June 2000 Chem. Pharm. Bull. 48(6) 861—864 (2000)

Synthesis of Arnottin I through a Palladium-Mediated Aryl–Aryl Coupling Reaction

Takashi HARAYAMA,* Hirotake YASUDA, Toshihiko AKIYAMA, Yasuo TAKEUCHI, and Hitoshi ABE

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-Naka, Okayama 700–8530, Japan.

Received January 31, 2000; accepted March 24, 2000

6*H*-Dibenzo[*b*,*d*]pyran-6-one, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one, and their derivatives were prepared *via* the palladium mediated aryl–aryl coupling reaction of aryl *ortho*-halobenzoate. The short step synthesis of arnottin I (1) was achieved by this method.

Key words arnottin I; palladium reagent; biaryl coupling reaction

Arnottin I (**1**) was isolated from *Xanthoxylum arnottianum* MAXIM.,[1] and thereafter, the total synthesis of **1** was used to identify the chemical structure.[2] The core of its structure involves the 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton which is the same as the gilvocarcins[3] and ravidomycin[4] (Chart 1). Since these compounds display biologically important properties[5] such as antitumor, antibacteria, or antivirus activity, our interests have been focused on the concise construction of the 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton.[6]

Recently, we demonstrated the aryl–aryl coupling reaction of amide type biaryl compounds using a palladium reagent,[7] and its application to the synthesis of nitidine[8] and chelerythrine.[9] This coupling reaction can be expected to be useful for the formation of other biaryl compounds such as the ester-linked biaryl compounds.

In this paper, we describe a palladium-mediated aryl–aryl coupling reaction[10] for the effective construction of 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one and the short step synthesis of arnottin I (**1**) as an application of this method.[11]

Internal Coupling Reaction of Phenyl Benzoate Derivatives In 1984, Ames and Opalko reported the intramolecular biaryl coupling reaction of both phenyl 2-bromobenzoate (**2**) and 2-bromophenyl benzoate (**3**).[12] In their report, the desired 6*H*-dibenzo[*b*,*d*]pyran-6-one (**4**)[12] was obtained from **2** using palladium (II) acetate ($Pd(OAc)_2$) (0.1 eq), triphenylphosphine (PPh_3), and sodium acetate (NaOAc) in *N*,*N*-dimethylacetamide (DMA), whereas **3** afforded no cyclized product **4** under the same reaction conditions (Chart 2).

In order to improve this unique biaryl coupling reaction, we investigated the reactivities of the corresponding iodo analogs **5**[13] and **6**,[14] which were supposed to be more highly reactive than the bromo compounds **2** and **3**. The results of the palladium-mediated reaction are summarized in Table 1. Initially, we examined $Pd(OAc)_2$ as a catalyst for the substrate **5**. It was found that the combination of a phosphine ligand and base was crucial for the yield of **4**. When PPh_3 was used as the ligand, sodium acetate gave a better result than silver carbonate (runs 1 and 2). While tri-(*o*-tolyl)phosphine ($P(2\text{-}Tol)_3$) lead to lower yield of **4** (runs 3 and 4), a bidentate phosphine ligand, 1,3-bis(diphenylphosphino)-propane (DPPP) gave **4** in good yield when it was used with

