A SYNTHESIS METHOD OF INDOLE-3-METHANAMINE AND/OR GRAMINE FROM INDOLE-3-CARBOXALDEHYDE, AND ITS APPLICATION FOR THE SYNTHESES OF BRASSININ, ITS 4-SUBSTITUTED ANALOGS, AND 1, 3, 4, 5-TETRAHYDROPYRROLO[4, 3, 2-*de*]QUINOLINE[1]

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Abstract——Simple conversion method of indole-3-carboxaldehyde into gramine and/or indole-3-methanamine was developed. The present method realized short step syntheses of brassinin, 4-iodo-, methoxy-, 4-methoxy-, and 4-*nitrobrassinin*, 4-methoxyindole-3-acetonitrile, and 1, 3, 4, 5-tetrahydropyrrolo[4, 3, 2-*de*]quinoline.

Various methods are reported[2] for the preparation of 3-substituted indoles. *Among them Mannich method via* 3-dimethylaminomethylindole (gramine) and Vilsmeier method *via* indole-3-carboxaldehyde are used most extensively.[2] In our continuing projects to attain simple syntheses of ergot alkaloids,[3] phytoalexins of Cruciferae,[4] *and various indole* natural products,[5] we needed a novel method which connect Vilsmeier and Mannich methods, making it possible to transform indole-3-carboxaldehyde (**1**) to indole-3-methanamine (**2**) or gramine (**3**) at one's will. *Although it has been the fundamental* desire in indole chemistry, no one has yet succeeded in finding a solution.[6] Now, we wish to report a simple method which meets our end.

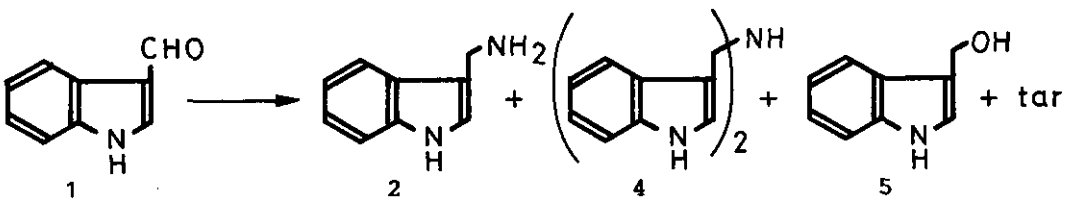
I. Simple method for converting indole-3-carboxaldehydes into gramines and/or indole-3-methanamines

Because of the intrinsic unstable nature of **2**, we examined various mild reactions for converting **1** to **2**, and finally reached to the reaction using ammonia (NH_3) or ammonium salts with boron hydride as a reducing agent. As can be seen from the typical results summarized in Table I, **2**, bis(indol-3-ylmethyl)amine (**4**), and indole-3-methanol (**5**) were generally produced with tars. Although further improvement is still necessary, the best yield (28%) of **2** was achieved under the reaction conditions of Entry 5.

We next turned our attention to transform indole-3-carboxaldehydes into the corresponding gramines, and successful results obtained are summarized in Tables II and III. Gramine (**3**) was obtained in 72~74% yield by the reaction of **1** with sodium borohydride ($NaBH_4$) in 50% aqueous dimethylamine (aq. Me_2NH)-methanol (MeOH) (1:1, v/v) in addition to 25~27% yield of **5** (Table II). In the case of 4-nitroindole-3-carboxaldehyde[7] (**6**), use of MeOH as co-solvent was not necessary. Thus, $NaBH_4$ reduction of **6** in 50% aq. Me_2NH afforded 3-dimethylaminomethyl-4-nitroindole (**7**), a key intermediate for indolactams,[8] in high yield together with minor production of 4-nitroindole-3-methanol (**8**) and 4-nitroindole[9] (**9**) (Table III, Entry 1). An attempt to raise the yield by forming iminium salt prior to the reduction was made by treating **6** with Me_2NH and $Me_2NH \cdot HCl$, but the result did not come up to the expectation (Entry 3). During these studies, alkaline treatment of **6** was found to produce **9**, quantitatively. This means that **9** became readily accessible from **1**[7a] in only two steps in 62% overall yield.[8]

We further examined to transform **3** into **2**.[6] First, **3** was converted to the quaternary ammonium salt with excess methyl iodide (MeI) in tetrahydrofuran (THF), and then it was reacted with aq. ammonia (NH_4OH) or sodium amide in an appropriate solvent for 2 h. The results shown in Table IV show that an amide anion did not afford good results (Entries 1~3). In cases

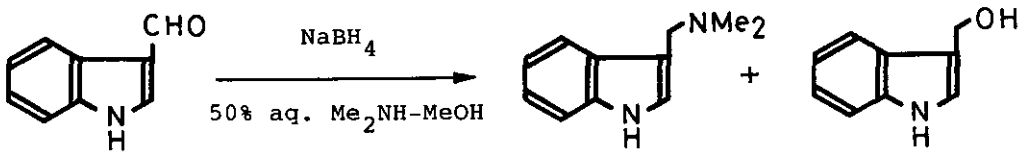
Table I. Preparation of Indole-3-methanamine from Indole-3-carboxaldehyde



Entry	Reaction			Conditions		Yield (%) of		
	Amine (mol. eq.)	Reducing Agent (mol. eq.)	Solvent	Temp. (°C)	Time (h)	2	4	5
1	NH_4OAc (5)	$NaBH_3CN$ (1.5)	AcOH	13	1.25	0	0	0
2	NH_4OAc (10)	$NaBH_3CN$ (1.6)	AcOH	reflux	21	12	0	0
3	NH_4OH (112)	$NaBH_4$ (3.1)	MeOH	14~18	20	9	13	72
4	NH_3 gas* (198)	$NaBH_4$ (3.1)	MeOH*	13~18	20	10	12	66
5	NH_4OH (108)	$NaBH_3CN$ (3.0)	AcOH	17~18	9	28	4	0

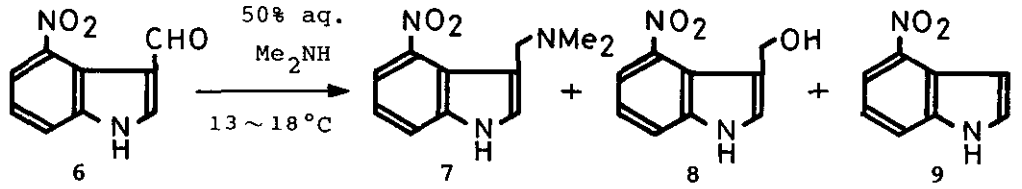
* NH_3 gas was saturated by bubbling into MeOH at room temperature.

