Synthesis of analogs of wasabi phytoalexin (methyl 1-methoxyindole-3-carboxylate)

SYNTHESIS OF ANALOGS OF WASABI PHYTOALEXIN (METHYL 1-METHOXYINDOLE-3-CARBOXYLATE)[1]

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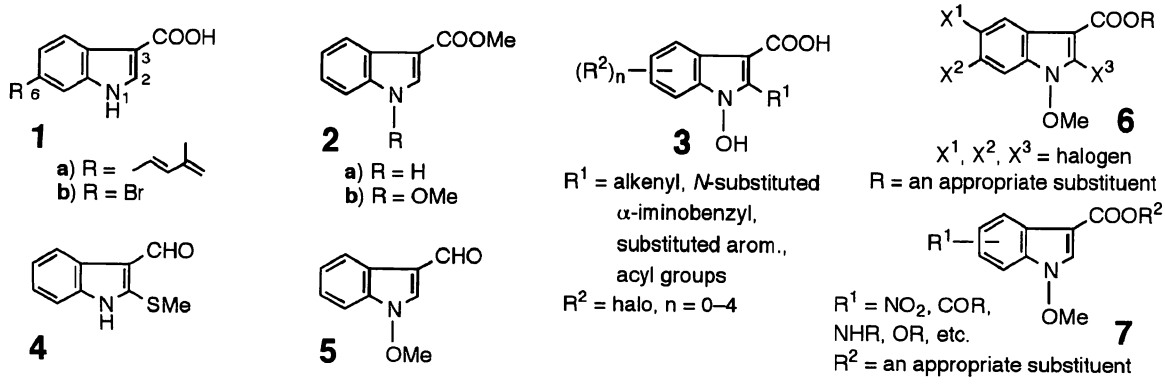
Abstract — Syntheses of wasabi phytoalexin analogs, such as 6-bromo-5-iodo, 2-bromo-5-iodo, 6-nitro, 5-chloroacetyl, and 6-chloroacetyl congeners, are reported. An interesting effect of the 1-methoxy group on the regioselectivity of electrophilic substitution reactions on indole nucleus is observed.

Indoles having a carboxy or a formyl group at the 3-position, including 1-hydroxy- or 1-methoxyindole derivatives, exhibit marked physiological activities in spite of their simple chemical structures.[2] Compounds (**1–3**)[2a-d] are a few representative examples (Scheme 1). Brassicanal A[3] (**4**) and 1-methoxyindole-3-carbaldehyde[3a] (**5**) are additional examples isolated by Takasugi[3] and co-workers as phytoalexins of plant family, *Cruciferae*. Recently, Pedras[4] and co-workers determined methyl 1-methoxyindole-3-carboxylate (**2b**) as a phytoalexin of Wasabi (*Wasabia japonica*, syn. *Eutrema wasabi*).
We have been much interested in determining the effect of 1-methoxy and 1-hydroxy groups on both the chemical reactivities[5] and biological activities[6] of indole compounds, aiming at preparing our own biologically active substances. From these points of view, we needed various kinds of analogs[7] of wasabi phytoalexin like **6** and **7** as shown in general formula.

