Synthesis of Bromoindole Alkaloids from *Laurencia brongniartii*

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A regioselective synthesis of *N*-carbomethoxy-2,3,5-tribromoindole (**6**) via a sequential one-pot bromination−aromatization−bromination of *N*-carbomethoxyindoline (**2**) is described. The process for the transformation of **2** into **6** permitted the isolation of stable reaction intermediates *N*-carbomethoxy-5-bromoindoline (**3**), *N*-carbomethoxy-5-bromoindole (**4**), and *N*-carbomethoxy-3,5-dibromoindole (**5**). Compound **6** was used to complete the total synthesis of the natural products **1b** and **1c**. In addition, bromination of *N*-carbomethoxyindole (**11**) afforded *N*-carbomethoxy-2,3,6-tribromoindole (**13**), from which the natural product **1a** was synthesized.

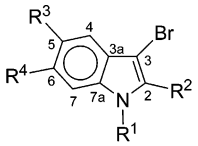
A wide variety of naturally occurring, biologically active brominated indole alkaloids have been isolated from marine invertebrates, including bryozoans, coelenterates, sponges, and tunicates.[1] Examples of these compounds are polybrominated indoles **1a**−**e** (Scheme 1). Compounds **1a**−**d** were isolated from *Laurencia brongniartii*,[2a] with **1c** and **1d** showing a wide-spectrum activity against Gram-positive bacteria.[2b] *N*-Methyl-2,3,5-tribromoindole (**1b**) has also been isolated from *Nitophyllum marginata*[2c] and *Aplysia dactylomela*,[2d] *N*-methyl-2,3,5,6-tetrabromoindole (**1d**) from *Ophiocoma erinaceus*,[2e] and 6-bromoindole (**1e**) from the palauan ascidian *Distaplia regina*.[2f]

Due to the potential of these compounds to develop antifungal and antibacterial agents,[3e] we report herein a general and simple method for the preparation of indoles **1a**−**c**. Although bromination of simple indoles with excess bromine has been extensively studied,[3a−f] comparatively little attention has been devoted to the reaction of indolines with bromine.[4] In this work we describe the high-yielding, regioselective bromination of *N*-carbomethoxyindoline (**2**) and *N*-carbomethoxyindole (**11**), employing excess Br_2 in CCl_4, which allowed the incorporation of bromine atoms at C-2, C-3, and C-5 and at C-2, C-3, and C-6, respectively.

Results and Discussion

We recently described a highly regioselective bromination reaction for the preparation of an indolylbromomalonate[5] using excess bromine in CCl_4. In the course of our studies toward the synthesis of biologically active indole derivatives, we sought a simple route to prepare polybrominated indoles **1a**−**d**. Although syntheses of **1a**, **1c**, and **1d** have been achieved,[3a,b,6] compound **1b** has not yet been synthesized. We thus aimed to develop a practical method to regioselectively introduce several bromine atoms into the indole nucleus, as well as the first total synthesis of *N*-methyl-2,3,5-tribromoindole (**1b**) through bromination of *N*-carbomethoxy-2,3-dihydroindole (**2**) (Scheme 2). We found that bromination of **2** in the presence of 8 equiv of Br_2 in CCl_4 afforded **6** in 96% yield. Although only 3 equiv of Br_2 are formally needed to achieve tribromination of the indole system, experiments containing less than 8 equiv of bromine gave mixtures of products and much lower yields of tribromoindole **6**. We also observed this trend in other reactions (see below) in which excess bromine gave consistently better yields and faster reactions. Deprotection of **6** was accomplished with NaH/MeOH under reflux to afford **7** in 90% yield. Finally, methylation of **7** gave natural product **1b** in 95% yield. The overall yield of **1b**, in three steps from **2**, was 83%. Bromination of **6** even in the presence of 16 equiv of Br_2 in CCl_4 was very slow at room temperature. The ^{1}H NMR spectrum of the reaction mixture showed, after two weeks, only a 25% conversion of **6** into **8**. Changing the solvent to AcOH[3a,b] and adding 8 equiv of Br_2 afforded **8** in 96% yield after 24 h at room temperature. Deprotection of **8** with NaH/MeOH afforded the natural product **1c** in 91% yield.

