Synthesis of 8-Oxoberbines and Related Benzolactams by $Pd(OAc)_2$-Catalyzed Direct Aromatic Carbonylation

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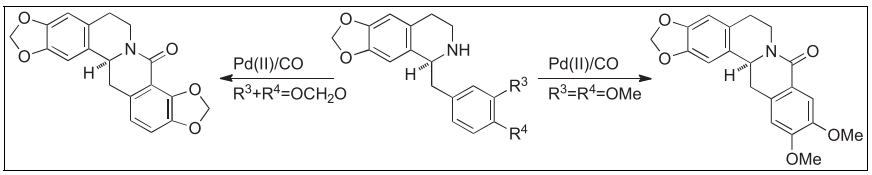

A variety of alkoxy-substituted benzolactams with a berbine or yohimbane skeleton were prepared from 1-benzyl-1,2,3,4-tetrahydroisoquinolines or 1-benzyl-1,2,3,4-tetrahydro-β-carbolines by a phosphine-free Pd(II)-catalyzed direct aromatic carbonylation in a $Pd(OAc)_2$-$Cu(OAc)_2$ catalytic system. The site selectivity was compared with that of the carbonylation with $Pd(OAc)_2$ or $Pd(OAc)_2$·2 PPh_3, respectively.

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INTRODUCTION

We recently reported $Pd(OAc)_2$-catalyzed carbonylation of amines using a $Pd(OAc)_2$-$Cu(OAc)_2$ catalytic system [1]. The method provides *N*,*N*′-dialkylureas from primary amines, oxazolidinones from 2-amino-1-alkanoles, and isoindolin-1-ones or tetrahydroisoquinolin-1-ones from secondary amines such as *N*-alkylbenzylamines or *N*-alkylphenethylamines. In the benzolactam formation, the chelation of a palladium species especially with a 3′,4′-methylenedioxy group generates *ortho*-palladation at the C-2′ position to conduct a CO group to the C-2′ (**i**), and in contrast, steric repulsion caused by a 3′,4′-dimethoxy group prefers the insertion of CO to the C-6′ (**ii**), as shown in Figure 1. Such effects are reflected in the products ratios. In this article, we describe a method for direct preparation of 8-oxoberbines and related benzolactams by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines and 1-benzyl-1,2,3,4-tetrahydro-β-carbolines in a $Pd(OAc)_2$-$Cu(OAc)_2$ catalytic system, which requires no phosphine ligands. Site selectivity of the carbonylation was compared with those of carbonylations using other palladium reagents such as $Pd(OAc)_2$ or $Pd(OAc)_2$·2 PPh_3 [2]. Some of the benzolactams obtained have been converted to protoberberine alkaloids [3, 4], which have been known to have a variety of biological activities [5a] including antileukemic and antitumor activities [5b].

RESULTS AND DISCUSSION

Substrates, 1-benzyltetrahydroisoquinolines **1**, were prepared in a conventional reaction sequence starting with the corresponding phenethylamines [6], and their carbonylation to the 8-oxoberbines was carried out by using the aforementioned phosphine-free Pd(II)-catalyst, $Pd(OAc)_2$ (5 mol %)-$Cu(OAc)_2$ (50 mol %) under carbon monoxide gas containing oxygen (Method A). Carbonylation with a stoichiometric amount of Pd(II)-reagent, $Pd(OAc)_2$ (Method B) or $Pd(OAc)_2$·2 PPh_3 (Method C) [2], was also examined for comparison. As shown in Scheme 1, carbonylation of **1a**–**d** with $Pd(OAc)_2$ (B) appeared to proceed via the most bulky cyclopalladation product which is probably in a dimeric form [7], and gave a mixture of benzolactams **2** and **3** in selectivities of 4:3 for a 3′,4′-methylenedioxy group (**b** and **d**) and exclusively **3** for a 3′,4′-dimethoxy group (**a** and **c**) (Table 1). The remarkable site selectivity of the latter may be accounted for by a steric repulsion so-called buttressing effect of the dimethoxy group [8]. Carbonylation with another Pd(II)-reagent, $Pd(OAc)_2$·2 PPh_3 (C) gave a 3:1 ratio of **2** and **3** for the dimethoxy, probably due to the more reduced steric hindrance compared with the dimeric cyclopalladation product in the use of $Pd(OAc)_2$ [7] (B), and only **2** for the methylenedioxy due to the more efficient chelation between Pd(II) and an oxygen atom of the neighboring alkoxy group [9]. Method A shows site selectivity between Methods B and

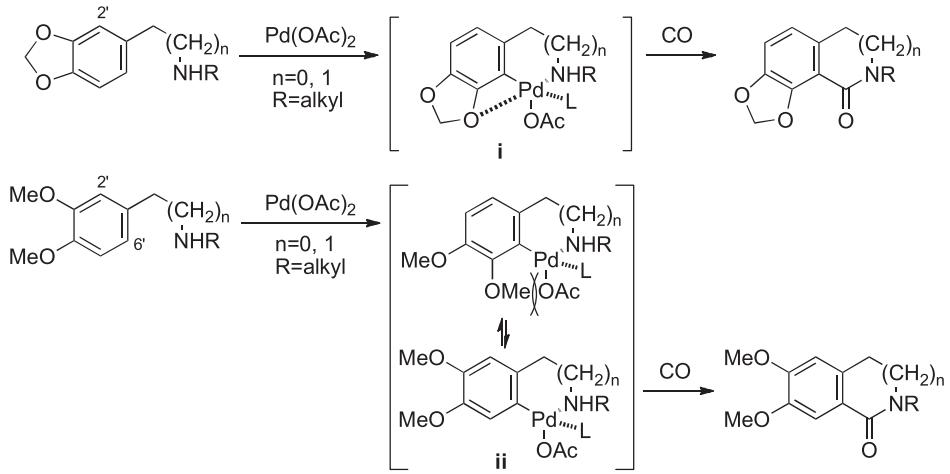


Figure 1. $Pd(OAc)_2$-catalyzed carbonylation.

