washed with brine (25 mL), dried ($MgSO_4$), and concentrated to an oil. The oil was chromatographed (silica gel, 25% ethyl acetate in hexanes) to give 570 mg (65%) of a 60:40 mixture of cis and trans glycidic esters, **11** and **7**, respectively: ^1H NMR (300 MHz, $CDCl_3$) δ 1.17–1.23 (3 H, 2 t), 1.69–1.96 (2 H, m), 3.14–3.42 (2 H, m), 3.23, 3.24, 3.26, 3.28 (6 H, 4 s), 4.08–4.18 (2 H, 2 q), 4.4–4.5 (1 H, 2 dd).

The mixture of esters (50 mg) was converted to the cis and trans tetrahydropyridazines **12** and **2** by using the method used for the chiral ester. The mixture of products was chromatographed (Sigmacell microcrystalline cellulose Type 50, ethanol–water, 8:1) to give the partially purified *cis*-tetrahydropyridazine **12**: ^1H NMR (300 MHz, D_2O) δ 2.03 (1 H, m, J = 2.9, 5.0, 21.5 Hz), 2.42 (1 H, m, J = 1.95, 5.3, 7.3, 21.5 Hz), 3.36 (1 H, dd, J = 1.95, 3.90 Hz), 4.22 (1 H, m, J = 1.2, 3.9, 5.0, 7.3 Hz), 6.6 (1 H, m, J = 1.2, 2.9, 5.3 Hz); R_f = 0.4 (silica gel, ethanol–1 N ammonium acetate buffer pH = 6.0, 5:1).

L-*trans*-3-Hydroxyproline (13). Methyl 5,5-dimethoxypent-2(*E*)-enoate 2(*R*),3(*S*)-oxide (**7**) (100 mg, 0.53 mmol) was dissolved in 20% aqueous methanol (4 mL), treated with potassium carbonate (81 mg, 0.59 mmol), and stirred for 2 h. The reaction mixture was then concentrated to give the potassium salt of the glycidic acid: ^1H NMR (300 MHz, D_2O) δ 1.71 (1 H, ddd, J = 5.6, 6.7, 14.5 Hz), 1.90 (1 H, ddd, J = 4.5, 5.6, 14.5), 2.96 (1 H, ddd, J = 2.1, 4.5, 6.7 Hz), 3.09 (1 H, d, J = 2.1 Hz), 3.26 (3 H, s), 3.27 (3 H, s), 4.55 (1 H, dd, J = 5.6, 5.6 Hz). The residue was dissolved in concentrated ammonia (37%, 3 mL), transferred to a Fisher-Porter tube, sealed, and heated at 40 °C for 15 h. The mixture was concentrated under vacuum to give a single product, the β-hydroxyamino acid **14**, by NMR: ^1H NMR (300 MHz, D_2O) δ 1.59 (2 H, pseudo t, J = approx. 6 Hz), 3.21 (3 H, s), 3.21 (3 H, s), 3.82 (1 H, dd, J = 4.6, 5.8 Hz), 3.90 (1 H, pseudo d, J = 4.6 Hz), 4.50 (1 H, dd, J = approx. 6 Hz); ^{13}C NMR (22.49 MHz, D_2O) δ 36.29 (t), 54.05 (q), 54.59 (q), 62.45 (d), 70.32 (d), 103.81 (d), 178.36 (s). The residue was dissolved in 50% aqueous ethanol (2 mL) and transferred to a gas burning tube containing a stirbar. A slow steady stream of hydrogen was bubbled through the mixture, which was then titrated to pH = 1.5 with trifluoroacetic acid and treated with Adam's catalyst (PtO_2, 10 mg). The reaction was stirred rapidly for 15 h at room temperature. TLC (silica gel, *n*-BuOH–AcOH–H_2O, 4:1:1, detected by chlorine:starch–iodide) showed formation of a single new product. The mixture was then titrated to pH = 7.0 (1 N KOH), filtered through a Celite pad, concentrated under vacuum, and chromatographed through weak anion (DEAE-Sephadex, OH^- form) and weak cation (IONAC, CGC-270, H^+ form) exchange resins to give 60 mg (87%) of the salt-free L-*trans*-3-hydroxyproline (**13**): ^1H NMR (300 MHz, D_2O–TFA) δ 1.7 (2 H, m), 3.15 (2 H, m), 3.92 (1 H, d, J = 2.2 Hz) 4.36 (1 H, m, J = 2.2 Hz); ^{13}C NMR (22.49 MHz, D_2O–TFA) δ 32.30, 44.99, 69.66, 74.61.

Registry No. 1, 75580-37-9; (3*S*,4*S*)-**2**, 77421-35-3; (±)-**2**, 120851-22-1; **3**·K, 120828-87-7; **4**, 40156-61-4; **5**, 61752-18-9; **6**, 120924-97-2; (2*R*,3*S*)-**7**, 120789-95-9; (±)-**7**, 120851-23-2; **8**, 120789-96-0; **9**, 120789-97-1; **10**, 120789-98-2; **11**, 120851-20-9; **12**, 120851-21-0; **13**, 4298-08-2; **14**, 120789-99-3; $OHCCH_2CH(OMe)_2$, 19060-10-7; $(MeO)_2P(O)CH_2COOMe$, 5927-18-4; $BrCH_2COOEt$, 105-36-2.

Metalated Heterocycles in the Synthesis of Ellipticine Analogues. A New Route to the 10*H*-Pyrido[2,3-*b*]carbazole Ring System

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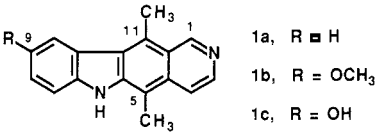
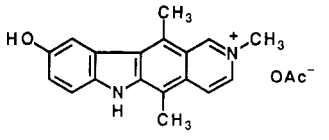
A synthesis of the 10*H*-pyrido[2,3-*b*]carbazole ring system is described, in which the key steps are regiospecific acylation of a 2-lithio-1-(phenylsulfonyl)indole (**7**) with 2,3-pyridinedicarboxylic anhydride (**8**), cyclization of the deprotected keto acid **10** to keto lactam **11** with acetic anhydride, and the addition of methyllithium to give, after reduction of the diol **12** with sodium borohydride, the target ring system. In this fashion, 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**3**) and the corresponding 7-methoxy (**4**) and 8-methoxy (**5**) derivatives were synthesized.

The 6*H*-pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), and related synthetic derivatives display pronounced anticancer activity in several animal and human tumor systems.[2] A derivative of 9-hydroxyellipticine (**1c**), namely, 2-methyl-9-hydroxyellipticinium acetate (**2**) ("elliptinium"), is currently undergoing extensive clinical trials, particularly in Europe, for the treatment of metastatic breast cancer, myeloblastic leukemia, and some solid tumors.[3] Moreover, these compounds exhibit multimodal action on DNA: (a) intercalation, (b) metabolism and subsequent covalent binding, (c) generation of oxygen radicals, and (d) the inhibition of topoisomerase II.[2a]



1a, R = H
1b, R = OCH_3
1c, R = OH



2

Consequently, since the initial discovery of the antitumor properties of the ellipticine alkaloids,[4] synthetic activity involving this ring system has been vigorous and unabated.[5,6]

(1) Recipient of the Dartmouth College Chandler T. White Prize for undergraduate research.

