Syntheses of melatonin and its derivatives

SYNTHESES OF MELATONIN AND ITS DERIVATIVES[1]

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Abstract — Two simple synthetic methods for melatonin are newly developed from tryptamine through intermediates, which are promising lead compounds for drug developing research. Novel chemical reactivities of melatonin in its bromination, lithiation, and acylation are also reported.

Melatonin[2] (**1**, Scheme 1) is a hormone secreted from pineal gland and is well known to control the circadian rhythms.[2] Its multimodality of biological activities[3] has recently been disclosed such as inhibition of Alzheimer β-fibrillogenesis,[3a] anti-aging properties relating to radical scavenging,[3b] antiproliferative effect on melanoma cells,[3c] etc.[3] Although several synthetic methods for **1** have been reported thus far,[4] they still have subjects to be improved in synthetic steps, overall yields, and economical efficiency. From the point of creating new biologically active compounds, we have engaged for some time in finding a novel synthetic method for **1** and proposed[1a] that it should involve value added intermediates as many as possible, which can function as lead compounds for drug developing. In this paper, we wish to describe the desired two synthetic methods for **1** from tryptamine (**2**) based on 1-hydroxyindole chemistry.[5] Interesting results of bromination, lithiation and subsequent reaction with an electrophile, and acylation of **1** are also reported.

Nb-Acetyl- (**3a**) and *Nb*-methoxycarbonyltryptamine (**3b**), readily available in quantitative yields from **2** by the respective reactions with either Ac_2O or methyl chloroformate,[5] were reduced with Et_3SiH[6] in TFA to afford the corresponding 2,3-dihydrotryptamines, (**4a**) and (**4b**), in 99 and 97% yields, respectively. Application of our 1-hydroxyindole synthetic method[5] to **4a**, using 30% H_2O_2 and $Na_2WO_4 \cdot 2H_2O$ as a catalyst,[5] provided **5a** in 66% yield. Under similar reaction conditions, **4b** provided **5b** in 65% yield. These two compounds, (**5a**) and (**5b**), are found to be promising lead compounds for inhibitors of blood platelet aggregation.[7]

We next examined nucleophilic substitution reaction[8] of **5a** in MeOH with acids having weak nucleophilic nature of the conjugated base and the results are summarized in Table 1. In cases where H_2SO_4 was employed, we could obtain **1** in no better than 17% yield (Entry 1) under variously examined reaction conditions. When the acid was changed to HF, the yield of **1** was dramatically improved to 55% (Entry 2). We finally found that BF_3 was an acid of choice (Entries 3–6). At an optimum reaction conditions shown in Entry 5, **1** was provided in 80% yield together with **3a** in 5% yield. In case of large scale production, however, their separations are not always easy due to their close *Rf* values. The synthetic **1** was identical with an authentic commercial sample. Consequently, four steps synthesis of **1** from **2** was established in 52% overall yield with 60% originality rate.[9]

Scheme 1

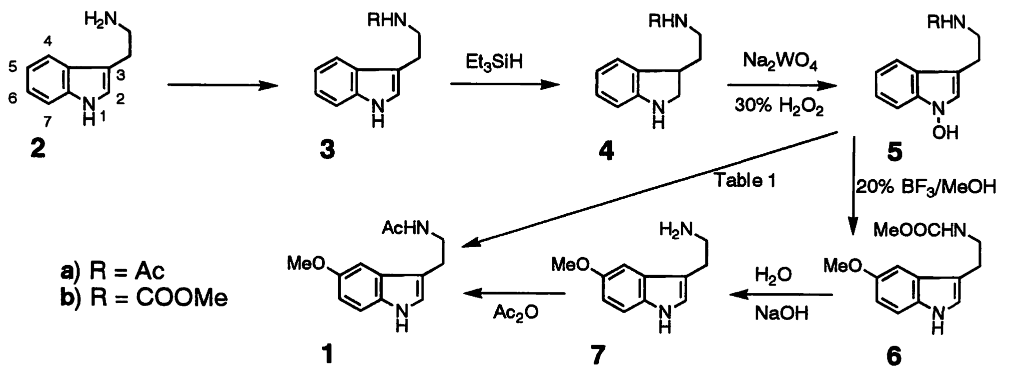


Table 1 5a $\xrightarrow[\text{MeOH}]{\text{Acid}}$ 1 + 3a

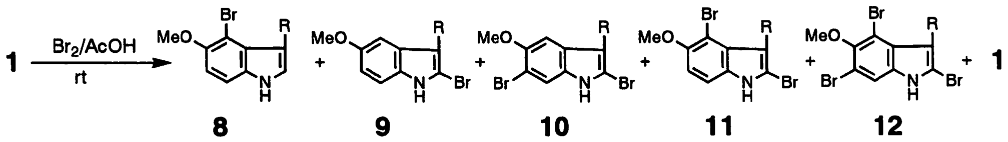
Entry	Reagent	Reaction Conditions		Yield (%) of	
		Temp. (°C)	Time (h)	1	3a
1	22% H_2SO_4	rt	24	17	10
2	11%HF	70	8	55	10
3	20%BF_3	52	4.5	54	5
4	"	70	2	65	5
5	"	reflux	2/3	80	5
6	"	reflux	0.5	72	3

