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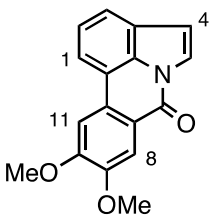
SIMPLE SYNTHESIS OF PRATOSINE AND HIPPADINE BY INTRAMOLECULAR PALLADIUM-CATALYZED CYCLIZATION AND DECARBOXYLATION

Hideaki Umemoto, Masashi Dohshita, Hiromi Hamamoto, and Yasuyoshi Miki*

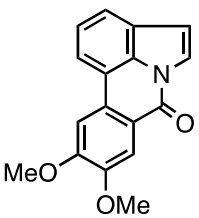
School of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577-8502, Japan

Abstract – The palladium-catalyzed cyclization of dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium acetate in hot 1,4-dioxane produced the 7*H*-pyrrolo[3,2,1-*de*]phenanthridine derivative, which was converted to pratosine by hydrolysis and decarboxylation. In a similar manner, hippadine was also prepared.

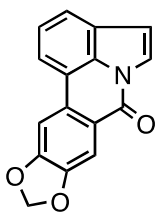
7*H*-Pyrrolo[3,2,1-*de*]phenanthridine alkaloids, pratosine,[1] hippadine,[2] and kalbretorine,[3] isolated from various species of *Amaryllidaceae* have significant biological activities; for example, hippadine inhibits fertility in male rats[4] and kalbretorine has an antitumor activity.[3] Pratosine and hippadine were mainly synthesized by three methods from the 2-protected indole,[5,6] indoline derivatives,[7] or 7-haloindoles and related compounds.[8,9] In a previous paper, we reported the synthesis of pratosine and hippadine by the palladium-catalyzed intramolecular cyclization of methyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2-carboxylate protected 2-position of the indole moiety by an ester group.[5] In this paper, we report the simple synthesis of pratosine and hippadine by the palladium-catalyzed intramolecular cyclization of dimethyl 1-(2-bromobenzyl)indole-2,3-dicarboxylates and decarboxylation.