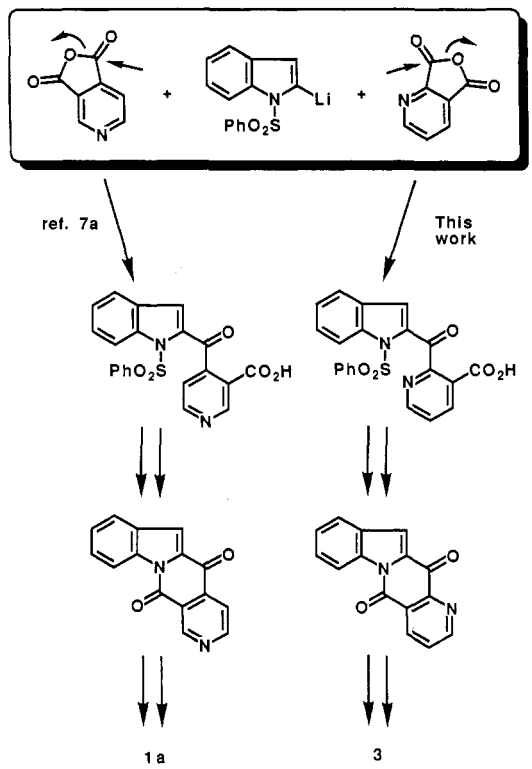
(2) For recent reviews, see: (a) Auclair, C. *Arch. Biochem. Biophys.* **1987**, *259*, 1. (b) Suffness, M.; Cardell, G. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. XXV, p 1. (c) Reference 4a.

(3) (a) Rouesse, J. G.; LeChevalier, T.; Caille, P.; Mondesir, J. M.; Garnier, H. S.; Levin, F. M.; Spielmann, M.; DeJager, R.; Amiel, J. L. *Cancer Treat. Rep.* **1985**, *69*, 707. (b) Caille, P.; Mondesir, J. M.; Droz, J. P.; Kerbrat, P.; Goodman, A.; Ducret, J. P.; Theodore, C.; Spielman, M.; Rouesse, J.; Amiel, J. L. *Cancer Treat. Rep.* **1985**, *69*, 901. (c) Sternberg, C. N.; Yagoda, A.; Casper, E.; Scoppetuolo, M.; Scher, H. I. *Anticancer Res.* **1985**, *5*, 415. (d) Einzig, A. I.; Gralla, R. J.; Leyland-Jones, B. R.; Kelsen, D. P.; Cibas, I.; Lewis, E.; Greenberg, E. *Cancer Invest.* **1985**, *3*, 235. (e) Reference 2a.

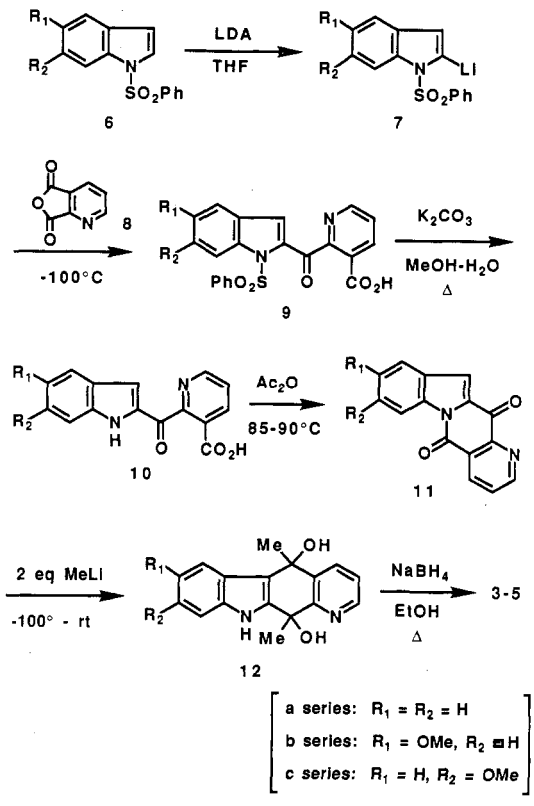
(4) (a) Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715. (b) Svoboda, G. H.; Poore, G. A.; Montfort, M. L. *J. Pham. Sci.* **1968**, *57*, 1720.

0022-3263/89/1954-3264$01.50/0

Scheme I

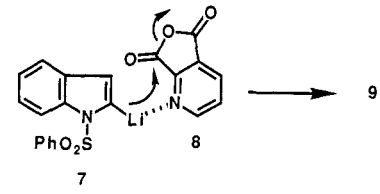


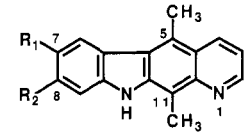
Scheme II



However, in contrast to synthetic and structure–activity studies focused on 6*H*-pyrido[4,3-*b*]carbazoles, very little attention has been directed towards the isomeric pyridocarbazoles.[5] In our ongoing program to develop efficient and general syntheses of pyridocarbazoles,[7] we describe herein a new approach to the construction of the pyrido[2,3-*b*]carbazole ring system,[8] exemplified by syntheses of the ellipticine analogues 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**3**), 7-methoxy-5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**4**), and 8-methoxy-5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**5**).

Scheme III





3, $R_1 = R_2 = H$

4, $R_1 = OCH_3$, $R_2 = H$

5, $R_1 = H$, $R_2 = OCH_3$

Our synthetic strategy parallels that which we devised to fashion ellipticine (**1a**),[7a] and both strategies are outlined in Scheme I. One obvious attractive feature of these synthetic routes is that a 2-lithioindole is common to both, and each approach is predicated on the regioselective acylation of this 2-lithioindole with a pyridinedicarboxylic anhydride (Scheme I).

Results and Discussion

Synthesis of 5,11-Dimethyl-10*H*-pyrido[2,3-*b*]carbazole (3). Our synthesis of **3** is shown in Scheme II. Indole was converted to 1-(phenylsulfonyl)indole (**6a**) in 91% yield as described earlier (*n*-BuLi; $PhSO_2Cl$).[9] Regiospecific C-2-lithiation of **6a** with lithium diisopropylamide (LDA) (THF, −70 → 20 °C, 3 h) followed by the rapid addition at −100 °C of 2,3-pyridinedicarboxylic anhydride (**8**)[10] gave keto acid **9a** in 83% yield. That this acylation is apparently regiospecific in the desired sense

(5) For reviews, see: (a) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. (b) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277. (c) Hewlins, M. J. E.; Oliveira-Campos, A.-M.; Shannon, P. V. R. *Synthesis* **1984**, *289*. (d) Barone, R.; Chanon, M. *Heterocycles* **1981**, *16*, 1357. (e) Sainsbury, M. *Synthesis* **1977**, 437.

