

SYNTHESES OF WASABI PHYTOALEXIN (METHYL 1-METHOXYINDOLE-3-CARBOXYLATE) AND ITS 5-IODO DERIVATIVE, AND THEIR NUCLEOPHILIC SUBSTITUTION REACTIONS ¹

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Abstract — A simple synthetic method for methyl 1-methoxyindole-3-carboxylate, a phytoalexin isolated from *Wasabia japonica*, syn. *Eutrema wasabi*, and its 5-iodo derivative is reported. They underwent nucleophilic substitution reactions selectively at the 2-position.

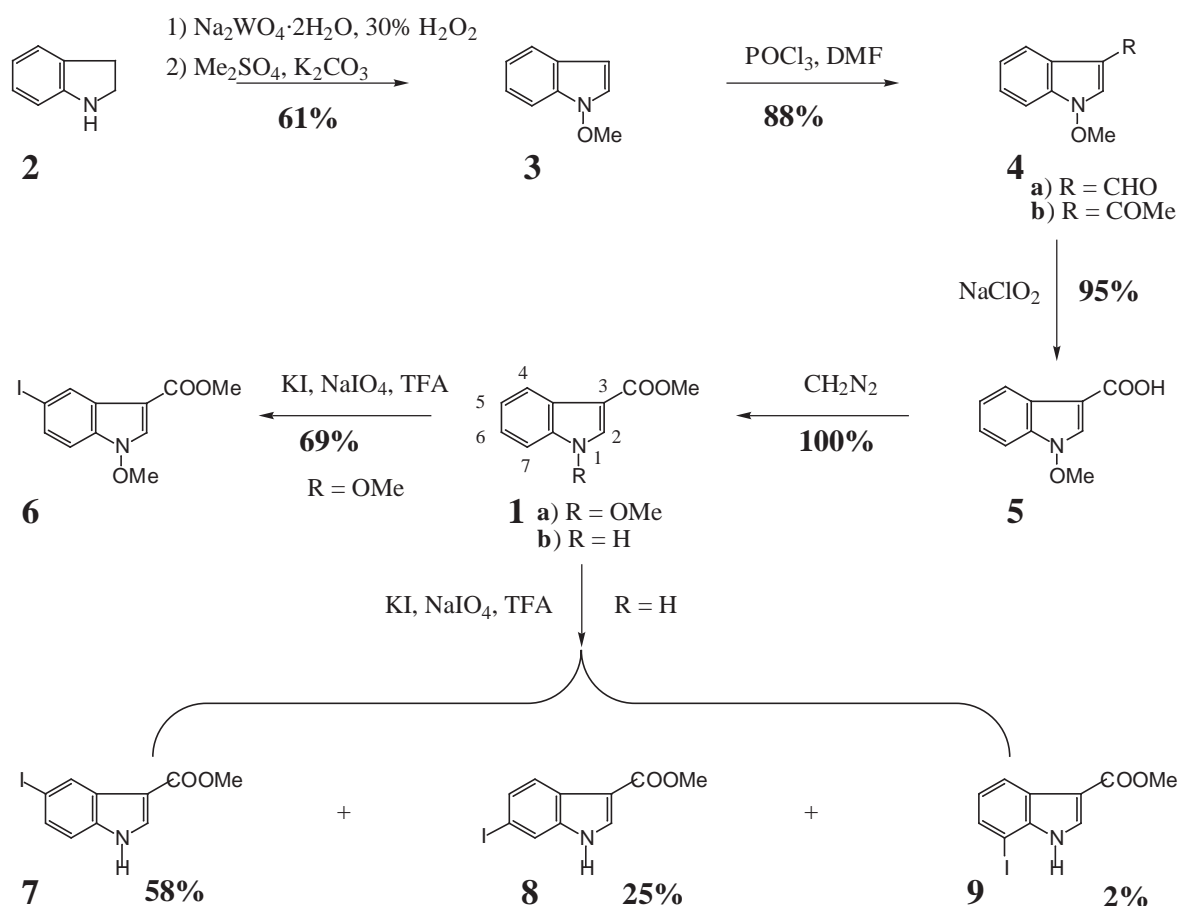
Soledade and co-workers² isolated methyl 1-methoxyindole-3-carboxylate³ (**1a**) from Wasabi (*Wasabia japonica*, syn. *Eutrema wasabi* as a phytoalexin (Scheme 1). They determined its structure by direct comparison with the authentic sample, obtained in 6% overall yield from indoline (**2**) in six steps without characterizing any intermediates at all. In the synthesis, our synthetic method for 1-methoxyindole (**3**) from **2** with NaWO₄·2H₂O and 30% H₂O₂⁴ was applied as a key step.² The compound (**1a**) itself had already been synthesized by Acheson and co-workers³ in ten steps from *o*-nitroaniline in poor overall yield.