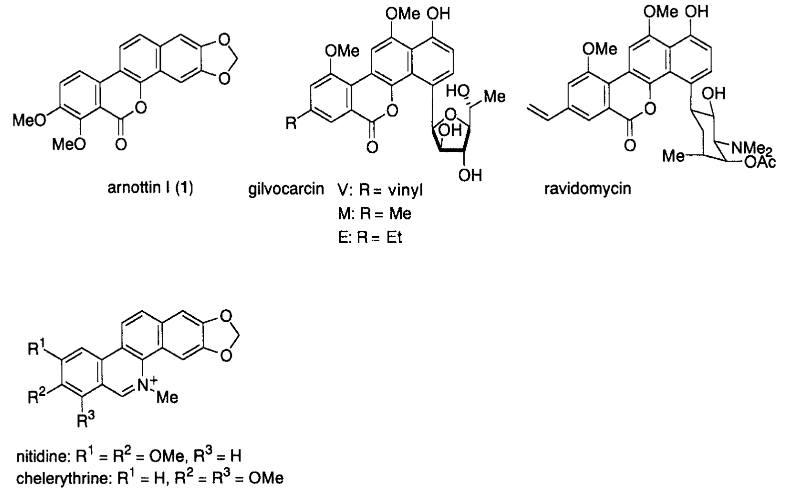


Chart 1

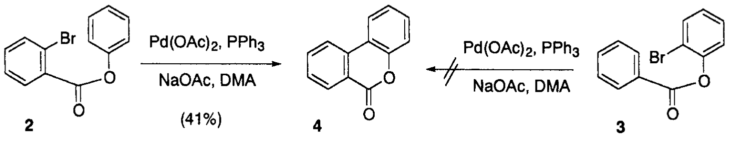


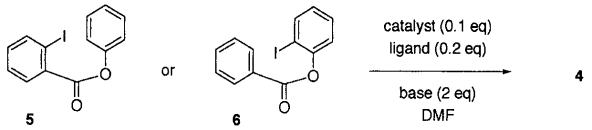
Chart 2

---

* To whom correspondence should be addressed. e-mail: harayama@pharm.okayama-u.ac.jp

NaOAc as the base (run 5). Interestingly, the best result was observed when no phosphine ligand was employed (run 7). The other catalysts such as bis(triphenylphosphine)palladium(II) chloride ($Pd(PPh_3)_2Cl_2$), palladium(II) acetylacetonate ($Pd(acac)_2$), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) afforded **4** in moderate yields (runs 8—11). On the other hand, the reaction of the ester **6** with $Pd(OAc)_2$, PPh_3, and NaOAc showed extremely poor reactivity (run 12).

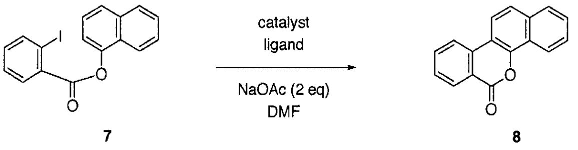
Table 1. Cyclization Reaction of Phenyl *o*-Iodobenzoate (**5**) and *o*-Iodophenyl Benzoate (**6**)



Run	Ester	Catalyst	Ligand	Base	Time (h)	Temp.	Yield (%) of **4**
1	**5**	$Pd(OAc)_2$	PPh_3	NaOAc	2	130 °C	73
2	**5**	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	24	Reflux	38
3	**5**	$Pd(OAc)_2$	$P(2\text{-Tol})_3$	NaOAc	4	Reflux	—[a]
4	**5**	$Pd(OAc)_2$	$P(2\text{-Tol})_3$	Ag_2CO_3	24	Reflux	36
5	**5**	$Pd(OAc)_2$	DPPP	NaOAc	2	Reflux	75
6[b]	**5**	$Pd(OAc)_2$	DPPP[c]	iso-Pr_2NEt	2	Reflux	—[d]
7	**5**	$Pd(OAc)_2$	None	NaOAc	1	Reflux	84
8	**5**	$Pd(PPh_3)_2Cl_2$	None	NaOAc	1.5	130 °C	66
9	**5**	$Pd(acac)_2$	None	NaOAc	1.5	130 °C	68
10	**5**	$Pd(acac)_2$	PPh_3	NaOAc	2.5	130 °C	57
11	**5**	$Pd(PPh_3)_4$	None	NaOAc	4	130 °C	54
12	**6**	$Pd(OAc)_2$	PPh_3	NaOAc	2	Reflux	6

a) Phenyl benzoate was detected on TLC. *b*) See ref. 7. *c*) Bu_3P (0.1 eq) was added as an additive. *d*) Phenyl benzoate was isolated in 65% yield.

