chloride salt[63] of **1a** was obtained: ^{1}H NMR (D_2O, external Me_4Si) δ 1.37–1.57 (m, 3 H), 1.80–2.10 (m, 4 H), 2.16–2.46 (m, 2 H), 3.94 (d, 2 H, J = 5.5 Hz), 4.07–4.37 (m, 1 H), ^{13}C NMR (D_2O, external Me_4Si) 14.6, 23.0, 27.5, 31.0, 42.3, 50.9 ppm.

Formation of diamine **1a** was confirmed by the preparation of the corresponding diacetyl derivative.[67] The dihydrochloride salt of **1a** (0.25 g, 1.34 mmol) was dissolved in methanol (2 mL) and made basic with a methanolic solution of sodium methoxide (0.07 g [3.04 mmol] of Na in 3 mL of methanol). To this mixture ether (50 mL) was added, and the insoluble material was removed by filtration. The filtrate was evaporated in vacuo, and the residue was triturated with ether (50 mL). Concentration of the ethereal solution gave 0.12 g (77%) of **1a**. Diamine **1a** was dissolved in pyridine (2 mL), acetic anhydride (0.32 g, 3.10 mmol) was added, and the resulting mixture was stirred (0.5h) at room temperature. Benzene (50 mL) was then added and the reaction mixture evaporated in vacuo to give 0.19 g of material. Recrystallization of the residue from benzene yielded 0.16 g (77%) of the diacetamide: mp 147–148 °C (lit.[64] mp 151 °C); IR (KBr) 3300, 1655, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 5 Hz), 1.34–1.46 (m, 6 H), 1.97 (s, 3 H), 1.98 (s, 3 H), 3.13–3.43 (m, 2 H), 3.78–4.08 (m, 1 H), 6.18–6.38 (br s, 1 H), 6.54–6.84 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 13.9, 22.5, 23.1, 23.4, 28.1, 32.4, 44.8, 50.2, 171.3 ppm.

Acid Hydrolysis of 4,5-Dihydro-4,5-*trans*-di-*n*-propyl-2-ethoxyimidazole (8d). Imidazoline **8d** (0.51 g, 2.58 mmol) was dissolved in 30% aqueous H_2SO_4 and then heated at reflux (18 h). The reaction was made basic (pH 14) with 20% aqueous NaOH and extracted with ether (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4), made acidic (pH 1) with 10% ethanolic HCl, and concentrated to dryness in vacuo to give 0.22 g (39%) of the dihydrochloride salt of **1d**. Reprecipitation of the residue from methanol (2 mL) by the addition of ether (50 mL) gave 0.17 g (30%) of the dihydrochloride of **1d** as a white solid: mp 218–220 °C. The product was identified by IR and ^{1}H NMR spectroscopy.

