Synthesis of Ellipticine by Hetaryne Cycloadditions − Control of Regioselectivity

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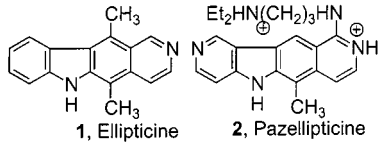
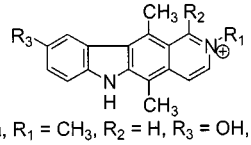
We have modified Gribble's and Moody's approaches to ellipticines by introducing substituents into the 3,4-didehydropyridine dienophile to control the key cycloaddition step. A chloro substituent at position 2 improved the yields and the regioselectivities of the cycloadditions and the overall efficiency of the synthesis of ellipticine.

Introduction

Ellipticine (**1**),[1] while possessing antitumor properties, is too toxic to be clinically useful, although phase II clinical trials have been reached by analogs such as pazellipticine (**2**), elliptinium (**3a**), datelliptium (**3b**), and BD-84 (**3c**).[2−4] Recently, attention has again been focused on the ellipticines, due to the finding that 9-hydroxyellipticine inhibits p53 phosphorylation and induces apoptosis,[5] and that *N*-quaternized derivatives show selective activity against p53-mutant cell lines[6]

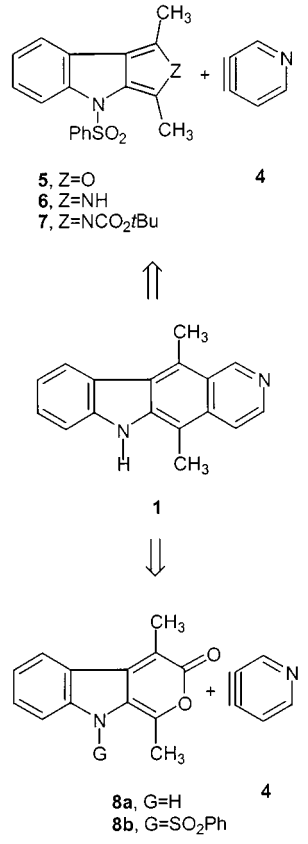


1, Ellipticine **2**, Pazellipticine



3a, $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$, Elliptinium
3b, $R_1 = CH_2CH_2N^+HEt_2$, $R_2 = H$, $R_3 = OH$, Datelliptium
3c, $R_1 = H$, $R_2 = NH(CH_2)_3N^+HEt_2$, $R_3 = CH_3O$, BD-84

Numerous procedures for the synthesis of ellipticines have been developed.[3,4,7−9] Because of our interest in cycloaddition reactions and aryne chemistry, we focused on Gribble's procedure,[10] which is based on the cycloaddition between 3,4-didehydropyridine (**4**) and an indoloisobenzofuran **5**, and also on Moody's procedure,[11,12] which is based on the cycloaddition between **4** and indolopyrone **8a** (Scheme 1). Although both these synthetic routes are short and convergent, they are of limited practical interest because of the low yields (≤ 20%) and the lack of regioselectivity of the cycloadditions. Variation of Gribble's strategy using dienes **6** and **7** produce similar results.[13] Davis and Gribble improved the yield and regioselectivity of the cycloaddition by use of 5,6-dihydropyridones, which have more asymmetric charge distributions, but this procedure requires an additional dehydrogenation step that has a yield of only 20%.[14]



5, Z=O
6, Z=NH
7, Z=NCO_2tBu

4

1

4

8a, G=H
8b, G=SO_2Ph

Scheme 1

Results and Discussion

It is known that the regiochemistry of some aryne cycloadditions can be controlled by the inductive and/or steric effect of a substituent near the triple bond.[15−23] To test whether this effect could improve the regioselectivity of the key cycloadditions with dienes **5**−**8a**[24] we carried out ex-

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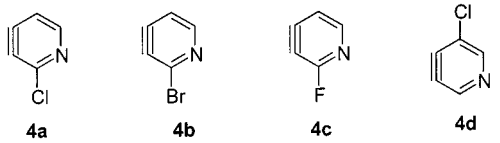
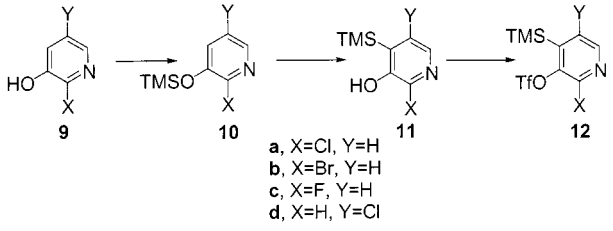
periments with pyridynes **4a**−**d**, which were selected because the directing groups F, Cl, and Br are relatively easy to introduce, allow modulation of the polarization and the steric hindrance, and are easy to remove after the cycloaddition, to afford the same compounds as prepared by Gribble and Moody.

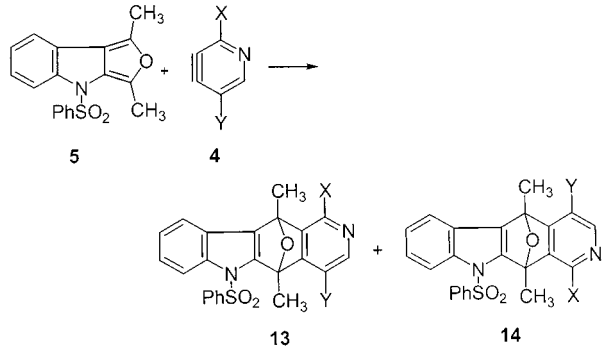


As precursors of pyridynes **4a**−**d**[25−29] we prepared the corresponding *o*-trimethylsilyl triflates[30] as shown in Scheme 2. 3-Hydroxypyridines **9a**−**d** were transformed into the corresponding trimethylsilyl derivatives **10a**−**d** by treatment with HMDS. Metalation of compounds **10a**−**c** at position 4, accomplished with LDA in THF, was followed by the migration of the trimethylsilyl group from the oxygen atom to position 4, affording pyridinols **11a**−**c**.[31−33] Metalation of **10d** under the same conditions afforded a 1:1 mixture of 5-chloro-3-hydroxy-4-(trimethylsilyl)pyridine (**11d**) and 5-chloro-3-hydroxy-2-(trimethylsilyl)pyridine (although metalation at position 4 seems to be favored on electronic grounds, this effect is cancelled by steric hindrance by the adjacent substituents[29,34−38]). However, the use of ether as solvent resulted in exclusive metalation of **10d** at position 4, giving **11d** in 83% yield. Treatment of compounds **11a**−**c** with triflic anhydride yielded the corresponding pyridyne precursors **12a**−**c**. For the transformation of **11d** into **12d** it was necessary to use *n*BuLi and *N*-(4-chloro-2-pyridyl)triflimide.