Scheme 1

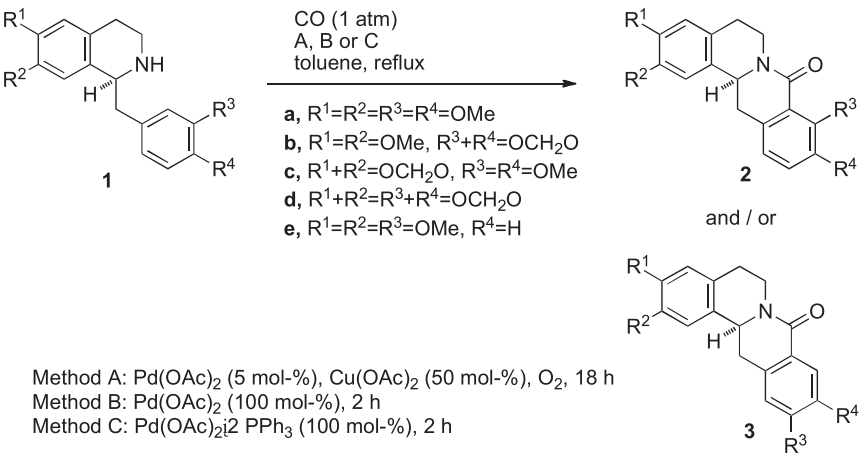


Table 1

Carbonylation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines **1**.

	NMR ratios of **2** and **3**[a,b]				
	A	B	C		
Method	**2:3**	**2:3**	**2:3**	Isolated yields of **2** or **3** (Method)	
1a, $R^1 = R^2 = R^3 = R^4 = OMe$	3:7	0:10	3:1	**2a**: 14% (A)	**3a**: 47% (A), 66% (B)
1b, $R^1 = R^2 = OMe$, $R^3 + R^4 = OCH_2O$	10:0	4:3	10:0	**2b**: 71% (A)	**3b**: 13% (B)
1c, $R^1 + R^2 = OCH_2O$, $R^3 = R^4 = OMe$	3:7	0:10	4:1	**2c**: 12% (A)	**3c**: 45% (A), 74% (B)
1d, $R^1 + R^2 = R^3 + R^4 = OCH_2O$	10:0	4:3	10:0	**2d**: 72% (A)	**3d**: 11% (B)
1e, $R^1 = R^2 = R^3 = OMe$, $R^4 = H$	1:1	0:10	2:1	**2e**: 32% (A)	**3e**: 36% (A), 62% (B)

[a]Isomer ratios in the crude reaction mixtures were determined by ^{1}H-NMR analysis.
[b]The ratio "0:10" or "10:0" shows that one of the two isomers was not detected.

C in Table 1. In other words, the $Pd(OAc)_2$-$Cu(OAc)_2$ system has both abilities of chelation and steric hindrance, proving that $Cu(OAc)_2$ works as not only an oxidant but also a ligand to Pd(II). Carbonylation of **1e** revealed that chelation ability of a 3′-monomethoxy group was lower than that of a 3′,4′-methylenedioxy group, and its steric

hindrance was smaller than that of a 3′4′-dimethoxy group, as expected. Consequently, it was found that methylenedioxybenzolactams **2b** and **2d** were selectively obtained in 71 and 72% isolated yields, and methoxybenzolactams **3a**, **3c** and **3e** were obtained in 36 ~ 47% yield, respectively, by the Method A carbonylation. In contrast, Method B carbonylation afforded methoxybenzolactams, **3a** (66%), **3c** (74%), and **3e** (62%), respectively.

The catalytic carbonylation of other substrates, 4′-methoxy, 2′,3′-dimethoxy and 3′,4′,5′-trimethoxybenzyl derivatives, **4g**, **4h**, and **4i**, gave the corresponding 8-oxoberbines **5g** (67%), **5h** (71%) and **5i** (61%), respectively (Scheme 2). Nonalkoxy-substituted benzolactam **5f** was obtained in 57% yield. Thus, the method should be useful for preparation of berbines and protoberberine alkaloids, as it was already reported that lithium aluminum hydride reduction of 8-oxobervines provided such alkaloids and related cyclic amines in good yields [4].

A similar site selectivity was reproduced in carbonylation of 1-benzyl-1,2,3,4-tetrahydro-β-carbolines **6** (Scheme 3, Table 2). Methylenedioxybenzolactam **8a** and methoxybenzolactam **7b**, which have a structural feature of yohimbine alkaloids [10], were isolated in 49 and 68% yields, respectively, by this Pd(II)-catalyzed carbonylation. Method B afforded **8a** in 67% yield.

The direct aromatic carbonylation is able to be conducted using substrates carrying a halogen atom. As shown in Scheme 4, bromides **9a** and **9b** were converted to 12-bromoberbines **10a** (76%) and **10b** (78%), respectively, together with a trace of **2a** or **3b** (<3%), which has been obtained by a Pd(0)-catalyzed carbonylation based on a halogen-metal exchange of the same bromides [4c].

Thus, by Pd(II)-catalyzed direct aromatic carbonylation using $Pd(OAc)_2$-$Cu(OAc)_2$ with the chelation-induced site selectivity, 1-benzyl-1,2,3,4-tetrahydroisoquinolines and 1-benzyl-1,2,3,4-tetrahydro-β-carbolines were converted to 8-oxoberbines **5a–i** and related benzolactams **7** and **8** with a yohimbane skeleton [10]. 8-Oxoberbines **10a,b** with a bromine atom were also prepared by the carbonylation. The method is promising as a widely applicable synthetic tool for nitrogen-containing heterocyclic compounds. Studies designed to use the method for the synthesis of other biologically active alkaloids are currently underway [11, 12].

