cally, the tetrahydropyrimidine ring in manzacidins A-C (1-3) may have been generated through a condensation between formic acid and an unusual amino acid like γ-amino-δ-hydroxyleucine.

Experimental Section

General Methods. Optical rotations were measured on a JASCO DIP-370 polarimeter. The IR and UV spectra were recorded on a JASCO A-102 and Shimadzu UV-220 spectrophotometer, respectively. ^1H and ^{13}C NMR spectra were recorded on a JEOL GX-270 and EX-400 spectrometers. FAB mass spectra were obtained on a JEOL HX-110 spectrometer using glycerol as a matrix. EI mass spectra were recorded on a JEOL DX-303 spectrometer. Wako C-300 silica gel (Wako Pure Chemical) was used for glass column chromatography, and TLC was carried out on Merck silica gel GF_{254}.

Collection, Extraction, and Separation. The sponge *Hymeniacidon* sp. was collected by SCUBA at Manza Beach, Okinawa island, and was kept frozen until used. The methanol extract (43 g) was dissolved in ethyl acetate and water (1:4, 200 mL) and then partitioned between ethyl acetate (400 mL × 3) and water (400 mL). The aqueous layer was subsequently extracted with 1-butanol (400 mL × 3). The 1-butanol-soluble fraction (6.3 g) was partially (2.0 g) subjected to flash column chromatography on silica gel (4.3 × 20 cm) eluted with chloroform/1-butanol/acetic acid/water (1.5:6:1:1). The fraction eluting from 560 to 780 mL was further purified by reversed-phase HPLC on ODS (Develosil ODS-5, Nomura Chemical, 10 × 250 mm; eluent acetonitrile/water/trifluoroacetic acid (22:78:0.1); flow rate 2.5 mL/min; UV detection at 254 nm) to give manzacidins A (1; 3.5×10^{-3}% yield, wet weight; t_R 24.6 min), B (2; 2.1×10^{-3}%; t_R 21.9 min), and C (3; 1.0×10^{-3}%; t_R 23.7 min).

Manzacidin A (1): colorless oil; $[\alpha]^{27}_D$ -28° (*c* 0.67, MeOH); IR (KBr) ν_{max} 3600-2800, 1710, 1685, 1625, 1400, 1320, 1205, 1190, and 1140 cm^{-1}; UV (MeOH) λ_{max} 209 (ε 5100) and 272 (5800) nm; ^1H and ^{13}C NMR (Table I); FABMS (positive) *m/z* 368 and 366 $(M + Na)^+$ and 346 and 344 $(M + H)^+$; exact mass found *m/z* 344.0251, calcd for $C_{12}H_{15}N_3O_4{}^{79}Br$ M + H 344.0246.

Manzacidin B (2): colorless oil; $[\alpha]^{22}_D$ -71° (*c* 0.43, MeOH); IR (KBr) ν_{max} 3600-2800, 1705, 1665, 1620, 1380, 1310, 1195, 1175, and 1125 cm^{-1}; UV (MeOH) λ_{max} 214 (ε 10300) and 273 (11600) nm; ^1H NMR (CD_3OD) δ_H 8.04 (1 H, s, H-13), 7.05 (1 H, d, *J* = 1.5 Hz, H-2), 6.98 (1 H, d, *J* = 1.5 Hz, H-4), 4.75 (1 H, br d, H-11), 4.46 (1 H, d, *J* = 2.2 Hz, H-10), 4.45 (1 H, d, *J* = 11.0 Hz, H-8a), 4.38 (1 H, d, *J* = 11.0 Hz, H-8b), and 1.44 (3 H, s, H_3-15); ^{13}C NMR (CD_3OD) δ_C 160.8 (s, C-6), 151.7 (d, C-13), 125.4 (d, C-2), 123.4 (s, C-5), 118.6 (d, C-4), 98.2 (s, C-3), 66.7 (t, C-8), 65.2 (d, C-10), 58.1 (s, C-9), and 23.7 (q, C-15); ^1H-^1H COSY correlations H-2/H-4, H-8a/H-8b, and H-10/H-11; HMBC correlations C-2/H-4, C-3/H-2, C-4/H-2, C-5/H-2, C-5/H-4, C-8/H_3-15, C-9/H_3-15, C-10/H_3-15, and C-15/H_2-8; FABMS (positive) *m/z* 384 and 382 $(M + Na)^+$ and 362 and 360 $(M + H)^+$; exact mass found *m/z* 360.0211, calcd for $C_{12}H_{15}N_3O_5{}^{79}Br$ M + H 360.0200.