Scheme 2

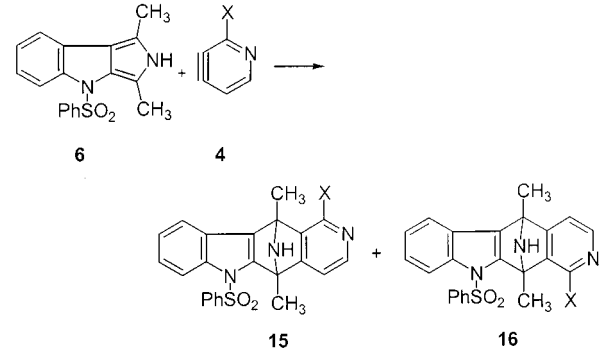
The key cycloadditions between **4a**−**d** and **5**−**8a** were carried out by generating the former in the presence of the latter, by treatment of compounds **12a**−**d** with CsF. We first studied the reactions of Gribble's diene **5** (Scheme 3, Table 1). When 2-chloro-3,4-didehydropyridine (**4a**) was generated in the presence of diene **5**, a mixture of adducts **13a** and **14a** was obtained in 2.4:1 ratio and in 88% yield (Entry 1); the products were identified after chromatographic separation by spectroscopic analysis and NOE experiments. To establish the relative importance of electronic and steric contributions we then changed the halogeno substituent at position 2 of the hetaryne. However, both bromo and fluoro abolished all regioselectivity (Entries 2 and 3). Similarly, a chloro at position 5 instead of at position 2 failed to invert the regioselectivity: Generation of **4d** in the presence of diene **5** gave a 1:1 mixture of **13d** and **14d** in 64% yield (Entry 4). Similar results were obtained with diene **6** (Scheme 4): There was modest regioselectivity with **4a** (Table 2, Entry 1) but not with **4b** (Entry 2). With the more crowded diene **7**, even **4a** failed to react regioselectively, giving a 1:1 mixture of regioisomers **17** and **18** in 52% yield (Scheme 5).



Scheme 3

Table 1. Cycloaddition of indoloisobenzofuran **5**

Entry	Diene	Hetaryne	Yield (%)	Ratio **13**/**14**
1	**5**	**4a** (X = Cl, Y = H)	88	2.4:1
2	**5**	**4b** (X = Br, Y = H)	40	1:1
3	**5**	**4c** (X = F, Y = H)	38	1.1:1
4	**5**	**4d** (X = H, Y = Cl)	64	1:1

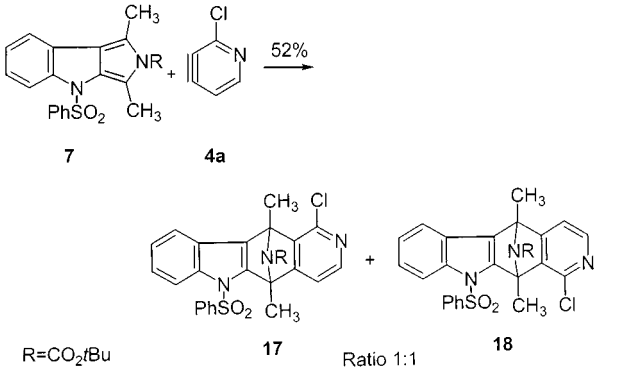


Scheme 4

Table 2. Cycloaddition of indolopyrrole **6**

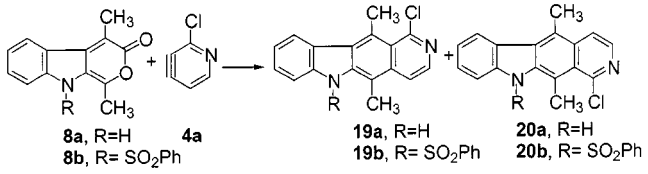
Entry	Diene	Hetaryne	Yield (%)	Ratio **15**/**16**
5	**6**	**4a** (X = Cl)	44	1.7:1
6	**6**	**4b** (X = Br)	28	1:1

Treatment of **4a** with Moody's pyrone (**8a**) also gave a 1:1 mixture of cycloadducts (**19a** and **20a**), with a yield of 21% (41% if the recovery of 20% of **8a** is taken into account; see Scheme 6). Finally, to make the diene more similar to dienes **5**−**7**, we protected the nitrogen atom of **8** with a phenylsulfonyl group by treatment with LiHMDS and



Scheme 5

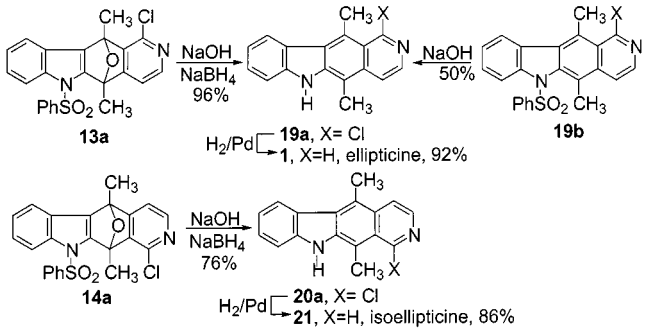
$ClSO_2Ph$ (78% yield). When **4a** was generated in the presence of diene **8b** the only product was a 20% yield of regioisomer **19b** (40% if recovery of 20% of **8a** is taken into account).



Scheme 6

We have found no explanation for the above results, other than the suggestion that they may be due to a delicate balance of factors including orbital overlapping, electrostatic interactions between the reaction centers, and steric and electrostatic interactions between the substituents in diene and dienophile (particularly the halogeno and the $PhSO_2$ group).

To complete the syntheses of ellipticine (**1**), **19a** was obtained in a remarkable 96% yield[39] from **13a** by treatment with NaOH and $NaBH_4$ (and also in 50% yield from **19b** by *N*-deprotection with NaOH), and was then subjected to hydrogenolysis, giving **1** in 92% yield (Scheme 7). Similarly, treatment of **14a** with NaOH and $NaBH_4$ gave a 76% yield of **20a**, which upon hydrogenolysis afforded an 86% yield of isoellipticine (**21**).



Scheme 7

Conclusion

To sum up, though the factors affecting the regioselectivity of the reported hetaryne cycloadditions are not understood, a chloro substituent at position 2 in the 3,4-didehydropyridine improves yield and regioselectivity. With this modification the overall yield of ellipticine from diene **5** was improved by a factor of 6 (from 9 to 55%).

