A Brief Total Synthesis of Eupolauramine

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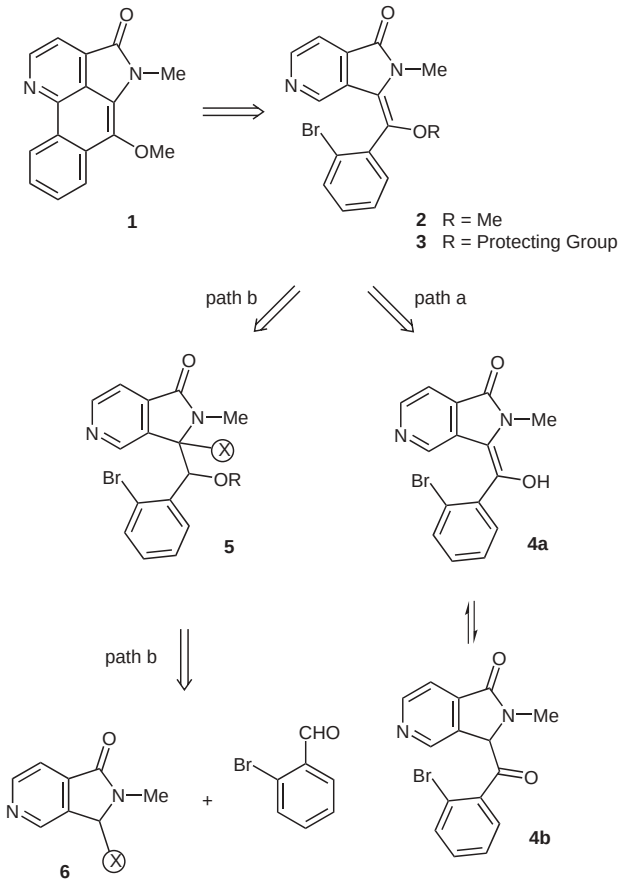
Abstract: A concise synthesis of the alkaloid eupolauramine has been achieved. The key step was a benzotriazolyl-mediated connection of a bromoaryl unit to the azaisoindolinone framework by an enol ether function. Free radical cyclization then provided the natural product.

Key words: alkaloids, carbanions, enols, ring closure, total synthesis

Eupolauramine (**1**) is a structurally unique azaphenanthrene alkaloid extracted from *Eupomatia* species.[1] This natural product was first isolated in 1972 by Taylor et al. from the bark of *Eupomatia laurina*[2] and is considered to be biogenetically derived from an oxoaporphine precursor, probably liriodenine.[3] Due to its architecturally sophisticated structure in conjunction with its low natural occurrence this alkaloid represents a challenging synthetic target and an interesting proving ground for organic chemists. Most of the synthetic routes to this phenanthrene lactam rely upon the construction of the benzo[*h*]quinoline unit equipped with appropriate functionalities, i.e. an ester-[4–7] or an acid[8] group on the pyridine unit, and a remote nitro-[4,5] or amino[6–8] function, able to secure the generation of the lactam ring. Eupolauramine was also obtained by decarboxylation of imbiline,[9] by sequential bromination of the azaphenanthrene lactam and ultimate replacement of the halogen atom by the methoxy functionality,[10] and by combining two photoinitiated processes, i.e. a $S_{RN}1$ reaction and a 6π-electron cyclization process, for the creation of the lactam- and azaphenanthrene ring systems.[11]

All these methods have been developed owing to the difficulties associated with the elaboration of the rather appealing intermediates **2** and **3**. Indeed, compounds **2** and **3** display all the mandatory structural specifications to straightforwardly reach the target natural alkaloid, i.e. the presence of an enol ether moiety integrated in an (aza)bromostilbenic unit likely to ensure the assemblage of the benzoquinoline ring system (retrosynthetic Scheme 1, path a). Unfortunately, all attempts to synthesize compound **2** by O-methylation of the enol form **4a** of the acylated compound **4b** were unrewarding and only the C-methylation product was obtained.[6,11] Furthermore, attempts to generate the azaphenanthrene unit embedded in the alkaloid skeleton by free radical cyclization of **4b** were fruitless. It then occurred to us that the creation of the enol ether unit (methylated or in some protected form) would be achievable by an olefination process applied to an azaisoindolinone precursor **5** equipped with a pendant hydroxybenzyl appendage on the benzylic position and a temporary blocking group X as well (retrosynthetic Scheme 1, path b). We assumed that such an adduct might in turn be obtained by sequential metallation of the azaisoindolinone derivative **6** and quenching with the appropriate aromatic aldehyde.



Scheme 1

Critical to the success of this strategy was then the ability to identify a temporary activating group X liable to allow and if feasible to facilitate the metallation/hydroxyalkylation sequence, to survive the O-substitution reaction and above all to be labile enough to promote the ultimate formation of the exocyclic enol function.

