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NOVEL SYNTHESES OF 1-HYDROXY-6- AND -5-NITROINDOLE-3-CARBALDEHYDES, AND THEIR DERIVATIVES AS DAIKON-PHYTOALEXIN ANALOGS[1]

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Abstract –1-Hydroxy-6- and -5-nitroindole-3-carbaldehydes are prepared for the first time from 1-methoxy-6- and -5-nitroindole-3-carbaldehydes, respectively, based on the discovery of novel methyl ether cleavage reaction. Utilizing them as common synthetic intermediates, syntheses of several daikon-phytoalexin analogs are achieved.

We have been much interested in the phytoalexins of plant family, *Cruciferae*,[2] because of their unique 1-alkoxyindole structures[3] and the fact we eat these vegetables at every meal. Therefore, it is important to determine whether these phytoalexins are good for our health. There is also a chance to find new biologically active compounds among analogs of the phytoalexins. So, we have thus far elaborated simple synthetic methods for 1-methoxyindole-3-carbaldehyde[4b] (**5a**, daikon[4c]-phytoalexin), brassicanal A,[4e] methyl 1-methoxyindole-3-carboxylate[5,6] (wasabi[5]-phytoalexin), and various kinds of analogs of wasabi-phytoalexin.[6] Now, we wish to report novel syntheses of 1-hydroxy-6- (**2a**) and -5-nitroindole-3-carbaldehydes (**9a**), and their derivatives (**10a**, **12**—**15**) as daikon-phytoalexin analogs.

We settled **2a** and **9a** as common synthetic intermediates to meet our end. In order to obtain **2a**, three routes were tried starting from indoline (**1**). Since 1-hydroxy-6-nitroindole (**3**) is readily available according to our method[7] in two steps from **1** (Scheme 1), Vilsmeier-Haack reaction of **3** was first attempted *in vain* to give disappointing results with formation of many products. As the second route, we examined the ether cleavage of 1-methoxy group in 1-methoxy-6-nitroindole-3-carbaldehyde (**5b**), which was prepared from **3** through 1-methoxy-6-nitroindole (**4**).[8] Although treatment of **5b** with trimethylsilyl iodide was unsuccessful, BBr_3 was found to provide **2a**. However, the yield was not improved to more than 40% under various examined reaction conditions.