As an alternative route, the reaction of **5b** with 20% BF_3 was examined in refluxing MeOH. Interestingly, the reaction was relatively faster than that of **5a** and, without any contamination of **3b**,[8d] **6** was obtained in 94% yield. Even if the formation of **3b** were observed by chance, the reaction would be suitable for large scale production because there are wide differences in *Rf* values between **6** and **3b**. Alkaline hydrolysis of **6** gave 5-methoxytryptamine[4f] (**7**) in 99% yield, which is known to be a potent agonist of serotonin.[4c] Acetylation of **7** with Ac_2O gave 92% yield of **1**. The final two steps could be carried out in 92% overall yield without isolation of **7**. As a result, six steps synthesis of **1** from **2** was established in 55% overall yield with 43% originality rate.[9]

With simple synthesis of **1** established, we examined its bromination taking into consideration that halogen containing melatonin derivatives had been utilized for various studies in brain chemistry.[10] A conventional bromination in AcOH with 0.95 mol eq. of Br_2 provided 4-bromo- (**8**), 2-bromo- (**9**), 2,4-dibromomelatonin[10a] (**11**), and unreacted **1** in 8, 28, 15, and 34% yields, respectively, as shown in Table 2 (Entry 1). When 2 mol eq. of Br_2 was employed, **1** reacted completely to afford **8**, 2,6-dibromomelatonin[10b] (**10**), and **11** in 10, 34, and 49% yields, respectively (Entry 2). The reaction with 3 mol eq. of Br_2 provided 2,4,6-tribromomelatonin (**12**) as a sole product in 60% yield (Entry 3). Structures of **8**—**11** except for **12** were determined by spectral data. As for **12**, however, 2,4,7-tribromomelatonin is an alternative possible candidate. Therefore, **12** was further converted to 1-acetyl derivative (**13**) in 53% yield by treatment with NaH, followed by the reaction with AcCl. Comparison of the ^{1}H-NMR spectrum of **12** with that of **13** clearly showed the anisotropy effect of 1-acetyl group on the singlet C(7)-proton by *ca.* 1 ppm, proving that **12** and **13** are 7-unsubstituted indoles.

It is interesting to note that the selective debromination of **11** could be realized in the following ways. Thus, upon reaction with **11** at room temperature, Mg/MeOH selectively removed the bromine atom at the 2 position to give **8** in 21% yield together with 44% yield of recovery, while such reagent systems as Mg/PrOH, Mg/THF, and Zn/AcOH/NH_4Cl did not react at all. Contrastively, *n*-BuLi in THF at −19℃, followed by the addition of H_2O, replaced the bromine atom at the 4-position for hydrogen to provide **9** in 51% yield together with unreacted **11** in 27% yield.

Table 2 R = CH_2CH_2NHAc



Entry	Bromine (mol eq)	Reaction Time (h)	Yield (%) of 8	9	10	11	12	1
1	0.95	5	8	28	0	15	0	34
2	1.9	2.5	10	0	34	49	0	0
3	3	2	0	0	0	0	60	0

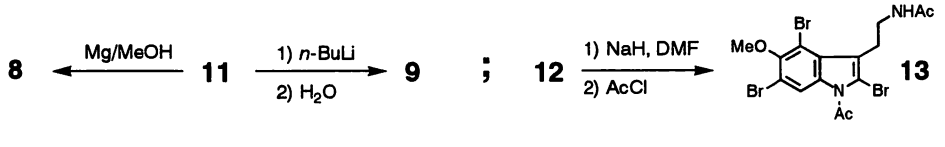
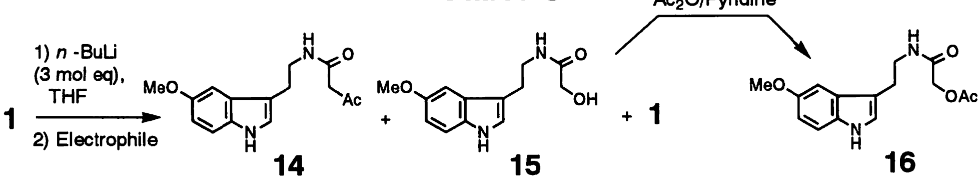