Manzacidin C (3): colorless oil; $[\alpha]^{22}_D$ +37° (*c* 0.23, MeOH); IR (KBr) ν_{max} 3600-2800, 1700, 1680, 1625, 1400, 1380, 1315, 1205, 1180 and 1135 cm^{-1}; UV (MeOH) λ_{max} 224 (ε 7500) and 273 (7700) nm; ^1H NMR (CD_3OD) δ_H 8.13 (1 H, s, H-13), 7.10 (1 H, d, *J* = 1.5 Hz, H-2), 6.94 (1 H, d, *J* = 1.5 Hz, H-4), 4.50 (1 H, m, H-11), 4.43 (1 H, d, *J* = 11.4 Hz, H-8a), 4.33 (1 H, d, *J* = 11.4 Hz, H-8b), 2.65 (1 H, m, H-10a), 2.07 (1 H, m, H-10b), and 1.50 (3 H, s, H_3-15); ^{13}C NMR (DMSO-d_6) δ_C 169.9 (s, C-16), 158.8 (s, C-6), 150.5 (d, C-13), 124.5 (d, C-2), 122.0 (s, C-5), 116.8 (d, C-4), 96.1 (s, C-3), 68.2 (t, C-8), 51.6 (s, C-9), 48.6 (d, C-11), 30.9 (t, C-10), and 23.0 (q, C-15); ^1H-^1H COSY correlations H-2/H-4, H-8a/H-8b, H-10a/H-11, H-10b/H-11, and H-10a/H-10b; FABMS (positive) *m/z* 344 and 346 $(M + H^+)$; exact mass found *m/z* 344.0262, calcd for $C_{12}H_{15}N_3O_4{}^{79}Br$ M + H 344.0246.

Methyl Ester 4. Manzacidin A (1, 0.6 mg) was treated with 5% hydrogen chloride in methanol (0.5 mL) under reflux for 30 min. Evaporation of the solvent afforded the methyl ester 4 (0.5 mg): ^1H NMR (CD_3OD) δ_H 8.14 (1 H, s, H-13), 7.05 (1 H, d, *J* = 1.8 Hz, H-2), 4.35 (1 H, d, *J* = 11.7 Hz, H-8a), 4.22 (1 H, d, *J* = 11.7 Hz, H-8b), 3.81 (3 H, s, MeO), 2.37 (1 H, dd, H-10a), 2.27 (1 H, dd, H-10b), and 1.48 (3 H, s, H_3-15); EIMS *m/z* 359, 357 (M^+, 1:1), 300, and 298 ($M^+ - COOCH_3$, 1:1).

Acknowledgment. We thank Mr. Z. Nagahama for his help in collecting the sponge and Dr. J. Fromont, James Cook University of North Queensland, for identification of the sponge.

Registry No. 1, 134029-41-7; 2, 134029-42-8; 3, 134107-38-3.

Supplementary Material Available: Copies of all spectra of manzacidins A-C (22 pages). Ordering information is given on any current masthead page.

Synthesis of an Unsymmetrical Naphthalein Indicator Dye from an Indole-6-sulfonamide

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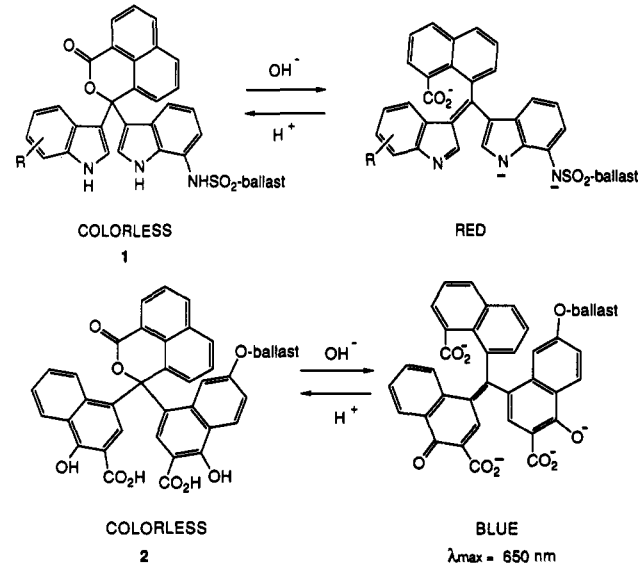
Received December 27, 1990

Naphthalein indicator dyes such as **1** and **2** can be used in integral format instant photography as opacification media to protect the latent image so that exposed film can be ejected immediately from the camera into ambient light.[1] These opacification dyes are designed to be colored



in the highly alkaline (pH ~14) photographic reagent while the chemistry of image development takes place but to begin to become colorless at pH ~12 to permit the image to be seen within 1-2 min. The dyes are designed to be completely colorless at the final system pH (close to neutrality) so that the color photograph can be viewed free from any residual visible absorptions of the opacification dyes. The position and nature of the substituents on the indole and naphthol moieties have a profound effect on the pK_a values of the indicator dyes.[2] The ballast groups are alkyl chains that limit the migration of the dyes. While working on indole naphthalein dyes of type 1, we required an efficient synthesis of indole sulfonamides. We report

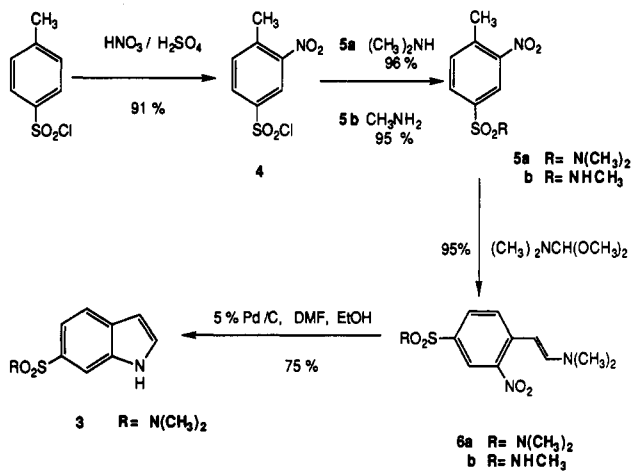
(1) Land, E. H. *Photogr. J.* **1974**, *7*, 1.