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Registry No. (±)-**1a**, 95647-75-9; (±)-**1a**·HCl, 95647-76-0; (±)-**1a** (diacetamide), 95648-07-0; **1b**·H_2SO_4, 95647-77-1; **1b**·2HCl, 15444-85-6; (±)-**1c**·H_2SO_4, 95647-78-2; (±)-**1c**·2HCl, 66427-25-6; (±)-**1d**·2HCl, 85782-34-9; *meso*-**1e**·H_2SO_4, 95647-79-3; *meso*-**1e**·2HCl, 28971-67-7; *meso*-**1f**·2HCl, 10027-80-2; **2a**, 592-41-6; **2b**, 115-11-7; **2c**, 624-64-6; **2d**, 14850-23-8; **2e**, 590-18-1; **2f**, 110-83-8; **2g**, 922-62-3; **2h**, 563-79-1; **3**, 420-04-2; **4**, 128-08-5; (±)-**5a**$_1$, 95647-80-6; (±)-**5a**$_2$, 95647-81-7; **5b**, 90304-06-6; (±)-**5c**, 85782-20-3; (±)-**5d**, 85782-24-7; (±)-**5e**, 85782-21-4; (±)-**5f**, 85782-23-6; (±)-**5g**, 95647-82-8; **5h**, 95647-83-9; (±)-**6a**, 95647-84-0; **6b**, 95647-85-1; (±)-**6c**, 95647-86-2; (±)-**6d**, 95647-87-3; (±)-**6e**, 95647-88-4; (±)-**6f**, 95647-89-5; (±)-**7a**, 95647-90-8; **7b**, 95647-91-9; **7c**, 95647-92-0; (±)-**7d**, 95673-89-5; *meso*-**7e**, 85782-30-5; **7f**, 85782-31-6; **7h**, 95647-93-1; (±)-**8a**, 95647-94-2; **8b**, 95647-95-3; (±)-**8c**, 85782-25-8; (±)-**8d**, 85782-29-2; (±)-**8e**, 95673-90-8; (±)-**8f**, 95647-96-4; **9a**, 95647-97-5; (±)-**9b**, 95647-98-6; (±)-**10**, 60933-67-7; (±)-**11**, 95647-99-7; (±)-**15**, 95648-00-3; (±)-**16**, 95648-01-4; (±)-**17**, 95648-02-5; (±)-**18**, 95648-03-6; (±)-**18**·PICRATE, 95648-05-8; (±)-**26**, 95648-06-9.

Supplementary Material Available: An expanded list (Table A) of the reaction of isourea salts **6** with bases is reported herein (1 page). Ordering information is given on any current masthead page.

Total Syntheses of Rivularins D_1 and D_3

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Contribution from the Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received June 13, 1984. Revised Manuscript Received February 5, 1985*

Abstract: Two of the recently discovered metabolites of *Rivularia firma* Womersley, (+)-3′,5,5′-tribromo-7′-methoxy-3,4′-bi-1*H*-indole (rivularin D_1) and (+)-2,3′,5,5′-tetrabromo-7′-methoxy-3,4′-bi-1*H*-indole (rivularin D_3), were synthesized in racemic form. 2-Methoxy-1-naphthalenamine, prepared by nitration of 2-methoxynaphthalene and reduction of the resulting 2-methoxy-1-nitronaphthalene, gave 5,8-dihydro-2-methoxy-1-naphthalenamine upon Birch reduction. Subsequent bromination, N-tosylation, ozonolysis, and acid-catalyzed cyclization furnished 5-bromo-7-methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-4-acetaldehyde, which was converted to 5-bromo-4-(5-bromo-1*H*-indol-3-yl)-7-methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indole with (4-bromophenyl)hydrazine. Hydrolytic detosylation and a bromination with pyridinium bromide perbromide gave (±)-rivularin D_1. A further bromination with *N*-bromosuccinimide led to (±)-rivularin D_3.

Two indole nuclei, which are connected directly to each other by bridging only two positions, can form 28 constitutional isomers. The historical indigo, the oldest known organic dye, can be regarded as a member of this class of compounds. It consists of two oxindole moieties linked to each other by a double bond, as in the most celebrated member, 2-(1,3-dihydro-3-oxo-2*H*-indol-2-ylidene)-1,2-dihydro-3*H*-indol-3-one, also known as indigotin. In addition to the 2,2′-internuclear connection of the indigotins there are the indirubins with 2,3′- and the isoindigotins with 3,3′-linkages.[1] The variety of these dyes is further enhanced by a number of substituents in the benzenoid portions. Whereas the dyes derived from herbal precursors appear to be devoid of substituents, those from the animal kingdom are likely to contain bromine and occasionally methoxy groups as well. Tyrian Purple, for instance, is 6,6′-dibromoindigo and was derived by the ancients from several species of mollusks of the genus *Murex*, whereas the 5,5′-7,7′-tetrabromo-6,6′-dimethoxyindigo is the most highly substituted indigotin described to date and was discovered, among other congeners, in the acorn worm *Ptychodera flava*.[2a–c]