Experimental Section

2-Chloro-3-(trimethylsilyloxy)pyridine (10a): HMDS (5.5 mL, 26.36 mmol) was added to 2-chloro-3-pyridinol (**9a**; 5.69 g, 43.93 mmol) and the mixture was heated at 80 °C for 45 min under a mild stream of argon (to remove the NH_3 formed). Evaporation of excess HMDS in vacuo yielded **10a** as an oil, which was used for the next reaction without purification; ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, 1 H), 7.16 (m, 2 H), 0.31 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 148.0 (C), 143.7(C), 141.6 (CH), 128.1 (CH), 123.1 (CH), −0.01 (CH_3).

2-Bromo-3-(trimethylsilyloxy)pyridine (10b): This compound was prepared as above, from 2-bromo-3-pyridinol (**9b**, 5.0 g, 28.7 mmol); ^{1}H NMR ($CDCl_3$): δ = 7.92 (m, 1 H), 7.20 (m, 2 H), 0.33 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 149.6 (C), 147.6 (CH), 136.4 (C), 127.3 (CH), 123.3 (CH), 0.29 (CH_3).

2-Fluoro-3-(trimethylsilyloxy)pyridine (10c): This compound was prepared as above, from 2-fluoro-3-pyridinol[40] (**9c**, 5.0 g, 28.7 mmol); ^{1}H NMR ($CDCl_3$): δ = 7.65 (m, 1 H), 7.18 (m, 1 H), 6.95 (m, 1 H), 0.23 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 155.4 (d, *J* = 237 Hz, C−F), 138.4 (d, *J* = 13.2 Hz, CH), 137.9 (d, *J* = 27.7 Hz, C), 130.6 (d, *J* = 4.9 Hz, CH), 121.7 (d, *J* = 4.2 Hz, CH), −0.31 (CH_3).

5-Chloro-3-(trimethylsilyloxy)pyridine (10d): This compound was prepared as above, from 5-chloro-3-pyridinol (**9d**, 11.3 g, 87.26 mmol); ^{1}H NMR ($CDCl_3$): δ = 8.20 (s, 1 H), 8.11 (s, 1 H), 7.15 (s, 1 H), 0.29 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 152.1 (C), 141.6 (CH), 140.4 (CH), 131.8 (C), 127.1 (CH), 0.02 (CH_3).

2-Chloro-3-hydroxy-4-(trimethylsilyl)pyridine (11a): A solution of **10a** (829 mg, 4.11 mmol) in dry THF (10 mL) was slowly added at −78 °C through a cannula to a solution of LDA, prepared from *n*BuLi (1.54 M, 3.5 mL, 5.34 mmol) and *i*Pr_2NH (0.83 mL, 5.88 mmol), and the temperature of the bath was then allowed to increase slowly to room temp. The mixture was poured into a 5% $NaHCO_3$ solution (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried with anhydrous Na_2SO_4. Evaporation of solvent in vacuo afforded a residue that was purified by chromatography (Et_2O/hexane, 1:2), giving **11a** (495 g, 60%) as a white solid; m.p. 104−106 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$): δ = 7.94 (d, *J* = 4.6 Hz, 1 H), 7.20 (d, *J* = 4.4 Hz, 1 H), 5.78 (br. s, 1 H), 0.34 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 152.0 (C), 140.6 (C), 137.6 (C), 136.9 (C), 128.8 (CH), −1.78 (CH_3); UV (EtOH): λ_{max} = 290 nm; IR (NaCl): $\tilde{\nu}$ = 1392, 1216 cm^{-1}; LRMS: *m*/*z* (%) = 203 (7), 201 (20) [M^+], 185 (36), 150 (100); HRMS for $C_8H_{12}ClNOSi$: calcd. 201.03767; found 201.03786; $C_8H_{12}ClNOSi$ (201.7): calcd. C 47.63, H 5.99, N 6.94; found C 48.01, H 6.05, N 6.97.

2-Bromo-3-hydroxy-4-(trimethylsilyl)pyridine (11b): This compound was prepared as above, from **10b** (7.0 g, 28.7 mmol) in 50% yield. White solid, m.p. 83−84 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$): δ =

7.94 (d, J = 4.1 Hz, 1 H), 7.22 (d, J = 4.1 Hz, 1 H), 0.35 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 153.2 (C), 141.0 (CH), 136.5 (C), 131.0 (C), 128.9 (CH), −1.8 (CH_3); UV (EtOH): λ_{max} = 292 nm; IR (NaCl): $\tilde{\nu}$ = 3495 (OH) cm^{-1}; LRMS: m/z (%) = 247 (5) [M$^+$], 245 (6) [M$^+$], 150 (100); HRMS for $C_8H_{12}BrNOSi$: calcd. 244.987154; found 244.987476.

2-Fluoro-4-(trimethylsilyl)-3-pyridinol (11c): This compound was prepared as above, from **10c** (5.37 g, 29.0 mmol) in 76% yield. White solid, m.p. 119−120 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$): δ = 7.69 (d, J = 4.7 Hz, 1 H), 7.12 (d, J = 4.7 Hz, 1 H), 0.34 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 152.5 (d, J = 236 Hz, C−F), 143.5 (d, J = 26 Hz, C), 140.5 (d, J = 3.5 Hz, C), 135.8 (d, J = 10.1 Hz, CH), 126.8 (d, J = 1.5 Hz, CH), −1.7 (CH_3); UV (EtOH): λ_{max} = 222, 282 nm; IR (NaCl): $\tilde{\nu}$ = 3391 cm^{-1}; LRMS: m/z (%) = 185 (31) [M$^+$], 170 (100); HRMS for $C_8H_{12}FNOSi$: calcd. 185.067221; found 185.067098.

5-Chloro-3-hydroxy-4-(trimethylsilyl)pyridine (11d): This compound was prepared as above, from **10d** (17.58 g, 87.26 mmol) in 83% yield. White solid, m.p. 137−138 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$): δ = 10.3 (s br., 1 H), 8.04 (s, 1 H), 8.00 (s, 1 H), 0.46 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 160.4 (C), 139.1 (C), 138.7 (CH), 135.9 (C), 133.0 (CH), 1.02 (CH_3); UV (EtOH): λ_{max} = 296 nm; IR (NaCl): $\tilde{\nu}$ = 1405 cm^{-1}; LRMS: m/z (%) = 201 (13) [M$^+$], 185 (55); HRMS for $C_8H_{12}ClNOSi$: calcd. 201.03767; found 201.03772.

