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NUCLEOPHILIC SUBSTITUTION REACTION OF *N*-2-(1-HYDROXY-INDOL-3-YL)ETHYLINDOLE-3-ACETAMIDE AND -1-HYDROXYIN-DOLE-3-ACETAMIDE[1]

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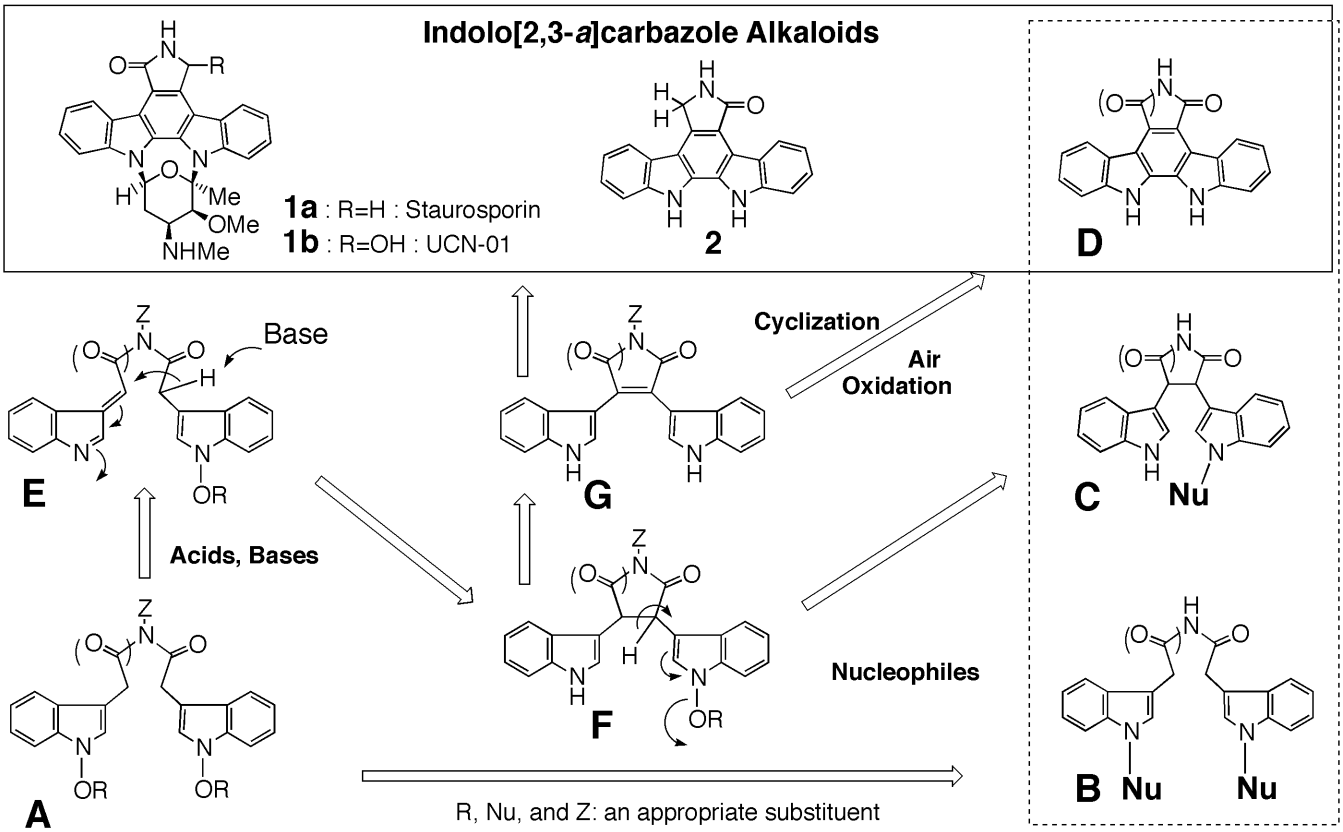
Abstract – Syntheses of *N*-2-(1-hydroxyindol-3-yl)ethyl-1-hydroxyindole-3-acetamide (**3a**) and -indole-3-acetamide (**4a**) are reported. They undergo nucleophilic substitution reaction at the 1-position upon reaction with indole in 85% formic acid to give new type compounds, *N*-2-[1-(indol-3-yl)indol-3-yl]ethylindole-3-acetamide (**13**), *N*-2-(indol-3-yl)ethyl- (**14**), and *N*-2-[1-(indol-3-yl)indol-3-yl]ethyl-1-(indol-3-yl)indole-3-acetamide (**15**).

We have disclosed that 1-alkoxytryptamines and -tryptophans undergo various kinds of new reactions thus far unprecedented[2] in indole chemistry. Nucleophilic substitution reaction at the 1-position on indole nucleus is one of them.[3]

In our ongoing project to develop new reactions characteristic to 1-hydroxy- and 1-alkoxyindole structures,[2] we have conceived the ideas as shown in general formula in Scheme 1. In the reaction of *N*-2-(1-alkoxyindol-3-yl)ethyl-1-alkoxyindole-3-acetamides (**A**) with appropriate reagents, we could obtain one of the possible products (**B**, **C**, and **D**) by controlling the reaction conditions and choosing substrate's structure (**A**). Type **B** product arises from direct substitution of **A** by nucleophiles at the 1-position of indole nucleus following the departure of 1-alkoxy group. Type **C** product would be provided through intermediates (**E** and **F**). If the intermediate (**G**) is generated from **F**, subsequent cyclization and air oxidation would lead it to **D**, which is a mother skeleton of indolo[2,3-*a*]carbazole alkaloids[4] such as staurosporin[4a] (**1a**), UCN-01[4b] (**1b**), **2**,[4c] and so on.