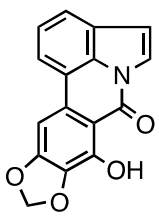
7*H*-pyrrolo[3,2,1-*de*]phenanthridine



pratosine



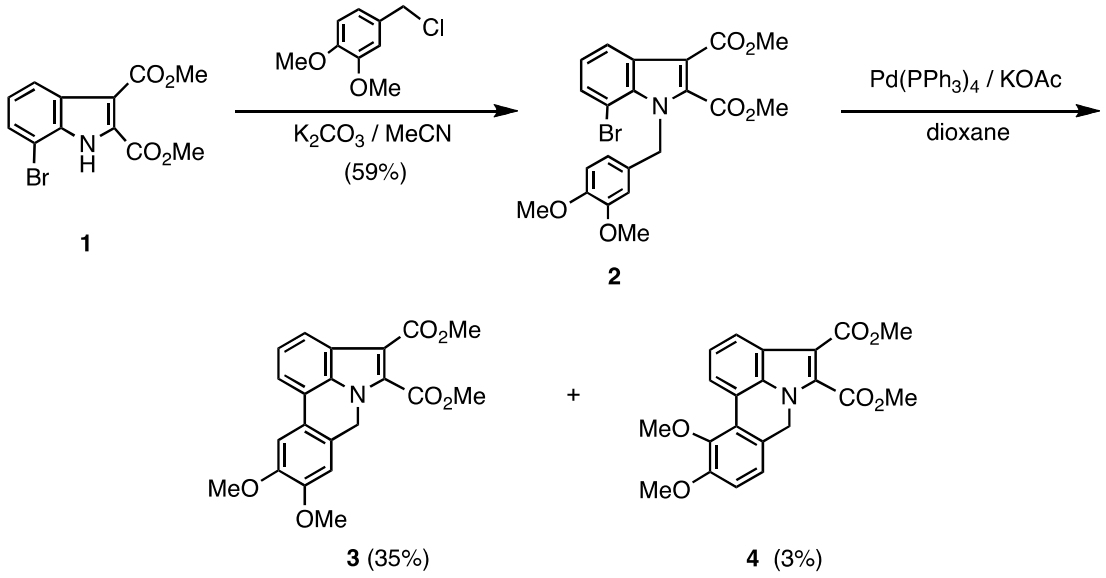
hippadine



kalbretorine

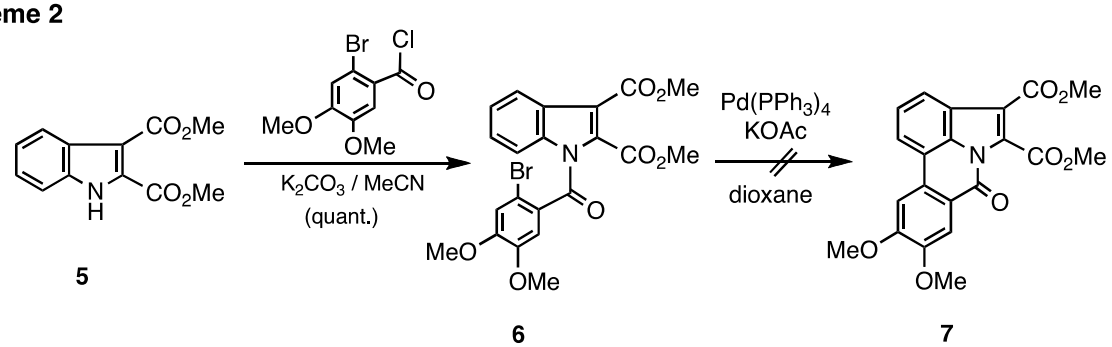
Dimethyl 7-bromoindole-2,3-dicarboxylate (**1**)[10] was converted to dimethyl 7-bromo-1-(3,4-dimethoxybenzyl)indole-2,3-dicarboxylate (**2**) by treatment with 3,4-dimethoxybenzyl chloride in the presence of potassium carbonate. The treatment of **2** with a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) ($(PPh_3)_4Pd$) in the presence of potassium acetate in hot dioxane gave a mixture of dimethyl 7*H*-9,10-dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**3**) and dimethyl 7*H*-10,11-dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**4**) in 35% and 3% yields, respectively (Scheme 1).

Scheme 1



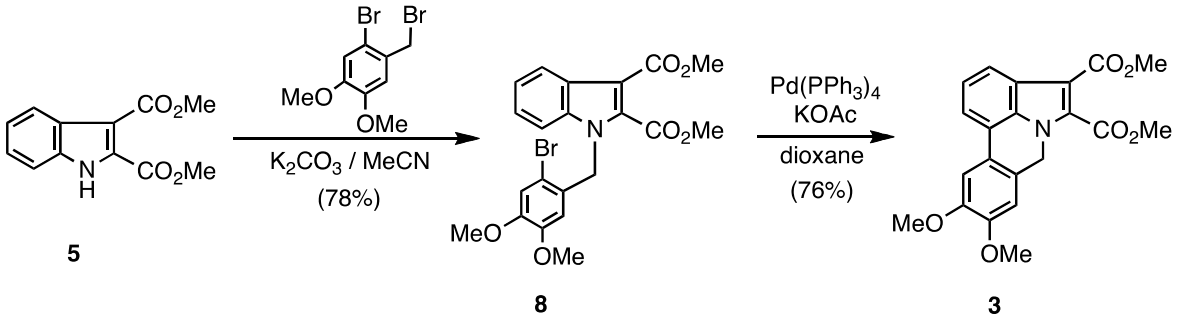
Dimethyl 9,10-dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridone-4,5-dicarboxylate (**7**) could not be isolated by treatment of dimethyl 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**6**), which was prepared from dimethyl indole-2,3-dicarboxylate (**5**) and 2-bromo-4,5-dimethoxybenzoyl chloride, in hot dioxane in the presence of $Pd(PPh_3)_4$ and potassium acetate. The starting material was recovered. The treatment of **6** in *N,N*-dimethylformamide instead of dioxane at 100 °C afforded **5**, which was produced by the hydrolysis of **6**, in low yield (Scheme 2).

