The Chemistry of Indoles. CIII.[1] Simple Syntheses of Serotonin, *N*-Methylserotonin, Bufotenine, 5-Methoxy-*N*-methyltryptamine, Bufobutanoic Acid, *N*-(Indol-3-yl)methyl-5-methoxy-*N*-methyltryptamine, and Lespedamine Based on 1-Hydroxyindole Chemistry

Masanori SOMEI,* Fumio YAMADA, Takashi KURAUCHI, Yoshiyuki NAGAHAMA, Masakazu HASEGAWA, Koji YAMADA, Sakiko TERANISHI, Haruhiko SATO, and Chikara KANEKO

Faculty of Pharmaceutical Sciences, Kanazawa University, 13–1 Takara-machi, Kanazawa 920–0934, Japan.
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Application of regioselective nucleophilic substitution reactions of 1-hydroxytryptamines to novel and simple syntheses of serotonin (1a), *N*-methylserotonin (1b), bufotenine (1c), 5-methoxy-*N*-methyltryptamine (2a), bufobutanoic acid (3a), *N*-(indol-3-yl)methyl-5-methoxy-*N*-methyltryptamine (4), and lespedamine (5) are described. Effective syntheses of 5-benzyloxytryptamine and 1-methoxy-2-oxindoles are also reported.

Key words 1-hydroxytryptamine; nucleophilic substitution reaction; serotonin; bufotenine; *N*-(indol-3-yl)methyl-5-methoxy-*N*-methyltryptamine; lespedamine

Tryptamine alkaloids such as serotonin[2] (**1a**, Chart 1), *N*-methylserotonin[3] (**1b**), bufotenine[4a,b] (**1c**), 5-methoxy-*N*-methyltryptamine[5] (**2a**), and melatonin[6] (**2b**) have marked physiological effects in spite of their simple chemical structures. Members of the alkaloid family are still increasing, thus bufobutanoic acid[7] (**3a**) and *N*-(indol-3-yl)methyl-5-methoxy-*N*-methyltryptamine[8] (**4**, Chart 2) have recently been isolated from *Ch'an Su* and the roots of *Antirhea lucida* (Sw.) HOOK (Rubiaceae), respectively. Lespedamine[9] (**5**, Chart 4) is an alkaloid isolated from *Lespedeza bicolor* var. *japonica* NAKAI.

From the viewpoint of developing novel biologically active substances, the tryptamine alkaloids seem to be attractive target compounds. Although synthetic methods for **1a**—**c**[2—4] and **2a**,**b**[6] have already been established, they require many steps starting from expensive indoles having an oxygen functional group at the 5-position. In the case of **5**, the unique 1-methoxyindole structure required chemists to devise an ingenious synthesis.[10] Generally speaking, the above syntheses are complex compared to the simple structures of the target compounds. How to prepare a simple target in a simple way is the most challenging ongoing subject in our group.

We have proposed 1-hydroxyindole hypotheses,[11] which could unify the biogenesis of many indole alkaloids by assuming 1-hydroxytryptamines (or 1-hydroxytryptophans) as common intermediates. In order to verify these hypotheses, we have created synthetic methods for the previously unknown 1-hydroxytryptamines.[12] We have also realized unprecedented nucleophilic substitution reactions in indole chemistry,[13] which had been predicted in the hypotheses.[11] These findings were successfully applied to two simple synthetic routes to melatonin[1] (**2b**), starting from **6b** and **6d** through **8b** and **8d**, respectively. The present paper is a full report of the previous communications[14] and describes further applications of the above findings to novel and simple syntheses of **1a**—**c**, **2a**, **3a**, **4**, and **5** from tryptamine (**6c**). An alternative synthesis of **5** through 1-methoxy-2-oxindole derivatives is also reported.

Syntheses of 1a, 1b, and 1c Syntheses of **1a**—**c** were achieved as follows. First, *N*-methoxycarbonyltryptamine (**6d**), readily and quantitatively available from **6c** by a conventional method, was converted to **7d** by reduction with triethylsilane[15] (Et_3SiH) in CF_3COOH (TFA) in 97% yield.[1] Next, our 1-hydroxyindole synthetic method,[12] employing 30% hydrogen peroxide (H_2O_2) in the presence of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) as a catalyst, was applied to **7d** to produce a 67% yield of 1-hydroxy-*N*-methoxycarbonyltryptamine[1] (**8d**), a potent inhibitor of blood platelet aggregation.[16] However, an attempt to obtain **8a** from **7a** by the 1-hydroxyindole synthetic method was unsuccessful because of the unstable nature of **8a**.

The desired regioselective nucleophilic hydroxylation at the 5-position was realized by reacting **8d** with 85% formic acid (HCOOH) at room temperature for 14 h to afford **9a** and **9b** in 54 and 8% yields, respectively. In the same reaction, when the reaction time was shortened to 20 min, **9b** and the corresponding 5-formyloxy compound (**9c**) were obtained in 24 and 40% yields, respectively. These observations suggest that formate is the initially introduced nucleophile into the 5-position. Subsequent treatment with 8% HCl in MeOH converted **9c** into **9b** in 60% yield.

Selective formation of **9a** in 69% yield was achieved upon treatment with 85% HCOOH at 80 °C when 1-methoxy derivative[17] (**10**) was employed as a substrate, prepared by methylation of **8d** with diazomethane (CH_2N_2). As in the case of **8d**, **10** afforded **9b** and **9c** in 25 and 38% yields, respectively, upon reaction with 85% HCOOH at room temperature with a short reaction time (15 min). Interconversions between **9a** and **9b** were readily carried out. Thus, treatment of **9b** with 85% HCOOH at room temperature for 48 h afforded **9a** in 69% yield, while alkaline hydrolysis of **9a** with 8% NaOH in MeOH gave **9b** in 76% yield. Subsequent hydrolysis of **9b** to **1a** proceeded in 73% yield by treatment with 10% NaOH in refluxing MeOH,[12c] while reduction of **9b** with lithium aluminium hydride ($LiAlH_4$) in refluxing Et_2O–THF afforded **1b** in 65% yield. Consequently, **1a** and **1b** are now available in five steps from **6c** in 26 and 23% overall yields, respectively. Since both the 1-hydroxyindole synthesis and nucleophilic substitution steps are our original reactions, the originality rates[18] of **1a** and **1b** are the same

* To whom correspondence should be addressed. e-mail: somei@dbs.p.kanazawa-u.ac.jp

(50%).

As long as 85% HCOOH was used, attempts to obtain **1c** were unsuccessful under various reaction conditions, starting from 1-hydroxy-*N*,*N*-dimethyltryptamine (**8e**) which was prepared from **6c** through **6e**[17] and **7e**[17] in 51% overall yield. However, more acidic condition such as 5% aqueous H_2SO_4 at reflux was found to convert **8e** into **1c**[4c] in 47% yield together with 16% yield of dehydroxylated product (**6e**). If the solvent was changed to MeOH under similar conditions, **8e** afforded **2e**, **1c**, and **6e** in 57, 7, and 11% yields, respectively. Comparing the ^{1}H-NMR spectrum of **2e** with those of the corresponding 1-acetyl (**11a**) and 1-formyl derivative (**11b**), an anisotropy effect of the 1-acyl group on the C-7 proton was observed by about 1 ppm. This clearly proved their structures. Subsequent cleavage of the methoxy group of **2e** with boron tribromide (BBr_3) in CH_2Cl_2–toluene resulted in an alternative route to **1c** in 63% yield. As a result, **1c** is available from **6c** in four steps in 24% overall yield with 60% originality rate.[18]

Synthesis of 3a Total synthesis of **3a** was achieved by three different routes by applying above results. The first route employed **9a** as an intermediate. The reaction of **9a** with benzyl bromide in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) afforded **12a** in 94% yield. Alkaline hydrolysis of **12a** with 10% NaOH in refluxing MeOH provided a 96% yield of 5-benzyloxytryptamine (**12b**).[19] With **12b**, a useful building block for preparing various serotonin derivatives in hand, we converted it to **3b** in 96% yield by reaction with succinic anhydride in THF. Confirmation of the carboxyl group in **3b** was shown by conversion to ester compound (**3d**) in 97% yield by methylation with CH_2N_2 at 0 °C. However, when the same methylation was carried out at room temperature, the yield of **3d** decreased to 57% and formation of the corresponding succinimide (**13a**) was observed in 30% yield. Finally, catalytic hydrogenation of **3b** over 10% Pd/C afforded **3a** in 99% yield. The spectroscopic data were identical with those reported in the literature.[8] Consequently, the first synthesis of **3a** was achieved in eight steps from **6c** in 25% overall yield with a 33% originality rate.

For the second route, a six-step synthesis of **3a** from **6c** in 13% overall yield with 43% originality rate was developed as follows. Compound **6c** was initially reacted with succinic anhydride in THF, followed by methylation with CH_2N_2 in a one pot procedure, to give methyl *N*-[2-(indol-3-yl)ethyl]succinamate (**14**) and *N*-[2-(indol-3-yl)ethyl]succinimide (**13b**) in 89 and 3% yields, respectively. Reduction of **14** with Et_3SiH in TFA provided the corresponding 2,3-dihydroindole (**15**) in 99% yield. Application of our 1-hydroxyindole synthetic method with $Na_2WO_4 \cdot 2H_2O$–30% H_2O_2 to **15** produced the desired 1-hydroxytryptamine (**16**) in 56% yield. Introduction of hydroxy group into the 5-position of **16** was achieved by treatment with 85% HCOOH to afford serotonin derivative (**3c**) in 38% yield together with a 21% yield of the corresponding 1-formyl compound (**3e**). Finally, the ester part of **3c** was hydrolyzed with 7% K_2CO_3 in MeOH at 50 °C to provide **3a** in 70% yield, though when the reaction was carried out at room temperature, **13c** was formed as a major product.

For the third route, **1a** was used as an intermediate. Although **1a** is known to react with acylating reagents at both side chain nitrogen and phenolic oxygen atoms,[20,21] we examined reaction conditions of **1a** with methyl chloroformate thoroughly and found that DMF is the solvent of choice to realize selective *N*-acylation to provide **9b**[20] in 94% yield. Based on this finding, **1a** was allowed to react with succinic anhydride in DMF at room temperature to afford **3a** in 84% yield without formation of the product derived from reaction at the phenolic oxygen atom. Thus, another six-step synthesis of **3a** from **6c** in 17% overall yield with 57% originality rate was developed.

