HETEROCYCLES, Vol. , No. , , pp. -,
Received, , Accepted, , Published online, (Please do not delete.)

CREATION OF NEW PROMOTERS FOR PLANT'S ROOT GROWTH: ITS APPLICATION FOR THE SYNTHESES OF VULCANINE AND BORRELINE, AND FOR COMBATING DESERTIFICATION AT GOBI DESERT IN INNER MONGOLIA[1#]

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Abstract – Various new 2-substituted indole-3-carbaldehydes are prepared. Structurally related alkaloids, vulcanine and borreline, are synthesized as well. Among the compounds, 2-haloindole-3-carbaldehydes are found to be potent promoters of plant's root growth. Its successful preliminary application is reported for making Gobi desert in Inner Mongolia full of plant.

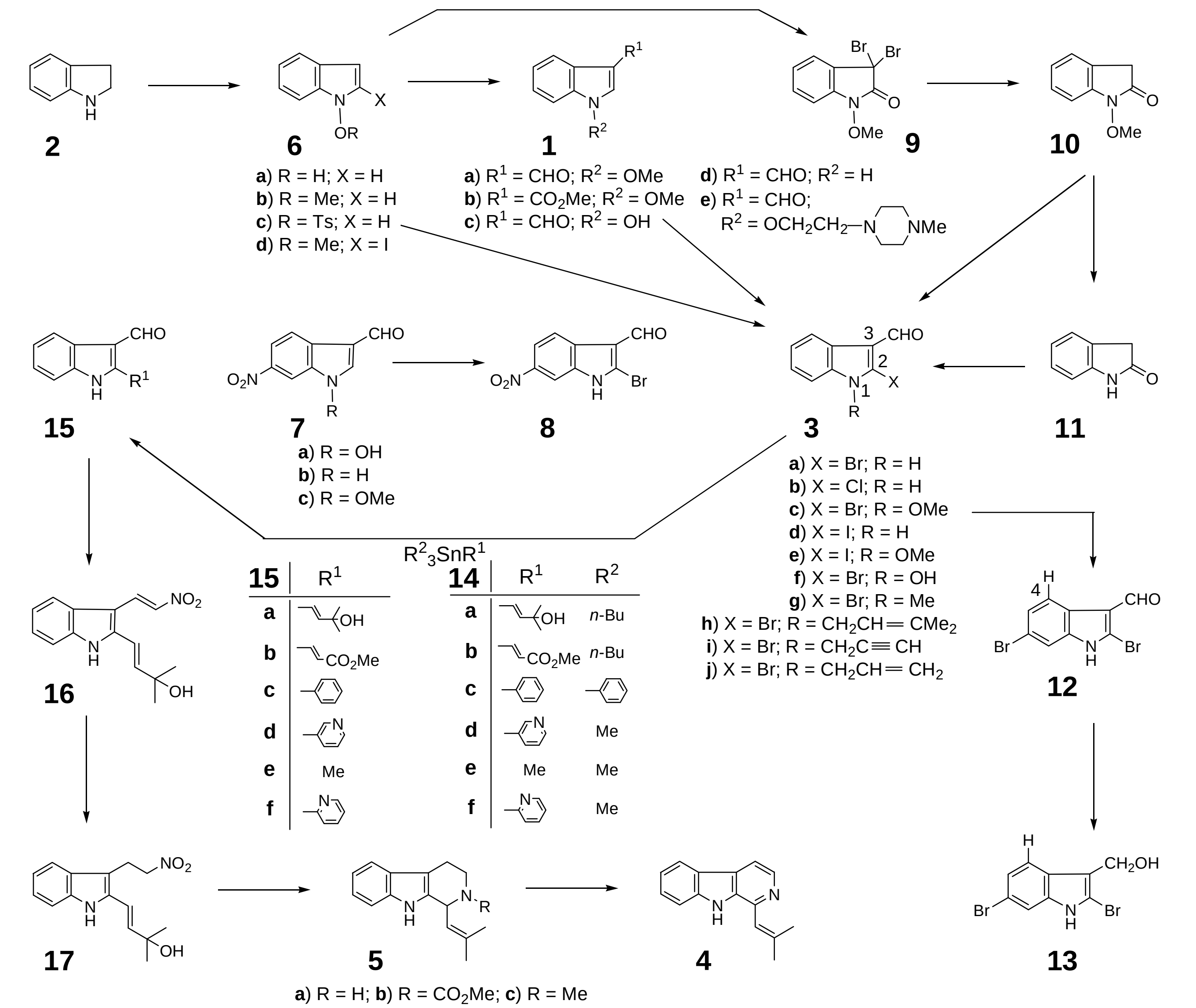
We have conceived an idea[3] that the metabolites of tryptophan have each own function *in vivo* and are promising targets for developing new drugs. In our project for discovering biologically active compounds among the metabolites, we have focused on the derivatives[4] of indole-3-carbaldehyde and indole-3-carboxylic acid, involving the corresponding 1-hydroxy- and 1-alkoxyindole derivatives, on the basis of our 1-hydroxyindole hypothesis.[3] During the study for about 25 years, we have found various types of plant growth regulators.[5] Other groups have found daikon[6] (*Raphanus sativus*, **1a**, Scheme 1) and wasabi (*Eutrema japonicum*) phytoalexins[7] (**1b**) which are good examples for the biologically active derivatives of indole-3-carbaldehyde and indole-3-carboxylic acid.

On the other hand, as for a starting material in a synthetic study, we make it a rule to utilize a bulk chemical.[8] Because when the target compound shows the expected biological activity, if it is needed widely by the ultimate customers, it should be manufactured in the factory and supplied in a large quantity. This is the reason why we have employed 2,3-dihydroindole (**2**) as a starting material throughout our study.

#dedicated to Prof. Dr. Ivar Ugi.

With an aim to discover plant’s root promoter, we chose 2-haloindole-3-carbaldehydes (**3a–j**) and their derivatives (**4, 5, 7, 8, 11—13, 15–17**) as target compounds. Part of this work was published as a preliminary communication.[1b] In this paper, we describe their syntheses from **2** and the application for the synthesis of closely related alkaloids, vulcanine[9] (**4**) and borreline[10] (**5c**). In addition, we have succeeded in creating potent activators for plant’s root growth. With these compounds in hand, we are now challenging to make Gobi desert in Inner Mongolia full of plant for preventing bai (yellow sand) from generation and for stopping global warming.

Scheme 1



I. Creation of New Promoters for Plant’s Root Growth

According to our synthetic method[3] for 1-hydroxyindole (**6a**) and its derivatives, 1-methoxyindole (**6b**) and 1-tosyloxyindole (**6c**) were prepared from **2** in 70 and 23% yields, respectively.[3] We then tried the synthesis of **3a** by the treatment of **6c** with $POBr_3$ based on the finding that **3b**[11] was produced by the reaction of **6c** with $POCl_3$ in 67% yield. In fact, however, **3a** was not obtained under various examined reaction conditions.

