at δ 7.65 (d), 7.35 (t), 7.15 (t), 6.77 (m) and 6.12 (m) totalling 24 H's; δ 5.2 (s, 2 H), 4.25 (q, 4 H; CH_2CH_3), 4.26 (AB, J = 10.5 Hz, 4 H), 1.2 (t, 6 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 172.5 (s, C=O), 139 (s), 138.3 (s), 134.3 (s), 131.1, 130.9, 130.0, 126.7, 126.1, 124.8, 61.8 (t), 55.8 (d), 53.8 (d), 52.6 (d), 14.2 (q).

Anal. Calcd for $C_{48}H_{40}O_4$: C, 84.71; H, 5.88; O, 9.41. Found: C, 84.68; H, 6.01.

Acknowledgment. This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences. We thank the NSF for the funding of two Shimadzu gas chromatographs (TFI-80-19684) and for partial funding of the EM-390 NMR (CHE 79-16449). We also thank D. L. Huser for some of the initial experiments.

Registry No. **5**, 89302-36-3; **6**, 89302-39-6; **7**, 89302-38-5; **8**, 89302-40-9; **10**, 89302-42-1; **12**, 89302-43-2; Na, 7440-23-5; Li, 7439-93-2; K, 7440-09-7; di-*tert*-butyl 9,9',10,10'-tetrahydro-9,9'-dianthroate, 89302-41-0; ethyl 1,4-dihydrobenzoate, 29246-24-0; *tert*-butyl 1,4-dihydrobenzoate, 61812-52-0; *tert*-butyl 1,4-dihydro-*p*-toluate, 89302-37-4; ethyl benzoate, 93-89-0; *tert*-butyl benzoate, 774-65-2; *tert*-butyl naphthoate, 66821-79-2; *tert*-butyl *p*-toluate, 13756-42-8; ethyl 9-anthroate, 1754-54-7; *tert*-butyl 9-anthroate, 1734-16-3; 9,10-dihydroanthracene, 613-31-0.

Rivularins. Preliminary Synthetic Studies

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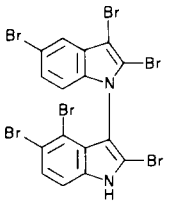
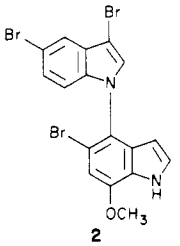
Received August 29, 1983

The 3,4'-biindole system of rivularin D has been synthesized from 1-(2,2-dimethoxyethyl)-2-methyl-3-nitrobenzene by consecutive Batcho–Leimgruber and Fischer indolizations. 5-Bromo-3-(2-methyl-3-nitrophenyl)-1*H*-indole could be converted to 5-bromo-1-methyl-3,4'-bi-1*H*-indole or 10-bromo-7-methyl-7*H*-naphth[2,1-*b*]indol-4-amine by heating with *N*,*N*'-dimethylformamide dialkyl acetal, followed by reduction with Raney nickel/hydrazine. In contrast to the generally operative alkylation mechanism which involves the alkoxy groups of the intermediate alkoxyimminium ion derived from the *N*,*N*-dialkylformamide dialkyl acetal, the N-methylation reactions presented here are shown to be unique examples where the N-methylation step is effected by the *N*-methyl groups of *N*,*N*-dimethylformamide dimethyl acetal.

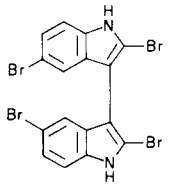
A number of brominated biindoles that exhibit a variety of nuclear connectivities and substitution patterns unprecedented among known naturally occurring biindoles were recently isolated from the blue-green alga *Rivularia firma* Womersley.[1] The size and location of the substituents generate atropisomerism, rendering most of these compounds optically active. Intended to suggest the source (Rivularia) and the chemical character (indole), the proposed generic term "rivularin" is a cumulative description of this class of compounds. The added letters A, B, C, and D represent 1–3', 1–4', 3–3', and 3–4' intramolecular linkages, respectively, between the indole nuclei.



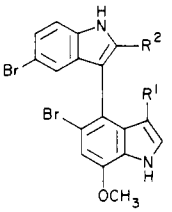
1
Rivularin A



2
Rivularin B



3
Rivularin C



4a : R^1 = Br, R^2 = H; Rivularin D_1

4b : R^1 = H, R^2 = Br; Rivularin D_2

4c : R^1 = R^2 = Br; Rivularin D_3

Of these biindoles, rivularin D_3 (**4c**) was of synthetic interest to us in view of its antiinflammatory activity. Our plan, therefore, consisted of the development of a reaction sequence that would first lead to the molecular rivularin D skeleton but also permit the synthesis of the 5,5'-dibromo-7-methoxy derivative from corresponding functionalized benzenoid precursors. The remaining two bromine substituents at the indole positions 2' and 3 would then have to be introduced in the final steps of the synthesis leading to racemic rivularin D_3.

The anticipated routes toward the monobrominated rivularin D nucleus (**7**), as outlined in Scheme I, were partial to the use of the two starting materials **5** and **10**, whose synthesis we had described recently.[2] Sequence A commences with a Fischer indolization of the enol ether **5**; the second indole would then be constructed by a Batcho–Leimgruber reaction from the resulting 5-bromo-3-(2-methyl-3-nitrophenyl)-1*H*-indole (**6**). The basic strategy in sequence B consists of the order reversal of the two indolizations.

In accordance with sequence A, **6** was prepared in acceptable yields, but the subsequent reaction with *N*,*N*-dimethylformamide dimethyl acetal proceeded with some unexpected results, which are summarized in Scheme II. Refluxing **6** in a mixture of *N*,*N*-dimethylformamide dimethyl acetal and *N*,*N*-dimethylformamide, followed by reductive cyclization of the resulting enamine, indeed gave rise to the expected biindole system, but the product (**8**) was N-methylated. Mass spectrometric proof for the N-methylation site in **8** was unavailable, since losses of bromine and methyl preceded further fragmentations, but the ^1H NMR spectrum revealed a singlet for H2 in one and a doublet of doublets for both H2 and H3 in the other indole moiety so that the structure of **8** was established.