Table II. Preparation of Gramine from Indole-3-carboxaldehyde



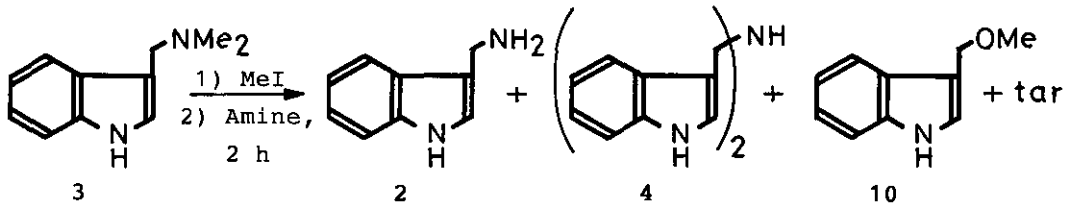
Entry	Reaction		Conditions		Yield (%) of	
	Me_2NH (mol. eq.)	$NaBH_4$ (mol. eq.)	Temp. (°C)	Time (h)	3	5
1	68	3.1	14 ~ 18	2.5	72	27
2	65	3.0	55 ~ 60	2.5	74	25

Table Ⅲ. Preparation of 4-Nitrogramine from 4-Nitroindole-3-carboxaldehyde



Entry	Reaction Conditions NaBH4 (mol. eq.)	Additives (mol. eq.)	Time (h)	Yield (%) of 7	8	9
1	9.1	–	20	86	9	2
2	3.1	–	2.5	80	18	0
3	3.0	$Me_2NH \cdot HCl$ (1.0)	2.5	75	23	0

Table Ⅳ. Preparation of Indole-3-methaneamine from Gramine



Entry	Reaction Conditions Solvent	Amine (mol. eq.)	Temp. (°C)	Yield (%) of 2	4	10
1	THF－H_2O (1:1)	$NaNH_2$ (21)	reflux	0	0	0
2	MeOH－H_2O (1:1)	$NaNH_2$ (20)	reflux	15	13	60
3	MeOH	$NaNH_2$ (21) and NH_4OH (249)	reflux	24	17	49
4	MeOH	NH_4OH (251)	reflux	56	39	4
5	Gramine itself* MeOH	NH_4OH (268)	reflux	27	6	5
6	*t*-BuOH	NH_4OH (249)	reflux	58	41	0
7	–	NH_4OH (468)	15	60	20	0
8	–	NH_4OH (463)	0	56	13	0

*Gramine was not methylated to ammonium salt prior to the reaction with ammonia, resulting in 59% yield of recovery of starting material.

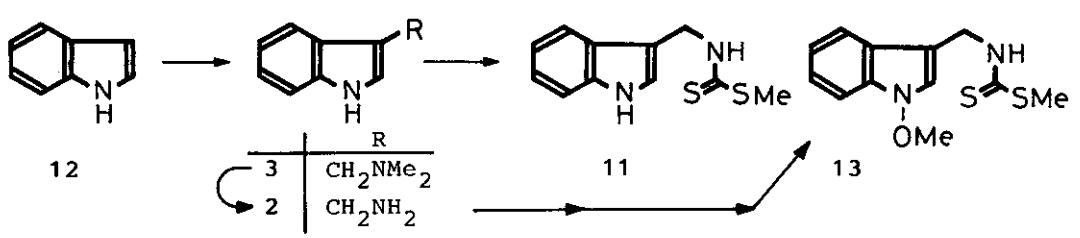
where MeOH was used as co-solvent (Entries 2~5), formation of 3-methoxymethylindole (**10**) was observed together with the desired **2** and **4**. *tert*-Butanol was the solvent of choice to avoid formation of **10**, and the yield of **2** was raised up to 58% (Entry 6). On the other hand, when **2** was heated in NH_4OH and MeOH at reflux for 2 h, **4** was produced[10] in 46% yield along with a 46% yield of the recovered **2**. Based on these results, treatment of the quaternary ammonium salt with NH_4OH at room temperature was finally found to be an effective reaction condition (Entry 7).

Since the spectral data of **2** and **4** were quite similar, their structures were confirmed unequivocally by leading them to the corresponding *N*b-acetyl derivatives, respectively.

Ⅱ. Syntheses of phytoalexins, their derivatives, and 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline

Brassinin (**11**),[4a] a phytoalexin of Cruciferae,[4b] is now readily available. Thus, gramine (**3**) was converted to **2** as described above, and subsequent reaction of **2** with carbon disulfide[4] (CS_2) and MeI completed simple three step synthesis of **11** from indole (**12**) in 53% overall yield (Scheme 1). On the other hand, our previous synthesis of methoxybrassinin[4a] (**13**) depended on the intermediate (**2**), which was prepared in poor overall yield (12%) from **1**. Now that **2** become easily available from both compounds, (**1**) and (**12**), this constitutes an improved seven step synthesis

Scheme 1



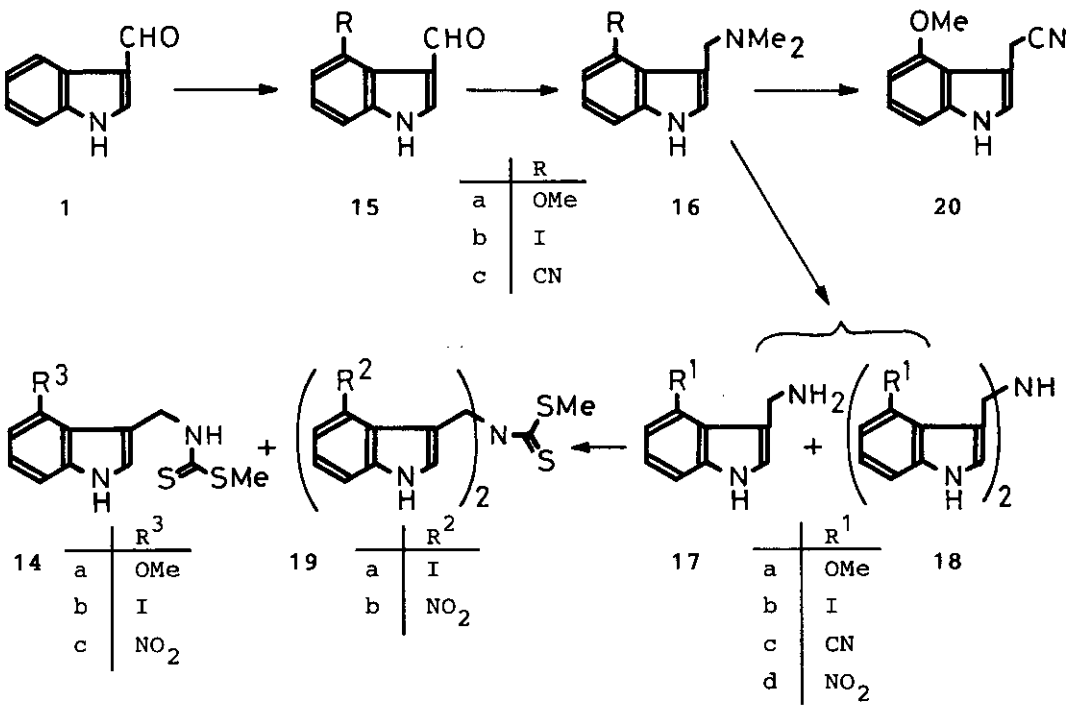
of **13** from **12** in 22% overall yield. Since Mannich reaction of indoles having various substituent at the benzene part can provide the corresponding gramines, derivatives of brassinin and methoxybrassin would be produced in quantity by applying the present method.

