Stereochemistry of 3-Alkylindole Dimerization: Acyclic δ_1,δ_1'-Tryptophan Dimers

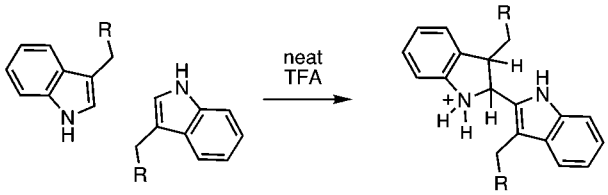
Casey C. McComas, Eric J. Gilbert, and David L. Van Vranken*

Department of Chemistry, University of California, Irvine, California 92697

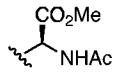
Received April 22, 1997

Under acidic conditions, 3-alkylindoles dimerize stereoselectively to produce racemic 2-(2′-indolyl)-3-alkylindolines **1**−**5** (eq 1). This Mannich-type reaction is a powerful tool in the synthesis of biindolyl natural products[1−3] and may even be important in the fluorogenic aging of corneal and lens proteins of the human eye.[4−7] While skatole dimer (**1**) has recently been shown to possess a trans stereochemistry,[8] tryptophan derivatives have been reported to dimerize in trifluoroacetic acid to afford one trans (**6a**) and one cis (**6b**) isomer. These assignments were made on the basis of differences between $J_{2,3}$ ^{1}H NMR coupling constants of the salts and free bases of **6a** and **6b**.[9−11] The seemingly disparate results obtained with tryptophan, as opposed to achiral 3-alkylindoles **1**−**5**,[1,12] have prevented the development of a consistent model for Mannich dimerization of 3-substituted indoles. We have reinvestigated the stereochemistry of tryptophan dimer formation in TFA and shown that the reaction follows the same pattern of reactivity as achiral 3-alkylindoles. In addition we have provided evidence that the indoline stereochemistry in tryptophan dimers is trans.

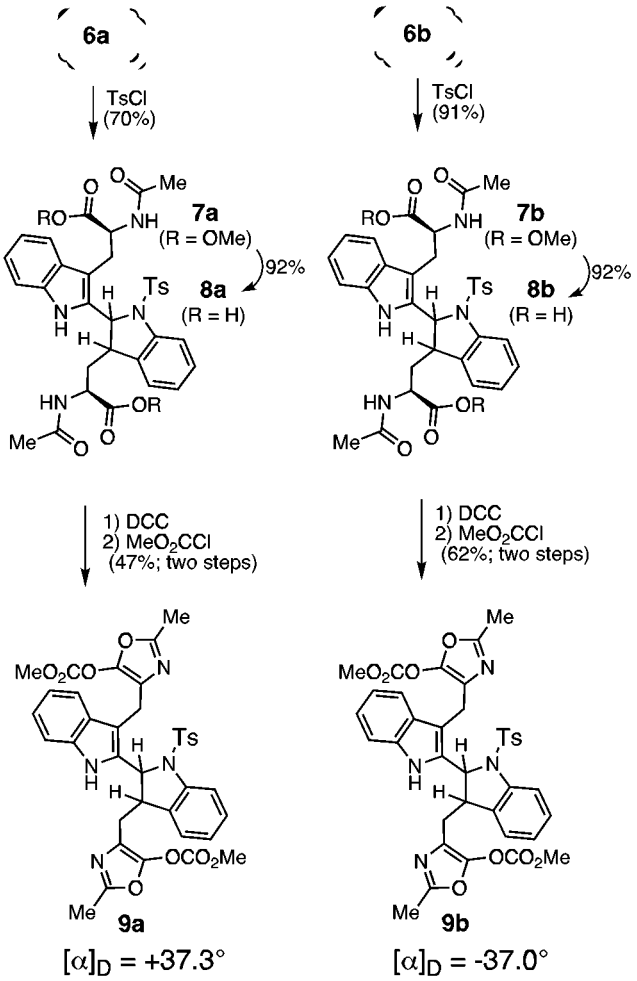
Our initial goal was to establish whether the indoline rings of **6a** and **6b** possessed the same or opposite relative stereochemistry by converting the α-amino acid moieties into achiral groups. *N*-Sulfonylation of **6a** and **6b** served to protect the indoline nitrogen and prevent facile photooxidation to the fluorescent ditryptophan (Scheme 1). The esters **7a** and **7b** were saponified with sodium hydroxide in aqueous THF to afford the diacids in over 90% yield, contaminated by a small amount of ethyl acetate. While decarboxylation of α-amino acids with lead tetraacetate is well-precedented, *N*-acetyltryptophan is a poor substrate for this reaction.[13] Similarly, attempts to cleave the corresponding β-acetamido alcohol with lead tetraacetate gave complex product mixtures.[14] As an alternative to oxidative cleavage we chose to convert the α-amino acid moieties into oxazoles via azalactone formation.[15] Azalactone formation proceeded easily with DCC in dioxane, although the bisazalactones were not sufficiently stable to isolate. The azalactones were directly converted to the more stable oxazoles by *O*-acylation with triethylamine and methyl chloroformate.[16] The yield for the two-step sequence of azalactone formation and acylation was 47% for **9a** and 62% for **9b**.