EXPERIMENTAL

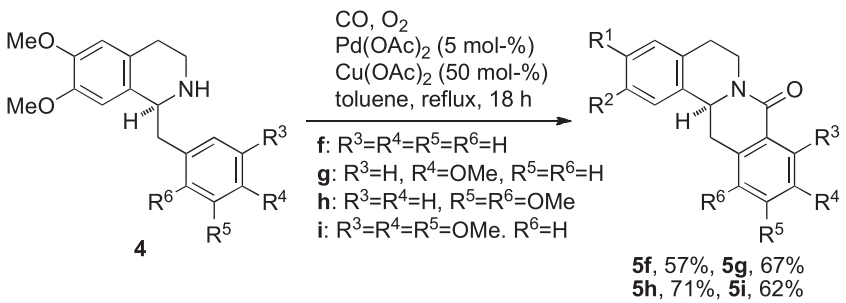
General remarks. Melting points were measured with a Yanagimoto micro melting point apparatus, and were uncorrected. The IR spectra were recorded with a JASCO IR-810 spectrometer. The LR- and HR-EI-MS spectra were determined with a JEOL JMS-HX110 or JEOL JMS-FABmate or JEOL JMS-700TZ mass spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-JX270 spectrometer (270 MHz). NMR samples were prepared using deuterio chloroform (99.8 atom % D, containing 0.03 % v/v tetramethylsilane (Aldrich). Chemical shifts were reported in ppm. TLC was carried out on a Merck Silica gel 60 PF_{254}. Elemental analyses were performed with Yanako MT-6 CHN CORDER and Dionex DX-500 at the Analytical Laboratory of Faculty of Pharmaceutical Science, Hokkaido University.

Tetrahydroisoquinolines **1a** (a colorless oil [13]), **1b** (a colorless oil [14]), **1c** [a colorless oil (lit. [15] mp 84°C)], **1d** [a colorless oil (lit. [16] mp 84–85°C)], **1e** (a colorless oil [16]), **4f** (a colorless oil [17]), **4g** [a colorless oil (lit. [18] HCl salt mp 200°C; lit. [19] HCl salt mp 202–203°C)], **4h** [a colorless oil (lit. [20] HCl salt mp 294°C)], and **4i** [a colorless oil][21] were prepared by Bischler–Napieralski cyclization of the corresponding *N*-phenethyl-α-phenylacetamides, followed by $NaBH_4$ reduction of the resultant 3, 4-dihydro derivatives, according to a modification [22] of the well-known reaction sequence [6].

3,4-Dimethoxybenzyl-1,2,3,4-tetrahydro-β-carboline (6a). *N*-Benzyl-*N*-[2-(3-indolyl)ethyl]-2-(3,4-dimethoxyphenyl)acetamide was prepared in 63% yield by *N*-acylation of *N*-benzyltryptamine, bp 190°C/0.15 torr (lit. [23] bp 160°C/0.01 torr) with 3,4-dimethoxyphenylacetyl chloride) and subjected to Bischler–Napieralski reaction with phosphorous oxychloride in boiling toluene for 3 h, followed by treatment with sodium borohydride in methanol to give the *N*-benzyl-1,2,3,4-tetrahydro-β-carboline as a light yellow oil (66%) after purification by a column chromatography on silica gel (ethyl acetate–hexane 4:1). The *N*-benzyl group was removed by treatment with 20% $Pd(OH)_2$ on carbon and ammonium formate in boiling ethanol–acetic acid (20:1), which is a modification of the known method [24], to give **6a** as a light yellow oil (91%) (lit. [25] mp 91°C; lit. [25, 26] mp 98°C; lit. [27] mp 130–131°C; Lit. [28] HCl salt mp 233°C; lit. [29] HCl salt mp 235–236°C); IR (neat): 3360 (NH), 1592, 1515 cm^{-1}.

^{1}H-NMR: δ 2.72–2.78 (m, 2H, 4-H), 2.95–3.11 (m, 3H, benzyl 2H and 3-H), 3.32 (dt, *J* = 12.5, 4.6, 4.6 Hz, 1H, 3-H), 3.79, 3.89

Scheme 2



Scheme 3

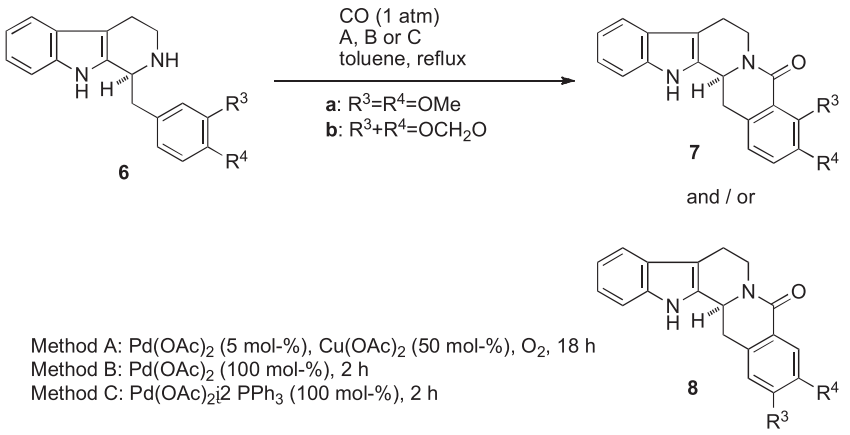


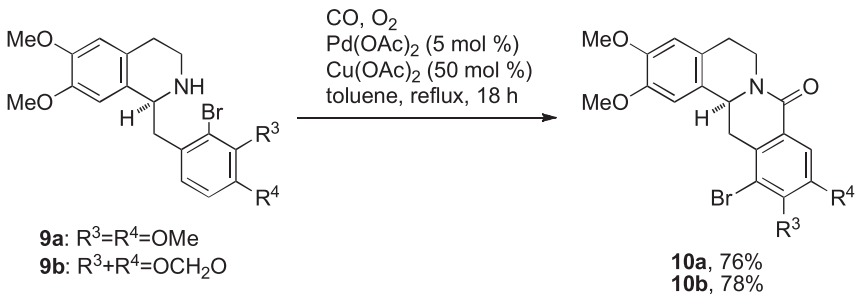
Table 2

Carbonylation of 1-benzyl-1,2,3,4-tetrahydro-β-carbolines **6**.