Figure 1



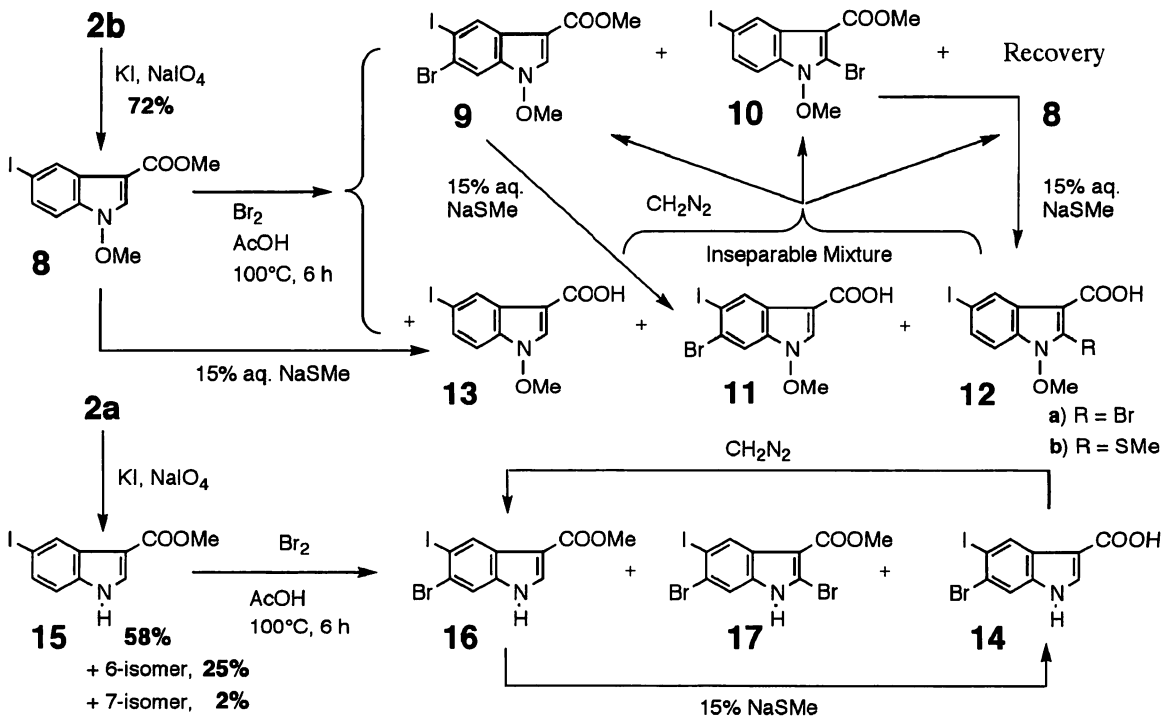
In the previous papers,[7] we established simple synthetic method for **2b** and its regioselective iodination to give methyl 5-iodo-1-methoxyindole-3-carboxylate[7a] (**8**). Based on these results, synthesis of methyl 6-bromo-5-iodo-1-methoxyindole-3-carboxylate (**9**), a representative of **6**, seemed to be easy. In fact, however, bromination of **8** gave complex mixtures of products under various reaction conditions.

Relatively clean reaction took place with Br_2 (1.3 mol eq.) in AcOH at 100°C to provide **9**, methyl 2-bromo-5-iodo-1-methoxyindole-3-carboxylate (**10**), 6-bromo- (**11**), 2-bromo-5-iodo-1-methoxyindole-3-carboxylic acid (**12a**), and 5-iodo-1-methoxyindole-3-carboxylic acid (**13**) in 17, 33, 6, 5, and 7% yields, respectively, together with 16% yield of unreacted **8**. Since the carboxylic acids (**11**, **12a**, and **13**) were inseparable, the mixture was methylated with diazomethane (CH_2N_2) to give **9**, **10**, and **8** in 6, 5, and 7% yields, respectively. Assuming that the methylation proceeded in a quantitative yield, the yields of **11**, **12a**, and **13** in the initial bromination products were estimated. Pure compound (**13**) was obtained in 38% yield by reacting **8** with 15% aq. NaSMe. Under similar reaction conditions, **9** provided **11** and **14** in 45 and 38% yields, respectively. In the same reaction of **10**, the expected compound (**12a**) was not produced at all, instead nucleophilic substitution reaction by methyl sulfide occurred at the 2-position to afford **12b** in 83% yield. As a result, pure **12a** has not been obtained yet.

On the other hand, bromination (1.3 mol eq.) of methyl 5-iodoindole-3-carboxylate (**15**) in AcOH at 100°C provided methyl 6-bromo- (**16**), 2,6-dibromo-5-iodoindole-3-carboxylate (**17**), and 6-bromo-5-iodoindole-3-carboxylic acid (**14**) in 48, 8, and 17% yields, respectively. In the same reaction, when 0.85 mol eq. of bromine was employed, **16** and **14** were produced in 56 and 18% yields, respectively, without formation of **17**. The structure of **14** was confirmed by the direct comparison with the sample obtained in 92% yield by the treatment of **16** with 15% NaSMe under reflux. Furthermore, methylation of **14** with CH_2N_2 in MeOH provided **16** in 90% yield.

