Acknowledgment. This investigation was supported by Grants CH-200 and CH-200A from the American Cancer Society, PHS Grant GM-30761 awarded by the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Merck Sharp and Dohme Research Laboratories. We thank the National Science Foundation for funds to purchase a Varian XL-300 NMR spectrometer, Dr. Catherine Costello (Massachusetts Institute of Technology), Dr. Frank Field (Rockefeller University), and Dr. Ronald L. Cerny (University of Nebraska—Lincoln) for the high-resolution mass spectra, and the Colorado State University Regional NMR Center for some high resolution NMR spectra. G.W.G is very grateful to American Cyanamid for an Academic Achievement Award and is especially indebted to Professor Marc Tius and his colleagues and students at the University of Hawaii at Manoa for their generous hospitality and Aloha spirit during a sabbatical year (1991–1992) when this manuscript was written.

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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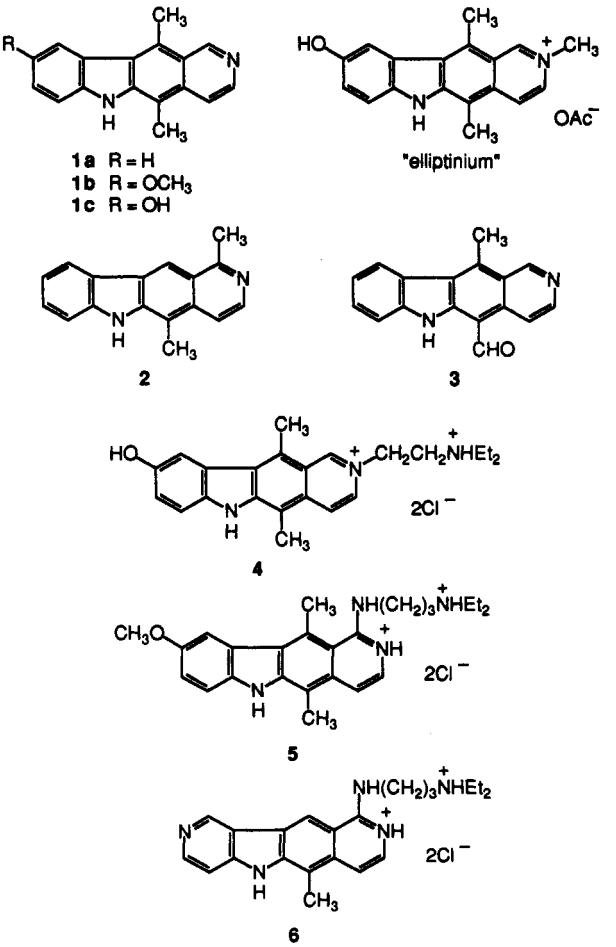
A general and efficient synthesis of the 6*H*-pyrido[4,3-*b*]carbazole ring system is described, in which the key steps are (1) regioselective acylation of a 2-lithio-1-(phenylsulfonyl)indole (**14**) with 3,4-pyridinedicarboxylic acid anhydride (**10**), (2) cyclization of the deprotected keto acid **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]



(1) For reviews of the synthesis and biological activity of pyridocarbazoles and related compounds, see: (a) Gribble, G. W. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1990; Vol. 39, p 1. (b) Auclair, C. *Arch. Biochem. Biophys.* **1987**, *259*, 1. (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. (d) Suffness, M.; Cordell, G. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. XXV, p 1. (e) For a recent example, see: Marsais, F.; Pineau, Ph.; Nivolliers, F.; Mallat, M.; Turck, A.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1992**, *57*, 565.

(2) (a) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690. (b) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.

(3) Gribble, G. W.; Fletcher, G. L.; Ketcha, D. M.; Rajopadhye, M. *J. Org. Chem.* **1989**, *54*, 3264.

(4) We have reported the synthesis of ellipticine in preliminary form: Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2810.

(5) We have also reported the synthesis of the related alkaloid 13-oxoellipticine (**3**): (a) Obaza-Nutaitis, J. A.; Gribble, G. W. *J. Nat. Prod.* **1986**, *49*, 449. (b) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 3831.

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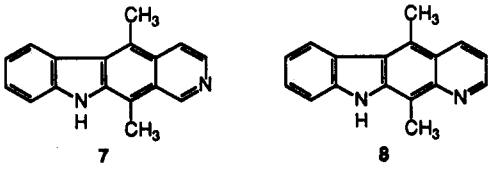


7 8

Our original strategy (Scheme I) revolved around the regioselective acylation of a 2-lithioindole **9** by 3,4-pyridinedicarboxylic acid anhydride (**10**),[6] followed by cyclization at the indole C-3 position, to eventually furnish ellipticine quinone **11**, which had previously been converted to ellipticine (**1a**).[7]

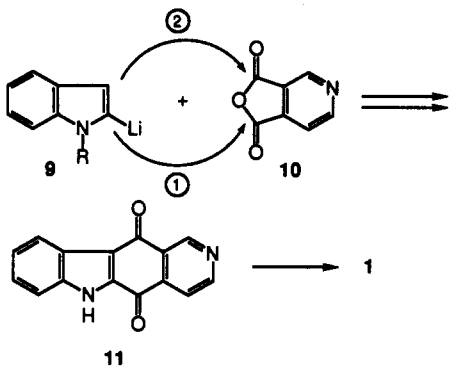
Results and Discussion

Synthesis of Ellipticine (1a). Our synthesis of the desired target keto acid **17** is illustrated in Scheme II. Indole (**12**) was converted to 1-(phenylsulfonyl)indole (**13**) in 91% yield by treatment with *n*-butyllithium in tetrahydrofuran (THF) followed by the addition of benzenesulfonyl chloride at −78 °C.[8] Later, it was found that the simple phase-transfer method of Illi is equally satisfactory.[9] Guided by the pioneering work of Sundberg,[10] we found that regiospecific 2-lithiation of **13** could be achieved with lithium diisopropylamide (LDA, THF, −75 → 0 °C, 2 h),[8] and the resulting solution of 2-lithio-1-(phenylsulfonyl)-indole (**14**) was rapidly treated with pyridine anhydride **10**[11] at −100 °C. This produced a mixture of N-protected keto acids **15** and **16** in 78% yield after crystallization from acetic acid, in a ratio of 92:8 (vide infra). The mixture of **15** and **16** could be separated by fractional crystallization from acetone since the minor keto acid **16** is completely insoluble in this solvent. The solubility difference between **15** and **16** parallels that between nicotinic acid and isonicotinic acid, the latter being more insoluble than the former.[12] More importantly, this solubility evidence suggested that the ring opening of anhydride **10** had indeed occurred as desired. Cleavage of the *N*-phenylsulfonyl protecting group was achieved with potassium carbonate in aqueous MeOH to afford keto acid **17** in essentially quantitative yield. A trace of what is probably the methoxy keto acid **18**, formed by conjugate addition of methoxide to the indole C-3 position, is present in the crude material by mass spectrometry.[13]

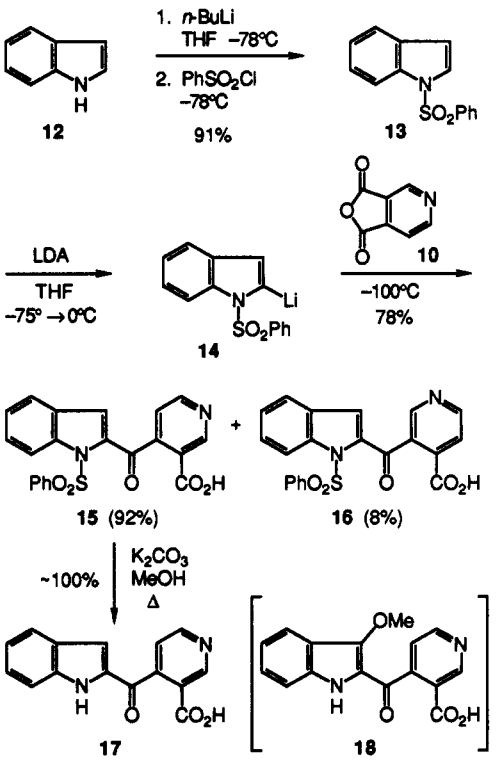
Unfortunately, all attempts to cyclize keto acid **17** to ellipticine quinone under Friedel–Crafts or related conditions on **17** or on the derived acid chloride[2b] were unsuccessful. However, under the action of hot acetic anhydride, keto acid **17** smoothly cyclized to the bright yellow-orange keto lactam **19** in virtually quantitative yield (Scheme III). The structure of **19** is supported by its reconversion to keto acid **17** with aqueous base at room temperature[14] and by its infrared spectrum, which shows carbonyl absorption at 1702 and 1675 cm^{-1} consistent with *N*-acylindole and aryl ketone chromophores, respectively.[15]

Although our failure to acquire quinone **11** was initially thought to be disastrous, we reasoned that keto lactam **19** should undergo an addition–fragmentation sequence to give **21** via **20**, since amides typically react this way with organolithium reagents.[16] Furthermore, *N*-indolylmethyl ketone **21** would be expected[17] to undergo C-3 cyclization to afford, after workup, diol **23**, *the same compound that results from addition of 2 equiv of methyllithium to el-*

Scheme I



Scheme II



(6) For an example of the regioselective ring opening of **10**, see: Bottaro, J. C.; Berchtold, G. A. *J. Org. Chem.* **1980**, *45*, 1176. For studies of the regioselective addition of nucleophiles to substituted phthalic anhydrides, see: Allahdad, A.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1855. Breau, L.; Kayser, M. M. *Can. J. Chem.* **1989**, *67*, 569.

