Reactions of the Cyclic Tautomer of 3-Indoleacetamides. Synthesis of N_b-Methyl-4,5,6-tribromo-3-indoleacetamide[1)]

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The cyclic tautomer (5) of N_b-methyl-3-indoleacetamide (4) has been prepared by dissolving 4 in phosphoric acid. The bromination of 5 with 1 or 2 mol of *N*-bromosuccinimide (NBS) or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) gave the 5-bromo- (8) and the 5,7-dibromo (9) derivatives. On the other hand, the 5-bromo derivative (11) was the major product of the bromination of the *N*-acetyl cyclic tautomer (6) even with 2 mol of NBS. The 5-nitro derivative (17) was obtained in excellent yield by the nitration of 6 with ammonium nitrate in trifluoroacetic anhydride (TFAA). Reduction of 17 followed by bromination gave the 4,6-dibromo derivative (19), which gave the tribromide (20) in the Sandmeyer reaction. The 4,5,6-tribromo-3-indoleacetamide (7), which is the indole moiety of a marine indole alkaloid, chartelline A, was obtained by the ring opening of 20. Furthermore, the oxidation of 5 with lead tetraacetate followed by acetylation gave the 5-acetoxy derivative (22). The selective hydrolysis and bromination of 22 gave the 4,6-dibromo-5-hydroxy derivative (24).

Keywords cyclic tautomer; 3-indoleacetamide; nitration; bromination; 4,5,6-tribromoindole; chartelline; *N*-bromosuccinimide; ammonium nitrate

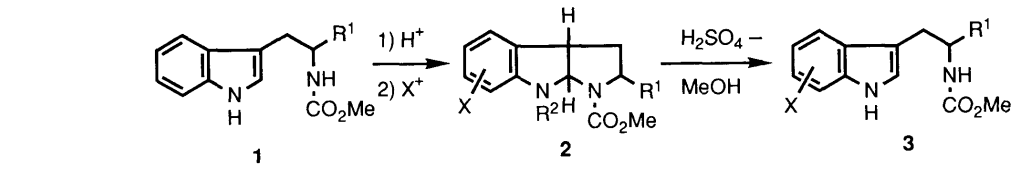
We have previously reported that the cyclic tautomer (**2**, X=H) could readily be obtained from N_b-acyltryptophans (**1**), and its electrophilic substitution reaction provided a convenient method for the preparation of the 5- and 6-substituted tryptophans (**3**) from tryptophan *via* **2**.[2)]

In this paper we describe the preparation and reactions of the cyclic tautomers (**5** and **6**) of the 3-indoleacetamide (**4**) and the synthesis of N_b-methyl-4,5,6-tribromo-3-indoleacetamide (**7**), which is the indole moiety of chartelline A, a unique indole alkaloid isolated from marine Bryozoa.[3)] Regioselective synthesis of 4,5,6-tribromo-3-indolecarbaldehyde and other tri- and tetrabromoindoles related to marine natural products has recently been reported by Ohta and Somei by different approaches.[4)]

When the indoleacetamide (**4**) was dissolved in 85% phosphoric acid at room temperature as in the case of **1**, the corresponding cyclic tautomer (**5**), mp 149—150 °C, was obtained in 56% yield. Acetylation of **5** with acetic anhydride–pyridine readily gave the 8-acetyl derivative (**6**). The ultraviolet (UV) spectrum of **5** showed an indoline chromophore (λ_{max} 243 and 296 nm) and its ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed a multiplet at 4.03 ppm due to the 3a proton and a doublet at 5.33 ppm due to the 8a proton. The NMR spectrum of the acetyl derivative (**6**) showed the presence of rotamers due to slow rotation of the C–N bond of the *N*-acetyl group; *i.e.*, two small peaks appeared at 4.07 (3a-H) and 5.90 (8a-H) ppm besides a broad peak at 3.95 ppm due to the 3a proton and a broad doublet at 6.33 ppm due to the 8a proton.[2d)]

The cyclic tautomer (**5**) was stable in acetic acid, compared with the cyclic tautomer (**2**, X, R^2=H, R^1=CO_2Me), which readily reverted to **1** in acetic acid.[2d)] However, the cyclic tautomers (**5** and **6**) reverted to the indole (**4**) on treatment with 10% sulfuric acid (H_2SO_4)–methanol (MeOH) at room temperature.

The bromination of **5** with *N*-bromosuccinimide (NBS)[2f)] (1 mol eq) in methylene chloride (CH_2Cl_2) at room temperture gave the 5-bromo derivative (**8**) in 90% yield along with the 5,7-dibromo derivative (**9**, 8%). The reaction with 2 mol eq of NBS gave **9** in 89% yield. The bromination of **5** with NBS (1 mol eq) in acetic acid (AcOH) at room temperature gave **8** (63%) and **9** (16%), while **9** (47%) and the 5,7-dibromo-3-indoleacetamide (**10**, 43%) were ob-



R^1=CO_2Me or H ; R^2=H or Ac ; X=H, 5-Br, 5-NO_2, 5-OH, 6-OH, 6-Br

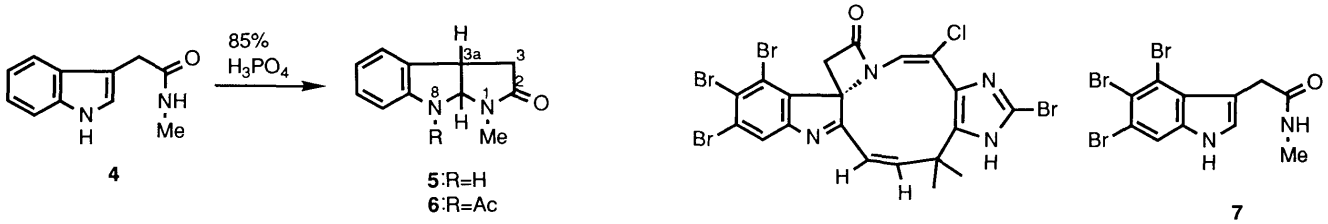


Chart 1

tained with 2 mol eq of NBS. The latter compound (**10**) was probably formed from **9** under these reaction conditions. The bromination of **8** with NBS (1 mol eq) in AcOH gave **9** (94%). The bromination of **5** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO)[5] in CH_2Cl_2 gave similar results (see Experimental). The bromination of **9** with NBS (1 mol eq) in AcOH did not give the tribromo derivative, and **9** was recovered.

