A Concise Total Synthesis of the Azaphenanthrene Alkaloid Eupolauramine

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A six-step total synthesis of the azaphenanthrene alkaloid eupolauramine **1** has been achieved using combinational metalation−cyclization tactics. The synthetic route involved first the construction of the azaisoindolinone **9** by aryne-mediated cyclization of he phosphorylated pyridocarboxamide **7** and subsequent dephosphorylation. Metalation of **9** followed by connection of the hydroxybenzyl appendage and E_1CB *anti*-elimination allowed the formation of the halogenoarylmethylene azaisoindolinone **4** in the exclusive *E*-form. Oxidative radical cyclization gave rise to the azaphenanthrene skeleton and regioselective bromination of **3** induced the incorporation of the bromine atom at the 6-position of the azaphenanthrene lactam. Ultimate replacement of the bromine atom of **2** by the methoxy functionality by sequential transmetalation, in situ oxidation, and *O*-methylation of the phenolic derivative **14** completed the synthesis of the target natural product eupolauramine.

Introduction

Eupolauramine **1** is a structurally unique azaphenanthrene alkaloid which has been isolated from the relic plant *Eupomatia laurina* (*Eupomatiaceae*) a small tree found on the coasts of Australia and New Guinea.[1] The origin of this natural product is still obscure but biogenetically it is considered to be derived from an oxoaporphine alkaloid precursor.[2] Despite the fact that eupolauramine has a close taxonomic relationship and structural similarity to the aristolactams, a class of fused phenanthrene lactams possessing interesting profiles of biological activity,[3] it appears to be devoid of any useful pharmacology. However, owing to both the intriguing structure of this alkaloid, which can be regarded in one sense as having a benzo[*h*]quinoline nucleus fused with a lactam ring, and also to its low natural occurrence, its elaboration has stimulated interest in the scientific community and attracted assorted synthetic efforts. As far as we are aware, seven total syntheses[4] and three formal syntheses[5] of this natural product have appeared in print. The main general approach to the synthesis of this architecturally sophisticated alkaloid relies upon the initial construction of the benzo[*h*]quinoline unit equipped with appropriate functionalization for subsequent manipulation to generate the lactam ring. Among all the reported routes, the most elegant and skillful of which is undoubtedly the Weinreb hetero Diels−Alder approach,[4a,c] where the elaboration of the pyridine moiety constitutes the key step in the assembly of the benzo[*h*]-quinoline ring system. However, provided that one disregards the need for photolysis equipment, the most expeditious synthesis of this natural product involves the combination of two photoinitiated processes under strictly anaerobic conditions, i.e., an intramolecular $S_{RN}1$ reaction to create the azaisoindolinone unit and a stilbene cyclization to generate the benzo[*h*]quinoline ring system.[4g]

We delineate here a tactically new six-step total synthesis of **1** that relies upon our long-standing experience in the field of enamides[6] and isoindolinone chemistry.[7]

Results and Discussion

Our approach to the synthesis of compound **1** is depicted in the retrosynthetic analysis shown in Scheme 1. The key steps were the synthesis of the fused aristolactam **3** with the pyridine embedded in the skeleton and the regioselective bromination of this azaphenanthrene

