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An Efficient Synthesis of C-11 Substituted 6H-Pyrido[4,3-b]Carbazoles

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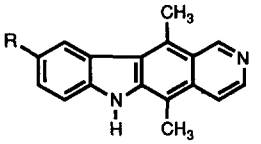
Abstract: A synthesis of the natural product 5-methyl-6H-pyrido[4,3-b]carbazole-11-methanol, 5 from the ketolactam 7 is described. Compound 7 was treated with one equivalent of MeLi followed by quenching of the reaction mixture with water to give the lactone 19. Compound 19 was treated with a number of organolithium reagents such as methyllithium, n-butyllithium, ethoxyvinyl lithium and the lithio derivative of formaldehyde diethyl mercaptal to give, after sodium borohydride reduction, 1, 15, 30, and 31 respectively. Compounds 30 and 31 were hydrolyzed and then reduced to give compounds 5 and 6 respectively, in an overall yield of 21%. Compounds 16 and 22 were identified as the intermediates in the Saulnier-Gribble synthesis of ellipticine.

INTRODUÇTION

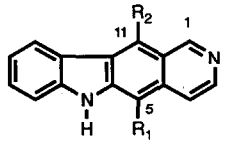
The alkaloid ellipticine **1** and its 9-oxygenated derivatives **2** and **3** are of considerable interest because of their antitumor properties in several experimental[1] and human[2] tumor systems. In a previous paper [3] we reported the synthesis and antitumor activity of 11-methyl-6H-pyrido[4,3-b]carbazole-5-methanol-N-methylcarbamate **4** and suggested a mechanism to account for the antitumor activity of ellipticine which differed from the one proposed by Auclair and Paoletti.[4] In our suggested mechanism we postulated that the methyl group at C-5 in ellipticine is the site of metabolic activation. However there was no compelling evidence to rule out activation at the alternate C-11 methyl group. Thus we were interested in preparing a number of compounds with substitution at the C-11 position of ellipticine and testing them for their antitumor properties. To synthesize some of our target compounds the need arose for substantial quantities of alcohols **5** and **6** which required the presence of an aldehyde or a ketone group at the C-11 position of ellipticine (Fig. 1).[5]

Compound **5** is a natural product which was first isolated in 1982 from the stem bark of *Strychnos dinklagei* by Koch et. al.[6] along with nine other alkaloids. Compound **5** was obtained in very small quantity as a non-crystalline solid and was characterized by means of a high resolution mass spectrum and a proton NMR spectrum. Suffness and Cardell[7] suggested that this compound be evaluated for anticancer activity, but up to the present time insufficient quantities have been available from natural sources. We now report the synthesis of **5** and a number of other C-11 substituted ellipticine analogs. In the course of this study directed toward the synthesis of C-11 substituted ellipticine derivatives we had occasion to identify the possible intermediates involved in Saulnier-Gribble synthesis of ellipticine.[8]

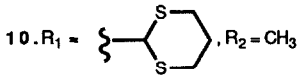
A number of methods are available for the synthesis of ellipticine and many of its analogs.[7,9] However functionalization at the C-11 position of ellipticine has not been reported. In 1982, Saulnier and Gribble reported a synthesis of ellipticine utilizing the ketolactam **7** which was obtained from indole in five steps. A conceptually similar synthesis of ellipticine has been reported by Joule[9b] using a quinone derivative **8**. The versatility of **7** and **8** has been illustrated in the synthesis of several dialkyl substituted pyrido[4,3-b]carbazoles.[10,11]



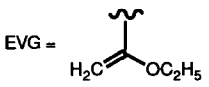
1. R = H
2. R = OH
3. R = OCH_3



4. R_1 = $CH_2OOCNHCH_3$, R_2 = CH_3
5. R_1 = CH_3, R_2 = CH_2OH
6. R_1 = CH_3, R_2 = $CHOHCH_3$



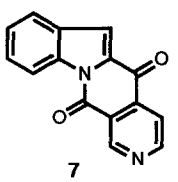
10. R_1 = , R_2 = CH_3



11. R_1 = $CH=CH_2$, R_2 = CH_3
12. R_1 = CHO, R_2 = CH_3
13. R_1 = CH_3, R_2 = CHO
14. R_1 = CH_3, R_2 = H
15. R_1 = CH_3, R_2 = Ethoxy Vinyl Group (EVG)

Fig. 1

We decided to use **7** as our starting material because it eliminates the need to prepare the pyridine lactone **9** required to synthesize **8**[9b] (Fig. 2). Compound **9** was prepared by Joule and co-workers[11] using pyridine-4-carboxylic acid in four steps in an overall yield of 20%.



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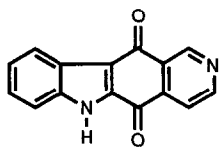
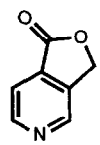