We have disclosed that 1-methoxyindoles having electron withdrawing group such as formyl (**4a**)^{3,5} and acetyl⁶ (**4b**) at the 3-position readily undergo nucleophilic substitution reactions⁷ regioselectively at the 2-position. Therefore, we have been much interested in **1a** and **4a,b** for determining whether their reactivities are correlated with antifungal activities or not. In this report, we wish to describe an effective and simple syntheses of **1a**, 1-methoxyindole-3-carboxylic acid (**5**), and 5-iodo derivative (**6**), as well as their nucleophilic substitution reactions comparing with those of **4a,b**.

First, we have succeeded in the synthesis of **1a** from **2** in only five steps with 51% overall yield. Thus, according to our previous report,⁴ 1-methoxyindole-3-carbaldehyde (**4a**), a phytoalexin found by Takasugi^{8a} and co-workers from plant family *Cruciferae*, was prepared in three steps with 54% overall yield from **2**. Further oxidation of **4a** with NaClO₂⁹ was successful to give 95% yield of **5** as stable colorless prisms melting at 173—174°C. These physical data are different from the reported off-white powder melting at 164—165°C (decomp) by Acheson and co-workers.³ Subsequent methylation of **5** with CH₂N₂ provided a quantitative yield of **1a** as stable colorless prisms, mp 45—46°C. These data are not consistent with the reported pink prisms,³ mp 39—40°C, either. These facts show that pure **1a** and **5** are now produced for the first time.

We next examined iodination of **1a** with KI and NaIO₄¹⁰ in TFA-H₂O. It is interesting to note that the desired methyl 5-iodo-1-methoxyindole-3-carboxylate (**6**) was produced predominantly in 69% yield,

Scheme 1



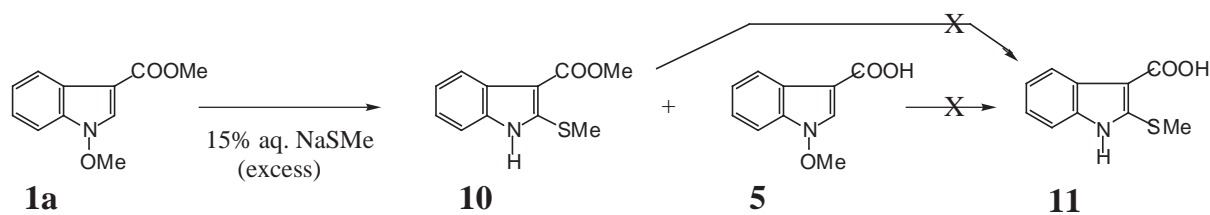
while under similar reaction conditions the iodination of methyl indole-3-carboxylate (**1b**) gave 5-iodo- (**7**), 6-iodo- (**8**), and 7-iodo compound (**9**) in 58, 25, and 2% yields, respectively. The results suggest that the introduction of 1-methoxy group would be an useful means for realizing regioselective electrophilic substitution reactions at the 5-position.

The structure of **6** was proved by comparing its $^1\text{H-NMR}$ spectrum with that of **1a**. The multiplet C(4)-proton of **1a**, readily discernible in the spectrum because of resonating at the lowest field among other proton signals due to the anisotropy effect of the methoxycarbonyl moiety, changed to *meta*-coupled doublet ($J = 2$ Hz) in the spectrum of **6**, proving it to be 5-substituted compound. Similar results were observed in the case of **7**. In the spectrum of **8**, the C(4)-proton is an *ortho*- and *para*-coupled double doublets ($J = 8$ and 0.5 Hz) showing it to be 6-substituted compound. The compound (**9**) is shown to be 7-substituted indole because the C(4)-proton appears as an *ortho*- and *meta*-coupled double doublets ($J = 8$ and 1 Hz).