	NMR ratios of **7** and **8**[a,b]				
	A	B	C		
Method	**7:8**	**7:8**	**7:8**	Isolated yields of **7** or **8** (Method)	
a, $R^3 = R^4$ = OMe	3:7	0:10	5:1	**7a**: 12% (A)	**8a**: 49% (A), 67% (B)
b, $R^3 + R^4 = OCH_2O$	10:0	1:1	10:0	**7b**: 68% (A)	**8b**: 22% (B)

[a]Isomer ratios in the crude reaction mixtures were determined by ^{1}H-NMR analysis.
[b]The ratio "0:10" or "10:0" shows that one of the two isomers was not detected.

Scheme 4



(each s, each 3H, OMe), 4.36 (t, J = 6.9 Hz, 1H, 1-H), 6.75 (d, J = 1.7 Hz, 1H, 2′-H), 6.80 (dd, J = 6.9, 1.7 Hz, 6′-H), 6.84 (d, J = 6.9 Hz, 5′-H), 7.06, 7.12 (each d, J = 7.6 Hz, 2H, 6- and 7-H), 7.21, 7.48 (each dd, J = 7.6, 1.7 Hz, each 1H, 5- and 8-H), 7.55 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 322 (M^+, 1.1), 185 (6.8), 171 (100), 144 (10), 115 (5.7); HR-MS calcd for $C_{20}H_{20}N_2O_2$ 322.1681; Found 322.1674.

3,4-(Methylenedioxy)-1,2,3,4-tetrahydro-β-carboline (6b). Similarly, *N*-benzyl-*N*-[2-(3-indolyl)ethyl]-2-(3,4-methylenedioxyphenyl) acetamide, mp 130–131°C (benzene), as colorless crystals (86%) was obtained and subjected to the Bischler–Napieralski reaction followed by sodium borohydride reduction to give *N*-benzyl-1,2,3,4-tetrahydro-*b*-carboline (75%). Removal of the *N*-benzyl group with 20% $Pd(OH)_2$ on carbon and ammonium formate [24] and purification of the crude product by a column chromatography on silica gel (20:1 ethyl acetate–methanol) afforded **6b** as a light yellow oil (68%) (lit. [28] HCl salt mp 271–273°C; lit. [30] HCl salt mp 273–274°C); IR (neat): 3582 (NH), 3402 (NH), 1606, 1502, 1498 cm^{-1}.

^{1}H-NMR: δ 2.72–2.78 (m, 2H, 4-H), 2.98, 3.00 (each s, each 1H, benzyl 2H), 3.00–3.07 (m, 1H, 3-H), 3.33 (dt, J = 12.5, 4.6, 4.6 Hz, 1H, 3-H), 4.30 (t, J = 6.9 Hz, 1H, 1-H), 5.97 (s, 2H, OCH_2O), 6.97 (dd, J = 7.9, 1.7 Hz, 1H, 6′-H), 6.78 (d, J = 1.7 Hz, 1H, 2′-H), 6.80 (d, J = 7.9 Hz, 1H, 5′-H), 7.09, 7.13 (each t, J = 7.9 Hz, 2H, 6- and 7-H), 7.24, 7.49 (each dd, J = 7.9, 1.7 Hz, each 1H, 5- and 8-H), 7.55 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 306 (M^+, 0.7), 305 (1.2), 185 (3.4), 171 (7.4), 135 (7.2), 115 (4.3); HR-MS calcd for $C_{19}H_{18}N_2O_2$ 306.1368; Found 306.1366.

A general procedure for Pd(II)-catalyzed carbonylation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines 1a–i and 1-benzyl-1,2,3,4-tetrahydro-β-carbolines 4a,b. Method A. A stirred suspension of freshly prepared amine (0.1 mmol), $Pd(OAc)_2$ (1.12 mg, 5 mol %), and $Cu(OAc)_2$ (9.2 mg, 50 mol %) in toluene (2 mL) was refluxed in an atmosphere of carbon monooxide (ca. 1–1.5 L) containing 6 mL air (corresponding to 0.05 mmol of oxygen) delivered from a toy balloon in an oil bath at 120°C for 18 h. The reaction mixture was cooled to room temperature and filtered through a pad of powdered anhydrous magnesium sulfate. The filtrate was concentrated, and the residue was analyzed by ^{1}H-NMR and purified by preparative silica gel TLC (2.5–5% methanol–dichloromethane) and/or crystallization.

Method B. A stirred mixture of amine (0.1 mmol) and $Pd(OAc)_2$ (22.4 mg, 100 mol %) in toluene (2 mL) was refluxed in an atmosphere of carbon monoxide in an oil bath at 120°C for 2 h. Method C: A stirred mixture of amine (0.1 mmol) and $Pd(OAc)_2{\cdot}2PPh_3$ [2] (74.9 mg, 100 mol %) in toluene (2 mL) was refluxed in an atmosphere of carbon monoxide in an oil bath at 120°C for 2 h. The products, 8-oxoberbines, **2a**, **3a**, **2b**, **3b**, **2c**, **2d**, **3e**, **5f**, **5g**, and **5h**, and 8-oxoindolobenzoquinilizidine, **7a** and **8a**, were known.

(±)-8-Oxotetrahydropalmatine (2a). Colorless crystals (14%); R_f 0.5 (5% methanol–dichloromethane); mp 171–172°C (ethanol) (lit. [17, 31] mp 167–168°C; lit. [5b] mp 169–170°C; lit. [21] mp 170–171°C; lit. [22] mp 171–172°C).

