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The Chemistry of Indoles. XXXIX.[1] A Facile Synthetic Method for 7-Substituted Indoles

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A simple four-step synthetic method for 7-iodo-, 7-bromo- and 7-chloroindole was established with high overall yield starting from 2,3-dihydroindole. Several 7-substituted indoles carrying a carbon side chain and 7-methoxyindole were also synthesized.

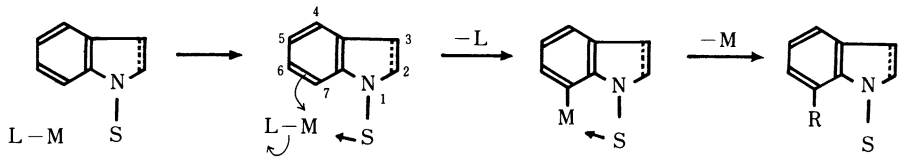
Keywords——thallation; 7-substituted indole; regioselective metalation; 7-iodoindole; 7-bromoindole; 7-chloroindole; 7-methoxyindole; methyl 3-(indol-7-yl)acrylate; 4-(indol-7-yl)-2-methyl-3-buten-2-ol; Heck reaction

For one possible approach to the construction of various types of structurally and biologically interesting indole alkaloids having a substituent at the 7-position,[2] 7-halogenoindoles are required as common building blocks. However, little work has been done on their syntheses and consequently they are available only through a laborious multistep route[3] with poor overall yield. In our continuing studies on regioselective functionalization of indoles,[4,5] we have elaborated a facile and regioselective synthetic method for 7-halogenoindoles, as reported in the preliminary communication.[6] In this report, we describe in detail these results and the syntheses of various 7-substituted indoles.

Regioselective Syntheses of 7-Halogenoindoles

In the previous paper, we reported that the thallation–palladation method[4] was a useful synthetic reaction for 4-substituted indoles with high regioselectivity. It was also shown that the regioselectivity was dramatically influenced by introduction of an extra substituent into the 2 or 3 position of the indole nucleus.[5] Based on these results, we designed the strategy shown in Chart 1. If a suitable ligand (S) is introduced at the indole (or 2,3-dihydroindole) nitrogen, the S group can coordinate to a metal reagent (metal (M)–leaving group (L)) putting the metal close to the 7-position. Consequently, metallation would occur regioselectively at the carbon-7 making the carbon susceptible to various functionalizations.

During examination of the feasibility of the strategy as planned, we soon recognized that thallation of 1-acyl-3-unsubstituted indoles with thallium tris-trifluoroacetate (TTFA) was unsuccessful because the compounds were quite sensitive to acids, and formed polymers.



S, ligand; M, metal; L, leaving group; R, suitable functional group.

Chart 1. Strategy for the Synthesis of 7-Substituted Indoles

However, in the 2,3-dihydroindole series, we could actualize our strategy by using TTFA and the acetyl group as M–L and S, respectively, though a methoxycarbonyl group could not function as the S group.

1-Acetyl-2,3-dihydroindole[7] (**2**) was produced in quantitative yield by the reaction of 2,3-dihydroindole (**1**) with refluxing acetic anhydride (Chart 2). Thallation of **2** was carried out with 1.6 mol eq of TTFA in trifluoroacetic acid[8] (TFA) at room temperature to give crude (1-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate) (**3**) as a crystalline residue, which was exposed to a vacuum to remove a trace amount of TFA. Although **3** could be isolated as a colorless crystalline powder, the crude residue (**3**) was subjected to the following reactions without further purification since we hoped to establish a simple one-pot procedure. When the residue was reacted with aqueous potassium iodide (KI), 1-acetyl-2,3-dihydro-7-iodoindole[9] (**4a**) was produced in 74% yield together with 1-acetyl-2,3-dihydro-5-iodoindole[10] (**5**) in 5% yield. It should be noted that when iodination was carried out in the mixed solvent of TFA and water (1 : 3, v/v) with KI, the yield of **5** significantly increased to 21%, whereas the yield of **4a** decreased to 42%.

