核転換反応の1-メトキシインドール-3-カルバアルデヒドの合成

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<td>doi</td>
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doi: 10.3987/COM-12-S(N)41
NUCLEOPHILIC SUBSTITUTION REACTION OF 1-METHOXYINDOLE-3-CARBALDEHYDE

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Abstract – 1-Methoxyindole-3-carbaldehyde is proved to be a versatile electrophile and reacts regioselectively at the 2-position with various types of nucleophiles providing 2-substituted indole-3-carbaldehydes.

Indole is one of the electron rich hetero-aromatics. This is the reason why electrophilic substitution reactions have been well studied in the indole chemistry (shown in general formula in Scheme 1, A). On the other hand, nucleophilic substitution reaction was not familiar until we developed 1-hydroxyindole chemistry. We demonstrated that a hydroxy or a methoxy group at the 1-position of indole skeleton functions as a good leaving group when at least one electron withdrawing group (ester, halogen) is present in the indole nucleus (Scheme 1, B). Since various types of 1-hydroxy- and 1-methoxyindoles are available, they can now be utilized as substrates for nucleophilic substitution reactions.

1-Methoxyindole-3-carbaldehyde (1, Scheme 2) is one of the simplest 1-methoxyindoles and a natural product, isolated from radish as a phytoalexin by Takasugi and co-workers. They also isolated another phytoalexin, brassicanal A (2), from Chinese cabbage. Taking these reports into consideration, we

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# Dedicated to the 77th birthday of Prof. Ei-ichi Negishi. ‡ Professor Emeritus of Kanazawa University. Present address: 56-7 Matsuhidai, Matsudo-shi, Chiba-ken, 270-2214, Japan.
came up with the idea that plant family *Brassicaceae* utilizes simple indole-3-carbaldehydes for not only protecting them from diseases and insects, but also promoting their growth.\(^8\) To examine the idea we needed many kinds of 2-substituted indole-3-carbaldehydes. In this paper, we wish to report the preparation of them, which are rarely available by electrophilic substitution reactions. Since we have established a rapid and high yield synthetic method\(^4\) for 1 employing our 1-hydroxyindole chemistry, we chose it as a starting material for nucleophilic substituion reactions.

I. Reaction of 1 with Sulfur- and Oxygen-Centered Nucleophiles

First of all, we tried potent nucleophiles such as sulfur- and oxygen-centered species and the results are summarized in Scheme 2. As expected, NaSMe reacted with 1 in refluxing MeOH for 2 h to give brassicanal A (2) in 94% yield. With this simple and successful synthesis of phytoalexin in hand, we next tried the reaction of 1 with NaOMe and NaOEt in refluxing MeOH and EtOH, respectively. The expected 2-methoxy- (3) and 2-ethoxyindole-3-carbaldehyde (4) were obtained in 90 and 95% yields, respectively. In reactions of 1 with sodium salt of ethylene glycol, 1,3-propanediol, glycerol, and \(N,N\)-dimethylethanol, the yield of the desired product decreased even though longer reaction time was employed. Thus, 5, 6, 7, and 8 were obtained in 50, 76, 30, and 36% yields, respectively. 2,2-Dimethyl-1,3-dioxolan-4-methanol also reacted with 1 in the presence of Na metal in \(N,N\)-dimethylformamide (DMF) to produce 9 in 57% yield. Hydrolysis of 9 with aqueous 6% HCl at room temperature (rt) afforded 7 in 63% yield.

Scheme 2. Reaction of 1 with Sulfur- and Oxygen-Centered Nucleophiles

When 3-methylbut-2-en-1-ol was reacted with 1 at rt for 24 h in the presence of NaH in DMF, the
expected 10a was not obtained. Instead of 10a, a 2:5 mixture of 2-oxindoles, 11 and 12, was obtained. Heating a MeOH solution of the mixture at reflux for 24 h transformed 12 into 11. By carrying out these reactions continually, 11 was prepared in 75% yield directly from 1. Since 12 is an unstable intermediate, its isolation as pure compound was not successful. However, 1H-NMR inspection of the crude reaction residue clearly showed the presence of 12. The mechanism of the formation of 11 is considered as follows. Initial production of 10a, followed by Claisen rearrangement to give 12, and subsequent liberation of formyl group of 12 result in the formation of 11. Similarly, the reaction of 1 with potassium salt of 2-methylbut-3-en-2-ol in hexamethylphosphoric triamide (HMPA) produced 26% yield of 13 through unstable intermediate 10b.

II. Reaction of 1 with Nitrogen-Centered Nucleophiles

Reactions of 1 with nitrogen containing heterocycles were examined in the presence of NaH in DMF at rt and the results are summarized in Scheme 3. Nucleophiles, such as pyrrole, indole, imidazole, and (8aS)-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione, afforded the expected products, 14, 15, 16, and 17 in 99, 95, 80, and 67% yields, respectively. In the reaction of 1 with benzimidazole, the reaction rate was slow and even after 5 days, the desired 18 was obtained in only 30% yield with starting material as the major product (62%).

The reactions of 1 with sodium salts of alicyclic amines are interesting to note. Although 19 and 20 were obtained in 71 and 26% yields in the respective reactions with pyrrolidine and piperidine, a significant amount of 3 was generated in both cases in 24 and 63% yields respectively. The reaction of 1 with piperazine provided 21 in 16% yield together with 48% yield of 3. Similar reaction with N-methylpiperazine afforded 22 in 13% yields in addition to 36% yield of 3.

The formation of 3 observed in the reactions utilizing these weak nucleophiles and NaH in DMF may be explained as follows (Scheme 4). The initial reductive cleavage of N–OMe bond in 1 with NaH by a or b path liberates indole-3-carbaldehyde (23) and MeOH. Hydride reduction of 3-formyl group and the liberation of MeOH is another possible mechanism. Excess NaH instantly convert MeOH into NaOMe. Once NaOMe is generated, it attacks the second molecule of 1 giving 3 and NaOMe, which in turn attacks the third molecule of 1, and infinite repetition of the processes leads to complete transformation of 1 to 3. In order to examine this explanation, treatment of 1 with NaH in DMF at rt was attempted proving the formation of 3 as a sole isolable product in 78% yield, though the formation of 23 was not detected at all.

The reaction of 1 with (R)-(–)-2-pyrrolidinemethanol in the presence of NaH afforded 2-[(R)-2-hydroxymethylpyrrolidin-1-yl]indole-3-carbaldehyde (24) in 14% yield together with a significant amount (23%) of unknown compound (MS m/z: 226 (M+)). In the same reaction, treatment of the crude reaction residue with Ac₂O provided 2-[(R)-2-acetoxymethylpyrrolidin-1-yl]indole-3-carbaldehyde (25)
Scheme 3. Reaction of 1 with Nitrogen-Centered Nucleophiles

Scheme 4

Scheme 5. Reaction of 1 with Carbon-Centered Nucleophiles
in 43% yield, which was converted to 24 by treatment with aqueous 8% NaOH in a quantitative yield.

**III. Reaction of 1 with Carbon-Centered Nucleophiles**

As for a carbon nucleophile, we chose KCN at first (Scheme 5). The reaction proceeded smoothly to give 26 in 98% yield. The reaction of 1 with acetone in the presence of KH in acetone–THF produced the expected 27 together with 28 in 51 and 29% yields, respectively. On the other hand, when aqueous 8% NaOH was used as base in acetone–MeOH, nucleophilic substitution reaction did not take place, instead the aldol reaction product (29) was obtained exclusively in 92% yield. The structure of 28 was proved through the conversion of 29 to 28 in 62% yield by the reaction with acetone in the presence of KH. Similar results were observed when 3-acetylpypyridine was used as a nucleophile. Thus, the reaction of 1 in the presence of KH in THF produced 30 and 31 in 74 and 9% yields, respectively.

Dimethyl malonate reacted with 1 using NaOMe in refluxing MeOH to give 32 and 33 in 46 and 13% yields, respectively. Treatment of 33 with NaOMe in refluxing MeOH afforded 32 in 64% yield.

