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NUCLEOPHILIC SUBSTITUTION REACTION OF 1-METHOXYINDOLE-3-CARBALDEHYDE^{1,‡}

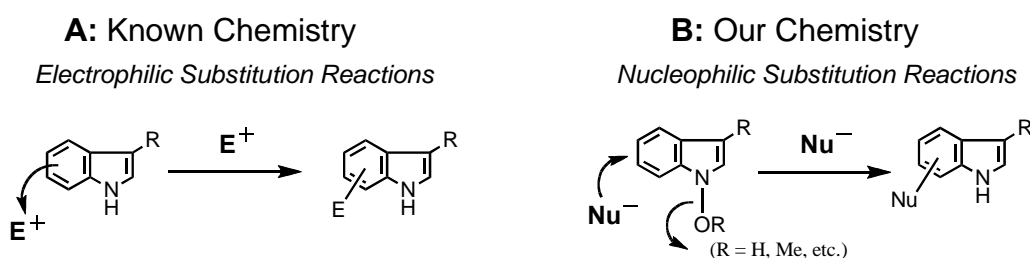
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Abstract – 1-Methoxyindole-3-carbaldehyde is proved to be a versatile electrophile and reacts regioselectively at the 2-position with various types of nucleophiles providing 2-substituted indole-3-carbaldehydes.

Indole is one of the electron rich hetero-aromatics. This is the reason why electrophilic substitution reactions have been well studied² in the indole chemistry (shown in general formula in Scheme 1, **A**). On the other hand, nucleophilic substitution reaction³ was not familiar until we developed 1-hydroxyindole chemistry.⁴ 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^{3b,4} (ester, halogen)^{3c} is present in the indole nucleus (Scheme 1, **B**). Since various types of 1-hydroxy- and 1-methoxyindoles are available,⁴ they can now be utilized as substrates for nucleophilic substitution reactions.

1-Methoxyindole-3-carbaldehyde⁵ (**1**, Scheme 2) is one of the simplest 1-methoxyindoles and a natural product, isolated from radish as a phytoalexin by Takasugi⁶ and co-workers. They also isolated another phytoalexin, brassicanal A (**2**), from Chinese cabbage.⁷ Taking these reports into consideration, we



Scheme 1

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.

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

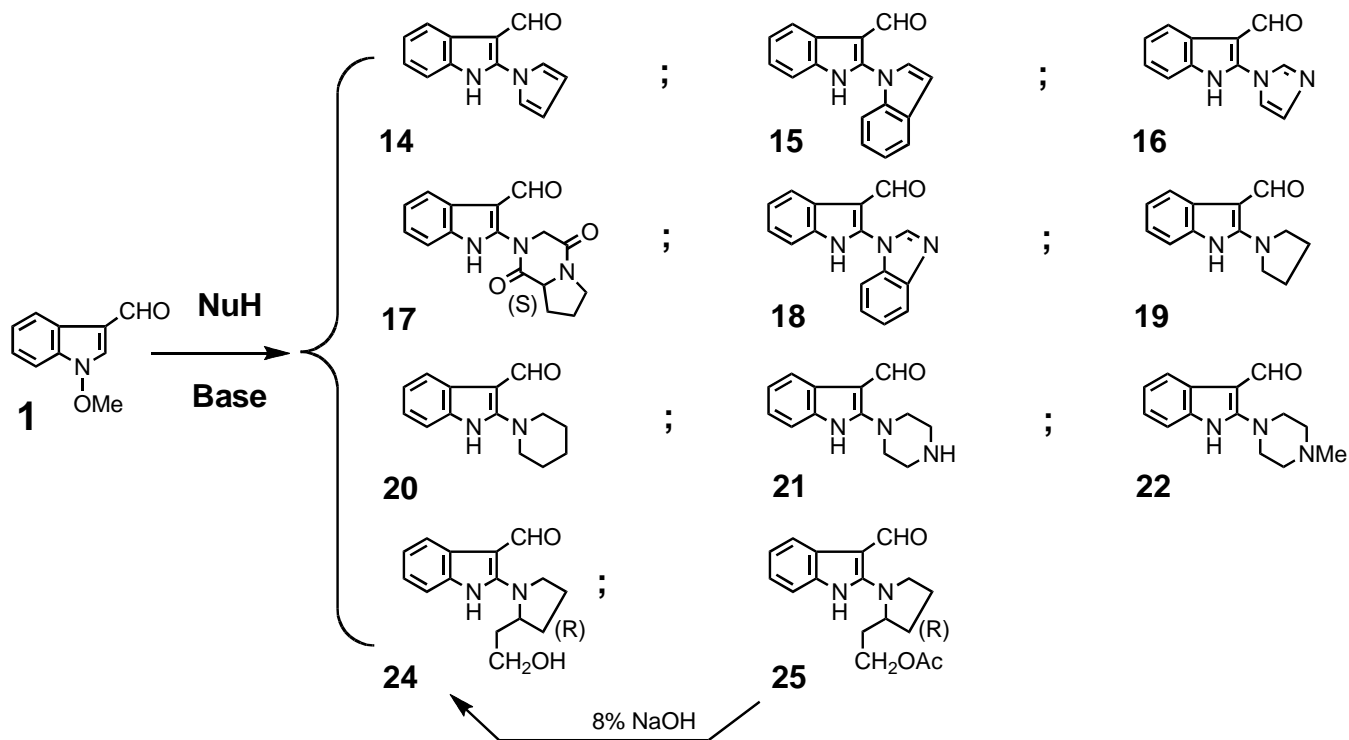
Reactions of **1** with nitrogen containing heterocycles were examined in the presence of NaH in DMF at rt and the results are summarized in Scheme 3. Nucleophiles, such as pyrrole, indole, imidazole, and (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione, afforded the expected products, **14**, **15**, **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**.

