Total Synthesis of Pyrano[3,2-e]indole Alkaloid
Fontanesine B by Double Cyclization Strategy

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Experimental Section

1. General Experimental
Melting points were recorded with a Yanaco MP3 and are uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometers. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Flash column chromatography was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

2. Experimental Procedure

General Procedure for the Synthesis of 4
A mixture of serotonin hydrochloride (2.55 g, 12 mmol) and aldehyde (10.0 mmol) in MeOH (150 mL) was stirred at room temperature for 0.5 h. Then to the mixture was added sodium cyanoborohydride (943 mg, 15 mmol) and stirred at room temperature for 1.5 h until the complete disappearance of starting material as indicated by TLC. After MeOH was removed by evaporation, saturated NaHCO$_3$ (150 mL) and AcOEt (150 mL) were added the residue. The whole was extracted with AcOEt (3 x 200 mL), washed with brine (2 x 150 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHCl$_3$/MeOH/Et$_3$N = 100/10/1) to give 4.

3-(2-Benzylaminoethyl)-1H-indol-5-ol (4a).
1.52 g, 57%: Pale yellow oil: IR (CHCl$_3$): 3296 cm$^{-1}$; H-NMR (500 MHz, CD$_3$OD): δ 9.91 (br s, 1H), 7.20-7.23 (m, 2H), 7.13-7.18 (m, 4H), 6.92 (s, 1H), 6.91 (d, J = 2.3 Hz, 1H), 6.67 (dd, J = 2.3, 8.6 Hz, 1H), 3.66 (s, 2H), 3.33 (br s, 1H), 2.79-2.87 (m, 4H); C-NMR (125 MHz, CD$_3$OD): δ 149.9, 139.0, 131.9, 128.2, 128.0, 126.9, 123.0, 111.5, 111.3, 111.2, 102.3, 52.9, 48.8, 24.7 (three carbons are overlapped); HRMS (ESI): calcd for C$_{17}$H$_{19}$N$_2$O [M+H]$: 267.1497, found 267.1497.

3-[2-(4-methoxybenzylaminoethyl)]-1H-indol-5-ol (4b).
1.54 g, 52%: Colorless powder: mp 138—139 ºC; IR (CHCl$_3$): 3481 cm$^{-1}$; H-NMR (500 MHz, CD$_3$OD): δ 7.13-7.15 (m, 3H), 6.96 (s, 1H), 6.87 (d, J = 2.3 Hz, 1H), 6.80-6.82 (m, 2H), 6.65 (dd, J = 2.3, 8.6 Hz, 1H), 3.72 (s, 2H), 3.70
(br s, 1H), 3.33 (s, 3H), 2.88 (s, 4H); \textit{C}-NMR (125 MHz, CD\textsubscript{3}OD): \(\delta\) 159.3, 149.9, 131.9, 129.9, 129.6, 127.9, 123.0, 113.6, 111.4, 111.2, 110.8, 102.2, 54.3, 52.1, 48.4, 24.4 (two carbons are overlapped); HRMS (ESI): calcd for C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}\[M+H\]+ 297.1603, found 297.1604.

3-[2-(2,4-Dimethoxybenzylamino)ethyl]-1H-indol-5-ol (4c).
1.50 g, 46%: Colorless powder: mp 139—140 °C; IR (CHCl\textsubscript{3}): 3479 cm\textsuperscript{–}1; H-NMR (500 MHz, CD\textsubscript{3}OD): \(\delta\) 7.19 (t, \(J = 8.6\) Hz, 2H), 7.09 (s, 1H), 6.85 (s, 1H), 6.70 (dd, \(J = 2.3, 8.6\) Hz, 1H), 6.48 (dd, \(J = 2.3, 8.6\) Hz, 1H), 6.44 (s, 1H), 4.05 (s, 2H), 3.75 (s, 3H), 3.61 (s, 3H), 3.18 (t, \(J = 6.9\) Hz, 2H), 3.06 (t, \(J = 7.4\) Hz, 2H); \textit{C}-NMR (125 MHz, CD\textsubscript{3}OD): \(\delta\) 159.3, 149.9, 131.9, 129.9, 129.6, 127.9, 123.0, 113.6, 111.4, 111.2, 110.8, 102.2, 54.3, 52.1, 48.4, 24.4 (two carbons are overlapped); HRMS (ESI): calcd for C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}\[M+H\]+ 297.1603, found 297.1604.