Scheme 1



1a: R^1 = Me, R^2 = R^4 = Br, R^3 = H
1b: R^1 = Me, R^2 = R^3 = Br, R^4 = H
1c: R^1 = H, R^2 = R^3 = R^4 = Br
1d: R^1 = Me, R^2 = R^3 = R^4 = Br
1e: R^1 = R^2 = R^3 = H, R^4 = Br

In order to gain information about the transformation process of **2** into **6**, indoline **2** was treated with excess bromine (8 equiv) and the reaction was monitored by ^{1}H NMR analysis. All the intermediate compounds were isolated and characterized spectroscopically. Thus, when **2** was reacted with bromine for 6 min, followed by treatment with a 10% aqueous solution of $NaHSO_3$ to quench excess unreacted bromine, the ^{1}H NMR spectrum of the mixture revealed quantitative transformation of **2** into 5-bromo derivative **3**. This regioselective bromination at C-5 is in agreement with the reactivity of a carbonyl-protected aniline.[7] The position of the bromine atom at C-5 was confirmed by X-ray diffraction of **3**, as shown in Figure 1. When **2** was reacted with bromine (8 equiv) for 1.5 h, the ^{1}H and ^{13}C NMR spectra of the crude material showed the presence of resonances characteristic for 3,5-dibromoindole **5**, which was formed by sequential bromination of the benzene ring, oxidation of the indoline to an indole, and C-3 bromination of the resulting indole. The ^{1}H NMR signals corresponding to 2,3,5-tribromoindole **6** appear after reaction for 2.5−4.5 h. Using these reaction conditions, 5-bromoindole **4** was not detected, probably due to its fast bromination under conditions of excess bromine. However, when indoline **3** was treated with only 1 equiv of Br_2 in CCl_4 for 2 h, a mixture of **4** and **5** (4:1) was obtained. Although a large number of methodologies for indolization of indolines have been

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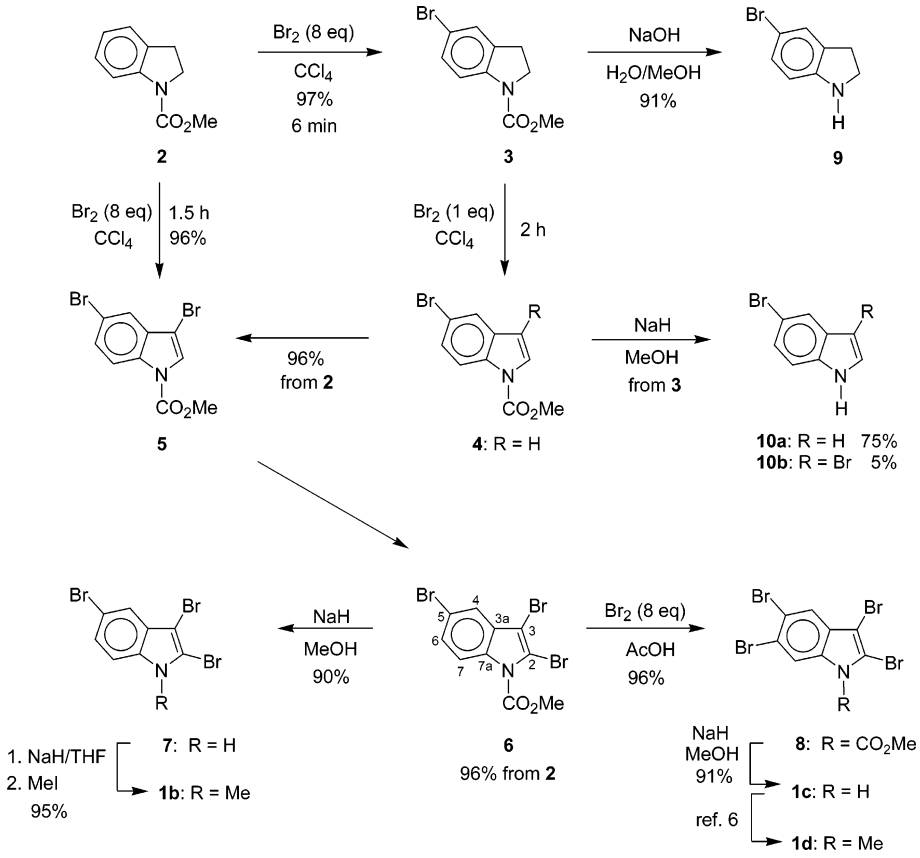
Scheme 2