Lacking the ene-1,4-dione moiety of the indigo dyes, biindoles with single-bond internuclear connections are colorless and have only recently come to light. A 7,7′-bi-1*H*-indole system is found in 11,11′-dihydroxy-12,12′-bicoronaridine, an alkaloid isolated from the plant *Bonafousia tetrastachya* (family *Apocynaceae*),[3a] 1,3′- and 3,3′-systems are present in the gliotoxin-related antibiotics chaetomin and the chaetocin family,[3b] and the rivularins, metabolites of the marine blue-green alga *Rivularia firma* Womersley, represent biindoles featuring 1,3′-, 1,4′-, 3,3′-, and 3,4′-intramolecular linkages. In contrast to the indigo dyes derived from plants, all rivularins contain anywhere from three to six bromine atoms and some exhibit an additional methoxy group.[4]

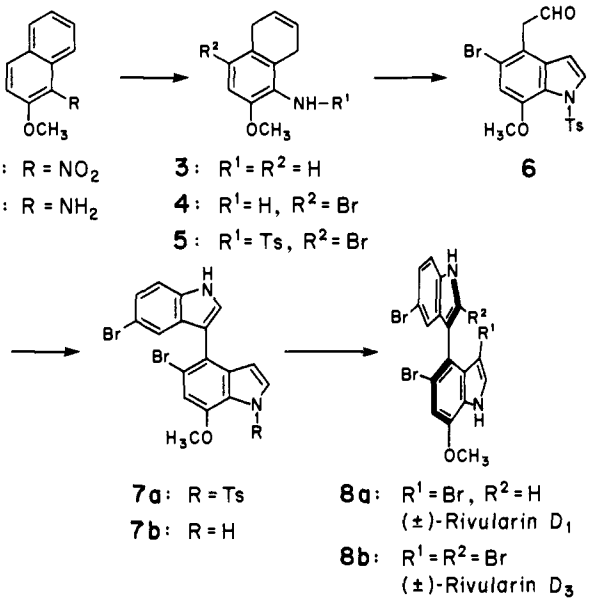
(1) Baker, J. T.; Duke, C. C. [*Conf.*], *4th, 1974 Food-Drugs Sea, Proc.* **1976**, 345–353.

(2) (a) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421–1443. (b) Higa, T.; Scheuer, P. J. *NATO Conf. Ser. 4* **1977**, *1*, 35–43. (c) Higa, T., Scheuer, P. J. *Heterocycles* **1976**, *4*, 227–233.

(3) (a) Damak, M.; Poupat, C.; Ahond, A. *Tetrahedron Lett.* **1976**, 3531–3534. (b) Turner, W. B.; Aldridge, D. C. "Fungal Metabolites II", Academic Press: New York, 1983; p 419.

0002-7863/85/1507-2943$01.50/0

Depending upon the site of the single-bond internuclear connection and the nature of the substituents, certain biindoles are suspected to be chiral due to atropisomerism and most rivularins indeed exhibit optical activity. The absolute configurations of rivularins A and D_3 (**8b**) were in fact established by Roentgen-diffraction



analyses as *S* and *R*, respectively.[5] Differing from rivularin D_3 only in their bromination patterns, rivularins D_1 (**8a**) and D_2 can thus be assumed to possess absolute configurations corresponding to that of D_3.[6]

Our interest in this class of compounds is based upon observed antiinflammatory activity of the crude algal extracts and the specific association of rivularin D_3 with this activity.[5] Rivularin D_1, a minor component of the metabolite fraction, was not examined in detail previously and became our major synthetic target.