4-Methoxybrassinin[4a,c] (**14a**) is also available in only four steps from **1** (Scheme 2). Thus, 4-methoxyindole-3-carboxaldehyde (**15a**), prepared according to our one pot synthetic method,[7b] was converted to 3-dimethylaminomethyl-4-methoxyindole[10] (**16a**) in 57% yield by the reaction with $NaBH_4$ in Me_2NH at room temperature for 2 h. Due to its instability, **16a** was reacted with MeI without purifying, and subsequent reaction with $NaBH_4$ in NH_4OH produced 4-methoxyindole-3-methanamine (**17a**) in 74% yield together with 13% yield of bis(4-methoxyindol-3-ylmethyl)amine (**18a**). Further reaction of **17a** with CS_2 and MeI afforded **14a** in 64% yield.

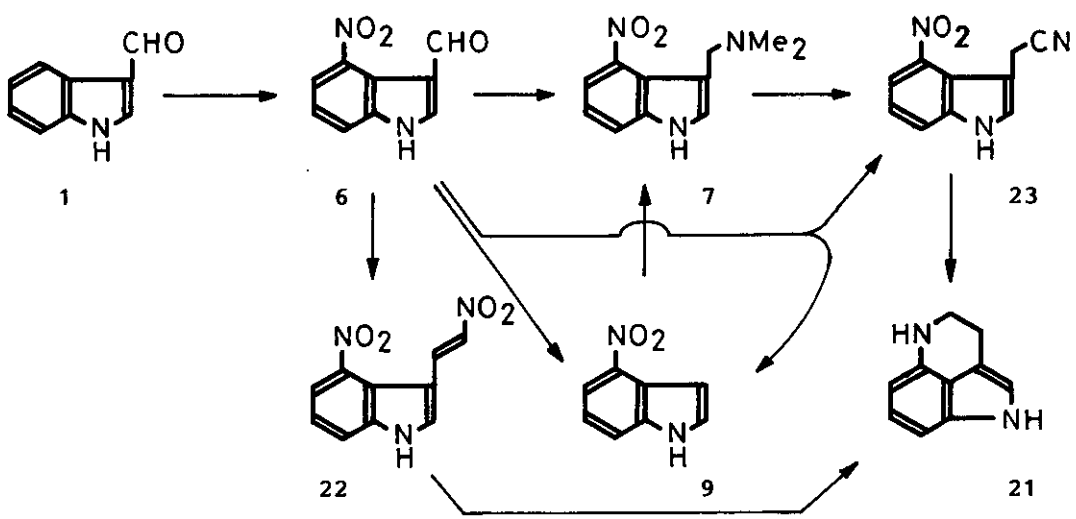
Similarly, 4-iodo-[8b] (**15b**) and 4-cyanoindole-3-carboxaldehyde[7b] (**15c**) afforded the corresponding 3-dimethylaminomethylindoles, (**16b**)[8b] and (**16c**), in 86 and 73% yields, respectively. Although **16c** afforded **17c** as a stable compound in 58% yield, **16b** generated unstable **17b**, which gradually collapsed to **18b** on standing or during purification by column chromatography. Therefore, the mixture of **17b** and **18b**, immediately after preparation from **16b**, was reacted with CS_2 and MeI to afford 4-iodobrassinin (**14b**) and methyl *N,N*-bis(4-iodoindol-3-ylmethyl)dithiocarbamate (**19a**) in 44 and 34% overall yields, respectively. Without isolating unstable **17d**, 4-nitrobrassinin (**14c**) and methyl *N,N*-bis(4-nitroindol-3-ylmethyl)dithiocarbamate (**19b**) were also produced from 3-dimethylaminomethyl-4-nitroindole (**7**) in 41 and 13% overall yields, respectively. Reaction of **18b** with CS_2 and MeI produced **19a** in 87% yield.

The present method effected three step synthesis of 4-methoxyindole-3-acetonitrile[11] (**20**), an aglycon of SF-2140,[12] in 81% overall yield from **1** through **15a** and then **16a**.

Scheme 2

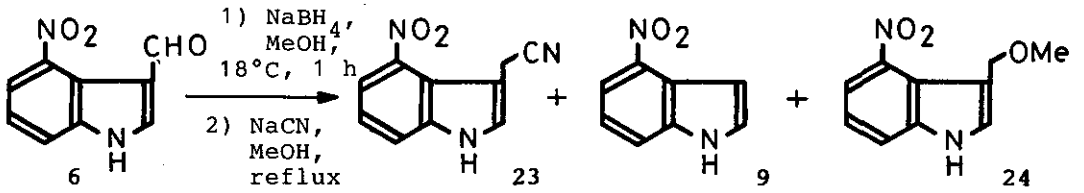


Scheme 3



The previous synthesis[5] of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**21**,[13] Scheme 3) met the trouble in the catalytic reduction step of nitrovinyl compound (**22**), due to its poor solubility to various solvents, which prevented **21** from multigram scale production. Although such problem did not exist in obtaining **21** by the reduction of 4-nitroindole-3-acetonitrile (**23**), it must be synthesized starting from the expensive[9] **9** through **7**. The present method achieved the preparation of **7** from **6**, which made possible to establish an improved and economical four step synthetic route to **21** (**1**→**6**→**7**→**23**→**21**). In addition, we found one-pot synthetic method for **23** by treating **6** sequentially with $NaBH_4$, and then with sodium cyanide in refluxing MeOH, as shown in Table V. Under the reaction conditions in the Entry 2, **23** was obtained in 35% yield along with a 56% yield of **9**, which could be returned[8b] to **7**.

Table V. Preparation of 4-Nitroindole-3-acetonitrile from 4-Nitroindole-3-carboxaldehyde



Entry	Reaction Conditions NaCN (mol. eq.)	Time (h)	Yield (%) of **23**	**9**	**24**
1	1.2	7	7	56	16
2	10.1	5	35	56	4
3	20.2	4	32	58	5

In summary, we developed a convenient method for converting indole-3-carboxaldehydes into indole-3-methanamines, gramines, and/or indole-3-acetonitrile. The present method would be widely used for aiming at shortening the synthetic steps of various indole derivatives.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (Ir) spectra were determined with a Shimadzu IR-420 spectrophotometer, and proton nuclear magnetic resonance (^{1}H-Nmr) spectra with a JEOL JNM-GSX 500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (Ms) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography (p-tlc) was performed on Merck Kiesel-gel GF_{254} (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.