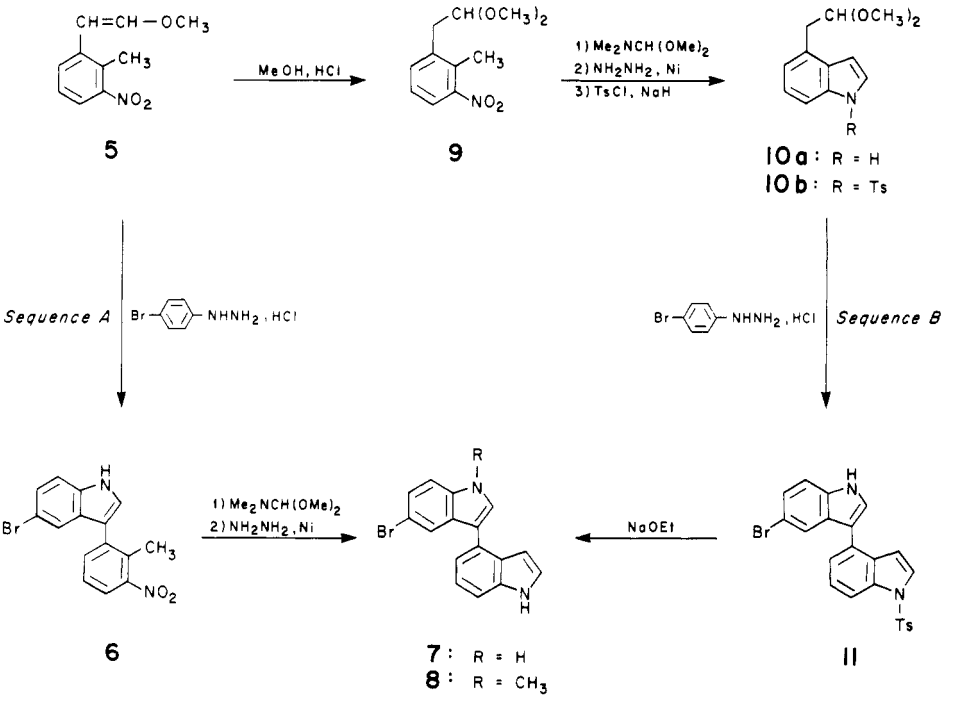
Hoping to prevent the N-methylation step during the Batcho–Leimgruber sequence, we prepared the *N*-acetyl,

(1) Norton, R. S.; Wells, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 3628.

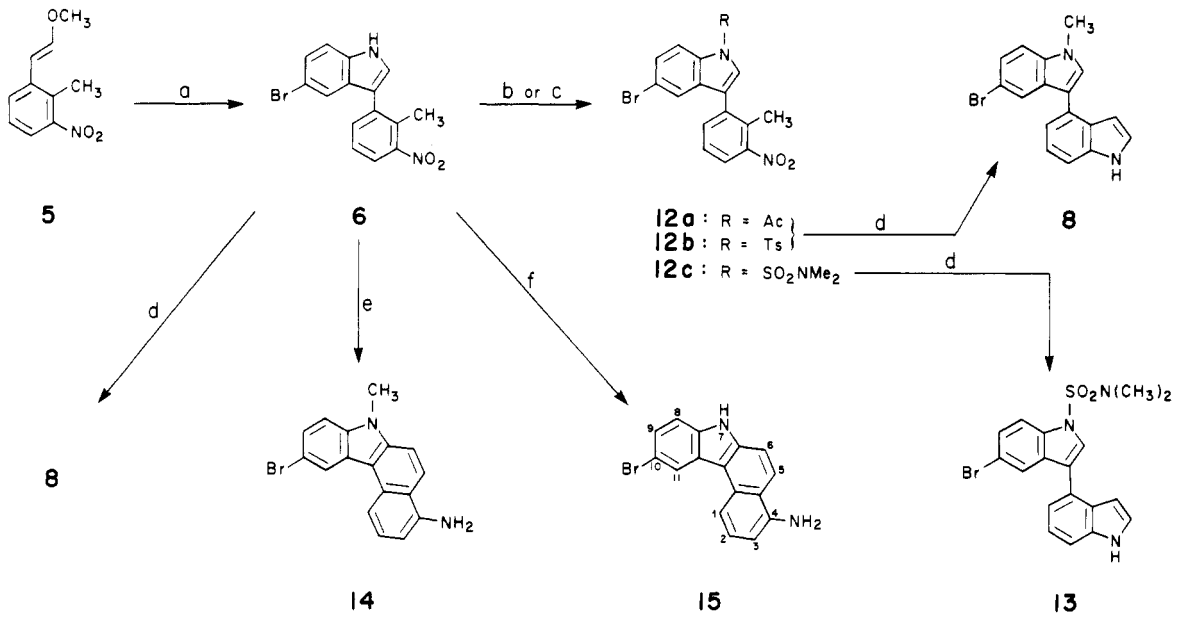
(2) Maehr, H.; Smallheer, J. *J. Org. Chem.* **1981**, *46*, 1752.

