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| journal or publication title | Heterocycles |
| volume | 53 |
| number | 8 |
| page range | 1725-1736 |
| year | 2000-08-01 |
| URL | http://hdl.handle.net/2297/4361 |

SYNTHESES OF MELATONIN AND ITS DERIVATIVES¹

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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.

Melatonin² (**1**, Scheme 1) is a hormone secreted from pineal gland and is well known to control the circadian rhythms.² Its multimodality of biological activities³ 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 Ac₂O or methyl chloroformate,⁵ were reduced with Et₃SiH⁶ in TFA to afford the corresponding 2,3-dihydrotryptamines, (**4a**) and (**4b**), in 99 and 97% yields, respectively. Application of our 1-hydroxyindole synthetic method⁵ to **4a**, using 30% H₂O₂ and Na₂WO₄·2H₂O 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 reaction⁸ 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 H₂SO₄ 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 BF₃ 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 *R_f* 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

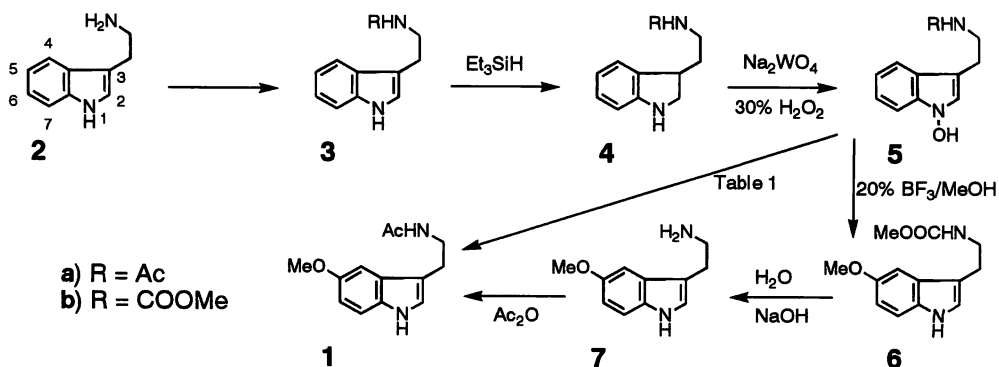


Table 1 5a $\xrightarrow[\text{MeOH}]{\text{Acid}}$ 1 + 3a

| Entry | Reagent | Reaction Conditions | | Yield (%) of | |
|-------|------------------------------------|---------------------|----------|--------------|----|
| | | Temp. (°C) | Time (h) | 1 | 3a |
| 1 | 22% H ₂ SO 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 |

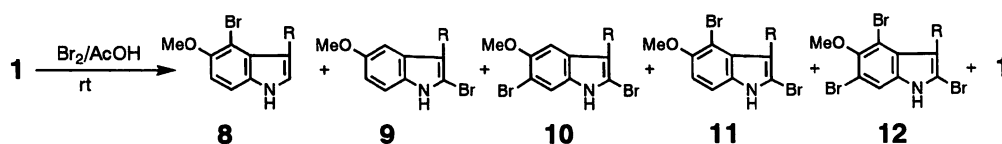
As an alternative route, the reaction of **5b** with 20% BF₃ was examined in refluxing MeOH. Interestingly, the reaction was relatively faster than that of **5a** and, without any contamination of **3b**,^{8d} **6** was obtained in 94% yield. Even if the formation of **3b** were observed by chance, the reaction would be suitable for large scale production because there are wide differences in *R_f* 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 Ac₂O 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 Br₂ 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 Br₂ 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 Br₂ 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-tri-

bromomelatonin 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 $^1\text{H-NMR}$ 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/NH₄Cl did not react at all. Contrastively, *n*-BuLi in THF at -19°C , followed by the addition of H₂O, 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 = CH₂CH₂NHAc



| Entry | Bromine (mol eq) | Reaction Time (h) | Yield (%) of | | | | | 1 |
|-------|------------------|-------------------|--------------|----------|-----------|-----------|-----------|----------|
| | | | 8 | 9 | 10 | 11 | 12 | |
| 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 |

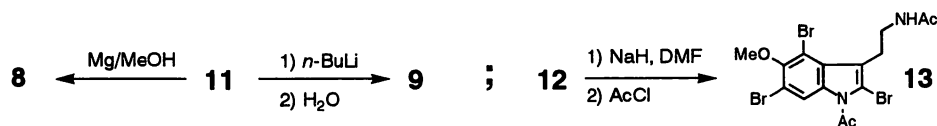
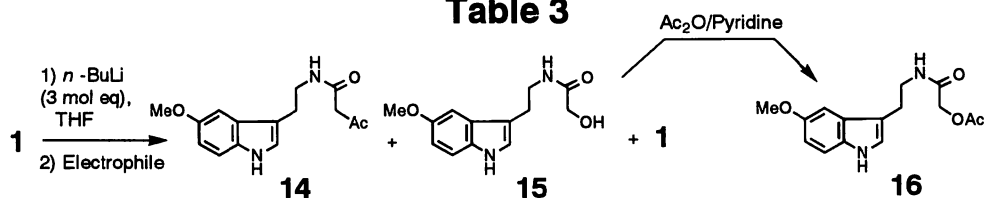