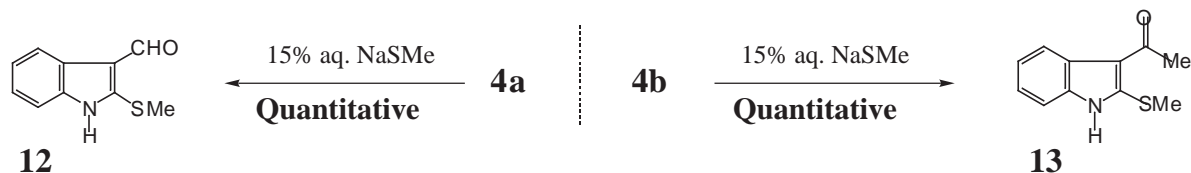
With **1a** and **6** in hand, their nucleophilic substitution reactions were examined. The reaction of **1a** with excess 15% aqueous NaSMe produced methyl 2-methylthioindole-3-carboxylate (**10**) and **5**, and the results are summarized in Table 1. Throughout these experiments, formation of 2-methylthioindole-3-carboxylic acid (**11**) was not observed. These facts indicate that once **5** is formed, it does not undergo nucleophilic substitution reaction, in addition hydrolysis of ester group of **10** to **11** does not occur because

of the resonance-stabilization by the lone pair electrons on the methylthio sulfur atom. Eventually, under the reaction conditions in the Entry 4, **10** was obtained in 70% yield. In contrast, under such milder conditions as refluxing in MeOH for 2 h, **4a** and **4b** reacted with 15% aqueous NaSMe to give brassicanal A^{8a,b} (**12**) and 2-methylthio-3-acetylindole⁶ (**13**) in quantitative yields, respectively.

Table 1



Entry	Solvent	Reaction Conditions		Yield (%) of	
		Temp (°C)	Time (h)	10	5
1	MeOH	reflux	2	0	47
2	MeOH	rt	48	5	94
3	DMF	reflux	3	22	72
4	DMF	60	6	70	29

