

HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 422 - 430. © 2018 The Japan Institute of Heterocyclic Chemistry
 Received, 31st January, 2018, Accepted, 22nd February, 2018, Published online, 26th February, 2018
 DOI: 10.3987/COM-18-S(T)30

A SHORT SYNTHESIS OF 9-FLUOROELLIPTICINE FROM 5-FLUOROINDOLE[‡]

Deborah A. Davis and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA. E-mail: ggribble@dartmouth.edu

Abstract – A synthesis of 9-fluoroellipticine (**1c**) from 5-fluoroindole (**6**) is described that features the regioselective lithiation of 5-fluoro-1-(phenylsulfonyl)indole (**7**) followed by chemoselective acylation of 3,4-pyridinedicarboxylic anhydride. Subsequent cyclization of keto acid **9** to keto lactam **10** with acetic anhydride and sequential treatment of **10** with methyllithium and sodium borohydride affords 9-fluoroellipticine.

INTRODUCTION

The 6*H*-pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), olivacine (**2**), and 17-oxoellipticine (**3**), isolated from plants of the *Ochrosia*, *Aspidosperma*, *Bleekeria*, and *Tabernaemontana* genera of the family *Apocynaceae*,¹ and from *Strychnos dinkagei* of the *Loganiaceae* family,² have been investigated for their anticancer activity for nearly 50 years³ (Figure 1). Accordingly, synthetic interest in these alkaloids continues to be intense and unabated.³⁻⁵

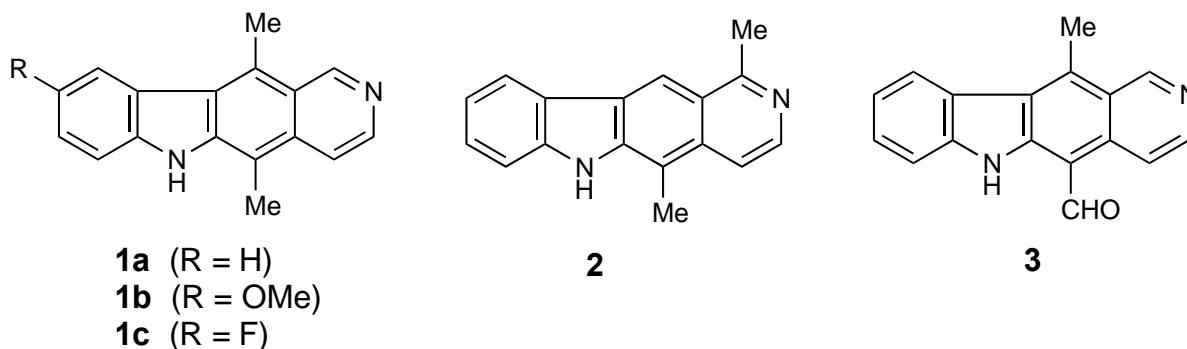


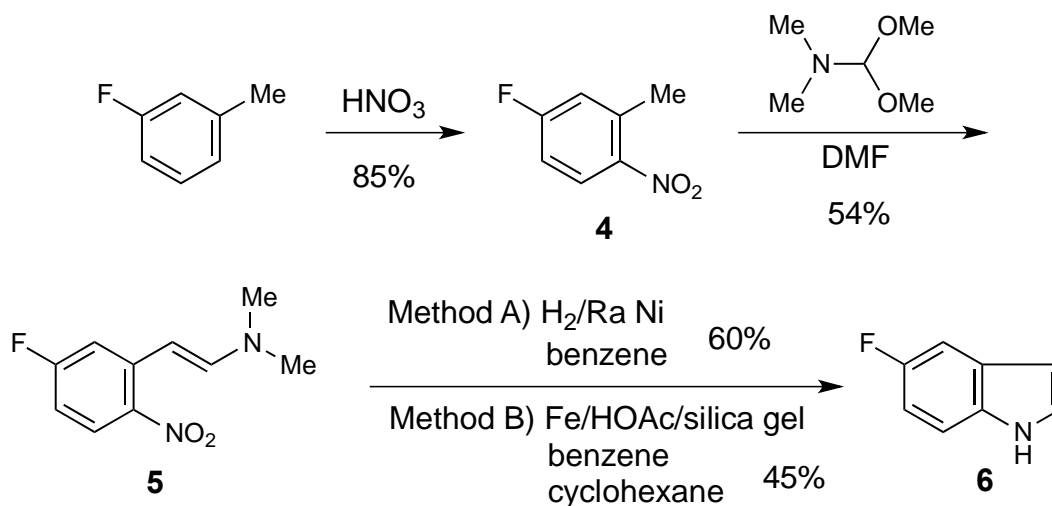
Figure 1

RESULTS AND DISCUSSION

A derivative of ellipticine, 9-fluoroellipticine (**1c**), is of special interest due to its ability to inhibit aryl hydrocarbon hydroxylase without expressing mutagenicity.⁶ Details on the synthesis of

