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Concise synthesis of pyrrolophenanthridine alkaloids using a Pd-mediated biaryl coupling reaction with regioselective C–H activation via the intramolecular coordination of the amine to Pd

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Abstract—The concise synthesis of *Amaryllidaceae* alkaloids, such as anhydrolycorinone, anhydrolycorin-7-one, assoanine, and oxoassoanine, which have a pyrrolophenanthridine skeleton, was achieved in moderate yield using the Pd-mediated biaryl coupling reaction of 1-(2-halobenzyl)-2,3-dihydroindole, which applied the regioselective C–H activation method with intramolecular coordination of the benzylamino group to Pd.

1. Introduction

The potentially useful pharmacological activities[1] and unique polycyclic structures of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids (e.g., **1**–**8**) have led to recent interest in developing new synthetic methods for these alkaloids.[2,3] Some of these attempts have involved an intramolecular aryl–aryl coupling reaction with a Pd reagent as the key step, including the dehydrogenation of two arenes with $Pd(OAc)_2$ in acetic acid,[4] a biaryl coupling reaction between a monobromoarene and an arene with a Pd reagent,[3,4a,5] and the intramolecular coupling of a bis-haloarene with a Pd reagent.[6] Recently, we reported a method of synthesizing several benzo[*c*]phenanthridine alkaloids using Pd-assisted aryl–aryl coupling reactions of 2-halo-*N*-naphthylbenzamides via the elimination of a hydrogen halide.[7] To examine the generality of this method, we tried to apply it to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids, especially anhydrolycorin-7-one (**3**)[1f] and oxoassoanine (**4**),[8a] which serve as advanced intermediates in the synthesis of other alkaloids.[4b,8b]

In this connection, Cai et al. reported that the reaction of 1-(2-bromobenzoyl)-2,3-dihydroindole (**9a**) using $Pd(OAc)_2$ and K_2CO_3 in DMA in the absence of a phosphine ligand afforded **3** in 55% yield.[5a,9] In our hands, the reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole (**9b**), which is expected to be more reactive than **9a**, under their reaction conditions did not produce **3**, even in the presence of a phosphine ligand. Miki et al. reported that the reaction of 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**10**) with $Pd(PPh_3)_4$ gave no coupling product.[3] Moreover, it has been reported that the biaryl coupling reaction of 1-(2-bromobenzyl)-2,3-diphenylindole (**11**) gave no coupling product,[4a] whereas the reaction of dimethyl 1-(2-bromobenzyl)indole-2,3-dicarboxylate (**12**) with $Pd(PPh_3)_4$ gave a coupling product (**13**).[3] These results seem somewhat contradictory (Scheme 1).

Recently, we developed a method of synthesizing a new skeletal compound, naphthobenzazepine, by regioselective C–H activation using the intramolecular coordination of a benzylamine to Pd.[11] We planned to apply this strategy to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids, such as anhydrolycorine (**1**)[1f,12a] and assoanine (**2**).[12b] Interconversion of **1** and **3** or **2** and **4** has already been accomplished by the air oxidation of **1** or **2**, and the $LiAlH_4$ reduction of **3** or **4**.[12] We envisioned that the intramolecular biaryl coupling reaction of 1-(2-halobenzyl)dihydroindole (**A**) using a Pd reagent would afford dihydropyrrolophenanthridine (**C**) directly, via an oxidative addition to Pd(0) and coordination of the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the C_7 position of the dihydroindole moiety [forming a four-membered palladacycle (**B**)][13,14] and the reductive elimination of Pd(0), as shown in Scheme 2. The details of the results are the subject of this paper.