Table 2. Cyclization Reaction of 1-Naphthyl *o*-Iodobenzoate (**7**)



Run	Catalyst	(mol eq)	Ligand	(mol eq)	Time (h)	Temp.	Yield (%) of **8**
1	$Pd(OAc)_2$	(0.1)	PPh_3	(0.2)	3	150°C	55
2	$Pd(OAc)_2$	(0.1)	None	—	2	Reflux	51
3	$Pd(PPh_3)_4$	(0.1)	None	—	5	130°C	49
4	$Pd(PPh_3)_2Cl_2$	(0.1)	None	—	5	130°C	59
5	$Pd(PPh_3)_2Cl_2$	(0.2)	None	—	3.5	130°C	70
6	$Pd(acac)_2$	(0.1)	PPh_3	(0.2)	1.5	130°C	59
7	$Pd(acac)_2$	(0.1)	None	—	2.5	130°C	72

Internal Coupling Reaction of 1-Naphthyl 2-Iodobenzoate and 1-Naphthyl 2,3-Dimethoxy-6-iodobenzoate As preliminary experiments for the synthesis of arnottin I, the reactivity of both naphthyl esters **7** and **9** was examined. These substrates were prepared by the esterification of benzoic acid derivatives with 1-naphthol. As shown in Table 2, the conversion of the ester **7** into the biaryl coupling product **8** was observed in all runs. When $Pd(OAc)_2$ was employed with PPh_3, the cyclized product **8** was generated in 55% yield (run 1). It was found that the effect of the phosphine ligand was negligible (run 2). Also, changing the catalyst to $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ did not have any notable effect (runs 3 and 4), but the use of 0.2 eq of the same catalyst lead to a slight improvement in the yield (run 5). While $Pd(acac)_2$ in the presence of PPh_3 gave **8** in only moderate yield (run 6), the best result was observed if this catalyst was used without the phosphine ligand (run 7).

Furthermore, our attempt at this coupling reaction of the ester-linked biaryl substrates was extended to the dimethoxy compound **9**. The results of the reaction are summarized in Table 3, in which results almost similar to those in Table 2 were observed. While the use of $Pd(OAc)_2$ gave **10** in moderate yields (runs 1 and 2), slightly higher yields were obtained when $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ was employed (runs 3 and 4). In this case, $Pd(acac)_2$ worked the most effectively to give **10** in up to 79% yield (runs 5 and 6).

Synthesis of Arnottin I Since the palladium-mediated coupling reaction of the ester-linked biaryl compounds was successful as already described, we planned the total synthesis of arnottin I utilizing this method. Our concise synthetic route is outlined in Chart 3.

The preparation of a key compound **11** should be realized by condensation between the carboxylic acid **12**[15] and naphthol **13** which was easily derived from commercially available 6,7-dimethoxy-α-tetralone (**14**) *via* several steps as shown in Chart 4. Thus, the demethylation of **14** followed by

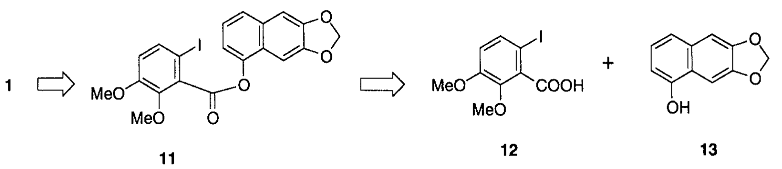


Chart 3

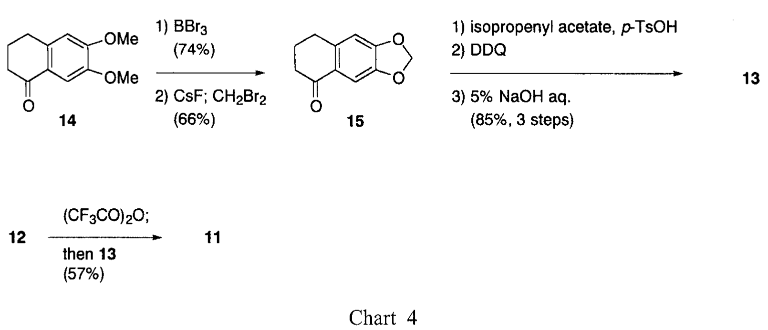
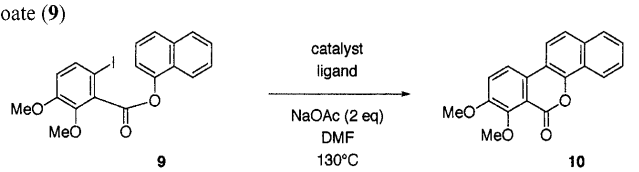