(7) (a) Taylor, D. A.; Baradarani, M. M.; Martinez, S. J.; Joule, J. A. *J. Chem. Res. (S)* **1979**, 387; (*M*) **1979**, 4801. (b) Ashcroft, W. R.; Beal, M. G.; Joule, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 994. (c) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.

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

(9) (a) Illi, V. O. *Synthesis* **1979**, 136. (b) Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215. (c) Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627.

(10) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324, for the 2-lithiation of 1-(phenylsulfonyl)indole with *tert*-butyllithium.

(11) (a) This material was readily prepared from the commercially available 3,4-pyridinedicarboxylic acid (cinchomeronic acid) using the procedure of Bachman, G. B.; Barker, R. S. *J. Org. Chem.* **1949**, *14*, 97. (b) Goldschmiedt, G.; Strache, H. *Monatsch.* **1890**, *10*, 156.

(12) We found that nicotinic acid is about 13 times more soluble in hot acetone than is isonicotinic acid; for similar data in other solvents, see: *Beilstein* **1935**, *22*, 38, 45.

(13) For a similar reaction, see: (a) Cooper, M. M.; Hignett, G. J.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3008. (b) Ashcroft, W. R.; Dalton, L.; Beal, M. G.; Humphrey, G. L.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2409.

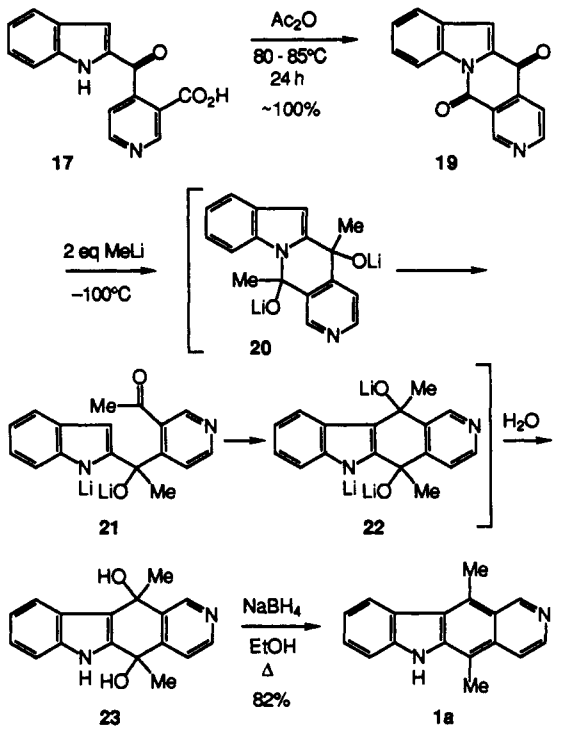
(14) *N*-Acylindoles are easily cleaved with base; cf.: Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand. B* **1976**, *30*, 853.

(15) By analogy, the corresponding 2-methylpyrrole–phthalic anhydride derived keto lactam exhibits carbonyl absorptions at 1708 and 1655 cm^{-1}: Cornforth, J. W.; Firth, M. E. *J. Chem. Soc.* **1958**, 1091.

(16) Micovic, V. M.; Mihailovic, M. Lj. *J. Org. Chem.* **1953**, *18*, 1190.

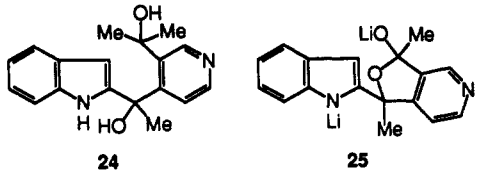
(17) For example, indolylmagnesium bromide reacts with acetophenone at C-3: Oddo, B.; Perotti, L. *Gazz. Chim. Ital.* **1930**, *60*, 13; *Chem. Abstr.* **1930**, *24*, 3785.

Scheme III



lipticine quinone 11. The execution of this experiment led precisely to this result and gave diol **23** as two unstable diastereomers, which, without purification, were treated with $NaBH_4$[7a] to give ellipticine (**1a**) in 82% yield from keto lactam **19** after flash chromatography. The overall yield of ellipticine from indole is thus 54% (six steps), representing one of the most efficient syntheses of this alkaloid.

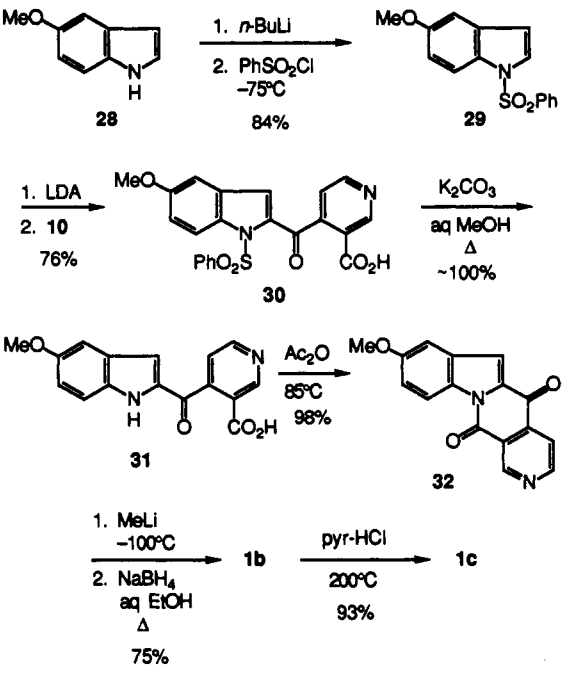
If the addition of methyllithium to keto lactam **19** is performed at −75 °C rather than −100 °C, the yield of ellipticine drops from 82% to 26%, which reflects the interception of ketone **21** by methyllithium to give diol **24**, which, in fact, can be isolated. It seems likely that **21** exists in equilibrium with lactol dianion **25**. Recently, Archer, in a meticulous examination of our proposed pathway (Scheme III), has confirmed the existence of intermediate **21** and has also isolated diol **24**.[18]



Several attempts to induce keto acids **15** or **17** to react with methyllithium in similar fashion to give diol **23** directly were unsuccessful.[19] For example, treatment of **15** with methyllithium (3 equiv, −78 °C) followed by acid workup gave **26** in 72% yield, and treatment of **17** with methyllithium (4.3 equiv, −60 → 25 °C) followed by acid workup gave lactone **27** in 72% yield.

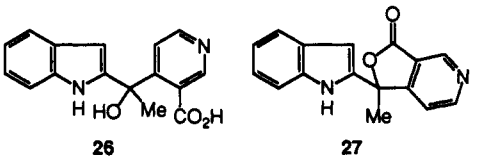
Using the same protocol, we have transformed the minor keto acid **16** into "isoellipticine" **7** in 85% yield,[2a] thus doubly confirming the regiochemistry of the acylation of

Scheme IV



2-lithioindole **14** with pyridine anhydride **10** (Scheme II).

Synthesis of 9-Methoxyellipticine (1b). An exactly analogous sequence to that described for ellipticine



(Schemes II and III) was used to convert 5-methoxyindole (**28**)[20] to 9-methoxyellipticine (**1b**) (Scheme IV). Noteworthy is the fact that none of the other regioisomeric keto acid could be detected (TLC, ^{13}C NMR) by analysis of the crude product **30**. The overall yield of 9-methoxyellipticine (**1b**) from **28** is 47%. Using the procedure of Brossi,[21] we converted **1b** into 9-hydroxyellipticine (**1c**).

Syntheses of 5,11-Disubstituted Ellipticine Derivatives and Olivacine (2). An important extension of our synthetic approach to 6*H*-pyrido[4,3-*b*]carbazoles was viewed as the differential introduction of substituents to the C-5 and C-11 positions. This variant on the main theme is essential for successful syntheses of olivacine (**2**) and 13-oxoellipticine (**3**). Moreover, it is known that many of the biologically active second-generation ellipticine derivatives have only a substituent at C-5.[1a]

In order to probe the relative reactivities of the two carbonyl groups in keto lactam **19**, we performed a model study. Treatment of keto lactam **19** with *n*-butyllithium (1 equiv, −100 °C) followed after 5 min by methyllithium (1 equiv, −100 °C) gave, after the usual sodium borohydride reduction of the diol intermediate, 5-*n*-butyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**34**) in 70% yield, and the 5,11-di-*n*-butyl derivative (**35**) in 18% yield.[5b] The structure of **34** was established from the results of classical nuclear Overhauser effect (NOE) experiments on ellipticine (**1a**), which confirmed the proton chemical shift assignments of the two (different) methyl groups, as illustrated in **36**. Thus, whereas the 2.8 ppm singlet had dis-

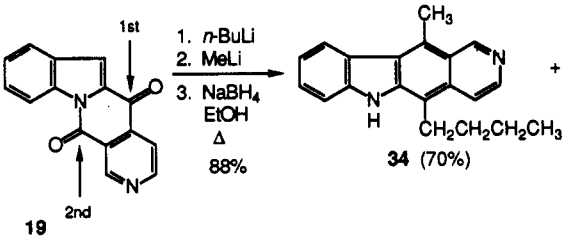
(18) (a) Modi, S. P.; Carey, J. J.; Archer, S. *Tetrahedron Lett.* **1990**, *31*, 5845. (b) Modi, S. P.; Michael, M. A.; Archer, S.; Carey, J. J. *Tetrahedron* **1991**, *47*, 6539.

(19) For summaries of this work, see: (a) Gribble, G. W. *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 1, p 43. (b) Gribble, G. W. *Synlett* **1991**, 289.

