HETEROCYCLES, Vol. 61, 2003, pp. 513 - 520
Received, 4th April, 2003, Accepted, 8th May, 2003, Published online, 13th May, 2003

SYNTHETIC STUDIES ON PYRROLOPHENANTHRIDONE SKELETON FROM 1-BENZOYL-7-IODODIHYDROINDOLE DERIVATIVES USING PALLADIUM-ASSISTED BIARYL COUPLING REACTIONS

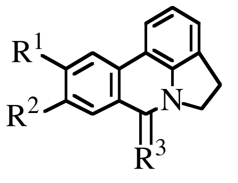
Takashi Harayama,* Hiroko Toko, Akihiro Hori, Taeko Miyagoe, Tomonori Sato, Hiromi Nishioka, Hitoshi Abe, and Yasuo Takeuchi

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1,
Okayama 700-8530, Japan.
e-mail:harayama@pharm.okayama-u.ac.jp

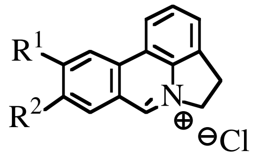
Abstract – The biaryl coupling reaction of 1-benzoyl-7-iododihydroindole derivatives using Pd reagent was examined. 1-[(1,3-Benzodioxol-5-yl)carbonyl]-7-iodo-2,3-dihydroindole gave 4,5-dihydro-7*H*-[1,3]dioxolo[4,5-*k*]pyrrolo[3,2,1-*de*]phenanthridin-7-one, which was formed by connection to a more hindered carbon, as a major product. 1-(3,4-Dimethoxybenzoyl)-7-iodo-2,3-dihydroindole gave oxoassoanine and 10,11-dimethoxy-4,5-dihydropyrrolo[3,2,1-*de*]-phenanthridin-7-one in an almost equal ratio.

Since pyrrolophenanthridine alkaloids (see Scheme 1) have significant biological activities[1] and unique polycyclic structures,[2] attention is still focused on the development of new synthetic methods for these alkaloids.[3] Some of these attempts have involved an intramolecular aryl-aryl coupling, in which a hydrogen halide is eliminated from the two aromatic components using a Pd reagent as a key step.[3d, 4] Recently, we reported a method of synthesizing several benzo[*c*]phenanthridine alkaloids using Pd-assisted biary coupling reactions of 2-halo-*N*-naphthylbenzamides *via* elimination of a hydrogen halide.[5] In order to examine the generality of this method, we tried to apply it to the synthesis of pyrrolophenanthridine alkaloids, especially anhydrolycorin-7-one (**1**)[6] and oxoassoanine (**2**),[7] which serve as advanced intermediates in the synthesis of other alkaloids.[8]

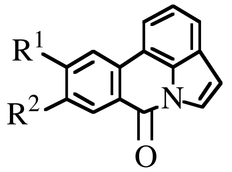
To synthesize pyrrolophenanthridine alkaloids, two routes (Routes A and B) are possible, as shown in Scheme 1. The biaryl coupling reactions of 1-(2-iodobenzoyl)-2,3-dihydroindole (**3**)[9] and 1-benzoyl-7-iodo-2,3-dihydroindole (**4**) were examined as a preliminary study of the synthesis of these alkaloids. The



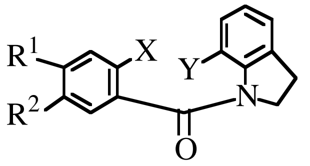
$R^1 + R^2 = OCH_2O$, $R^3 = O$: anhydrolycorin-7-one (**1**)
$R^1 = R^2 = OMe$, $R^3 = O$: oxoassoanine (**2**)
$R^1 + R^2 = OCH_2O$, $R^3 = H_2$: anhydrolycorine
$R^1 = R^2 = OMe$, $R^3 = H_2$: assoanine



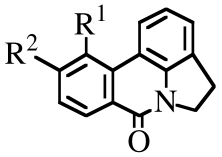
$R^1 + R^2 = OCH_2O$: anhydrolycorinium chloride
$R^1 = R^2 = OMe$: vasconine



