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SYNTHESIS AND CYTOTOXICITY OF NOVEL BIS-ELLIPTICINES AND BIS-ISOELLIPTICINES

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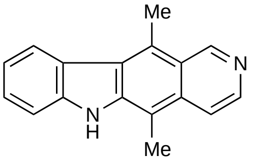
Abstract – A series of bis-ellipticines **7–9** and bis-isoellipticines **10–12** tethered through the indole nitrogen was synthesized and screened for antitumor cytotoxicity in the L-1210 murine leukemia assay. Activity was only displayed by 1,10-bis(6-ellipticinyl)-*n*-decane (**8**).

INTRODUCTION

The syntheses and biological activities of the alkaloid ellipticine (5,11-dimethyl-6*H*-pyrido-[4,3-*b*]carbazole) (**1**), isoellipticine (5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole) (**2**), related natural alkaloids, and synthetic derivatives have been of intense interest since the isolation of **1** in 1959.[1] Several all-encompassing reviews that survey the history and present status of the ellipticine field are available.[2] Likewise, the early syntheses of ellipticine, isoellipticine, and related ring systems have been summarized,[3] as have a selection of recent studies on ellipticine and its pronounced biological activity (Figure 1).[4]



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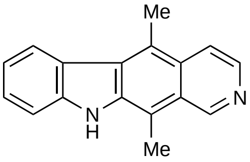

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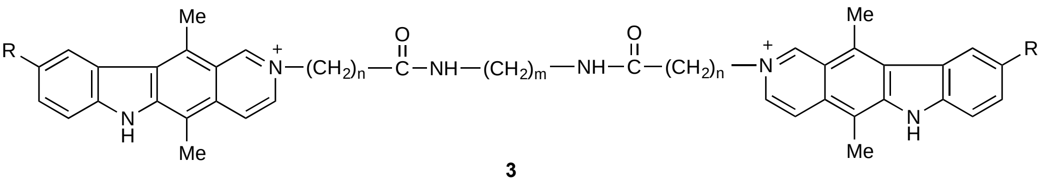
Figure 1

Despite the ubiquitous examples of both synthetic and (some) natural DNA intercalators and bis-intercalators,[5] only a few bis-ellipticines have been described. Roques synthesized a series of bis-ellipticines tethered via the pyridine nitrogen (N2) (**3**),[6] and Popp reported the synthesis of bis-ellipticine **4** with a *p*-xylene connecting unit[7] (Figure 2). Our own interest in potential DNA bis-intercalators has led to syntheses of 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane (**5**),[8] of semi-rigid tethered bis(9-aminoacridines),[9] and, more recently, of the three isomeric bis(aminocyclohexyl)methane acridines **6**.[10]



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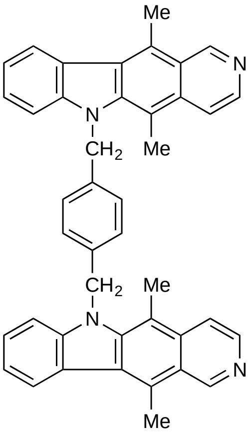
R = OH, OMe
n = 1, 2
m = 4, 6, 8, 10, 12



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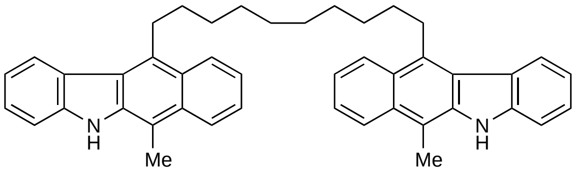

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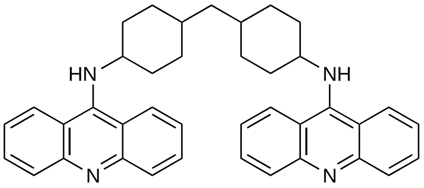

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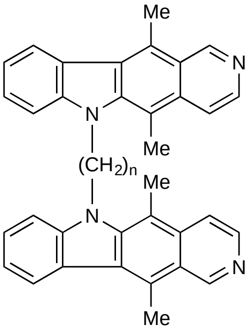
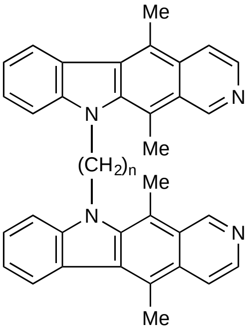
Figure 2

In continuation of our syntheses of ellipticine and related pyridocarbazoles,[11] we now report the syntheses and cytotoxicity of bis-ellipticines **7**–**9** and bis-isoellipticines **10**–**12** (Figure 3).