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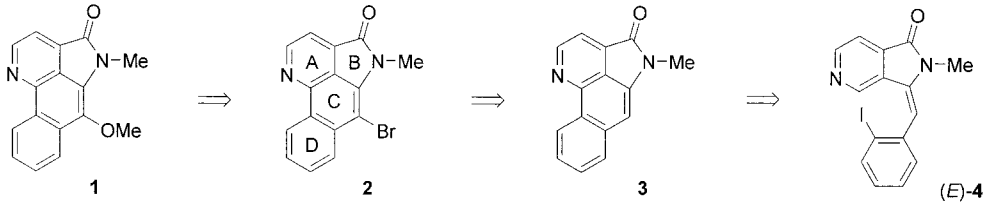
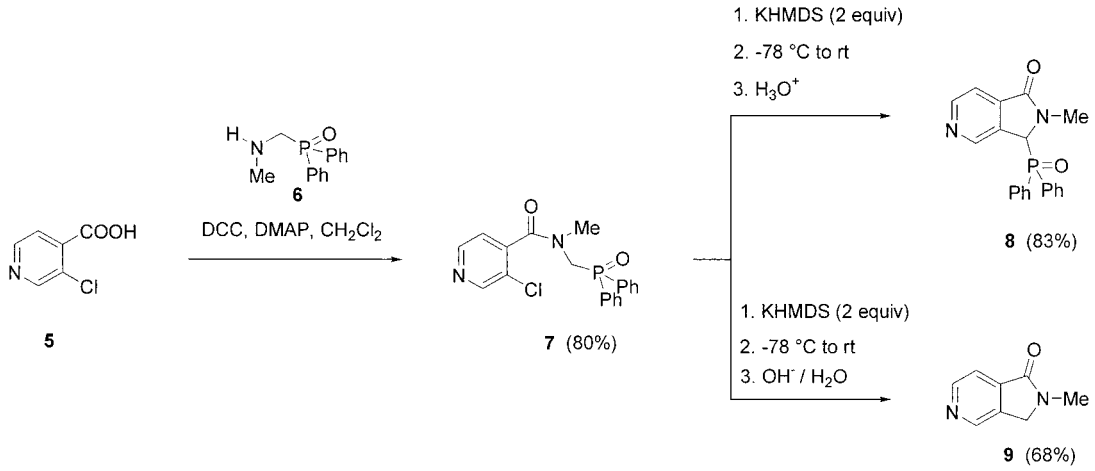
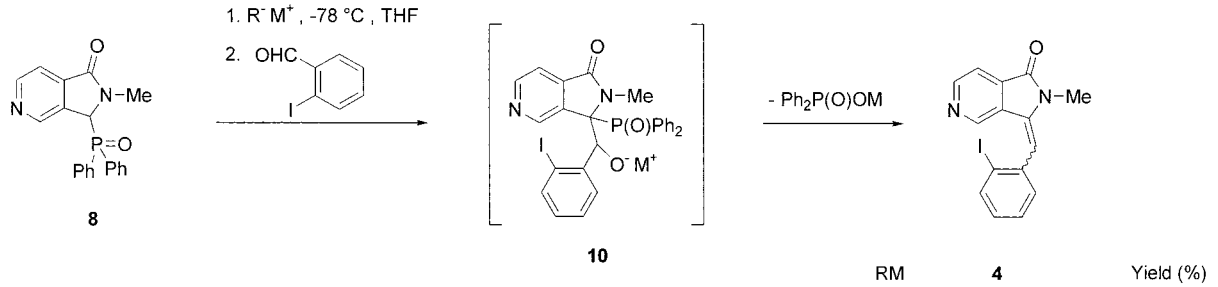
Scheme 1



Scheme 2



Scheme 3



RM	**4**	Yield (%)
KHMDS	*Z* / *E* 40:60	81
NaHMDS	*Z* / *E* 48:52	76
LHMDS	*Z* / *E* 38:62	83

lactam **3** with the hope that a halogen at C6 would serve as a useful leaving group, thus providing the site for aromatic nucleophilic substitution in ring C. Final displacement of the bromine atom of **2** by a methoxy group then should complete the synthesis of the target natural product **1**. Critical to the success of this strategy was the assembly of the azaindolinone **4** equipped with a halogenoarylmethylene unit with the mandatory *E*-stereochemistry required for the radically induced generation of the azaphenanthrene ring system. To reach this goal we first envisaged building up the arylmethyleneazaindolinone **4** under the agency of the Horner process between the phosphorylated azaindolinone **8** and 2-iodobenzaldehyde. We assumed that it could be possible by proper choice of the required base and solvent to control the stereochemical outcome of the reaction and then to force the reaction to produce exclusively the *E*-form of the enamide **4**. The first facet of the synthesis, the assembly of the phosphorylated isoindolinone **8** containing the pyridine unit was accomplished by taking advantage of our newly developed aryne-mediated cyclization applied to halogeno-*N*-(diphenylphosphinoylmethyl)benzamide derivatives.[8] For this purpose the required parent phosphorylated pyridocarboxamide **7** was initially synthesized by coupling *N*-[(diphenylphosphinoyl)methyl]-*N*-methylamine **6** with 3-chloroisonicotinic acid **5** (Scheme 2). Exposure of the phosphorylated chloroisonicotinamide derivative **7** to potassium bis(trimethylsilyl)amide (KHMDS, 2 equiv) at −78 °C in THF induced the regioselective formation of the phosphoryl-stabilized α-aminocarbanion and the concomitant formation of the pyridyne unit. Addition of the carbanion across the pyridyne moiety brought about the intramolecular arylation reaction and usual acidic workup delivered the phosphorylated azaisoindolinone **8** in an