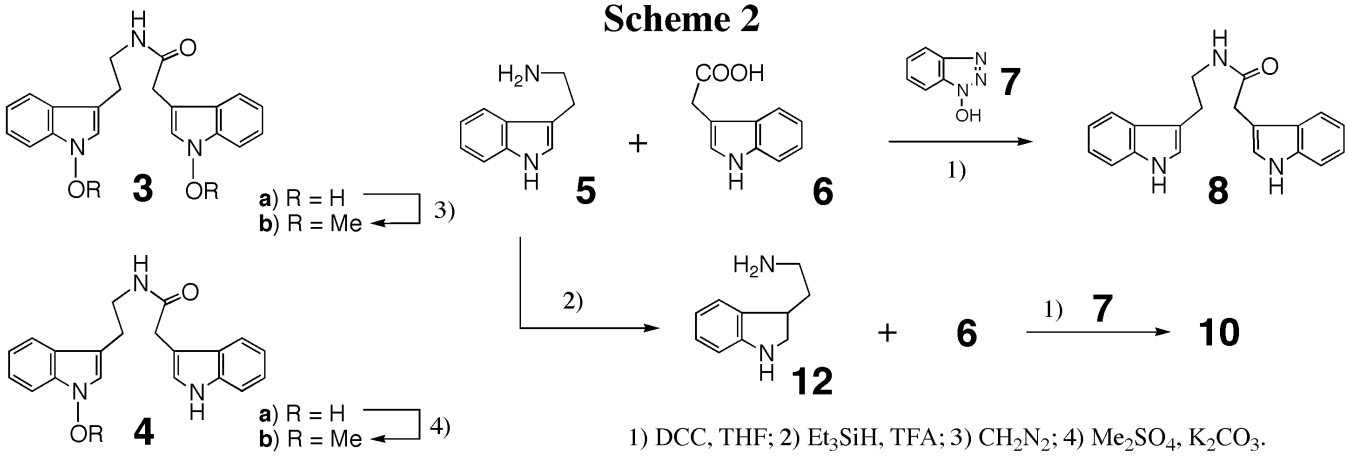
In order to verify the above ideas, we needed *N*-2-(1-hydroxyindol-3-yl)ethyl-1-hydroxyindole-3-acetamide (**3a**) and -indole-3-acetamide (**4a**) as substrates (Scheme 2). So, tryptamine (**5**) was reacted with indole-3-acetic acid (**6**) in the presence of DCC and 1-hydroxy-1,2,3-benzotriazole (**7**, HOBT) to

Scheme 1



provide *N*-2-(indol-3-yl)ethylindole-3-acetamide (**8**) in 81% yield. Then, the reduction of **8** with Et_3SiH[5] in CF_3COOH (TFA) was examined. Since the reduction with one mol eq. of Et_3SiH resulted in a significant amount of recovery, more than two mols eq. were used and the results are summarized in Table 1.

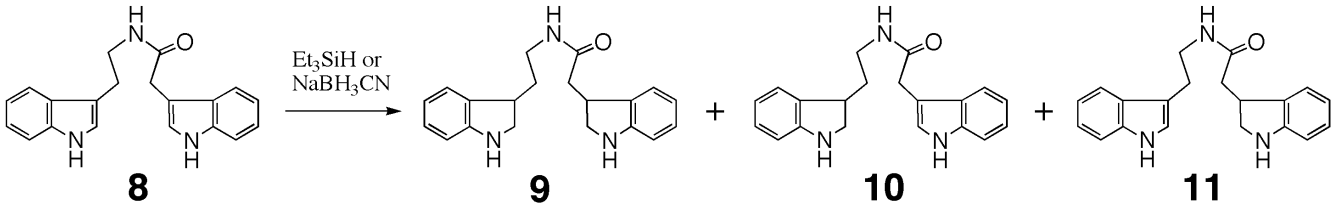
Scheme 2



As can be seen in Entries 1—5, the yield of *N*-2-(2,3-dihydroindol-3-yl)ethyl-2,3-dihydroindole-3-acetamide (**9**) varied depending on the amount of Et_3SiH, and finally under the reaction conditions described in Entry 4, **9** was obtained in 90% yield. In contrast $NaBH_3CN$ in AcOH (Entry 6) tends to favor the formation of *N*-2-(2,3-dihydroindol-3-yl)ethylindole-3-acetamide (**10**, 27%) together with a significant amount (13%) of *N*-2-(indol-3-yl)ethyl-2,3-dihydroindole-3-acetamide (**11**). It is interesting to

note that in the mixed solvent, AcOH–TFA (5:2, v/v), reduction with $NaBH_3CN$ resulted in the formation of **10** as a major product in 45% yield (Entry 7). Although regioselective reduction of the closely related compound, *N*-(indol-3-yl)methyl-*N*-methyltryptamine, was realized,[6] reaction conditions suitable for the selective reduction of **8** either to **10** or to **11** were not found.

Table 1. Reduction of *N*-2-(Indol-3-yl)ethylindole-3-acetamide



Entry	Reducing Agent (mol eq.)	Solvent	Reaction Temperature (°C)	Reaction Time (h)	Yield (%) of **9**	**10**	**11**	Recovery
1	Et_3SiH (2)	TFA	60	1.5	77	12	0	0
2	" (2.5)	"	60	1	75	10	0	0
3	" (3)	"	65	2	85	0	0	0
4	" (3)	"	65—75	4	90	0	0	0
5	" (5)	"	60	1	78	0	0	0
6	$NaBH_3CN$ (2)	AcOH	rt	3	9	27	13	38
7	"	AcOH–TFA (5:2, v/v)	rt	1.5	42	45	0	11

On the other hand, **10** was easily obtained when the following alternative route was employed (Scheme 2). Thus, 2,3-dihydrotryptamine (**12**) was prepared from tryptamine (**5**) by the reduction with Et_3SiH in TFA in 82% yield. Compound (**12**) was then condensed with indole-3-acetic acid (**6**) in the presence of DCC and **7** to afford **10** in 74% yield.

