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FIRST TOTAL SYNTHESIS OF (±)-FLUSTRAMINOL B

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Abstract – A first route for the synthesis of a 6-brominated marine alkaloid, flustraminol B (**1**), is reported using 2,6-dibromoindole (**3b**) as a key starting material. Bromine atoms were introduced regioselectively to **2b** using NBS. The crucial selective reductive cyclization of the corresponding 6-brominated-2,3-dioxindole (**7b**) was successfully controlled using Red-Al® in toluene, leading to 6-brominated pyrroloindole (**8**), which by selective *N*-methylation gave flustraminol B (**1**).

INTRODUCTION

The efficient regioselective bromination of indoles has attracted the interest of organic chemists in part, due to the growing number of brominated alkaloids that possessed the pyrroloindole skeleton.[1] These heterocyclic compounds are of particular interest due to possibilities for the discovery of new biologically active chemical entities. Since the low yields of brominated indole alkaloids obtained from original sources have thwarted progress toward this goal,[2] chemical synthesis has proven to be a viable alternative by which scarce natural products may be accessed in larger quantities.[3]

Electrophilic bromination of indoles is a strongly substrate-dependent process that may yield polybrominated derivatives.[4] Recently, we showed that bromination of *N*-carbomethoxyindoline and *N*-carbomethoxyindole using Br_2 in CCl_4 occurred to generate regioisomeric 2,3,5- or 2,3,6-tribrominated *N*-carbomethoxyindoles in good yields, respectively.[4b] These results caught our attention for two reasons. First, the possibility to direct a regioselective bromination at the benzene ring, and second because 2-brominated indoles are prone to react with oxidizing reagents to give oxindoles,[5] which in turn have

been successfully applied to the synthesis of pyrroloindole alkaloids.[6] In our efforts to prepare indole alkaloids, we applied an oxidative approach to indole and oxindole derivatives which allowed the construction of the 3-hydroxyoxindole framework.[7] Thus, the aim of the present work is to adapt this strategy to obtain brominated 3-hydroxyoxindole derivatives as intermediates for the first total synthesis of flustraminol B (**1**) isolated from the bryozoan *Flustra foliacea*[8] (Figure 1).

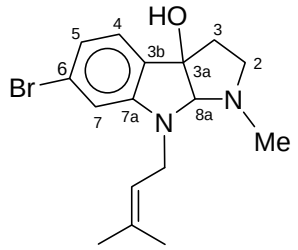

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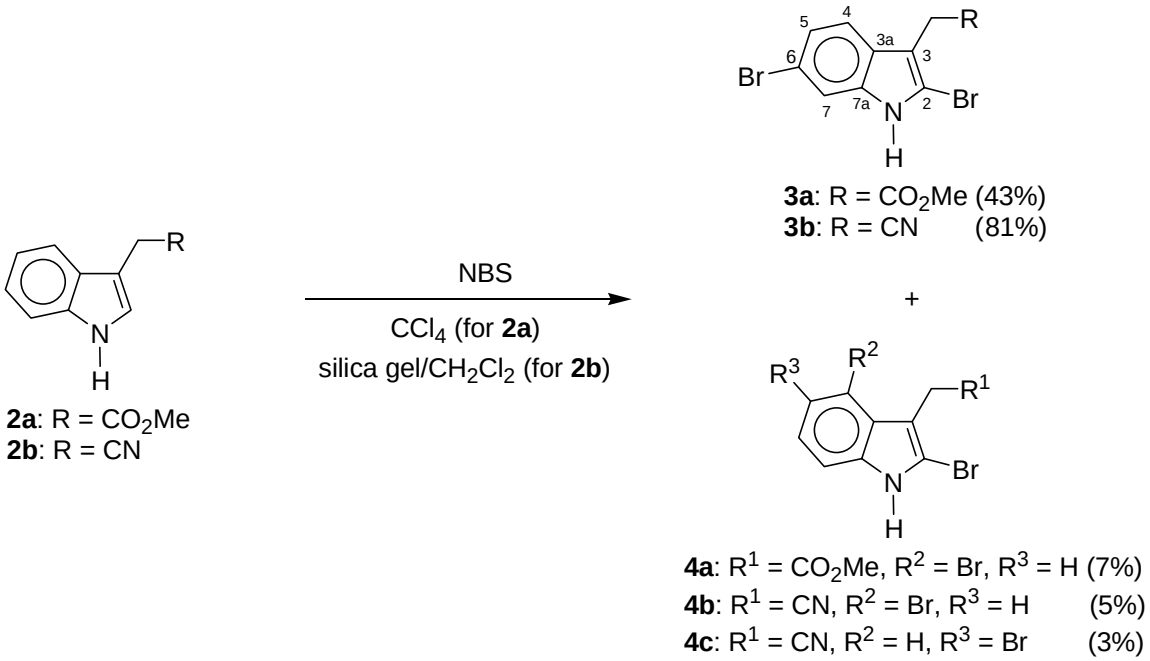
Figure 1

