

HETEROCYCLES, Vol. 60, No. 6, , pp. 1411 - 1418

Received, 14th February, 2003, Accepted, 4th April, 2003, Published online, 7th April, 2003

WATER-SOLUBLE MELATONINS: SYNTHESSES OF MELATONINS CARRYING A GLYCOSYL GROUP AT THE 1-POSITION¹

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Abstract – 1-(β -D-Xylopyranosyl)- (**2a**), 1-(β -D-glucoopyranosyl)- (**2b**), 1-(β -D-galactopyranosyl)- (**2c**), and 1-(α -D-arabinopyranosyl)melatonins (**3b**) are prepared as water-soluble melatonins starting from melatonin.

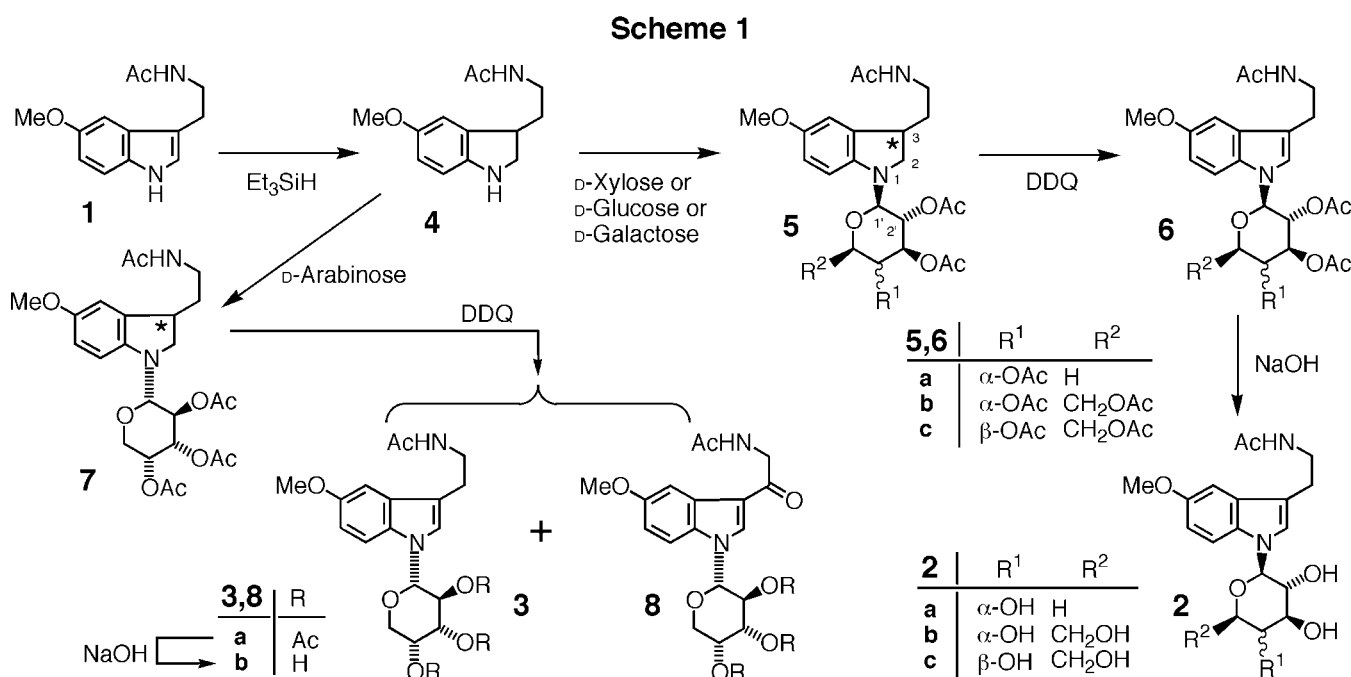
Regulation of the circadian rhythms,² inhibition of Alzheimer β -fibrillogenesis,^{3a} anti-aging properties relating to radical scavenging,^{3b} antiproliferative effect on melanoma cells,^{3c} and so on³ are well known biological activities³ reported for melatonin² (**1**, Scheme 1), a pineal gland hormone.

In our continuing project⁴ for developing new biologically active compounds based on indole nucleus, we have thus far succeeded in finding our own synthetic method⁴ for melatonin (**1**). With **1** in hand, we have now reached to the stage^{1c} for creating water-soluble melatonin^{1c} in order to examine whether such change in physical properties of **1** has a substantial effect on its biological activities. In this paper, we wish to report the results of our trial to produce 1-glycosylmelatonin derivatives (**2a–c**, **3b**), chosen as our targets among various candidates for water-soluble melatonins.

