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SULFUR-CONTAINING POLYBROMOINDOLES FROM THE RED ALGA LAURENCIA BRONGNIARTII

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Abstract. Six new polybromoindoles (**9-14**) have been isolated from the red alga *Laurencia brongniartii*. Two were optically active sulfoxides, the itomanindoles A (**12**) and B (**13**) and one was a bisindole (**14**). The structures of **12** and **14** were elucidated by X-ray analysis. The sulfoxides **12** and **13** were readily converted with diazomethane to the corresponding N-methyl derivatives. Treatment with acetic anhydride at room temperature gave the same indolenine (**24**) as the major product.

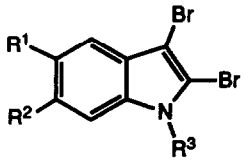
The genus *Laurencia* has been a favorite for chemical investigation since the 1960s. Numerous metabolites have been reported,[1] the most abundant being sesquiterpenes followed by non-terpenoid C_{15} acetogenins and diterpenes. Many of them are halogenated and are distinctive to the genus. Of the more than twenty species of *Laurencia* that have been studied so far, *L. brongniartii* is exceptional in that the usual metabolites are missing and that they contain instead polybromoindoles. Typically, the four bromoindoles (**1-4**) were found in algae collected in the Caribbean sea,[2] while four other sulfur-containing bromoindoles (**5-8**) were isolated from the same alga but of Taiwanese origin.[3] When we examined the constituents of *L. brongniartii* obtained from Okinawan waters, we found, in addition to compounds **5-8**, six new indoles (**9-14**), of which the sulfoxides (**12, 13**) and the bisindole (**14**) are particularly noteworthy. We now describe the details of the isolation and structure of these indoles together with some unexpected reactions of **12** and **13** which we have designated as itomanindoles A and B.[4]

Results and Discussion

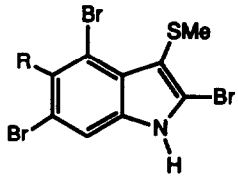
A fresh sample of *L. brongniartii* was thoroughly extracted with methanol. The ethyl acetate-soluble portion of the concentrated extract was chromatographed on NS gel,[5] silica gel, and finally on a Lobar Si-60 column to furnish indoles **5-14**. The known compounds **5-8** were identified by comparison of their spectroscopic data and melting points with those previously reported.[3] The 4,6-dibromo substitution pattern of compounds **5** and **7** was confirmed by the coupling constants (J = 1.5 Hz) of the *meta* aromatic protons and the acetylation-induced shift of the C7-proton. As shown previously with 4,6-dibromoindoles,[6] N-acetylation of these compounds caused a large downfield shift (~1 ppm) for one of the aromatic proton signals which was therefore assigned to the C7-proton (see acetyl derivatives **15-17, 19, 20** in Experimental Part).

All new indoles **9-14** were shown to possess 4,6-dibromo substituents. However, indole **9** contains an additional bromine atom as evidenced by mass spectral data. The third bromine atom is located at the C2 position since the ^{1}H NMR signal at δ 6.57 (dd, $J_{1\beta}$ = 2.1 Hz, $J_{3\gamma}$ = 0.8 Hz) must be due to the C3-proton on account of its typical long range coupling constants.

Indole **10** bears four bromine atoms as attested by the characteristic isotope peaks (M^+ at m/z 437, 435, 433, 431, and 429) in the EIMS. The ^{1}H NMR spectrum exhibited only two coupled *meta* aromatic proton signals



1 R^1 = Br, R^2 = H, R^3 = Me
2 R^1 = H, R^2 = Br, R^3 = Me
3 R^1 = R^2 = Br, R^3 = Me
4 R^1 = R^2 = Br, R^3 = H



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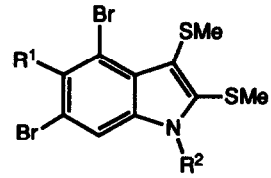
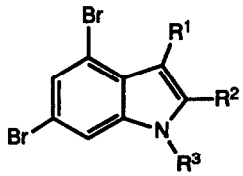
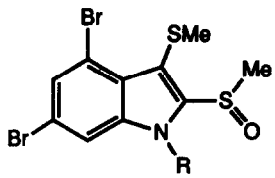
6 R = Br



7 R^1 = R^2 = H
8 R^1 = Br, R^2 = H
15 R^1 = H, R^2 = Ac
23 R^1 = H, R^2 = Me



9 R^1 = R^3 = H, R^2 = Br,
10 R^1 = R^2 = Br, R^3 = H
11 R^1 = R^3 = H, R^2 = SMe
16 R^1 = H, R^2 = Br, R^3 = Ac
17 R^1 = R^2 = Br, R^3 = Ac



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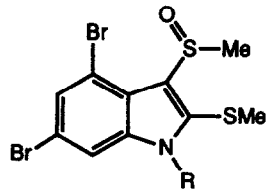
21 R = Me



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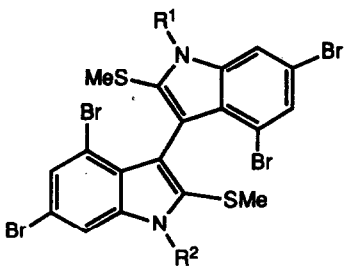
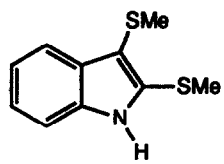
22 R = Me



14 R^1 = R^2 = H
19 R^1 = Ac, R^2 = H
20 R^1 = R^2 = Ac



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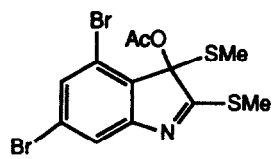


24

(δ 7.44 and 7.37) that shifted to δ 8.45 and 7.61 on acetylation. Thus, the compound must be a 2,3,4,6-tetrabromoindole.