$R^1 + R^2 = OCH_2O$: hippadine
$R^1 = R^2 = OMe$: pratosine

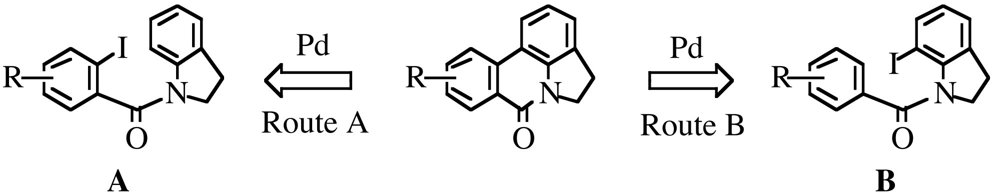


3 : $R^1=R^2=Y=H$, X=I
4 : $R^1=R^2=X=H$, Y=I
6 : $R^1=R^2=X=Y=H$
7 : $R^1+R^2=OCH_2O$, X=Br, Y=H
8 : $R^1+R^2=OCH_2O$, X=H, Y=I
9 : $R^1=R^2=OMe$, X=H, Y=I
11 : $R^1+R^2=OCH_2O$, X=Y=H
13 : $R^1=R^2=OMe$, X=Y=H



5 : $R^1=R^2=H$
10 : $R^1+R^2=OCH_2O$
12 : $R^1=R^2=OMe$

Fig. 1



Scheme 1

results are summarized in Table 1. The reaction of **3** with $Pd(OAc)_2$ in the presence of K_2CO_3 in DMA afforded 4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (**5**)[8b] in only 8% yield, while Cai *et al.* reported that the reaction of 1-(2-bromobenzoyl)-2,3-dihydroindole (**7**) with $Pd(OAc)_2$ in the presence of K_2CO_3 in DMA afford **1** in 55% yield.[4b, 10] In contrast, the reaction of **4** with $Pd(OAc)_2$, n-Bu_3P, 1,3-bis(diphenylphosphino)propane (DPPP), and Ag_2CO_3 in DMF under reflux for 30 min[5d] gave **5** in 79% yield along with 13% yield of 1-benzoyl-2,3-dihydroindole (**6**).[12] However, the reaction of **3** under the same conditions gave a mixture of **3** and an unidentified compound. Therefore, the coupling reaction of **8** or **9**, which involves an iodo group as a leaving group on the dihydroindole part, was examined using Route B, although the oxygen substituent(s) on the acid part may influence the cyclization position.[5b]

The starting materials (**8** and **9**) for the coupling reaction were prepared from 7-iododihydroindole[13] and piperonylic acid, and from 7-iododihydroindole and veratric acid, in 55% and 61% yield, respectively. Then, the reaction of **8**, which possesses a methylenedioxy group on a benzoyl part, and that of **9**, which possesses methoxy groups on a benzoyl part, using Pd reagent were investigated. The results are summarized in Table 2. Thus, reaction of **8** with n-Bu_3P, DPPP, and Ag_2CO_3[5d] afforded the coupling products (**1** and **10**) in the ratio of 1 to 6 in a total yield of 86% along with 12% yield of **11**. (see run 2 in Table 2) On the other hand, the reaction of **9** under the same reaction conditions gave the coupling

Table 1. Results of coupling reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole (**3**) and 1-benzoyl-7-iodo-2,3-dihydroindole (**4**) in DMF.

starting material	run	$Pd(OAc)_2$ (eq.)	phosphine (P/Pd)$^{a)}$	base$^{b)}$	temp.	time	yield (%)$^{c)}$ **5**	**6**	**SM**
3	1	1.0	-	K_2CO_3	reflux	30 min	8	7	-
	2	1.0	PPh_3 (2)	Ag_2CO_3	reflux	30 min	-	-	-
	3$^{d)}$	1.0	n-Bu_3P (1), DPPP (1)	Ag_2CO_3	reflux	30 min	-	-	-
	4$^{e)}$	0.1	-	AcOK	100°C	7 h	-	-	55
4	5	1.0	PPh_3 (2)	Ag_2CO_3	reflux	3 h	14	31	-
	6	1.0	n-Bu_3P (1), DPPP (1)	Ag_2CO_3	reflux	30 min	79	13	-
	7	0.2	n-Bu_3P (1), DPPP (1)	Ag_2CO_3	reflux	30 min	77	20	-
	8$^{e)}$	0.1	-	AcOK	100°C	3 h	46	-	25

a) Molar ratio between phosphine and Pd. *b)* 2 Eq. of base was added. *c)* Isolated yield. *d)* Mixture of **6** and unidentified compound was obtained. *e)* 2 Eq. of n-Bu_4NCl and 5.5 Eq. of AcOK were added. See reference 14.
SM : starting material. DPPP : 1,3-bis(diphenylphosphino)propane.