Indole-3-methanamine (**2**) from indole-3-carboxaldehyde (**1**)

Table I, Entry 5: $NaBH_3CN$ (95.4 mg, 1.52 mmol) was added to the solution of **1** (72.3 mg, 0.500 mmol) in AcOH (7.0 ml) and 29% NH_4OH (3.5 ml, 54 mmol) at 0°C. After stirring for 9 h at room temperature, brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract 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-29% NH_4OH (46:5:0.5, v/v) as a developing solvent. Under uv light, three bands were detected. Extraction from the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave the unreacted **1** (16.3 mg, 23%). Extraction from the middle band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **4** (3.0 mg, 4%). Extraction from the lower band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **2** (20.4 mg, 28%). The compound (**2**) was unstable and gradually collapsed to **4** and tars on standing. **2**: mp 98.0-101.0°C (colorless needles, recrystallized from CH_2Cl_2-hexane, lit.,[6] mp 104-107°C). Spectral data were identical with those of the reported ones. Ir (KBr): 3400, 3320, 1607, 1478, 1353, 1235, 1096, 734 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 3.99 (2H, s), 7.02 (1H, ddd, J=7.8, 6.8, and 1.0 Hz), 7.10 (1H, ddd, J=8.3, 6.8, and 1.0 Hz), 7.18 (1H, s), 7.34 (1H, d, J=7.8 Hz), 7.59 (1H, d, J=8.3 Hz). **4**: mp 115.0-117.0 °C (recrystallized from benzene-hexane, lit.,[10] mp 88°C). Ir (KBr): 3400, 3050, 2920, 1618, 1547, 1454, 1422, 1340, 1231, 1091, 1006, 740 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.03 (4H, s), 6.99 (2H, t, J=8.1 Hz), 7.10 (2H, t, J=8.1 Hz), 7.23 (2H, s), 7.35 (2H, d, J=8.1 Hz), 7.50 (2H, d, J=8.1 Hz). *Anal.* Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.31; H, 6.29; N, 14.90.

Gramine (3-dimethylaminomethylindole, **3**) from indole-3-carboxaldehyde (1)

Table Ⅱ, Entry 2: aqueous 50% Me_2NH (4.0 ml, 38.2 mmol) was added to the solution of **1** (85.0 mg, 0.586 mmol) in MeOH (4.0 ml) and stirred for 30 min at room temperature. $NaBH_4$ (66.5 mg, 1.76 mmol) was then added to the solution and the whole was heated at 55-60°C for 2.5 h with stirring. Brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a colorless solid, which was subjected to p-tlc on SiO_2 with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) as a developing solvent. Under uv light, two bands were detected. Extraction from the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave indole-3-methanol (**5**, mp 98.0-100.0°C, 23.9 mg, 25%). Extraction from the lower band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **3** (75.9 mg, 74%).

3-Dimethylaminomethyl-4-nitroindole (**7**) from 4-nitroindole-3-carboxaldehyde (**6**)

Table Ⅲ, Entry 2: $NaBH_4$ (53.0 mg, 1.40 mmol) was added to the solution of **6** (86.4 mg, 0.457 mmol) in aqueous 50% Me_2NH (4.0 ml, 38.2 mmol) at room temperature. After stirring at room temperature for 2.5 h, brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a yellow oil, which was subjected to p-tlc on SiO_2 with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) as a developing solvent. Under uv light, three bands were detected. Extraction from the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave the unreacted **6** (1.0 mg, 1%). Extraction from the middle band with CH_2Cl_2-MeOH (95:5, v/v) gave 4-nitroindole-3-methanol (**8**, 16.0 mg, 18%). Extraction from the lower band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **7**[8b] (80.3 mg, 80%). **8**: mp 150.0-152.0°C (orange prisms, recrystallized from AcOEt). Ir (KBr): 3520, 3240, 1624, 1505, 1388, 1324, 1296, 1121, 1086, 979, 731 cm^{-1}. ^1H-Nmr (CD_3OD) δ : 4.91 (2H, s), 7.24 (1H, t, J=8.3 Hz), 7.55 (1H, s), 7.73 (1H, dd, J=8.3 and 1.0 Hz), 7.84 (1H, dd, J=8.3 and 1.0 Hz). Ms *m/z*: 192 (M^+). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.24; H, 4.27; N, 14.40. In the Entry 1, 4-nitroindole[9] (**9**) was produced as a by-product. **9** was effectively prepared from **6** as follows.

4-Nitroindole (**9**) from 4-nitroindole-3-carboxaldehyde (**6**)

conc. HCl (1.0 ml) was added to the solution of **6** (40.8 mg, 0.215 mmol) in MeOH (2.0 ml) and heated at reflux for 1.5 h. After evaporation of the

solvent under reduced pressure, brine was added to the residue and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an orange solid. Purification by p-tlc on SiO_2 with CH_2Cl_2 as a developing solvent was performed. Extraction from the yellow band with CH_2Cl_2-MeOH (97:3, v/v) gave **9**[9] (34.6 mg, 99%).

Indole-3-methanamine (**2**) from gramine (**3**)

Table Ⅳ, Entry 4: MeI (0.11 ml, 1.77 mmol) was added to a solution of **3** (32.1 mg, 0.184 mmol) in anhydrous THF (2.0 ml) and stirred at room temperature for 1 h. After evaporation of the solvent *in vacuo*, MeOH (3.0 ml) and 29% NH_4OH (4.0 ml, 61 mmol) was added to the residue, and the resultant solution was refluxed for 2 h with stirring. Brine was added and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a colorless oil, which was subjected to p-tlc on SiO_2 with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) as a developing solvent. Under uv light, three bands were detected. Extraction from the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave 3-methoxymethylindole (**10**, 1.3 mg, 4%). Extraction from the middle band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **4** (10.0 mg, 39%). Extraction from the lower band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave **2** (15.0 mg, 56%).

Table Ⅳ, Entry 7: MeI (0.13 ml, 2.09 mmol) was added to a solution of **3** (34.2 mg, 0.197 mmol) in anhydrous THF (2.0 ml) and stirred at room temperature for 1 h. After evaporation of the solvent *in vacuo*, 29% NH_4OH (6.0 ml) was added to the residue, and the resultant solution was stirred at room temperature for 2 h. Gradually, an oily product separated out. Brine was added to the reaction mixture and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a colorless oil, which was subjected to p-tlc as described above. Under uv light, three bands were detected. Extraction from the upper band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) afforded unknown compound (5.3 mg), supposed to be tris(indol-3-ylmethyl)amine. Extraction from the middle band with the same solvent as above gave **4** (5.1 mg, 20%). Extraction from the lower band with the same solvent as above gave **2** (17.3 mg, 60%).

3-Acetylaminomethylindole from indole-3-methanamine (**2**)

Ac_2O (0.5 ml, 5.28 mmol) was added to the solution of **2** (18.8 mg, 0.128 mmol) in pyridine (1.0 ml, 12.4 mmol) and stirred at room temperature for 13 h. After evaporation of the solvent under reduced pressure, sat. aqueous $NaHCO_3$ was added to the residue and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a colorless oil. Purification by p-tlc on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent afforded 3-acetylaminomethylindole (22.5 mg, 93%). Mp 136.0-137.0 °C (colorless prisms, recrystallized from AcOEt, lit.,[6] mp 133-134°C). Ir (KBr): 3320, 1612, 1560, 1542, 1441, 1360, 1240, 1083, 1012, 739, 732 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.97 (3H, s), 4.60 (2H, d, J=5.4 Hz), 5.73 (1H, br s), 7.12-7.17 (2H, m), 7.22 (1H, dt, J=1.0 and 8.1 Hz), 7.38 (1H, d, J=8.1 Hz), 7.63 (1H, d, J=8.1 Hz), 8.42 (1H, br s). Ms *m/z*: 188 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.48; N, 14.89.