Indole **11** showed a molecular ion cluster at m/z 323, 321, and 319 in the EIMS, and the molecular formula $C_9H_7Br_2NS$ was deduced from the HR EIMS. The ^1H NMR spectrum displayed signals at δ 8.14 (1 H, brs, N-H), 7.36 (2 H, m, 5- and 7-H), 6.47 (1 H, dd, J = 2.0, 0.8 Hz, 3-H), and 2.51 (3 H, s, S-CH_3). These data define the structure of **11** as a 4,6-dibromo-2-(methylthio)indole.

Itomanindole A (**12**) was obtained as optically active crystals, mp 134-136 °C, $[\alpha]_D^{25}$ +8°. The molecular formula $C_{10}H_9Br_2NOS_2$ was deduced from HR EIMS. A strong IR absorption band at 1035 cm^{-1} announced the presence of a sulfoxide group. The ^1H NMR spectrum ($CDCl_3$) showed signals for two *meta*-disposed, coupled protons (δ 7.63, 7.48), a methylthio (δ 2.43), a methylsulfinyl (δ 3.08), and a highly deshielded proton (δ 11.21). These data suggest that **12** has a structure similar to **7** in which one of the methylthio groups is oxidized. Indeed, reduction of **12** with lithium aluminium hydride in THF gave **7** together with a small amount of 2,3-(dimethylthio)indole (**18**). In order to determine the position of the sulfoxide group and to uncover the origin of the acidic hydrogen atom which reacts with diazomethane (*vide infra*), a crystal was obtained by repeated recrystallization from chloroform-ethyl acetate and submitted to X-ray analysis. The resulting structure not only shows the sulfinyl group at the C2 position, but also reveals that a racemic pair of the molecules are united centrosymmetrically by two strong hydrogen bonds (Figure 1). The N...O interatomic distance (2.763(2) Å) is significantly shorter than that usually encountered.[7] It is worth remarking that the dimeric planar arrangement and the closeness of the juxtaposed molecules are reminiscent of paired bases in DNA.

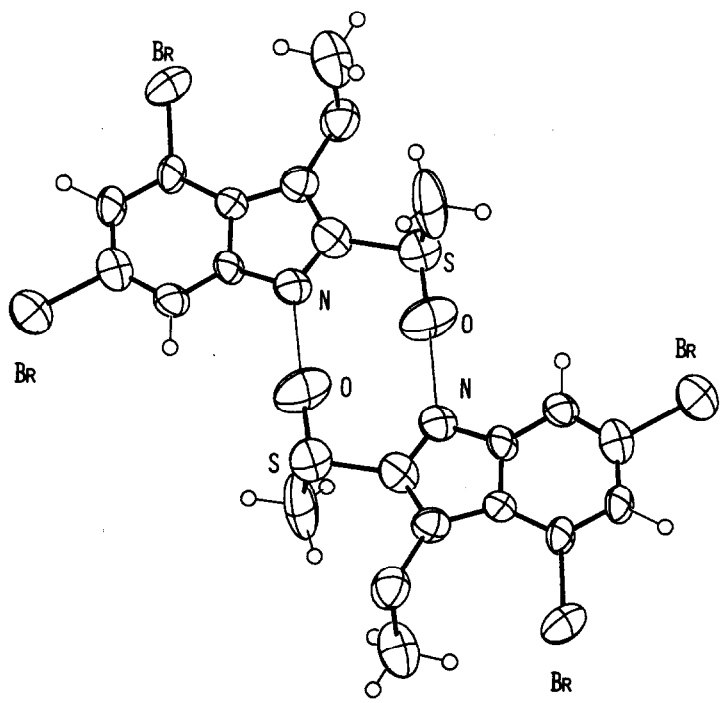


Fig. 1. Perspective drawing of the X-ray structure of a racemic pair of molecules (12) joined by two H-bonds.

Itomanindole B (13) was obtained as off-white crystals, mp 104-106 °C, $[\alpha]_D^{25}$ -38°. The molecular formula $C_{10}H_9Br_2NOS_2$ was determined by high resolution mass measurement at a (M^+ -O) ion and by the observation of a weak molecular ion cluster at m/z 385, 383, and 381 in the low resolution EIMS. A strong IR absorption band at 1030 cm^{-1} indicates a sulfinyl group. The ^1H NMR spectrum in deuterated DMSO exhibits signals [δ 12.02 (1 H, brs), 7.56 (1 H, d, J = 1.6 Hz), 7.49 (1 H, d, J = 1.7 Hz), 3.01 (3 H, s), 2.66 (3 H, s)] that parallel those displayed by **12**. Thus, itomanindole B is the isomeric sulfoxide **13**.