(6) For recent synthetic efforts, see: (a) Langendoen, A.; Koomen, G.-J.; Pandit, U. K. *Heterocycles* **1987**, *26*, 91. (b) Ross, B. S.; Archer, S. *Tetrahedron Lett.* **1986**, *27*, 5343. (c) Wijsmuller, W. F. A.; Wanner, M. J.; Koomen, G.-J.; Pandit, U. K. *Heterocycles* **1986**, *24*, 1795. (d) Narasimhan, N. S.; Dhavale, D. D. *Ind. J. Chem.* **1986**, *25B*, 12. (e) Nguyen, C. H.; Bisagni, E.; Lhoste, J.-M. *Can. J. Chem.* **1986**, *64*, 545. (f) Archer, S.; Ross, B. S.; P.-Matoccia, L.; Cioli, D. *J. Med. Chem.* **1987**, *30*, 1204. (g) Zee, S.; Su, H. *J. Chin. Chem. Soc.* **1987**, *34*, 135. (h) Sainsbury, M.; Smith, A. D.; Vong, K. K.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans 1* **1988**, 2945. (i) Larue, L.; Rivalle, C.; Muzard, G.; Paoletti, C.; Bisagni, E.; Paoletti, J. *J. Med. Chem.* **1988**, *31*, 1951. (j) Honda, T.; Kato, M.; Inoue, M.; Shimamoto, T.; Shima, K.; Nakanishi, T.; Yoshida, T.; Noguchi, T. *J. Med. Chem.* **1988**, *31*, 1295. (k) Hogan, I.; Jenkins, P.; Sainsbury, M. *Tetrahedron Lett.* **1988**, *29*, 6505.

(7) (a) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2810. (b) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690. (c) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 3831. (d) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518. (e) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451. (f) Obaza-Nutaitis, J. A.; Gribble, G. W. *J. Nat. Prod.* **1986**, *49*, 449.

(8) For the only other syntheses of this ring system, see: (a) Bergman, J.; Carlsson, R. *Tetrahedron Lett.* **1977**, 4663. (b) Bergman, J.; Carlsson, R. *Tetrahedron Lett.* **1978**, 4051. (c) Ashcroft, W. R.; Beal, M. G.; Joule, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 994. (d) Osman, A.; Hammam, A. S.; Khalil, Z. H.; Yanni, A. S. *Ind. J. Chem.* **1982**, *21B*, 325.

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

(10) This can be prepared from the commercially available 2,3-pyridinedicarboxylic acid (quinolinic acid) using the procedure of Dox, A. W. *J. Am. Chem. Soc.* **1915**, *37*, 1948. The anhydride **8** is also commercially available. We thank Ruetgers-Nease Chemical Co. for a gift of the diacid.

was indicated by the absence of the isomeric keto acid by thin-layer chromatography (TLC) and ^{13}C NMR spectroscopy. This contrasts with the reaction of **7a** with 3,4-pyridinedicarboxylic anhydride which leads to a 92:8 ratio of keto acids.[7a] The regiospecificity that is observed in the present case (**7a** + **8** → **9a**) may reflect prior nitrogen–lithium complexation, resulting in a "directed" acylation pathway (Scheme III), analogous to pyridine-directed deprotonation by alkyllithium reagents, examples of which are known.[11]

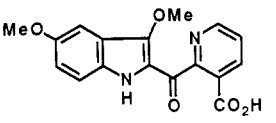
Although we were confident that the ring opening of anhydride **8** had proceeded in the desired fashion (→ **9a**), this fact could not be proved until the completion of the synthesis (since **3** is a known compound).

Cleavage of the benzenesulfonyl protecting group in **9a** was achieved with potassium carbonate (MeOH–H_2O, 3:1, reflux, 5 h) to give keto acid **10a** in essentially quantitative yield.[12] This was treated with hot acetic anhydride (85–90 °C, 21 h) to effect cyclization to the keto lactam **11a**, isolated as greenish golden crystals in 84% yield. The structure assigned to **11a** is fully supported by spectral and analytical data. Noteworthy is the ultraviolet spectrum of **11a**, which, upon the addition of hydroxide, changes to an ultraviolet spectrum of keto acid **10a**, as expected for an *N*-acylindole.[14]

Following our earlier protocol for transforming such keto lactams into pyridocarbazoles in essentially one maneuver,[7a] we treated keto lactam **11a** with methyllithium (2 equiv, −100 °C, THF) to afford a mixture of diols **12a**, which, without purification, was treated with sodium borohydride (EtOH, reflux, 25 h) to afford 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**3**) in 96% yield from **11a**. This material was identical with a sample of **3** synthesized by Bergman.[8a,b] The overall yield of **3** from indole is an extremely gratifying 60%.

Syntheses of Methoxy Derivatives 4 and 5. Prompted by the extraordinary biological activity of the A-ring-oxygenated ellipticine derivatives (e.g., **2**), we sought to extend our methodology to the syntheses of methoxy derivatives **4** and **5**. Our syntheses of **4** and **5** are also summarized in Scheme II.

For the synthesis of **4**, the required 5-methoxyindole is prepared by the procedure of Batcho and Leimgruber.[15] The subsequent *N*-benzenesulfonylation reaction to give **6b** can be performed either in the usual manner (*n*-BuLi; $PhSO_2Cl$)[9,16] in 84% yield, or, somewhat more conveniently, using a phase-transfer method[17] to give **6b** in 88% yield. Regioselective C-2 lithiation of **6b** with LDA followed by the addition of pyridine anhydride **8** gives keto acid **9b** in 82% yield. In contrast to the deprotection of **9a**, base-catalyzed hydrolysis of **9b** gives rise to the desired keto acid **10b** and a small amount of what is presumably the 3-methoxyindole keto acid **13** (MS, NMR). This



13

apparent nucleophilic conjugate addition to the indole 3-position was not completely unexpected.[7a,18] Because this impurity **13** proved to be difficult to remove from **10b**, we converted crude **10b** to keto lactam **11b** with hot acetic anhydride in 79% yield. Crystallization gave pure **11b**. The synthesis of **4** was completed by treating keto lactam **11b** with methyllithium followed by sodium borohydride. In this fashion, 5,11-dimethyl-7-methoxy-10*H*-pyrido[2,3-*b*]carbazole (**4**) was obtained in 33% purified yield from keto lactam **11b**.