(2) (a) Simon, M. S.; Waller, D. P. U.S. Patent 3,702,245, November 7, 1972. (b) Borror, A. L.; Chinoporos, E.; Filosa, M. P.; Herchen, S. R.; Petersen, C. P.; Stern, C. A.; Onan, K. D. *J. Org. Chem.* **1988**, *53*, 2047. (c) Borror, A. L.; Chinoporos, E.; Petersen, C. P. U.S. Patent 4,615,966, October 7, 1986.

0022-3263/91/1956-4576$02.50/0

here such a synthesis of 1*H*-indole-6-*N*,*N*-dimethylsulfonamide (**3**) and of the indicator dye **11**.[2c]

It was anticipated that the method of Batcho and Leimgruber[3] might be well-suited for the general preparation of indole-6-sulfonamides. We found, however, that, as described in the following text, the scope of the procedure was effectively limited to symmetrical tertiary sulfonamides. The synthesis of the sulfonamide series began with the nitration of *p*-toluenesulfonyl chloride to furnish 2-nitro-4-(chlorosulfonyl)toluene (**4**). Treatment



of **4** with aqueous dimethylamine cleanly produced **5a**, which was condensed smoothly with *N*,*N*-dimethylformamide dimethyl acetal[3] to form the desired styrene **6a** in 95% yield. However, analogous treatment of *N*-methylsulfonamide **5b** with *N*,*N*-dimethylformamide dimethyl acetal did not yield the desired 2-nitro-4-[(*N*-methylamino)sulfonyl]-β-(dimethylamino)styrene (**6b**), but instead led to a mixture of products that included 2-nitro-4-[(*N*,*N*-dimethylamino)sulfonyl]toluene (**5a**) and the corresponding styrene **6a**.[4]

Catalytic hydrogenation of enamine **6a** afforded the indole **3**. The synthesis of the corresponding secondary sulfonamide, 1*H*-indole-6-*N*-methylsulfonamide, is best achieved by the method of Borror[2b] via a 5-bromo-6-(chlorosulfonyl)indoline intermediate.

Acid-catalyzed condensation of indole **3** with naphthaldehydic acid[5] led to the naphthalide **7**. The structural assignment of **7** is based on ^{1}H, ^{13}C, ^{1}H–^{1}H COSY, and HETCOR experiments. Key to the assignment is the bond from the indole C-3 (δ_C 114.89, s) to the tertiary ring carbon C-10 (δ_C 76.23 (d), δ_H 7.47 (s, 1 H)) of the lactone. The indole C-2 (δ_C 126.87 (d), δ_H 7.62 (d, 1 H, J = 3)) bears a proton coupled to the indole NH that appears as a broad doublet at δ 11.84.[6]

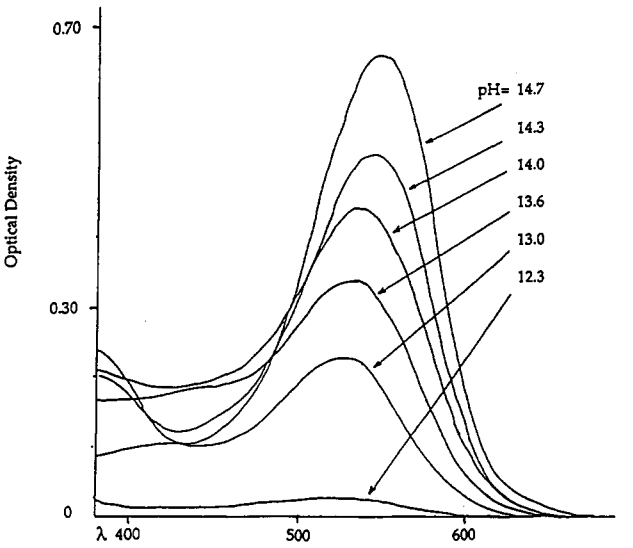


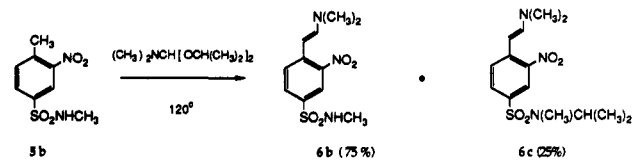
Figure 1. 11 (3.60×10^{-6}M) in 20% EtOH/KOH as a function of pH.

The coupling of **7** with a second indolyl component was effected using either of two related but discretely different strategies. Dehydrogenative oxidation of **7** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave upon workup the hydroxy lactone **8**, which was used without purification.[7] The opacification dye **11** was produced by direct treatment with 7-(hexadecylsulfonyl)amino-1*H*-indole[10] (**10**) in a 1:1 mixture of trifluoroacetic acid (TFA)/acetic acid. The structural assignment of **11** is based on ^{1}H and ^{13}C data and its performance as an indicator dye (see Figure 1). The lactone carbonyl C-11 appears at δ_C 166.11 (s) and the tertiary ring carbon C-10 at δ_C 85.76 (s).

