Synthesis of a New Pyrido[3,2-*b*]carbazole as an Ellipticine–Makaluvamine Hybrid

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Abstract: The first synthesis of pyrido[3,2-*b*]carbazole as an ellipticine–makaluvamine hybrid in 13 steps and 2% overall yield from commercially available 2,5-dimethoxyaniline is described.

Key words: heterocycles, Heck reaction, ring closure, homogeneous catalysis, polycycles

Ellipticine, a member of the pyrido[4,3-*b*]carbazole alkaloid family, first isolated in 1959 from the leaves of *Ochrosia elliptica* plant has been shown to possess anticancer activities against various tumors.[1] The main reason for the interest in ellipticine and analogues is its high efficiency against several types of cancer, limited toxic side effects, and complete lack of hematological toxicity.[2] Ellipticine is a DNA intercalating agent, and its high DNA binding affinity is thought to be mainly responsible for its pharmacological properties.[3–7] As a consequence ellipticine has proven to be a popular synthetic target, and a wide variety of routes have been reported.[8–13] Similarly, the structurally related aryl- and heteroaryl-annulated carbazoles have also received considerable synthetic attention.[14–18] Despite the great synthetic work developed around ellipticine, very little attention has been focused on its fusion with other biologically important molecules such as makaluvamine derivatives, which could lead to promising biological activities (Figure 1). The aim of the work reported herein was the synthesis of a pyrido[3,2-*b*]carbazole **1**, which can be seen as an ellipticine-makaluvamine hybrid.

Our approach for the synthesis of compound **1** involves a Pd-catalyzed Hartwig–Buchwald coupling between the aminotetrahydroquinoline **3** and 2-bromoiodobenzene followed by a Heck reaction to provide the carbazole ring.[19–22] After introduction of the ethylazido side chain at C-6, oxidation with the [bis(trifluoroacetoxy)iodo]benzene (PIFA) should afford the desired quinone that should be readily converted into carbazole **1** (Scheme 1).

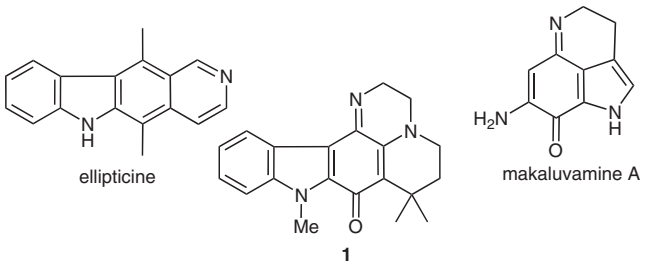
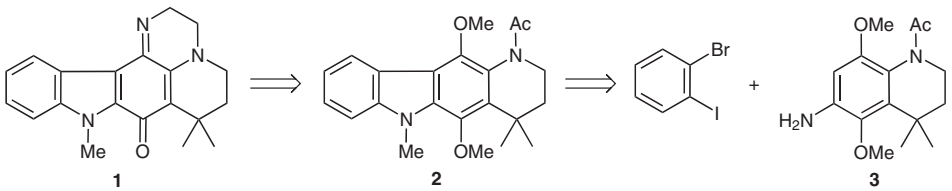


Figure 1 Structure of ellipticine, makaluvamine A, and pyrido[3,2-*b*]carbazole **1**

The required aminotetrahydroquinoline **3** was prepared in four steps from commercially available 2,5-dimethoxyaniline (**4**) (Scheme 2). The first step involves an N-alkylation of aniline **4** with 1-chloro-3-methylbut-2-ene in anhydrous pyridine at room temperature for three days to provide the amine **5** (70%). Cyclization of compound **5** was performed in excellent yield using concentrated sulfuric acid leading to bicycle **6**, which upon treatment with a mixture of acetic anhydride and pyridine (1:2) furnished the *N*-acetyl derivative **7**.[23] Nitration of **7** with extra pure nitric acid in dichloromethane afforded the nitro derivative **8** which was reduced to aminotetrahydroquinoline **3** by classic hydrogenation.