Chart 4

Table 3. Cyclization Reaction of 1-Naphthyl 6-Iodo-2,3-dimethoxybenzoate (**9**)



Run	Catalyst	(mol eq)	Ligand	(mol eq)	Time (h)	Yield (%) of **10**
1	Pd(OAc)$_2$	(0.2)	PPh$_3$	(0.4)	6.5	60
2	Pd(OAc)$_2$	(0.1)	None	—	16	58
3	Pd(PPh$_3$)4	(0.1)	None	—	5	64
4	Pd(PPh$_3$)$_2$Cl$_2$	(0.2)	None	—	10	65
5	Pd(acac)$_2$	(0.1)	PPh$_3$	(0.2)	3	79
6	Pd(acac)$_2$	(0.1)	None	—	4	76

Table 4. Cyclization Reaction of 6,7-Methylenedioxy-1-naphthyl 6-Iodo-2,3-dimethoxybenzoate (**11**)

$$\mathbf{11} \xrightarrow[\text{NaOAc (2 eq)}\ \text{DMF}]{\text{catalyst (0.1 eq)}\ \text{ligand (0.2 eq)}} \mathbf{1}$$

Run	Catalyst	Ligand	Time (h)	Temp. (°C)	Yield (%) of **1**
1	Pd(PPh$_3$)$_2$Cl$_2$	None	5	130	52
2	Pd(acac)$_2$	PPh$_3$	4	130	56
3	Pd(acac)$_2$	PPh$_3$	2	150	72
4	Pd(PPh$_3$)$_4$	None	3.5	130	58
5	Pd(PPh$_3$)$_4$	None	2	150	71

methylenation afforded **15**, and conversion into **13** was performed by Cushman's method[16)] involving the enol acetate formation, dehydrogenation, and hydrolysis. The esterification of **12** with trifluoroacetic anhydride was carried out to afford **11** in 57% yield.

The results of the internal biaryl coupling reaction of **11** in the presence of palladium reagent are summarized in Table 4. The formation of arnottin I was observed in all runs. Although this reaction at 130°C gave only moderate yields of **1** (runs 1, 2, and 4), a slightly higher temperature resulted in satisfactory yields (runs 3 and 5). Spectral data obtained from the synthetic material were in agreement with those for the natural product.

Conclusion We found that aryl *o*-halobenzoates could cyclize to give 6*H*-dibenzo[*b*,*d*]pyran-6-one, 6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one, and their derivatives using palladium reagent. The short step synthesis of arnottin I (**1**) was performed utilizing this internal aryl–aryl coupling reaction. Further studies on the mechanistic aspect and other application of this method are now underway in our laboratory.

Experimental

Melting points were measured with a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. NMR spectra were taken with a Varian VXR-500, VXR-200, or Hitachi R-1500 instrument with chemical shifts reported as δ ppm and couplings expressed in Hertz. Fast atom bombardment-mass spectra (FAB-MS) were obtained using a VG-70SE mass spectrometer. Elemental analyses were carried out on a Yanaco MT-5 CHN analyzer.

Phenyl 2-Iodobenzoate (**5**)[13)] and 2-Iodophenyl Benzoate (**6**)[14)] were prepared according to procedures reported in the literature.