0022-3263/84/1949-1549$01.50/0

Scheme I



Scheme II



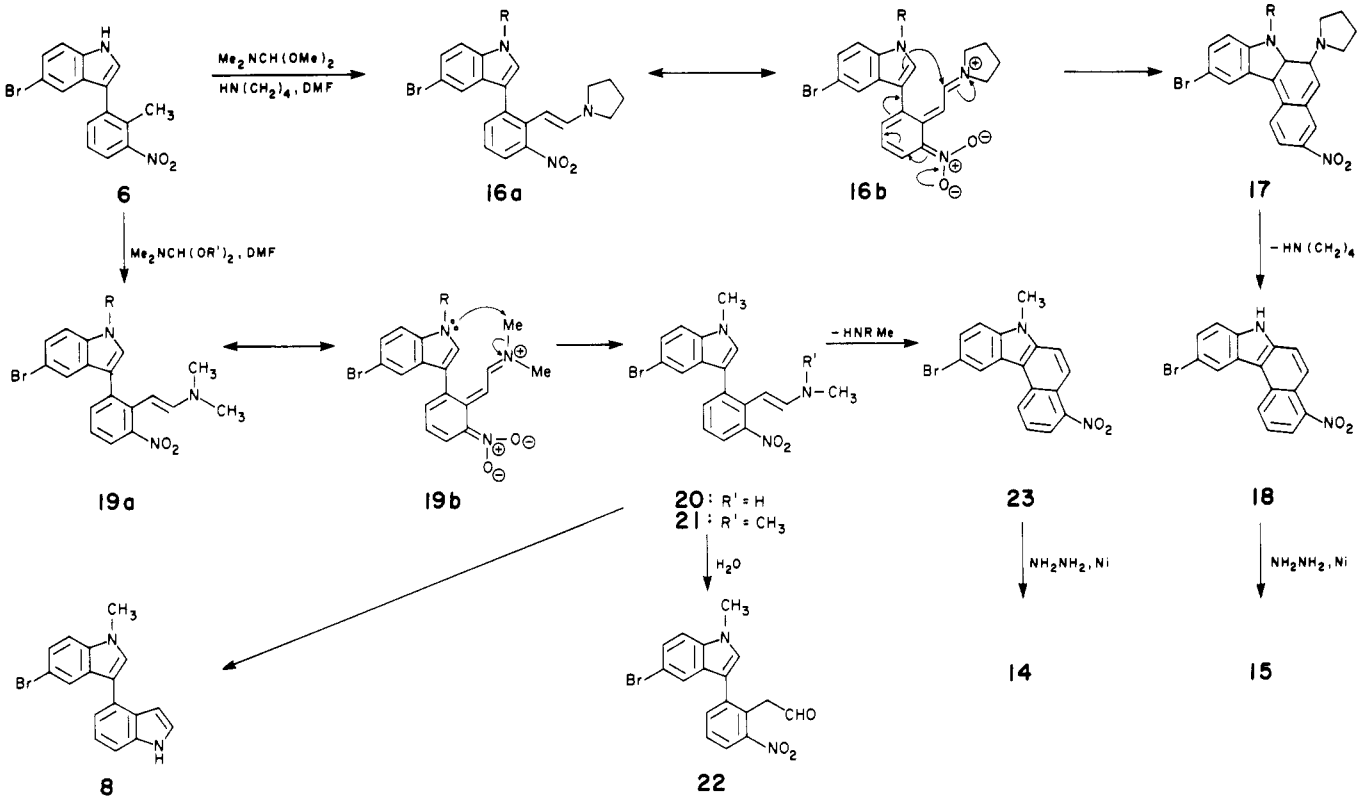
a, $NH_2NHC_6H_4Br$ / 2 N HCl / Me_2CHOH;
b, Ac_2O / AcONa;
c, NaH / DMF, RCl;
d, $Me_2NCH(OMe)_2$ / DMF, NH_2NH_2 / Raney Ni;
e, $Me_2NCH(OCHMe_2)_2$ / DMF, NH_2NH_2 / Raney Ni;
f, $Me_2NCH(OMe)_2$ / DMF / $HN(CH_2)_4$, NH_2NH_2 / Raney Ni;

N-tosyl, and, finally, the *N*-[(dimethylamino)sulfonyl] derivatives of **6** (**12a–c**). In the subsequent Batcho–Leimgruber reactions, derivatives **12a** and **12b**, however, lost the protective groups, yielding **8** much in the same way as did the unprotected indole derivative **6**. The sulfamide **12c**, generally known for exceptional solvolytic stability, survived the conditions of the Batcho–Leimgruber sequence and could be converted to the biindole **13**. The synthetic utility of **13** was limited in view of difficulties experienced in removing the protective group without loss of bromine or other decomposition.

N,*N*-Dimethylformamide dialkyl acetals are versatile alkylating agents[3] and have been employed successfully for the derivatization of carboxylic acids, phenols, thiols, and a host of heterocyclic compounds.[3,4] The mechanism of esterification of carboxylic acids has been thoroughly investigated and shown to involve an S_N2 attack at C-1 of the alkoxy group of the *N*,*N*-dimethylalkoxymethaniminium ion by the carboxylate anion.[5] It is therefore not surprising that bulky alkoxy groups, as in *N*,*N*-di-

(3) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
(4) Stanovnik, B.; Tišler, M.; Hribar, A.; Barlin, G. B.; Brown, D. *Aust. J. Chem.* **1981**, *34*, 1729.
(5) Brechbühler, H.; Büchi, H., Hatz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746.