The next N-arylation step was carried out by treatment of 6-aminotetrahydroquinoline **3** with 2-bromoiodobenzene under Hartwig–Buchwald catalytic conditions to afford the diarylamine **10** in satisfactory yield. Compound **10** was then efficiently cyclized to the corresponding pyrido[3,2-*b*]carbazole **2** by treatment with palladium acetate



Scheme 1 Retrosynthetic access to carbazole **1**

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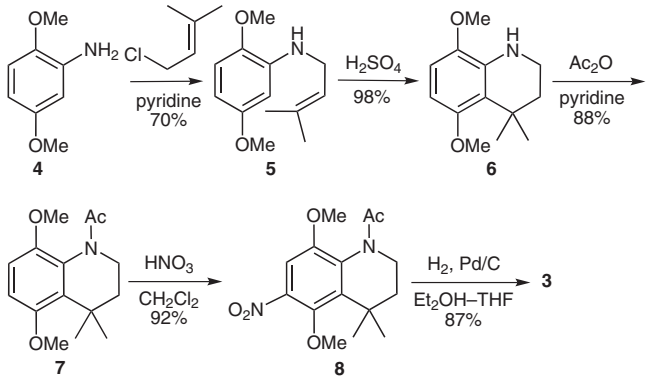
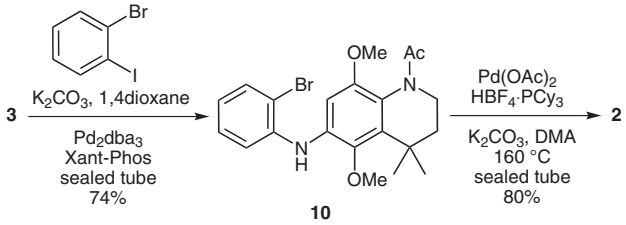


Scheme 2 Synthesis of aminotetrahydroquinoline **3**



Scheme 3 Synthesis of pyrido[3,2-*b*]carbazole **2**

as catalyst, PCy_3 as optimal ligand, and potassium carbonate as base in *N*,*N*-dimethylacetamide (DMA) at 160 °C (Scheme 3).[24]

Treatment of **2** with methyl iodide in the presence of sodium hydride in *N*,*N*-dimethylformamide led quantitatively to the *N*-methyl derivative **11**. Further chlorination through deprotonation with LDA at –78 °C followed by quenching of the resultant enolate with benzenesulfonyl chloride afforded chloroamide **12** (40%).[25] Chlorine displacement with sodium azide in *N*,*N*-dimethylformamide afforded the desired azido derivative, the amide group of which was reduced using BH_3·THF complex to yield compound **13** in 62% over two steps. Final oxidation with PIFA led to the desired quinone, which was further reduced by catalytic hydrogenation on Pd/C to give the desired imine **1** (Scheme 4).

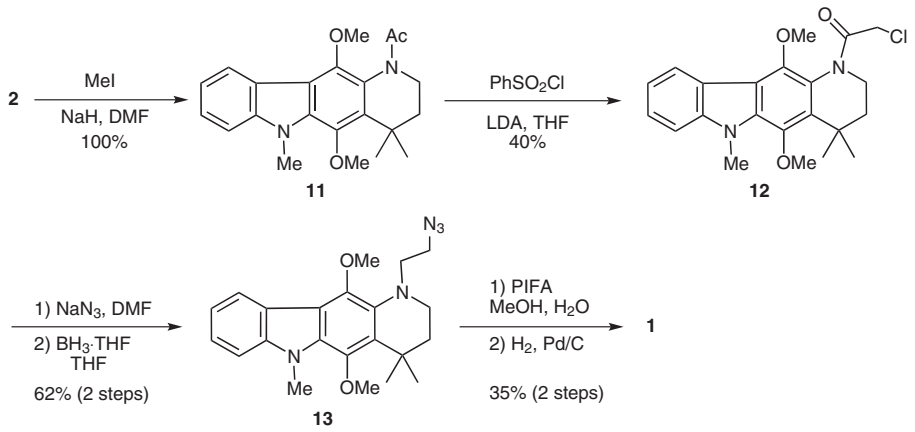
In conclusion, we have accomplished the synthesis of pyrido[3,2-*b*]carbazole **1** using a Hartwig–Buchwald coupling and Heck reaction as the key steps. The synthetic methodology developed in this work will be extended to access other interesting ellipticine analogues.

