consistent with the conclusions of the present study. They have observed predominant nucleophile (phosphate) trapping by the mitomycin C quinone methide (carbocation?) at low pH.[15a]

Experimental Section

Hydroquinones and their *O*-methylated derivatives were prepared according to the literature.[4,13] The kinetic studies were carried out in buffers prepared with doubly distilled water and adjusted to $\mu = 1.0$ with KCl. The following buffer systems were employed to hold pH: HCl/water, formic acid/formate (pK_a = 3.6), acetic acid/acetate (pK_a = 4.55), phosphate monobasic/phosphate dibasic (pK_a = 6.50), and boric acid/borate (pK_a = 9.2). These pK_a values were obtained at 30.0 ± 0.2 °C in $\mu = 1.0$ (KCl) aqueous solutions. Measurements of pH were made with a Radiometer GK2401C combination electrode.

Kinetic Studies of Hydrolysis. The hydrolytic studies of the hydroquinones were carried out in anaerobic aqueous buffers employing Thunberg cuvettes as previously described.[21] The *O*-methylated derivatives were studied in aerobic buffer.

Both aerobic and anaerobic studies were carried out as follows: A dimethyl sulfoxide stock of the compound to be studied was prepared fresh and 50 μL of this stock was added to 2.95 mL of buffer. The absorbance vs time data were collected on a UV–vis spectrophotometer in thermostated cells held at 30.0 ± 0.2 °C. These data were computer-fit to the two consecutive first-order equation for the general process A → B → C:[22]

$$\text{absorbance} = Xe^{-k_a t} + Ye^{-k_b t} + Z \tag{5}$$

$$X = \epsilon_A[A_0] - \epsilon_C[A_0] + (\epsilon_B[A_0] - \epsilon_C[A_0])[k_a/(k_b - k_a)]$$

$$Y = \epsilon_C[A_0] - \epsilon_B[A_0][k_a/(k_b - k_a)]$$

$$Z = \epsilon_C[A_0]$$

where $\epsilon_A[A_0]$, $\epsilon_B[A_0]$, and $\epsilon_C[A_0]$ are the maximum possible absorbances of A, B, and C in the process A → B → C, $[A_0]$ is the initial concentration of A, and ϵ's are extinction coefficients of A, B, and C. The first kinetic phase is designated by k_a and the second kinetic phase by k_b. The rate constants plotted on the pH–rate profiles (Figure 1–4) were obtained from the computer fits to the above equation, based on the difference between the data points and the computer-generated curve. Standard errors ranged from 4% for Figures 1 and 2 to 7% for Figures 3 and 4. The absorbance values plotted in Figure 5 were also obtained from such computer fits (absorbance at the conclusion of the first kinetic phase is X in the equation).

pK_a determinations for hydroquinones were carried out in anaerobic aqueous buffer employing Thunberg cuvettes. The pK_a determinations for the *O*-methylated analogues were carried out in aerobic buffers. Both aerobic and anaerobic pK_a determinations were made by computer-fitting absorbance vs pH data, obtained in $\mu = 1.0$ (KCl) 30.0 ± 0.2 °C aqueous buffer, to the following equation

$$\text{absorbance} = \frac{A_T a_H \epsilon_{HA} + A_T \epsilon_A K_a}{a_H + K_a} \tag{6}$$

where A_T is the total concentration of acid and conjugate base ([AH] + [A]), ϵ_{AH} is the extinction coefficient of the acid form, ϵ_A is the extinction coefficient of the conjugate base, a_H is the proton activity determined with a glass electrode, and K_a is the acid dissociation constant obtained from the fit.

^{1}H NMR Studies of Hydrolysis. An ^{1}H-NMR study of the hydrolysis of **1a** (0.015 M) was carried out in DMSO-d_6/0.05 M pD 6.95 phosphate buffer $\mu = 1.0$ (KCl) (3:1) with TSP-d_4 as the reference. The conversion of **1a** to **3a** corresponded to the following chemical shift changes: δ 4.80–4.96 (2-CH_2-X) and 4.02–4.04 (N(1)-CH_3). After 4 days, the final spectrum was that of **4a**: δ 4.86 (2-CH_2OH) and 4.07 (N(1)-CH_3).

An ^{1}H-NMR study of the hydrolysis of **1b** (0.05 M) was carried out in pD 4.00 acetate buffer $\mu = 1.0$ (KCl) under strict anaerobic conditions. The conversion of **1b** to **3b** corresponded to a shift from δ 4.80 to 4.95 for 2-CH_2-X. After several days, the final product **4b** was observed.

Acknowledgment. Funding from the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

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Syntheses and Diels–Alder Cycloaddition Reactions of 4*H*-Furo[3,4-*b*]indoles. A Regiospecific Diels–Alder Synthesis of Ellipticine

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Seven examples of the novel 4*H*-furo[3,4-*b*]indole ring system (**3–9**)—a stable, synthetic analogue of indole-2,3-quinodimethane—have been synthesized in 6–8 steps from simple indoles in overall yields of 21–28%. These 4*H*-furo[3,4-*b*]indoles undergo Diels–Alder reactions with several dienophiles (dimethyl acetylenedicarboxylate, *N*-phenylmaleimide, benzyne), including ethyl acrylate, which reacts regiospecifically with furoindole **4** to afford a single carbazole ester (**59**). This result, predicted by molecular orbital calculations, was used to design and execute a regiospecific Diels–Alder synthesis of the antitumor alkaloid ellipticine (**63**). Thus, the trimethylsilyl triflate-induced reaction between furoindole **4** and dihydropyridone **68b** is ≥99% regioselective and affords lactam **70b** in 89% yield. Further manipulation gives ellipticine (**63**) with no detectable (<1%) isoellipticine (**64**) in the crude product.

Over the past ten years, indole-2,3-quinodimethanes (**1**) and their stable cyclic analogues (**2**) have been the focus of considerable interest.[1] Although indole-2,3-quinodimethanes were earlier implicated by Bergman[2] and others[3,4] as intermediates in alkaloid synthesis, and by Hofheinz[5] in alkaloid rearrangement, it was the research of

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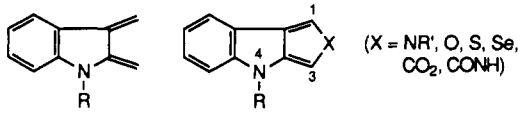
0022-3263/92/1957-5878$03.00/0

Marinelli[6] and, especially, of Magnus[7] that demonstrated the enormous utility of these intermediates in synthesis. More recently, other groups have described the generation and trapping of indole-2,3-quinodimethanes.[8-12]



1 2

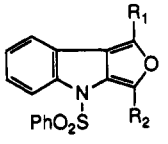
However, because these intermediates are not isolable, attention has turned to the development of synthetic analogues of indole-2,3-quinodimethanes, designed so as to exhibit greater stability and perhaps greater regioselectivity in cycloaddition reactions than their transient counterparts.[1] A number of research groups[13-20] have made important and elegant contributions to this area; notably Moody[13] and Pindur[14] exploiting pyrano[3,4-*b*]indol-3-ones (**2**, X = CO_2) and Sha[15] and Kreher[16] utilizing pyrrolo-[3,4-*b*]indoles (**2**, X = NR), following the pioneering work of Plieninger[21] and Welch[22] on these two rings systems, respectively.

When we began our work in this area in 1983, we focused on the then unknown 4*H*-furo[3,4-*b*]indole (**3**) ring system,[23] although the corresponding sulfur and selenium analogues were known,[24] but little studied. The alacrity with which furans undergo Diels–Alder reactions, in contrast to pyrroles, and the rich chemistry of isobenzofurans,[25] we believed portended a bright future for 4*H*-furo[3,4-*b*]indoles. Moreover, the projected stability of their Diels–Alder adducts, in contrast to those from pyrano[3,4-*b*]indol-3-ones, offered the possibility that one could manipulate these intermediate cycloadducts, thus extending the utility of 4*H*-furo[3,4-*b*]indoles in synthesis.

We now wish to disclose the full details of our studies with this ring system, culminating in a regiospecific Diels–Alder synthesis of the antitumor alkaloid ellipticine.[26]

Results and Discussion

Syntheses of 4-(Phenylsulfonyl)-4*H*-furo[3,4-*b*]-indoles. Our synthesis of the 4*H*-furo[3,4-*b*]indole ring system was patterned after the classical Paal–Knorr furan synthesis from 1,4-dicarbonyl compounds or their equivalents.[27] In our system, our target structures would necessarily be 2,3-disubstituted hydroxy ketone indoles, which should undergo cyclodehydration via a lactol intermediate to the target furoindoles.[28] In fact, this strategy has worked very well in most cases (vide infra). In order to explore the synthesis and reactivity of a range of substrates, we prepared several furoindoles (**3–9**), and, of these, only the synthesis of the dimethyl derivative **4** has been previously described in detail.[26c]



3 $R_1 = R_2 = H$
4 $R_1 = R_2 = Me$
5 $R_1 = Me$, $R_2 = H$
6 $R_1 = H$, $R_2 = Me$
7 $R_1 = Ph$, $R_2 = H$
8 $R_1 = H$, $R_2 = Ph$
9 $R_1 = Me$, $R_2 = Ph$

The synthesis of the parent compound **3** proved to be the most difficult of the series **3–9** (Scheme I). Commercially available indole-3-carboxaldehyde (**10**) was protected as the *N*-phenylsulfonyl derivative **11** and then reduced to alcohol **12** with $NaBH_4$. Regioselective dilithiation of **12** was achieved using *tert*-butyllithium (2.1 equiv) to give a deep-red solution of dianion **13**, which is presumably coordinated to both the alkoxide[29a] and the sulfonyl[29b] groups. Quenching this solution with D_2O af-

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(13) (a) Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 925. (b) May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 926. (c) Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2505. (d) May, C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 247. (e) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1407. (f) Moody, C. J.; Shah, P.; Knowles, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3249. (g) Moody, C. J.; Shah, P.; Knowles, P. *Tetrahedron Lett.* **1988**, *29*, 2693. (h) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 376. (i) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2463. (j) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673. (k) Jackson, P. M.; Moody, C. J. *Synlett* **1990**, 521. (l) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1667.
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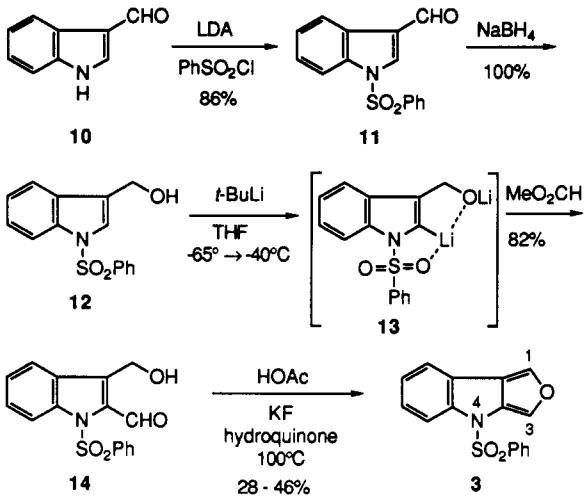
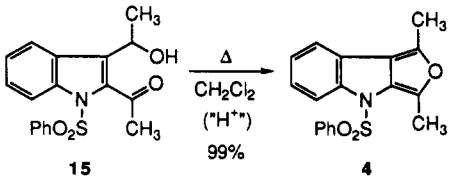
(27) For a modern example, see: Scott, L. T.; Naples, J. O. *Synthesis* **1973**, 209.
(28) For precedents, see: (a) Nishiyama, H.; Sasaki, M.; Itoh, K. *Chem. Lett.* **1981**, 1363. (b) Burton, L. P. J.; White, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 3226. (c) Reference 25.

Scheme I



forded the C-2 deuterated alcohol **12** in 77% yield (95% deuterium incorporation by MS and disappearance of a single peak at 125.3 ppm in the ^{13}C NMR spectrum). Treatment of dianion **13** with DMF gave hydroxy aldehyde **14** in variable yield (33–72%), and the use of TMEDA (2.2 equiv) and *N*-formylpiperidine resulted in only slight improvement. Subsequently, we found that using lithium diisopropylamide (LDA) as base and quenching **13** with methyl formate[30] gave **14** in 75–82% yield after recrystallization. The final step, ring closure to furoindole **3** by treatment of **14** with KF/hydroquinone/acetic acid, took considerable experimental work to achieve, and, in fact, remains erratic (28–46%). The cyclization of **14** to **3** can also be accomplished using trifluoroacetic acid (DMAP, Et_3N) in about the same yield (34%). Furoindole **3** is a stable, colorless solid, whose structure is supported by spectral and analytical data. The furan ring protons reveal the usual $^4J_{HH}$ = 1.3 Hz in the ^1H NMR spectrum.[31] Attempts to prepare the parent 4*H*-furo[3,4-*b*]indole by base cleavage of **3** (aqueous NaOH/MeOH or Me_3COK/THF) gave what appeared to be polymer. This is consistent with the lability of isobenzofurans.[25]

Noteworthy is the fact that the dimethyl analogue **4** forms much more readily from hydroxy ketone **15**[26c] than does **3** from hydroxy aldehyde **14**. This may be a consequence of the Thorpe–Ingold or "*gem*-dimethyl" effect,[32] wherein cyclization is increasingly favored both kinetically and thermodynamically by alkyl substitution in the open-chain substrate.[32d]



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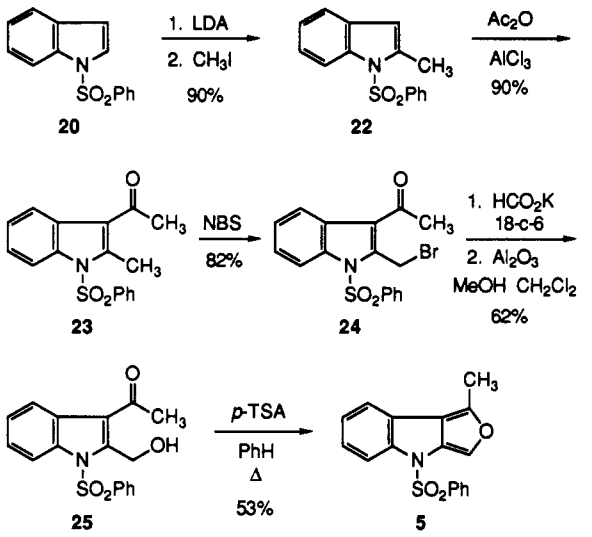
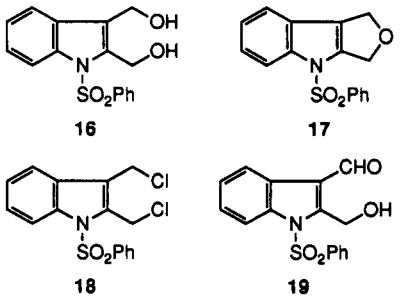
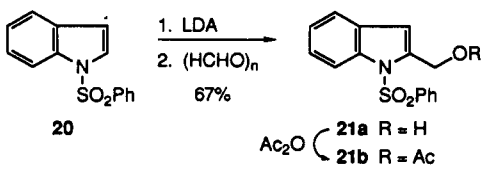
Scheme II



An alternative approach to furoindole **3** was briefly explored. Diol **16** could be prepared either by reducing **14** with $NaBH_4$ or by quenching dianion **13** with paraformaldehyde. However, efforts to prepare dihydrofuran **17** from diol **16** were largely unsuccessful. For example, reaction of diol **16** with $POCl_3$/DMF surprisingly gave dichloride **18** in 79% yield.