9-fluoroellipticine are lacking,⁶ and there is only one clearly defined synthesis of this derivative.⁷ We now describe a convenient synthesis of **1c** that utilizes our earlier synthesis of ellipticine.⁸

We prepared the requisite 5-fluoroindole using a modified Leimgruber-Batcho indole ring synthesis⁹ as shown in Scheme 1. Thus, 5-fluoro-2-nitrotoluene (**4**),¹⁰ prepared from 3-fluorotoluene and fuming nitric acid, was condensed with *N,N*-dimethylformamide dimethyl acetal to give enamine **5** in 54% yield. We found that the reaction of **5** with hydrogen gas in the presence of Raney nickel in benzene gave indole **6** in yields ranging from 48 to 60% (Method A). Alternatively, we found that **6** could be produced in 45% yield by treating **5** with iron and acetic acid in the presence of silica gel in a refluxing mixture of benzene and cyclohexane (Method B), a method developed by Borchardt for the synthesis of alkoxyindoles.¹¹

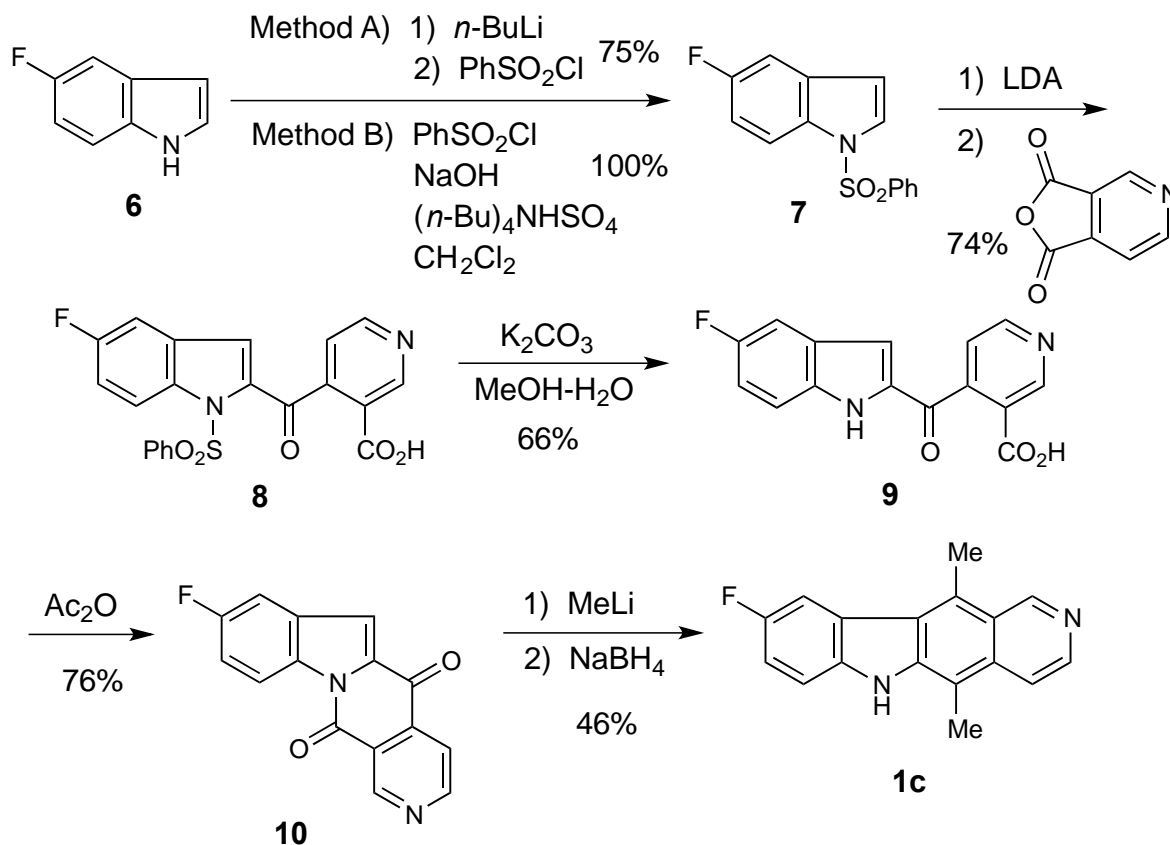


Scheme 1

With a supply of 5-fluoroindole (**6**) in hand, the stage was set for the synthesis of 9-fluoroellipticine (**1c**). Initial attempts to protect **6** as the 1-phenylsulfonyl derivative using butyllithium and quenching with benzenesulfonyl chloride (Method A) gave **7** in only 75% yield. However, we found that **6** could be protected quantitatively by using a simple modification of the Illi phase transfer method (Method B).¹² Thus, indole **6** and benzenesulfonyl chloride were added sequentially to a rapidly stirred suspension of powdered sodium hydroxide and tetra(*n*-butyl)ammonium hydrogen sulfate in methylene chloride (CH_2Cl_2) at 0 °C. After two hours, the mixture was filtered and concentrated to give 5-fluoro-1-(phenylsulfonyl)indole (**7**) in 28% overall yield from 3-fluorotoluene (Scheme 2).

Protected indole **7** was treated with lithium diisopropylamide (LDA) at low temperatures and then quenched with 3,4-pyridinedicarboxylic anhydride (cinchomeric anhydride) to give keto acid **8** in 74% yield after recrystallization. The deprotection of **8** was readily accomplished using potassium carbonate in aqueous methanol in 66% yield. The deprotected keto acid was then cyclized to keto lactam **10** in 76% yield by heating in neat acetic anhydride. Finally, 9-fluoroellipticine (**1c**) was prepared in two

steps from **10** in 46% yield first by the addition of methyl lithium (MeLi) at $-100\text{ }^{\circ}\text{C}$ followed by reduction with NaBH_4 . Thus, we were able to synthesize 9-fluoroellipticine in 17% overall yield from 5-fluoroindole.