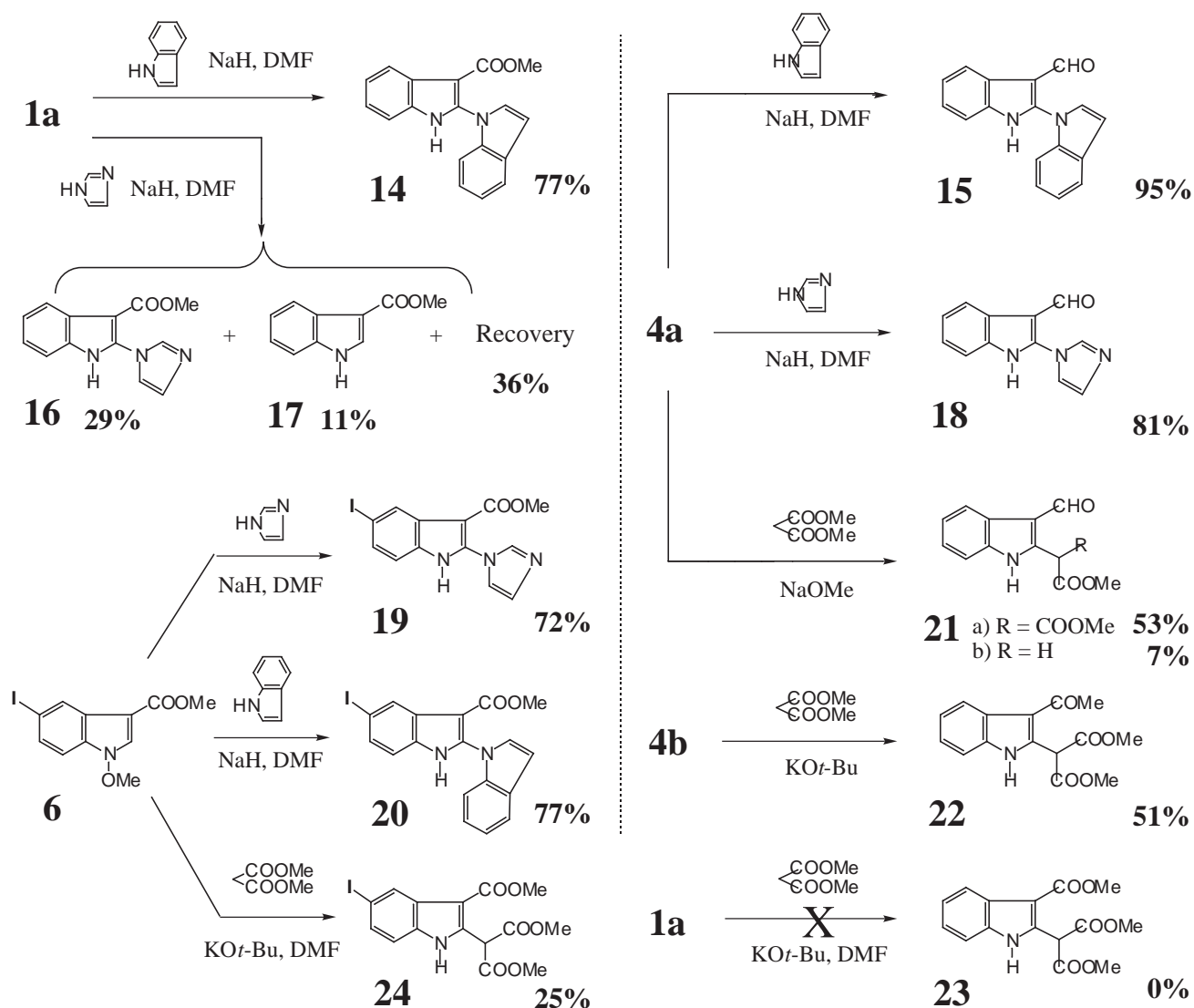


The reaction of **1a** with sodium indolyl in DMF at room temperature afforded methyl 2-(indol-1-yl)indole-3-carboxylate (**14**) in 77% yield, while the similar reaction of **4a** provided 2-(indol-1-yl)indole-3-carbaldehyde⁵ (**15**) in 95% yield (Scheme 2). Sodium imidazolyl reacted with **1a** in DMF at 60°C to afford methyl 2-(imidazol-1-yl)indole-3-carboxylate (**16**), methyl indole-3-carboxylate (**17**) and unreacted **1a** in 28, 11, and 36% yields, respectively. The corresponding reaction of **4a** with sodium imidazolyl provided 2-(imidazol-1-yl)indole-3-carbaldehyde⁵ (**18**) in 81% yield even at room temperature.

Remarkable enhancement in the reactivity of the nucleophilic substitution was observed by the introduction of halogen onto the indole ring. Thus, methyl 2-(imidazol-1-yl)-5-iodoindole-3-carboxylate (**19**) was produced in 72% yield in the reaction of **6** with sodium imidazolyl in DMF at 60°C, in contrast to the yield of 28% in the case of **16** as described above. In the reaction of **6** with the most reactive sodium indolyl, the yield (77%) of methyl 2-(indol-1-yl)-5-iodoindole-3-carboxylate (**20**) was almost the same as that of the corresponding reaction of **1a**.

As reported in the previous papers,^{6,11} sodium dimethylmalonate reacted smoothly with **4a** and **4b** giving **21a,b** and **22**, respectively. On the other hand, the reaction of **1a** with sodium dimethylmalonate did not form the desired **23** under various examined conditions, while similar KO^t-Bu promoted reaction of **6** provided **24** in 25% yield.

Scheme 2



In conclusion, we succeeded in establishing a simple five steps synthetic method for **1a** from **2**. Utilizing the route, **1a** and **5** were obtained in pure state for the first time. Regioselective preparation of 5-iodo derivative (**6**) was also successful. After examining some nucleophilic substitution reactions of 1-methoxyindoles reported in this paper, we have found the order of relative reactivity as $5 < 1a < 6 < 4b < 4a$, which correlates with the electron withdrawing ability of the 3-substituent. Comparisons of these reactivities and antifungal activities are now in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and $^1\text{H-NMR}$ spectra with either a JEOL JNM FX100S or 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.). Preparative thin-layer chromatography

(p-TLC) was performed on Merck Kiesel-gel GF₂₅₄ (Type 60)(SiO₂).

