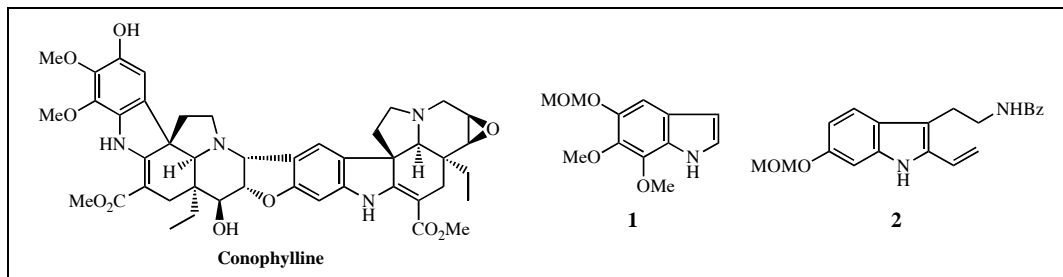


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Conophylline is a bisindole alkaloid of unique structure that shows anti-cancer and anti-diabetic activities. Two indole core structures of conophylline, namely 6,7-dimethoxy-5-methoxymethoxy-1H-indole (**1**), and *N*-benzoyl-*N*-[2-(6-methoxymethoxy-2-vinyl-1H-indol-3-yl)ethyl]amine (**2**) has been synthesized starting with substituted benzene derivatives.

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INTRODUCTION

Conophylline is a bisindole alkaloid isolated from the leaves of the tropical plant *Tabernaemontana divaricata* [1]. It shows anti-cancer activity against cells that express *K-ras* [2] and, more recently, effect on diabetes was disclosed [3]. We were interested in the anti-diabetic effect of conophylline that was unprecedented as a bisindole and considered that conophylline could be a new lead for the drugs and therapies toward diabetes.

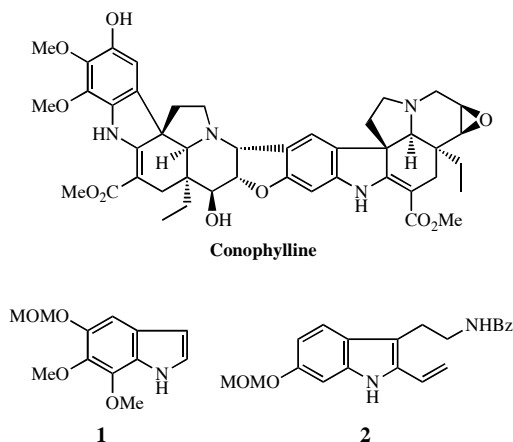


Figure 1

Conophylline has a unique structure comprising two indoles segmented *via* a central dihydrofuran [4]. The dihydrofuran seems crucial for the effect on diabetes, determining the spatial relationships of the indoles of both

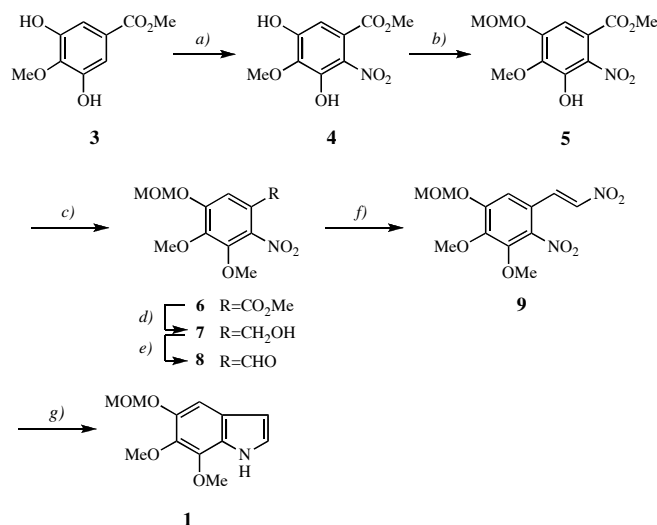
sides [3]. Our synthetic plan is to synthesize the left and the right indoles and assemble the two by constructing the central dihydrofuran. Herein we report a facile synthesis of trisubstituted indole **1** of the left wing and the right indole **2** appropriately functionalized and protected for the further elaboration.

RESULTS AND DISCUSSION

Synthesis of 6,7-dimethoxy-5-methoxymethoxy-1H-indole (1). As the left indole of conophylline has an array of two methoxyl and a hydroxyl substituents on the benzene ring, we started the synthesis of compound **1** with symmetrically substituted methyl 3,5-dihydroxy-4-methoxybenzoate **3** [5]. Compound **3** was dissymmetrized by the mono-nitration according to the method of Anuradha *et al.* using nickel nitrate [6] to give nitro derivative **4** in 70% yield. The differentiation of the two hydroxyl groups of compound **4** was successfully achieved as follows. The higher acidity of the hydroxyl group *para* to the nitro group of compound **4** facilitated the regioselective protection to give mono-methoxymethyl ether **5** in 54% yield (with 31% recovery of **4**). The remaining hydroxyl group was methylated with dimethyl sulfate to give dimethoxyphenol derivative **6** that is equipped with all necessary substituents on the left wing phenyl moiety in 97% yield. After extensive attempts including the conventional Fischer indole synthesis, the left wing indole was found to be accessible by the Magnus procedure [7], the cyclization of dinitro compound **9**. Thus, methyl ester **6** was treated with NaBH_4 to give (without reducing the nitro group) alcohol

7 (78% yield) that was further converted into the corresponding aldehyde **8** by MnO₂ oxidation (95% yield). The aldehyde **8** was condensed with nitromethane under the classical Henry reaction condition to give dinitro compound **9** in 92% yield and the subsequent reductive cyclization [7] proceeded smoothly to afford the desired 6,7-dimethoxy-5-methoxymethoxy-1*H*-indole (**1**) in 72% yield.