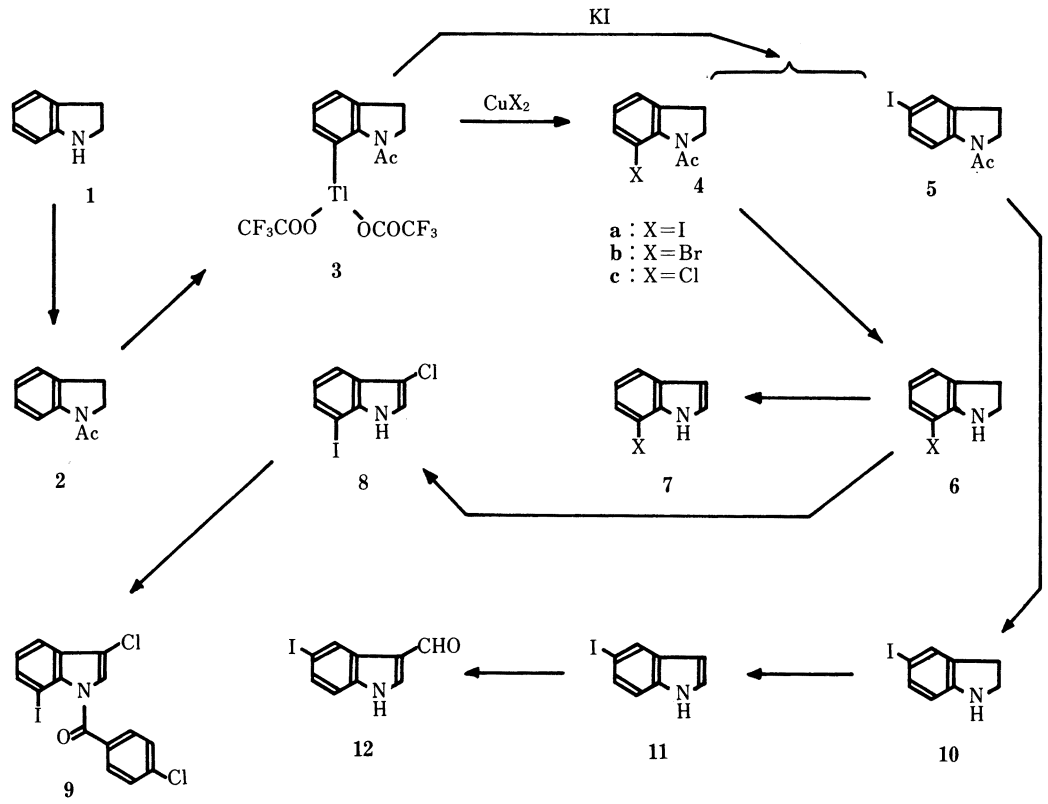


Chart 2

Although the reaction mechanism is unknown, these results of acidic iodination suggest that iodination should be carried out after removal of contaminating TFA from the thallated crystalline residue (**3**) as completely as possible.

Reaction of the thallated crystalline residue (**3**) with either cupric bromide or cupric chloride in *N*,*N*-dimethylformamide (DMF) afforded 1-acetyl-2,3-dihydro-7-bromo-[9] (**4b**) or -7-chloroindole (**4c**) in 62% and 42% yields, respectively, without the formation of the corresponding 5-halogenated compounds. Hydrolysis of 1-acetyl-2,3-dihydro-7-halo-

genoindoles (**4a**, **4b**, and **4c**) with aqueous sodium hydroxide afforded the corresponding 2,3-dihydro-7-halogenoindoles (**6a**, **6b**,[11] and **6c**) in 98%, 96%, and 93% yields, respectively.

Next, oxidation of the 2,3-dihydroindole (**6a**) to indole was examined by using active manganese dioxide (MnO_2),[12] *N*-chlorosuccinimide (NCS),[13] and *tert*-butylhypochlorite.[14] The reaction of **6a** with active MnO_2 in methylene chloride afforded the desired 7-iodoindole (**7a**) in only 13% yield, with the predominant formation of an unknown dimeric product (66%), whose mass spectrum (MS) showed the molecular ion peak at *m/z* 486. Oxidation of **6a** with NCS or *tert*-butylhypochlorite in the presence of triethylamine (NEt_3) afforded 3-chloro-7-iodoindole (**8**) together with recovery of **6a**; their ratios varied depending on the amount of the chlorinating reagent, but the formation of **7a** was not detected in the reaction mixtures. To our surprise, compound **8** was stable and its sodium salt, prepared by the action of sodium hydride in absolute DMF, was demonstrated to react with 4-chlorobenzoyl chloride, affording 3-chloro-1-(4-chlorobenzoyl)-7-iodoindole (**9**) in 62% yield. Further functionalization of **8** is in progress.

Finally, treatment of **6a** with oxygen in the presence of a catalytic amount of salcomine[15] in methanol at room temperature was found to afford **7a** cleanly in 77% yield. Under similar reaction conditions, **6b** and **6c** were successfully converted to the desired 7-bromo-[3a] (**7b**) and 7-chloroindole[3b] (**7c**) in 72% and 70% yields, respectively. Thus, 7-halogenoindoles are now readily available with high overall yield in four steps starting from **1**.

The structure of **5** was established as follows. Hydrolysis of **5** gave an 86% yield of 2,3-dihydro-5-iodoindole (**10**), which was converted to 5-iodoindole[16] (**11**) in 71% yield by salcomine-catalyzed oxidation with oxygen. Vilsmeier reaction of **11** with phosphorus oxychloride and DMF gave 5-iodo-3-indolecarbaldehyde (**12**) in 89% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5**, the C-7 proton signal appeared as a broad doublet ($J=8.4$ Hz) at a lower magnetic field than usual at δ 7.85 due to the anisotropic effect of the 1-acetyl group. In the compound **12**, the C-4 proton was deshielded by the 3-formyl group and resonated at a lower magnetic field (δ 8.88) as a doublet ($J=1.6$ Hz). These results clearly established the 5-substituted indole structure.

Syntheses of Various 7-Substituted Indoles

Since selective thallation of **2** was established as discussed above, we next examined direct introduction of a carbon side chain into the 7-position according to our thallation–palladation method.[4] Thus, **2** was thallated and the resulting crude residue (**3**) was treated with methyl acrylate in the presence of a catalytic amount of palladium acetate ($Pd(OAc)_2$) in DMF to afford methyl 3-(1-acetyl-2,3-dihydroindol-5-yl)acrylate (**13**) and methyl 3-(1-acetyl-2,3-dihydroindol-7-yl)acrylate (**14**) in 2% and 4% yields, respectively (Chart 3).