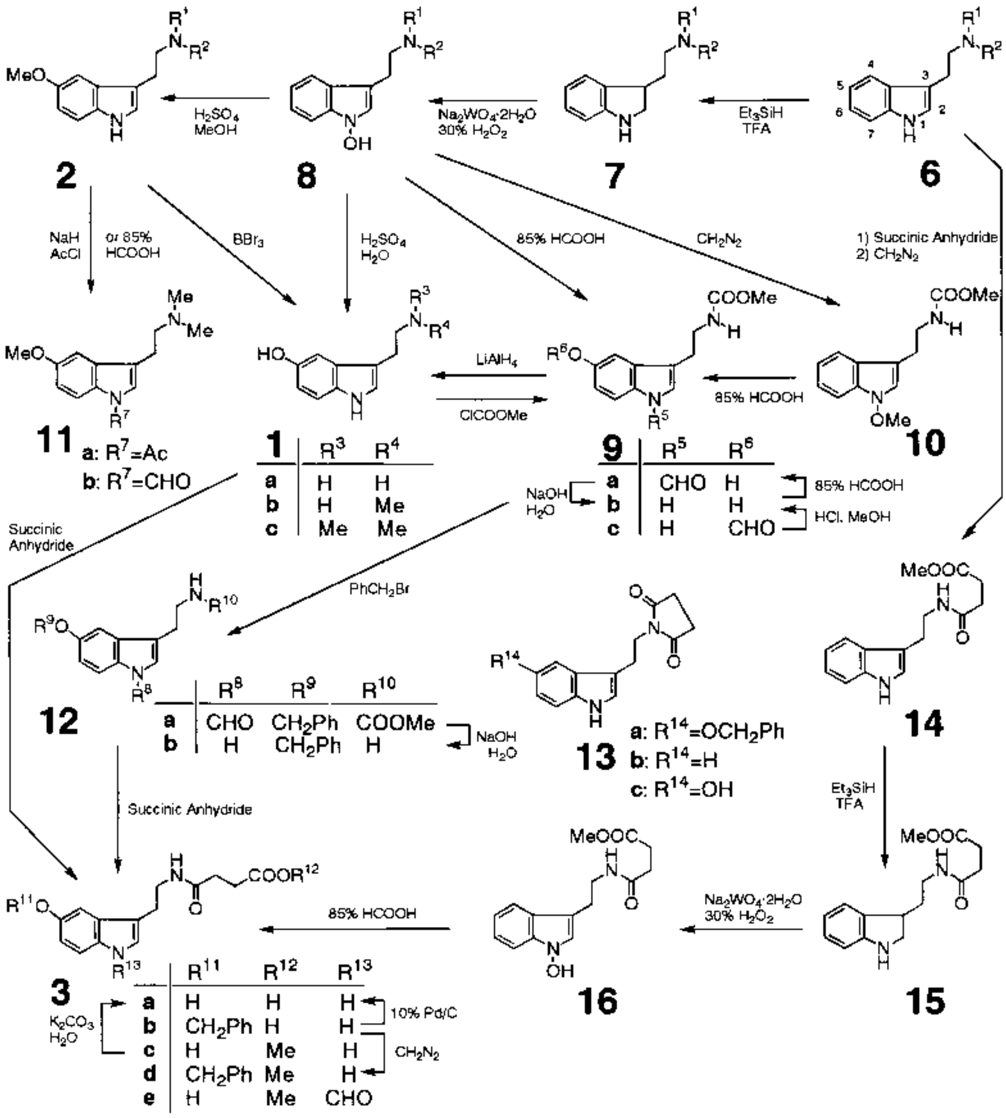
Synthesis of 4 and 2a Total synthesis of **4** was achieved by the following two routes (Chart 2). Our alkylation method for gramine[22] (**17**) with nucleophiles using tri-*n*-butylphosphine (Bu_3P) as a catalyst was successfully applied to **6a** in refluxing acetonitrile (MeCN) resulting in the formation of **18** in 73% yield. Next, preparation of **19a** was achieved in 71% yield when reduction of **18** was carried out with sodium cyanoborohydride[23] in AcOH–TFA (3 : 1, v/v). Interestingly, the use of AcOH alone as a solvent was not effective and led to the formation of **19a**, **19b**, and unreacted **18** in 28, 11, and 60% yields, respectively. The structure of **19a** was readily confirmed by its ^{1}H-NMR spectrum in which the methylene protons, connected to both the nitrogen atom and indole nucleus, were observed as a sharp AB quartet with a coupling constant of 13.4 Hz.

Selective reduction of the indole ring having a 2-aminoethyl side chain can be explained as shown in Chart 3. Generally, reduction of indole requires protonation at the 3-position and the resultant iminium carbon atom at the 2-position is attacked by hydride. In the case of **18**, rapid protonation initially occurs on the side chain basic nitrogen atom leading to an ammonium salt (**18A**). The slow second protonation can occur either at the 3- or 3′-positions, generating **18B** or **18C**, respectively. Formation of **18B** would be however energetically more favorable than **18C**, because the 3 position is further from the positively charged nitrogen atom than the 3′ position. Consequently the second proton approaching to the 3 position experiences less electrostatic repulsion.

Application of the 1-hydroxyindole synthetic method with $Na_2WO_4 \cdot 2H_2O$–30% H_2O_2 to **19a** gave the corresponding 1-hydroxyindole derivative (**20**) in 51% yield. Subsequent regioselective methoxylation of **20** by treatment with 10% H_2SO_4 in MeOH proceeded in 19% yield resulting in the first six-step total synthesis of **4**[24] from **6c** in 5% overall yield with 57% originality rate.

An alternative eight-step synthesis of **4** from **6c** in 24% overall yield with 44% originality rate is the following. Reduction of **6f** with Et_3SiH–TFA afforded **7f** in 95% yield. Oxidation of **7f** with $Na_2WO_4 \cdot 2H_2O$–30% H_2O_2 produced 1-hydroxy-*N*-methoxycarbonyl-*N*-methyltryptamine (**8f**) in 76% yield. Then, treatment of **8f** with 5% H_2SO_4 in refluxing MeOH gave **2f** in 48% yield. Hydrolysis of **2f** with 40% NaOH in refluxing MeOH afforded a 93% yield of **2a**, which is known as an alkaloid isolated from reed canary grass (*Phalaris arundinacea* L.).[5] Finally, our Bu_3P catalyzed reaction of **17** with **2a** in refluxing MeCN provided **4** in 78% yield.

Synthesis of 5 The first total synthesis of **5** by Acheson and co-workers[10] was carried out in thirteen steps from 2-nitroaniline (**21**) *via* such intermediates as **22** and **23** in 2.6% overall yield. We needed a simpler synthesis of **5** in order to



a: R^1=H, R^2=Me; **b**: R^1=Ac, R^2=H; **c**: R^1=R^2=H; **d**: R^1=COOMe, R^2=H; **e**: R^1=R^2=Me;
f: R^1=COOMe, R^2=Me.

Chart 1

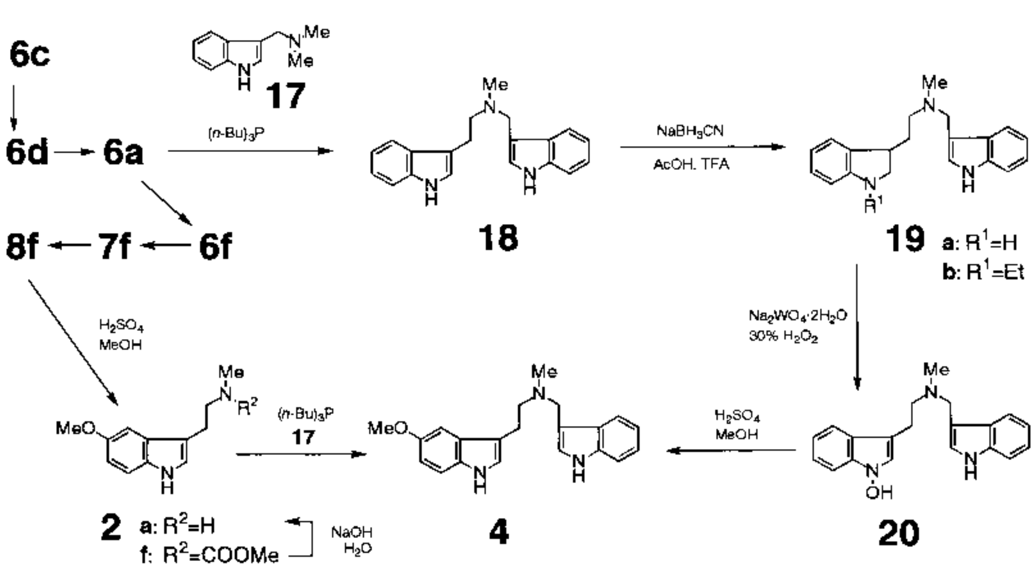


Chart 2

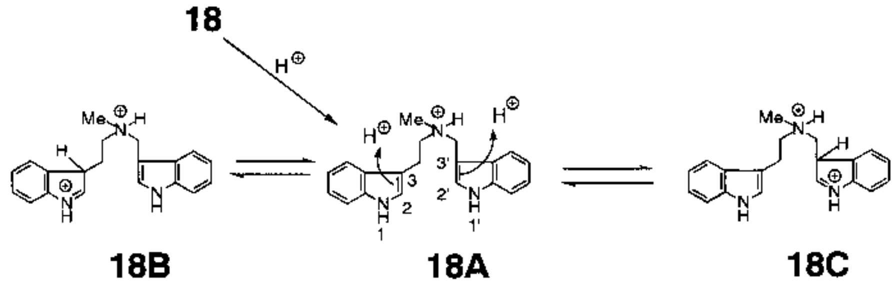


Chart 3

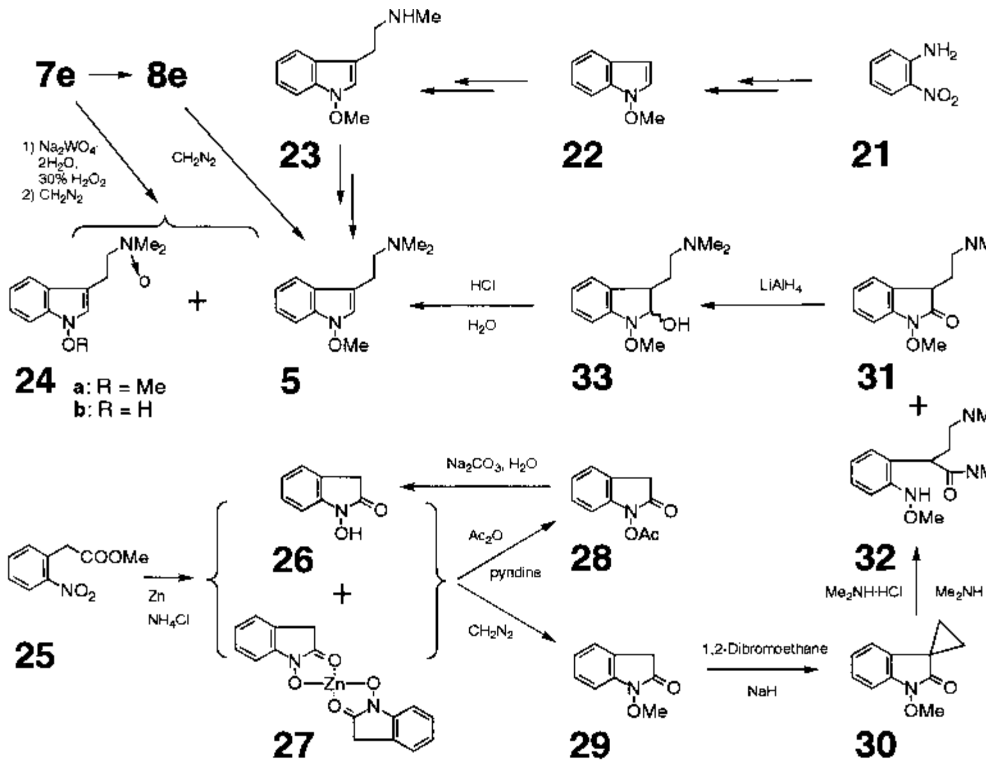


Chart 4

begin a study of its derivatives and their biological activity.

