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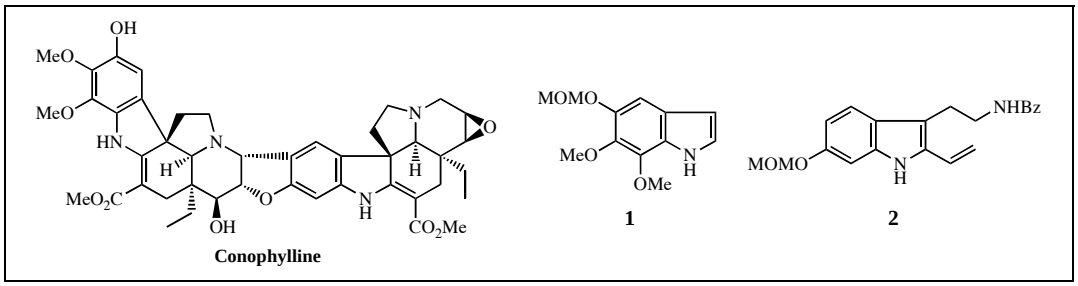

Conophylline is a bisindole alkaloid of unique structure that shows anti-cancer and anti-diabetic activities. Two indole core structures of conophylline, namely 6,7-dimethoxy-5-methoxymethoxy-1*H*-indole (**1**), and *N*-benzoyl-*N*-[2-(6-methoxymethoxy-2-vinyl-1*H*-indol-3-yl)ethyl]amine (**2**) has 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 unprecedent as a bisindole and considered that conophylline could be a new lead for the drugs and therapies toward diabetes.

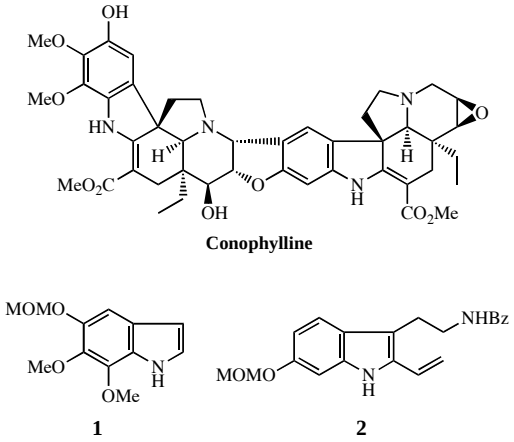


Figure 1

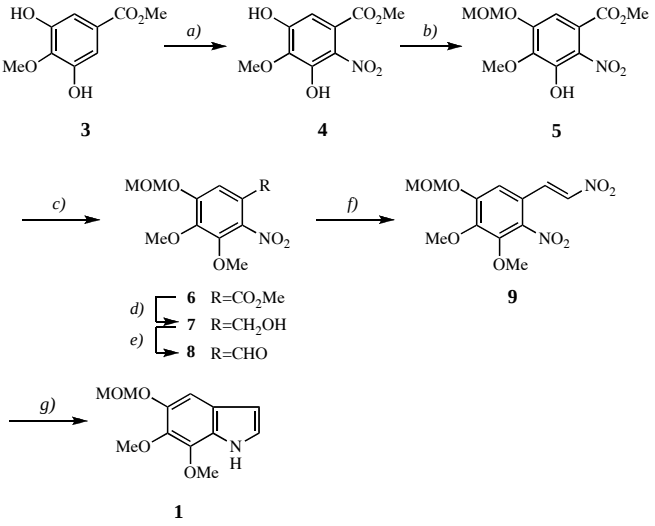
Conophylline has a unique structure comprising two indoles segmented *via* a central dihydrofuran [4]. The dihydrofuran seems crucial for the effect on diabetes, determining the spatial relationships of the indoles of both sides [3]. Our synthetic plan is to synthesize the left and the right indoles 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-1*H*-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 MnO_2 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