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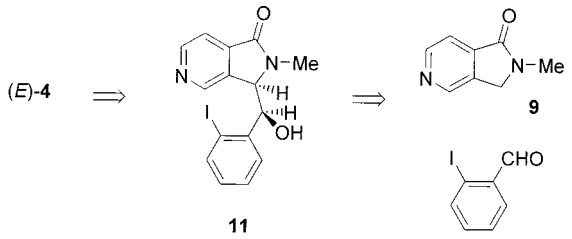
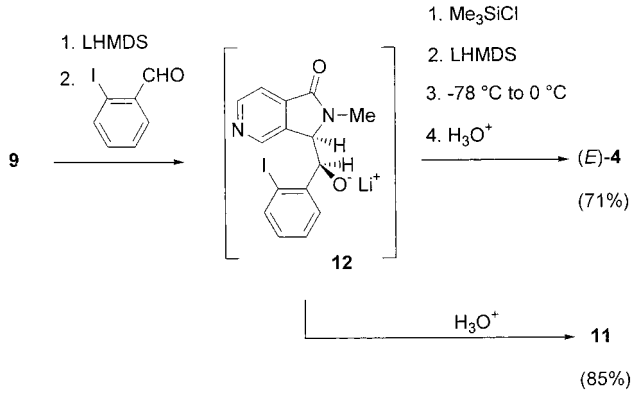
Scheme 4

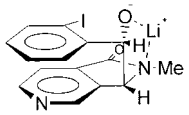


Scheme 5



excellent yield (Scheme 2). Horner reaction between the metalated isoindolinone **8** and 2-iodobenzaldehyde proceeded uneventfully to afford a fairly good yield of the 3-arylmethyleneazaisoindolinone **4** (Scheme 3). Somewhat disappointingly compound **4** was obtained in both of the difficulty separable *E*- and *Z*-forms, as unambiguously assigned from the NMR spectrum with the help of NOE experiments. Attempts to improve the proportion of the *E*-form by either employing different bases (KHMDS, LHMDS, NaHMDS, with or without crown-ethers) in order to change the counterion in the adduct **10** or varied solvents (ether, toluene, THF) met with no success, the least disappointing results (*E*/*Z* = 62:38) being obtained by making use of LHMDS in THF (Scheme 3). We then decided to switch our plans, and we thus set out to achieve an alternative strategy to secure the *E*-configuration of the key intermediate **4**. The present work originated from the following premises: (i) isoindolinones have been successfully metalated at the benzylic position of the heteroring system thus allowing the connection of a range of electrophiles at the 3 position of the lactam ring.[7a] Consequently, one could envisage the installation of a hydroxybenzyl appendage on the azaisoindolinone template by reaction of the anion derived from the phthalimidine **9** with 2-iodobenzaldehyde (retrosynthetic Scheme 4); (ii) it might be possible by proper choice of the metalating agent to control the diastereoselectivity of the addition of the metalated precursor derived from **9** to an aldehyde and thus force the formation of the *erythro* adduct **11**. Indeed, it has been shown on related systems that the relatively modest diastereoselectivity observed with lithiated species[9] could be dramatically improved by trans metalation with $MgBr_2$ prior to addition of the carbonyl derivative.[10] (iii) With *erythro* adduct **11** in hand it could be assumed that *O*-alkylation and E_1CB *anti*-elimination in the sequence would afford the desired enamide in the exclusive *E*-form.