Table 3

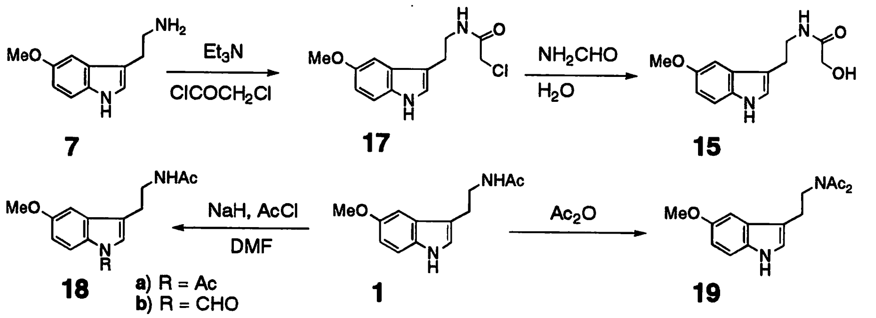


Entry	Electrophile (mol eq)	Gas	Reaction Time (h)	Yield (%) of 14	15	1
1	$MeCONMe_2$ (4)	Ar	5	30	0	66
2	"	"	6	23	4	43
3	–	O_2	1.5	–	16	76
4	–	"	5	–	36	39

Next, direct lithiation of **1** was examined with *n*-BuLi in THF under Ar at −18 ℃, followed by reaction with *N*,*N*-dimethylacetamide. The result was the formation of *Nb*-acetoacetyl- (**14**) and/or *Nb*-hydroxyacetyl-5-methoxytryptamine (**15**) as shown in Entries 1 and 2 (Table 3). Since the trace amount of oxygen contaminated in Ar seemed to be responsible for the formation of **15**, lithiation of **1** was carried out under oxygen atmosphere in the absence of an electrophile culminating in the formation of **15** in good yields (Entries 3 and 4). Further acetylation of **15** with Ac_2O/pyridine afforded 91% yield of *Nb*-acetoxy-acetyl-5-methoxytryptamine (**16**) proving the presence of a primary alcohol in the side chain.

The structure of **15** was confirmed by the following alternative synthesis (Scheme 2). The reaction of **7** with chloroacetyl chloride in the presence of Et_3N afforded 93% yield of **17**.[11] Subsequent heating of **17** in formamide/H_2O mixed solvent at reflux provided 87% yield of **15** which was identical with the sample obtained from the above lithiation method.

Scheme 2



Acylation of **1** is also worthy of mention. Thus, the initial treatment of **1** with NaH in DMF and subsequent reaction with AcCl provided 1-acetylmelatonin (**18a**) exclusively in 77% yield, while the reaction with refluxing Ac_2O afforded *Nb,Nb*-diacetyl-5-methoxytryptamine (**19**) in 92% yield. 1-Formylation of **1** occurred easily at room temperature by treatment with 85% HCOOH affording **18b** in 92% yield.

In conclusion, we have established two efficient and economical synthetic methods for **1** involving intermediates such as **2a**, **2b**, and **7**, which are promising lead compounds for future growth in drug developing studies. Furthermore, several novel chemical reactivities of **1** were found in its bromination, lithiation, and acylation. Utilizing the resultant building blocks, preparations of various derivatives of **1** and their biological evaluations are now in progress.

EXPERIMENTAL

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

***Nb*-Acetyl-2,3-dihydrotryptamine (4a) from *Nb*-Acetyltryptamine (3a)** — Et_3SiH (3.10 mL, 19.4 mmol) was added to a solution of **3a** (1.971 g, 9.76 mmol) in CF_3COOH (97 mL) and the mixture was heated at 60℃ for 3 h with stirring. After evaporation of the solvent, H_2O was added to the residue. The whole was made basic by adding 2N aqueous NaOH 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 MeOH–AcOEt (1:99, v/v) to give **4a** (1.970 g, 99%). **4a**: Colorless oil. IR (film): 3295, 1642 (br), 1556 (br), 747 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.83 (1H, m), 1.94 (3H, s), 1.95—2.06 (1H, m), 2.89 (1H, br s, disappeared on addition of D_2O), 3.21—3.42 (4H, m), 3.70 (1H, t, *J*=8.4 Hz), 5.77 (1H, br s), 6.66 (1H, d, *J*=7.6 Hz), 6.73 (1H, t, *J*=7.6 Hz), 7.04 (1H, t, *J*=7.6 Hz), 7.09 (1H, d, *J*=7.6 Hz). High resolution MS *m/z*: Calcd for $C_{12}H_{16}N_2O$: 204.1262. Found: 204.1269.