1-Methoxyindole-3-carboxylic acid (5) from 1-Methoxyindole-3-carbaldehyde (4a) — A solution of NaClO₂ (5.233 g, 57.86 mmol) and NaH₂PO₄·2H₂O (6.770 g, 43.40 mmol) in H₂O (30.0 mL) was added to a solution of **4a** (507 mg, 2.89 mmol) in *t*-BuOH (30.0 mL) and 2-methyl-2-butene (30.0 mL) at 0°C and the mixture was stirred for 39 h at rt. After addition of H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃ to give **5** (523 mg, 95%). **5**: mp 173–174°C (colorless prisms, recrystallized from AcOEt–hexane). IR (KBr): 2910 (br), 1664, 1512, 1450, 1325, 1265, 1220, 1085, 1010, 945, 740, 729, 716, 623 cm⁻¹. ¹H-NMR (CDCl₃) δ: 4.18 (3H, s), 7.31 (1H, dt, *J*=1.1, 7.6 Hz), 7.34 (1H, dt, *J*=1.1, 7.6 Hz), 7.49 (1H, dt, *J*=7.6, 1.1 Hz), 8.06 (1H, s), 8.24 (1H, dt, *J*=7.6, 1.1 Hz). MS *m/z*: 191 (M⁺). *Anal.* Calcd for C₁₀H₉NO: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.69; H, 4.75; N, 7.21.

Methyl 1-Methoxyindole-3-carboxylate (1a) from 5 — A solution of diazomethane in ether (30.0 mL) was added dropwise to a solution of **5** (252 mg, 1.32 mmol) in MeOH (8.0 mL) and the mixture was stirred for 1 h at rt. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1, v/v) to give **1a** (268 mg, 99%). **1a**: mp 45–46°C (colorless prisms, recrystallized from CHCl₃). IR (film): 3125, 2990, 1700 (br), 1520, 1490, 1455, 1440, 1375, 1330, 1260, 1210, 1150, 1120, 1088, 1027, 961, 775, 750, 730 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.91 (3H, s), 4.15 (3H, s), 7.28 (1H, dt, *J*=1, 7.8 Hz), 7.32 (1H, dt, *J*=1, 7.8 Hz), 7.46 (1H, dt, *J*=7.8, 1 Hz), 7.96 (1H, s), 8.17 (1H, dt, *J*=7.8, 1 Hz). High-resolution MS *m/z*: Calcd for C₁₁H₁₁NO₃: 205.0742. Found: 205.0739.

Methyl 5-Iodo-1-methoxyindole-3-carboxylate (6) from 1a — KI (607 mg, 3.66 mmol) and NaIO₄ (783 mg, 3.65 mmol) were added to a solution of **1a** (150 mg, 0.73 mmol) in TFA (4.0 mL) and H₂O (1.0 mL) and the mixture was stirred for 24 h at rt. After addition of ice and H₂O, the whole was extracted with CHCl₃–MeOH (9:1, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃ to give **6** (166 mg, 69%). **6**: pale yellow gum. IR (KBr): 1708, 1523, 1453, 1361, 1205, 1084 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.91 (3H, s), 4.13 (3H, s), 7.24 (1H, dd, *J*=8.8, 0.7 Hz), 7.58 (1H, brd, *J*=8.8 Hz), 7.90 (1H, s), 8.52 (1H, brs). High-resolution MS *m/z*: Calcd for C₁₁H₁₀NO₃I: 330.9707. Found: 330.9705.

Methyl 5-Iodo- (7), 6-Iodo- (8), and 7-Iodoindole-3-carboxylate (9) from Methyl indole-3-carboxylate (1b) — KI (1.700 g, 10.2 mmol) and NaIO₄ (2.192 g, 10.2 mmol) were added to a solution of **1b** (300 mg, 1.72 mmol) in TFA (8 mL) and H₂O (3 mL) and the mixture was stirred for 48 h at 20°C. After addition of ice and H₂O, the whole was extracted with CHCl₃–MeOH (9:1, v/v). The extract was washed successively with aq. 10% sodium thiosulfate and brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave solid, which was repeatedly column-chromatographed on SiO₂ with AcOEt–hexane (1:4–2:3, v/v) to give **9** (11 mg, 2%), **8** (131 mg, 25%), and **7** (300 mg, 58%) in the order of elution. **7**: mp 243.0–243.5°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3200, 1676, 1525, 1442, 1192, 1175 cm⁻¹. ¹H-NMR (CDCl₃–CD₃OD, 1:1) δ: 3.89 (3H, s), 7.16 (1H,