(±) **1** R = H
(±) **2** R = CO_2Me
(±) **3** R = CH_2NHAc
(±) **4** R = $CONMe_2$
(±) **5** R = $CH_2CH_2CO_2Me$ (1)

6a,b R = 

Scheme 1



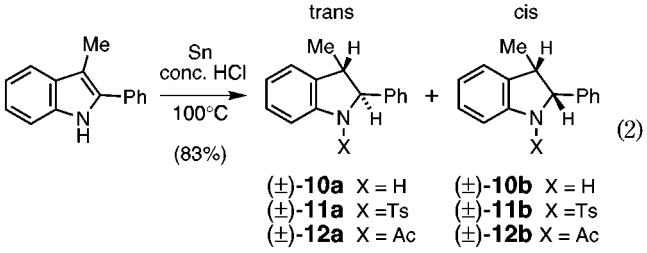
(1) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron Lett.* **1995**, *36*, 3945−3948.
(2) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.
(3) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500.
(4) Sigman, S. In *Progress in Tryptophan and Serotonin Research*; Schlossberger, H. G., Ed.; Walter de Gruyter & Co.: New York, 1984.
(5) Inoue, A.; Satoh, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 345.
(6) Wells-Knecht, M. C.; Huggins, T. G.; Dyer, D. G.; Thorpe, S. R.; Baynes, J. W. *J. Biol. Chem.* **1993**, *268*, 12348.
(7) Uma, L.; Sharma, Y.; Balasubramanian, D. *Photochem. Photobiol.* **1996**, *63*, 213.
(8) Stalick, W. M.; Mushrush, G. W.; Faour, S. Presented at the 213th National Meeting of the American Chemical Society, San Francisco, CA, 1997.
(9) Omori, Y.; Matsuda, Y.; Aimoto, S.; Shimonishi, Y.; Yamamoto, M. *Chem. Lett.* **1976**, 805.
(10) Hashizume, K.; Shimonishi, Y. In *Peptide Chemistry 1979*; Yonehara, H., Ed.; Protein Research Foundation: Tokyo, 1980.
(11) Hashizume, K.; Shimonishi, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3806−3810.
(12) Gilbert, E. J.; Ziller, J. W.; Van Vranken, D. L. *Tetrahedron*, accepted for publication.
(13) Needles, H. L.; Ivanetich, K. *Chem. Ind.* **1967**, 581.
(14) Apitz, G.; Jäger, M.; Jaroch, S.; Kratzel, M.; Schäffeler, L.; Steglich, W. *Tetrahedron* **1993**, *49*, 8223.
(15) Pines, S. H.; Karady, S.; Sletzinger, M. *J. Org. Chem.* **1968**, *33*, 1758.
(16) Steglich, W.; Höfle, G. *Chem. Ber.* **1969**, *102*, 883.

S0022-3263(97)00722-6 CCC: $14.00

The two indolines **9a** and **9b** were identical by all standard methods of characterization (mp, IR, LRMS, HRMS, and ^{1}H and ^{13}C NMR) except for optical rotation. Indoline **9a** had a specific rotation of +37.3° (c = 1.00, $CHCl_3$) whereas the opposite value was obtained for indoline **9b** ($[\alpha]_D = -37.0°$, c = 1.00, $CHCl_3$); **9a** and **9b** are clearly enantiomers. Thus *the dimerization of tryptophan is stereoselective, such that each diastereomer possesses the same relative indoline stereochemistry*. More importantly, it can now be stated with confidence that the dimerization of 3-alkylindoles (with a 3-methylene group) in TFA proceeds with complete control of stereoselectivity. It is unsafe to assume that skatole dimer, formed with stoichiometric sulfonic acids, and tryptophan dimers, formed in neat TFA, possess the same relative stereochemistry. In the intramolecular cyclization of 3-alkylindoles to form six-membered rings, stoichiometric sulfonic acids and neat TFA have been shown to afford products of kinetic and thermodynamic control, respectively.[12]