Scheme 2



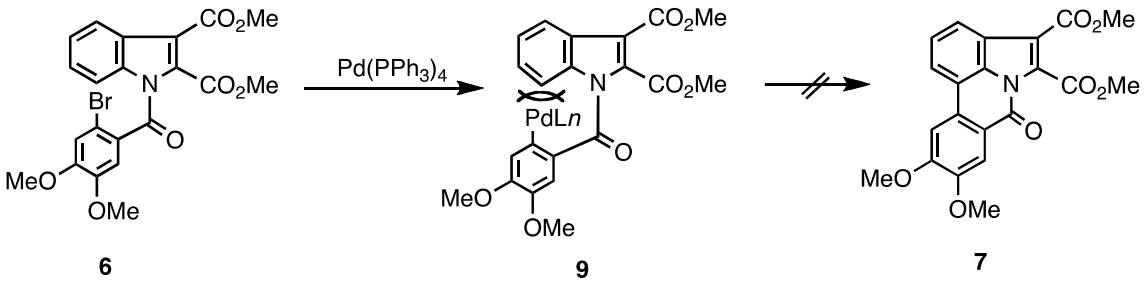
However, in a similar treatment described as **6**, dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**8**), which was obtained from dimethyl indole-2,3-dicarboxylate (**5**) and 2-bromo-4,5-dimethoxybenzyl bromide,[11] produced dimethyl 9,10-dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**3**) as the sole product in 76% yield (Scheme 3).

Scheme 3



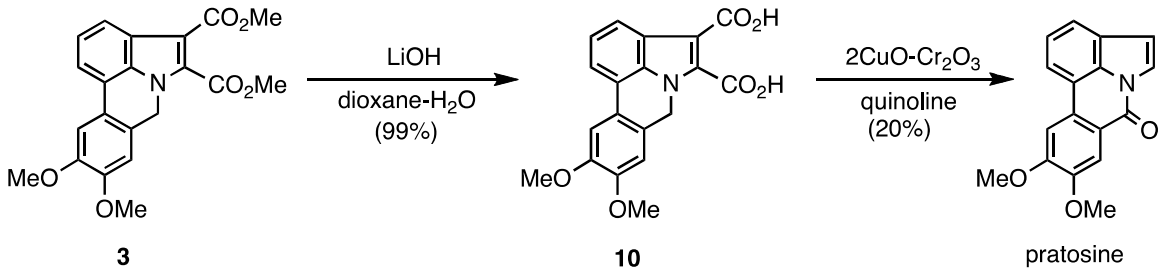
In order to investigate the negative reactivity of **6** on palladium-catalyzed intramolecular cyclization *via* Mizoroki-Heck reaction, **6** was subjected with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and potassium acetate in hot dioxane for 7 hours. In this case, the intermolecular coupling of **6** with phenylboronic acid was occurred and dimethyl 1-(4,5-dimethoxy-2-phenylbenzoyl)indole-2,3-dicarboxylate was obtained. Therefore, this result suggests that initial formation of the intermediate (**9**) is proceeded in the presence of $Pd(PPh_3)_4$ and potassium acetate, but the following intramolecular cyclization would not be occurred due to the steric hindrance. (Scheme 4) Even though the exact reaction mechanism is still not clear, the difficulty of the palladium-catalyzed intramolecular cyclization on C-7 position of 1-benzoylindole derivatives reported by Itahara may support the possibility of our suggestions.[12]

Scheme 4



The hydrolysis of **3** with LiOH gave the corresponding dicarboxylic acid (**10**), which could be converted into pratosine in 20% yield by treatment with copper chromite ($CuO\text{-}Cr_2O_3$) in hot quinoline (Scheme 5).