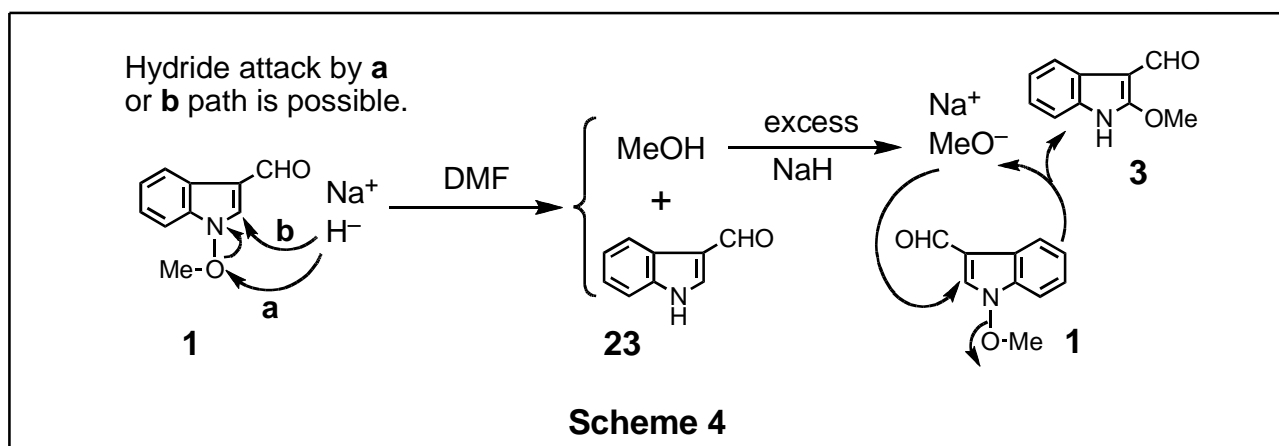
The formation of **3** observed in the reactions utilizing these weak nucleophiles and NaH in DMF may be explained as follows (Scheme 4). The initial reductive cleavage of *N*-OMe bond in **1** with NaH by **a** or **b** path liberates indole-3-carbaldehyde (**23**) and MeOH. Hydride reduction of 3-formyl 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.