Scheme 1



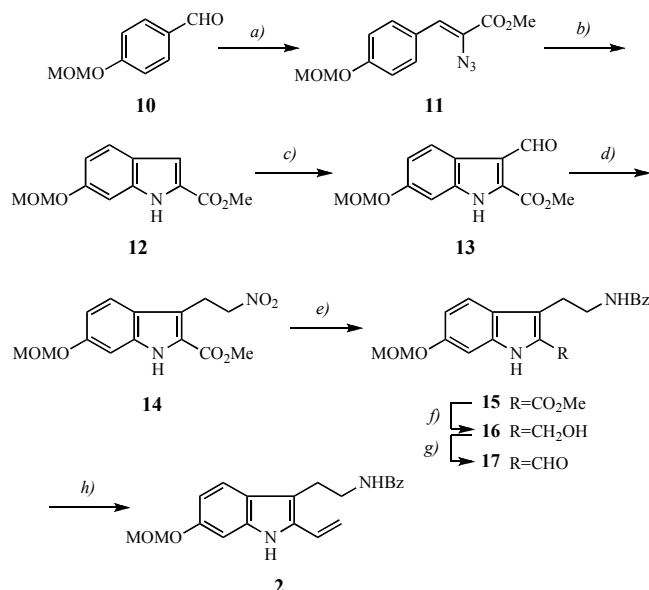
Reagents and conditions; a) Ni(NO₃)₂·6H₂O, PTSA, acetone; 70%, b) MOMCl, 2,6-lutidine, CH₂Cl₂, 0°C to r.t.; 54% (31% recovery), c) (MeO)₂SO₂, K₂CO₃, acetone, reflux; 97%, d) NaBH₄, THF, 0°C to r.t.; 78%, e) MnO₂, CH₂Cl₂, r.t.; 95%, f) MeNO₂, Et₃N, MeOH, 0°C; then NaOAc, Ac₂O, 50°C; 92%, g) Pd/C (10%), HOAc, H₂, MeOH, r.t.; 72%.

Synthesis of *N*-benzoyl-*N*-[2-(6-methoxymethoxy-2-vinyl-1*H*-indol-3-yl)ethyl]amine (2**).** The right indole **2** was synthesized by the Weidmann procedure [8], by cyclization of the azide compound **11**. Thus, 4-(methoxymethoxy)benzaldehyde (**10**) [9] was coupled with azidoacetate under strongly basic condition to give azide **11** in 74% yield. It was gratifying that the compound **11** gave indole **12** quantitatively simply by heating at reflux in toluene. The Vilsmeier formylation [10] was performed and aldehyde **13** was obtained in 56% yield (with 40% recovery of **12**). Condensation of aldehyde **13** with nitromethane was carried out according to the procedure of Young [11a] and Rodríguez [11b] and the subsequent olefin reduction was feasible by using NaBH₄ [11b,11c,11d] to give nitro compound **14** with an intact nitro group in 76% overall yield [12]. Reduction of the nitro group of **14** was carried out by hydrogenation with Pd/C and the resulting tryptamine was immediately protected by a benzoyl group in order to avoid the problematic lactam formation, affording the desired benzamide **15** in 77% yield. The methyl ester **15** was

transformed to aldehyde **17** by LAH reduction (89% yield) followed by MnO₂ oxidation (quantitative). The subsequent Wittig reaction of aldehyde **17** gave *N*-benzoyl-*N*-[2-(6-methoxymethoxy-2-vinyl-1*H*-indol-3-yl)ethyl]amine **2** in 81% yield.

Thus, the left and the right indoles of conophylline are now available in good overall yields. We are engaging in the side chain elaboration of the left indole **1** for the construction of the dihydrofuran junction between the left and the right indoles.

Scheme 2



Reagents and conditions; a) N₃CH₂CO₂Me, NaOMe, MeOH, 0°C to r.t.; 74%, b) toluene, reflux; quant., c) POCl₃, DMF, CH₂Cl₂, 0°C; 56% (40% recovery), d) MeNO₂, NH₄Cl, MeOH, r.t.; then NaBH₄, DMF, 0°C; 76%, e) Pd/C (10%), H₂, NH₄Cl, MeOH, r.t.; then BzCl, Et₃N, CH₂Cl₂, 0°C; 77%, f) LAH, THF, 0°C; 89%, g) MnO₂, CH₂Cl₂, r.t.; quant., h) CH₃PPh₃Br, KHMDS, THF, toluene, reflux; 81%.