2. Results and discussion

First, the Pd-catalyzed coupling reaction of 1-(2-bromobenzyl)-2,3-dihydroindole (**14**)[15] was examined as a preliminary study of the synthesis of these alkaloids

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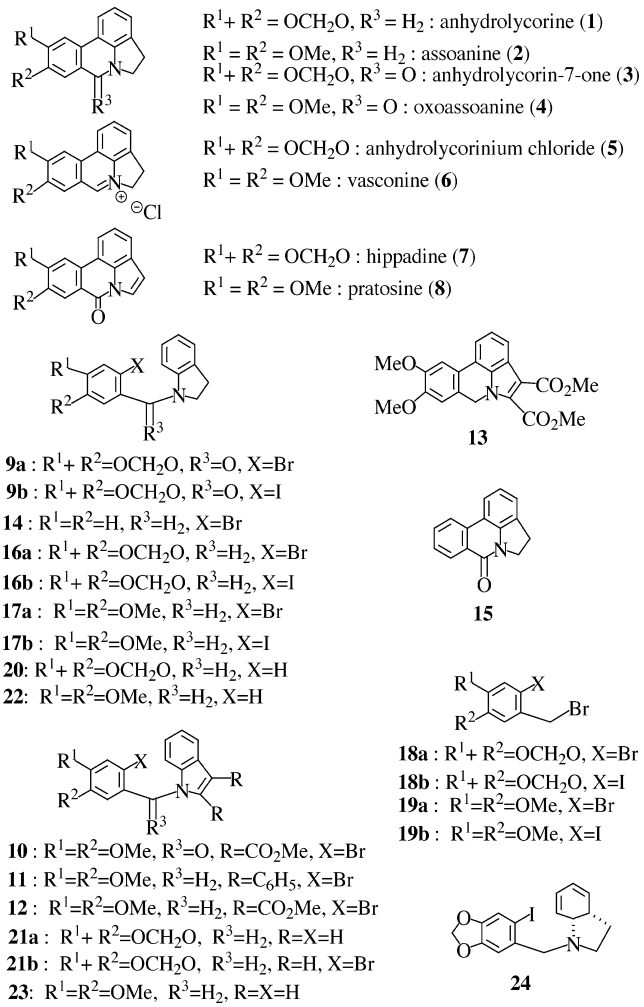
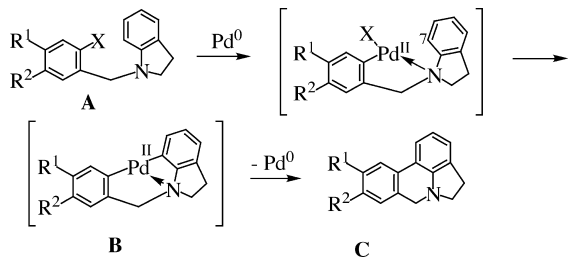


Scheme 1. Pyrrolophenanthridine alkaloids and related compounds.



Scheme 2. Strategy and proposed mechanism for synthesis of dihydropyrrolophenanthridine (**C**) from 1-(2-halobenzyl)dihydroindole (**A**).

(**1**–**4**). The reaction of **14** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave pyrrolophenanthridone (**15**) in 35% yield, along with 1-benzyl-2,3-dihydroindole (13% yield)[16] and 1-benzylindole (17% yield).[16] These results suggest that **15** was formed via a biaryl coupling reaction and concomitant oxidation, because 1-(2-iodobenzoyl)-2,3-dihydroindole gave **15** in only 8% yield[17] and alkaloids (**1** and **3**) readily undergo oxidation in air.[12] Therefore, this strongly implies that the synthetic strategy shown in Scheme 2 is applicable to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids.