On the other hand, the bromination of the *N*-acetyl cyclic tautomer (**6**) with NBS or TABCO did not proceed at room

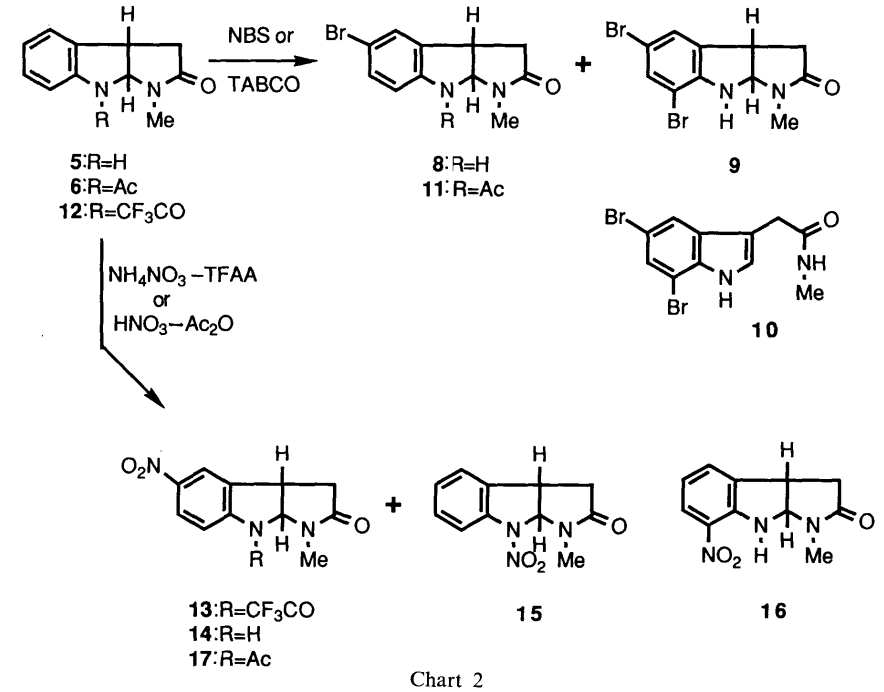


Chart 2

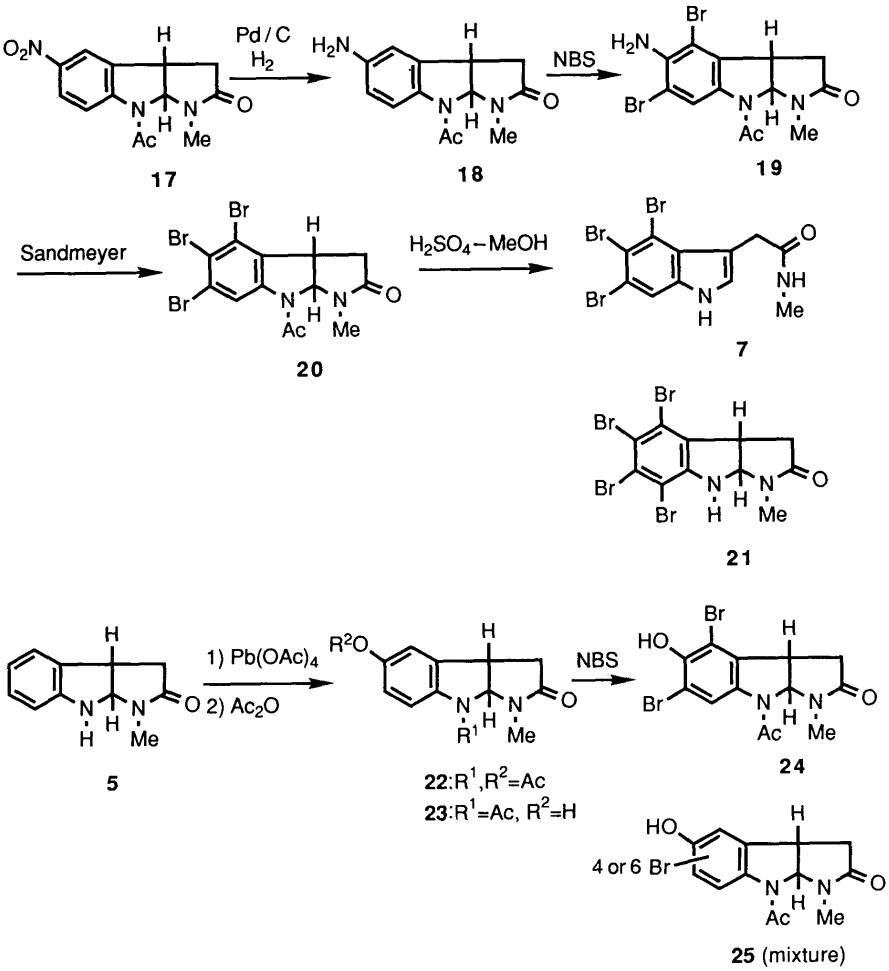


Chart 3

temperature in CH_2Cl_2 or AcOH. However, the bromination of **6** with NBS in AcOH at refluxing temperature gave the 5-bromo derivative (**11**) in 91% yield. The reaction of **6** using 2 mol eq of NBS in boiling AcOH gave only **11** and not the 5,7-dibromo derivative. The bromination of **6** with TABCO gave poorer results (see Experimental). It is interesting to note that the bromination of **2** (R^1, X=H, R^2=Ac) with NBS in AcOH and the chlorination of **2** (X=H, R^1=CO_2Me, R^2=Ac) with *N*-chlorosuccinimide (NCS) proceeded at room temperature to give the 5-substituted derivative in excellent yield,[2b,f] whereas **6** required the refluxing temperature of AcOH. The above result indicated that 4,5,6-tribromoindole could not be obtained by direct bromination of **8** or **11**.