described,[8] the use of bromine to carry out this transformation has not been studied. The indolization of **3** to afford **4** could occur either by bromination of **3** at the benzylic position and subsequent elimination of HBr or by bromine-induced oxidation of the *N*−C-2 amine bond to an iminum N═C-2 ion,[4e,9] followed by loss of H^+ from C-3 to form the indole-type functionality. The sequence for the transformation of **2** into **6** is now well established, as shown in Scheme 2. The key features of this synthesis are regioselective C-5 bromination[4c−e] of **2** followed by indoline oxidation and indole bromination at the C-2 and C-3 positions.

It is important to note that indoline **3** might be a good precursor for the facile syntheses of expensive 5-bromoindoline (**9**) and 5-bromoindole (**10a**). Thus, treatment of **3** with NaOH/H_2O/MeOH afforded **9**[10a] in 91% yield, while 5-bromoindole (**10a**)[10b] and 3,5-dibromoindole (**10b**) were also obtained from **3** in 75% and 5% overall yield, respectively.

In order to obtain 2,3,6-tribromoindoles, compound **11** was treated with 8 equiv of Br_2 in CCl_4 to afford **13** in 90% yield after 10 days of reaction (Scheme 3). The bromination process for the transformation of **11** into **13** via **12** requires bromination at positions C-2 and C-3 followed by bromination at position C-6.[3a,c,g] Deprotection of **13** with NaH/MeOH under reflux afforded **14** in 94% yield, which in turn was methylated to afford the natural product **1a** in 95% yield. The overall yield of **1a** from **11** was 80%. In addition, natural occurring **1d** could readily be obtained by *N*-alkylation of **1c**[6] or bromination at C-5 of **1a**.[3a]

Although compounds **1b** and **1c** are known, they have not yet been fully characterized by spectroscopic means. The position of the aromatic ring bromine atoms of **6** and **13** was confirmed by their ^{1}H NMR spectra, in which the signal for H-7 appears as a doublet at 7.91 ppm (J = 9.2 Hz) for **6** and at 8.24 ppm (J = 1.4 Hz) for **13**, downfield of all other aromatic protons due to deshielding of the C═O carbamate group.[5] Irradiation of H-7 allowed assignment of H-4 (7.59 ppm) and H-6 (7.41 ppm) for **6** and H-4 (7.32 ppm) and H-5 (7.42 ppm) for **13**. From this information and from ^{1}H−^{13}C heterocorrelated 2D NMR contour plots, the ^{13}C NMR spectra of the synthetic tribrominated indoles were assigned unequivocally. For the brominated indoles **1a** and **1d** the complete assignment of the ^{1}H and ^{13}C spectra has been described.[2a,3a] In particular, for the unambiguous assignment of the quaternary carbon atoms in this compounds, the T_1 values and H−C NOE difference spectroscopy were used.[11] In our case, for analogous brominated compounds **8** and **1c**, we assigned unequivocally all brominated and nonbrominated quaternary carbon atoms with the aid of 2D NMR spectra, mainly HMQC and HMBC, the substituent effects on the ^{13}C chemical shifts (SCS), and by comparison of these data with those of the indole derivatives synthesized in this work. Thus, δ values for H-4 in **1c** (7.73 ppm) and **8** (7.72 ppm) are quite similar, while δ values for H-7 vary from 8.38 ppm in **8** to 7.57 ppm in **1c** ($\Delta\delta$ = 0.81 ppm) due to the anisotropic effect of the carbamate carbonyl group on H-7 in **8**.[12a] In addition, a reliable approach for the examination of the 2D spectra was obtained using the C-7 resonance as a starting point due to its characteristic lower frequency.[12b] In addition, C-7a appears at higher frequency than C-3a in indole derivatives **4**−**7** (see Experimental Section) and the C-3 signal appears in the 90−92 ppm range for compounds **1a** and **1d**.[3a,11] With this information in hand and with detailed analysis of the HMBC contour plots, brominated and nonbrominated carbon atoms of indoles **8** and **1c** were assigned unequivocally. The key step for differentiation of quaternary carbon atoms C-3a, C-5, C-6, and C-7a was the HMBC $^2J_{C-H}$ and $^3J_{C-H}$ cross-peak values shown in Table S1.