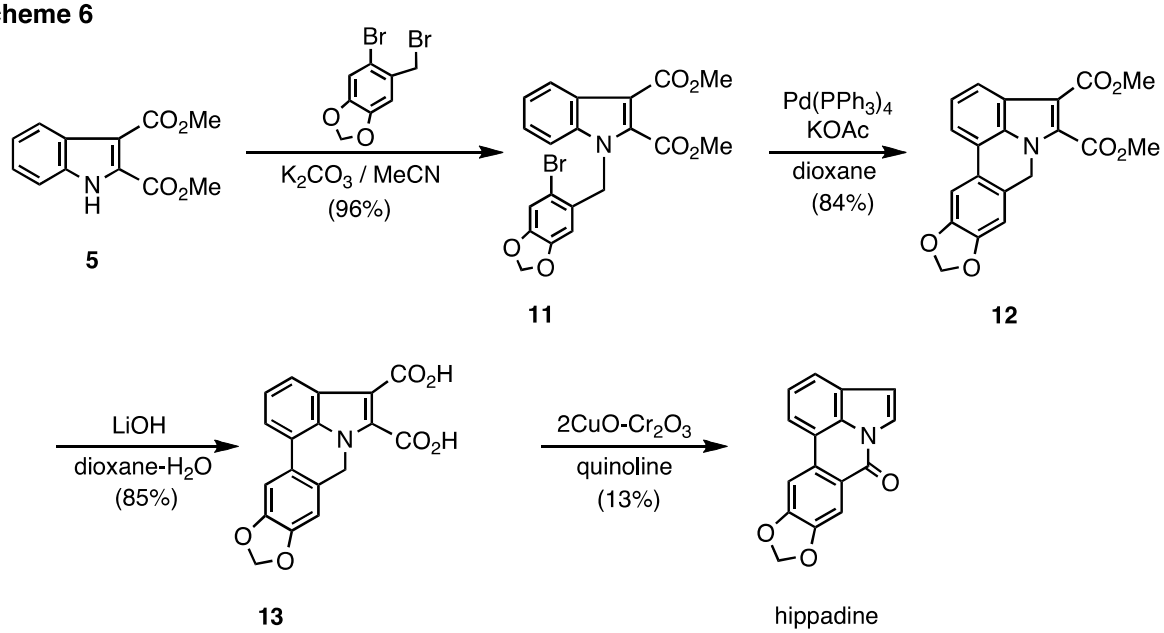
Scheme 5



3 **10** pratosine

The reaction of dimethyl indole-2,3-dicarboxylate (**5**) with 2-bromo-4,5-methylenedioxybenzyl bromide[13] afforded the dimethyl 1-(2-bromo-4,5-methylenedioxybenzyl)indole-2,3-dicarboxylate (**11**) (96%), which was treated with a catalytic amount of $(PPh_3)_4Pd$ in the presence of potassium acetate in hot dioxane to produce dimethyl 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**12**) (84%). In a manner similar to the synthesis of pratosine, the hydrolysis of **12** with LiOH gave the corresponding dicarboxylic acid (**13**) (85%), which could be converted into hippadine by the treatment with $CuO\text{-}Cr_2O_3$ in hot quinoline in 13% yield (Scheme 6).

Scheme 6



5 **11** **12** **13** hippadine

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EXPERIMENTAL

Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected.

The ^{1}H-NMR spectra were determined by a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded by a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded using a JEOL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh).

Dimethyl 7-Bromo-1-(4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (2)

A mixture of dimethyl 7-bromoindole-2,3-dicarboxylate (**1**)[10] (281 mg, 0.9 mmol), 4,5-dimethoxybenzyl chloride (202 mg, 1.1 mmol), and potassium carbonate (186 mg, 1.35 mmol) in acetone (3.6 mL) was refluxed for 22 h. Water was added to the mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 7 : 1) to give dimethyl 7-bromo-1-(4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**2**) (245 mg, 59%).

Mp. 110.5-111 °C (Et_2O). IR ($CHCl_3$) cm^{-1}: 1710, 1735. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (3H, s, OMe), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 3.92 (3H, s, OMe), 5.88 (2H, s, NCH_2), 6.48 (1H, dd, *J* = 8.5, 2 Hz, H-6'), 6.60 (1H, d, *J* = 2 Hz, H-2'), 6.74 (1H, d, *J* = 8.5 Hz, H-5'), 7.14 (1H, t, *J* = 8 Hz, H-5), 7.50 (1H, dd, *J* = 8, 1 Hz, H-6), 8.19 (1H, dd, *J* = 8, 1 Hz, H-4). *Anal*. Calcd for $C_{21}H_{20}BrNO_6$: C, 54.56; H, 4.36; N, 3.03. Found: C, 54.80; H, 4.44; N, 2.99.