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an argon atmosphere. THF was freshly distilled from benzophenone-sodium. All reagents and starting materials were purchased from commercial sources and used as received. All lithiation were carried out using Sigma-Aldrich LDA 2.0 M in THF–heptane–ethylbenzene. Analytical TLC analyses were carried out on silica gel F_{254} plates. Visualization was achieved by UV light (254 nm). Flash column chromatography was carried using Sigma-Aldrich Versaflash silica gel (particle size 20–45 μm). Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 300 FT spectrometer at r.t. (operating frequencies: ^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz). The chemical shifts (δ) for all compounds are listed in parts per million downfield from TMS using the NMR solvent as an internal reference. The reference values used for $CDCl_3$ were 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), or m (multiplet). Low-resolution mass (MS) were recorded on a Shimadzu GCMS-QP 2010 Gas Chromatograph Mass Spectrometer and reported in units of mass to charge (*m*/*z*). The mode of ionization used was electron-impact (EI, 70 eV) or chemical ionization (CI, methane reagent gas).

2,5-Dimethoxy-*N*-(3-methylbut-2-enyl)benzenamine (5)

To a solution of 2,5-dimethoxyaniline (**4**; 1.00 g, 6.50 mmol) in anhyd pyridine (10 mL) was added 1-chloro-3-methylbut-2-ene (0.88 mL, 7.80 mmol). The mixture was stirred and heated at reflux for 3 days. A solution of aq 1 M HCl (70 mL) was then added and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aq 1 M HCl (2 × 20 mL) and brine (30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to give compound **5** as a yellow oil; yield: 1.00 g (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 3.72 (d, *J* = 6.0 Hz, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.22 (br s, 1 H, NH), 5.40 (m, 1 H, C=CH), 6.20 (dd, *J* = 8.7, 2.7 Hz, 1 H_{arom}), 6.28 (d, *J* = 2.7 Hz, 1 H_{arom}), 6.70 (d, *J* = 8.7 Hz, 1 H_{arom}).



Scheme 4 Synthesis of pyrido[3,2-*b*]carbazole **1**

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0 (CH_3), 25.8 (CH_3), 41.6 (CH_2), 55.5 (OCH_3), 55.9 (OCH_3), 98.2 (CH_{arom}), 98.5 (CH_{arom}), 109.7 (CH_{arom}), 121.7 (CH_{arom}), 135.4 (C), 139.4 (C), 141.6 (C), 154.8 (C).

MS (EI): *m*/*z* = 138 ([M – $CH_2CHC(CH_3)_2$ – CH_3]$^+$, 100%), 221 ([M]$^+$, 58%), 206 ([M – CH_3]$^+$, 58%).

Anal. Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.59; H, 8.65; N, 6.33. Found: C, 70.21; H, 8.71; N, 6.21.

5,8-Dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (6)

A solution of 96% H_2SO_4 (5 mL) was cooled down to 0 °C. Then, the amine **5** (1.50 g, 6.78 mmol) was added portionwise over a 5 min period. The mixture was stirred for 20 min under continued cooling and basified using aq 25% NaOH until pH 9 and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 9:1) to give compound **6** as a brown oil; yield: 1.45 g (97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 6 H, 2 × CH_3), 1.82 (m, 2 H, CH_2), 3.26 (m, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.50 (br s, 1 H, NH), 6.20 (d, *J* = 8.7 Hz, 1 H_{arom}), 6.0 (d, *J* = 8.7 Hz, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2 (2 × CH_3), 32.1 (C), 38.0 (CH_2), 41.1 (CH_2), 55.3 (OCH_3), 55.8 (OCH_3), 98.5 (CH_{arom}), 107.0 (CH_{arom}), 118.7 (C), 135.7 (C), 141.2 (C), 153.9 (C).

MS (EI): *m*/*z* = 206 ([M – CH_3]$^+$, 100%), 221 ([M]$^+$, 50%), 176 ([M – 3 × CH_3]$^+$, 18%).

Anal. Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.65; H, 8.75; N, 6.21.