RESULTS AND DISCUSSION

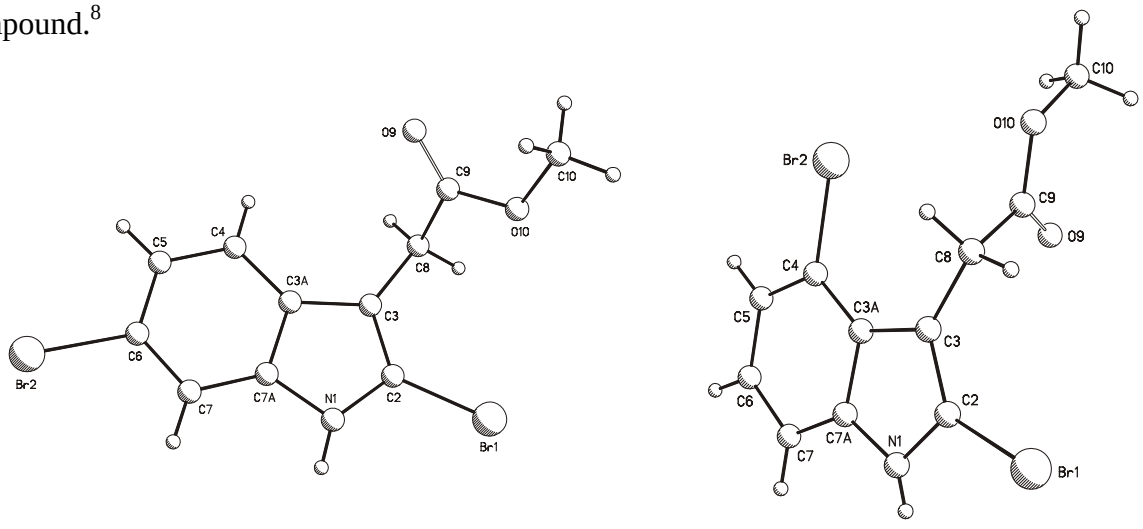
Oxindoles substituted with an acetonitrile or acetate group at C-3 are synthetically important as efficient precursors of pyrroloindoles upon reductive cyclization and were therefore seen as attractive precursors of **1**, following two parallel approaches. The first step in each approach for the synthesis of flustraminol B (**1**) involved a regioselective bromination of indoles (**2a**) and (**2b**) (Scheme 1). Although treatment of **2a** and **2b** with Br_2/CCl_4 or NBS/AcOH gave complex mixtures of products, fortunately, the use of NBS/CCl_4 for **2a** and NBS/silica gel/CH_2Cl_2 for **2b** produced hopeful results affording regioselectively 2,6-dibromoindole derivatives **3a** and **3b** in 43% and 81% yield, respectively, together with small amounts of undesired 2,4- and 2,5-dibromoindole derivatives (**4a**-**c**). The ^{1}H NMR spectra of **3a** and **3b** showed three aromatic proton spin-spin systems characteristic of indoles with a bromine atom either at position C-5 or C-6. The bromine atom was assigned at C-6 in **3a** and **3b** with the aid of HMQC measurements, which showed a correlation between the signals at 113.6-113.4 ppm, characteristic for C-7 in the ^{13}C NMR spectra, with those at 7.48 and 7.53 ppm in the ^{1}H NMR spectra.[4a,b,9] The position of the bromine atoms in **3a** and **4a** was confirmed from their X-ray structures (Figure 2, Table 1).

With this encouraging result in hand, we turned our attention toward the oxidation steps (Scheme 2). Treatment of **3a** and **3b** with TFA[5d,5e] furnished 6-bromooxindoles (**5a**) and **(5b**) in 67% and 68% yield, respectively. The subsequent oxidation of **5a** and **5b** was done with dimethyldioxirane[7] (DMD)/$NaHCO_3$ buffer to give 3-hydroxyoxindoles (**6a**) and (**6b**) in 99% and 97% yield, respectively. *N*-Alkylation of **6a** and **6b** with prenyl bromine (K_2CO_3/acetone, reflux 7 h) afforded oxindoles (**7a**) and (**7b**) in 98% and 89% yield, respectively. The X-ray structure for **7a** is shown in Figure 3 and the data are given in Table 1.