7, n = 8
8, n = 10
9, n = 12

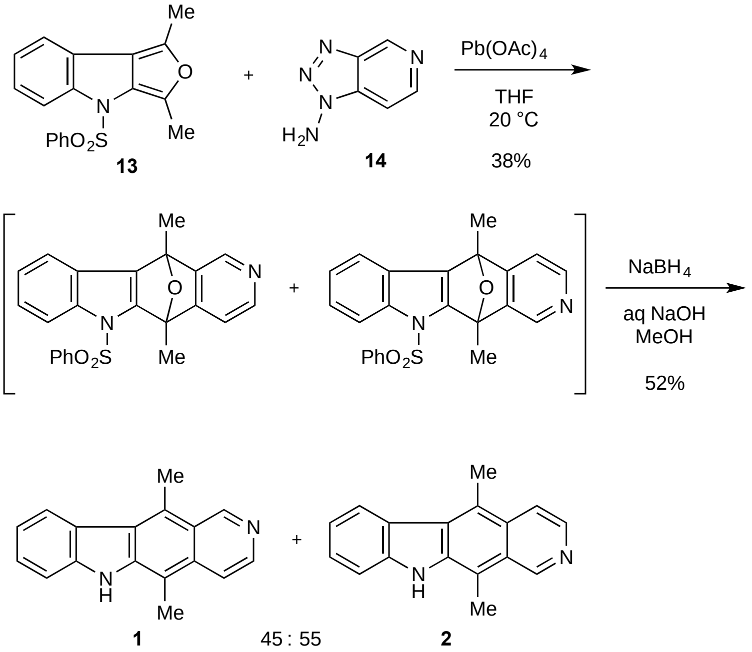


10, n = 8
11, n = 10
12, n = 12

Figure 3

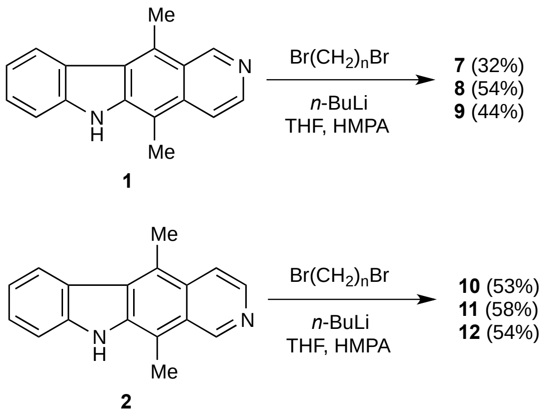
RESULTS AND DISCUSSION

We synthesized ellipticine (**1**) and isoellipticine (**2**) together in one pot in two steps using our earlier method (Scheme 1).[11] Thus, a Diels-Alder cycloaddition between 4-(phenylsulfonyl)-1,3-dimethyl-4*H*-furo[3,4-*b*]indole (**13**)[12] and 3,4-pyridyne, which was generated from 1-aminotriazolo[4,5-*c*]pyridine (**14**) and lead tetraacetate,[13] gave a mixture of cycloadducts in 38% yield. Deoxygenation[14] of the mixture with $NaBH_4$ in aqueous base afforded **1** and **2** (52% yield) in a ratio of 45:55, which were separated by flash chromatography and identified by comparison with authentic samples.[11]



Scheme 1

After some experimentation with different bases and solvents, we found that both **1** and **2** could be bis-alkylated with 1,ω-dibromoalkanes using *n*-BuLi/THF/HMPA to afford the desired bis-ellipticines **7**–**9** and bis-isoellipticines **10**–**12** in 33–54% and 53–58% yields, respectively (Scheme 2). The slightly greater stability of the ellipticinyl anion (hence lower reactivity) relative to the isoellipticinyl anion[15] may provide the explanation for the slightly higher yields of **10**–**12** from isoellipticine (**2**). Interestingly, in the absence of HMPA no alkylation was observed (with **1** and 1,10-dibromodecane), and Popp's conditions[7] (NaH, DMF) resulted in no alkylation. The modest yields of **7**–**12** are presumed to be due to the presence of monoalkylated side products, which were not isolated.



Scheme 2

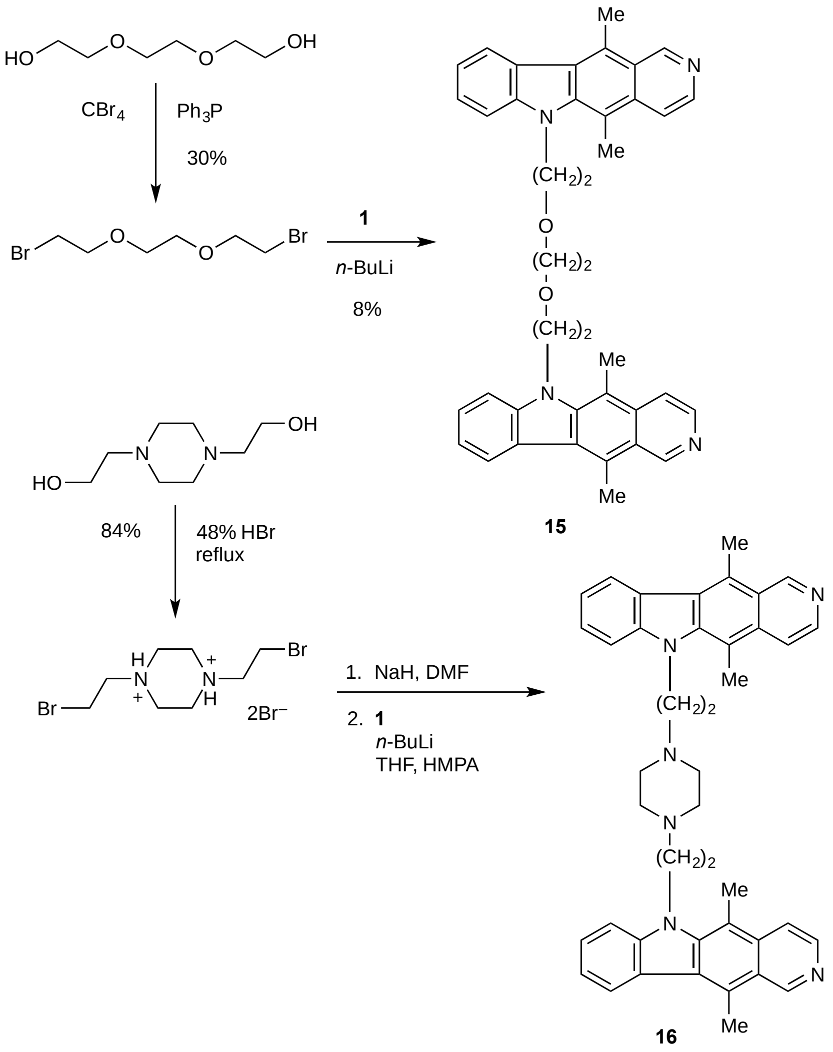
These six compounds, **7**–**12**, were screened *in vitro* against the L-1210 murine leukemia strain, but only bis-ellipticine **8** with the decyl tether exhibited (low) activity (Table 1). Kuhlmann has reported that a ten-carbon methylene tether maximizes DNA bis-intercalation and anti-tumor activity in ethidium dimers.[16] The bis-isoellipticine **11** with a decyl tether was inactive. It might be noted that isoellipticine was reported to be inactive in the L-1210 screen.[17]

Table 1. Antitumor activity of bis-ellipticines **7**–**9** and bis-isoellipticines **10**–**12**

Compound	L-1210 Activity *In vitro* IC_{50} µmol/mL
7	>0.015
8	0.011
9	>0.015
10	>0.015
11	>0.015
12	>0.015
1	0.00053
2	inactive[17]