Alternatively, and for larger scale preparation, the requisite change in oxidation state could be more satisfac-

(3) Batcho, A. D.; Leimgruber, W. *Org. Synth. 63*, 214.

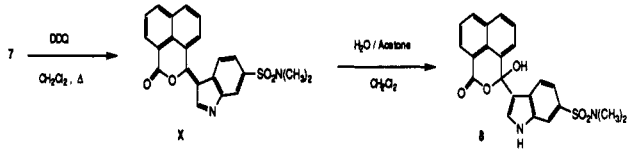
(4) The *N*,*N*-dimethylformamide dimethyl acetal methylates the secondary sulfonamide. See: (a) Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 211. (b) Brechbuhler, H.; Buchi, H.; Hotz, E.; Schreiber, J.; Eschenmoser, A. *Ibid.* 212. (c) Brechbuhler, H.; Buchi, H.; Hotz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746. In an attempt to suppress this side reaction, we briefly investigated the reaction of *N*,*N*-dimethylformamide diisopropyl acetal with **5b** at 120 °C. This led to a 3:1 mixture (NMR) of the desired styrene **6b** and 2-nitro-4-[(*N*-methyl-*N*-isopropylamino)sulfonyl]-β-(dimethylamino)styrene (**6c**).



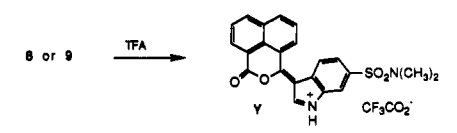
(5) Fuson, R. C.; Munn, G. *J. Am. Chem. Soc.* **1949**, *71*, 1870.

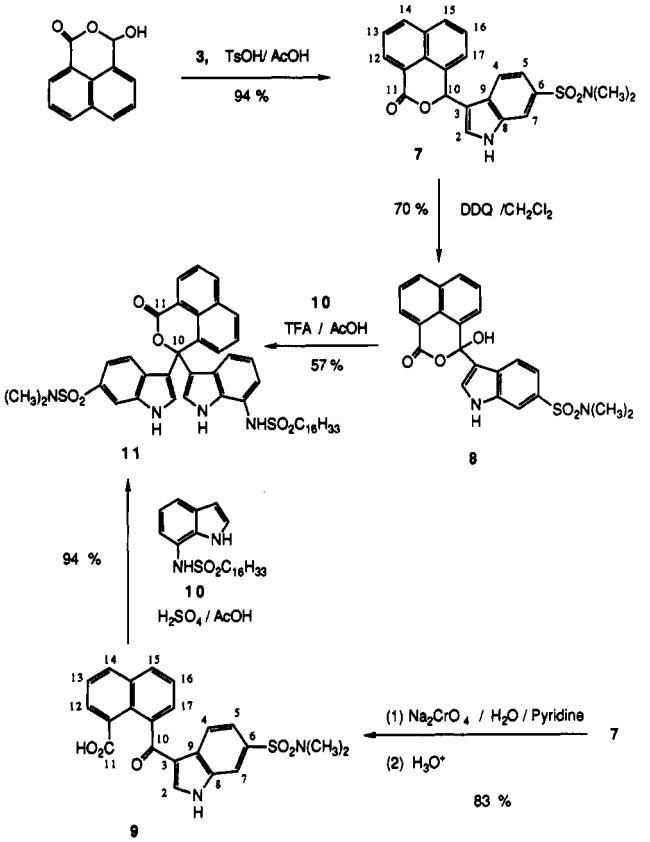
(6) Our assignments are consistent with the fact that substitution at C-3 in **7** would predict a downfield shift from the C-3 of indole **3** (δ 114.89 vs δ 102.64, respectively) and an upfield shift of C-2 in **7** compared to C-2 of indole **3** (δ 126.87 vs δ 130.54, respectively). See: Parker, R. G.; Roberts, J. D. *J. Org. Chem.* **1970**, *35*, 996. The NH of an unsubstituted indole such as **3** couples to both H-2 and H-3 with $J \sim 2$–3, and thus the coupling relationship of the indole proton of **7** is inconclusive for distinguishing between 2 and 3 substitution. See: Elvidge, J. A.; Foster, R. G. *J. Chem. Soc.* **1964**, 981.

(7) The formal product of the oxidation is **X**. It apparently is hydrated by water in the acetone of the workup (see Experimental Section) to **8**, which can be quantitatively converted to the isomeric keto acid **9**



by treatment with either 1 M NaOH or strong acid (TFA or sulfuric) followed, respectively, by acidification or dilution with water. Both **9** and **8** yield an identical bright red species assigned as **Y** when dissolved in TFA: ^{13}C NMR (TFA-*d*, 75 MHz) δ 174.81, 153.03, 148.87, 139.08, 136.09, 135.24, 133.91, 133.41, 130.51, 128.28, 126.16, 125.64, 125.05, 124.78, 121.94, 121.54, 114.68, 111.86, 110.66, 109.72, 32.66; ^{1}H NMR (TFA-*d*, 300 MHz) δ 9.38 (s, 1 H), 9.09 (d, J = 8 Hz, 1 H), 9.03 (dd, J = 1, 8 Hz, 1 H), 8.92 (d, J = 8 Hz, 1 H), 8.87 (d, J = 8 Hz, 1 H), 8.75 (d, J = 8 Hz, 1 H), 8.33 (d, J = 1 Hz, 1 H), 8.22 (dd, J = 8, 8 Hz, 1 H), 8.19 (dd, J = 8, 8 Hz, 1 H), 8.10 (dd, J = 1, 8 Hz, 1 H), 2.91 (s, 6 H). Y (or with the hydrogen sulfate counterion) is undoubtedly the reactive species in the final condensation step of either **8** or **9** with indole **10** to produce the indicator dye **11**.