1-Naphthyl 2-Iodobenzoate (7) To a solution of 2-iodobenzoic acid (1.12 g, 4.51 mmol) in dry tetrahydrofuran (THF) (20 ml) were added oxalyl chloride (0.79 ml, 9.02 mmol) and 2—3 drops of *N*,*N*-dimethylformamide (DMF) at 0 °C. After stirring for 1 h at room temperature, volatile materials were removed under reduced pressure to give a yellow residue which dissolved in dry pyridine (10 ml). To this mixture, 1-naphthol (617.6 mg, 4.28 mmol) was added, and stirred for 2 h at room temperature. The reaction mixture was poured into 10% HCl aqueous solution and extracted with AcOEt. The AcOEt layer was washed with 10% K_2CO_3 aqueous solution and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography with benzene-hexane (3 : 2) afforded **7** (1.40 g, 87%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1760 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.10—8.34 (11H, m). FAB-MS (positive ion mode) *m/z*: 375 $(M+1)^+$. *Anal.* Calcd for $C_{17}H_{11}IO_2$: C, 54.57; H, 2.96. Found: C, 54.29; H, 3.02.

1-Naphthyl 6-Iodo-2,3-dimethoxybenzoate (9) To a suspension of 6-iodo-2,3-dimethoxybenzoic acid (**12**)[15)] (110.8 mg, 0.360 mmol) in dry benzene (3 ml) was added trifluoroacetic anhydride (0.06 ml, 0.425 mmol). After stirring for 2 h at 60 °C, a solution of 1-naphthol (51.8 mg, 0.359 mmol) in dry benzene (3 ml) was added to the mixture and stirred for 2 h at 60 °C. The reaction mixture was cooled to room temperature and then diluted with ether. After neutralization with 5% NaOH aqueous solution and extraction with ether, the obtained ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the residue with benzene gave pure **9** (112.9 mg, 72%). For the analytical sample, recrystallization with benzene–hexane was carried out that left colorless prisms, mp 107—108°C. IR (KBr) cm^{-1}: 1750 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.90 (3H, s), 3.99 (3H, s), 6.78 (1H, d, *J*=8.8 Hz), 7.35—8.36 (8H, m). FAB-MS (positive ion mode) *m/z*: 435 $(M+1)^+$. *Anal.* Calcd for $C_{19}H_{15}IO_4$: C, 52.56; H, 3.48. Found: C, 52.39; H, 3.44.

6,7-Methylenedioxy-1-tetralone (15)[17)] To a solution of BBr_3 (20 ml) in dry CH_2Cl_2 (150 ml) was added 6,7-dimethoxy-1-tetralone (17.5 g, 85 mmol) at 0 °C. After stirring for 1 h at 0 °C, the ice bath was removed and the reaction mixture was stirred for 2 h. Water (15 ml) was slowly added at 0 °C, and after the exothermic reaction ceased, a 5% NaOH aqueous solution was added to make the reaction mixture basic. The aqueous layer was washed with CH_2Cl_2, made acidic with conc. HCl aqueous solution, and extracted with ether. After washing with brine and dried over $MgSO_4$, the solvent was removed under reduced pressure to give a residue which was subjected to silica gel column chromatography with hexane–AcOEt (1 : 1). 6,7-Dihydroxy-1-tetralone[18)] (11.3 g, 74%) was obtained as a pale yellow solid which was recrystallized with AcOEt–hexane that left pale yellow needles, mp 204—205 °C (lit.[18)] mp 195 °C). IR (KBr) cm^{-1}: 3520, 3200 (-OH), 1660 (C=O). ^{1}H-NMR (60 MHz, CD_3OD) δ: 1.90—2.92 (6H, m), 4.82 (2H, s), 6.65 (1H, s), 7.36 (1H, s). FAB-MS (positive ion mode) *m/z*: 179 $(M+1)^+$. *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.26; H, 5.72.