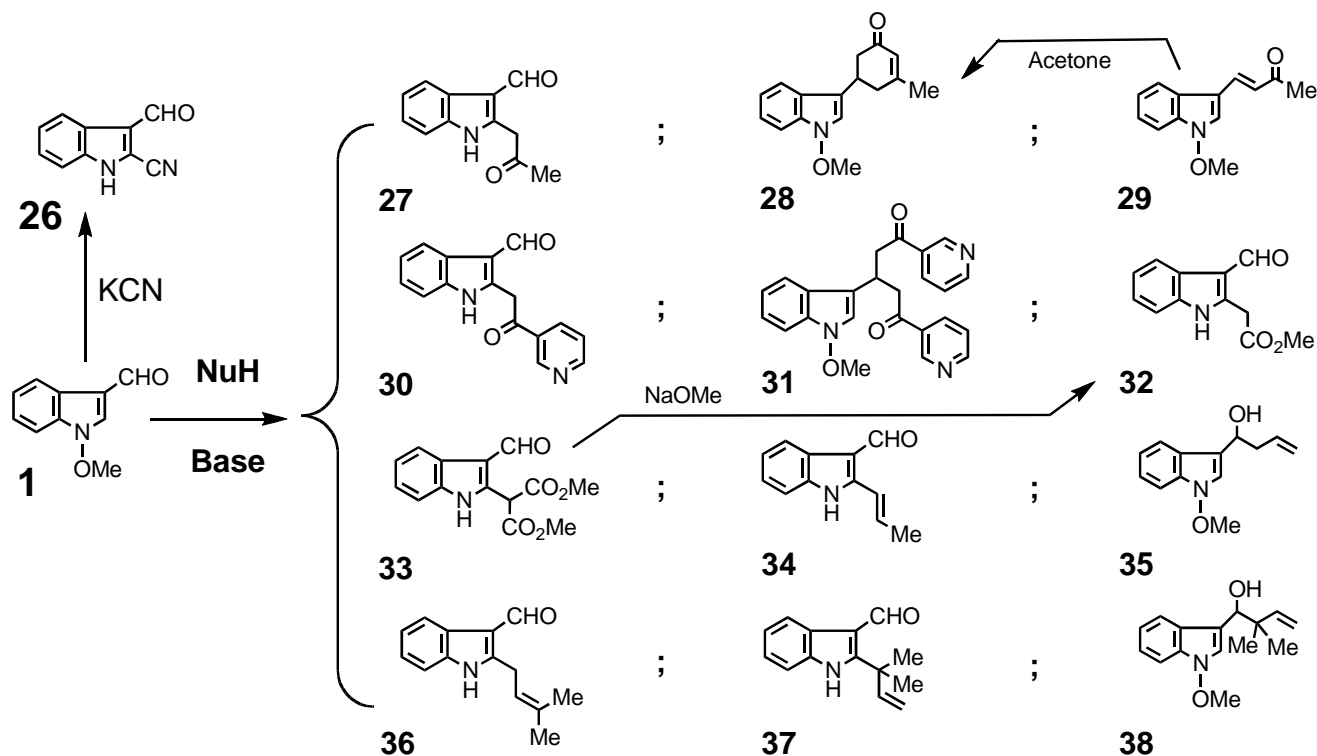
The reaction of **1** with (*R*)-(-)-2-pyrrolidinemethanol in the presence of NaH afforded 2-[(*R*)-2-hydroxymethylpyrrolidin-1-yl]indole-3-carbaldehyde (**24**) in 14% yield together with a

significant amount (23%) of unknown compound (MS m/z : 226 (M^+)). In the same reaction, treatment of the crude reaction residue with Ac_2O provided 2-[(*R*)-2-acetoxymethylpyrrolidin-1-yl]indole-3-carbaldehyde (**25**) in 43% yield, which was converted to **24** by treatment with aqueous 8% NaOH in a quantitative yield.