Scheme III



methylformamide dineopentyl acetal, do not esterify carboxylic acids. Assuming that the N-alkylation of the indole moiety in **6** proceeded by a similar mechanism, it appeared reasonable to select an acetal for the aminomethylenation of **6** possessing alkoxy groups of sufficient steric bulk to preclude N-alkylation. Thus, **6** was heated with *N,N*-dimethylformamide diisopropyl acetal in *N,N*-dimethylformamide, and the reaction mixture was subjected to reductive cyclization with Raney nickel and hydrazine. The resulting major reaction product, subsequently identified as **14**, was shown to contain a new ring system; moreover, this product was also methylated at the indole nitrogen. In an attempt to identify the N-methylating species, we repeated the aminomethylenation with *N,N*-dimethylformamide dimethyl acetal, pyrrolidine, and *N,N*-dimethylformamide and obtained 10-bromo-4-nitro-7*H*-naphth[2,1-*b*]indole (**18**), a product that had escaped the N-methylation step. In sharp contrast to the generally accepted mechanism of alkylations with *N,N*-dimethylformamide dialkyl acetals, the results observed here suggested the *N*-methyl groups of *N,N*-dimethylformamide dialkyl acetal to be the methyl donors. This hypothesis was not refuted when an aminomethylenation of **6** was attempted with reagents containing the *N*-methyl groups of *N,N*-dimethylformamide dialkyl acetal as the only possible methyl source. In this experiment, **6** was heated with *N,N*-dimethylformamide diisopropyl acetal and *N,N*-diethylformamide and furnished a mixture of 10-bromo-7-methyl-4-nitro-7*H*-naphth[2,1-*b*]indole (**23**) and the desmethyl analogue **18**.

The generation of the tetracyclic ring system **18** can be explained by assuming initial aminomethylenation of **6** by the methoxymethylenepyrrolidinium ion. In view of the much greater acidity of the indole NH as compared with the benzylic protons of the *o*-nitrotoluene moiety of **6**, this reaction may be preceded by an alcohol–indole or amine–indole exchange involving some form of an *N,N*-dimethylformamide acetal or aminal and **6**, which would give the N-substituted 5-bromo-3-[3-nitro-2-(2-pyrrolidin-1-ylethenyl)phenyl]-1*H*-indole (**16a**). It has previously been shown that systems such as 1-[2-[2-(2-methoxyethenyl)-6-nitrophenyl]ethenyl]pyrrolidine, which is similar to **16a**, cyclize by an ionic rather than electrocyclic process,[6] so that **18** and **23** are assumed to be formed by a mechanism involving ionic intermediates as well. Enamine **16a**, in its mesomeric form **16b**, could therefore undergo ring closure as illustrated in Scheme III, leading to 6a,7-dihydro-4-nitro-6-(1-pyrrolidinyl)naphth[2,1-*b*]indole (**17**), which, after β-elimination of pyrrolidine, yields **18**. Without added pyrrolidine, however, the reaction can take a different course, also shown in Scheme III. The initially resulting 2-[2-(5-bromo-1*H*-indol-3-yl)-6-nitrophenyl]-*N,N*-dimethylethenamine (**19a**) is subject to a methyl migration, either intermolecularly, yielding **21**, or intramolecularly, as shown in the mesomeric form **19b**, generating the rearrangement product **20**. Our attempts to isolate such enamine intermediates, either by adsorption or gel permeation chromatography, were not successful in view of their solvolytic instability; we merely obtained the (5-bromo-1-methyl-1*H*-indol-3-yl)-2-nitrobenzeneacetaldehyde **22**, proving that the methylation step precedes ring closure. In the presence of excess *N,N*-dimethylformamide dialkyl acetal, the enamine form shown in **20** is most likely stabilized by temporary N-blockage with an alkyl group such as *N,N*-dimethyl(alkoxymethyl), so that ring closure and β-elimination can occur as discussed in connection with the formation of **18** from **16**, leading to **23**, or the reaction can then proceed in the sense of the Batcho–Leimgruber sequence, yielding **8**. Minor changes

(6) Maehr, H.; Smallheer, J.; Blount, J. F.; Todaro, L. *J. Org. Chem.* **1981**, *46*, 5019.

in the reaction conditions apparently can alter the reaction course rather drastically.

The experiments described above clearly illustrate the inadequacy of sequence A for the synthesis of biindole **7**. In the alternate sequence B, therefore, the unbrominated indole ring was constructed initially from **9** via the Batcho–Leimgruber reaction as described,[2] and the resulting 4-(2,2-dimethoxyethyl)-1*H*-indole **10a** was then tosylated to enhance its stability against the acidic conditions necessary to accomplish the subsequent Fischer indolization. Thus, **10b** was converted to the tosylated biindole **11**, which furnished the desired model biindole **7** upon ethanolysis.

The studies described above have laid the groundwork for the total synthesis of rivularin D_3, the details of which will appear in the next paper in this series.

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 were obtained on 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. All solvent ratios are expressed in volume/volume. Melting points were determined on a Thermopan (Reichert) hot stage and are reported without corrections.

5-Bromo-3-(2-methyl-3-nitrophenyl)-1*H*-indole (6). A mixture of 1-(2-methoxyethenyl)-2-methyl-3-nitrobenzene[2] (**5**; 5 g, 25.88 mmol) in 2-propanol/2 M hydrochloric acid (1:1, 100 mL) was refluxed on a steam bath for 1 h. After cooling to room temperature, the solution was concentrated under reduced pressure to one-half of the original volume and extracted with dichloromethane. The extract was washed twice with water, dried ($MgSO_4$), and filtered, and the filtrate was evaporated. The resulting crude product was chromatographed on a column of Sephadex LH-20 with acetone as the mobile phase. The van Urk positive fractions (R_f 0.8, dichloromethane) were pooled and evaporated to give **6** as an amber, thick oil: yield 6.5 g (76%); IR (KBr) ν 3435 (NH), 1524 and 1355 (NO_2) cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 2.41 (s, 3, Me), 7.22 (d, 1, $J_{1,NH}$ = 2.5 Hz, H2), 7.34, 7.54 (AA'X, 3, $^1/_2\,J_{AX,meta} + {}^1/_2\,J_{AX,para}$ = 1.5 Hz, H6, H7, and H4, respectively), 7.37 (t, 1, J_{ortho} = 8.5 Hz, H5'), 7.58 (dd, 1, J_{ortho} = 8.5 and J_{meta} = 2 Hz, H4'), 7.81 (dd, 1, J_{ortho} = 8.5 and J_{meta} = 2 Hz, H6'), 8.40 (br s, 1, NH); mass spectrum, m/z (relative intensity) 330 (55, M^+), 313 (4, $M^+ - OH$), 300 (1, $M^+ - NO$), 283 (2, $M^+ - NO_2$), 284 (3, $M^+ - HNO_2$), 269 (3, $M^+ - NO_2 - CH_3$), 251 (4, $M^+ - Br$), 234 (100, $M,^+ - Br - OH$), 205 (39, $M^+ - Br - NO_2$), 204 (58, $M^+ - Br - HNO_2$); high-resolution mass spectrum calcd for $C_{15}H_{11}N_2O_2Br$, 330.0004 and 331.9985; found, m/z 329.9952 and 331.9922; calcd for $M^+ - Br - OH$, 234.0793; found, m/z 234.0793.