In order to determine the optical purity and configuration of the itomanindoles, synthetic samples were prepared. Reaction of **7** with sodium *meta*-periodate gave both itomanindoles A and B in 63 and 28% yield, respectively. However, when **7** was treated with the modified Sharpless reagent,[8] a single optically active product **12**, $[\alpha]_D^{25}$ +20.3°, was formed in 75% yield. The reaction was entirely regioselective, no trace of **13** being detected in the reaction mixture. Examination of the synthetic sample of **12**, which should have the R configuration, by NMR using the chiral solvating agent (R)-(-)-trifluoroanthrylethanol revealed that it was 80% optically pure.[9] Consequently, the reaction constitutes the first example of regioselective, asymmetric oxidation of prochiral sulfide substituents. Similarly, a natural sample of **12** was determined to have an enantiomeric excess of 2% of the R-configured isomer. The configuration and optical purity of **13** still remains to be elucidated.

Compound **14** was obtained as colorless crystals, mp 186-188 °C, by recrystallization from benzene-chloroform. The presence of four bromine atoms is shown by the molecular ion cluster at m/z 644, 642, 640, 638, and 636 in the EIMS. This information and the molecular formula $C_{18}H_{12}Br_4N_2S_2$ deduced from HR-EIMS suggest that it is a bisindole. The ^1H NMR spectrum exhibits only two coupled *meta*-related aromatic protons (δ 7.43, 7.35) and a methyl singlet (δ 2.33). The ^{13}C NMR spectrum shows one methyl and eight aromatic carbon resonances. These data corroborate the symmetric nature of the bisindole. Acetylation (Ac_2O/pyridine) of **14** gave the mono- (**19**) and diacetyl (**20**) derivatives. The ^1H NMR spectrum of **20** displays two aromatic (δ 8.53, 7.52) and two methyl proton signals (δ 3.03, 2.24), while **19** exhibits four signals arising from aromatic protons (δ 8.53, 7.52, 7.49, 7.35), three methyl protons (δ 3.02, 2.33, 2.22), and one N-H group (δ 8.46).

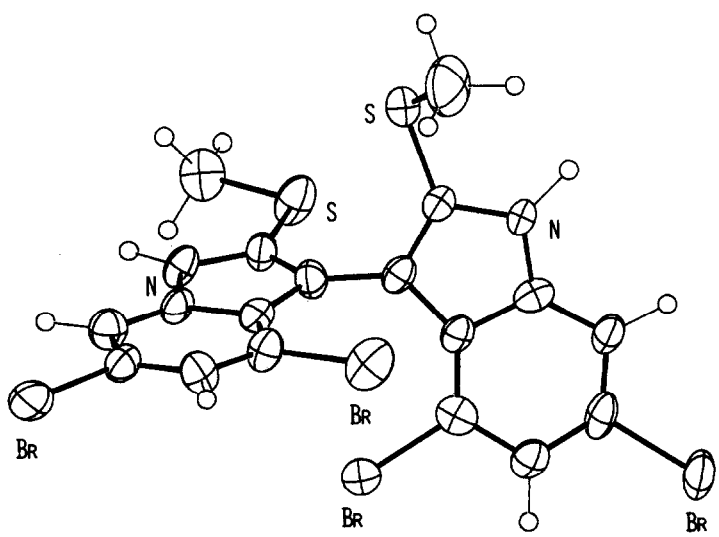


Fig. 2. Perspective drawing of the X-ray structure of bisindole 14

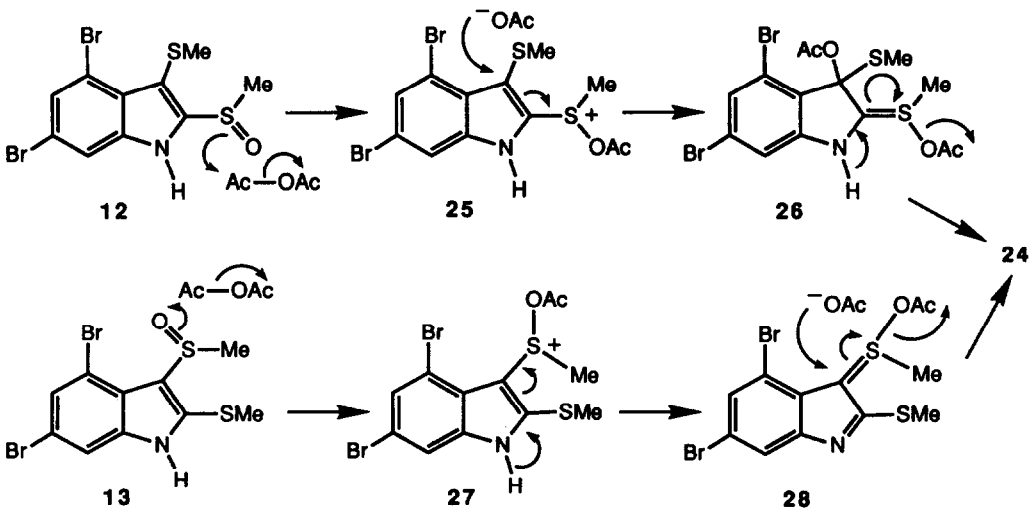
These data clearly point to the same 4,6-dibromo substitution pattern, and suggest that two molecules are connected either at the 3,3- or 2,2-positions. The matter was settled by the X-ray analysis of **14** (Figure 2). They are joined at the 3,3 positions and the two indole rings adopt a staggered conformation so that the angle between the mean planes is 73.6°.