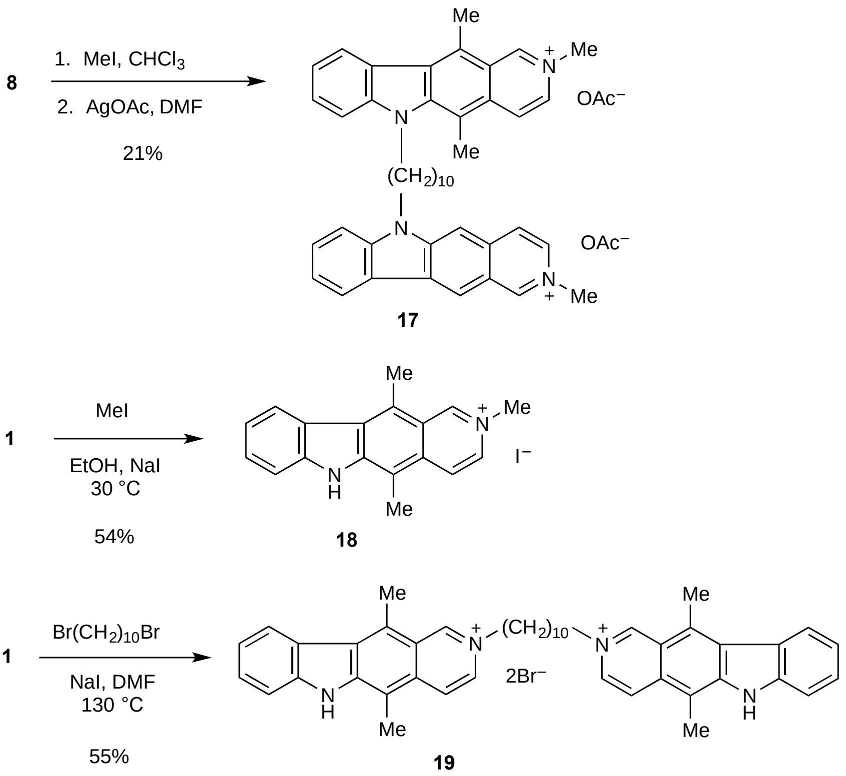
*Dose that reduces by 50% the cell growth relative to controls, 72 h after drug exposure at 37 °C.

Studies show that both polyether and polyamine tethers can exhibit higher DNA affinity than polymethylene tethers connected to different intercalating ring systems.[18] We therefore prepared 1,2-bis(2-bromoethoxy)ethane from triethylene glycol[19] and used it to bis-alkylate ellipticine (**1**) to give **15** in low yield (Scheme 3). Likewise, we synthesized 1,4-bis(2-bromoethyl)piperazine dihydrobromide[20] and attempted to alkylate ellipticine (**1**), but this was unsuccessful in affording any more than a trace of **16**. The problem with this bis-nitrogen mustard is that it may be prone to decomposition. Given these discouraging results we did not pursue the full characterization of these two compounds.



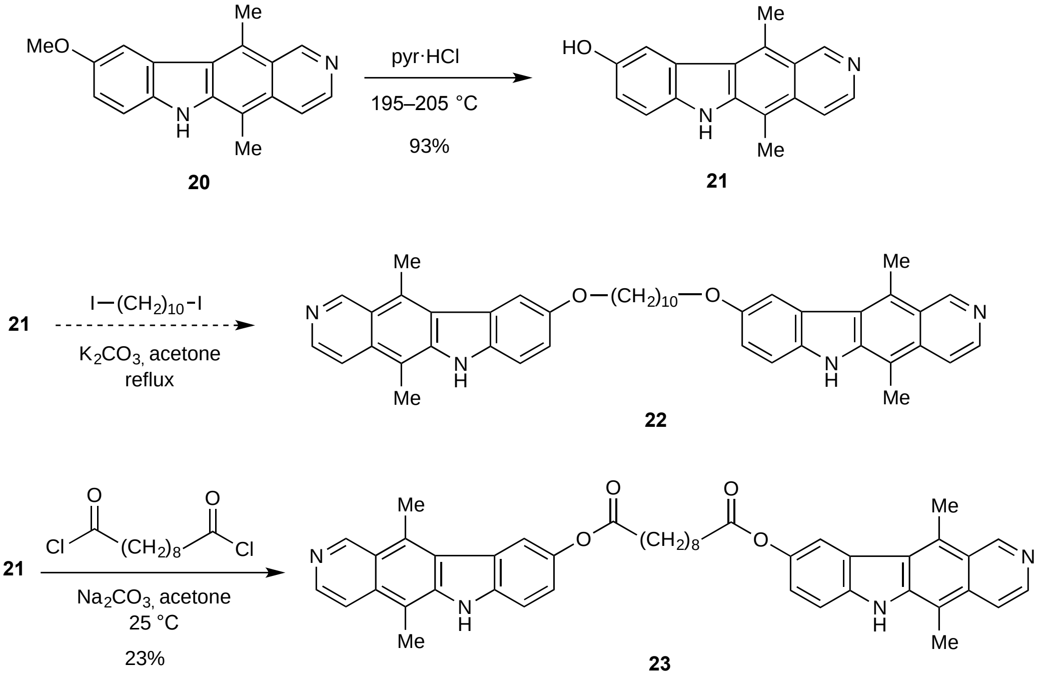
Scheme 3

It is known that water-soluble ellipticine salts have enhanced biological activity, exemplified by the therapeutic efficacy of 2-methyl-9-hydroxyellipticinium acetate.[2] Therefore, we methylated both pyridine nitrogens of bis-ellipticine **8** to give bis-ellipticinium acetate **17** (21% yield) (Scheme 4). For spectral comparison with **17** we methylated ellipticine to afford **18** (54% yield), and bis-alkylated ellipticine to give 2,2'-decamethylene-bis-ellipticinium dibromide **19** (55% yield).



Scheme 4

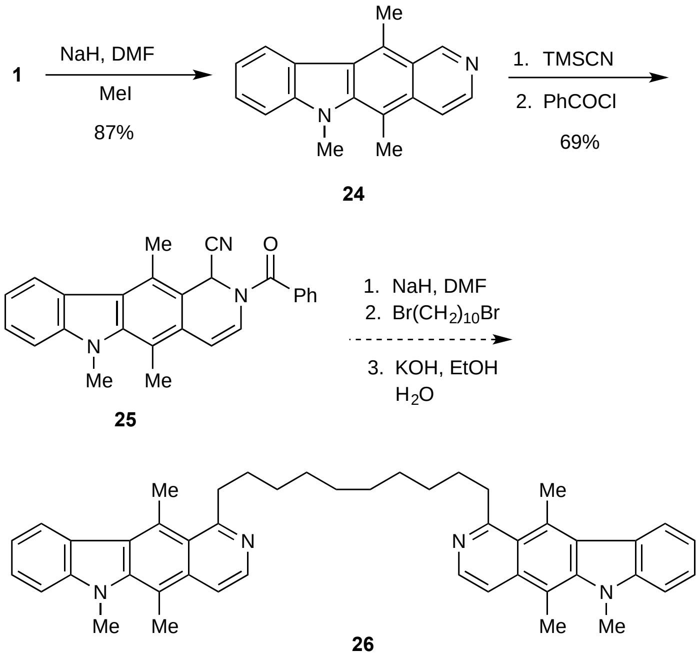
The 9-oxygenated ellipticine alkaloids 9-methoxyellipticine (**20**) and 9-hydroxyellipticine (**21**) are well studied and exhibit powerful anticancer activity. We demethylated **20** using the procedure of Brossi[21] to afford **21** in 93% yield. Attempts to alkylate **21** with 1,10-diiodododecane (K_2CO_3, acetone) yielded only traces of the anticipated bis-ether **22** (Scheme 5).