When 1 was reacted with allyltrimethylsilane in the presence of Bu₄NF in THF, 34 and 35 were obtained in 23 and 28% yields, respectively. In the similar reaction using (3-methylbut-2-en-1-yl)trimethylsilane, 36, 37, and 38 were produced in 7, 12, and 14% yields, respectively.

In conclusion, we have demonstrated that 1 is a good electrophile and reacts regioselectively at the 2-position with sulfur-, oxygen-, nitrogen-, and carbon-centered nucleophiles. Consequently, various types of 2-substituted indole-3-carbaldehydes become readily available, which are not accessible by employing electrophilic reactions. With 30 and 32 in hand as useful building blocks for the respective synthesis of natural products, goniomitine⁹ (39, Scheme 6) and caulerpin¹⁰ (40), the attempts are now in progress.

Biological evaluation of novel 2-substituted indole-3-carbaldehydes reported in this paper is also under investigation as sterilizer and plant growth regulator.⁸

**Scheme 6**

![Scheme 6](image)

**EXPERIMENTAL**

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 or Horiba FT-720 spectrophotometer, and ¹H-NMR spectra with a JEOL EX-270 or GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on Hitachi M-80 or JEOL JMS-SX 102A spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF₂₄₅ (Type 60) (SiO₂). Column
chromatography was performed on silica gel (SiO\(_2\), 100—200 mesh, from Kanto Chemical Co., Inc.) or activated alumina (Al\(_2\)O\(_3\), 300 mesh, from Wako Pure Chemical Industries, Ltd.) throughout the present study.

2-Methylthioindole-3-carbaldehyde (2) from 1-methoxyindole-3-carbaldehyde (1) — An aq. 15\% NaSMe (2.5 mL, 5.35 mmol) was added to a solution of 1 (43.7 mg, 0.25 mmol) in MeOH (4 mL) and heated at reflux for 2 h. After evaporation of solvent under reduced pressure, sat. aq. NH\(_4\)Cl was added. The whole was extracted with CH\(_2\)Cl\(_2\)–MeOH (95:5, v/v). The extract was washed with brine, dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure to leave an oil, which was column chromatographed on SiO\(_2\) with CH\(_2\)Cl\(_2\)–MeOH (99:1, v/v) to give 2 (44.6 mg, 94\%). 2: mp 233–234 °C (lit.,\(^7\) mp 210–213 °C colorless prisms, recrystallized from MeOH). IR (KBr): 1626, 1581, 1447, 1371, 1347, 1225, 848, 755, 657 cm\(^{-1}\). \(^1\)H-NMR (CD3OD) \(\delta\): 2.68 (3H, s), 7.19 (1H, ddd, \(J = 7.1, 7.0\), and 1.3 Hz), 7.22 (1H, ddd, \(J = 7.1, 7.0\), and 1.5 Hz), 7.38–7.42 (1H, m), 8.04–8.08 (1H, m), 10.04 (1H, s). MS \(m/z\): 191 (M\(^+\)). Anal. Calcd for C\(_{10}\)H\(_9\)NOS: C, 62.74; H, 4.74; N, 7.32. Found: C, 62.61; H, 4.80; N, 7.25.

2-Methoxyindole-3-carbaldehyde (3) from 1 — [General Procedure] (reaction with NaOMe): Na (136.5 mg, 5.93 mmol) was added to an ice-cooled anhydrous MeOH (2 mL) and stirred at rt for 5 min. To the resultant solution, a solution of 1 (40.1 mg, 0.23 mmol) in anhydrous MeOH (1 mL) was added. The mixture was refluxed for 2 h with stirring. After evaporation of solvent under reduced pressure, sat. aq. NH\(_4\)Cl was added. The whole was extracted with CH\(_2\)Cl\(_2\)–MeOH (95:5, v/v). The extract was washed with brine, dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure to leave an oil, which was column chromatographed on SiO\(_2\) with CH\(_2\)Cl\(_2\)–MeOH (97:3, v/v) to give 3 (35.9 mg, 90\%). 3: mp 251–252 °C (colorless plates, recrystallized from MeOH). IR (KBr): 1611, 1583, 1567, 1502, 1345, 1307, 1233, 1058, 745, 715 cm\(^{-1}\). \(^1\)H-NMR (CD3OD) \(\delta\): 4.19 (3H, s), 7.13 (1H, ddd, \(J = 6.1, 6.0\), and 1.5 Hz), 7.15 (1H, ddd, \(J = 6.1, 6.0\), and 1.5 Hz), 7.28 (1H, dd, \(J = 6.1\) and 1.5 Hz), 7.95 (1H, dd, \(J = 6.1\) and 1.5 Hz), 9.75 (1H, s). MS \(m/z\): 175 (M\(^+\)). Anal. Calcd for C\(_{10}\)H\(_9\)NO\(_2\): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.22; N, 7.98. [Second Procedure] (reaction with NaH): A solution of 1 (32.9 mg, 0.19 mmol) in anhydrous DMF (3 mL) was added to 60\% NaH (168.4 mg, 4.21 mmol) and stirred at rt for 17 h. After the same work-up as described in general procedure, 3 (25.8 mg, 78\%) was obtained.

2-Ethoxyindole-3-carbaldehyde (4) from 1 — In the general procedure for 3, Na (180.3 mg, 7.84 mmol), anhydrous EtOH (2 mL), and 1 (46.1 mg, 0.26 mmol) in anhydrous EtOH (2 mL) were used. After the same work-up and column chromatography, 4 (47.2 mg, 95\%) was obtained. 4: mp 227–228 °C (decomp., colorless prisms, recrystallized from MeOH). IR (KBr): 1604, 1573, 1485, 1364, 1344, 1234, 1050, 743, 657 cm\(^{-1}\). \(^1\)H-NMR (CD3OD) \(\delta\): 1.52 (3H, t, \(J = 7.1\) Hz), 4.47 (2H, q, \(J = 7.1\) Hz), 7.12 (1H, ddd, \(J = 7.3, 7.2\), and 1.7 Hz), 7.15 (1H, ddd, \(J = 7.3, 7.2\), and 1.5 Hz), 7.24–7.29 (1H, m), 7.93–7.98 (1H, m), 9.75 (1H, s). MS \(m/z\): 189 (M\(^+\)). Anal. Calcd for C\(_{11}\)H\(_{11}\)NO\(_2\): C, 69.82; H, 5.68; N, 7.40. Found: C, 69.82;
2-(2-Hydroxyethoxy)indole-3-carbaldehyde (5) from 1 — [General procedure] Na (105.4 mg, 4.58 mmol) was added to an ice-cooled anhydrous ethylene glycol (3 mL) and stirred at rt for 2.5 h. To the resultant solution, a solution of 1 (76.4 mg, 0.44 mmol) in anhydrous ethylene glycol (3 mL) was added and the mixture was heated at 60 °C for 19 h with stirring. Sat. aq. NH₄Cl was added and the whole was extracted with EtOAc. 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 CH₂Cl₂–MeOH (99:1, v/v) to give 1 (3.7 mg, 5%) and 5 (44.9 mg, 50%). 5: mp 188–190 °C (yellow prisms, recrystallized from MeOH). UV (MeOH) λ max nm (log ε): 304 (4.12), 267 (4.11), 244 (4.21). IR (KBr): 1608, 1545, 1345, 1258, 1233, 1070, 1052, 883, 750 cm⁻¹. ¹H-NMR (CD₃OD) δ: 3.96 (2H, ddd, J = 4.5, 3.7, and 1.4 Hz), 4.46 (2H, ddd, J = 4.5, 3.7, and 1.4 Hz), 7.13 (1H, ddd, J = 7.4, 7.3, and 1.7 Hz), 7.15 (1H, ddd, J = 7.4, 7.3, and 1.4 Hz), 7.25–7.29 (1H, m), 7.94–7.98 (1H, m), 9.82 (1H, s). MS m/z: 205 (M⁺). Anal. Calcd for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.08; H, 5.50; N, 6.86.

