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

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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, because of their unique 1-alkoxyindole structures 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 (5a, daikon-phytoalexin), brassicanal A, methyl 1-methoxyindole-3-carboxylate (wasabi-phytoalexin), and various kinds of analogs of wasabi-phytoalexin. 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 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). Although treatment of 5b with trimethylsilyl iodide was unsuccessful, BBr₃ was found to provide 2a. However, the yield was not improved to more than 40% under various examined reaction conditions.
Scheme 1

Table 1

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<th>Entry</th>
<th>DABCO (mol eq)</th>
<th>Reaction Temp. (°C)</th>
<th>Reaction Time (h)</th>
<th>2a Yield (%)</th>
<th>2b Yield (%)</th>
<th>5b Yield (%)</th>
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</table>

Figure 1

12: a) R = allyl, b) R = p-propargyl, c) R = CH₃CH₂CH₂Br, d) R = CH₂(C₆H₄)(CH₂)CH₂Br
13: a) R = allyl, b) R = p-propargyl, c) R = CH₃CH₂CH₂Br, d) R = CH₂(C₆H₄)(CH₂)CH₂Br
14: a) R¹ = H, R² = NO₂, b) R¹ = NO₂, R² = H
15: a) R¹ = H, R² = NO₂, R³ = 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 K₂CO₃ 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 BBr₃ 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. 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). It is interesting to note that when the above DABCO reaction was applied to daikon-phytoalexin (5a), 1-hydroxyindole-3-carbaldehyde³a (2c) and 1-{2-[4-(methyl)piperazin-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 nucleophilicity⁸ 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 K₂CO₃ 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 K₂CO₃ 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 ¹H-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 (SiO₂, 100–200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

**1-Benzylloxy-6-nitroindole (6) from 3** — A mixture of 3 (503.5 mg, 2.83 mmol), benzyl bromide (1.94 g, 11.3 mmol), and K₂CO₃ (1.56 g, 11.3 mmol) in MeOH (9.0 mL) was stirred at rt for 30 min. After addition of H₂O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ 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. ¹H-NMR (CDCl₃) 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 C₁₅H₁₂N₂O₃: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.25; H, 4.67; N, 10.25.

**1-Benzylloxy-6-nitroindole-3-carbaldehyde (7) from 6** — A mixture of POCl₃ (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 H₂O, the whole was made alkaline with saturated NaHCO₃ and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃ to give 7 (758.5 mg, 96%). 7: mp 154—156 °C (yellow powder, recrystallized from CHCl₃–hexane). IR (KBr): 1668, 1514, 1340 cm⁻¹. ¹H-NMR (CDCl₃) 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.*
Caled for C₁₆H₂₂N₂O₄: 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 BBr₃ in heptane (1M, 0.85 mL, 0.85 mmol) was added to a solution of 7 (50.2 mg, 0.17 mmol) in CHCl₃ (5.0 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at rt for 30 min. After addition of H₂O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃–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. ¹H-NMR (DMSO-d₆) 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). Anal. Caled for C₉H₆N₂O₄: 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 POCl₃ (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 H₂O, the whole was made alkaline with saturated NaHCO₃ and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with AcOEt–hexane (1:2, v/v) to give 5b (1.08 g, 94%). 5b: mp 180—182°C (yellow prisms, recrystallized from CHCl₃–hexane). IR (KBr): 1664, 1653, 1508, 1342 cm⁻¹. ¹H-NMR (CDCl₃) 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. Caled for C₁₀H₈N₂O₄: 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 BBr₃ — A solution of BBr₃ in heptane (1M, 4.63 mL, 4.63 mmol) was added to a solution of 5b (101.9 mg, 0.46 mmol) in CHCl₃ (10.0 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at rt for 20 h. After addition of H₂O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ successively with CHCl₃ and CHCl₃–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 H₂O, the whole was made acidic with 6% HCl and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃–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 H₂O₂, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃–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 Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–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. 

1H-NMR (DMSO-d₆) 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 D₂O). Anal. Calcd for C₉H₈NO₂: 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. 1H-NMR (CDCl₃) 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 C₁₆H₁₂N₅O₂: 287.1633. Found: 287.1636.