Next, to study the synthesis of pyrrolophenanthridine alkaloids, the starting materials (**16a**, **16b**, and **17a**) were prepared from dihydroindole and 2-bromobenzyl bromides (**18a**[18a] and **19a**[18b]) or 2-iodobenzyl bromides (**18b**)[19a] in the presence of *i*-Pr$_2$NEt in dry CH_3CN in 86–91% yield. The starting material (**17b**) was prepared from dihydroindole and 2-iodobenzyl bromide (**19b**)[19b] in ether in 77% yield. The intramolecular coupling reactions of 1-(2-bromobenzyl)dihydroindoles (**16a** and **17a**) using Pd were examined; the results are summarized in Tables 1 and 2. The reaction of **16a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave anhydrolycorin-7-one (**3**) in 45% yield (run 1 in Table 1),[12a] and the reaction in CH_3CN did not proceed (run 2 in Table 1). By contrast, the reaction of **16a** under an oxygen atmosphere, which was intended to accelerate the oxidation, afforded **3** in only 21% yield (run 3 in Table 1). In this connection, Knölker et al. recently reported that the reaction of iodo-tetrahydroindole (**24**) with $Pd(PPh_3)_4$ in DMF under air gave **3** in 29% yield via a coupling reaction and oxidation.[2h] The reaction of **16a** in degassed DMF under an Ar atmosphere gave anhydrolycorine (**1**)[12a] and **3**[20a] in 37 and 15% yields, respectively, along with **20** and **21a** (run 4 in Table 1). The reaction of **16a** using Ag_2CO_3 as a base produced only the oxidation product (**21b**) in 58% yield (run 7 in Table 1). The reaction using *i*-Pr$_2$NEt and DBU as a base did not proceed (runs 8 and 9 in Table 1). The reaction of **17a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave oxoassoanine (**4**)[12b] in 34% yield (run 1 in Table 2). The reaction of **17a** in degassed DMF under an Ar atmosphere gave assoanine (**2**)[20b] and **4** in 28 and 13% yields, respectively, along with **22** and **23** (run 4 in Table 2). The reaction of **16a** and **17a** using PCy_3 as a ligand gave the coupling products in better yield (run 5 in Table 1 and run 5 in Table 2).

To improve the yield, the biaryl coupling reaction of 1-(2-iodobenzyl)-2,3-dihydroindoles (**16b** and **17b**), which are more reactive than bromo compounds, was examined. The results are summarized in Tables 3 and 4. However, the yields were similar or lower than with bromo compounds. Unlike bromo compounds (**16a** and **17a**), with iodo compounds (**16b** and **17b**), Jeffery's conditions[21] gave the coupling products in higher yields (run 6 in Table 3, and run 4 in Table 4).

In conclusion, the concise synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids was accomplished by applying a strategy utilizing regioselective C–H activation via intramolecular coordination of the benzylamino group to Pd.[11]

3. Experimental

3.1. General

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 were recorded on a JNM-MY 60 FT (60 MHz) or a Varian VXR-200 (200 MHz) spectrometer. NMR spectra data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and

Table 1. Results of biaryl coupling reaction of 1-[(6-bromo-1,3-benzodioxol-5-yl)methyl)]-2,3-dihydroindole (**16a**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Base	Temp. (°C)	Time (h)	Yield (%)				
							1	**3**	**20**	**21a**	**21b**
1	B	20	P(*o*-tol)$_3$ (2)	K_2CO_3	125	3	Trace	45	19	6	—
2[c]	B	100	P(*o*-tol)$_3$ (2)	K_2CO_3	125	48	No reaction				
3[d]	C	20	P(*o*-tol)$_3$ (2)	K_2CO_3	125	3	—	21	Trace	8	—
4	A	10	P(*o*-tol)$_3$ (2)	K_2CO_3	125	1.5	37	15	23	16	—
5	A	10	Cy_3P (2)	K_2CO_3	125	1	50	6	17	8	—
6	A	10	*t*-Bu_3P (2)	K_2CO_3	125	8	6	33	—	13	—
7	B	20	P(*o*-tol)$_3$ (2)	Ag_2CO_3	125	5	—	—	—	—	58
8	A	10	P(*o*-tol)$_3$ (2)	*i*-Pr_2NEt	125	9	No reaction				
9	A	10	P(*o*-tol)$_3$ (2)	DBU	125	10	No reaction				
10[e]	B	20	—	K_2CO_3	100	31	—	3	—	—	—

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air, C:O_2) and 200 mol% of base was added.
[b] The molar ratio of the ligand and Pd.
[c] CH_3CN was used as a solvent.
[d] The starting material (**16a**) was recovered in 35% yield.
[e] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added. The starting material (**16a**) was recovered in 64% yield.