The lack of X-ray quality crystals prevented a direct determination of indoline stereochemistry, and the coupling constants provided no information about the relative stereochemistry of the indoline rings. Indeed, the $J_{2,3}$ coupling constants of 2,3-dialkylindolines are typically 8−9 Hz for both the cis and trans isomers. However, Anet has shown that when the indoline nitrogen is *N*-protected with nitrosyl or arylsulfonyl, cis-dialkylindolines exhibit a diagnostic $J_{2,3}$ coupling constant of 8−9 Hz, while the corresponding coupling constant in the trans isomer is less than 4 Hz.[17]

To confirm this relationship, we prepared 2-phenyl-3-methylindoline as a model system for comparison with **9a** and **9b**. Reduction of 3-methyl-2-phenylindole with tin in hydrochloric acid afforded the inseparable indolines **10a** and **10b** in a 1:10 ratio, respectively (eq 2).[18] *N*-Sulfonylation of the mixture of **10a** and **10b** with tosyl chloride in pyridine afforded the requisite model compounds **11a** and **11b**. Unfortunately, these diastereomers were not readily separable, so the indolines were *N*-acetylated to give **12a** and **12b**, which were easily separated by silica gel chromatography. The minor diastereomer **12a** and the major diastereomer **12b** were individually hydrolyzed (6 N methanolic HCl, 100 °C) and *N*-sulfonylated to afford pure samples of **11a** and **11b**.

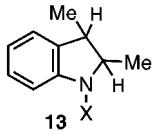


(2)

Gratifyingly, the coupling constants of the 2-phenyl-3-methylindolines **11a** and **11b** were consistent with the coupling constants observed by Anet for the corresponding 2,3-dimethylindolines, **13**. The unprotected indolines show little difference in the $J_{2,3}$ coupling constants (9.9 Hz for **10a** and 8.7 Hz for **10b**). However the *N*-tosylindolines show the marked difference predicted by Anet (3.5 Hz for **11a** and 9.6 Hz for **11b**). These results

(17) Anet, F. A. L.; Muchowski, J. M. *Chem. Ind.* **1963**, 81.
(18) Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *1979*, 4809.

Table 1. Diagnostic $J_{2,3}$ Coupling Constants in 2,3-Disubstituted Indolines



13

indoline	X	trans $J_{2,3}$ (Hz)	cis $J_{2,3}$ (Hz)
13	H	8.8	8.8
10	H	9.9	8.7
13	SO_2Ph	2.7	8.6
11	SO_2Ph	3.5	9.6

are also in agreement with the cis stereoselectivity previously reported for the tin reduction of 2,3-dialkylindoles.[18] On the basis of these results, we conclude that the coupling constants in 2-aryl-3-alkyl-*N*-tosylindolines provide a diagnostic correlation with relative stereochemistry. Returning to the *N*-tosyltryptophan dimers, the small $J_{2,3}$ coupling constants in $CDCl_3$ (1.6 Hz, 1.5 Hz, and 1.8 Hz for **7a**, **7b**, and **9a/b**) suggest that *both of these compounds are trans indolines*. The mechanistic origin of this stereoselectivity will be the subject of future work.

In conclusion, we have unambiguously demonstrated that the dimerization of tryptophan derivatives affords diastereomers with the same relative indoline stereochemistry. We have also shown that coupling constants in the *N*-tosyltryptophan dimers are consistent with a trans indoline stereochemistry. Thus, a consistent picture emerges for the intermolecular TFA-promoted dimerization of 3-alkylindoles, including tryptophan. The reaction is stereoselective and, based on ^{1}H NMR evidence, provides exclusively the trans indoline.

Experimental Section

All reactions were run under a nitrogen atmosphere. Tetrahydrofuran and diethyl ether were purified by distillation under a nitrogen atmosphere from the sodium ketyl of benzophenone prior to use. Methylene chloride and triethylamine were distilled from calcium hydride under a nitrogen atmosphere. All other solvents were used as purchased. Analytical TLC was performed using 0.25 mm EM silica gel 60 F_{254} plates. Elemental analyses were carried out by Atlantic Microlabs, Inc.

***N*-Tosyl-2,2′-indolylindoline 7a.** In a dry 25 mL round-bottom flask, **6a** (1.05 g, 2.00 mmol) was dissolved in pyridine (6 mL) and the temperature was reduced to 0 °C. Freshly recrystallized *p*-toluenesulfonyl chloride (0.57 g, 3.0 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature as stirring was continued for an additional 12 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 1 M $NaHSO_4$ (4 × 150 mL), and dried over $MgSO_4$. Filtration and concentration of the solvent *in vacuo* provided the crude product as a bright pink solid. Purification by silica gel chromatography (10% MeOH/$CHCl_3$) afforded **7a** (0.94 g, 70%) as a white solid.