Table 2

9 —1)→ **3a**

Entry	Reaction Time (min)	Yield (%) of **3a**
1	60	0
2	30	19
3	15	44
4	10	51

Table 3

10 —1)→ **4a**

Entry	Reaction Time (min)	Yield (%) of **4a**
1	30	47
2	15	55

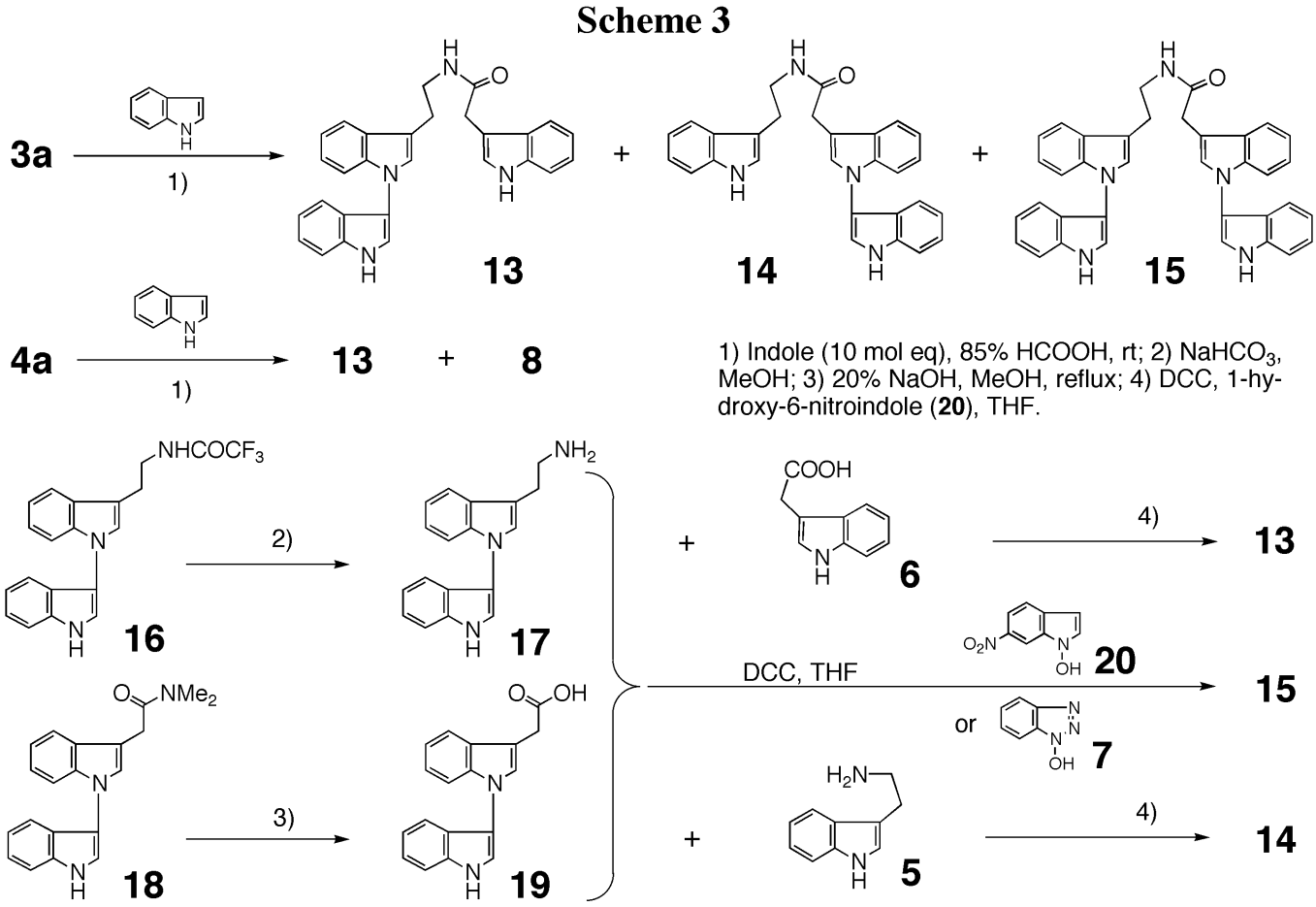
1) $Na_2WO_4 \cdot 2H_2O$ (0.2 mol eq), 30% H_2O_2 (10 mol eq), MeOH-H_2O (10:1, v/v), rt.

We next applied our 1-hydroxyindole synthetic method[2] to **9** using sodium tungstate and 30% hydrogen peroxide at room temperature. Generally speaking, long reaction time caused tar formation. As can be seen from Table 2, the yield of **3a** changed dramatically depending on the reaction time. The shorter the reaction time, the better the yield and finally **3a** was obtained in 51% yield under reaction conditions in Entry 4. Similar behavior was observed in the oxidation of **10** as shown in Table 3 and under reaction

conditions in Entry 2, **4a** was obtained in 55% yield. The structures of **3a** and **4a** were confirmed by leading them to the corresponding 1-methoxy derivatives, **3b** and **4b**, in 91 and 100% yields, respectively, by treating the former with CH_2N_2 and the latter with Me_2SO_4 and K_2CO_3.

With **3a** and **4a** in hand, we treated **3a** either with 85% formic acid (HCOOH) or with TFA. To the contrary to our expectation, regioselective nucleophilic introduction of hydroxy group into the 5-position,[2,7] generally observed in 1-hydroxytryptamine derivatives,[2,7] did not occur instead of forming a lot of spots, monitored on TLC, and tar. Employing indole as a nucleophile, we next examined the reaction of **3a** in 85% HCOOH and found that only the nucleophilic substitution reactions at the 1-position on indole nucleus took place giving such new type compounds as *N*-2-[1-(indol-3-yl)indol-3-yl]ethylindole-3-acetamide (**13**), *N*-2-(indol-3-yl)ethyl- (**14**), and *N*-2-[1-(indol-3-yl)indol-3-yl]ethyl-1-(indol-3-yl)indole-3-acetamide (**15**) in 7, 3, and 39% yields, respectively (Scheme 3). Under similar reaction conditions, **4a** provided **13** and **8** in the respective yields of 52 and 8%.