We then embarked on the synthesis of the azaisoindolinone **9**. This compound was readily obtained by applying a protocol recently developed in our laboratory which involves the basic treatment of the opened phosphorylated chloropyridylcarboxamide **7** as earlier mentioned followed by aqueous basic treatment (Scheme 2). This slight modification of the experimental protocol triggered off the formation of the azaisoindolinone **9** released from the phosphoryl appendage with an excellent yield. This one-pot procedure was considerably simpler than the earlier fortuitous approach reported in the literature.[11] Compound **9** was smoothly deprotonated with LHMDS at −78 °C in THF and subsequently quenched with 2-iodobenzaldehyde (Scheme 5). To our delight, classical workup delivered a single compound which was unambiguously identified as alcohol **11**. The ^1H NMR spectrum of this compound showed a coupling constant of 3.7 Hz between C3 and Cα protons which is in agreement with the *erythro* configuration,[9,10] and the structure of the *erythro* diastereoisomer **11** was ultimately confirmed by single crystal X-ray analysis. The high degree of diastereoselectivity observed in this process may be tentatively rationalized by the conjunction of two different phenomena attributable to the peculiar structure of the primary adduct **12**, i.e., the



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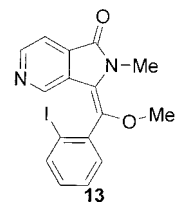
presence of the π-deficient pyridine unit which strongly facilitates π donor−acceptor interactions between the aromatic and heteroaromatic ring systems as well as the stabilization of the alkoxide by chelation of the lithium counterion embedded in a five-membered heteroring system. Since the stereochemical outcome of the reaction process bode well for preparing stereoselectively the desired enamide (*E*)-**4**, we envisioned performing the third and fourth phases of the synthesis with which we were concerned as a single one-pot reaction. For this purpose the transient oxanion **12** was *O*-silylated in situ with TMSCl (1 equiv) and subsequently treated in the sequel with LHMDS (1 equiv) at −78 °C. Warming to 0 °C was followed by acidic aqueous workup, and, gratifyingly, conducting the reaction according to this procedure afforded straightforwardly and solely the arylmethyleneazaindolinone (*E*)-**4** in good yield (Scheme 5). Curiously, all attempts to methylate alcohol **11** (via **12**) failed to afford the corresponding methyl ether which might have been oxidized to the enol ether **13**. Instead the



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dehydration product (*E*)-**4** was the major product of these methylation attempts. The exclusive formation of this

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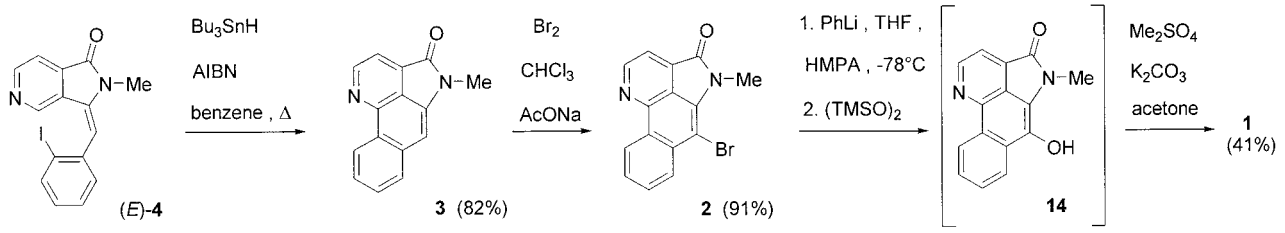
Scheme 6



stereoisomer was rewarding since its oxidative radical cyclization furnished the fused azaaristolactam **3** with a very satisfactory yield (Scheme 6). The radical reaction was performed by slow dropwise addition of a benzene solution of tributyltin hydride and AIBN to a refluxing benzene solution of (*E*)-**4** under argon. Since the subsequent chemical operation has precedent in related phenanthrenic systems,[12] we were reasonably optimistic about the chances of success for the regioselective bromination of azaaristolactam **3** necessary for introduction of the remaining functionality of eupolauramine **1**. The bromination reaction was carried out under classical conditions (Br_2, CH_2Cl_2, AcOH) thus allowing the predictable and exclusive incorporation of the bromine atom at the 6-position of the azaphenanthrene lactam as evidenced by the disappearance of C6 proton at δ 7.07 ppm in the ^{1}H NMR spectrum of **3**.