An attempt to prepare isomeric hydroxy aldehyde **19** by the application of Comins' methodology[33] to **11**, via in situ protection of the carbonyl group with the lithium salts of morpholine, *N*-methylpiperazine, or *N,N,N'*-trimethylethylenediamine, and then quenching with an electrophile (MeI, HCHO) failed. More recently, Comins encountered the same difficulty with **11**.[33b] In another approach to hydroxy aldehyde **19**, we found that 1-(phenylsulfonyl)-indole (**20**) could be lithiated with lithium diisopropylamide (LDA) and trapped with paraformaldehyde to give alcohol **21a** in good yield. Attempted formylation of both **21a** and the derived acetate **21b** with hexamethylenetetramine in trifluoroacetic acid, in a modified-Duff reaction,[34] was unsuccessful.



The synthesis of 1-methyl-4-(phenylsulfonyl)-4*H*-furo-[3,4-*b*]indole (**5**) is outlined in Scheme II. Methylation of 1-(phenylsulfonyl)indole (**20**) was achieved in excellent yield with LDA/MeI to give **22**. Acetylation[35] of **22** fol-

(33) (a) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. (b) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.

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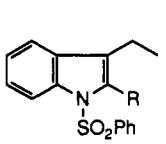
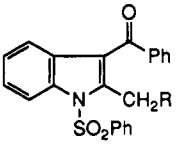
lowed by bromination and a two-step hydrolysis procedure using potassium formate and then methanol/alumina[36] gave hydroxy ketone **25**. Cyclization of **25** to furoindole **5** was effected with *p*-TsOH in refluxing benzene. The overall yield of **5** from indole is 21% (7 steps).

An alternative approach to **5** involved lithiation and hydroxymethylation (*s*-BuLi; HCHO) of 3-ethyl-1-(phenylsulfonyl)indole (**26**) to give alcohol **27** in 72% yield. Oxidation of **27** with activated MnO_2 gave aldehyde **28** in 70% yield. However, attempted bromination of **28** with NBS resulted in dehydrobromination to give the corresponding 3-vinylindole.

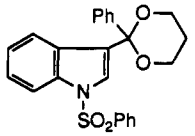


26 R = H
27 R = CH_2OH
28 R = CHO



29 R = H
30 R = Br
31 R = OH

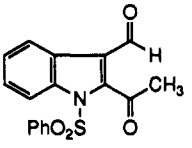
A similar protocol for the preparation of **5** was used to construct 1-phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**7**). Benzoylation of **22** followed by bromination of the resulting ketone **29** gave bromide **30**. The same two-step hydrolysis procedure[36] gave hydroxy ketone **31**, which conveniently cyclized to furoindole **7** after chromatography over silica gel and during rotary evaporation of the CH_2Cl_2 solvent. The overall yield of **7** from indole is 28% (6 steps). In an alternative approach to ketone **29**, we attempted to effect C-2 lithiation of ketal **32**, prepared from 3-benzoyl-1-(phenylsulfonyl)indole.[35] However, there was no evidence of lithiation after quenching with MeI or acetaldehyde.



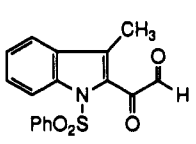
32

The synthesis of 3-methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**6**) is illustrated in Scheme III. Skatole (3-methylindole) (**33**) was protected as the *N*-phenylsulfonyl derivative **34**. Lithiation and quenching with acetaldehyde gave alcohol **35** in reasonable yield. Oxidation of **35** to ketone **36** with activated MnO_2, followed by the usual bromination and two-step hydrolysis, gave hydroxy ketone **38**. This material cyclized smoothly to furoindole **6** under the influence of excess BF_3·Et_2O in 79% yield. The overall yield of **6** from skatole is 26% (7 steps).

Attempts to oxidize the methyl group of **36** directly to **38** or to keto aldehyde **39** with SeO_2[37] appeared to give keto aldehyde **40**, whereas oxidation of **38** with PCC gave **39**.



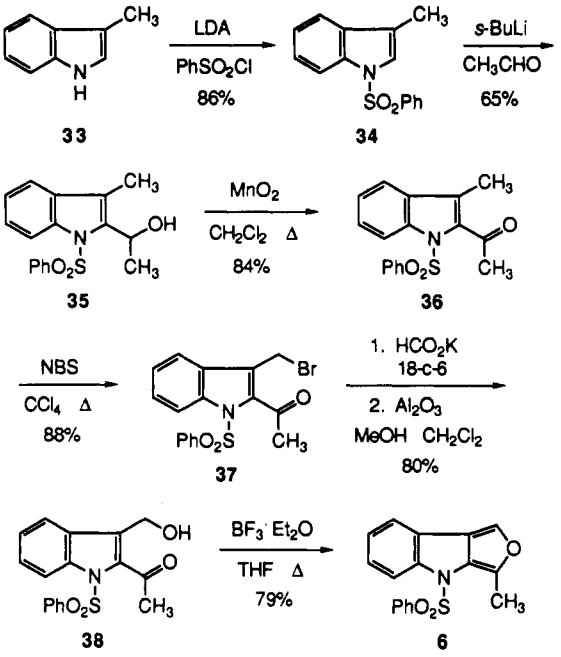
39



40

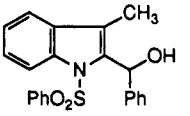
The synthesis of 3-phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**8**) exactly paralleled the synthesis of the

Scheme III

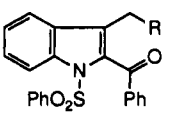


33 **34** **35** **36** **37** **38** **6**

3-methyl derivative **6** (cf. Scheme III). Thus, lithiation of **34** and quenching with benzaldehyde gave alcohol **41**. The standard sequence of oxidation, bromination, and hydrolysis gave hydroxy ketone **42c**. Ring closure to furoindole **8** was achieved in refluxing BF_3·Et_2O. The overall yield of **8** from skatole (**33**) is 21% (7 steps). Interesting, in contrast to the facile cyclization of the isomeric **31**, hydroxy ketone **42c** was relatively resistant to cyclization, as several different conditions (e.g., CF_3CO_2H, EtOH; $AlCl_3$, toluene; HCl, MeOH; Al_2O_3, toluene; *t*-BuLi, Ac_2O) failed to yield significant amounts of **8**. Likewise, attempts to cyclize bromide **42b** directly to **8** with silver trifluoroacetate were unsuccessful.

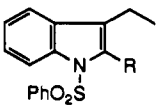


41

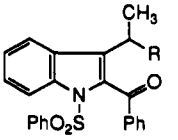


42a R = H
42b R = Br
42c R = OH

The synthesis of 1-methyl-3-phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**9**) utilized our previously developed methodology for the synthesis of dimethylfuroindole **4**.[26c] Thus, C-2 lithiation of 3-ethyl-1-(phenylsulfonyl)indole (**26**) with PhLi and quenching with benzaldehyde gave alcohol **43** in 72% yield. Oxidation, bromination, and hydrolysis with aqueous bicarbonate all proceeded in greater than 90% yield to give hydroxy ketone **46**. Ring closure to furoindole **9** occurred when **46** was heated in benzene. The overall yield of **9** from 3-ethylindole is 18% (6 steps) (or, from indole, the overall yield of **9** is 22% in 8 steps).



43 R = CHOHPh
44 R = COPh

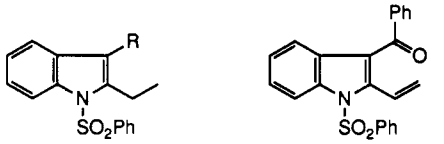


45 R = Br
46 R = OH

A brief approach to the synthesis of the isomeric 1-phenyl-3-methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole

(35) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.
(36) Liotta, C. L.; Harris, H. P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* **1974**, 2417.
(37) Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 7917.

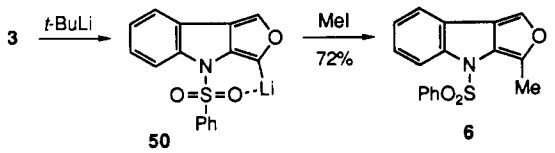
was undertaken. Quenching 2-lithio-1-(phenylsulfonyl)-indole with ethyl iodide gave **47**. Friedel–Crafts benzoylation gave ketone **48** in 69% yield. Unfortunately, attempts to brominate the methylene group of **48** led only to dehydrobromination and the formation of 2-vinylindole **49**.



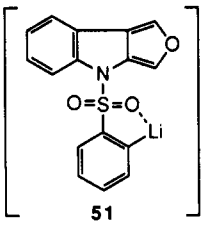
47 R = H
48 R = COPh

49

The susceptibility of furan to α-metalation[38] combined with the directed-metalating ability of sulfonyl groups[29b,38,39] suggested that it would be possible to lithiate regioselectively the C-3 position of furoindole **3**. Indeed, treatment of **3** with *tert*-butyllithium followed by quenching of the resulting anion **50** with MeI gave 3-methyl-1-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**6**) in 72% yield, identical to that prepared earlier (Scheme III), along with 13% of the isomeric **5**. The possibility exists that initial lithiation occurs to generate **51**, which undergoes transmetalation to give **50**, since this (intramolecular) rearrangement is known to occur with arenesulfonamides of N-substituted anilines.[40]



50 **6**



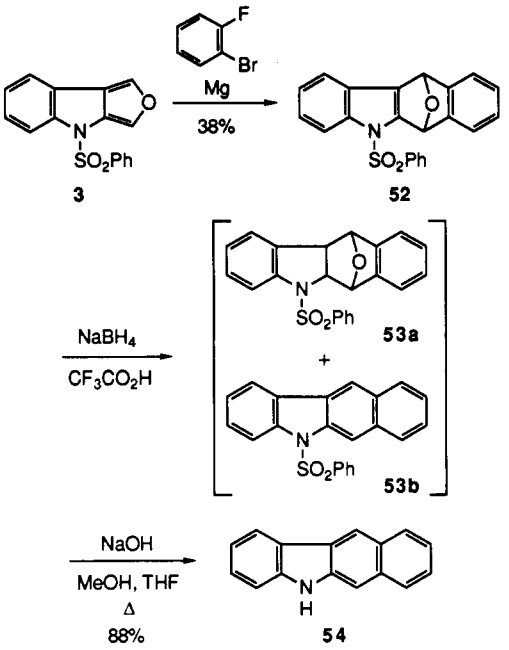
51

Diels–Alder Cycloaddition Reactions of Furo[3,4-*b*]indoles. As we discovered earlier with our study of the Diels–Alder cycloaddition reactions of 1,3-dimethylfuroindole **4**,[26c] these 1-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indoles behave very well as dienes in the Diels–Alder reaction.

Reaction of **3** with benzyne, as generated from 2-fluorobromobenzene and Mg,[41] gave adduct **52** (Scheme IV). Deoxygenation to the known 5*H*-benzo[*b*]carbazole (**54**) was accomplished with $NaBH_4/CF_3CO_2H$[42] followed by base treatment. Examination of the crude reaction mixture by mass spectrometry, prior to base treatment, indicated the presence of **53a** and **53b**.

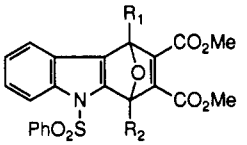
It is interesting to note that dimethylfuroindole **4** reacts with benzyne to give the corresponding Diels–Alder cycloadduct in 93% yield.[26c] It seems likely that the lower yield of **52** is due to competing metalation at the C-3 position of furoindole **3** by the Grignard reagent (cf. **50**) used to generate benzyne. Reaction of furoindoles **7** and **9** with dimethyl acetylenedicarboxylate (DMAD) afforded

Scheme IV



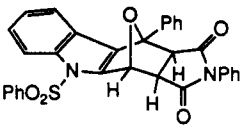
3 **52** **53a** **53b** **54**

cycloadducts **55** and **56** in 70% and 98% yield, respectively.

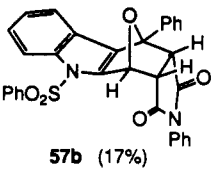


55 R_1 = Ph, R_2 = H
56 R_1 = Me, R_2 = Ph

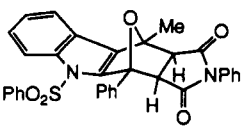
The reaction of furoindoles **7** and **9** with *N*-phenylmaleimide gave exo/endo mixtures (**57** and **58**). The isomeric structures were assigned from the ^1H NMR spectra. The exo isomer **57a** displays the low-field bridgehead proton as a singlet, whereas, in the endo isomer **57b**, this proton is split by the adjacent methine proton ($^3J_{HH}$ = 5.3 Hz). We also observed that the endo protons in **57a** are shielded relative to the exo protons in **57b**,[43] and the two ortho protons in the *N*-phenyl group are shielded in the endo isomer **57b**.[44] Similar NMR analysis confirmed the identities of **58a** and **58b**.