EXPERIMENTAL

Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. All products were dried under vacuum before anal. characterization. Column chromatography (CC): silica gel (60N, spherical, neutral; KANTO CHEMICAL CO, INC), aluminium oxide (activated, neutral, Brockmann I, standard grade, ~150 mesh, 58Å; ALDRICH). TLC: silica gel 60 F₂₅₄ (on glass; Merck), aluminium oxide 60 F₂₅₄ (on plastic sheet; Merck), visualization by UV light at 254 nm or staining with a soln. of H₃(PMo₁₂O₄₀)·nH₂O in EtOH. M.p.: Yanagimoto Melting Point Apparatus; uncorrected. Optical rotations: JASCO DIP-1000 digital polarimeter. IR spectra: JASCO IR A-100 FT-IR spectrometer; in cm⁻¹. NMR spectra (¹H and ¹³C): JEOL JNM-AL300 (300/75 MHz, resp.) spectrometer; J in Hz, δ in ppm rel. to residual solvent signals, spectra were recorded at

25°C. EI- and FAB-MS: JEOL JMS-BU20, JEOL JMS-700 mass spectrometers; in *m/z*.

Methyl 3,5-dihydroxy-4-methoxy-2-nitrobenzoate (4). PTSA (190 mg, 1.0 mmol) was added to a solution of methyl 3,5-dihydroxy-4-methoxybenzoate (**3**) [5] (1.98 g, 10 mmol) and Ni(NO₃)₂·6H₂O (3.19 g, 11 mmol) in anhydrous acetone (80 mL) at 0°C under Ar atmosphere. After stirring for 2 h, about half amount of acetone was removed *in vacuo*. The top clear layer of the resulting mixture was immediately applied to column chromatography on silica gel (CH₂Cl₂) to afford 1.70 g (70%) of **4** as a yellow amorphous solid. R_f 0.38 (AcOEt/*n*-hexane 2/1). M.p. 139~140 °C. IR (nujor): 3182, 2856, 1711, 1594, 1550, 1447, 1365, 1307, 1253, 1105, 1020, 988, 922, 870, 675, 607. ¹H-NMR(CD₃OD) δ: 3.92 (3H, s, PhOCH₃), 4.04 (3H, s, PhCO₂CH₃), 6.67 (1H, s, *H*-C(6)). ¹³C-NMR(CD₃OD) δ: 53.4, 61.3 (CH₃), 108.5 (CH), 126.2, 127.8, 135.7, 149.7, 155.1, 166.6 (C). HR-MS(EI) for C₉H₉NO₇ (M⁺), calcd. 243.0379, found 243.0383. Anal. Calcd. for C₉H₉NO₇: C, 44.45, H, 3.73, N, 5.76. Found: C, 44.18, H, 3.77, N, 5.97.

Methyl 3-hydroxy-4-methoxy-5-methoxymethoxy-2-nitrobenzoate (5). To a solution of compound **4** (486 mg, 2.0 mmol) and 2,6-lutidine (304 μL, 2.6 mmol) in CH₂Cl₂ (20 mL), a solution of MOMCl (167 μL, 2.2 mmol) in CH₂Cl₂ (20 mL) was dropwise at 0°C. After stirring for 10 h at r.t., H₂O (40 mL) was added to the reaction solution. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2×). The combined organic layer was washed with brine, dried over (Na₂SO₄), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH₂Cl₂, starting solution of crude was added 0.5 % HOAc) to afford 310 mg (54%) of **5** as a yellow solid along with 151 mg of compound **4** (31%: recovery), (recovery yield of **5**, 78%). R_f 0.1 (CH₂Cl₂). M.p. 90~91 °C. IR (KBr): 3372, 2959, 1722, 1590, 1545, 1339, 1269, 1242, 1066, 1003, 867, 775, 763, 735, 613. ¹H-NMR(CDCl₃) δ: 3.52 (3H, s, PhOCH₂OCH₃), 3.91 (3H, s, PhOCH₃), 3.97 (3H, s, PhCO₂CH₃), 5.31 (2H, s, PhOCH₂OCH₃), 6.97 (1H, s, *H*-C(6)) 9.91 (br, PhOH). ¹³C-NMR(CDCl₃) δ: 53.3, 56.8, 61.3 (CH₃), 95.0 (CH₂), 108.2 (CH), 125.6, 128.6, 139.4, 149.1, 154.8, 166.0 (C). HR-MS(EI) for C₁₁H₁₃NO₈ (M⁺), calcd. 287.0641, found 287.0629. Anal. Calcd. for C₁₁H₁₃NO₈: C, 46.00, H, 4.56, N, 4.88. Found: C, 46.00, H, 4.55, N, 4.96.