7a: mp 144−146 °C ($CHCl_3$); R_f = 0.54 (10% MeOH/$CHCl_3$); IR (KBr) 3379, 3287, 3060, 2953, 1742, 1659 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.30 (d, J = 8.7, 1H), 8.15 (d, J = 7.9, 1H). 7.67 (d, J = 8.3, 3H), 7.53 (d, J = 7.7, 1H), 7.31 (m, 9H), 5.28 (d, J = 1.9, 1H), 4.50 (m, 1H), 4.36 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 2.99 (m, 2H), 2.34 (s, 3H), 1.81 (s, 3H), 1.68 (s, 3H), 1.47 (m, 1H), 0.98 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.2, 172.5, 170.3, 169.5, 144.8, 140.8, 136.0, 135.8, 134.2, 134.0, 130.3, 128.9, 128.3, 127.1, 125.6, 125.1, 121.6, 119.0, 116.3, 111.9, 107.0, 79.6, 62.9, 53.9, 52.4, 52.3, 50.2, 46.2, 38.1, 26.5, 22.8, 22.5, 21.4; LRMS (FAB) m/z (relative intensity) 697 $[MNa]^+$, 674 (42) $[M]^+$, 545 (38), 259 (98), 130 (100); HRMS (FAB) calcd for $C_{35}H_{38}N_4O_8S$, 675.2488 $[MH]^+$, found 675.2495. Anal. Calcd for $C_{35}H_{38}N_4O_8S$: C, 62.29; H, 5.68; N, 8.31. Found: C, 62.15; H, 5.64; N, 8.23.

***N*-Tosyl-2,2′-indolylindoline 7b.** In a dry 25 mL round-bottom flask, **6b** (0.80 g, 1.5 mmol) was dissolved in pyridine (6 mL) and the temperature was reduced to 0 °C. Freshly recrystallized *p*-toluenesulfonyl chloride (0.38 g, 2.0 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature as stirring was continued for an additional 12 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 1 M $NaHSO_4$ (4 × 150 mL), and dried over $MgSO_4$. Filtration and concentration of the solvent *in vacuo* provided the crude product as a bright pink solid. Purification by silica gel chromatography (10% MeOH/$CHCl_3$) afforded **7b** (0.92 g, 91%) as a white solid.

7b: mp 144−145 °C ($CHCl_3$); $R_f = 0.56$ (10% MeOH/$CHCl_3$); IR (KBr) 3379, 3286, 3063, 2952, 2359, 2248, 1742, 1656 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.33 (d, $J = 7.5$, 1H), 8.28 (d, $J = 7.5$, 1H), 7.69 (m, 3H), 7.50 (d, $J = 8.0$, 1H), 7.40 (t, $J = 8.0$, 1H), 7.34 (d, $J = 8.0$, 2H), 7.25 (d, $J = 8.0$, 1H), 7.13 (t, $J = 7.5$, 1H), 7.05 (m, 2H), 6.98 (t, $J = 7.5$, 1H), 5.27 (s, 1H), 4.54 (m, 1H), 4.14 (m, 1H), 3.61 (s, 3H), 3.48 (s, 3H), 3.29 (m, 1H), 3.09 (m, 2H), 2.35 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H), 1.80 (m, 1H), 0.79 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 172.1, 169.8, 169.5, 144.6, 140.7, 135.7, 133.7, 132.6, 129.8, 128.7, 127.6, 127.0, 125.8, 124.5, 121.4, 118.7, 118.3, 116.3, 111.6, 106.8, 79.2, 63.6, 53.5, 52.0, 51.9, 48.6, 45.0, 37.2, 26.3, 22.4, 22.2, 21.0; LRMS (FAB) *m*/*z* (relative intensity) 697 $[MNa]^+$, 674 (60) $[M]^+$, 261 (30), 217 (100); HRMS (FAB) Calcd for $C_{35}H_{38}N_4O_8S$, 675.2488 $[MH]^+$, found 675.2476.

General Procedure for *N*-Tosyl-2,2′-indolylindoline Diacid 8a. A 25 mL round-bottom flask was charged with a solution of **7a** (0.82 g, 1.20 mmol) in THF (5 mL) followed by the addition of 2 M NaOH (4.0 mL, 8.0 mmol). The reaction mixture was stirred for 4 h at room temperature. After this time the reaction mixture was diluted with 1 M HCl (100 mL) and extracted with ethyl acetate (4 × 100 mL). The organics were combined and washed with H_2O (1 × 150 mL) amd brine (2 × 150 mL), and dried over $MgSO_4$. Filtration and concentration of the solvent *in vacuo* provided **8a** (0.48, 93%) as a yellow solid.