(±)-8-Oxoxylopinine (3a). Colorless crystals (47%); R_f 0.55 (5% methanol–dichloromethane); mp 191–192°C (benzene–diethyl ether) (lit. [32, 33] mp 187–188°C; lit. [34] mp 188–189°C; lit. [35] mp 190–192°C; lit. [36] mp 191°C; lit. [37] mp 191–192°C).

(±)-8-Oxosinactine (2b). Colorless crystals (71%); R_f 0.5 (5% methanol–dichloromethane); mp 199–202°C (methanol) (lit. [38] mp 198–200°C; lit. [22, 37] mp 198–202°C).

(±)-8-Oxoisosinactine (3b). Colorless crystals (13% in Method B); R_f 0.55 (5% methanol–dichloromethane); mp 175–176°C (ethyl acetate–diethyl ether) (lit. [34] mp 174–178°C; lit. [36] mp 175–176°C; lit. [37] mp 186–186.5°C).

(±)-8-Oxocanadine (2c). Colorless crystals (12%); R_f 0.5 (5% methanol–dichloromethane); mp 209–211°C (EtOH) [5] (lit. [39] mp 198–200°C; lit. [22] mp 198–202°C; lit. [17, 5b, 31] mp 217–218°C; lit. [21, 40] mp 222–223°C).

(±)-8-Oxoisocanadine (3c). Colorless crystals (45%); R_f 0.55 (5% methanol–dichloromethane); mp 221–224°C (methanol); IR (Nujol): 1638 (CO), 1605 cm^{-1}; ^{1}H-NMR: δ 2.71–2.95 (m, 4H, 5-, 5-, 6a-, 13b-H), 3.10 (dd, J = 15.5 Hz, 4.0 Hz, 1H, 13a-H), 3.94 (s, 6H, OMe), 4.80 (dd, J = 13.2, 4.0 Hz, 13a-H), 4.89–4.94 (m, 1H, 6b-H), 5.95 (s, 2H, 2,3-OCH_2O), 6.66 (s, 1H, 4-H), 6.70 (s, 2H, 1- and 12-H), 7.63 (s, 1H, 9-H) ppm; EI-MS (70 eV): m/z 353 (M^+, 100), 352 [$(M - H)^+$, 48.7], 337 [$(M - MeH)^+$, 2.7], 178 [$(MeO_3C_6H_3CH_2COH)^+$, 91.8], 177 [$(MeO_3C_6H_3CH_2CO)^+$, 8.9] 172 [$(OCH_2OC_6H_3CH_2CH_2NCH_2)^+$, 2.4]. Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98: H, 5.42; N, 3.96. Found: C, 67.79: H, 5.59; N, 3.88.

(±)-8-Oxostylopine (2d). Colorless crystals (72%); R_f 0.5 (5% methanol–dichloromethane); mp 267–270°C (methanol) (lit. [41] mp 250–252°C; lit. [22] mp 267–270°C).

2,3,10,11-Bis(methylenedioxy)-8-oxoberbine (3d). Colorless crystals (11% in Method B); R_f 0.55 (5% methanol–dichloromethane); mp 222–224°C (methanol). IR (Nujol): 1642 (CO), 1610, 1506, 1459 cm^{-1}; ^{1}H-NMR: δ 2.68–2.94 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.06 (dd, J = 15.5, 3.6Hz, 1H, 13a-H), 4.77 (dd, J = 13.2, 3.6 Hz, 1H, 13a-H), 4.88–4.93 (m, 1H, 6b-H), 5.95 (s, 2,3-OCH_2O), 6.00, 6.02 (each s, each 1H, 10,11-OCH_2O), 6.66, 6.67, 6.69 (each 1H, each s, Ar-H), 7.58 (1H, s, 9-H) ppm; EI-MS (70 eV): m/z 337 (M^+, 78.6), 322 (18.2), 308 (15.4), 162 (100), 134 (81.8). Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65: H, 4.48; N, 4.15. Found: C, 67.51: H, 4.67; N, 4.09.

2,3,9-Trimethoxy-8-oxoberbine (2e). Colorless crystals (32%); R_f 0.4 (3% methanol–dichloromethane); mp 211–212°C (methanol); IR (Nujol): 1650 (CO), 1612, 1596, 1514 cm^{-1}; ^{1}H-NMR: δ 2.73–3.11 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.07 (dd, J = 15.5, 3.3 Hz, 1H, 13a-H), 3.90 (s, 6H, OMe), 3.96 (s, 3H, OMe), 4.74 (dd, J = 13.2, 3.3 Hz, 1H, 13a-H), 5.03–5.08 (m, 1H, 6b-H), 6.68, 6.70 (each s, each 1H, 1- and 4-H), 6.84 (d, J = 7.6 Hz, 1H, 10-H), 6.94 (d, J = 8.6 Hz, 1H, 12-H) 7.38 (dd, J = 8.6, 7.6 Hz, 1H, 11-H) ppm. EI-MS (70 eV): m/z 339 (M^+, 86.8), 324 (27.0), 310 (13.3), 192 (9.4), 148 (100). Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.63; H, 6.31; N, 4.11.

2,3,11-Trimethoxy-8-oxoberbine (3e). Colorless crystals (36%); R_f 0.55 (3% methanol–dichloromethane); mp 153–154°C (methanol) [42] (lit. [43] mp 158–159°C).

2,3-Dimethoxy-8-oxoberbine (5f). Colorless crystals (57%); R_f 0.6 (5% methanol–dichloromethane); mp 142–144°C (methanol) (lit. [17] mp 139–140°C; lit. [36] mp 140–141°C; lit. [35] mp 141–142°C; lit. [43] mp 142°C; lit. [21b, 32] mp 143–144°C; lit. [34] mp 143–145°C; lit. [37] mp 144–145°C).

2,3,10-Trimethoxy-8-oxoberbine (5g). Colorless crystals (67%); R_f 0.55 (5% methanol–dichloromethane); mp 164–165°C (methanol) (lit. [43] mp 161–162°C).

2,3,11,12-Tetramethoxy-8-oxoberbine (5h). Colorless crystals (71%); R_f 0.4 (5% methanol–dichloromethane); mp 199–200°C (methanol) (lit. [44] mp 179–180°C).