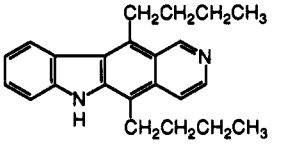
(20) (a) Batcho, A. D.; Leimgruber, W. *Chem. Abstr.* **1977**, *86*, 29624. (b) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214.

(21) Brossi, A.; Guthrie, R. W.; Kierstead, R. W. *Chem. Abstr.* **1976**, *84*, 105563y.

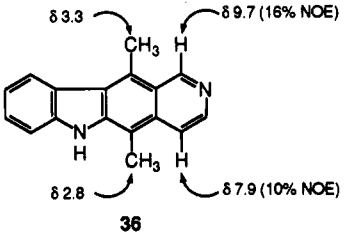
appeared from the ^1H NMR spectrum of **34**, the 3.3 ppm singlet remained. This model study clearly revealed that the ketone carbonyl group is attacked by an alkyllithium reagent first.



19 **34** (70%)

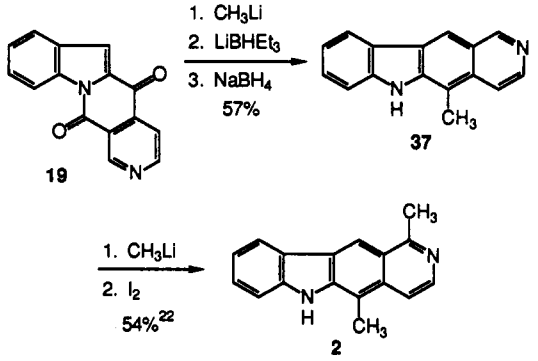


35 18%



36

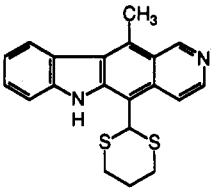
Our synthesis of olivacine (**2**) was achieved as follows. Treatment of keto lactam **19** sequentially with methyllithium and then Superhydride ($LiBHEt_3$) gave, after reduction of the intermediate diol, 11-demethylellipticine (**37**) in 57% yield, along with 30% ellipticine (**1a**). Kutney has previously converted **37** into olivacine (**2**).[22] The use of $NaBH_4$ or $LiAlH_4$ in this sequence was unrewarding. Attempts to prepare the parent 6*H*-pyrido[4,3-*b*]carbazole system by using 2 equiv of Superhydride or other hydride source (DIBAL, $NaBH_4$, Red-Al) have failed thus far.



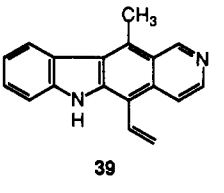
19 **37** **2**

We have also made use of the differential reactivity of the carbonyl groups in keto lactam **19** to synthesize the alkaloid 13-oxoellipticine (**3**).[5] Although treatment of **19** with the formyl anion equivalent 2-lithio-2-(trimethylsilyl)-1,3-dithiane, followed by methyllithium and reduction, afforded **38**, the yield was only 25%. Hydrolysis of **38** with $AgNO_3$/aqueous acetone furnished 13-oxoellipticine (**3**) in excellent yield. A better sequence involved the use of vinyllithium, in tandem with methyllithium, to give **39**, which was oxidatively cleaved using chromic acid to give 13-oxoellipticine (**3**) in 58% yield from **19**.[5a]

(22) Kutney, J. P.; Noda, M.; Lewis, N. G.; Monteiro, B.; Mostowicz, D.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 2426.

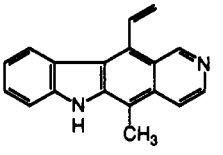


38

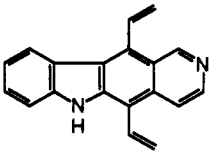


39

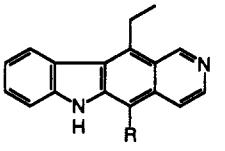
In similar fashion, keto lactam **19** was transformed into vinyl ellipticine derivatives **40** and **41**. Interestingly, under the standard reduction protocol ($NaBH_4$, EtOH), the C-11 vinyl group was reduced in part to afford the corresponding ethyl derivatives **42** and **43**. This overreduction was circumvented by employing $NaBH_4$ in *tert*-butyl alcohol, a reagent combination that presumably does not generate a more reactive alkoxyborohydride species.



40



41



42 R = CH_3
43 R = CH = CH_2

Synthesis of 6,11-Dimethyl-5*H*-benzo[*b*]carbazole (48). Finally, we have synthesized the benzo analogue **48** in 61% yield from 1-(phenylsulfonyl)indole (**13**) and phthalic anhydride (**44**) via keto lactam **47** (see the Experimental Section).

Summary

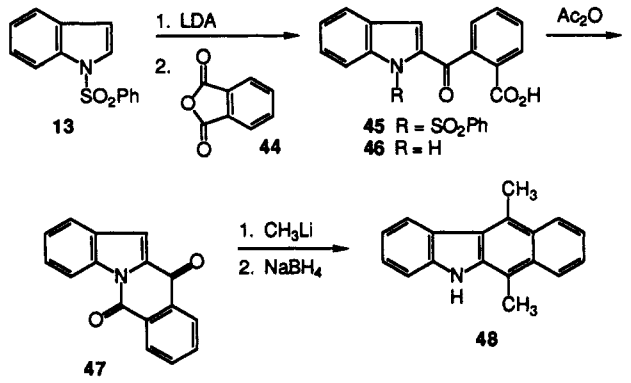
In summary, the regioselective acylation of 2-lithio-1-(phenylsulfonyl)indoles by 3,4-pyridinedicarboxylic acid anhydride, followed by the regioselective addition of organolithium reagents to the versatile keto lactam intermediates, affords a convenient and general route to the ellipticine family of alkaloids. Moreover, 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.

Experimental Section

3,4-Pyridinedicarboxylic Acid Anhydride (10). The procedure of Bachman and Barker was followed.[11a] A magnetically stirred mixture of 3,4-pyridinedicarboxylic acid (45.0 g, 0.269 mol) and Ac_2O (200 mL) was refluxed for 45 min. All of the solid dissolved, and the solution turned black. The Ac_2O was removed by distillation at 60–70 °C (10–20 Torr), and the product was then distilled to afford 38.3 g (96%) of **10** as a colorless solid: bp 114–117 °C (0.4 Torr); mp 75–76 °C (lit.[11b] mp 76–77 °C); IR (KBr) 3900, 1880, 1780, 1600, 1290, 1220, 891, 720, 680, 540; ^1H NMR ($CDCl_3$) δ 9.50 (s, 1 H), 9.38 (d, 1 H, J = 5.5 Hz), 8.03 (d, 1 H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0, 160.9, 156.5, 147.3, 138.5, 125.0, 118.3.

1-(Phenylsulfonyl)indol-2-yl 4-Carboxy-3-pyridyl Ketone (15). To a mechanically stirred solution of LDA (163 mmol) prepared from diisopropylamine (171 mmol) and *n*-BuLi (1.66 M in hexane; 98.3 mL, 163 mmol) in dry THF (215 mL) under Ar at −75 °C was added via syringe over 10 min a solution of **13** (40.00 g, 155.5 mmol) in dry THF (220 mL). The mixture was allowed to warm slowly to 10 °C over 3 h. The resulting 2-

Scheme V



lithioindole **14** precipitated as a colorless solid in a light orange solution. The mixture was cooled to −103 °C and treated as rapidly as possible via dropping funnel with a solution of pyridine anhydride **10** (24.34 g, 163.2 mmol) in dry THF (150 mL) while maintaining extremely efficient mechanical stirring and cooling (liquid N_2/dry ice/acetone mixture). The reaction mixture was stirred at −100 °C for 2.5 h, warmed to −50 °C over an additional 3 h, and then allowed to warm to room temperature over 12 h. After the solvent was removed by rotary evaporation, the resulting dark brown, oily solid was dissolved in H_2O (500 mL), and the solution was slowly acidified to pH 3 with 20% HCl with efficient stirring and cooling. The resulting white precipitate was collected by filtration after 15 min at 5 °C, washed with H_2O (3 × 150 mL), and thoroughly dried in vacuo to give 65.15 g of an off-white solid. This material was divided into two equal portions, and each one was treated with glacial HOAc (330 mL). The magnetically stirred mixture was boiled until nearly all of the solid material had dissolved (30–45 min) and then filtered by gravity (while hot) to remove a small amount of residual solids. The hot solution was immediately treated slowly with boiling H_2O (115 mL) until the resulting cloudy appearance persisted for about 5 s before fading. The hot mixture was allowed to stand at room temperature overnight and then cooled briefly at 10 °C. The product was collected by filtration, thoroughly washed with H_2O, and dried at 80 °C (0.5 Torr) to provide 49.69 g (combined, 2 crops each) (79%) of a mixture of protected keto acids **15** and **16** as fluffy white needles in a ratio of 92:8 (vide infra), mp 252–254 °C. This mixture (6.00 g) was treated with acetone (400 mL) and boiled for 20–30 min. Hot gravity filtration gave 0.45 g (8%) of regioisomer **16** which is totally insoluble in acetone, mp 274–275 °C dec (R_f 0.07, THF). The filtrate contained **15** (R_f 0.23, THF), which was best isolated by concentration to approximately half volume and collection (in 2–3 crops) to give **15** as colorless crystals: mp 263–264 °C; IR (KBr) 3440, 2390, 1735, 1680, 1605, 1535, 1450, 1340, 1185, 1045, 840 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 9.12 (s, 1 H), 8.92 (d, 1 H), 8.23–8.16 (m, 3 H), 7.80–7.55 (m, 6 H), 7.37 (t, 1 H), 7.26 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 184.4, 166.6, 153.7, 151.1, 147.5, 139.8, 138.9, 137.6, 135.2, 130.1, 129.8, 127.9, 127.7, 126.2, 125.3, 124.6, 124.1, 122.9, 116.0; MS *m/e* 406 (M^+) 265, 248, 141, 115, 77 (100%); UV (95% EtOH) λ_{max} 213, 244 (sh), 301 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, 61.89; H, 3.53; N, 6.79; S, 7.78.