*N*b-Acetylbis(indol-3-ylmethyl)amine from bis(indol-3-ylmethyl)amine (**4**)
Ac_2O (1.0 ml, 10.5 mmol) was added to the solution of **4** (11.8 mg, 0.043 mmol) in pyridine (2.0 ml, 24.8 mmol) and stirred at room temperature for 23 h. After evaporation of the solvent under reduced pressure, sat. aqueous $NaHCO_3$ was added to the residue and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a colorless oil. Purification by p-tlc on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent afforded *N*b-acetylbis(indol-3-ylmethyl)amine (13.2 mg, 97%). Colorless oil. Ir (film): 3400, 3260, 1610, 1453, 1420, 1353, 1230, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.26 (3H, s), 4.61 (2H, s), 4.85 (2H, s), 6.99 (1H, br s), 7.09-7.16 (3H, m), 7.19-7.27 (2H, m), 7.37 (1H, d, J=8.1 Hz), 7.41 (1H, d, J=8.1 Hz), 7.48 (1H, d, J=8.1 Hz), 7.73 (1H, d, J=8.1 Hz), 8.18 (1H, br s), 8.28 (1H, br s). High resolution ms *m/z*: Calcd for $C_{20}H_{19}N_3O$: 317.1527. Found: 317.1532.

3-Dimethylaminomethyl-4-methoxyindole (**16a**) from 4-methoxyindole-3-carboxaldehyde (**15a**)
15a (49.7 mg, 0.284 mmol) was dissolved in aqueous 50% Me_2NH (4.0 ml, 38.2 mmol) and stirred at room temperature for 30 min. $NaBH_4$ (34.8 mg, 0.92 mmol) was added to the solution and stirring was continued at room temperature for 2 h. Brine was added and the whole was extracted with CH_2Cl_2-

MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to p-tlc with $CHCl_3$-MeOH-29% NH_4OH (100:20:2, v/v) as a developing solvent. Under uv light, two bands were detected. Extraction from the upper band with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) gave 4-methoxyindole-3-methanol (9.7 mg, 19%). Extraction from the lower band with the same solvent as described above gave **16a** (33.3 mg, 57%). **16a**: mp 136.0-138.0°C (colorless *prisms*, *recrystallized* from acetone, lit.,[11] mp 142-143°C). Ir (KBr): 3090, 1586, 1510, 1465, 1240, 1080, 995, 729 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.32 (6H, s), 3.82 (2H, s), 3.91 (3H, s), 6.48 (1H, d, J=7.8 Hz), 6.94 (1H, dd, J=8.1 and 0.7 Hz), 6.98 (1H, d, J=2.2 Hz), 7.06 (1H, dd, J=8.1 and 7.8 Hz), 8.30 (1H, br s). Ms *m/z*: 204 (M^+). **16a** was a relatively unstable compound.

3-Dimethylaminomethyl-4-iodoindole (**16b**) from 4-iodoindole-3-carboxaldehyde (**15b**)

15b (1.1692 g, 4.3 mmol) was dissolved in aqueous 50% Me_2NH (100.0 ml, 955 mmol) and stirred at room temperature for 30 min. $NaBH_4$ (525.6 mg, 13.9 mmol) was added to the solution and stirring was continued at room temperature for 2 h. Brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil. Purification by *column chromatography* with $CHCl_3$-MeOH-29% NH_4OH (46:5:0.5, v/v) as an eluent afforded **16b**[8b] (1.119 g, 86%).

4-Cyano-3-dimethylaminomethylindole (**16c**) *from* 4-*cyanoindole*-3-carboxaldehyde (**15c**)

15c (83.9 mg, 0.49 mmol) was dissolved in aqueous 50% Me_2NH (4.0 ml, 38.2 mmol) and stirred at room temperature for 30 min. $NaBH_4$ (55.7 mg, 1.47 mmol) was added to the solution and stirring was continued at room temperature for 30 min. $NaBH_4$ (94.4 mg, 2.49 mmol) was added additionally to the solution and stirred at room temperature for 3 h. Brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography using sequencially CH_2Cl_2-MeOH (97:3, v/v) and $CHCl_3$-MeOH-29% NH_4OH (100:10:1, v/v) as an eluent. From the early part of the fractions, 4-cyanoindole-3-methanol (19.5 mg, 23%) was obtained. From the later part of the fractions, **16c** (72.0 mg, 73%) was obtained. 4-Cyanoindole-3-methanol: mp 145.

0-147.5°C (colorless prisms, recrystallized from MeOH). Ir (KBr): 3410, 3190, 2220, 1618, 1552, 1352, 1088, 990, 980, 796, 755 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 5.00 (2H, d, J=0.5 Hz), 7.22 (1H, dd, J=7.5 and 7.2 Hz), 7.45 (1H, dd, J=7.5 and 0.9 Hz), 7.48 (1H, s), 7.68 (1H, dd, J=7.2 and 0.9 Hz). Ms *m/z*: 172 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.76; H, 4.74; N, 16.21. **16c**: mp 173.5-176.5°C (decomp., colorless prisms, recrystallized from MeOH). Ir (KBr): 2820, 2220, 1617, 1467, 1455, 1360, 1347, 998, 825, 792, 764 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.36 (6H, s), 3.82 (2H, s), 7.17 (1H, dd, J=8.1 and 7.7 Hz), 7.23 (1H, d, J=1.8 Hz), 7.44 (1H, dd, J=7.7 and 0.9 Hz), 7.51 (1H, dd, J=8.1 and 0.9 Hz), 8.94 (1H, br s). Ms *m/z*: 199 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_3 \cdot 1/2H_2O$: C, 69.23; H, 6.74; N, 20.18. Found: C, 69.01; H, 6.57; N, 20.43.