Scheme 3. Reaction of **1** with Nitrogen-Centered Nucleophiles





Scheme 5. Reaction of 1 with Carbon-Centered Nucleophiles

III. Reaction of 1 with Carbon-Centered Nucleophiles

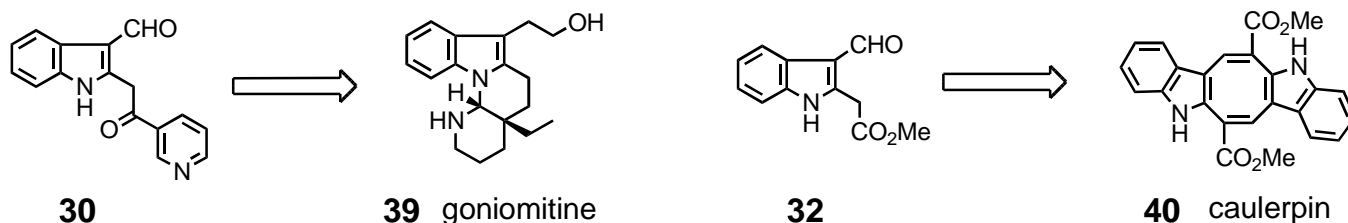
As for a carbon nucleophile, we chose KCN at first (Scheme 5). The reaction proceeded smoothly to give **26** in 98% yield. The reaction of **1** with acetone in the presence of KH in acetone–THF produced the expected **27** together with **28** in 51 and 29% yields, respectively. On the other hand, 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-acetylpyridine 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

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 (SiO₂, 100–200 mesh, from Kanto Chemical Co., Inc.) or activated alumina (Al₂O₃, 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. 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 an oil, which was column chromatographed on SiO₂ with CH₂Cl₂–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. ¹H-NMR (CD₃OD) δ: 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 C₁₀H₉NOS: 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_4Cl was added. The whole was extracted with CH_2Cl_2 –MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave an oil, which was column chromatographed on SiO_2 with CH_2Cl_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} . $^1\text{H-NMR}$ (CD_3OD) δ : 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 $\text{C}_{10}\text{H}_9\text{NO}_2$: 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} . $^1\text{H-NMR}$ (CD_3OD) δ : 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 $\text{C}_{11}\text{H}_{11}\text{NO}_2$: C, 69.82; H, 5.68; N, 7.40. Found: C, 69.82; H, 5.88; N, 7.31.

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. NH_4Cl was added and the whole was extracted with EtOAc. 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 CH_2Cl_2 –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} . $^1\text{H-NMR}$ (CD_3OD) 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 $\text{C}_{11}\text{H}_{11}\text{NO}_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.08; H, 5.50; N, 6.86.

2-(3-Hydroxypropyloxy)indole-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 (46:5:0.5, 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 C₁₂H₁₃NO₃·1/8H₂O: 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*=6.1, 5.6 and 3.9 Hz), 4.41 (1H, dd, *J*=9.8 and 6.1 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 C₁₂H₁₃NO₄: C, 61.27; H, 5.27; N, 5.95. Found: C, 60.97; H, 5.55; N, 6.00.

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) λ_{max} 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) λ_{max} 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-*d*₆) 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, ddd, *J*=7.5, 7.4, and 1.1 Hz), 7.19 (1H, ddd, *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, ddd, $J=7.7$, 1.1, and 0.6 Hz), 7.06 (1H, ddd, $J=7.7$, 7.6, and 1.1 Hz), 7.26 (1H, ddd, $J=7.7$, 7.6, and 1.1 Hz), 7.49 (1H, ddd, $J=7.7$, 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 109–109.5 °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, ddd, $J=14.5$, 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, td, $J=7.6$ 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-*d*₆ 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-*d*₆ 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-*d*₆ 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.