Scheme 3



The structure of **14** was determined by comparing it with the authentic sample prepared by condensing 1-(indol-3-yl)tryptamine (**17**) and 1-(indol-3-yl)indole-3-acetic acid (**19**). Compounds (**17** and **19**) were produced in 99 and 88% yields, respectively, by alkaline hydrolysis of *N*b-trifluoroacetyl-1-(indol-3-

yl)tryptamine (**16**) and *N*,*N*-dimethyl-1-(indol-3-yl)indole-3-acetamide (**18**), which were obtained according to our reported procedure.[3] When the condensation of **17** and **19** were carried out using **7** as an activating reagent for carboxylic acid, the yield of **15** was 65%. On the other hand, in case of utilizing 1-hydroxy-4-nitroindole[8] (**20**) instead of **7**, the yield of **15** was improved[2b] to 71%. Applying **20** as an activating reagent,[8] both condensations of **17** with **6** and **19** with **5** were successfully carried out to give authentic **13** and **14** in 88 and 61% yields, respectively.

In summary, we have found that 1-hydroxyindoles (**3a** and **4a**) undergo only the nucleophilic substitution reactions at the 1-position on indole nucleus upon reaction with indole in 85% HCOOH, resulting in the formation of type **B** compounds shown in Scheme 1. Treatments of **3a** and **4a** only with bases have been found to afford the recovery of starting materials. However, aiming at producing type **C** and **D** compounds, studies are now in progress employing *N*b-substituted tryptamines and indole-3-acetamides (type **A** compounds) as substrates.

EXPERIMENTAL

IR spectra were determined with a Shimadzu IR-420 or 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. PTLC was performed on Merck Kiesel-gel GF_{254} (Type 60)(SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

***N*-2-(Indol-3-yl)ethylindole-3-acetamide (8) from Tryptamine (5) and Indole-3-acetic Acid (6)** — A solution of **6** (1.00 g, 5.71 mmol) in anhydrous THF (10 mL) was added to a solution of DCC (1.41 g, 6.83 mmol) in anhydrous THF (16 mL). A solution of HOBT (926.0 mg, 6.85 mmol) in anhydrous THF (10 mL) was then added and the mixture was stirred at rt for 1 h. Thereafter, a solution of **5** (1.10 g, 6.87 mmol) in anhydrous THF (6 mL) was added and stirring was continued at rt for 4.5 h. Water was then added and the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). 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 **8** (1.47 g, 81%). **8**: mp 143.5—144.0°C (colorless powder, recrystallized from MeOH). IR (KBr): 3498, 1651, 1516 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.81 (2H, t, *J*=7.4 Hz), 3.32—3.35 (2H, m, collapsed to t, *J*=7.4 Hz, on addition of D_2O), 3.50 (2H, s), 6.95 (1H, dt, *J*=1.0, 7.5 Hz), 6.96 (1H, dt, *J*=1.1, 7.6 Hz), 7.05 (1H, dt, *J*=1.0, 7.5 Hz), 7.06 (1H, dt, *J*=1.1, 7.6 Hz), 7.08 (1H, d, *J*=2.2 Hz, collapsed to s on addition of D_2O), 7.16 (1H, d, *J*=2.2 Hz, collapsed to s on addition of D_2O), 7.32 (1H, dd, *J*=7.5, 1.0 Hz), 7.34 (1H, dd, *J*=7.6, 1.1 Hz), 7.51 (1H, d, *J*=7.5 Hz), 7.52 (1H, d, *J*=7.6 Hz), 7.92 (1H, br t, *J*=5.5 Hz, disappeared on addition of D_2O), 10.76 (1H, br s, disappeared on addition of D_2O), 10.83 (1H, br s, disappeared on addition of D_2O). MS *m/z*:

317 (M^+). *Anal*. Calcd for $C_{20}H_{19}N_3O \cdot 1/8H_2O$: C, 75.15; H, 6.07; N, 13.15. Found: C, 74.96; H, 6.04; N, 13.02.

***N*-2-(2,3-Dihydroindol-3-yl)ethylindole-3-acetamide (10), *N*-2-(2,3-Dihydroindol-3-yl)ethyl- (9), and *N*-2-(Indol-3-yl)ethyl-2,3-dihydroindole-3-acetamide (11) from 8 — [Entry 1]** Et_3SiH (0.05 mL, 0.32 mmol) was added to a solution of **8** (50.5 mg, 0.16 mmol) in TFA (1.6 mL) and the mixture was stirred at 60°C for 1.5 h. After evaporation of the solvent, the whole was made alkaline by adding 8% NaOH under ice cooling and extracted with $CHCl_3$–MeOH (95:5, v/v). 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 AcOEt–MeOH (99:1, v/v) to give **9** (38.9 mg, 77%) and **10** (11.9 mg, 12%). **9**: pale yellow gum. IR (film): 3319, 2929, 2854, 1653, 1606, 1487, 1464, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.20 (1H, m, disappeared on addition of D_2O), 1.71—1.78 (1H, m), 1.92—1.99 (1H, m), 2.34—2.54 (1H, m, disappeared on addition of D_2O), 2.35—2.41 (1H, m), 2.47—2.51 (1H, m), 3.20—3.42 (5H, m), 3.67 (1H, t, *J*=8.5 Hz), 3.69 (1H, t, *J*=8.5 Hz), 3.72—3.76 (1H, m), 5.67 (1H, br s, disappeared on addition of D_2O), 6.63 (2H, d, *J*=7.8 Hz), 6.68—6.74 (2H, m), 7.01—7.09 (4H, m). HRMS: Calcd for $C_{20}H_{23}N_3O$: 321.1841. Found: 321.1842. **10**: pale yellow gum. IR (film): 3286, 1655, 1525, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.90 (1H, br s, disappeared on addition of D_2O), 1.58—1.65 (1H, m), 1.79—1.86 (1H, m), 3.04 (1H, dd, *J*=8.9, 6.2 Hz), 3.14—3.19 (2H, m), 3.29—3.36 (1H, m), 3.51 (1H, t, *J*=8.9 Hz), 3.73 (2H, s), 5.88 (1H, br s, disappeared on addition of D_2O), 6.54 (1H, d, *J*=7.2 Hz), 6.66 (1H, dt, *J*=1.0, 7.2 Hz), 6.96—7.00 (2H, m), 7.13 (1H, d, *J*=2.5 Hz, collapsed to s on addition of D_2O), 7.15 (1H, ddd, *J*=8.1, 7.2, 1.0 Hz), 7.24 (1H, ddd, *J*=8.1, 7.2, 1.0 Hz), 7.41 (1H, dt, *J*=8.1, 1.0 Hz), 7.56 (1H, dd, *J*=8.1, 1.0 Hz), 8.25 (1H, br s, disappeared on addition of D_2O). HRMS: Calcd for $C_{20}H_{21}N_3O$: 319.1685. Found: 319.1681.