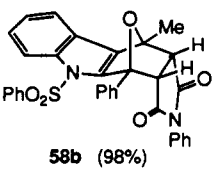
57a (54%)



57b (17%)



58a (2%)

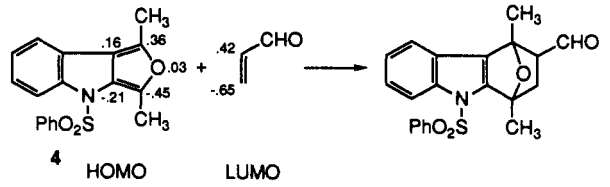


58b (98%)

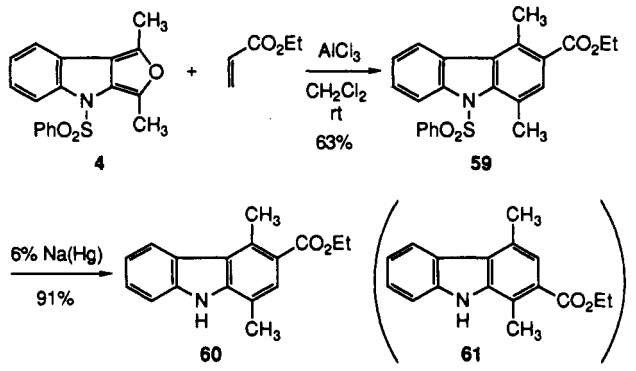
Before pursuing the Diels–Alder cycloaddition of furoindoles with unsymmetric dienophiles, we performed

(38) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.
(39) For recent examples, see: (a) Lamothe, M.; Anderson, M. B.; Fuchs, P. L. *Synth. Commun.* **1991**, *21*, 1675. (b) Alo, B. I.; Familoni, O. B.; Marsais, F.; Queguiner, G. *J. Heterocycl. Chem.* **1992**, *29*, 61.
(40) (a) Hellwinkel, D.; Supp, M. *Tetrahedron Lett.* **1975**, 1499. (b) Shafer, S. J.; Closson, W. D. *J. Org. Chem.* **1975**, *40*, 889.
(41) Newman, M. S.; Dali, H. M.; Hung, W. M. *J. Org. Chem.* **1975**, *40*, 262.
(42) Gribble, G. W.; Kelly, W. J.; Sibi, M. P. *Synthesis* **1982**, 143.
(43) For examples in bicyclo[2.2.1]heptane systems, see: (a) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346. (b) Bornstein, J.; Remy, D. E.; Shields, J. E. *Tetrahedron Lett.* **1974**, 4247.
(44) (a) Cava, M. P.; Pollack, N. M.; Mamer, O. A.; Mitchell, M. J. *J. Org. Chem.* **1971**, *36*, 3932. (b) Sasaki, T.; Kanematsu, K.; Iizuka, K.; Izumichi, N. *Tetrahedron* **1976**, *32*, 2879.

Scheme V



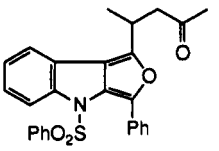
Scheme VI



molecular orbital calculations with the ground state of furoindole 4. The calculations employed the MOPAC series of programs[45] with the MINDO 3 hamiltonian.[46] No geometry optimization was attempted, but, rather, the coordinates of 4 were fixed at those provided by an X-ray crystallographic structure of 4.[47] There are 55 filled orbitals and SCF convergence was fast at the coordinates employed. The calculated electronic energy was 25692 eV and the heat of formation was calculated to be 57.3 kcal mol^{-1}. The sign and magnitude of each atomic orbital contribution to the ground-state HOMO of 4 is shown in Scheme V. The HOMO is clearly a π-type orbital and the largest electron density is centered on C-1 and C-3. If this result is matched with the coefficients for the LUMO of α,β-unsaturated carbonyl compounds, such as acrolein or acrylates,[48] then one predicts[49] the regiochemistry shown in Scheme V.

The reaction between furoindole 4 and ethyl acrylate was run in the presence of $AlCl_3$, to amplify both the rate[50] and the regioselectivity[51] of the cycloaddition reaction. Moreover, we anticipated that $AlCl_3$ would effect in situ bridge extrusion and aromatization of the Diels–Alder cycloadduct. As shown in Scheme VI, the product of this reaction was a single isomer (**59**), isolated in 63% yield. Examination of the crude reaction mixture by ^{13}C NMR failed to reveal more than a trace of the other isomer. Cleavage of the protecting group with buffered Na(Hg)[52] afforded the known carbazole ester **60**[53] in 91% yield, but not the known isomeric ester **61**.[53]

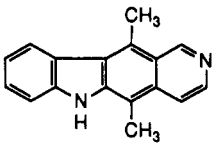
In contrast to the reaction between 4 and ethyl acrylate, reaction of furoindole 8 with 2-penten-2-one[54] in the presence of BF_3·Et_2O gave **62**, the product of electrophilic substitution.



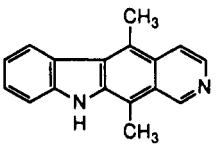
62

The application of cycloaddition reactions of furoindoles **3–9** to the synthesis of carbazole natural products will be described in due course.

Synthesis of Ellipticine. The antitumor pyrido[4,3-*b*]carbazole alkaloid ellipticine (**63**) and its derivatives have been the object of prodigious synthetic and biological study,[55] and one anticancer drug and several clinical candidates have emerged from this research.[55] An attractive synthetic route to ellipticine involves a Diels–Alder reaction between 3,4-pyridyne and indole-2,3-quinodimethane analogue **2**. Unfortunately, as we[26c] and Moody[13b,d] have discovered, this reaction is *not* regioselective but rather affords a ~1:1 mixture of ellipticine (**63**) and the nonbiologically active "isoellipticine" (**64**). Moreover, the combined yield of cycloadducts is less than 50%.



63



64

The very promising result obtained in the reaction between furoindole 4 and ethyl acrylate (Scheme VI) strongly suggested that an unsaturated valerolactam could serve as a regioselective 3,4-pyridyne synthetic equivalent in a Diels–Alder route to ellipticine. Indeed, as reported in preliminary form,[26d] this maneuver has now been realized.

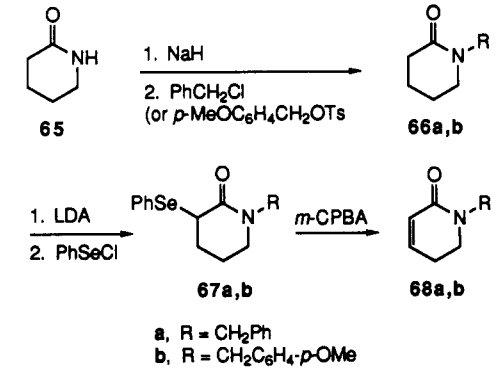
The target 5,6-dihydropyridone **68a** was prepared in straightforward fashion from commercially available δ-valerolactam (**65**) (Scheme VII). The known[56] lactam **66a** was converted into **68a** (27% yield from **65**) via phenyl selenide **67a** using the method of Zoretic.[57]

Initial attempts to accomplish the Diels–Alder cycloaddition between 1,3-dimethylfuroindole 4 and 5,6-dihydropyridone **68a** resulted in no reaction at room temperature and decomposition of **68a** at elevated temperatures. The use of Lewis acid promoters such as $AlCl_3$, BF_3·Et_2O, $TiCl_4$, $SnCl_4$, $EtAlCl_2$, Et_2AlCl, and $ZnCl_2$ only resulted in the decomposition of **68a**. Ultimately, the desired Diels–Alder reaction was accomplished using trimethylsilyl trifluoromethanesulfonate (TMSOTf) activation[58] to give, after basic workup, carbazole pyridone **70a** in 76% yield (Scheme VIII). While the product appeared to be the desired one (**70a**) with none of the regioisomer **71a** by NMR, we were unable to remove cleanly the *N*-benzyl group from **70a** or from the corresponding amine prepared by reducing **70a** with $LiAlH_4$.

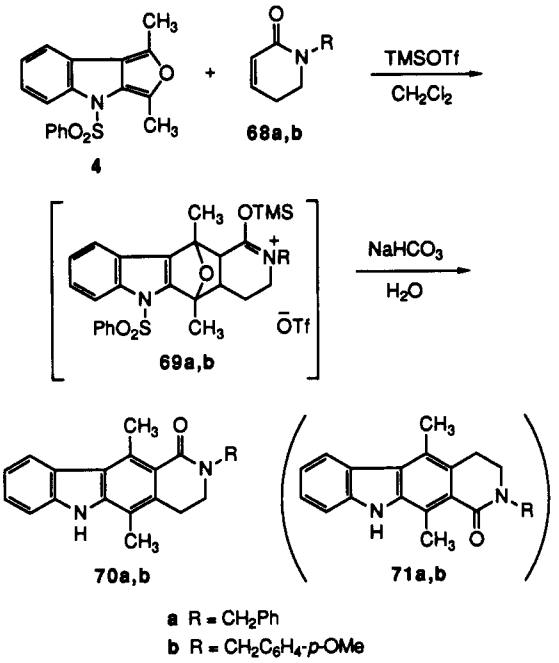
To circumvent this problem, we synthesized 1-(*p*-methoxybenzyl)-5,6-dihydropyridone (**68b**) from δ-valerolactam (**65**) in 50% yield (Scheme VII). Under the same Diels–Alder conditions developed for **68a**, pyridone **68b** reacted with dimethylfuroindole 4 in the presence of

(45) Stewart, J. J. P. *OCPE* Program No. 455.
(46) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285.
(47) Gribble, G. W.; Keavy, D. J.; Onan, K. D. Unpublished results.
(48) (a) Alston, P. V.; Ottenbrite, R. M.; Guner, O. F.; Shillady, D. D. *Tetrahedron* **1986**, *42*, 4403. (b) Kakushima, M. *Can. J. Chem.* **1979**, *57*, 2564.
(49) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.
(50) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(51) For a review, see: Laszlo, P.; Lucchetti, J. *Actual. Chim.* **1984**, 42. For a recent example, see: Ohgaki, E.; Motoyoshiya, J.; Narita, S.; Kakurai, T.; Hayashi, S.; Hirakawa, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3109.
(52) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(53) Govindachari, T. R.; Rajappa, S.; Sudarsanam, V. *Ind. J. Chem.* **1963**, *1*, 247.
(54) This prepared from the corresponding alcohol by Jones oxidation.
(55) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press, New York, 1990; Vol. 39, p 239.
(56) Räth, C. *Ann.* **1931**, *489*, 107.
(57) Zoretic P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587.
(58) Jung, M. E.; Vaccaro, W. D.; Buszek, K. R. *Tetrahedron Lett.* **1989**, *30*, 1893.

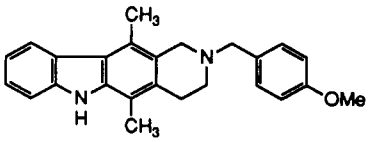
Scheme VII



Scheme VIII



TMSOTf to give **70b**, but only in 40% yield. Interestingly, when **4** and TMSOTf were added simultaneously to **68b**, no reaction occurred and the starting materials were recovered unchanged. After considerable experimentation, we found that the reaction between furoindole **4** and dihydropyridone **68b** in the presence of TMSOTf under carefully defined conditions ((1) allowing the lactam **68b** to react with TMSOTf for 1 h at 0 °C; (2) then adding furoindole **4** to this mixture at −40 °C; and (3) allowing the mixture to warm to room temperature over 18 h) afforded a single regioisomer (**70b**) in 89% yield. That this compound was indeed the desired regioisomer **70b** was proven by its conversion into ellipticine (**63**) by $LiAlH_4$ reduction to amine **72** and Pd/C-catalyzed tandem dehydrogenation/debenzylation to give ellipticine in 18% yield (78% based on unrecovered starting material).



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The absence of more than 1% of regioisomer **71b** from the Diels–Alder product was proven by subjecting the crude reaction mixture to the reduction/debenzylation sequence without any purification of intermediates. The resulting crude product was found by TLC to consist of only ellipticine (**63**), as no isoellipticine (**64**) could be detected under conditions that would have revealed as little as 1% **64** (by direct comparison with an artificial mixture of 99% **63** and 1% **64**).

Summary

The 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole ring system is reasonably easy to craft and several examples were synthesized from indole or skatole. These compounds undergo a variety of Diels–Alder reactions, including a highly regioselective cycloaddition reaction with dihydropyridones, leading ultimately to the first regioselective Diels–Alder synthesis of the antitumor pyrido[4,3-*b*]carbazole alkaloid ellipticine.

Experimental Section

Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Alkyllithium reagents were standardized prior to use by titration against diphenylacetic acid. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl under N_2 before use. Diethyl ether (Et_2O) was distilled from lithium aluminum hydride (LAH). *N,N*-Dimethylformamide (DMF), benzene, diisopropylamine, and HMPA were distilled from CaH_2. Methanol and EtOH were distilled from Na and CH_2Cl_2 was distilled from P_4O_{10}. Benzenesulfonyl chloride and *p*-TsCl were distilled, and PhSeCl was recrystallized from hexane prior to use. FC refers to flash column chromatography, and RC refers to radial chromatography. All chromatography utilized silica gel unless otherwise specified.

1-(Phenylsulfonyl)indole-3-carboxaldehyde (11) (Method A). To a −70 °C solution of LDA (1.06 equiv), prepared from *n*-BuLi (33.1 mL, 57.9 mmol, 1.75 M in hexane) and diisopropylamine (5.91 g, 58.4 mmol), under Ar with magnetic stirring was added a solution of **10** (7.90 g, 54.4 mmol) in dry THF (150 mL) via syringe. The mixture was allowed to warm to rt and stirred for 1.5 h. It was cooled to −70 °C, treated with $PhSO_2Cl$ (10.8 g, 61.1 mmol) via syringe, maintained at −70 °C for 2 h, and then allowed to warm to rt overnight. The mixture was concentrated in vacuo, and the residue was treated with CH_2Cl_2 (300 mL) and poured into 5% aqueous $NaHCO_3$ (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were washed with 3% aqueous $NaHCO_3$ (150 mL), H_2O (150 mL), and brine (2 × 250 mL), dried (K_2CO_3), and concentrated in vacuo to give 15.74 g of **11** as a yellow solid. Recrystallization from CH_2Cl_2/cyclohexane gave 10.05 g (65%) of **11** as an off-white solid, mp 157.5–158.5 °C (lit.[59] mp 158–158.5 °C). The mother liquor was concentrated in vacuo and chromatographed on Florisil (Et_2O) to afford an additional 3.32 g (21%) of **11**, homogeneous by TLC. This material was identical to a sample previously prepared in this laboratory.[59]

1-(Phenylsulfonyl)indole-3-carboxaldehyde (11) (Method B). Indole-3-carboxaldehyde (**10**) (9.4 g, 9.3 mmol) was added in one portion to an ice-cooled stirred mixture of n-Bu_4NHSO_4 (0.5 g) and crushed NaOH pellets (8 g) in CH_2Cl_2 (100 mL). This was followed immediately by the addition over 5 min of a solution of $PhSO_2Cl$ (14.1 g, 80 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at 0–5 °C for 25 min and then diluted with additional CH_2Cl_2 (50 mL) and stirred at rt for 1.5 h. The mixture was filtered and the solid was washed with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated in vacuo to give 24.0 g of solid, which was boiled with *i*-PrOH (ca. 100 mL), cooled to rt, and filtered to give 16.9 g (92%) of **11** as a colorless solid: mp 155–156 °C, identical (^1H NMR, TLC) to that prepared via method A.