5-Bromo-3,4'-bi-1*H*-indole (7). A solution of **11** (120 mg, 0.258 mmol) in 0.9 M ethanolic sodium ethoxide (1.5 mL) was heated at reflux temperature for 4 h. The product (**7**) gave a much more intense van Vrk coloration and moved slightly faster than **11** on TLC. The solution was poured into water. The precipitated solids were washed with water and dried, yielding crude **7** (52 mg, 64%). A pure sample was prepared by preparative TLC (dichloromethane): 100-MHz NMR ($CDCl_3$) δ 6.60 (dd, 1, $J_{2',3'}$ = 3 and $J_{3',NH}$ = 2 Hz, H3'), 7.15 (dd, 1, $J_{2',3'}$ = 3 and $J_{2',NH}$ = 2.5 Hz, H2'), 7.29 (m, 6, H2, H6, H7, H5', H6', H7'), 7.96 (s, 1, H4), 8.12 (br, 2 NH), mass spectrum, m/z (relative intensity) 310 (100, M^+), 282 (3, $M^+ - CH_2N$), 231 (33, $M^+ - Br$), 230 (76, $M^+ - HBr$), 203 (27, $M^+ - HBr - HCN$); high-resolution mass spectrum calcd for $C_{16}H_{11}N_2Br$, 310.0105 and 312.0086; found, 310.0114 and 312.0099.

5-Bromo-1-methyl-3,4'-bi-1*H*-indole (8) and 6-(5-Bromo-1-methyl-1*H*-indol-3-yl)-2-nitrobenzeneacetaldehyde (22). A mixture of **6** (800 mg, 2.42 mmol), *N,N*-dimethylformamide dimethyl acetal (1.2 mL), and DMF (3 mL) was stirred and heated in an oil bath (130 °C) under nitrogen for 48 h. The dark-red reaction mixture was evaporated under reduced pressure, and the resulting residue was redissolved in THF/methanol (1:1, 5 mL). To this stirred solution was added, at 45–50 °C and under nitrogen, $^1/_8$ teaspoonful of Raney nickel, followed by hydrazine hydrate (0.25 mL). The temperature was maintained at 45–50 °C, and two additional 0.25-mL portions of hydrazine hydrate were added after 30 and 90 min to the stirred suspension. The mixture was allowed to cool to room temperature 2 h after the last hydrazine addition and was filtered through a Celite pad. The filtrate and washings (dichloromethane) were evaporated, and the resulting crude product was purified by chromatography on a column of silica gel with dichloromethane–cyclohexane (4:1) as the mobile phase to yield **8** (0.44 g, 56%) as colorless prisms after recrystallization from aqueous ethanol: mp 147–148 °C; UV max ($CHCl_3$) 294–298 nm (ϵ 15 200), 305 (sh, ϵ 15 000); 100-MHz NMR ($CDCl_3$) δ 3.75 (s, 3, Me), 6.66 (dd, 1, $J_{2',3'}$ = 3 and $J_{3',NH}$ = 2 Hz, H3'), 7.21 (dd, 1, $J_{2',3'}$ = 3 and $J_{2',NH}$ = 2.5 Hz, H2'), 7.26 (m, 4, H2, H5', H6', H7'), 7.29, 7.31, 7.98 (ABX, 3, $J_{AB,ortho}$ = 8.5 and $J_{BX,meta}$ = 2 Hz, H7, H6, H4), 8.19 (br s, 1, NH); mass spectrum, m/z (relative intensity) 324 (100 M^+), 309 (2, $M^+ - CH_3$), 244 (44, $M^+ - HBr$), 230 (22, $M^+ - CH_3 - Br$), 299 (20, $M^+ - CH_3 - HBr$). Anal. Calcd for $C_{17}H_{13}N_2Br$: C, 62.79; H, 4.03; N, 8.61; Br, 24.57. Found: C, 62.67; H, 4.07; N, 8.51; Br, 24.82.

TLC analysis of the crude, dark red residue obtained prior to the reduction step exhibited the presence of two products. The minor one (R_f 0.86, dichloromethane) was identified as **23**; the major one was identified as **22** (R_f 0.34). Aldehyde **22**, a colorless substance, is formed during chromatography at the expense of the dark red enamine **20** or **21**. A small quantity of **22** was prepared by column chromatography (silica gel; cyclohexane–dichloromethane, 1:1) of the evaporated reaction mixture: 200-MHz NMR ($CDCl_3$) δ 3.85 (s, 1, Me), 4.08 (s, 2, CH_2), 7.08 (s, 1, H2'), 7.27 (d, 1, J_{ortho} = 8.5 Hz, H7'), 7.40 (dd, 1, J_{ortho} = 8.5 and J_{meta} = 2 Hz, H6'), 7.48 (d, 1, J_{meta} = 2 Hz, H4'), 7.54 (t, 1, J_{ortho} = 8 Hz, H4), 7.71 (d, 1, J_{ortho} = 8 Hz, H3), 8.09 (d, 1, J_{ortho} = 8 Hz, H5), 9.81 (s, 1, CHO).