Preobrazhenskaya⁵ and co-workers reported a synthetic method for 1-glycosylindoles without using any protecting group, consisting of heating indolines with an appropriate sugar component, followed by DDQ oxidation. So, we applied the procedure to meet our ends.

Melatonin⁴ (**1**), prepared through biologically active 1-hydroxytryptamines,⁶ was first converted to 2,3-dihydromelatonin (**4**) as reported^{4d,e} previously by reduction with Et₃SiH⁷ in CF₃COOH in 99% yield.^{4e} Although treatment of **4** with 3-mol eq. of D-xylose in refluxing MeOH afforded 1-glycosyl-2,3-dihydromelatonin, its isolation in pure state was difficult. The reaction mixture was therefore acetylated with Ac₂O-pyridine to afford a 1:1 mixture of diastereomers (**5a**) in 85% yield. Oxidation of the mixture with 1.2-mol eq. of DDQ in dioxane at room temperature produced **6a** as a single isomer in 56% yield.

To the contrary to the expected improvement, employment of 2-mol eq. of DDQ dropped the yield of **6a** down to 46% with formation of tar.



Similar reactions of **4** with D-glucose and D-galactose, followed by treatment with Ac₂O-pyridine, afforded **5b** and **5c** in 97 and 85% yields, respectively. Oxidations of **5b** and **5c** with 1-mol eq. of DDQ produced **6b** and **6c** in the respective yields of 87 and 80%. In these cases, the employment of 2-mol eq. of DDQ decreased the yields of **6b** and **6c** to 55 and 45% yields, respectively. The anomeric (C-1') protons in the ¹H-NMR spectra of **6a**—**c** clearly appeared as a doublet with a coupling constant of 9 Hz. Based on these data, their structures are confirmed to be 1-(β-D-glycosyl)melatonin and the diastereomers (**5a**—**c**) arise from the stereochemistry at the indole 3-position.

In the case of D-arabinose, **7** was obtained in 95% yield by the reaction with **4**, followed by treatment with Ac₂O-pyridine. An interesting fact is the formation of **8a** in 10% yield together with 43% yield of **3a** when the oxidation of **7** was carried out with 1.2-mol eq. of DDQ. 2-mol eq. of DDQ raised the yield of **8a** up to 34% together with 4% yield of **3a**. The anomeric protons of **8a** and **3a** appear as a doublet with a coupling constant of 9 Hz. Therefore, their *trans*-diaxial relationship to the neighboring C-2' proton is proved. Since D-arabinose has β-hydroxy group at the C-2' position, structures of **8a** and **3a** are confirmed to be 1-(α-D-glycosyl)melatonin derivatives. The difference in the anomeric configuration between **7** and **5a**—**c** seems to be the cause of their differences in the oxidation behavior.

Hydrolysis of ester group in **6a** was carried out with 8% aqueous NaOH to give the desired 1-(β-D-xylopyranosyl)melatonin (**2a**) in 83% yield. Similarly, alkaline hydrolysis of **6b**, **6c**, **3a**, and **8a** provided **2b**, **2c**, **3b**, and **8b** in 90, 93, 87, and 81% yields, respectively.

Biological evaluations of 1-glycosylmelatonins and syntheses of other types of water-soluble melatonins are now in progress.

EXPERIMENTAL

IR spectra were determined with a Shimadzu IR-420 or HORIBA FT-720 spectrophotometer and $^1\text{H-NMR}$ spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. PTLC was performed on Merck Kiesel-gel GF₂₅₄ (Type 60)(SiO₂). Column chromatography was performed on silica gel (SiO₂, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