Scheme 2

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 599 spectrometer and are referenced to the 1601 cm^{-1} band of polystyrene. ^1H NMR spectra (60 MHz) were recorded on a Varian EM-360A spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Varian XL-300 multinuclear Fourier transform spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS) using either TMS (d_{H} 0.00, d_{C} 0.00) or the solvent's residual proton or carbon signal (CDCl_3 : d_{H} 7.24, d_{C} 77.0; dimethyl sulfoxide- d_6 ($\text{DMSO-}d_6$): d_{H} 2.49, d_{C} 39.5; trifluoroacetic acid- d ($\text{TFA-}d$): d_{H} 11.5, d_{C} 116.6, 164.2) as an internal reference. The apparent multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), number of protons and coupling constants (hertz) are also reported. Unitary resolution mass spectra (MS) were obtained on a Finnigan 4023 GC/MS system. High-resolution mass spectra (HRMS) were recorded at the National Institutes of Health regional facility at the Massachusetts Institute of Technology. Ultraviolet (UV) spectra were recorded on a Hewlett

Packard 8451A diode array spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin-layer chromatography (TLC) was performed on pre-coated Silica Gel 60 F₂₅₄ plates from EM Reagents. Visualization was accomplished with 254 and 365 nm UV light, iodine vapor, ceric ammonium sulfate spray (3% in 10% sulfuric acid) or “van Urk’s reagent” spray (p-dimethylaminobenzaldehyde in ethanolic sulfuric acid). Flash chromatography was performed with EM Reagents Silica Gel 60 (230-400 mesh). All reactions were performed under a static head of predried (CaSO₄ tower) nitrogen or argon in glassware that had been dried for at least 12 h at 135 °C. Alkylolithium reagents were standardized prior to use by titration against diphenylacetic acid. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen immediately before use. Diethyl ether (Et₂O) was distilled from lithium aluminum hydride (LAH). *N,N*-Dimethylformamide (DMF), benzene, and diisopropylamine were distilled from CaH₂. MeOH and EtOH were distilled from sodium metal, and CH₂Cl₂ was distilled from P₂O₅. Benzenesulfonyl chloride and 3,4-pyridinedicarboxylic anhydride were distilled prior to use. Activated Raney nickel was obtained as a 50% slurry in water at pH = 10 and was used without further activation after washing with benzene. All other reagents were used as obtained.