In a previous study[7] we investigated several possibilities to assemble the biindole skeleton of rivularin D and reported a successful route to 5-bromo-3,4′-bi-1*H*-indole from 4-(2,2-dimethoxyethyl)-1-tosyl-1*H*-indole, prepared from 3-(2,2-dimethoxyethyl)-2-methylnitrobenzene by a Batcho–Leimgruber sequence, followed by a Fischer indolization[8] with (4-bromophenyl)hydrazine and detosylation. The syntheses of rivularins D_1 and D_3, as described here for the first time, follow a similar pattern of stepwise indolizations with 5-bromo-4-(5-bromo-1*H*-indol-3-yl)-7-methoxy-1-tosyl-1*H*-indole (**7a**) as key intermediate. The highly functionalized and *N*-protected 1*H*-indol-4-acetaldehyde (**6**), expeditiously prepared by a Plieninger indolization,[9] served as starting material for the Fischer indolization and was synthesized as follows. 2-Methoxynaphthalene was nitrated[10-12] regioselectively in acetic anhydride with fuming nitric acid. The desired 2-methoxy-1-nitronaphthalene (**1**) proved to be poorly soluble in acetic anhydride and precipitated from the reaction mixture at 0–5 °C.[13] Reduction of the nitro group with zinc–hydrochloric acid[14] furnished the hydrochloride of **2** and a subsequent Birch reduction led to the 5,8-dihydronaphthalene derivative **3**. Avoiding an excess of pyridinium bromide perbromide permitted regiospecific bromination of **3** with complete preservation of the olefin. Tosylation of the resulting **4** with triethylamine and tosyl chloride in situ afforded the sulfonamide **5** which was ozonized to the 5-bromo-3-[[(4-methylphenyl)sulfonyl]-amino]-1,2-benzenediacetaldehyde. Plieninger indolization of this dialdehyde yielded **6**. The 5-bromo-1*H*-indol-3-yl moiety was constructed with (*p*-bromophenyl)hydrazine hydrochloride by the Fischer method. Base hydrolysis of the biindole **7a** so obtained gave the detosylated biindole **7b** with all three required substituents at the benzenoid indole region appropriately positioned. The unsubstituted 3-position was brominated regiospecifically with pyridinium bromide perbromide in pyridine yielding crystalline (±)-rivularin D_1 (**8a**).

The additional bromination at the 2-position, as part of the synthesis of rivularin D_3, was more difficult to control in view of the required elevated temperature. A short treatment of **8a** with *N*-bromosuccinimide in dioxane at 65 °C, however, furnished (±)-rivularin D_3 as major component, obtained in crystalline form after chromatographic removal of the minor polybrominated impurities.

The spectroscopic data of racemic rivularins D_1 and D_3 were in agreement with the published values of the optically active forms but the observed antiinflammatory activities did not warrant further synthetic developments.

Experimental Section

IR (Digilab FTS-M), UV (Cary 14), and NMR spectra (Varian XL-100 and XL-200) were recorded with the indicated solvents, EI mass spectra (Varian MAT CH5) were obtained at an ionizing voltage of 70 eV and 250 °C ion-source temperature, and high-resolution data and FAB spectra were obtained in a VG instrument, ZAB-1F. R_f values pertain to TLC (silica gel 60 F-254 plates, E. Merck). Silica gel columns (Silica Woelm, 32–63 μm) were developed in the solvents stated. Solvent ratios are expressed in volume/volume. Solutions were dried with magnesium sulfate and evaporated under reduced pressure. Melting points were determined on a Thermopan (Reichert) hot stage and are reported without corrections.

2-Methoxy-1-nitronaphthalene (1). To an ice-cold solution of 2-methoxynaphthalene (75 g, 0.474 mol) in acetic anhydride (750 mL) was added fuming nitric acid (sp wt ca. 1.6, 21.6 mL) dropwise over a 30-min period at a temperature below 15 °C. The mixture was then stirred for 1 h at 0–5 °C and stored overnight at −20 °C. The deposited crystals were collected by filtration, washed thoroughly with water, and dried over potassium hydroxide under reduced pressure at 50 °C yielding **1** as yellow crystals (41.4 g, 43%): mp 127–128 °C (lit.[10] 128, 130 °C, recrystallized from acetic acid); 200-MHz NMR δ 4.05 (s, 1, OCH_3), 7.35 (d, 1, $J_{3,4}$ = 8.5 Hz, H3), 7.47 (t, 1, J_{ortho} = 8 Hz, H7), 7.61 (t, 1, J_{ortho} = 8 Hz, H6), 7.70 (d, 1, J_{ortho} = 8 Hz, H8), 7.85 (d, 1, J_{ortho} = 8 Hz, H5), 7.97 (d, 1, $J_{3,4}$ = 8.5 Hz, H4).

