Total Synthesis of (±)-Dragmacidin: A Cytotoxic Bis(indole)alkaloid of Marine Origin

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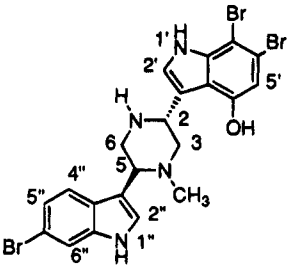
The total synthesis of the cytotoxic marine alkaloid, (±)-dragmacidin, *trans*-6,7-dibromo-3-[5-(6-bromo-1*H*-indol-3-yl)-4-methyl-2-piperazinyl]-1*H*-indol-4-ol, is described. The synthesis proceeds through the condensation of (6-bromoindol-3-yl)-α-(methylamino)acetonitrile with (6,7-dibromo-4-methoxyindol-3-yl)-α-oxoacetyl chloride. The product of this condensation was converted in two steps to an intermediate containing the central diketopiperazine ring which after reduction and deprotection gave the racemic natural product along with its *cis* isomer. An efficient preparation of 6,7-dibromo-4-methoxyindole is also presented.

Introduction

During the past years, a large number of marine natural products containing the indole nucleus have been isolated. The various structures of these indole alkaloids and their varied biological activities have been recently reviewed.[1] Although many marine natural products contain indole, derived biosynthetically from tryptamine, few contain an unoxidized piperazine ring between differently-substituted indole residues such as is found in the dragmacidins.[2] Dragmacidin itself was originally isolated from the deep water marine sponge *Dragmacidin* sp.[3] and, more recently, also obtained from a *Hexadella* sp.[4] along with several structurally related bisindoles, including topsentin C. The topsentins, which contain an imidazole ring between the indole residues, differ biosynthetically from the dragmacidins by virtue of a "head to head" assembly of tryptamine units rather than a "head to tail" assembly in the case of dragmacidin. Dragmacidin was reported to inhibit *in vitro* growth of P388 (murine leukemia) cells (IC_{50} = 15 μg/mL). It also inhibited growth of A-549 (human lung); HCT-8 (human colon); and MDAMB (human mammary) cancer cell lines (IC_{50} = 1–10 μg/mL).[3] A recent report demonstrates that dragmacidin also possesses antiinflammatory activity in both in vitro (inactivation of bee venom PLA_2) and in vivo (mouse ear edema test) assays.[5] Its structure was revised to *trans*-6,7-dibromo-3-[5-(6-bromo-1*H*-indol-3-yl)-4-methyl-2-piperazinyl]-1*H*-indol-4-ol (**1**).[3] Due to the interesting biological activity and chemical structure of dragmacidin and its low availability from nature, we undertook its total synthesis.



Dragmacidin, 1

Results and Discussion

In planning a total synthesis of a natural product target as a potential lead structure for a drug development program, both simplicity and convergence are important. A convergent route is economical and also allows for ready incorporation of structural modifications. Retrosynthetically, the piperazine unit in dragmacidin can best be viewed as derived from reduction of a 2,5-piperazinedione.[6] Recently, several methodologies have been developed for synthesis of naturally-occurring 2,5-piperazinedione alkaloids.[7] These involve either aldol condensation with 2,5-piperazinedione or its 1,4-diacetyl derivative[8,9] or acid- or base-catalyzed[10,11] or autoaminolytic cyclization of dipeptide esters.[12] With all these factors in mind, we proposed two retrosynthetic routes to the title compound as shown in Scheme 1.

Both routes lead to a common intermediate, 3,6-diindolyl-1-methyl-2,5-diketopiperazine, **2**, which upon reduction and *O*-demethylation would give racemic dragmacidin. By route A, we planned to construct the carbon skeleton in three steps from readily accessible starting materials by condensation of *N*-protected 6-bromoisatin, **4**, with 1,4-diacetyl-2,5-piperazinedione, **5**,[13] followed by *N*-methylation of the intermediate product and finally condensation with 6,7-dibromo-4-methoxyisatin **6**. Reduction and deprotection would give compound **2**.