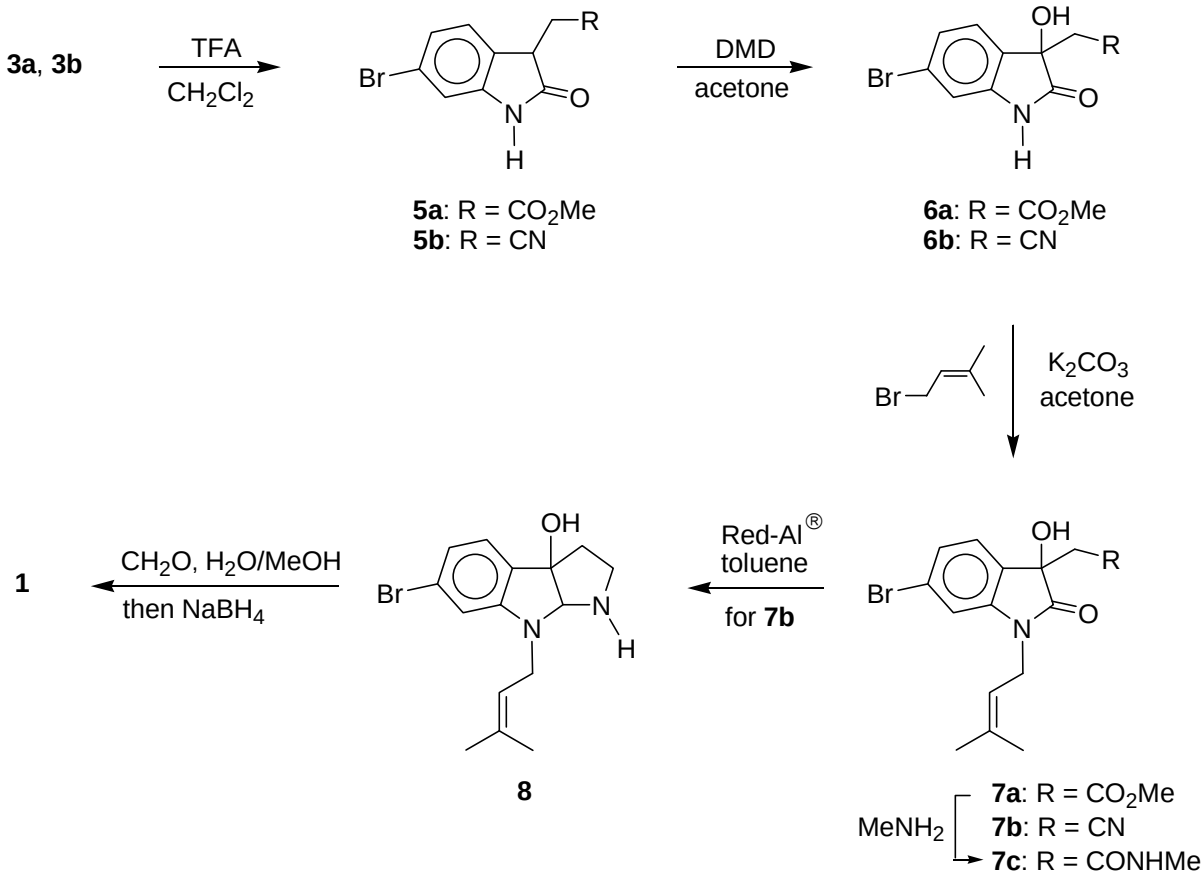
Scheme 1

In order to introduce the *N*-methyl group after the expected reductive annelation reaction, the acetamide derivative (**7c**) was prepared by treatment of **7a** with excess methylamine in water in 85% yield (Scheme 2). Since reductive annelation reactions conducted with $LiAlH_4$ led to reductive nucleophilic displacements of aromatic bromine atoms,[8,10] the more chemoselective alane[3c] and Red-Al®[6a] reagents were tested over scaffolds (**7a**-**7c**). While treatment of **7b** with Red-Al® at room temperature resulted in complete conversion within 3 h, to give the corresponding pyrroloindole (**8**) in 69% yield, only unidentifiable mixtures of products were obtained when **7a** and **7c** were treated with either alane or Red-Al® reagents. Finally, methylation of **8** by reductive amination[7] with $CH_2O/NaBH_4$ in MeOH afforded **1** in 53% yield. Compound (**1**) was obtained in 16% overall yield from **2b**. Pure **1** showed physical properties (IR, ^{1}H NMR, ^{13}C NMR, MS) consistent with those reported for the natural compound.[8]

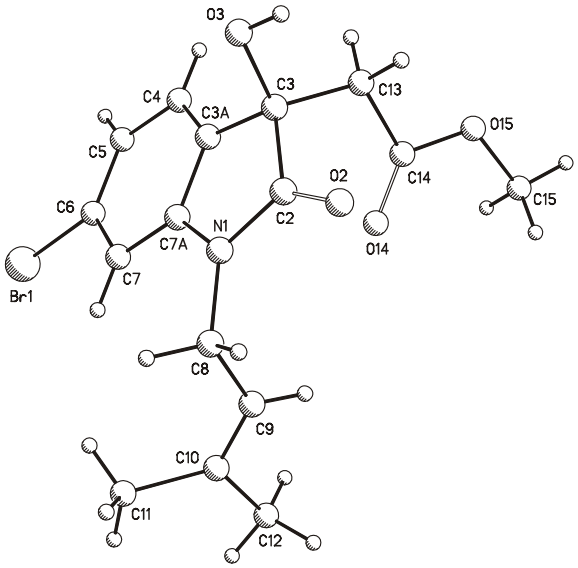


3a **4a**

Figure 2. X-Ray diffraction structures of **3a** and **4a**.



Scheme 2



7a

Figure 3. X-Ray diffraction structure of **7a**.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were 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 spectroscopic assignments 2D NMR spectra, HMQC and HMBC were used. Chemical shifts are reported as follows: chemical shift from TMS, integration, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet), 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. Microanalytical determinations were performed on a Perkin Elmer 2400 Series PCII apparatus. 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[11] was done using silica gel 60 (230-400 mesh) from Aldrich.