2-Methoxy-1-naphthalenamine hydrochloride (2·HCl). The reduction of **1** was conducted as described[14] and gave the hydrochloride of **2** as white needles, used without further purification: mp 179–182 °C dec; 200-MHz NMR δ 4.04 (s, 1, OCH_3), 7.48 (t, 1, J_{ortho} = 8 Hz, H6 or H7), 7.62 (t, 1, J_{ortho} = 8 Hz, H7 or H6), 7.60 (d, 1, J_{ortho} = 8.5 Hz, H3), 7.98 (d, 2, H4 and H5, J_{ortho} = 8 and 8.5 Hz), 8.12 (d, 1, J_{ortho} = 8 Hz, H8), 9.35 (br, 3, NH_2·HCl).

5,8-Dihydro-2-methoxy-1-naphthalenamine (3). A mixture of **2**·HCl (20 g, 0.0954 mol), absolute ethanol, ethanolic sodium ethoxide solution (2.66 M, 36 mL), and xylene (190 mL) was stirred and heated to reflux temperature in an oil bath (90 °C), and small pieces of sodium (10 g) were added during a 2-h period. The mixture was cooled to 60–70 °C and poured onto ice (ca. 600 g). The xylene layer was separated, washed with water 3 times, and evaporated. The residue was dissolved in ethanol and concentrated hydrochloric acid (20 mL) was added precipitating the salts of both **2** and **3**. The precipitate was washed with ethanol and ether and dried. The reduction process was repeated once more employing this mixture as described to yield **3**·HCl (12.4 g, 59%). The gradual disappearance of the starting material was followed by TLC (ethyl acetate–hexane, 1:4). The salt could be converted to the amine and then crystallized from methanol as colorless needles: mp 77–79 °C; 100-MHz NMR ($CDCl_3$) δ 3.10 and 3.36 (2 m, 4, H5, 8), 3.83 (s, 1, OCH_3), 5.88 (s, 2 H6, 7), 6.52, 6.79 (AB, 2, J_{ortho} = 8 Hz, H3,4); mass spectrum, *m/z* (relative intensity) 175 (100, $M^{+\cdot}$), 174 (33, M − H), 160 (67, M − CH_3).

(4) Norton, R. S.; Wells, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 3628–3635.
(5) Blount, J. F.; Daly, J. J.; Wells, R. J., unpublished results.
(6) Structures **8a** and **8b** are drawn according to a new convention with geometric stereodescriptors reflecting racemic character: Maehr, H. *J. Chem. Educ.* **1985**, *62*, 114–120.
(7) Maehr, H.; Smallheer, J. *J. Org. Chem.* **1984**, *49*, 1549–1553.
(8) For review references, see: Kutney, J. P. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 274.
(9) Plieninger, H.; Suhr, K. *Chem. Ber.* **1956**, *89*, 270–278.
(10) Yokoyama, M.; Iwata, K., Toyoshima, S. *Yakugaku Zasshi* **1958**, *78*, 123–125; Chem. Abstr. **1958**, *52*, 10986*c*.
(11) Wittkampf, L. *Chem. Ber.* **1884**, *14*, 393–395.
(12) Alcorn, P. G. E.; Wells, P. R. *Aust. J. Chem.* **1965**, *18*, 1391–1396.
(13) Although the yields of **1** were modest, this process was far superior to those using water[10] or acetic acid[11] as solvents which, in our hands, required complex separations of products nitrated at positions 1, 6, and 8. Nitromethane offers no advantage in terms of regioselectivity or ease of isolation.[12]
(14) Bradley, W.; Robinson, R. *J. Chem. Soc.* **1934**, 1484–1489.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.22; H, 7.38; N, 7.98.