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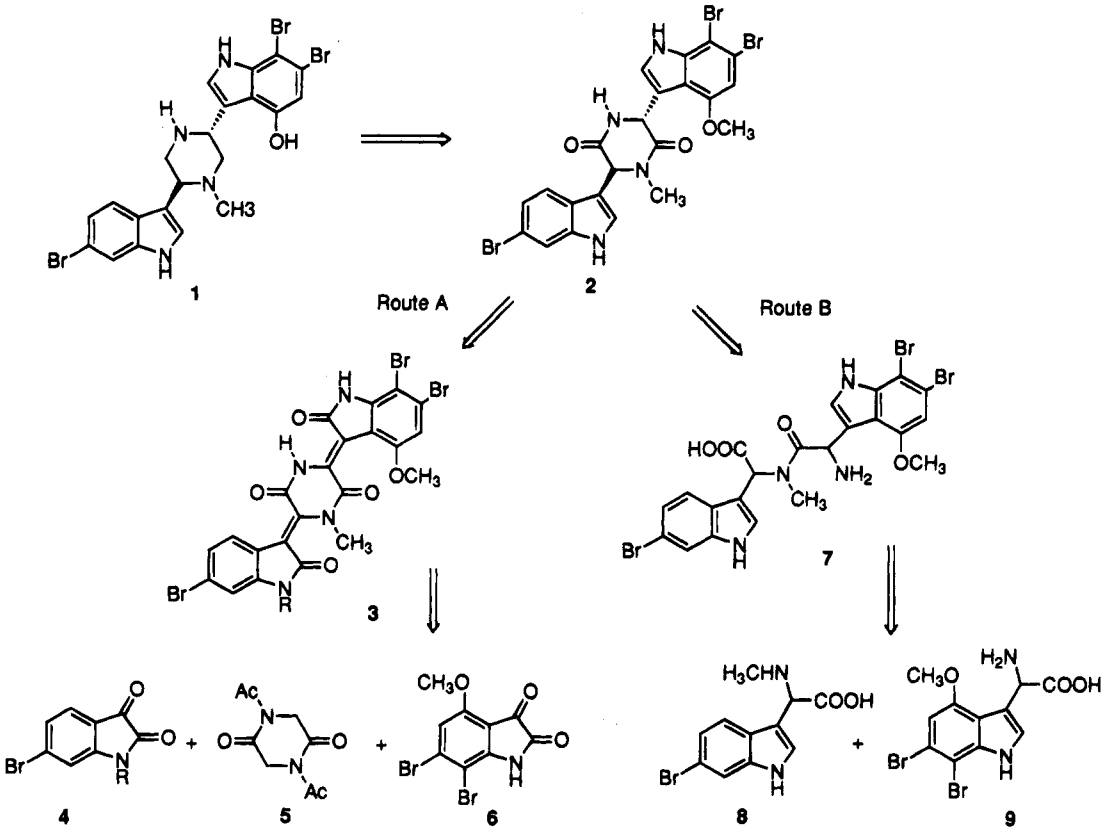
Scheme 1



The requisite isatins were prepared from 3-bromoaniline and 2,3-dibromo-5-methoxyaniline,[14] respectively, by treatment with chloral hydrate and hydroxylamine in the presence of strong acid using a modification of the literature methods.[15] Condensation of 2 equiv of isatin with **5** to give 3,6-bis(2-oxo-3-indolylidene)piperazine-2,5-dione has been previously reported.[16] By adjusting the ratio of reagents and careful choice of solvent, we were able to obtain primarily monocondensation in the reaction of **5** and 1 equivalent of isatin. Unfortunately, when the condensation was carried out with *N*-protected 6-bromoisatin, the desired monocondensation product was never obtained cleanly, despite many attempts using various solvents and bases. The condensation gave mixtures of desired product, bis product, and products which had not eliminated acetic acid. Because of the extreme insolubility of these compounds, no suitable method for purification could be found and we were forced to abandon this approach in favor of route B wherein the central diketopiperazine ring in compound **2** would be formed by cyclization of the dipeptide **7**. Dipeptide **7** would in turn be prepared from the two appropriately functionalized indolyl amino acids, **8** and **9**.

The known 6-bromoindole **4** was prepared *via* Batcho–Leimgruber indole synthesis from commercially available 4-bromo-2-nitrotoluene by reaction with dimethylformamide–dimethyl acetal followed by reduction of the intermediate enamine with hydrazine hydrate in the presence of Raney-Ni as catalyst.[17] This method of reduction was found to give better yields than the other reducing agents reported in the literature.[18]

Two methods for synthesis of previously unreported 6,7-dibromo-4-methoxyindole are shown in Scheme 2. This indole was initially obtained in modest yield by reduction of the corresponding isatin (which we had prepared for use in route A) with either borane–dimethyl sulfide complex or borane–tetrahydrofuran.[19] It was subsequently determined that the desired indole was available in excellent yields directly by reaction of 2,3-dibromo-5-methoxyaniline with chloroacetonitrile in the presence of boron trichloride and titanium tetrachloride followed by reduction with sodium borohydride in refluxing aqueous dioxane using the method of Sugasawa *et al.*[20]

