A CONCISE SYNTHESIS OF ARNOTTIN I *VIA* INTERNAL BIARYL COUPLING REACTION USING PALLADIUM REAGENT ¶

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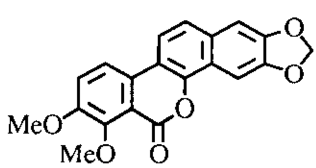
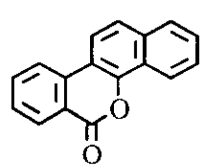
Abstract---Total synthesis of arnottin I (**1**) was accomplished *via* the internal aryl-aryl coupling reaction of iodo-ester (**2**) by the palladium-assisted cyclization reaction.

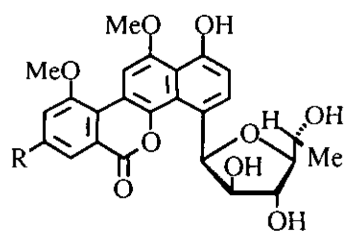
The structure of arnottin I (**1**) isolated from *Xanthoxylum arnottianum* Maxim.[1a] has recently been identified by its synthesis [1b] using the common intermediate for the synthesis of chelerythrine.[2] Its skeleton, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (A) is the same as that of gilvocarcin type, which has attracted much attention because of its high antitumor activity.[3] Thus, we developed a convenient and concise synthetic method for **1**. Since the internal cross coupling reaction with palladium catalyst has recently been utilized for the synthesis of condensed aromatic compounds,[4] we designed a synthetic plan for **1** involving an internal biaryl coupling reaction by Pd as a key reaction shown in Scheme 1.



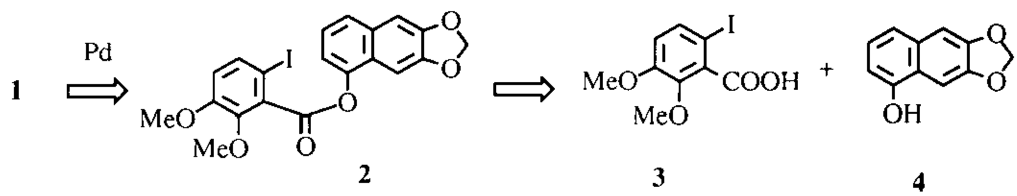
Arnottin I (**1**)



A



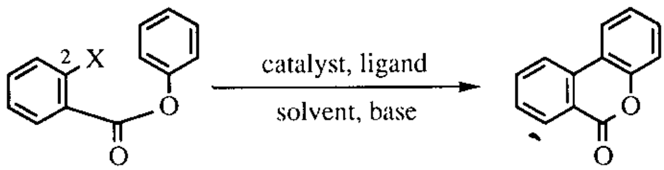
Gilvocarcin M : R = Me
V : R = Vinyl
E : R = Et



Scheme 1

¶ This paper is dedicated to the memory of the late Professor Syun-ichi Yamada

It was reported that an internal coupling reaction of bromo-ester (**5a**) with $Pd(OAc)_2$ (0.1 eq), triphenylphosphine (0.2 eq), and sodium acetate (2.4 eq) in dimethylacetoamide at 170°C gave cyclized product (**6**) in 41% yield.[5a] To improve the yield, cyclization reaction of **5** was examined using Pd(II) including purified $Pd(OAc)_2$,[6] ligand and base. The results, as summarized in Table I, indicated that iodo-ester (**5b**) is more reactive than bromo-ester (**5a**). Interestingly, the reaction of **5b** with $Pd(OAc)_2$ in the presence of bidentate ligand (DPPP) or without ligand provided **6** in a higher yield (see runs 7-9) in comparison with reaction of **5b** with other Pd reagents (see runs 10 -13). However, reaction of **5c**[7] was unfruitful.