1-(β -D-Triacetylxylopyranosyl)-2,3-dihydromelatonin (5a) from 4 — D-Xylose (112.5 mg, 0.75 mmol) was added to a solution of **4** (58.5 mg, 0.25 mmol) in MeOH (4.0 mL) and the mixture was refluxed for 2 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was dissolved in pyridine (3.0 mL, 37.0 mmol). To the resultant solution, Ac₂O (1.5 mL, 15.9 mmol) was added and the mixture was stirred at rt for 2.5 h. The solvent was evaporated under reduced pressure. After addition of H₂O to the residue, the whole was extracted with CHCl₃-MeOH (95:5, v/v). The extract was washed with 10% NH₄Cl and brine, dried over Na₂SO₄ and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ successively with CHCl₃-MeOH (99:1, v/v) and CHCl₃-MeOH (95:5, v/v) to give **5a** (105.3 mg, 85%). **5a**: pale yellow oil. IR (film): 1754, 1654 cm⁻¹. $^1\text{H-NMR}$ (CDCl₃) δ : 1.59—1.76 (2H, m), 1.93 (3/2H, s), 1.96 (3/2H, s), 1.99 (3/2H, s), 2.01 (3/2H, s), 2.04 (3H, s), 2.05 (3/2H, s), 2.06 (3/2H, s), 3.15—3.40 (5H, m), 3.66 (1/2H, t, $J=7.8$ Hz), 3.71 (1/2H, t, $J=7.5$ Hz), 3.73 (3H, s), 4.04—4.09 (1H, m), 4.81 (1/2H, d, $J=9.0$ Hz), 4.83 (1/2H, d, $J=9.0$ Hz), 4.96—5.02 (1H, m), 5.17 (1/2H, t, $J=9.0$ Hz), 5.19 (1/2H, t, $J=9.0$ Hz), 5.32 (1/2H, t, $J=9.0$ Hz), 5.33 (1/2H, t, $J=9.0$ Hz), 5.57 (1/2H, br t, $J=5.2$ Hz), 5.67 (1/2H, br t, $J=5.2$ Hz), 6.50 (1/2H, d, $J=8.6$ Hz), 6.51 (1/2H, d, $J=8.6$ Hz), 6.66 (1/2H, dd, $J=8.6, 2.5$ Hz), 6.67 (1/2H, dd, $J=8.6, 2.5$ Hz), 6.70 (1/2H, d, $J=2.5$ Hz), 6.75 (1/2H, d, $J=2.5$ Hz). HRMS m/z : Calcd for C₂₄H₃₂N₂O₉: 492.2108. Found: 492.2104. $[\alpha]_{\text{D}}^{25} +8.15^\circ$ (c=0.135, MeOH).

1-(β -D-Tetraacetylglucopyranosyl)-2,3-dihydromelatonin (5b) from 4 — In the same procedure as described in the preparation of **5a**, D-glucose (76.9 mg, 0.43 mmol), **4** (20.1 mg, 0.086 mmol), MeOH (1.5 mL), pyridine (1.5 mL, 18.5 mmol) and Ac₂O (0.75 mL, 7.9 mmol) were used. Column-chromatography was performed on SiO₂ with CHCl₃ to give **5b** (46.9 mg, 97%). **5b**: colorless oil. IR (film): 1751, 1655 cm⁻¹. $^1\text{H-NMR}$ (CDCl₃) δ : 1.61—1.67 (1H, m), 1.69—1.79 (1H, m), 1.94 (3/2H, s), 1.95 (3/2H, s), 1.99 (3H, s), 2.00 (3/2H, s), 2.01 (3/2H, s), 2.03—2.04 (3/2Hx4, each s), 3.15—3.40 (4H, m), 3.68 (1H, t, $J=8.8$ Hz), 3.74 (3H, s), 3.71—3.76 (1H, m), 4.03 (1/2H, dd, $J=12.2, 2.4$ Hz), 4.06 (1/2H,

dd, $J=12.2, 2.4$ Hz), 4.24 (1/2H, dd, $J=12.2, 3.2$ Hz), 4.26 (1/2H, dd, $J=12.2, 3.2$ Hz), 4.88 (1/2H, d, $J=9.1$ Hz), 4.89 (1/2H, d, $J=9.1$ Hz), 5.07 (1/2H, t, $J=9.0$ Hz), 5.08 (1/2H, t, $J=9.0$ Hz), 5.23 (1/2H, t, $J=9.0$ Hz), 5.24 (1/2H, t, $J=9.0$ Hz), 5.33 (1/2H, t, $J=9.0$ Hz), 5.34 (1/2H, t, $J=9.0$ Hz), 5.56 (1/2H, br t, $J=5.0$ Hz), 5.69 (1/2H, br t, $J=5.0$ Hz), 6.48 (1/2H, d, $J=8.5$ Hz), 6.50 (1/2H, d, $J=8.5$ Hz), 6.66 (1H, dd, $J=8.5, 2.4$ Hz), 6.71 (1/2H, d, $J=2.4$ Hz), 6.75 (1/2H, d, $J=2.4$ Hz). HRMS m/z : Calcd for $C_{27}H_{36}N_2O_{11}$: 564.2319. Found: 564.2324. $[\alpha]_D^{24} -5.76^\circ$ ($c=0.10$, MeOH).