4-(2,2-Dimethoxyethyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indole (10b). A solution of **10a** (104 mg, 0.507 mmol) in DMF (1 mL) was added dropwise to an ice-cooled solution of sodium hydride (50 mg) in DMF (1 mL). After the solution was stirred for 20 min, *p*-toluenesulfonyl chloride (300 mg) in DMF (1 mL) was added, and stirring was continued in the ice bath for 1 h and then at room temperature for 2 h. The mixture was poured into ice–water, the pH was adjusted to 9, and the product was extracted with dichloromethane. Evaporation of the water-washed and dried ($MgSO_4$) extract gave **10b** as viscous syrup (156 mg, 86%); 100-MHz NMR ($CDCl_3$) δ 2.33 (s, 3, CH_3), 3.08 (d, 2, J = 5.5 Hz, CH_2), 3.30 [s, 6, $(CH_3O)_2$], 4.57 (t, 1, J = 5.5 Hz, OCHO), 6.74 (d, $J_{2,3}$ = 4 Hz, H3), 7.10 (d, J_{ortho} = 7.5 Hz, H5), 7.21 and 7.76 (AA', BB', J_{ortho} = 8.5 Hz, C_6H_4), 7.24 (t, J_{ortho} = 7.5 Hz, H6), 7.57 (d, $J_{2,3}$ = 4 Hz, H2), 7.86 (d, J_{ortho} = 7.5 Hz, H7); mass spectrum, m/z (relative intensity) 328 (1, $M^+ - OCH_3$), 284 (1, $M^+ - CH(OCH_3)_2$, 91 (100).

5-Bromo-1'-[(4-methylphenyl)sulfonyl]-3,4'-bi-1*H*-indole (11). A mixture of **10b** (180 mg, 0.501 mmol), 4-bromophenylhydrazine hydrochloride (120 mg), 2-propanol (2 mL), and 2 M hydrochloric acid (2 mL) was heated on a steam bath under reflux for 30 min with occasional shaking. The mixture was evaporated under reduced pressure, and the residue was distributed between water (10 mL) and dichloromethane (10 mL). The aqueous phase was reextracted with dichloromethane, and the combined extracts were washed once with brine and dried ($MgSO_4$). The residue obtained upon evaporation was chromatographed on a column of Sephadex LH-20 with acetone as the mobile phase. Pooling and evaporation of the appropriate fractions (R_f 0.70, dichloromethane) gave **11** as an amber oil (133 mg, 0.286 mmol, 57%): 200-MHz NMR ($CDCl_3$) δ 2.36 (s, 3, Me), 6.75 (d, 1, $J_{2',3'}$ = 3.5 Hz, H3'), 7.25, 7.83 (AA', BB', 4, J_{ortho} = 8 Hz, H2, H3, H5, H6 of Ts), 7.29, (s, 2, H6, H7), 7.40 (s, 1, H2), 7.42, 7.88 (AA'X, 3, $^1/_2\,J_{AX,ortho} + {}^1/_2\,J_{A'X,meta}$ = 4.5 Hz, H5', H6', H7'), 7.60 (d, 1, $J_{2',3'}$ = 3.5 Hz, H2'), 7.82 (s, 1, H4), 8.39 (br s, 1, NH); mass spectrum, m/z (relative intensity) 464 (23, M^+), 309 (4, $M^+ - Ts$), 230 (100, $M^+ - Br$), 203 (30, $M^+ - Br - HCN$).

1-Acetyl-5-bromo-3-(2-methyl-3-nitrophenyl)-1*H*-indole (12a). 1-(2-Methoxyethenyl)-2-methyl-3-nitrobenzene (**5**; 1 g, 5.18 mmol) was converted to **6** as described and then dissolved in acetic anhydride (5 mL) without prior chromatography. After the addition of sodium acetate (1.11 g), the mixture was stirred and

heated in an oil bath (100 °C) for 3 h. The resulting solution was cooled to room temperature and poured into water. The crystals, which formed within a short time, were collected, washed with water and ethanol, and dried to yield **12a** as yellow clusters (1.37 g, 71% from **5**): mp 201–203 °C (after recrystallization from ethanol–dichloromethane); 100-MHz NMR ($CDCl_3$) δ 2.40 (s, 1, Me), 2.68 (s, 3, Ac), 7.39 (t, 1, J_{ortho} = 8 Hz, H5′), 7.43 (s, 1, H2), 7.40–7.60 (m, 3, H4, H6, H6′), 7.89 (dd, 1, J_{ortho} = 8 and J_{meta} = 2 Hz, H4′), 8.40 (d, 1, J_{ortho} = 8.5 Hz, H7); mass spectrum, *m/z* (relative intensity) 372 (25, M^+), 357 (2, $M^+ - CH_3$), 340 (2, $M^+ - CH_3OH$), 330 (42, $M^+ - COCH_2$), 313 (4, $M^+ - COCH_2 - OH$), 293 (2, $M^+ - Br$), 284 (4, $M^+ - COCH_2 - NO_2$), 283 (2, $M^+ - COCH_2 - HNO_2$), 269 (2, $M^+ - CH_3 - COCH_2 - NO_2$), 251 (5, $M^+ - COCH_2 - Br$), 234 (74, $M^+ - COCH_2 - Br - OH$), 205 (27, $M^+ - COCH_2 - NO_2 - Br$), 204 (39, $M^+ - COCH_2 - NO_2 - HBr$). Anal. Calcd for $C_{17}H_{13}BrN_2O_3$: C, 54.71; H, 3.51; N, 7.51; Br, 21.41. Found: C, 54.72; H, 3.34; N, 7.30; Br, 21.67.