The sulfinyl indoles **12** and **13** readily reacted with diazomethane to give N-methyl derivatives **21** and **22** in 95 and 72% yield, respectively. N-methylation was proved by Raney nickel reduction to 1-methylindole.[10] Normally, indoles are inert to diazomethane as they are not nucleophilic enough. In fact, treatment of **7** with excess diazomethane for 5 h gave the N-methyl derivative **23** but only in 6% yield. These results along with the NMR shift data demonstrate that the N-H group in **12** and **13** is rendered acidic by the dipolar sulfinyl group.

An unusual reaction of the sulfinyl indoles **12** and **13** was uncovered on acetylation. Surprisingly, both gave the same major product. Treatment of **12** with excess acetic anhydride and pyridine at room temperature for two days gave **15** and **24** in 11 and 41% yield, respectively. Some starting material (35%) was recovered. The product **15** was identical to that obtained by acetylation of **7**. The molecular formula $C_{12}H_{11}Br_2NO_2S_2$ of **24** was deduced from elemental analysis and LR EIMS (M^+ at m/z 427, 425, and 423). The IR spectrum shows a carbonyl absorption band at 1770 cm^{-1} which is higher than that of an N-acetyl derivative (*cf.* **15**: 1725 cm^{-1}). The spectrum also shows the sulfinyl group to be absent. The ^1H NMR spectrum displays three methyl singlets (δ 1.94, 2.14, and 2.65) and two aromatic doublets (δ 7.37 and 7.48), while the ^{13}C NMR spectrum shows six aromatic (δ 117.3, 122.0, 124.4, 131.0, 133.2, and 155.1), three methyl (δ 11.4, 13.7, and 20.3), and two carbon resonances [δ 92.4 (C-3) and 183.9 (C-2)]. Consequently, the indole nucleus can be ruled out in favor of the indolenine structure **24**.

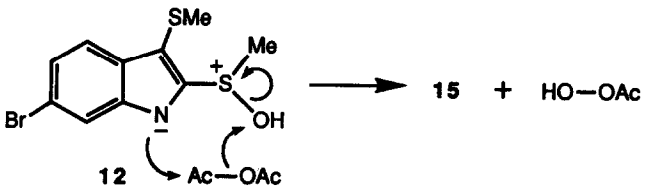
The sulfoxide **13** was more reactive toward acetic anhydride and gave **24** in 93% yield on reaction at room temperature for 12 h. The formation of **24** from both **12** and **13** can be rationalized by a rearrangement of the Pummerer-type.[11] Acetylation of the β- and γ-sulfoxide groups in **12** and **13** respectively produces the sulfonium cations **25** and **27**, which on deprotonation and attack by acetate afford *via* the intermediates **26** and **28**, the same product **24** (Scheme 1).

Scheme 1



The provenance of the minor product **15** is more difficult to account for. However, it can be supposed that **12** undergoes deoxygenation by addition of a molecule of acetic anhydride to the protonated sulfoxide-amide element with elimination of a molecule of peracetic acid to give **15** (Scheme 2). The fact that isomer **13** gives only **24** and none of **15** is understandable, since the required six-membered cyclic transition state is inaccessible.

Scheme 2



Conclusion

All the compounds reported here and elsewhere[3] are indoles bearing bromine substituents at the C4 and C6 positions. They contrast with the metabolites (**1-4**) found in the Caribbean alga,[2] which are brominated at the C2, C3, C5, and/or C6 positions. Nevertheless, *L. brongniartii* is the only known species of *Laurencia* which contains indoles to the exclusion of the halogenated sesquiterpenes and non-terpenoid C_{15} enynes usually found. Despite an extensive search we have detected no halogenated metabolites other than indoles. Interestingly, indole **1** has been isolated together with sesqui- and diterpenes from a sea hare sample (*Aplysia dactylomela*) collected off Puerto Rico.[12] It is obvious that these metabolites must have come from ingested *Laurencia*, but it is not known whether the indole and terpenoids originated from the same species.

The occurrence of sulfoxides as natural products is not common.[13] A recent example of marine origin, which complements compounds **12** and **13**, is the brominated indole eudistomin K sulfoxide.[14]

Experimental Part

Melting points were determined on a Mitamura Riken micromelting point apparatus and are uncorrected. Optical rotations were recorded on an Atago AA-5 digital polarimeter. IR spectra were taken on a Hitachi 260-10 infrared spectrometer. ^1H NMR spectra were measured on a JEOL JNM-PMX-60 and ^{13}C NMR spectra on a JEOL FX-90Q spectrometer. Mass spectra were recorded on a JEOL D-300 or DX-303 mass spectrometer. UV spectra were taken on a Jasco 610 spectrophotometer.

Unless otherwise stated, N-acetylation of indoles was carried out by allowing them to stand in excess acetic anhydride and pyridine at room temperature for 1-3 days.