Table 2. Results of coupling reaction of 1-benzoyl-7-iodo-2,3-dihydroindoles (**8** and **9**) in DMF$^{a)}$

starting material	run	$Pd(OAc)_2$ (eq.)	phosphine (P/Pd)$^{b)}$	base$^{c)}$	temp.	yield (%) (**1** +**10**)	**11**	ratio$^{d)}$ (**1** : **10**)
8	1	1.0	P(2-tol)$_3$ (2)	Ag_2CO_3	reflux	27	34	1 : 4.5
	2	1.0	n-Bu_3P (1), DPPP (1)	Ag_2CO_3	reflux	86	12	1 : 6
	3$^{e)}$	0.1	-	AcOK	100°C	64	-	1 : 1.7
						(**2** +**12**)	**13**	(**2** : **12**)
9	4	1.0	n-Bu_3P (1), DPPP (1)	Ag_2CO_3	reflux	97	2	1.3 : 1

a) All reactions were carried out in DMF for 2 h. *b)* Molar ratio between phosphine and Pd. *c)* 2 Eq. of base was used. *d)* Determined by ^{1}H-NMR spectral integration. *e)* 2 Eq. of n-Bu_4NCl and 5.5 Eq. of AcOK were used. **8** was recovered in 36% yield. See reference 14.

products (**2** and **12**) in an almost equal ratio. (see run 4 in Table 2) Interestingly, **10** was produced as a major product *via* connection to a more hindered carbon adjacent to the methylenedioxy group. The synthetic samples (**1** and **2**) were identified with the authentic samples of anhydrolycorin-7-one and oxoassoanine, respectively, by comparison of these physico-chemical data with the reported data. (see Expermental) The reaction mechanism for the regioselectivity of coupling reaction is now under investigation.

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 or JASCO FT/IR 350 spectrophotometer and ^{1}H-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or a Varian VXR-200 (200 MHz) or -500 (500 MHz) spectrometer, unless otherwise stated. NMR spectral data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on a Wako gel C-200. All the experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated to dryness under reduced pressure, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

1-Benzoyl-7-iodo-2,3-dihydroindole (4)

Benzoyl chloride (1.7 mL, 14.7 mmol) was added to a solution of 7-iodo-2,3-dihydroindole[13] (3.0 g, 12.2 mmol) in pyridine (30 mL) and the mixture was stirred for 1 h at rt. The reaction mixture was poured into 1N HCl and extracted with AcOEt. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (8 : 1) gave **4** (3.80 g, 89%) as colorless needles (hexane), mp 145.5-147°C. IR (KBr) cm^{-1}: 1650. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.07 (2H, t, *J*=7.5 Hz), 4.13 (2H, t, *J*=7.5 Hz), 6.83 (1H, dd, *J*=7.5, 7.5 Hz), 7.23 (1H, dd, *J*=7.5, 1.0 Hz), 7.47 (2H, dd, *J*=7.5, 7.5 Hz), 7.54 (1H, dddd, *J*=7.5, 7.5, 1.0, 1.0 Hz), 7.70 (1H, dd, *J*=7.5, 1.0 Hz), 7.79 (2H, dd, *J*=7.5, 1.0 Hz). *Anal.* Calcd for $C_{15}H_{12}NOI$: C, 51.60; H, 3.46; N, 4.01. Found: C, 51.62; H, 3.71; N, 3.90.

1-[(1,3-Benzodioxol-5-yl)carbonyl]-7-iodo-2,3-dihydroindole (8)

A few drops of dry DMF and oxalyl chloride (0.38 mL, 4.4 mmol) were added to a solution of piperonylic acid (365 mg, 2.2 mmol) in dry CH_2Cl_2 (40 mL) under ice-cooling and the mixture was stirred at the same temperature for 4 h. Then, the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of 7-iododihydroindole (650 mg, 2.65 mmol) in dry CH_2Cl_2 (8 mL) and dry pyridine (8 mL) and the mixture was stirred for 2 h at rt. The reaction mixture was poured into 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous sat. $NaHCO_3$ solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (2 : 1) gave **8** (475 mg, 55%) as colorless prisms (hexane-AcOEt), mp 158.5-161℃. IR (KBr) cm^{-1}: 1645. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.08 (2H, t, *J*=7.6 Hz), 4.14 (2H, t, *J*=7.6 Hz), 6.05 (2H, s), 6.82 (1H, dd, *J*=7.6, 7.6 Hz), 6.88 (1H, d, *J*=8.0 Hz), 7.23 (1H, dd, *J*=7.6, 0.9 Hz), 7.27 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=8.0, 1.8 Hz), 7.69 (1H, dd, *J*=7.6, 0.9 Hz). *Anal.* Calcd for $C_{16}H_{12}NO_3I$: C, 48.88; H, 3.08; N,3.56. Found: C, 48.84; H, 3.32; N, 3.34.

