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PREPARATION OF FIVE- AND SIX- MEMBERED CYCLIC KETONES BY THE PALLADIUM-CATALYZED CYCLIZATION REACTION. APPLICATION TO METHYL DIHYDROJASMONATE SYNTHESIS

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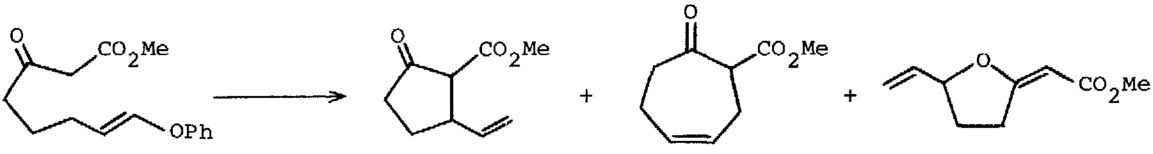
Summary: Methyl 3-oxo-8-phenoxy-6-octenoate (1) was cyclized using $Pd(OAc)_2$-PPh_3 as a catalyst to give 2-carbomethoxy-3-vinylcyclopentanone (2) and 2-carbomethoxy-4-cycloheptenone (3). The former was the main product in acetonitrile. 2-Alkylated 3-oxo-8-phenoxy-6-octenoates were converted mainly to the five-membered ketones. Based on this cyclization method, methyl dihydrojasmonate (8) was prepared from methyl 2-pentyl-3-oxo-8-phenoxy-6-octenoate (5). Methyl 3-oxo-9-phenoxy-7-nonenoate (10) was subjected to the palladium-catalyzed cyclization to afford 2-carbomethoxy-3-vinylcyclohexanone (11) *selectively without forming the eight-membered ketone* 12.

We had discovered the reaction of π-allylpalladium complex with carbanions as a useful method of carbon-carbon bond formation.[1] Since our discovery, a considerable progress in the synthetic application of the reactions of π-allylpalladium complexes or intermediates with carbanions as catalytic[2] or stoichiometric[3] process has been made. The reaction is particularly useful for the preparation of large and medium sized lactones and ketones.[4,5] In these cyclizations, formation of two allylic isomers is possible, but it was reported that the larger rings are preferentially formed rather than the smaller ones.[6] We now wish to report results of our studies aimed at preparing five- and six-membered cyclic ketones by the palladium-catalyzed intramolecular reaction of active methylene with allylic ether moiety.

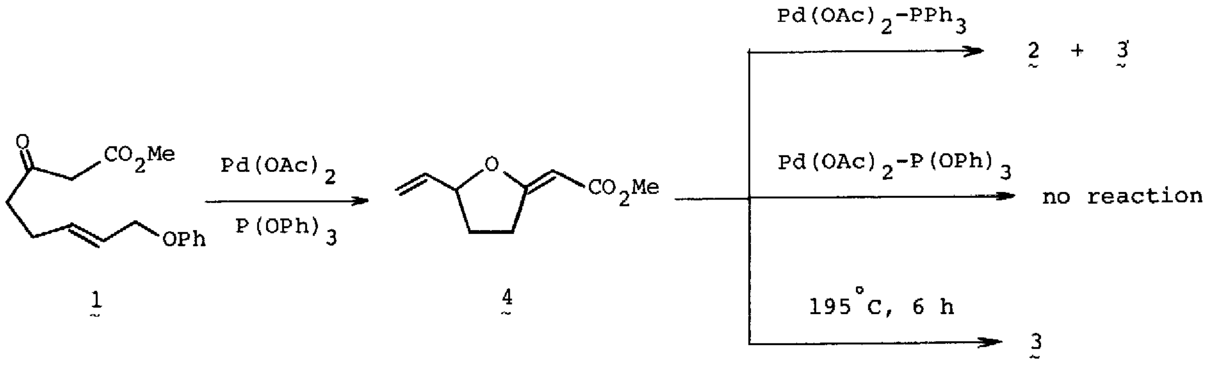
We have synthesized methyl (*E*)-3-oxo-8-phenoxy-6-octenoate (1) by the reaction of dianion of methyl acetoacetate with (*E*)-1-chloro-4-phenoxy-2-butene (77% yield), and carried out its cyclization using 5-10 mol% of $Pd(OAc)_2$-phosphine or phosphite as a catalyst at refluxing temperature of various solvents without using a base.