Methyl 3,4-dimethoxy-5-methoxymethoxy-2-nitrobenzoate (6). A mixture of compound **5** (144 mg, 0.5 mmol), (MeO)₂SO₂ (56.8 μL, 0.6 mmol), K₂CO₃ (138 mg, 1.0 mmol) in acetone (10 mL) was stirred at reflux for 12 h under Ar atmosphere. The resulting mixture was then filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH₂Cl₂ (20 mL) and washed with H₂O and brine, and the organic layer was dried over (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH₂Cl₂) to afford 147 mg (97%) of **6** as a pale yellow amorphous. R_f 0.66 (CH₂Cl₂). (M.p. 63~64 °C. IR (neat): 3133, 2870, 1735, 1543, 1339, 1233, 1156, 1111, 1068, 1012, 978, 923, 870, 807, 739. ¹H-NMR(CDCl₃) δ: 3.53 (3H, s, PhOCH₂OCH₃), 3.87 (3H, s, PhOCH₃), 3.96 (3H, s, PhOCH₃), 3.99 (3H, s, PhCO₂CH₃), 5.29 (2H, s, PhOCH₂OCH₃), 7.52 (1H, s, *H*-C(6)). ¹³C-NMR(CDCl₃) δ: 52.9, 56.6, 61.3, 62.6 (CH₃), 95.2 (CH₂), 112.7 (CH), 117.8, 141.0, 145.9, 147.2, 151.6, 163.0 (C). HR-MS(EI) for C₁₂H₁₅NO₈ (M⁺), calcd. 301.0798, found 301.0775.

(3,4-Dimethoxy-5-methoxymethoxy-2-nitrophenyl)methanol (7). To a solution of compound **6** (120 mg, 0.4 mmol) in

anhydrous MeOH (4 mL), NaBH₄ (152 mg, 4.0 mmol) was added little by little at 0°C under Ar atmosphere. After stirring for 3 h at r.t., the reaction solution was cooled to 0°C and neutralized with 1 N HCl. The resulting solution was extracted with CH₂Cl₂ (3×), and the combined organic layer was washed with brine, dried over (Na₂SO₄), and evaporated *in vacuo*. The residue was purified by column chromatography on aluminium oxide (CH₂Cl₂) to afford 85.2 mg (78%) of **7** as a yellow oil. R_f 0.09 (CH₂Cl₂). IR (neat): 2946, 1577, 1540, 1490, 1457, 1399, 1362, 1327, 1249, 1155, 1112, 964, 923, 881, 801. ¹H-NMR(CDCl₃) δ: 3.52 (3H, s, PhOCH₂OCH₃), 3.92 (3H, s, PhOCH₃), 3.99 (3H, s, PhOCH₃), 4.61 (2H, s, PhCH₂OH), 5.28 (2H, s, PhOCH₂OCH₃), 7.07 (1H, s, *H*-C(6)). ¹³C-NMR(CDCl₃) δ: 56.5, 61.1, 62.3 (CH₃), 61.1, 95.0 (CH₂), 111.6 (CH), 129.6, 139.1, 142.7, 146.8, 153.0 (C). HR-MS(EI) for C₁₁H₁₅NO₇ (M⁺), calcd. 273.0840, found 273.0848.

3,4-Dimethoxy-5-methoxymethoxy-2-nitrobenzaldehyde (8). A mixture of compound **13** (54.6 mg, 0.2 mmol) and MnO₂ (174 mg 2.0 mmol) in CH₂Cl₂ (3 mL) was stirred at r.t. for 3 h under Ar atmosphere. The resulting mixture was then filtered through *Celite*, and the *Celite* was washed with CH₂Cl₂. The filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (CH₂Cl₂) to afford 51.7 mg (95%) of **8** as pale yellow oil. R_f 0.66 (CH₂Cl₂). IR (neat): 3336, 1703, 1577, 1543, 1490, 1460, 1390, 1367, 1328, 1254, 1156, 1111, 1060, 1013, 963, 924, 879. ¹H-NMR(CDCl₃) δ: 3.54 (3H, s, PhOCH₂OCH₃), 4.00 (3H, s, PhOCH₃), 4.02 (3H, s, PhOCH₃), 5.32 (2H, s, PhOCH₂OCH₃), 7.46 (1H, s, *H*-C(6)), 9.85 (1H, s, PhCHO). ¹³C-NMR(CDCl₃) δ: 56.7, 61.4, 62.6 (CH₃), 95.2 (CH₂), 111.6, 185.7 (CH), 122.9, 141.0, 146.1, 148.5, 152.6 (C). HR-MS(EI) for C₁₁H₁₃NO₇ (M⁺), calcd. 271.0665, found 271.0692.