For the minor regioisomer **16**: IR (KBr) 3440, 2450, 1720, 1670, 1530, 1355, 1175, 1045, 960, 725 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 8.95 (d, 1 H), 8.85 (s, 1 H), 8.20–8.13 (m, 3 H), 7.83–7.56 (m, 6 H), 7.38 (t, 1 H), 7.29 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 184.4, 167.5, 153.7, 141.1, 139.3, 138.5, 138.3, 135.4, 133.4, 130.1, 129.5, 128.1, 127.6, 125.9, 125.4, 124.5, 123.5, 122.9, 115.9; MS *m/e* 406 (M^+), 265, 248, 141, 115, 77 (100); UV (95% EtOH) λ_{max} 214, 245 (sh), 300 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, 61.84; H, 3.50; N, 6.85; S, 7.89.

3-Carboxy-4-pyridyl 2-Indolyl Ketone (17). A magnetically stirred mixture of keto acid **15** (7.52 g, 18.5 mmol), K_2CO_3 (9.9 g, 72 mmol), MeOH (200 mL), and H_2O (70 mL) was refluxed under N_2 for 4.5 h. The mixture was cooled, and the solvent was removed in vacuo to give a light tan solid. This material was dissolved in H_2O (350 mL) and slowly acidified to pH 2–4 with 20% HCl while maintaining efficient cooling and stirring. The aqueous portion was then saturated with solid NaCl and extracted with EtOAc (3 × 250 mL). The combined extracts were washed with H_2O (2 × 200 mL) and brine (2 × 250 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 4.98 g (100%) of **17** as a light yellow solid after drying at 50–60 °C (0.2 Torr) (R_f 0.53, THF), mp 146–151 °C. This material was dissolved in acetone (100 mL), and the solution was concentrated to 50 mL and allowed to stand at room temperature for several hours and then in the refrigerator overnight. The product was collected by filtration, washed with hexane, and dried to give 3.81 g of pale yellow prisms, mp 152–157 °C dec. The mother liquor was further concentrated to afford an additional 0.77 g of **17**, mp 156–161 °C dec. Recrystallization from acetone gave the analytical sample: mp 159–162 °C dec; IR (KBr) 3475, 3320, 2440, 1710, 1642, 1522, 1416, 1309, 1246, 905, 819, 794, 738, 670, 577, 535, 473 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 12.10 (s, 1 H), 9.15 (s, 1 H), 8.93 (d, 1 H), 7.67–7.61 (m, 2 H), 7.49 (d, 1 H), 7.33 (t, 1 H), 7.08 (t, 1 H), 6.71 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 186.6, 166.4, 153.6, 151.1, 148.4, 139.0, 135.3, 127.4, 127.0, 125.6, 123.6, 122.6, 121.4, 113.4, 113.0; MS *m/e* 266 (M^+), 248, 220, 192, 164, 144, 116, 89 (100); UV (95% EtOH) λ_{max} 209, 228 (sh), 319 nm. Anal. Calcd for $C_{15}H_{10}N_2O_3S \cdot C_3H_6O$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.67; H, 4.95; N, 8.64.

Indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (19). The deprotected keto acid **17** (recrystallized, containing a mole of acetone of crystallization, vide supra) (3.50 g, 10.8 mmol) was heated under N_2 with magnetic stirring in Ac_2O (300 mL) at ca. 85 °C for 15 h and then at 85–90 °C for an additional 6 h. The Ac_2O was nearly completely removed by distillation at 50–60 °C (10–20 Torr). The residue was cooled and treated with H_2O (150 mL). After the ice-cooled mixture was stirred for 0.5 h, the product was collected by filtration, washed several times with H_2O, and dried at 40 °C (0.5 Torr) for 15 h to afford 2.70 g (100%) of keto lactam **19** as a light orange solid which was homogeneous by TLC (R_f 0.69, THF), mp 181–184 °C dec. This material was treated with acetone (250 mL) and heated for 2.5 h. At the end of this period all of the solid had dissolved, and the resulting bright orange solution was concentrated to 210 mL, allowed to slowly cool to room temperature, and then stored at 10 °C overnight. The product was collected by filtration, washed with hexane, and dried to give 2.17 g of **19** as yellow-orange prisms, mp 195–197 °C. The mother liquor was further concentrated to afford an additional 0.38 g of **19**. Recrystallization from acetone gave the analytical sample: mp 196–199 °C dec; IR (KBr) 3460, 1702, 1675, 1550, 1370, 1340, 1245, 750, 720 cm^{-1}; 360 MHz ^1H NMR (DMSO-d_6) δ 9.49 (s, 1 H), 9.13 (d, 1 H, J = 5.5 Hz), 8.53 (d, 1 H, J = 8.5 Hz), 8.03 (d, 1 H, J = 5.5 Hz), 7.90 (d, 1 H, J = 7.7 Hz), 7.85 (s, 1 H), 7.68 (t, 1 H), 7.46 (t, 1 H); ^{13}C NMR (DMSO-d_6) δ 174.6, 158.3, 155.2, 150.0, 138.7, 136.3, 133.6, 130.0, 128.3, 125.3, 124.7, 124.1, 118.3, 116.3; MS *m/e* 248 (M^+, 100), 220, 192, 164, 115, 88, 50; UV (95% EtOH) λ_{max} (log ε) 241 (4.56), 270 (sh) (4.33), 364 (sh) (4.21), 383 (4.27) nm; with added base, the UV spectrum obtained was identical with that of **17**. Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.26; H, 3.42; N, 11.22.

Ellipticine (1a). A magnetically stirred suspension of the keto lactam **19** (0.5173 g, 2.084 mmol) in dry THF (90 mL) was heated under Ar at 40–50 °C for 20–30 min to effect dissolution, and the resulting yellow-orange solution was then rapidly cooled to −102 °C and treated over 30 s via syringe with MeLi (1.62 M in Et_2O; 2.64 mL, 4.27 mmol). The resulting cloudy, light tan mixture was stirred at −105 to −98 °C for 1 h and then allowed to warm to 5 °C over 4.5 h. Distilled H_2O (5 mL) was added, the mixture was stirred for 5 min, and the THF was removed in vacuo to give diol **23** as a pale yellow viscous residue. This material was immediately treated under Ar with absolute EtOH (150 mL) and excess $NaBH_4$ (6 pellets, ca. 1.5 g) and then refluxed with magnetic stirring for 22 h. The $NaBH_4$ was added in 3 equal portions; 2 pellets initially, 2 more after 0.5 h, and the last 2 pellets after 20 h. After approximately 1 h at reflux, the reaction mixture became canary yellow and highly fluorescent. At the end of the 22-h reflux period, the reaction mixture was cooled and the solvent was removed in vacuo. The resulting yellow solid was treated with $CHCl_3$ (250 mL) and magnetically stirred for 5–10 min, followed by the addition of H_2O (200 mL). The phases were separated, and the aqueous portion was extracted with additional $CHCl_3$ (3 × 70 mL). The aqueous portion was extracted with additional $CHCl_3$ (100 mL), slowly acidified with concentrated HCl to pH 2, and then

basified with aqueous NaOH to pH 9–10. After separating the $CHCl_3$ layer, the aqueous portion was extracted again with $CHCl_3$ (1 × 100 mL). The combined $CHCl_3$ extracts were washed with H_2O (150 mL) and brine (2 × 300 mL), dried (K_2CO_3), and concentrated in vacuo to afford a bright yellow solid. This material was dissolved in dry THF (150 mL) and rotary evaporated onto silica gel. Flash chromatography over silica gel (30 cm column) with $CHCl_3$ (100 mL) followed by EtOAc provided 52.5 mg (9.5%) of an unidentified compound as a colorless solid, mp 224–229 °C, which may be 5-hydroxy-5,11-dimethyl-5,11-dihydro-6*H*-pyrido-[4,3-*b*]carbazole, the immediate product of diol **23** reduction. The high-resolution mass spectrum of this material exhibited M^+ = 264.1252 (calcd 264.1263 for $C_{17}H_{16}N_2O$), 249, 246, 234, 226. Further elution with 7:3 THF–EtOAc gave 0.4198 g (82%) of ellipticine (**1a**) as a bright yellow solid, mp 310–315 °C dec (lit.[23] mp 311–315 °C dec). Sublimation at ca. 200 °C (0.2 Torr) gave ellipticine as an amorphous yellow solid, mp 313–317 °C dec. This material was identical (IR, TLC, UV, MS, mmp) with an authentic sample of ellipticine. Recrystallization from MeOH gave bright lemon yellow needles: mp 311–315 °C dec; IR (KBr) 3470, 1620, 1605, 1470, 1415, 1387, 1324, 1308, 1264, 1248, 1029, 845, 812, 780, 740, 660, 598, 584, 497, 465 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 11.40 (s, 1 H), 9.70 (s, 1 H), 8.44 (d, 1 H, J = 6.1 Hz), 8.40 (d, 1 H, J = 8.3 Hz), 7.93 (d, 1 H, J = 6.1 Hz), 7.60–7.52 (m, 2 H), 7.30–7.25 (m, 1 H), 3.30 (s, 3 H), 2.80 (s, 3 H); 90-MHz ^{13}C NMR (DMSO-d_6) δ 149.6, 142.6, 140.4, 140.3, 132.4, 127.9, 127.0, 123.7, 123.3, 123.1, 121.9, 119.1, 115.7, 110.6, 107.9, 14.3, 11.9; MS m/e 246 (M^+, 100), 245, 231, 217, 123 (M^{2+}, 22), 109, 96, 51; UV (95% EtOH) λ_{max} 224, 238, 246 (sh), 276 (sh), 286, 294, 332 nm; (95% EtOH + 1% of added 20% HCl) λ_{max} 225 (sh), 240, 248 (sh), 306, 353 nm.