In summary, facile syntheses of natural products **1a**−**d** have been carried out. This method is efficient for the synthesis of indole derivatives containing bromine atoms at C-2, C-3, and C-5 or at C-2, C-3, and C-6.

Experimental Section

General Experimental Procedures. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were

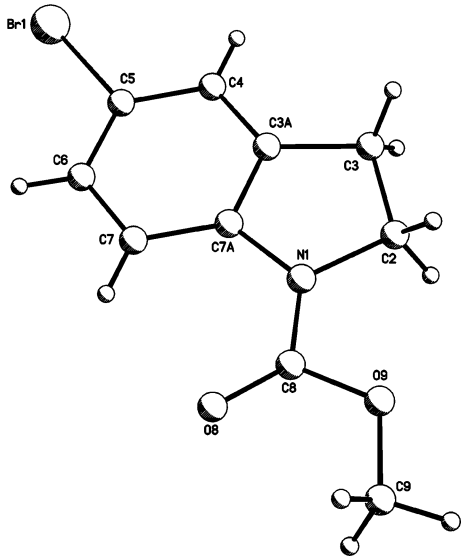
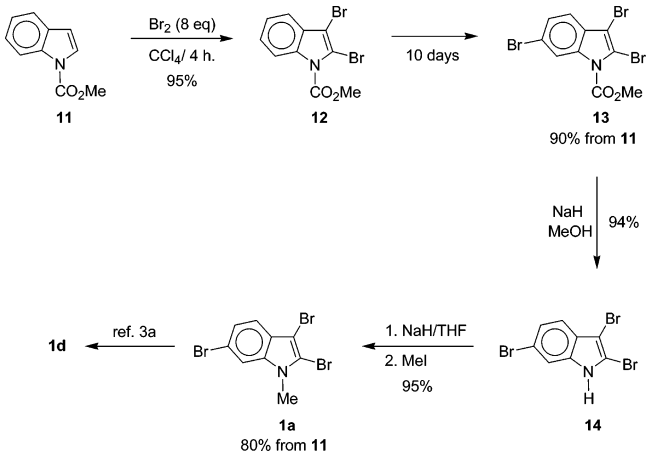


Figure 1. X-ray structure of **3**.

Scheme 3



recorded on a Perkin-Elmer 2000 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained on a JEOL Eclipse+ 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal reference. For complete NMR spectroscopic assignments, HMQC and HMBC experiments were used. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broad), coupling constants (Hz), and assignment. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Hewlett-Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-Mexico. Analytical thin-layer chromatography (TLC) was done on silica gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography[13] was done using silica gel 60 (230−400 mesh) from Aldrich.

General Procedure for the Preparation of Bromoindoles 3, 5, 6, 12, and 13. To a stirred solution of **2**[14] (0.1 g, 0.56 mmol) or **11**[15] (0.1 g, 0.57 mmol) in CCl_4 (20 mL) was added Br_2 (232 μL, 4.51 mmol for **2**, or 235 μL, 4.57 mmol for **11**) in CCl_4 (5 mL) over 5 min. The reaction mixture was stirred at room temperature for a specified period of time as follows: **3** (6 min), **5** (1.5 h), **6** (4.5 h), **12** (4 h), and **13** (10 days). The reaction mixture was treated with a 10% aqueous $NaHSO_3$ (25 mL) solution and stirred vigorously until the disappearance of the red color. The organic layer was separated and washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a pale brown solid, which was purified by crystallization.

5-Bromo-1-carbomethoxyindoline (3): prepared from **2** as colorless prisms (0.14 g, 97%); mp 117−118 °C (EtOAc/hexane); IR (KBr) ν_{max} 3114, 2985, 2952, 2919, 2851, 1703, 1483, 1447, 1393, 1334 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.61 (1H, br s, H-7), 7.36 (1H, d, J = 1.1 Hz, H-4), 7.30 (1H, dd, J = 8.4, 1.8 Hz, H-6), 3.93 (2H, t, J = 8.5 Hz, H-2), 3.73 (3H, br s, CH_3), 3.07 (2H, t, J = 8.8 Hz, H-3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 152.8 (CO_2Me), 141.6 (C-7a), 134.2 (C-3a), 129.6 (C-6), 127.7 (C-4), 115.4 (C-7), 113.8 (C-5), 52.5 (CH_3), 47.3 (C-2), 26.6 (C-3); EIMS m/z 257/255 [M$^+$] (77/77), 161 (13), 131 (57), 117 (100), 90 (36), 89 (87); FABHRMS m/z 254.9889 (calcd for $C_{10}H_{10}NO_2Br$, 254.9895).