Scheme 5

However, bis-acylation of **21** with sebacoyl dichloride afforded a low yield of bis-ester **23**.

Finally, we explored Reissert chemistry to possibly functionalize C-1 of ellipticine as Popp had reported for the synthesis of 1-cyanoellipticine and 1-carboxamidoellipticine.[22] To preclude undesirable reactions of the indole NH, we prepared the *N*-methyl ellipticine analogues shown in Scheme 6. Thus, *N*-6 methylation of **1** gave **24** in excellent yield. We prepared 6-methylellipticine (**24**) and converted it to Reissert analogue **25** in 69% yield, but attempts to functionalize C-1 with base (NaH and LDA) and 1,10-dibromodecane to give the desired bis-ellipticine **26** were unsuccessful. Mass spectral data indicated fragments of alkylated 6-methylellipticine but no indication that **26** had formed.



Scheme 6

In conclusion, we have prepared a series of bis-ellipticines **7**–**9** and bis-isoellipticines **10**–**12**, but only 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) displayed (low) activity in the L-1210 murine leukemia *in vitro* screen. Other attempts to synthesize different bis-ellipticines were only partially successful. Future work will be necessary to improve these endeavors including the synthesis of semi-rigid tethers.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 599 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Varian XL-300 Fourier Transform spectrometer. For ^{1}H NMR spectra, chemical shifts are reported in parts per million with tetramethylsilane as the internal standard. Low-resolution mass spectra were determined on a Finnigan EI-CI gas chromatograph-mass spectrometer.

High resolution EI, FEB, and FD spectra were obtained by Dr. Catherine E. Costello at the NIH Regional Facility at the Massachusetts Institute of Technology. Ultraviolet spectra were recorded on a Unicam SP-800A spectrophotometer. Flash chromatography was performed with EM Reagents Silica Gel 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck); spots were visualized under 254 nm ultraviolet light. The alkyllithium reagents were purchased from Aldrich and standardized by titration against 2,5-dimethoxybenzyl alcohol. Elemental analyses were obtained at Atlantic Microlabs, Atlanta, Georgia. All reactions were performed in oven-dried (110 °C) glassware under prepurified nitrogen or argon.

Preparation of 6-(phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydropyrido[4.3-*b*]carbazole and 10-(phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydro[3,4-*b*]carbazole. To a magnetically stirred solution of 4-(phenylsulfonyl)-1,3-dimethyl-4*H*-furo[3,4-*b*]indole (**13**, 1.00 g, 3.08 mmol) and 1-aminotriazolo[4,5-*c*]pyridine (**14**, 0.417 g, 3.09 mmol) in dry THF (30 mL) at 20 °C was added over 5 min via a solid addition funnel freshly recrystallized (from HOAc) $Pb(OAc)_4$ (1.373 g, 3.10 mmol). After 10 min, a second equivalent of $Pb(OAc)_4$ (1.420 g, 3.20 mmol) was added in the same manner. The reaction was stirred at 20 °C for 3 h, the Pb salts were removed by filtration, and the filtrate was concentrated in vacuo to afford an amorphous solid. Flash chromatography (1:4 EtOAc-CH_2Cl_2) gave high R_f by-products (0.447 g) as well as a mixture of cycloadducts (0.465 g, 38%) as an amorphous solid, which was homogeneous by TLC: (R_f 0.55, THF); UV (95% EtOH): λ_{max} = 239 nm; high-resolution mass spectrum: *m/z* Calcd for $C_{23}H_{18}N_2O_3S$: 402.1048. Observed: 402.1038.

Preparation of ellipticine (1) and isoellipticine (2). A magnetically stirred solution of the mixture of 6-(phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydropyrido[4,3-*b*]carbazole and 10-(phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydropyrido[3,4-*b*]carbazole (0.465 g, 1.43 mmol) in THF (5 mL) was treated with MeOH (15 mL), 50% aqueous NaOH (3 mL), and $NaBH_4$ (1 pellet, 0.3 g, 8 mmol). After 1 h at reflux, additional $NaBH_4$ (1 pellet, 0.3 g, 8 mmol) was added and the reaction was refluxed for 16 h. The resulting yellow-orange fluorescent mixture was allowed to cool to 20 °C, poured into saturated $NaHCO_3$ solution (100 mL), and extracted with $CHCl_3$ until the aqueous layer was not fluorescent. The usual workup afforded a yellow solid (0.250 g). Flash chromatography (CH_2Cl_2, then EtOAc) gave a mixture of **1** and **2** (0.147 g, 52%) as a yellow solid. Flash chromatography (9:1 EtOAc-Et_3N) gave pure **1** and **2** in a 45:55 ratio, respectively. Both were identical (IR, UV, TLC, mp) to authentic samples.[11c]

Preparation of 1,10-bis(6-ellipticinyl)-*n*-decane (8). To a magnetically stirred solution of ellipticine (**1**, 0.1017 g, 0.413 mmol) in dry THF (10 mL) and dry HMPA (0.5 mL) at -78 °C was added a solution of *n*-BuLi/hexane (0.99 M, 0.43 mL, 0.426 mmol) via syringe. After warming to 0 °C over 0.5 h and re-cooling to -78 °C, 1,10-dibromodecane (0.126 g. 0.420 mmol) was added via syringe as a solution in dry THF (1 mL), and this mixture was allowed to warm to 20 °C over 1 h. The reaction was then re-cooled to -78 °C, and treated via syringe with a solution of ellipticine anion (freshly prepared by treating ellipticine (**1**, 0.101 g, 0.410 mmol) in dry THF (8 mL) and dry HMPA (0.5 mL) at -78 °C with a solution of *n*-BuLi/hexane (0.99 M, 0.42 mL, 0.416 mmol), followed by warming to 0 °C over 1 h, and re-cooling to -78 °C). The resulting mixture was allowed to gradually warm to 20 °C overnight. The solvent was removed in vacuo, and the residue was treated with H_2O (75 mL) and $CHCl_3$ (75 mL), the layers were separated, the aqueous layer was further extracted with $CHCl_3$ (50 mL), acidified to pH = 2 with concentrated HCl, extracted with $CHCl_3$ (50 mL), basified to pH = 9–10 with 50% aqueous NaOH, and extracted with $CHCl_3$ (50 mL). This process was repeated twice, then the aqueous portion was neutralized to pH = 7–8, and extracted with $CHCl_3$ (2 x 25 mL). The combined extracts were concentrated in vacuo to 100 mL, washed with H_2O (10 x 50 mL), dried (K_2CO_3), filtered, and concentrated in vacuo to afford an orange solid (0.240 g). Flash chromatography (hexane, 100 mL; CH_2Cl_2, 100 mL; THF, 200 mL) gave **8** (0.140 g, 54%) as a dark yellow solid: mp 193–195 °C (dec.); rf (THF) = 0.20; ^{1}H NMR ($CDCl_3$): δ 9.7 (s, 2H), 8.5–8.2 (m, 4H), 7.9 (m, 2H), 7.5–7.2 (m, 6H), 4.4 (m, 4H), 3.1 (s, 6H), 2.9 (s, 6H), 1.8–0.9 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 149.5, 146.5, 144.3, 140.8, 140.6, 134.1, 133.6, 127.8, 124.6, 123.8, 123.5, 119.5, 115.6, 108.4, 107.9, 45.7, 30.2, 29.9, 29.2, 26.7, 15.6, 13.4; UV ($CHCl_3$): λ_{max} = 278 (sh), 289, 297, 333 nm, ($CHCl_3$ + HCl): λ_{max} = 307 nm; CI mass spectrum (isobutylene carrier gas): *m/z* 631 (MH^+); high resolution mass spectrum: *m/z* Calcd for $C_{44}H_{47}N_4$: 631.3801 (MH^+). Observed: 631.3796.