Extraction and Isolation. L. brongniartii (3.4 kg wet weight) was collected at Komesu, Itoman, Okinawa, in August, 1984. The fresh sample was extracted by soaking in methanol (4 l) overnight. After decanting the solution, the residue was submitted to the same extraction procedure four more times. The combined methanol extracts were evaporated. The resulting aqueous suspension was extracted with ethyl acetate to give a crude oil (13.3 g). The oil was chromatographed on NS gel[5] by successively eluting with methanol and ethyl acetate. The methanol eluate (11 g) was repeatedly chromatographed on silica gel (hexane-acetone) and on a Lobar Si-60 column (ethyl acetate) to furnish indoles **5-14**. The known indoles **5**, mp 102-105 °C; **6**, mp 112-114 °C; **7**, mp 108.5-110 °C; and **8**, mp 147-153 °C were obtained in amounts of 1713, 208, 959, and 111 mg, respectively. They were identified by comparison of their spectral data with those reported.[1]

1-Acetyl-4,6-dibromo-2,3-di(methylthio)indole (**15**). The acetyl derivative **15** was prepared from indole **7**. Mp 99-101 °C. IR (CCl_4) 1725, 1440, 1385, 1330, 1260, 1170, 1000, and 855 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 8.35 (1 H, d, J = 1.6 Hz), 7.59 (1 H, d, J = 1.6 Hz), 2.95 (3 H, s), 2.53 (3 H, s), and 2.43 (3 H, s). ^{13}C NMR ($CDCl_3$) δ 170.9, 141.4, 138.6, 131.4, 124.4, 119.5, 117.7, 114.5, 28.3, 21.7, and 21.4. EIMS m/z 411 (29), 409 (51), 407 (M^+, 26), 369 (55), 367 (94), 365 (49), 354 (23), 352 (42), 350 (25), 290 (16), 288 (31), 286 (17), and 47 (100 rel.%)

2,4,6-Tribromoindole (**9**). Yield 38 mg. Mp 106-113 °C (hexane-CCl_4). IR (KBr) 3420, 1605, 1495, 1470, 1410, 1380, 1320, 1280, 1170, 830, and 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.20 (1 H, br), 7.20 (2 H, m), and 6.57 (1 H, dd, J = 2.1, 0.8 Hz). EIMS m/z 357 (29), 355 (92), 353 (100), 351 (M^+, 33), 276 (16), 274 (29), 272 (15), 195 (17), and 193 (21 rel.%). HR EIMS m/z 350.7880. Calcd for $C_8H_4Br_3N$ 350.7893.

Acetyl derivative **16**: mp 114-114.5 °C (hexane-CCl_4); IR (KBr) 1705, 1515, 1430, 1385, 1370, 1285, 1235, 1160, 1035, 955, and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.45 (1 H, dd, J = 1.4, 0.7 Hz), 7.55 (1 H, d, J = 1.4 Hz), 6.82 (1 H, d, J = 0.6 Hz), and 2.86 (3 H, s).

2,3,4,6-Tetrabromoindole (**10**). Yield 33 mg. Mp 137-141 °C (hexane-CCl_4). IR (KBr) 3390, 1605, 1540, 1490, 1405, 1375, 1315, 1260, 1170, 930, and 835 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.45 (1 H, br), 7.44 (1 H, d, J = 1.4 Hz), and 7.37 (1 H, d, J = 1.5 Hz). EIMS m/z 437 (16), 435 (79), 433 (100), 431 (82), 429 (M^+, 18), 357 (8), 355 (27), 353 (23), 351 (10), 276 (10), 274 (17), and 272 (10 rel.%). HR EIMS m/z 432.6974. Calcd for $C_8H_3{}^{79}Br_2{}^{81}Br_2N$ 432.6962.

Acetyl derivative **17**: mp 176-178 °C. IR (KBr) 1705, 1430, 1375, 1260, 1200, 1160, 935, and 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.45 (1 H, d, J = 1.6 Hz), 7.61 (1 H, d, J = 1.5 Hz), and 2.83 (3 H, s). EIMS m/z 479 (1), 477 (5), 475 (8), 473 (5), 471 (M^+, 1), 437 (10), 435 (37), 433 (54), 431 (39), 429 (11), 356 (3), 354 (10), 352 (10), 350 (4), 274 (6), 272 (10), 270 (5), and 43 (100 rel.%).

4,6-Dibromo-2-(methylthio)indole (**11**). Yield 6 mg. Mp 59-61 °C (hexane-CCl_4). IR (KBr) 3420, 1610, 1495, 1465, 1425, 1375, 1325, 1285, 820, 760, and 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.14 (1 H, br), 7.36 (2 H, m), 6.47 (1 H, dd, J = 2.0, 0.8 Hz), and 2.51 (3 H, s). EIMS m/z 323 (51), 321 (96), 319 (M^+, 53), 308 (53), 306 (100), 304 (52), 227 (10), 225 (10), and 147 (38 rel.%). HR EIMS m/z 320.3638. Calcd for $C_9H_7{}^{79}Br^{81}BrNS$ 320.8645.

Itomanindole A (**12**). Yield 294 mg. Mp 134-136 °C (CHC_3). $[\alpha]_D^{25}$ +8.0° (c 1.56, $CHCl_3$). UV (EtOH) λ_{max} 234 (ϵ 20000) and 301 nm (ϵ 8000). IR (KBr) 3130, 1595, 1540, 1400, 1320, 1175, 1035, 955, 935, 845, and 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.21 (1 H, br), 7.63 (1 H, d, J = 1.6 Hz), 7.48 (1 H, d, J = 1.6 Hz), 3.08 (3 H, s), and 2.43 (3 H, s); (DMSO-d_6) δ 12.69 (1 H, br), 7.75 (1 H, d, J = 1.5 Hz), 7.54 (1 H, d, J = 1.5 Hz), 2.99 (3 H, s), and 2.33 (3 H, s). ^{13}C NMR (DMSO-d_6) δ 136.6, 129.3, 118.0, 116.1, 106.7, 105.9, 105.0, 97.4, 32.4, and 13.2. EIMS m/z 385 (13), 383 (20), 381 (M^+, 9), 369 (35), 367 (63), 365 (37), 354 (20), 352 (37), 350 (38), 348 (13), 290 (15), 288 (32), 286 (18), 94 (100), and 79 (67 rel.%). HR EIMS m/z 382.8465. Calcd for $C_{10}H_9{}^{79}Br^{81}BrNOS_2$ 382.8472.