We next examined the nitration of **5** with ammonium nitrate (NH_4NO_3) in trifluoroacetic anhydride (TFAA).[6] The reaction at 0 °C gave the 5-nitro-8-trifluoroacetyl derivative (**13**), which was converted to the 5-nitro derivative (**14**) by refluxing in MeOH. The reaction probably proceeded first to give **12**, which was isolated from the reaction at −60 °C, and **12** was nitrated to give **13**. On the other hand, the nitration of **5** with fuming nitric acid (HNO_3) in acetic anhydride at −10 °C gave the 8-nitro derivative (**15**, 21%), mp 130—131 °C, along with **6**. The structure of **15** was fully supported by spectral data and elemental analysis. Furthermore, **14** was obtained in 20% yield along with **5** (13%) and the 7-nitro derivative (**16**, 19%), when **15** was refluxed in MeOH. The nitration of **6** with fuming HNO_3 at −10 °C[2f] or with NH_4NO_3 in TFAA at room temperature gave the 5-nitro derivative (**17**) in 91% yield or 89% yield, and the 7-nitro derivative could not be obtained.

The catalytic hydrogenation of **13** and **14** in the presence of Pd–C in MeOH smoothly gave the corresponding amino derivatives, which were not stable and readily discolored in air. Similar catalytic hydrogenation of **17** gave the corresponding amine (**18**) which gave the 4,6-dibromo derivative (**19**) in 45% yield from **17** on bromination with NBS (2 mol eq) in AcOH. Sandmeyer reaction of **19** gave the tribromo derivative (**20**) in 86% yield. Ring opening of **20** with 10% H_2SO_4 in MeOH readily gave *N*-methyl-4,5,6-tribromo-3-indoleacetamide (**7**). On the other hand, the tetrabromide (**21**, 89%) was obtained by the Sandmeyer reaction for 5d at room temperature.

Oxidation of **5** with lead tetraacetate in trifluoroacetic acid (TFA) followed by reduction of the resulting quinoneimine with zinc[2b,g] and acetylation gave the 5-acetoxy-8-acetyl derivative (**22**) in 44% yield. The 6-acetoxy and other isomers could not be isolated. Selective hydrolysis of **22** with potassium carbonate (K_2CO_3) in MeOH smoothly gave the 5-hydroxy derivative (**23**). The bromination of **23** with NBS (2 mol eq) in CH_2Cl_2 gave the 4,6-dibromo derivative (**24**) in 70% yield along with the monobromo derivatives (**25**, 17%), which gave **24** (82%) on further bromination.

In conclusion, the cyclic tautomers (**5** and **6**) were found to be useful intermediates for the preparation of substituted 3-indoleacetamides.

Experimental

Melting points were measured with a Yamato MR-1 apparatus and are not corrected. The UV spectra were taken with Hitachi 323 and 340 spectrometers, and the infrared (IR) spectra with Hitachi 260-10 and 295 spectrometers. The mass spectra (MS) were recorded on Hitachi M-60 and 7M spectrometers, and the NMR spectra in $CDCl_3$ solution on JEOL JNM-GX-270, GSX-400, and GSX-500 apparatus using tetramethylsilane as an internal standard. Kieselgel (Merck, 300 mesh) was used for flash columns. Kieselgel 60 (Merck, 70—230 mesh) or Silica gel BW-820MH (Fuji-Davison) was used for open columns. Kieselgel GF_{254} type 60 (Merck) DCl Fertigplatten SILG-50 UV_{254} was used for preparative thin layer chromatography (TLC).

***N*$_b$-Methyl-3-indoleacetamide (4)** Methylamine (40% aqueous solution, 150 ml) was added to a solution of methyl 3-indoleacetate (106 g, 0.56 mol) in MeOH (350 ml) at room temperature, and the mixture was stirred for 15 h, then evaporated to leave a residue, which was recrystallized from AcOEt–hexane to give **4** (102 g, 97%). Recrystallization from AcOEt–hexane gave pale brown needles, mp 101—102 °C. UV λ_{max} (EtOH) nm (ε): 222 (25300), 273 (5480), 280 (6000), 289 (5100). IR ν_{max} (KBr) cm^{-1}: 3300 (NH), 1630 (CO). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.12; H, 6.44; N, 14.86.

1-Methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (5) **4** (10.0 g, 53.2 mmol) was dissolved in 85% phosphoric acid (70 ml) at room temperature. The solution was stirred for 17 h at room temperature, and then poured into chilled 20% Na_2CO_3 solution (300 ml). The mixture was extracted with CH_2Cl_2 and the extract was washed with saturated NaCl solution, and then dried. Evaporation of the solvent gave a residue (9.96 g), which was chromatographed on a silica gel column (500 g, AcOEt–hexane–MeOH, 40 : 1 : 1—60 : 1 : 2) to give **5** (5.64 g, 56%), **4** (1.6 g, 16%), and more polar products. Recrystallization of **5** from acetone–hexane gave colorless needles, mp 149—150 °C. UV λ_{max} (MeOH) nm (ε): 243 (6600), 296 (2500). IR ν_{max} (KBr) cm^{-1}: 1650 (CO). MS *m/z* (rel. intensity): 188 (M^+, 100), 130 (85). ^{1}H-NMR (270 MHz) δ: 2.62 (1H, dd, J=17.1, 2.4 Hz, 3-Ha), 2.85 (3H, s, NCH_3), 2.93 (1H, dd, J=17.1, 10.4 Hz, 3-Hb), 4.03 (1H, m, 3a-H), 4.56 (1H, br, 8-H), 5.33 (1H, d, J=7.6 Hz, 8a-H), 6.66—7.12 (4H, m, arom. H). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18, H, 6.43; N, 14.88. Found: C, 70.23; H, 6.51; N, 14.81.