In order to obtain **3a**, we next attempted to utilize 1-methoxy and 1-hydroxy derivatives, because we found the treatment of 1-hydroxy-6-nitroindole-3-carbaldehyde[12] (**7a**) with $POBr_3$ gave an 82% yield of 2-bromo-6-nitroindole-3-carbaldehyde (**8**) together with 6-nitroindole-3-carbaldehyde (**7b**, 11%). Therefore, **6b** was converted to **1a** in 90% yield as reported previously[3] by Vilsmeier-Haack reaction.

The desired 1-hydroxyindole-3-carbaldehyde (**1c**) was obtained by treating **1a** with KI in DMF-H_2O (3:1, v/v) at 160°C in 55% yield together with indole-3-carbaldehyde (**1d**) and unreacted **1a** in 3 and 33% yields, respectively. Quantitative production of **1c** was realized by the reaction of **1a** with DABCO (10 mol eq.) in DMF-H_2O (3:1, v/v) at 100°C. Interestingly, when the same reaction was carried out in DMF without a proton source, major product (61%) was 1-[2-(4-methylpiperazin-1-yl)ethoxy]indole-3-carbaldehyde (**1e**), and **1c** became a minor product (28%). The mechanism of the formation of **1e** was discussed in the previous paper.[4a] These new ether cleavage reactions were also applicable to 1-methoxy-6-nitroindole-3-carbaldehyde (**7c**). Thus, the former KI method gave **7a**, **7b**, and **7c** in 58, 4, and 22% yields, respectively, while the latter DABCO method[4a] provided **7a** in 90% yield.

Although bromination of **1a** with Br_2 in AcOH at 100°C afforded poor yield of 2-bromo-1-methoxyindole-3-carbaldehyde (**3c**, 15%) with a mixture of inseparable 5- and 6-bromocompounds, reaction of **1c** with $POBr_3$ in THF proceeded as expected and **3a** was obtained in 33% yield together with a 21% yield of **1d**.

In order to improve the yield of **3a**, alternative route[13a] was explored from **6b**. Bromination of **6b** with NBS in *t*-BuOH resulted in the formation of 3,3-dibromo-1-methoxy-2-oxindole[13a] (**9**) in 50% yield. Reductive debromination of **9** to 1-methoxy-2-oxindole[13a—c] (**10**) was carried out with Zn-AcOH at room temperature in 91% yield. Then, 1-methoxy group was removed by catalytic hydrogenation with 10% Pd/C and atmospheric hydrogen to afford 2-oxindole (**11**) in 95% yield, which is commercially available but an expensive chemical. Subsequent Vilsmeier reaction of **11** with $POBr_3$-DMF afforded **3a** in 77% yield.[1b] Application of the same reaction conditions to **10** provided (**3c**) in 84% yield.

2-Iodoindole-3-carbaldehyde (**3d**) was prepared in 62% yield by heating **3a** with CuI and KI in DMF though its separation from the unreacted **3a** was difficult. Preparation of 2-iodo-1-methoxyindole-3-carbaldehyde (**3e**) was carried out in 70% yield by the Vilsmeier reaction of 2-iodo-1-methoxyindole (**6d**), which was obtained according to our reported procedures from **2**.[14]

Treatment of **3c** with BBr_3 in anhydrous CH_2Cl_2 at 0°C provided 2-bromo-1-hydroxyindole-3-carbaldehyde (**3f**) in 14% yield in addition to 2,6-dibromoindole-3-carbaldehyde (**12**) and unreacted **3c** in 16 and 32% yields, respectively. Interestingly, the same reaction at reflux condition resulted in the predominant formation of **12** in 61% yield. The structure of **12** was determined by comparison of the

^{1}H-NMR spectrum with that of 2,6-dibromoindol-3-ylmethanol (**13**), which was produced by the reduction of **12** with $NaBH_4$ in 67% yield. The proton signal at the 4-position of **13** appeared at δ 7.55 (d, *J*=8.5 Hz), while the corresponding proton of **12** appeared at δ 8.19 (d, *J*=8.5 Hz). The observed anisotropy effect of the formyl group on **12** clearly proved their structures as shown in Scheme 1.

1-Substituted 2-bromoindole-3-carbaldehydes were easily prepared as follows. Thus, the reactions of **3a** with MeI, 3-methyl-2-butenyl bromide, propargyl bromide, and allyl bromide in the presence of *n*-Bu_4NBr and K_2CO_3 as a base provided 1-methyl- (**3g**), 1-(3-methyl-2-butenyl)- (**3h**), 1-propargyl- (**3i**), and 1-allyl-2-bromoindole-3-carbaldehydes (**3j**) in 98, 92, 91, and 98% yields, respectively.

II. Syntheses of Vulcanine and Borreline

In order to introduce a carbon side chain directly into the 2-position of **3a**, improved Heck reaction[15a,b] seemed to be promising among various palladium catalyzed cross coupling reactions.[15a-d] In fact, the Heck reaction of **3a** with 2-methyl-3-buten-2-ol gave the desired 2-(3-hydroxy-3-methyl-1-butenyl)-3-indolecarboxaldehyde (**15a**) in 0~15% yield under various examined reaction conditions: changes in concentrations of reactants and catalyst, reaction time, temperature.

On the other hand, modified Stille reaction[15c] was found to meet our end. Thus, **15a** was obtained in 87% yield upon treatment of **3a** with tributyl(3-hydroxy-3-methyl-1-butenyl)tin (**14a**) in the presence of *n*-Bu_4NCl and a catalytic amount of $Pd(OAc)_2$. Under similar reaction conditions, the reactions of **3a** with tin reagents, such as **14b—f**, afforded the corresponding **15b—f** in 67, 68, 38, 39, and 5% yields, respectively.

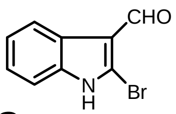
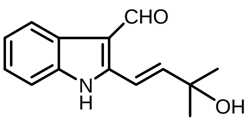
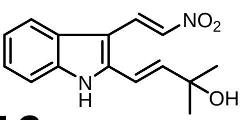
We next converted **15a** into (*E*,*E*)-2-methyl-4-[3-(2-nitrovinyl)indol-2-yl]-3-buten-2-ol (**16**) in 93% yield by the nitroaldol reaction with CH_3NO_2 and NH_4OAc as a catalyst. Subsequent reduction of **16** with $NaBH_4$ in MeOH afforded (*E*)-2-methyl-4-[3-(2-nitroethyl)indol-2-yl]-3-buten-2-ol (**17**) in 96% yield. With the desired **17** in hand, we next employed our reductive aminocyclization reaction.[16] Thus, the reaction of **17** with zinc in refluxing methanolic hydrochloric acid resulted in the formation of 1-(2-methyl-1-propenyl)-1,2,3,4-tetrahydro-β-carboline (**5a**) in 50% yield. Subsequent treatment of **5a** with *t*-BuOCl in THF generated vulcanine[9] (**4**) in 51% yield. On the other hand, the reaction of **5a** with ClCOOMe and Et_3N gave an 85% yield of 2-methoxycarbonyl-1-(2-methyl-1-propenyl)-1,2,3,4-tetrahydro-β-carboline (**5b**), which finally led to borrerine[10] (**5c**) in 70% yield by the reduction with $LiAlH_4$ in anhydrous THF.