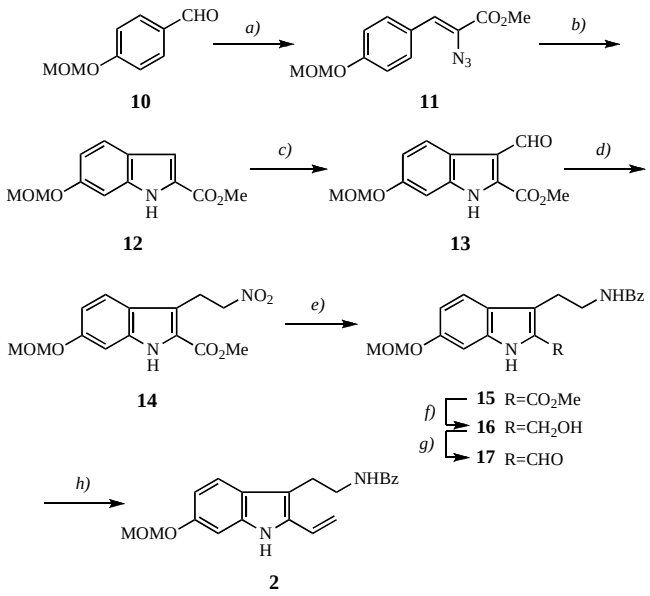


Reagents and conditions; *a)* $Ni(NO_3)_2$•$6H_2O$, PTSA, acetone; 70%, *b)* MOMCl, 2,6-lutidine, CH_2Cl_2, 0°C to r.t.; 54% (31%; recovery), *c)* $(MeO)_2SO_2$, K_2CO_3, acetone, reflux; 97%, *d)* $NaBH_4$, THF, 0°C to r.t.; 78%, *e)* MnO_2, CH_2Cl_2, r.t.; 95%, *f)* $MeNO_2$, Et_3N, MeOH, 0°C; then NaOAc, Ac_2O, 50°C; 92%, *g)* Pd/C (10%), HOAc, H_2, 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 $NaBH_4$ [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 MnO_2 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)* $N_3CH_2CO_2Me$, NaOMe, MeOH, 0°C to r.t.; 74%, *b)* toluene, reflux; quant., *c)* $POCl_3$, DMF, CH_2Cl_2, 0°C; 56% (40%; recovery), *d)* $MeNO_2$, NH_4Cl, MeOH, r.t.; then $NaBH_4$, DMF, 0°C; 76%, *e)* Pd/C (10%), H_2, NH_4Cl, MeOH, r.t.; then BzCl, Et_3N, CH_2Cl_2, 0°C; 77%, *f)* LAH, THF, 0°C; 89%, *g)* MnO_2, CH_2Cl_2, r.t.; quant., *h)* CH_3PPh_3Br, 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 F* $_{254}$ (on glass; *Merck*), aluminium oxide *60 F* $_{254}$ (on plastic sheet; *Merck*), visualization by UV light at 254 nm or staining with a soln. of $H_3(PMo_{12}O_{40})$·nH_2O 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 ^{13}C): *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-nitro-benzoate (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 $Ni(NO_3)_2 \cdot 6H_2O$ (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 (CH_2Cl_2) 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. ^{1}H-NMR(CD_3OD) δ: 3.92 (3H, s, PhOCH_3), 4.04 (3H, s, PhCO$_2$CH_3), 6.67 (1H, s, *H*-C(6)). ^{13}C-NMR(CD_3OD) δ : 53.4, 61.3 (CH_3), 108.5 (CH), 126.2, 127.8, 135.7, 149.7, 155.1, 166.6 (C). HR-MS(EI) for $C_9H_9NO_7$ (M^+), calcd. 243.0379, found 243.0383. Anal. Calcd. for $C_9H_9NO_7$: 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-nitro-benzoiate (5). To a solution of compound **4** (486 mg, 2.0 mmol) and 2,6-lutidine (304 μL, 2.6 mmol) in CH_2Cl_2 (20 mL), a solution of MOMCl (167 μL, 2.2 mmol) in CH_2Cl_2 (20 mL) was dropwised at 0°C. After stirring for 10 h at r.t., H_2O (40 mL) was added to the reaction solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). 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, 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 (CH_2Cl_2). M.p. 90~91 °C. IR (KBr): 3372, 2959, 1722, 1590, 1545, 1339, 1269, 1242, 1066, 1003, 867, 775, 763, 735, 613. ^{1}H-NMR($CDCl_3$) δ : 3.52 (3H, s, PhOCH$_2$OCH_3), 3.91 (3H, s, PhOCH_3), 3.97 (3H, s, PhCO$_2$CH_3), 5.31 (2H, s, PhOCH_2OCH$_3$), 6.97 (1H, s, H-C(6)) 9.91 (br, PhO*H*). ^{13}C-NMR($CDCl_3$) δ : 53.3, 56.8, 61.3 (CH_3), 95.0 (CH_2), 108.2 (CH), 125.6, 128.6, 139.4, 149.1, 154.8, 166.0 (C). HR-MS(EI) for $C_{11}H_{13}NO_8$ (M^+), calcd. 287.0641, found 287.0629. Anal. Calcd. for $C_{11}H_{13}NO_8$: 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-nitro-benzoate (6). A mixture of compound **5** (144 mg, 0.5 mmol), $(MeO)_2SO_2$ (56.8 μL, 0.6 mmol), K_2CO_3 (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 CH_2Cl_2 (20 mL) and washed with H_2O and brine, and the organic layer was dried over (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford 147 mg (97%) of **6** as a pale yellow amorphous. R_f 0.66 (CH_2Cl_2). (M.p. 63~64 °C. IR (neat): 3133, 2870, 1735, 