2,3,9,10,11-Pentamethoxy-8-oxoberbine (5i). A colorless oil (61%); R_f 0.5 (5% methanol–dichloromethane); IR (Nujol): 1646 (CO), 1592, 1558, 1414 cm^{-1}; ^{1}H-NMR: δ 2.73–3.02 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.15 (dd, J = 15.5, 3.6 Hz, 1H, 13a-H), 3.90 (s, 9H, 3 OMe), 3.91 (s, 6H, 2 OMe), 4.82 (dd, J = 13.5, 3.6 Hz, 1H, 13a-H), 4.82–4.95 (m, 1H, 6b-H), 6.32 (s, 1H, Ar-H), 6.70 (s, 2H, Ar-H) ppm; EI-MS (70 eV): m/z 399 (M^+, 4.2), 277 (100); HR-MS calcd for $C_{22}H_{25}NO_6$ 399.1681; Found 399.1702.

9,10-Dimethoxy-8-oxobenz[g]indolo[2,3-a]quinolizidine (7a). A colorless oil (12%); R_f 0.4 (3% methanol–dichloromethane) [45]; IR (neat): 3288 (NH), 1709 (CO), 1632, 1603, 1514 cm^{-1}; ^{1}H-NMR: δ 2.80–3.04 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.18 (dd, J = 15.1, 3.2 Hz, 1H, 13a-H), 3.85, 4.02 (each s, each 3H, 2 OMe), 4.86 (br. d, J = 12.4 Hz, 1H, 13a-H), 5.28 (dd, J = 12.8, 3.0 Hz, 1H, 6b-H), 6.92, 6.99 (each d, J = 8.2 Hz, each 1H, 11- and 12-H), 7.18, 7.21 (each t, J = 7.6 Hz, each 1H, 2- and 3-H), 7.38, 7.56 (each d, J = 7.6 Hz, each 1H, 1- and 4-H), 8.13 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 348 (M^+, 32.0), 331 (7.6), 277 (100), 199 (73), 178 (23.1), 171 (35.0), 152 (16.1); HR-MS: calcd for $C_{21}H_{20}N_2O_3$ 348.1474; Found 348.1471.

10,11-Dimethoxy-8-oxobenz[g]indolo[2,3-a]quinolizidine (8a). A colorless oil (49%); R_f 0.45 (3% methanol–dichloromethane) [21]; IR (neat): 3268 (NH), 1652 (CO), 1633, 1602, 1515 cm^{-1}; ^{1}H-NMR: δ 2.87–3.15 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.25 (dd, J = 15.5, 3.9 Hz, 1H, 13a-H), 3.92 (s, 6H, 2 OMe), 4.98 (dd, J = 12.9, 3.9 Hz, 1H, 13a-H), 5.20–5.30 (dd, 11.7, 3.0 Hz, 6b-H), 6.68 (s, 1H, 10-H), 7.13–7.25 (m, 2H, Ar-H), 7.38 (dd, J = 7.3, 1.3 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.68 (s, 1H), 8.14 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 348 (M^+, 100), 347 (36.4), 333 (24.5), 178 (16.6), 150 (21.1), 143 (2.4), 115 (2.2); HR-MS: calcd for $C_{21}H_{20}N_2O_3$ 348.1474; Found 348.1449.

(9,10-Methylenedioxy)-8-oxobenz[g]indolo[2,3-a]quinolizidine (7b). A colorless crystals (68%); R_f 0.4 (3% methanol–dichloromethane); mp 258°C (dec.) (chloroform); IR (neat):

3264 (NH), 1730 (CO), 1638, 1598, 1502, 1490 cm^{-1}; ^{1}H-NMR: δ 2.75–3.10 (m, 4H, 5-, 6a- and 13b-H), 3.47 (d, J = 15.1, 3.5 Hz, 1H, 13a-H), 4.94 (br. d, J = 13.2 Hz, 1H, 13a-H), 5.25 (br. d, J = 8.2 Hz, 1H, 6b-H), 6.09, 6.17 (each s, each 1H, OCH_2O), 6.72, 6.89 (each d, J = 8.1 Hz, 1H, 11, 12-H), 7.09, 7.14 (each t, J = 7.0 Hz, each 1H, 2- and 3-H), 7.16, 7.53 (each d, J = 7.0 Hz, each 1H, 1- and 4-H), 9.98 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 332 (M^+, 50.7), 317 (12.5), 301 (27.2), 213 (83.9), 199 (11.2), 171 (100), 135 (28.5), 115 (12.5); HR-MS: calcd for $C_{20}H_{16}N_2O_3$ 332.1162; Found 332.1143.

(10,11-Methylenedioxy)-8-oxobenz[g]indolo[2,3-a]quinolizidine (8b). A colorless oil (22% in Method B); R_f 0.45 (3% methanol–dichloromethane); IR (neat): 3258 (NH), 1710 (CO), 1634, 1598, 1502, 1466 cm^{-1}; ^{1}H-NMR δ 2.82–3.10 (m, 4H, 5-, 5-, 6a-H, 13b-H), 3.20 (dd, J = 15.5, 4.0 Hz, 1H, 13a-H), 4.96 (br, d, J = 13.5 Hz, 1H, 13a-H), 5.22 (br. d, J = 12.7 Hz, 1H, 6a-H), 6.65 (each s, each 1H, 12-H), 7.12, 7.20 (each t, J = 7.6 Hz, 2- and 3-H), 7.38, 7.56 (each d, J = 7.6 Hz, each 1H, 1- and 4-H), 7.63 (s, 1H, 9-H), 8.07 (br. s, 1H, NH) ppm; EI-MS (70 eV): m/z 332 (M^+, 46.3), 184 (22.1), 171 (25), 129 (25.4), 96 (100). HR-MS: calcd for $C_{20}H_{16}N_2O_3$ 332.1162; Found 332.1180.