Relatively few examples of indolylglycine derivatives have been reported in the literature and none with substitution on the indole ring system. Direct introduction of the amino acid side chain by use of a "glycine cation equivalent"[21] was unsuccessful with these indoles, probably due to the lower reactivity caused by the presence of the electron-withdrawing bromine substituents. Both indoles could be converted to the 3-indolylglyoxalates by reaction with oxalyl choride,[22] followed by reaction of the acid chloride with ethanol in the presence

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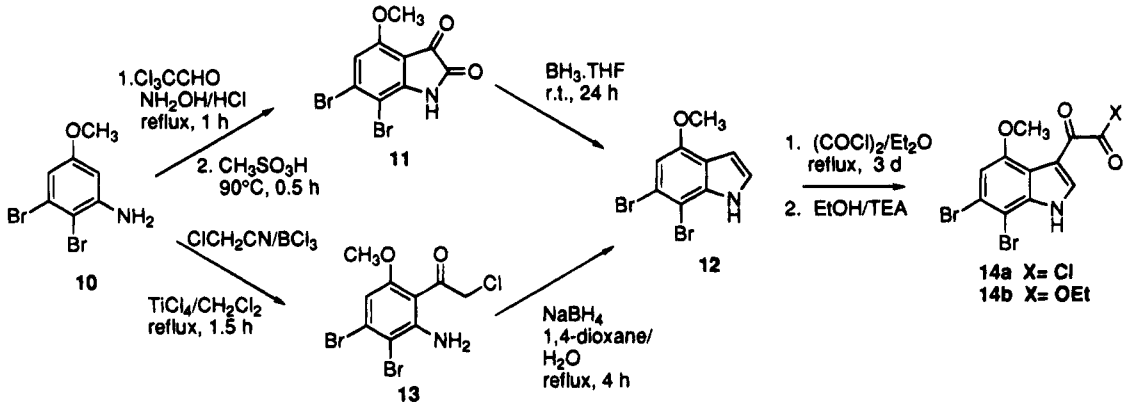
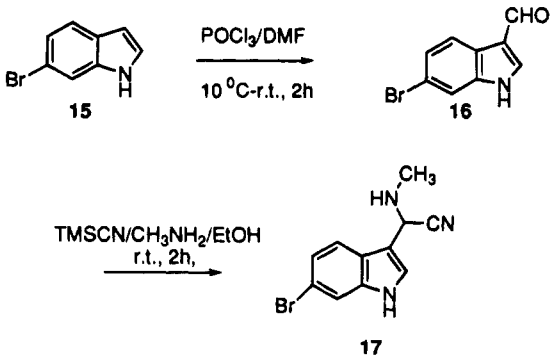
Scheme 2



Scheme 3



of triethylamine (see Scheme 2). This two-step procedure was superior to one-step reaction with ethyl oxalyl chloride.[23] Conversion of the ketones to the corresponding oximes was also straightforward;[24] however, no method for efficiently reducing the oxime to the amine without also attacking the aromatic bromines was identified.

Alternately, as illustrated in Scheme 3, indoles (exemplified here by 6-bromoimidole) could be converted in high yield to the indole-3-carboxaldehydes by Vilsmeier–Haack reaction with phosphorus oxychloride/dimethylformamide.[25] The aldehydes were then converted to the corresponding aminonitriles using a modified Strecker reaction[26] with trimethylsilyl cyanide in methanolic ammonia or ethanolic methylamine. These unstable aminonitriles readily reverted to the starting aldehydes on aqueous workup but could be isolated as their carbamate derivatives by treatment of the concentrated reaction mixture with ethyl chloroformate in the presence of triethylamine. All attempts to hydrolyze the protected amino nitriles to the target amino acids resulted in decomposition.

The solution to the problem ultimately came from modification of route B, as shown in Scheme 4, by eliminating the need for synthesis of the fully functionalized amino acid subunits. Instead of trapping with ethyl chloroformate, *N*-methylamino nitrile **17** was reacted directly with acid chloride **14a** to yield stable *N*-methylamide **18** in 92% yield. The next key intermediate, piperazinedione **20**, was obtained by hydrolysis of the nitrile with ammonium hydroxide/hydrogen peroxide in the presence of a phase transfer catalyst,[27] followed by intramolecular cyclization of the resulting ketoamide **19** in refluxing alcohol containing 30% aqueous ammonium hydroxide. This cyclization went very cleanly, and **20** was isolated as the sole product. Reduction of **20** with borane/tetrahydrofuran at 0 °C[28] afforded a mixture of *O*-methyldragmacidins **21a** and **21b** in a ratio of 4:1. It was apparent from the magnitude of the coupling constants observed for the H2 and H5 methine protons in the piperazine ring of **21a** (H5, δ 3.32, dd, J = 11.5, 3.5 Hz, and H2, δ 4.54, dd, J = 10.5, 2.5 Hz) that the piperazine ring was in a chair conformation with both indolyl substituents in an equatorial orientation. On the other hand, the coupling constants of H2 and H5 in **21b** (H5, δ 3.67, dd, J = 10.5, 3.6 Hz, and H2, δ 4.79, dd, J = 3.3, 3.8 Hz) show its conformation to have the 6-bromoindolyl in an equatorial orientation and the 6,7-dibromoindolyl in an axial orientation. The product ratio in this reduction was very dependent on the reaction temperature; e.g., reduction at room temperature gave a 1:1 mixture of **21a** and **21b**. This selectivity can be explained by elimination of the C2 hydroxyl group prior to 1,4-reduction.