For the synthesis of **5**, we prepared 1-(phenylsulfonyl)-6-methoxyindole (**6c**) from 2-(3-methoxyanilino)acetaldehyde diethyl acetal in 81% yield as previously described.[7e] The standard C-2 indole lithiation protocol and treatment of the resulting **7c** with pyridine anhydride **8** gave keto acid **9c** in 77% yield (Scheme II). Base cleavage of the *N*-benzenesulfonyl group gave **10c** in 96% yield (74% after recrystallization). Acetic anhydride treatment of keto acid **10c** effected cyclization in the usual manner to afford keto lactam **11c** in 96% yield. The synthesis of **5** was completed by treating keto lactam **11c** with methyllithium to give the diol **12c**, followed by exposure to sodium borohydride, which gave 5,11-dimethyl-8-methoxy-10*H*-pyrido[2,3-*b*]carbazole (**5**) in 33% yield after flash chromatography. Small amounts of what presumably is the isomeric 6*H*-pyrido[3,2-*b*]carbazole can be detected in the NMR spectra of **5** if keto lactam **11c** is not purified prior to reaction with methyllithium. This indicates that some of the isomeric keto acid forms during the acylation of **7c** with pyridine anhydride **8**, although no attempt was made to isolate this material.

The structures of **4** and **5** are fully substantiated by spectral and analytical data. Unfortunately, the yields of **4** and **5** from their respective keto lactams (**11b,c**) are lower than that for **3**. This distinction may reflect complexation of methyllithium with the methoxyl groups of **11b** and **11c** retarding carbonyl addition, although this point was not pursued. Alternatively, the electron-donating methoxyl groups could attenuate the electrophilicity of the carbonyl groups.

In summary, we have described a convenient, efficient, and versatile synthesis of the pyrido[2,3-*b*]carbazole ring system. The synthetic strategy is complementary to our earlier construction of the pyrido[4,3-*b*]carbazole (ellipticine) ring system,[7a] and both methodologies should be applicable to the synthesis of structural analogues for biological studies.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices or a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, or Desert Analytics, Tucson, AZ. Infrared spectra were recorded on a Perkin-Elmer 599 instrument. ^1H NMR spectra were obtained at 60 MHz with an Hitachi Perkin-Elmer R-24 or Varian EM-360 spectrometer, or with a Varian XL-300 Fourier transform NMR spectrometer operating at 300 MHz. Chemical shifts are reported in parts per million downfield from tetramethylsilane as the internal reference. ^{13}C NMR spectra were measured on a JEOL-FX60Q Fourier

(11) For a recent example and leading reference, see: Gribble, G. W.; Johnson, D. A. *Tetrahedron Lett.* **1987**, *28*, 5259.

(12) In an effort to shorten the preparation of keto acid **10a**, we explored the Katritzky indole metalation protocol (Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935). However, treatment of indole-1-carboxylic acid[13] with *tert*-butyllithium (2 equiv, −78 °C) followed by the addition of anhydride **8** (−100 °C) affords keto acid **10a** in only 15% yield after recrystallization.

(13) Boger, D. L.; Patel, M. *J. Org. Chem.* **1987**, *52*, 3934.

(14) Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand. B.* **1976**, *30*, 853.

(15) Batcho, A. D.; Leimgruber, W. *Chem. Abstr.* **1977**, *86*, 29624. Batcho, A. D., personal communication. Saulnier, M. G. Ph.D. Thesis, Dartmouth College, 1982, pp 174–176.

(16) For the preparation of **6b** using this method, see: Shepard, K. L.; Graham, S. L. *Eur. Pat. Appl.* EP 155,214; *Chem. Abstr.* **1986**, *104*, 109465*x*.

(17) (a) Illi, V. O. *Synthesis* **1979**, 136. (b) Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215.

(18) Joule has described an intramolecular version of this reaction: Cooper, M. M.; Hignett, G. J.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3008.

transform NMR spectrometer operating at 15 MHz or on a Varian XL-300 Fourier transform NMR spectrometer operating at 75 MHz. Low-resolution mass spectra were determined at 70 eV on a Finnigan EI-CI 4023 gas chromatograph–mass spectrometer. Ultraviolet (UV) spectra were recorded on a Unicam SP-800A spectrophotometer or on a Cary 15 or 219 instrument. "Flash chromatography" refers to the technique developed by Still.[19] Thin-layer chromatography (TLC) was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck). Spots were visualized under 254-nm ultraviolet light and/or by spraying with a solution of 3% aqueous ceric ammonium sulfate in 10% sulfuric acid followed by brief heating. The alkyllithium reagents were standardized by titration against 2,5-dimethoxybenzyl alcohol[20] or diphenylacetic acid.[21] Tetrahydrofuran was distilled from sodium/benzophenone and diisopropylamine was distilled over sodium hydride. For most of the lithiation procedures, a three-neck round-bottomed flask fitted with an internal thermometer, magnetic stirring bar, argon or nitrogen inlet adaptor, and rubber serum cap was used. All reactions were performed in oven-dried (130 °C) glassware under prepurified argon or nitrogen. Brine refers to a saturated aqueous solution of sodium chloride.

2,3-Pyridinedicarboxylic Acid Anhydride (8). A mixture of 2,3-pyridinedicarboxylic acid (3.34 g, 0.02 mol) and acetic anhydride (6.7 g, 0.066 mol) was gently heated until all the acid had dissolved, and then heated at reflux for 15 min. The solution was concentrated to about 3 mL and then cooled to 5 °C. The resulting solid was filtered, washed with CCl_4 (distilled from P_2O_5), and dried in vacuo to yield 2.56 g (86%) of **8**: mp 134–135 °C (lit.[10] mp 134 °C); IR (KBr) 3100, 1855, 1760, 1600, 1580, 1315, 1280, 1240, 890, 715, 540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, 1 H), 8.41 (d, 1 H), 7.86 (m, 1 H).

1-(Phenylsulfonyl)indol-2-yl 3-Carboxy-2-pyridyl Ketone (9a). To a magnetically stirred solution of lithium diisopropylamide (LDA) (0.082 mol) prepared from diisopropylamine (8.52 g, 11.8 mL, 0.084 mol) and *n*-butyllithium (1.60 M in hexane; 51.0 mL, 0.082 mol) in dry THF (108 mL) at −70 °C was added via syringe over 25 min a solution of 1-(phenylsulfonyl)indole (**6a**) (20.0 g, 0.0778 mol) in dry THF (100 mL). The resulting bright orange solution was allowed to warm to room temperature over 3 h. The mixture was then cooled to −100 °C (liquid N_2/dry ice/acetone/pentane bath) and treated as rapidly as possible via syringe with a solution of 2,3-pyridinedicarboxylic acid anhydride (**8**) (12.2 g, 0.082 mol) in dry THF (75 mL). The temperature of the reaction mixture rose to −80 °C upon addition, but was then recooled to −100 °C, maintained at this temperature for 1 h, and then allowed to warm slowly to room temperature overnight. The solvent was removed in vacuo from the resulting dark purple reaction mixture to afford a dark brown residue. This was dissolved in H_2O (400 mL) and slowly acidified to pH 2 with 20% HCl with efficient cooling and stirring. The resulting off-white precipitate was collected by filtration, washed with cold H_2O, and dried in vacuo to yield 26.8 g (83%) of **9a** as an off-white solid. Several crystallizations from acetone gave the analytical sample: mp 219–222 °C; IR (KBr) 3080, 2975, 1710, 1640, 1575, 1475, 1370, 1340, 1275, 1185 cm^{-1}; ^1H NMR (60 MHz, DMSO-d_6) δ 8.8 (d, 1 H), 8.35 (d, 1 H), 8.25–8.0 (m, 3 H), 7.8–7.4 (m, 6 H), 7.25–7.15 (m, 2 H); ^{13}C NMR (15 MHz, DMSO-d_6) δ 183.7, 167.0, 155.5, 149.9, 138.4, 138.0, 137.9, 137.6, 134.2, 134.0, 129.2, 128.0, 127.8, 127.1, 125.2, 124.3, 123.4, 121.8, 115.2; mass spectrum, *m/e* 406 (M^+), 265, 248, 115, 77; UV (EtOH) λ_{max} 220, 242, 298 nm.