3,5-Dibromo-1-carbomethoxyindole (5): prepared from **2** as a white powder (0.18 g, 96%); mp 119−120 °C (hexane/Et_2O); IR (KBr) ν_{max} 3145, 2963, 2920, 2856, 1745, 1444, 1369, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H, br d, J = 8.0 Hz, H-7), 7.65 (1H, d, J = 1.8 Hz, H-4), 7.63 (1H, br s, H-2), 7.46 (1H, dd, J = 8.8, 1.8 Hz, H-6), 4.04 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5 (CO_2-Me), 133.5 (C-7a), 131.2 (C-3a), 128.8 (C-6), 125.6 (C-2), 122.6 (C-4), 117.3 (C-5), 116.8 (C-7), 97.9 (C-3), 54.5 (CH_3); EIMS m/z 335/333/331 [M$^+$] (52/100/52), 291/289/287 (7/14/7), 280/288/286 (9/18/8), 276/274/272 (16/32/16), 210/208 (25/26), 195/193 (15/15); FABHRMS m/z 332.8823 (calcd for $C_{10}H_7NO_2Br_2$, 332.8823).

2,3,5-Tribromo-1-carbomethoxyindole (6): prepared from **2** as a white powder (0.223 g, 96%); mp 155−156 °C (hexane/Et_2O); IR (KBr) ν_{max} 3068, 2967, 2921, 2850, 1756, 1448, 1439, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (1H, d, J = 9.2 Hz, H-7), 7.59 (1H, d, J = 1.8 Hz, H-4), 7.41 (1H, dd, J = 8.8, 1.8 Hz, H-6), 4.09 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.4 (CO_2Me), 134.5 (C-7a), 130.1 (C-3a), 128.8 (C-6), 122.1 (C-4), 117.7 (C-5), 117.2 (C-7), 112.7 (C-2), 104.4 (C-3), 54.5 (CH_3); EIMS m/z 415/413/411/409 [M$^+$] (15/44/45/17), 371/369/367/365 (11/30/31/10), 356/354/352/350 (12/36/38/15), 290/288/286 (8/15/8), 194/192 (44/47), 59 (100); FABHRMS m/z 410.7932 (calcd for $C_{10}H_6NO_2Br_3$, 410.7928).

2,3-Dibromo-1-carbomethoxyindole (12): prepared from **11** as a white powder (0.180 g, 95%); mp 98−99 °C (hexane/Et_2O); IR (KBr) ν_{max} 3027, 2962, 2923, 2851, 1756, 1446, 1366, 1351, 1320, 1290 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, dd, J = 7.3, 1.1 Hz, H-7), 7.50 (1H, dd, J = 7.4, 1.8 Hz, H-4), 7.35 (1H, td, J = 7.3, 1.8 Hz, H-6), 7.31 (1H, td, J = 7.4, 1.1 Hz, H-5), 4.09 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8 (CO_2Me), 135.8 (C-7a), 128.6 (C-3a), 125.9 (C-6), 124.2 (C-5), 119.4 (C-4), 115.6 (C-7), 111.3 (C-2), 105.7 (C-3), 54.3 (CH_3); EIMS m/z 335/333/331 [M$^+$] (52/100/50), 291/289/287 (27/55/28), 276/274/272 (40/77/40), 210/208 (17/18), 195/193 (21/19), 114 (79); FABHRMS m/z 332.8823 (calcd for $C_{10}H_7NO_2Br_2$, 332.8823).