We have developed two synthetic routes to **5**. The first one is the simplest among the thus far reported syntheses.[10,25] Methylation of **8e**, obtained from **6c** in three steps, as described above, with CH_2N_2 resulted in **5** in 57% yield. Thus, **5** is now available in four steps from **6c** in 29% overall yield with 40% originality rate.

Interestingly, when the oxidation of **7e** with $Na_2WO_4 \cdot 2H_2O$–30% H_2O_2 and subsequent treatment with CH_2N_2 were performed in a one pot procedure, lespedamine *N*-oxide (**24a**) was obtained in 31% yield together with a 26% yield of **5**. Isolation of **24a** suggested the presence of the corresponding 1-hydroxy compound (**24b**) in the reaction mixture of the oxidation step. All attempts to isolate **24b** immediately after oxidation of **7e** failed due to its unstable nature.

To confirm the structure of **5** by an alternative synthesis, we established a second route starting from methyl 2-nitrophenylacetate (**25**).[14a)] Thus, treatment of **25** with zinc (Zn, 20 eq) and ammonium chloride (NH_4Cl) in MeOH for 3 h afforded **26** in 48% yield. When an excess amount of Zn was used or when a longer reaction time was employed, the yield of **26** decreased and a significant amount of **26** was consumed to form a Zn–complex (**27**). Based on its mass spectral data, the ratio of oxindole moiety to zinc in the complex was found to be 2 to 1. In addition, treatment of **27** with either Ac_2O–pyridine or CH_2N_2 afforded a good yield of 1-acetoxy- (**28**) or 1-methoxy-2-oxindole[25)] (**29**), respectively, proving the structure of **27**. Applying these observations, direct preparation methods for **28** and **29** in 70 and 77% yields, respectively, were established by treating the reaction products (a mixture of **26** and **27**), obtained after reduction of **25** with Zn–NH_4Cl, with either Ac_2O–pyridine or CH_2N_2. Hydrolysis of **28** with aq. Na_2CO_3 gave **26** in 94% yield.

With **29** in hand, it was allowed to react with ethylene dibromide in the presence of sodium hydride to afford a spiro compound (**30**) in 90% yield. Nucleophilic attack on the cyclopropane ring in **30** with aqueous dimethyl amine and its hydrochloride in DMF led to 1-methoxy-3-(2-*N*,*N*-dimethylaminoethyl)-2-oxindole (**31**) in 54% yield together with a 10% yield of the indole ring cleavage product (**32**). Subsequent reduction of **31** with $LiAlH_4$ in ether produced 2,3-dihydro-2-hydroxy-1-methoxyindole (**33**) in 62% yield as a mixture of diastereoisomers, which was found to be quite sensitive to acids. Thus, upon treatment with aq. HCl, **33** instantaneously collapsed to **5** in 95% yield. Based on this result, work-up of the reduction step was improved as follows. After reduction of **31** with $LiAlH_4$, the reaction mixture was treated briefly with aq. HCl. By this modification, **5** was prepared in 64% yield directly from **31**. As a result, the total synthesis of **5** was achieved in five steps with 24% overall yield from **25**.

In conclusion, we have reported that nucleophilic substitution reaction[13] of 1-hydroxytryptamines[12] can be utilized as a common and simple methodology for the preparations of serotonin congeners. Investigations of the scope and limitations of applicable nucleophiles for the substitution reaction are in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL JNM PMX60, JEOL JNM FX100S, or JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co. Inc.) or activated alumina (Al_2O_3, 300 mesh, from Wako Pure Chemical Industries, Ltd.). Preparative thin layer chromatography (p-TLC) was performed on Merck Kieselgel GF_{254} (type 60) (SiO_2).

***N*-Methyltryptamine (6a) from *N*-Methoxycarbonyltryptamine (6d)** $LiAlH_4$ (678.0 mg, 17.9 mmol) was added to a solution of **6d** (1.241 g, 5.69 mmol) in anhydrous THF (20.0 ml) and the mixture was refluxed for 4 h with stirring. After cooling, MeOH was added to the reaction mixture to destroy excess $LiAlH_4$ and then 10% aq. Rochelle salt was added. The whole was extracted with EtOAc and 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% aq. NH_3 (46 : 5 : 0.5, v/v) to give **6a** (932.1 mg, 94%). **6a**: mp 90—91 °C (colorless prisms, recrystallized from EtOAc–hexane). IR (KBr): 3300, 3130, 1618, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (1H, br s, disappeared on addition of D_2O), 2.44 (3H, s), 2.92 (2H, t, J=6.6 Hz), 2.98 (2H, t, J=6.6 Hz), 7.03 (1H, d, J=2 Hz, collapsed to s on addition of D_2O), 7.12 (1H, br t, J=8.1 Hz), 7.19 (1H, br t, J=8.1 Hz), 7.36 (1H, dt, J=8.1, 1 Hz), 7.63 (1H, br d, J=8.1 Hz), 8.19 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 174 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.58; H, 8.24; N, 16.02.

***N*-Methoxycarbonyl-*N*-methyltryptamine (6f) from 6a** A solution of ClCOOMe (320.3 mg, 3.4 mmol) in $CHCl_3$ (1.0 ml) was added to a solution of **6a** (188.5 mg, 1.1 mmol) in $CHCl_3$ (2.0 ml). To the resultant solution was added Et_3N (0.4 ml) at 0 °C with stirring. After additional stirring at room temperature for 23 h, sat. aq. $NaHCO_3$ was added to the reaction mixture and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1 : 1, v/v) to give **6f** (250.6 mg, 99%). **6f**: mp 88—89 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3270, 1672 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60 °C) δ: 2.82 (3H, s), 2.89 (2H, dt, J=0.7, 7.6 Hz), 3.47 (2H, t, J=7.6 Hz), 3.55 (3H, br s), 6.98 (1H, ddd, J=7.8, 7, 1 Hz), 7.06 (1H, ddd, J=8.1, 7, 1 Hz), 7.10 (1H, d, J=2.2 Hz), 7.33 (1H, dt, J=8.1, 1 Hz), 7.53 (1H, d, J=7.8 Hz), 10.66 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 232 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.30; H, 6.94; N, 12.07.

2,3-Dihydro-*N*,*N*-dimethyltryptamine (7e) from *N*,*N*-Dimethyltryptamine (6e) Et_3SiH (0.51 ml, 3.19 mmol) was added to a solution of **6e** (201.4 mg, 1.07 mmol) in TFA (20.0 ml) and the mixture was stirred at 55 °C for 2 h. After evaporation of the solvent under reduced pressure, the residual oil was made basic (pH 11) by adding 8% NaOH 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 SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **7e** (189.4 mg, 93%). **7e**: Colorless viscous oil. IR (film): 1610, 1488, 1465, 747 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.75 (1H, m), 1.98—2.04 (1H, m), 2.25 (6H, s), 2.30—2.43 (2H, m), 3.21 (1H, dd, J=8.6, 7.5 Hz), 3.28—3.34 (1H, m), 3.69 (1H, t, J=8.6 Hz), 3.72 (1H, br s, disappeared on addition of D_2O), 6.64 (1H, d, J=7.7 Hz), 6.72 (1H, dt, J=0.9, 7.7 Hz), 7.03 (1H, br t, J=7.7 Hz), 7.10 (1H, d, J=7.7 Hz). HR-MS *m/z*: Calcd for $C_{12}H_{18}N_2$: 190.1469. Found: 190.1478.

2,3-Dihydro-*N*-methoxycarbonyl-*N*-methyltryptamine (7f) from 6f Et_3SiH (1.40 ml, 8.8 mmol) was added to a solution of **6f** (681.8 mg, 2.94 mmol) in TFA (10.0 ml) and the mixture was stirred at 70 °C for 4 h. After evaporation of the solvent under reduced pressure, the residual oil was made basic (pH 10) by adding 30% aq. NaOH 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 EtOAc–hexane (1 : 1, v/v) to give **7f** (652.2 mg, 95%). **7f**: Colorless viscous oil. IR (film): 3350, 1686 (br) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 1.61—1.69 (1H, m), 1.89—1.97 (1H, m), 2.83 (3H, s), 3.08—3.16 (2H, m), 3.25 (1H, ddd, J=13.9, 8.6, 5.4 Hz), 3.33 (1H, ddd, J=13.9, 8.8, 6.4 Hz), 3.52—3.60 (1H, m), 3.59 (3H, s), 5.14 (1H, br s, disappeared on addition of D_2O), 6.48 (1H, br d, J=7.6 Hz), 6.53 (1H, dt, J=1, 7.3 Hz), 6.89 (1H, dddd, J=7.6, 7.3, 1, 0.5 Hz), 7.02 (1H, br d, J=7.3 Hz). HR-MS *m/z*: Calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1365.

2,3-Dihydro-*N*-methyltryptamine (7a) from 6a Et_3SiH (0.12 ml, 0.75 mmol) was added to a solution of **6a** (43.2 mg, 0.25 mmol) in TFA (2.0 ml) and the mixture was stirred at 60 °C for 4 h. After evaporation of the solvent under reduced pressure, the residual oil was made basic (pH 10) by adding 8% aq. NaOH 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 $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **7a** (38.2 mg, 87%). **7a**: Colorless oil. IR (film): 3300 (br), 1607 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.95 (2H, m, disappeared on addition of D_2O), 1.70—1.79 (1H, m), 1.99—2.08 (1H, m), 2.46 (3H, s), 2.63—2.73 (2H, m), 3.23 (1H, dd, J=8.8, 7.3 Hz), 3.30—3.38 (1H, m), 3.69 (1H, t, J=8.8 Hz), 6.65 (1H, d, J=7.3 Hz), 6.73 (1H, dt, J=1, 7.3 Hz), 7.03 (1H, br t, J=7.3 Hz), 7.09 (1H, d, J=7.3 Hz). HR-MS *m/z*: Calcd for $C_{11}H_{16}N_2$: 176.1313. Found: 176.1313.

1-Hydroxy-*N*,*N*-dimethyltryptamine (8e) from 7e A solution of $Na_2WO_4 \cdot 2H_2O$ (132.5 mg, 0.40 mmol) in H_2O (4.0 ml) was added to a solution of **7e** (378.9 mg, 1.98 mmol) in MeOH (40.0 ml). To the resultant solution was added 30% H_2O_2 (2.0 ml, 19.6 mmol) at 0 °C with stirring. After stirring at room temperature for 20 min, H_2O was added to the reaction mixture 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 SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give unreacted **7e** (19.1 mg, 5%) and **8e** (223.5 mg, 55%) in the order of elution. **8e**: mp 179.5—180.0 °C (colorless needles, recrystallized from MeOH–H_2O). IR (KBr): 1470, 1320, 840, 737 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.35 (6H, s), 2.64—2.68 (2H, m), 2.89—2.93 (2H, m), 6.99 (1H, ddd, J=8.1, 7.5, 0.9 Hz), 7.09 (1H, s), 7.13 (1H, ddd, J=8.1, 7.5, 0.9 Hz), 7.34 (1H, dt, J=8.1, 0.9 Hz), 7.50 (1H, dt, J=8.1, 0.9 Hz). MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.35; H, 8.04; N, 13.66.