2-(3-Hydroxypropyl)oxyindole-3-carbaldehyde (6) from 1 — Na (71.9 mg, 3.126 mmol) was added to an ice-cooled anhydrous 1,3-propanediol (1 mL) and stirred at rt for 5 min. To the resultant solution, a solution of 1 (105.9 mg, 0.60 mmol) in anhydrous 1,3-propanediol (2 mL) was added and the mixture was heated at 70 °C for 5 h with stirring. After the same work-up in the general procedure for 5 except for employing CHCl₃–MeOH–28%NH₃ (46:2:0.2, v/v) as an eluent, 6 (100.3 mg, 76%) was obtained. 6: mp 172–174 °C (yellow powder, recrystallized from CHCl₃). UV (MeOH) λ max nm (log ε): 305 (4.13), 267 (4.06), 244 (4.17), 211 (4.26). IR (KBr): 1605, 1480, 1450, 1348, 1237, 1054, 1007, 908, 874, 738, 715, 645 cm⁻¹. ¹H-NMR (CD₃OD) δ: 2.10 (2H, quint, J = 6.1 Hz), 3.79 (2H, t, J = 6.1 Hz), 4.53 (2H, t, J = 6.1 Hz), 7.11–7.17 (2H, m), 7.28 (1H, dd, J = 7.3 and 1.7 Hz), 7.95 (1H, dd, J = 5.6 and 2.4 Hz), 9.77 (1H, s). MS m/z: 219 (M⁺). Anal. Calcd for C₁₂H₁₃NO₃ ⋅ ½H₂O: C, 65.07; H, 5.92; N, 6.32. Found: C, 65.25; H, 5.94; N, 6.31.

2-(2,3-Dihydroxypropyloxy)indole-3-carbaldehyde (7) from 1 — Na (133.2 mg, 5.79 mmol) was added to a solution of glycerol (1 mL) in anhydrous DMF (1 mL) and the mixture was heated at 70 °C for 17 h. To the resultant solution, a solution of 1 (201.5 mg, 1.15 mmol) in anhydrous DMF (4 mL) was added and heated at 70 °C for additional 5 h. After the same work-up in the general procedure for 5 except for employing CHCl₃–MeOH–28%NH₃ (46:2:0.2, v/v) as an eluent, 7 (80.6 mg, 30%) was obtained. 7: mp 194.0–195.0 °C (yellow powder, recrystallized from MeOH-benzene). UV (MeOH) λ max nm (log ε): 304 (4.15), 267 (4.10), 244 (4.21), 210 (4.41). IR (KBr): 1608, 1560, 1486, 1460, 1360, 1239, 1124, 1062, 885, 748 cm⁻¹. ¹H-NMR (CD₃OD) δ: 3.70 (2H, d, J = 5.6 Hz), 4.06 (1H, dtd, J = 9.8 and 6.1 Hz), 4.41 (1H, dd, J = 9.8 and 3.9 Hz), 4.50 (1H, dd, J = 9.8 and 3.9 Hz), 7.11–7.17 (2H, m), 7.26–7.29 (1H, m), 7.94–7.97 (1H, m), 9.81 (1H, s). MS m/z: 235 (M⁺). Anal. Calcd for C₁₃H₁₄NO₄: C, H, 5.88; N, 7.31.
2-(2-N,N-Dimethylaminoethoxy)indole-3-carbaldehyde (8) from 1 — Na (156.4 mg, 6.80 mmol) was added to an ice-cooled anhydrous N,N-dimethylaminoethanol (3 mL) and stirred at rt for 5 min. To the resultant solution, a solution of 1 (240.8 mg, 1.37 mmol) in anhydrous THF (7 mL) was added and the mixture was heated at 70 °C for 2 h with stirring. After the same work-up in the general procedure for 5 except for employing CHCl₃–MeOH–28%NH₃ (46:2:0.2, v/v) as an eluent, 8 (114.1 mg, 36%) was obtained. 8: mp 148–149 °C (yellow plates, recrystallized from MeOH–H₂O). UV (MeOH) λmax nm (log ε): 304 (4.16), 267 (4.11), 244 (4.22), 210 (4.45). IR (KBr): 1601, 1580, 1485, 1348, 1238, 1238, 1045, 880, 734, 650 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.49 (6H, s), 2.85 (2H, t, J=4.2 Hz), 4.46 (2H, t, J=4.2 Hz), 7.15 (1H, dd, J=7.6 and 7.1 Hz), 7.19 (1H, d, J=7.6 Hz), 7.21 (1H, dd, J=7.8 and 7.1 Hz), 8.34 (1H, d, J=7.8 Hz), 9.96 (1H, s). MS m/z: 232 (M⁺). Anal. Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.28; H, 6.93; N, 12.00.

2-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxyindole-3-carbaldehyde (9) from 1 — Na (139.6 mg, 6.07 mmol) was added to (2,2-dimethyl-1,3-dioxolane-4-yl)methanol (2 mL) and the mixture was heated at 80 °C for 1.5 h. To the resultant solution, a solution of 1 (205.7 mg, 1.17 mmol) in anhydrous DMF (6 mL) was added and heated at 80 °C for additional 1 h. After addition of H₂O, the whole was made acidic with 6% HCl and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil (2.493 g), which was dissolved in pyridine (6 mL). To the resultant solution, Ac₂O (3 mL) was added and the mixture was stirred at rt for 1 h. After evaporation of the solvent, sat. aq. NaHCO₃ was added to the residue and the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CHCl₃–MeOH–28%NH₃ (100:1:0.1, v/v) to give 9 (183.5 mg, 57%). 9: mp 214–215 °C (red brown flakes, recrystallized from MeOH). UV (MeOH) λmax nm (log ε): 304 (4.16), 267 (4.11), 244 (4.23), 208 (4.43). IR (KBr): 1600, 1570, 1480, 1342, 1235, 1050, 835, 735, 655 cm⁻¹. ¹H-NMR (DMSO-d₆) δ: 1.31 (3H, s), 1.35 (3H, s), 3.87 (1H, dd, J=8.6 and 5.5 Hz), 4.13 (1H, dd, J=8.6 and 6.5 Hz), 4.41–4.46 (1H, m), 4.47–4.54 (2H, m), 7.10–7.15 (2H, m), 7.28–7.32 (1H, m), 7.89–7.93 (1H, m), 9.86 (1H, s), 12.13 (1H, br s). MS m/z: 275 (M⁺). Anal. Calcd for C₁₅H₁₇NO₄: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.43; H, 6.21; N, 5.11.

7 from 9 — 6% HCl (2 mL) was added to a solution of 9 (19.2 mg, 0.070 mmol) in MeOH (2 mL) and the mixture was stirred at rt for 0.5 h. Sat. aq. NaHCO₃ was added and the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CHCl₃–MeOH–28%NH₃ (46:10:1, v/v) to give 7 (10.4 mg, 63%).
3-(1,1-Dimethylallyl)-2-oxindole (11) through 3-(1,1-dimethylallyl)-3-formyl-2-oxindole (12) from 1 — 3-Methylbut-2-en-1-ol (350.3 mg, 4.0 mmol) in anhydrous DMF (1 mL) was added to 60% NaH (122.7 mg, 3.1 mmol) at rt and stirred for 10 min. To the resultant mixture, a solution of 1 (53.0 mg, 0.30 mmol) in anhydrous DMF (2 mL) was added and stirred at rt for 24 h. After addition of sat. aq. NH₄Cl, the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CH₂Cl₂ to give a 2:5 mixture (50.7 mg) of 11 and 12. The mixture was dissolved in MeOH (4 mL) and refluxed for 24 h. After evaporation of solvent, the resultant crude 11 was purified by column chromatography on SiO₂ with CH₂Cl₂ to give pure 11 (12.1 mg, 75%). 11: mp 149–150 °C (colorless leaves, recrystallized from MeOH–H₂O). IR (KBr): 1706, 1661, 1617, 1470, 1332, 1233, 920, 735, 680 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.12 (3H, s), 1.34 (3H, s), 3.25 (1H, s), 4.98 (1H, dd, J=17.5 and 1.0 Hz), 5.06 (1H, dd, J=10.7 and 1.0 Hz), 5.98 (1H, dd, J=17.5 and 10.7 Hz), 6.82 (1H, d, J=7.5 Hz), 6.95 (1H, d, J=7.5, 7.4, and 1.1 Hz), 7.19 (1H, d, J=7.7, 7.4, and 1.1 Hz), 7.31 (1H, d, J=7.7 Hz), 7.83 (1H, br s, disappeared on addition of D₂O). MS m/z: 201 (M⁺). Anal. Calcd for C₁₃H₁₅NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.68; H, 7.59; N, 6.92. 12: Unstable intermediate. ¹H-NMR (CDCl₃) δ: 1.22 (3H, s), 1.29 (3H, s), 5.02 (1H, dd, J=17.4 and 0.7 Hz), 5.16 (1H, dd, J=10.8 and 0.7 Hz), 6.13 (1H, dd, J=17.4 and 10.8 Hz), 6.90 (1H, d, J=7.7, 1.1, and 0.6 Hz), 7.06 (1H, dd, J=7.7, 7.6, and 1.1 Hz), 7.26 (1H, d, J=7.7, 7.6, and 1.1 Hz), 7.49 (1H, d, J=7.7, 1.1, and 0.6 Hz), 8.63 (1H, br s), 9.88 (1H, s).