The ultimate replacement of the bromine atom by the methoxy functionality proved far more problematic than we had anticipated. Indeed the lactam ring did not survive the nucleophilic aromatic substitution conditions usually employed, i.e., high-temperature reaction of arylhalide with alkali metal alkoxides in 2,4,6-collidine.[13] After experimenting a variety of reagents and conditions, we found that the only effective and reliable method proved to be by exploiting the prior transmetalation of **2** with phenyllithium, a weak nucleophilic metalating reagent sparing the pyridine ring.[14] The operation was effected at −78 °C in THF with HMPA used as a cosolvent[15] due to the poor solubility of **2** in the usual solvents. Attempted introduction of the hydroxyl group via quenching of the anion with molecular oxygen[16] gave only the debrominated compound and use of the more reactive electrophile trimethylborate ($B(OMe)_3$)[17] followed by an in situ oxidation of the boronic intermediate produced only traces of the azaphenanthrol lactam **14**. The hydroxy phenolic function was finally introduced by making use of bis(trimethylsilyl)peroxide as the electrophilic hydroxyl[18] albeit in moderate yield (Scheme 6) and at last *O*-methylation of the highly condensed phenolic derivative **14** led to the target natural product eupolauramine with an overall yield of 15% in the six steps.

In conclusion we have completed a new short and efficient synthesis of the azaphenanthrene alkaloid eupolauramine. The advantage of this synthesis lies in small number of synthetic steps and the ease of elaboration of the different partners involved in the assembly of this highly condensed alkaloid. This new conceptual approach also emphasizes the synthetic potential of α-aminocarbanions in annulation processes and the versatility of the phosphorylated temporary activating group. This strategy should be undoubtedly broadened to the synthesis of other polycyclic pyridine-containing natural products.

Experimental Section

General. All reactions were conducted under an argon atmosphere with magnetic stirring. Tetrahydrofuran (THF) was predried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar and stored over sodium wire before use. Melting points are uncorrected. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300, 75, and 121 MHz, respectively, on a Bruker AM 300 apparatus. Infrared spectra were recorded in a KBr pellet on a Perkin-Elmer 881. Elemental analyses were performed by the CNRS microanalysis center. For flash chromatography, Merck silica gel 60 (230−400 mesh ASTM) was used.

Materials. The *N*-(diphenylphosphinoylmethyl)methylamine **6**[6d] and 3-chloroisonicotinic acid **5**[19] were synthesized according to already reported procedures.

3-Chloro-*N*-(diphenylphosphinoylmethyl)-*N*-methylisonicotinamide (7). A solution of DCC (1.3 g, 6.4 mmol) and DMAP (74 mg, 0.6 mmol) in dry CH_2Cl_2 (20 mL) was added to a suspension of 3-chloroisonocotinic acid **5** (1 g, 6.4 mmol) in CH_2Cl_2 (40 mL) with vigorous stirring at 0 °C under Ar. The mixture was stirred for an additional 0.5 h, and a solution of the phosphorylated amine **6** (980 mg, 6.4 mmol) in CH_2Cl_2 (10 mL) was then slowly added. The mixture was stirred at room temperature for 2 h, cooled at 0 °C, filtered, and evaporated to dryness. The crude residue was then triturated with Et_2O, and the resulting white solid was collected by vacuum filtration and dissolved in the minimum acetone. The solution was kept in the refrigerator overnight and filtered to remove traces of DCU. Removal of the solvent under reduced pressure left a crude solid which was finally purified by recrystallization from hexane−toluene to yield 2.0 g (81%) of **7**: mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 4.40 (br. d, 2H), 3.30 (m, 2H), 6.66 (dd, J = 4.9, 0.5 Hz, 1H), 7.49−7.58 (m, 6H), 7.89−7.95 (m, 4H), 8.43 (d, J = 4.9 Hz, 1H), 8.53 (d, J = 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 37.7, 47.2 (d, J_{CP} = 76 Hz), 121.4, 128.8 (d, J_{CP} = 12.5 Hz), 127.5, 128.2 (d, J_{CP} = 98 Hz), 131.3 (d, J_{CP} = 10 Hz), 132.5, 142.4, 148.1, 149.8, 165.8; ^{31}P NMR ($CDCl_3$) δ 28.6; IR (KBr) 1648, 1190 cm^{-1}. Anal. Calcd for $C_{20}H_{18}ClN_2O_2P$: C, 62.43; H, 4.71, N, 7.28. Found: C, 62.59; H, 4.70, N, 7.42.