Intramolecular Cyclization of Dimethyl 7-Bromo-1-(4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (2): Dimethyl 7*H*-9,10-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (3) and 7*H*-10,11-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (4)

To a mixture of dimethyl 7-bromo-1-(4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**2**) (46 mg, 0.1 mmol) and potassium acetate (10 mg, 0.1 mmol) in dioxane (1.5 mL) was added $Pd(PPh_3)_4$ (6 mg, 0.05 mmol). The mixture was refluxed for 10 h under argon in the dark. Water was added to the reaction mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give dimethyl 7*H*-9,10-dimethoxypyrrolo[3,2,1-*de*]-phenanthridine-4,5-dicarboxylate (**3**) (13 mg, 35%) and 7*H*-10,11-dimethoxypyrrolo[3,2,1-*de*]-phenanthridine-4,5-dicarboxylate (**4**) (1 mg, 3%).

Dimethyl 7*H*-9,10-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (3): Mp 123-124 °C (AcOEt). IR ($CHCl_3$) cm^{-1}: 1709. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s, OMe), 3.96 (3H, s, OMe), 3.99 (3H, s, OMe), 4.02 (3H, s, OMe), 5.60 (2H, s, H-7), 6.66 (1H, s, H-8), 7.22 (1H, dd, *J* = 8, 7.5 Hz, H-2), 7.32 (1H, s, H-11), 7.47 (1H, dd, *J* = 7.5, 1 Hz, H-1), 7.78 (1H, dd, *J* = 8, 1 Hz, H-3). MS *m*/*z*: 381. HRMS *m*/*z*: Calcd for $C_{21}H_{19}NO_6$: 381.1212. Found: 381.1239. *Anal*. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 65.92; H, 5.08; N, 3.51.

7*H*-10,11-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (4): IR (Nujol) cm^{-1}: 1710. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (6H, s, OMe), 3.96 (3H, s, OMe), 4.02 (3H, s, OMe), 5.61 (2H, s, H-7), 6.90

(1H, d, *J* = 8 Hz, H-8 or H-9), 6.96 (1H, d, *J* = 8 Hz, H-9 or H-8), 7.28 (1H, t, *J* = 8 Hz, H-2), 7.89 (1H, d, *J* = 8 Hz, H-3), 8.46 (1H, d, *J* = 8 Hz, H-1). MS *m*/*z*: 381. HRMS *m*/*z*: Calcd for $C_{21}H_{19}NO_6$: 381.1212. Found: 381.1235.

Dimethyl 1-(2-Bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (6)

A mixture of dimethyl indole-2,3-dicarboxylate (**5**) (350 mg, 1.5 mmol), 2-bromo-4,5-dimethoxybenzoyl chloride (560 mg, 2 mmol), and potassium carbonate (311 mg, 2.25 mmol) in MeCN (7.5 mL) was refluxed for 1 h. Water was added to the mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography ($CHCl_3$) to give dimethyl 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**6**) (712 mg, quant.).

Mp 173-173.5 °C (*n*-hexane-AcOEt). IR (Nujol) cm^{-1}: 1746, 1708. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 3.95 (3H, s, OMe), 3.98 (3H, s, OMe), 7.00 (1H, s, H-6'), 7.08 (1H, d, *J* = 8.5 Hz, H-7), 7.10 (1H, s, H-3'), 7.28 (1H, ddd, *J* = 7.7, 7.3, 1.5 Hz, H-5 or H-6), 7.37 (1H, ddd, *J* = 8.5, 7.7, 1 Hz, H-6 or H-5), 8.18 (1H, dd, *J* = 7.3, 1 Hz, H-4).

Attempt to Synthesize Dimethyl 7*H*-9,10-Dimethoxy-7-oxopyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (7) by Intramolecular Cyclization of Dimethyl 1-(2-Bromo-4,5-dimethoxybenzoyl)-indole-2,3-dicarboxylate (6)

To a mixture of dimethyl 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**6**) (43 mg, 0.09 mmol) and potassium acetate (9 mg, 0.09 mmol) in dioxane (1.8 mL) was added $Pd(PPh_3)_4$ (5 mg, 0.05 mmol). The mixture was refluxed for 29 h under argon in the dark. Water was added to the reaction mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **6** (12mg, 28%)

Dimethyl 1-(2-Bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (8)

A mixture of dimethyl indole-2,3-dicarboxylate (**5**) (5.0 g, 22 mmol), 2-bromo-4,5-dimethoxybenzyl bromide (6.7 g, 22 mmol) and potassium carbonate (4.5 g, 32 mmol) in MeCN (43 mL) was refluxed for 6 h. Water was added to the mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 20 : 1) to give dimethyl 1-(4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**8**) (7.7 g, 78%).