General Procedure for the C4 Pictet–Spengler/Allylic Transposition
A mixture of 4 (5 mmol) and 3-methyl-2-butenal (0.72 mL, 7.5 mmol) in 2-propanol/Et\textsubscript{3}N (40 mL, v/v = 1/1) was heated under reflux with stirring until the complete disappearance of starting material as indicated by TLC. The mixture was cooled to rt. After addition of H\textsubscript{2}O (80 mL), the whole was extracted with AcOEt (3 x 150 mL), washed with brine (2 x 100 mL). The organic layer was dried over MgSO\textsubscript{4} and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane/Et\textsubscript{3}N = 50/10/1) to give 8.

N-Benzyl-2-(7,7-dimethyl-3,7-dihydropyrano[3,2-e]indol-1-yl)ethan-1-amine (8a).
1.3 g, 78%: Colorless powder: mp 110—112 °C; IR (CHCl\textsubscript{3}): 3481 cm\textsuperscript{–}1; H-NMR (500 MHz, CD\textsubscript{3}OD): \(\delta\) 7.17-7.24 (m, 5H), 7.05 (d, \(J = 8.6\) Hz, 1H), 6.94 (s, 1H), 6.86 (d, \(J = 10.3\) Hz, 1H), 6.56 (d, \(J = 8.6\) Hz, 1H), 5.56 (d, \(J = 8.6\) Hz, 1H), 3.75 (s, 3H), 3.69 (s, 2H), 2.98 (t, \(J = 7.5\) Hz, 2H), 2.81 (t, \(J = 6.9\) Hz, 2H), 1.34 (s, 6H); \textit{C}-NMR (125 MHz, CD\textsubscript{3}OD): \(\delta\) 146.1, 139.1, 133.1, 129.0, 128.2, 126.9, 124.1, 122.5, 120.2, 112.5, 112.1, 111.8, 111.2, 74.5, 52.9, 49.3, 26.8, 26.1 (four carbons are overlapped); HRMS (ESI): calcd for C\textsubscript{22}H\textsubscript{25}N\textsubscript{2}O \[M+H\]+ 333.1967, found 333.1967.
2-(7,7-Dimethyl-3,7-dihydropyrano[3,2-\(\epsilon\)]indol-1-yl)-N-(4-methoxybenzyl)ethan-1-amine (8b).

890 mg, 60%: Colorless powder: mp 97—100 °C; IR (CHCl\(_3\)): 3481 cm\(^{-1}\); H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.92 (br s, 1H), 7.20 (d, \(J = 9.2\) Hz, 2H), 7.07 (d, \(J = 9.2\) Hz, 1H), 6.94 (d, \(J = 2.3\) Hz, 1H), 6.90 (d, \(J = 10.3\) Hz, 1H), 6.83 (d, \(J = 8.6\) Hz, 2H), 6.71 (d, \(J = 8.6\) Hz, 1H), 5.60 (d, \(J = 9.8\) Hz, 1H), 3.78 (s, 3H), 3.76 (s, 2H), 3.05 (t, \(J = 6.9\) Hz, 2H), 2.95 (t, \(J = 6.9\) Hz, 2H), 1.43 (s, 6H); 13C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 158.7, 146.8, 132.6, 129.7, 129.4, 123.7, 122.9, 120.3, 114.0, 113.9, 113.2, 112.9, 111.3, 74.9, 55.4, 53.4, 49.7, 27.9, 27.3 (four carbons are overlapped); HRMS (ESI): calcd for C\(_{23}\)H\(_{27}\)N\(_2\)O\(_2\) [M+H]\(^+\) 363.2073, found 363.2070.