5-Fluoro-2-nitrotoluene (4). To a 250 mL 3-neck round bottom flask fitted with a dropping funnel, condenser, and thermometer was added, under nitrogen, 3-fluorotoluene (72 mL, 0.65 mol). The flask was cooled to -15 °C and with stirring fuming nitric acid (82 mL) was added over 3 h. The reaction was allowed to warm to 5 °C during the addition, during which time the solution gradually darkened. The mixture was stirred at 0 °C for an additional 5 h then heated at 55 °C for 30 min, during which time a brown gas was evolved. The solution was allowed to cool to room temperature then poured over 500 g of crushed ice to yield a pale yellow oil. The oil was separated from the aqueous phase then washed with 2 M NaOH (250 mL) and water (2 x 250 mL). The combined aqueous layer was extracted with 3 x 250 mL Et₂O and the combined organic phase was washed with saturated NaCl solution (500 mL), dried (Na₂SO₄), and concentrated in vacuo to yield 85 g (85%) of **4** after distillation: Bp 64–65 °C/1.5 Torr (lit.,¹⁰ bp 97–98 °C/10 Torr); IR (neat) 3090, 1595, 1530, 1480, 1340, 1270, 1230, 980, 865, 835, 820, 750, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 8.1 (m, 1H), 7.2 (m, 2H), 2.6 (s, 3H).

trans-β-Dimethylamino-5-fluoro-2-nitrostyrene (5). In a 1 L 3-neck flask fitted with a thermometer and a Vigreux column (which was connected to a condenser and a receiving flask) was placed **4** (84 g, 0.54 mol), *N,N*-dimethylformamide dimethyl acetal (100 g, 0.84 mol), and DMF (500 mL). The solution was heated with stirring in a 160 °C oil bath for 3 h, during which time the solution turned bright red and MeOH was collected in the receiving flask. The solution was allowed to cool and concentrated under reduced pressure to 100 mL. Storage of this residue at -10 °C for 1 h resulted in the precipitation of 65 g (2 crops, 54%) of **5** as red-purple needles: Mp 56–57 °C (lit.,⁹ mp 57.5–59 °C); IR (KBr) 2940,

1650, 1610, 1580, 1510, 1460, 1440, 1300, 1270, 1230, 1220, 1070, 1000, 950, 850, 790, 740 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.86 (m, 1H), 7.01 (m, 1H), 6.93 (m, 1H), 6.56 (m, 1H), 5.90 (m, 1H); ^{13}C NMR (CDCl_3) δ 164.6 (d, $J = 247.5$ Hz), 145.6, 140.6, 139.3 (d, $J = 10.2$ Hz), 128.4 (d, $J = 10.7$ Hz), 109.4 (d, $J = 17.5$ Hz), 109.1 (d, $J = 17.0$ Hz), 90.4, 40.6.

5-Fluoroindole (6, Method A). To a solution of **5** (10.0 g, 47.6 mmol) in benzene (100 mL) in a 500 mL Parr bottle was added a small spatula-full of Raney nickel. The suspension was shaken under an initial hydrogen pressure of 45 psi for 21 h. The catalyst was removed by filtration and washed well with benzene. The benzene phase was washed with 1 M H_2SO_4 (3 x 100 mL), water (3 x 100 mL), saturated aqueous NaHCO_3 solution (2 x 100 mL), and saturated aqueous NaCl solution (100 mL), then dried (Na_2SO_4) and concentrated to give a brown oil. Flash chromatography (CH_2Cl_2 -hexane, 1:1) yielded 3.83 g (60%) of the desired product: Mp 44–46 °C (lit.,⁹ mp 46–47 °C); IR (CHCl_3) 3400, 3050, 1720, 1680, 1450, 1400, 1340, 1330, 1270, 1120, 1110, 950 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.80 (broad m, 1H), 7.28 (m, 1H), 7.10 (m, 1H), 6.88 (m, 1H), 6.48 (m, 1H); ^{13}C NMR (CDCl_3) δ 157.9 (d, $J = 233.1$ Hz), 132.2, 128.2 (d, $J = 10.2$ Hz), 125.7, 111.4 (d, $J = 9.8$ Hz), 110.3 (d, $J = 25.4$ Hz), 105.3 (d, $J = 23.1$ Hz), 102.7 (d, $J = 4.3$ Hz).