Preparation of dibromoindoles 3a,**b and 4a-c.**

To a cooled solution of **2a** (0.30 g, 1.60 mmol) in CCl_4 (30 mL), or to a mixture of **2b** (0.25 g, 1.60 mmol) and silica gel (0.63 g, 1.04 mmol) in CH_2Cl_2 (30 mL), was added portionwise over 5 min NBS (0.58 g, 3.20 mmol) and the mixture was stirred at rt for 15 min for **2a** and 20 min for **2b**. The formed solid was filtered off and washed with CH_2Cl_2. The separated organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The resultant crude product was purified by flash column chromatography to provide **3a** and **4a** in the fractions eluted with EtOAc/hexane 1:19, and pure **3b**, and a mixture of **4b** and **4c**, in the fractions eluted with EtOAc/hexane 1:9. Compounds **4b** and **4c** were separated by extensive chromatography using silica gel impregnated with a 20% solution of $AgNO_3$ in MeCN[12] and eluting with EtOAc/hexane 3:7.

Methyl (2,6-dibromo-1*H*-indol-3-yl)acetate (3a). Prepared from **2a** as colorless prisms (0.24 g, 43%); mp 127-128 ºC (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.03 (1H, s, NH), 7.48 (1H, d, J = 1.6 Hz, H7), 7.43 (1H, d, J = 8.4 Hz, H4), 7.16 (1H, dd, J = 8.4, 1.7 Hz, H5), 3.71 (2H, s, H8), 3.60 (3H, s, CO_2CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.8 (CO_2Me), 136.7 (C-7a), 126.3 (C-3a), 122.4 (C-5), 120.0 (C-4), 114.5 (C-6), 113.4 (C-7), 111.1 (C-2), 107.7 (C-3), 51.8 (CO_2CH_3), 30.0 (C-8); IR (KBr) ν_{max} 2946, 1714, 1615, 1436, 1407, 1332 cm^{-1}; EIMS *m/z* 349/347/345 [M$^+$] (18/35/19), 290/288/286 (53/100/53), 209/207 (16/16), 128 (22); *Anal.* Calcd for $C_{11}H_9NO_2Br_2$: C 38.07; H 2.61; N 4.04. Found: C 38.33; H 2.54; N 3.71.

(2,6-Dibromo-1*H*-indol-3-yl)acetonitrile (3b). Prepared from **2b** as a white powder (0.40 g, 80%); mp 120-122 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.27 (1H, s, N-H), 7.62 (1H, d, J = 8.4 Hz, H-4), 7.53 (1H, d, J = 1.9 Hz, H-7), 7.27 (1H, dd, J = 8.4, 1.6 Hz, H-5), 4.03 (2H, s, H-8); ^{13}C NMR

(DMSO-d_6, 100 MHz) δ 136.6 (C-7a), 125.2 (C-3a), 122.8 (C-5), 119.4 (C-4), 118.0 (CN), 115.0 (C-6), 113.6 (C-7), 111.0 (C-2), 103.8 (C-3), 12.9 (C-8); IR (KBr) ν_{max} 3441, 3280, 2921, 1611, 1445, 1408 cm^{-1}; EIMS *m/z* 316/314/312 [M^+] (47/98/53), 235/233 (96/100), 154 (44), 127 (43), 100 (25); FABHRMS *m/z* 313.8882 (calcd for $C_{10}H_6N_2Br_2$, 313.8877); *Anal.* Calcd for $C_{10}H_6N_2Br_2$: C 38.25; H 1.93. Found: C 38.15; H 1.96.

Methyl (2,4-dibromo-1*H*-indol-3-yl)acetate (4a). Obtained from **2a** as colorless prisms (0.04 g, 7%); mp 152-154 ºC (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.26 (1H, s, N-H), 7.34 (1H, d, *J* = 8.1 Hz, H-7), 7.21 (1H, d, *J* = 7.3 Hz, H-5), 7.02 (1H, t, *J* = 8.1 Hz, H-6), 3.92 (2H, s, H-8), 3.64 (3H, s, CO_2CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.2 (CO_2Me), 137.3 (C-7a), 125.1 (C-3a), 123.6 (C-5), 122.8 (C-6), 113.2 (C-3), 111.9 (C-4), 110.7 (C-7), 107.3 (C-2), 51.5 (CO_2CH_3), 30.9 (C-8); IR (KBr) ν_{max} 3292, 1713, 1610, 1349, 1333 cm^{-1}; EIMS *m/z* 349/347/345 [M^+] (13/28/13), 290/288/286 (49/100/55), 209/207 (12/13), 128 (17); FABHRMS *m/z* 346.8976 (calcd for $C_{11}H_9NO_2Br_2$, 346.8980); *Anal*. Calcd for $C_{11}H_9NO_2Br_2$: C 38.07; H 2.61; N 4.04. Found: C 38.13; H 2.57; N 3.68.

(2,4-Dibromo-1*H*-indol-3-yl)acetonitrile (4b). Obtained from **2b** as a white powder (0.03 g, 5%); mp 171-173 ºC decomp. (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.54 (1H, s, N-H), 7.38 (1H, d, *J* = 8.1 Hz, H-7), 7.29 (1H, d, *J* = 7.9 Hz, H-5), 7.08 (1H, t, *J* = 8.1 Hz, H-6), 4.11 (2H, s, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 137.3 (C-7a), 124.2 (C-5), 124.0 (C-3a), 123.5 (C-6), 118.5 (C-2), 113.4 (CN), 111.4 (C-4), 111.1 (C-7), 103.6 (C-3), 14.6 (C8); IR (KBr) ν_{max} 2925, 2854, 1742, 1455 cm^{-1}; EIMS *m/z* 316/314/312 [M^+] (48/100/44), 236/234 (65/55), 154 (13), 127 (12); FABHRMS *m/z* 313.8868 (calcd for $C_{10}H_6N_2Br_2$, 313.8877).