N-(2,4-Dimethoxybenzyl)-2-(7,7-dimethyl-3,7-dihydropyrano[3,2-\(\epsilon\)]indol-1-yl)ethan-1-amine (8c).

911 mg, 46%: Colorless powder: mp 54—56 °C; IR (CHCl\(_3\)): 3479, 3309, 1732, 1614, 1589 cm\(^{-1}\); \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.24 (br s, 1H), 7.08 (d, \(J = 9.2\) Hz, 1H), 7.04 (d, \(J = 9.2\) Hz, 1H), 6.90 (s, 1H), 6.88 (d, \(J = 10.3\) Hz, 1H), 6.69 (d, \(J = 8.6\) Hz, 1H), 6.37-6.39 (m, 2H), 5.57 (d, \(J = 9.7\) Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.65 (s, 2H), 3.05 (t, \(J = 7.2\) Hz, 2H), 2.92 (t, \(J = 6.6\) Hz, 2H), 2.10 (br s, 1H), 1.43 (s, 6H); 13C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 160.2, 158.7, 146.7, 132.7, 130.5, 129.6, 123.9, 122.9, 120.6, 120.3, 113.8, 113.2, 112.8, 11.3, 103.7, 98.6, 74.9, 55.4, 55.2, 27.8, 27.3 (one carbon is overlapped); HRMS (ESI): calcd for C\(_{24}\)H\(_{29}\)N\(_2\)O\(_3\) [M+H]\(^+\) 393.2178, found 393.2178.

General Procedure for the Carbonylative Cyclization of 8 using Triphosgene, Et\(_3\)N and HBr

Triphosgene (149 mg, 0.5 mmol) was added to a mixture of 8 (1 mmol) and Et\(_3\)N (0.35 mL, 2.5 mmol) in toluene (100 mL) at room temperature and the mixture was heated at 70 °C with stirring for 0.5 h. After cooling to room temperature, HBr (30% in acetic acid, 0.3 mL) was added to the mixture and heated under reflux for 0.5 h. After cooling to room temperature and addition of H\(_2\)O (30 mL), the whole was extracted with AcOEt (3 x 70 mL), washed with brine (2 x 50 mL). The organic layer was dried over MgSO\(_4\) and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 3/1) to give 9 and 12.

9-Benzyl-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-\(\epsilon\)]pyrido[3,4-\(b\)]indol-8(3\(H\))one (9a).

18 mg, 5%: Colorless powder: mp 254—257 °C; IR (CHCl\(_3\)): 3460, 1641 cm\(^{-1}\); H-NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 11.50 (br s, 1H), 7.29-7.34 (m, 4H), 7.24 (t, \(J = 6.9\) Hz, 1H), 7.12 (d, \(J = 8.6\) Hz, 1H), 6.75 (d, \(J = 9.8\) Hz, 1H), 6.68
(d, J = 8.6 Hz, 1H), 5.67 (d, J = 9.8 Hz, 1H), 4.66 (s, 2H), 3.54 (t, J = 6.9 Hz, 2H), 3.08 (t, J = 6.9 Hz, 2H), 1.33 (s, 6H); ¹³C-NMR (125 MHz, DMSO-­d₆): δ 161.0, 146.6, 138.5, 133.7, 130.4, 129.1, 128.4, 128.1, 127.7, 121.4, 119.8, 116.7, 115.5, 113.3, 113.2, 75.5, 49.1, 47.6, 27.5, 22.5 (three carbons are overlapped); HRMS (ESI): calcd for C₂₃H₂₂N₂O₂ [M+H]+ 359.1760, found 359.1760.