Scheme 1

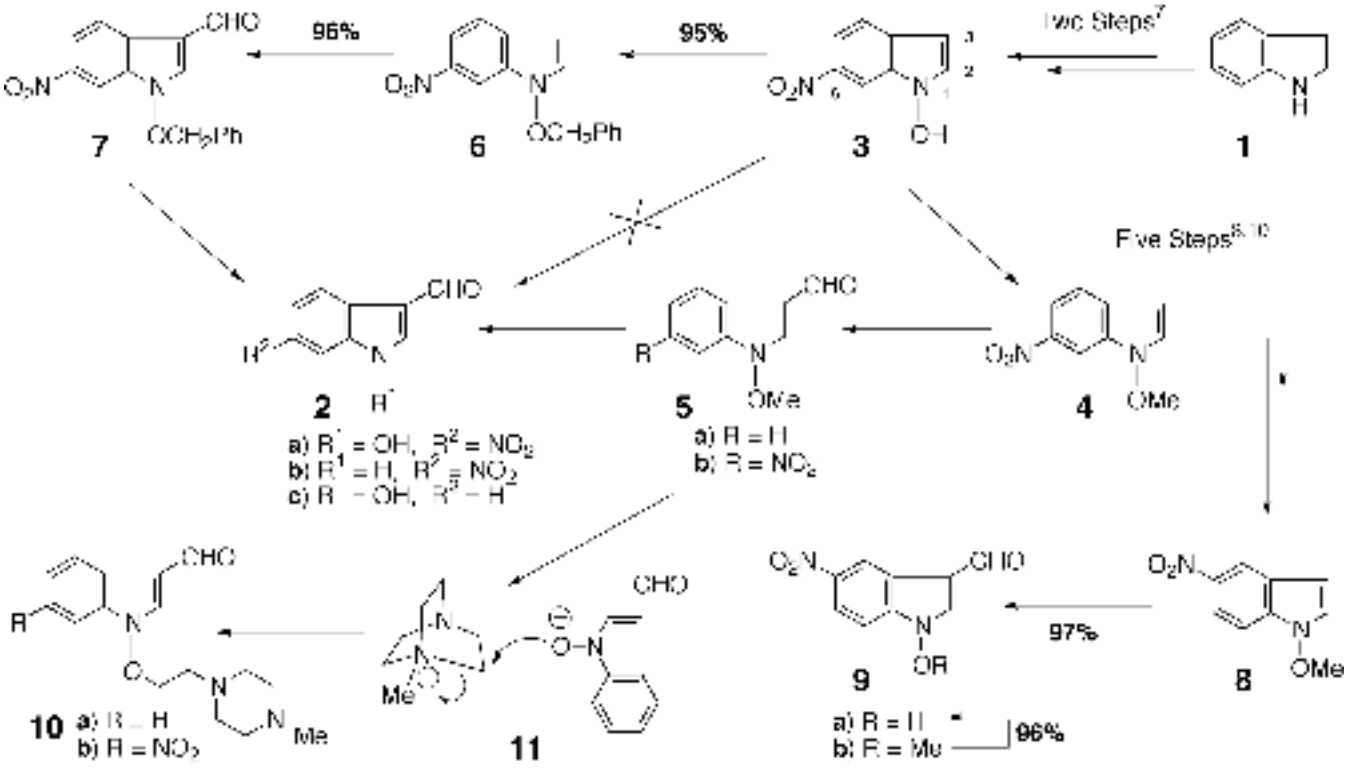
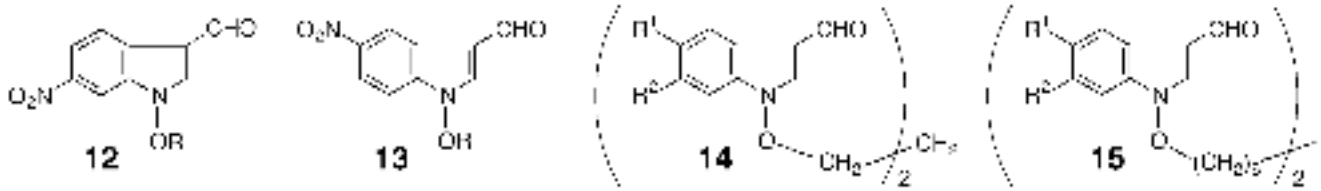


Table 1

5b → (DABCO, DMF) → **2a** + **2b** + Recovery

Entry	DABCO (mol eq)	Reaction Temp. (°C)	Reaction Time (h)	Yield (%) of **2a**	**2b**	**5b**
1	1	90	3	50	0	45
2	1	90	96	52	14	0
3	10	rt	168	44	0	55
4	10	90	3	90	0	0

Figure 1



a) R = allyl
b) R = propargyl
c) R = $CH_2CH_2CH_2Br$
d) R = $CH_2(CH_2)_{13}CH_2Br$

a) R = allyl
b) R = propargyl
c) R = $CH_2CH_2CH_2Br$
d) R = $CH_2(CH_2)_{13}CH_2Br$

a) R^1 = H, R^2 = NO_2
b) R^1 = NO_2, R^2 = H

a) R^1 = H, R^2 = NO_2
b) R^1 = NO_2, R^2 = H

We turned our attention to change the alkyl group on the 1-hydroxy oxygen from methyl to benzyl group. Treatment of **3** with benzyl bromide and K_2CO_3 afforded 1-benzyloxy-6-nitroindole (**6**) in 95% yield. Subsequent Vilsmeier-Haack reaction of **6** afforded 1-benzyloxy-6-nitroindole-3-carbaldehyde (**7**) in 96% yield. As expected, benzyl ether cleavage of **7** with BBr_3 was successful culminating in the formation of **2a** in 97% yield. As the third route, we conceived an idea to attack at the methyl carbon of 1-methoxy group in **5b** with base for producing **2a** relied on the acidic nature of 1-hydroxyindole compounds.[9] The idea was actually realized in the case where 1,4-diazabicyclo[2.2.2]octane (DABCO) was employed as a base and the results are summarized in Table 1.

When **5b** was treated with 1 mol eq. of DABCO in DMF at 90°C for 3 h, the desired product (**2a**) was obtained in 50% yield together with 45% yield of recovery (Entry 1). Prolonged heating at 90°C did not improve the yield of **2a** and formed its decomposed product (6-nitroindole-3-carbaldehyde, **2b**) in a significant yield (Entry 2). Treatment with excess amount of DABCO for long reaction time at room temperature afforded almost the same result as in the case of Entry 1 (Entry 3). On the basis of these observations, suitable reaction conditions shown in Entry 4 were finally found and now **2a** is available from **5b** in more than 90% yield.