(2,5-Dibromo-1*H*-indol-3-yl)acetonitrile (4c). Obtained from **2b** as a pale yellow powder (0.02 g, 3%); mp 172-173 ºC decomp. (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.31 (1H, s, N-H), 7.89 (1H, d, *J* = 1.1 Hz, H-4), 7.32 (1H, d, *J* = 8.8 Hz, H-7), 7.29 (1H, td, *J* = 8.1, 1.5 Hz, H-6), 4.03 (2H, s, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 134.7 (C-7a), 127.9 (C-3a), 124.7 (C-6), 120.0 (C-4), 118.1 (C-2), 113.2 (C-7), 112.6 (C-5), 111.8 (CN), 103.3 (C-3), 12.7 (C8); IR (KBr) ν_{max} 2927, 1744, 1413, 1336, 1176 cm^{-1}; EIMS *m/z* 316/314/312 [M^+] (48/100/47), 236/234 (54/47), 155 (8), 127 (8); FABHRMS *m/z* 313.8866 (calcd for $C_{10}H_6N_2Br_2$, 313.8877).

Preparation of oxindoles 5a and 5b.

To a solution of **3a** (0.51 g, 1.45 mmol), or to **3b** (0.46 g, 1.45 mmol) in CH_2Cl_2 (30 mL), were added 3.2 mL (37 mmol) of 90% aqueous TFA and the resulting mixture was stirred under reflux for 28 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 (100 mL). The organic phase was washed with a

saturated aqueous $NaHCO_3$ (3 x 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuum. The residue was purified by flash column chromatography eluting with EtOAc/hexane 3:1.

Methyl (6-bromo-2-oxo-2,3-dihydroindol-3-yl)acetate (5a). Obtained from **3a** as a white powder (0.28 g, 67%); mp 145-146 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (1H, br s, N-H), 7.14 (1H, dd, *J* = 8.0, 1.7 Hz, H-5), 7.09 (1H, d, *J* = 8.0 Hz, H-4), 7.08 (1H, d, *J* = 1.3 Hz, H-7), 3.74 (1H, dd, *J* = 7.5, 4.5 Hz, H-3), 3.70 (3H, s, CO_2CH_3), 3.08 (1H, dd, *J* = 17.2, 4.5 Hz, H-8a), 2.86 (1H, dd, *J* = 17.2, 7.5 Hz, H-8b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.4 (*C*ONH), 171.5 (*C*O_2Me), 143.1 (C-7a), 127.7 (C-3a), 125.5 (C-5), 125.5 (C-4), 121.9 (C-6), 113.6 (C-7), 52.3 (CO_2CH_3), 42.2 (C-3), 34.4 (C-8); IR (KBr) ν_{max} 3192, 3127, 1736, 1715, 1613, 1219, 1202 cm^{-1}; EIMS *m/z* 285/283 [M^+] (22/22), 253/251 (13/14), 225/223 (100/99), 197/195 (26/27), 145 (38), 116 (56), 89 (48); *Anal.* Calcd for $C_{11}H_9NO_3Br$: C 46.50; H 3.55; N 4.93. Found: C 46.55; H 3.47; N 4.44.

(6-Bromo-2-oxo-2,3-dihydroinodol-3-yl)acetonitrile (5b). Obtained from **3b** as a white powder (0.24 g, 68%); mp 169-170 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.80 (1H, s, N-H), 7.35 (1H, d, *J* = 8.1 Hz, H-4), 7.22 (1H, dd, *J* = 8.1, 1.9 Hz, H-5), 7.02 (1H, d, *J* = 1.9 Hz, H-7), 3.83 (1H, t, *J* = 5.9 Hz, H-3), 3.24 (1H, dd, *J* = 17.2, 5.9 Hz, H-8a), 3.08 (1H, dd, *J* = 17.2, 5.9 Hz, H-8b); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.3 (*C*ONH), 144.5 (C-7a), 126.5 (C-3a), 126.1 (C-4), 124.2 (C-5), 121.2 (C-6), 118.0 (CN), 112.4 (C-7), 41.0 (C-3), 17.4 (C-8); IR (KBr) ν_{max} 3445, 3198, 1708, 1607, 1451 cm^{-1}; EIMS *m*/*z* 227/225 [M^+-26] (60/61), 199/197 (23/23), 146 (100), 117 (62), 91 (26), 59 (37); FABHRMS *m/z* 250.9817 (calcd for $C_{10}H_7N_2OBr$, 250.9820); *Anal.* Calcd for $C_{10}H_7N_2OBr$: C 47.84; H 2.81; N 11.16. Found: C 48.15; H 2.82; N 10.69.

Preparation of 3-hydroxyoxindoles 6a and 6b.

To a solution of oxindole **5a** (0.14 g, 0.49 mmol), or **5b** (0.19 g, 0.77 mmol) in acetone (20 mL), was added $NaHCO_3$ (7 equiv for **5a**, and 3.5 equiv for **5b**). The resulting thick mixture was treated dropwise, over 10 min at rt, with a solution of oxone monopersulfate complex (5 equiv of $KHSO_5$ for **5a**, and 2.5 equiv for **5b**) and 5 mg of disodium EDTA in water (5 mL). After complete addition, the mixture was stirred at rt for additional 3 h. The acetone was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuum. The resulting crude product was purified by flash column chromatography with EtOAc/hexane 2:3.