Spectral data of **4** and **5c** are identical with those reported by Hesse and co-workers[9] and by Sakai and co-workers,[10] respectively.

III. Biological Evaluation for the Plant's Root Growth

Typical results, obtained after culturing the germinated seeds of rice (Nihonbare) and cucumber (Sagamihanpaku) at 25°C for 6 days, are shown in Table 1. In the case of aq. 3 ppm solution of **3a**, the average root length of the rice is 68% longer than that of the control (100%), while the average root length of cucumber is 113%. On the other hand, the effect of a 50 ppm aq. solution of **16** on the rice seeds was 168%. In the case of cucumber, a 3 ppm aq. solution of **16** promoted the root length up to 190%. Thus, almost all compounds described in this paper (**3—5**, **7**, **8**, **11—13, 15—17**) showed various degree of activity for plant's root promotion and we named them SOMRE compounds. Among them, SOMRE No. 1 (**3a**) and No. 4 (**3d**) have most potent activity. The detailed results will be reported elsewhere in due course.

Table 1. Average Root Length of Rice and Cucumber

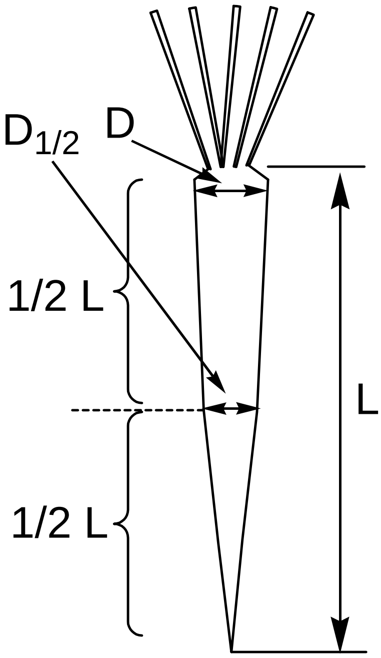
Plant and Root Length of the Control / Sample	**Rice** Control: 46.8 mm (100%)				**Cucumber** Control: 12.1 mm (100%)			
	Concentration of the Sample (ppm)				Concentration of the Sample (ppm)			
	50	12.5	3	0.8	50	12.5	3	0.8
 **3a**	14	**140**	**168**	**130**	100	**105**	**113**	98
 **15a**	**146**	**136**	**120**	100	100	100	**118**	101
 **16**	**168**	**133**	**113**	**109**	**120**	**180**	**190**	**114**

IV. Combating Desertification at Gobi Desert in Inner Mongolia

With new root growth encouragers (SOMRE compounds) in hand, we applied them to the wild plant *Calligonum alaschanicum* (a kind of sand jujube) and *Hedysarum scoparium* Fisch et C.A. Mey at Gobi desert in Inner Mongolia for combating desertification. After several trials in the desert, we have disclosed that the 2-bromo compounds (**3a**, **3c**: SOMRE No. 1, No. 3) have high germination rate and are suitable for any tested wild plant. 2-Iodocompounds (**3d**, **3e**: SOMRE No. 4, No. 5) have lower germination rate, but they are found to be more effective than the 2-bromo compounds as for the root growth.

On the other experiment at Gobi desert, seeds of *Calligonum alaschanicum* were divided into 5 groups and each group was dipped for 30 min into a 1, 3, 10 ppm aq. solution of **3a**, a 2 ppm aq. solution of indole-3-acetic acid (IAA, the reference), and H_2O (the control), respectively. Experiment farmland was divided into 5 parts as well. Seeds of each group were separately sprinkled to the divided farmlands on ditches of 5 cm depth and they were covered with sand. They were brought up for 73 days (from August 2 to October 14, 2005) under natural environment of the desert except for watering every one week. We then dug grown young plants and compared the average root length. The results are summarized in Table 2. As is evident from Table 2, the solutions of **3a** showed a remarkable effect on the plant's root growth. Especially, a 1 ppm aq. solution of **3a** encouraged the plant's root about 2 times longer and 8—15 times heavier than those of the reference and the control.

Table 2. Plant Growth for 73 Days at Gobi Desert in Inner Mongolia



Planting：August 2, 2005. Digging：October 14, 2005

Sample / Root	**Control**	**IAA** (2 ppm, **Reference**)	**3a** 10 ppm	**3a** 3 ppm	**3a** 1 ppm
Root Length (**L** cm)	**18.0**	21.0	**22.5**	**36.0**	**42.5**
Width (**D** mm)	**1.5**	1.2	1.5	**2.0**	**6.0**
$D_{1/2}$ (mm)	**1.0**	1.0	0.8	**2.0**	**4.0**
Weight (**mg**)	**620**	310	**360**	**1,390**	**4,980**

It is well known the plants grown from the seeds usually freeze to death during the severe cold winter at Gobi desert. In between May, 2006 and April, 2007, we have confirmed that the plants from the seeds treated with SOMRE No. 1 have not frozen to death, because they have three times longer root (53.2 cm) than the control (19.1 cm) and can survive through a year. In April, 2007, we dipped young plant's roots of 2,700 sand jujubes into the 1 ppm aq. solution of SOMRE No. 1 for 30 min and planted them at Gobi

desert of about 2 hectares. Under natural environment without artificial watering we observed their growth. Two months later, their survival rate is 87.9%, much better than 78.3% of the control group.
With these successful results in hand, we are now continuing preliminary field experiment to make Gobi desert green. Our compounds (SOMRE No. 1, No. 4, related compounds) make the wild plant's roots longer enough to reach to the ground water. They would change Gobi desert again to the area with full of plants as it was 300 years ago. They would be useful for preventing disastrous global warming and for production of more food as a new technology. We believe SOMRE compounds become "the medicine for the earth."

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with Shimadzu IR-420 and Horiba FT-720 spectrophotometers, UV spectra with a Shimadzu UV 2400 PC spectrophotometer, and ^{1}H-NMR spectra with JEOL FX-100, JEOL EX 270, and JEOL GSX 500 spectrometers, with tetramethylsilane as an internal standard. MS were recorded on Hitachi M-80 and JEOL JMS-SX 102A spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{245} (Type 60) (SiO_2). Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

1-Hydroxyindole-3-carbaldehyde (1c) and 1-[2-(4-methylpiperazin-1-yl)ethoxy]indole-3-carbaldehyde (1e) from 1-Methoxyindole-3-carbaldehyde (1a) — i) Method A: DABCO (1.05 g, 9.36 mmol) was added to a solution of **1a**[3,17] (159.8 mg, 0.91 mmol) in DMF (5 mL) and the mixture was heated at 100°C for 21 h with stirring. After addition of H_2O, the solution was made acidic (pH 4) with 6% HCl, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **1c** (41.4 mg, 28%). The aqueous layer was made basic (pH 10) with 8% NaOH and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **1e** (159.8 mg, 61%). **1c** and **1e** were identical with the samples prepared according to our previous paper.[4a] **1e**·2HCl: mp 220—230°C (decomp., pink powder, recrystallized from MeOH). IR (KBr): 1660cm^{-1}. ^{1}H-NMR (DMSO-d_6: D_2O=5:1, v/v) δ: 2.90 (3H, s), 3.41 (2H, t, J=4.9 Hz), 3.48 (8H, br s), 4.68 (2H, t, J=4.9 Hz), 7.37 (1H, dd, J=7.8, 7.1 Hz), 7.45 (1H, dd, J=7.8, 7.1 Hz), 7.71 (1H, d, J=7.8 Hz), 8.17 (1H, d, J=7.8 Hz), 8.66 (1H, s), 9.89 (1H, s). *Anal*. Calcd for $C_{16}H_{21}N_3O_2$·2HCl: C, 53.34; H, 6.43; N, 11.66. Found: C, 53.08; H, 6.41; N, 11.53.