1-(3,4-Dimethoxybenzoyl)-7-iodo-2,3-dihydroindole (9)

A few drops of dry DMF and oxalyl chloride (0.48 mL, 5.48 mmol) were added to a solution of veratric acid (500 mg, 2.74 mmol) in dry CH_2Cl_2 (50 mL) under ice-cooling and the mixture was stirred at the same temperature for 4 h. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of 7-iododihydroindole (806 mg, 3.29 mmol) in dry CH_2Cl_2 (2 mL) and dry pyridine (10 mL) and the whole was stirred for 2 h at rt. The reaction mixture was poured into 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous sat. $NaHCO_3$ solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (2 : 1) gave **9** (681 mg, 61%) as colorless needles (AcOEt), mp 201-202.5℃. IR (KBr) cm^{-1}: 1650. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.08 (2H, t, *J*=7.6 Hz), 3.93 (3H, s), 3.95 (3H, s), 4.17 (2H, t, *J*=7.6 Hz), 6.82 (1H, dd, *J*=7.5, 7.5 Hz), 6.92 (1H, d, *J*=8.1 Hz), 7.23 (1H, dd, *J*=7.5, 0.9 Hz), 7.38 (1H, d, *J*=1.9 Hz), 7.39 (1H, dd, *J*=8.1, 1.9 Hz), 7.70 (1H, dd, *J*=7.5, 0.9 Hz). *Anal.* Calcd for $C_{17}H_{16}NO_3I$: C, 49.90; H, 3.84; N,3.42. Found: C, 49.95; H, 4.12; N, 3.40.

General Procedure for the Coupling Reaction of 1-Benzoyldihydroindole Derivatives (runs 1~3 and 5~7 in Table 1, and runs 1, 2, and 4 in Table 2)

The 1-benzoyldihydroindole derivative (0.3 mmol) was reacted with $Pd(OAc)_2$, a phosphine ligand, and a base in dry DMF (8 mL) using $Pd(OAc)_2$ and the phosphine ligand in the ratios indicated in Tables 1 and 2, and 2 mol equivalents of base for the times and temperatures indicated in Tables. Then, the reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-$CHCl_3$-AcOEt (5 : 1 : 5) gave a mixture of coupling products and successive elution with the same solvent gave the dehalogeno-product or the starting material. The mixture of coupling products was separated by preparative TLC using a hexane-$CHCl_3$-AcOEt (3 : 5 : 1) solvent system. The upper zone gave the natural compounds (**1** and **2**), respectively. The lower zone gave the unnatural type of compounds (**10** and **12**), respectively.

General Procedure for the Coupling Reaction of 1-Benzoyldihydroindole Derivatives under Phosphine-free Conditions (runs 4 and 8 in Table 1, and run 3 in Table 2) [14]

The 1-benzoyldihydroindole derivative (0.3 mmol) was reacted with 0.1 equivalent of $Pd(OAc)_2$, 2 equivalents of n-Bu_4NCl, and 5.5 equivalents of KOAc in dry DMF (8 mL) for the times indicated in Tables 1 and 2 at 100°C. Then, the reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-$CHCl_3$-AcOEt (5 : 1 : 5) gave a mixture of coupling products and successive elution with the same solvent gave the dehalogeno-product or the starting material. The mixture of coupling products was separated by preparative TLC using a hexane-$CHCl_3$-AcOEt (3 : 5 : 1) solvent system. The upper zone gave **1** and the lower zone gave **10**.

4,5-Dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (5) : Colorless needles ($CHCl_3$-hexane), mp 170-171℃ (lit.,[8b] 89-90℃). IR (KBr) cm^{-1}: 1645. ^1H-NMR (500 MHz, $CDCl_3$) δ: 3.42 (2H, t, J=8.4 Hz), 4.48 (2H, t, J=8.4 Hz), 7.21 (1H, dd, J=7.6, 7.6 Hz), 7.32 (1H, br. d, J=7.6 Hz), 7.59 (1H, ddd, J=7.9, 7.9, 1.2 Hz), 7.75 (1H, ddd, J=7.9, 7.9, 1.2 Hz), 7.90 (1H, br. d, J=7.6 Hz), 8.19 (1H, br. d, J=7.9 Hz), 8.55 (1H, br. d, J=7.9 Hz). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N,6.33. Found: C, 81.66; H, 5.08; N, 6.28.