1-(β -D-Tetraacetylgalactopyranosyl)-2,3-dihydromelatonin (5c) from 4 — In the same procedure as described in the preparation of **5a**, D-galactose (231.2 mg, 1.28 mmol), **4** (100.2 mg, 0.43 mmol), MeOH (6.0 mL), pyridine (8.0 mL, 99.0 mmol), and Ac_2O (4.0 mL, 42.3 mmol) were used. Column-chromatography was performed on SiO_2 successively with $CHCl_3$ and $CHCl_3$ -MeOH (99:1 v/v) to give **5c** (205.4 mg, 85%). **5c**: colorless oil. IR (film): 1745, 1653 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 1.61—1.69 (1H, m), 1.70—1.80 (1H, m), 1.94 (3/2H, s), 1.96 (3/2H, s), 1.97 (3/2H, s), 1.98 (3/2H, s), 1.99 (3/2H, s), 2.01—2.02 (3/2Hx3, each s), 2.17 (3/2H, s), 2.19 (3/2H, s), 3.16—3.44 (4H, m), 3.71—3.77 (1H, m), 3.75 (3H, s), 3.96 (1H, t, $J=6.7$ Hz), 4.02—4.13 (2H, m), 4.83 (1/2H, d, $J=9.0$ Hz), 4.85 (1/2H, d, $J=9.0$ Hz), 5.14 (1/2H, dd, $J=9.0, 3.4$ Hz), 5.16 (1/2H, dd, $J=9.0, 3.4$ Hz), 5.39—5.40 (1/2Hx2, each t, $J=9.0$ Hz), 5.43 (1H, m), 5.54 (1/2H, br t), 5.61 (1/2H, br t), 6.50 (1H, t, $J=8.3$ Hz), 6.66 (1H, dd, $J=8.3, 2.4$ Hz), 6.70 (1/2 H, d, $J=2.4$ Hz), 6.74 (1/2H, d, $J=2.4$ Hz). HRMS m/z : Calcd for $C_{27}H_{36}N_2O_{11}$: 564.2319. Found: 564.2312. $[\alpha]_D^{24} +8.91^\circ$ ($c=0.10$, MeOH).

1-(α -D-Triacetylraabinopyranosyl)-2,3-dihydromelatonin (7) from 4 — In the same procedure as described in the preparation of **5a**, D-arabinose (208.2 mg, 1.39 mmol), **4** (64.9 mg, 0.28 mmol), MeOH (4.0 mL), pyridine (4.0 mL, 49.5 mmol), and Ac_2O (2.0 mL, 21.2 mmol) were used. The acetylated mixture was subjected to PTLC on SiO_2 developing twice with $CHCl_3$ -MeOH (97:3, v/v). Extraction of the band having an R_f value of 0.63—0.47 with $CHCl_3$ -MeOH (95:5, v/v) gave **7** (129.6 mg, 95%). **7**: colorless oil. IR (film): 1747, 1655 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 1.60—1.80 (2H, m), 1.93 (3/2H, s), 1.95 (3/2H, s), 1.99 (3/2H, s), 2.02 (3/2H, s), 2.03 (3/2H, s), 2.04 (3/2H, s), 2.17 (3/2H, s), 2.19 (3/2H, s), 3.17—3.48 (4H, m), 3.66—3.80 (2H, m), 3.74 (3H, s), 3.99 (1H, dd, $J=13.0, 2.0$ Hz), 4.76 (1/2H, d, $J=9.0$ Hz), 4.77 (1/2H, d, $J=9.0$ Hz), 5.13—5.18 (1H, m), 5.31 (1H, m), 5.41—5.45 (1H, m), 5.49 (1/2H, br t, $J=5.2$ Hz, disappeared on addition of D_2O), 5.58 (1/2H, br t, $J=5.2$ Hz, disappeared on addition of D_2O), 6.52 (1/2H, d, $J=8.6$ Hz), 6.53 (1/2H, d, $J=8.6$ Hz), 6.66 (1/2H, dd, $J=8.6, 2.7$ Hz), 6.67 (1/2H, dd, $J=8.6, 2.7$ Hz), 6.69 (1/2H, d, $J=2.7$ Hz), 6.74 (1/2H, d, $J=2.7$ Hz). HRMS m/z : Calcd for $C_{24}H_{32}N_2O_9$: 492.2108. Found: 492.2098. $[\alpha]_D^{25} -38^\circ$ ($c=0.10$, MeOH).