This novel methyl ether cleavage reaction with DABCO was successfully applied in 96% yield for the production of 1-hydroxy-5-nitroindole-3-carbaldehyde (**9a**) from 1-methoxy-5-nitroindole-3-carbaldehyde (**9b**), which is available from **1** in six steps through 1-methoxy-5-nitroindole (**8**).[3,10]

It is interesting to note that when the above DABCO reaction was applied to daikon-phytoalexin (**5a**), 1-hydroxyindole-3-carbaldehyde[3a] (**2c**) and 1-[2-(4-methylpiperazin-1-yl)ethoxy]indole-3-carbaldehyde (**10a**) were produced in 42 and 49% yields, respectively. The isolation of **10a** suggests the mechanism of the ether cleavage reaction. Thus, the nitrogen of DABCO first attacks the methyl carbon of 1-methoxy group in **5a** affording *N*-methylammonium salt (**11**) with oxide of **2c**. Then the oxide of **2c** attacks the carbon adjacent to the positively charged nitrogen of **11** resulting in the formation of **10a**. The difference of the nucleophilicity[9] between the oxides of **2c** and **2a** would be the major reason why the formation of **10b** was not observed at all in the reaction of **5b** with DABCO.

With **2a** and **9a** in hand, we next attempted the syntheses of several daikon-phytoalexin analogs (Figure 1). Treatment of **2a** with allyl bromide and propargyl bromide in the presence of K_2CO_3 provided the corresponding 1-allyloxy- (**12a**) and 1-propargyloxy derivatives (**12b**) in 93 and 93% yields, respectively. Upon the reaction of **2a** with 1,3-dibromopropane, **12c** and **14a** were produced in the respective yields of 91 and 9%. The dimer (**14a**) was readily obtained in 98% yield by either treating **12c** with **2a** or reacting 1,3-dibromopropane with two moles of **2a** in 93% yield. The reaction of **2a** with 1,12-dibromododecane afforded **12d** and **15a** in 85 and 15% yields, respectively.

Similarly, the reaction of **9a** with allyl bromide and propargyl bromide in the presence of K_2CO_3 provided the corresponding 1-allyloxy- (**13a**) and 1-propargyloxy derivatives (**13b**) in 90 and 92% yields, respectively. Upon the reaction of **9a** with 1,3-dibromopropane, **13c** and **14b** were obtained in the respective yields of 91 and 9%. The reaction of **9a** with 1,12-dibromododecane afforded **13d** and **15b** in 84 and 14% yields, respectively.

In summary, we have discovered a novel ether cleavage reaction of 1-methoxyindole derivatives with DABCO and successfully applied it for the first syntheses of 1-hydroxy-6- (**2a**) and -5-nitroindole-3-carbaldehyde (**9a**). Utilizing them as common intermediates, several kinds of 1-alkoxy-6- and -5-nitroindole-3-carbaldehydes were produced as analogs of daikon-phytoalexin (**5a**). Their biological evaluations and studies on the interactions of **14a**,**b** and **15a**,**b** with DNA are our ongoing projects.

EXPERIMENTAL

IR spectra were determined with a HORIBA FT-720 spectrophotometer and ^{1}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. Column chromatography was performed on silica gel (SiO_2, 100–200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

1-Benzyloxy-6-nitroindole (6) from 3 — A mixture of **3** (503.5 mg, 2.83 mmol), benzyl bromide (1.94 g, 11.3 mmol), and K_2CO_3 (1.56 g, 11.3 mmol) in MeOH (9.0 mL) was stirred at rt for 30 min. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:9, v/v) to give **6** (718.6 mg, 95%). **6**: mp 200—202 °C (yellow prisms, recrystallized from AcOEt–hexane). IR (KBr): 1508, 1487, 1333 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.24 (2H, s), 6.37 (1H, dd, *J*=3.3, 0.9 Hz), 7.24 (1H, d, *J*=3.3 Hz), 7.32—7.41 (5H, m), 7.59 (1H, d, *J*=8.8 Hz), 7.97 (1H, dd, *J*=8.8, 2.1 Hz), 8.23 (1H, d, *J*=2.1 Hz). *Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.25; H, 4.67; N, 10.25.