Table 3

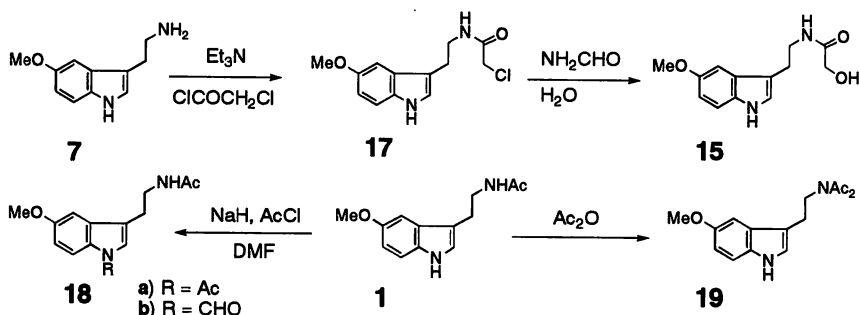


| Entry | Electrophile (mol eq) | Gas | Reaction Time (h) | Yield (%) of | | |
|-------|--------------------------|----------------|-------------------|--------------|-----------|----------|
| | | | | 14 | 15 | 1 |
| 1 | MeCONMe ₂ (4) | Ar | 5 | 30 | 0 | 66 |
| 2 | " | " | 6 | 23 | 4 | 43 |
| 3 | — | 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°C , followed by reaction with *N,N*-dimethylacetamide. The result was the formation of *Nb*-acetoacetyl- (**14**) and/or *Nb*-hydroxy-

acetyl-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*-acetoxyacetyl-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 $^1\text{H-NMR}$ 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°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 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} . $^1\text{H-NMR}$ (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 $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$: 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°C (colorless prisms, recrystallized from AcOEt-hexane). IR (KBr): 3407, 3345, 1716, 1521, 1247, 752 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$: 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 $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (500.0 mg, 1.53 mmol) in MeOH (150 mL)- H_2O (15.0 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 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} . $^1\text{H-NMR}$ (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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$: 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 $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (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} . $^1\text{H-NMR}$

(CD₃OD) 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 C₁₂H₁₄N₂O₃: 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. H₂SO₄ (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, H₂O was added under ice cooling and the whole was extracted with CH₂Cl₂–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was subjected to HPLC on SiO₂ 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, H₂O was added to the residue and the whole was made neutral by adding sat. NaHCO₃ under ice cooling and extracted with CH₂Cl₂–MeOH (95:5, v/v). After the same work-up and separation as described in Entry 1, **3a** (2.9 mg, 10%) and **1** (17.7 mg, 55%) were obtained.

Entry 5: 50% BF₃–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 CH₂Cl₂–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% BF₃–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 H₂O, the whole was made neutral by adding 40% aq. NaOH and extracted with CHCl₃. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃ to give **6** (1.50 g, 94%). **6**: mp 80–82 °C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 3330, 1670, 1536, 1486, 1035, 926, 775 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₁₃H₁₆N₂O₃: 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% BF₃–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 H₂O, the whole was made neutral by adding 40% aq. NaOH and extracted with CHCl₃. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃ 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 H₂O, the whole was extracted with CHCl₃–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} . $^1\text{H-NMR}$ (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 $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$: 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} . $^1\text{H-NMR}$ (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 $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{Br}\cdot 1/4\text{H}_2\text{O}$: 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} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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 $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{Br}$: 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} . $^1\text{H-NMR}$ (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 $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{Br}_2\cdot 1/4\text{H}_2\text{O}$: 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 CHCl₃–MeOH). IR (KBr): 3160 (br), 1610 (br), 1568 (br), 1465, 1433, 1045, 822 cm⁻¹. ¹H-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 C₁₃H₁₄N₂O₂Br₂·1/2CHCl₃: 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 Br₂ 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 Al₂O₃ with CHCl₃–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. ¹H-NMR (CD₃OD) 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 C₁₃H₁₃N₂O₂Br₃·1/2H₂O: 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 H₂O under ice cooling, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with 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 CHCl₃–hexane). IR (KBr): 3260, 1705, 1630, 1550, 1010 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₁₅H₁₅N₂O₃Br₃: 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 CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (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 anhydrous THF (3.0 mL) and the mixture was stirred at –19°C for 4.5 h under Ar atmosphere. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (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*-dimethyl-

acetamide (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} . $^1\text{H-NMR}$ (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 $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: 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} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) 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 $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3 \cdot 1/8\text{H}_2\text{O}$: 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} . $^1\text{H-NMR}$ (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 $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$: 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} . $^1\text{H-NMR}$ (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 $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl} \cdot 1/8\text{H}_2\text{O}$: 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 $\text{NH}_2\text{CHO-H}_2\text{O}$ (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} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) 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 $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3 \cdot 1/8\text{H}_2\text{O}$: 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} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 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 $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$: 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} . $^1\text{H-NMR}$ (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 third⁵ and the fourth⁸ 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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Received, 26th April, 2000