1-Hydroxy-*N*-methoxycarbonyl-*N*-methyltryptamine (8f) from 7f A solution of $Na_2WO_4 \cdot 2H_2O$ (20.6 mg, 0.06 mmol) in H_2O (0.5 ml) was added to a solution of **7f** (55.9 mg, 0.24 mmol) in MeOH (5.0 ml). To the resultant solution was added 30% H_2O_2 (0.25 ml, 2.5 mmol) at 0 °C with stirring. After stirring at room temperature for 40 min, H_2O was added to the reaction mixture and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1 : 1, v/v) to give **8f** (45.0 mg, 76%). **8f**: mp 107—108 °C (colorless prisms, recrystallized from Et_2O–hexane). IR (KBr): 3160, 1662, 1492 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 2.82 (3H, s), 2.88 (2H, dt, J=0.7, 7.6 Hz), 3.47 (2H, t, J=7.6 Hz), 3.56 (3H, s), 6.98 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.12 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.16 (1H, s), 7.32 (1H, d, J=8.1 Hz), 7.52 (1H, d, J=8.1 Hz), 10.76 (1H, s, disappeared on addition of D_2O). MS *m/z*: 248 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.98; H, 6.54; N, 11.22.

5-Hydroxy- (9b) and 1-Formyl-5-hydroxy-*N*-methoxycarbonyltryptamine (9a) from 1-Hydroxy-*N*-methoxycarbonyltryptamine (8d) A solution of **8d** (49.5 mg, 0.21 mmol) in 85% HCOOH (5.0 ml) was stirred at room temperature for 14 h. After evaporation of the solvent under reduced pressure, H_2O was added to the residue under ice cooling. 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 $CHCl_3$–MeOH–28%

aq. NH_3 (200 : 10 : 1, v/v) to give **9a** (29.7 mg, 54%) and **9b** (4.1 mg, 8%) in the order of elution. **9a**: mp 151—153 °C (colorless needles, recrystallized from MeOH–EtOAc). IR (KBr): 3290, 1682 (br), 1558, 1473 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 2.76 (2H, t, J=7.1 Hz), 3.30 (2H, q, J=7.1 Hz), 3.54 (3H, s), 6.80 (1H, dd, J=2.3, 8.8 Hz), 6.80 (1H, br s), 6.93 (1H, d, J=2.3 Hz), 7.48 (1H, br s), 7.93 (1H, br s), 8.99 (1H, br s), 9.18 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.60; H, 5.33; N, 10.76. **9b**: Colorless viscous oil. IR (film): 1686, 1525, 1262, 796 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.72 (2H, t, J=7.7 Hz), 3.21 (2H, dt, J=7.7, 5.6 Hz), 3.53 (3H, s), 6.58 (1H, dd, J=8.6, 2.4 Hz), 6.81 (1H, d, J=2.0 Hz), 7.02 (1H, d, J=2.4 Hz), 7.12 (1H, d, J=8.6 Hz), 7.18 (1H, br t, J=5.6 Hz), 8.60 (1H, s), 10.46 (1H, br s). HR-MS *m/z*: Calcd for $C_{12}H_{14}N_2O_3$: 234.1004. Found: 234.1019.

Compound 9a from 10 A solution of **10** (50.5 mg, 0.20 mmol) in 85% HCOOH (5.0 ml) was stirred at 80 °C for 20 min. Evaporation of the solvent under reduced pressure afforded an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (100 : 1 : 0.1, v/v) to give **9a** (36.8 mg, 69%).

Compound 9b and 5-Formyloxy-*N*-methoxycarbonyltryptamine (9c) from 8d A solution of **8d** (49.4 mg, 0.21 mmol) in 85% HCOOH (5.0 ml) was stirred at room temperature for 20 min. Evaporation of the solvent under reduced pressure afforded an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (100 : 1 : 0.1, v/v) to give unreacted **8d** (3.5 mg, 7%), **9c** (22.1 mg, 40%), and **9b** (11.7 mg, 24%) in the order of elution. **9c**: Colorless viscous oil. IR (film): 3400, 1703 (br), 1525, 1170, 780 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (2H, t, J=7.5 Hz), 3.24 (2H, q, J=7.5 Hz), 3.52 (3H, s), 6.89 (1H, dd, J=8.8, 2.5 Hz), 7.18 (1H, br t, J=8.8 Hz), 7.23 (1H, br d, J=2.5 Hz), 7.31 (1H, br d, J=2.5 Hz), 7.37 (1H, d, J=8.8 Hz), 8.54 (1H, s), 10,96 (1H, br s). HR-MS *m/z*: Calcd for $C_{13}H_{14}N_2O_4$: 262.0954. Found: 262.0945.

Compound 9b and 9c from 10 A solution of **10** (49.5 mg, 0.20 mmol) in 85% HCOOH (5.0 ml) was stirred at room temperature for 15 min. Evaporation of the solvent under reduced pressure afforded an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (100 : 1 : 0.1, v/v) to give **9c** (19.8 mg, 38%) and **9b** (11.5 mg, 25%) in the order of elution.

Compound 9b from 9c 6% HCl (0.1 ml) was added to a solution of **9c** (19.1 mg, 0.07 mmol) in MeOH (3.0 ml) at 0 °C and the mixture was stirred at room temperature for 20 min. To the reaction mixture was added H_2O under ice cooling and the whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (100 : 1 : 0.1, v/v) to give **9b** (10.2 mg, 60%).

Compound 9a from 9b A solution of **9b** (71.8 mg, 0.37 mmol) in 85% HCOOH (7.0 ml) was stirred at room temperature for 48 h. After evaporation of the solvent under reduced pressure, brine was added to the residue. The whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (200 : 10 : 1, v/v) to give **9a** (55.5 mg, 69%) and unreacted **9b** (7.2 mg, 10%) in the order of elution.

Compound 9b from 9a 8% NaOH (0.4 ml) was added to a solution of **9a** (41.2 mg, 0.15 mmol) in MeOH (3.6 ml) and the mixture was heated at 60 °C for 10 min. After cooling, the reaction mixture was made acidic (pH 3) by adding 6% HCl. The whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (200 : 10 : 1, v/v) to give unreacted **9a** (3.3 mg, 8%) and **9b** (28.0 mg, 76%) in the order of elution.

Serotonin (1a) from 9b 40% aq. NaOH (1.0 ml) was added to a solution of **9b** (51.5 mg, 0.22 mmol) in MeOH (3.0 ml) and the mixture was heated at reflux for 4 h with stirring. After cooling, the reaction mixture was made neutral (pH 7.0) by adding 6% HCl under ice cooling. The solvent was evaporated under reduced pressure to leave a brown oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (100 : 10 : 1, v/v) to give unreacted **9b** (8.9 mg, 17%) and **1a** (28.2 mg, 73%). Synthetic product (**1a**) and its hydrochloride (**1a**·HCl) were identical with the commercially available samples, respectively.

Compound 9b from 1a Methyl chloroformate (0.13 ml, 1.70 mmol) was added to a solution of serotonin hydrochloride (**1a**·HCl, 300.7 mg, 1.41 mmol) in DMF (15.0 ml) and pyridine (1.5 ml) at 0 °C with stirring. Stirring was continued at room temperature for an additional 1.5 h and H_2O was added. The whole was extracted with $CHCl_3$ and 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 (97 : 3, v/v) to give **9b** (310 mg, 94%).

1-Methoxy-*N*-methoxycarbonyltryptamine (10) from 8d An excess amount of ethereal CH_2N_2 was added to a solution of **8d** (39.1 mg, 0.17 mmol) in MeOH (2.0 ml) and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was column-chromatographed on SiO_2 with CH_2Cl_2–MeOH (99 : 1, v/v) to give **10** (34.3 mg, 83%). **10**: Colorless viscous oil. IR (film): 1705 (br), 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.93 (2H, t, J=6.6 Hz), 3.49 (2H, q, J=6.6 Hz), 3.66 (3H, s), 4.06 (3H, s), 4.76 (1H, br s), 7.10 (1H, s), 7.12 (1H, t, J=8.0 Hz), 7.25 (1H, t, J=8.0 Hz), 7.42 (1H, d, J=8.0 Hz), 7.57 (1H, d, J=8.0 Hz). HR-MS *m/z*: Calcd for $C_{13}H_{16}N_2O_3$: 248.1160. Found: 248.1163.

5-Methoxy-*N*,*N*-dimethyltryptamine (2e), 1c, and 6e from 8e *c*-H_2SO_4 (5.0 ml) was added to a solution of **8e** (421.2 mg, 2.06 mmol) in MeOH (45.0 ml) and the mixture was refluxed for 29 h with stirring. After cooling, the reaction mixture was made basic (pH 10) by adding 30% NaOH and the whole was extracted with $CHCl_3$–MeOH (95 : 5, v/v). The extract was dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 repeatedly with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) and acetone–hexane–28% aq. NH_3 (20 : 10 : 0.3, v/v) to give **6e** (44.2 mg, 11%), **2e** (256.4 mg, 57%), and **1c** (27.3 mg, 7%) in the order of elution. **2e**: mp 68—70 °C (colorless prisms, recrystallized from Et_2O–hexane). IR (KBr): 1625, 1589, 1477, 1463, 1438, 1216 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (6H, s), 2.61—2.66 (2H, m), 2.88—2.94 (2H, m), 3.86 (3H, s), 6.85 (1H, dd, J=8.8, 2.4 Hz), 6.99 (1H, d, J=2.2 Hz, collapsed to s on addition of D_2O), 7.05 (1H, d, J=2.4 Hz), 7.23 (1H, dd, J=8.8, 0.5 Hz), 7.97 (1H, br s). MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{13}H_8N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.49; H, 8.55; N, 12.76.

5-Methoxy-*N*-methoxycarbonyl-*N*-methyltryptamine (2f) from 8f A solution of **8f** (125.0 mg, 0.50 mmol) in 5% H_2SO_4 in MeOH (50 ml) was refluxed for 24 h with stirring. After cooling, the reaction mixture was made slightly alkaline (pH 7—8) by adding 30% aq. NaOH and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **6f** (11.3 mg, 11%), **2f** (63.3 mg, 48%), and unreacted **8f** (19.4 mg, 16%) in the order of elution. **2f**: mp 112—113 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3300, 1668, 1485, 1446 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 2.82 (3H, s), 2.86 (2H, m, A_2 part of A_2B_2), 3.47 (2H, m, B_2 part of A_2B_2), 3.56 (3H, s), 3.77 (3H, s), 6.72 (1H, dd, J=8.8, 2.4 Hz), 7.01 (1H, d, J=2.4 Hz), 7.04 (1H, d, J=2.4 Hz), 7.21 (1H, d, J=8.8 Hz), 10.36 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.02; H, 6.89; N, 10.63.

5-Methoxy-*N*-methyltryptamine (2a) from 2f 40% aq. NaOH (3.6 ml) was added to a solution of **2f** (40.1 mg, 0.15 mmol) in MeOH (6.0 ml) and the mixture was refluxed for 16 h with stirring. After cooling, H_2O was added to the reaction mixture and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **2a** (29.0 mg, 93%). **2a**: mp 108—109 °C (colorless prisms, recrystallized from EtOAc, lit.,[5] mp not reported). IR (KBr): 3320, 1584, 1465, 1435, 1211 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (1H, br s, disappeared on addition of D_2O), 2.45 (3H, s), 2.89—2.97 (4H, m, A_2B_2), 3.87 (3H, s), 6.86 (1H, dd, J=8.8, 2.4 Hz), 7.02 (1H, d, J=2.1 Hz, collapsed to s on addition of D_2O), 7.06 (1H, d, J=2.4 Hz), 7.25 (1H, d, J=8.8 Hz), 7.98 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.57; H, 7.89; N, 13.73.