3-(3-Methylbut-2-en-1-yl)-2-oxindole (13) from 1 — 2-Methylbut-3-en-2-ol (0.60 mL, 5.66 mmol) was added to a suspension of 35% KH (288.0 mg, 2.51 mmol) in HMPA (0.5 mL), and the whole was stirred at rt for 10 min. To the resultant solution, a solution of 1 (100.8 mg, 0.57 mmol) in HMPA (2.0 mL) was added and stirred at rt for 1 h. After addition of H₂O, the whole was made acidic by adding 6% HCl and extracted with EtOAc. 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 EtOAc–hexane (1:3, v/v) to give 13 (29.8 mg, 26%) and 3 (37.8 mg, 38%). 13: mp 109–110 °C (pale yellow prisms, recrystallized from EtOAc–hexane). IR (KBr): 1699, 1652, 1608, 1453, 1385, 1324, 1229, 821, 742 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.58 (3H, s), 1.67 (3H, s), 2.58 (1H, d, J=14.5, 7.5, and 6.5 Hz), 2.69–2.76 (1H, m), 3.46 (1H, dd, J=7.5 and 5.0 Hz), 5.11–5.16 (1H, m), 6.87 (1H, d, J=7.6 Hz), 7.00 (1H, td, J=7.6 and 1.1 Hz), 7.20 (1H, d, J=7.6 and 1.1 Hz), 7.23 (1H, d, J=7.6 Hz), 8.19 (1H, br s, disappeared on addition of D₂O). MS m/z: 201 (M⁺). Anal. Calcd for C₁₃H₁₅NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.51; H, 7.57; N, 6.83.

2-(Pyrrol-1-yl)indole-3-carbaldehyde (14) from 1 — [General procedure] A solution of pyrrole (71.4 mg, 1.06 mmol) in anhydrous DMF (1 mL) was added to 60% NaH (35.3 mg, 0.88 mmol) at 0 °C with stirring. After 10 min, a solution of 1 (49.9 mg, 0.28 mmol) in anhydrous DMF (2 mL) was added at 0 °C.
After stirring at rt for 3 h, sat. aq. NH₄Cl was added. The whole was extracted with CH₂Cl₂–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave solid, which was column chromatographed on SiO₂ with CH₂Cl₂–MeOH (99:1, v/v) to give 14 (59.1 mg, 99%). 14: mp 266–268 °C (decomp., colorless leaves, recrystallized from MeOH). IR (KBr): 1612, 1582, 1564, 1487, 1457, 1372, 1071, 726 cm⁻¹. ¹H-NMR (5% DMSO-d₆ in CDCl₃) δ: 6.44 (2H, dd, J=2.2 and 2.1 Hz), 7.22 (2H, dd, J=2.2 and 2.1 Hz), 7.25–7.30 (2H, m), 7.39–7.44 (1H, m), 8.25–8.30 (1H, m), 10.07 (1H, s), 12.04 (1H, br s, disappeared on addition of D₂O). MS m/z: 210 (M⁺). Anal. Calcd for C₁₃H₁₀N₂O: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.54; H, 4.87; N, 13.04.

2-(Indol-1-yl)indole-3-carbaldehyde (15) from 1 — In the general procedure for 14, indole (51.4 mg, 0.44 mmol) instead of pyrrole, 60% NaH (14.2 mg, 0.35 mmol), 1 (47.0 mg, 0.27 mmol), and 24 h as for reaction time were employed. After the same work-up except for employing EtOAc as an extraction solvent and CH₂Cl₂–hexane (1:1, v/v) as an eluent, 15 (66.4 mg, 95%) was obtained. 15: mp 259–260 °C (colorless leaves, recrystallized from MeOH). IR (KBr): 1615, 1578, 1555, 1486, 1449, 1381, 1355, 747, 736, 721 cm⁻¹. ¹H-NMR (5% DMSO-d₆ in CDCl₃) δ: 6.80 (1H, dd, J=3.4 and 0.9 Hz), 7.25 (1H, ddd, J=7.0, 6.8, and 1.1 Hz), 7.27–7.35 (3H, m), 7.46–7.51 (1H, m), 7.49 (1H, d, J=3.4 Hz), 7.60 (1H, ddd, J=8.2, 0.9, and 0.8 Hz), 7.71 (1H, ddd, J=8.9, 0.9, and 0.8 Hz), 8.29–8.34 (1H, m), 9.92 (1H, s), 12.29 (1H, br s, disappeared on addition of D₂O). MS m/z: 260 (M⁺). Anal. Calcd for C₁₇H₁₂N₂O: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.66; H, 4.60; N, 10.76.

2-(Imidazol-1-yl)indole-3-carbaldehyde (16) from 1 — In the general procedure for 14, imidazole (33.7 mg, 0.49 mmol) instead of pyrrole, 60% NaH (19.8 mg, 0.49 mmol), 1 (52.7 mg, 0.30 mmol), and 48 h as for reaction time were employed. After the same work-up except for employing EtOAc–MeOH (99:5, v/v) as an extraction solvent, Al₂O₃ as an adsorbent, and CH₂Cl₂–MeOH (97:3, v/v) as an eluent, 16 (51.3 mg, 80%) was obtained. 16: mp 233–234 °C (colorless needles, recrystallized from MeOH). IR (KBr): 1638, 1567, 1531, 1486, 1465, 1398, 1066, 1021, 748 cm⁻¹. ¹H-NMR (5% DMSO-d₆ in CDCl₃) δ: 7.28–7.36 (2H, m), 7.30 (1H, br d, J=1.2 Hz), 7.43–7.48 (1H, m), 7.56 (1H, br s), 8.14 (1H, br s), 8.24–8.29 (1H, m), 10.04 (1H, s), 12.44 (1H, br s, disappeared on addition of D₂O). MS m/z: 211 (M⁺). Anal. Calcd for C₁₂H₉N₃O•1/6MeOH: C, 67.48; H, 4.50; N, 19.40. Found: C, 67.45; H, 4.35; N, 19.21.