5-Fluoroindole (6, Method B). Using the method of Borchardt,¹¹ to a 500 mL three-neck round bottom flask were added 4.20 g (20.0 mmol) of **5**, silica gel (20 g), powdered iron (17 g), glacial acetic acid (120 mL), benzene (50 mL), and cyclohexane (150 mL). The mixture was heated at reflux with mechanical stirring under N_2 for 1 h. After 5 min, the mixture became very dark, but then faded to orange after 20 min. The reaction was allowed to cool to room temperature, then diluted with CH_2Cl_2 (200 mL) and filtered through a pad of Filter Cel. The filter cake was washed thoroughly with $\text{Et}_2\text{O}-\text{CH}_2\text{Cl}_2$ (1:9) and the combined organic phase washed with saturated aqueous sodium metabisulfite solution (2 x 300 mL), saturated aqueous NaHCO_3 solution (3 x 300 mL), saturated aqueous NaCl solution (2 x 300 mL), dried (Na_2SO_4), and concentrated to give 2.8 g of crude product. Flash chromatography (CH_2Cl_2 -hexane, 1:1) yielded 1.21 g (45%) of **6**: Mp 44–46 °C (lit.,⁹ mp 46–47 °C).

5-Fluoro-1-(phenylsulfonyl)indole (7, Method A). To a solution of 5-fluoroindole (**6**, 270 g, 20.0 mmol) in dry THF (60 mL) under nitrogen at -78 °C was added dropwise via syringe over 25 min $n\text{-BuLi}$ (2.22 M in hexane, 12.0 mL, 26.6 mmol). The solution was allowed to warm to room temperature during which time the resulting indole anion precipitated as a white solid. After the solution was recooled to -78 °C, benzenesulfonyl chloride (3.30 mL, 26.0 mmol) was added dropwise over 20 min, keeping the internal temperature below -70 °C. The resulting olive green solution was allowed to warm to room temperature overnight, poured into saturated aqueous NaHCO_3 solution (100 mL), and extracted with Et_2O (3 x 75 mL). The combined organic phase was washed with saturated aqueous NaHCO_3 solution (2 x 100 mL), saturated aqueous NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated

to yield 6.29 g of tan solid. Recrystallization from Et₂O gave 4.12 g (75%) of **7** as white crystals: Mp 133–134 °C; IR (KBr) 3170, 3100, 1590, 1460, 1440, 1360, 1340, 1210, 1180, 1090, 980, 840, 800, 790, 740, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 7.96 (m, 1H), 7.88 (m, 2H), 7.61 (m, 1H), 7.53 (m, 1H), 7.43 (m, 2H), 7.18 (m, 1H), 7.05 (m, 1H), 6.62 (m, 1H); ¹³C NMR (CDCl₃) δ 159.8 (d, *J* = 239 Hz), 137.9, 133.9, 131.7 (d, *J* = 10.2 Hz), 131.1, 129.3, 128.0, 126.6, 114.4 (d, *J* = 9.4 Hz), 112.7 (d, *J* = 25.5 Hz), 109.1 (d, *J* = 4.1 Hz), 106.9 (d, *J* = 23.9 Hz); MS *m/e* 275 (M⁺), 141, 134, 107, 77 (100%). Anal. Calcd for C₁₄H₁₀FNO₂S: C, 61.08; H, 3.66; N, 5.09; S, 11.64. Found: C, 61.19; H, 3.67; N, 5.08; S, 11.54.

5-Fluoro-1-(phenylsulfonyl)indole (7, Method B). To a rapidly stirred suspension of powdered NaOH (3.25 g, 81.3 mol) and tetra(*n*-butyl)ammonium hydrogen sulfate in CH₂Cl₂ (30 mL) was added **6** (3.50 g, 25.9 mmol) in CH₂Cl₂ (30 mL) in portions over 5 min at 0 °C. After stirring for 10 min, benzenesulfonyl chloride was added dropwise over 5 min. The mixture was stirred at room temperature for 5 h and then filtered. The filter cake was washed well with CH₂Cl₂ and the combined organic phases were evaporated to give an off white solid. Recrystallization from Et₂O/hexane yielded 7.15 g (100%) of **7** that was identical in all respects (TLC, IR, NMR) with a sample prepared by Method A: Mp 130–131 °C.