9-(4-Methoxybenzyl)-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-e]pyrido[3,4-b]indol-8(3H)-one (9b).
24 mg, 6%: Colorless powder: mp 186—187 °C; IR (CHCl₃): 3462, 1638 cm⁻¹; H-NMR (500 MHz, CDCl₃): δ 9.42 (br s, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 9.2 Hz, 1H), 6.86 (d, J = 9.2 Hz, 2H), 6.80 (d, J = 9.2 Hz, 1H), 6.73 (d, J = 9.7 Hz, 1H), 5.60 (d, J = 9.7 Hz, 1H), 4.72 (s, 2H), 3.80 (s, 3H), 3.60 (t, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 1.43 (s, 6H); ¹³C-NMR (125 MHz, CDCl₃): δ 161.3, 159.1, 147.1, 133.2, 130.1, 129.6, 129.4, 128.0, 121.6, 119.6, 116.9, 116.1, 114.1, 113.6, 112.5, 75.5, 55.4, 48.9, 47.1, 27.3, 22.8 (three carbons are overlapped); HRMS (ESI): calcd for C₂₄H₂₅N₂O₃ [M+H]+ 389.1865, found 389.1868.

9-(2,4-Dimethoxybenzyl)-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-e]pyrido[3,4-b]indol-8(3H)-one (9c).
8 mg, 2%: Colorless powder: mp 209—211 °C; IR (CHCl₃): 3460, 1719, 1687, 1638, 1614 cm⁻¹; H-NMR (500 MHz, CDCl₃): δ 9.86 (br s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 9.2 Hz, 1H), 6.76 (t, J = 9.5 Hz, 2H), 6.47 (d, J = 2.3 Hz, 1H), 6.44 (dd, J = 2.3, 8.6 Hz, 1H), 5.60 (d, J = 9.7 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.67 (t, J = 7.5 Hz, 2H), 3.14 (t, J = 6.9 Hz, 2H), 1.43 (s, 6H); ¹³C-NMR (125 MHz, CDCl₃): δ 161.6, 160.4, 158.7, 147.0, 133.4, 130.4, 129.9, 128.3, 121.6, 119.7, 118.1, 116.8, 115.8, 113.4, 112.7, 104.3, 98.6, 75.2, 55.5, 47.5, 44.0, 27.4, 22.9 (two carbons are overlapped); HRMS (ESI): calcd for C₂₅H₂₇N₂O₄ [M+H]+ 419.1971, found 419.1973.

2-Bromo-9-(2,4-dimethoxybenzyl)-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-e]pyrido[3,4-b]indol-8(3H)-one (12)
58 mg, 12%: Colorless powder: mp 189—191 °C; IR (CHCl₃): 3207, 1636 cm⁻¹; H-NMR (500 MHz, CDCl₃): δ 9.98 (br s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 6.77 (d, J = 9.2 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 6.45 (dd, J = 2.6, 8.1 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.69 (t, J = 7.6 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 1.43 (s, 6H); ¹³C-NMR (125 MHz, CDCl₃): δ 161.0, 146.6, 138.5, 133.7, 130.4, 129.1, 128.4, 128.1, 127.7, 121.4, 119.8, 116.7, 115.5, 113.3, 113.2, 75.5, 49.1, 47.6, 27.5, 22.5 (three carbons are overlapped); HRMS (ESI): calcd for C₂₃H₂₂N₂O₂ [M+H]+ 359.1760, found 359.1760.
Trichloromethyl (2-(7,7-dimethyl-3,7-dihydropyran[3,2-e]indol-1-yl)ethyl)(4-methoxybenzyl)carbamate (13b)

Triphosgene (312 mg, 1.05 mmol) was added to a mixture of 8b (1 mmol) and Et3N (0.35 mL, 2.5 mmol) in THF (40 mL) at room temperature and the mixture was stirring for 0.5 h. After addition of H2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over MgSO4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/10) to give 13b (460 mg, 88%) as a colorless powder.

Procedure for the C2 Pictet–Spengler Reaction of 13b

A solution of compound 13b (52 mg, 0.1 mmol) in DMSO was heated at 100 °C for 0.5 h. After removal of MeCN by evaporation, the resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 3/1—5:1) to give 9b (33 mg, 86%) as a colorless powder.