1-Benzyloxy-6-nitroindole-3-carbaldehyde (7) from 6 — A mixture of $POCl_3$ (1.25 mL, 13.6 mmol) and anhydrous DMF (7.5 mL, 96.4 mmol) was stirred at rt for 15 min. To the resulting mixture, a solution of **6** (718.6 mg, 2.68 mmol) in anhydrous DMF (35.0 mL) was added and the mixture was heated at 70 °C for 90 min with stirring. After addition of H_2O, the whole was made alkaline with saturated $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **7** (758.5 mg, 96%). **7**: mp 154—156 °C (yellow powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 1668, 1514, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.32 (2H, s), 7.29—7.32 (2H, m), 7.38—7.47 (3H, m), 7.67 (1H, s), 8.17 (1H, dd, *J*=8.8, 2.0 Hz), 8.27 (1H, d, *J*=2.0 Hz), 8.39 (1H, d, *J*=8.8 Hz), 9.88 (1H, s). *Anal.*

Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.56; H, 4.14; N, 9.38.

1-Hydroxy-6-nitroindole-3-carbaldehyde (2a) from 7 — A solution of BBr_3 in heptane (1M, 0.85 mL, 0.85 mmol) was added to a solution of **7** (50.2 mg, 0.17 mmol) in $CHCl_3$ (5.0 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at rt for 30 min. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **2a** (34.0 mg, 97%). **2a**: mp 211—213 °C (decomp, yellow fine needles, recrystallized from AcOEt–hexane). IR (KBr): 3113, 1595 (br), 1520, 1387, 1346, 1279 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.10 (1H, dd, *J*=8.7, 2.1 Hz), 8.26 (1H, d, *J*=8.7 Hz), 8.30 (1H, d, *J*=2.1 Hz), 8.77 (1H, s) 9.90 (1H, s). *Anal.* Calcd for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.18; H, 3.02; N, 13.40.

1-Methoxy-6-nitroindole-3-carbaldehyde (5b) from 4 — A mixture of $POCl_3$ (0.97 mL, 10.6 mmol) and anhydrous DMF (5.84 mL, 75.1 mmol) was stirred at rt for 15 min. To the resulting mixture, a solution of **4** (1.00 g, 5.2 mmol) in anhydrous DMF (15.0 mL) was added and the mixture was stirred at rt for 7 h. After addition of H_2O, the whole was made alkaline with saturated $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:2, v/v) to give **5b** (1.08 g, 94%). **5b**: mp 180—182°C (yellow prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 1664, 1653, 1508, 1342 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.28 (3H, s), 8.14 (1H, s), 8.22 (1H, dd, *J*=8.8, 2.0 Hz), 8.43 (1H, d, *J*=8.8 Hz), 8.45 (1H, d, *J*=2.0 Hz), 10.02 (1H, s). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.32; H, 3.61; N, 12.54.

1-Hydroxy-6-nitroindole-3-carbaldehyde (2a) from 1-Methoxy-6-nitroindole-3-carbaldehyde (5b): 1) with BBr_3 — A solution of BBr_3 in heptane (1M, 4.63 mL, 4.63 mmol) was added to a solution of **5b** (101.9 mg, 0.46 mmol) in $CHCl_3$ (10.0 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at rt for 20 h. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (95:5, v/v) to give unreacted **5b** (54.1 mg, 53%) and **2a** (37.7 mg, 40%) in the order of elution.

2) With DABCO — A solution of DABCO (231.0 mg, 2.06 mmol) in anhydrous DMF (2.0 mL) was added to a solution of **5b** (45.4 mg, 0.21 mmol) in anhydrous DMF (2.0 mL) and the mixture was stirred at 90 °C for 3 h. After addition of H_2O, the whole was made acidic with 6% HCl and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **2a** (38.3 mg, 90%).