2-Chloro-3-(trifluoromethanesulfonyloxy)-4-(trimethylsilyl)pyridine (12a): iPr$_2$EtN (3.1 mL, 17.80 mmol) and then, slowly, Tf_2O (2.8 mL, 23.73 mmol) were added at −80 °C to a solution of **11a** (2.39 g, 11.86 mmol) in dry CH_2Cl_2 (50 mL). After 1 h, the cooling bath was removed, and when the reaction mixture had reached room temp. it was poured into a dilute $NaHCO_3$ solution (50 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. Hexane was added to the residue, the remaining solid was removed by filtration, and the solution was chromatographed, affording **12a** (3.56 g, 90%) as an oil that solidified upon drying in vacuo; m.p. 51−53 °C; ^{1}H NMR ($CDCl_3$): δ = 8.35 (d, J = 4.7 Hz, 1 H), 7.40 (d, J = 4.7 Hz, 1 H), 0.44 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 148.6 (C), 147.6 (CH), 145.3 (C), 144.6 (C), 129.4 (CH), 118.5 (q, J = 320 Hz, CF_3), −0.86 (CH_3); UV (EtOH): λ_{max} = 274 nm; IR (NaCl): $\tilde{\nu}$ = 1217 cm^{-1}; LRMS: m/z (%) = 333 (1) [M$^+$], 318 (100), 185 (36); HRMS for $C_9H_{11}ClF_3NO_3SSi$: calcd. 332.98696; found 332.98689.

2-Bromo-3-(trifluoromethanesulfonyloxy)-4-(trimethylsilyl)pyridine (12b): Compound **12b** (4.50 g, 88%) was obtained from **11b** (3.36 g, 13.66 mmol) as an oil that solidified upon drying in vacuo; m.p. 61−62 °C; ^{1}H NMR ($CDCl_3$): δ = 8.33 (d, J = 4.6 Hz, 1 H), 7.41 (d, J = 4.6 Hz, 1 H), 0.44 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 148.2 (C), 147.9 (CH), 146.3 (C), 136.4 (C), 129.6 (CH), 118.4 (q, J = 320 Hz, CF_3), −0.6 (CH_3); UV (EtOH): λ_{max} = 274 nm; IR (NaCl): $\tilde{\nu}$ = 1355 cm^{-1}; LRMS: m/z (%) = 364 (2), 149 (100); HRMS for $C_9H_{12}BrF_3NO_3SSi$ [M$^+$(^{79}Br) + 1]: calcd. 377.944264; found 377.943347.

2-Fluoro-3-(trifluoromethanesulfonyloxy)-4-(trimethylsilyl)pyridine (12c): Compound **12c** (5.50 g, 87%) was obtained from **11c** (3.70 g, 20.0 mmol) as an oil; ^{1}H NMR ($CDCl_3$): δ = 8.03 (d, J = 4.7 Hz, 1 H), 7.21 (d, J = 4.7 Hz, 1 H), 0.31 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 154.4 (d, J = 244 Hz, C−F), 150.4 (C), 145.6 (d, J = 12.6 Hz, CH), 135.8 (d, J = 26.8 Hz, C), 127.7 (d, J = 4.4 Hz, CH), 118.6 (q, J = 321 Hz, CF_3); UV (EtOH): λ_{max} = 266 nm; IR (NaCl): $\tilde{\nu}$ = 1410 cm^{-1}; LRMS (FAB): m/z (%) = 317 (100) [M$^+$]; HRMS for $C_9H_{11}F_4NO_3SSi$: calcd. 317.01650; found 317.01925.

5-Chloro-3-(trifluoromethanesulfonyloxy)-4-(trimethylsilyl)pyridine (12d): Compound **12d** (3.8 g, 52%) was obtained from **11d** (4.4 g, 21.9 mmol) as an oil; ^{1}H NMR ($CDCl_3$): δ = 8.54 (s, 1 H), 8.48 (s, 1 H), 0.52 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 150.3 (C), 148.7 (CH), 141.5 (C), 139.9 (C), 138.6 (C), 118.4 (q, J = 320 Hz, CF_3), 0.5 (CH_3); UV (EtOH): λ_{max} = 280 nm; LRMS (FAB): m/z (%) = 333 (100) [M$^+$ + 1], 318 (18); $C_9H_{11}ClF_3NO_3SSi$ (333.8): calcd. C 32.38, H 3.32, N 4.19; found C 32.26, H 3.13, N 4.50.

General Procedure for the Cycloadditions: CsF and then, slowly, the hetaryne precursor **12** were added to a stirred suspension of the diene **5** in CH_3CN. Stirring was maintained at room temp. until consumption of **12** (TLC monitoring). The mixture was then filtered, the solvent was evaporated from the filtrate in vacuo, and the residue was chromatographed to obtain adducts.

Treatment of Furoindole 5 with 2-Chloro-3,4-didehydropyridine (4a): Treatment of furoindole **5**[10] (202 mg, 0.62 mmol), CH_3CN (8 mL) with CsF (1 g, 6.21 mmol) and **12a** (2.07 g, 6.21 mmol), followed by chromatography (silica gel; Et_2O/hexane, 1:2), afforded adducts **13a** (170 mg, 63%) and **14a** (70 mg, 26%).

Adduct 13a: M.p. 80−81 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$): δ = 8.04 (d, J = 4.6 Hz, 1 H), 7.98 (dd, J = 7.3 and 1.4 Hz, 2 H), 7.83 (dd, J = 7.3 and 1.4 Hz, 2 H), 7.45 (m, 4 H), 7.25 (m, 2 H), 7.12 (d, J = 4.6 Hz, 1 H), 2.37 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 165.4 (C), 154.7 (C), 149.3 (CH), 144.9 (C), 144.3 (C), 141.9 (C), 141.6 (C), 138.3 (C), 134.7 (CH), 129.8 (CH), 127.0 (CH), 126.3 (CH), 124.8 (CH), 124.1 (C), 120.1 (CH), 115.7 (CH), 114.7 (CH), 89.3 (C), 88.3 (C), 16.9 (CH_3), 16.1 (CH_3); UV (EtOH): λ_{max} = 246 nm; IR (NaCl): $\tilde{\nu}$ = 1181 cm^{-1}; LRMS: m/z (%) = 438 (9), 436 (23) [M$^+$], 295 (33); HRMS for $C_{23}H_{17}ClN_2O_3S$: calcd. 436.064842; found 436.066473.