3-Diphenylphosphinoyl-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-1-one (8) and 2-Methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (9). A solution of KHMDS (16 mL, 0.5 M in toluene, 8 mmol) was added dropwise to a solution of the phosphorylated amide **7** (1.54 g, 4 mmol) in

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THF (50 mL) at −78 °C under Ar. The mixture was stirred for 0.5 h and then allowed to warm to room temperature within 3 h.

For the preparation of the phosphorylated compound **8**, saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo, and the residue was treated with an additional 25 mL of MeOH and again concentrated in vacuo. The residue was triturated with Et_2O, filtered, and recrystallized from hexane−toluene to yield compound **8** (1.16 g, 83%): mp 194−195 °C; ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 5.49 (d, J = 10.6 Hz, 1H), 7.39−7.43 (m, 3H), 7.51−7.61 (m, 6H), 7.68−7.74 (m, 2H), 8.16 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 30.4, 62.8 (d, J_{CP} = 71 Hz), 117.3, 126.8 (d, J_{CP} = 98 Hz), 128.1 (d, J_{CP} = 99 Hz), 129.0 (d, J_{CP} = 12 Hz), 129.1 (d, J_{CP} = 12 Hz), 131.5 (d, J_{CP} = 9 Hz), 131.7 (d, J_{CP} = 9 Hz), 133.4 (d, J_{CP} = 2.5 Hz), 133.6 (d, J_{CP} = 2 Hz), 139.8, 145.5, 149.6, 166.9; ^{31}P NMR ($CDCl_3$) δ 30.0; IR (KBr) 1682, 1207 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_2O_2P$: C, 68.96; H, 4.92, N, 8.04. Found: C, 68.85; H, 5.05, N, 7.89.

For the synthesis of the dephosphorylated compound **9**, aqueous KOH (2.5 M, 4 mL) was added, and the mixture was stirred at room temperature within 15 min. Water was then added, and the mixture was extracted with Et_2O (3 × 20 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to a residue which was purified by flash column chromatography with acetone−hexanes (80:20). Recrystallization from hexane afforded compound **9** (946 mg, 68%): mp 88−89 °C (lit.[11] 82−84 °C); ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 3H), 4.42 (s, 2H), 7.63 (dd, J = 5.0, 0.9 Hz, 1H), 8.66 (d, J = 5.0 Hz, 1H), 8.73 (d, J = 0.9 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 29.6, 50.6, 117.3, 135.5, 140.4, 144.5, 149.2, 166.7.

(*Z*)- and (*E*)-3-(2-Iodobenzylidene)-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (4). A solution of the appropriate base (1 equiv) was added dropwise to a solution of **8** (696 mg, 2 mmol) in THF (20 mL) at −78 °C under Ar. The orange solution was kept at this temperature for 15 min, and a solution of 2-iodobenzaldehyde (464 mg, 2 mmol) in THF (5 mL) was then added by syringe. The reaction mixture was allowed to warm to room temperature over a period of 30 min followed by addition of aqueous NH_4Cl and extraction with Et_2O (100 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to a yellow oil which was purified by flash column chromatography with acetone−hexanes (80:20) as eluent to afford **4** as a mixture of (*E*)- and (*Z*)-isomers. The structure and the *E*/*Z* ratio were established by NOE difference experiments. The *N*-methyl H_3 (δ 3.46) showed a strong NOE to vinylic H (δ 6.46, 15%) for the (*E*)-isomer. **4**: ^{1}H NMR ($CDCl_3$, mixture of (*E*)- and (*Z*)-isomers) δ 2.96 (s, 3H, *Z*), 3.46 (s, 3H, *E*), 6.46 (s, 1H, *E*), 6.71 (s, 1H, *Z*), 7.02−7.16 (m, 1H, *Z* + *E*), 7.30−7.51 (m, 2H, *Z* + *E*), 7.68−7.73 (m, 1H, *Z* + *E*), 7.92 (dd, J = 8.0, 1.0 Hz, 1H, *Z*), 7.99 (dd, J = 8.0, 1.0 Hz, 1H, *E*), 8.38 (s, 1H, *E*), 8.70 (d, J = 4.9 Hz, 1H, *E*), 8.82 (d, J = 4.8 Hz, 1H, *Z*), 9.18 (s, 1H, *Z*).