torily achieved by treating the naphthalide **7** with sodium chromate in aqueous pyridine to give upon workup the keto acid **9**. The stability of the indolyl nucleus in the presence of chromium(VI) is unusual.[8] The structural assignment of **9** is based on ^{13}C, ^{1}H–^{1}H COSY, and HETCOR experiments. The carboxylic acid C-11 resonates at δ_C 169.55 (s) while the ketone C-10 appears at δ_C 190.93 (s). Keto acid **9** condensed smoothly with indole **10** in acetic acid in the presence of 1 molar equiv of sulfuric acid to furnish the dye **11** in 94% yield, maintaining a high degree of structural integrity with respect to the dissymmetry of the indolyl moieties about the *meso* carbon atom.

Figure 1 shows the spectral properties of **11** with respect to pH. The color change is instantaneous and completely reversible. The absence of an isosbestic point is presumably the result of the presence of two indoles and the hydrogen-bonded sulfonamide, all of which are ionizable in this pH range.

Experimental Section

2-Nitro-4-(chlorosulfonyl)toluene[9] (4). To a solution of 35.0 mL of concd nitric acid and 54.3 mL of concd sulfuric acid cooled with an ice/water bath was added 50.0 g (0.26 mol) of *p*-toluenesulfonyl chloride at such a rate that the temperature of the solution remained below 30 °C. When the addition was complete, the solution was allowed to warm to room temperature. After being stirred for 2 h, the reaction mixture was transferred to a separatory funnel and the lower acid layer was discarded. The organic layer was washed with ice-cold water and diluted with 50 mL of diethyl ether. The ethereal solution was washed consecutively with 100 mL of ice–water, 100 mL of 1% sodium carbonate, and twice with 100 mL of saturated brine. After being dried over magnesium sulfate, the solution was filtered and the filtrate was evaporated under reduced pressure to give a pale yellow oil that solidified upon standing (56.1 g, 91%). This material could be crystallized from ether to afford a white solid: mp 32–33 °C; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.11, 142.87, 141.66, 134.67, 130.41, 123.67, 20.90; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 8.60 (d, J = 2 Hz, 1 H), 8.17 (dd, J = 7, 2 Hz, 1 H), 7.67 (d, J = 7 Hz), 2.77 (s, 3 H); HRMS (EI$^+$) calcd for $C_7H_6NO_4SCl$ 234.9707, found 234.9706.

2-Nitro-4-[(*N*-methylamino)sulfonyl]toluene (5b). To 54 mL (0.63 mol) of a 40% solution of methylamine in water cooled in an ice bath was added a solution of 49.2 g (0.21 mol) of 2-nitro-4-(chlorosulfonyl)toluene in 200 mL of dichloromethane over 30 min. The mixture was stirred for 30 min at 0 °C and then warmed to room temperature. The organic layer was separated, washed with water (2 × 200 mL), dilute hydrochloric acid (2 × 200 mL), and 50% saturated sodium chloride solution (1 × 200 mL), dried over sodium sulfate, and filtered. Following concentration under reduced pressure to give an oil, crystallization from ethanol (150 mL) gave 42 g (88%) of 2-nitro-4-[(*N*-methylamino)sulfonyl]toluene: mp 92–93 °C; IR (KBr) 3340, 1520, 1340, 1180 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.17, 138.54, 138.36, 133.98, 131.01, 123.68, 29.32, 20.56; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (d, J = 1 Hz, 1 H), 7.98 (dd, J = 2, 8 Hz, 1 H), 7.54 (d, J = 8 Hz, 1 H), 4.58 (br q, J = 4 Hz, 1 H), 2.73 (s, 3 H), 2.69 (d, J = 4 Hz, 3 H); HRMS (EI$^+$) calcd for $C_8H_{10}N_2O_4S$ 230.0361, found 230.0364.

2-Nitro-4-[(*N*,*N*-dimethylamino)sulfonyl]toluene (5a). To 64 mL (0.318 mol) of a 25% solution of dimethylamine in water cooled in an ice bath was added a solution of 25.0 g (0.106 mol) of 2-nitro-4-(chlorosulfonyl)toluene in 150 mL of dichloromethane over 30 min. The mixture was stirred for 30 min at 0 °C and then warmed to room temperature. The organic layer was separated, washed with water (2 × 100 mL), dilute hydrochloric acid solution (2 × 100 mL), and 50% saturated sodium chloride solution (1 × 100 mL), and dried over sodium sulfate. Following filtration, the filtrate was evaporated under reduced pressure and the resulting solid was recrystallized from 2-propanol to give 24.9 g (96%) of 2-nitro-4-[(*N*,*N*-dimethylamino)sulfonyl]toluene: mp 90–91 °C; IR (KBr) 1530, 1340, 1160 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.21, 138.45, 135.26, 133.89, 131.35, 123.90, 37.86, 20.53; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (d, J = 2 Hz, 1 H), 7.89 (dd, J = 2, 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 2.79 (s, 6 H), 2.77 (s, 3 H); HRMS (EI$^+$) calcd for $C_9H_{12}N_2O_4S$ 244.0518, found 244.0509.