Adduct 14a: M.p. 185 °C (Et_2O); ^{1}H NMR ($CDCl_3$): δ = 8.05 (m, 2 H), 7.86 (m, 2 H), 7.40 (m, 4 H), 7.25 (m, 2 H), 7.04 (d, J = 4.6 Hz, 1 H), 2.50 (s, 3 H), 2.17 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 166.3 (C), 155.9 (C), 153.4 (C), 149.4 (CH), 142.6 (C), 142.3 (C), 141.2 (C), 138.3 (C), 134.6 (CH), 129.8 (CH), 127.1 (CH), 126.0 (CH), 124.6 (CH), 123.9 (C), 119.5 (CH), 115.9 (CH), 113.7 (CH), 90.8 (C), 86.6 (C), 17.6 (CH_3), 15.1 (CH_3); UV (EtOH): λ_{max} = 278 nm; IR (NaCl): $\tilde{\nu}$ = 1182 cm^{-1}; LRMS: m/z (%) = 438 (12), 436 (31) [M$^+$], 295 (61); HRMS for $C_{23}H_{17}ClN_2O_3S$: calcd. 436.064842; found 436.065156.

Treatment of Furoindole 5 with 2-Bromo-3,4-didehydropyridine (4b): Treatment of furoindole **5**[10] (100 mg, 0.31 mmol) with CsF (600 mg, 3.7 mmol) and **12b** (1.16 g, 3.1 mmol) in CH_3CN (4 mL), followed by chromatography (silica gel; Et_2O/hexane, 1:2), gave adducts **13b** (30 mg, 20%) and **14b** (30 mg, 20%).

Adduct 13b: M.p. 160−162 °C (EtOH); ^{1}H NMR ($CDCl_3$): δ = 8.01 (m, 2 H), 7.83 (m, 2 H), 7.55−7.25 (m, 6 H), 7.15 (d, J = 4.5 Hz, 1 H), 2.38 (s. 3 H), 2.28 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 164.3 (C), 154.3 (C), 149.0 (CH), 147.3 (C), 143.8 (C), 141.2 (C), 137.8 (C), 134.2 (CH), 131.2 (C), 129.3 (CH), 126.5 (CH), 125.8 (CH), 124.4 (CH), 123.7 (C), 119.7 (CH), 115.2 (CH), 114.4 (CH), 88.6 (C), 88.2 (C), 16.6 (CH_3), 15.6 (CH_3); UV (EtOH): λ_{max} = 222, 268 nm; IR (NaCl): $\tilde{\nu}$ = 1455, 1384 cm^{-1}; LRMS: m/z (%) = 482 (40) [M$^+$], 480 (38) [M$^+$], 341 (33), 339 (33); HRMS for $C_{23}H_{17}BrN_2O_3S$; calcd. 480.014326; found 480.015507.

Adduct 14b: M.p. 204 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$): δ = 8.05 (m, 4 H), 7.59−7.19 (m, 6 H), 7.08 (d, J = 4.5 Hz, 1 H), 2.53 (s. 3 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 165.2 (C), 155.3 (C), 149.2 (CH), 146.7 (C), 142.1 (C), 140.8 (C), 137.8 (C), 134.1

(CH), 131.9 (C), 129.3 (CH), 126.6 (CH), 125.6 (CH), 124.1 (CH), 123.4 (C), 119.0 (CH), 115.5 (CH), 113.4 (CH), 90.7 (C), 85.9 (C), 17.2 (CH_3), 14.6 (CH_3); IR (NaCl): $\tilde{\nu}$ = 1445, 1184 cm^{-1}; LRMS: *m/z* (%) = 482 (69) [M^+], 480 (63) [M^+], 341 (57), 339 (58); HRMS for $C_{23}H_{17}BrN_2O_3S$: calcd. 480.014326; found 480.013727.

Treatment of Furoindole 5 with 2-Fluoro-3,4-didehydropyridine (4c): Treatment of furoindole **5**[10] (101 mg, 0.31 mmol) with CsF (516 mg, 3.42 mmol) and **12c** (482 mg, 1.52 mmol) in CH_3CN (4 mL), followed by chromatography (silica gel; Et_2O), gave adducts **13c** (24 mg, 18%) and **14c** (26 mg, 20%).

Adduct 13c: ^1H NMR ($CDCl_3$): δ = 7.93 (dd, *J* = 1.1, 7.3 Hz, 1 H), 7.83 (dd, *J* = 0.9, 4.5 Hz, 1 H), 7.75 (m, 2 H), 7.50−7.18 (m, 6 H), 7.05 (m, 1 H), 2.24 (s, 3 H), 2.22 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 168.6 (C), 156.6 (d, *J* = 235 Hz, *C*−F), 154.6 (C), 147.1 (d, *J* = 13.0 Hz, CH), 143.9 (C), 141.2 (C), 138.3 (C), 134.0 (CH), 131.1 (d, *J* = 35.8 Hz, C), 129.3 (CH), 126.5 (CH), 125.7 (CH), 124.3 (CH), 123.7 (C), 119.5 (CH), 115.3 (CH), 113.4 (CH), 89.7 (C), 86.7 (C), 15.9 (CH_3), 15.8 (CH_3); LRMS: *m/z* (%) = 420 (4) [M^+], 279 (32), 141 (64), 77 (100); HRMS for $C_{23}H_{17}FN_2O_3S$: calcd. 420.094393; found 420.094512.

Adduct 14c: ^1H NMR ($CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1 H), 7.81−7.78 (m, 3 H), 7.48−7.15 (m, 6 H), 6.95 (m, 1 H), 2.36 (s, 3 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 169.6 (C), 156.6 (d, *J* = 236 Hz, *C*−F), 156.0 (C), 147.5 (d, *J* = 12.9 Hz, CH), 141.6 (C), 140.6 (C), 138.2 (C), 134.1 (CH), 130.5 (d, *J* = 34.6 Hz, C), 129.4 (CH), 126.6 (CH), 125.4 (CH), 124.2 (CH), 123.5 (C), 119.0 (CH), 115.5 (CH), 112.7 (CH), 89.1 (C), 87.1 (C), 17.0 (CH_3), 14.8 (CH_3); LRMS: *m/z* (%) = 420 (8) [M^+], 279 (100), 77 (100); HRMS for $C_{23}H_{17}FN_2O_3S$: calcd. 420.094393; found 420.094255.

Treatment of Furoindole 5 with 5-Chloro-3,4-didehydropyridine (4d): Treatment of furoindole **5**[10] (100 mg, 0.31 mmol) with CsF (470 mg, 3.1 mmol) and **12d** (1.02 g, 3.1 mmol) in CH_3CN (4 mL), followed by chromatography (silica gel; Et_2O/hexane, 1:2), gave cycloadducts **13b** (43 mg, 32%) and **14d** (43 mg, 32%).