1543, 1339, 1233, 1156, 1111, 1068, 1012, 978, 923, 870, 807, 739. ^{1}H-NMR($CDCl_3$) δ : 3.53 (3H, s, PhOCH$_2$OCH_3), 3.87 (3H, s, PhOCH_3), 3.96 (3H, s, PhOCH_3), 3.99 (3H, s, PhCO$_2$CH_3), 5.29 (2H, s, PhOCH_2OCH$_3$), 7.52 (1H, s, *H*-C(6)). ^{13}C-NMR($CDCl_3$) δ : 52.9, 56.6, 61.3, 62.6 (CH_3), 95.2 (CH_2), 112.7 (CH), 117.8, 141.0, 145.9, 147.2, 151.6, 163.0 (C). HR-MS(EI) for $C_{12}H_{15}NO_8$ (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), $NaBH_4$ (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 CH_2Cl_2 (3×), 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 aluminium oxide (CH_2Cl_2) to afford 85.2 mg (78%) of **7** as a yellow oil. R_f 0.09 (CH_2Cl_2). IR (neat): 2946, 1577, 1540, 1490, 1457, 1399, 1362, 1327, 1249, 1155, 1112, 964, 923, 881, 801. ^{1}H-NMR($CDCl_3$) δ : 3.52 (3H, s, PhOCH$_2$OCH_3), 3.92 (3H, s, PhOCH_3), 3.99 (3H, s, PhOCH_3), 4.61 (2H, s, PhCH_2OH), 5.28 (2H, s, PhOCH_2OCH$_3$), 7.07 (1H, s, *H*-C(6)). ^{13}C-NMR($CDCl_3$) δ : 56.5, 61.1, 62.3 (CH_3), 61.1, 95.0 (CH_2), 111.6 (CH), 129.6, 139.1, 142.7, 146.8, 153.0 (C). HR-MS(EI) for $C_{11}H_{15}NO_7$ (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 MnO_2 (174 mg 2.0 mmol) in CH_2Cl_2 (3 mL) was stirred at r.t. for 3 h under Ar atmosphere. The resuting mixture was then filtered through *Celite*, and the *Celite* was washed with CH_2Cl_2. The filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford 51.7 mg (95%) of **8** as pale yellow oil. R_f 0.66 (CH_2Cl_2). IR (neat): 3336, 1703, 1577, 1543, 1490, 1460, 1390, 1367, 1328, 1254, 1156, 1111, 1060, 1013, 963, 924, 879. ^{1}H-NMR($CDCl_3$) δ : 3.54 (3H, s, PhOCH$_2$OCH_3), 4.00 (3H, s, PhOCH_3), 4.02 (3H, s, PhOCH_3), 5.32 (2H, s, PhOCH_2OCH$_3$), 7.46 (1H, s, *H*-C(6)), 9.85 (1H, s, PhC*H*O). ^{13}C-NMR($CDCl_3$) δ : 56.7, 61.4, 62.6 (CH_3), 95.2 (CH_2), 111.6, 185.7 (CH), 122.9, 141.0, 146.1, 148.5, 152.6 (C). HR-MS(EI) for $C_{11}H_{13}NO_7$ (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 $MeNO_2$ in MeOH (1 mL), and Et_3N (10 μL) was added to this solution at 0°C under Ar atmosphere. After stirring for 2 h at the temperature, H_2O (5 mL) was added to the reaction solution. This mixture was extracted with CH_2Cl_2 (2×), and this combined organic layer was washed with brine, dried over (Na_2SO_4), and evaporated *in vacuo*. The residue was dissolved in Ac_2O (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 H_2O was then added to the resulting mixture. This mixture was extracted with CH_2Cl_2 (2×), and this 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 29.0 mg (92%) of **9** as a yellow amorphous. R_f 0.63 (CH_2Cl_2). M.p. 56~57 °C. IR (neat): 3109, 2957, 1638, 1576, 1533, 1490, 1343, 1273, 1223, 1171, 1092, 1014, 967, 922, 840. ^{1}H-NMR($CDCl_3$) δ : 3.55 (3H, s, PhOCH$_2$OCH_3), 3.99 (3H, s, PhOCH_3), 4.00 (3H, s, PhOCH_3), 5.30 (2H, s, PhOCH_2OCH$_3$), 7.13 (1H, s, *H*-C(6)), 7.46 (1H, d, *J* = 13.55 Hz, Ph–C*H*=CHNO$_2$), 7.85 (1H, d, *J* = 13.55 Hz, Ph–CH=C*H*NO$_2$). ^{13}C-NMR($CDCl_3$) δ : 56.7, 61.4, 62.5 (CH_3), 95.4 (CH_2), 109.2, 118.2, 139.6 (CH), 131.7, 141.2, 146.3, 146.8, 153.0 (C). HR-MS(EI) for $C_{12}H_{14}N_2O_8$ (M^+), calcd. 314.0750, found 314.0729. Anal. Calcd for $C_{12}H_{14}N_2O_8$: C, 45.86, H, 4.49, N, 8.91. Found: C, 45.93, H, 4.45, N, 8.74.