8



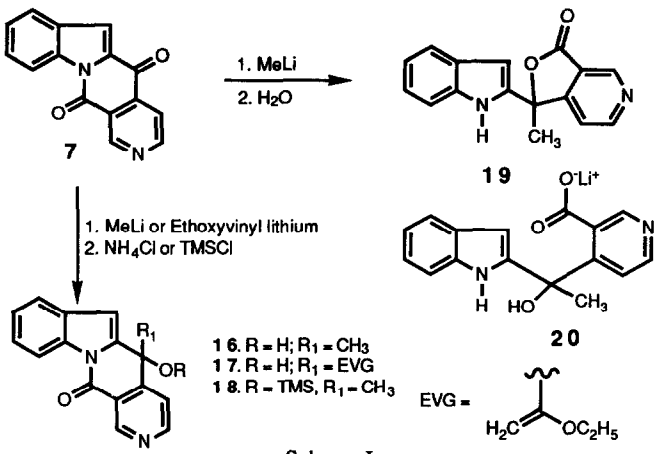
9

Fig. 2

It is reported that when the ketolactam **7** was treated with either one equivalent of 2-lithio-2-trimethylsilyl-1,3-dithiane[10] or vinyllithium[12] followed by 1 equivalent of methyllithium, a diol was obtained which was immediately reduced with $NaBH_4$ (ethanol, reflux) to give the corresponding C-5 substituted derivatives **10** and **11** respectively. Both **10** and **11** were then converted to 5-formylellipticine **12**.[10, 12] Our attempts to reverse the above order of addition of the organolithium reagents did not furnish the desired precursor of 11-formyl ellipticine **13**. When we treated the ketolactam with one equivalent of methyllithium followed by ethoxyvinyl lithium and $NaBH_4$ reduction step, ellipticine **1** and 11-norellipticine **14** were obtained along with a trace amount of the desired compound **15**. Ellipticine was an expected by-product based upon the work of Gribble[8] in which he demonstrated a lack of regiospecificity resulting from nucleophilic attack upon the ketolactam **7**.

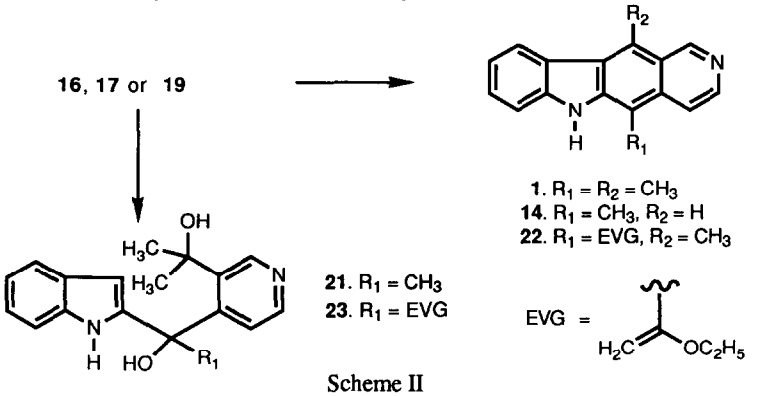
RESULTS AND DISCUSSION

When the ketolactam **7** was treated with one equivalent of MeLi or ethoxyvinyl lithium at -78 °C and the reaction was quenched with solid ammonium chloride, the lactam carbinols **16** and **17** were obtained as the major products (Scheme I). Similarly treatment of **7** with one equivalent of MeLi followed by quenching of the reaction mixture with TMSCl *in situ* gave the trimethylsilyl ether derivative **18** in good yield. However when the reaction mixture was quenched with water instead of solid NH_4Cl or TMSCl, lactone **19** was obtained as the main product. We believe that the LiOH produced during aqueous workup hydrolyzed the lactam **16** to give lithium salt of keto acid **20**. The salt **20** was water soluble and could not be extracted in organic solvents, but on acidification with concentrated HCl it underwent spontaneous cyclization to give the lactone **19**. The structure assigned to the lactone **19** is fully supported by spectral and analytical data. Conversion of lactam **16** to the lactone **19** in LiOH also went smoothly.



Scheme I

Lactam **16** and the lactone **19** were transformed to pyridocarbazoles essentially in one step.[7] When **16** and **19** were reduced with $NaBH_4$ in refluxing ethanol 11-norellipticine **14** was obtained in 54% yield (Scheme II). Treatment of lactone **19** with MeLi at low temperature followed by $NaBH_4$ reduction, gave ellipticine **1** in good yield. However when lactam **16** was treated similarly, ellipticine was obtained as a minor (5-10%) product. The major product of the reaction was diol **21** (75%). Similar results were obtained when **17** was subjected to the same reaction sequence i.e. treatment with MeLi followed by $NaBH_4$ reduction, to give pyrido[4,3-b]carbazole **22** in only 5% and diol **23** in 80% yield.