3-[1-(2-Iodophenyl)-1-hydroxymethyl]-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (11). A solution of LHMDS (1 M in hexanes, 2 mL, 2 mmol) was added dropwise to a solution of **9** (300 mg, 2 mmol) in THF (20 mL) with stirring under Ar at −78 °C. The mixture was stirred for an additional 15 min after which time a solution of 2-iodobenzaldehyde (466 mg, 2 mmol) in THF (5 mL) was added by syringe. The reaction mixture was stirred at −78 °C for a further 30 min, and then quenched with saturated NH_4Cl solution and finally extracted with three 30 mL portions of Et_2O and two 25 mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated on a rotary evaporator to afford **11** (640 mg, 83%) as a single diastereomer which was finally purified by recrystallization from EtOH: mp 195−196 °C; ^{1}H NMR (DMSO-d_6) δ 3.15 (s, 3H), 4.99 (d, J = 3.1 Hz, 1H), 5.26 (t, J = 4.0 Hz, 1H), 6.03 (d, J = 5.0 Hz, 1H), 7.20 (td, J = 7.5, 1.6 Hz, 1H), 7.32 (dd, J = 7.8, 1.5 Hz, 1H), 7.51 (td, J = 7.5, 1.6 Hz, 1H), 7.65 (d, J = 4.9 Hz, 1H), 7.73 (s, 1H), 7.97 (dd, J = 7.8, 1.0 Hz, 1H), 8.65 (d, J = 4.9 Hz, 1H);^{13}C NMR (DMSO-d_6) δ 27.7, 63.8, 72.4, 97.9, 116.7, 128.2, 129.2, 130.2, 136.4, 139.3, 141.0, 142.2, 144.9, 149.1, 166.2; IR (KBr) 3305, 1676 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2O_2I$: C, 47.39; H, 3.45, N, 7.37. Found: C, 47.21; H, 3.33, N, 7.45.

(*E*)-3-(2-Iodobenzylidene)-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (4) from 10. The metalation of (aza)isoindolinone **10** and subsequent trapping with 2-iodobenzaldehyde was conducted as described above. To the solution of oxanion **12** in THF at −78 °C was added freshly distilled Me_3SiCl (218 mg, 2 mmol), and the reaction mixture was warmed to room temperature over a period of 1 h. The mixture was recooled to −78 °C, treated with LHMDS (1 M in hexanes, 2 mL, 2 mmol), warmed again to room temperature, and finally quenched with aqueous NH_4Cl before extraction with Et_2O (3 × 20 mL) and CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the arylmethylene(aza)isoindolinone (*E*)-**4** which was purified by column chromatography on silica gel using hexanes−acetone (1:1) as eluent and finally recrystallized from hexane−toluene to obtain the pure product (*E*)-**4** (550 mg, 76%): mp 178−179 °C; ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H), 6.46 (s, 1H), 7.12 (dt, J = 7.3, 1.1 Hz, 1H), 7.43 (dt, J = 7.4, 1.0 Hz, 1H), 7.51 (dd, J = 7.6, 1.1 Hz, 1H), 7.73 (dd, J = 4.9, 1.2 Hz, 1H), 7.99 (dd, J = 8.0, 1.0 Hz, 1H), 8.37 (d, J = 1.2 Hz, 1H), 8.69 (d, J = 4.9 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 26.5, 100.7, 115.5, 116.9, 128.6, 130.1, 130.6, 136.0, 137.2, 138.6, 139.5, 144.7, 150.0, 164.8; IR (KBr) 1694 cm^{-1}. Anal. Calcd for $C_{15}H_{11}IN_2O$: C, 49.75; H, 3.06, N, 7.73. Found: C, 49.52; H, 3.15, N, 7.88.