Finally, to complete the synthesis, **21a** was *O*-demethylated with boron tribromide, smoothly affording racemic dragmacidin. The ^{1}H NMR chemical shifts and coupling constants of synthetic dragmacidin correspond to those reported for dragmacidin isolated from nature (Table 1).[2]

Experimental Section

Melting points are uncorrected. Mass spectra were measured by CI (NH_3) or DCI (NH_3) analytical methods. High-resolution accurate mass was run by DCI (NH_3).

6,7-Dibromo-4-methoxyisatin (11). To a hot solution (50–70 °C) of Na_2SO_4 (77.1 g) in water (130 mL) was added trichloroacetaldehyde (10.7 g, 0.0726 mol), followed by a hot mixture of aniline **10** (12.8 g, 0.0457 mol), EtOH (10 mL), NH_2-OH·HCl (9.56 g, 0.138 mol), and H_2O (45 mL). The mixture was treated with concd HCl (6 mL) and heated rapidly to a vigorous reflux for 1 h. The reaction was kept overnight at room temperature, and then the solid was collected by filtration and washed with water. Dry solid was partitioned between a mixture of ether and water. The organic layer was washed with water and brine and dried. After concentration,

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Scheme 4

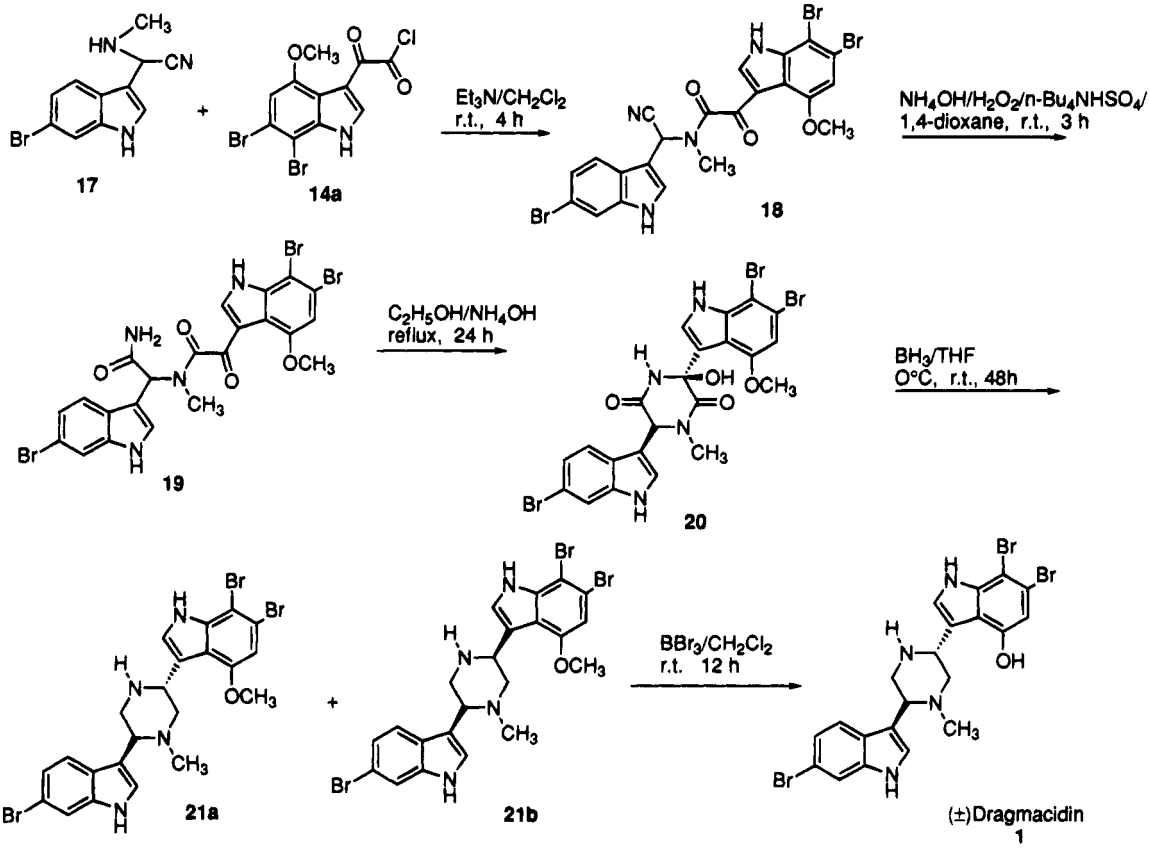

Table 1. ^{1}H NMR Data (Acetone-d_6) for Natural Dragmacidin, *O*-Methyldragmacidin (21a), and Synthetic Dragmacidin

C no.	natural dragmacidin[a]	21a[b]	synthetic dragmacidin[b]
2	4.35 (dd, 10.3, 2.3)	4.54 (dd, 10.4, 2.5)	4.34 (dd, 10.4, 2.5)
3(ax)	2.39 (dd, 10.3, 11.9)	2.20 (dd, 10.5, 11.5)	2.34 (dd, 10.4, 11.5)
3 (eq)	3.05 (bm)	3.02 (dd, 11.5, 3.5)	3.05 (dd, 11.5, 3.0)
5	3.46 (dd, 11.3, 3.9)	3.67 (dd, 10.5, 3.6)	3.46 (dd, 11.5, 3.5)
6(ax)	3.33 (dd, 11.9, 11.3)	3.22 (dd, 11.5, 10.5)	3.33 (dd, 11.5, 10.5)
6(eq)	3.13 (dd, 11.9, 3.9)	3.28 (dd, 11.5, 3.5,)	3.15 (dd, 11.5, 3.5,)
2′	7.27 (s)	7.33 (s)	7.26 (s)
5′	6.70 (s)	6.80 (s)	6.71 (s)