8-Acetyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (6) **5** (1.53 g, 8.1 mmol) was dissolved in acetic anhydride (15 ml) and pyridine (50 ml), and the mixture was stirred overnight. Usual work up gave **6** (1.89 g, 100%). Recrystallization from acetone–hexane gave colorless needles, mp 184—186 °C. UV λ_{max} (EtOH) nm (ε): 205 (25600), 243 (12900), 276 (2300). IR ν_{max} (KBr) cm^{-1}: 1700, 1655 (CO). ^{1}H-NMR (270 MHz) δ: 2.47 (3H, s, CH_3CO), 2.63 (1H, d-like, 3-Ha), 2.90 (3H, s, NCH_3), 2.95 (1H, m, 3-Hb), 3.95 (4/5H, br, 3a-H), 4.07 (1/5H, br, 3a-H), 5.90 (1/4H, br, 8a-H), 6.33 (3/4H, br d, 8a-H), 7.10—7.30 (4H, m, arom. H). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.18; N, 12.17. Found: C, 67.58; H, 6.11; N, 12.07.

Bromination of 5 1) NBS in CH_2Cl_2: NBS (104 mg, 1.1 eq) was added to a solution of **5** (100 mg, 0.532 mmol) in CH_2Cl_2 (6 ml) at room temperature, and the mixture was stirred for 5 min. The mixture was evaporated to leave a residue (216 mg), which was separated by flash column chromatography (SiO_2, 15 g, AcOEt–hexane–MeOH, 3 : 1 : 10—15 : 0 : 1) to give **8** (128 mg, 90%) and **9** (14.6 mg, 8%). Recrystallization of **8** from acetone–hexane gave colorless prisms, mp 187.5—188 °C. UV λ_{max} (MeOH) nm (ε): 253 (10400), 309 (2500). IR ν_{max} (KBr) cm^{-1}: 3300 (NH), 1660 (CO). MS *m/z* (rel. intensity): 268 (M^+, 100), 266 (M^+, 100). ^{1}H-NMR (270 MHz) δ: 2.59 (1H, dd, J=16.9, 2.2 Hz, 3-Ha), 2.84 (3H, s, NCH_3), 2.91 (1H, dd, J=16.9, 9.9 Hz, 3-Hb), 4.02 (1H, m, 3a-H), 4.62 (1H, br, NH), 5.34 (1H, d, J=8.1 Hz, 8a-H), 6.54 (1H, d, J=8.1 Hz, 7-H), 7.19 (1H, d, J=8.1 Hz, 6-H), 7.20 (1H, s, 4-H). *Anal.* Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.37; H, 4.04; N, 10.59. Recrystallization of **9** from acetone–hexane gave colorless needles, mp 240—243 °C. UV λ_{max} (EtOH) nm (ε): 212 (27900), 254 (10600), 315 (3200). IR ν_{max} (KBr) cm^{-1}: 3320 (NH), 1685 (CO). MS *m/z* (rel. intensity): 348 (M^+, 36), 346 (M^+, 70), 344 (M^+, 36), 42 (100). ^{1}H-NMR (270 MHz) δ: 2.58 (1H, dd, J=17.1, 2.8 Hz, 3-Ha), 2.88 (3H, s, NCH_3), 2.93 (1H, m, 3-Hb), 4.11 (1H, m, 3a-H), 4.80 (1H, s, NH), 5.40 (1H, dd, J=7.6, 2.4 Hz, 8a-H), 7.14 (1H, d, J=1.8 Hz, 6-H), 7.37 (1H, d, J=1.8 Hz, 4-H). The presence of the 4-H was supported by a difference nuclear Overhauser effect (NOE) experiment, which showed enhancements between 3a-H and 3-Ha (6.2%), 3a-H and 4-H (1.0%), and 3a-H and 8a-H (6.3%). *Anal.* Calcd for $C_{11}H_{10}Br_2N_2O$: C, 38.18; H, 2.91; N, 8.10. Found: C, 37.92; H, 2.88; N, 7.98.

Bromination of **8** (52 mg) with NBS (38 mg, 1.1 eq) in AcOH (2 ml) gave **9** (63 mg, 94%). Bromination of **5** (300 mg, 1.57 mmol) with NBS (597 mg, 2.0 eq) in CH_2Cl_2 (10 ml) at room temperature gave **9** (493 mg, 89%).

2) TABCO–CH_2Cl_2: TABCO (120 mg, 1.1 eq) was added to a solution

of **5** (50 mg, 0.266 mmol) in CH_2Cl_2 (5 ml) at room temperature. The mixture was stirred for 10 min, and worked up as above to give **8** (59 mg, 84%) and **9** (11 mg, 12%). The reaction of **5** (50 mg) with TABCO (229 mg, 2.1 eq) in CH_2Cl_2 (5 ml) gave **9** (91 mg, 99%).

3) NBS–AcOH: NBS (298 mg, 2.1 eq) was added to a solution of **5** (150 mg, 0.798 mmol) in AcOH (4 ml) at room temperature. The mixture was stirred for 30 min at room temperature and the solvent was evaporated off to leave a residue. The residue (522 mg) was chromatographed on a silica gel column (40 g, AcOEt–hexane (2 : 1)–AcOEt) to give **10** (118 mg, 43%) and **9** (129 mg, 47%). Recrystallization of **10** from acetone–hexane gave colorless powder, mp 170—172 °C. UV λ_{max} (EtOH) nm: 231, 284, 296, 307. IR ν_{max} (KBr) cm^{-1}: 3290 (NH), 1640 (CO). MS *m/z* (rel. intensity): 348 (M^+, 17), 346 (M^+, 33), 344 (M^+, 18), 288 (100). ^{1}H-NMR (400 MHz, in CD_3OD) δ: 2.71 (3H, s, NCH_3), 3.59 (2H, s, CH_2), 7.29 (1H, s, 2-H), 7.40 (1H, d, J=1.7 Hz, 4-H), 7.70 (1H, d, J=1.7 Hz, 6-H).

The reaction of **5** with NBS (1 eq) in AcOH gave **8** (63%) and **9** (16%).