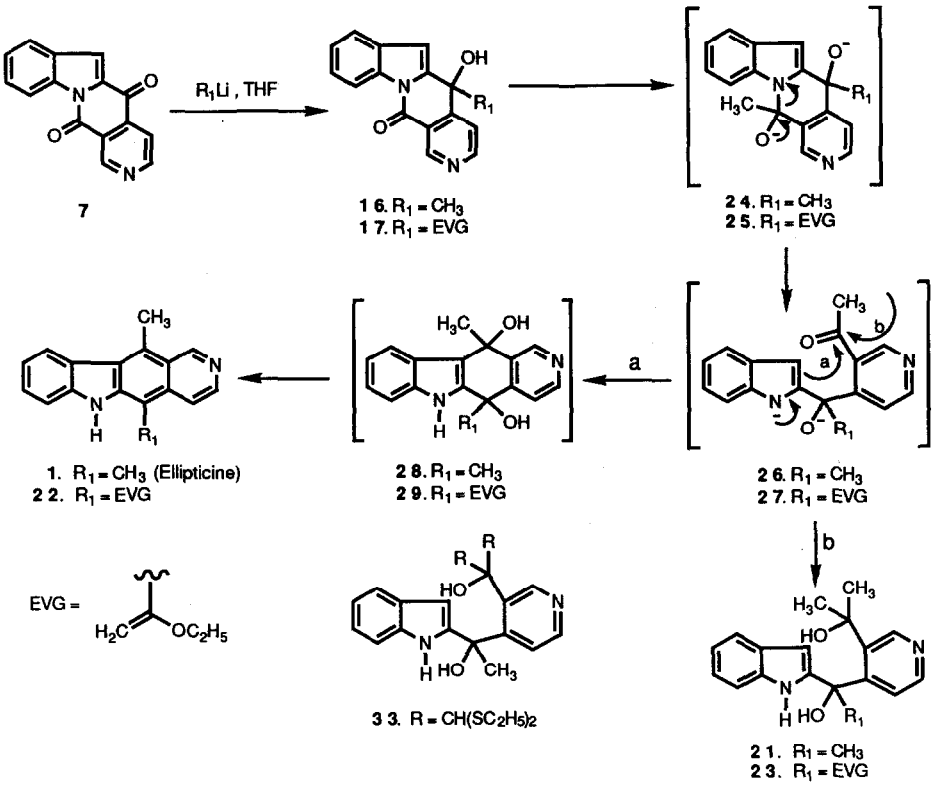
Scheme II

A possible explanation for the formation of **21** and **23** is shown in Scheme III. Addition of MeLi to either **16** or **17** would result in the formation of **24** and **25** which would break the lactam bond to give **26** and **27**, respectively. These compounds could either cyclize to give **28** and **29** (path a), followed by dehydration and aromatization to give pyrido[4,3-b]carbazole derivatives such as **1** and **22** or they could undergo nucleophilic attack by excess MeLi to give **21** and **23** (path b).

The formation of the tertiary carbinols **21** and **23** are the first direct evidence that **26** is an intermediate in the Saulnier-Gribble synthesis of ellipticine as suggested by these authors.[8] The isolation of lactams **16-18** in high yield is the evidence that **16** is the first intermediate in the Saulnier-Gribble synthesis of ellipticine.[8]

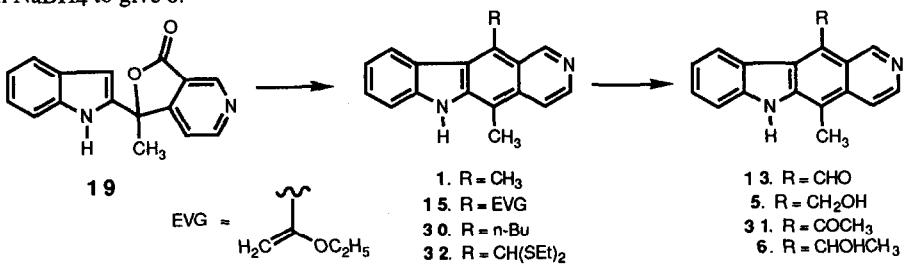
The lactone **19** proved to be a very useful compound for introducing functionality at the C-11 position of ellipticine.[12] A variety of primary and secondary organometallic lithium reagents were successfully added to the

lactone **19** at -30 °C to room temperature (Scheme IV). These adducts on $NaBH_4$ reduction gave the corresponding pyrido[4,3-b]carbazoles. For example when **19** was treated with an excess of MeLi, ethoxyvinyl



Scheme III

or n-BuLi at 0 °C, followed by $NaBH_4$ reduction, compounds **1**, **15**, and **30** were obtained, respectively, in good yield. The ethoxyvinyl derivative of ellipticine **15** was hydrolyzed in dil HCl to give **31** which in turn was reduced with $NaBH_4$ to give **6**.



Scheme IV

However addition of an aldehyde equivalent such as 2-lithio-1-trimethylsilyl-1,3-dithiane[13] or the lithio derivative of formaldehyde diethylmercaptal monosulfoxide[14] to either the lactone **19** or the lactams **16** and **18** was unsuccessful. Finally when the lactone **19** was treated a large excess of the lithio derivative of

formaldehyde diethylmercaptal followed by $NaBH_4$ (ethanol, reflux) reaction, compound **32** was isolated in 40-45% yield. Compound **31** was also obtained when lactam **18** was substituted for **19**. In this case the absence of diol **33** can be attributed to the steric factors involved in its formation.

Attempts to hydrolyze the thioacetal **32** with conventional reagents such as $HgCl_2$-HgO,[16] perchloric acid,[14a] $HgCl_2$-$CdCO_3$,[17] formic acid,[15] NCS-$AgNO_3$,[18] $AgNO_3$-ethanol,[19] NBS[20] failed completely or gave intractable mixtures. However, when the acetal **32** was treated with excess of bis(trifluoroacetoxy)iodobenze[21] in aqueous acetonitrile at room temperature, 11-formylellipticine **13** was obtained in high yield. Reduction of aldehyde **13** with $NaCNBH_3$ and a few drops of trifluoroacetic acid in ethanol at room temperature gave the alcohol **5** in almost quantitative yield as a crystalline yellow solid.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp open capilliary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained in the solvent indicated on a Varian XL-200 (200 MHz) or General Electric QE-300 spectrophotometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as the internal standard. The J values are reported in Hertz. Infrared spectra were recorded on a Perkin-Elmer Model 298 or a Perkin Elmer 1800 Fourier Transform infrared spectrophotometer or a Nicolet 20 SX spectrophotometer. Mass spectra were obtained on Hewlett-Packard HP 5987 GC/MS or Nermag R-10-10C mass spectrophotometer using isobutane or methane as the CI gas. The high resolution mass spectrum was performed at the Baker Laboratory, Cornell University, Ithaca, NY. Thin layer chromatography experiments were performed on pre-coated silica gel plastic plates (Kodak) with fluoroscent background. Spots were visualized under 254 nm ultraviolet light. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Despite careful drying some of the compounds retained water tenaciously. Proton signals attributed to water were observed in the NMR spectra.

For lithiation reactions, a three-neck round-bottom flask fitted with a magnetic stirring bar, argon or nitrogen inlet adapter, and rubber septum was used. All reactions were carried out in an atmosphere of dry nitrogen or argon and in flame-dried glassware. Tetrahydrofuran was distilled over sodium benzophenone ketyl immediately before use. Trimethylsilyl chloride was distilled over CaH before use. Methyl isocyanate, diisopropylamine and trifluoroacetic acid were distilled before use. All other commercially available compounds were used without further purification. Low temperature reactions were carried out in liquid nitrogen, Dry Ice and methanol bath.