[a] 360 MHz (as reported in refs 2 and 3). [b] 400 MHz, δ in ppm from internal TMS. Coupling constants J in Hz obtained after addition of TFA.

the resulting solid was added portionwise as a fine powder to CH_3SO_3H (60 mL) at 50 °C. After completion of addition, the mixture was heated to 90 °C for 30 min., followed by cooling to room temperature. Crude product was isolated by pouring the reaction into ice–water and filtering. The solid was washed with water and air dried. The crude product was recrystallized from ethanol to give isatin **11** (3 g) as a yellow solid in 20% yield: mp 255 °C dec; IR (KBr) 3150, 1754, 1736, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 7.00 (s, 1H), 7.80 (brs, 1H); MS *m/z* (NH_3 CI, rel inten) 353 ($(M + NH_4)^+$,100). Anal. Calcd for $C_9H_5Br_2NO_3$: C, 32.27; H, 1.50; N, 4.18; Br, 47.71. Found: C, 32.33; H, 1.45; N, 4.17; Br, 47.70.

6,7-Dibromo-4-methoxyindole (12). A. Chloroacetophenone **13** (24 g, 0.067 mol) in 90% aqueous dioxane (300 mL) was refluxed with sodium borohydride (92.5 g, 0.067 mol) for 4 h. The mixture was poured into water (1 L) containing 1 N HCl (100 mL). The solid was filtered out, dried, and recrystallized with ether–hexane to afford the indole **12** (18.5 g) in 90% yield: mp 250 °C dec; IR (KBr) 3300, 1607, 1522 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.93 (s, 3H), 6.67 (d, J = 3.2 Hz, 1H), 7.67 (s, 1H), 7.15 (d, J = 3.2 Hz, 1H), 8.33 (brs, 1H); MS, *m/z* (NH_3-CI, rel inten) 306 ($(M + 1)^+$, 100). Anal. Calcd for $C_9H_7Br_2NO$: C, 35.45; H, 2.31; N, 4.59; Br, 52.40. Found: C, 35.32; H, 2.30; N, 4.58; Br, 52.33.

B. To a solution of isatin **11** (10 g, 30 mmol) in THF (200 mL) was added BH_3/THF (1 M in THF, 75 mL, 75 mmol) dropwise. The mixture was stirred at room temperature overnight. After concentration under reduced pressure, the residue was subjected to flash chromatography to afford indole **12** (3.0 g) in 33% yield.