1-(β -D-Triacetylxylopyranosyl)melatonin (6a) from 5a — DDQ (64.0 mg, 0.28 mmol) was added to a solution of **5a** (115.7 mg, 0.24 mmol) in dioxane (5.0 mL) and the mixture was stirred at rt for 0.5 h. The

whole was made alkaline by adding 8% NaHCO₃ under ice cooling and 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 subjected to PTLC on SiO₂ developing three times with CHCl₃–MeOH (98:2, v/v). Extraction of the band having an *R_f* value of 0.71–0.58 with CHCl₃–MeOH (95:5, v/v) gave **6a** (65.0 mg, 56%). **6a**: pale yellow oil. IR (film): 1755, 1655 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.53 (3H, s), 1.93 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 2.77–2.84 (1H, m), 2.91–2.98 (1H, m), 3.39–3.46 (1H, m), 3.59 (1H, dd, *J*=11.5, 10.5 Hz), 3.66–3.74 (1H, m), 3.84 (3H, s), 4.29 (1H, dd, *J*=11.5, 5.6 Hz), 5.19 (1H, ddd, *J*=10.5, 9.5, 5.6 Hz), 5.29 (1H, t, *J*=9.0 Hz), 5.40 (1H, d, *J*=9.0 Hz), 5.44 (1H, dd, *J*=9.5, 9.0 Hz), 5.89 (1H, br t, disappeared on addition of D₂O), 6.89 (1H, dd, *J*=8.8, 2.4 Hz), 6.96 (1H, d, *J*=2.4 Hz), 7.07 (1H, s), 7.23 (1H, d, *J*=8.8 Hz). HRMS *m/z*: Calcd for C₂₄H₃₀N₂O₉: 490.1951. Found: 490.1945. [α]_D²⁴ –37.0° (c=0.10, MeOH).

1-(β-D-Tetraacetylglucopyranosyl)melatonin (6b) from 5b — In the same procedure as described in the preparation of **6a**, DDQ (84.2 mg, 0.32 mmol), **5b** (150.2 mg, 0.27 mmol), and dioxane (8.0 mL) were used. The crude product was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1 v/v) to give **6b** (130.7 mg, 87%). **6b**: yellow oil. IR (film): 1751, 1655 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.53 (3H, s), 1.94 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.78–2.85 (1H, m), 2.92–2.98 (1H, m), 3.40–3.47 (1H, m), 3.68–3.75 (1H, m), 3.85 (3H, s), 4.00 (1H, ddd, *J*=10.0, 4.9, 2.2 Hz), 4.17 (1H, dd, *J*=12.5, 2.2 Hz), 4.33 (1H, dd, *J*=12.5, 4.9 Hz), 5.26 (1H, dd, *J*=10.0, 9.5 Hz), 5.35 (1H, dd, *J*=9.5, 9.0 Hz), 5.45 (1H, t, *J*=9.5 Hz), 5.48 (1H, d, *J*=9.0 Hz), 5.92 (1H, br t, *J*=5.0 Hz), 6.90 (1H, dd, *J*=8.9, 2.3 Hz), 6.97 (1H, d, *J*=2.3 Hz), 7.08 (1H, s), 7.23 (1H, d, *J*=8.9 Hz). HRMS *m/z*: Calcd for C₂₇H₃₄N₂O₁₁: 562.2163. Found: 562.2149. [α]_D²⁵ –29.7° (c=0.10, MeOH).