Mp 108-109 °C (*n*-hexane-AcOEt). IR ($CHCl_3$) cm^{-1}: 1734, 1700. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (3H, s, OMe), 3.85 (3H, s, OMe), 3.95 (3H, s, OMe), 3.96 (3H, s, OMe), 5.44 (2H, s, NCH_2), 6.25 (1H, s, H-6'), 7.04 (1H, s, H-3'), 7.25-7.34 (3H, m, arom), 8.12-8.18 (1H, m, H-4). *Anal*. Calcd for $C_{21}H_{20}BrNO_6$: C, 54.56; H, 4.36; N, 3.03. Found: C, 54.79; H, 4.40; N, 2.79.

Intramolecular Cyclization of Dimethyl 1-(2-Bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate

(8): Dimethyl 7*H*-9,10-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (3)

To a mixture of dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**8**) (2.9 g, 6.3 mmol) and potassium acetate (620 mg, 6.3 mmol) in dioxane (100 mL) was added $Pd(PPh_3)_4$ (364 mg, 0.32 mmol). The mixture was refluxed for 24 h under argon in the dark. Water was added to the reaction mixture and the aqueous mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography (CH_2Cl_2) to give dimethyl 7*H*-9,10-dimethoxypyrrolo[3,2,1-*de*]-phenanthridine-4,5-dicarboxylate (**3**) (1.82 g, 76%).

7*H*-9,10-Dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylic Acid (10)

To a mixture of dimethyl 7*H*-9,10-dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**3**) (953 mg, 2.5 mmol) in a mixture of dioxane (15 mL) and water (15 mL) was added lithium hydroxide monohydrate (420 mg, 10 mmol) and the mixture was refluxed for 2 h. The mixture was acidified with a 10% hydrochloric acid aqueous solution, and the precipitate was collected by filtration to afford 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylic acid (**10**) (874 mg, 99%).

Mp 222 °C (decomp.) (THF). IR (Nujol) cm^{-1}: 3474, 3362, 1729, 1704. ^{1}H-NMR (DMSO-d_6) δ: 3.84 (3H, s, OMe), 3.90 (3H, s, OMe), 5.86 (2H, s, H-7), 7.02 (1H, s, H-8), 7.24 (1H, dd, *J* = 8, 7.5 Hz, H-2), 7.56 (1H, s, H-11), 7.74 (1H, dd, *J* = 7.5, 0.5 Hz, H-3 or H-1), 7.99 (1H, dd, *J* = 8, 0.5 Hz, H-1 or H-3). MS *m*/*z*: 353. HRMS *m*/*z*: Calcd for $C_{19}H_{15}NO_6$: 353.0899. Found: 353.0903.

Pratosine

A mixture of 7*H*-9,10-dimethoxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylic acid (**10**) (21 mg, 0.06 mmol) and copper chromite (2 mg) in quinoline (1 mL) was refluxed for 1 h. $CHCl_3$ was added to the mixture and the insoluble material was filtered through Celite to give a filtrate, which was washed with a 10% hydrochloric acid aqueous solution, then water and dried over Na_2SO_4. After filtration, the dried $CHCl_3$ solution was concentrated under reduced pressure to afford a residue, which was purified by column chromatography ($CHCl_3$) to give pratosine (3.3 mg, 20%).

Mp 234-235 °C (Et_2O-MeOH) (lit.,[1] 232-233 °C); IR (Nujol) cm^{-1}: 1670; ^{1}H-NMR ($CDCl_3$) δ: 4.07 (3H, s, OMe), 4.12 (3H, s, OMe), 6.90 (1H, d, *J* = 4 Hz, H-4), 7.48 (1H, t, *J* = 7.5 Hz, H-2), 7.64 (1H, s, H-8), 7.75 (1H, dd , *J* = 7.5, 0.5 Hz, H-3), 7.96 (1H, dd , *J* = 7.5, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.05 (1H, d, *J* = 4 Hz, H-5). HRMS *m/z* (M^+) *Anal*. Calcd for $C_{17}H_{13}NO_3$: 279.0895. Found: 279.0891.