***Nb*-Methoxycarbonyl-2,3-dihydrotryptamine (4b) from *Nb*-Methoxycarbonyltryptamine (3b)** — Et_3SiH (7.50 mL, 46.9 mmol) was added to a solution of **3b** (5.030 g, 23.0 mmol) in CF_3COOH (100 mL) and the mixture was heated at 60°C for 3 h with stirring. After evaporation of the solvent, H_2O was added to the residue. The whole was made basic by adding 2N aqueous NaOH 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 (95:5, v/v) to give **4b** (4.930 g, 97%). **4b**: mp 64—65℃ (colorless prisms, recrystallized from AcOEt-hexane). IR (KBr): 3407, 3345, 1716, 1521, 1247, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (1H, br s), 1.71—1.79 (1H, m), 1.96—2.04 (1H, m), 3.20—3.36 (4H, m), 3.66 (1H, t, *J*=8.0 Hz), 3.70 (1H, t, *J*=8.0 Hz), 4.82 (1H, br s), 6.64 (1H, d, *J*=7.5 Hz), 6.72 (1H, t, *J*=7.5 Hz), 7.03 (1H, t, *J*=7.5 Hz), 7.09 (1H, d, *J*=7.5 Hz). MS *m/z*: 220 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.31; H, 7.35; N, 12.65.

***Nb*-Acetyl-1-hydroxytryptamine (5a) from 4a** — 30% Aq. H_2O_2 (8.50 mL, 76.4 mmol) was added to a solution of **4a** (1.560g, 7.64 mmol) and $Na_2WO_4 \cdot 2H_2O$ (500.0 mg, 1.53 mmol) in MeOH (150 mL)–H_2O (15.0 mL) at 0℃ with stirring. Stirring was continued at rt for 30 min and then 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 MeOH-AcOEt (1:99, v/v) to give **5a** (1.104 g, 66%). **5a**: mp 138—139 °C (colorless prisms, recrystallized from AcOEt). IR (KBr): 3250, 3105, 1619, 1602, 1580, 743 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.89 (3H, s), 2.89 (2H, t, *J*=7.3 Hz), 3.43 (2H, t, *J*=7.3 Hz), 6.99 (1H, t, *J*=8.3 Hz), 7.10 (1H, s), 7.12 (1H, t, *J*=8.3 Hz), 7.34 (1H, d, *J*=8.3 Hz), 7.52 (1H, d, *J*=8.3 Hz). MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.53; N, 12.77.

***Nb*-Methoxycarbonyl-1-hydroxytryptamine (5b) from 4b** —30% Aq. H_2O_2 (1.0 mL, 9.18 mmol) was added to a solution of **4b** (201.9 mg, 0.92 mmol) and $Na_2WO_4 \cdot 2H_2O$ (63.2 mg, 0.18 mmol) in MeOH–H_2O (1:1, v/v, 22.0 mL) at 0°C with stirring. Stirring was continued at rt for 30 min and then 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 AcOEt-hexane (1:2, v/v) to give **5b** (237.4 mg, 65%). **5b**: mp 114—115 °C (colorless needles, recrystallized from CH_2Cl_2–hexane). IR (KBr): 3380, 3190, 1698, 1533, 1267, 983, 751 cm^{-1}. ^{1}H-NMR

(CD_3OD) δ: 2.89 (2H, t, *J*=7.5 Hz), 3.36 (2H, t, *J*=7.5 Hz), 3.61 (3H, s), 6.99 (1H, t, *J*=7.9 Hz), 7.09 (1H, s), 7.13 (1H, t, *J*=7.9 Hz), 7.34 (1H, d, *J*=7.9 Hz), 7.53 (1H, d, *J*=7.9 Hz). MS *m/z*: 234 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.40; H, 6.02; N, 11.90.

Melatonin (1) from *Nb*-acetyl-1-hydroxytryptamine (5a) — Entry 1: Conc. H_2SO_4 (2.0 mL) was added to a solution of **5a** (29.7 mg, 0.14 mmol) in MeOH (7 mL) at 0°C with stirring. After stirring at rt for 24 h, H_2O was added under ice cooling 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 HPLC on SiO_2 with AcOEt–hexane (3:1, v/v) to give **3a** (2.8 mg, 10%) and **1** (5.3 mg, 17%) in the order of elution. The obtained sample (**1**) was identical with a commercially available **1** in every respects.

Entry 2: 55% Aq. HF (2.0 mL) was added to a solution of **5a** (29.9 mg, 0.14 mmol) in MeOH (8.0 mL) under ice cooling and the mixture was heated at 70°C for 8 h. After evaporation of the solvent, H_2O was added to the residue and the whole was made neutral by adding sat. $NaHCO_3$ under ice cooling and extracted with CH_2Cl_2–MeOH (95:5, v/v). After the same work-up and separation as described in Entry 1, **3a** (2.9 mg, 10%) and **1** (17.7mg, 55%) were obtained.

Entry 5: 50% BF_3–methanol complex (2.0 mL) was added to a solution of **5a** (30.0 mg, 0.14 mmol) in MeOH (3.0 mL) under ice cooling and the mixture was refluxed for 40 min with stirring. After evaporation of the solvent, the whole was made neutral by adding 2N NaOH under ice cooling and extracted with CH_2Cl_2–MeOH (95:5, v/v). After the same work-up and separation as described in Entry 1, **3a** (1.4 mg, 5%) and **1** (25.5 mg, 80%) were obtained.