1 2 3 4

2-Carbomethoxy-3-vinylcyclopentanone (2) and 2-carbomethoxy-4-cycloheptenone (3) were obtained as the C-alkylated products. [2 bp 65-70°C/2 Torr; IR (film): 1756, 1722 (C=O), 1647 (C=C) cm^{-1}; NMR (CCl_4): δ 1.10-2.70 (m, 5H), 2.74-3.30 (m, 1H), 3.62 (s, 3H), 4.79-5.18 (m, 2H), 5.36-6.00 (m, 1H). 3 bp 65-70°C/2 Torr; IR (film): 1736, 1702 (C=O), NMR (CCl_4): δ 1.70-3.00 (m, 6H), 3.54 (s, 3H), 3.40-3.82, 12.55 (m, 1H, keto enol form), 5.27-5.70 (m, 2H)]. The ratio of 2 and 3 changed depending on the conditions as shown in the table. The nature of phosphine ligands was not crucial: PPh_3, PBu_3, and bis(diphenylphosphino)ethane [DIPHOS] gave similar ratios. The largest effect was observed by solvents. The desired 2 was obtained in 87% selectivity when acetonitrile or propionitrile was used (Exp. 8). Dioxane, benzene and THF gave the higher ratios of 3, but the conditions for the selective formation of 3 could not be found. The five-membered ketones were obtained predominantly when 2-alkylated derivatives were subjected to the cyclization. No seven-membered ketones were formed with the larger substituents (Exp. 10-13).

In addition to 2 and 3, formation of 2-carbomethoxymethylidene-5-vinyltetrahydrofuran (4) was detected as the O-alkylation product, which was rearranged to 2 and 3 during the reaction by the palladium catalyst.[7] This is the first example of the palladium-catalyzed O-alkylation of enolates. [4 IR (film): 1701 (C=O), 1639 (C=C); NMR (CCl_4): δ 1.40-3.36 (m, 4H), 3.57 (s, 3H), 4.53-4.97 (m, 1H), 5.01-5.45 (m, 3H), 5.58-6.20 (m, 1H)]. Interestingly, 4 was obtained selectively when triphenyl phosphite was used as the ligand (Exp. 1). This means that the Pd-phosphite catalyst has no catalytic activity for the rearrangement of 4 to 2 and 3. We confirmed that 4 was rearranged completely to 2 and 3 with $Pd(OAc)_2$-PPh_3. The ratios of 2 and 3 after the rearrangement were 87 : 13 in acetonitrile (1 h) and 45 : 55 in benzene (40 min). [3,3]Sigmatropic rearrangement of 4 in *N*-methylpyrrolidone at 195°C afforded 3 selectively as expected. These results suggest that 2 and 3 were formed directly from 1, and also *via* the formation of 4 and its rearrangement.

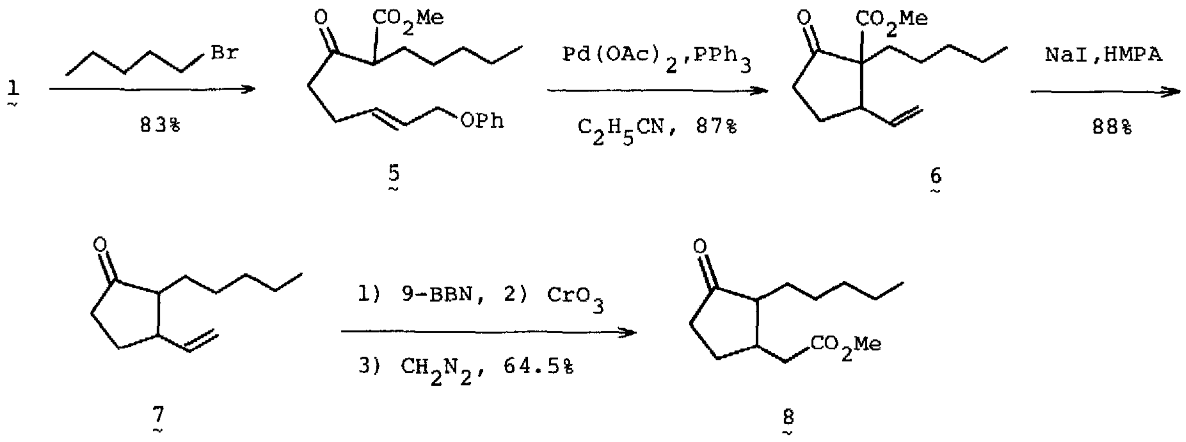


Based on the preferential formation of the five-membered ketones from the 2-alkylated keto esters, synthesis of methyl dihydrojasmonate (8) was carried out by the sequence of reactions, shown in the next page.