8a: mp 163−164 °C (dec) (ethyl acetate); $R_f = 0.72$ (75:15:10 *n*-BuOH/HOAc/H_2O); IR (KBr) 3369, 3064, 2923, 1721, 1644, cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.60 (s(br), 2H), 10.47 (s, 1H), 8.10 (d, $J = 7.5$, 1H), 8.04 (d, $J = 8.5$, 1H), 7.64 (m, 3H), 5.57 (d, $J = 8.0$, 1H), 7.35 (dt, $J = 1.0$, 8.0, 1H), 7.23 (m, 4H), 7.14 (t, $J = 7.5$, 1H), 7.02 (t, $J = 7.5$, 1H), 6.95 (t, $J = 7.5$, 1H), 5.31 (d, $J = 2.5$, 1H), 4.52 (m, 1H), 4.23 (m, 1H), 3.26 (m, 1H), 3.14 (m, 1H), 3.01 (m, 1H), 2.29 (s, 3H), 1.80 (s, 3H), 1.64 (s, 3H), 1.39 (m, 1H), 1.17 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.1, 173.6, 169.9, 169.6, 144.7, 140.9, 136.1, 135.8, 134.3, 133.9, 130.3, 128.9, 128.1, 127.8, 125.8, 124.9, 121.6, 119.3, 118.9, 116.1, 111.8, 108.1, 63.0, 53.8, 50.0, 46.0, 38.3, 26.7, 23.0, 22.5, 21.5; LRMS (FAB) *m*/*z* (relative intensity) 647 (100) $[M]^+$, 530 (65), 401 (22), 259 (35); HRMS (FAB) Calcd for $C_{33}H_{34}N_4O_8S$, 647.2175 $[MH]^+$, found 647.2180.

***N*-Tosyl-2,2′-indolylindoline Diacid 8b.** Isomer **7b** was saponified according to the general procedure to afford **8b** (0.72 g, 92%) as a yellow solid.

8b: mp 167−168 °C (dec) (ethyl acetate); $R_f = 0.70$ (75:15:10 *n*-BuOH/HOAc/H_2O); IR (KBr) 3369, 3064, 2923, 1733, 1650, cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.60 (s(br), 2H), 10.33 (s, 1H), 8.30 (d, $J = 8.0$, 1H), 8.05 (d, $J = 8.5$, 1H), 7.67 (m, 3H), 7.60 (d, $J = 7.5$, 1H), 7.40 (t, $J = 8.0$, 1H), 7.28 (d, $J = 8.0$, 2H), 7.23 (d, $J = 8.0$, 1H), 7.12 (m, 2H), 7.03 (t, $J = 7.5$, 1H), 6.98 (t, $J = 7.5$, 1H), 5.22 (s, 1H), 4.53 (m, 1H), 4.09 (m, 1H), 3.37 (m, 1H), 3.10 (m, 1H), 3.02 (d, $J = 11.5$, 1H), 2.32 (s, 3H), 1.81 (s, 3H), 1.80 (m, 1H), 1.79 (s, 3H), 0.70 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.8, 173.3, 169.8, 169.5, 144.8, 140.7, 135.9, 135.5, 133.5, 132.8, 129.8, 128.7, 127.6, 126.9, 126.0, 124.6, 121.5, 118.7, 118.6, 116.4, 111.7, 107.4, 63.5, 53.8, 48.5, 45.0, 37.1, 30.7, 22.5, 22.4, 21.1; LRMS (FAB) *m*/*z* (relative intensity) 647 (100) $[M]^+$, 530 (85), 391 (30), 259 (40); HRMS (FAB) Calcd for $C_{33}H_{34}N_4O_8S$, 647.2175 $[MH]^+$, found 647.2179.

Formation of *N*-Tosyl-2,2′-indolylindoline Bisazalactone and Conversion to the *N*-Tosyl-2,2′-indolylindoline Bisoxazole 9a. In a dry 25 mL flask, **8a** (0.40 g, 0.62 mmol) was dissolved in 5 mL of dry dioxane. Dicyclohexylcarbodiimide (0.25 g, 1.2 mmol) was added, and the reaction mixture was stirred at room temperature for 2.5 h. After this time a suspension had formed and ether (15 mL) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* to provide the unstable bisazalactone as a yellow solid that was used immediately in the next step without further purification.