General Procedure for the the Interrupted Phosgene Cyclization/Bischler–Napieralski-type Cyclization of 8

Triphosgene (312 mg, 1.05 mmol) was added to a mixture of 8 (1 mmol) and Et3N (0.35 mL, 2.5 mmol) in THF (40 mL) was added at room temperature and the mixture was stirring for 0.5 h. After addition of H2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over MgSO4 and concentrated in vacuo. The crude residue was used without further purification. A solution of the crude in DMSO was heated at 100 °C for 0.5 h. After removal of MeCN by evaporation, the resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 3/1—5:1) to give 9.

9a: 280 mg, 78%
9b: 253 mg, 65%
9c: 242 mg, 58%

![Chemical structure of 9c](image)

3,3-Dimethyl-7,9,10,11-tetrahydropyrano[3,2-e]pyrido[3,4-b]indol-8(3H)-one (10).

To a solution of compound 9c (42 mg, 0.1 mmol) in toluene was p-toluenesulfonylic acid (69 mg, 0.4 mmol) and heated at 100 °C for 16 h. After removal of toluene by evaporation, the resultant mixture was purified by silica gel column chromatography (AcOEt/hexane/CHCl3/MEOH/28% NH3 = 50/100/50/50/1) to give 10 (18 mg, 67%) as a colorless powder.

18 mg, 67%: Colorless powder: mp 149—150 °C; IR (CHCl3): 3460, 3421, 3229, 1719, 1663 cm–1; 1H-NMR (500 MHz, CDCl3): δ 9.09 (br s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 9.2 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.73 (br s, 1H), 5.64 (d, J = 10.3 Hz, 1H), 3.69-3.71 (m, 2H), 3.21 (t, J = 6.9 Hz, 2H), 1.45 (s, 6H); 13C-NMR (125 MHz, CDCl3): δ 163.0, 147.3, 133.0, 130.3, 127.2, 121.7, 119.5, 118.7, 116.6, 113.7, 112.5, 75.5, 42.2, 27.4, 23.0 (one carbon is overlapped); HRMS (ESI): calcd for C16H17N2O2 [M+H]+ 269.1290, found 269.1289.

![Chemical structure of 10](image)

4,4-Dimethyl-4,7,8,16-tetrahydro-10H-pyrano[3′,2′:4,5′]indolo[2′,3′:3,4]pyrido[2,1-b]quinazolin-10-one (Fontanesine B, 2).

To a solution of compound 10 (13 mg, 0.05 mmol) and anthranilic acid (8 mg, 0.06 mmol) in toluene was added POCl3 (18 mg, 0.12 mmol) at room temperature and the mixture was heated at 100 °C for 2 h. After removal of toluene by evaporation, the resultant mixture was purified by silica gel column chromatography (AcOEt/CHCl3 = 5/1) to give 2 (14 mg, 73%) as a pale yellow powder.

pale yellow powder; mp 261—263 °C; IR (CHCl3): 3396, 1668, 1660 cm–1; H-NMR (500 MHz, DMSO-d6): δ 11.71 (br s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.77 (td, J = 1.2, 6.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.43 (td, J = 1.2, 7.4 Hz, 1H), 7.12 (s, 1H), 6.93 (s, 1H), 6.53 (d, J = 9.7 Hz, 1H), 5.81 (d, J = 9.8 Hz, 1H), 4.38 (t, J = 6.9 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 1.34 (s, 6H); 13C-NMR (125 MHz, DMSO-d6): δ 161.1, 148.0, 146.8, 145.8, 135.0, 130.7, 128.5, 127.1, 127.0, 126.5, 121.5, 121.2, 119.8, 117.1, 116.1, 113.3, 113.2, 75.6, 41.1, 27.5, 21.3; HRMS (ESI): calcd for C23H20N3O2 [M+H]+ 370.1556, found 370.1557.