2,3,6-Tribromo-1-carbomethoxyindole (13): prepared from **11** as a white powder (0.211 g, 90%); mp 114−115 °C (hexane/Et_2O); IR (KBr) ν_{max} 2955, 2918, 2849, 1756, 1463, 1450, 1438, 1417, 1352 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (1H, d, J = 1.4 Hz, H-7), 7.42 (1H, dd, J = 8.4, 1.6 Hz, H-5), 7.32 (1H, d, J = 8.4 Hz, H-4), 4.10 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.3 (CO_2Me), 136.0 (C-7a), 127.5 (C-3a and C-5), 120.4 (C-4), 119.8 (C-6), 118.7 (C-7), 111.9 (C-2), 105.3 (C-3), 54.6 (CH_3); EIMS m/z 415/413/411/409 [M$^+$] (33/100/98/34), 371/369/367/365 (23/67/68/24), 356/354/352/350 (33/97/96/34), 290/288/286 (13/27/14), 194/192 (72/74), 59 (58); FABHRMS m/z 410.7914 (calcd for $C_{10}H_6NO_2Br_3$, 410.7928).

5-Bromo-1-carbomethoxyindole (4). To a stirred solution of **3** (0.1 g, 0.39 mmol) in CCl_4 (20 mL) was added Br_2 (20 μL, 0.39 mmol) in CCl_4 (10 mL) during 1 h, and stirring continued for another 1 h. The reaction mixture was worked up as usual to give a pale yellow powder. The ^{1}H NMR spectrum showed a 4:1 ratio of **4**:**5**. The mixture was purified by flash column chromatography eluting with EtOAc/hexane (1:20, v/v), to give **4** as a white powder: mp 54−55 °C (EtOAc/hexane); IR (KBr) ν_{max} 2954, 2924, 2853, 1742, 1450, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (1H, br d, J = 8.0 Hz, H-7), 7.66 (1H, d, J = 1.9 Hz, H-4), 7.57 (1H, br d, J = 3.7 Hz, H-2), 7.34 (1H, dd, J = 8.8, 1.8 Hz, H-6), 6.50 (1H, d, J = 3.7 Hz, H-3), 4.02 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4 (CO_2Me), 134.1 (C-7a), 132.4 (C-3a), 127.5 (C-6), 126.8 (C-2), 123.8 (C-4), 116.7 (C-7), 116.6 (C-5), 107.5 (C-3), 54.1 (CH_3); EIMS m/z 255/253 [M$^+$] (100/96), 210/208 (30/30), 196/194 (15/17), 130 (17), 115 (37); FABHRMS m/z 252.9748 (calcd for $C_{10}H_8NO_2Br$, 252.9738).

2,3,5,6-Tetrabromo-1-carbomethoxyindole (8). To a stirred solution of **6** (0.1 g, 0.24 mmol) in AcOH (10 mL) was added Br_2 (100 μL, 1.94 mmol). The reaction mixture was stirred at room temperature for 24 h and worked up as usual to give a pale brown solid, which was purified by washing it with hexane/Et_2O (4:1, v/v) to give **8** as a white

powder (114 mg, 96%); mp 176−177 °C (hexane/Et_2O); IR (KBr) ν_{max} 2955, 2921, 2851, 1746, 1434, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.38 (1H, s, H-7), 7.72 (1H, s, H-4), 4.11 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.1 (*C*O_2Me), 134.9 (C-7a), 129.1 (C-3a), 123.6 (C-4), 121.9 (C-6), 120.6 (C-7), 120.3 (C-5), 113.4 (C-2), 104.1 (C-3), 54.8 (CH_3); EIMS *m*/*z* 495/493/491/489/487 [M^+] (6/25/36/25/6), 449/447/445 (18/29/19), 434/432/430 (26/39/26), 274 (26), 272 (54), 112 (53), 59 (100); FABHRMS *m*/*z* 490.7028 (calcd for $C_{10}H_5NO_2Br_4$, 490.7013).

General Procedure for the Preparation of 1c, 7, and 14. To a stirred solution of the appropriate indole **6** (0.1 g, 0.243 mmol), **8** (0.1 g, 0.204 mmol), or **13** (0.1 g, 0.204 mmol) in MeOH (20 mL) was added NaH (2 molar equiv), and the mixture was heated under reflux for 2 h. After cooling to room temperature the MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with a saturated solution of NH_4Cl (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane (1:7, v/v).