ii) Method B: DABCO (386.3 mg, 3.45 mmol) was added to a solution of **1a** (61.2 mg, 0.35 mmol) in DMF–H_2O (3:1, v/v, 2 mL) and the mixture was heated at 100°C for 21 h with stirring. After addition of H_2O, the whole was made acidic (pH 4) with 6% HCl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **1c** (55.0 mg, 98%).

iii) Method C: KI (2.753 g, 16.6 mmol) was added to a solution of **1a** (32.3 mg, 0.19 mmol) in DMF–H_2O (3:1, v/v, 4 mL) and the mixture was heated at 160°C for 24 h with stirring. After the same work-up as described in the method B, unreacted **1a** (10.5 mg, 33%), **1d** (0.7 mg, 3%), and **1c** (16.3 mg, 55%) were obtained in the order of elution.

2-Bromoindole-3-carbaldehyde (3a) from 1-Hydroxyindole-3-carbaldehyde (1c) — A solution of **1c** (27.6 mg, 0.17 mmol) in anhydrous THF (3 mL) was added to $POBr_3$ (310.0 mg, 1.08 mmol) and the mixture was stirred at rt for 15 h. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:1, v/v) to give **3a** (12.6 mg, 33%) and **1d** (5.3 mg, 21%) in the order of elution. **3a**: mp 209—210.5°C[1b] (decomp., colorless needles, recrystallized from MeOH, lit.[18] mp 196—198°C). IR (KBr): 3100, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.96—7.54 (3H, m), 8.14—8.88 (1H, m), 9.82 (1H, s). MS *m/z*: 223 and 225 (M^+, ^{79}Br and ^{81}Br).

2-Bromoindole-3-carbaldehyde (3a) from 2-Oxindole (11) — A solution of $POBr_3$ (8 mL, 0.08 mol) in anhydrous $CHCl_3$ (20 mL) was added to anhydrous DMF (30 mL, 0.39 mol), and the mixture was stirred at rt for 25 min. To the resulting viscous solution was added a solution of **11** (4.06 g, 0.03 mol) in anhydrous $CHCl_3$ (60 mL), and then the mixture was stirred at rt for 13 h. During the above procedures, when magnetic stirring became difficult because of the increase in viscosity, supersonic wave generator was employed as an assistant. After cooling to 0°C, the whole was made basic by adding 40% aqueous NaOH and extracted with CH_2Cl_2–MeOH (9:1, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from MeOH to give **3a** (5.281 g, 77%).

2-Chloroindole-3-carbaldehyde (3b) from 1-Tosyloxyindole (6c) — A solution of Vilsmeier reagent (460.9 mg, 1.68 mmol), prepared from $POCl_3$ (767.6 mg, 5.01 mmol) and DMF (581.6 mg, 7.96 mmol), in DMF (0.5 mL) was added to a solution of **6c** (48.1 mg, 0.17 mmol) in DMF (1 mL) at 0°C and the mixture was stirred at rt for 5.5 h. The whole was made basic with 8% aqueous NaOH and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with CH_2Cl_2 to give **3b** (20.1 mg, 67%). Physical data were identical with those of the authentic sample.[11]

2-Bromo-1-methoxyindole-3-carbaldehyde (3c) from 1-Methoxy-2-oxindole (10)[4)] — Anhydrous DMF (9 mL) was added to a solution of $POBr_3$ (0.2 mL) in anhydrous $CHCl_3$ (6 mL) at 0°C and stirring was continued at rt for 15 min. To the resulting solution was added a solution of **10**[13] (236.3 mg, 1.45 mmol) in DMF (5 mL) at 0°C and the mixture was stirred at rt for 12 h. The whole was made basic with 8% aqueous NaOH and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:3, v/v) to give **3c** (307.5 mg, 84%). **3c**: mp 97—98°C (colorless needles, recrystallized from MeOH). IR (KBr): 1653 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.19 (3H, s), 7.31 (1H, ddd, *J*=7.6, 7.3, 1.2 Hz), 7.36 (1H, ddd, *J*=7.8, 7.3, 1.2 Hz), 7.45 (1H, dd, *J*=7.8, 1.2 Hz), 8.32 (1H, dd, *J*=7.6, 1.2 Hz), 9.98 (1H, s). MS m/z: 253 and 255 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_{10}H_8BrNO$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.02; H, 3.22; N, 5.33.

2-Iodoindole-3-carbaldehyde (3d) from 3a — KI (1.144 g, 6.89 mmol) and CuI (659.5 mg, 3.46 mmol) were added to a solution of **3a** (152.8 mg, 0.68 mmol) in DMF (15 mL) and the mixture was heated at 120°C for 48 h. After evaporation of the solvent under reduced pressure, H_2O was added to the residue. The whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:1, v/v) to give an inseparable mixture (151.9 mg) of **3a** and **3d** in a ratio of 1:3.1 (^1H-NMR analysis). The yields of **3a** and **3d** were calculated to be 29.8 mg (20%) and 122.1 mg (62%), respectively. To obtain 2 mg of pure **3d**, repeated HPLC and column-chromatography were required. **3d**: mp 224—226°C (colorless needles, recrystallized from MeOH). IR (KBr): 3138, 1639 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 7.19 (1H, td, *J*=7.5, 1.2 Hz), 7.22 (1H, td, *J*=7.5, 1.2 Hz), 7.42 (1H, dd, *J*=7.5, 1.2 Hz), 8.09 (1H, dd, *J*=7.5, 1.2 Hz), 9.72 (1H, s), 12.81 (1H, br s). High-resolution MS *m/z*: Calcd for C_9H_6INO: 270.9494. Found: 270.9478.

2-Iodo-1-methoxyindole-3-carbaldehyde (3e) from 2-Iodo-1-methoxyindole (6d) — $POCl_3$ (0.2 mL, 2.15 mmol) was added to DMF (2 mL, 25.8 mmol) at 0°C and the stirring was continued at rt for 15 min. To the solution was added a solution of **6d**[14] (137.1 mg, 0.50 mmol) in DMF (2 mL) at 0°C and the mixture was stirred at rt for 2 h. The whole was made basic with 8% aqueous NaOH and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under the reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:5, v/v) to give **3e** (105.6 mg, 70%). **3e**: mp 132—134°C (colorless needles, recrystallized from MeOH). IR (KBr): 1645 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.18 (3H, s), 7.29 (1H, t, *J*=7.3 Hz), 7.33 (1H, t, *J*=7.3 Hz), 7.46 (1H, d, *J*=7.3 Hz), 8.33 (1H, d, *J*=7.3 Hz), 9.79 (1H, s). MS *m/z*: 301 (M^+). *Anal*. Calcd for $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 40.33; H, 2.87; 4.47.