Itomanindole B (**13**). Yield 68 mg. Mp 104-106 °C ($CHCl_3$-MeOH). $[\alpha]_D^{25}$ -38° (c 0.328, 1:1 $CHCl_3$-MeOH). UV (EtOH) λ_{max} 233 (ϵ 29000) and 315 nm (ϵ 12000). IR (KBr) 3100-2900, 1600, 1545, 1420, 1380, 1320, 1270, 1180, 1030, 1000, 945, 840, and 740 cm^{-1}. ^1H NMR (DMSO-d_6) δ 12.02 (1 H, br), 7.56 (1 H, d, J = 1.6 Hz), 7.49 (1 H, d, J = 1.7 Hz), 3.01 (3 H, s), and 2.66 (3 H, s). ^{13}C NMR (DMSO-d_6) δ 130.8, 128.8, 117.7, 115.1, 105.2, 104.7, 104.0, 101.4, 31.2, and 6.5. EIMS m/z 385 (2), 383 (2), 381 (M^+, 1), 369 (14), 367 (26), 365 (12), 354 (7), 352 (14), 350 (8), 290 (7), 288 (13), 286 (8), 94 (100), and 79 (88 rel.%). HR EIMS m/z 366. 8504 (M^+ -O). Calcd for $C_{10}H_9{}^{79}Br^{81}BrNS_2$ 366.8523.

3,3-bis(4,6-Dibromo-2-methylthio)indole (**14**). Yield 209 mg. Mp 186-188 °C (hexane-$CHCl_3$). $[\alpha]_D^{25}$ 0° (c 0.5, $CHCl_3$). UV (EtOH) λ_{max} 236 (ϵ 50000) and 306 nm (ϵ 20000). IR (KBr) 3400, 1600, 1545, 1410, 1375,

1330, 1170, 940, and 835 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.43 (2 H, br), 7.43 (2 H, d, J = 1.4 Hz), 7.35 (2 H, d, J = 1.5 Hz), and 2.33 (6 H, s). ^{13}C NMR ($CDCl_3$) δ 137.5, 133.0, 127.8, 127.3, 115.9, 115.1, 113.9, 113.0, and 18.4. EIMS m/z 644 (7), 642 (24), 640 (32), 638 (21), 636 (M^+, 6), 548 (5), 546 (12), 544 (12), 542 (4), 452 (6), 450 (11), 448 (5), 371 (5), 369 (5), 290 (2), and 84 (100 rel.%). HR EIMS m/z 635.7170. Calcd for $C_{18}H_{12}{}^{79}Br_4N_2S_2$ 635.7175.

Acetylation of bisindole (14). A mixture of 14 (21.2 mg), pyridine (0.5 ml), and acetic anhydride (0.2 ml) was allowed to stand at room temperature for 45 h. After removing excess reagents under vacuum, the product mixture was chromatographed on a Lobar Si-60 column (4:1 hexane-ethyl acetate) to afford the monoacetyl derivative 19 (5.3 mg, 23%) and the diacetyl derivative 20 (8.9 mg, 37%) in addition to the starting material.

19: IR (CCl_4) 3460, 2920, 1720, 1380, 1265, 1235, 1155, and 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.53 (1 H, d, J = 1.6 Hz), 8.46 (1 H, br), 7.52 (1 H, d, J = 1.6 Hz), 7.49 (1 H, d, J = 1.6 Hz), 7.35 (1 H, d, J = 1.6 Hz), 3.02 (3 H, s), 2.33 (3 H, s), and 2.22 (3 H, s). EIMS m/z 686 (13), 684 (39), 682 (52), 680 (37), 678 (M^+, 11), 644 (14), 642 (37), 640 (52), 638 (35), 636 (11), 548 (10), 546 (24), 544 (22), 542 (8), 452 (14), 450 (23), 448 (13), and 43 (100 rel.%).

20: mp 247-250 °C (hexane-$CHCl_3$). IR (KBr) 1695, 1380, 1370, 1260, 1230, and 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.53 (2 H, d, J = 1.5 Hz), 7.52 (2 H, d, J = 1.5 Hz), 3.03 (6 H, s), and 2.24 (6 H, s). EIMS m/z 728 (7), 726 (20), 724 (24), 722 (16), 720 (M^+, 5), 686 (3), 684 (8), 682 (11), 680 (7), 678 (2), 644 (7), 642 (19), 640 (26), 638 (17), 636 (5), and 43 (100 rel.%).