In a dry 10 mL round-bottom flask, the bisazalactone (0.37 g, 0.61 mmol) was dissolved in 5 mL of THF. To this stirred solution was added triethylamine (0.34 mL, 2.4 mmol) via syringe followed by slow, dropwise addition of methyl chloroformate (0.19 mL, 2.4 mmol). The reaction mixture was stirred at room temperature for 4 h. After this time, the reaction mixture was diluted with 50 mL ether, washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), and dried over $MgSO_4$. Filtration and concentration of the solvent *in vacuo* provided the crude product. Purification by silica gel chromatography (33% Et_2O/benzene) afforded bisoxazole **9a** (0.28 g, 47%) as a white solid.

9a: $[\alpha]_D$ +37.3° (*c* = 1.00, $CHCl_3$); mp 119−120 °C (Et_2O/petroleum ether); $R_f = 0.38$ (10% Et_2O/petroleum ether); IR (CH_2Cl_2) 3048, 2978, 2296, 1786 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.61 (m, 3H), 7.37 (d, $J = 4.5$, 1H), 7.32 (m, 3H), 7.25 (d, $J = 8.0$, 1H), 7.03 (t, $J = 7.3$, 2H), 6.94 (d, $J = 7.5$, 1H), 6.92 (d, $J = 7.5$, 1H), 5.46 (d, $J = 4.0$, 1H), 3.89 (d, $J = 16.0$, 1H), 3.85 (d, $J = 16.0$, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.56 (m, 1H), 2.37 (dd, $J = 6.0$, 14.5, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.23, (s, 3H), 2.02 (dd, $J = 7.5$, 14.5, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 154.4, 151.6, 151.3, 145.8, 144.5, 144.3, 140.9, 136.0, 135.1, 133.8, 133.0, 129.6, 128.3, 127.2, 127.1, 125.2, 124.2, 121.6, 121.4, 118.9, 118.5, 118.4, 115.2, 111.4, 107.6, 62.4, 56.8, 56.7, 47.0, 29.0, 21.0, 19.1, 13.6 (a ^{13}C resonance is missing; we believe there may be overlapping signals in the 45−65 ppm region); LRMS (FAB) *m*/*z* (relative intensity) 749 $[MNa]^+$, 727 (62) $[MH]^+$, 571 (32), 307 (20), 154 (100); HRMS (FAB) Calcd for $C_{37}H_{34}N_4O_{10}S$, 727.2074 $[MH]^+$, found 727.2069. Anal. Calcd for $C_{37}H_{34}N_4O_{10}S$: C, 61.14; H, 4.72; N, 7.71. Found: C, 61.31; H, 4.80; N, 7.60.

Formation of *N*-Tosyl-2,2′-indolylindoline Bisazalactone and Conversion to the *N*-Tosyl-2,2′-indolylindoline Bisoxazole 9b. In a dry 25 mL flask, **8b** (0.50 g, 0.77 mmol) was dissolved in 5 mL of dry dioxane. Dicyclohexylcarbodiimide (0.32 g, 1.6 mmol) was added, and the reaction mixture was stirred at room temperature for 2.5 h. After this time a suspension had formed and ether (15 mL) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* to provide the unstable bisazalactone as a yellow solid that was used immediately in the next step without further purification.

In a dry 10 mL round-bottom flask, the bisazalactone (0.45 mL, 0.77 mmol) was dissolved in 5 mL of THF. To this stirred solution was added triethylamine (0.29 mL, 3.1 mmol) via syringe followed by slow, dropwise addition of methyl chloroformate (0.24 mL, 3.1 mmol). The reaction mixture was stirred at room temperature for 4 h. After this time the reaction mixture was diluted with 50 mL ether, washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), and dried over $MgSO_4$. Filtration and concentration of the solvent *in vacuo* provided the crude product. Purification of the crude product by silica gel chromatography (5:5:1 Et_2O/benzene/petroleum ether) afforded bisoxazole **9b** (0.35 g, 62%) as a white solid.