1-Benzoyl-2,3-dihydroindole (6) : Colorless needles (AcOEt), mp 120.5-122℃ (lit.,[12] 116-117℃).

Anhydrolycorin-7-one (1) : Colorless needles ($CHCl_3$-MeOH), mp 236-237℃ (lit.,[6a] 228-230℃, lit.,[6b] 232-234℃). The NMR data of the synthetic sample were identical with the reported data of the authentic sample.[6b]

4,5-Dihydro-7*H*-[1,3]dioxolo[4,5-*k*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (10) : Colorless needles ($CHCl_3$-MeOH), mp 243.5-246℃. IR (KBr) cm^{-1}: 1655. ^1H-NMR (500 MHz, $CDCl_3$) δ: 3.43 (2H, t, J=8.0 Hz), 4.73 (2H, t, J=8.0 Hz), 6.23 (2H, s), 7.09 (1H, d, J=8.5 Hz), 7.20 (1H, dd, J=8.0, 7.0 Hz), 7.33 (1H, dd, J=7.0, 1.0 Hz), 8.16 (1H, dd, J=8.0, 1.0 Hz), 8.18 (1H, d, J=8.5 Hz). *Anal.* Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N,5.28. Found: C, 72.48; H, 4.43; N, 5.37.

1-[(1,3-Benzodioxol-5-yl)carbonyl]-2,3-dihydroindole (11) : Colorless needles (ether), mp 123-124℃. IR (KBr) cm^{-1}: 1635. ^1H-NMR (200 MHz, $CDCl_3$) δ: 3.08 (2H, t, J=8.2 Hz), 4.07 (2H, t, J=8.2 Hz), 6.00 (2H, s), 6.83 (1H, d, J=8.0 Hz), 6.96-7.21 (6H, m). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 5.09; N,5.24. Found: C, 72.11; H, 5.18; N, 5.25.

Oxoassoanine (2) : Colorless needles ($CHCl_3$-MeOH), mp 272.5-274.5℃ (lit.,[7a] 247-250℃, lit.,[7b] 270-271℃). The NMR data of the synthetic sample were identical with the reported data of the authentic sample.[7]

10,11-Dimethoxy-4,5-dihydropyrrolo[3,2,1-*de*]phenanthridin-7-one (12) : Colorless prisims (AcOEt), mp 165-167℃. IR (KBr) cm^{-1}: 1640. ^1H-NMR (200 MHz, $CDCl_3$) δ: 3.43 (2H, t, J=8.4 Hz), 3.97 (3H, s), 4.03 (3H, s), 4.46 (2H, t, J=8.4 Hz), 7.22 (1H, d, J=8.8 Hz), 7.22 (1H, dd, J=8.4, 7.4 Hz), 7.35 (1H, dd, *J*=7.4, 1.0 Hz), 8.40 (1H, d, *J*=8.8 Hz), 8.69 (1H, dd, *J*=7.4, 1.0 Hz). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N,4.98. Found: C, 72.36; H, 5.48; N, 4.92.

1-(3,4-Dimethoxybenzoyl)-2,3-dihydroindole (13) : Colorless needles ($CHCl_3$-hexane), mp 135-137℃. IR (KBr) cm^{-1}: 1640. ^{1}H-NMR (200 MHz, $CDCl_3$) □: 3.12 (2H, t, *J*=8.3 Hz), 3.90 (3H, s), 3.94 (3H, s), 4.14 (2H, t, *J*=8.3Hz), 6.88-7.23 (7H, m) *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N,4.94. Found: C, 72.00; H, 6.23; N, 4.95.

ACKNOWLEDGEMENTS

The authors are indebted to the SC-NMR Laboratory of Okayama University for performing the NMR experiments.