Above results exhibited that the bromination of **15** proceeds regioselectively at the 6-position, while the

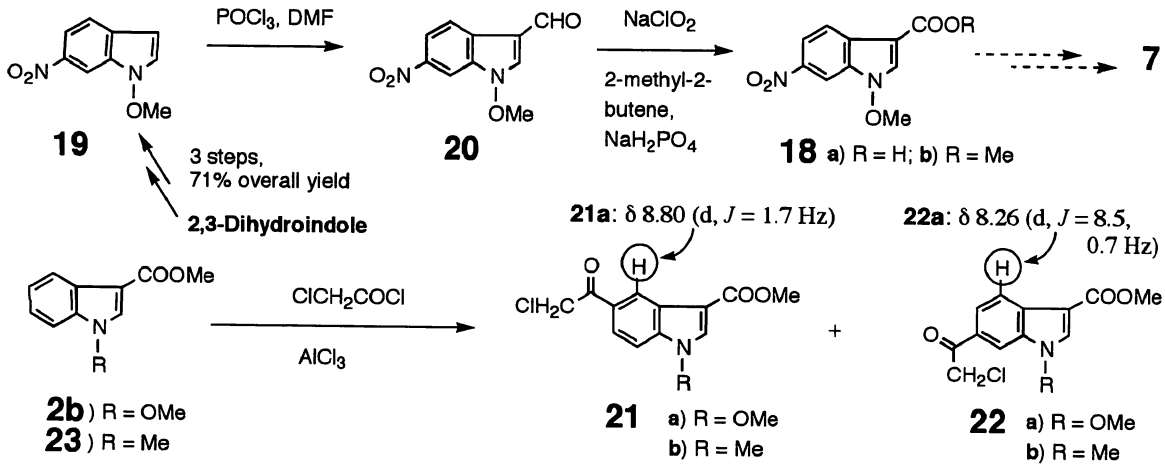
Scheme 1



introduction of methoxy group into the 1-position of **15** alters the reaction site and tends to favor the 2-po- sition. These observations are quite interesting considering the initial iodination of **2a** and **2b**. Thus, **2b** produced **8** exclusively in 72% yield,[7a] while **2a** afforded **15** together with 6- and 7-iodo isomers in 58, 25, and 2% yields.[7a] Further reaction examples would be needed for clarifying the effect of 1-methoxy group on the regioselectivity of electrophilic substitution reactions.

We next tried the preparation of methyl 1-methoxy-6-nitroindole-3-carboxylate (**18b**, Scheme 2) as a common intermediate for **7**, because the nitro group can easily be transformed into other functional groups such as amino, halogen, hydroxy, etc. According to our procedure,[8] 1-methoxy-6-nitroindole (**19**) was prepared from an industrial raw material, 2,3-dihydroindole, in three steps in 71% overall yield. Subsequent Vilsmeier reaction of **19** with $POCl_3$ and *N*,*N*-dimethylformamide provided a 94% yield of 1-methoxy-6-nitroindole-3-carbaldehyde (**20**), an analog of daikon phytoalexin[3a] (**5**). Oxidation of **20** to 1-methoxy-6-nitroindole-3-carboxylic acid (**18a**) was achieved in 92% yield by the treatment with $NaClO_2$[9] in the presence of 2-methyl-2-butene. Methylation of **18a** with CH_2N_2 in MeOH provided the desired **18b** in 99% yield.

Scheme 2



For the preparation of wasabi phytoalexin analogs having an acyl group, direct acylation of **2b** was examined. Thus, Friedel-Crafts acylation using chloroacetyl chloride and $AlCl_3$ in nitrobenzene at 100°C provided cleanly methyl 5-chloroacetyl- (**21a**) and 6-chloroacetyl-1-methoxyindole-3-carboxylate (**22a**) in 52 and 20% yields, respectively, and the ratio of **21a** to **22a** was 2.5:1. The acylated position of **21a** is determined by the presence of C4-H signal at 8.80 ppm (d, *J*=1.7 Hz) in its ^{1}H-NMR spectrum, while the corresponding C4-H signal of **22a** is observed at 8.26 ppm (d, *J*=8.5, 0.7 Hz) proving the 6-substituted indole structure.