1-(Phenylsulfonyl)-3-(hydroxymethyl)indole (12). To a solution of **11** (7.02 g, 24.6 mmol) in THF (160 mL) with magnetic stirring under Ar were added 95% EtOH (240 mL) and H_2O (30 mL). This solution was cooled to 0–5 °C and treated with $NaBH_4$ (1.02 g, 27.0 mmol) over 2–3 min in portions. The mixture was stirred at 0–5 °C for 75 min and then poured into a mixture of

(59) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

brine (150 mL) and H_2O (150 mL). Dichloromethane (200 mL) was added and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (2 × 300 mL), dried (K_2CO_3), and concentrated in vacuo to give 7.10 g (100%) of **12**, homogeneous by TLC, mp 93–95 °C. Recrystallization from CH_2Cl_2/cyclohexane/Et_2O gave the analytical sample, mp 82–83 °C: IR ($CHCl_3$) 3340, 1445, 1360, 1172, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 1 H), 4.76 (s, 2 H), 7.2–7.6 (m, 7 H), 7.88 (m, 2 H), 7.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 135.3, 133.8, 129.4, 129.3, 126.7, 125.0, 123.6, 123.4, 122.5, 119.9, 113.6, 57.0. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88; S, 11.16. Found: C, 62.62; H, 4.60; N, 4.82; S, 11.18.

1-(Phenylsulfonyl)-3-(hydroxymethyl)indole-2-carboxaldehyde (14). To a stirred solution of LDA, prepared from *n*-BuLi (93 mL, 110 mmol, 1.18 M in hexane) and diisopropylamine (11.1 g, 110 mmol), in THF (200 mL) was added dropwise under N_2 at −65 °C a solution of **12** (14.36 g, 50 mmol) in THF (75 mL) over 15 min. The reaction mixture was stirred at −75 °C for 90 min. The cooling bath was removed and the mixture was allowed to warm to rt and then stirred for 30 min. It was then cooled to −65 °C and treated via syringe with MeOCHO (15 g, 250 mmol) (two portions). The mixture was stirred overnight (−65 to −40 °C), the cooling bath was removed, and the mixture was allowed to warm to rt. The mixture was stirred at rt for 2 h and poured into saturated aqueous NH_4Cl (400 mL). The aqueous layer was extracted with EtOAc (200 mL). The organic extract was washed with H_2O (400 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo to give 16.0 g of **14** as an orange semisolid. Crystallization from *i*-PrOH gave 13.0 g (82%) (2 crops) of **14** as a tan solid, mp 122–123 °C. The analytical sample was prepared by crystallization from Et_2O/cyclohexane, mp 125.5–126 °C: IR (KBr) 3420, 1648, 1527, 1449 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (br s, 1 H), 4.76 (s, 2 H), 7.0–7.9 (m, 8 H), 8.2 (m, 1 H), 10.72 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 185.8, 137.2, 136.8, 135.7, 134.3, 133.7, 129.6, 129.2, 128.0, 126.4, 124.9, 122.1, 115.3, 55.3; HRMS calcd for M^+ 315.0565, found 315.0539. Anal. Calcd for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44; S, 10.17. Found: C, 61.02; H, 4.18; N, 4.38; S, 10.10.

4-(Phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (3). A mixture of **14** (0.177 g, 0.563 mmol), KF (4.6 mg), hydroquinone (1.5 mg), and HOAc (6.2 g) was heated at 100–105 °C for 3 h. The mixture was cooled to rt and then slowly added to a solution of $NaHCO_3$ (9.45 g) in H_2O (175 mL) with rapid stirring at 0–5 °C. To this were added Et_2O (150 mL) and CH_2Cl_2 (25 mL). The aqueous layer was extracted with additional Et_2O (2 × 50 mL) and then with CH_2Cl_2 (1 × 50 mL). The combined organic extracts were washed with H_2O (1 × 75 mL) and brine (2 × 100 mL), dried (K_2CO_3), and concentrated in vacuo to give a light red oil. Chromatography over Florisil (CH_2Cl_2) gave 76.9 mg (46%) of analytically pure **3** as a white solid, mp 145 °C dec: IR (KBr) 1450, 1369, 1179, 1092 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.98 (m, 1 H), 7.81–7.85 (m, 2 H), 7.77 (d, 1 H, J = 1.3 Hz), 7.61 (d, 1 H, J = 1.3 Hz), 7.48–7.58 (m, 2 H), 7.33–7.40 (m, 3 H), 7.23 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 144.2, 136.9, 133.7, 133.2, 131.0, 128.9, 127.4, 126.8, 124.4, 124.3 122.5, 121.8, 121.4, 115.1; MS m/z 297 (M^+), 204, 156, 128 (100), 101, 77; UV (EtOH) λ_{max} (log ϵ) 245 sh (4.13), 256 sh (4.08), 274 (3.71), 293 nm (3.69). Anal. Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71; S, 10.78. Found: C, 64.70; H, 3.77; N, 4.56; S, 10.70.

1-(Phenylsulfonyl)indole (20). This was prepared from indole in 94% yield by the method previously described.[60] In earlier preparations of **20**, we used a different procedure.[59]

[1-(Phenylsulfonyl)indol-2-yl]methanol (21a). A solution of LDA was generated under Ar at 0 °C by slowly adding *n*-BuLi (2.50 M in hexane, 8.90 mL, 22.2 mmol) to diisopropylamine (2.90 mL, 20.7 mmol) in THF (50 mL). The solution was stirred for 15 min at 0 °C, cooled to −78 °C, and treated dropwise with a solution of **20** (5.00 g, 19.4 mmol) in THF (10 mL) while keeping the internal temperature ≤−65 °C. The temperature was allowed to rise to 0 °C, and then the bright yellow solution was cooled to −78 °C and a slurry of paraformaldehyde (1.00 g, 33.3 mmol of CH_2O) in THF (5 mL) was rapidly added. Stirring was continued as the temperature was allowed to rise to rt overnight. The bright yellow homogeneous reaction mixture was poured into 5% aqueous $NaHCO_3$ (200 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed in succession with 10% aqueous $NaHCO_3$ (100 mL), H_2O (2 × 100 mL), brine (100 mL), decolorized with charcoal, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (CH_2Cl_2) gave 0.52 g of recovered **20** in addition to the product **21a** (4.03 g of viscous oil) which solidified on standing. Crystallization from Et_2O/hexane afforded colorless rhombohedra (3.32 g, 67%): mp 76.0–77.0 °C (lit.[61] mp 74 °C).

[1-(Phenylsulfonyl)indol-2-yl]methyl Acetate (21b). A solution of **21a** (0.30 g, 1.04 mmol), Ac_2O (0.12 mL, 1.27 mmol), and NaOAc (0.03 g, 0.36 mmol) in benzene (4 mL) under N_2 was heated at reflux for 9.5 h. The reaction was cooled to rt, 5% aqueous $NaHCO_3$ (30 mL) was added, and the mixture was stirred until no more gas evolution was observed. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Crystallization from Et_2O/hexane gave 0.32 g (94%) of **21b** as colorless needles: mp 86.5–87.5 °C. Anal. Calcd for $C_{17}H_{15}SO_4N$: C, 61.99; H, 4.59; N, 4.25; S, 9.73. Found: C, 62.05; H, 4.65, N, 4.25; S, 9.72.

2-Methyl-1-(phenylsulfonyl)indole (22). A stirred solution of LDA, prepared from 0.910 g (8.99 mmol) of diisopropylamine and *n*-BuLi (1.62 M in hexane, 9.39 mmol), in dry THF (20 mL) under Ar at −78 °C was treated with a solution of **20** (2.00 g, 7.77 mmol) in dry THF (20 mL) via syringe. The solution was allowed to warm to rt over 0.5 h and stirred for 2 h. The solution was cooled to −78 °C, treated with MeI (1.36 g, 9.63 mmol), allowed to warm to rt, and stirred for 15 h. The solution was then poured over ice (50 g) and treated with saturated NH_4Cl solution (50 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with H_2O (200 mL) and brine (2 × 200 mL), dried (K_2CO_3), and concentrated in vacuo to give a light tan oil. FC (CH_2Cl_2) and subsequent drying (40 °C, 0.1 Torr, 27 h) gave 1.89 g (90%) of **22** as a colorless oil, identical spectroscopically to a sample previously prepared in this laboratory:[59] ^1H NMR ($CDCl_3$) δ 8.37–8.24 (m, 1 H), 7.94–7.76 (m, 2 H), 7.67–7.20 (m, 6 H), 6.37 (s, 1 H), 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.8, 137.1, 136.8, 133.5, 129.5, 129.0, 125.9, 123.6, 123.3, 119.9, 114.2, 109.6, 15.5; MS m/z 271 (M^+), 130 (100).

3-Acetyl-2-methyl-1-(phenylsulfonyl)indole (23). A stirred suspension of $AlCl_3$ (0.83 g, 6.2 mmol) in dry CH_2Cl_2 (17 mL) under Ar was slowly treated with Ac_2O (0.67 g, 6.6 mmol). The solution was stirred at rt for 0.25 h and then treated with a solution of **22** (0.85 g, 3.1 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred for 0.5 h, poured over crushed ice (50 g), and extracted with CH_2Cl_2 (3 × 125 mL). The combined organic extracts were then washed with brine (250 mL), saturated aqueous $NaHCO_3$ (250 mL), and brine (250 mL), dried (K_2CO_3), and concentrated in vacuo. The crude product (mp 118–121 °C) was recrystallized from Et_2O/hexane to give 0.86 g (90%) of **23** as colorless crystals: mp 131.5–132 °C; IR (KBr) 1672, 1554, 1475, 1453, 1379, 1180, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.49–7.32 (m, 9 H), 2.92 (s, 3 H), 2.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.1, 142.8, 138.8, 136.0, 134.3, 129.5, 126.9, 126.5, 124.8, 124.4, 120.9, 120.7, 114.5, 32.1, 14.2. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 65.08; H, 4.87; N, 4.40; S, 10.23.

3-Acetyl-2-(bromomethyl)-1-(phenylsulfonyl)indole (24). A stirred solution of **23** (3.13 g, 9.99 mmol), NBS (1.83 g, 10.3 mmol), and benzoyl peroxide (53.9 mg) in CCl_4 (125 mL) was heated at reflux under Ar for 0.5 h. The suspension was allowed to cool to rt, filtered, and concentrated in vacuo to give **24** as colorless crystals. The residue from the filtration was stirred for 12 h with CCl_4 (175 mL), filtered, and concentrated in vacuo to give additional **24**. The combined solids were recrystallized from Et_2O/hexane to give 3.20 g (82%) of **24** as colorless crystals: mp 133.5–134.5 °C; IR (KBr) 1669, 1531, 1450, 1376, 1181, 1071 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29–7.86 (m, 4 H), 7.79–7.28 (m, 5 H), 5.47 (s, 2 H), 2.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 195.4, 140.7, 138.2, 136.0, 134.6, 129.4, 127.1, 126.3, 126.2, 124.8, 121.5, 121.4, 114.9, 32.2,

(60) Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627.

(61) Caixach, J.; Capell, R.; Galvez, C.; Gonzalez, A.; Roca, N. *J. Heterocycl. Chem.* **1979**, *16*, 1631.

22.0; MS m/z 393, 391, 312. Anal. Calcd for $C_{17}H_{14}BrNO_3S$: C, 52.05; H, 3.60; Br, 20.37; N, 3.57; S, 8.17. Found: C, 52.09; H, 3.62; Br, 20.44; N, 3.51; S, 8.10.

3-Acetyl-2-(hydroxymethyl)-1-(phenylsulfonyl)indole (25). A stirred solution of **24** (2.00 g, 5.10 mmol), anhydrous KOCHO (2.63 g, 31.2 mmol), and 18-crown-6 (107 mg) in MeCN (85 mL) was heated at reflux under Ar for 18 h. The suspension was filtered, concentrated in vacuo, digested with 5% MeOH in CH_2Cl_2 (150 mL), treated with Al_2O_3 (activity I neutral, 12.1 g), and stirred for 72 h under Ar. The suspension was filtered, the Al_2O_3 was washed with CH_2Cl_2 (3 × 65 mL), and the combined organic filtrate was concentrated in vacuo to give a yellow semicrystalline solid. FC (1:1 EtOAc/hexane) gave 1.04 g (62%) of **25**. Recrystallization from Et_2O gave the analytical sample: mp 114–115 °C; IR (KBr) 3512, 1667, 1537, 1454, 1384, 1185, 1159, 1019 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16–7.22 (m, 9 H), 5.19 (s, 2 H), 2.74 (s, 3 H), 2.52 (s, 1 H, exchangeable in D_2O); ^{13}C NMR ($CDCl_3$) δ 197.1, 145.3, 138.1, 135.8, 134.5, 129.5, 126.9, 126.2, 125.8, 124.7, 122.9, 121.0, 115.1, 54.9, 31.8. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.73. Found: C, 62.19; H, 4.64; N, 4.14; S, 9.59.

1-Methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (5). A stirred solution of **25** (34.0 mg, 0.103 mmol) in dry benzene (15 mL) was treated with p-TsOH–H_2O (1.0 mg). The solution was heated at reflux for 15 min. The solution was concentrated in vacuo and subjected to RC (CH_2Cl_2) to give 17.0 mg (53%) of **5**: mp 151.5–152.5 °C; IR (KBr) 2932, 1455, 1374, 1267, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99–7.82 (m, 3 H), 7.60–7.17 (m, 7 H), 2.51 (s, 3 H); MS m/z 311 (M^+), 170 (100).

1-(Phenylsulfonyl)-3-ethylindole (26). This compound was prepared in two steps in 97% yield from **19** as previously described,[35] or in one step from 3-ethylindole as described below. This procedure is an improvement over that previously described.[26c] To a stirred solution of 3-ethylindole (33.30 g, 229.3 mmol) in dry THF (400 mL) under Ar at −70 °C was added n-BuLi (1.33 M in hexane, 176 mL, 234 mmol) via syringe. The solution was allowed to warm to 0 °C over 1.25 h, cooled to −70 °C, and treated slowly with $PhSO_2Cl$ (49.8 g, 282 mmol). The solution was allowed to warm to rt and stirred for 14 h. The solution was then poured into saturated $NaHCO_3$ solution (200 mL), and the aqueous layer was extracted with Et_2O (6 × 300 mL). The combined organic extracts were concentrated in vacuo to give **26** as white crystals. Recrystallization from Et_2O gave 61.0 g (93%) of **26**: mp 124.0–124.5 °C (lit.[62] mp 125.0–125.5 °C); IR (KBr) 2976, 1455, 1367, 1191, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06–7.75 (m, 3 H), 7.51–7.14 (m, 7 H), 2.66 (q, J = 7.5 Hz, 2 H), 1.30 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.2, 135.3, 133.5, 131.0, 129.1, 126.6, 125.4 124.6, 123.0, 121.9, 119.4, 113.6, 18.1, 13.1; MS m/z 285 (M^+), 270, 145, 144 (100), 143, 115, 77.