For the diol **23**: MS m/e 280 (M^+), 265, 262, 247 (100), 219, 149, 123, 96 (found, M^+, 280.1202, $C_{17}H_{16}N_2O_2$ requires, M^+, 280.1212).

5-Methoxy-2-nitrotoluene. The procedure of Blaikie and Perkin was used.[24] To a 2-L three-neck Morton round-bottomed flask equipped with a reflux condenser, 500-mL addition funnel, N_2 inlet adapter, and mechanical stirring unit were added absolute MeOH (350 mL) and freshly cut Na (31.3 g, 1.36 mol). The mixture was stirred under N_2 for several hours until all of the sodium had dissolved. The colorless suspension of sodium methoxide which resulted was then cooled to 0–5 °C and treated over 15 min with a solution of 3-methyl-4-nitrophenol (102 g, 0.666 mol) in absolute MeOH (185 mL). There resulted a yellow-orange precipitate which was stirred for an additional 15 min and then treated over 10 min with dimethyl sulfate (171.8 g, 1.36 mol). Considerable heat was evolved, and cooling (0–5 °C) was maintained during the addition. The mixture was refluxed for 1 h, cooled, most of the solvent was removed in vacuo, and the residue was treated with H_2O (600 mL). After the mixture was cooled for 1 h, the product was collected by filtration, washed with 5% aqueous $NaHCO_3$ (200 mL) and H_2O (2 × 200 mL), and dried at 20–25 °C (1 Torr) to afford 95.72 g (86%) of 5-methoxy-2-nitrotoluene as an off-white fluffy solid (R_f 0.42, PhH), mp 48–48.5 °C (lit.[24] mp 55 °C). This material was used directly for the next reaction as described below.

***trans*-β-(Dimethylamino)-5-methoxy-2-nitrostyrene.** The procedure of Batcho and Leimgruber was used.[20] A magnetically stirred solution of 5-methoxy-2-nitrotoluene (93.7 g, 0.561 mol) and *N,N*-dimethylformamide dimethyl acetal (83.5 g, 0.701 mol) in *N,N*-dimethylformamide (300 mL) was heated for 21 h in a 2-L round-bottomed flask fitted with a heating mantle, a 20-cm Vigreux distillation head, a downward condenser, and receiver connected to a nitrogen inlet via a mineral oil bubbler. The heat input was adjusted so that the MeOH evolved during the course of reaction distilled slowly and the head temperature did not exceed 66 °C (63 mL of distillate was collected in this manner). The reddish brown solution was cooled and concentrated in vacuo at 70–75 °C to afford 160 g of a red viscous oil. This was treated with anhydrous MeOH (308 mL) and stored under N_2 at −5 °C for 3 h. The resulting crystalline material was collected by filtration, washed with hexane, and dried at 20 °C (1 Torr) to give 83.8 g (67%) of enamine, mp 65.5–66.5 °C (lit.[20] mp 67.5–69 °C). The mother liquor was concentrated in vacuo, treated with MeOH (40 mL), stored at −5 °C for 4 days, and then cooled further to −78 °C to yield 9.7 g (8%) of additional enamine, mp 58–60 °C. The enamine was immediately used in the next reaction as described below: ^{13}C NMR ($CDCl_3$) δ 162.5, 144.7, 138.7, 138.5, 128.0, 109.0, 107.4, 92.2, 55.4, 40.5.

5-Methoxyindole (28). The procedure of Batcho and Leimgruber was used.[20] A solution of the above enamine (20.0 g, 90.0 mmol) in benzene (200 mL) and 5% Pd/C (0.39 g) was hydrogenated (3 atm) at 25 °C in a 1-L autoclave using a Parr apparatus. After being shaken for 27 h, the catalyst was removed by filtration through a bed of Celite and was thoroughly extracted with benzene. The combined benzene extracts from three identical runs were washed successively with cold 1 M aqueous H_2SO_4 (2 × 150 mL), H_2O (150 mL), and cold 1 M aqueous K_2CO_3 (150 mL). The combined aqueous portions were treated with brine (200 mL) and extracted with additional benzene (3 × 150 mL). The combined benzene extracts were washed with brine (350 mL), dried (Na_2SO_4), and concentrated in vacuo to give 31.4 g of a greenish-brown viscous oil which solidified on standing. TLC of this substance showed the product **28** (R_f 0.22, PhH) and a small amount of origin material. Distillation gave 26.9 g (68%) of **28** as a colorless solid, mp 55–56 °C (lit.[20] mp 56.5–57.5 °C); bp 110 °C (0.2 Torr). This material was used directly for the next reaction as described below.

1-(Phenylsulfonyl)-5-methoxyindole (29). To a magnetically stirred solution of 5-methoxyindole (**28**) (7.08 g, 48.1 mmol) in dry THF (7.0 mL) under Ar at 75 °C was added dropwise via syringe over 5 min *n*-BuLi (1.65 M in hexane; 30.6 mL, 50.5 mmol). The cooling bath was removed, and the solution was stirred for 45 min while warming to 0 °C. The resulting indole anion precipitated as a white solid in a cloudy colorless solution. After the suspension was recooled to −75 °C, benzenesulfonyl chloride (9.35 g, 52.9 mmol) was added neat via syringe over 5 min, keeping the internal temperature below −70 °C. The resulting pale yellow mixture was allowed to warm slowly to room temperature overnight, poured into 5% aqueous $NaHCO_3$ (200 mL), and extracted with CH_2Cl_2 (4 × 75 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (2 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo to give 14.35 g of a light orange solid. This material was dissolved in 6:1 Et_2O–CH_2Cl_2 (200 mL), and the solution was concentrated to 50 mL. After cooling slowly to room temperature and then further in the cold, the product was collected by filtration, washed with cyclohexane, and dried to give 10.8 g (78%) of **29** as a colorless solid, mp 95–96 °C (lit.[25] mp 98–99 °C). An additional 0.81 g (6%) of **29** was obtained from the mother liquor; ^{13}C NMR ($CDCl_3$) δ 156.3, 138.1, 133.5, 131.6, 129.5, 129.0, 126.9, 126.5, 114.2, 113.6, 109.3, 103.6, 55.5.

1-(Phenylsulfonyl)-5-methoxyindol-2-yl 3-Carboxy-4-pyridyl Ketone (30). To a magnetically stirred solution of LDA (27.4 mmol) prepared from diisopropylamine (2.96 g, 29.3 mmol) and *n*-BuLi (1.60 M in hexane; 17.1 mL, 27.4 mmol) in dry THF (35 mL) under Ar at −75 °C was added via syringe over 4 min a solution of **29** (7.50 g, 26.1 mmol) in dry THF (40 mL). The resulting bright orange reaction mixture was allowed to warm slowly to 15 °C over 3 h. The deep red mixture was cooled to −100 °C and treated as rapidly as possible with a solution of pyridine anhydride **10** (4.24 g, 28.5 mmol) in dry THF (30 mL) while maintaining very efficient stirring and cooling (liquid N_2/dry ice/acetone mixture). The resulting cloudy, light tan reaction mixture was stirred at −100 °C for 1 h and then allowed to warm very slowly to room temperature overnight. After the solvent was removed by rotary evaporation, the resulting dark tan solid residue was dissolved in H_2O (150 mL) and the solution was slowly acidified to pH 2 with 20% HCl with efficient cooling and stirring. The resulting colorless precipitate was collected by filtration after 15 min at 5 °C, thoroughly washed with H_2O, and dried in vacuo to give 23.3 g of an off-white solid. This material was divided into two equal portions, and each one was treated with acetone (140 mL). The mixture was boiled until nearly all of the solid material had dissolved and then filtered by gravity (while hot)

(23) Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903.
(24) Blaikie, K.; Perkin, W. H., Jr. *J. Chem. Soc.* **1924**, *125*, 296.
(25) Sundberg, R. J.; Parton, R. L. *J. Org. Chem.* **1976**, *41*, 163.

to remove a small amount of residual solids. The hot filtrate was concentrated to 50 mL, allowed to cool slowly to room temperature, and then stored at 5–10 °C for 2 days to afford 5.50 g of **30** as colorless prisms, mp 220–224 °C dec. An additional 3.18 g of **30** was obtained from a second and third crop (R_f 0.18, THF). Thus, the combined yield of **30** was 76%. Crystallization from acetone gave the analytical sample as large, colorless prisms: mp 226–228 °C dec; IR (KBr) 2470, 1720, 1680, 1534, 1451, 1219, 1175, 1027, 960, 940, 848, 811, 750, 725, 685 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 9.11 (s, 1 H), 8.91 (d, 1 H, J = 5 Hz), 8.13–8.08 (m, 3 H), 7.76–7.64 (m, 3 H), 7.55 (d, 1 H, J = 5 Hz), 7.22–7.19 (m, 2 H), 7.15 (s, 1 H), 3.76 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 183.4, 165.9, 156.4, 153.0, 150.5, 146.8, 138.3, 137.5, 134.4, 133.8, 129.4, 128.4, 127.1, 125.5, 123.3, 122.2, 118.5, 116.4, 104.9, 55.5; MS m/e 436 (M^+), 392, 372, 353, 312, 295, 278, 263, 235, 208, 94, 77 (100); UV (95% EtOH) λ_{max} 217, 303 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, 60.62; H, 4.49; N, 5.63; S, 6.51.