The structure of **13** was readily proved by the fact that the palladium-catalyzed Heck reaction[17] of **5** with methyl acrylate gave **13** in 96% yield. On the other hand, the structure of **14** was proved as follows. First, **6a** was led to methyl 3-(2,3-dihydroindol-7-yl)acrylate (**15**) in 90% yield by means of the Heck reaction with methyl acrylate. Treatment of **15** with acetic anhydride and pyridine afforded **14** in 94% yield. Subsequent catalytic hydrogenation of **15** over 10% palladium on carbon at ordinary atmospheric pressure gave an 84% yield of 4*H*-1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]quinoline-4-one (**16**), which was identical with an authentic sample prepared by the cyclization of 1-(3-chloropropionyl)-2,3-dihydroindole.[18] For further structural confirmation, **15** was subjected to salcomine-catalyzed oxidation with oxygen to afford in 71% yield the known methyl 3-(indol-7-yl)acrylate (**17**),[5] which had been alternatively prepared starting from methyl 3-methyl-2-nitrobenzoate (**18**) *via* 7-indolecarbaldehyde (**19**).

It is notable that the thallation–palladation reaction of **2** afforded a poor result, while the Heck reaction of **6a** gave a satisfactory result. The formation of **3** was unambiguously proved

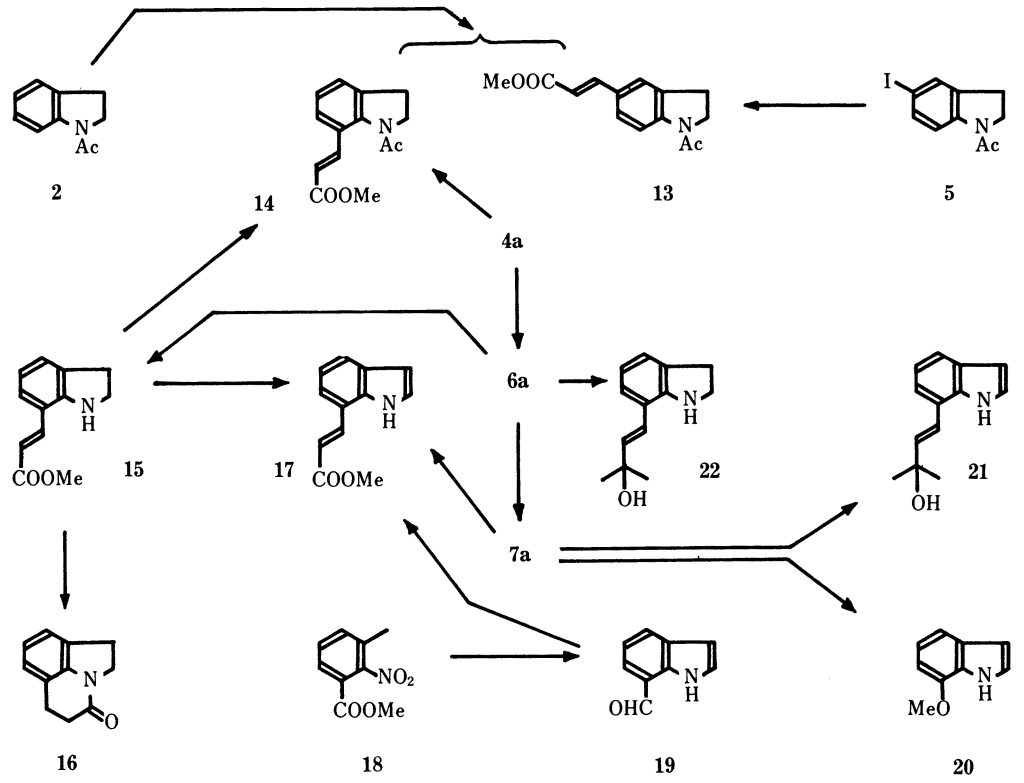


Chart 3

by its high-yield conversion to the corresponding 7-iodo compound (**4a**), as discussed above. Therefore, the above results suggest that the thallium–palladium exchange can not occur effectively at the 7-position of **3**, probably because palladium requires a strictly square-planar ligand field. The acetyl group on the sp^3 nitrogen can neither satisfy this requirement nor function as a ligand, but acts only as a sterically congesting group making the formation of the corresponding palladium complex unfavorable. Support for these assumptions has been furnished by the result of the Heck reaction of **4a** with methyl acrylate, providing **14** and **2**, and recovery of **4a** in 5%, 14%, and 60% yields, respectively, while **6a** successfully afforded **15** under similar reaction conditions.

The versatility of 7-halogenoindoles was shown by the following reactions using **7a** as a representative substrate. Thus, the treatment of **7a** with sodium methoxide in DMF in the presence of cuprous iodide[19] afforded 7-methoxyindole[20] (**20**) in 76% yield. The structure of **20** was unequivocally established by an alternative synthesis starting from 3-methoxy-2-nitrotoluene by the use of the improved Leimgruber–Batcho method.[21] The synthesis of 8-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline starting from **20** has already been reported.[22] On the other hand, the Heck reaction of **7a** with methyl acrylate successfully afforded **17** in 90% yield. When 2-methyl-3-buten-2-ol was used as an olefin component, **7a** produced 4-(indol-7-yl)-2-methyl-3-buten-2-ol (**21**) in 48% yield, together with recovery of **7a** in 33% yield. Similarly, the Heck reaction of **6a** with 2-methyl-3-buten-2-ol proceeded smoothly to give 4-(2,3-dihydroindol-7-yl)-2-methyl-3-buten-2-ol (**22**) in 74% yield.

