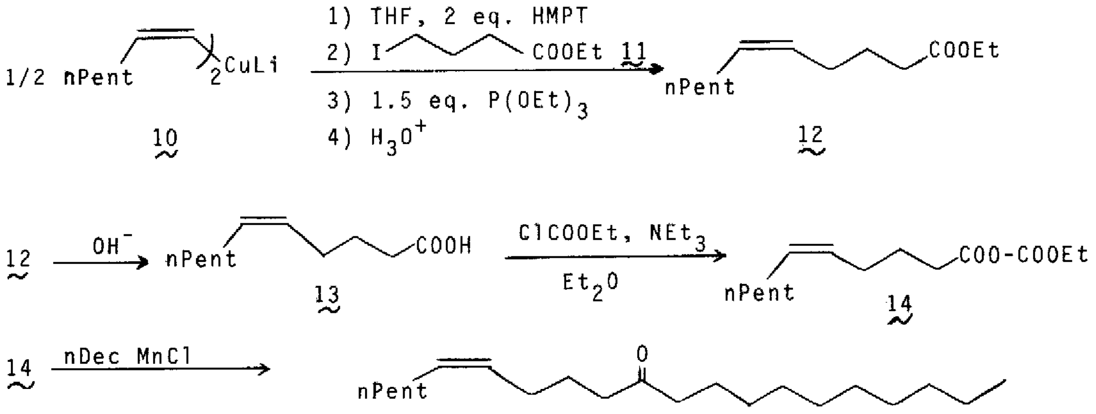
8 92% yield

9

exo-Breviconin

b.p. 46°/0.1 mmHg. n_D^{20} 1.4512. IR (neat) 3020, 1660, 1060, 725 cm^{-1} ^{1}H NMR (CCl$_4$/TMS) 5.22 (m, 2H) 3.94 (s,4H) 1.22 (s,3H). ^{13}C NMR (CDCl$_3$/TMS) 131.8, 128.8 (C=C) 110.1 (CH$<^{O}_{O}$) 64.5 (CH$_2$O).

The synthesis of the sex pheromone of the Douglas-fir tussock moth, Orgyia pseudotsugata[1,8], 15, is based on the same synthetic method :



15 73% overall yield

Cuprate 10, prepared by addition of 1250 ml (56 mmol) of acetylene to an ethereal solution of nPent$_2$CuLi (25 mmol), is alkylated, as above, by 11.6 g (48 mmol) of the iodide 11. The crude ester 12 is saponified (KOH 10N, 24h, 20°C) to afford 7.7 g (87% yield) of pure acid 13, which is transformed quantitatively into the mixed anhydride 14[9]. The crude anhydride is then added, at -40°C, to a suspension of 45 mmol of n-decyl manganese chloride[10] in a mixture of 30 ml THF, 30 ml Et$_2$O and 120 ml hexane. The mixture is stirred 2h at room temperature, then hydrolysed with 80 ml HCl 2N. The crude pheromone 15 contained some n-eicosane, which is removed by filtration on 100 g silica gel (first elution with hexane to remove $C_{20}H_{22}$, then with Et$_2$O to recover the product 15). Distillation

through a 10 cm Vigreux column afforded 10.8g (84 % yield) of pure pheromone **15** :
b.p. 161-162°/0.05 mmHg . n_D^{20} 1.4565. IR (neat) 3015, 1720, 1660, 725 cm^{-1}
^{1}H NMR (CCl_4/TMS) 5.32 ppm (m, 2H) 2.32 (t, 4H). ^{13}C NMR ($CDCl_3$/TMS) 211.4 (C=O) 131.2, 129.0 (C=C).

These syntheses illustrate the efficiency of our method for the simple preparation of pheromones in high yield and very high isomeric purity(>99.9%)

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