Bromination of 6 1)NBS–AcOH: NBS (426 mg, 1.1 eq) was added to a solution of **6** (500 mg, 2.17 mmol) in AcOH (8 ml) and the mixture was refluxed for 1 h, and allowed to cool. Then 20% K_2CO_3 solution (30 ml) was added, and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated NaCl solution and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (35 g, AcOEt–hexane (3 : 1—5 : 1)) to give **11** (610 mg, 91%). Recrystallization of **11** from acetone–hexane gave a colorless powder, mp 198—201 °C. UV λ_{max} (EtOH) nm (ε): 206 (19200), 252 (18100), 285 (2600), 293 (2300). IR ν_{max} (KBr) cm^{-1}: 1695, 1670 (CO). MS *m/z* (rel. intensity): 310 (M^+, 84), 308 (M^+, 85), 268 (100), 266 (99). ^{1}H-NMR (270 MHz) δ: 2.44 (3H, s, CH_3CO), 2.61 (1H, d-like, 3-Ha), 2.89 (3H, s, NCH_3), 2.94 (1H, m, 3-Hb), 3.94 (2/3H, br t, 3a-H), 4.05 (1/3H, br, 3a-H), 5.87 (1/3H, br, 8a-H), 6.31 (2/3H, br d, 8a-H), 7.38 (1H, d, J=1.8 Hz, 4-H), 7.40 (1H, dd, J=7.6, 1.8 Hz, 6-H), 7.02 (2/3H, br d, 7-H), 7.93 (1/3H, br s, 7-H). *Anal.* Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.51; H, 4.24; N, 9.06. Found: C, 50.34; H, 4.21; N, 8.99.

The same compound was obtained by acetylation of **8** with acetic anhydride–pyridine. The reaction of **6** with NBS (2 eq) in boiling AcOH gave **11** (80%) and the dibromide was not obtained.

2) TABCO–CH_2Cl_2: TABCO (98 mg, 1.1 eq) was added to a solution of **6** (50 mg, 0.217 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred overnight at room temperature to give **6**, and the mixture was refluxed for 16 h. The solvent was evaporated off to leave a residue, which was subjected to flash column chromatography (SiO_2, 10 g, AcOEt) to give **11** (37 mg, 56%), and **6** (15 mg, 31%).

Nitration of 5 1)NH_4NO_3–TFAA at −10 °C: NH_4NO_3 (22 mg, 1.05 eq) was added to a solution of **5** (50 mg, 0.266 mmol) in TFAA (3 ml) at −60 °C. The mixture was stirred for 6.5 h at −10 °C, then was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (5 g, AcOEt–hexane (2 : 1—1 : 0)) to give **13** (67 mg, 88%). Recrystallization from acetone–hexane gave a colorless powder, mp 233—236 °C. UV λ_{max} (EtOH) nm: 225, 306; (EtOH–NaOH) nm: 225, 315, 365. IR ν_{max} (KBr) cm^{-1}: 1720, 1680 (CO). MS *m/z* (rel. intensity): 329 (M^+, 100), 260 (57). ^{1}H-NMR (270 MHz) δ: 2.80 (1H, br d, J=17.4 Hz, 3-Ha), 2.88 (3H, s, NCH_3), 3.03 (1H, dd, J=17.1, 8.6 Hz, 3-Hb), 4.20 (1H, t-like, J=7.3 Hz, 3a-H), 6.26 (1H, br, 8a-H), 7.70—8.45 (1H, br, 7-H), 8.19 (1H, dd, J=2.4, 1.2 Hz, 4-H), 8.29 (1H, dd, J=8.9, 2.2 Hz, 6-H); at 50 °C: 2.78 (1H, br d, J=17.1 Hz, 3-Ha), 2.87 (3H, s, NCH_3), 3.00 (1H, dd, J=17.1, 8.5 Hz, 3-Hb), 4.16 (1H, dd, J=8.2, 7.0 Hz, 3a-H), 6.24 (1H, d, J=7.0 Hz, 8a-H), 8.02 (1H, br d, 7-H), 8.17 (1H, dd, J=2.4, 1.2 Hz, 4-H), 8.28 (1H, dd, J=8.9, 2.4 Hz, 6-H). *Anal.* Calcd for $C_{13}H_{10}F_3N_3O_4$: C, 47.43; H, 3.06; N, 12.76. Found: C, 47.38; H, 3.07; N, 12.79.

When the reaction was quenched after 30 min at −60 °C under the above conditions, **12**, mp 117—118 °C (MeOH), was obtained in 99% yield. UV λ_{max} (EtOH) nm: 250, 275, 283. IR ν_{max} (KBr) cm^{-1}: 1700, 1670 (CO). MS *m/z* (rel. intensity): 284 (M^+, 100), 215 (70). ^{1}H-NMR (270 MHz) δ: 2.72 (1H, br d, 3-Ha), 2.86 (3H, s, NCH_3), 2.95 (1H, dd, J=17.1, 8.5 Hz, 3-Hb), 4.07 (1H, br, 3a-H), 6.15 (1H, br, 8a-H), 7.24—7.96 (3H, m, 4,5,6-H), 8.03 (1H, br, 7-H). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 54.79; H, 3.90; N, 9.89.

2) NH_4NO_3–TFAA at 0 °C: NH_4NO_3 (223 mg, 1.05 eq) was added to a solution of **5** (500 mg, 2.66 mmol) in TFAA (8 ml) at 0 °C. The mixture was stirred for 6.5 h at 0 °C, and poured into ice-water (50 ml). This mixture was extracted with CH_2Cl_2 and the extract was washed with H_2O and dried. Evaporation of the solvent gave a residue (crude **13**, 865 mg), which was dissolved in MeOH (50 ml). The solution was refluxed for 1.5 h and evaporated to leave a residue, which was chromatographed on a silica gel column (35 g, AcOEt–acetone (1 : 0—1 : 1—0 : 1)) to give **14** (610 mg, 98%). Recrystallization from MeOH gave a yellow powder, mp 234—237 °C. UV λ_{max} (EtOH) nm (ε): 201 (22300), 230 (5600), 243 (4700), 304 (2400), 314 (3400), 369 (14500). IR ν_{max} (KBr) cm^{-1}: 3300 (NH), 1685 (CO). MS *m/z* (rel. intensity): 233 (M^+, 100), 175 (70). ^{1}H-NMR (270 MHz) δ: 2.66 (1H, dd, J=17.7, 2.5 Hz, 3-Ha), 2.88 (3H, s, NCH_3), 3.04 (1H, dd, J=17.1, 9.8 Hz, 3-Hb), 4.09 (1H, m, 3a-H), 5.33 (1H, br, NH), 5.50 (1H, d, J=7.9 Hz, 8a-H), 6.60 (1H, d, J=8.9 Hz, 7-H), 8.01 (1H, br, 4-H), 8.07 (1H, dd, J=8.9, 0.6 Hz, 6-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.71; H, 4.74; N, 17.96.