2,3,5,6-Tetrabromoindole (1c): obtained from **8** as a pale brown powder (0.08 g, 91%); mp 153−154 °C (EtOAc/hexane); IR (KBr) ν_{max} 3380, 2924, 2854, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (1H, br s, N−H), 7.73 (1H, s, H-4), 7.57 (1H, s, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (C-7a), 128.4 (C-3a), 123.4 (C-4), 119.2 (C-6), 117.1 (C-5), 115.6 (C-7), 112.4 (C-2), 93.9 (C-3); EIMS *m*/*z* 437/435/433/431/429 [M^+] (16/64/100/64/17), 356/354/352/350 (15/38/38/13), 275/273/271 (23/41/22), 137 (34), 86 (43); FABHRMS *m*/*z* 432.6965 (calcd for $C_8H_3NBr_4$, 432.6958).

2,3,5-Tribromoindole (7): obtained from **6** as a pale brown powder (0.077 g, 90%); mp 150−151 °C (EtOAc/hexane); IR (KBr) ν_{max} 2918, 2850, 1635, 1456, 1434, 1325 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (1H, br s, N−H), 7.61 (1H, d, J = 1.1 Hz, H-4), 7.29 (1H, dd, J = 8.8, 1.8 Hz, H-6), 7.13 (1H, d, J = 8.8 Hz, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.4 (C-7a), 129.2(C-3a), 126.6 (C-6), 121.6 (C-4), 114.7 (C-5), 112.3 (C-7), 111.4 (C-2), 93.8 (C-3); EIMS *m*/*z* 357/355/353/351 [M^+] (33/100/99/35), 276/274/272 (27/55/27), 249/247/245 (7/13/7), 195/193 (19/19), 114 (37); FABHRMS *m*/*z* 354.7860 (calcd for $C_8H_4NBr_3$, 354.7853).

2,3,6-Tribromoindole (14): obtained from **13** as a pale brown powder (0.080 g, 94%); mp 74−75 °C (EtOAc/hexane); IR (film) ν_{max} 3408, 1719, 1612, 1442, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (1H, br s, N−H), 7.44 (1H, d, J = 1.1 Hz, H-7), 7.34 (1H, d, J = 8.4 Hz, H-4), 7.29 (1H, dd, J = 8.4, 1.4 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3 (C-7a), 126.7 (C-3a), 124.8 (C-5), 120.3 (C-4), 117.3 (C-6), 113.8 (C-7), 110.8 (C-2), 94.9 (C-3); EIMS *m*/*z* 351/353/355/357 [M^+] (19/57/56/18), 272/274/276 (18/35/17), 97 (27), 71 (74), 57 (100); FABHRMS *m*/*z* 354.7853 (calcd for $C_8H_4NBr_3$, 354.7853).

5-Bromoindoline (9). To a stirred solution of **3** (0.1 g, 0.39 mmol) in MeOH (20 mL) was added a 20% aqueous solution of NaOH (10 mL), and the mixture was heated under reflux for 2 h. The MeOH was evaporated in vacuo, and the residue was diluted with EtOAc (100 mL). The organic phase was washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane (1:7, v/v) to give **9**[10b] as a pale brown powder (0.07 g, 91%); mp 39−40 °C (EtOAc/hexane) (lit.[10c] mp 36−40 °C); IR (film) ν_{max} 3386, 2933, 2856, 1604, 1486, 1471, 1248 cm^{-1}; ^1H NMR and MS in agreement with published values; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8 (C-7a), 131.9 (C-3a), 129.9 (C-6), 127.7 (C-4), 110.7 (C-7), 110.2 (C-5), 48.0 (C-2), 29.8 (C-3).

Procedure for the Preparation of 10a and 10b. To a stirred solution of **3** (0.1 g, 0.39 mmol) in CCl_4 (20 mL) was added Br_2 (20 μL, 0.39 mmol) in CCl_4 (10 mL) over 1 h, and stirring at room temperature continued for another 1 h. The reaction mixture was worked up as usual to give a pale yellow solid, which was dissolved in MeOH (20 mL), NaH (2 molar equiv) was added, and the mixture was heated under reflux for 2 h. After cooling to room temperature the MeOH was evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with a saturated solution of NH_4Cl (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane (1:7, v/v).