5-Methoxy-*Nb*-methoxycarbonyltryptamine (6) from 5b — Example 1 (g scale): 50% BF_3–methanol complex (10.0 mL) was added to a solution of **5b** (1.50 g, 6.41 mmol) in MeOH (100 mL) and the mixture was refluxed for 40 min with stirring. After addition of ice and H_2O, the whole was made neutral by adding 40% aq. NaOH and 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 **6** (1.50 g, 94%). **6**: mp 80—82 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3330, 1670, 1536, 1486, 1035, 926, 775 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.94 (2H, t, *J*=6.7 Hz), 3.52 (2H, q, *J*=6.7 Hz), 3.66 (3H, s), 3.87 (3H, s), 4.77 (1H, br s), 6.87 (1H, dd, *J*=8.7 and 2.3 Hz), 7.01 (1H, d, *J*=2.3 Hz), 7.03 (1H, br s), 7.26 (1H, d, *J*=8.7 Hz), 7.94 (1H, br s). 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, 62.74; H, 6.44; N, 11.10.

Example 2 (10 g scale): 50% BF_3–methanol complex (180.0 mL) was added to a solution of **5b** (9.64 g, 41.2 mmol) in MeOH (500 mL) and the mixture was refluxed for 30 min with stirring. After addition of ice and H_2O, the whole was made neutral by adding 40% aq. NaOH and 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 **6** (8.52 g, 83%).

5-Methoxytryptamine (7) from 6 — 20% Aq. NaOH (1.0 mL) was added to a solution of **6** (51.2 mg, 0.20 mmol) in MeOH (1.0 mL) and the mixture was refluxed for 4 h with stirring. After addition of ice and 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 (46:5:0.5, v/v) to give **7** (38.8 mg, 99%). **7**: mp 124—126°C (lit.,[4f] mp 120°C, colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 2880 (br), 1586, 1490, 790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.88 (2H, t, *J*=6.7 Hz), 3.03 (2H, t, *J*=6.7 Hz), 3.87 (3H, s), 6.86 (1H, dd, *J*=8.8, 2.4 Hz), 7.03 (1H, d, *J*=2.4 Hz), 7.05 (1H, d, *J*=2.4 Hz), 7.26 (1H, d, *J*=8.8 Hz), 7.91 (1H, br s). *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.14; H, 7.43; N, 14.50.

Melatonin (1) from 7 — Ac_2O (3.0 mL, 31.7 mmol) was added to a solution of **7** (918.0 mg, 4.83 mmol) in pyridine (6.0 mL) and the mixture was stirred at rt for 40 min. After evaporation of the solvent under reduced pressure, the whole was made alkaline by adding 2N aq. NaOH 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 (99:1, v/v) to give **1** (1.03 g, 92%).

4-Bromomelatonin (8), 2-bromomelatonin (9), 2,6-dibromomelatonin (10), 2,4-dibromomelatonin (11), and 2,4,6-tribromomelatonin (12) from 1 — **Entry 1**: A 0.57 M solution of Br_2 in AcOH (1.55 mL, 0.95 mmol) was added to a solution of **1** (217.5 mg, 0.92 mmol) in AcOH (10 mL) and the mixture was stirred for 5 h at rt. After addition of H_2O, the whole was made basic by adding 40% aq. NaOH 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 successively with AcOEt and $CHCl_3$–MeOH (99:1, v/v) to give unreacted **1** (73.8 mg, 34%), **9** (82.4 mg, 28%), **11**[10a] (56.5 mg, 15%), and **8** (24.5 mg, 8%) in the order of elution. **8**: mp 171—173 °C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3210, 1655, 1630, 1540, 1240, 775 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s), 3.25 (2H, t, *J*=6.6 Hz), 3.63 (2H, q, *J*=6.6 Hz), 3.92 (3H, s), 5.63 (1H, br s), 6.92 (1H, d, *J*=8.8 Hz), 7.09 (1H, br s), 7.27 (1H, d, *J*=8.8 Hz), 8.05 (1H, br s). MS *m/z*: 312, 310 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_2O_2Br \cdot 1/4H_2O$: C, 49.46; H, 4.95; N, 8.87. Found: C, 49.57; H, 4.70; N, 8.74. **9**: mp 148—149°C (colorless prisms, recrystallized from $CHCl_3$–MeOH). IR (KBr): 3230 (br), 1625, 1580, 1485, 1210, 743 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.78 (3H, s), 2.73 (2H, t, *J*=7.0 Hz), 3.19 (2H, q, *J*=7.0 Hz), 3.76 (3H, s), 6.73 (1H, dd, *J*=8.5, 2.4 Hz), 7.01 (1H, d, *J*=2.4 Hz), 7.17 (1H, d, *J*=8.5 Hz), 7.96 (1H, t, *J*=7.0 Hz), 11.50 (1H, s). MS *m/z*: 312, 310 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.07; H, 4.77; N, 8.83. **11**[10a]: mp 177—179 °C (pale brown powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3410, 1648, 1530, 1245, 790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (3H, s), 3.21 (2H, t, *J*=6.5 Hz), 3.61 (2H, q, *J*=6.5 Hz), 3.91 (3H, s), 5.72 (1H, br s), 6.89 (1H, d, *J*=8.8 Hz), 7.21 (1H, d, *J*=8.8 Hz), 8.41 (1H, br s). MS *m/z*: 392, 390, 388 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_2Br_2 \cdot 1/4H_2O$: C, 39.57; H, 3.70; N, 7.10. Found: C, 39.56; H, 3.59; N, 6.76.