3) HNO_3–Ac_2O: **5** (50 mg, 0.266 mmol) was added to a chilled solution of fuming HNO_3 (d=1.50, 0.014 ml) in acetic anhydride (1.4 ml) at −10 °C, and the mixture was stirred for 1 h at the same temperature. Work-up as above gave **15** (13 mg, 21%) and **6** (39 mg, 64%). Recrystallization of **15** from AcOEt–hexane gave pale yellow needles, mp 130—131 °C. UV λ_{max} (EtOH) nm (ε): 271 (6400), 282 (7400), 291 (7700). IR ν_{max} (KBr) cm^{-1}: 1710 (CO), 1535, 1475 (NO_2). ^{1}H-NMR (500 MHz) δ: 2.59 (1H, dd, J=17.3, 2.8 Hz, 3-Ha), 3.02 (1H, dd, J=17.3, 10.2 Hz, 3-Hb), 3.07 (3H, s, NCH_3), 4.25 (1H, t-like, 3a-H), 6.51 (1H, d, J=8.0 Hz, 8a-H), 7.27 (1H, d, J=8.3 Hz, 4-H), 7.31 (1H, t, J=8.3 Hz, 6-H), 7.41 (1H, m, 5-H), 7.86 (1H, d, J=8.3 Hz, 7-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.78; H, 4.84; N, 17.84.

Reaction of 15 in Boiling MeOH A solution of **15** (100 mg, 0.429 mmol) in MeOH (8 ml) was refluxed for 23 h. Evaporation of the solvent gave a residue, which was separated by flash column chromatography (SiO_2, 8 g, AcOEt–hexane (5 : 1—1 : 0)) to give **14** (20 mg, 20%), **15** (10 mg, 10%), **16** (19 mg, 19%), and **5** (10 mg, 13%). Recrystallization of **16** from AcOEt–hexane gave pale yellow needles, mp 214—216 °C. UV λ_{max} (EtOH) nm: 238, 277, 398. IR ν_{max} (KBr) cm^{-1}: 3420 (NH), 1685 (CO), 1510, 1450 (NO_2). ^{1}H-NMR (500 MHz) δ: 2.65 (1H, dd, J=17.3, 2.2 Hz, 3-Ha), 2.92 (3H, s, NCH_3), 3.01 (1H, dd, J=17.3, 9.9 Hz, 3-Hb), 4.09 (1H, ddd, J=9.9, 8.8, 2.2 Hz, 3a-H), 5.56 (1H, d, J=8.8 Hz, 8a-H), 6.76 (1H, dd, J=8.5, 7.2 Hz, 5-H), 7.31 (1H, d, J=7.2 Hz, 4-H), 7.37 (1H, br, NH), 7.90 (1H, d, J=8.8 Hz, 6-H).

Nitration of 6 NH_4NO_3 (730 mg, 1.05 eq) was added gradually to a solution of **6** (2.00 g, 8.70 mmol) in TFAA (30 ml) under ice cooling. The mixture was stirred for 3 h at room temperature, then poured into ice-water (150 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and dried. Evaporation of the solvent gave a residue (2.68 g), which was recrystallized from acetone–hexane to give **17** (2.13 g, 89%) as cotton-like crystals, mp 239.5—241.5 °C. UV λ_{max} (EtOH) nm (ε): 205 (4300), 229 (9900), 318 (12400). IR ν_{max} (KBr) cm^{-1}: 1695 sh, 1670 (CO), 1515, 1480 (NO_2). MS *m/z* (rel. intensity): 275 (M^+, 49), 233 (100). ^{1}H-NMR (270 MHz) δ: 2.52 (3H, s, CH_3CO), 2.73 (1H, d-like, 3-Ha), 2.92 (3H, s, NCH_3), 3.02 (1H, dd, J=17.5, 9.3 Hz, 3-Hb), 4.10 (1H, br, 3a-H), 6.30 (1H, br, 8a-H), 7.10—7.60 (1H, br, 7-H), 8.14 (1H, br, 4-H), 8.24 (1H, dd, J=8.2, 1.8 Hz, 6-H); at 50 °C: 2.50 (3H, s, CH_3CO), 2.70 (1H, d-like, 3-Ha), 2.91 (3H, s, NCH_3), 3.00 (1H, dd, J=17.4, 9.2 Hz, 3-Hb), 4.06 (1H, t-like, 3a-H), 6.20 (1H, br, 8a-H), 7.62 (1H, br, 7-H), 8.11 (1H, d, J=2.1 Hz, 4-H), 8.21 (1H, dd, J=8.9, 2.1 Hz, 6-H). *Anal.* Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.77; N, 15.16.

Compound **17** was also obtained by the acetylation of **14** with acetic anhydride–pyridine. The nitration of **6** with fuming HNO_3 (d=1.5) at −10 °C gave **17** in 91% yield.