(8aS)-2-(3-Formylindol-2-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (17) from 1 — In the general procedure for 14, (8aS)-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (551.9 mg, 3.58 mmol) instead of pyrrole, 60% NaH (143.1 mg, 3.58 mmol), 1 (201.4 mg, 1.15 mmol), and 6 h as for reaction time were employed. After the same work-up except for employing CH₂Cl₂–MeOH (95:5, v/v) as an eluent, 17 (229.4 mg, 67%) was obtained. 17: mp 231–233 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1701, 1680, 1608, 1577, 1469, 1406, 1351, 1314, 1206, 769 cm⁻¹. ¹H-NMR (5% DMSO-d₆ in CDCl₃) δ: 1.96–2.07 (1H, m), 2.07–2.15 (1H, m), 2.21–2.30 (1H, m), 2.42–2.49 (1H, m),
3.61–3.73 (2H, m), 4.19 (1H, d, \(J=16.1\) Hz), 4.42 (1H, t, \(J=8.1\) Hz), 4.86 (1H, d, \(J=16.1\) Hz), 7.24–7.31 (2H, m), 7.39–7.43 (1H, m), 8.41–8.46 (1H, m), 10.07 (1H, s), 11.80 (1H, br s, disappeared on addition of D\(_2\)O). MS \(m/z\): 297 (M⁺). Anal. Calcd for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_3\): C, 64.64; H, 5.08; N, 14.13. Found: C, 64.57; H, 5.06; N, 14.03.

2-(Benzimidazol-1-yl)indole-3-carbaldehyde (18) from 1 — In the general procedure for 14, benzimidazole (75.3 mg, 0.64 mmol) instead of pyrrole, 60% NaH (22.3 mg, 0.56 mmol), 1 (49.0 mg, 0.28 mmol), and 5 days as for reaction time were employed. After the same work-up except for employing EtOAc as an eluent, 18 (21.8 mg, 30%) was obtained together with 1 (30.3 mg, 62%). 18: mp 278–280 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1657, 1562, 1490, 1472, 1451, 1392, 1213, 741 cm\(^{-1}\). \(^1\)H-NMR (5% DMSO-\(d_6\) in CDCl\(_3\)) \(\delta\): 7.34–7.40 (2H, m), 7.41–7.46 (2H, m), 7.50–7.54 (1H, m), 7.58–7.63 (1H, m), 7.89–7.94 (1H, m), 8.31–8.36 (1H, m), 8.42 (1H, m), 9.95 (1H, s), 12.60 (1H, br s, disappeared on addition of D\(_2\)O). MS \(m/z\): 261 (M⁺). Anal. Calcd for C\(_{16}\)H\(_{11}\)N\(_3\)O: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.72; H, 4.16; N, 15.98.

2-(Pyrrolidin-1-yl)indole-3-carbaldehyde (19) from 1 — In the general procedure for 14, pyrrolidine (414.5 mg, 5.83 mmol) instead of pyrrole, 60% NaH (219.8 mg, 5.50 mmol), 1 (49.3 mg, 0.28 mmol), and 6 h as for reaction time were employed. After the same work-up except for employing CH\(_2\)Cl\(_2\)–MeOH (95:5, v/v) as an eluent, 3 (11.8 mg, 24%) and 19 (42.7 mg, 71%) were obtained. 19: mp 343 °C (decomp., colorless leaves, recrystallized from MeOH). IR (KBr): 1625, 1608, 1591, 1563, 1477, 1454, 1410, 1370, 1352, 1327, 742, 670 cm\(^{-1}\). \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\): 2.00–2.07 (4H, m), 3.45–3.61 (4H, m), 6.95–7.00 (2H, m), 7.11–7.16 (1H, m), 8.01–8.07 (1H, m), 9.79 (1H, s), 10.82 (1H, br s, disappeared on addition of D\(_2\)O). MS \(m/z\): 214 (M⁺). Anal. Calcd for C\(_{13}\)H\(_{14}\)N\(_2\)O: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.62; H, 6.58; N, 12.98.

2-(Piperidin-1-yl)indole-3-carbaldehyde (20) from 1 — In the general procedure for 14, piperidine (467.2 mg, 5.49 mmol) instead of pyrrole, 60% NaH (211.2 mg, 5.28 mmol), 1 (47.5 mg, 0.27 mmol), and 6 h as for reaction time were employed. After the same work-up except for employing CH\(_2\)Cl\(_2\)–MeOH (97:3, v/v) as an eluent, 20 (16.0 mg, 26%) and 3 (30.0 mg, 63%) were obtained. 20: mp 262–263 °C (decomp., colorless leaves, recrystallized from MeOH). IR (KBr): 1597, 1563, 1444, 1382, 1241, 743 cm\(^{-1}\). \(^1\)H-NMR (CD\(_3\)OD) \(\delta\): 1.70–1.81 (6H, m), 3.58–3.63 (4H, m), 7.02–7.08 (2H, m), 7.13–7.17 (1H, m), 7.90 (1H, br s), 9.77 (1H, s). MS \(m/z\): 228 (M⁺). Anal. Calcd for C\(_{14}\)H\(_{16}\)N\(_2\)O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.57; H, 6.95; N, 12.04.

2-(Piperazin-1-yl)indole-3-carbaldehyde (21) from 1 — A solution of piperazine (797.2 mg, 9.25 mmol) in anhydrous DMF (8 mL) was added to 60% NaH (369.7 mg, 9.24 mmol, washed with hexane) under ice cooling and stirring was continued at rt for 1 h. To the resultant solution, a solution of 1 (81.0 mg, 0.46 mmol) in anhydrous DMF (2 mL) was added and the mixture was heated at 60 °C for 3 h with
stirring. After addition of H2O, the whole was extracted with EtOAc. 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–MeOH–28%NH3 (46:2:0.2, v/v) to give 3 (38.6 mg, 48%) and 21 (16.7 mg, 16%). 21: mp 198–200 °C (yellow flakes, recrystallized from MeOH-benzene). UV (MeOH) λmax nm (log ε): 329 (4.02), 275 (4.16), 255 (4.33), 219 (4.38). IR (KBr): 1595, 1565, 1465, 1375, 1230, 995, 745, 657 cm-1. 1H-NMR (CD3OD) δ: 3.02 (4H, t, J=5.0 Hz), 3.59 (4H, t, J=5.0 Hz), 7.05–7.09 (2H, m), 7.18–7.20 (1H, m), 7.88 (1H, br s), 9.82 (1H, s). MS m/z: 229 (M+). Anal. Calcd for C13H15N3O: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.96; H, 6.51; N, 17.95.

2-(4-Methylpiperazin-1-yl)indole-3-carbaldehyde (22) from 1 — A solution of 1-methylpiperazine (4.630 g, 46.2 mmol) in anhydrous DMF (4 mL) was added to 60% NaH (1.836 g, 45.9 mmol, washed with hexane) under ice cooling and stirring was continued at rt for 1 h. To the resultant solution, a solution of 1 (201.5 mg, 1.15 mmol) in anhydrous DMF (4 mL) was added and the mixture was heated at 65 °C for 1 h with stirring. After addition of H2O, the whole was made acidic with 6% HCl and extracted with EtOAc. 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–MeOH–28%NH3 (46:5:0.5, v/v) to give 3 (72.8 mg, 36%) and 22 (36.2 mg, 13%). 22: mp 229–230 °C (brown powder, recrystallized from MeOH–benzene). UV (MeOH) λmax nm (log ε): 329 (4.06), 274 (4.18), 255 (4.36), 219 (4.40). IR (KBr): 1570, 1380, 1365, 1249, 1147, 993, 903, 830, 748, 663 cm-1. 1H-NMR (CDCl3) δ: 2.42 (3H, s), 2.71 (4H, t, J=4.6 Hz), 3.69 (4H, t, J=4.6 Hz), 7.11 (1H, ddd, J=8.1, 6.4, and 1.1 Hz), 7.18 (1H, ddd, J=7.1, 6.4, and 1.2 Hz), 7.22 (1H, dd, J=8.1 and 1.2 Hz), 7.96 (1H, dd, J=7.1 and 1.1 Hz), 8.88 (1H, br s), 10.06 (1H, s). MS m/z: 243 (M+). Anal. Calcd for C14H17N3O: C, 69.11; H, 7.04; N, 17.27. Found: C, 68.87; H, 6.95; N, 17.18.