2,3-Dimethoxy-1-methoxymethoxy-4-nitro-5-(2-nitroethenyl)benzene (9). Compound **8** (27.1 mg, 0.1 mmol) was dissolved in 55% solution of MeNO₂ in MeOH (1 mL), and Et₃N (10 μL) was added to this solution at 0°C under Ar atmosphere. After stirring for 2 h at the temperature, H₂O (5 mL) was added to the reaction solution. This mixture was extracted with CH₂Cl₂ (2×), and this combined organic layer was washed with brine, dried over (Na₂SO₄), and evaporated *in vacuo*. The residue was dissolved in Ac₂O (1 mL), and NaOAc (0.8 mg, 0.01 mmol) was added to this solution. This mixture was stirred for 3 h at 50°C under Ar atmosphere, and H₂O was then added to the resulting mixture. This mixture was extracted with CH₂Cl₂ (2×), and this combined organic layer was washed with brine, dried over (Na₂SO₄), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH₂Cl₂) to afford 29.0 mg (92%) of **9** as a yellow amorphous. R_f 0.63 (CH₂Cl₂). M.p. 56~57 °C. IR (neat): 3109, 2957, 1638, 1576, 1533, 1490, 1343, 1273, 1223, 1171, 1092, 1014, 967, 922, 840. ¹H-NMR(CDCl₃) δ: 3.55 (3H, s, PhOCH₂OCH₃), 3.99 (3H, s, PhOCH₃), 4.00 (3H, s, PhOCH₃), 5.30 (2H, s, PhOCH₂OCH₃), 7.13 (1H, s, *H*-C(6)), 7.46 (1H, d, *J* = 13.55 Hz, Ph-CH=CHNO₂), 7.85 (1H, d, *J* = 13.55 Hz, Ph-CH=CHNO₂). ¹³C-NMR(CDCl₃) δ: 56.7, 61.4, 62.5 (CH₃), 95.4 (CH₂), 109.2, 118.2, 139.6 (CH), 131.7, 141.2, 146.3, 146.8, 153.0 (C). HR-MS(EI) for C₁₂H₁₄N₂O₈ (M⁺), calcd. 314.0750, found 314.0729. Anal. Calcd. for C₁₂H₁₄N₂O₈: C, 45.86, H, 4.49, N, 8.91. Found: C, 45.93, H, 4.45, N, 8.74.

6,7-Dimethoxy-5-methoxymethoxy-1H-indole (1). A mixture of compound **9** (31.4 mg, 0.1 mmol) and Pd/C (10%, 3.1 mg) in HOAc/MeOH (17%, 1 mL) was stirred at r.t. for 5 h under H₂ atmosphere. The mixture was then filtered through

Celite, and the *Celite* was washed with CH_2Cl_2 . The filtrate was diluted with CH_2Cl_2 and washed with saturated NaHCO_3 and brine. The organic layer was dried over (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford 17.0 mg (72%) of **1** as a white solid. R_f 0.27 (CH_2Cl_2). M.p. 74~75 °C. IR (KBr): 3341, 3109, 2932, 1581, 1464, 1311, 1221, 1141, 1109, 1060, 1031, 990, 906, 873, 852, 749, 591, 560. $^1\text{H-NMR}$ (CDCl_3) δ : 3.56 (3H, s, $\text{ArOCH}_2\text{OCH}_3$), 3.92 (3H, s, ArOCH_3), 4.07 (3H, s, ArOCH_3), 5.23 (2H, s, $\text{ArOCH}_2\text{OCH}_3$), 6.43 (1H, dd, $J = 2.56$, 2.56 Hz, $H-C(3)$), 7.11 (1H, s, $H-C(4)$), 7.13 (1H, dd, $J = 2.56$, 2.56 Hz, $H-C(2)$), 8.19 (br, $H-N(1)$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 56.1, 61.0, 61.5 (CH_3), 96.4 (CH_2), 102.8, 102.9, 124.1 (CH), 123.8, 125.5, 138.6, 138.8, 146.3 (C). HR-MS(EI) for $\text{C}_{12}\text{H}_{15}\text{NO}_4$ (M^+), calcd. 237.1004, found 237.1001.

Methyl (Z)-2-azido-3-(4-methoxymethoxyphenyl)propenoate (11). To anhydrous MeOH (150 mL), Na metal (4 g) was added at 0°C, and stirred at the temperature to finish the resolution. To this solution, a solution of 4-(methoxymethoxy)benzaldehyde (**10**) [9] (9.96 g, 60 mmol) and methyl azidoacetate (20.7 g, 180 mmol) in anhydrous MeOH (50 mL) was dropwise at -10°C under Ar atmosphere, and warmed to r.t. gradually. After stirring for 12 h at r.t., the reaction mixture was cooled to 0°C and added ice cold H_2O (200 mL). MeOH was removed *in vacuo*, and the aqueous layer was extracted with CH_2Cl_2 (3 \times). The combined organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford 11.2 g (74%) of **11** as a yellow amorphous. R_f 0.74 (CH_2Cl_2). IR (neat): 2953, 2359, 2119, 1713, 1602, 1508, 1437, 1376, 1322, 1240, 1175, 1152, 1079, 992, 833. $^1\text{H-NMR}$ (CDCl_3) δ : 3.48 (3H, s, OCH_2OCH_3), 3.90 (3H, s, CO_2CH_3), 5.21 (2H, s, OCH_2OCH_3), 6.88 (1H, s, Ph-CH=C), 7.04 (2H, d, $J = 8.81$ Hz, $H-C(3)$), 7.78 (2H, d, $J = 8.81$ Hz, $H-C(2)$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 52.8, 56.1 (CH_3), 94.1 (CH_2), 116.0, 125.5, 132.3 (CH), 123.5, 127.0, 158.0, 164.2 (C). HR-MS (EI) for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_4$ (M^+), calcd. 263.0906, found 263.0910.