1-(β-D-Tetraacetylgalactopyranosyl)melatonin (6c) from 5c — In the same procedure as described in the preparation of **6a**, DDQ (65.8 mg, 0.29 mmol), **5c** (136.2 mg, 0.24 mmol), and dioxane (8.0 mL) were used. The crude product was column-chromatographed on SiO₂ successively with CHCl₃–MeOH (99:1 v/v) and AcOEt to give **6c** (108.7 mg, 80%). **6c**: colorless oil. IR (film): 1751, 1655 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.55 (3H, s), 1.94 (3H, s), 2.01 (3H, s), 2.04 (3H, s), 2.26 (3H, s), 2.81–2.87 (1H, m), 2.93–2.99 (1H, m), 3.40–3.47 (1H, m), 3.68–3.75 (1H, m), 3.85 (3H, s), 4.17 (1H, dd, *J*=13.5, 9.0 Hz), 4.20 (1H, dd, *J*=9.0, 5.0 Hz), 4.22 (1H, dd, *J*=13.5, 5.0 Hz), 5.27 (1H, dd, *J*=10.4, 3.2 Hz), 5.44 (1H, d, *J*=9.0 Hz), 5.51 (1H, dd, *J*=10.4, 9.0 Hz), 5.56 (1H, d, *J*=3.2 Hz), 5.92 (1H, br t, *J*=5.0 Hz), 6.90 (1H, dd, *J*=8.8, 2.5 Hz), 6.97 (1H, d, *J*=2.5 Hz), 7.12 (1H, s), 7.27 (1H, d, *J*=8.8 Hz). HRMS *m/z*: Calcd for C₂₇H₃₄N₂O₁₁: 562.2163. Found: 562.2163. [α]_D²⁵ –22° (c=0.10, MeOH).

1-(α-D-Triacetyl-rabinopyranosyl)melatonin (3a) and 3-[2-(Acetylamino)acetyl]-1-(α-D-triacetyl-rabinopyranosyl)-5-methoxyindole (8a) from 7 — [Entry 1] In the same procedure as described in

the preparation of **6a**, DDQ (65.8 mg, 0.29 mmol), **7** (136.2 mg, 0.24 mmol), and dioxane (8.0 mL) were used and stirring was continued for 1 h. The crude product was subjected to PTLC on SiO₂ developing twice with CHCl₃–MeOH–28% NH₃ (46:1:0.1, v/v). Extraction of the band having an *R_f* value of 0.63–0.52 with CHCl₃–MeOH (95:5, v/v) gave **3a** (62.1 mg, 43%). Extraction of the band having an *R_f* value of 0.37–0.32 with CHCl₃–MeOH (95:5, v/v) gave **8a** (15.0 mg, 10%). **3a**: colorless oil. IR (film): 1749, 1655 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.55 (3H, s), 1.94 (3H, s), 2.04 (3H, s), 2.26 (3H, s), 2.80–2.87 (1H, m), 2.93–2.99 (1H, m), 3.39–3.47 (1H, m), 3.68–3.76 (1H, m), 3.85 (3H, s), 3.93 (1H, dd, *J*=13.4, 0.7 Hz), 4.20 (1H, dd, *J*=13.4, 2.0 Hz), 5.27 (1H, dd, *J*=10.3, 3.4 Hz), 5.35 (1H, d, *J*=9.0 Hz), 5.44 (1H, ddd, *J*=3.4, 2.0, 0.7 Hz), 5.55 (1H, dd, *J*=10.3, 9.0 Hz), 5.92 (1H, br t, *J*=5.5 Hz disappeared on addition of D₂O), 6.89 (1H, dd, *J*=9.0, 2.4 Hz), 6.97 (1H, d, *J*=2.4 Hz), 7.13 (1H, s), 7.26 (1H, d, *J*=9.0 Hz). HRMS *m/z*: Calcd for C₂₄H₃₀N₂O₆: 490.1951. Found: 490.1952. [α]_D²⁶ +2.78° (c=0.09, MeOH).

[Entry 2] In the same procedure as described in the preparation of **6a**, DDQ (66.8 mg, 0.29 mmol), **7** (72.4 mg, 0.15 mmol), and dioxane (5.0 mL) were used. After the same work-up and separation as described in the Entry 1, **3a** (3.1 mg, 4%) and **8a** (25.5 mg, 34%) were obtained. **8a**: colorless oil. IR (film): 1749, 1653 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.66 (3H, s), 2.04 (3H, s), 2.11 (3H, s), 2.33 (3H, s), 3.89 (3H, s), 3.96 (1H, dd, *J*=13.4, 1.0 Hz), 4.25 (1H, dd, *J*=13.4, 2.0 Hz), 4.63 (1H, dd, *J*=18.0, 4.0 Hz), 4.68 (1H, dd, *J*=18.0, 4.5 Hz), 5.29 (1H, dd, *J*=10.0, 3.4 Hz), 5.43 (1H, d, *J*=9.0 Hz), 5.48 (1H, ddd, *J*=3.4, 2.0, 1.0 Hz), 5.62 (1H, dd, *J*=10.0, 9.0 Hz), 6.66 (1H, br t, disappeared on addition of D₂O), 6.98 (1H, dd, *J*=9.0, 2.4 Hz), 7.38 (1H, d, *J*=9.0 Hz), 7.82 (1H, d, *J*=2.4 Hz), 8.03 (1H, s). HRMS (FAB⁺) *m/z*: Calcd for C₂₄H₂₉N₂O₁₀: 505.1823 (MH⁺). Found: 505.1821. [α]_D²⁸ +3.88° (c=0.12, MeOH).