[Entry 4] Et_3SiH (0.73 mL, 4.49 mmol) was added to a solution of **8** (473.9 mg, 1.50 mmol) in TFA (5 mL) and the mixture was stirred at 65—75°C for 4 h. After the same work-up as described in Entry 1, the resultant residue was column-chromatographed on SiO_2 with AcOEt–MeOH (95:5, v/v) to give **9** (429.4 mg, 90%).

[Entry 6] $NaBH_3CN$ (95%, 20.9 mg, 0.32 mmol) was added to a solution of **8** (50.0 mg, 0.16 mmol) in AcOH (1.5 mL) at 0°C and the mixture was stirred at rt for 3 h. After addition of H_2O, the whole was made alkaline by adding 8% NaOH under ice cooling and extracted with $CHCl_3$–MeOH (95:5, v/v). After the same work-up as described in Entry 1, the resultant residue was subjected to PTLC on SiO_2 with AcOEt–MeOH (97:3, v/v) as a developing solvent. Extractions of four bands having an *Rf* value of 0.84—0.72, 0.68—0.61, 0.58—0.38, and 0.33—0.23 with AcOEt–MeOH (95:5, v/v) gave unreacted **8** (19.0 mg, 38%), **10** (13.8 mg, 27%), **11** (6.6 mg, 13%), and **9** (4.7 mg, 9%), respectively. **11**: pale yellow gum. IR (film): 3400, 3288 (br), 1651 (br), 1531, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, br s,

disappeared on addition of D_2O), 2.35 (1H, dd, *J*=14.4, 7.9 Hz), 2.46 (1H, dd, *J*=14.4, 6.0 Hz), 2.91—3.00 (2H, m), 3.20 (1H, dd, *J*=8.6, 5.0 Hz), 3.56—3.67 (2H, m), 3.70 (1H, t, *J*=8.6 Hz), 3.70—3.77 (1H, m), 5.49 (1H, br t, disappeared on addition of D_2O), 6.61 (1H, d, *J*=7.6 Hz), 6.67 (1H, dt, *J*=0.9, 7.6 Hz), 6.97 (1H, d, *J*=2.4 Hz, collapsed to s on addition of D_2O), 7.02 (1H, t, *J*=7.6 Hz), 7.05 (1H, t, *J*=7.6 Hz), 7.12 (1H, dt, *J*=0.9, 7.6 Hz), 7.20 (1H, dt, *J*=0.9, 7.6 Hz), 7.36 (1H, d, *J*=7.6 Hz), 7.57 (1H, d, *J*=7.6 Hz), 8.05 (1H, br s, disappeared on addition of D_2O). HRMS: Calcd for $C_{20}H_{21}N_3O$: 319.1685. Found: 319.1682.

[Entry 7] $NaBH_3CN$ (95%, 20.9 mg, 0.32 mmol) was added to a solution of **8** (50.0 mg, 0.16 mmol) in AcOH (1 mL) and TFA (0.4 mL) at 0°C and the mixture was stirred at rt for 1.5 h. After the same work-up as described in Entry 1, the resultant residue was subjected to PTLC on SiO_2 developing three times with AcOEt–hexane (10:1, v/v). Extractions of three bands having an *Rf* value of 0.74—0.69, 0.59—0.51, and 0.45—0.36 with AcOEt–MeOH (95:5, v/v) gave unreacted **8** (5.4 mg, 11%), **10** (22.7 mg, 45%), and **9** (21.0 mg, 42%), respectively.

2,3-Dihydrotryptamine (12) from 5 — Et_3SiH (0.15 mL, 0.94 mmol) was added to a solution of **5** (100.0 mg, 0.63 mmol) in TFA (1.0 mL) and the mixture was stirred at 68—71°C for 4 h. After evaporation of the solvent, the whole was made alkaline by adding 8% NaOH under ice cooling and extracted with $CHCl_3$–MeOH (95:5, v/v). 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–28% NH_3 (46:5:0.5, v/v) to give **12** (83.0 mg, 83%). **12**: pale yellow gum. IR (film): 3367, 1606, 1568, 1487, 1358, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.03 (3H, br s, disappeared on addition of D_2O), 1.65—1.77 (1H, m), 1.98 (1H, dtd, *J*=13.3, 7.6, 5.5 Hz), 2.81 (2H, t, *J*=7.6 Hz), 3.22 (1H, dd, *J*=8.7, 7.5 Hz), 3.31—3.37 (1H, m), 3.69 (1H, t, *J*=8.7 Hz), 6.64 (1H, d, *J*=7.5 Hz), 6.72 (1H, dt, *J*=0.8, 7.5 Hz), 7.02 (1H, t, *J*=7.5 Hz), 7.08 (1H, d, *J*=7.5 Hz). HRMS: Calcd for $C_{10}H_{14}N_2$: 162.1157. Found: 162.1163.