Dimethyl 7*H*-9,10-Methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (12)

A mixture of dimethyl indole-2,3-dicarboxylate (**5**) (2.33 g, 10 mmol), 2-bromo-4,5-methylenedioxy-benzyl bromide (3.54 g, 12 mmol), and potassium carbonate (2.07 g, 15 mmol) in MeCN (23 mL) was refluxed for 2 h. The insoluble material was filtered through Celite to give a filtrate. The filtrate was concentrated under reduced pressure to afford dimethyl 1-(2-bromo-4,5-methylenedioxybenzyl)-indole-2,3-dicarboxylate (**11**) (4.26 g, 96%), which was used in next step without purification.

IR (KBr) cm^{-1}: 1733, 1708; ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3Hx2, s, CO_2Me), 5.43 (2H, s, CH_2), 5.88 (2H, s, CH_2), 6.05 (1H, s, arom), 7.04 (1H, s, arom), 7.2-7.35 (2H, m, arom), 8.2-8.3 (1H, m, arom).

To a mixture of dimethyl 1-(2-bromo-4,5-methylenedioxybenzyl)indole-2,3-dicarboxylate (**11**) (5.13 g, 11.5 mmol) and potassium acetate (1.35 g, 13.8 mmol) in dioxane (230 mL) was added $Pd(PPh_3)_4$ (0.66 g, 0.58 mmol). The mixture was refluxed for 6 h under argon in the dark. Water was added to the reaction mixture and the aqueous mixture was extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was recrystallized from AcOEt to give dimethyl 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**12**) (3.54 g, 84%).

Mp 209-210 °C (AcOEt); IR (Nujol) cm^{-1}: 1710, 1692; ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s, CO_2Me), 4.01 (3H, s, CO_2Me), 5.60 (2H, s, NCH_2), 6.02 (2H, s, O-CH_2-O), 6.65 (1H, s, H-8 or H-11), 7.21 (1H, t, J = 7 Hz, H-2), 7.33 (1H, s, H-11 or H-8), 7.43 (1H, br d, J = 7 Hz, H-1), 7.78 (1H, br d, J = 7 Hz, H-3). HRMS *m/z* (M^+) *Anal*. Calcd for $C_{20}H_{15}NO_6$: 366.0978. Found: 366.0965.

Hippadine

To a mixture of dimethyl 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**12**) (912 mg, 2.5 mmol) in a mixture of dioxane (12.5 mL) and water (12.5 mL) was added lithium hydroxide monohydrate (525 mg, 12.5 mmol), and the mixture was refluxed for 5 h. The mixture was acidified with a 10% hydrochloric acid aqueous solution and the precipitate was collected by filtration to afford 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylic acid (**13**) (720 mg, 85%).

IR (KBr) cm^{-1}: 1693; ^{1}H-NMR ($CDCl_3$) δ: 5.82 (2H, s, CH_2), 6.08 (2H, s, CH_2), 6.99 (1H, s, H-8 or H-11), 7.21 (1H, t, J = 7 Hz, H-2), 7.65 (1H, s, H-11 or H-8), 7.69 (1H, d, J = 7 Hz, H-1 or H-3), 7.95 (1H, br d, J = 7 Hz, H-3 or H-1). HRMS *m/z* (M^+) *Anal*. Calcd for $C_{18}H_{12}NO_6$: 338.0665. Found: 368.0675.

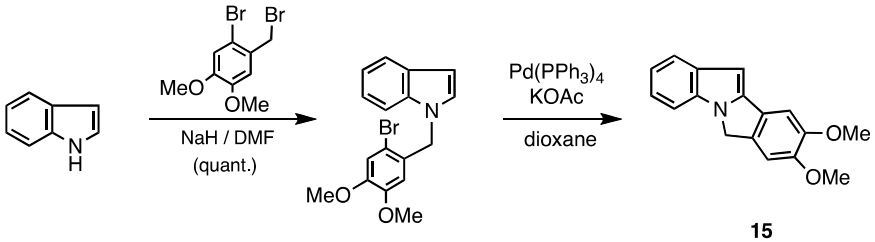
A mixture of 7*H*-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylic acid (**13**) (51 mg, 0.15 mmol) and copper chromite (9 mg) in quinoline (1.5 mL) was heated at 220 °C for 2.5 h. $CHCl_3$ was added to the mixture and the insoluble material was filtered through Celite to give a filtrate, which was washed with a 10% hydrochloric acid aqueous solution, then water and dried over Na_2SO_4. After filtration, the dried $CHCl_3$ solution was concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give hippadine (5 mg, 13%).