***N*-(4-Bromo-5,8-dihydro-2-methoxy-1-naphthalenyl)-4-methylbenzenesulfonamide (5).** Triethylamine (6.0 g, 0.059 mol) was added to a solution of **3**·HCl (12.4 g, 0.0586 mol) in pyridine (100 mL). The mixture was cooled to 0–5 °C and, under vigorous stirring, a solution of pyridinium bromide perbromide (20.6 g, technical grade) in pyridine (100 mL) was added dropwise. Stirring for 5 min was followed by the addition of triethylamine (6.0 g) and *p*-tosyl chloride (13.5 g, 0.071 mol). The ice bath was removed and stirring continued overnight at room temperature. Addition of water precipitated 22 g (92%) of the sulfonamide **5**. Recrystallization from ethanol–diethyl ether afforded beige prisms: mp 205–206 °C; 200-MHz NMR ($CDCl_3$) δ 2.41 (s, 1, CH_3 of Ts), 3.13 (s, 1, OCH_3), 3.33, 3.76 (2 m, 4, H5, 8) 5.88 (m, 2, H6, 7), 6.01 (s, 1, NH), 6.77 (s, 1, H3), 7.23, 7.56 (AA′, BB′, 4, J_{ortho} = 8 Hz, C_6H_4 of Ts). Anal. Calcd for $C_{18}H_{18}BrNO_3S$: C, 52.95; H, 4.44; N, 3.43; Br, 19.57. Found: C, 53.26; H, 4.56; N, 3.39; Br, 19.37.

5-Bromo-7-methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-4-acetaldehyde (6). A solution of **5** (13 g, 0.0318 mol) in tetrahydrofuran–dichloromethane (1:1, 500 mL) was treated with ozone −78 °C for 1 h. The solution was purged with nitrogen and methyl sulfide (6.5 mL) was added at −78 °C. The mixture was allowed to come to room temperature and the solvents were evaporated. The residue was redissolved in toluene (250 mL), oxalic acid dihydrate (1.5 g) was added, and the mixture was heated on the steam bath with occasional shaking for 1 h and cooled to room temperature. Washing the toluene solution to neutrality with water and evaporation gave a residue which was chromatographed on silica gel (dichloromethane) to yield 4.32 g (32%) of aldehyde **6** as colorless rosettes: mp 175–185 °C dec; 100-MHz NMR ($CDCl_3$) δ 2.40 (s, 1, CH_3 of Ts), 3.70 (s, 1, OCH_3), 3.99 (d, 2, $J_{1,2}$ = 2 Hz, H2), 6.56 (d, 1, $J_{2',3'}$ = 4 Hz, H3′), 6.89 (s, 1, H6), 7.26, 7.72 (AA′, BB′, 4, J_{ortho} = 8 Hz, C_6H_4 of Ts), 7.87 (d, 1, $J_{2',3'}$ = 4 Hz, H2′); mass spectrum, *m/z* (relative intensity) 421 (42, $M^+\cdot$), 392 (100, M − CHO), 328 (2, M − CHO − SO_2), 313 (2, M − CHO − Br), 312 (2, M − CHO − HBr), 266 (2, M − Ts), 238 (61, 5-bromo-7-methoxy-4-methylene-4*H*-indole conjugate acid); calcd for $C_{18}H_{16}{}^{79}BrNO_4S$ 420.9976, found 420.9983.