1-(5,8-Dimethoxy-4,4-dimethyl-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (7)

To a solution of **6** (1.00 g, 4.50 mmol) in anhyd pyridine (1.82 mL, 22.60 mmol) under argon atmosphere, was added dropwise Ac_2O (7.69 mL, 81.40 mmol). The mixture was stirred for 18 h at r.t. A solution of aq 1 M HCl (70 mL) was then added and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed several times with aq 1 M HCl and finally with brine (30 mL). The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to give compound **7** as a brown solid; yield: 1.04 g (88%); mp 82–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.76 (m, 2 H, CH_2), 1.98 (s, 3 H, $COCH_3$), 2.90 (br s, 1 H, CH_aH$_b$), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.64 (br s, 1 H, CH$_a$$H_b$), 6.73 (d, *J* = 3.3 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (NCH_3), 28.3 (CH_3), 28.6 (CH_3), 34.6 (CH_2), 41.4 (C), 43.0 (CH_2), 55.6 (OCH_3), 55.9 (OCH_3), 109.1 (CH), 109.6 (CH), 129.2 (C), 130.0 (C), 147.0 (C), 152.9 (C), 172.1 (C=O).

MS (EI): *m*/*z* = 232 ([M – OCH_3]$^+$, 100%), 206 ([M – $COCH_3$ + 1]$^+$, 91%), 263 ([M]$^+$, 38%).

Anal. Calcd for $C_{15}H_{21}NO_3$ (263.34): C, 68.42; H, 8.04; N, 5.32. Found: C, 69.05; H, 8.31; N, 5.21.

1-(5,8-Dimethoxy-4,4-dimethyl-6-nitro-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (8)

A solution of **7** (2.00 g, 9.00 mmol) in anhyd CH_2Cl_2 (20 mL) was cooled down to 0 °C under argon atmosphere. Extra pure HNO_3 (0.48 mL, 10.80 mmol) was added carefully and the mixture was allowed to stir at 0 °C for 2 h before hydrolysis over ice. The product was extracted with EtOAc (3 × 20 mL) and the combined organic layers were successively washed with aq $NaHCO_3$ (50 mL) and brine (30 mL), and dried ($MgSO_4$). The solvent was then removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to give compound **8** as a yellow solid; yield: 2.15 g (92%); mp 120–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.77 (m, 2 H, CH_2), 2.02 (s, 3 H, $COCH_3$), 3.12 (m, 1 H, CH_aH$_b$), 3.81 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.40 (m, 1 H, CH$_a$$H_b$), 7.29 (s, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 ($COCH_3$), 27.9 (CH_3), 29.4 (CH_3), 35.7 (C), 41.4 (CH_2), 41.9 (CH_2), 56.2 (CH_3), 62.4 (CH_3), 106.4 (CH_{arom}), 134.2 (C), 136.2 (C), 140.7 (C), 147.7 (C), 148.4 (C), 171.3 (C=O).

MS (EI): *m*/*z* = 266 ([M – $COCH_3$]$^+$, 100%), 251 ([M – $COCH_3$ – CH_3]$^+$, 90%), 277 ([M – OCH_3]$^+$, 79%), 308 ([M]$^+$, 50%).

Anal. Calcd for $C_{15}H_{20}N_2O_2$ (308.34): C, 58.43; H, 6.54; N, 9.09. Found: C, 58.31; H, 6.48; N, 8.98.

1-(6-Amino-5,8-dimethoxy-4,4-dimethyl-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (3)

A solution of **8** (1.00 g, 3.20 mmol) in mixture of EtOH–THF (1:1, 20 mL) was hydrogenated (15 psi) over Pd/C (200 mg) for 18 h at r.t. The catalyst was filtered on Celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to give compound **3** as a brown solid; yield: 780 mg (87%); mp 138–140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.74 (m, 2 H, CH_2), 1.93 (s, 3 H, $COCH_3$), 3.01 (m, 1 H, CH_aH$_b$), 3.73 (s, 6 H, 2 × OCH_3), 3.52 (m, 1 H, CH$_a$$H_b$), 6.30 (s, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 ($COCH_3$), 27.5 (CH_3), 30.0 (CH_3), 35.2 (C), 40.5 (CH_2), 41.3 (CH_2), 55.6 (OCH_3), 60.4 (OCH_3), 98.4 (CH), 119.6 (C), 135.1 (C), 138.8 (C), 139.6 (C), 149.9 (C), 172.2 (C=O).

MS (EI): *m*/*z* = 278 ([M]$^+$, 100%), 221 ([M – CH_3 – $COCH_3$]$^+$, 68%), 263 ([M – CH_3]$^+$, 39%).

Anal. Calcd for $C_{15}H_{22}N_2O_3$ (221.30): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.81; H, 8.01; N, 10.04.