2-Nitro-4-[(*N*,*N*-dimethylamino)sulfonyl]-β-(dimethylamino)styrene (6a). A solution of 5.0 g (0.02 mol) of 2-nitro-4-[(*N*,*N*-dimethylamino)sulfonyl]toluene (**5a**) in 5.5 mL (0.04 mol) of *N*,*N*-dimethylformamide dimethyl acetal was heated to 100 °C and maintained for 4 h. The red mixture was concentrated under reduced pressure and allowed to stand overnight, whereupon crystalline material separated. Diethyl ether (20 mL) was added, and the solid was collected by suction filtration. The product was washed with diethyl ether (2 × 20 mL) and dried under vacuum to give 5.8 g (95%) of a brick-red solid: mp 128–130 °C; IR (KBr) 1590, 1540, 1330, 1150 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.61, 143.03, 140.42, 130.35, 127.32, 125.93, 123.86, 89.67, 40.93, 37.97; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 1 Hz, 1 H), 7.57 (m, 2 H), 7.18 (d, J = 13 Hz, 1 H), 5.92 (d, J = 13 Hz, 1 H), 3.01 (s, 6 H), 2.73 (s, 6 H); HRMS (EI$^+$) calcd for $C_{12}H_{17}N_3O_4S$ 299.0940, found 299.0951.

1*H*-Indole-6-*N*,*N*-dimethylsulfonamide (3). To a solution of 10.0 g (0.033 mol) of 2-nitro-4-[(*N*,*N*-dimethylamino)-sulfonyl]-β-(dimethylamino)styrene (**6a**) in 200 mL of ethanol and 50 mL of *N*,*N*-dimethylformamide was added 1.0 g of 5% palladium on carbon. The mixture was hydrogenated (45 psig) for 18 h. The slurry was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane (100 mL), washed with dilute hydrochloric acid (3 × 100 mL) and 50% saturated sodium chloride solution (1 × 100 mL), and dried over sodium sulfate. Following filtration, the filtrate was evaporated under reduced pressure to give a crystalline residue that was recrystallized from 2-propanol to give 5.6 g (75%) of 1*H*-indole-6-*N*,*N*-dimethylsulfonamide: mp 152–154 °C; IR (KBr) 3400, 1330, 1150 cm^{-1}; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 135.64 (s, C-8), 131.79 (s, C-9), 130.54 (d, C-2), 127.78 (s, C-6), 121.44 (d, C-4), 118.63 (d, C-5), 112.94 (d, C-7), 102.70 (d, C-3), 38.67 (q); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91 (br s, NH), 7.99 (s, 1 H), 7.76 (d, J = 7 Hz, 1 H), 7.48 (m, 2 H), 6.65 (br s, 1 H), 2.70 (s, 6 H); HRMS (EI$^+$) calcd for $C_{10}H_{12}N_2O_2S$ 224.0619, found 224.0617.

3-(3-Oxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-yl)-1*H*-indole-

(8) Albright, J. D., Goldman, L. *J. Org. Chem.* **1965**, *30*, 1107.
(9) Murata, S. *Yamaguchi Daigaku Kogakubu Gakuho* **1961**, *12*, 132.

6-*N*,*N*-dimethylsulfonamide (7). The two solid reactants, 1*H*-indole-6-*N*,*N*-dimethylsulfonamide (12.0 g, 0.0536 mol) and 1,8-naphthaldehydic acid[5] (10.7 g, 0.0536 mol), were taken up in 50 mL of glacial acetic acid, and the thick tan suspension was heated to 80 °C. A dark solution was obtained, whereupon the catalyst *p*-toluenesulfonic acid (12% in acetic acid, 14.6 mL, 15.6 g, 0.0106 mol) was added in a steady stream. An exotherm of 10 °C was observed. The reaction mixture was maintained at 90–95 °C for 15 min then let cool slowly to 25 °C over 45 min. Solids separated by crystallization and were collected by suction filtration, washed with a minimum amount of acetic acid, and dried to give 20.5 g (94% of theory) of the off-white naphthalide 7, mp 231–233 °C: IR (KBr) 3368, 1715, 1330, 1140 cm^{-1}; ^{13}C NMR (DMSO, 75 MHz) δ 163.64 (s, C-11), 135.54 (s, C-8), 134.00 (d, C-12), 131.82 (s, C-9), 130.33 (s), 129.94 (d, C-16), 128.74 (d, C-17), 128.23 (s), 127.70 (s, C-6), 127.15 (d, C-15), 126.87 (d, C-2), 126.63 (d, C-13), 124.26 (d, C-14), 120.24 (s), 119.40 (d, C-4), 118.13 (d, C-5), 114.89 (s, C-3), 112.49 (d, C-7), 76.23 (d, C-10), 37.64 (q); ^1H NMR (DMSO, 300 MHz) δ 11.84 (b d, NH), 8.40 (dd, *J* = 1, 8 Hz, C12-H), 8.37 (dd, *J* = 1, 8 Hz, C17-H), 8.07 (d, *J* = 8 Hz, C15-H), 7.89 (d, *J* = 1 Hz, C7-H), 7.82 (dd, *J* = 7, 8 Hz, C13-H), 7.62 (d, *J* = 3 Hz, C2-H), 7.60 (dd, *J* = 7,8 Hz, C16-H), 7.47 (s, C10-H), 7.42 (d, *J* = 8 Hz, C4-H), 7.34 (dt, *J* = 1,7 Hz, C14-H), 7.30 (dd, *J* = 1,8 Hz, C5-H), 2.56 (s, 6 H); HRMS (FAB^+) calcd for $C_{22}H_{19}N_2O_4S$ 407.1066, found 407.1090.