6,7-Dimethoxy-5-methoxymethoxy-1*H*-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 H_2 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}H-NMR($CDCl_3$) δ : 3.56 (3H, s, $ArOCH_2OCH_3$), 3.92 (3H, s, $ArOCH_3$), 4.07 (3H, s, $ArOCH_3$), 5.23 (2H, s, $ArOCH_2OCH_3$), 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}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 $C_{12}H_{15}NO_4$ (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 dropwised at −10°C under Ar atmosphere, and warmed to r.t. gradually. After sitirring for 12 h at r.t., the reaction mixture was cooled to 0°C and added ice cold H_2O (200mL). MeOH was removed *in vacuo*, and the aqueous layer was extracted with CH_2Cl_2 (3×). 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}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–C*H*=C), 7.04 (2H, d, *J* = 8.81 Hz, *H*-C(3)), 7.78 (2H, d, *J* = 8.81 Hz, *H*-C(2)). ^{13}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 $C_{12}H_{13}N_3O_4$ (M^+), calcd. 263.0906, found 263.0910.

Methyl 6-methoxymethoxy-1*H*-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 (CH_2Cl_2/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}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}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 $C_{12}H_{13}NO_4$: C, 61.27, H, 5.57, N, 5.95. Found: C, 61.19, H, 5.50, N, 5.89.

Methyl 3-formyl-6-methoxymethoxy-1*H*-indole-2-carboxylate (13). To a solution of DMF (3 mL) in anhydrous CH_2Cl_2 (20 mL), $POCl_3$ (1 mL) was dropwised 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 be 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×). The combined organic layer was dried over (Na_2SO_4), and evaporated *in vacuo*. The residue and filtered crystalline was mixed and washed with CH_2Cl_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 (CH_2Cl_2/MeOH 50/1). M.p. 194~196 °C. IR (KBr): 3174, 1714, 1637, 1577, 1526, 1378, 1360, 1248, 1213, 1147, 1078, 986, 838. ^{1}H-NMR (DMSO-D6) 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, C*H*O). ^{13}C-NMR (DMSO-D6) 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 $C_{13}H_{13}NO_5$: 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-1*H*-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×), 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×). The organic layer was washed with brine (2×), 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 (CH_2Cl_2/MeOH 50/1). M.p. 122~123 °C. IR (KBr): 3324, 1690, 1629, 1549, 1459, 1380, 1336, 1254, 1214, 1150, 1101, 1074, 999. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (3H, s, OCH_2OCH_3), 3.76 (2H, t, *J* = 7.33 Hz, $CH_2CH_2NO_2$), 3.95 (3H, s, CO_2CH_3), 4.67 (2H, t, *J* = 7.33 Hz, $CH_2CH_2NO_2$), 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}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 $C_{14}H_{16}N_2O_6$: 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-1*H*-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×), 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}H-NMR ($CDCl_3$) δ: 3.41 (2H, t, *J* = 6.97 Hz, C*H*$_2$CH$_2$NHBz), 3.48 (3H, s, OCH$_2$OC*H*$_3$), 3.77 (2H, dt, *J* = 6.97, 6.97 Hz, CH$_2$C*H*$_2$NHBz), 3.86 (3H, s, CO$_2$C*H*$_3$), 5.19 (2H, s, OC*H*$_2$OCH$_3$), 6.83 (br, CH$_2$CH$_2$N*H*Bz), 6.86 (1H, dd, *J* = 8.80, 2.20 Hz, *H*-C(5)), 7.03 (1H, d, *J* = 2.20 Hz, *H*-C(7)), 7.32-7.46 (3H, m, *H*-Ph), 7.59 (1H, d, *J* = 8.80 Hz, *H*-C(4)), 7.67-7.69 (2H, m, *H*-Ph), 8.94 (br, *H*-N(1)) ^{13}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 $C_{21}H_{23}N_2O_5$ (MH^+), calcd. 383.1607, found 383.1615.