d, $J=8.5$ Hz), 7.48 (1H, dd, $J=8.5$, 2 Hz), 7.84 (1H, s), 8.44 (1H, d, $J=2$ Hz). MS m/z : 301 (M^+). *Anal.* Calcd for $C_{10}H_8NO_2I$: C, 39.88; H, 2.67; N, 4.65. Found: C, 39.89; H, 2.59; N, 4.70. **8**: mp 238.0—238.5°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3200, 1670, 1513, 1198, 1050, 802 cm^{-1} . 1H -NMR ($CDCl_3$ - CD_3OD , 9:1) δ : 3.91 (3H, s), 7.48 (1H, dd, $J=8$, 2 Hz), 7.76 (1H, dd, $J=2$, 0.5 Hz), 7.84 (1H, s), 7.88 (1H, dd, $J=8$, 0.5 Hz). MS m/z : 301 (M^+). *Anal.* Calcd for $C_{10}H_8NO_2I$: C, 39.88; H, 2.67; N, 4.65. Found: C, 39.92; H, 2.57; N, 4.63. **9**: mp 154.5—155.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3210, 1675, 1444, 1300, 1190, 780, 720 cm^{-1} . 1H -NMR ($CDCl_3$ - CD_3OD , 9:1) δ : 3.90 (3H, s), 6.98 (1H, dd, $J=8$, 7.4 Hz), 7.60 (1H, dd, $J=7.4$, 1 Hz), 7.96 (total 1H, s and d, $J=3$ Hz), 8.11 (1H, dd, $J=8$, 1 Hz). MS m/z : 301 (M^+). *Anal.* Calcd for $C_{10}H_8NO_2I$: C, 39.88; H, 2.67; N, 4.65. Found: C, 39.69; H, 2.51; N, 4.70.

Methyl 2-Methylthioindole-3-carboxylate (10) from 1a — Excess 15% aqueous sodium thiomethoxide (9.0 mL) was added to a solution of **1a** (62 mg, 0.30 mmol) in DMF (3.0 mL) and the mixture was stirred for 6 h at 60°C. After addition of H_2O , the whole was made acidic by adding aqueous 1N HCl with ice-cooling and extracted with AcOEt. The extract 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 (99:1, v/v) to give **10** (47 mg, 70%) and **5** (17 mg, 29%) in the order of elution. **10**: mp 105—107°C (colorless fine needles, recrystallized from $CHCl_3$ -hexane). IR (KBr): 3300, 1660 (br), 1450, 1200, 1068, 758 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 2.63 (3H, s), 3.96 (3H, s), 7.18 (1H, t, $J=7.8$ Hz), 7.22 (1H, t, $J=7.8$ Hz), 7.32 (1H, d, $J=7.8$ Hz), 8.03 (1H, d, $J=7.8$ Hz), 8.45 (1H, br s). MS m/z : 221 (M^+). *Anal.* Calcd for $C_{11}H_{11}NO_2S \cdot 1/2H_2O$: C, 57.39; H, 5.21; N, 6.08. Found: C, 57.65; H, 5.02; N, 5.96.

Methyl 2-(Indol-1-yl)indole-3-carboxylate (14) from 1a — A solution of indole (19 mg, 0.16 mmol) in anhydrous DMF (2.0 mL) was added to 60% NaH (4.8 mg, 0.12 mmol) with ice-cooling and the mixture was stirred for 15 min at rt. To the resultant solution, a solution of **1a** (17 mg, 0.08 mmol) in anhydrous DMF (1.0 mL) was added and the mixture was stirred for 16 h at rt. After addition of H_2O , 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, which was column-chromatographed on SiO_2 with $CHCl_3$ -hexane (1:1, v/v) to give **14** (18 mg, 77%). **14**: mp 159—160°C (colorless prisms, recrystallized from $CHCl_3$ -hexane). IR (KBr): 3210, 1658, 1560, 1465, 1442, 1204, 1141, 1090 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 3.76 (3H, s), 6.72 (1H, dd, $J=3.4$, 0.7 Hz), 7.20 (1H, dt, $J=1.7$, 7.1 Hz), 7.24 (1H, dt, $J=1.7$, 7.1 Hz), 7.33—7.36 (2H, m), 7.37—7.40 (2H, m), 7.43 (1H, d, $J=3.4$ Hz), 7.68 (1H, dd, $J=7.1$, 1.7 Hz), 8.24—8.26 (1H, m), 8.71 (1H, br s, disappeared on addition of D_2O). MS m/z : 290 (M^+). *Anal.* Calcd for $C_{18}H_{14}N_2O_2 \cdot 1/3H_2O$: C, 72.97; H, 4.95; N, 9.46. Found: C, 72.74; H, 4.84; N, 9.41.

