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AN EFFICIENT SYNTHETIC METHOD OF METHYL (±)-JASMONATE

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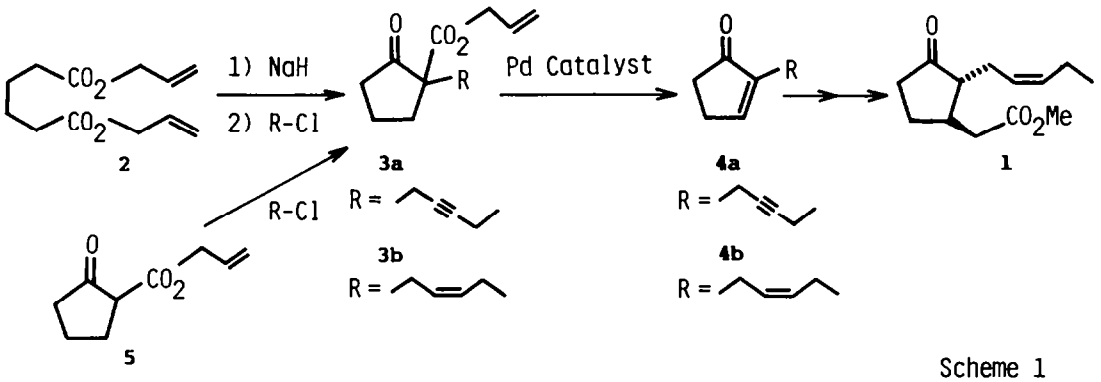
Abstract - An efficient synthetic method of methyl (±)-jasmonate is described. 2-Pentynyl-2-cyclopentenone, the key intermediate in this route, was synthesized by applying the palladium-catalyzed enone formation from allyl β-keto carboxylate as a key reaction.

INTRODUCTION

Methyl (±)-jasmonate (**1**) is an important constituent[1] for characteristic odor of Jasmine oil, and very useful in perfume industry. Therefore, many synthetic routes to this compoumd have been reported,[2] but most of these routes are not satisfactory, particularly from a standpoint of its commercial production. We have directed our attention to develop an efficient synthetic method for methyl (±)-jasmonate (**1**) from cheaply available materials.

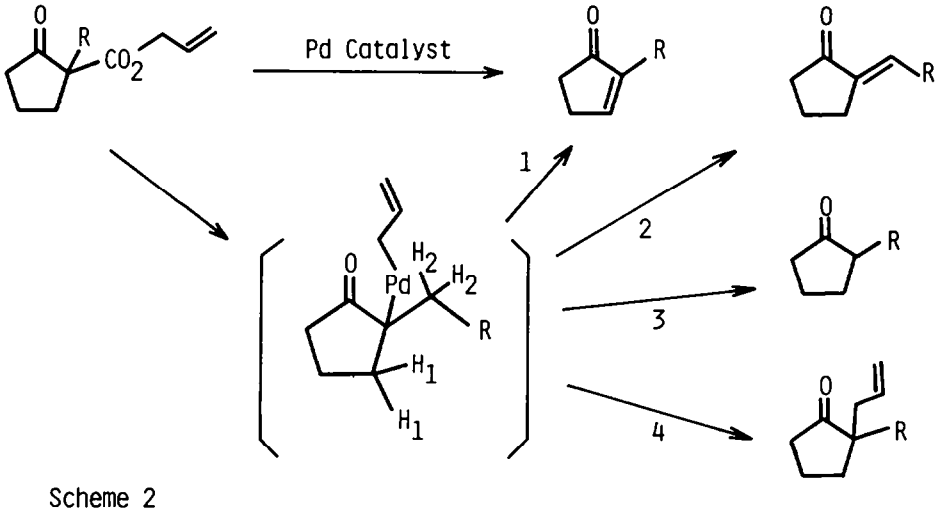
Recently, we have reported a novel synthetic method of α,β-unsaturated ketones by the palladium catalyzed decarboxylation-dehydrogenation reaction of allyl β-keto carboxylates.[3] We applied this reaction to the synthesis of 2-(cis-2-pentenyl)-2-cyclopentenone (**4b**), which is an important intermediate for the synthesis of **1**. In this paper, we wish to report an efficient procedure for producing methyl (±)-jasmonate starting from cheaply available adipate by the sequence of reactions shown below.