1-Acetyl-5-methoxy-*N*,*N*-dimethyltryptamine (11a) from 2e A solution of **2e** (50.0 mg, 0.23 mmol) in DMF (2.0 ml) was added to 60% NaH (26.4 mg, 0.66 mmol, washed with dry benzene) at 0 °C with stirring. After additional stirring for 15 min at room temperature, a solution of AcCl (68.8 mg, 0.88 mmol) in DMF (1.0 ml) was added to the resultant solution and the mixture was stirred at room temperature for 4 h. After the reaction mixture was made basic (pH 9—10) by adding 8% aq. NaOH, the whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **11a** (30.0 mg, 50%) and unreacted **2e** (13.5 mg, 27%) in the order of elution. **11a**: Colorless viscous oil. IR (film): 1690, 1598, 1476 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.23 (6H, s), 2.56 (2H, t, J=7.6 Hz), 2.57 (3H, s), 2.78 (2H, t, J=7.6 Hz), 3.81 (3H, s), 6.91 (1H, dd, J=9, 2.4 Hz), 7.08 (1H, d, J=2.4 Hz), 7.60 (1H, s), 8.18 (1H, d, J=9 Hz).

HR-MS *m/z*: Calcd for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1518.

1-Formyl-5-methoxy-*N*,*N*-dimethyltryptamine (11b) from 2e A solution of **2e** (40.4 mg, 0.18 mmol) in 85% HCOOH (4.0 ml) was heated at 80 °C for 86 h with stirring. After evaporation of the solvent under reduced pressure, the residue was subjected to p-TLC on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v). Under UV light, two bands were detected. Extraction from the upper band with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) afforded **11b** (22.5 mg, 50%). Extraction from the lower band with the same solvent as above afforded unreacted **2e** (13.0 mg, 32%). **11b**: Colorless viscous oil. IR (film): 1708, 1602 cm^{-1}. ^1H-NMR (DMSO-d_6, 60 °C) δ: 2.37 (6H, s), 2.76 (2H, t, J=7.5 Hz), 2.86 (2H, t, J=7.5 Hz), 3.83 (3H, s), 6.96 (1H, dd, J=8, 2.7 Hz), 7.15 (1H, d, J=2.7 Hz), 7.60 (1H, s), 8.06 (1H, br s), 9.20 (1H, br s). HR-MS *m/z*: Calcd for $C_{14}H_{18}N_2O_2$: 246.1367. Found: 246.1368.

***N*-Methylserotonin (1b) from 9b** $LiAlH_4$ (59.9 mg, 1.58 mmol) was added to a solution of **9b** (31.2 mg, 0.13 mmol) in anhydrous Et_2O–THF (1 : 1, v/v, 4.0 ml) and the mixture was refluxed for 26 h with stirring. After cooling, MeOH was added to the reaction mixture to destroy excess $LiAlH_4$. After evaporation of the solvent under reduced pressure, the residual oil was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (5 : 1 : 1, v/v) to give **1b** (16.4 mg, 65%). **1b**: Colorless viscous oil.[3] IR (film): 3380, 3280, 1618, 1578, 1460 cm^{-1}. ^1H-NMR (CD_3OD) δ: 2.38 (3H, s), 2.82—2.90 (4H, m, A_2B_2), 6.66 (1H, dd, J=8.5, 2.4 Hz), 6.92 (1H, dd, J=2.4, 0.5 Hz), 7.00 (1H, s), 7.15 (1H, dd, J=8.5, 0.5 Hz). HR-MS *m/z*: Calcd for $C_{11}H_{14}N_2O$: 190.1106. Found: 190.1106.

5-Hydroxy-*N*,*N*-dimethyltryptamine (1c, Bufotenine) from 8e *c*-H_2SO_4 (1.0 ml) was added to a solution of **8e** (31.2 mg, 0.15 mmol) in H_2O (19.0 ml) and the mixture was refluxed for 6 h with stirring. After cooling, the reaction mixture was made neutral by adding sat. aq. $NaHCO_3$ and the whole was extracted with $CHCl_3$–MeOH (95 : 5, v/v). The extract was 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% aq. NH_3 (46 : 5 : 0.5, v/v) to give **6e** (4.5 mg, 16%) and **1c** (14.7 mg, 47%) in the order of elution. **1c**: mp 146—147 °C (colorless prisms, recrystallized from EtOAc, lit.,[3] mp 146—147 °C). IR spectrum was identical with that of the reported chart.[3] ^1H-NMR (CD_3OD) δ: 2.41 (6H, s), 2.73 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 6.66 (1H, dd, J=8.6, 2.4 Hz), 6.90 (1H, dd, J=2.4, 0.5 Hz), 7.00 (1H, s), 7.15 (1H, dd, J=8.6, 0.5 Hz). MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.48; H, 8.17; N, 13.58. Iodomethylate: mp 218—219 °C (colorless prisms, recrystallized from MeOH, lit.,[3] mp 214—215 °C). IR (KBr): 1620, 1584, 1475 cm^{-1}. ^1H-NMR (CD_3OD) δ: 3.19—3.26 (2H, m), 3.24 (9H, s), 3.57—3.62 (2H, m), 6.71 (1H, dd, J=8.5, 2.4 Hz), 6.94 (1H, dd, J=2.4, 0.5 Hz), 7.15 (1H, s), 7.19 (1H, dd, J=8.5, 0.5 Hz). *Anal.* Calcd for $C_{13}H_{19}N_2OI$: C, 45.10; H, 5.53; N, 8.09. Found: C, 44.98; H, 5.66; N, 7.80. Monopicrate: mp 185—186 °C (orange prisms, recrystallized from MeOH, lit.,[3] mp 179—180 °C). IR (KBr): 1626, 1609, 1561, 1333 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.85 (6H, s), 2.98 (2H, t, J=8.1 Hz), 3.29 (2H, t, J=8.1 Hz), 6.64 (1H, dd, J=8.5, 2.4 Hz), 6.87 (1H, d, J=2.4 Hz), 7.13 (1H, d, J=2.4 Hz, collapsed to s on addition of D_2O), 7.16 (1H, d, J=8.5 Hz), 8.59 (2H, s), 8.64 (1H, s, disappeared on addition of D_2O), 9.15 (1H, br s, disappeared on addition of D_2O), 10.63 (1H, br s, disappeared on addition of D_2O). *Anal.* Calcd for $C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$: C, 49.88; H, 4.42; N, 16.16. Found: C, 49.84; H, 4.38; N, 15.90.

Compound 1c from 2e 1 M solution of BBr_3 in toluene (5.7 ml, 5.7 mmol) was added to a solution of **2e** (245.4 mg, 1.13 mmol) in CH_2Cl_2 (12.0 ml) at −15 °C and the mixture was stirred at −15 °C for an additional 4 h. After addition of ice and H_2O, the mixture was made basic (pH 8—9) by adding 30% aq. NaOH. The whole was extracted with $CHCl_3$–MeOH (9 : 1, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give unreacted **2e** (58.5 mg, 24%) and **1c** (145.4 mg, 63%) in the order of elution.

5-Benzyloxy-1-formyl-*N*-methoxycarbonyltryptamine (12a) from 9a A solution of benzyl bromide (217.7 mg, 1.27 mmol) in anhydrous DMF (1.0 ml) was added to a mixture of K_2CO_3 (165.3 mg, 1.20 mmol) and **9a** (104.3 mg, 0.39 mmol) in anhydrous DMF (2.0 ml), and the whole was stirred at room temperature for 2.5 h. After addition of H_2O, the whole was extracted with $CHCl_3$–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 EtOAc–hexane (1 : 4, v/v) to give **12a** (132.1 mg, 94%). **12a**: pale yellow oil. IR (film): 3300, 1700, 1600, 1478 cm^{-1}. ^1H-NMR (DMSO-d_6, 90 °C) δ: 2.81 (2H, t, J=7.2 Hz), 3.32 (2H, q, J=7.2 Hz), 3.54 (3H, s), 5.16 (2H, s), 6.84 (1H, br s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.24 (1H, d, J=2.4 Hz), 7.31 (1H, t, J=7.7 Hz), 7.38 (2H, t, J=7.7 Hz), 7.47 (2H, d, J=7.7 Hz), 7.55 (1H, s), 8.04 (1H, br d, J=8.8 Hz), 9.24 (1H, br s). HR-MS *m/z*: Calcd for $C_{20}H_{20}N_2O_4$: 352.1423. Found: 352.1421.

5-Benzyloxytryptamine (12b) from 12a 40% aq. NaOH (2.0 ml) was added to a solution of **12a** (174.9 mg, 0.50 mmol) in MeOH (6.0 ml) and the mixture was refluxed for 4 h with stirring. After addition of H_2O, the whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (46 : 2 : 0.2, v/v) to give **12b** (126.5 mg, 96%). **12b**: mp 97.5—99.5 °C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 1585, 1490, 1465, 1205, 1010 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.51 (2H, br s, disappeared on addition of D_2O), 2.86 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 5.11 (2H, s), 6.94 (1H, dd, J=2.5, 8.8 Hz), 7.02 (1H, d, J=2.5 Hz), 7.14 (1H, d, J=2.5 Hz), 7.25 (1H, d, J=8.8 Hz), 7.31 (1H, br t, J=7.7 Hz), 7.38 (2H, br t, J=7.7 Hz), 7.48 (2H, br d, J=7.7 Hz), 7.94 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 266 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_2O \cdot 1/8H_2O$: C, 76.02; H, 6.85; N, 10.43. Found: C, 76.10; H, 6.81; N, 10.49.

***N*-[2-(5-Benzyloxyindol-3-yl)ethyl]succinamic Acid (3b) from 12b** Succinic anhydride (22.6 mg, 0.22 mmol) was added to a solution of **12b** (49.0 mg, 0.18 mmol) in anhydrous THF (4.0 ml) and the mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–AcOH (46 : 5 : 0.5, v/v) to give **3b** (64.6 mg, 96%). **3b**: mp 145—147 °C (colorless plates, recrystallized from MeOH–$CHCl_3$). IR (KBr): 3400, 1710, 1610, 1545, 1195 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.41—2.44 (2H, m), 2.63—2.66 (2H, m), 2.95 (2H, t, J=6.6 Hz), 3.61 (2H, q, J=6.6 Hz), 5.11 (2H, s), 5.75 (1H, br t, J=6.6 Hz), 6.96 (1H, dd, J=8.8, 2.2 Hz), 7.02 (1H, d, J=2.2 Hz), 7.11 (1H, d, J=2.2 Hz), 7.28 (1H, t, J=8.8 Hz), 7.32 (1H, t, J=7.7 Hz), 7.39 (2H, br t, J=7.7 Hz), 7.48 (2H, d, J=7.7 Hz), 8.02 (1H, br s, disappeared on addition of D_2O). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.73; H, 6.02; N, 7.57.