Methyl 2-(Imidazol-1-yl)indole-3-carboxylate (16) from 1a — A solution of imidazole (80 mg, 1.17 mmol) in anhydrous DMF (2.0 mL) was added to 60% NaH (21 mg, 0.88 mmol) with ice-cooling and the mixture was stirred for 15 min at rt. To the resultant solution, a solution of **1a** (60 mg, 0.29 mmol) in anhydrous DMF (3.0 mL) was added and the mixture was stirred for 25 h at 60°C. After addition of H_2O , 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 solid, which was recrystallized from MeOH to

give **16** (15 mg). Mother liquor was subjected to p-TLC on SiO₂ with CHCl₃–MeOH (95:5, v/v) as a developing solvent. Under UV light, three bands were detected. Extraction of the band (*R_f* value: 0.96—0.80) with CHCl₃–MeOH (9:1, v/v) afforded unreacted **1a** (21 mg, 36%). Extraction with the same solvent as above, 5.6 mg (11%) of **1b** was obtained from the band (*R_f* value: 0.68—0.50). Similarly, further crop of **16** (5 mg) was obtained from the band (*R_f* value: 0.29—0.18). Total yield of **16** was 20 mg (28%). **16**: mp 265—266°C (colorless needles, recrystallized from MeOH). IR (KBr): 1691, 1460, 1345, 1215, 1060, 745, 720 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 3.75 (3H, s), 7.11 (1H, s), 7.24 (1H, dt, *J*=1.2, 7.3 Hz), 7.27 (1H, dt, *J*=1.2, 7.3 Hz), 7.44 (1H, dt, *J*=1.2, 7.3 Hz), 7.60 (1H, t, *J*=1.2 Hz), 8.04 (1H, dd, *J*=7.3, 1.2 Hz), 8.11 (1H, s). MS *m/z*: 241 (M⁺). *Anal.* Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.59; H, 4.60; N, 17.29.

Methyl 2-(Imidazol-1-yl)-5-iodoindole-3-carboxylate(19) from 6 — A solution of imidazole (34 mg, 0.51 mmol) in anhydrous DMF (1.0 mL) was added to 60% NaH (15 mg, 0.38 mmol) with ice-cooling and the mixture was stirred for 10 min at rt. To the resultant solution, a solution of **6** (42 mg, 0.12 mmol) in anhydrous DMF (2.0 mL) was added and the mixture was stirred for 23 h at 62°C. After addition of H₂O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with AcOEt–hexane (2:1, v/v) to give **19** (36 mg, 72%). **19**: mp 271—272°C (colorless prisms, recrystallized from MeOH). IR (KBr): 1692, 1490, 1441, 1218, 1161, 1062 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 3.76 (3H, s), 7.11 (1H, s), 7.30 (1H, d, *J*=8.5 Hz), 7.54 (1H, dd, *J*=8.5, 1.7 Hz), 7.61 (1H, br s), 8.12 (1H, s), 8.29 (1H, s, disappeared on addition of D₂O), 8.35 (1H, d, *J*=1.7 Hz). MS *m/z*: 367 (M⁺). *Anal.* Calcd for C₁₃H₁₀N₃O₂I: C, 42.52; H, 2.73; N, 11.44. Found: C, 42.38; H, 2.76; N, 11.16.

Methyl 2-(Indol-1-yl)-5-iodoindole-3-carboxylate (20) from 6 — A solution of indole (18 mg, 0.15 mmol) in anhydrous DMF (2.0 mL) was added to 60% NaH (4.7 mg, 0.12 mmol) with ice-cooling and the mixture was stirred for 15 min at rt. To the resultant solution, a solution of **6** (26 mg, 0.08 mmol) in anhydrous DMF (1.5 mL) was added and the mixture was stirred for 17.5 h at rt. After addition of H₂O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–hexane (2:1, v/v) to give **20** (25 mg, 77%). **20**: mp 192—194°C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 1668, 1558, 1273, 1204, 1144 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.78 (3H, s), 6.72 (1H, d, *J*=3.4 Hz), 7.16 (1H, d, *J*=8.6 Hz), 7.22 (1H, dt, *J*=1.7, 7.1 Hz), 7.25 (1H, dt, *J*=1.7, 8.1 Hz), 7.37 (1H, d, *J*=8.1 Hz), 7.43 (1H, d, *J*=3.4 Hz), 7.60 (1H, dd, *J*=8.6, 1.7 Hz), 7.68 (1H, dd, *J*=8.1, 1.7 Hz), 8.59 (1H, d, *J*=1.7 Hz), 8.83 (1H, s, disappeared on addition of D₂O). MS *m/z*: 416 (M⁺). *Anal.* Calcd for C₁₈H₁₃N₂O₂I·1/2H₂O: C, 50.84; H, 3.29; N, 6.59. Found: C, 50.80; H, 3.04; N, 6.46.