CsF (47.5 g, 313 mmol) was added to a solution of 6,7-dihydroxy-1-tetralone (11.2 g, 62.6 mmol) in DMF (250 ml) and the resulting mixture was stirred for 3 h at room temperature. After dibromomethane (6.7 ml) was added, the mixture was stirred for 2 h at 100°C and cooled to room temperature. AcOEt was added to dilute the mixture, and then any undissolved solid was removed by filtration. The filtrate was washed with 5% NaOH aqueous solution and brine, dried over $MgSO_4$, and concentrated to give a residue which was subjected to silica gel column chromatography with benzene. Recrystallization with hexane was carried out to leave **15** (7.83 g, 66%) as colorless needles, mp 75—76 °C (hexane) (lit.[17)] mp 74—76°C). IR (KBr) cm^{-1}: 1665, 1250, 1035. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.09 (2H, m), 2.59 (2H, t, *J*=6.6 Hz), 2.88 (2H, t, *J*=6.1 Hz), 6.00 (2H, s), 6.66 (1H, s), 7.47 (1H, s). FAB-MS (positive ion mode) *m/z*: 191 $(M+1)^+$. *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.57; H, 5.26.

6,7-Methylenedioxy-1-naphthol (13)[19)] A mixture of **15** (1.90 g, 10 mmol), isopropenyl acetate (60 ml), and *p*-toluenesulfonic acid (*p*-TsOH) monohydrate (304 mg, 1.6 mmol) was refluxed for 3 h under an argon atmosphere. After cooling to room temperature, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.72 g, 12 mmol) was added to the mixture, which was stirred for 1 h at 90 °C. After cooling, the mixture was diluted with CH_2Cl_2, successively washed with 10% $NaHCO_3$, 5% HCl aqueous solution, and brine, then dried over $MgSO_4$. Evaporation of the solvent gave a residue which was dissolved in a mixture of ethanol (60 ml) and 10% NaOH aqueous solution (30 ml). The mixture was stirred for 90 min at 80 °C and then diluted with ether. The mixture was washed with 10% HCl aqueous solution and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude residue which was purified by silica gel column chromatography with benzene to afford pure **13** (1.60 g, 85%) as colorless needles, mp 137—138 °C (benzene–hexane) (lit.[19b)] 124 °C, lit.[19c)] 133—134 °C). IR (KBr) cm^{-1}: 3350, 1245, 1040. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.18 (1H, s), 6.04 (2H, s), 6.68 (1H, dd, J=7.5, 1.0 Hz), 7.09 (1H, s), 7.15 (1H, dd, J=8.0, 7.5 Hz), 7.26 (1H, d, J=8.0 Hz), 7.48 (1H, s). FAB-MS (positive ion mode) *m/z*: 189 $(M+1)^+$, 188 (M^+). *Anal.* Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.28. Found: C, 70.25; H, 4.47.

6,7-Methylenedioxy-1-naphthyl 6-Iodo-2,3-dimethoxybenzoate (11) To a suspension of **12**[15)] (449.4 mg, 1.46 mmol) in dry benzene (6 ml) was added trifluoroacetic anhydride (0.42 ml, 2.97 mmol). After stirring for 2 h at 60 °C, a solution of **13** (274.5 mg, 1.46 mmol) in dry benzene (6 ml) was added to the mixture and stirred for 2 h at 60 °C. The reaction mixture was cooled to room temperature and then diluted with ether. After neutralization with 5% NaOH aqueous solution and extraction with ether, the combined ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the residue with benzene gave **11** as a crude solid. Recrystallization with benzene–hexane was carried out to leave pure **11** (293.8 mg, 57%) as colorless prisms, mp 175.5 °C. IR (KBr) cm^{-1}: 1750 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.93 (3H, s), 4.01 (3H, s), 6.06 (2H, s), 6.81 (1H, d, J=8.5 Hz), 7.16 (1H, s), 7.37—7.39 (2H, m), 7.57 (1H, d, J=8.5 Hz), 7.59—7.62 (2H, m). FAB-MS (positive ion mode) *m/z*: 479 $(M+1)^+$. *Anal.* Calcd for $C_{20}H_{15}IO_6$: C, 50.23; H, 3.16. Found: C, 49.92; H, 3.22.

Typical Procedure for Internal Biaryl Coupling Reaction Base (0.882 mmol), phosphine ligand (0.076 mmol), and palladium reagent (0.037 mmol) were successively added to a solution of ester (0.368 mmol) in dry DMF (4 ml). The reaction mixture was then heated in an oil bath. After cooling to room temperature, the mixture was diluted with AcOEt. Undissolved materials were removed by filtration and then the filtrate was poured into 10% HCl aqueous solution. The organic layers were combined and washed with brine. Evaporation of the solvent gave a residue which was purified by silica gel chromatography with benzene–hexane.