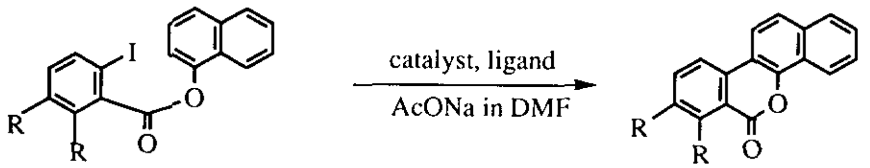
5a X=Br
5b X=I
5c X=OTf

6

Table 1. Results of Cyclization Reaction of Phenyl 2-Substituted Benzoate (5) [a)]

starting material	run	catalyst	equiv.	ligand	solvent	base	time	temp.	yield of **6** (%)
5a	1	$Pd(OAc)_2$	0.1	PPh_3	DMF	NaOAc	2 h	reflux	61
	2	$Pd(OAc)_2$	0.1	—	DMF	NaOAc	48 h	reflux	59
	3	$Pd(OAc)_2$	0.5	PPh_3	DMF	NaOAc	2 h	reflux	15
	4	$Pd(OAc)_2$	0.1	PPh_3	benzene	NaOAc	2 h	reflux	— b)
5b	5	$Pd(OAc)_2$	0.1	PPh_3	DMF	NaOAc	1.5 h	reflux	68
	6	$Pd(OAc)_2$	0.1	POT	DMF	Ag_2CO_3	24 h	reflux	38
	7	$Pd(OAc)_2$	0.1	DPPP	DMF	NaOAc	2 h	reflux	75
	8	$Pd(OAc)_2$	0.1	—	DMF	NaOAc	1 h	reflux	84
	9	$Pd(OAc)_2$	0.1	—	DMF	NaOAc	5 h	130°C	84
	10	$Pd(PPh_3)_2Cl_2$	0.1	—	DMF	NaOAc	1.5 h	130°C	66
	11	$Pd(acac)_2$	0.1	—	DMF	NaOAc	1.5 h	130°C	68
	12	$Pd(acac)_2$	0.1	PPh_3	DMF	NaOAc	2.5 h	130°C	57
	13	$Pd(PPh_3)_4$	0.1	—	DMF	NaOAc	4 h	130°C	54
5c	14	$Pd(OAc)_2$	0.1	PPh_3	DMF	$^{i}Pr_2NEt$	8 h	reflux	12
	15	$Pd(OAc)_2$	0.1	—	DMF	NaOAc	3.5 h	reflux	— c)
	16	$Pd(OAc)_2$	0.1	DPPP	DMF	$^{i}Pr_2NEt$	3 h	reflux	20
	17	$Pd(PPh_3)_2Cl_2$	0.27	—	DMA	NaOPiv	10 h	80°C	22 d)
	18	$Pd(PPh_3)_2Cl_2$	0.1	—	DMF	$^{i}Pr_2NEt$	8 h	reflux	22 e)
	19	$Pd(acac)_2$	0.1	DPPP	DMF	$^{i}Pr_2NEt$	24 h	reflux	— f)
	20	$Pd(PPh_3)_4$	0.1	—	DMF	$^{i}Pr_2NEt$	4 h	reflux	— g)

a) All reactions were carried out using Pd catalyst and ligand in a ratio of 1:2 and 2 mol equivalent of base. b) **5b** was recovered in 45% yield. c) Acetate (**5**, X=OAc) was obtained in 24% yield. d) See reference 5c). Hydrolysis product (**5**, X=OH) was obtained in 21% yield. e) Phenyl benzoate was obtained in 40% yield together with 8% yield recovered **5c**. f) Phenyl benzoate was obtained in 90% yield. g) Phenyl benzoate and **5c** were obtained in 23 and 41% yields, respectively.

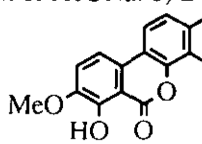


7a R=H 8a R=H
7b R=OMe 8b R=OMe

Table 2. Results of Cyclization Reaction of 1-Naphthyl Benzoate (7) [a)]

starting material	run	catalyst	equiv.	ligand	time	temp.	yield of **8** (%)
7a	1	$Pd(OAc)_2$	0.1	PPh_3	3 h	150°C	55
	2	$Pd(OAc)_2$	0.1	—	4 h	130°C	48
	3	$Pd(OAc)_2$	0.1	—	2 h	reflux	51
	4	$Pd(PPh_3)_2Cl_2$	0.1	—	5 h	130°C	59
	5	$Pd(PPh_3)_2Cl_2$	0.2	—	3.5 h	130°C	70
	6	$Pd(acac)_2$	0.1	PPh_3	1.5 h	130°C	59
	7	$Pd(acac)_2$	0.1	—	2.5 h	130°C	72
	8	$Pd(PPh_3)_4$	0.1	—	5 h	130°C	49
7b	9	$Pd(OAc)_2$	0.1	—	16 h	130°C	58
	10	$Pd(OAc)_2$	0.1	—	2 h	reflux	47 [b)]
	11	$Pd(PPh_3)_2Cl_2$	0.1	—	5 h	130°C	60
	12	$Pd(acac)_2$	0.1	—	4 h	130°C	76
	13	$Pd(acac)_2$	0.1	PPh_3	3 h	130°C	79
	14	$Pd(PPh_3)_4$	0.1	—	5 h	130°C	64