Table 2. Results of biaryl coupling reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-2,3-dihydroindole (**17a**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						2	**4**	**22**	**23**
1[c]	B	20	P(*o*-tol)$_3$ (2)	125	3	Trace	34	11	10
2[d]	B	10	P(*o*-tol)$_3$ (2)	125	7	Trace	25	9	10
3[e]	B	10	P(*o*-tol)$_3$ (2)	160	1	Trace	30	2	17
4	A	10	P(*o*-tol)$_3$ (2)	140	2	28	13	28	18
5	A	10	Cy_3P (2)	125	1	45	13	26	3

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO_3 was added.
[b] The molar ratio of the ligand and Pd.
[c] The starting material (**17a**) was recovered in 9% yield.
[d] The starting material (**17a**) was recovered in 21% yield.
[e] DMA was used as a solvent.

the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out with Merck silica gel (230–400 mesh) and Wako activated alumina (300 mesh). All the experiments were carried out in an argon atmosphere, unless otherwise noted, and the extract was washed with brine, dried over anhydrous K_2CO_3, and filtered, and the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

3.2. Coupling reaction of 1-(2-bromobenzyl)-2,3-dihydroindole (14) with palladium reagent

To a solution of **14** (58 mg, 0.2 mmol) in DMF (1.5 ml) were added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (5.3 mg, 0.02 mmol), and K_2CO_3 (55 mg, 395 mmol), and the

Table 3. Results of biaryl coupling reaction of 1-[(6-iodo-1,3-bezodioxol-5-yl)methyl]-2,3-dihydroindole (**16b**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						1	**3**	**20**	**21a**
1	B	20	P(*o*-tol)$_3$ (2)	125	2.5	Trace	43	17	14
2	A	5	P(*o*-tol)$_3$ (2)	125	3.5	34	16	21	12
3	A	5	Cy_3P (2)	125	1.5	48	12	21	12
4	A	5	*n*-Bu_3P (2)	125	3.5	35	10	25	16
5	A	5	*t*-Bu_3P (2)	125	1	41	13	24	13
6	A	5	—	115	3.5	50	11	17	12
7[c]	B	20	—	100	24	Trace	51	19	Trace
8[d]	B	20	—	100	2.3	Trace	47	13	Trace
9	A	5	DPPP	125	2	29	11	27	11

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO_3 was added.
[b] The molar ratio of the ligand and Pd.
[c] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added.
[d] 100 mol% of *n*-Bu_4NCl and 550 mol% of AcOK were added.

Table 4. Results of biaryl coupling reaction of 1-(2-iodo-4,5-dimethoxybenzyl)-2,3-dihydroindole (**17b**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						2	**4**	**22**	**23**
1	B	5	P(*o*-tol)$_3$ (2)	125	2	Trace	35	16	13
2	A	5	P(*o*-tol)$_3$ (2)	125	2.5	28	15	25	15
3	A	5	Cy_3P (2)	125	1	24	10	33	4
4[c]	A	5	—	115	4	43	6	22	11
5[d]	A	5	—	155	4	37	6	3	19

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO3 was added.
[b] The molar ratio of the ligand and Pd.
[c] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added.
[d] 100 mol% of *n*-Bu_4NCl and 550 mol% of AcOK were added.

reaction mixture was stirred for 1.6 h at 125 °C. Then, the mixture was diluted with AcOEt and the precipitate was removed by filtration. The filtrate was washed with aqueous 5% NaOH solution and brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography through Al_2O_3. Elution with hexane–AcOEt (200:1) gave a mixture of 1-benzyl-2,3-dihydroindole[16] and 1-benzylindole.[16] Elution with hexane–AcOEt (1:1) gave 4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (**15**) (19 mg, 35%). Moreover, a mixture of 1-benzyl-2,3-dihydroindole and 1-benzylindole was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane gave 1-benzyl-2,3-dihydroindole (6 mg, 13%) and successive elution with the same solvent gave 1-benzylindole (9 mg, 17%).