Methyl 6-methoxymethoxy-1H-indole-2-carboxylate (12). A solution of compound **11** (5.26 g, 20 mmol) in toluene (300 mL) was stirred at reflux for 12 h. The reaction solution was then evaporated *in vacuo*. Recrystallization from toluene afforded 4.69 g (quant.) of **11** as a white crystalline. R_f 0.56 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50/1). M.p. 106~107 °C. IR (KBr): 3311, 2952, 2897, 1699, 1629, 1524, 1445, 1253, 1209, 1148, 1121, 1076, 1004, 824. $^1\text{H-NMR}$ (CDCl_3) δ : 3.51 (3H, s, CH_2OCH_3), 3.93 (3H, s, CO_2CH_3), 5.23 (2H, s, OCH_2OCH_3), 6.90 (1H, dd, $J = 8.81$, 2.20 Hz, $H-C(5)$), 7.10 (1H, d, $J = 2.20$ Hz, $H-C(7)$), 7.16 (1H, d, $J = 0.92$ Hz, $H-C(3)$), 7.56 (1H, d, $J = 8.81$ Hz, $H-C(4)$), 8.98 (br, $H-N(1)$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 51.9, 56.0 (CH_3), 94.9 (CH_2), 97.5, 109.0, 113.1, 123.4 (CH), 122.7, 126.5, 137.8, 156.3, 162.4 (C). MS (EI) m/z 235 (M^+). Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_4$: C, 61.27, H, 5.57, N, 5.95. Found: C, 61.19, H, 5.50, N, 5.89.

Methyl 3-formyl-6-methoxymethoxy-1H-indole-2-carboxylate (13). To a solution of DMF (3 mL) in anhydrous CH_2Cl_2 (20 mL), POCl_3 (1 mL) was dropwise at 0°C under Ar atmosphere and stirred for 30 min at the temperature and for further 30 min at r.t. The solution was then cooled to 0°C and compound **12** (1.18 g, 5.0 mmol) was added little by little. After stirring for 30 min at the temperature and for further 30 min at r.t., the reaction solution was cooled to 0°C again, and the reaction was quenched by the addition of saturated NaHCO_3 (30

mL), followed by stirring for 1 h at r.t. CH_2Cl_2 was removed *in vacuo* and the pale yellow crystalline precipitated was filtered and the filtrate was extracted with AcOEt (3 \times). The combined organic layer was dried over (Na_2SO_4), and evaporated *in vacuo*. The residue and filtered crystalline was mixed and washed with $\text{CH}_2\text{Cl}_2/n$ -hexane (50%) solution to afford 0.73 g (56%) of **13** as a pale yellow crystalline. The filtrate was evaporated, and the residue was purified by column chromatography on silica gel (3.3% MeOH/ CH_2Cl_2) to recover 0.47 g of **12** (40% recovery) (recovery yield of **13**, 92%). R_f 0.45 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50/1). M.p. 194~196 °C. IR (KBr): 3174, 1714, 1637, 1577, 1526, 1378, 1360, 1248, 1213, 1147, 1078, 986, 838. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 3.41 (3H, s, OCH_2OCH_3), 3.98 (3H, s, CO_2CH_3), 5.24 (2H, s, OCH_2OCH_3), 7.02 (1H, dd, $J = 8.79$, 2.20 Hz, $H-C(5)$), 7.15 (1H, d, $J = 2.20$ Hz, $H-C(7)$), 8.12 (1H, d, $J = 8.79$ Hz, $H-C(4)$), 10.57 (s, CHO). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 52.6, 55.6 (CH_3), 94.2 (CH_2), 98.1, 115.7, 123.2, 187.6 (CH), 118.7, 119.7, 131.7, 136.8, 155.8, 160.5 (C). MS (EI) m/z 263 (M^+). Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: C, 59.31, H, 4.98, N, 5.32. Found: C, 59.01, H, 4.98, N, 5.31.

Methyl 3-(2-nitroethyl)-6-methoxymethoxy-1H-indole-2-carboxylate (14). Compound **13** (1.32 g, 5 mmol) and NH_4OAc (385 mg, 5.0 mmol) was added to 55% solution of MeNO_2 in MeOH (30 mL) and stirred for 48 h at r.t. under Ar atmosphere. The resulting mixture was then added H_2O (30 mL), and MeOH was removed *in vacuo*. The aqueous layer was extracted with AcOEt (2 \times), and the organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. This crude compound was dissolved in DMF (10 mL) and cooled to 0°C. To this solution was added NaBH_4 (200 mg) little by little and stirred for 1 h. The reaction solution was then neutralized with 1 M HCl and extracted with AcOEt (2 \times). The organic layer was washed with brine (2 \times), dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (2% MeOH/ CH_2Cl_2) to afford 1.17 g (76%) of **14** as a white solid. R_f 0.49 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50/1). M.p. 122~123 °C. IR (KBr): 3324, 1690, 1629, 1549, 1459, 1380, 1336, 1254, 1214, 1150, 1101, 1074, 999. $^1\text{H-NMR}$ (CDCl_3) δ : 3.50 (3H, s, OCH_2OCH_3), 3.76 (2H, t, $J = 7.33$ Hz, $\text{CH}_2\text{CH}_2\text{NO}_2$), 3.95 (3H, s, CO_2CH_3), 4.67 (2H, t, $J = 7.33$ Hz, $\text{CH}_2\text{CH}_2\text{NO}_2$), 5.22 (2H, s, OCH_2OCH_3), 6.93 (1H, dd, $J = 8.79$, 2.20 Hz, $H-C(5)$), 7.04 (1H, d, $J = 2.20$ Hz, $H-C(7)$), 7.57 (1H, d, $J = 8.79$ Hz, $H-C(4)$), 10.98 (br, $H-N(1)$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 51.9, 56.0 (CH_3), 23.2, 75.2, 94.8 (CH_2), 97.4, 113.3, 121.0 (CH), 118.1, 122.7, 123.1, 136.6, 156.8, 161.8 (C). MS (EI) m/z 308 (M^+). Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6$: C, 54.54, H, 5.23, N, 9.09. Found: C, 54.62, H, 5.14, N, 9.07.