(8a*S*)-2-(3-Formylindol-2-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (17) from 1 — In the general procedure for **14**, (8a*S*)-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-*d*₆ 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 D₂O). MS *m/z*: 297 (M⁺). *Anal.* Calcd for C₁₆H₁₅N₃O₃: 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. ¹H-NMR (5% DMSO-*d*₆ in CDCl₃) δ: 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 D₂O). MS *m/z*: 261 (M⁺). *Anal.* Calcd for C₁₆H₁₁N₃O: 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

CH₂Cl₂–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. ¹H-NMR (DMSO-*d*₆) δ: 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 D₂O). MS *m/z*: 214 (M⁺). *Anal.* Calcd for C₁₃H₁₄N₂O: 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 CH₂Cl₂–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. ¹H-NMR (CD₃OD) δ: 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 C₁₄H₁₆N₂O: 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) λ_{max} 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) λ_{max} nm (log ϵ): 329 (4.06), 274 (4.18), 255 (4.36), 219 (4.40). IR (KBr): 1570, 1380, 1365, 1249, 1228, 1147, 993, 903, 830, 748, 663 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) 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 $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}$: 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 H_2O , the whole was extracted with EtOAc. 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–28% NH_3 (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) λ_{max} nm (log ϵ): 322 (4.17), 269 (4.23), 258 (4.40), 217 (4.36). $[\alpha]_{\text{D}}^{24}$: –59 ($c=0.5$, MeOH). IR (KBr): 1560, 1368, 1238, 1040, 742, 662 cm^{-1} . $^1\text{H-NMR}$ (CD_3OD) δ : 2.11–2.25 (4H, m), 3.55–3.63 (1H, m), 3.69 (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), 7.11–7.13 (1H, m), 8.10 (1H, br s), 9.70 (1H, s). MS m/z : 244 (M^+). *Anal.* Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 1/8\text{H}_2\text{O}$: 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 CH_2Cl_2 –hexane). UV (MeOH) λ_{max} nm (log ϵ): 348 (4.30), 281 (4.18), 276 (4.26), 272 (4.17), 242 (3.81), 209 (4.57). $[\alpha]_{\text{D}}^{30}$: –702 ($c=0.36$, MeOH). IR (KBr): 1635, 1426, 1390, 1308, 1262, 1222, 1095, 1060, 1009, 922, 745 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) 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 $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$: 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, Ac_2O (2 mL) was added and the mixture was stirred at rt for 0.5 h. After evaporation of the solvent, sat. aq. NaHCO_3 was added to the residue and the whole was extracted with CH_2Cl_2 –MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave 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, dd, *J*=7.6 and 1.0 Hz), 9.82 (1H, br s), 9.88 (1H, 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 (99.5:0.5, 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) λ_{max} 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 C₁₆H₁₇NO₂•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) λ_{max} 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-*d*₆) 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*=7.2, 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 *R_f* 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 *R_f* 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 mg, 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, dd, *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, ddd, *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 C₁₂H₁₁NO: 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. ¹H-NMR (CD₃OD) δ: 2.62–2.73 (2H, m), 4.05 (3H, s), 4.96 (1H, t, *J*=6.7 Hz), 5.01 (1H, ddt, *J*=10.2, 2.1, and 1.1 Hz), 5.07 (1H, ddt, *J*=17.1, 2.1, and 1.5 Hz), 5.85 (1H, ddt, *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 C₁₃H₁₅NO₂: 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 Bu₄NF•3H₂O (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. 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 subjected to p-TLC on SiO₂ with CHCl₃–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–H₂O). IR (KBr): 1627, 1580, 1461, 1381, 1232 cm^{-1} . ¹H-NMR (CDCl_3) δ : 1.77 (3H, s), 1.84 (3H, d, $J=1.5$ Hz), 3.88 (2H, d, $J=7.3$ Hz), 5.40 (1H, tq, $J=7.3$ and 1.5 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 D₂O), 10.23 (1H, s). MS m/z : 213 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}$: 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_2Cl_2 –hexane). IR (KBr): 3160, 1621, 1581, 1440, 1369 cm^{-1} . ¹H-NMR (CDCl_3) δ : 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), 8.52 (1H, br s, disappeared on addition of D₂O), 10.47 (1H, s). MS m/z : 213 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}$: 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} . ¹H-NMR (CDCl_3) δ : 1.07 (3H, s), 1.08 (3H, s), 1.57 (1H, br s, disappeared on addition of D₂O), 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 $\text{C}_{15}\text{H}_{19}\text{NO}_2$: 245.1416. Found; 245.1415.

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