1-(6-(2-Bromophenylamino)-5,8-dimethoxy-4,4-dimethyl-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (10)

To a solution of **3** (300 mg, 1.08 mmol) in anhyd 1,4-dioxane (8 mL) in a resealable Schlenk tube under argon atmosphere were added successively 2-bromoiodobenzene (0.21 ml, 1.62 mmol), XantPHOS (25 mg, 0.04 mmol), and K_2CO_3 (2.98 g, 21.58 mmol). The flask was capped with a rubber septum and degassed with argon. Pd_2dba_3 (19 mg, 0.02 mmol) was then added and the tube was sealed and the contents were stirred at reflux for 18 h. The mixture was then diluted with EtOAc (20 mL), filtered trough a plug of Celite, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to give compound **10** as a brown solid; yield: 340 mg (74%); mp 135–137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.74 (m, 1 H, CH_aH$_b$), 1.82 (m, 1 H, CH$_a$$H_b$), 2.04 (s, 3 H, $NCOCH_3$), 3.02 (br s, 1 H, CH_cH$_d$), 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.60 (br s, 1 H, CH$_c$$H_d$), 6.31 (s, 1 H_{arom}), 6.79 (m, 1 H_{arom}), 6.83 (s, 1 H_{arom}), 7.26 (m, 2 H_{arom}), 7.57 (d, *J* = 9 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 ($COCH_3$), 28.0 (CH_3), 29.9 (CH_3), 35.0, (C), 40.8 (CH_2), 41.7 (CH_2), 55.9 (OCH_3), 61.1 (OCH_3), 102.6 (C), 112.4 (C), 115.5 (CH), 121.1 (CH), 123.5 (C),

128.3 (CH), 133.1 (CH), 133.3 (C), 135.1 (C), 140.8 (CH), 144.2 (C), 149.5 (C), 171.8 (C=O).

MS (EI): *m*/*z* = 434 ([M, Br^{81}]$^+$, 100%), 432 ([M, Br^{79}]$^+$, 100%), 419 ([M – CH_3, Br^{81}]$^+$, 62%), 417 ([M – CH_3, Br^{79}]$^+$, 60%), 377 ([M – $COCH_3$ – CH_3 + H, Br^{81}]$^+$, 60%), 375 ([M – $COCH_3$ – CH_3 + H, Br^{79}]$^+$, 60%).

Anal. Calcd for $C_{21}H_{25}BrN_2O_3$ (433.35): C, 58.21; H, 5.82; N, 6.46. Found: C, 58.36; H, 5.79; N, 6.47.

1-(5,11-Dimethoxy-4,4-dimethyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]carbazol-1(6*H*)-yl)ethanone (2)

Crushed K_2CO_3 (96 mg, 0.69 mmol), compound **10** (100 mg, 0.23 mmol), $Pd(OAc)_2$ (15 mg, 0.07 mmol), and PCy_3/HBF_4 (52 mg, 0.14 mmol) were placed in a 10 mL screw-cap vial equipped with a magnetic stir bar. The vial was purged with argon and anhyd degassed DMA (8 mL) was added. The reaction mixture was then heated at 130 °C for 24 h. The mixture was then diluted with EtOAc (15 mL) and filtered trough a plug of Celite. The organic layer was washed with brine (2 × 10 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to give compound **2** as a brown solid; yield: 57 mg (70%); mp 280–283 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.79 (m, 1 H, CH_aH$_b$), 1.90 (m, 1 H, CH$_a$$H_b$), 2.10 (s, 3 H, $NCOCH_3$), 3.14 (m, 1 H, CH_cH$_d$), 3.86 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.74 (m, 1 H, CH$_c$$H_d$), 7.25 (m, 1 H_{arom}), 7.44 (m, 2 H_{arom}), 8.25 (m, 1 H_{arom}), 8.47 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (COCH_3), 27.7 (CH_3), 30.2 (CH_3), 35.4 (C), 40.8 (CH_2), 41.1 (CH_2), 60.6 (OCH_3), 61.4 (OCH_3), 110.7 (CH), 116.2 (C), 120.1 (CH), 122.4 (C), 122.7 (CH), 124.0 (C), 125.9 (CH), 131.7 (C), 133.0 (C), 139.4 (C), 139.9 (C), 145.8 (C), 172.6 (C=O).

MS (EI): *m*/*z* = 321 ([M – OCH_3]$^+$, 100%), 352 ([M]$^+$, 44%).