Adduct 13d: M.p. 217 °C; ^1H NMR ($CDCl_3$): δ = 8.24 (s, 1 H), 8.10 (s, 1 H), 8.00 (m, 1 H), 7.84 (m, 2 H), 7.57−7.22 (m, 6 H), 2.36 (s. 3 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 157.1 (C), 155.5 (C), 148.6 (CH), 148.4 (C), 141.9 (C), 141.0 (C), 137.9 (C), 137.1 (CH), 134.2 (CH), 129.4 (CH), 126.6 (CH), 125.7 (CH), 124.3 (CH), 123.9 (C), 123.6 (C), 119.4 (CH), 115.3 (CH), 88.6 (C), 87.9 (C), 16.4 (CH_3), 16.0 (CH_3); UV (EtOH): λ_{max} = 244 nm; IR (NaCl): $\tilde{\nu}$ = 1372, 1185 cm^{-1}; LRMS: *m/z* (%) = 436 (33) [M^+], 295 (65); HRMS for $C_{23}H_{17}ClN_2O_3S$: calcd. 436.064842; found 436.063183; $C_{23}H_{17}ClN_2O_3S$ (436.9): calcd. C 63.23, H 3.92, N 6.41; found C 63.00, H 3.94, N 6.08.

Adduct 14d: M.p. 220 °C; ^1H NMR ($CDCl_3$): δ = 8.19 (s, 1 H), 8.15 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 2 H), 7.56−7.23 (m, 6 H), 2.49 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 156.3 (C), 153.8 (C), 149.1 (C), 148.6 (CH), 143.5 (C), 141.0 (C), 137.9 (C), 136.1 (CH), 134.1 (CH), 129.3 (CH), 126.6 (CH), 125.8 (CH), 124.7 (C), 124.2 (CH), 123.4 (C), 119.3 (CH), 115.4 (CH), 90.3 (C), 85.9 (C), 17.0 (CH_3), 14.9 (CH_3); UV (EtOH): λ_{max} = 246 nm; IR (NaCl): $\tilde{\nu}$ = 1372, 1185 cm^{-1}; LRMS: *m/z* (%) = 436 (8) [M^+], 295 (39); HRMS for $C_{23}H_{17}ClN_2O_3S$: calcd. 436.064842; found 436.063982.

Treatment of Pyrroloindole 6 with 2-Chloro-3,4-didehydropyridine (4a): Treatment of pyrroloindole **6**[13] (57 mg, 0.17 mmol) with CsF (300 mg, 2.0 mmol) and **12a** (586 mg, 1.7 mmol) in CH_3CN (2 mL), followed by chromatography (silica gel; EtOAc/hexane, 4:1), gave adducts **15a** (11 mg, 16%) and **16a** (21 mg, 28%).

Adduct 15a: M.p. 97 °C (Et_2O/hexane); ^1H NMR ($CDCl_3$): δ = 7.97−7.90 (m, 2 H), 7.73−7.70 (m, 2 H), 7.49−7.18 (m, 6 H), 6.97 (d, *J* = 4.5 Hz, 1 H), 2.23 (s. 3 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 165.8 (C), 156.8 (C), 148.2 (CH), 147.0 (C), 144.9 (C), 141.9 (C), 141.3 (C), 138.4 (C), 134.1 (CH), 132.3 (C), 129.3 (CH), 126.4 (CH), 125.6 (CH), 124.3 (CH), 119.7 (CH), 115.3 (CH), 114.5 (CH), 72.2 (C), 70.1 (C), 16.8 (CH_3), 15.9 (CH_3); UV (EtOH): λ_{max} = 220, 246 nm; IR (NaCl): $\tilde{\nu}$ = 1441 cm^{-1}; LRMS: *m/z* (%) = 435 (82) [M^+], 294 (100); HRMS for $C_{23}H_{18}ClN_3O_2S$: calcd. 435.080827; found 435.080756.

Adduct 16a: ^1H NMR ($CDCl_3$): δ = 8.28 (m, 2 H), 7.73 (m, 2 H), 7.55−7.19 (m, 7 H), 2.76 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 162.0 (C), 152.5 (C), 151.9 (C), 150.7 (C), 149.8 (CH), 142.5 (C), 141.9 (C), 137.4 (C), 134.3 (CH), 129.4 (CH), 126.9 (CH), 126.4 (CH), 125.0 (CH), 124.3 (C), 120.4 (CH), 120.0 (CH), 116.9 (CH), 77.2 (C), 72.1 (C), 24.6 (CH_3), 20.3 (CH_3); UV (EtOH): λ_{max} = 246, 302 nm; IR (NaCl): $\tilde{\nu}$ = 3446, 1373 cm^{-1}; LRMS: *m/z* (%) = 435 (56) [M^+], 294 (100); HRMS for $C_{23}H_{18}ClN_3O_2S$: calcd. 435.080827; found 435.079151.

Treatment of Pyrroloindole 6 with 2-Bromo-3,4-didehydropyridine (12b): Pyrroloindole **6**[13] (183 mg, 0.56 mmol), CsF (855 mg, 5.66 mmol), and **12b** (2.1 g, 5.64 mmol) in CH_3CN (8 mL) gave adducts **15b** (41 mg, 15%) and **16b** (34 mg, 13%) after chromatography (silica gel; EtOAc/CH_2Cl_2, 1:2).

Adduct 15b: M.p. 82−90 °C (Et_2O /hexane); ^1H NMR ($CDCl_3$): δ = 7.95 (m, 1 H), 7.86 (d, *J* = 4.5 Hz, 1 H), 7.71 (m, 1 H), 7.50−7.11 (m, 7 H), 6.98 (d, *J* = 4.5 Hz, 1 H), 2.23 (s. 3 H), 2.10 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 164.9 (C), 159.8 (C), 150.3 (C), 148.5 (CH), 145.9 (C), 143.2 (C), 139.4 (C), 138.7 (C), 134.1 (CH), 131.2 (C), 129.4 (CH), 126.5 (CH), 127.5 (CH), 124.3 (CH), 119.8 (CH), 115.4 (CH), 114.7 (CH), 71.9 (C), 70.5 (C), 17.1 (CH_3), 16.0 (CH_3); UV (EtOH): λ_{max} = 224, 248 nm; IR (NaCl): $\tilde{\nu}$ = 1370 cm^{-1}; LRMS: *m/z* (%) = 481 (60) [M^+], 479 (57) [M^+], 340 (98), 338 (100), 77 (28); HRMS for $C_{23}H_{18}BrN_3O_2S$: calcd. 479.030310; found 479.030097.