Anal. Calcd for $C_{21}H_{14}N_2O_5S$: C, 62.06; H, 3.47; N,6.89; S, 7.89. Found: C, 62.15; H, 3.77; N, 6.63; S, 7.60.

3-Carboxy-2-pyridyl 2-Indolyl Ketone (10a). A mixture of keto acid **9a** (1.99 g, 4.90 mmol), K_2CO_3 (2.63 g, 19.0 mmol), H_2O (20 mL), and MeOH (53 mL) was refluxed under N_2 with magnetic stirring for 5 h. The yellow-orange mixture was allowed to cool to room temperature, and the solvent was removed in vacuo to give a bright yellow solid. This was dissolved in H_2O (220 mL) and slowly acidified to pH 2–3 with 20% HCl while maintaining efficient cooling and stirring. The aqueous layer was extracted with ethyl acetate (200 mL) and saturated with solid NaCl and then further extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to give 1.30 g (100%) of **10a** as a yellow solid (R_f 0.18, THF), mp 193–197 °C. Crystallization from acetone gave the analytical sample as yellow crystals: mp 195–198 °C; IR (KBr) 3350, 1700, 1640, 1575, 1520, 1335, 1260 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1 H), 8.84 (dd, 1 H, J = 4.8, 1.4 Hz), 8.38 (dd, 1 H, J = 7.9, 1.4 Hz), 7.72 (dd, 1 H, J = 8.1, 4.8 Hz), 7.64 (d, 1 H, J = 8.2 Hz), 7.50 (d, 1 H, J = 8.2 Hz), 7.31 (t, 1 H, J = 7.3, 7.8 Hz), 7.08 (t, 1 H, J = 7.1, 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.5, 166.3, 157.0, 151.5, 138.2, 138.1, 134.7, 126.9, 126.5, 125.8, 124.8, 122.0, 120.4, 112.7, 120.0; mass spectrum, *m/e* 266 (M^+), 144, 116, 89, 40 (100); UV (EtOH) λ_{max} 225, 315 nm.

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.28; H, 4.02; N, 10.40.

Indolo[1,2-*b*][1,6]naphthyridine-5,12-quinone (11a). A solution of keto acid **10a** (2.90 g, 0.011 mol) in acetic anhydride (225 mL) was heated at 85–92 °C under N_2 for 21 h. The dark purple reaction mixture was allowed to cool to room temperature. The resulting precipitate was collected by filtration, washed with cold H_2O, and dried in vacuo to afford 2.30 g (84%) of **11a** as green-gold crystals (R_f 0.56, THF), mp 240–244 °C. Recrystallization from acetone gave the analytical sample: mp 259–262 °C; IR (KBr) 3100, 1690, 1610, 1585, 1555, 1380, 1345, 1260, 1240, 1140, 880, 740, 725, 690, 385 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.08 (dd, 1 H, J = 1.7, 4.7 Hz, H-2), 8.68 (dd, 1 H, J = 1.7, 8.1 Hz, H-4), 8.49 (d, 1 H, J = 8.3 Hz, H-7), 7.93 (dd, 1 H, J = 4.7, 8.1 Hz, H-3), 7.89 (d, 1 H, J = 8.7 Hz, H-10), 7.79 (s, 1 H, H-11), 7.65 (t, 1 H, J = 7.4, 7.8 Hz, H-8), 7.44 (t, 1 H, J = 7.3, 7.8 Hz, H-9); mass spectrum, *m/e* 248 (M^+, 100), 220, 192, 164, 115, 88, 50; UV (95% EtOH) λ_{max} 225, 266, 375 nm; the addition of aqueous NaOH to the cuvette gave a UV spectrum identical with that of **10a**.

Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.24; H, 3.42; N, 10.92.

5,11-Dimethyl-10*H*-pyrido[2,3-*b*]carbazole (3). A magnetically stirred suspension of keto lactam **11a** (1.56 g, 6.29 mmol) in dry THF (325 mL) under N_2 at −101 °C was treated over 30 s via syringe with methyllithium (1.05 M in Et_2O, 12.3 mL, 12.9 mol). The resulting mixture was stirred at −101 °C for 1 h and then allowed to warm slowly to room temperature overnight. Distilled H_2O (15 mL) was added to the orange-brown suspension, and this was stirred for 15 min. The THF was then removed in vacuo to give crude diol **12a** as a brown viscous residue. This was immediately treated under N_2 with 95% EtOH (455 mL) and excess sodium borohydride pellets (7 pellets, ca. 2.1 g) and then refluxed with magnetic stirring for 25 h. The sodium borohydride was added in 5 portions: 3 pellets initially, one pellet after every 2 h over the next 6 h, and the last pellet after 20 h. After approximately 2 h at reflux, the solution had become a light orange and was fluorescent. At the end of the 25-h reflux period, the reaction mixture was cooled to room temperature and the solvent was removed in vacuo to provide an orange-green residue. This was suspended in H_2O (150 mL) and continuously extracted over 3 days with CH_2Cl_2. After 1 day, the aqueous layer was acidified with concentrated HCl to pH 2 and then basified with 20% aqueous KOH to pH 8–9. After 3 days, the $CHCl_2$ layer was washed with brine (2 × 50 mL), dried (K_2CO_3), and evaporated in vacuo to give an orange-yellow solid. This was dissolved in hot MeOH (110 mL), concentrated to 50 mL, allowed to cool to room temperature, and then stored at 5 °C for 2 days. The resulting precipitate was collected by filtration, washed with cold MeOH, and dried in vacuo to provide 0.82 g (53%) of **3** as yellow needles (R_f 0.62, THF), mp 217–221 °C. Flash chromatography of the filtrate on silica gel with EtOAc gave an additional 0.67 g (total yield 96%; 29% overall yield from indole) of **3** as orange-yellow crystals. This material was identical (TLC, IR, mmp) with a sample provided by Dr. Jan Bergman:[8a,b] IR (KBr) 3000, 1635, 1615, 1585, 1490, 1460, 1410, 1380, 1355, 1315, 1300, 1260, 1225, 1200, 1080, 850, 775, 745, 640 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1 H), 8.95 (dd, J = 1.5, 4 Hz, 1 H, H-2) 8.64 (dd, J = 1.6, 8.6 Hz, 1 H, H-4), 8.34 (d, J = 7.6 Hz, 1 H, H-6), 7.64 (d, J= 7.3 Hz, 1 H, H-9), 7.56 (t, J = 7.3 Hz, 1 H, H-8), 7.38 (dd, J = 4.3, 8.6 Hz, 1 H, H-3), 7.26 (t, J = 7.3 Hz, 1 H, H-7), 3.10 (s, 3 H, 5-Me), 3.02 (s, 3 H, 11-Me); ^{13}C NMR (75 MHz, DMSO-d_6)