(R)-(–)-2-(2-Hydroxymethylpyrrolidin-1-yl)indole-3-carbaldehyde (24) and an unknown compound from 1 — A solution of (R)-(–)-2-pyrrolidinemethanol (597.6 mg, 5.92 mmol) in anhydrous DMF (3 mL) was added to 60% NaH (469.5 mg, 11.7 mmol, washed with hexane) under ice cooling and stirring was continued at rt for 1 h. To the resultant solution, a solution of 1 (206.6 mg, 1.18 mmol) in anhydrous DMF (4 mL) was added and the mixture was stirred at rt for 0.5 h. After addition of H2O, the whole was extracted with EtOAc. 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–MeOH–28%NH3 (46:2:0.2, v/v) to give 24 (39.4 mg, 14%) and unknown compound (61.1 mg, 23%). 24: mp 187.0–188.5 °C (purple prisms, recrystallized from MeOH). UV (MeOH) λmax nm (log ε): 322 (4.17), 269 (4.23), 258 (4.40), 217 (4.36). [α]D24: –59 (c=0.5, MeOH). IR (KBr): 1560, 1368, 1238, 1040, 742, 662 cm-1. 1H-NMR (CD3OD) δ: 2.11–2.25 (4H, m), 3.55–3.63 (1H, m), 3.69 (1H, br s), 7.02–7.04 (2H, m), 7.37 (1H, dd, J=11.5 and 5.6 Hz), 3.73 (1H, dd, J=11.5 and 5.6 Hz), 3.74–3.80 (1H, m), 4.21 (1H, br s), 7.02–7.04 (2H, m).
m), 7.11–7.13 (1H, m), 8.10 (1H, br s), 9.70 (1H, s). MS m/z: 244 (M⁺). *Anal.* Calcd for C₁₄H₁₆N₂O₂•1/₈H₂O: C, 68.20; H, 6.54; N, 11.36. Found: C, 68.34; H, 6.59; N, 11.40. Unknown compound: mp 221–223 °C (pale brown prisms, recrystallized from CH₂Cl₂–hexane). UV (MeOH) λ_max: 348 (4.30), 281 (4.18), 276 (4.26), 272 (4.17), 242 (3.81), 209 (4.57). [α]D₃₀: –702 (c=0.36, MeOH). IR (KBr): 1635, 1426, 1390, 1308, 1262, 1222, 1095, 1060, 1009, 922, 745 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.63–1.73 (1H, m), 1.94–2.04 (2H, m), 2.25–2.32 (1H, m), 3.58–3.76 (4H, m), 4.48 (1H, d, J=12.3 Hz), 7.03 (1H, dd, J=7.5 and 7.3 Hz), 7.12 (1H, dd, J=7.9 and 7.3 Hz), 7.29 (1H, d, J=7.5 Hz), 7.39 (1H, d, J=7.9 Hz), 7.41 (1H, s). MS m/z: 226 (M⁺). *Anal.* Calcd for C₁₄H₁₄N₂O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.29; H, 6.16; N, 12.31.

(R)-(−)-2-(2-Acetoxymethylpyrrolidin-1-yl)indole-3-carbaldehyde (25) from 1 — In the same procedure as described for 24, (R)-(−)-2-pyrrolidinemethanol (586.5 mg, 5.80 mmol), 60% NaH (229.8 mg, 5.74 mmol, washed with hexane), 1 (202.4 mg, 1.15 mmol) were used. After the same work-up as for 24, the resultant residue was dissolved into pyridine (4 mL). To the resultant solution, Ac₂O (2 mL) was added and the mixture was stirred at rt for 0.5 h. After evaporation of the solvent, sat. aq. NaHCO₃ was added to the residue and the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CH₂Cl₂–MeOH (98:2, v/v) to give 25 (143.3 mg, 43%). 25: mp 156–157 °C (pale gray prisms, recrystallized from CH₂Cl₂–hexane). UV (MeOH) λ_max nm (log ε): 321 (4.17), 268 (4.24), 257 (4.40), 217 (4.40). [α]D₃₀: –69 (c=0.18, MeOH). IR (KBr): 1742, 1600, 1562, 1375, 1224, 1045, 922, 748, 667 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.00–2.22 (4H, m), 2.19 (3H, s), 3.49–3.55 (1H, m), 3.74 (1H, dd, J=11.5 and 9.2 Hz), 3.75–3.80 (1H, m), 4.06–4.13 (1H, m), 4.48 (1H, dd, J=11.5 and 2.5 Hz), 7.11 (1H, td, J=7.6 and 1.2 Hz), 7.15 (1H, td, J=7.6 and 1.0 Hz), 7.22 (1H, dd, J=7.6 and 1.2 Hz), 8.26 (1H, br s), 9.82 (1H, s), 9.88 (1H, br s). MS m/z: 286 (M⁺). *Anal.* Calcd for C₁₆H₁₈N₂O₃: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.33; H, 6.27; N, 9.79.

24 from 25 — Aq. 8% NaOH (1 mL) was added to a solution of 25 (21.5 mg, 0.075 mmol) in DMF (1 mL) and the mixture was stirred at rt for 1 h. After addition of H₂O, the whole was extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave 24 (18.5 mg, 100%) as crystals.

2-Cyanoindole-3-carbaldehyde (26) from 1 — A solution of KCN (76.5 mg, 1.17 mmol) in H₂O (1 mL) was added to a solution of 1 (37.3 mg, 0.21 mmol) in DMF (4 mL) and heated at 75–80 °C for 2 h with stirring. After evaporation of solvent under reduced pressure, sat. aq. NH₄Cl was added and the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CH₂Cl₂–MeOH (99:5, v/v) to give 26 (35.6 mg, 98%). 26: mp 228–230 °C (decomp.,
colorless prisms, recrystallized from MeOH). IR (KBr): 2230, 1647, 1575, 1447, 1436, 1380, 654, 640 cm⁻¹. ¹H-NMR (CD₃OD) δ: 7.37 (1H, ddd, J=8.1, 7.1, and 1.0 Hz), 7.47 (1H, ddd, J=8.4, 7.1, and 1.2 Hz), 7.53 (1H, ddd, J=8.4, 1.0, and 0.9 Hz), 8.23 (1H, ddd, J=8.1, 1.2, and 0.9 Hz), 10.20 (1H, s). MS m/z: 170 (M⁺). Anal. Calcd for C₁₀H₆N₂O: C, 70.58; H, 3.55; N, 16.45. Found: C, 70.45; H, 3.84; N, 16.46.

1-(3-Formylindol-2-yl)propan-2-one (27) and 5-(1-methoxyindol-3-yl)-3-methylcyclohex-2-enone (28) from 1 — Under Ar atmosphere, a solution of acetone (0.88 ml, 11.9 mmol) in anhydrous THF (1 mL) was added to a suspension of 35% KH (1.33 g, 11.6 mmol, washed with benzene) in anhydrous THF (5 mL) with stirring under ice cooling. After gas evolution ceased, a solution of 1 (102.9 mg, 0.59 mmol) in anhydrous THF (6 mL) was added to the resultant solution and the mixture was stirred at rt for 6 h. After addition of H₂O, the whole was made acidic with NH₄Cl and extracted with CH₂Cl₂–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 CH₂Cl₂–MeOH (98:2, v/v) to give 28 (42.9 mg, 29%) and 27 (61.3 mg, 51%) in the order of elution. 27: mp 133–135 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1712, 1628, 1469, 1394, 1188, 740 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.39 (3H, s), 4.43 (2H, s), 7.25–7.31 (2H, m), 7.40–7.45 (1H, m), 8.07-8.12 (1H, m), 9.99 1H, br s, disappeared on addition of D₂O), 10.28 (1H, s). MS m/z: 201 (M⁺). Anal. Calcd for C₁₂H₁₁NO₂: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.45; N, 7.13. 28: mp 70–71 °C (pale brown prisms, recrystallized from hexane). UV (MeOH) λmax nm (log ε): 290 (3.72), 277 (3.70), 224 (4.60). IR (KBr): 1645, 1440, 1368, 1239, 1205, 1021, 953, 880, 738 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.02 (3H, s), 2.57 (1H, dd, J=18.1 and 6.2 Hz), 2.60 (1H, dd, J=16.3 and 12.1 Hz), 2.71 (1H, dd, J=18.1 and 4.6 Hz), 2.81 (1H, dd, J=16.3 and 4.2 Hz), 3.60–3.68 (1H, m), 4.07 (3H, s), 6.00 (1H, s), 7.07 (1H, s), 7.12 (1H, ddd, J=7.9, 7.0, and 0.9 Hz), 7.26 (1H, ddd, J=8.2, 7.0, and 0.7 Hz), 7.43 (1H, dd, J=8.2 and 0.9 Hz), 7.51 (1H, dd, J=7.9 and 0.7 Hz). MS m/z: 255 (M⁺). Anal. Calcd for C₁₃H₁₃NO₂•1/8H₂O: C, 74.61; H, 6.65; N, 5.44. Found: C, 74.76; H, 6.87; N, 5.32.