In conclusion, simple 7-substituted indoles are now readily accessible from 2,3-dihydroindole (**1**). With these compounds in hand, we are currently investigating the syntheses of 7-substituted natural indole alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL JNM-PMX60 or FX100S spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kieselgel GF_{254} (Type 60) (SiO_2). Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

1-Acetyl-2,3-dihydro-7-iodoindole (4a) and 1-Acetyl-2,3-dihydro-5-iodoindole (5) from 1-Acetyl-2,3-dihydroindole (2)——A 0.88 M solution of TTFA (32.8 ml, 1.6 mol eq) in TFA[8] was added to a solution of **2** (2.908 g) in TFA (29.0 ml) and stirring was continued at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue was dried *in vacuo* at room temperature. By this work-up, the oily residue was transformed into a crystalline residue (**3**). [By the addition of a small amount of TFA to the residue, followed by filtration and washing with 1,2-dichloromethane, (1-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate) (**3**) could be isolated as a colorless crystalline powder. **3**: mp 135—140 °C. IR (KBr): 1670 (br), 1613, 1211, 1137, 837, 805, 723 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, d, J=12 Hz), 3.09 (2H, dt, J=76, 8 Hz), 4.12 (2H, br s), 7.09 (1H, dt, J=268, 7 Hz), 7.27 (1H, dd, J=1050, 7 Hz), 7.29 (1H, dd, J=112, 7 Hz).] A solution of KI (23.912 g) in H_2O (160 ml) was added to the crystalline residue (**3**) and stirring was continued at room temperature for 2 h. After addition of CH_2Cl_2–MeOH (95 : 5, v/v) to the reaction mixture, the whole was filtered through SiO_2 to remove solid precipitates. The organic layer was separated and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed successively with 5% aqueous sodium thiosulfate and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to column chromatography on SiO_2 with AcOEt–*n*-hexane (1 : 1, v/v) as an eluent. From the early fractions, **4a** (3.843 g, 74%) was obtained. From the later fractions, **5** (254.5 mg, 5%) was obtained.

4a: mp 128.0—128.5 °C (lit.[9] mp 119—120 °C, colorless prisms, recrystallized from AcOEt). IR (KBr): 1654, 1589, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.98 (2H, t, J=7.4 Hz), 4.05 (2H, t, J=7.4 Hz), 6.62 (1H, t, J=7.2 Hz), 7.06 (1H, br d, J=7.2 Hz), 7.51 (1H, br d, J=7.2 Hz). MS *m/z*: 287 (M^+). *Anal.* Calcd for $C_{10}H_{10}INO$: C, 41.84; H, 3.51; N, 4.88. Found: C, 41.74; H, 3.50; N, 4.73.

5: mp 142.5—143.5 °C (lit.[10] mp 139.5—140.5 °C, colorless prisms, recrystallized from AcOEt). IR (KBr): 1650, 1581 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, br s), 3.09 (2H, t, J=7.8 Hz), 3.98 (2H, br t, J=7.8 Hz), 7.26—7.48 (2H, m), 7.85 (1H, br d, J=8.4 Hz). MS *m/z*: 287 (M^+). *Anal.* Calcd for $C_{10}H_{10}INO$: C, 41.84; H, 3.51; N, 4.88. Found: C, 42.00; H, 3.52; N, 4.69.

1-Acetyl-2,3-dihydro-7-bromoindole (4b) from 2——A 0.88 M solution of TTFA (17.1 ml, 1.6 mol eq) in TFA was added to a solution of **2** (1.504 g) in TFA (15.0 ml) and stirring was continued at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (20.0 ml). A solution of cupric bromide (8.358 g) in DMF (55.0 ml) was added to the above solution and the whole was stirred at room temperature for 3 h. After evaporation of the solvent under reduced pressure, CH_2Cl_2–MeOH (95 : 5, v/v) and brine were added to the residue and the whole was filtered to remove precipitates. The organic layer was separated, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in benzene. The resulting benzene solution was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a crystalline solid, which was purified by column chromatography on SiO_2 with CH_2Cl_2–AcOEt (95 : 5, v/v) as an eluent to give **4b** (1.381 g, 62%). mp 115.0—115.5 °C (lit.[9] mp 116—117 °C, colorless prisms, recrystallized from AcOEt–*n*-hexane). IR (KBr): 1666, 1451, 1383 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 2.99 (2H, t, J=7.2 Hz), 4.13 (2H, t, J=7.2 Hz), 6.79 (1H, t, J=7.2 Hz), 7.06 (1H, br d, J=7.2 Hz), 7.26 (1H, br d, J=7.2 Hz). MS *m/z*: 241, 239 (M^+). *Anal.* Calcd for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.20; N, 5.83. Found: C, 50.30; H, 4.18; N, 5.93.

1-Acetyl-2,3-dihydro-7-chloroindole (4c) from 2——A 0.88 M solution of TTFA (45.0 ml, 2.1 mol eq) in TFA was added to a solution of **2** (3.000 g) in TFA (30.0 ml) and stirring was continued at 45—55 °C for 4 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (20.0 ml). A solution of cupric chloride (10.178 g) in DMF (100 ml) was added to the above solution and the whole was stirred at 45—55 °C for 4.5 h. After evaporation of the solvent under reduced pressure, CH_2Cl_2–MeOH (95 : 5, v/v) and brine were added to the residue and the whole was filtered to remove precipitates. The organic layer was separated, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on SiO_2 with AcOEt–CH_2Cl_2–*n*-hexane (1 : 2 : 5, v/v) as an eluent to give **4c** (1.511 g, 42%). mp 99.0—100.0 °C (colorless prisms, recrystallized from *n*-hexane). IR (KBr): 1666, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.96 (2H, t, J=7.2 Hz), 4.10 (2H, t, J=7.2 Hz), 6.70—7.20 (3H, m). MS *m/z*: 197, 195 (M^+). *Anal.* Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.14; H, 5.11; N, 7.05.