1-Hydroxyindole-3-carbaldehyde (2c) and 1-[2-(4-Methylpiperazin-1-yl)ethoxy]indole-3-carbaldehyde (10a) from 5a — A mixture of **5a** (156.9 mg, 0.90 mmol) and DABCO (990.4 mg, 8.80

mmol) in anhydrous DMF (5.0 mL) was stirred at 100 °C for 12 h. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **2c** (60.2 mg, 42%). The acidic water layer was made alkaline with 8% NaOH and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **10a** (125.5 mg, 49%). **2c**: mp 154—156 °C (decomp, pale yellow prisms, recrystallized from AcOEt–hexane). IR (KBr): 3107, 1616 (br), 1558 (br), 1516, 1309, 1238 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.26 (1H, dt, *J*=1.3, 7.3 Hz), 7.34 (1H, dt, *J*=1.3, 7.3 Hz), 7.52 (1H, d, *J*=7.3 Hz), 8.11 (1H, d, *J*=7.3 Hz), 8.43 (1H, s), 9.84 (1H, s), 12.20 (1H, br s, disappeared on addition of D_2O). *Anal.* Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.86; H, 4.37; N, 8.66. **10a**: colorless viscous oil. IR (film): 2939, 2802, 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 2.80—2.90 (8H, m), 2.86 (2H, t, *J*=5.3 Hz), 4.44 (2H, t, *J*=5.3 Hz), 7.33 (1H, dt, *J*=2.0, 7.3 Hz), 7.38 (1H, dt, *J*=2.0, 7.3 Hz), 7.50 (1H, dd, *J*=2.0, 7.3 Hz), 7.96 (1H, s), 8.30 (1H, dd, *J*=2.0, 7.3 Hz), 9.98 (1H, s). HRMS *m/z*: Calcd for $C_{16}H_{21}N_3O_2$: 287.1633. Found: 287.1636.

1-Methoxy-5-nitroindole-3-carbaldehyde (9b) from 8 — A mixture of $POCl_3$ (1.0 mL, 10.9 mmol) and anhydrous DMF (6.0 mL, 77.2 mmol) was stirred at rt for 15 min. To the resulting mixture, a solution of **8** (1.02 g, 5.31 mmol) in anhydrous DMF (15.0 mL) was added and the mixture was heated at 60 °C for 2 h with stirring. After addition of H_2O, the whole was made alkaline with 8% NaOH and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **9b** (1.13 g, 97%). **9b**: mp 183—185 °C (beige powder, recrystallized from $CHCl_3$). IR (KBr): 1672, 1657, 1525, 1329 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (3H, s), 7.57 (1H, d, *J*=9.0 Hz), 8.05 (1H, s), 8.28 (1H, dd, *J*=9.0, 2.2 Hz), 9.23 (1H, d, *J*=2.2 Hz), 10.03 (1H, s). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.41; H, 3.59; N, 12.73.

1-Hydroxy-5-nitroindole-3-carbaldehyde (9a) from 9b — A mixture of **9b** (50.2 mg, 0.23 mmol) and DABCO (260.3 mg, 2.32 mmol) in anhydrous DMF (2.0 mL) was heated at 100 °C for 3 h with stirring. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **9a** (48.5 mg, 96%). **9a**: mp 222—225 °C (decomp, yellow fine needles, recrystallized from MeOH–$CHCl_3$). IR (KBr): 1618, 1585, 1560, 1512, 1365, 1331, 1292 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.73 (1H, d, *J*=9.0 Hz), 8.21 (1H, dd, *J*=9.0, 2.2 Hz), 8.70 (1H, s), 8.98 (1H, d, *J*=2.2 Hz), 9.94 (1H, s). *Anal.* Calcd for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.35; H, 2.93; N, 13.63.

1-Allyloxy-6-nitroindole-3-carbaldehyde (12a) from 2a — A mixture of **2a** (110.2 mg, 0.54 mmol), K_2CO_3 (295.2 mg, 2.1 mmol), and allyl bromide (642.5 mg, 5.3 mmol) in MeOH (10.5 mL) and H_2O (1 mL) was stirred at rt for 3 h. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **12a** (122.1 mg, 93%). **12a**: mp 120—122 °C (yellow needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 1666 (br), 1508, 1346 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.97 (2H, d, *J*=6.6 Hz), 5.36 (1H, dd, *J*=10.3, 0.5 Hz), 5.40 (1H, dd, *J*=17.1, 0.5 Hz), 6.20 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz), 8.17 (1H, dd, *J*=8.8, 2.0 Hz), 8.32 (1H, d, *J*=8.8 Hz), 8.48 (1H, d, *J*=2.0 Hz), 8.99 (1H, s), 9.95 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.29; H, 4.09; N, 11.23.