1-Methylitomanindole A (21). To 12 (16.4 mg) was added an excess of ethereal solution of diazomethane, and the solution was kept standing for 1.5 h. After evaporation of solvent, the residue was recrystallized from acetone to furnish 1-methylitomanindole A (21) (16.2 mg, 95%) as colorless crystals: mp 117.5-118.5 °C. $[\alpha]_D^{25}$ -6.9° (c 0.54, $CHCl_3$). UV (EtOH) λ_{max} 238 (ϵ 31000) and 306 nm (ϵ 11000). IR (CCl_4) 2930, 1595, 1465, 1450, 1440, 1420, 1405, 1355, 1335, 1190, 1060, 965, 950, and 880 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.48 (2 H, s), 4.11 (3 H, s), 3.06 (3 H, s), and 2.40 (3 H, s). ^{13}C NMR ($CDCl_3$) δ 141.4, 140.8, 128.7, 124.3, 117.9, 115.7, 112.2, 110.9, 41.6, 31.1, and 22.9. EIMS m/z 399 (55), 397 (97), 395 (48), 367 (56), 365 (100), 363 (49), 354 (27), 352 (50), 348 (30), 336 (21), 334 (28), and 332 (15 rel.%). HR EIMS m/z 394.8625. Calcd for $C_{11}H_{11}{}^{79}Br_2NOS_2$ 394.8648.

1-Methylitomanindole B (22). To a stirred solution of 13 (40.3 mg) in methanol (4 ml) was added an excess of ethereal diazomethane. The mixture was stirred for 1 h. After evaporation of solvent, the residue was chromatographed on silica gel (6:1 chloroform-ethyl acetate) to give 1-methylitomanindole B (22) (30.0 mg, 72%) as a colorless glassy material: $[\alpha]_D^{25}$ 0° (c 0.6, $CHCl_3$). UV (EtOH) λ_{max} 235 (ϵ 39000) and 305 nm (ϵ 11000). IR (CCl_4) 2530, 1595, 1445, 1420, 1405, 1320, 1300, 1185, 1080, 1060, 865, and 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.52 (1 H, d, J = 1.5 Hz), 7.44 (1 H, d, J = 1.4 Hz), 3.68 (3 H, s), 3.16 (3 H, s), and 2.50 (3 H, s). EIMS m/z 431 (5), 429 (9), 427 (M^+, 5), 415 (7), 413 (10), 411 (5), 383 (17), 381 (30), 379 (16), 368 (7), 366 (12), 364 (6), 352 (54), 350 (100), and 348 (56 rel.%).

Reduction of 1-methylitomanindole A (21) *with Raney nickel*. To a stirred solution of 21 (97.7 mg) in ethanol was added an excess of a suspension of freshly prepared Raney nickel in ethanol. The mixture was stirred for 1 h and filtered through a pad of silica gel. The residue of the filtrate was purified on a silica gel column (3:1 hexane-chloroform) to afford 1-methylindole (18.4 mg, 57%) as a colorless oil. UV (MeOH) λ_{max} 220 (ϵ 28000) and 282 nm (ϵ 4900). IR (CCl_4) 3060, 2950, 2880, 1610, 1510, 1490, 1480, 1465, 1420, 1350, 1330, 1320, 1240, 1080, and 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.66 (1 H, m), 7.35-7.1 (3 H, complex), 7.05 (1 H, d, J = 2.8 Hz), 6.50 (1 H, d, J = 2.8 Hz), and 3.77 (3 H, s). These data were identical with those of a commercial sample (Kanto Chemicals).

Reduction of 1-methylitomanindole B (22) *with Raney nickel*. Compound 22 (13.5 mg) was similarly treated with Raney nickel as above to give 1-methylindole (1.7 mg, 38%) which was identical with an authentic sample.

Reduction of itomanindole A (12) *with LiAlH$_4$*. To a suspension of $LiAlH_4$ (65 mg) in tetrahydrofuran (6 ml) was added a solution of 12 (10 mg) in the same solvent (4 ml), and the mixture was stirred for 1 h. After quenching the reaction by adding a dilute hydrochloric acid solution, the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated, and the residue was chromatographed on a Lobar Si-60 (4:1 hexane-ethyl acetate) to give 1.0 mg (10%) of 7, and 0.5 mg (9%) of 18 as an oil. Some sulfoxide 12 was recovered (4.2 mg). Compound 7 was identified by comparing TLC and IR with those of an authentic sample. Compound 18 was identical by TLC and IR spectrum with a product obtained by the same reaction on 7.

18: IR (KBr) 3390, 2920, 1430, 1325, 1220, 1030, 965, 905, 835, 800, and 745 cm^{-1}. ^1H NMR (CCl_4) δ 7.96 (1 H, br), 7.40 (1 H, m), 7.3-6.8 (3 H, complex), 2.49 (3 H, s), and 2.31 (3 H, s).

Reaction of 4,6-dibromo-2,3-di(methylthio)indole (7) *with diazomethane*. To a solution of 7 (70 mg) in methanol (5 ml) was added an excess of ethereal solution of diazomethane. The mixture was stirred for 1 h and concentrated to remove most ether. Fresh diazomethane solution was added, and the mixture was allowed to react for 1 h. This procedure was repeated four times. The residue from the reaction mixture was chromatographed on a Lobar Si-60 column (4:1 hexane-ethyl acetate) to give 4,6-dibromo-2,3-dimethylthio-1-methylindole (23) (4.6 mg, 6%). IR (CCl_4) 2930, 1595, 1450, 1405, 1325, 1305, 1275, 1180, 1080, 970, and 960 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.44 (1 H, d, J = 1.4 Hz), 7.37 (1 H, d, J = 1.4 Hz), 3.84 (3 H, s), 2.43 (3 H, s), and 2.38 (3 H, s). EIMS m/z 383 (60), 381 (100), 379 (M^+, 51), 368 (22), 366 (40), 364 (22), 304 (39), 302 (74), 300 (41), 289 (16), 287 (41), and 285 (34 rel.%).