a) All reactions were carried out using Pd catalyst and ligand in a ratio of 1:2 and 2 mol equivalent of AcONa. b) Demethylated compound (**B**) was obtained in 30% yield.



(**B**)

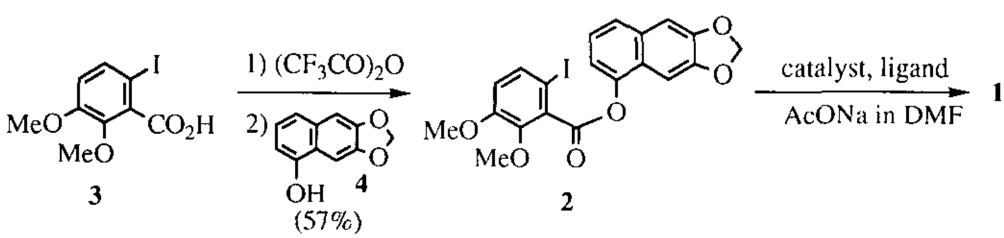


Table 3. Results of Cyclization Reaction of 6,7-Methylenedioxy-1-naphthyl 2,3-Dimethoxy-6-iodobenzoate (**2**) to Arnottin I (**1**)[a)]

run	catalyst	equiv.	ligand	time	temp.	yield of **1** (%)
1	$Pd(PPh_3)_2Cl_2$	0.1	—	5 h	130°C	52
2	$Pd(acac)_2$	0.1	PPh_3	4 h	130°C	56
3	$Pd(acac)_2$	0.1	PPh_3	2 h	150°C	72
4	$Pd(PPh_3)_4$	0.1	—	3.5 h	130°C	58
5	$Pd(PPh_3)_4$	0.1	—	2 h	150°C	71

a) All reactions were carried out using Pd catalyst and ligand in a ratio of 1:2 and 2 mol equivalent of AcONa.

Next, the internal coupling reaction of naphthyl benzoate (7)[8] to tetracyclic compound (**8**) was examined. As shown in Table 2, $Pd(acac)_2$ and/or $Pd(PPh_3)_2Cl_2$ were more effective than $Pd(OAc)_2$ or $Pd(PPh_3)_4$ in the synthesis of **8**.

Finally, **1** was synthesized according to the synthetic plan shown in Scheme 1. Thus, ester (**2**) was prepared from acid (**3**)[9] and naphthol (**4**)[11] in 57% yield by Parish's method.[10] Palladium-assisted internal biaryl coupling reaction of **2** provided the cyclization product in a high yield as shown in Table 3 (see runs 3 and 5). The synthetic sample was identified with the authentic sample of arnottin I (**1**).

In conclusion, the present method using the Pd reagent is convenient for preparing benzonaphthopyranone derivatives (**A**).

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7. Triflate ester (**5c**) was prepared from salicylaldehyde *via* three steps in total yield of 51% ; i) reaction with Tf_2O, ii) oxidation with $NaClO_2$ and H_2O_2 in aqueous MeCN, and iii) reaction with $(COCl)_2$, followed by phenol.
8. Naphthyl ester (**7b**) was prepared from acid (**3**)[9] in 72% yield by successive treatment with $(CF_3CO)_2O$ and 1-naphthol in benzene at 60°C.[10]
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11. Naphthol (**4**) was prepared from 6,7-dimethoxy-1-tetralone *via* five steps in total yield of 15%; i) demethylation with BBr_3, ii) methylenation with CH_2Br_2 in the presence of CsF, iii) enol acetylation with isopropenyl acetate, iv) dehydrogenation with DDQ, and v) hydrolysis with 5% NaOH.[12]
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