1-Propargyloxy-6-nitroindole-3-carbaldehyde (12b) from 2a — A mixture of **2a** (100.4 mg, 0.49 mmol), K_2CO_3 (269.2 mg, 1.95 mmol), and propargyl bromide (1.15 g, 9.65 mmol) in MeOH (6.5 mL) and H_2O (1.0 mL) was stirred at rt for 5 h. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–hexane (1:2, v/v) to give **12b** (110.7 g, 93%). **12b**: mp 189—193 °C (yellow fine needles, recrystallized from AcOEt). IR (KBr): 2125, 1664, 1500, 1354 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (1H, t, *J*=2.3 Hz), 5.26 (2H, d, *J*=2.3 Hz), 8.18 (1H, dd, *J*=8.8, 2.2 Hz), 8.34 (1H, d, *J*=8.8 Hz), 8.53 (1H, d, *J*=2.2 Hz), 9.02 (1H, s), 9.98 (1H, s). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{12}H_8N_2O_4 \cdot 1/8H_2O$: C, 58.48; H, 3.37; N, 11.37. Found: C, 58.39; H, 3.34; N, 11.10.

1-(3-Bromopropoxy)-6-nitroindole-3-carbaldehyde (12c) and 1,3-Bis(3-formyl-6-nitroindol-1-yloxy)propane (14a) from 2a — A mixture of **2a** (51.8 mg, 0.25 mmol), K_2CO_3 (140.3 mg, 1.02 mmol) and 1,3-dibromopropane (508.6 mg, 2.52 mmol) in DMF (5.0 mL) was stirred at rt for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (99:1, v/v) to give **12c** (74.8 mg, 91%) and **14a** (5.1 mg, 9%) in the order of elution. **12c**: mp 110.5—112.5 °C (yellow prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 1670, 1512, 1344 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (2H, quint, *J*=6.1 Hz), 3.70 (2H, t, *J*=6.1 Hz), 4.59 (2H, t, *J*=6.1 Hz), 8.14 (1H, s), 8.22 (1H, dd, *J*=8.8, 2.2 Hz), 8.44 (1H, d, *J*=8.8 Hz), 8.47 (1H, d, *J*=2.2 Hz), 10.03 (1H, s). *Anal.* Calcd for $C_{12}H_{11}BrN_2O_4$: C, 44.06; H, 3.39; N, 8.56. Found: C, 44.04; H, 3.37; N, 8.38. **14a**: mp 251—252 °C (decomp, pale yellow powder, recrystallized from $CHCl_3$–MeOH). IR (KBr): 1662, 1510, 1338 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.40 (2H, quint, *J*=6.2 Hz), 4.74 (4H, t, *J*=6.2 Hz), 8.18 (2H, dd, *J*=8.8, 2.1 Hz), 8.35 (2H, d, *J*=8.8 Hz), 8.57 (2H, d, *J*=2.1 Hz), 9.11 (2H, s), 9.98 (2H, s). MS *m/z*: 452 (M^+). *Anal.* Calcd for $C_{21}H_{16}N_4O_8 \cdot 1/2H_2O$: C, 54.67; H,

3.71; N, 12.14. Found: C, 54.75; H, 3.56; N, 12.02.

1-(12-Bromododecyloxy)-6-nitroindole-3-carbaldehyde (12d) and 1,12-Bis(3-formyl-6-nitroindol-1-yloxy)dodecane (15a) from 2a — A mixture of **2a** (50.9 mg, 0.25 mmol), K_2CO_3 (136.6 mg, 0.99 mmol), and 1,12-dibromododecane (406.3 mg, 1.24 mmol) in DMF (5.0 mL) was stirred at rt for 40 min. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (2:1, v/v) and $CHCl_3$ to give **12d** (94.7 mg, 85%) and **15a** (10.4 mg, 15%) in the order of elution. **12d**: mp 84—85 °C (yellow prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 2918, 1672, 1512, 1336 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29—1.45 (14H, m), 1.54 (2H, quint, *J*=7.4 Hz), 1.86 (2H, quint, *J*=6.8 Hz), 1.87 (2H, quint, *J*=6.8 Hz), 3.41 (2H, t, *J*=6.8 Hz), 4.39 (2H, t, *J*=6.8 Hz), 8.10 (1H, s), 8.21 (1H, dd, *J*=8.8, 2.2 Hz), 8.41 (1H, d, *J*=2.2 Hz), 8.42 (1H, d, *J*=8.8 Hz), 10.02 (1H, s). *Anal.* Calcd for $C_{21}H_{29}N_2O_4Br$: C, 55.63; H, 6.45; N, 6.18. Found: C, 55.52; H, 6.46; N, 6.05. **15a**: mp 134—135 °C (yellow powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 2924, 1662, 1512, 1336 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33—1.45 (12H, m), 1.56 (4H, quint, *J*=6.8 Hz), 1.88 (4H, quint, *J*=6.8 Hz), 4.40 (4H, t, *J*=6.8 Hz), 8.19 (2H, s), 8.21 (2H, dd, *J*=8.8, 2.0 Hz), 8.41 (2H, d, *J*=8.8 Hz), 8.41 (2H, d, *J*=2.0 Hz), 9.99 (2H, s). *Anal.* Calcd for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92; N, 9.68. Found: C, 61.95; H, 5.91; N, 9.49.