2,6-Dibromoindole-3-carbaldehyde (12) with/without 2-Bromo-1-hydroxyindole-3-carbaldehyde

(3f) from 2-Bromo-1-methoxyindole-3-carbaldehyde (3c) — i) Method A: BBr_3 (2 mL, 21.2 mmol) was added to a solution of **3c** (50.0 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0°C and the mixture was refluxed for 21 h with stirring. The mixture was poured into an ice water and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **12** (36.3 mg, 61%). **12**: mp 269—270°C (decomp., colorless prisms, recrystallized from MeOH). IR (KBr): 3082, 1631 cm^{-1}. ^1H NMR (CD_3OD) δ: 7.35 (1H, dd, *J*=8.5, 1.8 Hz), 7.56 (1H, d, *J*=1.8 Hz), 8.04 (1H, d, *J*=8.5 Hz), 9.91 (1H, s). ^1H NMR ($CDCl_3$) δ: 7.41 (1H, dd, *J*=8.5, 1.2 Hz), 7.51 (1H, d, *J*=1.2 Hz), 8.17 (1H, d, *J*=8.5 Hz), 8.76 (1H, br s), 10.01 (1H, s). MS *m/z*: 301, 303, and 305 (M^+ $^{79}Br_2$, $^{79}Br^{81}Br$, and $^{81}Br_2$). *Anal*. Calcd for $C_9H_5Br_2NO$: C, 35.68; H, 1.66; N, 4.62. Found: C, 35.64; H, 1.72; N, 4.57.

ii) Method B: BBr_3 (4.0 mL, 42.3 mmol) was added to a solution of **3c** (97.0 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0°C and the mixture was stirred at rt for 24 h. After the same work-up as described in the Method A, the crude product was column-chromatographed on SiO_2 with $CHCl_3$ to give unreacted **3c** (30.8 mg, 32%), **12** (18.2 mg, 16%), and **3f** (12.7 mg, 14%) in the order of elution. **3f**: mp 192—194°C (decomp., colorless needles, recrystallized from AcOEt–hexane). IR (KBr): 1630 cm^{-1}. ^1H-NMR (CD_3OD) δ: 7.27 (1H, dd, *J*=7.8, 7.3 Hz), 7.34 (1H, *J*=7.8, 7.3 Hz), 7.50 (1H, d, *J*=7.8 Hz), 8.16 (1H, d, *J*=7.8 Hz), 9.86 (1H, s). High-resolution MS *m/z*: Calcd for $C_9H_6{}^{79}BrNO_2$: 238.9582. Found: 238.9579. Calcd for $C_9H_6{}^{81}BrNO_2$: 240.9561. Found: 240.9556.

2-Bromo-1-methylindole-3-carbaldehyde (3g) from 3a — A solution of MeI (969.2 mg, 6.83 mmol) in THF (10 mL) was added to a mixture of **3a** (1.07 g, 4.75 mmol), Bu_4NBr (306.9 mg, 0.952 mmol), and K_2CO_3 (3.55 g, 25.7 mmol) in THF (60 mL), and the mixture was stirred at rt for 5 h. After addition of brine, the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with CH_2Cl_2 to give **3g** (1.11 g, 98%). **3g**: mp 118—118.5°C (colorless prisms, recrystallized from hexane). IR (KBr): 1638 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 7.14—7.36 (3H, m), 8.14—8.36 (1H, m), 9.98 (1H, s). MS *m/z*: 237 and 239 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; N, 5.88. Found: C, 50.44; H, 3.35; N, 6.09.

2-Bromo-1-(3-methyl-2-buten-1-yl)indole-3-carbaldehyde (3h) from 3a — A solution of prenyl bromide (1.06 g, 7.17 mmol) in THF (10 mL) was added to a mixture of **3a** (1.02 g, 4.54 mmol), Bu_4NBr (300.8 mg, 0.933 mmol), and K_2CO_3 (3.57 g, 25.8 mmol) in THF (60 mL), and the mixture was stirred at rt for 6 h. After the same work-up as described in the preparation of **3g**, 1.22 g (92%) of **3h** was obtained. **3h**: 78.5—79°C (colorless needles, recrystallized from hexane). IR (KBr): 1650 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.75 (3H, d, *J*=1.2 Hz), 1.92 (3H, d, *J*=1.2 Hz), 4.83 (2H, d, *J*=7.0 Hz), 5.18 (1H, th, *J*=7.0, 1.2 Hz), 7.11—7.35 (3H, m), 8.15—8.39 (1H, m). 10.00 (1H, s). MS m/z: 291 and 293 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.58; H, 4.84; N, 4.80.

2-Bromo-1-propargylindole-3-carbaldehyde (3i) from 3a — A solution of propargyl bromide (826.6 mg, 6.95 mmol) in THF (10 mL) was added to a mixture of **3a** (1.00 g, 4.50 mmol), Bu_4NBr (280.1 mg, 0.88 mmol), and K_2CO_3 (3.19 g, 23.1 mmol) in THF (40 mL), and the mixture was stirred at rt for 22 h. After addition of brine, the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from MeOH to give **3i** (1.01 g) as colorless flakes. The mother liquor was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (3:2, v/v) as a developing solvent. Extraction of the band having an *Rf* value of 0.35—0.43 with CH_2Cl_2–MeOH (95:5, v/v) gave **3i** (60.9 mg). Total yield of **3i** was 1.07 g (91%). **3i**: mp 151.5—152.5°C. IR (KBr): 1636 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (1H, t, *J*=2.5 Hz), 5.00 (2H, d, *J*=2.5 Hz), 7.14—7.54 (3H, m), 8.14—8.39 (1H, m), 10.00 (1H, s). MS *m/z*: 261 and 263 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_{12}H_8BrNO$: C, 54.98; H, 3.08; N, 5.34. Found: C, 54.82; H, 2.98; N, 5.47.

1-Allyl-2-bromolindole-3-carbaldehyde (3j) from 3a — A solution of allyl bromide (108.0 mg, 0.89 mmol) in THF (2 mL) was added to a mixture of **3a** (100.3 mg, 0.45 mmol), Bu_4NBr (29.3 mg, 0.09 mmol), and K_2CO_3 (307.8 mg, 2.23 mmol) in THF (6 mL), and the mixture was stirred at rt for 1 h. After the same work-up as described in the preparation of **3g**, 115.3 mg (98%) of **3j** was obtained. **3j**: mp 87—88°C (colorless prisms, recrystallized from $CHCl_3$). IR (KBr): 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.90 (2H, ddd, *J*=5.0, 1.8, 1.2 Hz), 5.23 (1H, dt, *J*=17.0, 1.8 Hz), 5.26 (1H, dt, *J*=10.5, 1.2 Hz), 5.94 (1H, ddt, *J*=17.0, 10.5, 5.0 Hz), 7.26—7.33 (3H, m), 8.31—8.34 (1H, m), 10.06 (1H, s). MS *m/z*: 263 and 265 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_{12}H_{10}BrNO\cdot1/4H_2O$: C, 53.65; H, 3.94; N, 5.21. Found: C, 53.84; H, 3.73; N, 5.21.