5-Bromoindole (10a): obtained from **3** as a white powder (0.057 g, 75%); mp 91−92 °C (EtOAc/hexane) (lit.[10a] mp 91 °C); IR (KBr) ν_{max} 3412, 2919, 2850, 1627, 1443, 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (1H, br s, N−H), 7.76 (1H, br s, H-4), 7.26 (1H, dd, J = 8.8, 1.9 Hz, H-6), 7.22 (1H, d, J = 8.5 Hz, H-7), 7.17 (1H, t, J = 2.6 Hz, H-2), 6.48 (1H, t, J = 2.2 Hz, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.5 (C-7a), 129.8 (C-3a); 125.5 (C-2), 125.0 (C-6), 123.3 (C-4), 113.2 (C-5), 112.6 (C-7), 102.4 (C-3); EIMS *m*/*z* 197/195 [M^+] (100/96), 116 (87), 89 (34).

3,5-Dibromoindole (10b): obtained from **3** as a white powder (0.005 g, 5%); mp 80−81 °C (EtOAc/hexane); IR (KBr) ν_{max} 2969, 2927, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (1H, br s, N−H), 7.72 (1H, d, J = 1.8 Hz, H-4), 7.32 (1H, dd, J = 8.8, 1.9 Hz, H-6), 7.24 (1H, d, J = 8.5 Hz, H-7), 7.22 (1H, d, J = 2.5 Hz, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.1 (C-7a), 128.7 (C-3a), 126.3 (C-6), 124.7 (C-2), 122.0 (C-4), 114.1 (C-5), 113.1 (C-7), 91.1 (C-3); EIMS *m*/*z* 277/275/273 [M^+] (51/100/51), 196/194 (49/50), 115 (54); FABHRMS *m*/*z* 274.8759 (calcd for $C_8H_5NBr_2$, 274.8768).

General Procedure for the Preparation of 1a and 1b. To a solution of **7** or **14** (0.1 g, 0.283 mmol) in THF (10 mL) were added NaH (4.2 mmol) and MeI (3.4 mmol), followed by stirring in an ice-cooled bath for 45 min. The mixture was diluted with EtOAc (100 mL), and the organic layer was washed with brine (2 × 20 mL), dried over Na_2SO_4, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane (1:7, v/v).

2,3,6-Tribromo-1-methylindole (1a): obtained from **14** as a pale brown powder (0.099 g, 95%); mp 90−91 °C (EtOAc/hexane) (lit.[2a] mp 90.5−91 °C); IR (film) ν_{max} 2937, 1607, 1561, 1497, 1461, 1416, 1331, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (1H, d, J = 1.5 Hz, H-7), 7.31 (1H, d, J = 8.4 Hz, H-4), 7.24 (1H, d, J = 8.4, 1.8 Hz, H-5), 3.70 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9 (C-7a), 125.9 (C-3a), 124.2 (C-5), 120.2 (C-4), 116.8 (C-5), 115.7 (C-2), 112.7 (C-7), 93.1 (C-3), 32.6 (CH_3); EIMS *m*/*z* 371/369/367/365 [M^+] (38/99/100/34), 356/354/352/350 (6/18/19/7), 290/288/286 (6/13/7), 249/247/245 (5/10/5, 194/192 (17/18), 128 (24), 87 (21); FABHRMS *m*/*z* 366.8018 (calcd for $C_9H_6NBr_3$, 366.8030).

2,3,5-Tribromo-1-methylindole (1b): obtained from **7** as white crystals (0.098 g, 95%); mp 121−122 °C (EtOAc/hexane) (lit.[2a] mp 120−122 °C); IR (KBr) ν_{max} 2921, 2851, 1631, 1463, 1420, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (1H, d, J = 1.8 Hz, H-4), 7.30 (1H, dd, J = 8.7, 1.8 Hz, H-6), 7.12 (1H, d, J = 8.8 Hz, H-7), 3.75 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.2 (C-7a), 128.6 (C-3a), 126.0 (C-6), 121.6 (C-4), 116.5 (C-2), 114.4 (C-5), 111.3 (C-7), 92.2 (C-3), 32.7 (CH_3); EIMS *m*/*z* 371/369/367/365 [M^+] (34/100/95/34), 356/354/352/350 (3/9/9/3), 290/288/286 (6/14/7), 289/287/285 (6/9/4), 249/247/245 (4/8/4, 209/207 (15/16), 194/192 (14/16); FABHRMS *m*/*z* 366.8035 (calcd for $C_9H_6NBr_3$, 366.8030).

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Supporting Information Available: Heteronuclear long-range coupling constants for **1c** and **8** (Table S1) and X-ray data for compound **3** (Tables S2 and S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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