9b: $[\alpha]_D$ −37.0° (*c* = 1.00, $CHCl_3$); mp 119−121 °C (Et_2O/petroleum ether); $R_f = 0.38$ (10% Et_2O/petroleum ether); IR (CH_2Cl_2) 3048, 2978, 2296, 1786 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.61 (m, 3H), 7.37 (d, $J = 4.5$, 1H), 7.32 (m, 3H), 7.25 (d, $J = 8.0$, 1H), 7.03 (t, $J = 7.3$, 2H), 6.94 (d, $J = 7.5$, 1H), 6.92 (d, $J = 7.5$, 1H), 5.46 (d, $J = 4.0$, 1H), 3.89 (d, $J = 16.0$, 1H), 3.85 (d, $J = 16.0$, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.56 (m, 1H), 2.37 (dd, $J = 6.0$, 14.5, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.23, (s, 3H), 2.02 (dd, $J = 7.54$, 14.5, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.7, 154.4, 151.6, 151.3, 145.8, 144.5, 144.3, 140.8, 136.0, 135.1, 133.8, 133.0, 129.6, 128.3, 127.2, 127.1, 125.2, 124.1, 121.6, 121.4, 118.9, 118.5, 118.4, 115.2, 111.4, 107.6, 62.4, 56.8, 56.6, 47.0, 29.0, 21.0, 19.1, 13.6 (a ^{13}C resonance is missing; we believe there may be overlapping signals in the 45−65 ppm region); LRMS (FAB) *m*/*z* (relative intensity) 749 $[MNa]^+$, 727 (100) $[MH]^+$, 571 (65), 154 (50); HRMS (FAB) Calcd for $C_{37}H_{34}N_4O_{10}S$, 727.2073 $[MH]^+$, found 727.2078. Anal. Calcd for $C_{37}H_{34}N_4O_{10}S$: C, 61.14; H, 4.72; N, 7.71. Found C, 61.20; H, 4.74; N, 7.76.

***cis*- and *trans*-2,3-Dihydro-3-methyl-2-phenylindole (10a and 10b).** To 2-phenylskatole (1.91 g, 9.24 mmol) in ethanol (42 mL) were added mossy tin (10.9 g, 92.4 mmol) and 12 N HCl (42.0 mL). The reaction mixture was stirred at 100 °C for 22 h. Upon cooling to room temperature, the reaction mixture

was decanted from the residual tin. Addition of 3 N NaOH (75 mL) to the mixture resulted in a white precipitate that was filtered off. The white precipitate was stirred with hot ethyl acetate and filtered again. The aqueous layer was extracted with ethyl acetate (4 × 25 mL). All the organic layers were combined, washed with H_2O (2 × 20 mL) and brine (1 × 30 mL), and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded an inseparable mixture of cis and trans indolines **10b** and **10a** as a 10:1 mixture (1.78 g, 94%) as determined by ^{1}H NMR.

***trans*-*N*-Acetyl-2,3-dihydro-3-methyl-2-phenylindole (12a) and *cis*-*N*-Acetyl-2,3-dihydro-3-methyl-2-phenylindole (12b).** To the mixture of *cis*- and *trans*-2,3-dihydro-3-methyl-2-phenylindoles **10a** and **10b** (0.39 g, 1.9 mmol) in pyridine (6.0 mL) was added acetic anhydride (0.58 g, 5.7 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. The residue was taken up into methylene chloride (100 mL) and washed with 1 N HCl (2 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was preadsorbed on silica gel and purified by silica gel chromatography (15−30% EtOAc/hexane) to afford *trans*-*N*-acetylindoline **12a** (0.050 g, 10%) and *cis*-*N*-acetylindoline **12b** (0.26 g, 53%).

12a: mp 149−150 °C (CH_2Cl_2); R_f = 0.45 in 20% EtOAc/hexane; IR (KBr) 3067, 3033, 2964, 2865, 1649 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (m, 1H), 7.27 (m, 4H), 7.10 (m, 4H), 4.85 (s, 1H), 3.19 (m, 1H), 2.01 (s, 3H), 1.44 (d, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 142.6, 142.5, 134.7, 129.1, 127.9, 127.7, 124.8, 124.1, 116.9, 72.0, 46.5, 24.2, 22.7 (a ^{13}C resonance is missing; we believe there may be overlapping signals in the 120−130 ppm region); MS (CI) 251 (100), 209 (98), 194 (81), 132 (75); HRMS (CI) calcd for $C_{17}H_{17}NO$, 251.1310, found 251.1307. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.33; H, 6.84; N, 5.53.

12b: mp 107−110 °C (CH_2Cl_2); R_f = 0.35 in 20% EtOAc/hexane; IR (KBr) 3038, 2975, 2965, 2861, 1647 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.9, 1H), 7.28 (m, 4H), 7.09 (m, 2H), 7.03 (m, 2H), 5.34 (d, J = 9.5, 1H), 3.93 (m, 1H), 2.02 (s, 3H), 0.92 (d, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 143.3, 138.1, 134.6, 128.6, 127.9, 127.8, 126.7, 124.1, 123.3, 116.4, 68.9, 39.8, 24.2, 13.9; MS (CI) 251 (99), 209 (100), 194 (79), 132 (69); HRMS (CI) calcd for $C_{17}H_{17}NO$, 251.1310, found 251.1306. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.34; H, 6.88; N, 5.61.