Methyl 3-[2-(benzoylamino)ethyl]-6-methoxymethoxy-1H-indole-2-carboxylate (15). Compound **14** (124 mg, 0.4 mmol) and NH_4Cl (107 mg, 2.0 mmol) was dissolved in MeOH (12 mL). Pd/C (10%, 12.4 mg) was added to this solution and stirred at r.t. for 18 h under H_2 atmosphere. The resulting mixture was then filtered through *Celite*, and the *Celite* was washed with CH_2Cl_2 . The filtrate was dried over (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and added Et_3N (390 μL , 2.8 mmol) at 0°C. BzCl (70 μL , 0.6 mmol) was added to this solution immediately and stirred for 30 min. To the reaction solution, H_2O was added at 0°C, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 \times), and the combined organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (50%

AcOEt/*n*-hexane) to afford 118 mg (77%) of **15** as a white solid. R_f 0.41 (AcOEt/*n*-hexane 1/1). M.p. 156~157 °C. IR (KBr): 3313, 2971, 2924, 2853, 1691, 1640, 1542, 1459, 1377, 1257, 1146, 1068, 1016, 461. $^1\text{H-NMR}$ (CDCl_3) δ : 3.41 (2H, t, $J = 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 3.48 (3H, s, OCH_2OCH_3), 3.77 (2H, dt, $J = 6.97, 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 3.86 (3H, s, CO_2CH_3), 5.19 (2H, s, OCH_2OCH_3), 6.83 (br, $\text{CH}_2\text{CH}_2\text{NHBz}$), 6.86 (1H, dd, $J = 8.80, 2.20$ Hz, $H\text{-C}(5)$), 7.03 (1H, d, $J = 2.20$ Hz, $H\text{-C}(7)$), 7.32-7.46 (3H, m, $H\text{-Ph}$), 7.59 (1H, d, $J = 8.80$ Hz, $H\text{-C}(4)$), 7.67-7.69 (2H, m, $H\text{-Ph}$), 8.94 (br, $H\text{-N}(1)$) $^{13}\text{C-NMR}$ (CDCl_3) δ : 51.7, 55.9 (CH_3), 24.1, 41.2, 94.8 (CH_2), 97.4, 112.9, 121.4, 126.8, 128.3, 131.1 (CH), 122.4, 122.7, 123.1, 134.5, 136.9, 156.7, 162.8, 167.5 (C). HR-MS (FAB) for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5$ (MH^+), calcd. 383.1607, found 383.1615.

N-Benzoyl-N-[2-(2-hydroxymethyl-6-methoxymethoxy-1H-indol-3-yl)ethyl]amine (16). To a solution of compound **15** (76.6 mg, 0.2 mmol) in anhydrous THF (2 mL), LAH (75.9 mg, 2.0 mmol) was added little by little at 0°C under Ar atmosphere. After stirring for 2 h at the temperature, $\text{H}_2\text{O}/\text{THF}$ (50%) solution was added carefully to quench the reaction, and the resulting mixture was filtered to remove the inorganic salt. The filtrate was extracted with AcOEt (3 \times), and the organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt) to afford 63.0 mg (89%) of **16** as a white solid. R_f 0.42 (AcOEt). M.p. 89~92 °C. IR (nujor): 3033, 1644, 1575, 1530, 1147, 1074, 1005, 917, 709. $^1\text{H-NMR}$ (CD_3OD) δ : 3.05 (2H, t, $J = 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 3.45 (3H, s, OCH_2OCH_3), 3.59 (2H, t, $J = 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 4.69 (2H, s, CH_2OH), 5.14 (2H, s, OCH_2OCH_3), 6.73 (1H, dd, $J = 8.80, 2.20$ Hz, $H\text{-C}(5)$), 7.01 (1H, d, $J = 2.20$ Hz, $H\text{-C}(7)$), 7.36-7.48 (3H, m, $H\text{-Ph}$), 7.46 (1H, d, $J = 8.80$ Hz, $H\text{-C}(4)$), 7.70-7.73 (2H, m, $H\text{-Ph}$) $^{13}\text{C-NMR}$ (CD_3OD) δ : 56.1 (CH_3), 24.9, 42.3, 56.4, 94.8 (CH_2), 99.4, 111.4, 120.0, 128.2, 129.5, 132.5 (CH), 110.3, 125.1, 135.4, 135.8, 137.9, 155.1, 170.4 (C). HR-MS (FAB) for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4$ (M^+), calcd. 354.1580, found 354.1611.