Table. Cyclization of Methyl 3-Oxo-8-phenoxy-6-octenoate and Its 2-Alkyl Derivatives[a]

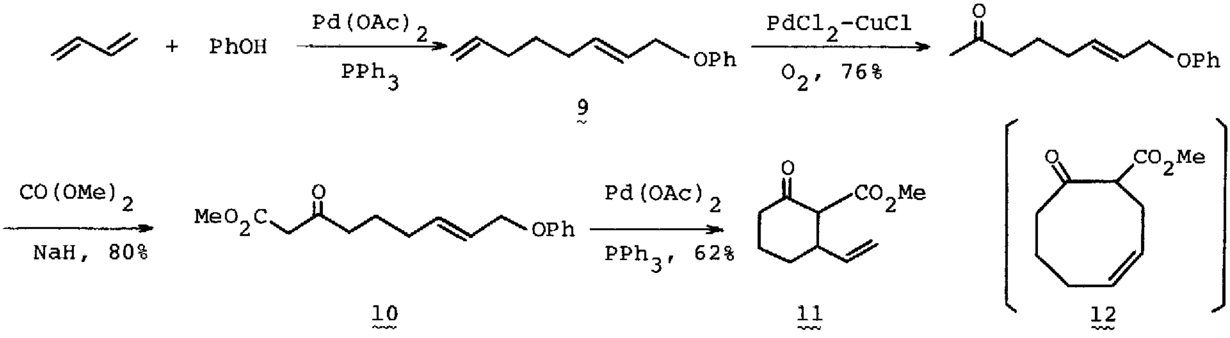
No	R	Solvent	Ligand	Ratios[b]				Time
				2	3	4	Others	(h)
1	H	CH_3CN	$P(OPh)_3$	0	0	100	0	8
2	H	CH_3CN	DIPHOS	76	12	0	12	12
3	H	CH_3CN	PBu_3	85	15	0	0	1
4	H	dioxane	PPh_3	46	51	0	3	1/3
5	H	benzene	"	44	49	0	7	2/3
6	H	THF	"	37	57	0	6	8
7	H	acetone	"	60	27	0	13	2.5
8	H	CH_3CN	"	87(59%)[c]	13	0	0	1
9	CH_3	CH_3CN	"	95(72%)	5	0	0	1/4
10	C_2H_5Ph	CH_3CN	"	(70%)				1/4
11	n-C_5H_{11}	C_2H_5CN	"	(87%)				3
12	Z-$CH_2CH{=}CHC_2H_5$	C_2H_5CN	"	(79%)				2
13	$CH_2C{\equiv}CC_2H_5$	C_2H_5CN	"	(74%)				1.5

a) Reactions were carried out at refluxing temperature of the solvents with $Pd(OAc)_2$ (5-10 mol%) and ligands (20-35 mol%). b) Determined by gas chromatography. c) Isolated yields.



Alkylation of 1 with pentyl bromide (83%), followed by cyclization with $Pd(OAc)_2$-PPh_3 in boiling propionitrile for 3 h produced the five-membered ketone 6 in 87% yield. 6 was decarbomethoxylated with NaI in HMPA at 100°C to give 7 (88%). Hydroboration of 7 gave the diol, which was oxidized to the keto acid and then methylated with diazomethane to afford methyl dihydrojasmonate (8) in 64.5% overall yield.

Then methyl 3-oxo-9-phenoxy-7-nonenoate (10) was prepared from the butadiene telomer 9 by the following way, and subjected to the palladium-catalyzed cyclization. 2-Carbomethoxy-3-vinylcyclohexanone (11) was obtained in nearly 90% selectivity using $Pd(OAc)_2$ with PPh_3, DIPHOS, or $P(OPh)_3$ in acetonitrile, benzene, or dioxane without forming the eight-membered ketone 12.



Application of these cyclization methods to syntheses of more complex molecules of natural origin is under active investigation.

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