1- Hydroxy-6-nitroindole-3-carbaldehyde (7a) from 1-Methoxy-6-nitroindole-3-carbaldehyde (7c) — i) Method A: The formation of **7a** in 90% yield by the reaction of **7c** with DABCO was reported in the preceding paper.[12]

ii) Method B: A solution of KI (960.0 mg, 5.78 mmol) in H_2O (1 mL) was added to a solution of **7c** (32.8 mg, 0.15 mmol) in DMF (3 mL), and the mixture was heated at 120°C for 36 h with stirring. After evaporation of the solvent under reduced pressure, AcOEt was added to the residue. The same work-up of the organic layer as described in the Method A gave unreacted **7c** (7.3 mg, 22%), **7b** (1.1 mg, 4%), and **7a** (17.9 mg, 58%) in the order of elution. **7a** is identical with the authentic sample.[12]

2-Bromo-6-nitroindole-3-carbaldehyde (8) from 7a — $POBr_3$ (529.4 mg, 1.85 mmol) was added to a solution of **7a** (60.9 mg, 0.30 mmol) in anhydrous THF (4 mL) and the mixture was stirred at rt for 5 h. After evaporation of the solvent, H_2O was added to the residue, and the whole was extracted with

$CHCl_3$–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:1, v/v) to give **8** (65.3 mg, 82%) and **7b** (6.2 mg, 11%) in the order of elution. **8**: mp 296—298°C (decomp., colorless prisms, recrystallized from AcOEt). IR (KBr): 1631 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.12 (1H, dd, *J*=8.8, 1.6 Hz), 8.24 (1H, d, *J*=8.8 Hz), 8.27 (1H, d, *J*=1.6 Hz), 9.95 (1H, s). The proton at the 1-position did not appear. MS *m/z*: 268 and 270 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_9H_5BrN_2O_3$: C, 40.18; H, 1.87; N, 10.41. Found: C, 40.16; H, 1.93; N, 10.47.

3,3-Dibromo-1-methoxy-2-oxindole (9) from 1-methoxyindole (6b) — NBS (3.637 g, 20.43 mmol) was added to a solution of **6b** (1.001g, 6.81 mmol) in *t*-BuOH (70 mL) and the mixture was stirred at rt for 30 min. After evaporation of the solvent, H_2O was added to the residue. The whole was extracted with benzene. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a yellow solid, which was column-chromatographed on SiO_2 with CH_2Cl_2–hexane (2:1, v/v) to give **9** (1.281 g, 59%). **9**: mp 73—75°C (pale yellow prisms, recrystallized from CH_2Cl_2–hexane). IR (KBr): 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (3H, s), 6.95 (1H, dd, *J*=7.7, 1.5 Hz), 7.15 (1H, br dt, *J*=1.5, 7.7 Hz), 7.34 (1H, br dt, *J*=1.5, 7.7 Hz), 7.56 (1H, dd, *J*=7.8, 1.5 Hz). MS *m/z*: 319, 321, and 323 (M^+, ^{79}Br and ^{81}Br). *Anal*. Calcd for $C_9H_7Br_2NO_2$: C, 33.64; H, 2.18; N, 4.36. Found: C, 33.51; H, 2.09; N, 4.51.

1- Methoxy-2-oxindole (10) from 9 — Zink powder (103.2 mg, 1.6 mmol) was added to a solution of **9** (50.5 mg, 0.16 mmol) in AcOH (5 mL) and the mixture was stirred at rt for 1.5 h. Unreacted Zn was filtered off and washed with CH_2Cl_2–MeOH (95:5, v/v). H_2O was added to the combined washing and the filtrate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with CH_2Cl_2 to give **10** (16.6 mg, 65%). Spectral data are identical with the authentic sample prepared according to our previous procedures.[13a,b]

2-Oxindole (11) from 10 — A solution of **10** (155.3 mg, 0.95 mmol) in MeOH (10 mL) was hydrogenated in the presence of 10% Pd/C (50 mg) at rt and 1 atm for 1 h. Catalyst was filtered off and the filtrate was evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO_2 with CH_2Cl_2 to give **11** (120.4 mg, 95%), whose physical data were identical with the commercially available sample.

2,6-Dibromoindol-3-ylmethanol (13) from 12 — $NaBH_4$ (150.0 mg, 3.95 mmol) was added to a solution of **12** (65.2 mg, 0.22 mmol) in MeOH (10 mL), and the mixture was stirred at rt for 1 h. After evaporation of the solvent under reduced pressure, AcOEt was added to the residue. The whole was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **13** (44.2 mg, 67%). **13**:

colorless oil. IR (film): 3398, 3213, 1614 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (1H, br s), 4.80 (2H, s), 7.26 (1H, dd, *J*=8.5, 1.7 Hz), 7.43 (1H, d, *J*=1.7 Hz), 7.55 (1H, d, *J*=8.5 Hz), 8.18 (1H, br s). High-resolution MS *m/z*: Calcd for $C_9H_7{}^{79}Br_2NO$: 302.8895. Found: 302.8915. Calcd for $C_9H_7{}^{79}Br^{81}BrNO$: 304.8874. Found: 304.8852. Calcd for $C_9H_7{}^{81}Br_2NO$: 306.8854. Found: 306.8829.

***E*-2-(3-Hydroxy-3-methyl-1-butenyl)indole-3-carbaldehyde (15a) from 3a — General Procedure:** A solution of **3a** (405.4 mg, 1.81 mmol), (3-hydroxy-3-methyl-1-butenyl)tributyltin (**14a**, 1.00 g, 2.81 mmol), $Pd(OAc)_2$ (42.3 mg, 0.19 mmol), and Bu_4NCl (1.00 g, 3.61 mmol) in DMF (6 mL) was heated at 115—120°C for 3 h with stirring. After evaporation of the solvent under reduced pressure, brine was added, and the whole was extracted with AcOEt–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (2:1, v/v) to give **15a** (362.1 mg, 87%). **15a**: mp 194—195°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3165, 2975, 1614 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.47 (6H, s), 6.75 (1H, d, *J*=16.0 Hz), 7.02—7.48 (3H, m), 7.20 (1H, d, *J*=16.0 Hz), 7.99—8.23 (1H, m), 10.18 (1H, s). MS *m/z*: 229 (M^+). *Anal*. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.17; H, 6.60; N, 6.32.

Methyl (*E*)-3-(3-Formylindol-2-yl)acrylate (15b) from 3a — In the general procedure for **15a**, **3a** (102.2 mg, 0.46 mmol), 2-(methoxycarbonyl)vinyltributyltin (**14b**, 254.2 mg, 0.68 mmol), $Pd(OAc)_2$ (12.1 mg, 0.05 mmol), and Bu_4NCl (248.6 mg, 0.90 mmol) were used. After the same work-up as described in the preparation of **15a**, 70.2 mg (67%) of **15b** was obtained. **15b**: mp 261—262°C. IR (KBr): 3050, 1703, 1628 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 3.72 (3H, s), 6.95 (1H, d, *J*=16.0 Hz), 7.25—7.49 (3H, m), 8.50 (1H, d, *J*=16.0 Hz), 8.59—8.77 (1H, m), 10.71 (1H, s). The NH proton signal was not observed. MS *m/z*: 229 (M^+). *Anal*. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.89; H, 4.76; N, 6.04.