3.2.1. 4,5-Dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (15). Colorless needles, mp 168–170 °C ($CHCl_3$–hexane), (lit.[17] 170–171 °C).

3.2.2. 1-Benzyl-2,3-dihydroindole. Pale yellow oil, (lit.[16] oil). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 2.88–3.44 (4H, m, C_2–H and C_3–H), 4.23 (2H, s, Ar–CH_2N), 6.45–7.33 (9H, m, Ar–H).

3.2.3. 1-Benzylindole. Colorless plates, mp 38.5–40 °C (Et_2O), (lit.[16] 43–44 °C). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 5.33 (2H, s, Ar–CH_2N), 6.55 (1H, d, J=3.4 Hz, C_3–H), 7.04–7.33 (9H, m, Ar–H), 7.62 (1H, d, J=3.4 Hz, C_2–H).

3.3. General procedure for the synthesis of starting materials (16a, 16b and 17a)

To a solution of 2-halobenzyl bromides (**18a**,[18a] **18b**,[19b] and **19a**[18b]) (3.00 mmol) in dry CH_3CN (8 ml) were added dihydroindole (425 mg, 3.60 mmol), Et_4NI (116 mg, 0.45 mmol), and *i*-Pr_2NEt (2.1 ml, 12.3 mmol), and the reaction mixture was stirred for 30 min at 70 °C. The mixture was diluted with AcOEt and the entire organic layer was washed with aqueous 5% NaOH solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography through silica gel.

3.3.1. 1-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]-2,3-dihydroindole (16a). Elution with AcOEt–hexane (1:20) gave **16a** (302 mg, 91%), colorless plates, mp 66–67 °C (Et_2O). IR (KBr) cm^{-1}: 1245, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.3 Hz, C_3–H), 3.41 (2H, t, J=8.3 Hz, C_2–H), 4.21 (2H, s, Ar–CH_2N), 5.95 (2H, s, $C_{2'}$–H), 6.43 (1H, dd, J=0.9, 7.8 Hz, C_7–H), 6.68 (1H, ddd, J=0.9, 7.4, 7.8 Hz, C_5–H), 6.96 (1H, s, $C_{4'}$–H), 7.03 (1H, s, $C_{7'}$–H), 7.01–7.12 (2H, m, C_4–H and C_6–H). FAB-MS *m*/*z*: 331 $(M)^+$, 333 $(M+2)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 58.04; H, 4.42; N, 4.28.

3.3.2. 1-[(6-Iodo-1,3-benzodioxol-5-yl)methyl]-2,3-dihydroindole (16b). Elution with AcOEt–hexane (1:10) gave **16b** (324 mg, 86%), colorless needles, mp 74.5–75.5 °C (Et_2O). IR (KBr) cm^{-1}: 1250, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (2H, t, J=8.1 Hz, C_3–H), 3.40 (2H, t, J=8.1 Hz, C_2–H), 4.15 (2H, s, Ar–CH_2N), 5.96 (2H, s, $C_{2'}$–H), 6.43 (1H, dd, J=1.0, 8.0 Hz, C_7–H), 6.68 (1H, ddd, J=1.0, 7.2, 7.6 Hz, C_5–H), 6.97 (1H, s, $C_{4'}$–H), 7.06 (1H, dd, J=7.6, 8.0 Hz, C_6–H), 7.11 (1H, d, J=7.2 Hz, C_4–H), 7.28 (1H, s, $C_{7'}$–H). FAB-MS *m*/*z*: 379 $(M)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.91; H, 3.97; N, 3.88.