Dimethyl 2-(5-Iodo-3-methoxycarbonylindol-2-yl)malonate (24) from 6 — A solution of dimethyl malonate (96 mg, 0.72 mmol) in anhydrous DMF (8.0 mL) was added to KO^{*t*}-Bu (81 mg, 0.72 mmol) and the mixture was stirred for 10 min at rt. To the resultant solution, a solution of **6** (60 mg, 0.18 mmol) in anhydrous DMF (4.0 mL) was added and the mixture was stirred for 9 h at 72°C. After addition

of H₂O and ice, the whole was extracted with AcOEt–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO₂ with CHCl₃–hexane (4:1, v/v) as a developing solvent. Extraction of the band (*R_f* value: 0.87–0.65) with CHCl₃ gave unreacted **6** (24 mg, 40%). Extraction of the band (*R_f* value: 0.45–0.23) with CHCl₃ gave **24** (20 mg, 25%). **24**: mp 159–160°C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 1729 (br), 1691, 1436, 1260, 1085, 1023 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.81 (6H, s), 3.96 (3H, s), 6.23 (1H, s), 7.20 (1H, d, *J*=8.6 Hz), 7.54 (1H, dd, *J*=8.6, 1.7 Hz), 8.46 (1H, d, *J*=1.7 Hz), 9.70 (1H, brs). High-resolution MS *m/z*: Calcd for C₁₅H₁₄NO₆I: 430.9860. Found: 430.9866.

REFERENCES AND NOTES

1. a) Dedicated to the 77th birthday of Prof. Sho Ito. b) This is Part 98 of a series entitled “The Chemistry of Indoles”. Part 97: F. Yamada, A. Goto, and M. Somei, *Heterocycles*, 2000, **53**,
2. M. Soledade, C. Pedras, and J. L. Sorensen, *Phytochemistry*, 1998, **49**, 1959. These authors did not cite us in spite of using our 1-methoxyindole synthetic method.⁴ Other recent unfair example is the following: D. L. Boger, H. Keim, B. Oberhauser, E. P. Schreiner, and C. A. Foster, *J. Am. Chem. Soc.*, 1999, **121**, 6197.
3. R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc. Perkin Trans. 1*, 1978, 1117.
4. M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905; Review: M. Somei, *Heterocycles*, 1999, **50**, 1157 and references cited therein.
5. F. Yamada, D. Shinmyo, and M. Somei, *Heterocycles*, 1994, **38**, 273 and see the reference 2 in the paper.
6. M. Somei, M. Nakajou, T. Teramoto, A. Tanimoto, and F. Yamada, *Heterocycles*, 1999, **51**, 1949.
7. M. Somei, H. Morikawa, K. Yamada, and F. Yamada, *Heterocycles*, 1998, **48**, 1117; J. A. Joule, “Progress in Heterocyclic Chemistry”, Vol. 11, ed. by G. W. Gribble and T. L. Gilchrist, Elsevier Science Ltd., Oxford, 1999, pp. 45–65; M. Hasegawa, K. Yamada, Y. Nagahama, and M. Somei, *Heterocycles*, 1999, **51**, 2815. See also references, 4 and 5.
8. a) M. Takasugi, K. Monde, N. Katsui, and A. Shirata, *Bull. Chem. Soc. Japan*, 1988, **61**, 285; M. Takasugi, *Kagaku to Seibutu*, 1993, **31**, 22 and references cited therein. b) Synthesis of **12**: M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **61**, 1877.
9. B. S. Bal, W. E. Childers, Jr., and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091.
10. H. O. Wirth, O. Konigstein, and W. Kern, *Liebigs Ann. Chem.*, 1960, **634**, 84; D. L. Mattern and X. Chen, *J. Org. Chem.*, 1991, **56**, 5903.
11. M. Somei, F. Yamada, and G. Yamamura, *Chem. Pharm. Bull.*, 1998, **46**, 191.