Methyl *N*-[2-(5-Benzyloxyindol-3-yl)ethyl]succinamate (3d) and *N*-[2-(5-Benzyloxyindol-3-yl)ethyl]succinimide (13a) from 3b An excess amount of ethereal CH_2N_2 was added to a solution of **3b** (166.0 mg, 0.45 mmol) in MeOH (5.0 ml) at room temperature and stirring was continued for 10 min. After evaporation of the solvent under reduced pressure, the residual oil was column-chromatographed with $CHCl_3$–MeOH (99 : 1, v/v) to give **13a** (47.5 mg, 30%) and **3d** (98.7 mg, 57%) in the order of elution. **3d**: mp 108—110 °C (colorless needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 3390, 1725, 1658 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.40 (2H, t, J=6.8 Hz), 2.65 (2H, t, J=6.8 Hz), 2.92 (2H, t, J=6.6 Hz), 3.58 (2H, q, J=6.6 Hz), 3.65 (3H, s), 5.11 (2H, s), 5.67 (1H, br t, J=6.6 Hz), 6.95 (1H, dd, J=8.6, 2.4 Hz), 7.04 (1H, d, J=2.2 Hz), 7.13 (1H, d, J=2.4 Hz), 7.27 (1H, d, J=8.6 Hz), 7.32 (1H, t, J=7.4 Hz), 7.39 (2H, t, J=7.4 Hz), 7.48 (2H, d, J=7.4 Hz), 7.98 (1H, br s). *Anal.* Calcd for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.43; H, 6.34; N, 7.31. **13a**: mp 172—174 °C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3380, 1767, 1690 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.62 (4H, s), 3.01 (2H, t, J=7.6 Hz), 3.81 (2H, t, J=7.6 Hz), 5.12 (2H, s), 6.93 (1H, dd, J=8.8, 2.4 Hz), 7.06 (1H, d, J=2.4 Hz), 7.23 (1H, s), 7.24 (1H, d, J=8.8 Hz), 7.31 (1H, br t, J=7.6 Hz), 7.38 (2H, t, J=7.6 Hz), 7.51 (2H, d, J=7.6 Hz), 7.90 (1H, br s). *Anal.* Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.15; H, 5.72; N, 7.98.

Compound 3d from 3b An excess amount of ethereal CH_2N_2 was added to a solution of **3b** (99.6 mg, 0.27 mmol) in MeOH (3.0 ml) at 0 °C and stirring was continued for 10 min at 0 °C. After evaporation of the solvent under reduced pressure, the residual oil was column-chromatographed with $CHCl_3$–MeOH (99 : 1, v/v) to give **3d** (101.0 mg, 97%).

Bufobutanoic Acid (3a) from 3b A solution of **3b** (54.2 mg, 0.15 mmol) in MeOH (3.0 ml) was hydrogenated in the presence of 10% Pd/C (53.4 mg) at room temperature and 1 atm for 1 h. Catalyst was filtered off and the filtrate was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–AcOH (46 : 5 : 0.5, v/v) to give **3a** (40.4 mg, 99%). **3a**: Pale brown oil. IR (film): 3390, 1710, 1620, 1580, 1540, 1485, 1460, 1365, 1185, 938, 800 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.32 (2H, t, J=7.2 Hz), 2.43 (2H, t, J=7.2 Hz), 2.70 (2H, t, J=7.6 Hz), 3.28 (2H, q, J=7.6 Hz), 6.58 (1H, dd, J=8.6, 2.2 Hz), 6.81 (1H, d, J=2.2 Hz), 7.02 (1H, d, J=2.2 Hz), 7.11 (1H, d, J=8.6 Hz), 7.94 (1H, t, J=7.6 Hz), 8.60 (1H, br s, disappeared on addition of D_2O), 10.45 (1H, s). HR-MS *m/z*: Calcd for $C_{14}H_{16}N_2O_4$: 276.1110. Found: 276.1109. Spectral data are identical with the reported values.[8]

***N*-[2-(Indol-3-yl)ethyl]succinimide (13b) and Methyl *N*-[2-(Indol-3-yl)ethyl]succinamate (14) from 6c** Succinic anhydride (750.8 mg, 7.50 mmol) was added to a solution of **6c** (1.00 g, 6.25 mmol) in anhydrous THF (50.0 ml) and the mixture was stirred at room temperature for 20 min. After evaporation of the solvent, the residue was dissolved in MeOH (10.0 ml) and excess ethereal CH_2N_2 was added to the resultant solution. After stirring at room temperature for 5 min, the solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99 : 1, v/v) to give **13b** (50.3 mg, 3%) and **14** (1.53 g, 89%) in the order of elution. **13b**: mp 178—180 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 1770, 1690 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.61 (4H, s), 3.06 (2H, t, J=7.6 Hz), 3.83 (2H, t, J=7.6 Hz), 7.09 (1H, d, J=2.4 Hz), 7.13 (1H, ddd, J=8.0, 7.0, 1.0 Hz), 7.19 (1H, ddd, J=8.0, 7.0, 1.0 Hz), 7.35 (1H, d, J=8.0 Hz), 7.67 (1H, d, J=8.0 Hz), 8.02 (1H, br s). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.31; H, 5.79; N, 11.59. **14**: mp 118—120 °C (colorless needles, recrystallized from $CHCl_3$). IR (KBr): 1723, 1650, 1545, 1230, 740 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.40 (2H, t, J=6.8 Hz), 2.65 (2H, t, J=6.8 Hz), 2.97 (2H, t, J=6.8 Hz), 3.60 (2H, q, J=6.8 Hz), 3.66 (3H, s), 5.67 (1H, br s), 7.06 (1H, d, J=2.4 Hz), 7.13 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.38 (1H, dt, J=8.1, 1.0 Hz), 7.61 (1H, dd, J=8.1, 1.0 Hz), 8.07 (1H, br s). MS m/z: 274 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_3 \cdot 1/8H_2O$: C, 65.14; H, 6.65; N, 10.13. Found: C, 65.07; H, 6.61; N, 10.27.

***N*-[2-(5-Hydroxyindol-3-yl)ethyl]succinimide (13c) from 3c** 14% aq. K_2CO_3 (3.0 ml) was added to a solution of **3c** (72.6 mg, 0.25 mmol) in MeOH (3.0 ml) and the mixture was stirred at room temperature for 40 min. AcOH was added to the reaction mixture until the pH of the whole became 5.0. Evaporation of the solvent under reduced pressure left brown solid, which was column-chromatographed with EtOAc–hexane (1 : 2, v/v) to give **13c** (16.7 mg, 26%). **13c**: mp 219—221 °C (colorless needles, recrystallized from $CHCl_3$–MeOH). IR (KBr): 3400, 3300, 1763, 1680 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.61 (4H, s), 2.76—2.79 (2H, m), 3.55—3.58 (2H, m), 6.59 (1H, dd, J=8.6, 2.2 Hz), 6.84 (1H, d, J=2.2 Hz), 7.07 (1H, d, J=2.2 Hz), 7.12 (1H, d, J=8.6 Hz), 8.63 (1H, s, disappeared on addition of D_2O), 10.51 (1H, s). MS m/z: 258 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_3 \cdot 1/8H_2O$: C, 64.54; H, 5.51; N, 10.75. Found: C, 64.59; H, 5.35; N, 10.61.

Methyl *N*-[2-(2,3-Dihydroindol-3-yl)ethyl]succinamate (15) from 14 Et_3SiH (0.12 ml, 0.73 mmol) was added to a solution of **14** (100.1 mg, 0.36 mmol) in TFA (5.0 ml) and the mixture was stirred at 60 °C for 4 h. After evaporation of the solvent, the whole was made basic by adding saturated $NaHCO_3$ under ice cooling and extracted with $CHCl_3$–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 $CHCl_3$–MeOH (97 : 3, v/v) to give **15** (99.6 mg, 99%). **15**: mp 74—75 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 1724, 1645 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.73—1.81 (1H, m), 1.95—2.02 (1H, m), 2.43 (2H, t, J=6.8 Hz), 2.63—2.68 (2H, m), 3.26—3.41 (4H, m), 3.68 (3H, s), 3.70 (1H, t, J=8.8 Hz), 5.82 (1H, br s), 6.65 (1H, d, J=7.5 Hz), 6.73 (1H, dt, J=1.0, 7.5 Hz), 7.04 (1H, br t, J=7.5 Hz), 7.09 (1H, br d, J=7.5 Hz). MS m/z: 276 (M^+). *Anal.* Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.22; H, 7.37; N, 10.04.

Methyl *N*-[2-(1-Hydroxyindol-3-yl)ethyl]succinamate (16) from 15 A solution of $Na_2WO_4 \cdot 2H_2O$ (24.1 mg, 0.07 mmol) in H_2O (1.0 ml) was added to a solution of **15** (100.6 mg, 0.36 mmol) in MeOH (10.0 ml) and then 30% H_2O_2 (0.37 ml, 3.64 mmol) was added to the reaction mixture at 0 °C. After stirring at room temperature for 1 h, H_2O was added to the reaction mixture and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with EtOAc–hexane (1 : 1, v/v) and $CHCl_3$–MeOH (99 : 1, v/v) to give **16** (59.4 mg, 56%) and unreacted **15** (6.6 mg, 7%) in the order of elution. **16**: mp 151.5—153.5 °C (colorless needles, recrystallized from EtOAc–hexane). IR (KBr): 3370, 1715, 1640, 1555, 740 cm^{-1}. ^1H-NMR (CD_3OD) δ: 2.45 (2H, t, J=6.8 Hz), 2.58 (2H, t, J=6.8 Hz), 2.90 (2H, t, J=7.2 Hz), 3.45 (2H, t, J=7.2 Hz), 3.65 (3H, s), 6.99 (1H, t, J=8.0 Hz), 7.11 (1H, s), 7.13 (1H, t, J=8.0 Hz), 7.34 (1H, d, J=8.0 Hz), 7.53 (1H, d, J=8.0 Hz). MS m/z: 290 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_4 \cdot 1/8H_2O$: C, 61.58; H, 6.29; N, 9.58. Found: C, 61.57; H, 6.18; N, 9.41.

Methyl *N*-[2-(5-Hydroxyindol-3-yl)ethyl]succinamate (3c) and Methyl *N*-[2-(1-Formyl-5-hydroxyindol-3-yl)ethyl]succinamate (3e) from 16 A solution of **16** (134.6 mg, 0.46 mmol) in 85% HCOOH (40.0 ml) was stirred at 50 °C for 50 min. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with EtOAc–hexane (1 : 1, v/v) and $CHCl_3$–MeOH (99 : 1, v/v) to give **3e** (30.6 mg, 21%) and **3c** (50.6 mg, 38%) in the order of elution. **3c**: Colorless oil. IR (film): 3320, 1730, 1645 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.42 (2H, t, J=6.3 Hz), 2.69 (2H, t, J=6.3 Hz), 2.91 (2H, t, J=6.3 Hz), 3.51 (2H, q, J=6.3 Hz), 3.73 (3H, s), 5.66 (1H, br t, J=6.3 Hz), 6.07 (1H, br s, disappeared on addition of D_2O), 6.82 (1H, dd, J=8.8, 2.5 Hz), 7.00 (1H, d, J=2.5 Hz), 7.06 (1H, d, J=2.5 Hz), 7.22 (1H, d, J=8.8 Hz), 7.91 (1H, br s, disappeared on addition of D_2O). HR-MS m/z: Calcd for $C_{15}H_{18}N_2O_4$: 290.1267. Found: 290.1264. **3e**: mp 178—180 °C (colorless needles, recrystallized from MeOH–$CHCl_3$). IR (KBr): 3350, 1727, 1697, 1648 cm^{-1}. ^1H-NMR (DMSO-d_6, 90 °C) δ: 2.36 (2H, t, J=7.5 Hz), 2.50 (2H, t, J=7.5 Hz), 2.74 (2H, t, J=7.5 Hz), 3.36 (2H, q, J=7.5 Hz), 3.58 (3H, s), 6.80 (1H, dd, J=8.7, 2.2 Hz), 6.93 (1H, d, J=2.2 Hz), 7.47 (1H, s), 7.70 (1H, br s), 7.93 (1H, br s), 9.00 (1H, br s), 9.18 (1H, br s). MS m/z: 318 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.29; H, 5.63; N, 8.73.