Scheme 1

RESULTS

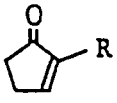
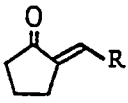
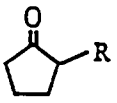
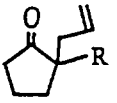
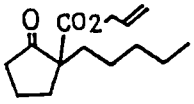
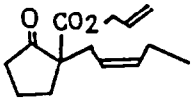
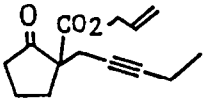
The β-keto esters **3a** and **3b** were prepared from diallyl adipate (**2**) and 2-pentynyl chloride[4] or cis-2-pentenyl chloride[4] respectively by Dieckmann condensation-alkylation sequence using NaH as a base in 85-90% yield. Also **3a** and **3b** were synthesized by alkylation of allyl 2-oxo-cyclopentanecarboxylate (**5**) with the corresponding alkyl chlorides in 90-95% yield. The next step is the conversion of β-keto esters **3a** and **3b** to the cyclopentenone **4a** and **4b** by the palladium-catalyzed decarboxylation-dehydrogenation reaction. Three competitive reactions proceed by the palladium-catalyzed reaction of allyl 2-oxo-1-alkylcyclopentanecarboxylate. They are the decarboxylation-dehydrogenation to give 2-alkyl-2-cyclopentenone (reaction 1, Scheme 2), the decarboxylation-protonation to 2-alkylcyclopentanone (reaction 3), and the decarboxylation-allylation to 2-allyl-2-alkylcyclopentanone (reaction 4). Selectivity for these three reactions can be controlled by careful selection of reaction conditions. Previous studies with other substrates suggest that it is possible to carry out the decarboxylation-dehydrogenation reaction as a main path under certain conditions. In addition, the decarboxylation-dehydrogenation produces 2-alkyl-2-cyclopentenone (reaction 1) and 2-alkylidenecyclopentanone (reaction 2) which are the endo-exo isomers. Thus there is a possibility of forming four compounds by the palladium-catalyzed reaction as shown in Scheme 2, and it is important to find optimum conditions for selective formation of the required 2-alkyl-2-cyclopentenone.



Scheme 2

At first, the selectivity for the endo and exo double bonds was investigated. In the case of the 2-pentenyl derivative of β-keto ester **3b**, the endo/exo ratio was 55/27. After several attempts to increase the endo selectivity, we found that the endo/exo ratios changed considerably depending on the structure of 2-alkyl groups. As shown in Table 1, the highest endo/exo ratio of 85/5 was obtained with 2-pentynyl group by using $Pd(OAc)_2$ and dppe [bis(diphenylphosphino)ethane] as a catalyst. Also the ratio was 65/16 with 2-pentyl. Thus, 2-pentynyl compound **3a** was found to be the suitable one for the present purpose.

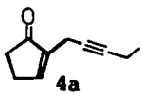
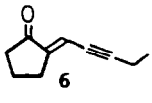
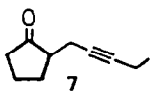
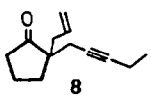
Table 1. Reaction of Allyl 2-Oxocyclopentanecarboxylate Derivatives with Pd-dppe Catalyst[a]

Run	Substrate	Product Yield (%)[b,c]			
					
1		65	16	5	0
2		55	27	7	1
3		85	5	4	1

a. Reactions were carried out with 5 mol% of $Pd(OAc)_2$ and dppe in boiling CH_3CN under N_2.
b. All products were identified by NMR and IR spectra.
c. GLC yield.