8-Acetyl-5-amino-4,6-dibromo-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (19) from 17 A mixture of **17** (1.96 g, 7.13 mmol), MeOH (50 ml), 10% Pd–C (300 mg), and concentrated HCl (2 drops) was hydrogenated for 4.5 h under an H_2 atmosphere and at atmospheric pressure. The mixture was filtered and the filtrate was evaporated to leave a residue, which was dissolved in H_2O (20 ml) and CH_2Cl_2 (50 ml). The aqueous layer was basified with 20% K_2CO_3 solution and extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was dried and evaporated to leave a crude amine (**18**, 1.91 g). UV λ_{max} (EtOH) nm: 268, 312. NBS (2.66 g, 2.1 eq) was added gradually to a solution of the above **18** in AcOH (20 ml), and the mixture was stirred overnight at room temperature. Then 20% K_2CO_3 solution was added to the solution to make it alkaline under ice-cooling. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 solution was washed with saturated NaCl solution and dried. Evaporation of the solvent gave a residue, which was subjected to silica gel flash column chromatography (120 g, AcOEt–hexane–MeOH (20 : 2 : 1—20 : 1 : 2)) to give **19** (1.30 g, 45%). Recrystallization from MeOH gave a colorless powder, mp 234—237 °C. UV λ_{max} (EtOH) nm (ε): 212 (27800), 265 (14900), 324 (4700). IR ν_{max} (KBr) cm^{-1}: 3460, 3340

(NH), 1690 (CO). MS *m/z* (rel. intensity): 405 (M^+, 53), 403 (M^+, 100), 401 (M^+, 50), 363 (39), 361 (78), 359 (40). ^{1}H-NMR (270 MHz) δ: 2.40 (3H, s, CH_3CO), 2.92 (3H, s, NCH_3), 2.8—3.1 (2H, m, 3-H_2), 3.93 (1H, br, 3a-H), 4.52 (2H, br, 5-NH_2, exchangeable), 5.90 (1/3, br s, 8a-H), 6.28 (2/3H, br, 8a-H), 7.21 (2/3H, br, 7-H), 8.19 (1/3H, br, 7-H). *Anal.* Calcd for $C_{13}H_{13}Br_2N_3O_2$: C, 38.74; H, 3.25; N, 10.42. Found: C, 38.69; H, 3.27; N, 10.36.

1-Acetyl-4,5,6-tribromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (20). Sandmeyer Reaction of 19 $NaNO_2$ (22 mg, 1.3 eq) was added gradually to a solution of **19** (100 mg, 0.248 mmol) in 48% HBr solution (3 ml) at 0 °C, and the mixture was stirred for 30 min. CuBr (75 mg, 2.1 eq) was added to the mixture at 0 °C, and the whole was stirred for 4.5 h at the same temperature. AcOEt and 20% K_2CO_3 solution (15 ml) were then added and the aqueous solution was extracted with AcOEt. The combined AcOEt solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave a residue, which was chromatographed on a silica gel column (7 g, CH_2Cl_2–MeOH (100 : 1)) to give **20** (100 mg, 86%). Recrystallization from MeOH gave pale yellow needles, mp 214—215 °C. UV λ_{max} (EtOH) nm (ε): 224 (34400), 255 (13100), 294 (2000), 304 (1600). IR ν_{max} (KBr) cm^{-1}: 1720, 1680 (CO). MS *m/z* (rel. intensity): 470 (M^+, 14), 468 (M^+, 39), 466 (M^+, 40), 464 (M^+, 14), 428 (24), 426 (71), 424 (73), 422 (25), 42 (100). ^{1}H-NMR (270 MHz) δ: at 40 °C: 2.43 (3H, s, CH_3CO), 2.92 (5H, br, NCH_3, $3H_2$), 4.10 (1H, t-like, 3a-H), 6.15 (1H, br, 8a-H), 7.44 (1/3H, s, 7-H), 7.70 (2/3H, br, 7-H). *Anal.* Calcd for $C_{13}H_{11}Br_3N_2O_2$: C, 33.44; H, 2.34; N, 6.00. Found: C, 33.69; H, 2.44; N, 6.14.

When the reaction mixture after the addition of CuBr (3 eq) was stirred for 5 d at room temperature, and treated as above, the tetrabromide (**21**), mp 228.5—229.5 °C (from CH_2Cl_2–hexane), was obtained in 89% yield. UV λ_{max} (EtOH) nm: 228, 263, 305, 327. IR ν_{max} (KBr) cm^{-1}: 3280 (NH), 1660 (CO). MS *m/z* (rel. intensity): 508 (M^+, 2), 506 (M^+, 9), 504 (M^+, 14), 502 (M^+, 10), 500 (M^+, 3), 450 (17), 448 (66), 446 (100), 444 (68), 442 (18). Exact MS Calcd for $C_{11}H_8{}^{79}Br_4N_2O$: 499.7369. Found: 499.7361; Calcd for $C_{11}H_8{}^{79}Br_3{}^{81}BrN_2O$: 501.7349. Found: 501.7333; Calcd for $C_{11}H_8{}^{79}Br_2{}^{81}Br_2N_2O$: 503.7329. Found: 503.7322; Calcd for $C_{11}H_8{}^{79}Br^{81}Br_3N_2O$: 505.7309. Found: 505.7305; Calcd for $C_{11}H_8{}^{81}Br_4N_2O$: 507.7289. Found: 507.7274. ^{1}H-NMR (270 MHz) at 55 °C δ: 2.71 (1H, dd, J=18.0, 4.0 Hz, 3-Ha), 2.90 (3H, s, NCH_3), 2.98 (1H, dd, J=18.0, 10.4 Hz, 3-Hb), 4.14 (1H, ddd, J=10.2, 8.2, 4.2 Hz, 3a-H), 5.02 (1H, br, NH, exchangeable), 5.47 (1H, d, J=8.2 Hz, 8a-H).

***N*$_b$-Methyl-4,5,6-tribromo-3-indoleacetamide (7)** A solution of **20** (310 mg, 0.664 mmol) in 10% H_2SO_4–MeOH (8 ml) was stirred overnight at room temperature, then 20% K_2CO_3 solution (30 ml) was added under ice-cooling. The mixture was extracted with AcOEt. The AcOEt solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave crude **7** (272 mg, 96%). Recrystallization from AcOEt–hexane gave colorless needles, mp 207—210.5 °C. UV λ_{max} (EtOH) nm (ε): 204 (21200), 237 (48000), 283 (5600), 294 (6000), 306 (4900). IR ν_{max} (KBr) cm^{-1}: 3400 (NH), 1630 (CO). MS *m/z* (rel. intensity): 428 (M^+, 6), 426 (M^+, 16), 424 (M^+, 17), 422 (M^+, 6), 370 (33), 368 (99), 366 (100), 364 (35). ^{1}H-NMR (500 MHz, in CD_3OD) δ: 2.70 (3H, s, NCH_3), 3.84 (2H, s, CH_2), 7.31 (1H, s, 2-H), 7.74 (1H, s, 7-H). *Anal.* Calcd for $C_{11}H_9Br_3N_2O$: C, 31.09; H, 2.13; N, 6.59. Found: C, 31.16; H, 2.21; N, 6.68.

