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# A NOVEL SYNTHESIS OF ROYAL JELLY ACIDS AND QUEEN SUBSTANCE BY THE FIVE CARBON HOMOLOGATION USING β-VINYL-β-PROPIOLACTONE

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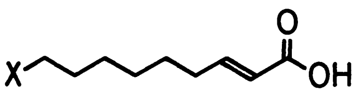
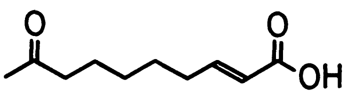
10-Hydroxy-(E)-2-decenoic acid, (E)-2-decenedioic acid (Royal jelly acids), and 9-oxo-(E)-2-decenoic acid (queen substance) were synthesized *via* 10-hydroxy-3-decenoic acid and 9,9-ethylenedioxy-3-decenoic acid, respectively, prepared easily by the regioselective ring-opening reaction of β-vinyl-β-propiolactone with Grignard reagents in the presence of copper(I) catalyst.

Several α,β-unsaturated $C_{10}$ acids play important roles on honey bee. Royal jelly, the sole neutrient of queen bee larve, contains free fatty acids, called royal jelly acids, two of which are 10-hydroxy-(E)-2-decenoic acid (1) as the major component and (E)-2-decenedioic acid (2) as a minor one.1) The acid 2 has been also found to possess antibiotic2) and antitumor activities.3) Queen substance, 9-oxo-(E)-2-decenoic acid (3) is a well-Known pheromone secreted by queen honey bee and inhibits ovary developments in the worker bees and queen rearing within the colony.4)

Because of their biological importance, a number of syntheses for these acids have been published.5,6) In this communication, we wish to report a new synthetic method for these three acids utilizing the reaction of β-vinyl-β-propiolactone (4) with Grignard reagents in the presence of copper(I) catalyst.7) The salient feature in the present route is the five carbon homologation by the regioselective ring-opening of the lactone 4 with properly functionalized $C_5$ Grignard reagents to furnish 3-decenoic acid derivatives which are isomerized easily to desired (E)-2-decenoic acid ones under a basic condition.



1 X=$CH_2OH$ 2 X=$CO_2H$



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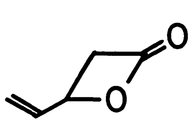

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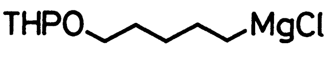
Royal jelly acid 1 was prepared *via* 10-hydroxy-3-decenoic acid (6) which was easily obtained by the copper-catalyzed reaction of the lactone 4 with 5-tetrahydropyranyloxypentyl Grignard reagent (5). The hydroxy group of 5-chloropentanol was protected by converting to tetrahydropyranyl ether8) (98% yield, bp 105 ∿ 106 °C/1.8 mmHg), followed by treatment with Mg in refluxing THF to afford Grignard reagents 5 in 85% yield. Then, Grignard reagent 5 was added dropwise into a mixture of 4 and copper(I) iodide (2 mol%) in THF-$Me_2S$ (16:1) at -78 °C, and stirred for 1 h. After treatment of the reaction mixture with aq HCl-MeOH, the acid 6[8] was obtained as a colorless oil in 86% yield. The base-catalyzed isomerization of 6 to 1 in a refluxing solution of 5N KOH for 3 h afforded a mixture of 1 and 6 in a ratio of 3:2, determined by NMR spectrum. Recrystalization of the mixture in $CH_2Cl_2$ at -20 °C gave preferentially the desired acid 1. Evaporation of the mother liquor, followed by isomerization and recrystalization gave pure 1[8] in a combined yield of 65% (mp 63 ∿ 64 °C, lit.[1] 62 °C).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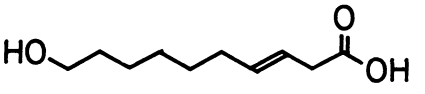
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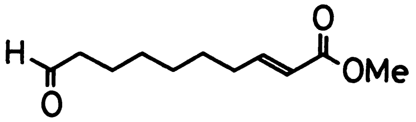
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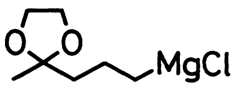
Royal jelly acid 1 was converted easily to the other one 2 as follows. Esterification of 1 with diazomethane and subsequent oxidation with pyridinum chlorochromate gave methyl 9-formyl-(E)-2-nonenoate (7)[8] in 75% yield. Oxidation of 7 with siliver oxide and saponification furnished 2[8] in 92% yield (mp 168 ∿ 169 °C, lit.[5c] mp 168 ∿ 170 °C).

In a similar manner, queen substance 3 was synthesized easily from 5-chloro-2-pentanone and the lactone 4. Ketalization of 5-chloro-2-pentanone with ethylene glycol gave 4,4-ethylenedioxypentyl chloride[8] (84% yield, bp 104 ∿ 105 °C/33 mmHg). The Grignard reagent (8), prepared from the ketalized chloride and Mg in 70% yield, was added into a mixture of 4 and copper(I) iodide in THF-$Me_2S$ (20:1) at -78 °C. After stirring for 1 h at -78 °C, the reaction mixture was evaporated, and the magnesium salt of 9,9-ethylenedioxy-3-decenoic acid (9)[8] was refluxed in 5N NaOH for 3 h. Acidification and separation by silica gel TLC ($CH_2Cl_2$-AcOEt-AcOH) gave 9-oxo-3-decenoic acid (10)[8] and 3[8] in 37% and 46% yield, respectively. Ketalization of 10 and isomerization gave 3 in a combined yield of 63% (mp 54 ∿ 55 °C, lit[6b] 53 ∿ 54 °C).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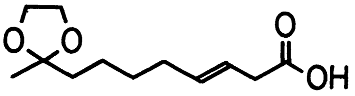
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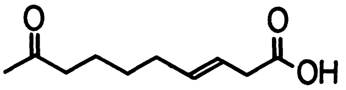
10

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8) All products gave satisfactory NMR and IR spectra.

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