5-Methoxyindol-2-yl 3-Carboxy-4-pyridyl Ketone (31). A magnetically stirred mixture of the protected keto acid **30** (6.72 g, 15.4 mmol), K_2CO_3 (8.75 g, 63.3 mmol), MeOH (180 mL), and H_2O (60 mL) were refluxed under N_2 for 5 h. The mixture was cooled, and the solvent was removed in vacuo to give a dark oil. This material was dissolved in H_2O (300 mL) and slowly acidified to pH 2–3 with 20% HCl while maintaining efficient cooling and stirring. The aqueous portion was then saturated with NaCl and extracted with EtOAc (4 × 100 mL). The combined extracts were washed with H_2O (2 × 100 mL) and brine (2 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 4.55 g (100%) of **31** as a light yellow solid after drying at 30 °C (0.5 Torr) (R_f 0.27, THF), mp 144–149 °C. This material was dissolved in acetone (125 mL), heated to boiling, and filtered by gravity (while hot) to remove a small amount of residual solids. The hot filtrate was concentrated to 70 mL, allowed to cool slowly to room temperature overnight, and then stored at 5–10 °C for 2 h. The product was collected by filtration, washed with cyclohexane, and dried to give 1.92 g of **31** as a pale yellow solid, mp 158–161 °C dec. The mother liquor was further concentrated to afford (in 2 crops) an additional 1.51 g of **31**. Crystallization from acetone gave the analytical sample as light yellow prisms: mp 163–166 °C dec; IR (KBr) 3320, 2460, 1726, 1638, 1525, 1452, 1411, 1165, 1015, 902, 842, 801, 754, 732, 669, 600, 536 cm^{-1}; 360-MHz ^1H NMR (DMSO-d_6) δ 13.7–13.4 (broad s, 1 H), 12.0 (s, 1 H), 9.15 (s, 1 H), 8.93 (d, 1 H, J = 5.6 Hz), 7.63 (d, 1 H, J = 5.6 Hz), 7.39 (d, 1 H, J = 10.0 Hz), 7.07 (d, 1 H, J = 2.4 Hz), 7.00 (dd, 1 H, J = 10.0 and 2.4 Hz), 6.61 (s, 1 H), 3.75 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 185.5, 165.8, 154.1, 153.0, 150.6, 147.8, 135.1, 133.9, 127.2, 125.1, 121.9, 118.0, 113.7, 111.5, 102.5, 55.3; MS m/e 296 (M^+), 278 (100), 263, 235, 207, 179, 164, 152, 139, 119, 102, 77, 50; UV (95% EtOH) λ_{max} 218, 321 nm. Anal. Calcd for $C_{16}H_{12}N_2O_4S \cdot {}^1/_2C_3H_6O$: C, 64.61; H, 4.65; N, 8.61. Found: C, 64.91; H, 4.72; N, 8.80.

8-Methoxyindolo[1,2-b][2,7]naphthyridine-5,12-quinone (32). The deprotected keto acid **31** (recrystallized; containing 0.5 mol of acetone of crystallization) (2.47 g, 7.59 mmol) was heated under N_2 with magnetic stirring in Ac_2O (190 mL) at ca. 85 °C for 26 h. The Ac_2O was nearly completely removed by distillation at 50–60 °C (10–20 Torr). The residue was cooled and treated with H_2O (200 mL). After the ice-cooled mixture was stirred for 0.5 h, the product was collected by filtration, washed several times with H_2O, and dried at 40 °C (0.5 Torr) to afford 2.06 g (98%) of methoxy keto lactam **32** as a light yellow-orange solid which was homogeneous by TLC (R_f 0.66, THF), mp 238–241 °C dec. This material (1.85 g) was treated with acetone (500 mL), heated for 2 h, and filtered by gravity (while hot) to remove 0.85 g of **32**, mp 254–255 °C dec. An additional 0.83 g of **32** (mp 246–249 °C dec) was obtained by concentrating the filtrate to 120 mL and allowing the product to slowly crystallize over several hours. Recrystallization of the former material from acetone gave the analytical sample: mp 258–259 °C dec; IR (KBr) 1704, 1677, 1550, 1486, 1443, 1375, 1340, 1261, 1220, 1183, 1025, 863, 823, 775, 724, 683, 557, 371 cm^{-1}; 360-MHz ^1H NMR (HOAc-d_4) δ 9.63 (s, 1 H), 9.15 (d, 1 H, J = 5.8 Hz), 8.53 (d, 1 H, J = 9.4 Hz), 8.20 (d, 1 H, J = 5.8 Hz), 7.77 (s, 1 H), 7.33–7.27 (m, 2 H), 3.90 (s, 3 H); MS m/e 278 (M^+, 100), 263, 235, 207, 144, 125; UV (95% EtOH) λ_{max} (log ϵ) 248 (4.37), 292 (4.27), 375 (sh) (4.05), 385 (4.06) nm; with added base, the UV spectrum obtained was identical with that of **31**. Anal. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.02; H, 3.65; N, 10.11.

9-Methoxyellipticine (1b). A magnetically stirred suspension of the methoxy keto lactam **32** (141.8 mg, 0.5095 mmol) in dry THF (50 mL) was heated under Ar at 50 °C for 45 min to effect complete dissolution, and the resulting yellow-orange solution was then rapidly cooled to −100 °C and treated over 10–15 s via syringe with MeLi (1.62 M in Et_2O; 0.64 mL, 1.04 mmol). The resulting tan mixture was stirred at −100 °C for 1 h and then allowed to warm to 15 °C overnight. Distilled H_2O (4 mL) was added, the mixture was stirred for 10 min, and the THF was removed in vacuo to give the derived diol as a tan viscous residue. This material was immediately treated under Ar with absolute EtOH (75 mL) and excess $NaBH_4$ (5 pellets, ca. 1.25 g) and then refluxed with magnetic stirring for 6.5 h. The $NaBH_4$ was added in portions: 2 pellets initially and 1 every 1.5 h thereafter. After approximately 1 h at reflux, the reaction mixture became yellow and highly fluorescent. At the end of the 6.5-h reflux period, the reaction mixture was cooled and the solvent was removed in vacuo. The resulting solid residue was treated with $CHCl_3$ (250 mL) and magnetically stirred for 5 min followed by the addition of H_2O (200 mL). The mixture was slowly acidified with 20% HCl to pH 2 and then basified with aqueous 2 N NaOH to pH 10. After separating the $CHCl_3$ layer, the aqueous portion was partitioned overnight with fresh $CHCl_3$ (150 mL). The aqueous portion was then extracted further with $CHCl_3$ (3 × 75 mL). The combined $CHCl_3$ extracts were washed with H_2O (150 mL) and brine (2 × 250 mL), dried (K_2CO_3), and concentrated in vacuo to afford 140.0 mg of an orange-brown solid after drying at 65 °C (0.1 Torr). This material was dissolved in 1:1 EtOAc–THF and rotary evaporated onto silica gel. Flash chromatography over silica gel (20-cm column) with EtOAc (175 mL) followed by 2:1 EtOAc–THF gave 99.5 mg (75%)[26] of 9-methoxyellipticine (**1b**) as yellow-orange crystals (R_f 0.28, THF). Recrystallization from EtOAc gave **1b** as yellow-brown crystals, mp 275–278 °C dec (lit.[23] mp 280–285 °C dec). This material was identical in all respects (TLC, IR, UV, MS, mmp 275–279 °C dec) with a sample of naturally occurring 9-methoxyellipticine: IR (KBr) 3450, 1624, 1600, 1482, 1435, 1400, 1296, 1252, 1220, 1143, 1024, 802, 686, 589, 455 cm^{-1}; MS m/e 276 (M^+, 100), 275, 261, 218, 138, 116, 109, 102, 96, 88; UV (95% EtOH) λ_{max} 243, 276 (sh), 291, 306 (sh), 335, 351 (sh), 397 nm; (95% EtOH + 1% of added 20% HCl) λ_{max} 225 (sh), 245, 252 (sh), 276, 312, 356, 377 nm.