4-Methoxyindole-3-methanamine (**17a**) from 4-methoxyindole-3-carboxaldehyde (**15a**) *via* unstable 3-dimethylaminomethyl-4-methoxyindole (**16a**)

15a (51.8 mg, 0.296 mmol) was dissolved in aqueous 50% Me_2NH (5.0 ml, 47.6 mmol) and stirred at room temperature for 30 min. $NaBH_4$ (33.7 mg, 0.891 mmol) was added to the solution and stirring was continued at room temperature for 2 h. Brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. THF (5.0 ml) was added to the residue and then MeI (0.19 ml, 3.05 mmol) was added. After stirring at room temperature for 3 h, MeOH (15.0 ml) and 29% NH_4OH (20.0 ml) were added and the whole was refluxed for 2 h. After cooling, brine was added and the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was subjected to column chromatography on SiO_2 with $CHCl_3$-MeOH-29% NH_4OH (100:15:1.5, v/v) as an eluent. From the early part of the fractions, 4-methoxyindole-3-methanol (2.6 mg, 5%) was obtained. From the middle part of the fractions, bis(4-methoxyindol-3-ylmethyl)amine (**18a**, 6.2 mg, 13%) was obtained. From the later part of the fractions, **17a** (38.4 mg, 74%) was obtained. **17a**: mp 140.0-141.5°C (decomp., pale yellow prisms, recrystallized from MeOH-benzene). Ir (KBr): 3360, 1583, 1513, 1459, 1446, 1434, 1363, 1258, 1245, 1084, 924, 739 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 3.92 (2H, s), 3.94 (3H, s), 6.50 (1H, d, J=7.5 Hz), 6.95 (1H, d, J=7.5 Hz), 7.00 (1H, s), 7.02 (1H, t, J=7.5 Hz). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.67; H, 6.82; N, 15.61. High resolution ms *m/z*: Calcd for $C_{10}H_{12}N_2O$: 176.0949. Found: 176.0959. **17a** was a relatively unstable com-

pound. **18a**: mp 167.0-168.0°C (crystallized by MeOH-CH_2Cl_2, but decomposed during recrystallization and/or handling). Ir (KBr):3330, 1613, 1580, 1508, 1446, 1357, 1256, 1251, 1078, 960, 743, 731 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 3.55 (6H, s), 3.98 (4H, s), 6.43 (2H, d, J=7.8 Hz), 6.96 (2H, dd, J=7.8 and 1.0 Hz), 7.00 (2H, t, J=7.8 Hz), 7.06 (2H, s). *Ms m/z*: 335 (M^+).

4-Cyanoindole-3-*methanamine* (**17c**) and bis(4-cyanoindol-3-ylmethyl)amine (**18c**) from 4-cyano-3-dimethylaminomethylindole (**16c**)

MeI (0.10 ml, 1.60 mmol) was added to a stirred solution of **16c** (31.7 mg, 0.159 mmol) in THF (10.0 ml) and stirring was continued at 22°C for 1 h. After evaporation of the solvent *in vacuo*, MeOH (10.0 ml) and 29% NH_4OH (5.0 ml, 76 mmol) were added to the residue and the resultant solution was refluxed for 2 h. After cooling, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil. The oil consisted of four products. Separation was carried out repeatedly using column chromatography and p-tlc (on SiO_2 with AcOEt-hexane (1:2, v/v) or $CHCl_3$-MeOH-29% NH_4OH (100:10:1, v/v) as an eluent or developing solvent). In the order of increasing polarity, 4-cyano-3-methoxymethylindole (1.6 mg, 5%), **18c** (2.8 mg, 11%), **16c** (6.6 mg, 20%), and **17c** (13.7 mg, 50%) were isolated. **17c**: mp 133.0-135.0°C (pale yellow prisms, recrystallized from AcOEt-hexane). Ir (KBr): 3028, 2940, 2220, 1615, 1584, 1345, 1124, 930, 760 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.17 (2H, d, J=0.7 Hz), 7.22 (1H, dd, J=8.3 and 7.5 Hz), 7.44 (1H, s), 7.45 (1H, dd, J=7.5 and 0.9 Hz), 7.67 (1H, dd, J=8.3 and 0.9 Hz). *Ms m/z*: 171 (M^+). *Anal.* Calcd for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.19; H, 5.36; N, 24.35. **18c**: mp 198.0-200.0°C (colorless needles, recrystallized from MeOH-H_2O). Ir (KBr): 3310, 3270, 2211, 1616, 1440, 1428, 1346, 749 cm^{-1}. ^{1}H-Nmr (d_6-DMSO) δ : 4.12 (4H, s), 7.21 (2H, dd, J=8.3 and 7.4 Hz), 7.47 (2H, dd, J=7.4 and 0.8 Hz), 7.55 (2H, d, J=2.0 Hz), 7.71 (2H, dd, J=8.3 and 0.8 Hz), 11.52 (2H, s). Ms *m/z*: 325 (M^+). *Anal.* Calcd for $C_{20}H_{15}N_5$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.98; H, 4.46; N, 21.38. 4-Cyano-3-methoxymethylindole: mp 121.0-122.0°C (colorless plates, recrystallized from ether-hexane). Ir (KBr): 3330, 2230, 1620, 1448, 1439, 1352, 1102, 1082, 940, 741 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 3.54 (3H, s), 4.82 (2H, d, J=0.5 Hz), 7.22 (1H, dd, J=8.2 and 7.3 Hz), 7.38 (1H, d, J=2.5 Hz), 7.51 (1H, dd, J=7.3 and 0.9 Hz), 7.58 (1H, dd, J=8.2 and 0.9 Hz), 8.43 (1H, br s). Ms *m/z*: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.21; H, 5.45; N, 15.03.

4-Methoxybrassinin (**14a**) from 4-methoxyindole-3-methanamine (**17a**)
Carbon disulfide (0.03 ml, 0.5 mmol) was added to the solution of **17a** (41.1 mg, 0.233 mmol) in pyridine (3.0 ml, 37.3 mmol) and Et_3N (2.1 ml, 15.0 mmol) at 0°C, and stirred for 1 h, then MeI (0.03 ml, 0.48 mmol) was added, and stirring was continued at 0°C for additional 1 h. H_2O (10.0 ml) was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a yellow oil. Purification by column chromatography on SiO_2 with CH_2Cl_2 as an eluent afforded **14a**[4] (40.0 mg, 64%). **14a**: Colorless oil. All spectral data were identical with those of natural product.[4c]

4-Iodobrassinin (methyl 4-iodoindol-3-ylmethyldithiocarbamate, **14b**) and methyl *N,N*-bis(4-iodoindol-3-ylmethyl)dithiocarbamate (**19a**) from 3-dimethylaminomethyl-4-iodoindole (**16b**)
MeI (0.26 ml, 4.17 mmol) was added to a stirred solution of **16b** (122.0 mg, 0.407 mmol) in THF (6.0 ml) and stirring was continued at 27°C for 1 h. After evaporation of the solvent *in vacuo*, MeOH (20.0 ml) and 29% NH_4OH (60.0 ml, 921 mmol) were added to the residue and the resultant solution was refluxed for 1 h. After cooling, the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an orange oil. Based on its ^{1}H-nmr spectrum, the oil was found to be a mixture of **17b** and **18b**, but every attempt to isolate **17b** failed due to its strong tendency to dimerize to **18b** during chromatography. Therefore, the oil was immediately dissolved in the mixed solvent of pyridine (10.0 ml, 124 mmol) and triethylamine (3.5 ml, 25 mmol). Carbon disulfide (0.05 ml, 0.83 mmol) was added to the resultant solution and stirring was continued at 0°C for 1 h, and then MeI (0.05 ml, 0.80 mmol) was added. After stirring at 0°C for 1 h, H_2O was added, and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an orange oil. Column chromatography was performed on SiO_2 with ether-hexane (3:1, v/v) as an eluent. **14b** (64.7 mg, 44%) was obtained from the early part of the fractions, and **19a** (43.0 mg, 34%) from the later part of the fractions. **14b**: mp 134.0-135.0°C (decomp., colorless prisms, recrystallized from CH_2Cl_2-hexane). Ir (KBr): 3310, 3270, 1503, 1418, 1386, 1331, 1246, 1089, 1035, 925, 899, 774, 742 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 25°C, rotational isomers existed) δ : 2.62 (12/5H, s), 2.73 (3/5H, s), 4.97 (2/5 H, d, J=4.9 Hz), 5.19 (8/5H, d, J=4.9 Hz), 6.92 (1H, t, J=8.1 Hz), 7.32