5-Hydroxy-5-methyl-indolo[1,2-b][2,7]naphthyridin-12-one (16). A solution of ketolactam **7**[8] (283 mg, 1.14 mmol) in 40 mL of dry THF was cooled to -78 °C. Methyl lithium (0.8 mL, 1.55M in diethyl ether, 1.2 mmol) was added dropwise by syringe. The solution was allowed to warm to -10 °C over 3 h. Solid ammonium chloride (600 mg, 11.2 mmol) was added. The mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue was partitioned between water and chloroform (3x50mL). The chloroform extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 300 mg of crude product. Flash chromatography on silica gel (1:1 hexane-ethyl acetate) gave 230 mg (76%) of lactam **16**: mp 122-125 °C; IR (KBr) λ 3366, 1696, 1598, 1454, 1357, 1328, 1247, 1159, 1112, 973, 884, 819, 788, 753, 670 cm^{-1}; NMR ($CDCl_3$) δ 8.97 (1 H, s, H_1), 8.41 (1 H, d, J = 5.0, H_1), 8.29 (1H, d, J = 2.6, H), 8.26 (1 H, d, J = 2.2, H), 7.58 (1 H, d, J = 5.4, H), 7.49-7.47 (1 H, m), 7.45-7.19 (2 H, m), 6.78 (1 H, s, H_6), 5.16 (1H, br s, OH), 1.70 (3 H, s, CH_3); MS, m/e 265 (M+1). Anal. Calcd for $C_{16}H_{12}N_2O_2$.0.5 H_2O: C, 70.33; H, 4.76; N, 10.26. Found: C, 70.20; H, 4.69; N, 10.04.

5-Hydroxy-5-(1-ethoxyethenyl)-indolo[1,2-b][2,7]naphthyridin-12-one (17). A solution of ethoxyvinyl lithium, prepared by adding t-BuLi (2.8 mL, 1.7 M in pentane, 4.7 mmol) by syringe to a solution of ethylvinyl ether (2.8 mL, 6.0 mmol) in 10 mL THF at -78 °C, was added by cannula to a solution of ketolactam **7**[8] (500 mg, 2.0 mmol) in 100 mL of dry THF at -78 °C. The resulting solution was stirred at -78 °C for 4 h and then was quenched by adding solid NH_4Cl (10 g). The reaction mixture was allowed to warm to room temperature and the THF was removed under reduced pressure. The light brown residue was partitioned between $CHCl_3$ and a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted twice with additional $CHCl_3$. The organic extracts were combined, washed with water and dried over K_2CO_3. The oily residue obtained after solvent removal was chromatographed on silica gel using hexane-ethyl acetate (15:85) as eluent to give **17** (483 mg, 75%) as a yellow solid: mp 71-72 °C; IR (KBr) λ 1700, 1596, 1452, 1370, 1356,

1329, 1229, 752 cm^{-1}; NMR ($CDCl_3$) δ 9.37 (1 H, s), 8.72 (1 H, d, J = 5.4, H), 8.52 (1 H, d, J = 8.0, H), 7.62 (1 H, d, J = 5.4, H), 7.58-7.54 (1 H, m), 7.36-7.25 (2 H, m), 6.83 (1 H, s, H_5), 4.65 (1 H, d, J = 2.8, vinyl H), 4.16 (1 H, d, J = 2.8, vinyl H), 3.59 (2 H, q, $\underline{CH_2}CH_3$), 1.00 (3 H, t, $CH_2\underline{CH_3}$); MS, m/e 321 (M+1). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.04; N, 8.75. Found: C, 71.02; H, 5.08; N, 8.60.

5-Hydroxy-5-trimethylsilyloxy-indolo[1,2-b][2,7]naphthyridin-12-one (18). To a stirred solution of keto lactam **7**[8] (248 mg, 0.1 mmol) in 50 mL of dry THF at -78 °C was added methyllithium (1 mL, 1.55M in diethylether, 0.15 mmol) by syringe. The solution was stirred at -78 °C for 1 h and then warmed gradually to -10 °C. Trimethylsilyl chloride (2 mL, 1.6 mmol) was added by syringe in one portion and the resulting solution was stirred for an additional 30 min at room temperature. The mixture was neutralized by adding aqueous $NaHCO_3$ solution. The solvents were removed under pressure and the residue was partitioned between water and chloroform. The aqueous layer was thoroughly extracted with $CHCl_3$ (3x50 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to give an oil. This oil was chromatographed on silica gel (hexane-ethyl acetate (9:1)) to give 0.27 g (80%) of the product **18**. An analytical sample was obtained by recrystallization from ether-hexane: mp 143-145 °C; IR (KBr) λ 2975, 2960, 1680, 1590, 1450, 1420, 1375, 1330, 1245, 1160, 1100, 1090, 1005, 960, 850, 750 cm^{-1}; NMR ($CDCl_3$) δ 9.53 (1 H, s, H_1), 8.88 (1 H, d, J = 5.2, H_3), 8.65 (1 H, d, J = 8.0), 7.68 (1 H, d, J = 5.2, H_4), 7.62-7.58 (1 H, m), 7.46-7.33 (2 H, m), 6.84 (1 H, s, H_6), 1.85 (3 H, s, CH_3), 1.57 (s, H_2O), -0.18 (9H, s, $Si(CH_3)_3$); MS, m/e 337 (M+1). Anal. Calcd for $C_{19}H_{20}N_2O_2Si.0.2\ H_2O$: C, 67.13; H, 5.95; N, 8.24. Found: C, 67.04; H, 5.98; N, 8.31.