12-Bromo-2,3,10,11-tetramethoxy-8-oxoberbine (10a). From **9a** [22]; colorless crystals (76%); R_f 0.6 (3% methanol–dichloromethane); mp 166–167.5°C (ethanol); IR (Nujol): 1649 (CO), 1594, 1561, 1510 cm^{-1}; ^{1}H-NMR: δ 2.70–3.06 (m, 4H, 5- and 13-H), 3.52 (dd, J = 16.1, 4.0 Hz, 1H, 6a-H), 3.90 (s, 3H, OMe), 3.92 (s, 6H, 2 OMe), 3.94 (s, 3H, OMe), 4.82 (dd, J = 13.5, 4.0 Hz, 1H, 13a-H), 4.93 (dd, J = 8.1, 3.0 Hz, 1H, 6b-H), 6.70, 6.75, 7.73 (each s, each 1H, 1-, 4- and 9-H) ppm; EI-MS (70 eV): m/z 449, 447 (M^+, 79 and 100), 434, 432 (23 and 30), 418, 416 (22 and 19), 258, 256 (24 and 23), 230, 228 (43 and 43), 190 (13), 149 (16). Anal. Calcd. for $C_{21}H_{22}NO_5Br$: C, 56.27; H, 4.95; N, 3.12; Br, 17.82. Found: C, 56.07; H, 5.19; N, 3.07; Br, 17.87.

12-Bromo-2,3,10,11-tetramethoxy-8-oxoberbine (10b). From **9b** [22] colorless crystals (78%); R_f 0.6 (3% methanol–dichloromethane); mp 220–221°C (ethanol); IR (Nujol): 1651, 1607, 1524 cm^{-1}; ^{1}H-NMR: δ 2.68 (dd, J = 16.3, 13.4 Hz, 1H, 5b-H), 2.78 (t, J = 11.7 Hz, 1H, 5a-H), 2.92, 2.98 (AB type, J = 11.7 Hz, 2H, 13-H), 3.46 (dd, J = 16.6, 3.7 Hz, 1H, 13a-H), 3.90, 3.93 (each s, each 3H), 4.79 (dd, J = 13.5, 3.7 Hz, 1H, 13a-H), 4.92 (br. d, J = 8.2 Hz, 1H, 6b-H), 6.11 (s, 2H, OCH_2O), 6.69, 6.71, 7.59 (each s, each 1H, 1, 4- and 9-H) ppm; EI-MS (70 eV): m/z 433, 431 (M^+, 88 and 100), 418, 416 (30 and 36), 402, 400 (29 and 25), 244, 242 (34 and 34), 214, 212 (52 and 53), 190 (18), 133 (45). Anal. Calcd. for $C_{21}H_{18}NO_5Br$: C, 55.57; H, 4.20; N, 3.24; Br, 18.48. Found: C, 55.61; H, 4.24; N, 3.00; Br, 18.66.

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REFERENCES AND NOTES

[1] (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. J Am Chem Soc 2004, 126, 14342; (b) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. J Org Chem 2006, 71, 5951.

[2] Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. J Chem Soc 1965, 3632.

[3] (a) Manske, R. H. F.; Ashford, W. R. In The Alkaloids; Manske, R. H. F.; Holmes, H. L., Eds.; Academic Press: New York, 1954; Vol. 4, p 77; (b) Santavy F. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12, p 333; (c) Santavy, F. In The Alkaloids; Manske, R. H. F.; Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, p 385; (d) Bhakuni, D. S.; Jain S. In The Alkaloids; Brossi, A., Ed.; Academic Press: Orlando, FL, 1986; Vol. 28, p 95; (e) Hanaoka M. In The Alkaliids; Brossi, A., Ed.; Academic Press: Orlando, FL, 1988; Vol. 33; p 141.

[4] Synthesis of 8-oxoberbines with Pd(0), see: (a) Pandey, G. D.; Tiwari, K. P. Synth Commun 1979, 9, 895; (b) Pandey, C. D.; Tiwari, K. P. Tetrahedron 1981, 37, 1213; (c) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. J Org Chem 1999, 64, 6583. With $Co_2(CO)_8$ and $Fe_3(CO)_{12}$, see: (d) Trifonov, L. S.; Orehovats, A. S.; Tetrahedron Lett 1985, 26, 3159.

[5] (a) Leitaoda-Cunha, E. V.; Fechine, I. M.; Guedes, D. N.; Barbosa-Filho, J. M.; de Silva, M. S. In The Alkaloids; Cordell, G. A., Ed.; Elsevier Academic Press: Amsterdam, 2005; Vol. 62, p 1; (b) Matulenko, M. A.; Meyers, A. I. J Org Chem 1996, 61, 573.

[6] (a) Whaley, W. M.; Govindachari, T. R. Inorg React 1951, 6, 74; (b) Deulofeu, V.; Comin, J.; Vernengo, M. J. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, 1963; Vol. 10, p 401.

[7] For *ortho*-palladation products with $Pd(OAc)_2$ of benzylic amines and β-phenethylamines having hydrogen on their nitrogen atoms, see: (a) Fuchita, Y.; Tsuchiya, H. Polyhedron 1993, 12, 2079; Inorg Chim Acta 1993, 209, 229; (b) Vicente, J.; Saura-Llamas, I.; Palin, M. J.; Jones, P. G.; Ramírez de Arellano, M. C. Organometallics 1997, 16, 826.

[8] (a) Liang, C. D. Tetrahedron Lett 1986, 27, 1971; (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. Bull Chem Soc Jpn 1997, 70, 3117; (c) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. J Org Chem 2000, 65, 1475.