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(20) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *Chem. Commun.* **1980**, 88.
(21) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

148.0 (C-2), 144.5, 142.9, 140.3, 132.5 (C-4), 126.8 (C-8), 125.7, 123.6 (C-6), 123.1, 122.7, 121.1, 118.8 (C-7), 116.9 (C-3), 111.5, 110.5 (C-9), 14.5, 11.7;[22] mass spectrum m/e 246 (M^+), 231, 123, 109, 58 (100), 44; UV (EtOH) λ_{max} 235, 281, 292, 304, 328, 345, 398 nm; (EtOH and 1% of added 20% HCl) λ_{max} 242, 250 sh, 303, 367 nm.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.79; H, 5.87; N, 11.32.

1-(Phenylsulfonyl)-5-methoxyindole (6b). To a magnetically stirred mixture of tetra-*n*-butylammonium hydrogen sulfate (0.43 g, 1.27 mmol), crushed sodium hydroxide (6.2 g, 153 mmol), and CH_2Cl_2 (75 mL) at 0–5 °C was added a solution of 5-methoxyindole[15] (7.9 g, 53.7 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 10 min and then treated dropwise with a solution of benzenesulfonyl chloride (10.8 g, 61.3 mmol) in CH_2Cl_2 (45 mL), keeping the temperature below 35 °C. The reaction mixture was stirred at room temperature for 5 h and filtered. The filter cake was washed with CH_2Cl_2 (70 mL), and the solvent was evaporated in vacuo to give an off-white solid, which was recrystallized from Et_2O–CH_2Cl_2 (5:1) to give 13.6 g of **6b** (88%) as off-white crystals: mp 99–100 °C (lit.[23] mp 98–99 °C).

1-(Phenylsulfonyl)-5-methoxyindol-2-yl 3-Carboxy-2-pyridyl Ketone (9b). To a magnetically stirred solution of LDA (13.7 mmol) prepared from diisopropylamine (1.48 g, 2.05 mL, 14.7 mmol) and *n*-butyllithium (1.30 M in hexane; 10.5 mL, 13.7 mmol) in dry THF (17.5 mL) under argon at −75 °C was added via syringe over 6–7 min a solution of 1-(phenylsulfonyl)-5-methoxyindole (**6b**) (3.75 g, 13.1 mmol) in dry THF (20 mL). The resulting orange reaction mixture was allowed to warm to room temperature slowly over 3 h. The reaction mixture was then cooled to −100 °C and treated as rapidly as possible via syringe with a solution of 2,3-pyridinedicarboxylic acid anhydride (**8**) (2.12 g, 14.2 mmol) in dry THF (30 mL). The internal temperature rose to −60 °C, the reaction was cooled immediately to −100 °C, the resulting tan reaction mixture was stirred at −100 °C for 1 h, and then allowed to warm to room temperature slowly overnight. The solvent was removed in vacuo to afford a green-black residue, which was dissolved in H_2O (210 mL) and acidified to pH 2–3 with 20% HCl while maintaining efficient cooling and stirring. The precipitate was collected by filtration, washed with H_2O, and dried in vacuo to obtain 4.65 g (82%) of **9b** as a tan solid. Crystallization from acetone gave 2.35 g (41%) of **9b** as tan prisms (R_f 0.18, THF). Two additional recrystallizations from acetone gave the analytical sample as off-white prisms: mp 165–170 °C; IR (KBr) 3100, 1740, 1700, 1675, 1619, 1592, 1535, 1452, 1355, 1220, 1075, 1052, 730, 685, 605, 590, 562, 472 cm^{-1}; ^1H NMR (60 MHz, DMSO-d_6) δ 8.80 (d, 1 H), 8.85–7.82 (m, 6 H), 7.75–7.35 (m, 4 H), 7.15 (s, 1 H), 3.75 (s, 3 H) 2.08 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.4, 167.6, 156.7, 155.9, 149.6, 139.2, 138.0, 137.9, 134.6, 133.4, 132.3, 129.6, 129.3, 127.4, 125.4, 122.4, 117.8, 116.6, 105.0, 55.7; mass spectrum, m/e 436 (M^+), 392, 295, 263, 251 (100), 208, 77; UV (95% EtOH) λ_{max} 228, 301 nm.

Anal. Calcd for $C_{22}H_{16}N_2O_6S \cdot C_3H_6O$: C, 60.72; H, 4.48; N, 5.66; S, 6.48. Found: C, 60.59; H, 4.61; N, 5.62; S, 6.51.

5-Methoxyindol-2-yl 3-Carboxy-2-pyridyl Ketone (10b). A magnetically stirred mixture of keto acid **9b** (1.97 g, 4.52 mmol), K_2CO_3 (2.50 g, 18.1 mmol), methanol (55 mL), and H_2O (20 mL) was refluxed under N_2 for 5 h. The mixture was cooled, and the solvent was removed in vacuo to yield a yellow solid. This was dissolved in H_2O (150 mL) and slowly acidified to pH 2 with 20% HCl while maintaining efficient cooling and stirring. The aqueous layer was saturated with NaCl and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 1.16 g (87%) of **10b** as a yellow solid, mp 170–180 °C. This was dissolved in acetone (50 mL), heated to boiling, and filtered by gravity (while hot) to remove a small amount of residual solids. The hot filtrate was concentrated to 5–10 mL, allowed to cool slowly to room temperature and then stored at 5–10 °C. The product was collected by filtration, washed with cyclohexane, and dried in vacuo to give 0.70 g (52%) of **10b** as yellow crystals, mp 184–187 °C. Two additional recrystallizations from acetone gave the analytical sample: mp 191–194 °C; IR (KBr) 3340, 2920, 1700, 1635, 1575, 1540, 1445, 1260, 1215 cm^{-1}; ^1H NMR (60 MHz, DMSO-d_6) δ 11.95 (s, 1 H), 8.78 (d, 1 H), 8.35 (d, 1 H), 7.80–7.40 (m, 2 H), 7.35 (s, 1 H), 7.05 (s, 1 H), 6.65 (s, 1 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.2, 166.4, 157.0, 154.0, 151.5, 138.1, 135.0, 133.6, 127.2, 126.5, 124.8, 117.6, 113.7, 111.4, 102.4, 55.2; mass spectrum, m/e 326 (**13** impurity), 308, 296 (M^+, 100), 278, 263, 235, 179, 152, 139, 119, 102; UV (95% EtOH) λ_{max} 322 nm.

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.12; H, 4.29; N, 9.22.