Preparation of 1,8-bis(6-ellipticinyl)-*n*-octane (7). This compound was prepared in an analogous fashion to 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) using 1,8-dibromooctane in 32% yield after flash chromatography: mp 295–298 °C (dec.); rf (THF) = 0.20; ^{1}H NMR ($CDCl_3$): δ 9.7 (s, 2H), 8.5–8.4 (m, 4H), 7.9 (d, 2H), 7.6–7.2 (m, 6H), 4.5 (t, 4H), 3.3 (s, 6H), 3.0 (s, 6H), 1.9–0.8 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 151.4, 149.6, 144.4, 140.9, 135.7, 128.1, 126.9, 125.4, 124.0, 123.7, 119.7, 115.8, 108.6, 105.0, 45.9, 34.2, 30.3, 21.1, 14.8, 13.6; UV ($CHCl_3$): λ_{max} = 279 (sh), 288, 296, 332 nm, ($CHCl_3$ + HCl): λ_{max} = 310 nm); CI mass spectrum (isobutylene carrier gas): *m/z* 603 (MH^+); high resolution mass spectrum: *m/z* Calcd for $C_{42}H_{43}N_4$: 603.3488 (MH^+). Observed: 603.3466; Anal. Calcd for $C_{42}H_{44}N_4$+1/2 mol H_2O: C, 82.49; H, 7.04; N, 9.16. Found: C, 82.70; H, 7.26; N, 9.05.

Preparation of 1,12-bis(6-ellipticinyl)-*n*-dodecane (9). This compound was prepared in an analogous fashion to 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) using 1,12-dibromododecane in 44% yield after flash chromatography: mp 174–176 °C (dec.); rf (THF) = 0.20; ^{1}H NMR ($CDCl_3$): δ 9.7 (s, 2H), 8.5–8.3 (m, 4H), 7.9 (d, 2H), 7.5–7.2 (m, 6H), 4.5 (t, 4H), 3.2 (s, 6H), 2.0 (s, 6H), 1.9–1.2 (m, 20H); ^{13}C NMR ($CDCl_3$): δ 151.1, 146.0, 144.3, 135.7, 135.1, 133.9, 130.8, 128.1, 127.9, 125.4, 124.2, 123.0, 120.6, 117.5, 109.1, 45.9, 34.1, 30.3, 29.4, 26.8, 21.1, 15.0, 13.7; UV ($CHCl_3$): λ_{max} = 277 (sh), 284, 333 nm, ($CHCl_3$ + HCl): λ_{max} = 308 nm; CI mass spectrum (isobutylene carrier gas): *m/z* 659 (MH^+); high resolution mass spectrum: *m*/*z* Calcd for $C_{46}H_{51}N_4$: 659.4114 (MH^+). Observed: 659.4127.

Preparation of 1,8-bis(10-isoellipticinyl)-*n*-octane (10). This compound was prepared in an analogous fashion to 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) 1,8-dibromooctane in 53% yield after flash chromatography: mp 215–218 °C (dec.); rf (THF) 0.25; ^{1}H NMR ($CDCl_3$): δ 9.6 (s, 2H), 8.5–8.3 (m, 4H), 7.9 (m, 2H), 7.5–7.2 (m, 6H), 4.5 (t, 4H), 3.1 (broad s, 12H), 2.0–1.2 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 148.8, 145.1, 139.0, 138.9, 129.4, 127.6, 127.5, 126.8, 125.8, 124.4, 123.3, 119.3, 116.5, 110.9, 108.6, 46.0, 29.8, 29.1, 26.7, 14.9, 13.4; UV ($CHCl_3$): λ_{max} = 284, 320 nm, ($CHCl_3$ + HCl): λ_{max} = 303 nm; IR (KBr): 3680 (m), 2980 (s), 2940 (s), 2860 (m), 1620 (m), 1600 (s), 1480 (s), 1400 (s), 1360 (m), 1200 (s), 990 (s), 800 (m), 750 (s) cm^{-1}; FAB mass spectrum ($HOCH_2CH_2OH$ matrix): *m/z* 603 (MH^+); high resolution mass spectrum: *m/z* Calcd for $C_{42}H_{43}N_4$: 603.3488. Observed: 603-3460; Anal. Calcd for $C_{42}H_{43}N_4$+1 mol H_2O: C, 81.26; H, 7.14; N, 9.02. Found: C, 81.23; H, 6.92; N, 8.84.

Preparation of 1,10-bis(10-isoellipticinyl)-*n*-decane (11). This compound was prepared in an analogous fashion to 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) using 1,10-dibromodecane in 58% yield after flash chromatography: mp 140–143 °C; rf (THF) 0.27; ^{1}H NMR ($CDCl_3$): δ 9.7 (s, 2H), 8.4–8.1 (m, 6H), 7.6–7.2 (m, 6H), 4.4 (t, 4H), 3.1 (broad s, 12H), 1.8–1.7 (m, 4H), 1.4–1.1 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 145.3, 145.2, 139.3, 132.2, 132.1, 129.6, 129.2, 128.7, 126.2, 124.8, 122.6, 119.9, 112.5, 108.9, 46.0, 30.0, 29.3, 29.1, 26.7, 15.0, 13.5; UV ($CHCl_3$): λ_{max} = 275 (sh), 285, 321 nm, ($CHCl_3$ + HCl): λ_{max} = 303 nm; IR (KBr): 3400 (m), 2920 (s), 2840 (m), 1640 (m), 1610 (s), 1590 (m), 1470 (s), 1400 (s), 740 (s) cm^{-1}; CI mass spectrum (isobutylene carrier gas): *m/z* 631 (MH^+); high resolution mass spectrum: *m/z* Calcd for $C_{44}H_{47}N_4$: 631.3801 (MH^+). Observed: 631.3819; Anal. Calcd for $C_{44}H_{46}N_4$+4/3 mol H_2O: C, 80.70; H, 7.49; N, 8.55. Found: C, 80.58; H, 7.36; N, 8.23.