2-Amino-3,4-dibromo-6-methoxy-α-chloroacetophenone (13). To a stirred solution of **10** (32 g, 0.17 mol) in CH_2Cl_2 (300 mL) cooled in an ice bath was added dropwise successively, boron trichloride (1 M in CH_2Cl_2, 180 mL, 0.18 mol), chloroacetonitrile (14.3 g, 0.19 mol), and titanium tetrachloride (1 M in CH_2Cl_2, 190 ml, 0.19 mol). The resulting mixture was refluxed for 1.5 h. After being cooled to room temperature, the mixture was carefully poured into a mixture of ice and 20% HCl (700 mL). The organic solvent was distilled. The residue was heated on a water bath (90 °C) for 30 min. After the solution was cooled to room temperature, the solid was filtered off and partitioned between ether (1.4 L) and 1 N NaOH (500 mL). The organic layer was separated and washed with brine, dried over Na_2SO_4, and concentrated. The resulting solid was recrystallized from ethanol to afford **13** (55 g) in 90% yield: mp 169 °C; IR (KBr) 3476, 3326, 1652, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 4.73 (s, 2H), 6.53 (s, 1H), 7.13 (brs, 2H); MS *m/z* (NH_3-CI, rel inten) 375 ($(M + NH_4)^+$, 100), 358 ($(M + 1)^+$, 30). Anal. Calcd for $C_9H_8Br_2NO_2Cl$: C, 30.24; H, 2.26; N, 3.92, Br, 44.71; Cl, 9.92. Found: C, 30.29; H, 2.20; N, 3.86; Br, 44.89; Cl, 9.96.

[(6,7-Dibromo-4-methoxy)indol-3-yl]-α-oxoacetyl chloride (14a). Indole **12** (16.2 g, 0.053 mol) in anhydrous ether (150 mL) was refluxed with oxalyl chloride (8.1 g, 0.063 mol) for 3 days. Hexane (150 mL) was added. The yellow solid was filtered off and washed with hexane several times and then dried under vacuum to give **14a** (16.6 g) in 79% yield: mp 264.7 °C dec; IR (KBr) 3165, 1708, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.00 (s, 1H), 8.12 (s, 1H); MS *m/z* (NH_3-CI, rel inten) 395 ($(M^+ + 1$, 100).

6-Bromoindole-3-carboxaldehyde (16). Phosphorus oxychloride (7 g, 0.0457 mol) was added dropwise to DMF (10 mL)

cooled in an ice bath. The mixture was kept at 0 °C for 30 min. A solution of 6-bromoindole (**15**) (7.2 g, 0.0367 mol) in DMF (36 mL) was then added dropwise, keeping the reaction temperature below 10 °C. After a further 3 h at 20 °C, the syrupy solid was poured into ice–water (300 g), neutralized with 1 N NaOH, and then left standing overnight. The crude solid was collected by filtration and recrystallized from ethanol to afford **16** (7.6 g) in 93% yield: mp 205 °C; IR (KBr) 3160–2087 (brs), 1640, 1574, 1524 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.39 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 10.03 (s, 1H), 11.35 (brs, 1H); MS m/z (NH_3-CI, rel inten) 241 ($(M + NH_4)^+$, 100), 224 ($(M + 1)^+$, 93). Anal. Calcd for C_9H_6NOBr: C, 48.25; H, 2.70; N, 6.25; Br, 35.66. Found: C, 48.17; H, 2.66; N, 6.25; Br, 35.69.

(6-Bromoindol-3-yl)(methylamino)acetonitrile (17). To a suspension of **16** (10 g, 0.045 mol) in methanol (50 mL) cooled in an ice bath were added methylamine (8 M in ethanol, 10 mL, 0.08 mol) and trimethylsilyl cyanide (5.0 g, 0.05 mol) successively. The mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dried in vacuo to afford **17** in quantitative yield: mp 97.8 °C; IR (KBr) 3400, 2170, 1642, 1614, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.50 (s, 1H), 5.02 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.52 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 8.32 (brs, 1H); MS m/z (NH_3-CI, rel inten) 237 (M^+ – CN, 100). Anal. Calcd for $C_{11}H_{10}N_3Br$: C, 50.02; H, 3.82; N, 15.91; Br, 30.25. Found: C, 49.92; H, 3.77; N, 15.75; Br, 30.72.

6,7-Dibromo-*N*-[(6-bromo-indol-3-yl)cyanomethyl]-4-methoxy-*N*-methyl-α-oxoindole-3-acetamide (18). To a solution of compound **17** (8.3 g, 0.032 mol) and triethylamine (3.3 g, 0.032 mol) in CH_2Cl_2 (200 mL) cooled in an ice bath was added a solution of **14a** (12.5 g, 0.032 mol) in a mixture of CH_2Cl_2 (200 mL) and ether (50 mL) dropwise. After 1 h, the mixture was washed with water and brine, dried over Na_2SO_4, and concentrated. The resulting solid was washed with ether to afford **18** (18 g) in 91% yield: mp 280° C dec; IR (KBr) 3170, 2246, 1706, 1656, 1570, 1518 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.98 (s, 3H), 3.92 (s, 3H), 7.08 (s, 1H), 7.26 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.78 (s, 1H), 8.10 (s, 1H), 10.80 (brs, 1H), 11.5 (bs, 1H); MS m/z (NH_3-CI, rel inten) 644/642/640/638 ($(M + NH_4)^+$, 18/56/5/16), 627/625/623/621 ($(M + 1)^+$, 32/95/100/32). Anal. Calcd for $C_{22}H_{15}N_4Br_3O_3 \cdot H_2O$: C, 41.22; H, 2.67; N, 8.74; Br, 37.39. Found: C, 41.01; H, 2.32; N, 8.55; Br, 37.75.