3-Ethyl-2-(hydroxymethyl)-1-(phenylsulfonyl)indole (27). A stirred solution of **26** (3.00 g, 10.5 mmol) in dry THF (40 mL) at −70 °C under Ar was treated with s-BuLi (1.41 M in cyclohexane, 9.00 mL, 12.7 mmol) via syringe. The solution was allowed to warm slowly to rt (45 min) and cooled to −70 °C, TMEDA was added (1.91 mL, 1.47 g, 12.6 mmol), and the solution was stirred for 1.5 h. The solution was then treated with a solution of paraformaldehyde formed by bubbling dry gaseous paraformaldehyde into THF (45 mL) for 0.5 h. The quenched reaction mixture was then allowed to warm slowly (45 min) to rt, stirred for 3 h, poured into 10% NH_4Cl solution (300 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were concentrated in vacuo, redigested with CH_2Cl_2 (200 mL), washed with brine (200 mL), dried (K_2CO_3), and concentrated in vacuo to provide 3.29 g of a yellow oil. FC (CH_2Cl_2) provided 2.39 g of **27** (72%) as a pale yellow oil that crystallized on standing. Recrystallization from Et_2O/hexane provided the analytical sample: mp 84–85 °C; IR (KBr) 3555, 1455, 1365, 1181, 1002 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20–8.06 (m, 1 H), 7.85–7.51 (m, 3 H), 7.61–7.23 (m, 6 H), 4.90 (d, J = 7.5 Hz, 2 H), 3.23 (t, J = 7.5 Hz, 1 H), 2.77 (q, J = 7.5 Hz, 2 H), 1.23 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 134.6, 133.8, 129.7, 129.2, 126.2, 125.7, 125.3, 123.6, 119.5, 114.6, 54.9, 17.4, 15.2; MS m/z 315 (M^+), 156, 144 (100), 115, 77. Anal. Calcd for $C_{17}H_{18}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.58; H, 5.46; N, 4.39; S, 10.13.

1-(Phenylsulfonyl)-3-ethylindole-2-carboxaldehyde (28). A stirred solution of **27** (2.28 g, 7.23 mmol) in dry CH_2Cl_2 (250 mL) was treated with MnO_2 (6.40 g, 73.6 mmol) and heated at reflux for 36 h. The suspension was cooled to rt and filtered, and the filtrate was saved. The residue was placed in a Soxhlet continuous extraction apparatus and extracted with CH_2Cl_2 (250 mL) for 12 h. The extract was combined with filtrate and concentrated in vacuo to provide an oil that crystallized on standing. Recrystallization from Et_2O/hexane gave 1.59 g (70%) of **28** as colorless analytically pure crystals: mp 120–121 °C; IR (KBr) 2923, 1677, 1550, 1448, 1357, 1127 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.67 (s, 1 H), 8.31–6.98 (m, 9 H), 3.05 (q, J = 7.5 Hz, 2 H), 1.19 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.7, 138.8, 137.8, 136.8, 134.0, 132.4, 129.8, 129.1, 129.0, 126.6, 124.7, 121.5, 116.0, 18.1, 14.4; MS m/z 313 (M^+), 172, 77. Anal. Calcd for $C_{17}H_{16}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 65.23; H, 4.85; N, 4.45; S, 10.30.

3-Benzoyl-2-methyl-1-(phenylsulfonyl)indole (29). A stirred suspension of $AlCl_3$ (2.27 g, 17.0 mmol) in dry CH_2Cl_2 (50 mL) under Ar was treated with PhCOCl (2.36 g, 16.8 mmol). The solution was stirred at rt for 0.25 h and then treated with a solution of **22** (2.24 g, 8.25 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred for 0.25 h, poured over ice (150 g), and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then washed with brine (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL), dried (K_2CO_3), and concentrated in vacuo to give a clear oil. The crude oil was subjected to FC (CH_2Cl_2) to provide 2.69 g (86%) of **29** as a clear oil which crystallized on standing. Recrystallization from Et_2O/hexane gave the analytical sample: mp 130.5–132.0 °C; IR (KBr) 3074, 1659, 1602, 1556, 1453, 1384, 1235, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35–8.19 (m, 1 H), 7.95–6.99 (m, 13 H), 2.64 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.9, 141.0, 138.8, 138.8, 135.9, 134.2, 133.2, 129.5, 128.6, 128.1, 126.5, 124.8, 124.1, 120.7, 120.4, 114.3, 14.6; MS m/z 375 (M^+), 234, 105, 77. Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73; S, 8.54. Found: C, 70.31; H, 4.60; N, 3.70; S, 8.48.

3-Benzoyl-2-(bromomethyl)-1-(phenylsulfonyl)indole (30). A stirred solution of **29** (2.06 g, 5.49 mmol), NBS (1.04 g, 5.84 mmol), and benzoyl peroxide (50 mg) in CCl_4 (125 mL) was heated at reflux under Ar for 1.75 h. The suspension was cooled to 5 °C, filtered, and concentrated in vacuo to give **30** as a clear oil. The oil was triturated with Et_2O/hexane to give colorless crystals. Recrystallization from Et_2O/hexane gave 2.22 g (89%) of **30** as colorless crystals: mp 156.5–158.5 °C dec; IR (KBr) 1651, 1555, 1444, 1390, 1249, 1196 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31–7.14 (m, 14 H), 5.25 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 192.2, 139.3, 138.2, 138.1, 135.8, 134.5, 133.6, 129.6, 129.4, 128.6, 127.4, 127.1, 126.2, 124.3, 122.9, 121.5, 114.7, 21.4; MS m/z 248, 220, 77. Anal. Calcd for $C_{22}H_{16}BrNO_3S$: C, 58.15; H, 3.55; Br, 17.59; N, 3.08; S, 7.06. Found: C, 58.23; H, 3.60; Br, 17.64; N, 3.08; S, 7.01.

1-Phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (7). A stirred solution of **30** (1.79 g, 3.95 mmol), anhydrous KOCHO (2.0457 g, 4.5026 mmol), and 18-crown-6 (133 mg) in MeCN (75 mL) was heated at reflux under Ar for 18 h. The suspension was filtered, concentrated in vacuo, digested with 5% MeOH in CH_2Cl_2 (106 mL), treated with Al_2O_3 (activity I neutral, 9.90 g), and stirred for 72 h under Ar. The suspension was filtered, the Al_2O_3 was washed with CH_2Cl_2 (3 × 65 mL), and the combined organic filtrate was concentrated in vacuo to give a light orange oil. The oil was digested with CH_2Cl_2 (300 mL) and heated at reflux for 36 h. FC (CH_2Cl_2) gave 996 mg (68%) of **7** as colorless crystals. Recrystallization from Et_2O gave the analytical sample: mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 1 H), 7.91–7.79 (m, 6 H), 7.52–7.23 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 144.3, 143.4, 136.7, 134.7, 134.0, 130.7, 129.0, 128.9, 127.9, 127.5, 126.9, 124.9, 124.3, 123.2, 122.5, 122.4, 116.9, 115.0. Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75; S, 8.58. Found: C, 70.69; H, 4.06; N, 3.71; S, 8.67.

2-Phenyl-2-[1-(phenylsulfonyl)indol-3-yl]-1,3-dioxolane (32). A stirred solution of 3-benzoyl-1-(phenylsulfonyl)indole[35] (2.00 g, 5.53 mmol) in dry benzene (50 mL) was treated with 1,3-propanediol (4.80 g, 64 mmol) and heated at reflux with removal of H_2O (Dean–Stark trap) for 20 h. The solution was cooled to rt, washed with 1 M NaOH (2 × 100 mL), H_2O (50 mL), and brine (50 mL), dried (K_2CO_3), and concentrated in vacuo to

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give 2.85 g (88%) of **32** as an off-white solid melting at 159–161 °C. Recrystallization from Et_2O/hexane afforded 1.68 g (77%) of the analytical sample as colorless platelets: mp 163.0–164.0 °C; ^1H NMR ($CDCl_3$) δ 8.10–7.81 (m, 5 H), 7.75–7.19 (m, 10 H), 4.09 (t, J = 6.0 Hz, 4 H), 1.98–1.75 (m, 2 H); MS m/z 419 (M^+), 342 (100), 192, 130, 100, 85, 77, 57. Anal. Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34; S, 7.64. Found: C, 68.83; H, 5.12; N, 3.29; S, 7.59.

3-Methyl-1-(phenylsulfonyl)indole (34). A stirred solution of LDA, prepared from diisopropylamine (12.0 g, 118 mmol) and *n*-BuLi (1.6 M in hexane, 74.8 mL, 119 mmol), in dry THF (30 mL) at −78 °C under Ar was treated with a solution of **33** (12.90 g, 96.2 mmol) in dry THF (200 mL). The solution was stirred for 0.5 h, allowed to warm to rt over 1 h, stirred for 2.5 h, cooled to −78 °C, and treated via syringe with $PhSO_2Cl$ (13.8 mL, 108 mmol). The solution was stirred for 0.5 h, allowed to warm slowly (12 h) to rt, and treated with saturated NH_4Cl solution (25 mL). The mixture was poured into saturated NH_4Cl solution (200 mL) and treated with CH_2Cl_2 (200 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (K_2CO_3) and concentrated in vacuo to give a clear oil that crystallized on standing. Recrystallization from Et_2O/hexane gave 22.89 g (86%) of **34** as colorless crystals: mp 117.5–119 °C; IR (KBr) 1446, 1365, 1275, 1174, 1006 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17–7.78 (m, 3 H), 7.54–7.20 (m, 7 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 135.1, 133.4, 131.6, 129.0, 126.5, 124.5, 123.0, 122.9, 119.3, 118.7, 113.5, 9.5. This material was identical to a sample previously prepared by another method in our laboratory.[59]

1-[3-Methyl-1-(phenylsulfonyl)indol-2-yl]ethanol (35). A stirred solution of **34** (2.99 g, 11.0 mmol) in dry THF (50 mL) under Ar at −70 °C was treated via syringe with *s*-BuLi (1.22 M in cyclohexane, 12.9 mmol). The pale yellow solution was stirred at −70 °C for 15 min, allowed to warm to rt (45 min), and stirred for 3.5 h. A precipitate separated from the solution. The suspension was cooled to −70 °C and treated via syringe with freshly distilled MeCHO (1.30 mL, 22.3 mmol). The solution was allowed to warm slowly to rt (14 h), treated with saturated NH_4Cl solution (25 mL), poured into saturated NH_4Cl solution (100 mL), and treated with CH_2Cl_2 (150 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried (K_2CO_3), and concentrated in vacuo to give an oil. FC (CH_2Cl_2) provided 2.24 g (65%) of **35** as a yellow oil: IR (neat) 3550, 3078, 2991, 1590, 1481, 1453, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17–8.00 (m, 1 H), 7.89–7.68 (m, 2 H), 7.48–7.16 (m, 6 H), 5.45 (q, J = 7.5 Hz, 1 H), 3.68 (bs, 1 H), 2.29 (s, 3 H), 1.71 (d, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.8, 136.5, 133.5, 131.3, 128.9, 126.3, 125.1, 123.7, 119.4, 119.1, 115.1, 63.4, 23.4, 9.5. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.74; H, 5.44; N, 4.42; S, 10.15.

2-Acetyl-3-methyl-1-(phenylsulfonyl)indole (36). A stirred solution of **35** (2.95 g, 9.34 mmol) in dry CH_2Cl_2 (175 mL) was treated with activated black MnO_2 (12.21 g, 140 mmol) and heated at reflux for 24 h. The suspension was cooled to rt and filtered, the residue was washed with CH_2Cl_2 (3 × 25 mL), and the combined organic filtrate was concentrated in vacuo to give a clear oil. FC (CH_2Cl_2) gave 2.46 g (84%) of **36** as a colorless crystalline solid. An additional 0.09 g (3%) was obtained by continuous extraction with CH_2Cl_2 (300 mL) of the filtration residue in a Soxhlet extractor, concentration of the resultant solution in vacuo, and RC (CH_2Cl_2) of the residue. Recrystallization from Et_2O gave the analytical sample: mp 115.5–117 °C; ^1H NMR ($CDCl_3$) δ 8.09–7.91 (m, 1 H), 7.64–7.16 (m, 8 H), 2.66 (s, 3 H), 2.20 (s, 3 H). Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 65.24; H, 4.88; N, 4.43; S, 10.28.

2-Acetyl-3-(bromomethyl)-1-(phenylsulfonyl)indole (37). A stirred suspension of **36** (2.50 g, 7.98 mmol), NBS (1.50 g, 8.44 mmol), and benzoyl peroxide (46.7 mg) in CCl_4 (90 mL) was heated at reflux under Ar for 3 h. Additional NBS (81 mg, 0.46 mmol) was added and the suspension heated at reflux for 1 h. The suspension was then cooled to rt, filtered, and concentrated in vacuo to give a yellow oil. Trituration with Et_2O induced crystallization and afforded 2.76 g (88%) of **37** as a crystalline solid. Recrystallization from Et_2O gave 2.30 g (73%) of **37** as colorless crystals: mp 137–138 °C; IR (KBr) 1688, 1554, 1448, 1363, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 1 H), 7.66 (d, J = 8.9 Hz, 2 H), 7.56 (d, J = 7.0 Hz, 1 H), 7.49–7.26 (m, 5 H), 4.53 (s, 2 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 195.4, 137.7, 136.8, 135.4, 134.2, 128.9, 127.7, 127.1, 125.1, 124.8, 120.9, 115.9, 32.2, 20.5. Anal. Calcd for $C_{17}H_{14}BrNO_3S$: C, 52.05; H, 3.60; Br, 20.37; N, 3.57; S, 8.17. Found: C, 52.15; H, 3.63; Br, 20.29; N, 3.52; S, 8.13.