2,3-Dihydro-7-iodoindole (6a) from 4a——A 40% aqueous NaOH solution (2.0 ml) was added to a solution of **4a** (199.7 mg) in MeOH (2.0 ml) and the whole was heated under reflux for 30 min with stirring. After cooling of the reaction mixture, water was added and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as an eluent to give **6a** (167.0 mg, 98%) as a

colorless oil. IR (film): 3360, 1605, 1571 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.92—3.29 (2H, m), 3.40—3.75 (3H, m, on addition of D_2O, 1H disappeared), 6.30 (1H, t, J=7.4 Hz), 6.91 (1H, br d, J=7.4 Hz), 7.22 (1H, br d, J=7.4 Hz). High resolution MS m/z: Calcd for C_8H_8IN: 244.9702. Found: 244.9727.

7-Bromo-2,3-dihydroindole (6b) from 4b——A 40% aqueous NaOH solution (2.0 ml) was added to a solution of **4b** (106.3 mg) in MeOH (2.0 ml) and the whole was heated under reflux for 30 min with stirring. After cooling of the reaction mixture, H_2O was added and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as an eluent to give **6b** (84.5 mg, 96%) as a colorless oil. IR (film): 3380, 1608, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.02—3.24 (2H, m, A_2 part of A_2B_2), 3.51—3.72 (2H, m, B_2 part of A_2B_2), 3.70 (1H, br s, disappeared on addition of D_2O), 6.54 (1H, dd, J=8.0, 7.2 Hz), 7.01 (1H, dd, J=7.2, 1.2 Hz), 7.14 (1H, dd, J=8.0, 1.2 Hz). High resolution MS m/z: Calcd for C_8H_8BrN: 196.9840 and 198.9821. Found: 196.9857 and 198.9845.

7-Chloro-2,3-dihydroindole (6c) from 4c——A 40% aqueous NaOH solution (1.0 ml) was added to a solution of **4c** (105.9 mg) in MeOH (1.0 ml) and the whole was heated under reflux for 30 min with stirring. After cooling of the reaction mixture, H_2O was added and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as an eluent to give **6c** (77.6 mg, 93%) as a colorless oil. IR (film): 3380, 1610, 1583 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (1H, br s, disappeared on addition of D_2O), 2.98—3.21 (2H, m, A_2 part of A_2B_2), 3.52—3.73 (2H, m, B_2 part of A_2B_2), 6.60 (1H, t, J=7.7 Hz), 6.92—7.08 (2H, m). High resolution MS m/z: Calcd for C_8H_8ClN: 153.0345. Found: 153.0363.

7-Iodoindole (7a) from 6a——Oxygen was bubbled into a solution of **6a** (268.8 mg) and salcomine (36.6 mg) in MeOH (55.0 ml) at room temperature for 5 h with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 3, v/v) as an eluent to give **7a** (205.3 mg, 77%). mp 55.0—56.0 °C (colorless plates, recrystallized from hexane). IR (KBr): 3390, 1606, 1554 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 6.46 (1H, d, J=3.0 Hz), 6.65 (1H, t, J=7.5 Hz), 7.15 (1H, d, J=3.0 Hz), 7.32 (1H, dd, J=7.5, 1.2 Hz), 7.43 (1H, dd, J=7.5, 1.2 Hz). MS m/z: 243 (M^+). *Anal.* Calcd for C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.63; H, 2.41; N, 5.52.

7-Bromoindole (7b) from 6b——Oxygen was bubbled into a solution of **6b** (61.1 mg) and salcomine (10.4 mg) in MeOH (12.0 ml) at room temperature for 11 h with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as a developing solvent to give **7b** (44.4 mg, 72%). mp 45.0—45.5 °C (lit.[3a] mp 42—43 °C, colorless prisms, recrystallized from *n*-hexane). IR (KBr): 3400, 1613, 1559 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (1H, dd, J=3.2, 2.2 Hz), 6.99 (1H, t, J=7.7 Hz), 7.25 (1H, dd, J=3.2, 2.2 Hz), 7.35 (1H, dd, J=7.7, 0.7 Hz), 7.58 (1H, br d, J=7.7 Hz), 8.28 (1H, br s). MS m/z: 197, 195 (M^+). *Anal.* Calcd for C_8H_6BrN: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.89; H, 2.99; N, 7.01.

7-Chloroindole (7c) from 6c——Oxygen was bubbled into a solution of **6c** (46.7 mg) and salcomine (10.1 mg) in MeOH (10.0 ml) at room temperature for 4 h with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as a developing solvent to give **7c** (32.1 mg, 70%). mp 59.0—59.5 °C (lit.[3b] mp 57—58 °C, colorless plates, recrystallized from *n*-hexane). IR (KBr): 3400, 1620, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.57 (1H, dd, J=3.3, 2.1 Hz), 7.02 (1H, t, J=7.6 Hz), 7.18 (1H, dd, J=7.6, 1.2 Hz), 7.25 (1H, dd, J=3.3, 2.1 Hz), 7.53 (1H, dd, J=7.6, 1.2 Hz), 8.31 (1H, br s). *Anal.* Calcd for C_8H_6ClN: C; 63.38; H, 3.99; N, 9.24. Found: C, 63.23; H, 3.96; N, 9.23.