***N*-[2-Amino-1-(6-bromoindol-3-yl)-2-oxoethyl]-6,7-dibromo-4-methoxy-*N*-methyl-α-oxoindole-3-acetamide (19).** To a solution of **18** (10 g, 0.016 mol) in 90% aqueous 1,4-dioxane (200 mL) were added n-Bu_4NHSO_4 (600 mg), H_2O_2 (30%, 20 mL), and 1 N NaOH (20 mL) successively. The mixture was stirred at room temperature for 3 h and then poured into water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water and brine, dried, and concentrated. The resulting residue was triturated with CH_2Cl_2 and filtered to give **19** (9.5 g) in 92% yield: mp 252 °C dec; IR (KBr) 1660, 1608, 1572, 1538, 1510 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.82 (s, 3H), 3.92 (s, 3H), 6.60 (s, 1H), 7.18 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 8.15 (s, 1H), 10.6 (brs, 1H), 11.04 (bs, 1H); MS m/z (NH_3-DCI, rel inten) 662/660/658/656 ($(M + NH_4)^+$, 40/100/96/36), 645/643/641/639 ($(M + 1)^+$, 12/29/38/14). Anal. Calcd for $C_{22}H_{17}Br_3N_4O_4$: C, 41.22; H, 2.67; N, 8.74; Br, 37.39. Found: C, 41.20; H, 2.82; N, 8.58; Br, 37.46.

6-(6-Bromoindol-3-yl)-3-[(6,7-dibromo-4-methoxy)indol-3-yl]-3-hydroxy-1-methyl-2,5-piperazinedione (20). A solution of **19** (6.5 g, 0.01 mol) in ethanol (40 mL) was refluxed with 30% aqueous ammonium hydroxide (10 mL) for 2 h. The white solid which precipitated was collected by filtration, washed with ethanol, and dried to afford **20** (4 g) in 62% yield: mp 279 °C (dec); IR (KBr) 3286, 1662, 1610, 1570 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.84 (s, 3H), 3.86 (s, 3H), 5.46 (s, 1H), 7.38 (s, 1H, OH), 7.48 (d, J = 8.7 Hz, 1H), 7.58 (s, 1H), 7.62 (s, 1H), 7.64 (s, 1H), 8.21 (d, J = 8.7 Hz, 1H), 11.3 (brs, 1H), 11.5 (brs, 1H); MS m/z (NH_3-DCI, rel inten) 645/643/641/639 ($(M + 1)^+$, 1/4/6/2), 627/625/623/621 ($(M - H_2O)^+$, 34/100/98/35). Anal. Calcd for $C_{22}H_{17}Br_3N_4O_4$: C, 41.22; H, 2.67; N, 8.74; Br, 37.39. Found: C, 40.85; H, 2.91; N, 8.34; Br, 37.46.