5-Bromo-3-(2-methyl-3-nitrophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indole (12b). Sodium hydride (0.4 g, 50% in mineral oil) was added to DMF (5 mL) at 0 °C under stirring, followed by a solution of crude **6** (DMF/dichloromethane, 2 mL, 1:1) prepared from 1 g of **5** (5.18 mmol) as described for the preparation of **12a**. The resulting deep red solution was stirred for 20 min at 0 °C. A solution of *p*-toluenesulfonyl chloride (1.3 g) in DMF (5 mL) was added, and stirring was continued at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture lost its red color during this time and was poured into a mixture of ice and aqueous sodium carbonate solution. The mixture was then extracted with diethyl ether; the ether phase was washed repeatedly (water) and dried ($MgSO_4$), yielding **12b** as an orange syrup (2.16 g, 86% from **5**), which was used without further purification: 100-MHz NMR ($CDCl_3$) δ 2.28 (s, 3, Me of Ts), 2.37 (s, 3, Me), 7.26, 7.77 (AA′, BB′, 4, J_{ortho} = 8 Hz, H2, H6 and H3, H5 of Ts), 7.37 (t, 1, J_{ortho} = 8 Hz, H5′), 7.35–7.55 (m, 3, H4, H6, H6′), 7.55 (s, 1, H2), 7.85 (m, 1, H4′), 7.93 (d, 1, J_{ortho} = 8.5 Hz, H7); mass spectrum, *m/z* (relative intensity) 484 (21, M^+), 388 (3, $M^+ - Br - OH$), 330 (16), 329 (7, $M^+ - Ts$), 313 (2), 312 (3, $M^+ - Ts - OH$), 282 (3, $M^+ - Ts - HNO_2$), 250 (5, $M^+ - Ts - Br$), 249 (2, $M^+ - HBr$), 234 (29, $M^+ - Ts - Br - CH_3$), 204 (30, $M^+ - Ts - Br - NO_2$), 203 (30).

5-Bromo-3-1*H*-indol-4-yl-*N*,*N*-dimethyl-1*H*-indole-1-sulfonamide (13). The indole derivative **12c** was prepared from **5** (1 g, 5.18 mmol) as described for **12b** by using *N*,*N*-dimethylsulfamoyl chloride (0.9 g) instead of tosyl chloride and dichloromethane for extractions. The crude **12c** was treated with *N*,*N*-dimethylformamide dimethyl acetal, and the resulting product was reduced and purified as described for the preparation of **8**, yielding **13** (0.45 g, 21% from **5**) as colorless needles: mp 197–199 °C (after recrystallization from aqueous ethanol); UV max (ethanol) 218 nm (ϵ 67 300), 292 (ϵ 12 600); 200-MHz NMR (Me_2SO-d_6) δ 2.90 (s, 6, Me_2N), 6.43 (d, 1, $J_{2',3'}$ = 3 Hz, H3′), 7.24, 7.49 (AA′X, 3, $^1/_2\,J_{AX,ortho} + {}^1/_2\,J_{A'X,meta}$ = 5 Hz, H6′, H7′, H5′), 7.46 (d, 1, $J_{2',3'}$ = 3 Hz, H2′), 7.58 (dd, 1, J_{ortho} = 9 and J_{meta} = 2 Hz, H6), 7.83 (d, 1, J_{meta} = 2 Hz, H4), 7.87 (s, 1, H2), 7.97 (d, 1, J_{ortho} = 9 Hz, H7), 11.35 (br s, NH); mass spectrum, *m/z* (relative intensity) 417 (40, M^+), 309 (45, $M^+ - SO_2NMe_2$), 230 (100, $M^+ - SO_2NMe_2 - Br$), 229 (29, $M^+ - SO_2NMe_2 - HBr$). Anal. Calcd for $C_{18}H_{16}BrN_3O_2S$: C, 51.68; H, 3.85; N, 10.04. Found: C, 51.44; H, 3.91; N, 9.62.

10-Bromo-7*H*-naphth[2,1-*b*]indol-4-amine (15). A suspension of **18** (1.78 g, 5.22 mmol) in THF–methanol (1:1, 20 mL) was reduced with Raney Nickel ($^1/_2$ teaspoonful) and hydrazine hydrate (three 1-mL portions) as described for the preparation of **8**. Evaporation of filtrate and washings furnished crystalline **15** without chromatography. Recrystallization from methanol gave yellow needles, (1.56 g, 96%): mp 245–256 °C dec; UV max (2-propanol) 201 nm (ϵ 48 300), 224 (24 700), 260 (53 400), 296 (sh, 9200), 302 (sh, 8100), 334 (sh, 11 900), 347 (15 100), 374 (8600); 200-MHz NMR ($CDCl_3$–Me_2SO-d_6, 20:1) δ 4.45 (br s, 2, NH_2), 6.80 (d, 1, J_{ortho} = 8 Hz, H1), 7.48 (s, 2 H8, H9), 7.49 (t, 1, J_{ortho} = 8 Hz, H2), 7.61 (d, 1, J_{ortho} = 9 Hz, H6), 7.91 (d, 1, J_{ortho} = 9 Hz, H5), 8.08 (d, 1, J_{ortho} = 8 Hz, H3), 8.60 (s, 1, H11); mass spectrum, *m/z* (relative intensity) 310 (100, M^+), 282 (4, $M^+ - CNH_2$), 231 (37, $M^+ - Br$), 204 (39, $M^+ - Br - HCN$). Anal. Calcd for $C_{16}H_{11}BrN_2$: C, 61.76; H, 3.56; N, 9.00; Br, 25.68. Found: C, 62.35; H, 3.64; N, 8.42; Br, 25.34.