***N*-Benzoyl-*N*-[2-(2-hydroxymethyl-6-methoxymethoxy-1*H*-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, H_2O/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×), 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}H-NMR (CD_3OD) δ: 3.05 (2H, t, *J* = 6.97 Hz, C*H*$_2$CH$_2$NHBz), 3.45 (3H, s, OCH$_2$OC*H*$_3$), 3.59 (2H, t, *J* = 6.97 Hz, CH$_2$C*H*$_2$NHBz), 4.69 (2H, s, C*H*$_2$OH), 5.14 (2H, s, OC*H*$_2$OCH$_3$), 6.73 (1H, dd, *J* = 8.80, 2.20 Hz, *H*-C(5)), 7.01 (1H, d, *J* = 2.20 Hz, *H*-C(7)), 7.36-7.48 (3H, m, *H*-Ph), 7.46 (1H, d, *J* = 8.80 Hz, *H*-C(4)), 7.70-7.73 (2H, m, *H*-Ph) ^{13}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 $C_{20}H_{22}N_2O_4$ (M^+), calcd. 354.1580, found 354.1611.

***N*-Benzoyl-*N*-[2-(2-formyl-6-methoxymethoxy-1*H*-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}H-NMR (CD_3OD) δ: 3.36 (2H, t, *J* = 6.97 Hz, C*H*$_2$CH$_2$NHBz), 3.45 (3H, s, OCH$_2$OC*H*$_3$), 3.66 (2H, t, *J* = 6.97 Hz, CH$_2$C*H*$_2$NHBz), 5.20 (2H, s, OC*H*$_2$OCH$_3$), 6.80 (1H, dd, *J* = 8.80, 2.20 Hz, *H*-C(5)), 7.03 (1H, d, *J* = 2.20 Hz, *H*-C(7)), 7.36-7.50 (3H, m, *H*-Ph), 7.68 (1H, d, *J* = 8.80 Hz, *H*-C(4)), 7.64-7.77 (2H, m, *H*-Ph), 9.85 (1H, s, C*H*O) ^{13}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 $C_{20}H_{21}N_2O_4$ (MH^+), calcd. 353.1501, found 353.1504.

***N*-Benzoyl-*N*-[2-(6-methoxymethoxy-2-vinyl-1*H*-indol-3-yl)ethyl]amine (2)** .To a suspension of CH_3PPh_3Br (179 mg, 0.5 mmol) in anhydrous THF (1 mL), KHMDS (0.5 *M* in toluene, 1.0 mL) was dropwised at r.t. under Ar atmosphere. After stirring for 15 min, this solution was dropwised 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×). 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}H-NMR ($CDCl_3$) δ: 3.09 (2H, t, *J* = 6.60 Hz, C*H*$_2$CH$_2$NHBz), 3.51 (3H, s, OCH$_2$OC*H*$_3$), 3.71 (2H, dt, *J* = 6.60, 6.60 Hz, CH$_2$C*H*$_2$NHBz), 5.18 (1H, d, *J* = 11.36 Hz, –CH=C*H*$_a$H$_b$), 5.21 (2H, s, OC*H*$_2$OCH$_3$), 5.41 (1H, d, *J* = 17.60 Hz, –CH=CH$_a$*H*$_b$), 6.13 (br, CH$_2$CH$_2$N*H*Bz), 6.80 (1H, dd, *J* = 11.36, 17.60 Hz, –C*H*=CH$_2$), 6.84 (1H, dd, *J*=8.80, 2.20 Hz, *H*-C(5)), 7.05 (1H, d, *J* =2.20 Hz, *H*-C(7)), 7.34-7.49 (3H, m, *H*-Ph), 7.68 (1H, d, *J* = 8.80 Hz, *H*-C(4)), 7.62-7.65 (2H, m, *H*-Ph), 8.04 (br, *H*-N(1)). ^{13}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 $C_{21}H_{22}N_2O_3$ (M^+), calcd. 350.1630, found 350.1620.

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