6*H*-Dibenzo[*b*,*d*]pyran-6-one (**4**): Colorless needles, mp 92—94 °C (hexane) (lit.[20)] 92—93 °C). IR (KBr) cm^{-1}: 1730 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.36 (1H, td, J=8.0, 1.0 Hz), 7.39 (1H, dd, J=8.0, 1.0 Hz), 7.50 (1H, ddd, J=8.5, 7.5, 1.5 Hz), 7.60 (1H, td, J=7.5, 1.0 Hz), 7.84 (1H, ddd, J=7.5, 7.0, 1.5 Hz), 8.09 (1H, dd, J=8.0, 1.5 Hz), 8.15 (1H, d, J=8.0 Hz), 8.42 (1H, dd, J=8.0, 1.0 Hz). FAB-MS (positive ion mode) *m/z*: 197 $(M+1)^+$. *Anal.* Calcd for $C_{13}H_8O_2$: C, 79.58; H, 4.11. Found: C, 79.29; H, 4.41.

6*H*-Benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**8**): Colorless needles, mp 191 °C (hexane) (lit.[21)] mp 191 °C). IR (KBr) cm^{-1}: 1730 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.37—8.57 (10H, m). FAB-MS (positive ion mode) *m/z*: 247 $(M+1)^+$. *Anal.* Calcd for $C_{17}H_{10}O_2$: C, 82.91; H, 4.09. Found: C, 82.74; H, 4.36.

7,8-Dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**10**): Colorless needles, mp 185—187 °C (benzene). IR (KBr) cm^{-1}: 1740 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.00 (3H, s), 4.05 (3H, s), 7.47 (1H, d, J=9.0 Hz), 7.56—7.64 (2H, m), 7.72 (1H, d, J=9.0 Hz), 7.86 (1H, d, J=8.0 Hz), 7.94 (1H, d, J=9.0 Hz), 7.99 (1H, d, J=9.0 Hz), 8.57 (1H, d, J=8.0 Hz). FAB-MS (positive ion mode) *m/z*: 307 $(M+1)^+$. *Anal.* Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.16; H, 4.72.

Arnottin I (**1**): Colorless prisms, mp 294—297 °C ($CHCl_3$) (lit.[2)] mp 292—297 °C). IR (KBr) cm^{-1}: 1750. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.99 (3H, s), 4.03 (3H, s), 6.10 (2H, s), 7.14 (1H, s), 7.45 (1H, d, J=8.5 Hz), 7.54 (1H, d, J=8.5 Hz), 7.84 (1H, d, J=9.0 Hz), 7.85 (1H, s), 7.89 (1H, d, J=9.0 Hz).

Acknowledgement This work was supported in part by a grant-in-aid from the Ministry of Education, Science, Sports and Culture, Japan (No. 11672103 to T. H.). The authors are indebted to Professor T. Ishikawa, Faculty of Pharmaceutical Sciences, Chiba University, for providing us with the spectral data of arnottin I, and to the SC-NMR Laboratory of Okayama University for doing the high field NMR experiments.