1-(1H-Indol-2-yl)-1-methyl-furo[3,4-c]pyridine-3(1H)-one (19). (a) A solution of ketolactam **7**[7] (1.0 g, 4.0 mmol) in 200 mL of dry THF was cooled to -100 °C. Methyllithium (2.88 mL, 1.55M in diethyl ether, 4.0 mmol) was added dropwise by syringe. The orange solution was allowed to warm to 10 °C over a 4 h period. The resulting green solution was quenched by the addition of 40 mL of water. The solvent was removed in vacuo and the residue was diluted with 100 mL of distilled water. The basic aqueous phase was washed with $CHCl_3$ (3x50 mL) and discarded. The aqueous phase was acidified to pH 2 with concentrated HCl and was then extracted with $CHCl_3$ (4x50 mL). The extracts were combined, dried (Na_2SO_4) and concentrated to give a light green oil. Further concentration at 0.1 mm for 18 h gave 660 mg (62%) of lactone **19** as a foam. An analytical sample was obtained by recrystallization from $CHCl_3$: mp 170-172 °C; IR (KBr) λ 3380, 1770, 1650, 1620, 1455, 1385 cm^{-1}; NMR ($CDCl_3$) δ 9.01 (1 H, s), 8.90 (1 H, br s), 8.77 (1 H, d, J = 5.0), 7.39 (1 H, d), 7.25 (1 H, d), 7.15 (1 H, t), 7.10 (1 H, t), 6.50 (1 H, s), 2.05 (3 H, s, $\underline{CH_3}$); MS, m/e 265 (M+1). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.73; H, 4.54; N, 10.61. Found: C, 72.61; H, 4.58; N, 10.60.

(b) Lithium hydroxide (30 mg, 0.72 mmol) was added to a suspension of lactam **16** (20 mg, 0.75 mmol) in 4 mL of 90% aqueous THF. The mixture was stirred at room temperature under argon until there was no starting material left, as judged by TLC. The solvents were removed in vacuo and the solid residue was taken up in water. The aqueous layer was extracted with $CHCl_3$ (3x20 mL). The combined extracts were evaporated and the residue was triturated with ether to give **19** (15 mg, 75%) which was identical in all respects with the sample prepared above.

5-Methyl-6H-pyrido[4,3-b]carbazole (14). A solution of lactone **19** (26 mg, 0.1 mmol) and sodium borohydride (131 mg, 3.4 mmol) in 20 mL of absolute ethanol was heated to reflux overnight. The solution was cooled to room temperature and then ethanol was removed under vacuum. The residue was partitioned between water and $CHCl_3$ with vigorous stirring for 30 min. The organic layer was separated and the aqueous phase was thoroughly extracted with $CHCl_3$ (2x50 mL). The organic layers were combined, washed with water, dried (Na_2SO_4) and concentrated to give 13 mg (54%) of the desired compound **14**: mp 270-275 °C (lit[22] 275-277 °C). Lactam **16** was also converted to **14** using the above procedure in 60% yield.

5,11-Dimethyl-6H-pyrido[4,3-b]carbazole (Ellipticine) (1). A solution of lactone **19** (78 mg, 0.3 mmol) in 16 mL of dry THF was stirred and cooled to 0 °C. MeLi (0.47 mL, 1.55 M in diethyl ether, 0.7 mmol) was added via syringe over 20 seconds. The solution was stirred at 0 °C for 1 h and was then quenched with water. The reaction mixture was concentrated under reduced pressure to furnish a brown semi-solid which was dissolved in absolute ethanol (65 mL). Sodium borohydride (558 mg, 15 mmol) was added at intervals (278 mg initially followed by 140 mg after 1 h and another 140 mg after 4 h) while refluxing the reaction

overnight. The reaction mixture was concentrated to a green semi-solid and the residue was partitioned between water and chloroform. The aqueous phase was thoroughly extracted with chloroform. The organic extracts were combined, washed with water and dried (Na_2SO_4). The oily residue obtained after removal of solvent was chromatographed with hexane-ethyl acetate (1:3) as eluent to give 56 mg (75%) of ellipticine as a yellow solid. The material so obtained was identical in all respects (IR, NMR, MS, mp 311-315 °C dec) with an authentic sample of ellipticine.

5,11-dimethyl-6H-pyrido[4,3-b]carbazole (1) and α-(1-Methyl)-α-(1H-indol-2-yl)-3-[(dimethyl)hydroxymethyl]-4-pyridine (2-ethanol) (21). Methyllithium (1.3 mL, 1.55 M in diethyl ether, 0.44 mmol) was added to a solution of lactam **17** (55 mg, 0.22 mmol) in 20 mL of dry THF at -78 °C. The mixture was stirred for 12 h before being quenched by water. The solution was concentrated and the residue was taken up in 40 mL of absolute ethanol and sodium borohydride (160 mg, 4.2 mmol). The mixture was heated to reflux for 8 h and then stirred at room temperature overnight. Ethanol was removed under reduced pressure and the residue was taken up in water. The yellow precipitate was filtered, washed with water and dried to give 5 mg (10%) of ellipticine which was identical in all aspect with the authentic sample. The aqueous phase was thoroughly extracted with $CHCl_3$. The combined organic layers were washed with a brine solution, dried (Na_2SO_4) and concentrated to give an oil, which was characterized as the diol **21** (43 mg, 70%). All attempts to purify this material for an analytical sample by either crystallization or chromatography gave decomposition products. IR (KBr) λ 3223, 2978, 1605, 1457, 1310, 1229, 1094, 1052, 839, 744 cm^{-1}; NMR ($CDCl_3$) δ 8.95 (1 H, s, NH), 8.45 (1 H, s, H_1), 8.28 (1 H, d, J = 5.4), 7.45 (1 H, d, J = 7.2, H_3), 7.30 (1 H, d, J = 7.2, H_4), 7.25-7.07 (2 H, m), 6.09 (1 H, s, indole-H_3), 3.82-3.42 (2 H, br, OH), 2.02 (3 H, s, CH_3), 1.62 (3 H, s, CH_3); MS, m/e 297 (M+1); HR-MS calcd for $C_{18}H_{20}N_2O_2$: 296.1526, found: 296.1525.