5-Fluoro-1-(phenylsulfonyl)indol-2-yl 3-carboxy-4-pyridyl ketone (8). To a magnetically stirred solution of lithium diisopropylamide (5.50 mmol) prepared from diisopropylamine (3.25 mL, 5.50 mmol) and *n*-BuLi (2.22 M in hexane, 2.50 mL, 5.55 mmol), in dry THF (15 mL) at -78 °C was added via syringe over 5 min a solution of **7** (1.38 g, 5.00 mmol) in THF (15 mL). The orange solution was allowed to warm to room temperature over 3 h then cooled to -100 °C and treated as rapidly as possible with a solution of 3,4-pyridinedicarboxylic anhydride (0.83 g, 5.6 mmol) in THF (15 mL) while maintaining efficient stirring and cooling. The solution was stirred at -100 °C for 1 h and then allowed to warm to room temperature over 12 h. The solvents were removed by rotary evaporation and then the dark residue was dissolved in water (50 mL), cooled to 0 °C, and slowly acidified with dilute HCl. The resulting tan precipitate was collected, washed well with water, and dried in vacuo to yield 2.01 g of crude product. Recrystallization from acetone yielded 1.57 g (74%) of **8** as a white solid: Mp 232–233 °C; IR (KBr) 3580, 1750, 1685, 1540, 1460, 1380, 1360, 1300, 1220, 1180, 1060, 960, 730, 605 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 9.11 (s, 1H), 8.90 (d, *J* = 5.2 Hz, 1H), 8.21 (m, 1H), 8.18 (m, 2H), 7.77 (m, 1H), 7.69 (m, 2H), 7.55 (m, 1H), 7.52 (m, 1H), 7.47 (m, 1H), 7.18 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 183.6, 166.5, 165.7, 153.1, 146.6, 140.1, 139.1, 138.3, 135.5, 135.1, 134.6, 129.5, 128.2, 127.1, 125.4, 122.6, 122.2, 109.5, 107.8, 103.6, 101.3; MS *m/e* 424 (M⁺), 380, 360, 283, 266, 141, 77 (100%); Anal. Calcd for C₂₁H₁₄FN₂O₅S: C, 59.43; H, 3.09; N, 6.61. Found: C, 59.22; H, 3.31; N, 6.46.

5-Fluoroindol-2-yl 3-carboxy-4-pyridyl ketone (9). A magnetically stirred solution of the keto-acid **8** (1.50 g, 3.54 mmol), K₂CO₃ (2.00 g, 14.6 mmol), and water (15 mL) in MeOH (45 mL) was refluxed for

4.5 h. After cooling, the solvents were evaporated to give a dark residue which was dissolved in water (100 mL), cooled to 0 °C, and slowly acidified with dilute HCl. The precipitate was collected by filtration, washed well with water, and dried in vacuo to yield 0.67 g (66%) of **9** as a yellow solid, which was used without purification in the next reaction. Recrystallization from acetone gave the analytical sample: Mp 150–153 °C; IR (KBr) 3350, 1725, 1640, 1530, 1255, 1170, 800, 760, 665, 605 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 12.24 (s, 1H), 9.19 (s, 1H), 8.97 (d, *J* = 4.9 Hz, 1H), 7.71 (d, *J* = 5.0 Hz, 1H), 7.62 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.34 (m, 1H), 7.21 (m, 1H), 6.70 (s, 1H), 4.02 (s, MeOH from reaction); ¹³C NMR (DMSO-*d*₆) δ 185.8, 165.5, 158.8, 155.8, 151.3 (d, *J* = 172 Hz), 148.2, 136.2, 135.1, 128.5, 127.7, 126.9 (d, *J* = 10.5 Hz), 125.5, 122.3, 115.2 (d, *J* = 27.3 Hz), 114.2 (d, *J* = 9.7 Hz), 111.7 (d, *J* = 5.0 Hz), 106.7 (d, *J* = 22.9 Hz); MS *m/e* 284 (M⁺), 266, 238, 210, 182, 162, 134, 89; UV (95% EtOH) 214, 315 nm. Anal. Calcd for C₁₅H₉FN₂O₃ + 2 MeOH: C, 58.20; H, 4.92; N, 8.04. Found: C, 58.49; H, 3.58; N, 7.43.