Methyl (6-bromo-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetate (6a). Obtained from **5a** as a white powder (0.15 g, 99%); mp 172-173 ºC (CH_2Cl_2/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.45 (1H, s,

N-H), 7.28 (1H, d, *J* = 7.9 Hz, H-4), 7.13 (1H, dd, *J* = 7.9, 1.7 Hz, H-5), 6.95 (1H, d, *J* = 1.7 Hz, H-7), 6.25 (1H, s, OH), 3.40 (3H, s, CO_2CH_3), 3.06 and 2.96 (2H, AB system, *J* = 16.1 Hz, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.7 (*C*ON-H), 169.2 (*C*O_2Me), 144.3 (C-7a), 130.3 (C-3a), 125.9 (C-4), 124.0 (C-5), 121.9 (C-6), 112.4 (C-7), 72.3 (C-3), 51.3 (CO_2CH_3), 41.0 (C-8); IR (KBr) ν_{max} 3332, 2919, 1720, 1619, 1199, 1178 cm^{-1}; EIMS *m/z* 283/281 [M^+-18] (100/97), 252/250 (51/51), 224/222 (78/59), 196/194 (51/52), 115 (62), 88 (48), 58 (53); FABHRMS *m/z* 298.9798 (calcd for $C_{11}H_{10}NO_4Br$, 298.9793).

(6-Bromo-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetonitrile (6b). Obtained from **5b** as a white powder (0.20 g, 97%); mp 217-218 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.7 (1H, s, N-H), 7.40 (1H, d, *J* = 7.7 Hz, H-4), 7.26 (1H, dd, *J* = 8.0, 1.5 Hz, H-5), 7.03 (1H, d, *J* = 1.5 Hz, H-7), 6.72 (1H, s, OH), 3.07 and 3.00 (2H, AB system, *J* = 16.6 Hz, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.5 (*C*ONH), 143.3 (C-7a), 129.1 (C-3a), 126.0 (C-4), 124.7 (C-5), 122.7 (C-6), 116.9 (CN), 112.9 (C-7), 71.8 (C-3), 25.8 (C-8); IR (KBr) ν_{max} 3286, 1717, 1612, 1446, 823 cm^{-1}; EIMS *m/z* 250/248 [M^+] - 18 (100/92), 222/220 (38/30), 141 (62), 114 (93), 87 (33), 57 (47); FABHRMS *m/z* 266.9761 (calcd for $C_{10}H_7N_2O_2Br$, 266.9769); *Anal.* Calcd for $C_{10}H_7N_2O_2Br$: C 44.97; H 2.64; N 10.49. Found: C 45.13; H 2.70; N 10.69.

Preparation of prenyloxindoles 7a and 7b. To a solution of **6a** (0.08 g, 0.25 mmol) in acetone (10 mL), or **6b** (0.81 g, 3.03 mmol) in acetone (50 mL), were added 2.5 equiv of prenyl bromide and 2.5 equiv of K_2CO_3, and the mixture was heated under reflux for 7 h. After cooling to rt, the solid was filtered off and washed with acetone (2 x 10 mL), the volatiles were evaporated under reduced pressure and the residue was dissolved with EtOAc (100 mL). The organic layer was washed with brine (2 x 20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuum. The crude product was purified by crystallization.

Methyl [6-bromo-3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetate (7a). Obtained from **6a** as colorless prisms (0.09 g, 99%); mp 130-131 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (1H, d, *J* = 7.7 Hz, H-4), 7.12 (1H, dd, *J* = 7.7, 1.5 Hz, H-5), 6.86 (1H, d, *J* = 1.5 Hz, H-7), 5.07 (1H, tm, *J* = 6.6 Hz, H-9), 4.46 (1H, br s, OH), 4.21 (1H, dd, *J* = 15.4, 6.6 Hz, H-8a), 4.16 (1H, dd, *J* = 15.4, 6.6 Hz, H-8b), 3.57 (3H, s, CO_2CH_3), 2.89 and 2.86 (2H, AB system, *J* = 16.1, Hz, H-13), 1.74 and 1.67 (6H, 2s, Me-11, Me-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9 (*C*ON), 170.6 (*C*O_2Me), 144.5 (C-7a), 137.8 (C-10), 128.4 (C-3a), 125.9 (C-5), 125.4 (C-4), 123.9 (C-6), 117.4 (C-9), 113.0 (C-7), 73.3 (C-3), 52.2 (CO_2CH_3), 41.2 (C-13), 38.5 (C-8), 25.8 and 18.3 (Me-11, Me-12); IR (KBr) ν_{max} 3358, 2982, 2970, 2958, 1737, 1698, 1610 cm^{-1}; EIMS *m/z* 369/367 [M^+] (11/11), 351/349 (10/10), 292/290 (11/10), 226 (61), 241/239 (25/27), 69 (100); *Anal.* Calcd for $C_{16}H_{18}NO_4Br$: C 52.19; H 4.93; N 3.80. Found: C 52.17; H 4.96; N 3.46.