5,5′-Dibromo-7′-methoxy-1′-[(4-methylphenyl)sulfonyl]-3,4′-bi-1*H*-indole (7a). A mixture of **6** (4.50 g, 10.66 mmol), (4-bromophenyl)-hydrazine hydrochloride (2.46 g, 11.0 mmol), sodium acetate (3.6 g, 44 mmol), and absolute ethanol (100 mL) was stirred and heated to reflux in an oil bath under nitrogen for 30 min. Heating and stirring was continued overnight after the addition of zinc chloride (15 g). The mixture was cooled to room temperature and poured into water. The precipitate was collected, washed with water, resuspended in 5% aqueous sodium hydrogen carbonate, again washed with water, and dried. Chromatography on Sephadex LH-20 (acetone) gave 3.9 (63.7%) of **7a** as an amber foam upon evaporation of the solvent: 100-MHz NMR ($CDCl_3$) δ 2.43 (s, 1, CH_3 of Ts), 3.75 (s, 1, OCH_3) 6.31 (d, 1, $J_{2',3'}$ = 4 Hz, H3′), 6.99 (s, 1, H6′), 7.27 (d, 1, $J_{2,NH}$ = 3 Hz, H2), 7.33 (s, 2, H6, 7), 7.44 (s, 1 H4), 7.29, 7.77 (AA′, BB′, 4, J_{ortho} = 8.5 Hz, C_6H_4 of Ts), 7.77 (d, 1, $J_{2',3'}$ = 4 Hz, H2′), 8.40 (br, 1, NH); mass spectrum, *m/z* (relative intensity) 572 (7, $M^+\cdot$); calcd for $C_{24}H_{18}{}^{79}Br_2NOS$ 571.9405, found 571.9441; calcd for $C_{24}H_{18}{}^{79}Br^{81}BrNOS$ 573.9385, found 573.9386; calcd for $C_{24}H_{18}{}^{81}Br_2NOS$ 575.9365, found 575.9396.

5,5′-Dibromo-7′-methoxy-3,4′-bi-1*H*-indole (7b). A solution of **7a** (3.9 g, 6.79 mmol) in a mixture of absolute ethanol (25 mL) and 2.66 M ethanolic sodium ethoxide (10 mL) was stirred and heated under nitrogen at reflux for 4 h). The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate 3 times. The combined extracts were washed once with water, dried, and evaporated. The residue was chromatographed on silica gel (ethyl acetate–hexane, 1:4) to yield 1.5 g (53%) of **7b** as a light amber syrup: R_f 0.44 (diethyl ether–hexane, 2:1); 200-MHz NMR ($CDCl_3$) δ 4.02 (s, 1, OCH_3), 6.22 (t, 1, $J_{2'3'} = J_{NH,3'}$ = 3 Hz, H3′), 6.97 (s, 1, H6′), 7.12 (t, 1, $J_{2'3'} = J_{NH,2'}$ = 3 Hz, H2′), 7.32 (s, 2, H6,7), 7.35 (d, 1, $J_{2,NH}$ = 3 Hz, H2), 7.54 (s, 1, H4), 8.28 (br, 1, NH), 8.38 (br, 1, NH); mass spectrum, *m/z* (relative intensity) 418 (100, $M^+\cdot$), 403 (18, M − CH_3), 339 (2, M − Br), 338 (2, M − HBr), 324 (30, M − Br − CH_3), 323 (13, M − HBr − CH_3), 245 (22, M − 2Br − CH_3); calcd for $C_{17}H_{12}{}^{79}Br^{81}BrN_2O$ 419.9296, found 419.9291.