Bufobutanoic Acid (3a) from 3c 14% aq. K_2CO_3 (2.0 ml) was added to a solution of **3c** (18.1 mg, 0.062 mmol) in MeOH (2.0 ml) at 0 °C and the mixture was stirred at 50 °C for 1 h. The whole was made acidic by adding 6% HCl under ice cooling and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–AcOH (46 : 5 : 0.5, v/v) to give unreacted **3c** (2.5 mg, 14%) and **3a** (12.1 mg, 70%) in the order of elution.

Compound 3a from 1a Succinic anhydride (63.5 mg, 0.64 mmol) was added to a solution of serotonin hydrochloride (**1a**·HCl, 103.9 mg, 0.49 mmol) in DMF (5.0 ml) and pyridine (0.5 ml) at room temperature and stirring was continued for 10 h. After evaporation of solvent under reduced pressure, the residual oil was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–AcOH (46 : 5 : 0.5, v/v) to give **3a** (113.0 mg, 84%) and unreacted **1a** (12.7 mg, 15%) in the order of elution.

***N*-Indol-3-ylmethyl-*N*-methyltryptamine (18) from 6a** A solution of n-Bu_3P (23.0 mg, 0.11 mmol) in MeCN (3.0 ml) was added to a mixture of **6a** (36.4 mg, 0.21 mmol) and gramine (**17**, 44.3 mg, 0.25 mmol) and the resultant solution was refluxed for 15 h under Ar atmosphere with stirring. After evaporation of the solvent under reduced pressure, the residual oil was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **18** (46.3 mg, 73%), **17** (6.8 mg), and unreacted **6a** (9.5 mg, 26%) in the order of elution. **18**: mp 119—121 °C (colorless prisms, recrystallized from acetone–hexane). IR (KBr): 3400, 1619, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.81 (2H, m, A_2 part of A_2B_2), 3.03 (2H, m, B_2 part of A_2B_2), 3.81 (2H, s), 6.97 (1H, d, J=2.5 Hz), 7.06—7.13 (3H, m), 7.15—7.21 (2H, m), 7.32 (1H, d, J=8.3 Hz), 7.34 (1H, d, J=8.1 Hz), 7.54 (1H, d, J=8.1 Hz), 7.72 (1H, d, J=7.8 Hz), 7.95 (1H, br s, disappeared on addition of D_2O), 8.09 (1H, br s, disappeared on addition of D_2O). MS m/z: 303 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.11; H, 7.08; N, 13.60.

1-Ethyl- (19b) and/or 2,3-Dihydro-*N*-indol-3-ylmethyl-*N*-methyltryptamine (19a) from 18: Method A: $NaBH_3CN$ (308.9 mg, 4.92 mmol) was added to a solution of **18** (298.8 mg, 0.98 mmol) in AcOH (12.0 ml) and TFA (4.0 ml) and the mixture was stirred for 13 h at room temperature. After addition of H_2O, the mixture was made basic (pH 10) by adding 8% aq. NaOH and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **19a** (213.0 mg, 71%). **19a**: Colorless viscous oil. IR (film): 3390, 1606, 1485, 1457 cm^{-1}. ^1H-NMR (CD_3OD) δ: 1.72—1.80 (1H, m), 2.02—2.10 (1H, m), 2.29 (3H, s), 2.52 (1H, ddd, J=12.2, 10.7, 5.1 Hz), 2.61 (1H, ddd, J=12.2, 10.7, 5.6 Hz), 3.07 (1H, dd, J=8.9, 7.1 Hz), 3.18—3.25 (1H, m), 3.51 (1H, t, J=8.9 Hz), 3.76 (1H, d, J=13.4 Hz), 3.80 (1H, d, J=13.4 Hz), 6.64 (1H, d, J=7.3 Hz), 6.65 (1H, dt, J=1, 7.3 Hz), 6.96 (1H, br t, J=7.3 Hz), 6.99 (1H, br d, J=7.3 Hz), 7.03 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.10 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.19 (1H, s), 7.35 (1H, dt, J=8.1, 1 Hz), 7.62 (1H, dt, J=8.1, 1 Hz). HR-MS m/z: Calcd for $C_{20}H_{23}N_3$: 305.1892. Found: 305.1895.

Method B: $NaBH_3CN$ (39.8 mg, 0.63 mmol) was added to a solution of **18** (25.5 mg, 0.08 mmol) in AcOH (2.0 ml) and the mixture was stirred for 7 h at room temperature After addition of H_2O, the mixture was made basic (pH 10) by adding 8% aq. NaOH and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **19b** (3.1 mg, 11%), **19a** (7.1 mg, 28%), and unreacted **18** (15.3 mg, 60%). **19b**: Colorless viscous oil. IR (film): 3410, 1603, 1486, 1455 cm^{-1}. ^1H-NMR (CD_3OD) δ: 1.10 (3H, t, J=7.2 Hz), 1.70—1.78 (1H, m), 2.01—2.09 (1H, m), 2.32 (3H, s), 2.52 (1H, ddd, J=12.2, 10.8, 4.9 Hz), 2.63 (1H, ddd,

J=12.2, 10.8, 5.6 Hz), 2.84 (1H, dd, J=8.7, 7 Hz), 3.01 (1H, dq, J=13.2, 7.2 Hz), 3.09—3.16 (1H, m), 3.10 (1H, dq, J=13.2, 7.2 Hz), 3.34 (1H, t, J=8.7 Hz), 3.77 (1H, d, J=13.4 Hz), 3.83 (1H, d, J=13.4 Hz), 6.48 (1H, d, J=7.3 Hz), 6.59 (1H, dt, J=1, 7.3 Hz), 6.95 (1H, d, J=7.3 Hz), 7.00 (1H, br t, J=7.3 Hz), 7.03 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.10 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.20 (1H, s), 7.36 (1H, dt, J=8.1, 1 Hz), 7.62 (1H, dt, J=8.1, 1 Hz). HR-MS m/z: Calcd for $C_{22}H_{27}N_3$: 333.2205. Found: 333.2201.

1-Hydroxy-*N*-indol-3-ylmethyl-*N*-methyltryptamine (20) from 19a A solution of $Na_2WO_4 \cdot 2H_2O$ (54.3 mg, 0.16 mmol) in H_2O (2.8 ml) was added to a solution of **19a** (213.0 mg, 0.70 mmol) in MeOH (28.0 ml). To the resultant solution was added 30% H_2O_2 (0.72 ml, 7.05 mmol) at 0 °C with stirring. After stirring at room temperature for 1 h, Me_2S (0.6 ml, 8.2 mmol) was added to the reaction mixture cautiously under ice-cooling. Stirring was continued at room temperature for 30 min and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **20** (113.9 mg, 51%). **20**: mp 173—174 °C (decomp., colorless prisms, recrystallized from acetone). IR (KBr): 3380, 1540, 1451 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.24 (3H, s), 2.65 (2H, t, J=7.8 Hz), 2.88 (2H, t, J=7.8 Hz), 3.71 (2H, s), 6.92 (1H, ddd, J=7.8, 7.1, 1 Hz), 6.95 (1H, ddd, J=7.8, 7.1, 1 Hz), 7.06 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.10 (1H, ddd, J=8.1, 7.1, 1 Hz), 7.21 (1H, d, J=2.1 Hz), 7.22 (1H, s), 7.30 (1H, d, J=8.1 Hz), 7.34 (1H, d, J=8.2 Hz), 7.40 (1H, d, J=7.8 Hz), 7.61 (1H, d, J=7.8 Hz), 10.87 (1H, br s, disappeared on addition of D_2O), 10.97 (1H, br s, disappeared on addition of D_2O). MS m/z: 319 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_3O \cdot 1/8H_2O$: C, 74.68; H, 6.66; N, 13.06. Found: C, 74.65; H, 6.65; N, 12.90.

***N*-Indol-3-ylmethyl-5-methoxy-*N*-methyltryptamine (4) from 2a** A solution of n-Bu_3P (22.9 mg, 0.11 mmol) in MeCN (5.0 ml) was added to a mixture of **2a** (57.3 mg, 0.28 mmol) and gramine (**17**, 59.6 mg, 0.34 mmol) and the resultant solution was refluxed for 24 h under an Ar atmosphere with stirring. After evaporation of the solvent under reduced pressure, the residual oil was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **4** (73.0 mg, 78%), **17** (12.1 mg), and unreacted **2a** (12.0 mg, 21%) in the order of elution. **4**: Colorless viscous oil (lit.,[7] amorphous whitish powder). Although IR and ^{1}H-NMR data differ slightly from the reported values,[7] we found that proton signals shift markedly depending on the deuterated solvent and concentration. The data of ^{13}C-NMR are completely identical with the reported values.[7] IR ($CHCl_3$): 3450 (br), 2780, 1621, 1585, 1483, 1451 cm^{-1}. ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ: 2.40 (3H, s), 2.81 (2H, m, A_2 part of A_2B_2), 3.00 (2H, m, B_2 part of A_2B_2), 3.79 (3H, s), 3.85 (2H, s), 6.82 (1H, dd, J=8.8, 2.5 Hz), 6.95 (1H, s), 6.97 (1H, d, J=2.5 Hz), 7.11 (1H, ddd, J=8.1, 7, 1 Hz), 7.17 (1H, s), 7.18 (1H, ddd, J=8.1, 7, 1 Hz), 7.23 (1H, d, J=8.8 Hz), 7.37 (1H, dt, J=8.1, 1 Hz), 7.69 (1H, dt, J=8.1, 1 Hz). HR-MS m/z: Calcd for $C_{21}H_{23}N_3O$: 333.1841. Found: 333.1852.

Compound 4 from 20 A solution of **20** (29.8 mg, 0.09 mmol) in 10% H_2SO_4 in MeOH (4.0 ml) was refluxed for 6 h with stirring. After cooling, the reaction mixture was made basic (pH 10) by adding 20% aq. NaOH and the whole was extracted with $CHCl_3$–MeOH (9 : 1, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **4** (5.8 mg, 19%), **18** (2.6 mg, 9%), and unreacted **20** (15.9 mg, 53%) in the order of elution.