[6-Bromo-3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetonitrile (7b). Obtained from **6b** as pale yellow prisms (0.91 g, 89%); mp 142-143 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (1H, d, *J* = 8.1 Hz, H-4), 7.31 (1H, dd, *J* = 8.0, 1.5 Hz, H-5), 7.00 (1H, d, *J* = 1.5 Hz, H-7), 5.11 (1H, t, *J* = 6.6 Hz, H-9), 4.38 (1H, s, OH), 4.30 (1H, dd, *J* = 15.4, 6.6 Hz, H-8a), 4.21 (1H, dd, *J* = 15.4, 6.6 Hz, H-8b), 3.06, 2.71 (2H, AB system, *J* = 16.4 Hz, H-13), 1.81 and 1.74 (6H, 2s, Me-11, Me-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2 (N-*C*O), 143.6 (C-7a), 138.7 (C-10), 126.8 (C-5), 126.7 (C-3a), 125.8 (C-4), 124.8 (C-6), 116.8 (C-9), 115.3 (CN), 113.6 (C-7), 72.6 (C-3), 38.8 (C-8), 27.5 (C-13), 25.8 and 18.7 (Me-11, Me-12); IR (KBr) ν_{max} 3350, 1713, 1607, 1486, 1432 cm^{-1}; EIMS *m/z* 318/316 [M^+-18] (15/15), 250/248 (38/37), 69 (100); FABHRMS *m/z* 334.0327 (calcd for $C_{15}H_{15}N_2O_2Br$, 334.0317); *Anal.* Calcd for $C_{15}H_{15}N_2O_2Br$: C 53.75; H 4.51; N 8.36. Found: C 53.65; H 4.46; N 7.96.

Methyl[6-bromo-3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetamide (7c). To a solution of **7a** (0.15 g, 0.41 mmol) in MeOH (10 mL) was added 40% aqueous $MeNH_2$ (0.6 mL). The mixture was stirred at rt for 84 h, diluted with EtOAc (100 mL) and washed with a saturated aqueous of NH_4Cl (3 x 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuum. The resulting crude product was purified by flash column chromatography with EtOAc to give **7c** as a pale yellow oil (0.129 g, 86%), which solidified on standing in toluene as a white powder; mp 119-121 °C (toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (1H, d, *J* = 7.9 Hz, H-4), 7.18 (1H, dd, *J* = 7.9, 1.5 Hz, H-5), 6.91 (1H, d, *J* = 1.4 Hz, H-7), 6.17 (1H, br q, *J* = 4.8 Hz, N-H), 5.10 (1H, br t, *J* = 6.8 Hz, H-9), 4.23 (1H, dd, *J* = 16.3, 6.6 Hz, H-8a), 4.19 (1H, dd, *J* = 16.3, 7.0 Hz, H-8b), 2.83 (3H, d, *J* = 4.8 Hz, NH*Me*), 2.73 and 2.48 (2H, AB system, *J* = 15.0 Hz, H-13), 1.80 and 1.72 (6H, 2s, Me-11, Me-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7 (*C*ON), 170.7 (*C*O_2NHMe), 143.6 (C-7a), 137.8 (C-10), 129.0 (C-3a), 125.9 (C-5), 125.4 (C-4), 123.4 (C-6), 117.2 (C-9), 112.8 (C-7), 74.0 (C-3), 41.4 (C-13), 38.3 (C-8), 26.3 (CH_3N), 25.6 (C-11), 18.2 (C-12); IR (KBr) ν_{max} 3358, 2926, 1718, 1652, 1606, 1486, 1434, 1374 cm^{-1}; EIMS *m/z* 369/367 [M^+] (6/6), 226 (50), 89 (18), 69 (100), 53 (25). FABHRMS *m/z* 367.0661 (calcd for $C_{16}H_{19}N_2O_3Br$, 367.0657).

6-Bromo-3a-hydroxy-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (8). To a cooled solution of **7b** (0.60 g, 1.80 mmol) in dry toluene (20 mL) was added 1.1 mL (3.60 mmol) of a 65% solution of Red-Al® in toluene. The resulting mixture was stirred at rt for 3 h. A 10% aqueous solution of NaOH was added followed by 100 mL of EtOAc. The organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 1:9 to give **8** (0.40 g, 70%) as a white powder; mp 76-78 °C (EtOAc/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (1H, d, *J* = 7.7 Hz, H-4), 6.77 (1H, dd, *J* = 7.7, 1.4 Hz, H-5), 6.51 (1H, d, *J* = 1.5 Hz, H-7), 5.16 (1H, dd, *J* = 7.4, 6.3 Hz, H-10), 4.68 (1H, s, H-8A),

3.80 (1H, dd, *J* = 15.7, 7.3 Hz, H-9A), 3.71 (1H, dd, *J* = 15.4, 6.4 Hz, H-9B), 3.08 (1H, ddd, *J* = 11.3, 6.3, 3.7 Hz, H-2A), 2.77 (1H, ddd, *J* = 10.2, 9.9, 6.6 Hz, H-2B), 2.14 (2H, m, H-3A, H-3B), 1.73 (6H, s, Me-12, Me-13); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7 (C-7a); 136.3 (C-11), 130.8 (C-3b), 125 (C-4), 124.0 (C-6), 120.1 (C-5), 119.5 (C-10), 109.6 (C-7), 90.7 (C-8a), 88.1 (C-3a), 45.8 (C-2), 42.9 (C-9), 42.6 (C-3), 25.9 and 18.2 (Me-11, Me-12); IR (KBr) ν_{max} 3903, 2966, 2924, 2855, 1671, 1604, 1485, 1445 cm^{-1}; FABHRMS *m/z* 323.0750 (calcd for $C_{15}H_{19}N_2OBr$, 323.0759).