3-Fluoroindolo[1,2-*b*][2,7]naphthyridine-6,11-quinone (10). A solution of keto-acid **9** (0.67 g, 2.36 mmol) in acetic anhydride (100 mL) was heated at 80 °C for 26 h. The bulk of the solvent was removed by distillation at reduced pressure. Water (75 mL) was then added and the mixture was stirred at 0 °C for 30 min. Filtration yielded 0.50 g of a brown solid which was recrystallized from acetone to yield 0.48 g (76%) of **10** as a yellow-green solid in two crops: Mp 200–202 °C; IR (KBr) 1715, 1680, 1560, 1380, 1340, 1270, 1195, 1020, 960, 890, 730, 690, 605 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 9.46 (s, 1H), 9.13 (d, *J* = 3.7 Hz, 1H), 8.48 (m, 1H), 8.00 (d, *J* = 4.1 Hz, 1H), 7.75 (s, 1H), 7.52 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 174.8, 161.1, 155.4, 150.1, 149.0 (d, *J* = 160 Hz), 138.7, 134.9, 132.9, 121.1, 119.1, 109.3 (d, *J* = 24.1 Hz), 118.3 (d, *J* = 11.2 Hz), 117.9 (d, *J* = 9.5 Hz), 115.4 (d, *J* = 4.5 Hz), 114.9 (d, *J* = 4.2 Hz); MS *m/e* 266 (M⁺, 100%), 238, 210, 182, 149, 133, 77, 50; UV (95% EtOH) 212, 242, 270 (sh), 356, 365 (sh) nm; addition of NaOH produced a spectrum identical to that of **9**. Anal. Calcd for C₁₅H₇FN₂O₂: C, 67.67; H, 2.65; N, 10.52. Found: C, 67.67; H, 2.80; N, 10.24.

9-Fluoroellipticine (1c). A magnetically stirred solution of keto-lactam **10** (0.99 g, 3.76 mmol) in THF (200 mL) was cooled to -110 °C and treated over 30 s with MeLi (1.40 M in Et₂O, 6.50 mL, 9.02 mmol) while maintaining efficient cooling. The solution was stirred at this temperature for 1 h and then allowed to warm to room temperature over 15 h, during which time the solution became forest green in color. Water (15 mL) was then added, the solution was stirred an additional 15 min and the THF was removed by rotary evaporation. The brown-green residue was dissolved in absolute EtOH (200 mL), treated with excess NaBH₄ (30 pellets, 9 g), and refluxed for 18 h. The NaBH₄ was added in four portions during the reaction period; after 30 min the solution became fluorescent orange. The mixture was cooled and concentrated to yield a brown solid. This residue was dissolved in CHCl₃ (250 mL) and treated with H₂O (200 mL). The layers were separated and the aqueous phase acidified to pH 3 with

dilute HCl, extracted with CHCl₃ (2 x 100 mL), basified to pH 10 with dilute NaOH, and extracted with CHCl₃ continuously for 24 h. The combined organic phases were dried (Na₂SO₄) and adsorbed onto silica gel. Flash chromatography (EtOAc) yielded 0.48 g (46%) of **1c** as a bright yellow powder. Recrystallization from MeOH provided the analytical sample: Mp 320–325 °C (dec); IR (KBr) 3450, 1630, 1600, 1480, 1405, 1305, 1265, 1195, 1140, 1025, 950, 810, 795 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.37 (s, 1H), 9.68 (s, 1H), 8.41 (m, 1H), 8.11 (m, 1H), 7.89 (m, 1H), 7.53 (m, 1H), 7.40 (m, 1H), 3.20 (s, 3H), 2.73 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 156.4 (d, *J* = 231 Hz), 153.4, 149.9, 148.9, 141.3, 139.1, 138.5, 132.6, 128.8, 117.8, 115.9 (d, *J* = 6.0 Hz), 114.5 (d, *J* = 24.8 Hz), 111.4 (d, *J* = 9.3 Hz), 111.3 (d, *J* = 9.0 Hz), 109.7 (d, *J* = 24.7 Hz), 14.2, 11.9; MS *m/e* 264 (M⁺, 100%), 249, 132, 118, 111, 105, 57, 44, 40; HRMS *m/e* Calcd. (M⁺) 264.10628, obsd. 264.10930; UV (95% EtOH) 208, 226 (sh), 273, 280, 297 (sh), 330 (sh) nm, (95% EtOH + 1% dil. HCl) 208, 233 (sh), 262 (sh), 300, 350 (sh) nm; Anal. Calcd for C₁₇H₁₃FN₂·0.25 MeOH: C, 76.09; H, 5.18; N, 10.29. Found: C, 76.10; H, 5.09; N, 10.43.

ACKNOWLEDGEMENT

We acknowledge Dartmouth College for support of this work.