Adduct 16b: M.p. 206 °C (dec); ^1H NMR ($CDCl_3$): δ = 7.95 (d, *J* = 8.1 Hz, 1 H), 7.88 (d, *J* = 4.5 Hz, 1 H), 7.78 (m, 2 H), 7.48−7.11 (m, 6 H), 6.98 (d, *J* = 4.5 Hz, 1 H), 2.36 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 166.4 (C), 157.9 (C), 148.8 (CH), 146.9 (C), 145.2 (C), 140.9 (C), 138.3 (C), 134.0 (CH), 132.5 (C), 129.3 (CH), 126.6 (CH), 125.4 (CH), 124.0 (CH), 123.9 (C), 119.1 (CH), 115.6 (CH), 113.8 (CH), 74.3 (C), 68.1 (C), 17.9 (CH_3), 14.6 (CH_3); UV (EtOH): λ_{max} = 250, 280 nm; IR (NaCl): $\tilde{\nu}$ = 1370 cm^{-1}; LRMS: *m/z* (%) = 481 (100) [M^+], 479 (93) [M^+], 340 (65), 338 (67), 77 (22); HRMS for $C_{23}H_{18}BrN_3O_2S$: calcd. 479.030310; found 479.032522.

Treatment of Pyrroloindole 7 with 2-Chloro-3,4-didehydropyridine (4a): Treatment of compound **7**[13] (66 mg, 0.15 mmol) with CsF (280 mg, 1.85 mmol) and **12a** (520 mg, 1.55 mmol) in CH_3CN (2 mL), followed by chromatography (silica gel; Et_2O/hexane, 1:2), gave adducts **17** (22 mg, 26%) and **18** (22 mg, 26%).

Adduct 17: Oil; ^1H NMR ($CDCl_3$): δ = 7.99 (d, *J* = 4.5 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.83 (m, 2 H), 7.43 (m, 2 H), 7.36−7.15 (m, 4 H), 7.08 (d, *J* = 4.6 Hz, 1 H), 2.59 (s, 3 H), 2.42 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 164.6 (C), 155.2 (C), 154.1 (C), 148.4 (CH), 144.8 (C), 142.8 (C), 141.5 (C), 141.3 (C), 137.4 (C), 133.9 (CH), 129.1 (CH), 126.9 (CH), 125.8 (CH), 124.4 (CH), 124.3 (C), 119.5 (CH), 115.7 (CH), 114.4 (CH), 81.9 (C), 74.3 (C), 74.1 (C), 28.3 (CH_3), 17.1 (CH_3), 16.4 (CH_3); IR (NaCl): $\tilde{\nu}$ =

1710 cm^{-1}; LRMS: *m/z* (%) = 434 (22) [$M^+ - CO_2tBu$], 294 (61), 57 (100).

Adduct 18: Oil; ^1H NMR ($CDCl_3$): δ = 7.98−7.94 (m, 2 H), 7.82 (m, 2 H), 7.45−7.12 (m, 6 H), 6.99 (d, *J* = 4.6 Hz, 1 H), 2.74 (s, 3 H), 2.31 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ = 164.8 (C), 155.3 (C), 155.2 (C), 148.5 (CH), 143.0 (C), 142.9 (C), 142.4 (C), 141.2 (C), 137.7 (C), 133.9 (CH), 129.1 (CH), 126.8 (CH), 125.7 (CH), 124.2 (CH), 124.0 (C), 119.0 (CH), 115.9 (CH), 113.1 (CH), 81.9 (C), 77.1 (C), 71.5 (C), 28.2 (CH_3), 17.4 (CH_3), 15.3 (CH_3); IR (NaCl): $\tilde{\nu}$ = 1708 cm^{-1}; LRMS: *m/z* (%) = 434 (22) [$M^+ - CO_2tBu$], 294 (61) [$M^+ - CO_2tBu - SO_2Ph$], 57 (100) [CO_2tBu].

1,4-Dimethyl-9-(phenylsulfonyl)pyrano[3,4-*b*]indol-3-one (8b): LiHMDS (0.125 M, 6.3 mL, 0.79 mmol) was slowly added to a solution of **8a**[41] (140 mg, 0.66 mmol) in dry THF (15 mL) at −20 °C. After this had been heated for 20 min, $PhSO_2Cl$ (0.14 mL, 1.05 mmol) was added and the mixture was stirred overnight at −20 °C. H_2O (25 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was chromatographed (silica gel; Et_2O/hexane, 1:1), affording **8b** (180 mg, 78%) as a yellow solid; m.p. 132−138 °C; ^1H NMR ($CDCl_3$): δ = 8.09 (d, *J* = 8.3 Hz, 1 H), 7.94 (m, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.61−7.16 (m, 6 H), 2.72 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 163.6 (C), 152.2 (C), 145.5 (C), 143.2 (C), 133.9 (CH), 133.8 (C), 131.6 (CH), 128.5 (CH), 127.7 (C), 127.5 (CH), 126.7 (CH), 125.3 (CH), 123.5 (C), 120.3 (CH), 111.5 (C), 19.9 (CH_3), 12.2 (CH_3); UV (EtOH): λ_{max} = 220, 266, 370 nm; IR (NaCl): $\tilde{\nu}$ = 1712 (C=O), 1447 cm^{-1}; LRMS: *m/z* (%) = 353 (7) [M^+], 212 (100); HRMS for $C_{19}H_{15}NO_4S$: calcd. 353.072180; found 353.071709.

Treatment of Pyrone 8a with 2-Chloro-3,4-didehydropyridine: Pyrone **8a**[41] (36 mg, 0.169 mmol), CsF (300 mg, 1.98 mmol), and **12a** (565 mg, 1.70 mmol) in CH_3CN (3 mL) gave a 1:1 mixture of adducts **19a** and **20a** (10 mg, 21%) after chromatography (silica gel; CH_2Cl_2/EtOAc, 19:1).

Treatment of 1,4-Dimethyl-9-(phenylsulfonyl)pyrano[3,4-*b*]indol-3-one (8b) with 2-Chloro-3,4-didehydropyridine (4a) to give 1-Chloro-6-(phenylsulfonyl)ellipticine (19b): Compound **8b** (56 mg, 0.16 mmol), CsF (265 mg, 1.75 mmol), and **12a** (530 mg, 1.58 mmol) in dioxane (3 mL) gave adduct **19b** (14 mg, 20%) after chromatography (silica gel; EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$): δ = 8.35 (d, *J* = 5.8 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 5.8 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.48−7.27 (m, 3 H), 7.00−6.90 (m, 4 H), 3.13 (s, 3 H), 3.07 (s, 3 H); LRMS: *m/z* (%) = 420 (1) [M^+], 279 (14).