10 from 6 and 12 — In the same procedure and work-up as described in the preparation of **8**, **6** (58.4 mg, 0.33 mmol) in anhydrous THF (0.6 mL), DCC (82.6 mg, 0.40 mmol) in anhydrous THF (0.8 mL), HOBT (54.1 mg, 0.40 mmol) in anhydrous THF (1.4 mL), and **12** (64.8 mg, 0.41 mmol) in anhydrous THF (1.5 mL) were used. Column-chromatography was performed with $CHCl_3$–MeOH–28% NH_3 (46:5:0.5, v/v) to give **10** (79.2 mg, 79%).

***N*-2-(1-Hydroxyindol-3-yl)ethyl-1-hydroxyindole-3-acetamide (3a) from 9** — A solution of $Na_2WO_4{\cdot}2H_2O$ (48.2 mg, 0.15 mmol) in H_2O (1.0 mL) was added to a solution of **9** (124.7 mg, 0.73 mmol) in MeOH (6.0 mL). A solution of 30% H_2O_2 (828.9 mg, 21.9 mmol) in MeOH (4.0 mL) was then added at 0°C and the mixture was stirred at rt for 10 min. Water was added 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 an oil, which was column-chromatographed on SiO_2 successively with AcOEt–hexane (1:1, v/v) and AcOEt to give **3a** (130.6 mg, 51%). **3a**: mp 191.0—192.0°C (decomp, colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3363, 3199, 1610, 1550 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.79 (2H, t, *J*=7.5 Hz), 3.26—3.40 [2H, appeared at 3.39 (2H, t, *J*=7.5 Hz) on addition of D_2O], 3.48 (2H, s), 6.97 (1H, t, *J*=7.8 Hz), 6.97 (1H, t, *J*=7.7 Hz), 7.12 (1H, t, *J*=7.8 Hz), 7.12 (1H, t, *J*=7.7 Hz), 7.21 (1H, s), 7.25 (1H, s), 7.31 (1H, d, *J*=7.8 Hz), 7.32 (1H, d, *J*=7.7 Hz), 7.51 (1H, d, *J*=7.8 Hz), 7.52 (1H, d, *J*=7.7 Hz), 8.01 (1H, br t, *J*=5.4 Hz, disappeared on addition of D_2O), 11.03 (2H, br s, disappeared on addition of D_2O). HRMS (FAB$^+$): Calcd for $C_{20}H_{20}N_3O_3$ (MH^+): 350.1504. Found: 350.1504. *Anal.* Calcd for $C_{20}H_{19}N_3O_3 \cdot 1/2H_2O$: C, 67.02; H, 5.63; N, 11.72. Found: C, 66.81; H, 5.42; N, 11.60.

***N*-2-(1-Methoxyindol-3-yl)ethyl-1-methoxyindole-3-acetamide (3b) from 3a** — Excess CH_2N_2 in Et_2O was added to a solution of **3a** (4.6 mg, 0.017 mmol) in MeOH (1.0 mL) and the mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (2:1, v/v) to give **3b** (4.5 mg, 91%). **3b**: colorless gum. IR (film): 3408, 3298, 2935, 1647, 1523 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (2H, t, *J*=6.5 Hz), 3.48 (2H, q, *J*=6.5 Hz, collapsed to t on addition of D_2O), 3.65 (2H, s), 3.93 (3H, s), 4.01 (3H, s), 5.71 (1H, br s, disappeared on addition of D_2O), 6.56 (1H, s), 7.02 (1H, s), 7.06 (1H, dt, *J*=0.9, 7.8 Hz), 7.11 (1H, dt, *J*=0.9, 7.8 Hz), 7.21 (1H, dt, *J*=0.9, 7.8 Hz), 7.27 (1H, dt, *J*=0.9, 7.8 Hz), 7.34 (1H, d, *J*=7.8 Hz), 7.43 (1H, d, *J*=7.8 Hz), 7.45 (1H, d, *J*=7.8 Hz), 7.46 (1H, d, *J*=7.8 Hz). HRMS: Calcd for $C_{22}H_{23}N_3O_3$: 377.1739. Found: 377.1747.

***N*-2-(1-Hydroxyindol-3-yl)ethylindole-3-acetamide (4a) from 10** — In the same procedure and work-up as described in the preparation of **3a**, $Na_2WO_4 \cdot 2H_2O$ (93.5 mg, 0.283 mmol) in H_2O (2.0 mL), **10** (452.0 mg, 1.42 mmol) in MeOH (11 mL), 30% H_2O_2 (1.61 g, 42.6 mmol) in MeOH (9.0 mL) were used. Column-chromatography was performed with $CHCl_3$–MeOH–28% NH_3 (46:1:0.1, v/v) to give **4a** (258.6 mg, 55%). **4a**: colorless viscous gum. IR (film): 3400, 1624, 1537, 741 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.79 (2H, t, *J*=7.4 Hz), 3.31—3.33 [2H, m, appeared at 3.33 (2H, t, *J*=7.4 Hz) on addition of D_2O], 3.50 (2H, s), 6.96 (1H, t, *J*=7.8 Hz), 6.97 (1H, t, *J*=7.7 Hz), 7.06 (1H, t, *J*=7.8 Hz), 7.12 (1H, t, *J*=7.7 Hz), 7.16 (1H, d, *J*=2.2 Hz, collapsed to s on addition of D_2O), 7.21 (1H, s), 7.32 (1H, d, *J*=7.8 Hz), 7.34 (1H, d, *J*=7.7 Hz), 7.52 (1H, d, *J*=7.8 Hz), 7.52 (1H, d, *J*=7.7 Hz), 7.94 (1H, br t, *J*=5.6 Hz, disappeared on addition of D_2O), 10.83 (1H, br s, disappeared on addition of D_2O), 11.00 (1H, br s, disappeared on addition of D_2O). HRMS: Calcd for $C_{20}H_{19}N_3O_2$: 333.1477. Found: 333.1491.