3.3.3. 1-(2-Bromo-4,5-dimethoxybenzyl)-2,3-dihydroindole (17a). Elution with AcOEt–hexane (1:10) gave **17a** (282 mg, 91%), colorless plates, mp 68–69 °C (Et_2O). IR (KBr) cm^{-1}: 1260, 1030. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.3 Hz, C_3–H), 3.38 (2H, t, J=8.3 Hz, C_2–H), 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.23 (2H, s, Ar–CH_2N), 6.51 (1H, dd, J=1.0, 7.8 Hz, C_7–H), 6.68 (1H, ddd, J=1.0, 7.2, 7.4 Hz, C_5–H), 7.00 (1H, s, $C_{6'}$–H), 7.05 (1H, s, $C_{3'}$–H), 7.07 (1H, dd, J=7.4, 7.8 Hz, C_6–H), 7.12 (1H, d, J=7.2 Hz, C_4–H). FAB-MS *m*/*z*: 347 $(M)^+$, 349 $(M+2)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.53; H, 5.08; N, 3.92.

3.3.4. 1-(2-Iodo-4,5-dimethoxybenzyl)-2,3-dihydroindole (17b). To a solution of **19b**[19b] (1.43 g, 4.00 mmol) in ether (10 ml) was added dihydroindole (858 mg, 7.20 mmol) and the reaction mixture was stirred for 1.5 h at rt. After evaporation of solvent, the residue dissolved in $CHCl_3$ was subjected to column chromatography through silica gel. Elution with $CHCl_3$ gave **17b** (1.21 g, 77%), colorless prisms, mp 93–94 °C (Et_2O). IR (KBr) cm^{-1}: 1255, 1025. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.2 Hz, C_3–H), 3.40 (2H, t, J=8.2 Hz, C_2–H), 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.20 (2H, s, Ar–CH_2–N), 6.50 (1H, dd, J=7.8 Hz, C_7–H), 6.70 (1H, dd, J=7.2, 7.4 Hz, C_5–H), 6.99 (1H, s, $C_{6'}$–H), 7.09 (1H, dd, J=7.4, 7.8 Hz, C_6–H), 7.12 (1H, d, J=7.2 Hz, C_4–H), 7.27 (1H, s, $C_{3'}$–H). FAB-MS *m*/*z*: 395 $(M)^+$. Anal. calcd for $C_{17}H_{18}INO_2$: C, 51.66; H, 4.59; N, 3.54. Found: C, 51.57; H, 4.75; N, 3.47.

3.4. General procedure for the coupling reaction of 1-halobenzyldihydroindole derivatives (16 and 17) in the presence of phosphine ligand

Each compound (**16** or **17**) (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 200 mol% of base for the times and temperatures indicated in the tables. Then, the reaction mixture was diluted with AcOEt and the precipitate was removed by filtration. The filtrate was washed with aqueous 5% NaOH solution and brine. The residue from **16** was dissolved in $CHCl_3$ and subjected to column chromatography through Al_2O_3. Elution with hexane–AcOEt (50:1) gave **20** and elution with hexane–AcOEt (30:1) gave **21a**. Moreover, elution with hexane–AcOEt (15:1) gave **1** and elution with AcOEt gave **3**.

3.4.1. Anhydrolycorine (1). Pale yellow prisms, 110–112.5 °C (EtOH), (lit.[20a] 108–111 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (2H, t, J=7.9 Hz, C_4–H), 3.33 (2H, t, J=7.9 Hz, C_5–H), 4.07 (2H, s, C_7–H), 5.97 (2H, s, OCH_2O), 6.64 (1H, s, C_8–H), 6.76 (1H, dd, J=7.3, 7.3 Hz, C_2–H), 7.01 (1H, dd, J=1.0, 7.3 Hz, C_3–H), 7.16 (1H, s, C_{11}–H), 7.28 (1H, dd, J=1.0, 7.3 Hz, C_1–H). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.49; H, 5.43; N, 5.35.