1-Allyloxy-5-nitroindole-3-carbaldehyde (13a) from 9a — A mixture of **9a** (50.5 mg, 0.25 mmol), K_2CO_3 (136.0 mg, 0.98 mmol), and allyl bromide (297.2 mg, 2.46 mmol) in MeOH (5.25 mL) and DMF (0.5 mL) was stirred at rt for 3 h. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (95:5, v/v) to give **13a** (54.3 mg, 90%) and unreacted **9a** (4.6 mg, 9%) in the order of elution. **13a**: mp 132 °C (colorless fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 1666, 1508, 1367, 1335 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.82 (2H, ddd, *J*=6.8, 1.1, 0.8 Hz), 5.36 (1H, ddt, *J*=17.1, 1.0, 1.1 Hz), 5.44 (1H, ddt, *J*=10.3, 1.0, 0.8 Hz), 6.12 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz), 7.56 (1H, d, *J*=9.0 Hz), 7.98 (1H, s), 8.28 (1H, dd, *J*=9.0, 2.2 Hz), 9.23 (1H, d, *J*=2.2 Hz), 10.02 (1H, s). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_4 \cdot 1/8H_2O$: C, 58.01; H, 4.16; N, 11.27. Found: C, 58.21; H, 4.03; N, 11.25.

1-Propargyloxy-5-nitroindole-3-carbaldehyde (13b) from 9a — A mixture of **9a** (51.2 mg, 0.25 mmol), K_2CO_3 (137.5 mg, 0.99 mmol), and propargyl bromide (591.6 mg, 4.97 mmol) in MeOH (5.25 mL) and DMF (0.5 mL) was stirred at rt for 5 h. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (95:5, v/v) to give **13b** (55.7 mg, 92%) and unreacted **9a** (3.9

mg, 8%) in the order of elution. **13b**: mp 199—201 °C (pale yellow prisms, recrystallized from $CHCl_3$–MeOH). IR (KBr): 3309, 2129, 1672, 1525, 1516, 1333 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.73 (1H, t, *J*=2.4 Hz), 4.97 (2H, d, *J*=2.4 Hz), 7.61 (1H, d, *J*=9.0 Hz), 8.13 (1H, s), 8.28 (1H, dd, *J*=9.0, 2.2 Hz), 9.25 (1H, d, *J*=2.2 Hz), 10.05 (1H, s). *Anal.* Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.86; H, 3.26; N, 11.43.

1-(3-Bromopropoxy)-5-nitroindole-3-carbaldehyde (13c) and 1,3-Bis(3-formyl-5-nitroindol-1-yl-oxy)propane (14b) from 9a — A mixture of **9a** (50.4 mg, 0.24 mmol), K_2CO_3 (135.3 mg, 0.98 mmol), and 1,3-dibromopropane (495.0 mg, 2.45 mmol) in DMF (5.0 mL) was stirred at rt for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **13c** (73.0 mg, 91%) and **14b** (5.4 mg, 9%) in the order of elution. **13c**: mp 88—89 °C (pale yellow plates, recrystallized from $CHCl_3$–hexane). IR (KBr): 3101, 1662, 1522, 1329 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (2H, quint, *J*=6.4 Hz), 3.70 (2H, t, *J*=6.4 Hz), 4.56 (2H, t, *J*=6.4 Hz), 7.61 (1H, d, *J*=9.0 Hz), 8.05 (1H, s), 8.30 (1H, dd, *J*=9.0, 2.0 Hz), 9.24 (1H, d, *J*=2.0 Hz), 10.04 (1H, s). *Anal.* Calcd for $C_{12}H_{11}N_2O_4Br$: C, 44.06; H, 3.39; N, 8.56. Found: C, 43.98; H, 3.32; N, 8.57. **14b**: mp 233—235 °C (decomp, yellow powder, recrystallized from acetone). IR (KBr): 3107, 1668, 1516, 1331 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.34 (2H, quint, *J*=6.4 Hz), 4.68 (4H, t, *J*=6.4 Hz), 7.89 (2H, d, *J*=9.0 Hz), 8.24 (2H, dd, *J*=9.0, 2.2 Hz), 9.00 (2H, d, *J*=2.2 Hz), 9.01 (2H, s), 9.99 (2H, s). MS *m/z*: 452 (M^+). *Anal.* Calcd for $C_{21}H_{16}N_4O_8 \cdot 1/2H_2O$: C, 54.67; H, 3.71; N, 12.14. Found: C, 54.50; H, 3.55; N, 12.06.