9-Methoxyindolo[1,2-*b*][1,6]naphthyridine-5,12-quinone (11b). The keto acid **10b** (0.400 g, 1.35 mmol) was heated under N_2 with magnetic stirring in neat acetic anhydride (17 mL) at 85–90 °C for 27 h. The mixture was allowed to cool slowly to room temperature and then stored at 5–10 °C for 4 days. The precipitate was collected by filtration, washed with cold H_2O, and dried in vacuo to give 0.30 g (80%) of **11b** as golden crystals (R_f 0.54, THF), mp 208–212 °C. Recrystallization from acetone gave the analytical sample: mp 215–218 °C; IR (KBr) 3060, 1685, 1620, 1550, 1385, 1340, 1270, 1215, 810, 725, 385 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 9.07 (dd, 1 H, J = 1.6, 4.7 Hz, H-2), 8.66 (dd, 1 H, J = 1.6, 8.0 Hz, H-4), 8.37 (d, 1 H, J = 9 Hz, H-7), 7.92 (dd, 1 H, J = 4.7, 8.0 Hz, H-3), 7.70 (s, 1 H, H-11), 7.39 (d, 1 H, J = 2.5 Hz, H-10), 7.26 (dd, 1 H, J = 2.5, 9 Hz, H-8),3.85 (s, 3 H, CH_3O); mass spectrum, m/e 278 (M^+, 100), 263, 235, 207, 125; UV (95% EtOH) λ_{max} 222, 247, 375, 390 nm; with added base (5% aqueous NaOH) the UV spectrum was identical with that of **10b**.

Anal. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 68.91; H, 3.48; N, 10.08.

5,11-Dimethyl-7-methoxy-10*H*-pyrido[2,3-*b*]carbazole (4). A magnetically stirred suspension of methoxy keto lactam **11b** (0.25 g, 0.90 mmol) in dry THF (150 mL) was heated under argon at 50 °C for 1 h to effect nearly complete dissolution. The resulting green-gold solution was cooled to −100 °C and treated over 30 s via syringe with methyllithium (1.05 M in Et_2O; 1.74 mL, 1.83 mmol). This was stirred at −100 °C for 1 h and then allowed to warm slowly to room temperature overnight. Distilled H_2O (7 mL) was added to the dark green reaction mixture, it was stirred for 10 min, and then the THF was removed in vacuo to give the diol **12b** as a dark green viscous residue. This was immediately treated under argon with absolute ethanol (135 mL) and excess sodium borohydride (7 pellets, ca. 2.1 g) and refluxed with magnetic stirring for 23.5 h. The sodium borohydride was added in 6 portions: two pellets initially, one pellet every 2 h for the next 8 h, and one pellet after 21.5 h. After approximately 1 h, the solution had become light tan and was fluorescent. At the end of the 23.5-h reflux period, the reaction mixture was cooled and the solvent was removed in vacuo to obtain a yellow-orange residue. This was dissolved in H_2O (150 mL) and continuously extracted with CH_2Cl_2 over 2 days, during which time the aqueous layer was acidified to pH 2 with concentrated HCl and then basified to pH 8-9 with 20% KOH on four separate occasions. After the 2-day extraction period, the CH_2Cl_2 was removed from the dark green highly fluorescent reaction mixture to obtain a brown residue. This was dissolved in methanol (75 mL), heated to boiling, concentrated to 15–20 mL, cooled slowly to room temperature overnight, and then stored at 5–10 °C for 1 day. There was collected by filtration 0.046 g (19%) of **4** as fluffy green-yellow crystals (R_f 0.67, THF). The filtrate was flash chromatographed on silica gel with CH_2Cl_2 followed by EtOAc to afford an additional 0.036 g (14%) (total yield 33%, 8% overall from 5-methoxyindole) of **4** as bright yellow fluffly needles: mp 197–199 °C. Recrystallization from EtOH gave the analytical sample: mp 196–197 °C; IR (KBr) 3180, 2940, 1620, 1580, 1490, 1475, 1435, 1225, 1020, 815, 805, 765 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.89 (dd, 1 H, J = 1.5, 3.9 Hz, H-2), 8.68 (dd, 1 H,

(22) For compound **3**, ^1H NMR, ^{13}C NMR, HETCOR, and APT spectra were recorded on a Varian XL-300 spectrometer (conc. 125 mg/0.6 mL DMSO-d_6). The attached proton test (APT) on **3**, using a delay of 7 ms, gave a spectrum (aromatic region) with eight positive peaks for the quaternary carbons and seven negative peaks for the carbons bonded to hydrogen (viz. C-2, 3, 4, 6, 7, 8, and 9). Examination of the 2D heteronuclear chemical shift correlation spectrum (HETCOR) permitted assignments of ^{13}C resonances based on previously assigned ^1H resonances obtained from the 1D spectrum. Interpretation of the ^{13}C spectrum further led to the characterization of ^1H resonances (notably H-7 and H-8) via HECTOR. Our assignments compare favourably with spectral data reported for the isomeric pyrido[4,3-*b*]carbazoles (ellipticines): Mansour, T. S.; Wong, T. C.; Kaiser, E. M. *Org. Magn. Reson.* **1983**, *21*, 71. Commenges, G.; Rao, R. C. *Heterocycles* **1988**, *27*, 1395.

(23) Sundberg, R. J.; Parton, R. L. *J. Org. Chem.* **1976**, *41*, 163.

J = 1.5, 8.6 Hz, H-4), 7.84 (d, 1 H, J = 2.6 Hz, H-6), 7.50 (d, 1 H, J = 8.8 Hz, H-9), 7.37 (dd, 1 H, J = 3.9, 8.6 Hz, H-3), 7.17 (dd, 1 H, J = 2.6, 8.8 Hz, H-8), 3.90 (s, 3 H, OMe), 3.13 (s, 3 H, 5-Me), 2.92 (s, 3 H, 11-Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 148.2, 144.4, 141.0, 137.6, 132.8, 125.9, 123.4, 122.8, 120.8, 116.9, 115.0, 111.3, 111.0, 107.7, 55.8, 14.6, 11.6; mass spectrum, m/e 276 (M^+), 261, 218, 138, 116, 102; UV (EtOH) λ_{max} 239, 275, 290, 317, 347, 420 nm; (EtOH + 1% of 20% HCl) λ_{max} 227, 247, 312, 372 nm.

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.02; H, 5.88; N, 10.06.