2-Acetyl-3-(hydroxymethyl)-1-(phenylsulfonyl)indole (38). A stirred solution of **37** (2.00 g, 5.10 mmol), anhydrous KOCHO (2.71 g, 32.2 mmol), and 18-crown-6 (98.6 mg) in MeCN (82 mL) was heated at reflux under Ar for 46 h. The suspension was filtered, concentrated in vacuo, digested with 5% MeOH in CH_2Cl_2 (152 mL), treated with Al_2O_3 (activity I neutral, 12.0 g), and stirred for 72 h under Ar. The suspension was filtered, the Al_2O_3 was washed with CH_2Cl_2 (3 × 70 mL), and the combined organic filtrates were concentrated in vacuo to give a slightly yellow oil that crystallized on standing. Recrystallization from Et_2O gave 1.20 g (72%) of **38**, mp 124–125 °C. RC (CH_2Cl_2) of the mother liquor gave an additional 135 mg (8%) of **38**: IR (KBr) 3498, 1665, 1552, 1448, 1366, 1175, 1006 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 1 H), 7.59–7.22 (m, 8 H), 4.59 (d, J = 6.5 Hz, 2 H), 2.93 (t, J = 6.5 Hz, 1 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.7, 138.2, 137.5, 134.9, 134.2, 131.8, 129.7, 128.7, 128.0, 127.0, 125.2, 121.3, 116.2, 54.9, 32.1. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.73. Found: C, 62.06; H, 4.64; N, 4.25; S, 9.79.

3-Methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (6). A stirred solution of **38** (0.304 g, 0.923 mmol) in dry THF (20 mL) was treated with $BF_3{\cdot}Et_2O$ (0.90 mL, 7.32 mmol) and heated at reflux for 2 h. The solution was cooled to rt, poured over ice (25 g), and treated with saturated aqueous $NaHCO_3$ (25 mL) and CH_2Cl_2 (25 mL), the layers were separated, and the organic layer was extracted with additional CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried (K_2CO_3), and concentrated in vacuo to give crude material. RC (CH_2Cl_2) gave 0.229 g (79%) of **6** as colorless crystals. Recrystallization from Et_2O gave the analytical sample: mp 146–148 °C dec; IR (KBr) 3156, 1457, 1366, 1186 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 2 H), 7.49–7.42 (m, 2 H), 7.38–7.27 (m, 3 H), 7.24–7.18 (m, 2 H), 2.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.2, 136.4, 135.1, 133.5, 128.8, 128.4, 128.3, 127.2, 126.9, 124.8, 123.2, 122.6, 122.1, 116.8, 13.2; MS m/z 311 (M^+), 170, 128 (100). Anal. Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50; S, 10.30. Found: C, 65.45; H, 4.22; N, 4.44; S, 10.22.

[3-Methyl-1-(phenylsulfonyl)indol-2-yl]phenylmethanol (41). A stirred solution of **34** (9.00 g, 33.1 mmol) in dry THF (150 mL) under Ar at −70 °C was treated via syringe with *s*-BuLi (1.22 M in cyclohexane, 32.0 mL, 39.0 mmol). The pale yellow solution was stirred at −70 °C for 15 min, allowed to warm to rt (45 min), and stirred for 3.5 h. A precipitate formed, and the suspension was cooled to −70 °C and treated via syringe with freshly distilled PhCHO (4.1 mL, 40.3 mmol). The solution was allowed to warm slowly to rt (14 h), poured into saturated NH_4Cl solution (300 mL), and treated with CH_2Cl_2 (200 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 150 mL). The combined organic extracts were concentrated in vacuo, redigested with CH_2Cl_2 (200 mL) and brine (200 mL), dried (K_2CO_3), and concentrated in vacuo to give an oil. FC (CH_2Cl_2) of the oil provided 9.16 g (73%) of **41** as a pale yellow oil: IR (neat) 3514, 3064, 2925, 1603, 1531, 1494, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–8.13 (m, 1 H), 7.69–7.07 (m, 14 H), 6.59 (d, J = 7.5 Hz, 1 H), 4.29 (d, J = 7.5 Hz, 1 H), 2.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.7, 138.1, 136.7, 136.3, 133.4, 130.8, 128.8, 128.2, 126.9, 126.3, 125.6, 125.4, 123.6, 120.4, 119.3, 114.8, 67.8, 9.5. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71; S, 8.49. Found: C, 69.99; H, 5.02; N, 3.56; S, 8.09.

2-Benzoyl-3-methyl-1-(phenylsulfonyl)indole (42a). A stirred solution of **41** (2.18 g, 5.77 mmol) in dry CH_2Cl_2 (55 mL) was treated with 8.65 g (99.4 mmol) of activated black MnO_2 and heated at reflux under Ar for 10 h. The suspension was cooled to rt and filtered, and the residue was washed with CH_2Cl_2 (3 × 25 mL). The combined organic filtrate was concentrated in vacuo to afford a yellow oil. Trituration with Et_2O induced crystallization. Recrystallization from CH_2Cl_2/hexane gave 1.40 g (65%) of **42a** as colorless platelets. The filtration residue was subjected to continuous extraction with CH_2Cl_2 (300 mL) in a Soxhlet extractor for 48 h. The organic extract was concentrated in vacuo,

digested with mother liquor from the initial recrystallization, and concentrated via heating on a steam bath to afford an additional 0.57 g (26%) of crystalline **42a**. Further recrystallization from CH_2Cl_2 gave the analytical sample: mp 140.5–141 °C; IR (KBr) 1664, 1602, 1587, 1456, 1373, 1262, 1184 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–7.24 (m, 14 H), 2.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.4, 138.3, 136.6, 136.3, 133.8, 133.5, 133.4, 131.2, 129.5, 128.9, 128.6, 127.2, 126.8, 124.7, 124.3, 120.4, 115.2, 9.3. Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73; S, 8.54. Found: C, 70.24; H, 4.59, N, 3.70; S, 8.45.

2-Benzoyl-3-(bromomethyl)-1-(phenylsulfonyl)indole (42b). A stirred solution of **42a** (0.3517 g, 0.9368 mmol), NBS (0.1845 g, 1.036 mmol), and benzoyl peroxide (15 mg) in CCl_4 (15 mL) was heated at reflux under Ar for 1.5 h. The suspension was then cooled to 0 °C, filtered and concentrated in vacuo to give 0.407 g (96%) of a slightly yellow crystalline solid that was homogeneous by TLC (CH_2Cl_2). Recrystallization from Et_2O gave 0.35 g (82%, two crops) of **42b** as a colorless crystalline solid: mp 169–170 °C; IR (KBr) 1659, 1600, 1450, 1380, 1263, 1203, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1 H), 7.94 (d, J = 7.9 Hz, 2 H), 7.87 (d, J = 7.9 Hz, 2 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.66–7.60 (m, 1 H), 7.55–7.35 (m, 7 H), 4.48 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 137.6, 136.7, 136.1, 134.8, 134.2, 134.0, 129.7, 129.1, 128.7, 128.5, 127.3, 127.1, 124.6, 122.8, 120.7, 115.0, 21.2. Anal. Calcd for $C_{22}H_{16}BrNO_3S$: C, 58.16; H, 3.55; Br, 17.59; N, 3.08; S, 7.06. Found: C, 58.24; H, 3.59; Br, 17.51; N, 3.06; S, 7.00.

2-Benzoyl-3-(hydroxymethyl)-1-(phenylsulfonyl)indole (42c). A stirred solution of **42b** (3.00 g, 6.60 mmol), anhydrous KOCHO (3.38 g, 40.2 mmol), and 18-crown-6 (123 mg) in MeCN (106 mL) was heated at reflux under Ar for 18 h. The suspension was filtered, concentrated in vacuo, digested with 5% MeOH in CH_2Cl_2 (200 mL), treated with Al_2O_3 (activity I neutral, 14.80 g), and stirred for 36 h under Ar. The suspension was filtered, the Al_2O_3 was washed with CH_2Cl_2 (100 mL), and the combined organic filtrate was concentrated in vacuo to give a slightly yellow oil was homogeneous by TLC (1:1 EtOAc/hexane). FC (1:1 EtOAc/hexane) gave 2.30 g (89%) of **42c** as colorless crystals. Recrystallization from Et_2O gave the analytical sample: mp 114–116 °C dec; IR (KBr) 3410, 1664, 1596, 1447, 1368, 1261, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30–7.22 (m, 14 H), 4.62 (s, 2 H), 2.25 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 189.5, 138.0, 136.5, 136.3, 136.2, 134.7, 134.0, 133.6, 129.5, 129.2, 128.9, 128.5, 128.2, 127.0, 124.6, 121.0, 115.1, 55.1. Anal. Calcd for $C_{22}H_{17}NO_4S$: C, 67.51; H, 4.38; N, 3.58; S, 8.19. Found: C, 67.35; H, 4.30; N, 3.56; S, 8.20.

3-Phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (8). A stirred solution of **42c** (0.175 g, 0.447 mmol) in dry THF (20 mL) was treated with $BF_3{\cdot}Et_2O$ (0.98 mL, 8.0 mmol) and heated at reflux for 2 h under Ar. The solvent was continuously dried by means of cycling though a Soxhlet extractor containing 4-Å molecular sieves. After 2 h the reaction was judged to be incomplete and an additional (0.46 mL, 3.7 mmol) portion of $BF_3{\cdot}Et_2O$ was added via syringe. The solution was heated at reflux for an additional 2 h, poured over ice (20 g), and treated with a solution of cold aqueous 3% NaOH (25 mL). The solution was then treated rapidly with CH_2Cl_2 (25 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (100 mL), dried (K_2CO_3), and concentrated in vacuo to give a yellow semisolid. RC (CH_2Cl_2) gave 85.0 mg (51%) of **8** as analytically pure colorless crystals: mp 148.5–149.5 °C; ^1H NMR ($CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 1 H), 7.86 (d, J = 7.3 Hz, 2 H), 7.52–7.28 (m, 8 H), 7.22 (t, J = 7.6 Hz, 2 H), 7.13 (t, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 146.3, 139.0, 135.5, 134.8, 130.1, 129.9, 128.3, 128.3, 128.2, 128.0, 127.8, 127.4, 127.3, 125.6, 124.8, 123.4, 122.0, 118.7. Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.76. Found: C, 70.57; H, 4.13; N, 3.68.

3-Ethyl-2-(hydroxybenzyl)-1-(phenylsulfonyl)indole (43). A stirred solution of **26** (8.00 g, 28.0 mmol) in dry THF (100 mL) was treated at −70 °C under Ar with PhLi (2.47 M in cyclohexane; 31 mmol). The mixture was stirred for 0.5 h and slowly warmed to rt over 0.5 h. The mixture was stirred at rt for 2 h, cooled to −65 °C, and treated with PhCHO (4.5 g, 42 mmol). The solution was warmed to rt over 0.5 h and stirred for 14 h. The solution was poured into saturated aqueous $NaHCO_3$ (250 mL) and extracted with CH_2Cl_2 (4 × 400 mL). The combined organic extracts were concentrated in vacuo, the resultant oil was digested with CH_2Cl_2 (500 mL), and the digest was stirred for 1 h with saturated aqueous sodium metabisulfite solution (200 mL). The organic layer was washed with H_2O (500 mL) and brine (500 mL), dried (K_2CO_3), and concentrated in vacuo to give a yellow oil that started to crystallize on standing. Benzene was added and, after crystallization was complete, the crystals were separated and the mother liquor was subjected to FC to give additional material. The combined yield of **43** was 7.93 14.5; MS m/z 391 (M^+). Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.62; H, 5.44; N, 3.58; S, 8.25.

2-Benzoyl-3-ethyl-1-(phenylsulfonyl)indole (44). A stirred solution of **43** (2.00 g, 5.11 mmol) in dry CH_2Cl_2 (60 mL) was treated with 8.11 g (93.3 mmol) of activated MnO_2. The suspension was heated at reflux for 16 h. The mixture was then cooled to rt and filtered. The residual solid was washed with CH_2Cl_2 (3 × 100 mL), transferred to a Soxhlet extractor, and subjected to continuous extraction with CH_2Cl_2 (400 mL) for 22 h. The combined organic extract was concentrated in vacuo to give 1.99 g (100%) of **44** as a pale yellow solid. Recrystallization from Et_2O gave 1.85 g (93%) of the analytical sample as colorless crystals: mp 142.5–143 °C; IR (KBr) 1664, 1604, 1453, 1378, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26–7.22 (m, 14 H), 2.67 (q, J = 7.5 Hz, 2 H), 1.14 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.5, 138.4, 136.6, 136.3, 133.8, 133.3, 133.0, 131.1, 130.3, 129.5, 128.7, 128.5, 127.2, 126.6, 124.3, 120.5, 115.5, 17.7, 14.6. Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60; S, 8.23. Found: C, 70.83; H, 4.94; N, 3.60; S, 8.26.

2-Benzoyl-3-(1-bromoethyl)-1-(phenylsulfonyl)indole (45). A stirred solution of **44** (3.84 g, 9.86 mmol), NBS (1.77 g, 9.94 mmol), and benzoyl peroxide (27 mg) in CCl_4 (70 mL) was heated at reflux under Ar for 3 h. The reaction mixture was cooled to 5 °C and the insoluble succinimide was removed by filtration and washed with CCl_4 (3 × 50 mL). The combined extract was concentrated in vacuo and the residue dried (25 Torr) to provide **45** as an off-white solid. Recrystallization from Et_2O/hexane provided 4.14 g (90%) of analytically pure **45** as colorless crystals: mp 112–114 °C; IR (KBr) 1673, 1603, 1454, 1381, 1263, 1187, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21–7.74 (m, 6 H), 7.66–6.89 (m, 8 H), 5.22 (q, J = 7.5 Hz, 1 H), 2.03 (d, J = 7.5 Hz, 3 H). Anal. Calcd for $C_{23}H_{18}BrNO_3S$: C, 58.98; H, 3.87; Br, 17.06; N, 2.99; S, 6.84. Found: C, 58.93; H, 3.88; Br, 17.04; N, 2.94; S, 6.85.

2-Benzoyl-3-(1-hydroxyethyl)-1-(phenylsulfonyl)indole (46). A solution of **45** (1.57 g, 3.86 mmol) in THF (50 mL) was treated with $NaHCO_3$ (0.392 g, 4.66 mmol) and H_2O (10 mL) at rt under Ar. The suspension was stirred at rt for 48 h. The solvent was partially removed in vacuo, and the residue was treated with CH_2Cl_2 (150 mL) and saturated aqueous $NaHCO_3$ (150 mL). The layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O (300 mL) and brine (300 mL), dried (K_2CO_3), and concentrated in vacuo to give a clear oil. Further drying (0.25 Torr) gave 1.29 g (97%) of **46** as a colorless foam. FC (2:1 hexane/EtOAc) and drying at 50 °C/0.1 Torr gave the analytical sample: mp 118 °C dec; IR (KBr) 3612, 3022, 1673, 1605, 1454, 1378, 1259, 1182 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22–7.75 (m, 6 H), 7.59–7.26 (m, 8 H), 4.99 (q, J = 6.0 Hz, 1 H), 2.41 (br s, 1 H), 1.42 (d, J = 6.0 Hz, 3 H); MS m/z 405 (M^+). Anal. Calcd for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45; S, 7.91. Found: C, 68.23; H, 4.78; N, 3.43; S, 7.85.