5-(1-Ethoxyethenyl)-11-methyl-6H-pyrido[4,3-b]carbazole (22) and α-(1-Ethoxyethenyl)-α-(1H-indol-2-yl)-3-[(dimethyl)hydroxymethyl]-4-pyridinemethanol (23). Methyllithium (2.0 mL, 1.4 M in diethylether, 2.8 mmol) was added to a stirred solution of ethoxyvinyl lactam **17** (263 mg, 0.8 mmol) in dry THF (75 mL) at -78 °C. The mixture was stirred at -78 °C for 1 h and then warmed gradually to room temperature over a period of 4 h. The reaction mixture was quenched with 10 mL of water and the solvent was removed under reduced pressure. The aqueous residue was dissolved in 10 mL of absolute ethanol and was then concentrated using a rotary evaporator to azeotrope most of the remaining water. The resulting yellow semi-solid was dissolved in 200 mL of absolute ethanol. Sodium borohydride (1.8 g, 47 mmol) was added at intervals (900 mg initially followed by 450 mg after 1 h and another 450 mg after 4 h) while refluxing the solution overnight. The reaction was cooled to room temperature and then concentrated to a yellow residue. The residue was partitioned between 200 mL water and 200 mL of $CHCl_3$. The two phases were stirred vigorously for 30 min and then separated. The aqueous phase was extracted with $CHCl_3$ (2x75 mL). The organic extracts were combined and were washed with brine, dried (Na_2SO_4) and concentrated to give a light brown oil. Flash chromatography of the oil using ethylacetate-hexane (7:3) gave two products. The major product was **23** (217 mg, 75%). An analytical sample of **23** was obtained as a colorless solid by recrystallization from $CHCl_3$: mp 186-188 °C; IR (KBr) λ 3330, 2976, 1596, 1455, 1065, 798, 745, 727, 687 cm^{-1}; NMR ($CDCl_3$) δ 9.79 (1 H, br s), 8.57 (1 H, s), 8.23 (1 H, d, J = 5.3, H), 7.41 (1 H, d, J = 7.6, H), 7.31 (1 H, d, J = 7.6, H), 7.00-6.87 (2 H, m), 5.99 (1 H, s, indolic-H_3), 4.21 (1 H, d, J = 1.7, vinyl H), 3.88 (1 H, d, J = 1.7, vinyl H), 3.76 (2 H, q, $\underline{CH_2}CH_3$), 3.30 (2 H, s), 1.62 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 1.13 (3 H, t, $CH_2\underline{CH_3}$); MS, m/e 353 (M+1). Anal. Calcd for $C_{21}H_{24}N_2O_3.1.5\ H_2O$: C, 66.55; H, 6.38; N, 7.39. Found: C, 66.18; H, 6.46; N, 7.42.

The minor product **22** (12 mg, 5%) was obtained as an oil: NMR ($CDCl_3$) δ 9.73 (1 H, s), 8.61 (1 H, br s), 8.46 (1 H, d), 8.38 (1 H, d), 8.03 (1 H, d), 7.51 (2 H, m), 7.34 (1 H, t), 4.90 (1 H, d), 4.61 (1 H, d), 4.15 (2 H, q), 3.35 (3 H, s, CH_3), 1.50 (3 H, t); MS, m/e 303 (M+1).

11-n-Butyl-5-methyl-6H-pyrido[4,3-b]carbazole (30). To a stirred solution of lactone **19** (100 mg, 0.38 mmol) in dry THF (20 mL) at -60 °C was added n-BuLi (1.5 mL, 2.5 M in hexane, 3.75 mmol). The reaction mixture was stirred for 6 h with gradual warming to room temperature. Excess n-BuLi was decomposed by addition of water (2 mL). The solvent was removed in vacuo and the residue was taken up in absolute ethanol (30 mL) and sodium borohydride (160 mg, 4.2 mmol). The mixture was heated to reflux overnight. After removal of the solvent, the residue was partitioned between water and $CHCl_3$. The aqueous

layer was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and concentrated to give a dark oil which was purified by silica gel chromatography with ethyl acetate-hexane (2:3) as eluent to give **30** (75 mg, 69%): mp 272-275 °C; IR (KBr) λ 3440, 2950, 1600, 1465, 1405, 1245, 735 cm^{-1}; NMR ($CDCl_3$) δ 9.70 (1 H, s, H_1), 8.49 (1 H, d, J = 5.8, H_3), 8.27-8.17 (2 H, m), 7.86 (1 H, d, J = 5.8, H_4), 7.52-7.49 (2 H, m), 7.35-7.28 (1 H, m), 3.76 (2 H, t, Ar-CH_2), 2.77 (3 H, s, Ar-CH_3), 1.95-1.62 (4 H, m), 1.04 (3 H, t, CH_3); MS, m/e 289 (M+1). Anal. Calcd for $C_{20}H_{20}N_2.0.4\ H_2O$: C, 81.30; H, 6.91; N, 9.48. Found: C, 81.24; H, 6.96; N, 9.44.