5-Acetoxy-8-acetyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (22) A solution of lead tetraacetate (9.43 g, 2.0 eq) in CH_2Cl_2 (60 ml) was added gradually to a solution of **5** (2.00 g, 10.6 mmol) in TFA (25 ml) under ice-cooling. The mixture was stirred for 20 min, then Zn powder (5.0 g) was added under ice-cooling. Stirring was continued for 30 min. Water (100 ml) was then added and the mixture was extracted with CH_2Cl_2. The aqueous solution was made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave a residue (crude 5-hydroxy-1-methylhexahydropyrroloindol-2-one, 1.48 g), which was dissolved in Ac_2O (15 ml) and pyridine (50 ml). The solution was stirred overnight at room temperature. Work-up as usual gave **22** (1.35 g, 44%), mp 158.5—161.5 °C (from acetone–hexane), as colorless cotton like crystals. UV λ_{max} (EtOH) nm (ε): 205 (9600), 246 (11900), 281 (2000), 286 (1900); (EtOH–NaOH): 273, 312 nm. IR ν_{max} (KBr) cm^{-1}: 1757, 1705, 1670 (CO). MS *m/z* (rel. intensity): 288 (M^+, 29), 204 (100). ^{1}H-NMR (270 MHz) at 50 °C δ: 2.28 (3H, s, CH_3CO), 2.43 (3H, s, CH_3CO), 2.60 (1H, d, J=17.4 Hz, 3-Ha), 2.89 (3H, s, NCH_3), 2.90 (1H, m, 3-Hb), 3.96 (1H, br t, 3a-H), 6.23 (1H, br, 8a-H), 6.99 (2H, m, 4- and 6-H), 7.20 (1H, br, 7-H). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.39; H, 5.56; N, 9.63.

8-Acetyl-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (23) A mixture of **22** (930 mg, 3.23 mmol) and K_2CO_3 (7.0 g, 15 eq) in MeOH (50 ml) was stirred for 2 h at room temperature. The solvent was evaporated off to leave a residue, which was placed on top of a silica gel column (30 g). Elution with CH_2Cl_2–MeOH (10 : 1) gave **23** (740 mg, 93%). Recrystallization from aqueous MeOH gave colorless prisms, mp 279—283.5 °C. UV λ_{max} (EtOH) nm (ε): 202 (24200), 252 (13200), 295 (3400); (EtOH–10%NaOH): 273, 312 nm. IR ν_{max} (KBr) cm^{-1}: 3195 (OH), 1680 (CO). MS *m/z* (rel. intensity): 246 (M^+, 100). ^{1}H-NMR (270 MHz, in CD_3OD) δ: 2.42 (3H, s, CH_3CO), 2.53 (1H, br t, 3-Ha), 2.84 (3H, s, NCH_3), 2.95 (1H, dd, J=17.2, 9.0 Hz, 3-Hb), 3.94 (2/3H, br t, 3a-H), 4.05 (1/3H, br t, 3a-H), 6.11 (1/3H, d, J=6.6 Hz, 8a-H), 6.29 (2/3H, d, J=6.7 Hz, 8a-H), 6.73 (2H, m, 4- and 6-H), 7.14 (2/3H, d, J=8.5 Hz, 7-H), 7.75 (1/3H, d, J=8.2 Hz, 7-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.13; H, 5.82; N, 11.30.

Bromination of 23. Formation of 8-Acetyl-4,6-dibromo-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (24) and 8-Acetoxy-6(4)-bromo-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (25) NBS (76 mg, 2.1 eq) was added to a solution of **23** (50 mg, 0.203 mmol) in CH_2Cl_2 (5 ml) at room temperature and the mixture was stirred for 24 h at the same temperature. The solvent was evaporated off to leave a residue, which was chromatographed on a silica gel column (8 g, AcOEt–hexane–MeOH (60 : 1 : 1)) to give **24** (57 mg, 70%) from the first eluent and **25** (11 mg, 17%) from the second eluent.

Recrystallization of **25** from MeOH gave a colorless powder, mp 235.5—238 °C. UV λ_{max} (EtOH) nm: 254, 304; (EtOH–NaOH): 275, 324. IR ν_{max} (KBr) cm^{-1}: 1670 (CO). MS *m/z* (rel. intensity): 326 (M^+, 96), 324 (M^+, 100). The NMR spectrum showed a mixture of the 4- and 6-bromo derivatives.

Recrystallization of **24** from MeOH gave a colorless powder, mp 219—220 °C. UV λ_{max} (EtOH) nm: 217, 254, 304; (EtOH–NaOH): 278, 332. IR ν_{max} (KBr) cm^{-1}: 3200 (OH), 1690 (CO). MS *m/z* (rel. intensity): 406 (M^+, 42), 404 (M^+, 84), 402 (M^+, 43), 364 (49), 362 (100), 360 (54). Exact MS Calcd for $C_{13}H_{12}{}^{79}Br_2N_2O_3$: 401.9215. Found: 401.9198. Calcd for $C_{13}H_{12}{}^{79}Br^{81}BrN_2O_3$: 403.9195. Found: 403.9192. Calcd for $C_{13}H_{12}{}^{81}Br_2N_2O_3$: 405.9175. Found: 405.9170. ^{1}H-NMR (270 MHz, CD_3OD) at 40 °C δ: 2.42 (3H, s, $COCH_3$), 2.43 (1H, m, 3-Ha), 2.90 (3H, s, NMe), 2.99 (1H, dd, J=16.9, 9.0 Hz, 3-Hb), 4.09 (1H, br t, 3a-H), 6.22 (1H, br d, 8a-H), 7.90 (1H, br, 7-H).

Bromination of **25** with NBS (1.1 eq) in CH_2Cl_2 at room temperature gave **24** in 82% yield.

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References and Notes

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