5-n-Butyl-11-methyl-6H-pyrido[4,3-b]carbazole (34) and 5,11-Di-n-butyl-6H-pyrido[4,3-b]carbazole (35). A magnetically stirred suspension of the keto lactam **19** (225.5 mg, 0.9084 mmol) in dry THF (40 mL) was heated under Ar at 40–50 °C for 20–30 min to effect complete dissolution and the resulting yellow-orange solution was then rapidly cooled to −102 °C and treated over 20 s via syringe with n-BuLi (1.70 M in hexane; 0.54 mL, 0.92 mmol). The mixture was stirred for 4–5 min at −100 °C, and then MeLi (1.62 M in Et_2O; 0.57 mL, 0.92 mmol) was added rapidly via syringe. The reaction mixture was stirred at −100 °C for 1 h and then allowed to warm slowly to 5 °C over an additional 1.5 h. Distilled H_2O (5 mL) was added, the mixture was stirred for 5 min, and the THF was removed in vacuo to give the derived diol mixture. This material was immediately treated under Ar with absolute EtOH (75 mL) and excess $NaBH_4$ (5 pellets, ca. 1.25 g) and then refluxed with magnetic stirring for 22 h. The $NaBH_4$ was added in portions: 2 pellets initially, 1 more after 40 min, and the last 2 pellets after 20 and 21 h. After approximately 1 h at reflux, the reaction mixture became yellow and highly fluorescent. At the end of the 22-h reflux period, the mixture was cooled and the solvent was removed in vacuo. The resulting yellow solid residue was treated with $CHCl_3$ (150 mL) and H_2O (100 mL) and stirred for 1 h. The phases were separated, and the aqueous portion was extracted with additional $CHCl_3$ (3 × 75 mL). Ethyl acetate (200 mL) was then added to the aqueous phase, and the mixture was stirred overnight. The phases were separated, and the aqueous portion was extracted with fresh EtOAc (100 mL). All of the organic extracts were combined, washed with brine (2 × 250 mL), dried (K_2CO_3), and concentrated

(26) The yield is based on ca. 94% purity of lactam **32**, since mass spectroscopy indicated 6% of a C-6 methoxy keto lactam in the crude sample of **32** used in this experiment.

in vacuo to afford a yellow solid. This material was dissolved in dry THF and rotary evaporated onto silica gel. Flash chromatography over silica gel with EtOAc provided 55.8 mg (18%) of 5,11-di-*n*-butyl-6*H*-pyrido[4,3-*b*]carbazole (**35**) as a yellow solid, mp 201–206 °C (R_f 0.50, THF). Further elution with ethyl acetate gave 182.7 mg (70%) of 5-*n*-butyl-11-methyl-6*H*-pyrido[4,3-*b*]-carbazole (**34**) as a yellow solid (R_f 0.40, THF), decomposes at 303 °C (begins to lose crystallinity at ca. 283 °C).

For **34**: IR (KBr) 3470, 2960, 2935, 2875, 1615, 1598, 1468, 1408, 1373, 1316, 1300, 1257, 1240, 1019, 836, 807, 726, 583, 463 cm^{-1}; partial 360-MHz ^1H NMR (DMSO-d_6) δ 11.38 (s, 1 H), 9.71 (s, 1 H), 8.43–8.38 (m, 2 H), 7.93 (d, 1 H, J = 6.0 Hz), 7.59–7.53 (m, 2 H), 7.28–7.24 (m, 1 H), 3.28 (s, 3 H), 0.94 (t, 3 H, J = 7.3 Hz); UV (95% EtOH) λ_{max} 225, 239 (sh), 246 (sh), 276 (sh), 286.5, 295, 333 nm; (95% EtOH + 1% of added 20% HCl) λ_{max} 225 (sh), 240, 249 (sh), 307, 354 nm; MS m/e 288 (M^+), 245 (100) (found, M^+, 288.1656, $C_{20}H_{20}N_2$ requires, M^+, 288.1627). Anal. Calcd for $C_{20}H_{20}N_2 \cdot {}^6/_{10}H_2O$: C, 80.29; H, 7.14; N, 9.36. Found: C, 80.26; H, 7.15; N, 9.10.

For **35**: IR (KBr) 3430, 2940, 2865, 1602, 1462, 1410, 1379, 1321, 1263, 1245, 800, 730, 462 cm^{-1}; UV (95% EtOH) λ_{max} 223, 240 (sh), 276 (sh), 286, 294, 333 nm; MS m/e 330 (M^+), 287 (100) (found, M^+, 330.2103, $C_{23}H_{26}N_2$ requires, M^+, 330.2096).

11-Demethylellipticine (37). To a magnetically stirred solution of keto lactam **19** (500 mg, 2.01 mmol) in dry THF (75 mL) at −100 °C was added MeLi (1.05 M in Et_2O, 1.9 mL, 2.00 mmol) via syringe. After 5 min at −100 °C, $LiBHEt_3$ (1.0 M in THF, 2.0 mL, 2.00 mmol) was added via syringe. The reaction mixture was allowed to warm gradually to 20 °C overnight, then H_2O (5 mL) was added, and after 5 min the THF was removed in vacuo. The residue was dissolved in EtOH (100 mL), treated with $NaBH_4$ (2 pellets, 600 mg, 16 mmol), and heated to reflux. Additional $NaBH_4$ (4 pellets, 1.2 g, 32 mmol) was added over 20 h. After 48 h at reflux, the mixture was allowed to cool to 20 °C, the solvent was removed in vacuo, and the residue was treated with H_2O (200 mL) and $CHCl_3$ (200 mL). The layers were separated, and the aqueous phase was acidified (pH = 2) with concd HCl, extracted with $CHCl_3$ (1 × 100 mL), basified (pH = 9–10) with 50% aqueous NaOH, and extracted with $CHCl_3$ (1 × 100 mL). This process was repeated twice, and then the aqueous portion was neutralized (pH = 7–8) and extracted with $CHCl_3$ (1 × 100 mL). The combined extracts were dried (K_2CO_3) and concentrated in vacuo to afford a yellow solid (532 mg). Flash chromatography (hexane, 200 mL; CH_2Cl_2, 250 mL; EtOAc, 500 mL) gave both 11-demethylellipticine (**37**; 264 mg, 57%) [R_f = 0.33 (THF); mp 274–275 °C (lit.[27] mp 275–277 °C); ^{13}C NMR ($CDCl_3$) δ 153.6, 142.6, 140.9, 132.2, 127.7, 125.3, 123.5, 122.4, 121.4, 119.2, 119.1, 117.0, 116.0, 111.2, 110.6, 12.2; UV (95% EtOH) λ_{max} 272 (sh), 283, 293, 327 nm; (95% EtOH + HCl) λ_{max} 305, 349 nm; MS m/e (rel int) 232 (M^+, 100), 217 (M − Me, 2), 166 (M^{2+}, 23)] and ellipticine (**1a**; 148.4 mg, 30%), which was identical by TLC to a known sample.

5,11-Divinyl-6*H*-pyrido[4,3-*b*]carbazole (41). To a magnetically stirred solution of keto lactam **19** (75.0 mg, 0.302 mmol) in dry THF (15 mL) at −100 °C was added via syringe vinyllithium (1.94 M in THF, 0.31 mL, 0.60 mmol). After 1 h at −90 °C, the mixture was allowed to warm to 25 °C over 2.5 h. Water (3 mL) was added, and after 5 min the solvent was removed in vacuo. The residue was treated with *t*-BuOH (50 mL) and $NaBH_4$ powder (26.2 mg, 0.693 mmol) and heated to reflux. After 24 h at reflux, the solvent was removed in vacuo, and the residue was treated with H_2O (25 mL) and continuously extracted with $CHCl_3$ for 3 days. The $CHCl_3$ extract was concentrated in vacuo to afford an orange solid (88.6 mg). Flash chromatography (hexane, 100 mL; EtOAc, 200 mL; 2:1 EtOAc/THF, 150 mL) gave **41** (50.7 mg, 62%) cleanly as a yellow solid which was recrystallized from MeOH: R_f = 0.52 (THF); mp 243–245 °C; IR (KBr) 3340 (m), 3100 (m), 2940 (m), 1655 (m), 1600 (s), 1470 (s), 1250 (s), 1100 (m), 1000 (m), 750 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.6 (s, 1 H), 8.5–8.3 (m, 2 H), 7.8 (d, 1 H, J = 6.1 Hz), 7.5–7.2 (m, 5 H), 6.05 (dd, 1 H, J = 9.9 and 1.5 Hz), 5.9 (dd, 1 H, J = 10.8 and 1.5 Hz), 5.85 (dd, 1 H, J = 17.9 and 1.5 Hz), 5.7 (dd, J = 16.5 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 151.1, 141.8, 141.1, 139.4, 132.6, 132.0, 131.4, 127.7, 124.2, 123.9, 122.9, 122.2, 121.7, 120.6, 120.1, 119.9, 116.2, 110.4, 106.0; UV (95% EtOH) λ_{max} 290, 337 nm; (95% EtOH + HCl) λ_{max} 308, 354 nm; HRMS calcd for $C_{19}H_{14}N_2$ 270.1157, observed 270.1159. Anal. Calcd for $C_{19}H_{14}N_2 \cdot {}^2/_5H_2O$: C, 82.23; H, 5.37; N, 10.09. Found: C, 82.09; H, 5.44; N, 10.11.

5-Methyl-11-vinyl-6*H*-pyrido[4,3-*b*]carbazole (40). To a magnetically stirred solution of keto lactam **19** (75.0 mg, 0.302 mmol) in dry THF (15 mL) at −100 °C was added via syringe MeLi (1.0 M in Et_2O, 0.30 mL, 0.30 mmol). After 5 min, vinyllithium (1.94 M in THF, 0.16 mL, 0.31 mmol) was added via syringe. After 1 h at −90 °C, the mixture was allowed to warm to 25 °C over 3 h. Water (5 mL) was added, and after 5 min the solvent was removed in vacuo. The residue was treated with *t*-BuOH (50 mL) and $NaBH_4$ powder (22.9 mg, 0.605 mmol) and heated to reflux. After 23 h at reflux, the solvent was removed in vacuo, and the residue was treated with H_2O (25 mL) and $CHCl_3$ (30 mL). The aqueous layer was acidified (pH = 2) with concd HCl, extracted with $CHCl_3$ (30 mL), basified (pH = 10–11) with 50% aqueous NaOH, and extracted with $CHCl_3$ (30 mL). This process was repeated until the aqueous layer was clear. The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford an orange solid (97.7 mg). Flash chromatography (hexane, 100 mL; 1:1 EtOAc–hexane, 600 mL; EtOAc, 100 mL) gave **40** (36.1 mg, 46%) [R_f = 0.44 (THF); mp 283–285 °C dec; IR (KBr) 3140 (m), 3070 (m), 2980 (m), 1600 (s), 1470 (s), 1410 (s), 1250 (s), 1090 (m), 750 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.6 (s, 1 H), 8.6–8.4 (m, 2 H), 7.8–7.2 (m, 5 H), 6.1 (dd, 1 H, J = 9.9 and 1.5 Hz), 5.8 (dd, 1 H, J = 16.5 and 1.5 Hz), 2.7 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.5, 142.8, 140.6, 140.5, 140.4, 132.4, 132.3, 129.7, 127.5, 127.2, 123.7, 123.4, 119.4, 119.1, 115.8, 110.8, 109.9, 12.1; UV (95% EtOH) λ_{max} 275 (sh), 286, 292, 331 nm; (95% EtOH + HCl) λ_{max} 307, 353 nm; HRMS calcd for $C_{18}H_{14}N_2$ 258.1157, observed 258.1134] and ellipticine (**1a**; 9.7 mg, 13%). Anal. Calcd for $C_{18}H_{14}N_2 \cdot {}^2/_3H_2O$: C, 79.97; H, 5.72; N, 10.36. Found: C, 79.98; H, 5.52; N, 10.49.