11-(1-Ethoxyethenyl)-5-methyl-6H-pyrido[4,3-b]carbazole (15). A solution of ethoxyvinyl lithium was prepared by adding t-BuLi (2.2 mL, 1.7 M in pentane, 3.7 mmol) by syringe to a solution of ethylvinyl ether (2.2 mL, 4.7 mmol) at -78 °C. The solution was stirred for 30 min and the dry ice-acetone bath was replaced with an ice bath (0 °C). A solution of lactone **19** (200 mg, 0.76 mmol) in 10 mL of dry THF was added to the ethoxyvinyl lithium solution and the reaction mixture was stirred at room temperature for 4 h. Excess lithium reagent was quenched with 10 mL of water. The solvent was removed under reduced pressure and the residue was taken up in absolute ethanol (80 mL). Sodium borohydride (450 mg, 11.84 mmol) was added and the mixture was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and water. Two phases were separated and the aqueous phase was extracted with $CHCl_3$ (2x100 mL). The combined extracts were washed with a brine solution, dried (Na_2SO_4) and concentrated to give 215 mg (94%) of **17** as an oil. An analytical sample was obtained by crystallization in methanol-ether, as a bright yellow solid: mp 228-231 °C; IR (KBr) λ 1469, 1408, 1275, 1245, 1060, 818, 750 cm^{-1}; NMR ($CDCl_3$) δ 9.64 (1 H, s, H_1), 8.48 (1 H, d, J = 6.2, H_3), 8.24 (1 H, d, J = 8.0, H_{11}), 8.11 (1 H, br s, NH), 7.83 (1 H, d, J = 6.0, H_4), 7.50-7.44 (2 H, m), 7.24 (1 H, m), 4.94 (1 H, d, J = 2.2, vinyl H), 4.55 (1 H, d, J = 2.2, vinyl H), 4.22 (2 H, q, $\underline{CH_2}CH_3$), 2.80 (3 H, s, Ar-CH_3), 1.58 (s, H_2O), 1.42 (3 H, t, $CH_2\underline{CH_3}$); MS, m/e 303 (M+1). Anal. Calcd for $C_{20}H_{18}N_2O.0.25\ H_2O$: C, 78.28; H, 6.08; N, 9.13. Found: C, 78.29; H, 6.13; N, 9.14.

11-Acetyl-5-methyl-6H-pyrido[4,3-b]carbazole (31). 11-Ethoxyvinyl-5-Methyl-6H-pyrido[4,3-b]carbazole **15** (20 mg, 0.07 mmol) was dissolved in 1 mL of methanol. One mL of aqueous 6M HCl was added and the resulting solution was stirred at room temperature for 4 h. Methanol was removed under reduced pressure and the aqueous residue was made basic by the addition of saturated $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ (3x20 mL). The combined extracts were washed with water, dried (Na_2SO_4) and concentrated to give **31** (16 mg, 88%) as a yellow solid. An analytical sample was obtained by recrystallization from methanol: mp 283-285 °C; IR (KBr) λ 1699, 1597, 1466, 1405, 1247, 744 cm^{-1}; NMR ($CDCl_3$) δ 11.27(1H, s, NH), 9.13 (1 H, s, H_1), 8.39 (1 H, d, J = 6.2, H_3), 7.86 (1 H, d, J = 6.0, H), 7.78 (1 H, d, J = 7.6, H), 7.49-7.44 (2 H, m), 7.17-7.10 (2H, m), 3.21 (s, H_2O), 2.83 (3 H, s, Ar-CH_3), 2.81 (3 H, s, CH_3); MS, m/e 275 (M+1). Anal. Calcd for $C_{18}H_{14}N_2O.0.25\ H_2O$: C, 77.53; H,5.15; N, 10.04. Found: C, 77.19; H, 5.34; N, 9.87.

11-(1-Hydroxyethyl)-5-methyl-6H-pyrido[4,3-b]carbazole (6). Sodium borohydride (250 mg, 6.6 mmol) was added to a solution of **31** (121 mg, 0.4 mmol) in 40 mL of absolute ethanol at 50 °C. The mixture was stirred at 50 °C for 8 h and then at room temperature overnight. Ten mL of 10% aqueous NaOH solution was added and the aqueous layer was extracted with chloroform (3x50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give 115 mg (97%) of the alcohol **6**. Recrystallization in methanol provided the analytical sample: mp > 300 °C; IR (KBr) λ 3320, 1599, 1467, 1418, 1411, 1246, 1072, 724 cm^{-1}; NMR (DMSO-d_6) δ 11.39 (1 H, s, NH), 10.27 (1 H, s, H_1), 8.44 (1 H, d, J = 8.2, H), 8.38 (1 H, d, J = 6.2, H_3), 7.91 (1 H, d, J = 6.0, H_4), 7.58-7.50 (2 H, m), 7.27-7.22 (1 H, m), 6.43 (1 H, q, J = 6.6, $\underline{CH}CH_3$), 5.89 (1 H, s, OH), 2.29 (3 H, s, Ar-CH_3), 1.79 (3 H, d, J = 6.6, $CH\underline{CH_3}$); MS, m/e 277 (M+1). Anal. Calcd for $C_{18}H_{16}N_2O.0.33\ H_2O$: C, 76.59; H,5.78; N, 9.99. Found: C, 76.78; H, 5.99; N, 9.86.

5-Methyl-11-[2,2-bis(ethylthio)methanal]-6H-pyrido[4,3-b]carbazole (32).

(a) To a solution of 1,1-bis(ethylthio)methane[15] (1.05 g, 7.72 mmol) in 15 mL of dry THF at -30 °C was added n-BuLi (6.4 mL, 2.5 M in hexane, 0.62 mmol) by syringe. The solution was stirred for 1 h at -30 °C and then was treated with solid lactone **19** (240 mg, 0.11 mmol). The resulting orange solution was kept at -30 °C

