

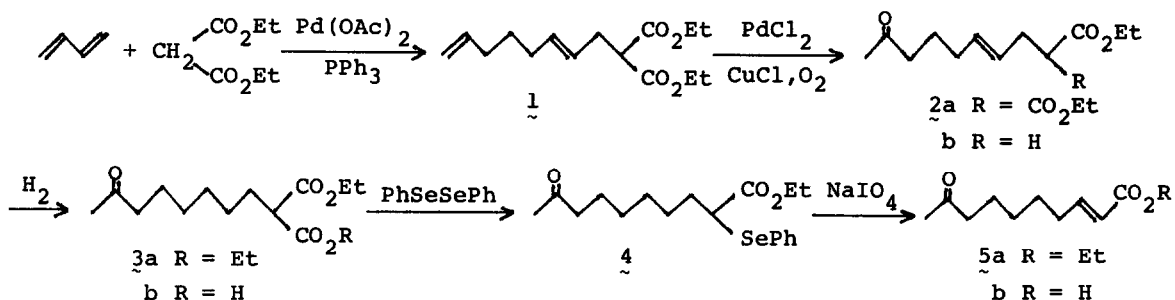
SIMPLE SYNTHESIS OF QUEEN SUBSTANCE FROM THE BUTADIENE TELOMER

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Two types of useful synthetic reactions catalyzed by palladium compounds are known. (I) Telomerization of butadiene with various nucleophiles catalyzed by palladium phosphine complexes¹ (II) Oxidation of olefins to carbonyl compounds using bivalent palladium salt and copper salt.² We now wish to report the application of the palladium catalyzed reactions to the synthesis of queen substance (5b), a well-known honey bee pheromone, by the following sequence.



Several synthetic methods for queen substance have been reported.⁴ These methods are mostly based on elongation of short carbon chain compounds. The present method utilizes the butadiene telomer 1 which has exactly right carbon numbers and suitable functionality for the facile synthesis of queen substance.

Palladium catalyzed telomerization of butadiene with malonate has been reported.⁵ Butadiene and diethyl malonate reacted to give diethyl 2,7-octadienyl malonate 1 in 95% yield (bp 105-107°C/0.5 mm) using palladium acetate and triphenylphosphine as a catalyst. The selective oxidation of the terminal olefin to the methyl ketone without attacking the internal olefin was achieved by using PdCl₂ in the presence of CuCl as an oxidizing agent.^{3,6} A mixture of CuCl (5.94 g, 60 mmol) and PdCl₂ (1.06 g, 6 mmol), and water (2.1 ml) in DMF (15 ml) was shaken under oxygen atmosphere until absorption of oxygen stopped. Then the malonate 1 (15.9 g, 59.3 mmol) was added and the mixture was shaken at a room temperature for 10 hr. The progress of the oxidation was monitored by TLC. After the usual work-up, the methyl ketone 2a was isolated by distillation [11.4 g, 67%, bp 145-150°C/2 mm; NMR δ 6.2-6.5 (2H, br), 4.85 (4H, q, J = 8 Hz), 3.8 (1H, d, d, J = 8 & 9), 2.1-3.2 (6H, br), 2.4 (3H, s), 1.5 (6H, t, J = 8); IR (neat) 1725 cm⁻¹].

The removal of one ester group and the migration of the double bond at 4-position to the conjugated position is the simplest way to queen substance. After protecting the ketone of 2b, the double bond migration was attempted by using various catalysts such as strong bases, $\text{RhCl}(\text{PPh}_3)_3$, RuCl_3 , and H_2PtCl_6 , but all attempts did not give the desired product cleanly.

Then the double bond of 2a was reduced by using palladium on carbon to give the saturated keto ester 3a in a high yield. A novel preparative method for α,β -unsaturated esters from saturated esters by introduction of phenylselenyl group with subsequent oxidative removal has been reported.^{7,8} The group is usually introduced via the reaction of phenylselenyl bromide with carbanion generated from saturated esters with lithium diisopropylamide. We found a convenient modified method for the conversion of alkylmalonate to α,β -unsaturated ester. The malonate 3a was converted quantitatively into the half ester 3b by treating with one equivalent of KOH in ethanol and subsequent acidification with 3N HCl. The half ester 3b (258 mg, 1 mmol) was converted into sodium salt with one equivalent of NaH in dry toluene, and diphenyldiselenide (374 mg, 1.2 mmol) was added. The mixture was refluxed for 3 hr. Ethyl 9-keto-2-phenylselenyldecanoate 4 was isolated as an oil after column chromatography [175 mg, 47%; NMR δ 6.9-7.4 (5H, br, phenyl), 3.95 (2H, q, $J = 7$ Hz), 3.38 (1H, t, $J = 7$), 2.1-2.5 (2H, br), 2.0 (3H, s), 1.12 (3H, t, $J = 7$); IR (neat) 1730, 1580, 740, 690 cm^{-1}]. This method of introduction of phenylselenyl group can be carried out without protecting the ketone and without using a strong base.

The oxidative removal of the phenylselenyl group from 4 (137 mg, 0.37 mmol) was carried out by the established method^{7,8} using NaIO_4 (235 mg, 1.1 mmol) to give ethyl 9-keto-2-decenoate 5a [71.7 mg, 91%; NMR δ 6.79 (1H, dt, $J = 16.2$ & 7 Hz), 5.65 (1H, dt, $J = 16.2$ & 1), 4.07 (2H, q, $J = 7.0$), 2.0-2.5 (4H, br), 2.0 (3H, s), 1.22 (3H, t, $J = 7$); IR (neat) 1720, 1655, 980 cm^{-1}]. The trans configuration of the double bond was fully confirmed by the NMR spectrum. Hydrolysis of 5a with dilute KOH solution produced queen substance as colorless crystals, which was identified by melting point (53-55°C, reported, 54.5-55.5°C)⁹, undepressed with an authentic sample.

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