REFERECES AND NOTES

1. a) S. C. Chattopadhyay, U. Chattopadhyay, P. P. Marthur, K. S. Saini, and S. Ghosal, *Planta Med.*, 1983, **49**, 252; b) G. R. Petti, V. Gaddamidi, A. Goswani, and G. M. Cragg, *J. Nat. Prod.*, 1984, **47**, 796; c) S. Ghosal, R. Lochan, Ashutosh, Y. Kumar, and R. S. Srivastava, *Phytochemstry*, 1985, **24**, 1825; d) R. K. Y. Zee-Cheng, S.-J. Yan, and C. C. Chen, *J. Med. Chem.,* 1978, **21**, 199; e) C. C. Chen and R. K. Y. Zee-Cheng, *Heterocycles*, 1981, **15**, 1275.
2. a) O. Hoshino, “The Alkaloids” Vol. 51, ed. by G. A. Cordell, Academic Press, New York, **1998**, pp. 323-424; b) J. R. Lewis, *Nat. Prod. Rep.*, 2000, **17**, 57; c) J. R. Lewis, *Nat. Prod. Rep.*, 1998, **15**, 107.
3. a) S. E. Wolkenberg and D. L. Boger, *J. Org. Chem.*, 2002, **67**, 7361; b) D. L. Boger and S. E. Wolkenberg, *J. Org. Chem.*, 2000, **65**, 9120; c) D. C. Harrowven, D. Lai, and M. C. Lucas, *Synthesis*, **1999**, 1300 and references cited therein; d) A. Padwa, M. A. Brodney, B. Liu, and K. Satake, T. Wu, *J. Org. Chem.*, 1999, **64,** 3595; d) Y. Miki, H. Shirokoshi, and K. Matsushita, *Tetrahedron Lett.*, 1999, **40**, 4347 and references cited therein.
4. a) D.C. Black, P. A. Keller, and N. Kumar, *Tetrahedron*, 1993, **49**, 151; b) H. W. Shao and J. C. Cai, *Chinese Chem. Lett.*, 1996, **7**, 13; c) A. P. Kozikowsky and D. Ma, *Tetrahedron Lett.*, 1991, **32**, 3317; d) S. J. Garden, J. C. Torres, and A. C. Pinto, *J. Braz. Chem. Soc.*, 2000, **11**, 441.
5. a) T. Harayama, T. Akiyama, H. Akamatsu, K. Kawano, H. Abe, and Y. Takeuchi, *Synthesis*, **2001**, 444; b) T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, and Y. Takeuchi, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 523; c) T. Harayama and K. Shibaike, *Heterocycles*, 1998, **49**, 191; d) T. Harayama, T. Akiyama, Y. Nakano, H. Nishioka, H. Abe, and Y. Takeuchi, *Chem. Pharm. Bull.*, 2002, **50**, 519; e) T. Harayama, T. Akiyama, Y. Nakano, K. Shibaike, H. Akamatsu, A. Hori, H. Abe, and Y. Takeuchi, *Synthesis*, **2002**, 237; f) T. Harayama, T. Sato, Y. Nakano, H. Abe, and Y. Takeuchi, *Heterocycles*, 2003, **59**, 293; g) T. Harayama, A. Hori, Y. Nakano, T. Akiyama, H. Abe,

and Y. Takeuchi, *Heterocycles*, 2002, **58**, 159.

6. a) S. Ghosal, P. H. Rao, D. K. Jaiswal, Y. Kumar, and A. W. Frahm, *Phytochemistry*, 1981, **20**, 2003; b) H. Hara, O. Hoshino, and B. Umezawa, *Tetrahedron Lett.*, **1972**, 5031.
7. a) J. M. Llabres, F. Viladoma, J. Bastida, C. Codina, and M. Rubiralta, *Phytochemistry*, 1986, **25**, 2637; b) J. S. Parnes, D. S. Carter, L. J. Kurz, and L. A. Flippin, *J. Org. Chem.*, 1994, **59**, 3497.
8. a) M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1990, **31**, 1523; b) R. H. Hutchings and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 1004; c) D.C. Black, P. A. Keller, and N. Kumar, *Tetrahedron Lett.*, 1989, **30**, 5807.
9. W. Carruthers and N. Evans, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1523.
10. Phosphine ligand is generally required for the Heck-type reaction of bromoarene[11] and we could not reproduce the Cai's results.[4b] In this connection, the reaction of dimethyl 1-(2-bromobenzoyl)indole-2,3-dicarboxylate with $Pd(PPh_3)_4$ gave no coupling product.[3d]
11. a) R. F. Heck, *Organic Reactions*, ed. by W. G. Dauben, John Wiley & Sons, Inc., New York, **1982**, Vol. 27, pp. 345-390; b) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2.
12. T. A. Crabb and S. L. Soilleux, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1381.
13. M. Somei, Y. Saida, T. Funamoto, and T. Ohta, *Chem. Pharm. Bull.*, 1987, **35**, 3146.
14. a) T. Jeffery, *J. Chem. Soc., Chem. Commun.*, **1984**, 1287; b) T. Jeffery, *Tetrahedron*, 1996, **52**, 10113.