1-(12-Bromododecyloxy)-5-nitroindole-3-carbaldehyde (13d) and 1,12-Bis(3-formyl-5-nitroindol-1-yloxy)dodecane (15b) from 9a — A mixture of **9a** (51.4 mg, 0.25 mmol), K_2CO_3 (137.9 mg, 1.0 mmol), and 1,12-dibromododecane (410.2 mg, 1.25 mmol) in DMF (5.0 mL) was stirred at rt for 40 min. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and $CHCl_3$–MeOH (99:1, v/v) to give **13d** (95.6 mg, 84%) and **15b** (10.0 mg, 14%) in the order of elution. **13d**: mp 60—61 °C (pale yellow prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 2927, 2850, 1653, 1525, 1329 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28—1.46 (12H, m), 1.49—1.57 (4H, m), 1.82—1.89 (4H, m), 3.41 (2H, t, *J*=6.8 Hz), 4.36 (2H, t, *J*=6.8 Hz), 7.54 (1H, d, *J*=9.0 Hz), 8.01 (1H, s), 8.27 (1H, dd, *J*=9.0, 2.2 Hz), 9.24 (1H, d, *J*=2.2 Hz), 10.03 (1H, s). MS *m/z*: 454 (M^+), 452 (M^+). *Anal.* Calcd for $C_{21}H_{29}N_2O_4Br \cdot 1/8H_2O$: C, 55.36; H, 6.47; N, 6.15. Found: C, 55.27; H, 6.39; N, 6.17. **15b**: mp 150—151 °C (pale yellow fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 2931, 1655, 1523, 1329 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.26—1.36 (12H, m), 1.46 (4H, quint, *J*=6.8 Hz), 1.75 (4H, quint, *J*=6.8 Hz), 4.42 (4H, t, *J*=6.8 Hz), 7.80 (2H, d, *J*=9.0 Hz),

8.24 (2H, dd, *J*=9.0, 2.2 Hz), 8.95 (2H, s), 8.98 (2H, d, *J*=2.2 Hz), 9.97 (2H, s). MS *m/z*: 578 (M^+). *Anal.* Calcd for $C_{30}H_{34}N_4O_8 \cdot 1/2H_2O$: C, 61.32; H, 6.00; N, 9.53. Found: C, 61.35; H, 5.86; N, 9.49.

1,3-Bis(3-formyl-6-nitroindol-1-yloxy)propane (14a) from 12c — A mixture of **12c** (10.4 mg, 0.03 mmol), **2a** (6.6 mg, 0.03 mmol), and K_2CO_3 (8.9 mg, 0.06 mmol) in DMF (1.0 mL) was stirred at rt for 90 min. After addition of H_2O, the whole was made acidic with 6% HCl and resulting precipitates (**14a**, 11.0 mg) were collected by filtration and washed with AcOEt. Water was added to the combined filtrate and washing, and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **14a** (3.1 mg). The total yield of **14a** was 14.1 mg (98%).

1,3-Bis(3-formyl-6-nitroindol-1-yloxy)propane (14a) from 2a—A mixture of **2a** (30.5 mg, 0.15 mmol), K_2CO_3 (41.1 mg, 0.30 mmol), and 1,3-dibromopropane (14.9 mg, 0.07 mmol) in DMF (1.0 mL) was stirred at rt for 90 min. After addition of H_2O, the whole was made acidic with 6% HCl and resulting precipitates (**14a**, 22.4 mg) were collected by filtration and washed with AcOEt. Water was added to the combined filtrate and washing, and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **14a** (8.8 mg). The total yield of **14a** was 31.2 mg (93%).

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