2-Phenylindole-3-carbaldehyde (15c) from 3a — In the general procedure for **15a**, **3a** (41.1 mg, 0.18 mmol), tetraphenyltin (**14c**, 117.3 mg, 0.27 mmol), $Pd(OAc)_2$ (4.3 mg, 0.02 mmol), and Bu_4NCl (97.7 mg, 0.35 mmol) were used. After the same work-up and column-chromatgraphy as described in the preparation of **15a**, **15c** (27.7 mg, 68%) and **3a** (3.9 mg, 10%) were obtained in the order of elution. **15c**: mp 260.5—263°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3120, 1628 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 7.18—7.90 (8H, m), 8.53—8.91 (1H, m), 10.25 (1H, s). MS *m/z*: 221 (M^+). *Anal*. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.51; H, 4.92; N, 6.35.

2-(3-Pyridyl)indole-3-carbaldehyde (15d) from 3a — In the general procedure for **15a**, **3a** (103.1 mg, 0.46 mmol), (3-pyridyl)trimethyltin (**14d**, 221.0 mg, 0.91 mmol), $Pd(OAc)_2$ (9.7 mg, 0.04 mmol), and Bu_4NCl (261.3 mg, 0.94 mmol) were used. After the same work-up and column-chromatgraphy as described in the preparation of **15a**, **15d** (39.1 mg, 38%), **15e** (10.9 mg, 15%), and **1d** (5.5 mg, 8%) were obtained in the order of elution. **15d**: mp 246—246.5°C (colorless needles, recrystallized from MeOH). IR (KBr): 3430, 3130, 1628 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 7.28—7.70 (4H, m), 8.14 (1H, ddd, *J*=8.0, 2.2, 1.8 Hz), 8.75—8.96 (2H, m), 9.27 (1H, dd, *J*=2.2, 0.8 Hz), 10.41 (1H, s). MS *m/z*: 222 (M^+). *Anal*. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.48; H, 4.77; N, 12.50.

2-Methylindole-3-carbaldehyde (15e) from 3a — In the general procedure for **15a**, **3a** (467.8 mg, 2.09 mmol), tetramethyltin (**14e**, 562.2 mg, 3.12 mmol), $Pd(OAc)_2$ (42.7 mg, 0.19 mmol), and Bu_4NCl (1.34 g, 4.84 mmol) were used. After the same work-up and column-chromatgraphy as described in the preparation of **15a**, **15e** (130.0 mg, 39%) and **1d** (18.1 mg, 6%) were obtained in the order of elution. **15e**: mp 204—205°C (colorless needles, recrystallized from MeOH). IR (KBr): 3250, 1635 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.63 (3H, s), 6.89—7.39 (3H, m), 7.79—8.12 (1H, m), 9.82 (1H, s). MS *m/z*: 159 (M^+). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.50; H, 5.62; N, 8.82.

2-(2-Pyridyl)indole-3-carbaldehyde (15f) from 3a — In the general procedure for **15a**, **3a** (100.5 mg, 0.45 mmol), **14f** (1.07 g, 4.43 mmol), $Pd(OAc)_2$ (10.9 mg, 0.05 mmol), and Bu_4NCl (246.1 mg, 0.89 mmol) were used. After the same work-up and column-chromatgraphy as described in the preparation of **15a**, unreacted **3a** (21.4 mg, 21%), **15f** (5.0 mg, 5%), **15e** (0.5 mg, 1%), and **1d** (2.4 mg, 4%) were obtained in the order of elution. **15f**: mp 225.5—226.5°C (colorless needles, recrystallized from MeOH). IR (KBr): 3060, 1619 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 7.12—7.70 (4H, m), 7.75 (1H, dd, *J*=7.5, 2.0 Hz), 8.70 (1H, dt, *J*=8.0, 1.0 Hz), 8.65—8.78 (1H, m), 8.78—8.98 (1H, m), 11.04 (1H, s). MS *m/z*: 222 (M^+). *Anal*. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.42; H, 4.38; N, 12.83.

(*E*,*E*)-2-Methyl-4-[3-(2-nitrovinyl)indol-2-yl]-3-buten-2-ol (16) from 15a — NH_4OAc (736.1 mg, 9.50 mmol) was added to a solution of **15a** (435.7 mg, 1.90 mmol) in $MeNO_2$ (26 mL) and the mixture was heated at 90°C for 4 h with stirring. After cooling to rt, the resulting precipitates (**16**, 406.1 mg) were collected by filtration and washed with MeOH. The filtrate and washings were combined and H_2O was added. The whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO_2 with CH_2Cl_2–MeOH (95:5, v/v) to give **16** (75.7 mg). Total yield of **16** was 481.8mg (93%). **16**: mp 246.5—247°C (decomp., red needles, recrystallized from MeOH). IR (KBr): 3250, 1578, 1360 cm^{-1}. ^{1}H NMR (pyridine-d_5) δ: 1.55 (6H, s), 7.02 (1H, d, *J*=16.0 Hz), 7.26—7.59 (4H, m), 7.85—8.05 (1H, m), 8.52 (1H, d, *J*=13.2 Hz), 8.77 (1H, d, *J*=13.2 Hz). MS *m/z*: 272 (M^+). *Anal*. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.97; H, 5.89; N, 10.46.

(*E*)-2-Methyl-4-[3-(2-nitroethyl)indol-2-yl]-3-buten-2-ol (17) from 16 — $NaBH_4$ (173.5 mg, 4.59 mmol) was added to a solution of **16** (206.0 mg, 0.76 mmol) in MeOH (30 mL) and the mixture was stirred at rt for 1 h. After addition of AcOEt, the whole was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with

AcOEt–hexane (1:1, v/v) to give **17** (199.5 mg, 96%). **17**: mp 122.5—123°C (colorless prisms, recrystallized from benzene). IR (KBr): 3520, 3310, 1554, 1380 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.23 (6H, s), 3.48 (2H, t, *J*=7.5 Hz), 4.62 (2H, t, *J*=7.5 Hz), 6.31 (1H, d, *J*=16.0 Hz), 6.71 (1H, d, *J*=16.0 Hz), 6.83—7.52 (4H, m). MS *m/z*: 274 (M^+). *Anal*. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.89; H, 6.58; N, 10.23.