Flustraminol B (1). To a solution of **8** (0.14 g, 0.42 mmol) in MeOH (10 mL) was added CH_2O (0.30 mL, 3.70 mmol) and the mixture stirred at rt for 3 h. The mixture was cooled and $NaBH_4$ (0.07 g, 1.84 mmol) was added, then warmed to rt and stirred for 1 h. The volatiles were evaporated, water (50 mL) was added and extracted with Et_2O (3 x 20 mL). The organic phase was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography eluting with EtOAc/MeOH 9:1 to give **1** (0.08 g, 53%) as a pale brown oil, whose IR, ^{1}H NMR, ^{13}C NMR and MS were in agreement with those reported for the natural compound.[8] Although **1** is known, its spectroscopic data are incomplete and ambiguous. Thus, NMR data for **1** follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (1H, d, *J* = 7.9 Hz, H-4), 6.83 (1H, dd, *J* = 7.9, 1.4 Hz, H-5), 6.62 (1H, d, *J* = 1.4 Hz, H-7), 5.18 (1H, br t, *J* = 6.9 Hz, H-10), 4.36 (1H, s, H-8a), 3.86 (1H, dd, *J* = 17.1, 5.9 Hz, H-9A), 3.81 (1H, dd, *J* = 17.1, 6.2 Hz, H-9B), 2.82 (1H, ddd, *J* = 9.5, 6.6, 4.4 Hz, H-2A), 2.64 (1H, td, *J* = 9.2, 6.3 Hz, H-2B), 2.54 (1H, br s, OH), 2.53 (3H, s, Me-14), 2.28 (1H, ddd, *J* = 11.5, 8.1, 7.0 Hz, H-3A), 2.13 (1H, ddd, *J* = 11.5, 6.2, 4.8 Hz, H-3B), 1.72 (6H, s, Me-12, Me-13); ^{13}C NMR **(**$CDCl_3$, 100 MHz) δ 152.4 (C-7a), 135.5 (C-11), 131.5 (C-3b), 124.6 (C-4), 123.8 (C-6), 120.9 (C-5), 119.9 (C-10), 111.4 (C-7), 95.7 (C-8a), 88.0 (C-3a), 53.1 (C-2), 47.6 (C-9), 40.3 (C-3), 38.7 (Me-14), 25.8 and 18.3 (Me-11, Me-12).

X-Ray diffraction analysis of 3a, 4a, 7a, and 7b. The studies were done on a Bruker Smart 6000 CCD using Mo radiation (λ = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. The data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. An empirical absorption correction was applied. The structures for compounds **4a** and **7a** were solved by direct methods using the SHELXS-97[13] program while for compounds **3a** and **7b**, the SIR02[14] software was used. Both programs are included in the WINGX v1.6[15] package. The structural refinement was carried out by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. The deposition number for **3a** is 644066, that for **4a** is 644067 and that for **7a** is 644068. Data for **7b**, having disordered[16] prenyl methyl groups, are not detailed in Table 1, but were also deposited under CCDC

number 644069.

Table 1. X-Ray data collection and processing parameters for **3a**, **4a** and **7a**.

Compound	**3a**	**4a**	**7a**
Formula	$C_{11}H_9O_2NBr_2$	$C_{11}H_9O_2NBr_2$	$C_{16}H_{18}O_4NBr$
Size (mm^3)	0.49x0.36x0.24	0.57x0.46x0.22	0.60x0.46x0.40
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	*Pcab*	$P2_1/n$	$P2_1/n$
a (Å)	8.106(2)	8.424(1)	9.2538(8)
b (Å)	14.898(3)	10.485(1)	20.093(2)
c (Å)	19.751(4)	13.462(2)	9.9130(8)
a (°)	90	90	90
β (°)	90	97.666(3)	112.943(2)
γ (°)	90	90	90
V ($Å^3$)	2385.2(9)	1178.3(2)	1697.4(3)
D_{calcd} (g cm^{-3})	1.93	1.51	1.44
Z	8	4	4
M (mm^{-1})	6.8(Mo K_α)	3.5(Mo K_α)	2.4(Mo K_α)
T (K)	298	298	298
$2\theta_{range}$ (°)	2.06 – 26.01	2.47 – 25.98	2.56 – 25.99
Total reflections	15970	7503	11251
Unique reflections	2331	2316	3323
R_{int} (%)	0.0001	0.05	0.0001
Observed reflections	1052 $I \geq 4\sigma(I)$	1631 $I \geq 4\sigma(I)$	2013 $I \geq 4\sigma(I)$
Parameters	150	149	208
R (%), R_w (%)	3.5, 7.5	3.8, 8.7	3.6, 8.4
e_{max} ($eÅ^{-3}$)	0.30	0.70	0.31

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