Reaction of itomanindole A (12) *with acetic anhydride*. A mixture of 12 (50 mg), pyridine (0.15 ml), and acetic anhydride (0.3 ml) was allowed to stand at room temperature for two days. After evaporation, the residue was chromatographed on a Lobar Si-60 column (2:1 hexane-ethyl acetate) to give 15 (5.7 mg, 11%) and 3-acetoxy-4,6-dibromo-2,3-di(methylthio)indolenine (24) (22.7 mg, 41%). Some 12 was recovered (17.9 mg, 35%). Compound 24 was obtained as colorless crystals, mp. 121-123.5 °C, by recrystallization from hexane-chloroform. 24: UV (EtOH) λ_{max} 252 (ϵ 11000) and 305 nm (ϵ 3400). IR (CCl_4) 1770, 1595, 1510, 1435, 1390, 1370, 1215, 1200, 1170, 1140, 1075, 1045, 940, 930, and 865 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.48 (1 H, d, J = 1.6 Hz), 7.37 (1 H, d, J = 1.6 Hz), 2.65 (3 H, s), 2.14 (3 H, s), and 1.94 (3 H, s). ^{13}C NMR ($CDCl_3$) δ 183.9, 167.4, 155.1, 133.2, 131.0, 124.4, 122.0, 117.3, 92.4, 20.3, 13.7, and 11.4. EIMS m/z 427 (5), 425 (10), 423 (M^+, 5), 380 (53), 378 (84), 376 (42), 338 (54), 336 (100), 334 (51), 322 (34), 320 (64), and 318 (33 rel.%). Found: C 33.76, H 2.56, N 3.29, Br 37.64, S 14.82. Calcd for $C_{12}H_{11}Br_2NO_2S_2$: C 33.90, H 2.61, N 3.30, Br 37.59, S 15.08.

Reaction of itomanindole B (13) *with acetic anhydride*. A mixture of 13 (8.9 mg), pyridine (0.15 ml), and acetic anhydride (0.3 ml) was allowed to stand at room temperature for 12 h. After concentration under vacuum, the residue was chromatographed on a Lobar Si-60 column (4:1 hexane-ethyl acetate) to give 9.2 mg (93%) of a compound, mp 123.5-125.5 °C, identical with 24 in all respects.

Synthesis of racemic itomanindoles A and B. To a solution of 7 (100 mg) in methanol (20 ml) was added 0.05 M sodium *meta*-periodate solution (14 ml). The mixture was stirred at room temperature for 1.5 h, poured into saturated sodium chloride solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed on silica gel (chloroform-ethyl acetate) to give 12 (46 mg, 44%), 13 (20.3 mg, 19%), and 7 (29.4 mg, 29%). The synthetic products were identified by comparing TLC, IR, and NMR spectra with those of natural samples.

Synthesis of R-(+)-itomanindole A (12). Compound 7 (183.5 mg) was treated with the modified Sharpless reagent (titanium tetraisopropoxide, (R,R)-diethyltartrate, water, and cumene hydroperoxide in dichloromethane) according to Kagan's procedure.[7] The reaction product was purified over silica gel (2:1 chloroform-ethyl acetate)

to afford **12** (143.5 mg, 75%) as a white solid, $[\alpha]_D^{25}$ +20.3° (c 0.62, $CHCl_3$). This product was identical to an authentic sample of **12** as attested by IR and NMR spectra. The optical purity of the synthetic sample was estimated to be 80% by recording its ^1H NMR spectrum by using the chiral solvating agent, (R)-(-)-trifluoroanthrylethanol.

Crystallographic data: Data were collected at room temperature on automatic four-circle Philips PW1100 (**12**) and Nonius CAD4 (**14**) diffractometers with monochromated MoKα radiation (λ = 0.71069 Å). Both structures were solved by direct methods[15] and refined by full matrix least-squares analysis with XRAY76[16] (**12**) and XTAL-2.4[17] (**14**) programs. All coordinates of hydrogen atoms were calculated.

12, $C_{10}H_9NOS_2Br_2$, m = 383.1. Monoclinic, space group $P2_1/n$, a = 9.5702(15), b = 9.5502(9), c = 14.5651(14) Å, β = 103.10(1)°, Z = 4, Dc = 1.96 gr·cm^{-3}, μ = 6.48 mm^{-1}, Fooo = 744. R = ωR = 0.072 (ω = 1) for 1184 observed reflections (|Fo| > 4σ(Fo) and |Fo| > 4).

14, $C_{18}H_{12}N_2S_2Br_4$, m = 640.0. Monoclinic, space group $P2_1/c$, a = 8.9038(6), b = 17.2963(12), c = 14.125(2) Å, β = 106.36(1)°, Z = 4, Dc = 2.04 gr·cm^{-3}, μ = 7.84 mm^{-1}, Fooo = 1244. R = 0.073 (ωR = 0.067; ω = $1/\sigma^2$(Fo)) for 2227 observed reflections (|Fo| > 4σ(Fo)).

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

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