Preparation of 1,12-bis(10-isoellipticinyl)-*n*-dodecane (12). This compound was prepared in an analogous fashion to 1,10-bis(6-ellipticinyl)-*n*-decane (**8**) using 1,12-dibromododecane in 54% yield after flash chromatography: mp 163–165 °C (dec.); rf (THF) 0.27; ^{1}H NMR ($CDCl_3$): δ 9.6 (s, 2H), 8.4–8.3 (m, 4H), 7.9 (d, 2H), 7.5–7.2 (m, 6H), 4.4 (t, 4H), 3.0 (broad s, 12H), 1.8–1.7 (m, 4H), 1.4–1.2 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 148.8, 145.0, 138.8, 138.6, 129.3, 127.5, 127.3, 126.7, 125.7, 124.4, 123.2, 119.3, 116.5, 110.6, 108.6, 46.0, 30.2, 29.9, 29.4, 29.2, 26.8, 14.9, 13.3; UV ($CHCl_3$): λ_{max} = 275 (sh), 286, 321 nm, ($CHCl_3$ + HCl): λ_{max} = 304 nm; IR (KBr): 3420 (w), 2940 (s), 2850 (m), 1610 (w), 1600 (s), 1480 (s), 1440 (s), 750 (s) cm^{-1}; FAB mass spectrum ($HOCH_2CH_2OH$ matrix): *m/z* 659 (MH^+); high resolution mass spectrum: *m/z* Calcd for $C_{46}H_{51}N_4$: 659.4114 (MH^+). Observed: 659.4103; Anal. Calcd for $C_{46}H_{50}N_4$+4/3 mol H_2O: C, 80.90; H, 7.77; N, 8.20. Found: C, 81.16; H, 7.62; N, 8.10.

Preparation of 1,2-bis(2-bromoethoxy)ethane. To a magnetically stirred solution of triethylene glycol (3.375 g, 22.47 mmol) and CBr_4 (15.82 g, 47.7 mmol) in CH_2Cl_2 (50 mL) at 25 °C was added gradually over 10 min Ph_3P (12.51 g, 47.7 mmol). The resulting mixture was stirred at 25 °C for 15 h, then poured into 1:1 hexane-Et_2O (200 mL). The resulting white precipitate was removed by filtration, and the filtrate was concentrated in vacuo to afford a yellow liquid (11.57 g). Flash chromatography (hexane, 200 mL; Et_2O, 150 mL; CH_2Cl_2, 150 mL) gave a liquid product that was passed through basic Al_2O_3. The filtrate was concentrated in vacuo to afford the product (1.82 g, 30%) as a colorless liquid: ^1H NMR ($CDCl_3$): δ 3.8 (t, 4H), 3.6 (s, 4H), 3.4 (t, 4H); ^{13}C NMR ($CDCl_3$): δ 71.2, 70.5, 30.5; IR (neat): 2880 (s), 1360 (m), 1280 (s), 1110 (broad, s), 670 (m) cm^{-1}.

Preparation of 1,2-bis[2-(6-ellipticinyl)ethoxy]ethane (15). To a magnetically stirred solution of ellipticine (**1**, 50.0 mg, 0.203 mmol) in a mixture of dry THF (10 mL) and dry HMPA (2 mL) at -78 °C was added via syringe *n*-BuLi (1.01 M in hexane, 0.21 mL, 0.212 mmol). The resulting mixture was allowed to warm to 25 °C over 40 min, re-cooled to -78 °C, and treated via syringe with a solution of 1,2-bis(2-bromoethoxy)ethane (56.0 mg, 0.203 mmol) in dry THF (3 mL). This mixture was allowed to warm to 25 °C over 1 h, re-cooled to -78 °C, and treated with a solution of freshly generated ellipticine anion [prepared from ellipticine (**1**, 50.0 mg, 0.203 mmol) in dry THF (10 mL) and dry HMPA (2 mL) at -78 °C and *n*-BuLi (1.01 M in hexane, 0.22 mL, 0.222 mmol), which was allowed to warm to 25 °C over 30 min then re-cooled to -78 °C]. The resulting mixture was allowed to warm to 25 °C overnight, then poured into H_2O (35 mL) and extracted with $CHCl_3$ (3 x 30 mL). The aqueous phase was acidified (pH = 2) with concentrated HCl, extracted with $CHCl_3$ (30 mL), basified (pH = 10–11) with aqueous NaOH, and extracted with $CHCl_3$ (30 mL). This process was repeated until the aqueous portion was clear. The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford an orange solid (307 mg). Flash chromatography (hexane, 100 mL; CH_2Cl_2, 100 mL; EtOAc, 400 mL; 1:1 THF-EtOAc, 300 mL) gave **15** (10.9 mg, 8.4%) as an orange solid: ^1H NMR ($CDCl_3$): δ 9.8 (s, 2H), 8.4–8.2 (m, 4H), 7.8 (d, 2H), 7.5–7.1 (m, 6H), 4.5 (t, 4H), 3.8 (t, 4H), 3.5 (s, 4H), 3.1 (s, 6H), 2.8 (s, 6H); UV ($CHCl_3$): λ_{max} = 278, 288, 295 nm, ($CHCl_3$ + HCl): λ_{max} = 310 nm; FAB mass spectrum (3-nitrobenzyl alcohol matrix): *m/z* 607 (MH^+).

Preparation of *N,N*'-bis(2-bromoethyl)piperazine dihydrobromide.[20b] From a solution of *N,N*'-bis(2-hydroxyethyl)piperazine (6.00 g, 34.4 mmol) in 48% HBr (50 mL) was distilled HBr (15 mL). The remaining mixture was stirred at reflux for 24 h, then allowed to cool to 25 °C. Most of the solvent was removed in vacuo, and to the resulting residue was added acetone (40 mL). This mixture was refrigerated overnight, and the resulting precipitate was collected and dried in vacuo to afford the product (13.31 g, 84%) as a white solid: mp >240 °C [Lit.[20a] mp 240–260 °C (dec.)].