Entry 2: A 0.61 M solution of Br_2 in AcOH (6.70 mL, 4.09 mmol) was added to a solution of **1** (499.5 mg, 2.15 mmol) in AcOH (15.0 mL) and the mixture was stirred at rt for 2.5 h. After the same work-up as described in Entry 1, the resultant residue was repeatedly column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (99:1, v/v) to give **10**[10b] (285.4 mg, 34%), **11** (409.1 mg, 49%), and **8** (65.8 mg, 10%) in the order of elution. **10**[10b]: mp 146—148°C (colorless prisms, recrystallized from $CHCl_3$ – MeOH). IR (KBr): 3160 (br), 1610 (br), 1568 (br), 1465, 1433, 1045, 822 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.76 (3H, s), 2.75 (2H, t, *J*=7.0 Hz), 3.21 (2H, q, *J*=7.0 Hz), 3.84 (3H, s), 7.19 (1H, s), 7.45 (1H, s), 7.94 (1H, t, *J*=7.0 Hz), 11.63 (1H, br s). MS *m/z*: 392, 390, 388 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_2Br_2 \cdot 1/2CHCl_3$: C, 36.02; H, 3.22; N, 6.23. Found: C, 36.01; H, 3.06; N, 5.98.

Entry 3: A 1 M solution of Br_2 in AcOH (3.04 mL, 3.04 mmol) was added to a solution of **1** (236.1 mg, 1.02 mmol) in AcOH (17.0 mL) and the mixture was stirred at rt for 2 h. After the same work-up as described in Entry 1, the resultant residue was column-chromatographed on Al_2O_3 with $CHCl_3$–AcOEt–hexane (4:1:4, v/v) to give **12** (286.5 mg, 60%). **12**: mp 122—125 °C (decomp, colorless powder, recrystallized from MeOH). IR (KBr): 3350, 1650, 1540, 1023 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.90 (3H, s), 3.13 (2H, t, *J*=6.9 Hz), 3.45 (2H, t, *J*=6.9 Hz), 3.84 (3H, s), 7.49 (1H, s). *Anal.* Calcd for $C_{13}H_{13}N_2O_2Br_3 \cdot 1/2H_2O$: C, 32.67; H, 2.74; N, 5.86. Found: C, 32.76; H, 2.78; N, 5.69.

1-Acetyl-2,4,6-tribromomelatonin (13) from 12 — A solution of **12** (85.0 mg, 0.18 mmol) in anhydrous DMF (1.5 mL) was added to 60% NaH (23.4 mg, 0.58 mmol, washed with dry benzene) at 0°C with stirring. To the resultant solution was added a solution of AcCl (66.4 mg, 0.85 mmol) in DMF (0.5 mL) and the mixture was stirred at rt for 24 h. After addition of H_2O under ice cooling, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (2:1, v/v) to give unreacted **12** (26.1 mg, 31%) and **13** (49.5 mg, 53%) in the order of elution. **13**: mp 165—168°C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3260, 1705, 1630, 1550, 1010 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (3H, s), 2.86 (3H, s), 3.30 (2H, t, *J*=7.1 Hz), 3.59 (2H, q, *J*=7.1 Hz), 3.90 (3H, s), 5.62 (1H, br s), 8.58 (1H, s). *Anal.* Calcd for $C_{15}H_{15}N_2O_3Br_3$: C, 35.26; H, 2.96; N, 5.48. Found: C, 35.26; H, 2.92; N, 5.44.

4-Bromomelatonin (8) from 11 — Finely chopped Mg (319.5 mg, 13.1 gram atom) was added to a solution of **11** (50.4 mg, 0.13 mmol) in MeOH (10 mL) and the mixture was stirred at rt for 2.5 h. The whole was made acidic by adding 2N aq. HCl 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 (99:1, v/v) to give unreacted **11** (21.9 mg, 44%) and **8** (8.5 mg, 21%) in the order of elution.

2-Bromomelatonin (9) from 11 — A 1.58 M *n*-BuLi solution in hexane (0.25 mL, 0.39 mmol) was added to a solution of **11** (50.3 mg, 0.13 mmol) in anhydous THF (3.0 mL) and the mixture was stirred at –19°C for 4.5 h under Ar atmosphere. After addition of H_2O under ice cooling, 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 (99:1, v/v) to give **9** (20.5 mg, 51%) and unreacted **11** (13.4 mg, 27%) in the order of elution.