1-(Phenylsulfonyl)-6-methoxyindol-2-yl 3-Carboxy-2-pyridyl Ketone (9c). To a magnetically stirred solution of LDA (27.4 mmol) prepared from diisopropylamine (2.96 g, 4.10 mL, 29.3 mmol) and *n*-butyllithium (1.49 M in hexane; 18.4 mL, 27.4 mmol) in dry THF (35 mL) under argon at −75 °C was added via syringe over 5–7 min a solution of 1-(phenylsulfonyl)-6-methoxyindole (**6c**)[7e] (7.50 g, 26.1 mmol) in dry THF (40 mL). The resulting bright yellow solution was stirred at −75 °C for 1 h and then allowed to warm to room temperature over 3.5 h. The reaction mixture was cooled to −100 °C and treated rapidly via syringe with a solution of 2,3-pyridinedicarboxylic anhydride (**8**) (4.25 g, 28.5 mmol) in dry THF (50 mL). The temperature rose to −60 °C, and the color changed from orange to yellow brown. The reaction mixture was recooled to −100 °C, stirred at this temperature for 1.5 h, and then allowed to warm slowly to room temperature overnight. The solvent was removed in vacuo, H_2O (100 mL) was added, and the mixture was acidified to pH 3 with 20% aqueous HCl while cooling and stirring. The solid was collected by filtration and dried in vacuo to afford 9.65 g (85%) of **9c** as an off-white solid. Crystallization from acetone and then from benzene gave the analytical sample: mp 213 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (d, 1 H, J = 4.6 Hz), 8.29 (d, 1 H, J = 7.8 Hz), 8.11 (d, 2 H, J = 7.6 Hz), 7.15 (s, 1 H), 7.00 (dd, 1 H, J = 8.9, 2.3 Hz), 3.90 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 160.2, 155.9, 150.7, 140.5, 137.9 137.8, 136.7, 134.3, 129.4, 128.3, 127.1, 125.3, 124.6, 123.8, 121.6, 114.1, 98.9, 55.7; mass spectrum, m/e 295 (M^+ − $PhSO_2$), 251, 236, 180, 77, 57; UV (EtOH) λ_{max} 208, 328 nm.

Anal. Calcd for $C_{22}H_{16}N_2O_6S$: C, 60.55; H, 3.70; N, 6.42; S, 7.35. Found: C, 60.61; H, 3.72; N, 6.39, S, 7.30.

6-Methoxyindol-2-yl 3-Carboxy-2-pyridyl Ketone (10c). A magnetically stirred mixture of keto acid **9c** (86.6 mg, 0.20 mmol), K_2CO_3 (110 mg, 0.80 mmol), methanol (6 mL), and H_2O (2 mL) was refluxed for 7 h. The mixture was allowed to cool and then concentrated in vacuo. Water (10 mL) was added, and the mixture was acidified to about pH 2 at 0 °C with 15% HCl. The yellow product obtained was filtered, washed with water, and dried in vacuo to give 43.0 mg (75%) of **10c**. Recrystallization from EtOH–H_2O gave 24.7 mg of analytically pure **10c**: mp 205 °C dec; IR (KBr) 3220, 1710, 1590, 1540, 1265, 1200 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1 H), 8.82 (dd, J = 1.5, 4.7 Hz, 1 H), 8.34 (dd, J = 1.5, 8 Hz, 1 H), 7.70 (dd, J = 4.7, 8.1 Hz, 1 H), 7.50 (d, J = 9.1 Hz, 1 H), 6.89 (d, J = 2 Hz, 1 H), 6.73 (dd, J = 2.5, 8.9 Hz, 1 H), 6.67 (d, J = 1.5 Hz, 1 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.5, 166.4, 158.8, 157.0, 151.3, 139.5, 138.0, 134.0, 126.6, 124.6, 123.8, 121.4, 112.9, 112.4, 93.7, 55.1; mass spectrum, m/e 296 (M^+), 278, 263, 252, 237, 174, 119, 91 (100), 78; UV (EtOH) λ_{max} 344, 218 nm.

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.61; H, 3.99; N, 9.25.

8-Methoxyindolo[1,2-*b*][1,6]naphthyridine-5,12-quinone (11c). The keto acid **10c** (0.83 g, 2.8 mmol) was heated with acetic anhydride (60 mL) at 85 °C under N_2 overnight. After 2 h some solid formed and additional acetic anhydride (25 mL) was added. The reaction mixture was allowed to cool to room temperature and stored in a freezer overnight, and the solid was collected by filtration to give 0.42 g (54%) of **11c** as orange crystals, mp 288–289 °C. An additional 0.33 g (42%) (total yield 96%) of material was obtained from the filtrate by concentration in vacuo and the addition of H_2O (15 mL): IR (KBr) 1695, 1680, 1620, 1555, 1500, 1390, 1355 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (dd, 1 H, J = 1.4, 4.7 Hz, H-2), 8.68 (dd, 1 H, J = 1.4, 8 Hz, H-4), 8.04 (d, 1 H, J = 2.2 Hz, H-7), 7.93 (dd, 1 H, J = 4.7, 8 Hz, H-3), 7.80 (d, 1 H, J = 8.8 Hz, H-10), 7.75 (s, 1 H, H-11), 7.09 (dd, 1 H, J = 2.2, 8.8 Hz, H-9), 3.91 (s, 3 H, CH_3O); mass spectrum, m/e 278 (M^+, 100), 263, 235, 207, 77; UV (95% EtOH) λ_{max} 220, 242, 273, 426 nm; with added KOH, λ_{max} 265, 345 nm.

Anal. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 68.84; H, 3.63; N, 10.04.

5,11-Dimethyl-8-methoxy-10*H*-pyrido[2,3-*b*]carbazole (5). A magnetically stirred suspension of methoxy keto lactam **11c** (0.290 g, 1.04 mmol) in dry THF (350 mL) under argon was cooled to −105 °C and treated rapidly with methyllithium (1.05 M; 2.33 mL, 2.45 mmol). The mixture was stirred at −100 °C for 2 h and allowed to warm slowly to room temperature overnight. The solvent was removed in vacuo, and the residue was treated with ethanol (200 mL) and excess sodium borohydride (8 pellets, ca. 2.4 g) and then refluxed under argon for 3 days. The solvent was removed in vacuo, and the residue was subjected to continuous extraction with $CHCl_3$. This extract was concentrated in vacuo and flash chromatographed (silica gel; CH_2Cl_2/EtOAc eluent) to give 0.096 g (33%) of **5**, mp 244–245 °C. Recrystallization from EtOH gave the analytical sample: mp 255 °C; IR (KBr) 3440, 3160, 3080, 1625, 1590, 1450, 1410, 1285, 1170 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (s, 1 H), 8.87 (dd, 1 H, J = 1.6, 4.2 Hz, H-2), 8.69 (dd, 1 H, J = 1.6, 8.6 Hz, H-4), 8.22 (d, 1 H, J = 8.8 Hz, H-6), 7.41 (dd, 1 H, J = 4.0, 8.6 Hz, H-3), 7.02 (d, 1 H, J = 2.2 Hz, H-9), 6.84 (dd, 1 H, J = 2.4, 8.5 Hz, H-7), 3.89 (s, 3 H, OMe), 3.10 (s, 3 H, 5-Me), 2.90 (s, 3 H, 11-Me); mass spectrum, m/e 276 (M^+, 100), 262, 233, 219; UV (95% EtOH) λ_{max} 234, 278, 298 sh, 308, 354, 390 nm; with added HCl, λ_{max} 240, 249, 262 sh, 310 sh, 320, 390 nm.

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 77.72; H, 5.79; N, 10.08.

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