Attempted preparation of *N,N*'-bis[2-(6-ellipticinyl)ethyl]piperazine (16). To a magnetically stirred solution of ellipticine (85.2 mg, 0.346 mmol) in a mixture of dry THF (15 mL) and dry HMPA (2 mL) at -78 °C was added via syringe *n*-BuLi (1.01 M in hexane, 0.40 mL, 0.404 mmol). The resulting solution was allowed to warm to 25 °C over 40 min, then recooled to -78 °C. Simultaneously, in another vessel, *N*,*N*'-bis(2-bromoethyl)piperazine dihydrobromide (0.80 mg, 0.173 mmol) was suspended in dry DMF, and treated with NaH (60% dispersion in oil, 16.8 mg, 0.420 mol). After 20 min, this solution was transferred via syringe to the vessel containing the ellipticine anion. The resulting solution was allowed to warm to 25 °C overnight, then poured into water (60 mL), extracted with $CHCl_3$ (2 x 35 mL), acidified (pH = 2) with hydrochloric acid, extracted with $CHCl_3$ (35 mL), basified (pH = 10-11) with aqueous NaOH, and extracted with $CHCl_3$ (35 mL). This process was repeated until the aqueous phase was clear. The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford an orange solid (98.0 mg). TLC (THF) indicated that only ellipticine was present.

Preparation of 1,10-bis[6-(2-methylellipticinium)]decane diacetate (17). To a stirred solution of 1,10-bis(6-ellipticinyl)decane (**8**, 13.3 mg, 0.0211 mmol) in $CHCl_3$ (4 mL) at 25 °C was added in one portion MeI (7 μL, 15.9 mg, 0.112 mmol). The resulting mixture was stirred at 25 °C for 24 h, then centrifuged. The supernatant was removed by pipette, and the resulting residue was dried in vacuo to afford an orange solid (9.5 mg, 49%). This solid, presumed to be 1,10-bis[6-(2-methylellipticinium)]decane diiodide, was dissolved in DMF (1 mL) directly in the centrifuge tube. To this was added in one portion AgOAc (2.0 mg, 0.012 mmol). The resulting solution was stirred at 25 °C for 24 h, then Et_2O (2 mL) was added, and the mixture was refrigerated overnight. The resulting precipitate was collected and dried in vacuo to afford **17** as a yellow solid (1.7 mg, 21%): FAB mass spectrum (aqueous $HOCH_2CH_2OH$ matrix): *m/z* 661 ($MH^+ – 2$ OAc); UV (95% EtOH): $\lambda_{max} = 253$, 284 (sh), 312, 370 nm. The small quantity precluded further study.

Preparation of 2-methylellipticinium iodide (18). A solution of ellipticine (**1**, 49.4 mg, 0.201 mmol) and MeI (0.02 mL, 0.32 mmol) in EtOH (10 mL) with a catalytic amount of NaI was magnetically stirred at 30 °C for 3 days. The resulting precipitate was collected and dried in vacuo to afford **18** as a deep yellow solid (41.8 mg, 54%): mp >360 °C (beginning of decomposition) (Lit.[17] mp ca. 360 °C (dec.); UV (95% EtOH): $\lambda_{max} = 309$ nm.

Preparation of 2,2'-decamethylene-bis-ellipticinium bromide (19). A solution of ellipticine (**1**, 128.2 mg, 0.530 mmol) and 1,10-dibromodecane (78.4 mg, 0.261 mmol) in DMF (20 mL) with a catalytic amount of NaI was magnetically stirred at 130 °C for 3 days. The resulting precipitate was collected and dried in vacuo to afford **19** as a yellow solid (113 mg, 55%): mp 345–347 °C (dec.); UV (95% EtOH): $\lambda_{max} = 310$ nm; mass spectrum: *m/z* 710 ($M^+ – Br$), 631 ($M^+ – 2\ Br$), 316 ($M^{+2} – 2\ Br$).

Preparation of 9-hydroxyellipticine (21).[21] A mixture of 9-methoxyellipticine (**20**, 152.7 mg, 0.553 mmol) and commercial pyridine hydrochloride (2.92 g, 25.3 mmol) was heated at 195–205 °C for 45 min.

This mixture was allowed to cool to 25 °C, and diluted with brine (20 mL). The resulting precipitate was collected and dissolved in hot H_2O (45 mL), filtered, cooled to 25 °C, and slowly added to stirred saturated aqueous $NaHCO_3$ (16 mL). The resulting precipitate was collected, washed with cold H_2O, and dried in vacuo. The dried solids were placed in a Soxhlet apparatus and extracted with THF for 24 h. The extract was concentrated in vacuo to afford an orange solid. Flash chromatography (hexane, 100 mL; CH_2Cl_2, 100 mL; EtOAc, 100 mL; 2:1 EtOAc-THF, 150 mL; THF, 100 mL) gave **21** (0.135 g, 93%) as a yellow solid: mp 304–305 °C (Lit.[21] mp 307–309 °C); mass spectrum: *m/z* (relative intensity) 262 (M^+, 100), 247 (20), 131 (M^{+2}, 19); IR (KBr): 3400 (broad, s), 2950 (s), 1600 (s), 1480 (s), 1400 (m), 1215 (s), 1100 (broad, s), 800 (m), 610 (s) cm^{-1}; UV (95% EtOH): λ_{max} = 242, 276, 296, 332 nm, (95% EtOH + HCl): λ_{max} = 315, 370 nm.

Attempted preparation of 1,10-bis(9-elliptinyloxy)decane (22). To a magnetically stirred suspension of 9-hydroxyellipticine (**21**, 27.4 mg, 0.104 mmol) and K_2CO_3 (30 mg, 0.22 mol) in dry acetone (10 mL) at 25 °C was added in one portion 1,10-diiododecane (20.9 mg, 0.053 mol). The resulting mixture was stirred at 25 °C for 24 h, then at reflux for 6 h. Additional K_2CO_3 (about 800 mg) was added, and the mixture was stirred at reflux for 4 h, then at 25 °C for 24 h. H_2O (10 mL) was added, and the whole was extracted with $CHCl_3$ (3 x 50 mL). The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford an orange solid (55.3 mg). Flash chromatography (hexane, 75 mL; CH_2Cl_2, 75 mL; THF, 150 mL; MeOH, 75 mL) gave three product fractions (weights: 4.1 mg, 6.6 mg, 7.4 mg – in order of elution). Due to the small quantities obtained, characterization was not successful.