***N*-2-(1-Methoxyindol-3-yl)ethylindole-3-acetamide (4b) from 4a** — K_2CO_3 (23.0 mg, 0.17 mmol) and Me_2SO_4 (0.01 mL, 0.10 mmol) were added to a solution of **4a** (11.1 mg, 0.03 mmol) in MeOH (0.5 mL) and the mixture was stirred at rt for 1 h. Water was added 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 an oil,

which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:5:0.5, v/v) to give **4b** (11.5 mg, 100%). **4b**: pale yellow oil. IR (film): 3402, 3278, 2927, 1653, 1525, 741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (2H, t, *J*=6.4 Hz), 3.47 (2H, q, *J*=6.4 Hz, collapsed to t on addition of D_2O), 3.69 (2H, s), 3.91 (3H, s), 5.73 (1H, br t, *J*=6.4 Hz, disappeared on addition of D_2O), 6.52 (1H, s), 6.94 (1H, d, *J*=2.4 Hz, collapsed to s on addition of D_2O), 7.05 (1H, dt, *J*=0.9, 7.7 Hz), 7.12 (1H, dt, *J*=0.9, 7.7 Hz), 7.21 (1H, dt, *J*=0.9, 7.7 Hz), 7.23 (1H, dt, *J*=0.9, 7.7 Hz), 7.34 (1H, d, *J*=7.7 Hz), 7.38 (1H, d, *J*=7.7 Hz), 7.44 (1H, d, *J*=7.7 Hz), 7.50 (1H, d, *J*=7.7 Hz), 8.13 (1H, br s, disappeared on addition of D_2O). HRMS: Calcd for $C_{21}H_{21}N_3O_2$: 347.1634. Found: 347.1633.

***N*-2-[1-(Indol-3-yl)indol-3-yl]ethylindole-3-acetamide (13), *N*-2-(Indol-3-yl)ethyl- (14), and *N*-2-[1-(Indol-3-yl)indol-3-yl]ethyl-1-(indol-3-yl)indole-3-acetamide (15) from 3a** — A solution of **3a** (50.6 mg, 0.15 mmol) and indole (169.9 mg, 1.45 mmol) in 85% HCOOH (6.0 mL) was stirred at rt for 3 h. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 successively with AcOEt–hexane (1:1, v/v) and $CHCl_3$–MeOH–28% NH_3 (46:1:0.1, v/v) to give **15** (30.9 mg, 39%), **14** (2.0 mg, 3%), and **13** (4.4 mg, 7%) in the order of elution. **13:** pale yellow oil. IR (film): 3408, 3276, 1651, 1527, 1458, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.87 (2H, t, *J*=6.2 Hz), 3.55 (2H, q, *J*=6.2 Hz, collapsed to t on addition of D_2O), 3.68 (2H, s), 5.82 (1H, br t, *J*=6.2 Hz, disappeared on addition of D_2O), 6.31 (1H, s), 6.83 (1H, d, *J*=2.4 Hz, collapsed to s on addition of D_2O), 6.85—6.88 (1H, m), 6.99—7.05 (2H, m), 7.10 (1H, dt, *J*=1.7, 7.2 Hz), 7.14 (1H, dt, *J*=1.7, 7.2 Hz), 7.15 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O), 7.17 (1H, dd, *J*=7.2, 1.7 Hz), 7.23 (1H, ddd, *J*=7.2, 1.7, 0.8 Hz), 7.32 (1H, d, *J*=7.2 Hz), 7.33 (1H, dt, *J*=1.7, 7.2 Hz), 7.49 (1H, ddd, *J*=7.2, 1.7, 0.8 Hz), 7.53 (1H, d, *J*=7.2 Hz), 7.54 (1H, dt, *J*=1.7, 7.2 Hz), 7.65 (1H, br s, disappeared on addition of D_2O), 8.43 (1H, br s, disappeared on addition of D_2O). HRMS (FAB^+): Calcd for $C_{28}H_{25}N_4O$ (MH^+): 433.2028. Found: 433.2027. **14:** pale yellow gum. IR (film): 3402, 3278, 1651, 1525, 741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (2H, t, *J*=6.1 Hz), 3.55 (2H, q, *J*=6.1 Hz), 3.76 (2H, s), 5.85 (1H, br t, *J*=6.1 Hz), 6.34 (1H, d, *J*=2.2 Hz, collapsed to s on addition of D_2O), 7.04 (1H, s), 7.04 (1H, dt, *J*=1.0, 7.6 Hz), 7.11 (1H, dt, *J*=1.0, 7.6 Hz), 7.12 (1H, dt, *J*=1.0, 7.6 Hz), 7.17 (1H, dt, *J*=1.0, 7.6 Hz), 7.18 (1H, dd, *J*=7.6, 1.0 Hz), 7.20 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O), 7.22 (1H, dt, *J*=1.0, 7.6 Hz), 7.27 (1H, dd, *J*=7.6, 1.0 Hz), 7.30 (1H, dt, *J*=1.0, 7.6 Hz), 7.33 (1H, dt, *J*=7.6, 1.0 Hz), 7.48 (1H, d, *J*=7.6 Hz), 7.49 (1H, d, *J*=7.6 Hz), 7.57 (1H, dt, *J*=7.6, 1.0 Hz), 7.58 (1H, s, disappeared on addition of D_2O), 8.49 (1H, br s, disappeared on addition of D_2O). HRMS: Calcd for $C_{28}H_{24}N_4O$: 432.1950. Found: 432.1969. **15**: pale yellow gum. IR (film): 3398, 3269, 1651, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (2H, t, *J*=6.3 Hz), 3.63 (2H, q, *J*=6.3 Hz, collapsed to t on addition of D_2O), 3.80 (2H, s), 6.01 (1H, br t, *J*=6.3 Hz, disappeared on addition of D_2O), 6.75 (1H, s), 6.99 (1H, d, *J*=2.4 Hz, collapsed to s on addition of

D_2O), 7.00 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O), 7.03—7.16 (8H, m), 7.21—7.24 (1H, m), 7.25—7.29 (2H, m), 7.32 (1H, d, *J*=7.7 Hz), 7.34 (1H, d, *J*=7.7 Hz), 7.42 (1H, d, *J*=7.7 Hz), 7.44 (1H, d, *J*=7.7 Hz), 7.56—7.60 (2H, m), 8.10 (1H, br s, disappeared on addition of D_2O), 8.15 (1H, br s, disappeared on addition of D_2O). HRMS (FAB^+): Calcd for $C_{36}H_{30}N_5O$ (MH^+): 548.2451. Found: 548.2437.