1-Methyl-3-phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (9). A stirred solution of **46** (1.13 g, 3.29 mmol) in dry benzene (60 mL) was heated at reflux under N_2 for 12 h. The solution was then cooled to rt and concentrated in vacuo. The residue was digested with CH_2Cl_2 (60 mL) and the organic solution was treated with saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 75 mL) and the combined organic extracts were washed with H_2O (150 mL) and brine (150 mL), dried (K_2CO_3), and concentrated in vacuo to give a yellow solid. FC gave analytically pure **9** (0.44 g, 41%) as colorless crystals: mp 157 °C dec; IR (KBr) 3068, 2922, 1675, 1455, 1370, 1186 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21–7.74 (m, 3 H), 7.54–6.75 (m, 11 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.8, 140.3, 136.8, 134.8, 133.4, 130.1, 128.4, 128.3, 127.8, 127.7, 127.5, 127.3, 126.5, 125.4, 124.3, 120.9, 120.2, 118.4, 13.5; MS m/z 387 (M^+). Anal. Calcd for $C_{23}H_{17}NO_3S$: C, 71.30; H, 4.42; N, 3.61; S, 8.27. Found: C, 71.21; H, 4.42; N, 3.58; S, 8.34.

2-Ethyl-1-(phenylsulfonyl)indole (47). To a stirred solution of LDA, prepared from diisopropylamine (0.73 g, 7.2 mmol) and *n*-BuLi (1.62 M in hexane, 6.72 mmol), in dry THF (13 mL) under Ar at −70 °C was added a solution of **20** (1.66 g, 6.45 mmol) in dry THF (13 mL). The mixture was stirred for 1.5 h, allowed to warm to rt over 15 h, cooled to −70 °C, and treated with EtI (1.24 g, 7.95 mmol) in dry THF (13 mL). The mixture was allowed to warm to rt, stirred for 14 h, poured over ice (60 g), and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were concentrated in vacuo, and the resultant oil was digested with CH_2Cl_2 (60 mL), washed with H_2O (60 mL) and brine (60 mL), dried (K_2CO_3), and concentrated in vacuo to give a yellow oil. The crude oil was passed through a silica pad (CH_2Cl_2), and then subjected to FC (1:1 CH_2Cl_2/hexane) to give 1.44 g (78%) of **47** which crystallized on standing. Recrystallization from Et_2O/hexane gave the analytical sample: mp 96–97.5 °C; IR (KBr) 2968, 1592, 1568, 1450, 1430, 1369, 1222, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28–8.04 (m, 1 H), 7.82–7.67 (m, 2 H), 7.51–7.13 (m, 5 H), 6.39 (s, 1 H), 3.03 (q, *J* = 7.5 Hz, 2 H), 1.32 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.7 139.1, 137.2, 133.5, 129.7, 129.1, 126.1, 123.8, 123.4, 120.1, 114.6, 107.8, 22.4, 13.0; MS *m/z* 285 (M^+), 144. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.21. Found: C, 67.46; H, 5.30; N, 4.90; S, 11.30.

3-Benzoyl-2-ethyl-1-(phenylsulfonyl)indole (48). A stirred suspension of $AlCl_3$ (5.50 g, 41.2 mmol) in dry CH_2Cl_2 (150 mL) at rt was treated with PhCOCl (2.91 g, 20.7 mmol) over 10 min under Ar. The solution was stirred for 15 min and then treated with a solution of **47** (1.97 g, 6.90 mmol) in CH_2Cl_2 (60 mL). The solution was stirred for 3 h and poured over ice (150 g), and the aqueous layer was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic extracts were washed with brine (500 mL), saturated $NaHCO_3$ (500 mL), H_2O (500 mL), and brine (2 × 500 mL), dried (K_2CO_3), and concentrated in vacuo. FC (CH_2Cl_2) gave 1.85 g (69%) of **48** as a clear colorless oil which crystallized on standing. Recrystallization from Et_2O/hexane gave the analytical sample: mp 130–131 °C; IR (neat) 1654, 1600, 1582, 1450, 1377, 1266, 1240, 1180, 1061 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41–8.27 (m, 1 H), 7.98–7.10 (m, 13 H), 3.16 (q, *J* = 7.5 Hz, 2 H), 1.32 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.9, 147.4, 138.7, 135.8, 134.1, 133.1, 129.4, 128.5, 128.3, 126.3, 124.7, 124.0, 120.6, 120.4, 114.9, 20.8, 15.9; MS *m/z* 389 (M^+), 248 (100), 105 (100), 77. Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60; S, 8.23. Found: C, 71.01; H, 4.97; N, 3.55; S, 8.20.

Reaction of Furoindole 3 with Benzyne. 5-(Phenylsulfonyl)-6,11-epoxy-6,11-dihydro-5*H*-benzo[*b*]carbazole (52). A mixture of **3** (133 mg, 0.448 mmol) and Mg (37.4 mg) in dry THF (7 mL) was heated to reflux under Ar with stirring. To this was added dropwise over 15 min a solution of *o*-bromofluorobenzene (87.4 mg, 0.499 mmol) in dry THF (6 mL). The mixture was refluxed for 3.25 h, cooled, treated with 5% aqueous NH_4Cl (1 mL), and poured into additional 5% NH_4Cl (100 mL). Extraction with CH_2Cl_2 and the usual workup gave a residue. FC (cyclohexane/CH_2Cl_2 1:1) gave 63.8 mg (38%) of **52** as an off-white solid, mp 164–166 °C dec, as well as 26.0 mg (20%) of **3**. Recrystallization from Et_2O/CH_2Cl_2/pentane (1:1:1) gave the analytical sample of **52**: mp 165.5 °C; IR (KBr) 1480, 1449, 1441, 1368, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57–8.05 (m, 3 H), 6.75–7.55 (m, 10 H), 6.31 (s, 1 H), 6.13 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 156.0, 148.5, 147.5, 139.8, 139.3, 137.7, 133.9, 129.0, 126.7, 125.7, 125.4, 124.5, 123.8, 121.0, 119.8, 119.7, 114.5, 81.4, 81.3; MS *m/z* 373 (M^+), 232 (100), 216, 204, 203, 176, 77; HRMS *m/z* 373.0744 (M^+, calcd 373.0773). Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75; S, 8.59. Found: C, 70.74; H, 4.05; N, 3.73; S, 8.52.

Deoxygenation of 52. 5*H*-Benzo[*b*]carbazole (54). A mixture of **52** (57.0 mg, 0.153 mmol), $NaBH_4$ (35 mg), and THF (6 mL) at 0–5 °C under N_2 was treated dropwise over 1 h with a solution of CF_3CO_2H (2.1 g) in dry THF (4 mL). Also added in portions over this 1-h period was additional $NaBH_4$ (100 mg). The mixture was allowed to warm to rt overnight and then poured into H_2O (100 mL) and extracted with CH_2Cl_2 (1 × 150 mL). To the aqueous layer was added saturated aqueous $NaHCO_3$ (100 mL), and this was extracted with additional CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (2 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo to give a residue. TLC indicated two products in about equal amounts, and analysis of the crude product by MS suggested that **53a** and **53b** were present. This crude product was dissolved in THF (5 mL) and MeOH (15 mL) and treated with 50% aqueous NaOH (3 mL) and H_2O (3 mL). The mixture was heated at reflux for 48 h, cooled, and acidified with concd HCl. Chloroform (75 mL) was added and the mixture was poured into saturated aqueous $NaHCO_3$ (150 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (4 × 25 mL) and benzene (1 × 30 mL). The combined organic extracts were washed with H_2O (1 × 40 mL) and brine (2 × 60 mL), dried (K_2CO_3), and concentrated in vacuo to give 38.8 mg of **54**, essentially homogeneous by TLC (fluorescent). FC (1:2 cyclohexane/CH_2Cl_2) gave 29.2 mg (88%) of **54** as a colorless solid, mp 285–288 °C. Recrystallization from benzene gave colorless plates, mp 332–333 °C dec (lit.[63] mp 330–331 °C). The UV spectrum was an exact match with the published spectrum:[64] UV (EtOH) λ_{max} 230, 264 (sh), 268, 282, 292, 317, 331, 373, 390 nm; ^1H NMR (360 MHz, DMSO-d_6) δ 11.21 (s, 1 H), 8.68 (s, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.06 (d, *J* = 7.8 Hz, 1 H), 8.00 (d, *J* = 8.5 Hz, 1 H), 7.86 (s, 1 H), 7.52–7.42 (m, 3 H), 7.40–7.33 (m, 1 H), 7.24–7.16 (m, 1 H); MS *m/z* 217 (M^+, 100), 216, 189, 163, 108, 94.

2,3-Dicarbomethoxy-1-methyl-4-phenyl-5-(phenylsulfonyl)-1,4-dihydrocarbazole 1,4-Endoxide (56). General Procedure for Cycloaddition Reactions. A stirred solution of **9** (75.0 mg, 0.194 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.11 g, 0.77 mmol) in dry benzene (10 mL) was heated at reflux for 12 h. The solution was then cooled to rt, concentrated in vacuo, and purified by RC (CH_2Cl_2) to give 101 mg (98%) of **56** as a colorless crystalline solid. Recrystallization from Et_2O gave the analytical sample as colorless crystals: mp 158 °C dec; IR (KBr) 1741, 1722, 1629, 1432, 1372, 1247, 1187, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 1 H), 7.63–7.25 (m, 13 H), 3.86 (s, 3 H), 2.71 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 162.9, 158.4, 157.7, 153.3, 144.3, 140.7, 138.4, 133.8, 133.4, 129.2, 129.0, 128.4, 128.0, 126.7, 125.4, 124.2, 124.1, 119.8, 115.4, 96.6, 90.2, 52.6, 52.3, 15.9. Anal. Calcd for $C_{31}H_{23}NO_7S$: C, 65.77; H, 4.38; N, 2.64; S, 6.05. Found: C, 65.69; H, 4.39; N, 2.61; S, 6.14.

2,3-Dicarbomethoxy-1-phenyl-5-(phenylsulfonyl)-1,4-dihydrocarbazole 1,4-Endoxide (55). This was prepared from **7** and DMAD by the general procedure described above. Recrystallization from Et_2O gave 0.124 g (70%) of **55** as colorless crystals: mp 115 °C dec; IR (KBr) 1726, 1642, 1433, 1372, 1312, 1249, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz), 7.75–7.68 (m), 7.59–7.42 (m), total integration 14 H, 6.47 (s, 1 H), 3.84 (s, 3 H), 3.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.9, 158.4, 158.4, 151.6, 140.2, 138.4, 137.4, 134.2, 133.0, 129.9, 129.4, 129.0, 128.6, 127.0, 125.2, 125.2, 124.3, 120.3, 114.8, 99.2, 82.9, 52.5, 52.2.

***N*-Phenyl-1,4-epoxy-1-phenyl-1,2,3,4-tetrahydro-5-(phenylsulfonyl)-2,3-carbazoledicarboximides 57a,b.** These were prepared from **7** and *N*-phenylmaleimide by the general procedure described above. RC (CH_2Cl_2) of the crude reaction mixture effected separation of the exo–endo adducts. For **57a** (54%): ^1H NMR ($CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 7.7 Hz, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H), 7.61–7.30 (m, 11 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.3 Hz, 2 H), 6.27 (s, 1 H), 3.39, 3.32 (AB q, *J* = 6.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.5, 171.8, 146.8, 140.7, 137.3, 134.5, 133.5, 131.6, 130.0, 129.6, 129.0, 128.7, 128.6, 128.5, 126.9, 126.4, 125.8, 125.5, 124.4, 122.9, 120.4, 114.7, 93.2, 79.4, 52.6, 52.6.

For **57b** (17%): ^1H NMR ($CDCl_3$) δ 8.02 (d, *J* = 6.9 Hz, 2 H), 7.94 (d, *J* = 7.5 Hz, 2 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.58–7.39 (m, 6 H), 7.30–7.23 (m, 3 H), 7.19–7.06 (m, 4 H), 6.36 (d, *J* = 5.3 Hz, 1 H), 6.16 (ddd, *J* = 6.8, 1.3, 1.3 Hz, 2 H), 4.29 (dd, *J* = 7.7, 5.3 Hz, 1 H), 4.10 (d, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.9, 144.4, 140.7, 137.2, 135.4, 134.3, 132.1, 130.7, 129.4, 129.2, 128.8, 128.6, 128.2, 127.2, 127.1, 125.7, 125.5, 124.7, 123.6, 120.6, 114.6, 92.4, 78.4, 52.2, 51.3.

***N*-Phenyl-1,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydro-5-(phenylsulfonyl)-2,3-carbazoledicarboximides 58a,b.** These were prepared from **9** and *N*-phenylmaleimide by the general procedure described above. RC (CH_2Cl_2) of the crude reaction mixture effected separation of the exo–endo adducts. For

(63) (a) Buu-Hoi, N. P.; Saint-Ruf, G. *J. Chem. Soc. C* **1966**, 924. (b) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1969**, *25*, 227.
(64) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1952**, 1658.

58b (76%): IR (KBr) 1717, 1499, 1449, 1378, 1185, 1058, 963, 736, 710, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1 H), 7.63–7.01 (m, 16 H), 6.18 (d, J = 7.4 Hz, 2 H), 4.29, 3.71 (AX q, J = 7.7 Hz, 2 H), 2.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 171.1, 145.3, 141.5, 137.6, 135.9, 133.9, 133.6, 130.6, 129.1, 129.0, 128.8, 128.6, 128.1, 127.8, 126.8, 125.8, 125.6, 124.6, 122.9, 120.3, 115.5, 93.1, 85.9, 55.5, 55.3, 18.6. The exo adduct (2%) was identified by high sensitivity ^1H NMR. Analysis of the soft cuts (22%) by ^1H NMR demonstrated the presence of nearly pure endo adduct. Anal. Calcd for $C_{33}H_{25}N_2O_5S$: C, 70.70; H, 4.32. Found: C, 70.61; H, 4.39.