1-Methoxy-5-nitroindole-3-carbaldehyde (9b) from 8 — A mixture of POCl₃ (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 H₂O₂, the whole was made alkaline with 8% NaOH and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃ to give 9b (1.13 g, 97%). 9b: mp 183—185 °C (beige powder, recrystallized from CHCl₃). IR (KBr): 1672, 1657, 1525, 1329 cm⁻¹. 1H-NMR (CDCl₃) 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 C₁₉H₁₉N₂O₂: 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 H₂O₂, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (95:5, v/v) to give 9a (48.5 mg, 96%). 9a: mp 222—225 °C (decomp, yellow fine needles, recrystallized from MeOH–CHCl₃). IR (KBr): 1618, 1585, 1560, 1512, 1365, 1331, 1292 cm⁻¹. 1H-NMR (DMSO-d₆) 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 C₉H₆N₂O₂: 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$_2$CO$_3$ (295.2 mg, 2.1 mmol), and allyl bromide (642.5 mg, 5.3 mmol) in MeOH (10.5 mL) and H$_2$O (1 mL) was stirred at rt for 3 h. After addition of H$_2$O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na$_2$SO$_4$, 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$_2$O$_4$: 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$_2$CO$_3$ (269.2 mg, 1.95 mmol), and propargyl bromide (1.15 g, 9.65 mmol) in MeOH (6.5 mL) and H$_2$O (1.0 mL) was stirred at rt for 5 h. After addition of H$_2$O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na$_2$SO$_4$, 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}$H$_{10}$N$_2$O$_4$·1/8H$_2$O: 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$_2$CO$_3$ (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$_2$O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na$_2$SO$_4$, 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$_{15}$H$_9$BrN$_2$O$_4$: 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}$N$_2$O$_8$·1/2H$_2$O: C, 54.67; H,
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), K₂CO₃ (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 H₂O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ successively with CHCl₃−hexane (2:1, v/v) and CHCl₃ 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 CHCl₃−hexane). IR (KBr): 2918, 1672, 1512, 1336 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₃₁H₆₂N₂O₅Br: 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 CHCl₃−hexane). IR (KBr): 2924, 1662, 1512, 1336 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₃₈H₇₄N₄O₈: 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), K₂CO₃ (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 H₂O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ successively with CHCl₃ and CHCl₃−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 CHCl₃−hexane). IR (KBr): 1666, 1508, 1367, 1335 cm⁻¹. ¹H-NMR (CDCl₃) 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, ddt, 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 C₁₃H₁₀N₂O₄·1/8H₂O: 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), K₂CO₃ (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 H₂O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ successively with CHCl₃ and CHCl₃−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 CHCl₃-MeOH). IR (KBr): 3309, 2129, 1672, 1525, 1516, 1333 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₁₃H₈N₂O₄: 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-yloxy)propane (14b) from 9a — A mixture of 9a (50.4 mg, 0.24 mmol), K₂CO₃ (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 H₂O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃-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 CHCl₃-hexane). IR (KBr): 3101, 1662, 1522, 1329 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₁₂H₁₄N₂O₄Br: 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. ¹H-NMR (DMSO-d₆) 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 C₁₂H₁₆N₂O₄·1/2H₂O: C, 54.67; H, 3.71; N, 12.14. Found: C, 54.50; H, 3.55; N, 12.06.

1-(12-Bromododecxyloxy)-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), K₂CO₃ (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 H₂O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ successively with CHCl₃ and CHCl₃-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 CHCl₃-hexane). IR (KBr): 2927, 2850, 1653, 1525, 1329 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₂₁H₂₉N₂O₄Br·1/8H₂O: 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 CHCl₃-hexane). IR (KBr): 2931, 1655, 1523, 1329 cm⁻¹. ¹H-NMR (DMSO-d₆) 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.*
Calcld for C₉H₈N₄O₆·1/2H₂O: 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 K₂CO₃ (8.9 mg, 0.06 mmol) in DMF (1.0 mL) was stirred at rt for 90 min. After addition of H₂O, 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 Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃ 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), K₂CO₃ (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 H₂O, 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 Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1, v/v) to give 14a (8.8 mg). The total yield of 14a was 31.2 mg (93%).

REFERENCES