Preparation of bis(9-ellipticine) 1,10-decanedioate (23). To a magnetically stirred suspension of 9-hydroxyellipticine (**21**, 40.0 mg, 0.153 mmol) and Na_2CO_3 (160 mg, 1.51 mmol) in acetone (15 mL) at 25 °C was added in one portion via syringe sebacoyl chloride (16 µL, 18 mg, 0.075 mmol). The resulting mixture was stirred at 25 °C for 4 days, then poured into H_2O (25 mL) and extracted with $CHCl_3$ (4 x 30 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford an orange solid (32.6 mg). The aqueous portion was continuously extracted with $CHCl_3$ to furnish additional product (16.8 mg: Total: 49.4 mg). Flash chromatography of the combined solids (hexane, 100 mL; CH_2Cl_2, 100 mL; EtOAc, 300 mL; 2:1 EtOAc-THF, 150 mL; THF, 200 mL; MeOH, 100 mL) gave recovered 9-hydroxyellipticine (**21**, 18.8 mg, 47%) and **23** (11.9 mg, 23%) as an orange solid: FAB mass spectrum (MeOH $HOCH_2CH_2OH$ matrix): *m/z* 691 (MH^+); IR (KBr): 1740 (s), 1600 (s), 1480 (s), 1220 (m), 1100 (m) cm^{-1}.

Preparation of 6-methylellipticine (24). To a magnetically stirred solution of ellipticine (**1**, 500 mg, 2.03 mmol) in a mixture of dry THF (80 mL) and dry HMPA (8 mL) was added via syringe *n*-BuLi (1.4 M in hexane, 1.60 mL, 2.24 mmol). The resulting solution was allowed to warm to 25 °C over 1.5 h, then re-cooled to -78 °C. To this was added via syringe methyl iodide (0.13 mL, 2.09 mmol), and the resulting solution was allowed to warm to 25 °C overnight. The reaction mixture was poured into H_2O (100 mL) and extracted with $CHCl_3$ (4 x 75 mL). The combined extracts were concentrated in vacuo to 150 mL, and then washed with H_2O (10 x 75 mL). The organic phase was dried (K_2CO_3), filtered, and concentrated in vacuo to afford **24** (460.7 mg, 87%) cleanly as a yellow solid: R_f = 0.27 (THF); mp 209–210 °C (Lit.[23] mp 211–212 °C); mass spectrum: *m/z* (relative intensity) 260 (M^+, 49), 245 (M – Me, 22), 130 (M^{+2}, 8); ^1H NMR ($CDCl_3$): δ 9.6 (s, 1H), 8.4 (d, 1H), 8.2 (d, 1H), 7.8 (d, 1H), 7.5 (t, 1H), 7.3–7.2 (m, 2H), 4.0 (s, 3H), 3.1 (s, 3H), 2.9 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 149.7, 145.1, 141.9, 140.9, 134.4, 128.8, 127.1, 123.9, 123.6, 119.7, 116.0, 115.9, 108.6, 108.4, 106.2; UV (95% EtOH): λ_{max} = 278 (sh), 282, 294, 336 nm, (95% EtOH + HCl): λ_{max} = 309 nm.

Preparation of 2-benzoyl-1-cyano-6-methyl-1,2-dihydroellipticine (25). To a magnetically stirred solution of 6-methylellipticine (**23**, 125.0 mg, 0.481 mmol) in dry CH_2Cl_2 (10 mL) at 25 °C was added TMSCN (0.16 mL, 120 mg, 1.20 mmol) followed by benzoyl chloride (0.14 mL, 170 mg, 1.20 mmol). The resulting solution was stirred at 25 °C for 23 h, then the solvent was removed in vacuo. EtOH (5 mL) was added, and the resulting solid was collected and dried in vacuo to afford **25** (130.3 mg, 69%) cleanly as a yellow solid: R_f = 0.61 (THF); mp 174–175 °C; UV (95% EtOH): λ_{max} = 269, 332 nm; IR (KBr): 3060 (m), 2950 (m), 1680 (s), 1640 (s), 1580 (m), 1470 (m), 1345 (s), 1280 (s), 1170 (m), 990 (m), 730 (s), 690 (s) cm^{-1}; mass spectrum: *m/z* (relative intensity) 260 (100), 105 (54); high resolution mass spectrum: Calcd for $C_{18}H_{16}N_2$: 260.1313. Observed: 260.1390; Calcd for C_7H_5O: 105.0340. Observed: 105.0349; ^1H NMR ($CDCl_3$): δ 8.2 (d, 1H), 7.6–7.2 (m, 8H), 6.6 (d, 1H), 6.4 (d, 1H), 5.3 (s, 1H), 4.0 (s, 3H), 2.9 (s, 3H), 2.7 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.5, 142.8, 140.6. 132.4, 131.9, 129.3, 128.5, 128.0, 126.6, 125.6, 125.0, 123.1, 122.6, 122.3, 119.6, 116.8, 115.8, 114.1, 108.8, 103.4, 42.7, 33.4, 15.9, 14.8; Anal. Calcd for $C_{26}H_{21}N_3O \cdot 1/4\ H_2O$: C, 78.77; H, 5.59; N, 10.60. Found: C, 78.85; H, 5.45; N, 10.60.

Attempted preparation of 1,12-bis[1-(6-methylellipticinyl)]dodecane (26). Representative procedure for the attempted preparation of C-1 tethered bis-ellipticines. To a magnetically stirred solution of 2-benzoyl-1-cyano-6-methyl-1,2-dihydroellipticine (**25**, 40.0 mg, 0.102 mmol) and 1,12-dibromododecane (16.8 mg, 0.511 mmol) in dry THF (8 mL) at 25 °C was added NaH (60% dispersion in oil, 0.260 mmol). The resulting mixture was stirred at 25 °C for 2 days, then the solvent was removed in vacuo. To the resulting yellow residue was added H_2O (5 mL), 95% EtOH (10 mL), and KOH (370 mg), and this mixture was stirred at reflux for 24 h. The reaction mixture was poured into H_2O (20 mL), extracted with $CHCl_3$ (3 x 20 mL), acidified (pH = 2) with HCl, extracted with $CHCl_3$ (20 mL), basified (pH = 10–11) with aqueous NaOH, and extracted with $CHCl_3$ (20 mL). The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford a yellow solid (59.4 mg). Flash chromatography gave a yellow solid (42.4 mg) which was recrystallized from CH_2Cl_2: R_f = 0.30

(THF); mass spectrum: *m/z* (relative intensity) 303 (100), 286 (59), 258 (40), 243 (31); FAB mass spectrum: *m/z* 304; ^{1}H NMR (DMSO): δ 8.4–8.2 (m), 7.9 (d), 7.5–7.2 (m), 6.8 (broad, s), 4.1 (s), 3.2 (s), 3.0 (s), 1.5 (m), 1.3–1.2 (m); ^{13}C NMR (DMSO): δ 156.2, 144.9, 141.0, 138.6, 134.9, 128.4, 127.5, 125.4, 124.0, 122.6, 119.7, 119.3, 117.0, 109.5, 109.2, 104.9, 33.9, 25.4, 18.8, 14.0.

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