3-Carbethoxy-1,4-dimethyl-9-(phenylsulfonyl)carbazole (59). A stirred solution of **4** (196 mg, 0.603 mmol) in dry CH_2Cl_2 (6 mL) was treated at 0 °C under Ar with a suspension of $AlCl_3$ (80.6 mg, 6.0 mmol) and ethyl acrylate (0.09 mL, 0.83 mmol) in CH_2Cl_2 (4 mL). The mixture turned red and was stirred for 3 min, poured over ice (200 g), and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were washed with brine (250 mL), H_2O (250 mL), and brine (250 mL), dried (K_2CO_3), and concentrated in vacuo to afford a brown oil that began to crystallize. The oil was subjected to RC to give 155 mg (63%) of **59** as a crystalline solid, which gave the following after recrystallization from Et_2O/hexane: mp 136–136.5 °C; IR (KBr) 1714, 1574, 1449, 1362, 1209, 1178, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1 H), 7.85 (d, J = 9.0 Hz, 1 H), 7.80 (s, 1 H), 7.44 (t, J = 9.0 Hz, 1 H), 7.34–7.26 (m, 2 H), 7.13–7.05 (m, 4 H), 4.43 (q, J = 7.5 Hz, 2 H), 2.84 (s, 3 H), 2.78 (s, 3 H), 1.45 (t, J = 7.5 Hz, 3 H).

3-Carbethoxy-1,4-dimethylcarbazole (60). A stirred solution of **59** (49.1 mg, 0.120 mmol) in dry degassed EtOH (4 mL) at 0 °C was treated with $NaHPO_4$ (22.1 mg, 0.155 mmol) and 6% Na/Hg amalgam (236 mg). The suspension was stirred for 4 h and treated with additional 6% Na/Hg amalgam (119 mg). The suspension was stirred for 2 h and filtered through Celite, and the cake was washed with EtOH (3 × 15 mL) and THF (3 × 15 mL). The combined filtrate was concentrated in vacuo and subjected to RC to afford 29.0 mg (91%) of **60** as colorless crystals which were recrystallized from Et_2O/hexane: mp 152.5–153.0 °C (lit.[53] mp 150–152 °C); UV (EtOH) λ_{max} 239, 246.5, 274, 310 (sh), 321 (sh), 336 (sh) (literature[53] reports 245, 275, 310, 335). Literature[53] values for 2-carbethoxy-1,4-dimethylcarbazole: mp 118–120 °C; UV (EtOH) λ_{max} 250, 305, 352.

***N*-(*p*-Methoxybenzyl)-2-piperidone (66b).** To a suspension of NaH (97%, 1.10 g, 45.8 mmol) in dry Et_2O (50 mL) at −78 °C was added dropwise with mechanical stirring a solution of *p*-methoxybenzyl alcohol (5.70 mL, 45.5 mmol) in Et_2O (50 mL). The solution was stirred for 30 min; then a solution of freshly distilled *p*-TsCl (8.70 g, 45.6 mmol) in Et_2O (50 mL) was added. The thick mixture was stirred an additional 1 h at −78 °C and then added dropwise to a solution of the sodium salt of δ-valerolactam (prepared from **65** (90%, 5.01 g, 45.5 mmol) and NaH (97%, 1.25 g, 52.1 mmol) at 0 °C) in dry Et_2O (250 mL) at −78 °C. The cooling bath was removed and the solution was stirred for an additional 12 h and then poured into H_2O (300 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 200 mL), and the combined organic extract was washed with saturated aqueous $NaHCO_3$ (300 mL), H_2O (2 × 300 mL) and brine (2 × 300 mL), dried (Na_2SO_4), and concentrated to give an oil. Distillation yielded 7.57 g (68%) of **66b** as a colorless liquid: bp 135–145 °C/0.2 Torr; IR (neat) 3080, 3010, 2950, 2880, 2850, 1635, 1515, 1495, 1250, 1175, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (d, 2 H, J = 8.7 Hz), 6.75 (d, 2 H, J = 8.7 Hz), 4.46 (s, 2 H), 3.69 (s, 3 H), 3.20 (m, 2 H), 2.37 (m, 2 H), 1.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.2, 158.5, 130.1, 129.0, 113.5, 54.8, 54.8, 49.0, 46.6, 32.1, 22.8, 21.0.

***N*-(*p*-Methoxybenzyl)-5,6-dihydro-2-pyridone (68b).** To a stirred solution of LDA prepared from diisopropylamine (9.40 mL, 67.1 mmol) and *n*-BuLi (2.30 M in hexane, 29.0 mL, 66.7 mmol) in THF (75 mL) at −78 °C was added a solution of **66b** (7.01 g, 32.0 mmol) in THF (75 mL) dropwise over 30 min. The solution was stirred for 35 min; then a solution of PhSeCl (6.12 g, 32.0 mmol) and HMPA (7.0 mL, 41 mmol) in THF (75 mL) was added dropwise over 30 min. The orange solution was kept cold for 30 min and then allowed to warm to rt and poured into H_2O (500 mL). The aqueous solution was extracted with Et_2O (3 × 100 mL); then the organic extract was washed with 10% NaOH (300 mL), H_2O (300 mL), 10% HCl (300 mL), H_2O (300 mL), and brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo to give an amber oil. Purification by FC (9:1 hexane/Et_2O, then 1:1 hexane/Et_2O) yielded 11.31 g (95%) of **67b**. This product was dissolved in CH_2Cl_2 (125 mL) and added to a stirred solution of *m*-CPBA (~50%, 14 g) in CH_2Cl_2 (125 mL) at 0 °C. The mixture was allowed to warm slowly to rt over 12 h and then poured into saturated aqueous $NaHCO_3$ (300 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), H_2O (200 mL), and brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to give an amber oil. Distillation yielded 5.14 g (78%) of **68b** as a colorless liquid, bp 180–185 °C/1.0 Torr, that crystallized as white needles after drying in vacuo: mp 45–46 °C; IR (neat) 3000, 2940, 2830, 1660, 1605, 1505, 1235, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, 2 H, J = 8.7 Hz), 6.79 (d, 2 H, J = 8.7 Hz), 6.47 (dt, 1 H, J = 9.7, 4.1 Hz), 5.91 (d, 1 H, J = 9.8 Hz); 4.47 (s, 2 H), 3.71 (s, 3 H), 3.22 (m, 2 H), 2.23 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 158.7, 140.2, 129.7, 128.6, 114.5, 112.9, 55.7, 54.4, 48.8, 23.9; MS m/z 217 (M^+, 100), 202, 186, 121, 96. Anal. Calcd for $C_{13}H_{15}NO_2$ + 0.25 H_2O: C, 70.41; H, 7.04; N, 6.31. Found: C, 70.96; H, 7.07; N, 6.27.

2-(*p*-Methoxybenzyl)-3,4-dihydro-5,11-dimethyl-1-oxopyrido[4,3-*b*]carbazole (70b). To a solution of **68b** (0.50 g, 2.3 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added freshly prepared TMSOTf[65] (0.55 mL, 2.8 mmol). The colorless solution was stirred at 0 °C for 1 h and then cooled to −40 °C, and **4**[26c] (0.50 g, 1.5 mmol) was added and the mixture was stirred while being warmed to rt over a period of 16 h. The purple colored solution was then diluted with CH_2Cl_2 to 25 mL and added to saturated aqueous $NaHCO_3$ (25 mL), and the resultant solution was stirred for 3 h. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extract was washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to give a tan solid. FC (CH_2Cl_2, then 1:1 CH_2Cl_2/EtOAc) yielded 0.48 g (89%) of **70b** as an off-white solid. Recrystallization from CH_2Cl_2/hexane gave the analytical sample: mp 235–236 °C dec; IR ($CHCl_3$) 3660, 3020, 2950, 2850, 1640, 1600, 1510, 1420, 1390, 1325, 1240, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.78 (s, 1 H), 8.17 (d, 1 H, J = 7.9 Hz), 7.47 (d, 1 H, J = 8.1 Hz), 7.31 (m, 1 H), 7.23 (d, 2 H, J = 8.6 Hz), 7.13 (m, 1 H), 6.79 (d, 2 H, J = 8.6 Hz), 4.68 (s, 2 H), 3.71 (s, 3 H), 3.39 (m, 2 H), 3.16 (s, 3 H), 2.86 (m, 2 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.3, 158.7, 140.4, 140.1, 135.1, 135.0, 130.2, 129.1, 124.8, 124.5, 123.0, 122.9, 121.3, 120.6, 119.3, 113.8, 112.6, 110.7, 55.1, 49.3, 44.7, 26.8, 18.6, 12.9; MS m/z 384 (M^+, 100), 369, 276, 263, 235, 207, 192, 121, 91, 77; UV (95% EtOH) λ_{max} 240, 250, 270, 282 nm. Anal. Calcd for $C_{25}H_{24}N_2O_2$ + H_2O: C, 74.60; H, 6.51; N, 6.96. Found: C, 75.65; H, 6.11; N, 7.29.

2-(*p*-Methoxybenzyl)-1,2,3,4-tetrahydro-5,11-dimethylpyrido[4,3-*b*]carbazole (72). To a solution of **70b** (0.1051 g, 0.274 mmol) in THF (15 mL) was added LAH (0.013, g 0.34 mmol). After the initial exothermic reaction subsided, the mixture was refluxed for 3 h and then cooled, diluted to 50 mL with CH_2Cl_2, and poured into ice–H_2O (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and adsorbed onto silica gel. FC (1:1 CH_2Cl_2/EtOAc) yielded 0.0791 g (78%) of **72** as a tan solid: ^1H NMR (DMSO-d_6) δ 10.94 (s, 1 H), 8.10 (d, 1 H, J = 8.0 Hz), 7.48 (d, 1 H, J = 8.0 Hz), 7.33 (m, 1 H), 7.28 (d, 2 H, J = 8.5 Hz), 7.10 (m, 1 H), 6.90 (d, 2 H, J = 8.5 Hz), 3.74 (s, 3 H), 3.65 (s, 2 H), 3.62 (s, 2 H), 2.82 (m, 2 H), 2.63 (m, 2 H), 2.55 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 158.2, 140.2, 137.9, 130.4, 130.2, 129.9, 125.3, 124.3, 123.8, 123.5, 122.0, 118.9, 118.1, 114.5, 113.6, 110.6, 79.2, 61.6, 54.9, 49.7, 27.7, 14.8, 12.7; MS m/z 370 (M^+), 369, 355, 262, 248, 247, 221 (100), 204, 121.

Ellipticine (63). A solution of **72** (0.0316 g, 0.110 mmol) and 10% Pd/C (0.0046 g) in decalin (2 mL) was refluxed for 24 h and then filtered through a pad of filter cel. The filter pad was washed well with EtOAc and the solution adsorbed onto silica gel. FC initially with EtOAc to remove the starting material (0.0214 g) and then 7:3 EtOAc/THF yielded 0.0053 g (18% yield, 78% based on unrecovered starting material) of **63** that was identical with an authentic sample of ellipticine by TLC, IR, and UV.

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A Versatile and Efficient Construction of the 6*H*-Pyrido[4,3-*b*]carbazole Ring System. Syntheses of the Antitumor Alkaloids Ellipticine, 9-Methoxyellipticine, and Olivacine and Their Analogues

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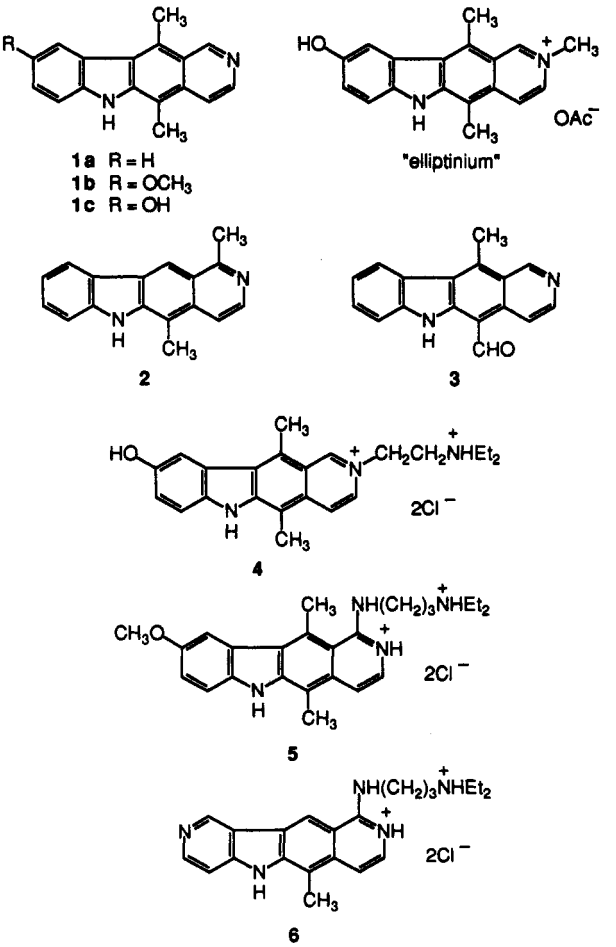
A general and efficient synthesis of the 6*H*-pyrido[4,3-*b*]carbazole ring system is described, in which the key steps are (1) regioselective acylation of a 2-lithio-1-(phenylsulfonyl)indole (**14**) with 3,4-pyridinedicarboxylic acid anhydride (**10**), (2) cyclization of the deprotected keto acid **17** to keto lactam **19** with acetic anhydride, and (3) the addition of methyllithium to give, after reduction of the intermediate diol **23** with sodium borohydride, the target ring system. In this fashion, ellipticine (**1a**), 9-methoxyellipticine (**1b**), and 9-hydroxyellipticine (**1c**) were synthesized in excellent overall yields from indole. The use of Superhydride, in place of 1 equiv of methyllithium, provided a synthesis of olivacine (**2**), and the use of phthalic anhydride in the sequence allowed for the preparation of 6,11-dimethylbenzo[*b*]carbazole (**48**). The overall yields of ellipticine (**1a**) (54%) and 9-methoxyellipticine (**1b**) (47%) in six steps from their respective indoles represent one of the most efficient syntheses of these antitumor alkaloids.

The *Ochrosia* and *Aspidosperma* 6*H*-pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), 9-hydroxyellipticine (**1c**), and olivacine (**2**) are potent antitumor agents, and "elliptinium" is used clinically as a drug to treat advanced breast cancer, myeloblastic leukemia, and some solid tumors.[1] More recently, 13-oxoellipticine (**3**) was isolated from a *Strychnos* tree.[1a] Recent years have witnessed the development of second-generation ellipticine-derived antitumor agents, including the new clinical candidates datelliptium (**4**), retelliptine (**5**), and pazelliptine (**6**).[1a] Interestingly, these compounds exhibit multimodal action on DNA: (a) intercalation, (b) metabolism and subsequent covalent binding, (c) generation of oxygen radicals, and (d) inhibition of topoisomerase II.[1a-d]

In previous papers, we have described in full our approach to the syntheses of the isomeric 10*H*-pyrido[3,4-*b*]carbazole (**7**)[2] and 10*H*-pyrido[2,3-*b*]carbazole (**8**)[3] ring systems. We now wish to disclose the complete details of our construction of the 6*H*-pyrido[4,3-*b*]carbazole (ellipticine) ring system.[4,5]



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