(1/5H, br s), 7.39 (1H, d, J=8.1 Hz), 7.43 (4/5H, br s, NH), 7.44 (1H, d, J=2.4 Hz), 7.62 (1H, d, J=8.1 Hz), 7.89 (1/5H, br s, NH), 8.24 (4/5H, br s). Ms *m/z*: 362 (M^+). *Anal.* Calcd for $C_{11}H_{11}IN_2S_2$: C, 36.47; H, 3.06; N, 7.73. Found: C, 36.48; H, 3.03; N, 7.64. **18b**: mp 191.0-191.5°C (pale yellow needles, recrystallized from MeOH-H_2O). Ir (KBr): 3375, 1613, 1538, 1413, 1324, 1173, 1081, 1035, 829, 758, 744, 734 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.18 (4H, s), 6.79 (2H, t, J=7.9 Hz), 7.36 (2H, s), 7.37 (2H, dd, J=7.9 and 0.9 Hz), 7.43 (2H, dd, J=7.9 and 0.9 Hz). Ms *m/z*: 527 (M^+). *Anal.* Calcd for $C_{18}H_{15}I_2N_3$: C, 41.01; H, 2.87; N, 7.97. Found: C, 40.93; H, 2.97; N, 7.66. **19a**: mp 153.0-154.0°C (decomp., colorless prisms, recrystallized from MeOH-H_2O). Ir (KBr): 3350, 1613, 1547, 1478, 1408, 1328, 1274, 1229, 1184, 1155, 1039, 893, 760, 725 cm^{-1}. ^{1}H-Nmr (d_6-DMSO) δ : 2.60 (3H, s), 5.45 (2H, s), 5.69 (2H, s), 6.83 (2H, t, J=7.5 Hz), 7.11 (1H, s), 7.26 (1H, s), 7.39-7.46 (4H, m). Anal. Calcd for $C_{20}H_{17}I_2N_3S_2$: C, 38.91; H, 2.78; N, 6.81. Found: C, 38.99; H, 2.96; N, 6.62.

4-Nitrobrassinin (methyl 4-nitroindol-3-ylmethyldithiocarbamate, **14c**) and methyl *N,N*-bis(4-nitroindol-3-ylmethyl)dithiocarbamate (**19b**) from 3-dimethylaminomethyl-4-nitroindole (**7**)

MeI (1.40 ml, 22.4 mmol) was added to a stirred solution of **7** (473.2 mg, 2.161 mmol) in THF (20.0 ml) and stirring was continued at 25°C for 2 h. After evaporation of the solvent *in vacuo*, MeOH (50.0 ml) and 29% NH_4OH (150.0 ml, 2.30 mol) were added to the residue and the resultant solution was refluxed for 1 h. After cooling, the whole was extracted with CH_2Cl_2. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a brown solid which was dissolved in the mixed solvent of pyridine (30.0 ml, 373 mmol) and Et_3N (10.0 ml, 71.7 mmol). Carbon disulfide (0.20 ml, 3.32 mmol) was added to the resultant solution and stirring was continued at 0°C for 1 h, and then MeI (0.20 ml, 3.21 mmol) was added. After stirring at 0°C for 1 h, H_2O was added, and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown oil. Column chromatography was performed repeatedly on SiO_2 with CH_2Cl_2 or CH_2Cl_2-MeOH (99:1, v/v) as eluents. In the order of increasing polarity, **9** (14.1 mg, 4%), **24** (16.6 mg, 4%), **14c** (248.2 mg, 41%), and **19b** (62.1 mg, 13%) were obtained. **14c**: mp 154.0-155.0°C (decomp., yellow prisms, recrystallized from MeOH-H_2O). Ir (KBr): 3325, 3155, 1511, 1496, 1362, 1320, 1296, 1118, 1082, 1056, 924, 731 cm^{-1}. ^{1}H-Nmr (CD_3OD,

25°C, *rotational isomers existed*) δ : 2.57 (18/7H, s), 2.64 (3/7H, s), 4.94 (2/7H, s), 5.11 (12/7H, s), 7.25 (1H, t, J=8.1 Hz), 7.56 (1H, s), 7.76 (1H, d, J=8.1 Hz), 7.93 (1H, d, J=8.1 Hz). Ms *m/z*: 281 (M^+). *Anal.* Calcd for $C_{11}H_{11}N_3O_2S_2$: C, 46.96; H, 3.94; N, 14.94. Found: C, 47.10; H, 3.86; N, 15.06. **19b**: mp 170.0-171.0°C (orange prisms, recrystallized from MeOH). Ir (KBr): 3360, 1658, 1510, 1477, 1411, 1361, 1323, 1268, 1231, 1160, 1115, 1045, 798, 727 cm^{-1}. ^{1}H-Nmr (d_6-DMSO) δ : 2.61 (3H, s), 5.28 (2H, s), 5.52 (2H, s), 7.24 (1H, t, J=6.9 Hz), 7.26 (1H, t, J=6.9 Hz), 7.32 (1H, s), 7.39 (1H, s), 7.79-7.85 (4H, m). Ms *m/z*: 455 (M^+). *Anal.* Calcd for $C_{20}H_{17}N_5O_4S_2$: C, 52.74; H, 3.76; N, 15.37. Found: C, 52.49; H, 3.98; N, 15.09.

An attempt to isolate 4-nitroindole-3-methanamine (**17d**) and bis(4-nitroindol-3-ylmethyl)amine (**18d**) from 3-dimethylaminomethyl-4-nitroindole (**7**) MeI (0.26 ml, 4.17 mmol) was added to a stirred solution of **7** (88.3 mg, 0.403 mmol) in THF (8.0 ml) and stirring was continued at 30°C for 1 h. After evaporation of the solvent *in vacuo*, MeOH (20.0 ml) and 29% NH_4OH (60.0 ml, 921 mmol) were added to the residue and the resultant solution was refluxed for 2 h. After cooling, the whole was extracted with CH_2Cl_2. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a brown oil, which was subjected to column chromatography repeatedly on SiO_2 with CH_2Cl_2-MeOH-29% NH_4OH (100:15:1.5, v/v) as an eluent. In the order of increasing polarity, **9** (7.7 mg, 12%), **24** (7.6 mg, 9%), **18d** (6.4 mg, 9%), and **17d** (31.9 mg, 41%) were obtained. **17d** was unstable and collapsed to **18d** and tars during chromatography and/or handling. Further attempts to characterize **17d** are in progress. **17d**: mp 122.0-123.5°C (crystallized by MeOH-CH_2Cl_2, orange crystals). Ir (KBr): 3360, 1558, 1510, 1503, 1358, 1317, 1287, 936, 784, 734 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.06 (2H, s), 7.24 (1H, t, J=7.8 Hz), 7.53 (1H, s), 7.75 (1H, d, J=7.8 Hz), 7.92 (1H, d, J=7.8 Hz). High resolution ms *m/z*: Calcd for $C_9H_9N_3O_2$: 191.0692. Found: 191.0686. **18d**: mp 174.0-176.0°C (dark orange prisms, crystallized from MeOH-CH_2Cl_2). Ir (KBr): 3350, 1555, 1507, 1354, 1318, 1289, 730 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.13 (4H, s), 7.23 (2H, t, J=8.4 Hz), 7.55 (2H, s), 7.76 (2H, dd, J=8.4 and 1.1 Hz), 7.91 (2H, dd, J=8.4 and 1.1 Hz). **18d** were relatively unstable compound and M^+ peak was not observed in its mass spectrum.