***cis*-*N*-(*p*-Toluenesulfonyl)-2,3-dihydro-3-methyl-2-phenylindole (11b).** To *cis*-*N*-acetylindoline **12b** (0.500 g, 1.99 mmol) in methanol (10 mL) was added 12 N HCl (10 mL). The mixture was stirred at 100 °C for 5 h. Upon cooling to room temperature, the mixture was basified to pH 9 with 3 N NaOH. The mixture was then extracted with ethyl acetate (4 × 20 mL). The organic layers were combined, washed with H_2O (2 × 10 mL) and brine (1 × 30 mL), and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the cis indoline **10b** (0.40 g, 1.9 mmol) which was carried on directly by taking up into methylene chloride (7.0 mL). *p*-Toluenesulfonyl chloride (0.56 g, 2.9 mmol) and triethylamine (0.39 g, 3.9 mmol) were added, and the reaction mixture was stirred for 12 h at room temperature. Methylene chloride (50 mL) was added to the reaction mixture which was then washed with 0.5 N HCl (1 × 20 mL), H_2O (2 × 10 mL), and brine (1 × 30 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded a residue that was preadsorbed on silica gel and purified by silica gel chromatography (10% EtOAc/hexane) to afford *cis*-*N*-tosylindoline **11b** (0.55 g, 78%).

11b: mp 140−142 °C (CH_2Cl_2); R_f = 0.35 in 10% EtOAc/hexane; IR (KBr) 3034, 2966, 2864, 1351, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0, 1H), 7.54 (d, J = 8.1, 2H), 7.26 (m, 1H), 7.19 (m, 3H), 7.13 (d, J = 8.0, 2H), 7.06 (m, 3H), 6.99 (d, J = 7.3, 1H), 5.35 (d, J = 9.6, 1H), 3.46 (m, 1H), 2.34 (s, 3H), 0.80 (d, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 142.1, 137.7, 136.2, 135.9, 129.4, 128.1, 127.9, 127.7, 127.3, 126.9, 124.4, 123.9, 115.3, 70.1, 39.7, 21.5, 14.0; MS (CI) 363 (40), 208 (100), 130 (26); HRMS (CI) calcd for $C_{22}H_{21}NSO_2$, 363.1292, found 363.1290. Anal. Calcd for $C_{22}H_{21}NSO_2$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.65; H, 5.88; N, 3.84.

***trans*-*N*-(*p*-Toluenesulfonyl)-2,3-dihydro-3-methyl-2-phenylindole (11a)**. To *trans*-*N*-acetylindoline **12a** (0.18 g, 0.71 mmol) in methanol (3 mL) was added 12 N HCl (3 mL). The reaction mixture was stirred at 100 °C for 5 h. Upon cooling to room temperature, the mixture was basified to pH 9 with 3 N NaOH. The solution was extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with H_2O (2 × 10 mL) and brine (1 × 25 mL), and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the trans indoline **10a** (0.115 g, 79%) which was carried on directly by taking up in to methylene chloride (2 mL). *p*-Toluenesulfonyl chloride (0.160 g, 0.84 mmol) and triethylamine (0.113 g, 1.12 mmol) were added, and the reaction mixture was stirred at room temperature for 12 h. Methylene chloride (50 mL) was added, and the mixture was washed with 0.5 N HCl (1 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 30 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded a residue that was preadsorbed on silica gel. Purification by silica gel chromatography (10% EtOAc/hexane) afforded *N*-tosylindoline **11a** (0.123 g, 61%).

11a: mp 117−120 °C (CH_2Cl_2); R_f = 0.35 in 10% EtOAc/hexane; IR (KBr) 3035, 2955, 2923, 1349, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1, 1H), 7.60 (d, J = 8.2, 2H), 7.28 (m, 7H), 7.18 (d, J = 8.1, 2H), 7.04 (m, 1H), 4.70 (d, J = 3.5, 1H), 3.10 (m, 1H), 2.36 (s, 3H), 0.89 (d, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.6, 141.3, 135.7, 134.8, 129.4, 128.6, 128.1, 127.6, 127.2, 125.8, 124.3, 124.2, 115.6, 72.9, 46.1, 21.9, 21.5; MS (CI) 363 (41), 208 (100), 193 (19), 130 (16); HRMS (CI) calcd for $C_{22}H_{21}NSO_2$, 363.1292, found 363.1295. Anal. Calcd for $C_{22}H_{21}NSO_2$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.62; H, 5.83; N, 3.85.

Acknowledgment. This work is supported by the Camille and Henry Dreyfus Foundaton, the National Science Foundation (CHE-9523521), and the National Institute of Health (GM-54523).

Supporting Information Available: ^{1}H NMR data are provided for **7b**, **8a**, and **8b** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970722H