References

1) Ishii H., Ishikawa T., Haginiwa J., *Yakugaku Zasshi*, **97**, 890—900 (1977).
2) Ishii H., Ishikawa T., Murota M., Aoki Y., Harayama T., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1019—1022.
3) Hatano K., Higashide E., Shibata M., Horii S., Mizuno K., *Agric. Biol. Chem.*, **44**, 1157—1163 (1980); Horii S., Fukase H., Mizuta E., Hatano K., Mizuno K., *Chem. Pharm. Bull.*, **28**, 3601—3611 (1980); Balitz D. M., O'Herron F. A., Bush J., Vyas D. M., Nettleton D. E., Grulich R. E., Brander W. T., Doyle T. W., Arnold E., Crardy J., *J. Antibiot.*, **34**, 1544—1555 (1981); Nakano H., Matsuda Y., Ito K., Ohkubo S., Morimoto M., Tomota F., *ibid.*, **34**, 266—270 (1981); Takahashi K., Yoshida M., Tomita F., Shirahata K., *ibid.*, **34**, 271—275 (1981).
4) Findlay J. A., Liu J.-S., Radics L., Rakhit S., *Can. J. Chem.*, **59**, 3018—3020 (1981); Sehgal S. N., Czerkawski H., Kudelski A., Pandev K., Saucier R., Vézina C., *J. Antibiot.*, **36**, 355—361 (1983).
5) Wei T. T., Chan J. A., Roller P. P., Weiss U., Stroshane R. M., White R. J., Byrne K. M., *J. Antibiot.*, **35**, 529—532 (1982); Wei T. T., Byrne K. M., Warnick-Pickle D., Greenstein M., *ibid.*, **35**, 545—548 (1982); Singh K., *ibid.*, **37**, 71—73 (1984).
6) Syntheses of gilvocarcins have been reported: Deshpande P. P., Martin O. R., *Tetrahedron Lett.*, **31**, 6313—6316 (1990); Matsumoto T., Hosoya T., Suzuki K., *J. Am. Chem. Soc.*, **114**, 3568—3570 (1992); Hosoya T., Takashiro E., Matsumoto T., Suzuki K., *ibid.*, **116**, 1004—1015 (1994), and references cited therein.
7) Harayama T., Akiyama T., Nakano Y., *Chem. Pharm. Bull.*, **45**, 1723—1725 (1997).
8) Harayama T., Akiyama T., Nakano Y., Shibaike K., *Heterocycles*, **48**, 1989—1993 (1998); Harayama T., Shibaike K., *ibid.*, **49**, 191—195 (1998).
9) Harayama T., Akiyama T., Kawano K., *Chem. Pharm. Bull.*, **44**, 1634—1636 (1996).
10) Review on palladium-mediated coupling reaction: Tsuji J., "Palladium Reagents and Catalysts," John Wiley and Sons Inc., New York, 1995, pp. 125—252; Knight D. W., "Comprehensive Organic Synthesis," Vol. 3, ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, pp. 481—520.
11) A preliminary communication of this work has been published: Harayama T., Yasuda H., *Heterocycles*, **46**, 61—64 (1997).
12) Ames D. E., Opalko A., *Tetrahedron*, **40**, 1919—1925 (1984).
13) Singh A., Andrews L. J., Keefer R. M., *J. Am. Chem. Soc.*, **84**, 1179—1185 (1962).
14) Buchan S., McCombie H., *J. Chem. Soc.*, **1931**, 137—144.
15) Dyke S. F., Tiley E. P., *Tetrahedron*, **31**, 561—568 (1977).
16) Wang G., Cushman M., *Synth. Commun.*, **21**, 989—996 (1991).
17) Ninomiya I., Naito T., Ishii H., Ishida T., Ueda M., Harada K., *J. Chem. Soc., Perkin Trans 1*, **1975**, 762—764.
18) Momose T., Oya H., Ohkura Y., Iwasaki M., *Chem. Pharm. Bull.*, **2**, 119—122 (1954).
19) *a*) Takao N., Kamigauchi M., Sugiura M., Ninomiya I., Miyata O., Naito T., *Heterocycles*, **16**, 221—225 (1981); *b*) Dallacker F., Schneider P., *Chem. Ztg.*, **110**, 455—458 (1986); *c*) Zjawiony J., Peterson J. R., *Org. Prep. Proced. Int.*, **23**, 163—172 (1991).
20) Alo B. I., Kandil A., Patil P. A., Sharp M. J., Siddiqui M. A., Snieckus V., Josephy P. D., *J. Org. Chem.*, **56**, 3763—3768 (1991).
21) Chatterjea J. N., Bhakta S. C., Chattopadhyay A. K., *J. Indian Chem. Soc.*, **51**, 757—762 (1974).