4-Methoxyindole-3-acetonitrile (**20**) from 3-dimethylaminomethyl-4-methoxyindole (**16a**)

KCN (206.7 mg, 3.174 mmol) was added to the solution of **16a** (59.0 mg, 0.289 mmol) in DMF (2.0 ml) and H_2O (2.0 ml) and heated at reflux for 1 h. H_2O was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a yellow oil. Purification by p-tlc on SiO_2 with AcOEt-hexane (1:2, v/v) afforded **20** (46.0 mg, 86%). **20**: mp 145.0-146.0°C (colorless prisms, recrystallized from $CHCl_3$-hexane, lit.,[12] mp 136°C, lit.,[11] mp 141-142°C). Spectral data were identical with the reported ones. Ir (KBr): 3360, 2270, 1617, 1590, 1509, 1355, 1260, 1091, 752, 733 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 3.92 (3H, s), 4.05 (2H, d, J=1.0 Hz), 6.50 (1H, d, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz), 7.09 (1H, t, J=1.0 Hz), 7.12 (1H, t, J=8.0 Hz), 8.08 (1H, br s). Ms *m/z*: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.98; H, 5.41; N, 15.11.

Preparation of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline[13] (**21**)

1) A solution of 4-nitroindole-3-acetonitrile[8b] (**23**, 50.8 mg, 0.253 mmol) in AcOEt (10.0 ml) was hydrogenated over 10% Pd/C (53.4 mg) at 69-73°C and 78-80 atm for 7 h. After removal of the catalyst by filtration, the solvent was evaporated off under reduced pressure to leave a crystalline solid, which was subjected to column chromatography on SiO_2 with ether-benzene (1:9, v/v) as an eluent. From the early part of the fractions, **21** (22.7 mg, 57%) was obtained. From the later part of the fractions, 4-aminoindole-3-acetonitrile[8b] (17.4 mg, 40%) was obtained. **21**: mp 135.0-136.0°C (colorless prisms, recrystallized from ether-hexane, lit.,[13] mp 132.5-133.5°C). Spectral data were identical with the reported ones. Ir (KBr): 3310, 3150, 1611, 1510, 1322, 1067, 1038, 731 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 3.02 (2H, dt, J=1.0 and 5.7 Hz), 3.47 (2H, t, J=5.7 Hz), 6.23 (1H, d, J=7.5 Hz), 6.71 (1H, br s), 6.72 (1H, t, J=7.5 Hz), 6.96 (1H, t, J=7.5 Hz), 7.78 (1H, br s). Ms *m/z*: 158 (M^+).

2) A solution of 4-aminoindole-3-acetonitrile[8b] (15.4 mg, 0.09 mmol) in AcOEt (10.0 ml) was hydrogenated over 10% Pd/C (10.1 mg) at 70-76°C and 90-95 atm for 8 h. After removal of the catalyst by filtration, the solvent was evaporated off under reduced pressure to leave a crystalline solid. Purification by column chromatography on SiO_2 with ether-benzene (1:9, v/v) as an eluent afforded 3.0 mg (21%) of **21**. Further elution with the same solvent afforded unreacted starting material (10.9 mg, 71%).

3) A solution of 4-nitro-3-(2-nitrovinyl)indole[5] (**22**, 50.5 mg, 0.21 mmol) in AcOEt (10.0 ml) was hydrogenated over 10% Pd/C (52.4 mg) at 70-76°C

and 61-69 atm for 7 h. After usual work-up and purification by column chromatography, as described above, 11.6 mg (35%) of **21** was obtained.
4) A solution of 4-azido-3-(2-nitrovinyl)indole[5] (50.0 mg, 0.218 mmol) in AcOEt (15.0 ml) was hydrogenated over 10% Pd/C (52.3 mg) at 70-76°C and 69-70 atm for 7 h. After usual work-up and purification by column chromatography, as described above, 6.6 mg (19%) of **21** was obtained.

4-Nitroindole-3-acetonitrile (**23**) from 4-nitroindole-3-carboxaldehyde (**6**) Table V, Entry 2: $NaBH_4$ (9.6 mg, 0.25 mmol) was added to the solution of **6** (40.0 mg, 0.21 mmol) in MeOH (4.0 ml) at room temperature. After stirring at room temperature for 1 h, NaCN (104.6 mg, 2.13 mmol) was added and the whole was heated at reflux for 5 h. Brine was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave crystalline solid, which was subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent. From the early part of the fractions, 4-nitroindole (**9**, 19.1 mg, 56%) was obtained. From the middle part of the fractions, **23** (14.7 mg, 35%) was obtained. From the later part of the fractions, 3-methoxymethyl-4-nitroindole (**24**, 1.8 mg, 4%) was obtained. **23**: mp 204.5-205.0 °C (yellow prisms, recrystallized from MeOH). Ir (KBr): 3390, 2225, 1633, 1515, 1316, 1110, 802, 728 cm^{-1}. ^{1}H-Nmr (CD_3OD) δ : 4.11 (2H, s), 7.29 (1H, t, J=8.0 Hz), 7.61 (1H, s), 7.79 (1H, dd, J=8.0 and 1.0 Hz), 7.96 (1H, dd, J=8.0 and 1.0 Hz). Ms *m/z*: 201 (M^+). *Anal.* Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.85; H, 3.58; N, 20.94. **24**: mp 104.5-105.5 °C (dark yellow prisms, recrystallized from CH_2Cl_2-hexane). Ir (KBr): 3173, 1620, 1513, 1503, 1376, 1313, 1069, 892, 728 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 3.43 (3H, s), 4.75 (2H, s), 7.25 (1H, t, J=8.3 Hz), 7.44 (1H, br d, J=2.4 Hz), 7.63 (1H, d, J=8.3 Hz), 7.88 (1H, d, J=8.3 Hz), 8.55 (1H, br s). Ms *m/z*: 206 (M^+). *Anal.* Calcd for $C_{10}H_{10}N_2O_3 \cdot 1/6H_2O$: C, 57.42; H, 4.98; N, 13.39. Found: C, 57.53; H, 4.76; N, 13.41.

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