5-Methyl-4,5-dihydrobenzo[*h*]pyrrolo[3,4,5-*d*,*e*]quinolin-4-one (3). To a solution of *(E)*-**4** (362 mg, 1 mmol) in dry degassed benzene (500 mL), refluxing under Ar, was added a solution of *n*-Bu_3SnH (378 mg, 1.3 mmol) and AIBN (164 mg, 1 mmol) in dry degassed benzene (50 mL) by syringe over a period of 30 min. Once addition had finished, refluxing was kept up for a further 3 h. The benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (100 mL). The solution was washed with hexane (3 × 50 mL) and concentrated in vacuo to a solid residue which was recrystallized from EtOH to afford **3** (147 mg, 63%): mp 191−192 °C (lit.[4c] 182 °C dec); ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H), 7.07 (s, 1H), 7.63−7.67 (m, 2H), 7.84 (dd, J = 7.0, 2.5 Hz, 1H), 7.90 (d, J = 4.7 Hz, 1H), 8.98 (dd, J = 6.8, 2.5 Hz, 1H), 9.21 (d, J = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.7, 105.7, 117.1, 123.9, 126.3, 128.4, 128.8, 129.3, 133.6, 136.0, 137.2, 144.7, 151.7, 167.2; IR (KBr) 1706 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30, N, 11.96. Found: C, 77.03; H, 4.41, N, 11.75.

6-Bromo-5-methyl-4,5-dihydrobenzo[*h*]pyrrolo[3,4,5-*d*,*e*]quinolin-4-one (2). A solution of Br_2 (144 mg, 0.9 mmol) in $CHCl_3$ (10 mL) was added dropwise to a vigorously stirred suspension of AcONa (74 mg, 0.9 mmol) in a solution of (aza)aristolactam **3** (140 mg, 0.6 mmol) in $CHCl_3$ (30 mL). The mixture was stirred at room temperature for 1 h. Triethylamine (5 mL) was then added, and the organic phase was successively treated with aqueous NaOH (10%, 3 × 10 mL) and aqueous sodium thiosulfate (10%, 3 × 10 mL), washed with water and brine, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure to afford crude **2** (167 mg, 89%) which was finally purified by recrystallization from MeOH: mp 244−245 °C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 7.69 (dt, J = 7.5, 1.1 Hz, 1H), 7.77 (dt, J = 7.7, 1.4 Hz, 1H), 7.89 (d, J = 4.6 Hz, 1H), 8.36 (dt, J = 8.2, 1.1 Hz, 1H), 8.99 (dd, J = 7.7, 1.4 Hz, 1H), 9.19 (d, J = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.2, 102.3, 117.1, 121.9, 123.8, 126.7, 127.2, 127.6, 129.3, 130.0, 132.4, 134.3, 143.9, 151.6, 167.4; IR (KBr) 1711 cm^{-1}. Anal. Calcd for $C_{15}H_9BrN_2O$: C, 57.53; H, 2.90, N, 8.95. Found: C, 57.32; H, 2.73, N, 9.05.

Preparation of Eupolauramine (1) from the 6-Hydroxy-5-methyl-4,5-dihydrobenzo[*h*]pyrrolo[3,4,5-*d*,*e*]quinolin-4-one (14). A solution of the brominated compound **2** (100 mg, 0.32 mmol) in a mixture of THF (40 mL) and HMPA (5 mL) was cooled to −78 °C and treated with PhLi (1.8 M in cyclohexane/ether, 0.37 mL, 0.67 mmol). The resulting solution

was maintained at −78 °C for 30 min, at which time neat bis(trimethylsilyl) peroxide[20] (266 mg, 1.5 mmol) was added. The temperature bath was removed, and the mixture was allowed to warm to room temperature with stirring. The resulting solution was quenched with saturated NH_4Cl, the volatiles were removed in vacuo, and the crude material was dissolved in 5% HCl−MeOH (2 mL) and allowed to stir at room temperature (10 min). The mixture was then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to give the crude phenol **14** which was directly methylated following the Weinreb's protocol[4c] to provide, after chromatography on silica using AcOEt as eluent, 35 mg of synthetic eupolauramine **1** with analytical and spectral data matching those reported for the natural product.

(20) Ricci, A.; Taddei, M. *Synthesis* **1986**, 633.

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Supporting Information Available: X-ray crystallographic data and an ORTEP drawing of compound **11** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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