3-Chloro-7-iodoindole (8) from 6a——A solution of NCS (3.052 g) in CH_2Cl_2 (50.0 ml) was added to a solution of **6a** (1.397 g) in CH_2Cl_2 (10.0 ml) and NEt_3 (8.0 ml), and the mixture was stirred at room temperature for 1 h. The whole was washed with 2 N HCl, then with brine, and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residual oil was purified by column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as an eluent to give **8** (1.030 g, 65%). mp 58.0—58.5 °C (colorless prisms, recrystallized from CCl_4). IR (KBr): 3380, 1608, 771, 733 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 6.76 (1H, dd, J=8.1, 7.0 Hz), 7.18 (1H, s), 7.40 (1H, dd, J=8.1, 1.3 Hz), 7.42 (1H, dd, J=7.0, 1.3 Hz). MS m/z: 279, 277 (M^+). *Anal.* Calcd for C_8H_5ClIN: C, 34.63; H, 1.82; N, 5.05. Found: C, 34.46; H, 1.68; N, 4.99.

3-Chloro-1-(4-chlorobenzoyl)-7-iodoindole (9) from 8——A solution of **8** (198.8 mg) in absolute DMF (2.0 ml) was added to NaH (prepared by washing 50% NaH (41.5 mg, 1.2 mol eq) with absolute benzene) with stirring at room temperature. Stirring was continued for 5 min, then a solution of 4-chlorobenzoyl chloride (164.0 mg) in benzene (1.0 ml) was added and the whole was stirred at room temperature for 14.5 h. Aqueous saturated $NaHCO_3$ was added and the whole was extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a crystalline solid, which was subjected to column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (4 : 6, v/v) as an eluent. From the early fractions, the starting material (52.5 mg, 27%) was recovered. From the later fractions, **9** (185.9 mg, 62%) was obtained. mp 149.0—150.0 °C (colorless prisms, recrystallized from CH_2Cl_2–*n*-hexane). IR (KBr): 1703, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.98 (1H, t, J=7.4 Hz), 7.12 (1H, s), 7.40 (2H, d, J=8.0 Hz), 7.46—7.64 (1H, m), 7.68—7.89 (1H, m), 7.76 (2H, d, J=8.0 Hz). MS m/z: 419, 417, 415 (M^+). *Anal.* Calcd for $C_{15}H_8Cl_2INO$: C, 43.30; H, 1.94; N, 3.37. Found: C, 43.49; H, 1.81; N, 3.31.

2,3-Dihydro-5-iodoindole (10) from 5——A 40% aqueous NaOH solution (1.0 ml) was added to a solution of **5** (27.4 mg) in MeOH (1.0 ml) and the mixture was heated under reflux for 30 min under an argon atmosphere with stirring. After the reaction mixture had cooled, the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1 : 1, v/v) as an eluent to give **10** (20.1 mg, 86%) as a colorless oil. IR (film): 3380, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.89 (2H, t, J=8.3 Hz), 3.41 (2H, t, J=8.3 Hz), 6.33 (1H, d, J=8.1 Hz), 7.17 (1H, br d, J=8.1 Hz), 7.27 (1H, br s). MS *m/z*: 245 (M^+). High resolution MS *m/z*: Calcd for C_8H_8IN: 244.9702. Found: 244.9754.

5-Iodoindole (11) from 10——Oxygen was bubbled into a solution of **10** (33.4 mg) and salcomine (48.0 mg) in MeOH (6.0 ml) at room temperature for 5 h with stirring. After evaporation of the solvent, the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (7 : 3, v/v) as a developing solvent. Under ultraviolet (UV) light, two bands were detected on the whole luminescent plate. Extraction of the band at *Rf* 0.88—0.77 with CH_2Cl_2–MeOH (95 : 5, v/v) afforded **11** (23.6 mg, 71%). Extraction of the band at *Rf* 0.32—0.24 with the same mixed solvent afforded the starting material (3.1 mg, 9%). **11**: mp 103.0—103.5 °C (colorless prisms, recrystallized from *n*-hexane). IR (film): 3410, 796, 761 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.45—6.51 (1H, m), 7.13—7.25 (2H, m), 7.44 (1H, dd, J=8.6, 1.6 Hz), 7.98 (1H, br s), 8.16 (1H, br s). MS *m/z*: 243 (M^+). *Anal.* Calcd for C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.60; H, 2.45; N, 5.62.

5-Iodo-3-indolecarbaldehyde (12) from 11——A solution of **11** (23.2 mg) in absolute DMF (0.6 ml) was added to stirred Vilsmeier reagent, prepared by mixing $POCl_3$ (26.7 mg) with ice-cooled absolute DMF (0.5 ml), and stirring was continued at room temperature for 17 h. Ice and H_2O were added and the whole was made alkaline by adding 2 N NaOH, and then extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a crystalline solid, which was purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as an eluent to give **12** (23.0 mg, 89%). mp 237.0—238.0 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3060, 1619 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 7.19 (1H, d, J=8.4 Hz), 7.49 (1H, dd, J=8.4, 1.6 Hz), 7.99 (1H, s), 8.88 (1H, d, J=1.6 Hz), 9.98 (1H, s). MS *m/z*: 271 (M^+). *Anal.* Calcd for C_9H_6INO: C, 39.88; H, 2.23; N, 5.17. Found: C, 39.89; H, 2.21; N, 4.88.