3.4.2. Anhydrolycorin-7-one (3). Pale brown needles, mp 236–237 °C ($CHCl_3$–MeOH), (lit.[20a] 232–234 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.33 (2H, t, J=8.3 Hz, C_4–H), 4.38 (2H, t, J=8.3 Hz, C_5–H), 6.05 (2H, s, OCH_2O), 7.10 (1H, dd, J=7.6, 7.6 Hz, C_2–H), 7.20 (1H, dd, J=1.2, 7.6 Hz, C_3–H), 7.43 (1H, s, C_{11}–H), 7.64 (1H, dd, J=1.2, 7.6 Hz, C_1–H), 7.82 (1H, s, C_8–H). Anal. calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.46; H, 4.38; N, 5.21.

3.4.3. 1-[(1,3-Benzodioxol-5-yl)methyl]-2,3-dihydroindole (20). Pale yellow oil, (lit.[19a] oil). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.96 (2H, t, J=8.2 Hz, C_3–H), 3.29 (2H, t, J=8.2 Hz, C_2–H), 4.16 (2H, s, Ar–CH_2N), 5.95 (2H, s, $C_{2'}$–H), 6.51 (1H, d, J=7.6 Hz, Ar–H), 6.63–7.11 (6H, m, Ar–H). FAB-MS m/z: 253 $(M)^+$.

3.4.4. 1-[(1,3-Benzodioxol-5-yl)methyl]indole (21a). Colorless needles, mp 82–83 °C (petr. ether). IR (KBr) cm^{-1}: 1235, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.22 (2H, s, Ar–CH_2N), 5.91 (2H, s, $C_{2'}$–H), 6.53 (1H, d, J=3.4 Hz, C_3–H), 6.59 (1H, d, J=1.4 Hz, $C_{4'}$–H), 6.63 (1H, dd, J=1.4, 7.8 Hz, $C_{6'}$–H), 6.73 (1H, d, J=7.8 Hz, $C_{7'}$–H), 7.10 (1H, ddd, J=1.4, 6.8, 6.8 Hz, C_5–H), 7.12 (1H, d, J=3.4 Hz, C_2–H), 7.18 (1H, ddd, J=1.4, 6.8, 8.2 Hz, C_6–H), 7.30 (1H, dd, J=1.4, 8.2 Hz, C_7–H), 7.64 (1H, dd, J=1.4, 6.8 Hz, C_4–H). FAB-MS m/z: 251 $(M)^+$. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.32; H, 5.45; N, 5.49.

3.4.5. 1-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]indole (21b). The residue of run 7 in Table 1 was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane–AcOEt (20:1) gave **21b**, colorless needles, mp 124.5–125.5 °C (hexane). IR (KBr) cm^{-1}: 1240, 1035. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.29 (2H, s, Ar–CH_2–N), 5.89 (2H, s, $C_{2'}$–H), 6.06 (1H, d, J=3.5 Hz, C_3–H), 6.58 (1H, d, J=3.5 Hz, C_2–H), 7.04 (1H, s, $C_{4'}$–H), 7.12 (1H, s, $C_{7'}$–H), 7.13 (1H, ddd, J=1.0, 7.0, 8.0 Hz, C_5–H), 7.19 (1H, ddd, J=1.0, 7.0, 8.0 Hz, C_6–H), 7.25 (1H, dd, J=1.0, 8.0 Hz, C_7–H), 7.66 (1H, dd, J=1.0, 8.0 Hz, C_4–H). FAB-MS m/z: 329 $(M)^+$, 331 $(M+2)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 58.26; H, 3.66; N, 4.24. Found: C, 58.27; H, 3.93; N, 4.11.