(E)-4-(1-Methoxyindol-3-yl)but-3-en-2-one (29) from 1 — Aq. 8% NaOH (0.5 mL) was added to a solution of 1 (103.0 mg, 0.59 mmol) in MeOH-acetone (1:1, v/v, 2 mL) and the mixture was stirred at rt for 6 h. After evaporation of solvent under reduced pressure, brine was added. The whole was extracted with EtOAc. 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 CH₂Cl₂–MeOH (99:1, v/v) to give 29 (116.5 mg, 92%). 29: pale yellow oil. IR (film): 1670, 1580 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.37 (3H, s), 4.16 (3H, s), 6.77 (1H, d, J=16.1 Hz), 7.26 (1H, ddd, J=8.1, 7.1, and 1.1 Hz), 7.34 (1H, ddd, J=8.2, 7.1, and 1.1 Hz), 7.52 (1H, ddd, J=8.2, 1.1, and 0.9 Hz), 7.86 (1H, d, J=16.1 Hz), 7.92 (1H, ddd, J=8.1, 1.1, and 0.9 Hz), 8.00 (1H, s). High resolution MS m/z: Calcd for C₁₃H₁₃NO₂: 215.0946. Found:
215.0941.

28 from 29 — Under Ar atmosphere, a solution of acetone (0.7 ml, 9.53 mmol) in anhydrous THF (1 mL) was added to a suspension of 35% KH (1.026 g, 8.98 mmol, washed with benzene) in anhydrous THF (5 mL) with stirring under ice cooling. After gas evolution ceased, a solution of 29 (102.3 mg, 0.48 mmol) in anhydrous THF (6 mL) was added to the resultant solution and the mixture was stirred at rt for 1 h. After addition of H2O, the whole was made acidic with 6% HCl and extracted with CH2Cl2–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 column chromatographed on SiO2 with CH2Cl2–MeOH (98:2, v/v) to give 28 (75.2 mg, 62%).

3-[2-(3-Formylindol-2-yl)acetyl]pyridine (30) and 1,5-di(pyrid-3-yl)-3-(1-methoxyindol-3-yl)pentane-1,5-dione (31) from 1 — Under Ar atmosphere, a solution of 3-acetylpyridine (88.1 mg, 0.72 mmol) in anhydrous THF (2 mL) was added to 35% KH (66.1 mg, 0.58 mmol, washed with hexane) with stirring under ice cooling. After gas evolution ceased, a solution of 1 (83.2 mg, 0.47 mmol) in anhydrous THF (2 mL) was added to the resultant solution and the mixture was stirred at rt for 40 min. After addition of H2O, the whole was made acidic with 6% HCl and extracted with CH2Cl2–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–MeOH–28%NH3 (46:2:0.2, v/v) to give 1 (4.2 mg, 5%), 31 (16.5 mg, 9%), and 30 (93.1 mg, 74%) in the order of elution. 30: mp 208–210 °C (orange needles, recrystallized from MeOH). UV (MeOH) λmax nm (log ε): 301 (4.08), 266 (4.15), 244 (4.31), 212 (4.57). IR (KBr): 1698, 1628, 1580, 1460, 1390, 1218, 1000, 977, 758 cm−1. 1H-NMR (DMSO-d6) δ: 5.09 (2H, s), 7.18–7.24 (2H, m), 7.48 (1H, dd, J=6.9 and 1.1 Hz), 7.65 (1H, ddd, J=8.0, 4.7, and 1.0 Hz), 8.10 (1H, d, J=7.2 Hz), 8.45 (1H, ddd, J=8.0, 2.2, and 1.9 Hz), 8.87 (1H, dd, J=4.7 and 2.2 Hz), 9.31 (1H, dd, J=1.9 and 1.0 Hz), 10.08 (1H, s), 12.04 (1H, br s). MS m/z: 264 (M+). Anal. Calcd for C16H12N2O2: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.51; H, 4.46; N, 10.40.

31: yellow oil. IR (KBr): 1682, 1582, 1447, 1418, 1360, 1275, 1223, 739, 700 cm−1. 1H-NMR (CDCl3) δ: 3.51 (2H, dd, J=16.6 and 6.6 Hz), 3.62 (2H, dd, J=16.6 and 7.1 Hz), 4.00 (3H, s), 4.37 (1H, tt, J=7.1 and 6.6 Hz), 7.12 (1H, dd, J=8.1 and 5.8 Hz), 7.18 (1H, s), 7.24 (1H, dd, J=8.1 and 5.8 Hz), 7.38 (1H, d, J=8.1 Hz), 7.42 (2H, dd, J=7.8 and 4.9 Hz), 7.61 (1H, d, J=8.1 Hz), 8.24 (2H, ddd, J=7.8, 1.6, and 1.5 Hz), 8.76 (2H, dd, J=4.9 and 1.5 Hz), 9.16 (2H, d, J=1.6 Hz). MS m/z: 399 (M+). High resolution MS m/z: Calcd for C24H21N3O3: 399.1581. Found: 399.1580.

Methyl 2-(3-formylindol-2-yl)acetate (32) and dimethyl 2-(3-formylindol-2-yl)malonate (33) and from 1 — A solution of dimethyl malonate (85.6 mg, 0.65 mmol) in anhydrous MeOH (1 mL) was added to a NaOMe solution in anhydrous MeOH (prepared by dissolving Na (12.0 mg, 0.52 mmol) in anhydrous MeOH (0.5 mL)) and stirred at rt for 1 h. To the resultant solution, a solution of 1 (49.8 mg,
0.28 mmol) in anhydrous MeOH (2 mL) was added and the mixture was refluxed for 30 min with stirring. After addition of H₂O, the whole was made acidic with 6% HCl and extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CH₂Cl₂–MeOH (99:1, v/v) to give 1 (13.3 mg, 27%), 33 (10.5 mg, 13%), and 32 (31.6 mg, 46%) in the order of elution. 32: mp 116–118 °C (colorless leaves, recrystallized from MeOH–H₂O). IR (KBr): 1730, 1644, 1465, 1451, 1438, 1389, 1305, 1215, 1163, 1024, 756, 749 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.82 (3H, s), 4.29 (2H, s), 7.26–7.31 (1H, m), 7.39–7.44 (1H, m), 8.14–8.19 (1H, m), 9.88 (1H, s), 10.24 (1H, s). MS m/z: 217 (M⁺), 185, 158. Anal. Calcd for C₁₂H₁₁NO₃: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.44; H, 5.06; N, 6.48. 33: mp 162–163 °C (colorless needles, recrystallized from MeOH). IR (KBr): 1757, 1734, 1626, 1449, 1384, 1325, 1238, 1147, 743 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.83 (6H, s), 5.84 (1H, s), 7.30 (1H, ddd, J = 7.2, 7.1, and 1.5 Hz), 7.33 (1H, ddd, J = 7.1, 7.1, and 1.6 Hz), 7.44–7.48 (1H, m), 8.14–8.19 (1H, m), 9.85 (1H, br s), 10.31 (1H, s). MS m/z: 275 (M⁺), 243. Anal. Calcd for C₁₄H₁₃NO₅: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.25; H, 4.71; N, 5.04.