1-(2-Methyl-1-propenyl)-1,2,3,4-tetrahydro-β-carboline (5a) from 17 — A solution of **17** (174.9 mg, 0.64 mmol) in THF (19.5 mL) was added to a mixture of Zn powder (897.2 mg, 13.7 mmol) [washed with 6% HCl (4 mL)] in 6% HCl (6.5 mL) at 0°C and the mixture was refluxed for 5 min with stirring. Unreacted Zn was filtered off and the filtrate was evaporated under reduced pressure. The residue was made basic by adding 8% aqueous NaOH and the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:2:0.2, v/v) to give **5a** (22.5 mg, 50%). **5a**: mp 160—161°C (colorless prisms, recrystallized from CH_2Cl_2, lit.,[10] mp 158—159°C). IR (KBr): 3400, 1092 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, d, *J*=1.2 Hz), 1.88 (3H, d, *J*=1.2 Hz), 2.65—2.89 (2H, m), 2.89—3.55 (2H, m), 4.83 (1H, br d, *J*=9.5 Hz), 5.26 (1H, dt, *J*=9.5, 1.2 Hz), 6.92—7.33 (3H, m), 7.33—7.53 (1H, m), 7.64 (1H, br s). MS *m/z*: 226 (M^+). *Anal*. Calcd for $C_{15}H_{18}N_2\cdot 1/4H_2O$: C, 78.05; H, 8.07; N, 12.13. Found: C, 78.47; H, 8.09; N, 11.84.

2-Methoxycarbonyl-1-(2-methyl-1-propenyl)-1,2,3,4-tetrahydro-β-carboline (5b) from 5a — A solution of $ClCO_2Me$ (38.6 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **5a** (54.0 mg, 0.24 mmol) and Et_3N (80.0 mg, 0.79 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at rt for 2 h. Saturated $NaHCO_3$ was added and the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was recrystallized from MeOH to give **5b** (47.5 mg) as colorless prisms. The mother liquor was subjected to p-TLC on SiO_2 with CH_2Cl_2–MeOH (95:5, v/v) as a developing solvent. Extraction from the band having an *Rf* value of 0.93—1.00 with CH_2Cl_2–MeOH (95:5, v/v) gave **5b** (10.3 mg). Total yield of **5b** was 58.7 mg (85%). **5b**: mp 186—189°C (lit.,[10] mp 180—181°C). IR (KBr): 3400, 3040, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.77 (3H, d, *J*=1.4 Hz), 1.98 (3H, d, *J*=1.4 Hz), 2.64—2.88 (2H, m), 2.88—3.37 (1H, m), 3.73 (3H, s), 4.39 (1H, d, *J*=12.5 Hz), 5.30 (1H, d, *J*=10.0 Hz), 5.88 (1H, d, *J*=10.0 Hz), 6.91—7.32 (3H, m), 7.36—7.52 (1H, m), 7.59 (1H, br s). High-resolution MS *m/z*: Calcd for $C_{17}H_{20}N_2O_2$: 284.1524. Found: 284.1526.

Borrerine (5c) from 5b — $LiAlH_4$ (98.6 mg, 2.60 mmol) was added to a solution of **5b** (46.3 mg, 0.16 mmol) in THF (8 mL) at 0°C and the mixture was refluxed for 5 h with stirring. After addition of MeOH and 10% aqueous Rochelle salt under ice cooling, the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:5:0.5, v/v) as a developing solvent. Extraction from the band having an *Rf* value of 0.74—0.90 with $CHCl_3$–MeOH–28% aq. NH_3 (46:5:0.5, v/v) gave **5c** (28.2 mg, 70%). **5c**: mp 105—106°C (colorless prisms, recrystallized from hexane, lit.,[10] mp 102—103°C). IR (KBr): 3200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, d, *J*=1.2 Hz), 1.88 (3H, d, *J*=1.2 Hz), 2.48—3.29 (4H, m), 4.05 (1H, dt, *J*=9.5, 1.2 Hz), 5.18 (1H, br d, *J*=9.5 Hz), 6.92—7.34 (3H, m), 7.34—7.63 (2H, m). High-resolution MS *m/z*: Calcd for $C_{16}H_{20}N_2$: 240.1625. Found: 240.1630.

Vulcanine (4) from 5a — A solution of *t*-BuOCl (42.4 mg, 0.39 mmol) in THF (1 mL) was added to a suspension of **5a** (37.0 mg, 0.16 mmol) and powdered NaOH (32.1 mg, 0.80 mmol) in THF (4 mL) and the mixture was stirred at rt for 64 h. H_2O was added and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with AcOEt–hexane (1:1, v/v) as a developing solvent. Extraction from the band having an *Rf* value of 0.47—0.65 with AcOEt gave **4** (18.5 mg, 51%). **4**: pale yellow oil. IR ($CHCl_3$): 1645, 1623, 1567, 1492, 1452, 1420, 1380, 1316, 1235 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, d, *J*=1.2 Hz), 2.01 (3H, d, *J*=1.2 Hz), 6.60 (1H, t, *J*=1.2 Hz), 7.28 (1H, ddd, *J*=8.1, 6.4, 1.7 Hz), 7.51 (1H, ddd, *J*=8.1, 1.7, 1.0 Hz), 7.53 (1H, ddd, *J*=8.1, 6.4, 1.0 Hz), 7.82 (1H, d, *J*=5.4 Hz), 8.11 (1H, d, *J*=8.1 Hz), 8.46 (1H, d, *J*=5.4 Hz), 8.57 (1H, br s, disappeared on addition of D_2O). ^{13}C-NMR ($CDCl_3$) δ: 20.5, 26.7, 111.9, 113.0, 119.0, 120.3, 121.6, 121.8, 128.8, 129.5, 134.0, 136.8, 140.7, 140.8, 143.8. UV λmax (MeOH) nm (log ε): 214 (4.36), 239 (4.49), 260 (sh, 4.23), 292 (4.14), 356 (3.79). MS *m/z*: 222 (M^+), 207, 182, 103. High-resolution MS *m/z*: Calcd for $C_{15}H_{14}N_2$: 222.1157. Found: 222.1154. **4**·HCl: mp 189—192°C (yellow needles, recrystallized from Et_2O–MeOH, lit.,[9] mp 103°C). IR (KBr): 3340, 1640, 1599, 1442, 761 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.93 (3H, d, *J*=1.2 Hz), 2.22 (3H, d, *J*=1.2 Hz), 6.74 (1H, t, *J*=1.2 Hz), 7.47 (1H, ddd, *J*=8.1, 6.8, 1.0 Hz), 7.76 (1H, dt, *J*=8.3, 1.0 Hz), 7.80 (1H, ddd, *J*=8.3, 6.8, 1.0 Hz), 8.35 (1H, d, *J*=6.4 Hz), 8.41 (1H, dt, *J*=8.1, 1.0 Hz), 8.55 (1H, d, *J*=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 20.9, 26.6, 113.9, 114.2, 116.6, 121.5, 123.0, 124.1, 129.5, 133.1, 134.8, 135.2, 137.4, 145.4, 152.5. *Anal*. Calcd for $C_{15}H_{14}N_2$·HCl·1/4H_2O: C, 68.44; H, 5.93; N, 10.64. Found: C, 68.51; H, 5.83; N, 10.68.

ACKNOWLEDGMENTS

The authors express their cordial gratitude to Dr. Y. Kamuro (Nissan Chemical Ind. Ltd.) for the biological test (rice and cucumber). They are deeply indebted to Mr. T. Minamide, a member of “The NPO Juridical Person for Making the World Desert Green” for observing the root growth for 73 days in the hottest season at Gobi desert in Inner Mongolia.

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