The residue from **17** was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane–AcOEt (15:1) gave **22**. Successive elution with the same solvent gave **23** and **2**, and elution with AcOEt gave **4**.

3.4.6. Assoanine (2). Pale yellow needles, mp165.5–168 °C (EtOH), (lit.[20b] 175–176 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.03 (2H, t, J=7.8 Hz, C_4–H), 3.34 (2H, t, J=7.8 Hz, C_5–H), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.12 (2H, s, C_7–H), 6.67 (1H, s, C_8–H), 6.78 (1H, dd, J=7.4, 7.6 Hz, C_2–H), 7.01 (1H, dd, J=1.0, 7.4 Hz, C_3–H), 7.19 (1H, s, C_{11}–H), 7.34 (1H, dd, J=1.0, 7.6 Hz, C_1–H). FAB-MS m/z: 268 $(M+1)^+$.

3.4.7. Oxoassoanine (4). Colorless needles, mp 271–273 °C ($CHCl_3$–MeOH), (lit.[20b] 270–271 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.43 (2H, t, J=8.3 Hz, C_4–H), 4.04 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.49 (2H, t, J=8.3 Hz, C_5–H), 7.20 (1H, dd, J=7.4, 7.6 Hz, C_2–H), 7.28 (1H, d, J=1.0, 7.4 Hz, C_3–H), 7.52 (1H, s, C_{11}–H), 7.80 (1H, d, J=1.0, 7.8 Hz, C_1–H), 7.93 (1H, s, C_8–H). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.43; H, 5.57; N, 5.03.

3.4.8. 1-(3,4-Dimethoxybenzyl)-2,3-dihydroindole (22). Colorless needles, mp 77–78 °C (petr. ether). IR ($CHCl_3$) cm^{-1}: 1260, 1030. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.97 (2H, t, J=8.0 Hz, C_3–H), 3.33 (2H, t, J=8.0 Hz, C_2–H), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.21 (2H, s, Ar–CH_2N), 6.62–7.14 (7H, m, Ar–H). FAB-MS m/z: 269 $(M)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 7.07; N, 5.19.

3.4.9. 1-(3,4-Dimethoxybenzyl)indole (23). Colorless needles, mp 61.5–62.5 °C (hexane). IR (KBr) cm^{-1}: 1255, 1025. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.25 (2H, s, Ar–CH_2N), 6.53 (1H, d, J=3.6 Hz, C_3–H), 6.66–6.70 (2H, m, $C_{2'}$–H and $C_{6'}$–H), 6.78 (1H, d, J=8.6 Hz, $C_{5'}$–H), 7.10 (1H, ddd, J=6.8, 7.2 Hz, C_5–H), 7.11 (1H, d, J=3.6 Hz, C_2–H), 7.18 (1H, ddd, J=1.4, 7.2, 8.0 Hz, C_6–H), 7.31 (1H, d, J=8.0 Hz, C_7–H), 7.64 (1H, dd, J=1.4, 6.8 Hz, C_4–H). FAB-MS m/z: 267 $(M)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.28; H, 6.26; N, 5.20.

3.5. General procedure for the coupling reaction of 1-(2-iodobenzyl)dihydroindole derivatives (16b and 17b) under phosphine-free conditions (runs 6–8 in Table 3, and runs 4 and 5 in Table 4)

The 1-(2-iodobenzyl)dihydroindole derivative (0.3 mmol) was reacted with 0.05 mol% of $Pd(OAc)_2$, 100 mol% of n-Bu_4NCl, and 300 mol% of K_2CO_3 or 550 mmol% of

AcOK in dry DMF (4 ml) for the times and at temperature indicated in Tables 3 and 4. Then, the reaction mixture was diluted with ether and the precipitates were removed by filtration. Then, the reaction mixture was diluted with AcOEt and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography and the products (**2**, **4**, **22**, and **23**) shown in Tables 3 and 4 were separated by the methods mentioned before.

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