10-Bromo-4-nitro-7*H*-naphth[2,1-*b*]indole (18). A solution of **6** (7 g, 21.1 mmol) in DMF (15 mL), *N*,*N*-dimethylformamide dimethyl acetal (3.75 mL), and pyrrolidine (2.4 mL) was stirred and heated at reflux temperature under nitrogen. After 3 h, additional *N*,*N*-dimethylformamide dimethyl acetal (3.75 mL) and pyrrolidine (2.4 mL) were added, and heating was continued for a total of 7.5 h. The solvents were evaporated under reduced pressure; the residue was redissolved in dichloromethane and filtered through a short column of Sephadex LH-20 with acetone as the mobile phase. The fractions with R_f 0.49 (dichloromethane–cyclohexane, 4:1) were pooled and evaporated. Trituration of the residue with methanol gave yellow solids (2.5 g, 35%), which were recrystallized from methanol, yielding **18** as yellow needles: mp 236–238 °C; UV max ($CHCl_3$) 260 nm (ϵ 47 200), 319 (9600), 367–369 (8500); 200-MHz NMR ($CDCl_3$ + Me_2SO-d_6, 20:1) δ 7.52 (s, 2 H8, H9), 7.71 (t, 1, J_{ortho} = 8 Hz, H2), 7.83 (d, 1, J_{ortho} = 9 Hz, H6), 8.01 (d, 1, J_{ortho} = 8 Hz, H3), 8.34 (d, 1, J_{ortho} = 9 Hz, H5), 8.54 (s, 1, H11), 8.86 (d, 1, J_{ortho} = 8 Hz, H1), 11.21 (br s, NH); mass spectrum, *m/z* (relative intensity) 340 (100, M^+), 339 (2, $M^+ - H$), 310 (13, $M^+ - NO$), 294 (10, $M^+ - NO_2$), 282 (51, $M^+ - NO - CO$), 267 (11, $M^+ - NO_2 - HCN$), 261 (2, $M^+ - Br$), 231 (6, $M^+ - Br - NO$), 215 (88, $M^+ - Br - NO_2$), 214 (77, $M^+ - Br - HNO_2$). Anal. Calcd for $C_{16}H_9N_2O_2Br$: C, 56.33; H, 2.66; N, 8.21; Br, 23.42. Found: C, 56.48; H, 2.86; N, 8.47; Br, 23.59.

10-Bromo-7-methyl-7*H*-naphth[2,1-*b*]indol-4-amine (14) and 10-Bromo-7-methyl-4-nitro-7*H*-naphth[2,1-*b*]indole (23). A solution of **6** (0.6 g, 1.81 mmol) in DMF (3 mL) and *N*,*N*-dimethylformamide diisopropyl acetal (1.5 mL) was stirred and heated at reflux under nitrogen in an oil bath (130 °C) for 70 h. The solvents were evaporated under reduced pressure, and the crude **23** was reduced with Raney nickel/hydrazine as described for the preparation of **8**. Trituration of the residue with dichloromethane gave **14** as a yellow, crystalline residue (126 mg, 21%), mp 256 °C dec. The mother liquor contained additional **14** [R_f 0.27 (ethyl acetate–hexane, 1:1)], which was not isolated: UV max (2-propanol) 203 nm (ϵ 31 400), 255–256 (19 450), 263 (43 900), 300 (7750), 338–340 (sh, 10 000), 352 (11 750), 380 (6250); 100-MHz NMR (Me_2SO-d_6) δ 4.00 (s, 3, Me), 5.81 (br s, 2, NH_2), 6.72 (d, 1, J_{ortho} = 8 Hz, H3), 7.43 (t, 1, J_{ortho} = 8 Hz, H2), 7.56 (dd, 1, J_{ortho} = 9 and J_{meta} = 2 Hz, H9), 7.60 (d, 1, J_{ortho} = 9 Hz, H8), 7.74 (d, 1, J_{ortho} = 9 Hz, H6), 7.88 (d, 1, J_{ortho} = 8 Hz, H1), 8.24 (dd, 1, J_{ortho} = 9 Hz, H5), 8.61 (dd, 1, J_{meta} = 2 Hz, H11); mass spectrum, *m/z* (relative intensity) 324 (100, M^+), 309 (10, $M^+ - CH_3$), 296 (4, $M^+ - CH_2N$), 245 (7, $M^+ - Br$) 244 (8, $M^+ - HBr$); high-resolution mass spectrum calcd for $C_{17}H_{13}N_2Br$: 324.0261 and 326.0237; found, *m/z* 324.0263 and 326.0243.

A small portion of crude **23** was purified by chromatography on a silica gel column, with cyclohexane–dichloromethane, 1:1, as the mobile phase [R_f 0.83 (same system)] and recrystallized from acetone–methanol: mp 224–225 °C; UV max ($CHCl_3$) 268 (ϵ 35 285), 293 (sh, 10 700), 319 (6550), 380 nm (6500); 100-MHz NMR (Me_2SO-d_6) δ 4.04 (s, 1, Me), 7.68 (dd, 1, J_{ortho} = 8.5, J_{meta} = 1.5 Hz, H9), 7.77 (d, 1, J_{ortho} = 8.5 Hz, H8), 7.84 (t, 1, J_{ortho} = 8 Hz, H2), 8.13 (d, 1, J_{ortho} = 9.5 Hz, H6), 8.14 (d, 1, J_{ortho} = 8 Hz, H3), 8.30 (d, 1, J_{ortho} = 9.5 Hz, H5), 8.78 (dd, 1, J_{meta} = 1.5 Hz, H11), 9.11 (d, 1, J_{ortho} = 8 Hz, H1); mass spectrum, *m/z* (relative intensity) 354 (100, M^+), 324 (14, $M^+ - NO$), 308 (10, $M^+ - NO_2$), 296 (42, $M^+ - NO - CO$), 281 (5, $M^+ - NO - CO - CH_3$). Anal. Calcd for $C_{17}H_{11}BrN_2O_2$: C, 57.49; H, 3.12; N, 7.89; Br, 22.50. Found: C, 56.99; H, 3.17; N, 7.88; Br, 22.21.

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