1-Chloroellipticine (19a) from 13a: NaOH (100 mg) and $NaBH_4$ (60 mg, 1.59 mmol) were added to a solution of **13a** (99 mg, 0.22 mmol) in THF (4 mL) and the mixture was refluxed for 2 h. Conc. HCl (2 mL) was then added and the mixture was stirred at room temp. for 1 h. A 10% NaOH solution was added to achieve a pH > 7 and the mixture was extracted with 20% CH_2Cl_2/*i*PrOH. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography (silica gel; CH_2Cl_2/EtOAc, 95:5), affording **19a** (61 mg, 96%) as a yellow solid; m.p. 257 °C (dec.); ^1H NMR ([D$_6$]DMSO): δ = 11.56 (s, 1 H), 8.35 (d, *J* = 7.9 Hz, 1 H), 8.11 (d, *J* = 5.8 Hz, 1 H), 7.91 (d, *J* = 5.8 Hz, 1 H), 7.56 (m, 2 H), 7.26 (m, 1 H), 3.42 (s, 3 H), 2.77 (s, 3 H); ^{13}C NMR ([D$_6$]DMSO): δ = 149.6 (C), 142.8 (C), 140.4 (C), 138.2 (CH), 135.7 (C), 128.7 (C), 127.6 (CH), 126.1 (C), 124.3 (CH), 122.9 (C), 120.4 (CH), 119.4 (C), 116.7 (CH), 110.9 (CH), 109.5 (C), 21.1 (CH_3), 12.9 (CH_3); IR (NaCl): $\tilde{\nu}$ = 2926 (NH) cm^{-1}; LRMS: *m/z* (%) = 282 (34) [M^+ + 2], 281 (25) [M^+ + 1], 280 (100) [M^+], 265 (30); HRMS for $C_{17}H_{13}ClN_2$: calcd. 280.076726; found 280.077091.

1-Chloroellipticine (19a) from 19b: A 50% solution of NaOH (1 mL) was added to **19a** (14 mg, 0.033 mmol) in THF (1 mL) and the mixture was refluxed for 2 h. Conc. HCl (1 mL) was then added and the solution was stirred at room temp. for 1 h. A 10% solution of NaOH was added to achieve a pH > 7 and the mixture was extracted with 20% CH_2Cl_2/*i*PrOH. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography (silica gel; CH_2Cl_2/EtOAc, 95:5), affording **19a** (5 mg, 50%) as a yellow solid.

4-Chloroisoellipticine (20a): A 10% solution of NaOH (1 mL) and $NaBH_4$ (20 mg, 0.53 mmol) were added to a solution of **14a** (54 mg, 0.12 mmol) in THF/MeOH (1:1) (2 mL). The mixture was refluxed for 2 h, then cooled to room temp., treated with conc. HCl (2 mL), and stirred at room temp. for 1 h. NaOH (10%) was added to achieve a pH > 7 and the mixture was extracted with CH_2Cl_2. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was chromatographed (silica gel; Et_2O) to afford **20a** (26 mg, 76%) as a yellow solid; m.p. 226 °C; ^1H NMR ($CDCl_3$): δ = 8.23 (d, *J* = 7.5 Hz, 1 H), 8.09 (s, 1 H), 8.05 (d, *J* = 5.5 Hz, 1 H), 7.82 (d, *J* = 5.6 Hz, 1 H), 7.43 (m, 2 H), 7.20 (m, 1 H), 3.04 (s, 3 H), 3.00 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 142.5 (C), 141.0 (C), 140.2 (C), 136.6 (CH), 132.7 (C), 128.0 (CH), 126.4 (C), 124.5 (CH), 124.6 (C), 124.0 (C), 123.7 (C), 120.0 (CH), 117.4 (CH), 111.5 (C), 110.6 (CH), 17.7 (CH_3), 15.7 (CH_3); UV (EtOH): λ_{max} = 234, 288 nm; IR (NaCl): $\tilde{\nu}$ = 3447 cm^{-1}; LRMS: *m/z* (%) = 282 (33) [M^+ + 2], 281 (25) [M^+ + 1], 280 (100) [M^+]; HRMS for $C_{17}H_{13}ClN_2$: calcd. 280.07673; found 280.07670.

Ellipticine (1): Anhydrous NaOAc (40 mg, 0.5 mmol) and 10% Pd/C (6 mg, 0.005 mmol) were added to a solution of **19a** (14 mg, 0.05 mmol) in AcOH (2 mL). The air in the flask was replaced with H_2 (1 atm) and the mixture was stirred overnight. The solution was filtered through Celite and 10% NaOH solution was added to the filtrate to achieve a pH > 7. The mixture was extracted with 20% CH_2Cl_2/*i*PrOH, the organic phase was dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was chromatographed (silica gel; Et_2O/hexane, 1:1), affording ellipticine (**1**, 11 mg, 92%) as a yellow solid; m.p. 250−252 °C (ref.[13] 243−250 °C); ^1H NMR ($CDCl_3$): δ = 9.66 (s, 1 H), 8.43 (d, *J* = 6.0 Hz, 1 H), 8.30 (d, *J* = 7.8 Hz, 1 H), 8.10 (m, 1 H), 7.79 (d, *J* = 6.1 Hz, 1 H), 7.43 (m, 2 H), 7.25 (m, 1 H), 3.23 (s, 3 H), 2.70 (s, 3 H); LRMS: *m/z* (%) = 246 (100) [M^+], 231 (32).

Isoellipticine (21): Isoellipticine (**21**, 11 mg, 86%) was obtained from **20a** (25 mg, 0.09 mmol), anhydrous NaOAc (80 mg, 0.97 mmol), and 10% Pd/C (10 mg, 0.009 mmol) as a yellow solid; m.p. 308−310 °C (ref.[13] 312−314 °C); ^1H NMR ($CDCl_3$): δ = 9.55 (s, 1 H), 8.43 (d, *J* = 6.1 Hz, 1 H), 8.33 (d, *J* = 7.8 Hz, 1 H), 8.09 (s br., 1 H), 7.96 (d, *J* = 6.1 Hz, 1 H), 7.45 (m, 2 H), 7.23 (m, 2 H), 3.11 (s, 3 H), 2.86 (s, 3 H); LRMS: *m/z* (%) = 246 (100) [M^+].

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