The second problem is how to suppress the decarboxylation-protonation (reaction 3, Scheme 2). It was found that amount of 2-pentynylcyclopentanone (7) increased by decreasing amounts of the catalyst as shown in Table 2. The cyclopentanone 7 was produced as high as 33% by using 1 mol% of the catalyst. In order to increase the formation of **4a**, we tried various palladium compounds and ligands, and finally we obtained satisfactory results with 0.5-1.0% $Pd(OAc)_2$ by the use of PPh_3 as a ligand (Table 3). Also the ratio of $PPh_3/Pd(OAc)_2$ is an important factor for the selectivity of the reaction as shown in Figure 1 and Table 3. When the ratio became higher than three, the allylation (reaction 4) was the main path of the reaction.[5] The smaller ratios favor the formation of **4a**, and even in the absence of PPh_3, a high ratio of **4a** was obtained. The best selectivity for **4a** was obtained by the ratios from 1 to 1.5.

Table 2. Reaction of **2a**. Effect of Amounts of the Catalyst.[a]

Run	Catalyst Amount (mol%)	Reaction Time (h)	Product Yield (%)[b,c]			
			 **4a**	 **6**	 **7**	 **8**
1	5	0.5	85	5	4	1
2	2	2.5	70	5	14	1
3	1	10	60	3	33	2

a. Reactions were carried out in boiling CH_3CN under N_2.
b. All products were identified by NMR and IR spectra.
c. GLC yield.

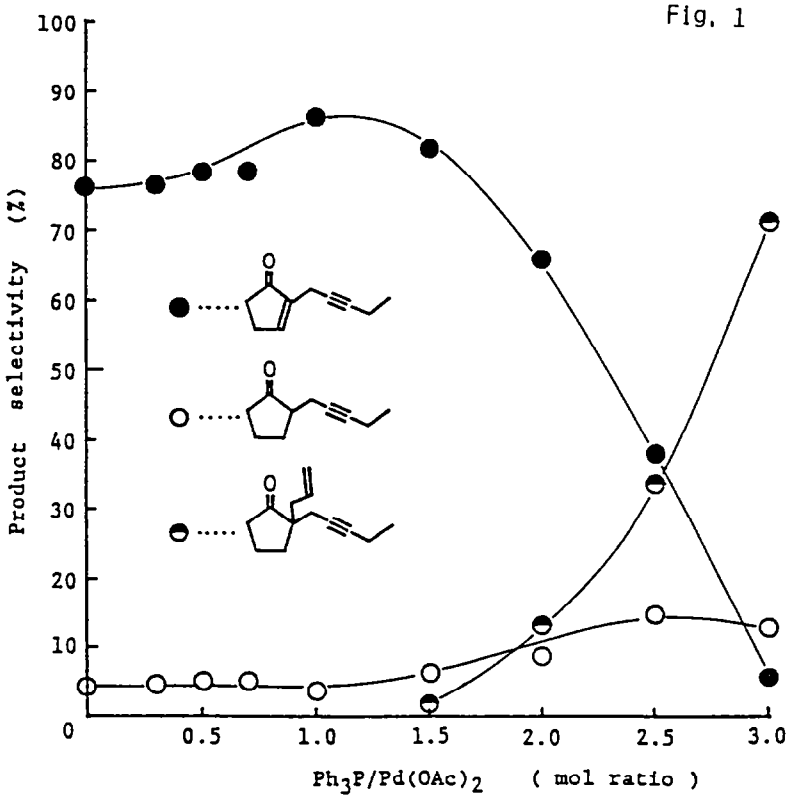
Table 3. Reaction of 3a. Effect of Various Palladium Catalysts[a]