for 1 h and then warmed gradually to room temperature. After 4 h the reaction was quenched with 2 mL of water. The solvent was removed under reduced pressure and the residue was taken up in 50 mL of absolute ethanol. Sodium borohydride (1 pellet, 160 mg, 4.2 mmol) was added and the reaction mixture was heated under reflux for 8 h under argon. The solution was cooled to room temperature. The solvents were removed *in vacuo*. The residue was partitioned between water and $CHCl_3$. The aqueous layer was thoroughly extracted with $CHCl_3$ (3x75 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to give 245 mg of the crude product. Purification by silica gel chromatography with hexane-ethyl acetate (9:1) as eluent gave 150 mg (45%) of the product **32**: mp 256-258 °C (dec.); IR (KBr) λ 3140, 2940, 1615, 1595, 1460, 1410, 1370, 1320, 1260, 1245, 1145 cm^{-1}; NMR ($CDCl_3$) δ 10.51 (1 H, s, H_1), 8.51 (1 H, d, J = 6.2, H_3), 8.32 (1 H, t), 7.83 (1 H, d, J = 6.2, H_4), 7.52-7.47 (2 H, m), 7.33-7.27 (2 H, m), 6.68 (1 H, s, ($\underline{CH}SEt)_2$), 2.77 (3 H, s, $\underline{CH_3}$), 2.72-2.64 (4H, q, ($\underline{CH_2}CH_3)_2$), 1.24-1.16 (6H, t. ($CH_2\underline{CH_3})_2$); MS, m/e 367 (M+1). Anal. Calcd for $C_{21}H_{22}N_2S_2.0.5\ H_2O$: C, 67.20; H, 6.00; N, 7.47. Found: C, 67.43; H, 6.09; N, 7.56.

(b) A solution of lithio derivative of formaldehyde diethylmercaptal was prepared by carefully adding n-BuLi (1.2 mL, 2.5 M in hexane, 0.19 mmol) to a solution of 1,1-bis(ethylthio)methane (0.43 g, 3.2 mmol) in 8 mL of dry THF at -30 °C. After 1 h of additional stirring, the lactam **18** (45.1 mg, 0.13 mmol) was added in one portion. An orange-yellow colored solution resulted. The reaction was allowed to warm to room temperature over 2 h and then was quenched with water. The solution was concentrated under reduced pressure to dryness. The residue was dissolved in 45 mL of absolute ethanol. To this solution KF (140 mg, 2.41 mmol) and $NaBH_4$ (160 mg, 0.42 mmol) was added. The mixture was heated to reflux for 2 h. The solution was cooled to room temperature and then concentrated to give a semi-solid residue. The residue was partitioned between water and $CHCl_3$. The aqueous layer was thoroughly extracted with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Flash chromatography on silica gel with hexane-ethylacetate (2:1) as eluent gave 22 mg (45%) of the product **32** as a yellow solid: mp 256-257 °C (dec) which was identical in all respect with the sample described above.

5-Methyl-11-formyl-6H-pyrido[4,3-b]carbazole (13). To a suspension of **32** (53 mg, 0.15 mmol) in 35 mL of 90% aqueous acetonitrile bis(trifluoroacetoxy)-iodobenzene (370 mg, 0.89 mmol) was added at room temperature. The resulting orange solution was stirred until the reaction was over as judged by TLC. A saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture. The precipitate was collected by filtration and the yellow solid was washed with water, followed by methanol-ether (1:5) mixture and dried to give 21 mg (56%) of the product. The filtrate was extracted with $CHCl_3$/MeOH (9:1) (4x30 mL). The combined organic solution was washed with brine, dried (Na_2SO_4).and concentrated to give an additional 11 mg (29%) of the product **13** in a total yield of 85%: mp 320-330 °C (dec); IR (KBr) λ 1675, 1640, 1600, 1420, 1245, 1065, 1020, 810, 745 cm^{-1}; NMR (DMSO-d_6) δ 11.53 (1 H, s H_1), 10.36 (1 H, s, CHO), 8.63 (1 H, d, J = 8.0 Hz, H_{10}), 8.54 (1 H, d, J = 5.8, H_3), 8.06 (1 H, d, J = 5.8, H_4), 7.62 (2 H, m, H_7, H_9), 7.26 (1 H, m, H_8), 3.67(s, H_2O), 2.91 (3 H, s, CH_3); MS, m/e 261 (M+1). Anal. Calcd for $C_{17}H_{12}N_2O.0.5\ H_2O$: C, 75.84; H, 4.83; N, 10.41. Found: C, 75.71; H, 4.53; N, 10.42.

5-Methyl-11-methanol-6H-pyrido[4,3-b]carbazole (5). A clear solution was obtained by mixing aldehyde **13** (21 mg, 0.08 mmol) in 20 mL of absolute ethanol and a few drops of trifluoroacetic acid. Sodium cyanoborohydride (100 mg, 1.59 mmol) was added in one portion and the resulting yellow solution was stirred at room temperature overnight. The solution was concentrated and the residue was taken up in 100 mL of 10% MeOH in $CHCl_3$. The organic layer was washed successively with an aqueous solution of $NaHCO_3$, water, and a brine solution. After drying (Na_2SO_4) and concentrating under vacuum alcohol **5** (18.8 mg, 89%) was obtained as a yellow solid. An analytical sample of **5** was obtained by silica gel chromatography with $CHCl_3$-MeOH (9:1) as eluent: mp 312-320 °C (dec.); IR (KBr) λ 3240, 3050, 2900, 2870, 1600, 1465, 1410, 1245, 1035, 995, 810, 740 cm^{-1}; NMR (DMSO-d_6)[23] δ 11.50 (1 H, s, $\underline{NH}$), 9.78 (1 H, s, H_1), 8.42 (2 H, d, J = 6.4, H_3, H_{10}), 7.94 (1 H, d, J = 6.0, H_4), 7.59-7.52 (2 H, m, H_7, H_9), 7.29-7.21 (1 H, t, H_8), 5.58 (3 H, br s, $\underline{CH_2}OH$), 2.82 (3 H, s, $\underline{CH_3}$); MS, m/e 263 (M+1). Anal. Calcd for $C_{17}H_{14}N_2O.0.67\ H_2O$: C, 74.45; H, 5.58; N, 10.21. Found: C, 74.60; H, 5.24; N, 10.41.

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