***trans*-6,7-Dibromo-3-[5-(7-bromo-1*H*-indol-3-yl)-4-methyl-2-piperazinyl]-4-methoxy-1*H*-indole (21).** To a stirring suspension of **20** (7 g, 0.011 mol) in THF (100 mL) cooled in an ice bath was added BH_3/THF (1 M in THF, 100 mL, 0.1 mol) dropwise. The mixture was stirred at room temperature for 3 days. The reaction was quenched by careful addition of 1 N HCl (50 mL) at 0 °C. After a further 2 h, the solvent was removed. The residue was washed with ether (200 mL) and partitioned between ethyl acetate (100 mL) and saturated $NaHCO_3$ (50 mL). The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting solid was purified by flash chromatography (eluted with $CHCl_3$/MeOH 10:1) on silica gel to afford **21a** (2.42 g) and **21b** (0.6 g) in a total of 46% yield. **21a:** mp 230 °C dec; IR (KBr) 3426, 3254, 1608, 1570, 1542, 1490, 1454, 1426 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.04 (s, 3H), 2.20 (dd, J = 11.5, 10.5 Hz, 1H), 3.02 (dd, J = 11.5, 3.5 Hz, 1H), 3.22 (dd, J = 11.5, 10.5 Hz, 1H), 3.28 (dd, J = 11.5, 2.5 Hz, 1H), 3.32 (dd, J = 11.5, 3.5 Hz), 4.01 (s, 3H), 4.54 (dd, J = 10.5, 2.5 Hz, 1H), 6.80 (s, 1H), 7.13 (dd, J = 8.6, 1.5 Hz, 1H), 7.33 (s, 1H), 7.34 (dd, J = 1.5 Hz, 1H), 7.60 (dd, J = 1.5 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 10.3 (brs, 1H), 10.4 (brs, 1H); MS m/z (NH_3-DCI, rel inten) 600/599/597/595 ($(M + 1)^+$, 60/100/96/30); HRMS for $C_{22}H_{22}N_4Br_3O$ (M + 1, 3 × ^{79}Br) calcd 594.934 370, found 594.933 299. Anal. Calcd for $C_{22}H_{21}N_4Br_3O$: C, 44.25; H, 3.54; N, 9.38; Br, 40.14. Found: C, 44.13; H, 3.42; N, 9.17; Br, 40.10. **21b:** mp 221 °C dec; IR (KBr) 3428, 1606, 1568, 1538, 1490, 1452, 1420 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.08 (s, 3H), 2.85 (dd, J = 11.5, 3.6 Hz, 1H), 2.90 (dd, J = 11.5, 3.0 Hz, 1H), 3.20 (dd, J = 10.5, 11.5 Hz, 1H), 3.35 (dd, J = 11.5, 3.8 Hz, 1H), 3.67 (dd, 10.5, 3.6 Hz, 1H), 4.00 (s, 3H), 4.79 (dd, J = 3.3, 3.8 Hz, 1H), 6.86 (s, 1H), 7.10 (dd, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.60 (s, 1H), 7.75 (dd, J = 8.7 Hz, 1H), 7.89 (s, 1H), 10.35 (brs, 1H), 10.52 (brs, 1H); MS m/z (NH_3-DCI, rel inten) 600/599/597/595 ($M + 1)^+$, 86/98/100/40); HRMS for $C_{22}H_{22}N_4Br_3O$ (M + 1, 3 × ^{79}Br) calcd 594.934 370, found 594.933 461. Anal. Calcd for $C_{22}H_{21}N_4Br_3O$: C, 44.25; H, 3.54; N, 9.38; Br, 40.14. Found: C, 44.02; H, 3.42; N, 9.12; Br, 40.18.

trans-6,7-Dibromo-3-[5-(6-bromo-1*H*-indol-3-yl)-4-methyl-2-piperazinyl]-1*H*-indol-4-ol [(±)-Dragmacidin]. To a solution of *O*-methyldragmacidin (21a) (1.0 g, 1.7 mmol) in CH_2Cl_2 (300 mL) cooled in an ice bath was added BBr_3 (1 M in CH_2Cl_2, 20 mL) dropwise. After 1 h the mixture was allowed to warm to room temperature and then stirred overnight. Water (50 mL) was added to quench the reaction. Then 1 N NaOH (100 mL) was added, and the mixture was extracted with ethyl acetate. The extracts were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting product was subjected to flash chromatography eluted with $CHCl_3$/MeOH 10:1 to afford (±)-**1** (0.85 g) in 86% yield: mp 215 °C dec; IR (KBr) 3445, 1610, 1575, 1540, 1490, 1454 cm^{-1}. ^1H NMR (actone-d_6) δ 2.04 (s, 3H), 2.34 (dd, J = 11.5, 10.4 Hz, 1H), 3.05 (dd, J = 11.5, 3.5 Hz, 1H), 3.15 (dd, J = 11.5, 3.5 Hz, 1H), 3.33 (dd, J = 10.5, 11.5 Hz, 1H), 3.46 (dd, J = 11.5, 3.5 Hz, 1H), 4.34 (dd, J = 10.4, 2.5 Hz, 1H), 6.71 (s, 1H), 7.12 (dd, J = 8.6, 1.4 Hz, 1H), 7.26 (s, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 1.4 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 10.5 (brs, 1H), 10.68 (brs, 1H) MS m/z (NH_3-DCI, rel inten) 587/585/583/581 ($(M + 1)^+$, 30/100/92/8); HRMS for $C_{21}H_{20}Br_3N_4O$ (M + H, 3 × ^{79}Br) calcd 580.917 377, found 580.917 453. Anal. Calcd for $C_{21}H_{19}Br_3N_4O$: C, 43.26; H, 3.28; N, 9.38; Br, 41.11. Found: C, 43.18; H, 3.23; N, 9.46; Br, 41.10.