Run	Catalyst	Cat. Amount (mol%)	Ligand	Ligand Amount (mol%)	Solvent	Reaction Time (h)	Product Yield(%)[b,c] 4a	6	7	8
1	$Pd(OAc)_2$	5.0	2,2'-Dipyridyl	5.0	CH_3CN	3	51	3	38	8
2	"	1.0	PPh_3	2.0	"	1	67	4	10	13
3	"	"	"	1.0	"	"	86	6	3	0.4
4	"	0.5	"	0.75	"	"	83	5	5	2
5	"	"	None	-	"	2	80	5	4	0
6	"	1.0	PPh_3	1.5	t-BuOH	"	70	4	11	5
7	"	"	"	"	toluene	"	72	4	7	9
8	$Pd(acac)_2$	0.5	"	0.75	CH_3CN	4	77	4	9	3

a. Reactions were carried out in boiling solvents under N_2.
b. All products were identified by NMR and IR spectra.
c. GLC yield.

Moreover, the cyclopentenone formation proceeded in various solvents such as tert. butyl alcohol and toluene by using PPh_3 as a ligand, but the most satisfactory results were obtained in acetonitrile as shown in Table 3. The reaction proceeded smoothly in boiling acetonitlile.

Fig. 1



Based on these results, the β-keto ester **3a** was converted to the cyclopentenone **4a** in 80-85% yields. And then, the cyclopentenone **4a** was hydrogenated with a Lindlar catalyst under atmospheric pressure of hydrogen at room temperature to give the key intermediate **4b** in 95% yield. The cyclopentenone **4b** was easily transformed into methyl (±)-jasmonate (**1**) by two-step sequence. The Michael addition of methyl malonate to **4b** gave the adduct in 98% which was converted to **1** by saponification-decarboxylation in 90% yield.

Thus methyl (±)-jasmonate (**1**) was synthesized in higher than 60% total yield for over all six steps from cheaply available adipic acid.

EXPERIMENTAL

IR spectra were determined on a HITACHI 260-30 spectrometer. NMR spectra were recorded with tetramethylsilane as an internal standard on a JEOL-FX 100 (100 MHz) spectrometer.

Allyl 1-(2-pentynyl)-2-oxocyclopentanecarboxylate (**3a**)

a)From diallyl adipate

To a stirred suspension of NaH (4.30 g of 64.5% mineral oil dispersion, 0.117 mol) in dry toluene (140 mL) was added allyl alcohol (2.14 g) at room temperature under nitrogen atmosphere. To the mixture was added dropwise diallyl adipate (23.89 g, 0.105 mol) over 1 h, and the resulting mixture was heated at 90 °C for 3 h. Then allyl alcohol was removed from this mixture azeotropically. When allyl alcohol was not detected in the reaction mixture, 2-pentynyl chloride (10.58 g, 0.102 mol) was added dropwise to the resulting mixture over 10 min at 100 °C. After being stirred for 3-4 h, the mixture was cooled to room temperature, and then quenched with 10% aq HCl. The organic layer was washed with sat.$NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated.

The residue was distilled to give **3a**. (21.96 g, 87% yield from diallyl adipate): bp 131-133 °C/4 mmHg, IR (neat) 3060, 2950, 1740, 1720, 1640, 1305, 1140, 1095, 980, 920, 865, 775 cm^{-1}. NMR ($CDCl_3$) δ = 0.98 (t, 3H, J=7 Hz), 1.75-2.50 (m, 8H), 2.47 (t, 2H, J=1 Hz), 4.43 (d, 2H, J=5 Hz), 4.96-5.30 (m, 2H), 5.40-5.96 (m, 1H). Anal. Calcd for $C_{15}H_{20}O_3$: C,72.55; H, 8.12. Found: C, 72.59; H, 8.10.

b) From allyl 2-oxocyclopentanecarboxylate (**5**)

A mixture of **5** (295 g, 1.67 mol), K_2CO_3 (692.4 g, 5.01 mol) and 2-pentynyl chloride (221 g, 2.11 mol) in dry acetone (1500 mL) was refluxed for 7-8 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was distilled to give **3a** (371 gm 88% yield from **5**).