3-[(8-Carboxy-1-naphthalenyl)carbonyl]-1*H*-indole-6-*N*,*N*-dimethylsulfonamide (9). The naphthalide 7 (15.0 g, 0.0369 mol) was taken up in 45 mL of pyridine. The mixture was heated to 40–45 °C to obtain a brown solution that was cooled to 30 °C then treated with a solution of sodium chromate (6.0 g, 0.037 mol, *caution*: toxic; see MSDS) in 22.5 mL of water. The mixture was stirred at 30–35 °C for 2 h, and a thick golden yellow suspension gradually formed. The mixture was cooled to 10 °C and was treated with concentrated hydrochloric acid (84 mL, 1.0 mol) over 5–10 min so that the temperature was maintained below 35 °C. Following completion of the addition, the mixture was heated slowly to 45 °C over 30 min, maintained at temperature for 3 h, and allowed to cool slowly to 25 °C over 1 h. The pale beige insolubles were collected by suction filtration, washed successively with 150 mL of 10% hydrochloric acid and 3 × 50 mL of water, and, after drying, afforded 14.4 g of a beige powder. The crude material (alternatively, without drying) was taken up in 320 mL of 0.5 M sodium hydroxide and stirred for 30 min at 25 °C. Insolubles were separated by suction filtration, and the pale yellow filtrate was acidified (while being stirred) by the dropwise addition of 30 mL of 6 M hydrochloric acid while the temperature was maintained at 25–30 °C. The creamy white solid precipitate was collected by suction filtration, washed, and dried to give 13.8 g of the keto acid 9. Final purification was effected by stirring the material in 145 mL of glacial acetic acid for 2 h at 75 °C. The suspension was cooled to 35 °C, and insolubles were collected by suction filtration and dried to give 13.0 g (83% of theory) of the white solid 9, mp 268 °C dec; IR (KBr) 3203, 3175, 1684, 1593, 1330, 1155 cm^{-1}; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 190.93 (s, C-10), 169.55 (s, C-11), 138.25 (d), 135.70 (s, C-8), 134.31 (s), 131.93 (d), 131.24 (s, C-9), 131.14 (d), 129.64 (s), 129.14 (d), 128.91 (d), 128.57 (s), 126.96 (s), 125.46 (d), 125.28 (d), 122.15 (d, C-4), 120.25 (d, C-5), 116.47 (s, C-3), 112.51 (d, C-7), 37.73 (q); ^1H NMR (DMSO-d_6, 300 MHz) δ 12.75 (s, CO_2H), 12.40 (s, NH), 8.40 (d, *J* = 8 Hz, C4-H), 8.24 (b s, C2-H), 8.21 (dd, *J* = 1, 7 Hz, 1 H), 8.19 (d, *J* = 8 Hz, 1 H), 7.95 (b s, C7-H), 7.89 (dd, *J* = 1, 7 Hz, 1 H), 7.85 (dd, *J* = 1, 7 Hz, 1 H), 7.66 (dd, *J* = 7, 8 Hz, 1 H), 7.64 (dd, *J* = 7, 8 Hz, 1 H), 7.59 (d, *J* = 8 Hz, C5-H), 2.64 (s, 6 H); MS *m*/*e* (FB^+) 423. Anal. Calcd for $C_{22}H_{18}N_2O_5S$: C, 62.55; H, 4.29; N, 6.63; S, 7.59. Found: C, 62.14; H, 4.56; N, 6.34; S, 7.68.