Anal. Calcd for $C_{21}H_{24}N_2O_3$ (352.44): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.32; H, 6.91; N, 7.90.

1-(5,11-Dimethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]carbazol-1(6*H*)-yl)ethanone (11)

Under an inert atmosphere, a solution of **2** (200 mg, 0.57 mmol) in anhyd DMF (10 mL) was cooled to 0 °C in an ice bath. NaH (30 mg, 0.79 mmol) was then added portionwise and the mixture was stirred for 30 min and then MeI (0.05 mL, 0.85 mmol) was added. The resulting mixture was warmed to r.t. over 2 h. The mixture was poured onto ice and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed successively with brine (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to give compound **11** as a brown solid; yield: 210 mg (~100%); mp 186–188 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.75 (m, 1 H, CH_aH$_b$), 1.86 (m, 1 H, CH$_a$$H_b$), 2.06 (s, 3 H, $COCH_3$), 3.21 (m, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.12 (s, 3 H, NCH_3), 4.63 (m, 2 H, CH_2), 7.27 (t, *J* = 9 Hz, 1 H_{arom}), 7.42 (d, *J* = 9 Hz, 1 H_{arom}), 7.50 (t, *J* = 9 Hz, 1 H_{arom}), 7.27 (t, *J* = 9 Hz, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (COCH_3), 26.6 (CH_3), 30.4 (CH_3), 31.4 (C), 35.8 (NCH_3), 40.4 (CH_2), 40.9 (CH_2), 60.7 (OCH_3), 63.6 (OCH_3), 108.8 (CH), 116.5 (C), 119.8 (CH), 121.8 (C), 122.6 (CH), 123.5 (C), 125.9 (CH), 133.0 (C), 133.4 (C), 141.1 (C), 142.0 (C), 146.1 (C), 172.3 (C=O).

MS (EI): *m*/*z* = 335 ([M – OCH_3]$^+$, 100%), 366 ([M]$^+$, 65%).

Anal. Calcd for $C_{22}H_{26}N_2O_3$ (366.46): C, 72.11; H, 7.15; N, 7.64. Found: C, 70.21; H, 6.99; N, 7.55.

2-Chloro-1-(5,11-dimethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]carbazol-1(6*H*)-yl)ethanone (12)

To a stirred solution of **11** (100 mg, 0.27 mmol) in THF (5 mL) cooled at –10 °C under an argon atmosphere was added LDA (0.15 mL, 1.1 equiv, 0.3 mmol, 2.0 M in THF–heptane–ethylbenzene). After completion of the addition, the mixture was stirred for 30 min at –10 °C, and then $PhSO_2Cl$ (42 μL, 0.636 mmol) was added. The reaction mixture was stirred at –10 °C for 2 h and allowed to warm slowly to r.t. before adding dropwise to a sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford the crude product, which were purified by column chromatography (cyclohexane–EtOAc, 8:2) to give compound **12** as a brown solid; yield: 210 mg (99%); mp 186–188 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.80 (m, 1 H, CH_aH$_b$), 1.96 (m, 1 H, CH$_a$$H_b$), 3.30 (m, 1 H, C$H_cH_d$), 3.83 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.14 (s, 3 H, NCH_3), 4.15 (d, *J* = 15 Hz, 1 H, CH_eH$_f$), 1.96 (d, *J* = 15 Hz, 1 H, CH$_e$$H_f$), 3.30 (m, 1 H, C$H_cH_d$), 7.28 (m, 1 H_{arom}), 7.43 (m, 1 H_{arom}), 7.53 (m, 1 H_{arom}), 8.22 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 (CH_3), 30.4 (CH_3), 31.5 (C), 35.8 (COCH_3), 40.8 (CH_2), 41.5 (CH_2), 42.5 (CH_2), 60.9 (OCH_3), 63.6 (OCH_3), 105.8 (C), 108.9 (CH), 116.5 (C), 119.9 (CH), 121.4 (C), 122.3 (C), 122.5 (CH), 126.1 (CH), 133.7 (C), 141.6 (C), 142.1 (C), 145.0 (C), 167.9 (C=O).

MS (CI): *m*/*z* = 402 ([M + 1]$^+$, 100%).

Anal. Calcd for $C_{22}H_{25}ClN_2O_3$ (400.91): C, 65.91; H, 6.29; N, 6.99. Found: C, 66.05; H, 6.33; N, 6.89.