***Nb*-Acetoacetyl-5-methoxytryptamine (14) from 1** — A 1.58 M *n*-BuLi solution in hexane (0.85 mL, 1.34 mmol) was added to a solution of **1** (105.5 mg, 0.45 mmol) in anhydrous THF (4.0 mL) and the mixture was stirred at –19°C for 4 h under Ar atmosphere. To the mixture was added *N,N*-dimethylacetamide (0.15 mL, 1.84 mmol) and the resultant mixture was stirred at –19°C for additional 1 h under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic by adding 2N aq. HCl 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 AcOEt to give **14** (36.9 mg, 30%) and unreacted **1** (69.3 mg, 66%) in the order of elution. **14**: Colorless oil. IR (film): 3300, 1710, 1640, 1540, 1215, 1170, 800 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.96 (2H, t, *J*=7.0 Hz), 3.37 (2H, s), 3.61 (2H, q, *J*=7.0 Hz), 3.87 (3H, s), 6.87 (1H, dd, *J*=8.5, 2.4 Hz), 6.93 (1H, br s), 7.03 (1H, d, *J*=2.4 Hz), 7.05 (1H, d, *J*=2.4 Hz), 7.26 (1H, d, *J*=8.5 Hz), 7.95 (1H, br s). High resolution MS *m/z*: Calcd for $C_{15}H_{18}N_2O_3$: 274.1318. Found: 274.1319.

***Nb*-Hydroxyacetyl-5-methoxytryptamine (15) from 1** — A 1.58 M *n*-BuLi solution in hexane (0.85 mL, 1.34 mmol) was added to a solution of **1** (106.5 mg, 0.46 mmol) in anhydrous THF (4.0 mL) and the mixture was stirred at –18°C for 4 h under Ar atmosphere. Then, the mixture was stirred at –18°C for 1 h under O_2 atmosphere. After addition of H_2O under ice cooling, the whole was made acidic by adding 2N aq. HCl 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 (99:1, v/v) to give unreacted **1** (41.6 mg, 39%) and **15** (41.5 mg, 36%) in the order of elution. **15**: mp 142—143°C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3320, 3180, 1628, 1483, 1220, 1060, 805 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.80 (2H, t, *J*=7.3 Hz), 3.38 (2H, q, *J*=7.3 Hz), 3.76 (3H, s), 3.79 (2H, d, *J*=5.6 Hz, collapsed to s on addition of D_2O), 5.47 (1H, t, *J*=5.6 Hz, disappeared on addition of D_2O), 6.71 (1H, dd, *J*=8.8, 2.4 Hz), 7.06 (1H, d, *J*=2.4 Hz), 7.11 (1H, d, *J*=2.4 Hz), 7.21 (1H, d, *J*=8.8 Hz), 7.78 (1H, br t, *J*=7.3 Hz), 10.63 (1H, br s). MS *m/z*: 248 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_3 \cdot 1/8H_2O$: C, 62.33; H, 6.44; N, 11.18. Found: C, 62.46; H, 6.31; N, 11.14.

***Nb*-Acetoxyacetyl-5-methoxytryptamine (16) from 15** — Acetic anhydride (0.5 mL, 5.28 mmol) was added to a solution of **15** (30.1 mg, 0.12 mmol) in pyridine (1.0 mL) and the mixture was stirred at rt for 1 h. After evaporation of the solvent under reduced pressure, the whole was made basic by adding sat. aq. $NaHCO_3$ 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 $CHCl_3$-hexane (1:2, v/v) to give **16** (32.1 mg, 91%). **16**: Colorless oil. IR (film): 3310, 1745, 1662, 1545, 1220, 1060, 800, 752 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.97 (3H, s), 2.98 (2H, t, *J*=6.6 Hz), 3.64 (2H, q, *J*=6.6 Hz), 3.86 (3H, s), 4.52 (2H, s), 6.19 (1H, br s), 6.88 (1H, dd, *J*=8.8, 2.4 Hz), 7.04 (1H, br s), 7.04 (1H, d, *J*=2.4 Hz), 7.27 (1H, d, *J*=8.8 Hz), 7.98 (1H, br s). High–resolution MS *m/z*: Calcd for $C_{15}H_{18}N_2O_4$: 290.1267. Found: 290.1264.