REFERENCES AND NOTES

- (a) S. Goodwin, A. F. Smith, and E. C. Horning, *J. Am. Chem. Soc.*, **1959**, **81**, 1903; (b) J. Bruneton and A. Cavé, *Phytochemistry*, **1972**, **11**, 846; (c) K. N. Kilminster, M. Sainsbury, and B. Webb, *Phytochemistry*, **1972**, **11**, 389; (d) A. Ahond, H. Fernandez, M. Julia-Moore, C. Poupat, V. Sánchez, P. Potier, S. K. Kan, and T. Sévenet, *J. Nat. Prod.*, **1981**, **44**, 193; (e) A. A. Salim, M. J. Garson, and D. J. Craik, *J. Nat. Prod.*, **2004**, **67**, 1719; (f) A. R. Carroll, R. Addepalli, G. Fechner, J. Smith, G. P. Guymer, P. I. Forster, and R. J. Quinn, *J. Nat. Prod.*, **2008**, **71**, 1063.
- (a) S. Michel, F. Tillequin, M. Koch, and L. A. Assi, *J. Nat. Prod.*, **1980**, **43**, 294; (b) S. Michel, F. Tillequin, and M. Koch, *Tetrahedron Lett.*, **1980**, **21**, 4027; (c) S. Michel, F. Tillequin, and M. Koch, *J. Chem. Soc., Chem. Commun.*, **1987**, 229.
- For reviews, see (a) C. M. Miller and F. O. McCarthy, *RSC Adv.*, **2012**, **2**, 8883; (b) M. Stiborova and E. Frei, *Curr. Med. Chem.*, **2014**, **21**, 575; (c) G. W. Gribble, 'Synthesis and Antitumor Activity of Ellipticine Alkaloids and Related Compounds' in *The Alkaloids: Chemistry and Pharmacology*; ed. by A. Brossi, Academic Press: New York, 1990; pp. 239–352.
- For reviews, see (a) M. Sainsbury, *Synthesis*, **1977**, 437; (b) G. W. Gribble and M. G. Saulnier, *Heterocycles*, **1985**, **23**, 1277.
- For recent studies, see (a) M. G. Ferlin, C. Marzano, V. Gandin, S. Dall'Acqua, and L. D. Via, *ChemMedChem*, **2009**, **4**, 363; (b) C. M. Miller, E. C. O'Sullivan, K. J. Devine, and F. O.

- McCarthy, [Org. Biomol. Chem.](#), 2012, **10**, 7912; (c) F. M. Deane, E. C. O'Sullivan, A. R. Maguire, J. Gilbert, J. A. Sakoff, A. McCluskey, and F. O. McCarthy, [Org. Biomol. Chem.](#), 2013, **11**, 1334; (d) E. G. Russell, J. Guo, E. C. O'Sullivan, C. M. O'Driscoll, F. O. McCarthy, and T. G. Cotter, [Invest. New Drugs](#), 2016, **34**, 15; (e) M. Stiborová, J. Poljaková, E. Martinková, L. Bořek-Dohalská, T. Edkschlager, R. Kizek, and E. Frei, [Interdiscip. Toxicol.](#), 2011, **4**, 92; (f) W. J. Andrews, T. Panova, C. Normand, O. Gadad, I. G. Tikhonova, and K. I. Panov, [J. Biol. Chem.](#), 2013, **288**, 4567; (g) T. Nishiyama, N. Hatae, M. Mizutani, T. Yoshimura, T. Kitamura, M. Miyano, M. Fujii, N. Satsuki, M. Ishikura, S. Hibino, and T. Choshi, [Eur. J. Med. Chem.](#), 2017, **136**, 1.
6. (a) P. Lesca, P. Lecointe, D. Pelaprat, C. Paoletti, and D. Mansuy, [Biochem. Pharmacol.](#), 1980, **29**, 3231; (b) P. Lesca, P. Lecointe, C. Paoletti, and D. Mansuy, [Chem. Biol. Interact.](#), 1979, **25**, 279.
 7. R. J. Hall, P. Dharmasena, J. Marchant, A.-M. F. Oliveira-Campos, M.-J. R. P. Queiroz, M. M. Raposo, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1879.
 8. M. G. Saulnier and G. W. Gribble, [J. Org. Chem.](#), 1982, **47**, 2810.
 9. A. D. Batcho and W. Leimgruber, [Org. Synth.](#), 1985, **63**, 214.
 10. G. Schiemann, [Chem. Ber.](#), 1929, **62**, 1794.
 11. A. K. Sinhababu and R. T. Borchardt, [J. Org. Chem.](#), 1983, **48**, 3347.
 12. V. O. Illi, [Synthesis](#), 1979, 136.