3′,5,5′-Tribromo-7′-methoxy-3,4′-bi-1*H*-indole ((±)-Rivularin D_1, 8a). A solution of pyridinium bromide perbromide (0.86 g) in pyridine (10 mL) was added dropwise, with stirring, to a solution of **7b** (1.0 g, 2.38 mmol) in pyridine (10 mL) at 0–5 °C. Stirring was continued for 5 min after completion of the addition. The mixture was then distributed between water and diethyl ether; the ether layer was washed twice with water and evaporated. Redissolving the residue in dichloromethane, filtering the solution through a short column of silica gel, and solvent evaporation gave crystalline **8a** which could be recrystallized from chloroform (0.43 g, 36%): R_f 0.48 (diethyl ether–hexane, 2:1); mp 220–223 °C dec (lit.[4] mp 220–223 °C of optically active form); IR (KBr) 3425 (NH), 1615, 1560, 1480, 1440, 1400, 1380, 1280, 1270, 1100, 1000, 770 cm^{-1}; UV max (acetonitrile) 300 (sh, ϵ 11 550), 291 (13 100), 285 (sh, 12 600); 200-MHz NMR ($CDCl_3$) δ 4.02 (s, 1, OCH_3), 7.01 (s, 1, H6′), 7.14 (d, 1, $J_{2',NH}$ = 3 Hz, H2′), 7.21 (d, 1, $J_{2,NH}$ = 3 Hz, H2), 7.31 (s, 2, H6,7), 7.39 (s, 1, H4), 8.33 (br, 1, NH), 8.53 (br, 1, NH); mass spectrum, *m/z* (relative intensity) 496 (23, $M^+\cdot$), 481 (1, M − CH_3), 401 (6, M − CH_3 − HBr), 338 (77, M − 2Br), 323 (68, M − CH_3 − 2Br). Anal. Calcd for $C_{17}H_{11}Br_3N_2O$: C, 40.92; H, 2.22; N, 5.61. Found: C, 40.62; H, 2.25; N, 5.83.

2,3′5,5′-Tetrabromo-7′-methoxy-3,4′-bi-1*H*-indole ((±)-Rivularin D_3, 8b). A solution of **8a** (25 mg, 0.050 mmol) in 1,4-dioxane (1.5 mL) was stirred at room temperature while a solution of *N*-bromosuccinimide (10.8 mg, 0.06 mmol) in dioxane (0.5 mL) was added dropwise. The resulting solution was immersed into an oil bath of 65 °C and stirred for 15 min. The mixture was then cooled and distributed between diethyl ether and 10% aqueous sodium carbonate solution. The ether phase was combined with two additional ether extracts, dried, and evaporated. Pure **8b** was obtained by preparative-layer chromatography as beige prisms (20 mg, 69%) which were recrystallized from dichloromethane–hexane: R_f 0.54 (diethyl ether–hexane, 2:1); mp 180 °C dec (lit.[4] mp 178–179 °C dec, of optically active form); IR (KBr) 3420, 1620, 1560, 1450, 1410, 1280, 1140, 1010, 800 cm^{-1}; UV max (acetonitrile) 299 (sh, ϵ 13 900), 290 (16 800), 280 nm (sh, 15 800); 200-MHz NMR ($CDCl_3$) δ 4.02 (s, 3, OCH_3) 7.01 (s, 1, H6′), 7.18 (d, 1, $J_{2',NH}$ = 3 Hz, H2′), 7.32 (s, 2, H6, 7), 7.36 (s, 1, H4), 8.35 (br, 1, NH), 8.68 (br, 1, NH); mass spectrum, *m/z* (relative intensity) 574 (2, $M^+\cdot$), 559 (1, M − CH_3), 495 (1, M − Br), 494 (5, M − HBr), 480 (1, M − CH_3 − Br) 479 (2, M − CH_3 − HBr), 401 (5, M − CH_3 − 2Br); calcd for $C_{17}H_{11}{}^{79}Br_3{}^{81}BrN_2O$ (FAB, M + H) 576.7584, found 576.7594.

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Registry No. 1, 4900-66-7; **2**·HCl, 6271-82-5; **3**, 95739-82-5; **3**·HCl, 95739-83-6; **5**, 95739-84-7; **6**, 95739-85-8; **7a**, 95739-86-9; **7b**, 95739-87-0; **8a**, 95739-88-1; **8b**, 95739-89-2; 2-methoxynaphthalene, 93-04-9; (4-bromophenyl)hydrazine hydrochloride, 622-88-8.