[9] A catalytic version of the Method C carbonylation of **1d** with $Pd(OAc)_2{\cdot}2\ PPh_3$ [20] (20 mol %) in the presence of oxygen (70 mol %) gave **2d** 18 h later in a similar selectivity (72%) to that of Method C, when the initial dark-reddish color of the reaction mixture due to the Pd(II) ion was kept during the carbonylation. Similar carbonylation of **1d** with $Pd(PPh)_4$ (20 mol%)-AcOH (40 mol %), $Pd_2(dba)_3$ (10 mol %)-PPh_3 (40 mol %)-AcOH (40 mol %), or $Pd(OH)_2$ (20%) on carbon or $Pd(acac)_2$ (20 mol %) with PPh_3 (40 mol %) and AcOH (40 mol %) also produced **2d** in 50–70%. However, an identical treatment for carbonylation of **1d** with $Pd_2(dba)_3$ (5 mol %) gave no benzolactams but a mixture of 6,7,3′,4′-bis(methylenedioxy)-1-benzylisoquinoline and its 3,4-dihydro derivative in a ratio of 1:9 almost quantitatively.

[10] (a) Monteiro H. J. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. 11, p 145; (b) Toke, L.; Szantay, C. Heterocycles 4, 251 (1976); (c) Szantay, C.; Blasko, G.; Honty, K.; Dornyei, G. In The Alkaloids; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 27, p 131, 407; (d) Chen F.-E.; Huang, J. Chem Rev 2005, 105, 4671.

[11] (±)-Nuevamine, which is one of the isoquinoline alkaloids having a five-membered benzolactam, could not be obtained by the method A or C, but formed by the method (B) with 3 equiv of palladium(II) acetate in boiling toluene almost as a single product (>95%) in 73% isolated yield, mp 206.2–208.9°C (methanol). For isolation and synthesis of the alkaloid, see; (a) Moniot, J. L.; Hindenlang, D. M. Shamma, M. J Org Chem 1979, 44, 4347; (b) Valencia, E.; Freyer, A. J.; Shamma, M. Tetrahedron Lett 1984, 25, 599; (c) Alonso, R.; Castedo, L.; Dominguez, D. Tetrahedron Lett 1985, 26, 2925; (d) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. Tetrahedron 2004, 60, 6169; (e) Wakchaure, R. B.; Easwar, S.; Puranik, V.; Argade, N. P. Tetrahedron 2008, 64, 1786.

[12] (a) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. J Org Chem 2007, 72, 2008; (b) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. Eur J Org Chem 2009, 1173.

[13] Hahn, G.; Kely, W. Ber 1937, 70, 685.

[14] Mehra, K.; Grag, H. S.; Bhakuni, D. S.; Khanna, N. M. Ind J Chem 14B, 1976, 844.

[15] Haworth, R. D.; Perkin, W. H., Jr.; Rankin, J. Perkin J Chem Soc 1924, 125, 1686.

[16] Buck, J. S.; W. R. Perkin Jr, Stevens, T. S. J Chem Soc 1925, 1462.

[17] Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Venugopal, D. J Org Chem 1992, 57, 6716.

[18] Bick, I. R. C.; Clezy, P. S.; Vernengo, M. J. J Chem Soc 1960, 4928.
[19] Tomita, M.; Fujita, E.; Murai, F. Yakugaku Zasshi 1951, 71, 1035.
[20] Chakravati, S.; Swaminathan, M. J Ind Chem Soc 1934, 11, 107.
[21] (a) Shono, K.; Usui, Y.; Mizutani, T.; Hamaguchi, H. Tetrahedron Lett 1980, 21, 3073; (b) Shono, K.; Hamaguchi, H.; Sasaki, M.; Figita, S.; Nagami, K. J Org Chem 1983, 48, 1621.
[22] Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. J Org Chem 1999, 64, 6583.
[23] Nowak, W.; Gerlach, H. Liebigs Ann Chem 1993, 153.
[24] Ram, S.; Spicer, L. D. Synth Commun 1987, 17, 415.
[25] Potts, K. T.; Robinson, R. J Chem Soc 1955, 2675.
[26] Hahn, G.; Hansel, A. Ber 1938, 71, 2192.
[27] Kanaoka, Y. Chem Pharm Bull 1959, 7, 597.
[28] Kametani, T.; Takeshita, M.; Satoh, F. Yakugaku Zasshi 1974, 94, 261.
[29] Hahn, G.; L. Bárwald, Schales, O.; Werner, H. Ann Chem 1935, 520, 107.
[30] Short, H.; Freifelder, M.; Stone, G. R. J Org Chem 1961, 26, 2560.
[31] Nimgirawath, S.; Ponghusabun, O. Aust J Chem 1994, 47, 951.
[32] Singh, K. N. Tetrahedron Lett 1998, 39, 4391.
[33] Comins, D. L.; Thakker, P. M.; Baevsky, M. F. Tetrahedron 1997, 53, 16327.
[34] Lenz, G. J Org Chem 1974, 39, 2846.
[35] Ninomiya, I.; Naito, T.; Takasugi, H. J Chem Soc Perkin Trans 1975, 1720.
[36] Pandey, G. D.; Tiwari, K. P. Tetrahedron 1981, 37, 1213.
[37] Orito, K.; Satoh, Y.; Nishizawa, H.; Harada, R.; Tokuda, M. Org Lett 2000, 2, 2535.
[38] Govindachari, T. R.; Nagarajan, K.; Charubala, R. Pai, B. R. Ind J Chem 1970, 8, 763.
[39] Perkin, W. H.; Jr., Ray, J. N.; Stauton, J.; Hist, M.; Robinson, R. J Chem Soc 1925, 127, 740.
[40] Haworth, R. D.; Pinder, A. R.; Robinson, R. Nature 1950, 165, 529.
[41] Chrzanowska, M. J Nat Prod 1995, 58, 401.
[42] Naito, T.; Katsumi, K.; Toda, Y.; Ninomiya, I. Heterocycles 1983, 20, 775.
[43] Brown, D. B.; Dyke, S. F. Tetrahedron 1966, 22, 2429.
[44] Greenslade, D.; Ramage, R. Tetrahedron 1977, 33, 927.
[45] Meyers, A. I.; Hellring, S. J Org Chem 1982, 47, 2229.