2-(2-Pentynyl)-2-cyclopentenone (**4a**)

To a solution of PPh_3 (251.9 mg, 0.962 mmol) in CH_3CN (500 mL) was added $Pd(OAc)_2$ (143.6 mg, 0.641 mmol) at 80 °C under nitrogen. Then the β-keto ester **3a** (30 g, 0.128 mmol) was added dropwise to the mixture over 30 min. The resulting mixture was heated at 80 °C for 30 min, and concentrated in vacuo. The residue was distilled to give **4a** (17.26 g, 86% purity, 81% yield): bp. 72-78 °C/1 mmHg; IR (neat) 2200, 1700, 1635, 1610, 1240, 1195, 1030, 1000 cm^{-1}. NMR ($CDCl_3$) δ = 1.11 (t, 3H, J=7.0 Hz), 2.1-3.3 (m, 8H), 7.7-7.9 (m, 1H).

By-products were separated by preparative gas chromatography, and their structures were determined as follows.

2-(2-Pentynyl)cyclopentanone (**7**): IR (neat) 1735, 1400, 1155, 1015, 1000, 925 cm^{-1}; NMR ($CDCl_3$) δ = 1.05 (t, 3H, J=6.5 Hz), 1.50-2.60 (m, 11H).

2-Allyl-2-(2-pentynyl) cyclopentanone (**8**): IR (neat) 1735, 1630, 1320, 1265, 1185, 1155, 995, 785 cm^{-1}; NMR ($CDCl_3$) δ = 1.05 (t, 3H, J=6.5 Hz), 1.60-2.40 (m, 12H), 4.80-5.90 (m, 3H).

2-(2-Pentynylidene)cyclopentanone (**6**): IR (neat) 2200, 1715, 1615, 1225, 1203, 1160, 825; NMR ($CDCl_3$) δ = 1.19 (t, 3H, J=6.5 Hz), 1.70-2.75 (m, 8H), 6.00-6.15 (m, 1H).

2-(cis-2-Pentenyl)-2-cyclopentenone (**4b**)

A mixture of the purified **4a** (108.7 g, 0.734 mol) and Lindlar catalyst (5.4 g) in n-BuOH (200 mL) was stirred at room temperature under 1 atm of H_2. After the hydrogen-uptake ceased in 2 h, the mixture was filtered and the filtrate was concentrated. The residue was distilled to give **4b** (104.3 g, 95% yield): bp. 85-90 °C/3 mmHg; IR (neat) 1700, 1625, 1402, 1348, 1239, 1195, 1046, 1000, 790 cm^{-1}; NMR (CCl_4) δ = 0.95 (t, 3H, J=7.5 Hz), 1.8-2.8 (m, 8H), 5.0-5.5 (m, 2H), 7.0-7.2 (m, 1H).

Michael-addition of methyl malonate to **4a**

A mixture of **4b** (812.6 g, 5.417 mol), dimethyl malonate (1073.5 g, 8.132 mmol), and NaOMe (17.6 g, 0.326 mmol) in MeOH (500 mL) was stirred at 0 °C for 10 h under nitrogen. Then the mixture was quenched with aq HCl (185 mL). The organic layer was concentrated by distillation under reduced pressure to give crude ester (1621.5 g, 93.2% purity, 98.9% yield). This crude ester was used in the next reaction without purification.

Methyl (±)-jasmonate (**1**)

A mixture of the crude ester of the Michael addition (1621 g, 93.2% purity, 5.357 mmol) and adipic acid (625.7 g, 4.286 mmol) was heated at 190 °C for 6 h. Then the mixture was washed with aq. $NaHCO_3$ and distilled to give methyl (±)-jasmonate (**1**) (1080 g, 4.826 mmol, 90% yield). bp. 130-135 °C/1 mmHg; IR (neat) 1735, 1195, 1165 cm^{-1}. NMR ($CDCl_3$) δ = 0.95 (t, 3H, J=7 Hz), 1.6-2.8 (m, 12H), 3.65 (s, 3H), 5.0-5.55 (m, 2H).

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