N-Benzoyl-N-[2-(2-formyl-6-methoxymethoxy-1H-indol-3-yl)ethyl]amine (17). Compound **16** (70.8 mg, 0.2 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL), and MnO_2 (17.4 mg, 2.0 mmol) was added to this solution under Ar atmosphere. After stirring for 2 h at r.t., the reaction mixture was then filtered through *Celite*, and the *Celite* was washed with CH_2Cl_2 . The filtrate was dried over (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (50% AcOEt/*n*-hexane) to afford 70.2 mg (quant.) of **17** as a white solid. R_f 0.57 (AcOEt/*n*-hexane 2/1). M.p. 152~153 °C. IR (KBr): 3419, 3296, 1646, 1546, 1439, 1310, 1232, 1198, 1148, 1073, 1013, 698. $^1\text{H-NMR}$ (CD_3OD) δ : 3.36 (2H, t, $J = 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 3.45 (3H, s, OCH_2OCH_3), 3.66 (2H, t, $J = 6.97$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 5.20 (2H, s, OCH_2OCH_3), 6.80 (1H, dd, $J = 8.80, 2.20$ Hz, $H\text{-C}(5)$), 7.03 (1H, d, $J = 2.20$ Hz, $H\text{-C}(7)$), 7.36-7.50 (3H, m, $H\text{-Ph}$), 7.68 (1H, d, $J = 8.80$ Hz, $H\text{-C}(4)$), 7.64-7.77 (2H, m, $H\text{-Ph}$), 9.85 (1H, s, CHO) $^{13}\text{C-NMR}$ (CD_3OD) δ : 56.3 (CH_3), 24.6, 42.7, 95.8 (CH_2), 98.5, 114.1, 123.3, 128.2, 129.5, 132.6, 181.6 (CH), 124.2, 127.9, 134.0, 135.6, 140.8, 159.1, 170.4 (C). HR-MS (FAB) for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4$ (MH^+), calcd. 353.1501, found 353.1504.

N-Benzoyl-N-[2-(6-methoxymethoxy-2-vinyl-1H-indol-3-yl)ethyl]amine (2). To a suspension of $\text{CH}_3\text{PPh}_3\text{Br}$ (179 mg, 0.5 mmol) in anhydrous THF (1 mL), KHMDS (0.5 M in toluene, 1.0 mL) was dropwise at r.t. under Ar atmosphere. After

stirring for 15 min, this solution was dropwise to a solution of compound **17** (35.3 mg, 0.1 mmol) in anhydrous THF (1 mL) under Ar atmosphere, and this reaction mixture was stirred at reflux for 18 h. The resulting solution was then quenched by addition of H_2O (2 mL), and extracted with CH_2Cl_2 (3 \times). The combined organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on aluminium oxide (50% AcOEt/*n*-hexane) to afford 28.5 mg (81%) of **2** as a colorless oil (unstable to light). R_f 0.54 (AcOEt/*n*-hexane 1/1). IR (neat): 3479, 3115, 3041, 2841, 1729, 1574, 1539, 1345, 1309, 1248, 1149, 1072, 1004, 898, 845, 805, 694. $^1\text{H-NMR}$ (CDCl_3) δ : 3.09 (2H, t, $J = 6.60$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 3.51 (3H, s, OCH_2OCH_3), 3.71 (2H, dt, $J = 6.60, 6.60$ Hz, $\text{CH}_2\text{CH}_2\text{NHBz}$), 5.18 (1H, d, $J = 11.36$ Hz, $-\text{CH}=\text{CH}_a\text{H}_b$), 5.21 (2H, s, OCH_2OCH_3), 5.41 (1H, d, $J = 17.60$ Hz, $-\text{CH}=\text{CH}_a\text{H}_b$), 6.13 (br, $\text{CH}_2\text{CH}_2\text{NHBz}$), 6.80 (1H, dd, $J = 11.36, 17.60$ Hz, $-\text{CH}=\text{CH}_2$), 6.84 (1H, dd, $J = 8.80, 2.20$ Hz, $H\text{-C}(5)$), 7.05 (1H, d, $J = 2.20$ Hz, $H\text{-C}(7)$), 7.34-7.49 (3H, m, $H\text{-Ph}$), 7.68 (1H, d, $J = 8.80$ Hz, $H\text{-C}(4)$), 7.62-7.65 (2H, m, $H\text{-Ph}$), 8.04 (br, $H\text{-N}(1)$) $^{13}\text{C-NMR}$ (CDCl_3) δ : 55.9 (CH_3), 23.8, 40.5, 95.2, 110.9 (CH_2), 97.9, 111.1, 119.5, 125.1, 126.8, 128.4, 131.3 (CH), 112.5, 123.9, 132.8, 134.5, 137.0, 154.8, 167.5 (C). HR-MS (EI) for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3$ (M^+), calcd. 350.1630, found 350.1620.

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