Similar results were already reported by Nakatsuka[10] and co-workers in the chloroacetylation of methyl 1-methylindole-3-carboxylate (**23**). In their experiment, however, **21b** and **22b** were obtained as an

inseparable mixture. Based on the ratio of the following Baeyer-Villiger oxidation products, the ratio of **21b** to **22b** could be estimated to be 3:1. Similar Friedel-Crafts acylation of indoles having an electron withdrawing group has been reported by several researchers. [11] Comparing these results, it would be safe to say that the introduction of a methoxy group into the 1-position prefers the 6-substitution to 5-substitution in Friedel-Crafts acylation.

In conclusion, introduction of a methoxy group into the 1-position is found to influence significantly the regiochemistry of electrophilic substitution reactions on indole nucleus. With key building blocks such as **9**, **10**, **15**, **18**, **21a**, and **22a** in hand, preparations of various kinds of wasabi phytoalexin analogs are now in progress to conduct structure-activity relationship study.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrophotometer, and ^{1}H-NMR spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

Methyl 6-Bromo- (9), 2-Bromo-5-iodo-1-methoxyindole-3-carboxylate (10), 6-Bromo- (11), 2-Bromo- (12a), and 5-iodo-1-methoxyindole-3-carboxylic acid (13) from Methyl 5-Iodo-1-methoxyindole-3-carboxylate (8) — A solution of Br_2 (3.8 mL, 0.76 mmol) in AcOH was added to a solution of **8** (192.7 mg, 0.58 mmol) in AcOH (10mL) and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$-MeOH (9:1, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with $CHCl_3$-hexane (1:1, v/v) and then with $CHCl_3$ to give **10** (80 mg, 33%), **9** (40.7 mg, 17%), **8** (30.1 mg, 16%), and a mixture fraction (**11**, **12a**, and **13**, 45.6 mg) in the order of elution. **9**: mp 142.5—143.0°C (colorless fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1695, 1517, 1446, 1205 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s), 4.14 (3H, s), 7.79 (1H, s), 7.90 (1H, s), 8.69 (1H, s). MS *m/z*: 410 (M^+: Br^{81}), 408 (M^+: Br^{79}). *Anal.* Calcd for $C_{11}H_9NO_3BrI$: C, 32.22; H, 2.21; N, 3.42. Found: C, 32.28; H, 2.22; N, 3.43. **10**: mp 158—159°C (colorless fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1722, 1498, 1195, 1178, 1016 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s), 4.14 (3H, s), 7.22 (1H, d, *J*=8.5 Hz), 7.59 (1H, dd, *J*=8.5, 1.5 Hz), 8.50 (1H, d, *J*=1.5 Hz). MS *m/z*: 410 (M^+: Br^{81}), 408 (M^+: Br^{79}). *Anal.* Calcd for $C_{11}H_9NO_3BrI \cdot 1/2H_2O$: C, 31.53; H, 2.17; N, 3.34. Found: C, 31.21; H, 2.19; N, 3.28. Pure samples, (**11**) and (**13**), were obtained from **9** and **8**, respectively, by the reaction with 15% aq. NaSMe as shown below.

Separation of 11, 12a, and 13 as Methylated Products, (9), (10), and (8) — Excess CH_2N_2 in Et_2O was added to a solution of the mixture fraction (**11**, **12a**, and **13**, 45.6 mg), obtained in the above experiment, in MeOH (5.0 mL) and the whole was stirred at rt for 10 min. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$-hexane (1:2, v/v) to give **10** (11.9 mg, 5%), **9** (14.0 mg, 6%), and **8** (12.6 mg, 7%).