Mp 215-216 °C (*n*-hexane-acetone) (lit.,[2] 209-210 °C); IR (Nujol) cm^{-1}: 1673; ^{1}H-NMR ($CDCl_3$) δ: 6.17 (2H, s, CH_2), 6.90 (1H, d, J = 4 Hz, H-4), 7.48 (1H, t, J = 8 Hz, H-2), 7.66 (1H, s, H-8), 7.76 (1H, dd, J = 8, 0.5 Hz, H-3), 7.92 (1H, dd, J = 8, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.04 (1H, d, J = 4 Hz, H-5). HRMS *m/z* (M^+) *Anal*. Calcd for $C_{16}H_9NO_3$: 263.0582. Found: 263.0579.

REFERENCES

1. S. Ghosal, K. S. Saini, and A. W. Frahm, *Phytochemistry*, 1983, **22**, 2305.

2. S. Ghosal, P. H. Rao, D. K. Jaiswal, Y. Kumar, and A. W. Frahm, *Phytochemistry*, 1981, **20**, 2003; A. A. Ali, M. K. Mesbah, and A. W. Frahm, *Planta Med.*, 1981, **43**, 407.
3. S. Ghosal, R. Lochan, Ashutosh, Y. Kumar, and R. S. Srivastava, *Phytochemistry*, 1985, **24**, 1825.
4. S. Chattopadhyay, U. Chattopadhyay, P. P. Mathur, K. S. Saini, and S. Ghosal, *Planta Med.*, 1983, **49**, 252.
5. Y. Miki, H. Shirokoshi, and K. Matsushita, *Tetrahedron Lett.*, 1999, **40**, 4347, and references cited therein.
6. C. G. Hartung, A. Fecher, B. Chapell, and V. Snieckus, *Org. Lett.*, 2003, **5**, 1899.
7. A. Padwa, M. Dimitroff, A. W. Watersoon, and T. Wu, *J. Org. Chem.*, 1998, **63**, 3986; D. St. C. Black, P. A. Keller, and N. Kumar, *Tetrahedron Lett.*, 1989, **30**, 5807.
8. D. W. Robbins, T. A. Boebel, and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 4068; U. V. Mentzel, D. Tanner, and J. E. Tønder, *J. Org. Chem.*, 2006, **71**, 5807; J. C. Torres, A. C. Pinto, and S. J. Garden, *Tetrahedron*, 2004, **60**, 9889; H.-J. Knölker and S. Filani, *Synlett*, 2003, 1752; O. Tsuge, T. Hatta, and H. Tsuchiyama, *Chem. Lett.*, 1998, 155; R. H. Hutchings and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 1004; M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, D. C. R. Hockless, J. W. Holman, R. W. Read, and A. W. Wu, *J. Chem. Soc., Chem. Commun.*, 1995, 2551; M. Iwao, H. Takehara, S. Obata, and M. Watanabe, *Heterocycles*, 1994, **38**, 1717; T. Sakamoto, A. Yasuhara, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1993, **36**, 2597; M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1990, **31**, 1523.
9. Recent report of synthesis of pratosine and hippadine: M. D. Ganton and M. A. Kerr, *Org. Lett.*, 2005, **7**, 4777.
10. Y. Miki, K. Matsushita, H. Hibino, and H. Shirokoshi, *Heterocycles*, 1999, **51**, 1585.
11. R. O. Hutchins, A. Abdel-Magid, Y. P. Stercho, and A. Wambsgans, *J. Org. Chem.*, 1987, **52**, 702.
12. T. Itahara, *Synthesis*, 1979, 151.
13. A. Padwa, J. E. Cochran, and C. O. Kappe, *J. Org. Chem.*, 1996, **61**, 3706.
14. Palladium-catalyzed cyclization of 1-(3-bromo-4,5-dimethoxybenzyl)indole (**14**) exclusively gave the 6*H*-isoindolo[2,1-*a*]indole derivative (**15**) in 61% yield. This was similar to the results reported by Black.[15]



14 **15**

15. D. St. C. Black, P. A. Keller, and N. Kumar, *Tetrahedron*, 1993, **49**, 151.