Methyl 3-(1-Acetyl-2,3-dihydroindol-5-yl)acrylate (13) and Methyl 3-(1-Acetyl-2,3-dihydroindol-7-yl)acrylate (14) from 2——A 0.88 M solution of TTFA (1.13 ml, 1.6 mol eq) in TFA was added to a solution of **2** (99.6 mg) in TFA (1.0 ml) and stirring was continued at room temperature for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in DMF (2.0 ml). $Pd(OAc)_2$ (11.5 mg) and a solution of freshly distilled methyl acrylate (159.4 mg) were added, and the whole was heated at 120 °C for 30 min with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on SiO_2 with AcOEt–CH_2Cl_2–*n*-hexane (1 : 1 : 2, v/v) as an eluent. From the early fractions, the starting material (32.8 mg, 33%) was recovered. From the later fractions, a mixture of **13** and **14** was obtained. The mixture was separated by p-TLC on SiO_2 with CH_2Cl_2–Et_2O (9 : 1, v/v) as a developing solvent. Under UV light, two bands were detected. Extraction of the upper band at *Rf* 0.61—0.57 with CH_2Cl_2–MeOH (95 : 5, v/v) afforded **14** (5.8 mg, 4%). Extraction of the lower band at *Rf* 0.52—0.44 with the same mixed solvent afforded **13** (3.5 mg, 2%).

13 from 5——A solution of **5** (48.5 mg), freshly distilled methyl acrylate (51.3 mg), $Pd(OAc)_2$ (5.3 mg), and NEt_3 (0.5 ml) in DMF (3.0 ml) was heated at 110 °C for 30 min with stirring. After cooling of the reaction mixture, AcOEt was added and the whole was filtered to remove solid precipitates. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **13** (39.9 mg, 96%). mp 179.5—180.5 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1711, 1659, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 3.19 (2H, t, J=8.3 Hz), 3.78 (3H, s), 4.09 (2H, t, J=8.3 Hz), 6.30 (1H, d, J=15.9 Hz), 7.26—7.41 (2H, br m), 7.61 (1H, d, J=15.9 Hz), 8.16 (1H, br d, J=8.8 Hz). MS *m/z*: 245 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.57; H, 6.19; N, 5.70.

14 from 4a——A solution of **4a** (99.1 mg), freshly distilled methyl acrylate (91.2 mg), $Pd(OAc)_2$ (10.2 mg), and NEt_3 (0.5 ml) in DMF (3.0 ml) was heated at 115 °C for 30 min with stirring. After cooling of the reaction mixture, solid precipitates were removed by filtration. The filtrate was concentrated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2–Et_2O (95 : 5, v/v) as a developing solvent. Under UV light, three dark bands were detected. Extraction of the upper band at *Rf* 0.51—0.40 with CH_2Cl_2–MeOH (95 : 5, v/v) afforded the starting material (59.2 mg, 60%). Extraction of the middle band at *Rf* 0.37—0.31 with the same mixed solvent afforded **2** (7.6 mg, 14%). Extraction of the lower band at *Rf* 0.21—0.14 with the same mixed solvent afforded **14** (4.6 mg, 5%). Compound **14** was identical with the sample prepared by the acetylation of **15**.

14 from Methyl 3-(2,3-Dihydroindol-7-yl)acrylate (15)——Acetic anhydride (0.5 ml) was added to a solution of **15** (20.5 mg) in pyridine (1.0 ml) and the mixture was stirred at room temperature for 17 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2–MeOH (95 : 5, v/v). The solution was washed successively with aqueous saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **14** (23.2 mg, 94%). mp 123.0—124.0 °C (colorless needles, recrystallized from Et_2O–*n*-hexane). IR

(KBr): 1712, 1655, 1626 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, br s), 3.04 (2H, t, J=7.6 Hz), 3.79 (3H, s), 4.17 (2H, t, J=7.6 Hz), 6.31 (1H, d, J=16.1 Hz), 7.10 (1H, t, J=7.3 Hz), 7.24 (1H, br d, J=7.3 Hz), 7.43 (1H, br d, J=7.3 Hz), 7.69 (1H, d, J=16.1 Hz). MS m/z: 245 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.60; H, 6.17; N, 5.66.

15 from 6a——A solution of **6a** (53.7 mg), freshly distilled methyl acrylate (58.7 mg), $Pd(OAc)_2$ (5.1 mg), and NEt_3 (0.5 ml) in DMF (3.0 ml) was heated at 120 °C for 30 min with stirring. After cooling, AcOEt was added to the reaction mixture and the whole was filtered to remove solid precipitates. The filtrate was washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **15** (40.0 mg, 90%). mp 86.0—87.0 °C (yellow prisms, recrystallized from ether–*n*-hexane). IR (KBr): 3370, 1690, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.06 (2H, t, J=8.5 Hz), 3.39—4.08 (1H, br s, disappeared on addition of D_2O), 3.64 (2H, t, J=8.5 Hz), 3.79 (3H, s), 6.27 (1H, d, J=16.1 Hz), 6.68 (1H, t, J=7.6 Hz), 7.03—7.21 (2H, m), 7.70 (1H, d, J=16.1 Hz). MS m/z: 203 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.71; H, 6.45; N, 6.76.

4*H*-1,2,5,6-Tetrahydropyrrolo[3,2,1-*ij*]quinoline-4-one (16) from 15——A solution of **15** (795.0 mg) in MeOH (50.0 ml) was hydrogenated over 10% Pd–C (203.2 mg) at room temperature and atmospheric pressure for 1.75 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to leave a crude product, which was purified by column chromatography on SiO_2 with ether as an eluent to give **16** (567.3 mg, 84%). mp 111.0—112.0 °C (lit.[17] mp 112—113 °C, colorless prisms, recrystallized from *n*-hexane). IR (KBr): 1649, 1485, 1394 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.63 (2H, t, J=7 Hz), 2.96 (2H, t, J=7 Hz), 3.17 (2H, t, J=8 Hz), 4.00 (2H, t, J=8 Hz), 6.76—7.12 (3H, m). MS m/z: 173 (M^+). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.42; H, 6.43; N, 7.88.