32 from 33 — A solution of 33 (56.1 mg, 0.19 mmol) in anhydrous MeOH (2 mL) was added to a NaOMe solution in anhydrous MeOH (prepared by dissolving Na (8.9 mg, 0.38 mmol) in anhydrous MeOH (0.5 mL)) and the mixture was refluxed for 2 h with stirring. After addition of H₂O, the whole was made acidic with 6% HCl and extracted with CH₂Cl₂–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 CH₂Cl₂–MeOH (98:2, v/v) as a developing solvent. Extraction of the band having an Rf value of 0.63–0.52 with CH₂Cl₂–MeOH (95:5, v/v) afforded 33 (4.3 mg, 8%). Extraction of the band having an Rf value of 0.47–0.27 with CH₂Cl₂–MeOH (95:5, v/v) afforded 32 (28.6 mg, 64%).

2-[(E)-Propen-1-yl]indole-3-carbaldehyde (34) and 1-(1-methoxyindol-3-yl)but-3-en-1-ol (35) from 1 — Under an Ar atmosphere, a solution of 1 (54.1 mg, 0.31 mmol) in anhydrous THF (4 mL) was added to a mixture of Bu₄NF•3H₂O (106.8 mg, 0.34 mmol, dried for 2 h under reduced pressure) and molecular sieve (4 angstrom, 353.4 mg, flame dried, 1 h). To the mixture, allyltrimethylsilane (0.15 mL, 0.94 mmol) was added and stirred at rt for 6 h. After addition of sat. aq. NH₄Cl, the whole was extracted with CH₂Cl₂–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 column chromatographed on SiO₂ with CH₂Cl₂–hexane (7:3, v/v) to give 35 (18.9, 28%), 34 (13.3 mg, 23%), and unknown product (8.8 mg) in the order of elution. 34: mp 217–218 °C (yellow prisms, recrystallized from MeOH). IR (KBr): 1628, 1585, 1463, 1382, 1245, 948, 749, 740 cm⁻¹. ¹H-NMR (CD₃OD) δ: 2.03 (3H, ddd, J = 6.8 and 1.7 Hz), 6.66 (1H, dq, J = 15.9 and 6.8 Hz), 7.03 (1H, dq, J = 15.9 and 1.7 Hz), 7.17 (1H, ddd, J = 7.8, 7.1, and 0.9 Hz), 7.23 (1H,
dd, $J=8.1, 7.1,$ and $1.3$ Hz), $7.37$ (1H, ddd, $J=8.1, 1.0,$ and $0.9$ Hz), $8.11$ (1H, ddd, $J=7.8, 1.3,$ and $0.9$ Hz), $10.12$ (1H, s). MS $m/z$: 185 (M$^+$), 170. Anal. Calcd for C$_{12}$H$_{11}$NO: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.77; H, 6.09; N, 7.51. 35: colorless oil. IR (film): 1638, 1450, 1438, 1350, 1319, 1226, 1092, 1046, 1031, 1010, 1000, 979, 954, 917, 758, 739 cm$^{-1}$. $^1$H-NMR (CD$_3$OD) $\delta$: 2.62–2.73 (2H, m), 4.05 (3H, s), 4.96 (1H, d, $J=7.0$ Hz), 5.85 (1H, ddd, $J=17.1, 10.2,$ and $7.0$ Hz), 7.05 (1H, ddd, $J=7.9, 7.1,$ and $0.9$ Hz), 7.19 (1H, ddd, $J=8.2, 7.1,$ and $1.1$ Hz), 7.34 (1H, s), 7.38 (1H, ddd, $J=8.2, 0.9,$ and $0.7$ Hz), 7.67 (1H, ddd, $J=7.9, 1.1,$ and $0.7$ Hz). High resolution MS $m/z$: Calcd for C$_{13}$H$_{15}$NO$_2$: 217.1102. Found: 217.1101.

2-(3,3-Dimethylallyl)- (36), 2-(1,1-dimethylallyl)indole-3-carbaldehyde (37), and 2,2-dimethyl-1-(1-methoxyindol-3-yl)but-3-en-1-ol (38) from 1 — Under an Ar atmosphere, a solution of 1 (53.5 mg, 0.31 mmol) in anhydrous THF (4 mL) was added to a mixture of Bu$_4$NF•3H$_2$O (108.5 mg, 0.34 mmol, dried for 2 h under reduced pressure) and molecular sieve (4 angstrom, 416.4 mg, flame dried, 1 h). To the mixture, (3-methylbut-2-en-1-yl)trimethylsilane (0.20 mL, 1.1 mmol) was added and stirred at rt for 3 h. After addition of sat. aq. NH$_4$Cl, the whole was extracted with CH$_2$Cl$_2$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO$_2$ with CHCl$_3$–hexane (7:3, v/v) as a developing solvent. Extraction of the band having an $R_f$ value of 0.65–0.58, 0.58–0.50, 0.49–0.43, 0.42–0.37 with CHCl$_3$–MeOH (95:5, v/v) afforded 38 (10.6 mg, 14%), unreacted 1 (20.5 mg, 38%), 37 (7.7 mg, 12%), and 36 (4.4 mg, 7%), respectively. 36: mp 149–150 °C (colorless needles, recrystallized from MeOH–H$_2$O). IR (KBr): 1627, 1580, 1461, 1381, 1232 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 1.77 (3H, s), 1.84 (3H, d, $J=1.5$ Hz), 3.88 (2H, d, $J=7.3$ Hz), 5.40 (1H, t, $J=7.3$ Hz), 7.24 (1H, ddd, $J=8.5, 7.1,$ and $1.3$ Hz), 7.27 (1H, ddd, $J=8.5, 7.1,$ and $1.3$ Hz), 7.33–7.36 (1H, m), 8.21–8.26 (1H, m), 8.47 (1H, br s, disappeared on addition of D$_2$O), 10.23 (1H, s). MS $m/z$: 213 (M$^+$). Anal. Calcd for C$_{14}$H$_{15}$NO: C, 78.84; H, 7.09; N, 6.54. Found: C, 78.97; H, 7.16; N, 6.52. 37: mp 194–195 °C (colorless needles, recrystallized from CH$_2$Cl$_2$–hexane). IR (KB): 3160, 1621, 1581, 1440, 1369 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 1.69 (6H, s), 5.292 (1H, d, $J=17.5$ Hz), 5.294 (1H, d, $J=10.6$ Hz), 6.23 (1H, dd, $J=17.5$ and $10.6$ Hz), 7.25 (1H, ddd, $J=8.8, 7.3,$ and $1.5$ Hz), 7.28 (1H, ddd, $J=8.8, 7.3,$ and $1.5$ Hz), 7.35–7.38 (1H, m), 8.35–8.39 (1H, m), 8.47 (1H, br s, disappeared on addition of D$_2$O), 10.47 (1H, s). MS $m/z$: 213 (M$^+$). Anal. Calcd for C$_{14}$H$_{15}$NO: C, 78.84; H, 7.09; N, 6.54. Found: C, 78.63; H, 7.13; N, 6.49. 38: colorless oil. IR (film): 1634, 1449, 1355, 1093, 1043, 1034, 1009, 955, 912, 662, 639 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 1.07 (3H, s), 1.08 (3H, s), 1.57 (1H, br s, disappeared on addition of D$_2$O), 4.08 (3H, s), 4.82 (1H, s), 5.14 (1H, dd, $J=17.4$ and $1.3$ Hz), 5.15 (1H, dd, $J=10.8$ and $1.3$ Hz), 6.04 (1H, dd, $J=17.4$ and $10.8$ Hz), 7.10 (1H, ddd, $J=8.1, 7.1,$ and $0.9$ Hz), 7.23 (1H, ddd, $J=8.2, 7.1,$ and $0.9$ Hz), 7.25 (1H, s), 7.41 (1H, ddd, $J=8.2, 0.9,$ and $0.8$ Hz), 7.66 (1H, ddd, $J=8.1, 0.9,$ and $0.8$ Hz). High resolution MS $m/z$: Calcd for C$_{15}$H$_{19}$NO$_2$: 245.1416. Found: 245.1415.
REFERENCES AND NOTES