13 and 8 from 4a — A solution of **4a** (14.6 mg, 0.04 mmol) and indole (51.4 mg, 0.44 mmol) in 85% HCOOH (1.0 mL) was stirred at rt for 3 h. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). 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–28% NH_3 (46:1:0.1, v/v) to give **13** (9.9 mg, 52%) and **8** (1.1 mg, 8%).

1-(Indol-3-yl)tryptamine (17) from *N*b-Trifluoroacetyl-1-(indol-3-yl)tryptamine (16) — Sat. aq. $NaHCO_3$ (3.0 mL, 3.15 mmol) was added to a solution of **16** (53.1 mg, 0.14 mmol) in MeOH (6.0 mL) and the mixture was stirred at 60°C for 8 h. After addition of H_2O, the whole was extracted with $CHCl_3$. 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–28% NH_3 (46:5:0.5, v/v) to give **17** (39.2 mg, 99%). **17**: mp 175.0—177.0°C (decomp, pale yellow plates, recrystallized from $CHCl_3$). IR (KBr): 3350, 3284, 1585, 1565, 1454, 1238, 746, 737 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (2H, br s, disappeared on addition of D_2O), 3.00 (2H, t, *J*= 6.6 Hz), 3.11 (2H, t, *J*= 6.6 Hz), 7.11—7.20 (3H, m), 7.21 (1H, s), 7.29 (1H, ddd, *J*=8.2, 7.1, 1.1 Hz), 7.31—7.35 (1H, m), 7.38 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O), 7.44—7.49 (2H, m), 7.67—7.70 (1H, m), 8.30 (1H, br s, disappeared on addition of D_2O). MS *m/z* : 275 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_3 \cdot 1/4H_2O$: C, 77.25; H, 6.12; N, 15.02. Found: C, 77.34; H, 6.10; N, 14.94.

1-(Indol-3-yl)indole-3-acetic Acid (19) from *N*,*N*-Dimethyl-1-(indol-3-yl)indole-3-acetamide (18) — 40% NaOH (7.0 mL) was added to a solution of **18** (55.8 mg, 0.18 mmol) in MeOH (7.0 mL) and the mixture was refluxed for 16 h with stirring. After addition of H_2O, the whole was extracted with $CHCl_3$. 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 (90:10, v/v) to give **19** (44.7 mg, 88%). **19**: mp 172.0—173.0°C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3361, 1698, 1246, 1217, 742 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.76 (2H, s), 7.05 (1H, t, *J*=7.6 Hz), 7.09 (1H, dt, *J*=1.1, 7.6 Hz), 7.13 (1H, dt, *J*=1.1, 7.6 Hz), 7.20 (1H, t, *J*=7.6 Hz), 7.23 (1H, d, *J*=7.6 Hz), 7.28 (1H, d, *J*=7.6 Hz), 7.45 (1H, s), 7.51 (1H, d, *J*=7.6 Hz), 7.62 (1H, d, *J*=7.6 Hz), 7.68 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O), 11.40 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 290 (M^+). *Anal.* Calcd for $C_{18}H_{14}N_2O_2 \cdot 1/4H_2O$: C, 73.33; H, 4.96; N, 9.50. Found: C, 73.29; H, 4.84; N, 9.52.

13 from 6 and 17 — A solution of **6** (10.0 mg, 0.057 mmol) in anhydrous THF (1.0 mL) was added to

a solution of DCC (14.1 mg, 0.07 mmol) in anhydrous THF (1.0 mL). A solution of 1-hydroxy-6-nitroindole (12.2 mg, 0.07 mmol) in anhydrous THF (1.3 mL) was then added and the mixture was stirred at rt for 1 h. Thereafter, a solution of **17** (18.8 mg, 0.07 mmol) in anhydrous THF (1.2 mL) was added and stirring was continued at rt for 2 h. The precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to leave a solid which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:1:0.1, v/v) to give **13** (21.6 mg, 88%).

14 from 5 and 19 — In the same procedure and work-up as described in the preparation of **13**, **19** (20.9 mg, 0.07 mmol) in anhydrous THF (1.5 mL), DCC (17.8 mg, 0.09 mmol) in anhydrous THF (1.5 mL), 1-hydroxy-6-nitroindole (**20**, 15.4 mg, 0.09 mmol) in anhydrous THF (1.0 mL), and **5** (13.8 mg, 0.09 mmol) in anhydrous THF (1.0 mL) were used to give **14** (18.9 mg, 61%).

15 from 17 and 19 — In the same procedure and work-up as described in the preparation of **13**, **19** (10.3 mg, 0.04 mmol) in anhydrous THF (1.0 mL), DCC (8.8 mg, 0.04 mmol) in anhydrous THF (1.0 mL), 1-hydroxy-6-nitroindole (7.6 mg, 0.04 mmol) in anhydrous THF (1.0 mL), and **17** (11.7 mg, 0.04 mmol) in anhydrous THF (1.0 mL) were used. Column-chromatography was performed with $CHCl_3$–MeOH–28% NH_3 (46:0.5:0.05, v/v) to give **15** (13.8 mg, 71%).

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