1-(2-Azidoethyl)-5,11-dimethoxy-4,4,6-trimethyl-2,3,4,6-tetrahydro-1*H*-pyrido[3,2-*b*]carbazole (13)

Under an inert atmosphere, NaN_3 (105 mg, 1.8 mmol) was added to a solution of **12** (40 mg, 0.10 mmol) in anhyd DMF (3 mL). After completion of the addition, the mixture was heated to reflux for 2 h. After hydrolysis with sat. aq $NaHCO_3$ (30 mL), the product was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the desired azido compound, which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.79 (m, 1 H, CH_aH$_b$), 1.90 (m, 1 H, CH$_a$$H_b$), 3.30 (m, 1 H, C$H_cH_d$), 3.55 (d, *J* = 18Hz, 1 H, CH_eH$_f$), 3.84 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.13 (s, 3 H, NCH_3), 4.35 (d, *J* = 18Hz, 1H, CH$_e$$H_f$), 4.64 (m, 1 H, CH$_c$$H_d$), 7.27 (m, 1 H_{arom}), 7.45 (m, 1 H_{arom}), 7.53 (m, 1 H_{arom}), 8.25 (m, 1 H_{arom}).

Under an inert atmosphere, a solution of BH_3·THF complex (0.22 mL, 1 M solution in THF, 0.22 mmol) was added dropwise to a solution of the above azide (30 mg, 0.073 mmol) in anhyd THF at 0 °C. After completion of the addition, the reaction mixture was then heated to reflux for 2 h. After pouring the mixture onto ice, the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were successively washed with H_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and brine (20 mL). The organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to give compound **13** as a brown oil; yield: 13 mg (45%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 6 H, 2 × CH_3), 1.70 (m, 2 H, CH_2), 3.15 (m, 2 H, CH_2), 3.31 (m, 2 H, CH_2), 3.63 (m, 2 H, CH_2), 3.83 (s, 3 H, NCH_3), 3.90 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 7.20 (m, 1 H_{arom}), 7.34 (m, 1 H_{arom}), 7.44 (m, 1 H_{arom}), 8.21 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 (2 × CH_3), 30.27 (NCH_3), 30.7 (C), 31.9 (C), 33.4 (CH_2), 38.5 (CH_2), 41.5 (CH_2), 43.4 (CH_2),

59.0 (OCH_3), 61.9 (OCH_3), 108.8 (CH), 118.9 (CH), 121.8 (C), 122.5 (CH), 123.8 (C), 125.4 (CH), 127.8 (C), 131.9 (C), 136.7 (C), 142.7 (C), 143.3 (C).

MS (CI): *m*/*z* = 394, ($[M + 1]^+$, 100%).

Anal. Calcd for $C_{22}H_{27}N_5O_2$ (393.49): C, 67.15; H, 6.92; N, 17.80. Found: C, 67.31; H, 7.00; N, 17.25.

6,6,8-Trimethyl-2,5,6,8-tetrahydro-1,3a,8-triazaindeno[1,2-*a*]phenalen-7(1*H*,8*H*)-one (1)

To a suspension of **13** (40 mg, 0.10 mmol) in mixture of H_2O–MeOH (9:1, 5 mL) at r.t. was added PIFA (130 mg, 0.30 mmol) and the mixture was stirred for 2 h at r.t.. Then, H_2O (10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the desired quinone used, which was used without further purification. A solution of the above quinone in a mixture of EtOH–THF (1:1, 20 mL) was hydrogenated (15 psi) over Pd/C (8 mg) for 5 h at r.t. The catalyst was filtered on a pad of Celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to give compound **1** as a red oil; yield: 11 mg (35% for 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 6 H, 2 × CH_3), 1.83 (m, 2 H, CH_2), 3.28 (m, 4 H, 2 × CH_2), 4.15 (m, 2 H, CH_2), 4.19 (s, 3 H, NCH_3), 7.37 (m, 3 H, 3 H_{arom}), 8.48 (m, 1 H_{arom}).

MS (EI): *m*/*z* = 304 ($[M - CH_3]^+$, 100%), 319 ($[M]^+$, 41%).

Anal. Calcd for $C_{20}H_{21}N_3O$ (319.41): C, 75.21; H, 6.63; N, 13.16. Found: C, 75.36; H, 6.68; N, 12.99.

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