3-[1-[7-[(Hexadecylsulfonyl)amino]-1*H*-indol-3-yl]-3-oxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-yl]-1*H*-indole-6-*N*,*N*-dimethylsulfonamide (11). The two reactants, keto acid 9 (16.0 g, 0.0379 mol) and 7-[(hexadecylsulfonyl)amino]-1*H*-indole[10] (10; (15.9 g, 0.0378 mol), were taken up in 225 mL of glacial acetic acid, and the suspension was stirred slowly for 15 min. A solution of sulfuric acid (3.7 g (96+ %), 0.0376 mol) in 15 mL of glacial acetic acid was added dropwise over 15 min, and then the mixture was heated to 35 °C and was stirred for 24 h at 35 °C. The suspension was cooled to 25 °C; in one portion, 180 mL of methanol was added, and the mixture was stirred vigorously for 30 min after which an essentially complete solution was obtained. The mixture was cooled to 10 °C and stirred slowly for 2 h. Filtration by suction separated 0.9 g of insolubles shown (HPLC) to be largely unconverted keto acid 9. The filtrate was added slowly to 1.3 L of cold water (stirred mechanically) to precipitate a faintly pink colored solid. After 1.5 h, the solids were collected by suction filtration, washed with water, and dried in the air overnight. Final drying was effected in vacuo at 70 °C to give 29.2 g (94% of theory) of the pale pink dye 11: TLC R_f 0.6 (silica gel eluted with 1:2 ethyl acetate/dichloromethane); mp 203–204 °C; IR (KBr) 3354, 1702, 1330, 1150 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.11 (C=O), 135.89, 134.30, 133.32, 132.40, 129.94, 129.02, 128.74, 128.59, 128.34, 128.02, 127.66, 126.46, 126.36, 125.94, 121.65, 120.86, 120.60, 120.29, 119.30, 119.08, 118.56, 117.76, 112.63, 85.76 (C-10), 51.00, 38.02, 31.92, 29.70, 29.66, 29.62, 29.52, 29.36, 29.30, 29.12, 28.20, 23.39, 22.69, 14.12; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.41 (b s, 1 H), 9.37 (b s, 1 H), 8.42 (d, *J* = 7 Hz, 1 H), 8.20 (d, *J* = 7 Hz, 1 H), 7.95 (d, *J* = 7 Hz, 1 H), 7.93 (b s, 1 H), 7.65 (dd, *J* = 8, 8 Hz, 1 H), 7.53 (d, *J* = 7 Hz, 1 H), 7.41 (dd, *J* = 8, 8 Hz, 1 H), 7.33 (b s, 1 H), 7.05–7.25 (m, 3 H), 6.86 (d, *J* = 7 Hz, 1 H), 6.5 (m, 2 H), 6.26 (b s, 1 H), 3.01 (b t, *J* = 8 Hz, 2 H), 2.64 (s, 6 H), 1.72 (m, 2 H), 1.1–1.4 (m, 26 H), 0.82 (t, *J* = 7 Hz, 3 H); HRMS (FAB^+) calcd for $C_{22}H_{19}N_2O_4S$ 825.3720, found 825.3740; HPLC 98.4% wt 11 (0.4% wt 10, 1.3% wt symmetrical dye derived from 10); HPLC method column, Rainin C18 (5 μm), 25 × 0.46 cm; flow rate, 1.0 mL/min; detector, 254 nm, retention time, 21.1 min; elution solvents, A water/methanol = 900/100, B methanol/acetonitrile = 800/200 (A and B buffered, 0.01 M ammonium acetate); gradient, 70–100% B in 20 min.

DDQ Oxidation of 7. Naphthalide 7 (22.0 g, 0.054 mol) was taken up with 13.62 g (0.060 mol) of DDQ in 550 mL of dichloromethane and heated at reflux under argon for 4.5 h. Additional DDQ (2.7 g, 0.012 mol) was added together with 200 mL of dichloromethane, and the mixture was maintained at temperature for an additional 6 h. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The brown residue was dissolved in 100 mL of chloroform and 50 mL of acetone, and to this 500 mL of hexanes was slowly added to precipitate a tan solid that was collected by suction filtration and washed with hexanes to afford 15.3 g (70%) of 8. This material (TLC, 5% methanol/dichloromethane, predominantly one component with R_f = 0.15) was used without purification to prepare 11. An analytical sample was purified by column chromatography on silica gel (elution with 1–5% MeOH in CH_2Cl_2) to provide a pale yellow solid, mp > 250 °C: IR (KBr) 3425, 1745 cm^{-1}; UV (CH_2Cl_2) λ 224 (ε = 55300), λ 280 (ε = 14700), λ 330 (ε = 6500); MS *m*/*e* 405 (M^+ − 18). For reasons that remain unclear, it was not possible to obtain NMR spectra of this compound[7] with any fine detail. Only broad absorptions were obtained over a temperature range of −70 to 100 °C. Anal. Calcd for $C_{22}H_{18}N_2O_5S$: C, 62.55; H, 4.29; N, 6.63; S, 7.59. Found: C, 62.97; H, 4.04; N, 6.73; S, 8.03.

Preparation of 11 from 8 and 10. A slurry of 12.72 g (0.0314 mol) of 8 and 13.23 g (0.0314 mol) of indole 10[10] was stirred under argon in 220 mL of dry glacial acetic acid and cooled to 10 °C. Trifluoroacetic acid (220 mL) was slowly added to the stirred mixture so as to hold the temperature below 15 °C. When the addition was complete, the slurry was allowed to warm to 21 °C and to stir for 18 h. During this period, a solution was gradually obtained. The reaction mixture was poured into 4.4 L of stirred ice–water. The resulting precipitate was collected, washed with water, and air dried to afford 24.7 g (95%) of a tan cake. This solid was taken up in 250 mL of dichloromethane, and insoluble materials (2.0 g) were removed by filtration. The filtrate was placed on a Waters Prep 500 HPLC (2 silica gel columns), eluted with 4 L of dichloromethane, 4 L each of 0.5, 1.0, and 1.5% methanol in dichloromethane, and 11 (14.7 g, 57% of theory, 99% area by HPLC) was obtained.

Supplementary Material Available: ^{13}C or ^1H NMR spectra of 1a, 3a, 4, 5a, 5b, 6a, 7, and 9 (9 pages). Ordering information is given on any current masthead page.

(10) Huyffer, P. U.S. Patent 3,772,329, November 13, 1973.