1-Hydroxy-2-oxindole (26) from Methyl 2-Nitrophenylacetate (25) Zn (314.6 mg, 4.81 mg atom) was added to a solution of **25** (46.1 mg, 0.23 mmol) and NH_4Cl (49.3 mg, 0.92 mmol) in MeOH (2.0 ml) and H_2O (0.5 ml) and the mixture was stirred at room temperature for 3 h. To the reaction mixture, CH_2Cl_2–MeOH (95 : 5, v/v) was added. The precipitates were filtered off through thin SiO_2 layer and washed with CH_2Cl_2–MeOH (95 : 5, v/v). The filtrate and washings were combined and evaporated under reduced pressure to leave the residue, which was made acidic by adding 0.3% aq. HCl 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 subjected to p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) to give **26** (16.8 mg, 48%). **26**: mp 200.5—202.0 °C (colorless prisms, recrystallized from CH_2Cl_2–MeOH, lit.,[25] mp 199—201 °C). IR (KBr): 1675, 1617 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.35 (1H, br s), 3.43 (2H, s), 6.65—7.41 (4H, m).

Zinc Complex of 1-Hydroxy-2-oxindole (27) from 25 Zn (6.405 g, 98 mg atom) was added to a solution of **25** (1.018 g, 5.2 mmol) and NH_4Cl (1.084 g, 20.2 mmol) in MeOH (40 ml) and H_2O (10 ml) and the mixture was stirred at room temperature for 3 h. The precipitates were filtered off through filter paper and washed with hot MeOH. The filtrate and washings were combined and evaporated under reduced pressure to dryness. Acetone was added to the residue, and the precipitates were removed through thin SiO_2 layer. The filtrate was evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from CH_2Cl_2–MeOH (95 : 5, v/v) to give **27** (243.7 mg, 26%) as colorless prisms. **27**: mp >300 °C. IR (KBr): 1630, 1605 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 3.28 (4H, s), 6.62—7.38 (8H, m). HR-MS m/z: Calcd for $C_{16}H_{12}N_2O_4Zn$: 360.0087 and 362.0057. Found: 360.0109 and 361.9963.

1-Acetoxy-2-oxindole (28) from 25 Zn (6.590 g, 100 mg atom) was added to a solution of **25** (1.035 g, 5.4 mmol) and NH_4Cl (1.137 g, 21.2 mmol) in MeOH (40 ml) and H_2O (10 ml) and the mixture was stirred at room temperature for 3 h. The precipitates were filtered off through filter paper and washed with hot MeOH. The filtrate and washings were combined and evaporated under reduced pressure to dryness. To the residue, pyridine (20 ml) and Ac_2O (10 ml) were added and the mixture was stirred at room temperature for 4 h. After evaporation of the solvent under reduced pressure, H_2O was added to the residue and the whole was extracted with CH_2Cl_2. 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–Et_2O (10 : 1, v/v) to give **28** (709.9 mg, 70%). **28**: mp 97—99 °C (colorless prisms, recrystallized from Et_2O–hexane). IR (KBr): 1807, 1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.55 (2H, s), 6.50—7.35 (4H, m). MS m/z: 191 (M^+). *Anal.* Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.00; H, 4.72; N, 7.04.

Compound 26 from 28 A solution of **28** (104.2 mg, 0.54 mmol) in sat. aq. Na_2CO_3 (10 ml) was heated at 100 °C for 30 min with stirring. After cooling, the reaction mixture was made acidic by adding 18% aq. HCl and the resultant precipitates (**26**, 16.5 mg) were collected by filtration. The filtrate 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 Et_2O–CH_2Cl_2 (3 : 2, v/v) to give further crop of **26** (59.8 mg). Total yield of **26** was 76.3 mg (94%).

1-Methoxy-2-oxindole (29) from 25 Zn (823.5 mg, 12.6 mg atom) was added to a solution of **25** (121.0 mg, 0.62 mmol) and NH_4Cl (130.4 mg, 2.43 mmol) in MeOH (5.0 ml) and H_2O (1.2 ml) and the mixture was stirred at room temperature for 3 h. The precipitates were filtered off through filter paper and washed with hot MeOH. The filtrate and washings were combined and evaporated under reduced pressure to dryness and the residue was dissolved in MeOH (5.0 ml). To the resultant solution, ethereal CH_2N_2 was added until the gas evolution was not observed. After evaporation of the solvent under reduced pressure, the residual oil was subjected to p-TLC on SiO_2 with CH_2Cl_2–MeOH (97 : 3, v/v) to give **29** (78.0 mg, 77%). **29**: mp 84.5—86.0 °C (colorless prisms, recrystallized from Et_2O, lit.,[25] mp 84—86 °C). IR (KBr): 1712, 1617 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (2H, s), 3.95 (3H, s), 6.65—7.42 (4H, m). MS m/z: 163 (M^+).

1-Methoxy-2-oxindole-3-spirocyclopropane (30) from 29 A solution of **29** (103.4 mg, 0.63 mmol) in anhydrous DMF (2.5 ml) was added to 50% NaH (62.8 mg, 1.30 mmol, washed with dry benzene) at 0 °C with stirring. To the resultant solution was added a solution of ethylene dibromide (144 mg, 2.5 mmol) in DMF (1.5 ml) and the mixture was stirred at room temperature for 4 h. After addition of H_2O under ice cooling, the whole was extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with Et_2O–hexane to give **30** (108.7 mg, 90%). **30**: Colorless viscous oil. IR (film): 1723, 1619 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.17—1.54 (2H, m), 1.54—1.87 (2H, m), 3.92 (3H, s), 6.41—7.21 (4H, m). HR-MS m/z: Calcd for $C_{11}H_{11}NO_2$: 189.0789. Found: 189.0795.

1-Methoxy-3-(2-*N*,*N*-dimethylaminoethyl)-2-oxindole (31) and 2-(2-*N*-Methoxyaminophenyl)-*N*,*N*-dimethyl-4-(*N*,*N*-dimethylamino)butylamide (32) from 30 50% aq. Me_2NH (12.0 ml, 107 mmol) was added to a solution of **30** (404.4 mg, 2.1 mmol) and $Me_2NH \cdot HCl$ (1.614 g, 19.5 mmol) in DMF (28 ml) and the mixture was sealed in a tube. The whole was heated at 65±5 °C for 20 h with stirring. After cooling, the reaction mixture was made basic with 0.8% NaOH and the whole was extracted with benzene. 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% aq. NH_3–1,2-dichloroethane (46 : 5 : 0.5 : 2.5, v/v) to give **31** (270.3 mg, 54%) and **32** (60.0 mg, 10%) in the order of elution. **31**: Colorless viscous oil. IR (film): 1727, 1616 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.69—2.50 (4H, A_2B_2, m), 2.06 (6H, s), 3.32 (1H, t, J=5.6 Hz), 3.86 (3H, s), 6.57—7.29 (4H, m). HR-MS m/z: Calcd for $C_{13}H_{18}N_2O_2$: 234.1367. Found: 234.1375. **32**: Colorless viscous oil. IR (film): 3480, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.57 (4H, m), 2.32 (6H, s), 2.73 (3H, s), 2.86 (3H, s), 3.66 (3H, s), 3.90 (1H, dd, J=8.8, 5.2 Hz), 6.50—7.30 (4H, m), 6.93 (1H, br s). HR-MS m/z: Calcd for $C_{15}H_{25}N_3O_2$: 279.1944. Found: 279.1937.

2,3-Dihydro-2-hydroxy-3-[2-(*N*,*N*-dimethylamino)ethyl]-1-methoxyindole (33) from 31 $LiAlH_4$ (9.6 mg, 0.25 mmol) was added to a solution of **31** (54.1 mg, 0.23 mmol) in anhydrous Et_2O (9.0 ml) and the mixture was stirred at room temperature for 2 h. After addition of MeOH at 0 °C to the reaction mixture to destroy excess $LiAlH_4$, 10% aq. Rochelle salt 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 evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **33** (34.0 mg, 62%). **33**: Colorless viscous oil. IR (film): 3340, 1612, 1596, 1475, 1463 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.84—2.75 (5H, m), 2.25 (6H, s), 3.82 (3H, s), 4.60 and 4.92 (total 1H, each d, J=8 Hz), 5.83 (1H, br s), 6.44—7.15 (4H, m). HR-MS m/z: Calcd for $C_{13}H_{20}N_2O_2$: 236.1523. Found: 236.1539.

Lespedamine (5) from 31 $LiAlH_4$ (10.1 mg, 0.25 mmol) was added to a solution of **31** (54.0 mg, 0.23 mmol) in anhydrous Et_2O (10 ml) and the mixture was stirred at room temperature for 3.5 h. After addition of MeOH at 0 °C to the reaction mixture to destroy excess $LiAlH_4$, the mixture was made acidic by adding 6% HCl. The whole was then made basic with 8% NaOH and 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 subjected to p-TLC on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **5** (32.4 mg, 64%). **5**: Colorless viscous oil. IR ($CHCl_3$): 1460 cm^{-1} (lit.,[8] 1459 cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 2.37 (6H, s), 2.65 (2H, t, J=8 Hz), 2.93 (2H, t, J=8 Hz), 4.05 (3H, s), 7.10 (1H, dt, J=0.9, 7.8 Hz), 7.10 (1H, s), 7.23 (1H, dt, J=0.9, 7.8 Hz), 7.40 (1H, dd, J=7.8, 0.9 Hz), 7.57 (1H, dd, J=0.9, 7.8 Hz). HR-MS m/z: Calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1416. IR and ^{1}H-NMR spectra are identical with those of natural product reported in the literature.[8] Picrate: mp 161—163 °C (lit.,[8] mp 160—162 °C).

Compound 5 from 33 Three drops of 6% HCl were added to a solution of **33** (33.7 mg, 0.14 mmol) in MeOH (5.0 ml) at room temperature with stirring. After 10 min, the reaction mixture was made basic with 0.8% NaOH 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 subjected to p-TLC on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **5** (29.7 mg, 95%).

Compound 5 and Lespedamine *N*-Oxide (24a) from 7e A solution of $Na_2WO_4 \cdot 2H_2O$ (15.5 mg, 0.05 mmol) in H_2O (0.5 ml) was added to a solution of **7e** (43.9 mg, 0.23 mmol) in MeOH (5.0 ml). To the resultant solution was added 30% H_2O_2 (0.24 ml, 2.3 mmol) at 0 °C with stirring. After stirring at room temperature for 30 min, excess ethereal CH_2N_2 was added and stirring was continued for 30 min. H_2O was added to the reaction mixture and the whole was extracted with $CHCl_3$–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 $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **5** (13.1 mg, 26%) and **24a** (17.0 mg, 31%) in the order of elution. **24a**: Colorless viscous oil. IR (film): 1644 (br), 1453 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (6H, s), 3.37—3.40 (2H, m), 3.57—3.60 (2H, m), 4.06 (3H, s), 7.13 (1H, ddd, J=7.9, 7.5, 1.1 Hz), 7.18 (1H, s), 7.25 (1H, ddd, J=7.9, 7.5, 1.1 Hz), 7.42 (1H, dt, J=7.9, 1.1 Hz), 7.59 (1H, dt, J=7.9, 1.1 Hz). HR-MS m/z: Calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1370.

Compound 5 from 8e Excess ethereal CH_2N_2 was added to a solution of **8e** (13.1 mg, 0.06 mmol) in MeOH (5.0 ml) and stirring was continued at room temperature for 30 min. After removal of the solvent under reduced pressure, the residue was subjected to p-TLC on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46 : 5 : 0.5, v/v) to give **5** (8.0 mg, 57%).

References and Notes

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Originality rate is the result of the following calculation:
originality rate (%)=100×[number of newly developed steps+1]÷[total number of synthetic steps+1]
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