6-Bromo-5-Iodo-1-methoxyindole-3-carboxylic acid (11) and 14 from 9 — Excess 15% aq. NaSMe (8 mL) was added to a solution of **9** (51.8 mg, 0.13 mmol) in MeOH (3 mL) and the mixture was refluxed for 2 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic (pH 1) by adding 8% HCl and extracted with EtOAc. The extract 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 $CHCl_3$-MeOH-AcOH (46:1:0.1, v/v) to give **11** (22.5 mg, 45%) and **14** (17.8 mg, 38%) in the order of elution. **11**: mp 275—280°C (decomp, colorless fine needles, recrystallized from $CHCl_3$-MeOH). IR (KBr): 1658, 1520, 1217 cm^{-1}. ^1H-NMR (5% CD_3OD in $CDCl_3$) δ: 4.14 (3H, s), 7.80 (1H, s), 7.93 (1H, s), 8.71 (1H, s). MS *m/z*: 397 (M^+: Br^{81}), 395 (M^+: Br^{79}). *Anal.* Calcd for $C_{10}H_7NO_3BrI$: C, 30.33; H, 1.78; N, 3.54. Found: C, 30.54; H, 1.85; N, 3.52.

5-Iodo-1-methoxy-2-methylthioindole-3-carboxylic acid (12b) from 10 — Excess 15% aq. NaSMe (2 mL) was added to a solution of **10** (23.8 mg, 0.06 mmol) in MeOH (2 mL) and the mixture was refluxed for 1 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with EtOAc-MeOH (9:1, v/v). The extract 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 $CHCl_3$-MeOH-AcOH (46:1:0.5, v/v) to give **12b** (17.4 mg, 83%). **12b**: mp 167—168°C (decomp, colorless fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1668, 1492, 1205 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.68 (3H, s), 4.16 (3H, s), 7.21 (1H, dd, *J*=8.5, 0.7 Hz), 7.61 (1H, dd, *J*=8.5, 1.5 Hz), 8.62 (1H, dd, *J*=1.5, 0.7 Hz). High-Resolution MS *m/z*:: Calcd for $C_{11}H_{10}NO_3IS$: 362.9426. Found: 362.9429.

5-Iodo-1-methoxyindole-3-carboxylic acid (13) from 8 — Excess 15% aq. NaSMe (5.0 mL) was added to a solution of **8** (32.2 mg, 0.9 mmol) in MeOH (2 mL) and the mixture was refluxed for 1 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with EtOAc-MeOH (95:5, v/v). The extract 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 $CHCl_3$-MeOH-AcOH (46:1:0.1, v/v) to give **13** (11.7 mg, 38%). **13**: mp 211—213°C (colorless fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1670, 1525, 1220 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 4.13 (3H, s), 7.42 (1H, d, *J*=8.6 Hz), 7.58 (1H,dd, *J*=8.6, 1.7 Hz), 8.35 (1H, s), 8.39 (1H, d, *J*=1.7 Hz). MS *m/z*: 317 (M^+). *Anal.* Calcd for $C_{10}H_8NO_3I \cdot 1/2\ H_2O$: C, 36.83; H, 2.78; N, 4.30. Found: C, 36.95; H, 2.57; N, 4.35.

Methyl 6-Bromo- (16), 2,6-Dibromo-5-iodoindole-3-carboxylate (17), and 6-Bromo-5-iodoindole-3-carboxylic acid (14) from 15 — [**Method 1**] A solution of Br_2 (2.2 mL, 0.43 mmol) in AcOH was added to a solution of **15** (100.8 mg, 0.33 mmol) in AcOH (5.0 mL), and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$-MeOH (9:1, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with acetone-benzene (1:9, v/v) and then with CH_2Cl_2-hexane (2:1, v/v) to give **17** (12.7 mg, 8%), **16** (61.5 mg, 48%), and **14** (20.5 mg, 17%) in the order of elution. **16**:

mp 262.5—263°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3270, 1677, 1520, 1441, 1198, 1053 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.82 (3H, s), 7.88 (1H, s), 8.12 (1H, s), 8.52 (1H, s), 12.10 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 381 (M^+: Br^{81}), 279 (M^+: Br^{79}). *Anal.* Calcd for $C_{10}H_7NO_2BrI$: C, 31.61; H, 1.86; N, 3.69. Found: C, 31.74; H, 1.73; N, 3.74. **17**: mp 275—277°C (colorless fine needles, recrystallized from $CHCl_3$-MeOH). IR (KBr): 3226, 1681, 1504, 1430, 1382, 1062 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s), 7.74 (1H, s), 8.47 (1H, s), 13.05 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 460 (M^+: 2 x Br^{81}), 458 (M^+: Br^{81}, Br^{79}), 456 (M^+: 2 x Br^{79}). *Anal.* Calcd for $C_{10}H_6NO_2Br_2I \cdot 1/4H_2O$: C, 25.92; H, 1.41; N, 3.02. Found: C, 25.80; H, 1.44; N, 2.95. **14**: mp 224—226°C (decomp, brown prisms, recrystallized from EtOAc-MeOH). IR (KBr): 3249, 1637, 1531, 1186 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.85 (1H, s), 8.02 (1H, s), 8.54 (1H, s), 11.96 (1H, br s, disappeared on addition of D $_2O$). MS *m/z*: 367 (M^+: Br^{81}), 365 (M^+: Br^{79}). *Anal.* Calcd for $C_9H_5NO_2BrI \cdot 1/2H_2O$: C, 28.82; H, 1.61; N, 3.74. Found: C, 28.68; H, 1.51; N,3.67.

[**Method 2**] A solution of Br_2 in AcOH (1.5 mL, 0.30 mmol) was added to a solution of **15** (108.3 mg, 0.36 mmol) in AcOH (5.0 mL), and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After the same work-up and column-chromatography as described in the [**Method 1**], **16** (76.9 mg, 56%) and **14** (23.8 mg, 18%) were obtained.

Methyl 6-Bromo-5-iodoindole-3-carboxylate (16) from 14 — Excess CH_2N_2 in Et_2O was added to a solution of **14** (13.0 mg, 0.036 mmol) in MeOH (10 mL) and the mixture was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$-MeOH (95:5, v/v) to give **16** (12.1 mg, 90%).

6-Bromo-5-iodoindole-3-carboxylic acid (14) from 16 — Excess 15% aq. NaSMe (8.0 mL) was added to a suspension of **16** (50.9 mg, 0.13 mmol) in MeOH (3 mL) and the mixture was refluxed for 2 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with $CHCl_3$-MeOH (9:1, v/v). The extract 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 $CHCl_3$-MeOH (95:5, v/v) to give **14** (45.3 mg, 92%).

1-Methoxy-6-nitroindole-3-carboxylic acid (18a) from 20 — A solution of sodium chlorite (1.186 g, 13.1 mmol) and sodium dihydrogen phosphate (1.535 g, 9.84 mmol) in H_2O (6 mL) was added to a solution of **20** (144.4 mg, 0.66 mmol) and 2-methyl-2-butene (3.0 mL) in DMF (10 mL), and the mixture was stirred at rt for 1.5 h. The whole was made acidic (pH 3) by adding 8% HCl under ice cooling, and extracted with EtOAc. The extract 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 $CHCl_3$-MeOH-AcOH (46:1:0.1, v/v) to give **18a** (143.2 mg, 92%). **18a**: mp 232.5—233°C (pale yellow fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1682, 1516, 1348, 1221 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.23 (3H, s), 8.11 (1H, dd, *J*=9.0, 2.0 Hz), 8.24 (1H, d, *J*=9.0 Hz), 8.46 (1H, d, *J* =2.0 Hz), 8.77 (1H, s). MS *m/z*: 236 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O_5$: C, 50.85; H, 3.41; N, 11.86. Found: C, 50.64; H, 3.40; N, 11.83.

Methyl 1-Methoxy-6-nitroindole-3-carboxylate (18b) from 18a — Excess CH_2N_2 in Et_2O was added to a suspension of **18a** (11.1 mg, 0.047 mmol) in MeOH (2.0 mL) and the mixture was

stirred at rt for 15 min. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed on SiO_2 with $CHCl_3$-hexane (2:1, v/v) to give **18b** (11.6 mg, 99%). **18b**: mp 155.5—156°C (pale yellow fine needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1716, 1514, 1352, 1213 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.94 (3H, s), 4.23 (3H, s), 8.16 (1H, dd, *J*=9.0, 2.0 Hz), 8.18 (1H, s), 8.28 (1H, d, *J*=9.0 Hz), 8.43 (1H, d, *J*=2.0 Hz). MS *m/z*: 250 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O_5 \cdot 1/8H_2O$: C, 52.33; H, 4.09; N, 11.10. Found: C, 52.21; H, 4.05; N, 11.11.