1-(Phenylsulfonyl)indol-2-yl 2-Carboxyphenyl Ketone (45). To a magnetically stirred solution of LDA (0.032 mol), prepared from diisopropylamine (3.54 g, 0.035 mol) and *n*-BuLi (21.9 mL of 1.46 M solution in hexane, 0.032 mol), in dry THF (50 mL) under N_2 at −78 °C was added via syringe over 10 min a solution of 1-(phenylsulfonyl)indole (**13**) (7.50 g, 0.029 mol) in THF (4.0 mL). The mixture was stirred at −75 °C for 2 h and allowed to warm slowly to 10 °C over 1 h. The mixture was recooled to −78 °C, a solution of freshly sublimed phthalic anhydride (4.44 g, 0.030 mol) in THF (40 mL) was added rapidly via syringe, and the mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure, and the residue was taken up in H_2O (100 mL), cooled to 0 °C, and acidified to pH 2–3 by the dropwise addition of 20% aqueous HCl. The resulting solid was filtered and dried to afford 11.1 g (95%) of **45** as a light tan powder. Recrystallization from acetone afforded 8.41 g of **45**: mp 212–213 °C; IR (KBr) 3320, 1705, 1670, 1340, 1180, 1050, 750, 725, 660, 580 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.3–7.1 (m, 8 H), 6.9 (s, 1 H); MS m/e 405 (M^+), 265, 247 (100), 219, 190, 165, 89, 77; UV (95% EtOH) λ_{max} 217, 245 (sh), 267 (sh), 276 (sh), 295 nm. Anal. Calcd for $C_{22}H_{15}NO_5S$: C, 65.17; H, 3.73; N, 3.46; S, 7.91. Found: C, 65.24; H, 3.77; N, 3.45; S, 7.87.

2-Carboxyphenyl 2-Indolyl Ketone (46). A solution of keto acid **45** (3.98 g, 9.83 mmol) in MeOH (100 mL), H_2O (35 mL), and K_2CO_3 (5.42 g, 0.039 mol) was refluxed under N_2 for 24 h. The MeOH was removed by rotary evaporation, and the resulting flocculent white suspension was taken up in water (300 mL), cooled to 0 °C, and acidified to pH 2–3 with 20% aqueous HCl. The mixture was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a yellow solid which was recrystallized from acetone to afford 2.42 g (93%) of **46**: mp 234–235 °C dec; IR (KBr) 3200, 1705, 1605, 1515, 1390, 1270, 1245, 835, 740 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.3–6.9 (m, 8 H), 6.7 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 188.7, 167.5, 142.3, 139.1, 137.1, 132.8, 130.6, 128.8, 128.4, 126.5, 123.6, 121.4, 121.1, 113.3, 112.0, 111.6; UV (95% EtOH) λ_{max} 225 (sh), 315 nm. Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.43; H, 4.22; N, 5.27.

Indolo[1,2-*b*]isoquinoline-6,11-quinone (47). A suspension of keto acid **46** (0.511 g, 1.93 mmol) in Ac_2O (100 mL) was heated at 90 °C under N_2 for 24 h, allowed to cool to room temperature,

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and placed in a freezer overnight. Filtration afforded 0.27 g (56%) of keto lactam **47**. The filtrate was evaporated under reduced pressure, and the residue was recrystallized from acetone to afford an additional 0.11 g (24%) of keto lactam **47** (80% total): mp 217–218 °C dec; IR (KBr) 1690, 1660, 1550, 1370, 1335, 1310, 1240, 750, 710 cm^{-1}; ^{13}C NMR (acetone-d_6) δ 175.4, 159.0, 137.0, 134.3, 133.9, 133.5, 133.4, 131.0, 129.7, 129.2, 128.5, 126.8, 125.2, 123.6, 117.1, 116.3; MS *m/e* 247 (M^+, 100), 219, 190, 164, 149, 115, 95, 76; UV (95% EtOH) λ_{max} 225 (sh), 240, 265, 360 nm. Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.69; H, 3.70; N, 5.65.

6,11-Dimethyl-5*H*-benzo[*b*]carbazole (48). To a solution of keto lactam **47** (0.289 g, 1.17 mmol) in dry THF (50 mL) at −78 °C was added slowly MeLi (3.38 mL of 0.76 M in ether, 2.57 mmol). The resulting dark green solution was stirred for 2 h at −78 °C and allowed to warm to room temperature over an additional 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in 95% EtOH (40 mL). Sodium borohydride (2 pellets) was added, and the mixture was refluxed for 24 h. The solvent was removed under reduced pressure, and the residue was taken up in H_2O (15 mL), acidified with glacial HOAc, and then neutralized with 10% aqueous NaOH. Extraction with $CHCl_3$ (4 × 100 mL), drying (Na_2SO_4), and concentration in vacuo gave crude **48**. Recrystallization from CCl_4 gave 0.250 g (87%) of **48**: mp 211–213 °C (lit.[7a] mp 211–212 °C), which was identical (IR, UV, TLC) to a sample previously prepared in this laboratory:[28] IR (KBr) 3415, 1630, 1610, 1475, 1460, 1390, 1365, 1320, 1300, 1240, 745, 710 cm^{-1}; MS *m/e* 245 (M^+, 100), 230, 215, 202, 149, 115; UV (95% EtOH) λ_{max} 234, 248 (sh), 271, 282 (sh), 297 nm.

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Substrate Specificity and Carbohydrate Synthesis Using Transketolase

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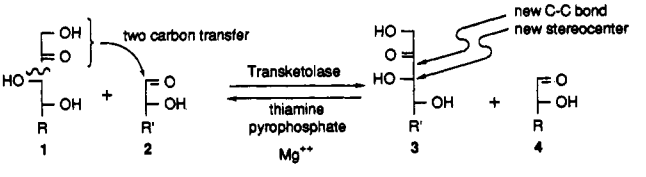
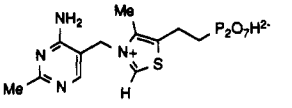
This paper describes the use of the enzyme transketolase as a catalyst in organic synthesis. The properties of transketolase from both yeast and spinach were investigated. The yeast enzyme was found to be more convenient for routine use. Examination of the substrate specificity of yeast transketolase demonstrated that the enzyme accepts a wide variety of 2-hydroxy aldehydes as substrates. A practical protocol for transketolase-catalyzed condensation of hydroxypyruvic acid with these aldehydes has been developed and used for the synthesis of four carbohydrates: L-idose, L-gulose, 2-deoxy-L-xylohexose, and L-xylose.

This paper describes our studies of the use of transketolase (EC 2.2.1.1) (TK) in organic synthesis. As part of the oxidative pentose phosphate pathway, TK transfers a two-carbon ketol unit from a donor ketose (**1**) to an acceptor aldose (**2**) (Scheme I).[1] The reaction is reversible, and the products of the reaction, a ketose homologated by two carbons (**3**) and an aldose shortened by two carbons (**4**), can also function as reaction partners. The TK-catalyzed two-carbon transfer reaction shown in Scheme I requires the presence of the cofactors thiamine pyrophosphate (TPP, **5**) and magnesium(II).[2]

To drive the equilibrium established by TK, Srere et al. used β-hydroxypyruvic acid (HPA) (**6**) (Scheme II) as the ketol donor.[3] This strategy coupled the formation of the glycolyl–TPP complex **9** with the decarboxylation of HPA and rendered the complete reaction irreversible. Scheme II shows the catalytic cycle for the TK-mediated condensation of HPA (**6**) and α-hydroxy aldehyde **10**. Addition

Scheme I. Transketolase-Catalyzed Interconversion of Carbohydrates





Thiamine pyrophosphate (TPP) **5**

of the anion of TPP (**7**) to HPA results in the formation of intermediate **8**. This adduct loses CO_2 and generates the glycolyl–thiamine pyrophosphate adduct **9**. The adduct, represented by two canonical forms, **9a** and **9b**, is nucleophilic and adds to substrate **10** to afford **11**.[4] Fragmentation of **11** then regenerates the TPP anion **7**,

(1) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1985; p 76.
(2) Datta, A.; Racker, E. *J. Biol. Chem.* **1961**, *236*, 624.
(3) Srere, P.; Cooper, J. R.; Tabachnick, M.; Racker, E. *Arch. Biochim. Biophys.* **1958**, *74*, 295. Compare: de la Haba, G.; Lafer, I. G.; Racher, E. *J. Biol. Chem.* **1955**, *214*, 409.
(4) For a review of thiamine chemistry see: Kluger, R. *Chem. Rev.* **1987**, *87*, 863.

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