Methyl 3-(Indol-7-yl)acrylate (17) from 15——Oxygen was bubbled into a solution of **15** (50.0 mg) and salcomine (8.0 mg) in MeOH (10.0 ml) at room temperature for 4 h with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (7:3, v/v) as a developing solvent. Under UV light, two dark bands were detected on the whole luminescent plate. Extraction of the band at *Rf* 0.48—0.22 with CH_2Cl_2–MeOH (95:5, v/v) afforded **17** (35.0 mg, 71%). Extraction of the band at *Rf* 0.19—0.10 with the same mixed solvent afforded the recovered starting material (7.5 mg, 15%). **17**: mp 97.0—98.0 °C (pale yellow prisms, recrystallized from ether–*n*-hexane). Spectral data were identical with those of the authentic sample reported in our previous paper.[5]

Methyl 3-(Indol-7-yl)acrylate (17) from 7a——A solution of **7a** (50.8 mg), freshly distilled methyl acrylate (60.9 mg), $Pd(OAc)_2$ (5.6 mg), and NEt_3 (0.5 ml) in DMF (3.0 ml) was heated at 108 °C for 30 min with stirring. After cooling of the reaction mixture, AcOEt was added and the whole was filtered to remove solid precipitates. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid, which was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **17** (37.7 mg, 90%) as pale yellow prisms. Compound **17** was identical with a sample prepared from 7-indolecarbaldehyde[5] (**19**) by means of the Wittig reaction.

7-Methoxyindole (20) from 7a——A solution of **7a** (36.9 mg) in absolute DMF (3.0 ml) and cuprous iodide (58.4 mg) were added to an absolute methanol solution of sodium methoxide, prepared by dissolving sodium (57.6 mg) in absolute MeOH (1.0 ml). The whole was heated at 120 °C for 1 h with stirring. After evaporation of the solvent under reduced pressure, CH_2Cl_2–MeOH (95:5, v/v) and water were added to the residual oil and the whole was filtered through SiO_2 to remove precipitates. The organic layer was separated, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (2:1, v/v) as a developing solvent to give **20**[19] (16.9 mg, 76%) as a colorless oil. IR (film): 3405, 1628, 1584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 6.36—6.46 (1H, m), 6.47 (1H, dd, J=7.8, 1.8 Hz), 6.87 (1H, t, J=7.8 Hz), 6.93—7.05 (1H, m), 7.12 (1H, dd, J=7.8, 1.8 Hz), 8.10 (1H, br s). High resolution MS m/z: Calcd for C_9H_9NO: 147.0684. Found: 147.0702.

4-(Indol-7-yl)-2-methyl-3-buten-2-ol (21) from 7a——A mixture of **7a** (200.7 mg), freshly distilled 2-methyl-3-buten-2-ol (213.9 mg), $Pd(OAc)_2$ (18.7 mg), NEt_3 (1.0 ml), and tetra-*n*-butylammonium bromide (53.3 mg) in DMF (5.0 ml) was heated at 100 °C for 30 min with stirring. After cooling of the reaction mixture, AcOEt was added and the whole was filtered to remove solid precipitates. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane (1:1, v/v) as an eluent. From the early fractions, the starting material (65.8 mg, 33%) was recovered. From the later fractions, **21** (80.3 mg, 48%) was obtained. **21**: mp 123.0—127.0 °C (colorless needles, recrystallized from CH_2Cl_2–*n*-hexane). IR (KBr): 3480, 3240, 1604, 1117 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.44 (6H, s), 6.41 (1H, d, J=3.2 Hz), 6.42 (1H, d, J=16.2 Hz), 6.93 (1H, t, J=7.5 Hz), 6.94 (1H, d, J=16.2 Hz), 7.18 (1H, br d, J=7.5 Hz), 7.19 (1H, d, J=3.2 Hz), 7.40 (1H, dd, J=7.5, 1.3 Hz). *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.41; H, 7.47; N, 6.94.

4-(2,3-Dihydroindol-7-yl)-2-methyl-3-buten-2-ol (22) from 6a——A mixture of **6a** (2.264 g), freshly distilled 2-methyl-3-buten-2-ol (3.838 g), $Pd(OAc)_2$ (692.0 mg), NEt_3 (20.0 ml), and tetra-*n*-butylammonium bromide (1.896 g) in DMF (20.0 ml) was heated at 100—110 °C for 30 min with stirring. After cooling of the reaction mixture, AcOEt was added and the whole was filtered to remove solid precipitates. The filtrate was washed with brine, dried over Na_2SO_4,

and concentrated to leave an oil, which was subjected to column chromatography on SiO_2 with CH_2Cl_2 and then ether as eluents to give **22** (1.382 g, 74%). mp 85.0—86.5 °C (colorless prisms, recrystallized from ether). IR (KBr): 3290, 1598, 1451 cm^{-1}. ^1H-NMR (CD_3OD) δ: 1.38 (6H, s), 2.96 (2H, t, J=8.0 Hz), 3.46 (2H, t, J=8.0 Hz), 6.16 (1H, d, J=16.0 Hz), 6.52 (1H, d, J=16.0 Hz), 6.60 (1H, t, J=7.5 Hz), 6.91 (1H, br d, J=7.5 Hz), 6.01 (1H, br d, J=7.5 Hz). MS m/z: 203 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.57; H, 8.31; N, 6.92.

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