1-Methoxy-6-nitroindole-3-carbaldehyde (20) from 1-Methoxy-6-nitroindole (19) — $POCl_3$ (0.97 mL, 10.4 mmol) was added to dry DMF (5.8 mL, 63 mmol) at 0°C and stirring was continued for 15 min. A solution of **19** (1.00 g, 5.2 mmol) in dry DMF (15 mL) was added to the resultant mixture at 0°C. After stirring at rt for 7 h, H_2O was added to the reaction mixture at 0°C and the whole was made basic (pH 10) by adding sat. aq. $NaHCO_3$. After stirring at rt for 30 min maintaining pH 10 by adding sat. aq. $NaHCO_3$, the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave yellow solid, which was column-chromatographed on SiO_2 with EtOAc-hexane (1:2, v/v) to give **20** (1.08 g, 94%). **20**: mp 180—182°C (yellow prisms, recrystallized from $CHCl_3$-hexane). IR (KBr): 1664, 1653, 1508, 1342 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.28 (3H, s), 8.14 (1H, s), 8.22 (1H, dd, *J*=8.8, 2.0 Hz), 8.43 (1H, d, *J*=8.8 Hz), 8.45 (1H, d, *J*=2.0 Hz), 10.02 (1H, s). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.32; H, 3.61; N, 12.54.

Methyl 5-Chloroacetyl- (21a) and Methyl 6-Chloroacetyl-1-methoxyindole-3-carboxylate (22a) from 2b — Anhydrous $AlCl_3$ (392.7 mg, 2.94 mmol) and then a solution of chloroacetyl chloride (166.1 mg, 1.47 mmol) in nitrobenzene (0.4 mL) was added successively to a solution of **2b** (100.5 mg, 0.49 mmol) in nitrobenzene (1 mL) and the mixture was heated at 100°C for 15 min with stirring. After addition of H_2O with stirring under ice cooling, the solvent was evaporated under reduced pressure. The residue was made basic (pH 11) by adding 8% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with CH_2Cl_2 and $CHCl_3$ to give **22a** (26.9 mg, 20%) and **21a** (71.3 mg, 52%) in the order of elution. **21a**: mp 138—139 °C (pale brown prisms, recrystallized from $CHCl_3$-hexane). IR (KBr): 1700, 1610, 1218, 1178 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 4.18 (3H, s), 4.84 (2H, s), 7.55 (1H, dd, *J*=8.7, 1.0 Hz), 8.01 (1H, dd, *J*=8.7, 1.7 Hz), 8.03 (1H, s), 8.80 (1H, d, *J*=1.7 Hz). MS *m/z*: 283 (M^+: Cl^{37}), 281 (M^+: Cl^{35}). *Anal.* Calcd for $C_{13}H_{12}NO_4Cl \cdot 1/8H_2O$: C, 54.99; H, 4.35; N, 4.96. Found: C, 54.83; H, 4.29; N, 4.84. **22a**: mp 156—158 °C (colorless prisms, recrystallized from $CHCl_3$-hexane). IR (KBr): 1695, 1616, 1437, 1387, 1197 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 4.21 (3H, s), 4.79 (2H, s), 7.85 (1H, dd, *J*=8.5, 1.5 Hz), 8.12 (1H, s), 8.16 (1H, dd, *J*=1.5, 0.7 Hz), 8.26 (1H, dd, *J*=8.5, 0.7 Hz). High Resolution MS *m/z*: Calcd. for $C_{13}H_{12}NO_4Cl$: 283.0425 (M^+: Cl^{37}) and 281.0455 (M^+: Cl^{35}). Found: 283.0427 and 281.0427.

REFERENCES AND NOTES

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