1-(β-D-Xylopyranosyl)melatonin (2a) from 6a — 8% NaOH (0.5 mL) was added to a solution of **6a** (29.9 mg, 0.06 mmol) in MeOH (1.0 mL) and the mixture was stirred at rt for 1 h. After evaporation of the solvent under reduced pressure, brine was added to the residue and the whole was extracted with AcOEt–MeOH (95:5, v/v). The extract was dried over Na₂SO₄ and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with AcOEt–MeOH (97:3, v/v) to give **2a** (18.5 mg, 83%). **2a**: colorless oil. IR (film): 3321, 2920, 1633, 1483, 1454, 1232, 1051 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 1.81 (3H, s), 2.75 (2H, t, *J*=7.6 Hz), 3.33 (2H, t, *J*=7.6 Hz), 3.34–3.41 (2H, m), 3.44–3.51 (1H, m), 3.68 (1H, dt, *J*=5.6, 8.8 Hz), 3.74–3.79 (1H, m), 3.77 (3H, s), 5.08 (1H, d, *J*=4.6 Hz, disappeared on addition of D₂O), 5.10 (1H, d, *J*=5.6 Hz, disappeared on addition of D₂O), 5.14 (1H, d, *J*=4.6 Hz, disappeared on addition of D₂O), 5.21 (1H, d, *J*=9.0 Hz), 6.76 (1H, dd, *J*=8.8, 2.4 Hz), 7.02 (1H, d, *J*=2.4 Hz), 7.20 (1H, s), 7.37 (1H, d, *J*=8.8 Hz), 7.91 (1H, br t, disappeared on addition of D₂O). HRMS *m/z*: Calcd for C₁₈H₂₄N₂O₆: 364.1634. Found: 364.1629. [α]_D²⁵ –22.0° (c=0.093, MeOH).

1-(α -D-Arabinopyranosyl)melatonin (3b) from 3a — In the same procedure as described in the preparation of **2a**, 8% NaOH (0.5 mL), **3a** (28.7 mg, 0.06 mmol), and MeOH (1.0 mL) were used and stirring was continued for 15 min. The crude product was subjected to PTLC on SiO₂ developing twice with CHCl₃–MeOH (85:15, v/v). Extraction of the band having an *R_f* value of 0.59–0.49 with CHCl₃–MeOH (85:15, v/v) gave **3b** (18.5 mg, 87%). **3b**: colorless oil. IR (film): 3354, 2933, 1641, 1558, 1485, 1232, 1085 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.91 (3H, s), 2.88 (2H, t, *J*=7.1 Hz), 3.46 (2H, br t, *J*=7.1 Hz), 3.70 (1H, dd, *J*=9.4, 3.3 Hz), 3.83 (1H, dd, *J*=12.9, 1.2 Hz), 3.83 (3H, s), 3.97 (1H, ddd, *J*=3.3, 2.4, 1.2 Hz), 3.98 (1H, dd, *J*=12.9, 2.4 Hz), 4.22 (1H, t, *J*=9.0 Hz), 5.18 (1H, d, *J*=9.0 Hz), 6.80 (1H, dd, *J*=9.0, 2.4 Hz), 7.05 (1H, d, *J*=2.4 Hz), 7.23 (1H, s), 7.44 (1H, d, *J*=9.0 Hz). HRMS (FAB⁺) *m/z*: Calcd for C₁₈H₂₅N₂O₆: 365.1713 (MH⁺). Found: 365.1727. [α]_D²⁶ –15.5° (c=0.10, MeOH).