***Nb*-Chloroacetyl-5-methoxytryptamine (17) from 7** — A solution of chloroacetyl chloride (127.7 mg, 1.13 mmol) in $CHCl_3$ (1.0 mL) was added to a solution of **7** (103.2 mg, 0.54 mmol) in $CHCl_3$ (2.0 mL) and Et_3N (0.3 mL, 2.15 mmol). The mixture was stirred at rt for 1 h. After addition of H_2O under ice cooling, 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 $CHCl_3$ to give **17** (134.3 mg, 93%). **17**: mp 130—131°C (lit.,[9] mp 125—127°C, colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3300, 1650, 925, 805 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.99 (2H, t, J=6.8 Hz), 3.65 (2H, q, J=6.8 Hz), 3.88 (3H, s), 4.03 (2H, s), 6.68 (1H, br s), 6.89 (1H, dd, J=8.8, 2.4 Hz), 7.04 (2H, d, J=2.4 Hz), 7.28 (1H, d, J=8.8 Hz), 7.96 (1H, br s). MS m/z: 268, 266 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_2O_2Cl \cdot 1/8H_2O$: C, 58.05; H, 5.71; N, 10.41. Found: C, 58.04; H,5.57; N, 10.45.

***Nb*-Hydroxyacetyl-5-methoxytryptamine (15) from 17** — A solution of **17** (50.0 mg, 0.19 mmol) in NH_2CHO–H_2O (10:1, v/v, 2.2 mL) was heated at 120°C for 3 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 (99:1, v/v) to give **15** (40.3 mg, 87%).

1-Acetylmelatonin (18a) from 1 —A solution of **1** (103.2 mg, 0.45 mmol) in anhydrous DMF (4.0 mL) was added to 60% NaH (35.5 mg, 0.89 mmol, washed with dry benzene) at 0°C with stirring. To the resultant solution was added a solution of AcCl (124.2 mg, 1.58 mmol) in DMF (1.0 mL) and the mixture was stirred at rt for 5 h. After addition of H_2O under ice cooling, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt to give unreacted **1** (10.7 mg, 10%) and **18a** (93.9 mg, 77%) in the order of elution. **18a**: mp 135—137 °C (colorless prisms,, recrystallized from $CHCl_3$–hexane). IR (KBr): 3250, 1712, 1638, 1390, 1260 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.81 (3H,s), 2.58 (3H, s), 2.77 (2H, t, J=7.0 Hz), 3.36 (2H, q, J=7.0 Hz), 3.81 (3H, s), 6.92 (1H, dd, J=8.9, 2.4 Hz), 7.13 (1H, d, J=2.4 Hz), 7.63 (1H, s), 8.01 (1H, br t, J=7.0 Hz), 8.19 (1H, d, J=8.9 Hz). 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, 64.96; H, 6.53; N, 10.18.

***Nb*-Acetyl-1-formyl-5-methoxytryptamine (18b) from 1**— Compound (**1**) (23.2 mg, 0.10 mmol) was dissolved in 85% HCOOH (5.0 mL, 111 mmol) and the solution was stirred at rt for 94 h. Evaporation of the solvent under reduced pressure afforded an oil, which was column-chromatographed on SiO_2 with CH_2Cl_2–MeOH (97:3, v/v) to give **18b** (23.9 mg, 92%) and unreacted **1** (1.2 mg, 5%) in the order of elution. **18b**: Colorless oil. IR (film): 3275, 1705, 1653, 1477, 1386, 1240, 1040, 783 cm^{-1}. ^1H-NMR (DMSO-d_6, 120°C) δ: 1.80 (3H, s), 2.81 (2H, dt, J=5.8, 1.0 Hz), 3.38 (2H, dt, J=4.8, 5.8 Hz), 3.82 (3H, s), 6.94 (1H, dd, J=7.5, 2.4 Hz), 7.14 (1H, d, J=2.4 Hz), 7.51 (1H, br s), 7.52 (1H, s), 8.03 (1H, d, J=7.5 Hz), 9.23 (1H, s). High resolution MS m/z: Calcd for $C_{14}H_{16}N_2O_3$: 260.1159. Found: 260.1151.

***Nb*-Acetylmelatonin (19) from 1** — A solution of **1** (49.4 mg, 0.21 mmol) in Ac_2O (1.0 mL) was refluxed for 2 h with stirring. After evaporation of the solvent under reduced pressure, the whole was made alkaline by adding 2N aq. NaOH 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 (99:1, v/v) to give **19** (53.5 mg, 92%). **19**: mp 158—159°C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3340, 1690 (br), 1590, 1375, 1260, 1170, 830, 820 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.33 (6H, s), 2.99—3.02 (2H, m), 3.88 (3H, s), 3.92—3.95 (2H, m), 6.87 (1H, dd, J=8.8, 2.4 Hz), 6.98 (1H, d, J=2.4 Hz), 7.13 (1H, d, J=2.4 Hz), 7.26 (1H, d, J=8.8 Hz), 7.92 (1H, br s). MS m/z: 274 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.43; H, 6.56; N, 10.21.

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In the synthesis of **1**, the reactions developed by us are utilized in the third[5] and the fourth[8] steps. Originality rate is the result of the following calculation.
Originality Rate (%) = 100 x [Number of Newly Developed Steps + 1] ÷ [Total Number of Synthetic Steps + 1]

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