1-(β -D-Glucopyranosyl)melatonin (2b) from 6b — In the same procedure as described in the preparation of **2a**, 8% NaOH (0.5 mL), **6b** (18.5 mg, 0.03 mmol), and MeOH (1.0 mL) were used and stirring was continued for 0.5 h. The crude product was column-chromatographed with AcOEt–MeOH (95:5 v/v) to give **2b** (11.7 mg, 90%). **2b**: yellow oil. IR (film): 3392, 2924, 1635, 1485, 1074, 1032 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.91 (3H, s), 2.88 (2H, t, *J*=7.3 Hz), 3.45 (2H, t, *J*=7.3 Hz), 3.47 (1H, dd, *J*=9.5, 8.8 Hz), 3.54 (1H, ddd, *J*=9.5, 5.0, 2.0 Hz), 3.57 (1H, dd, *J*=9.0, 8.8 Hz), 3.69 (1H, dd, *J*=12.1, 5.6 Hz), 3.82 (3H, s), 3.86 (1H, dd, *J*=12.2, 2.0 Hz), 3.88 (1H, t, *J*=9.0 Hz), 4.52 (1H, br s), 5.34 (1H, d, *J*=9.0 Hz), 6.81 (1H, dd, *J*=8.8, 2.4 Hz), 7.05 (1H, d, *J*=2.4 Hz), 7.21 (1H, s), 7.39 (1H, d, *J*=8.8 Hz). HRMS (FAB⁺) *m/z*: Calcd for C₁₉H₂₇N₂O₇: 365.1819 (MH⁺). Found: 365.1823. [α]_D²⁷ –16.8° (c=0.10, MeOH).

1-(β -D-Galactopyranosyl)melatonin (2c) from 6c — In the same procedure as described in the preparation of **2a**, 8% NaOH (0.5 mL), **6c** (44.5 mg, 0.08 mmol), and MeOH (1.0 mL) were used and stirring was continued for 15 min. Column-chromatography was performed with CHCl₃–MeOH (85:15 v/v) to give **2c** (29.1 mg, 93%). **2c**: colorless oil. IR (film): 3363, 2927, 1633, 1483, 1088, 1041 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.91 (3H, s), 2.88 (2H, t, *J*=7.1 Hz), 3.46 (2H, br t, *J*=7.1 Hz), 3.68 (1H, dd, *J*=9.0, 2.4 Hz), 3.71–3.79 (3H, m), 3.82 (3H, s), 3.99 (1H, d, *J*=2.4 Hz), 4.22 (1H, t, *J*=9.0 Hz), 5.27 (1H, d, *J*=9.0 Hz), 6.80 (1H, dd, *J*=8.8, 2.4 Hz), 7.05 (1H, d, *J*=2.4 Hz), 7.25 (1H, s), 7.46 (1H, d, *J*=8.8 Hz). HRMS (FAB⁺) *m/z*: Calcd for C₁₉H₂₇N₂O₇: 395.1818 (MH⁺). Found: 395.1807. [α]_D²⁷ –8.6° (c=0.10, MeOH).

3-[2-(Acetylamino)acetyl]-1-(α -D-arabinopyranosyl)-5-methoxyindole (8b) from 8a — In the same procedure as described in the preparation of **2a**, 8% NaOH (0.5 mL), **8a** (10.6 mg, 0.02 mmol), and MeOH (1.0 mL) were used and stirring was continued for 30 min. Column-chromatography was performed with CHCl₃–MeOH (85:15 v/v) to give **8b** (6.4 mg, 81%). **8b**: colorless oil. IR (film): 3398, 2924, 1641, 1525, 1086 cm⁻¹. ¹H-NMR (CD₃OD) δ : 2.07 (3H, s), 3.72 (1H, dd, *J*=9.0, 3.3 Hz), 3.84 (3H, s), 3.87 (1H, dd, *J*=12.4, 1.1 Hz), 3.99 (1H, ddd, *J*=3.3, 2.0, 1.1 Hz), 4.04 (1H, dd, *J*=12.4, 2.0 Hz), 4.22

(1H, t, $J=9.0$ Hz), 4.54 (1H, d, $J=17.5$ Hz), 4.61 (1H, d, $J=17.5$ Hz), 5.30 (1H, d, $J=9.0$ Hz), 6.90 (1H, dd, $J=9.0, 2.4$ Hz), 7.62 (1H, d, $J=9.0$ Hz), 7.77 (1H, d, $J=2.4$ Hz), 8.39 (1H, s). HRMS (FAB⁺) m/z : Calcd for C₁₈H₂₃N₂O₇: 379.1506 (MH⁺). Found: 379.1499.

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