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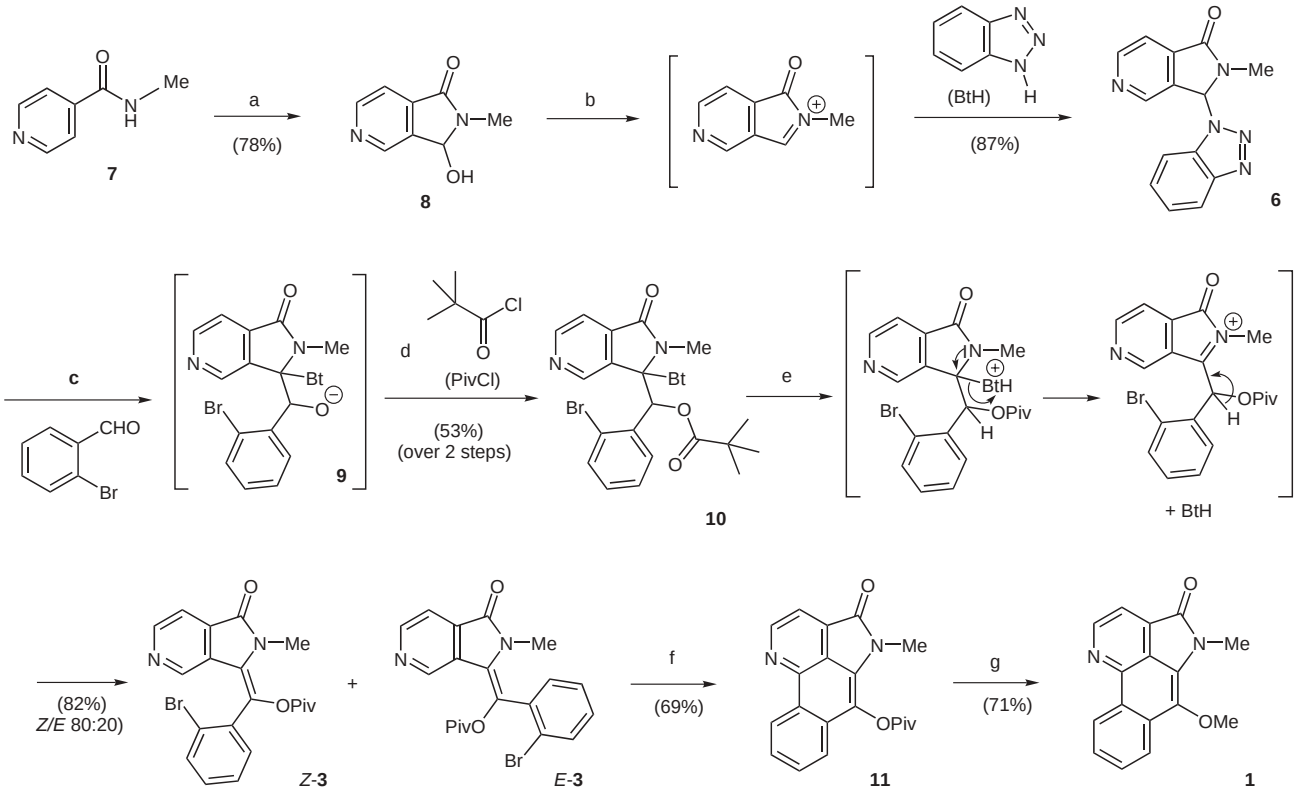
The choice of benzotriazole, which has proved to be of widespread applicability as a synthetic auxiliary in a multitude of synthetic endeavors,[12] originated from the following premises: (i) the benzotriazolyl ring system has been indiscriminately involved in the generation of stabilized and non stabilized α-aminocarbanionic species;[13] (ii) *N*-benzotriazolylmethylcarboxamides have been shown to be excellent candidates for the generation of *N*-acylenamines under basic or acidic conditions.[14] Consequently, we embarked on the synthesis of the azaisoindolinone **6** equipped with the benzotriazolyl unit. The assembly of this polynitrogenated compound was accomplished by a two step sequence involving the quenching with dimethylformamide (DMF) of the dilithiated species generated by treatment with *n*-butyllithium (BuLi) of the isonicotinamide derivative **7** (Scheme 2). Exposure of the N,O-hemiacetal **8**[15] to a catalytic amount of *para*-toluenesulfonic acid (*p*TSA) then induced the formation of the iminium salt which was trapped as it is formed with an excess of benzotriazole to provide the desired azaisoindolinone **6**. This compound was smoothly deprotonated with BuLi in tetrahydrofuran (THF) at –78 °C and then allowed to react with 2-bromobenzaldehyde. At this stage we opted for the interception of the transient oxanion **9** with the highly reactive pivaloyl chloride. In fact we anticipated that the bulky pivaloyl group (Piv) could play a double role. Its presence in the adduct **10** could have a steric impact on the subsequent elimination process leading to **3** and force in particular the exocyclic olefinic system to adopt the more favorable *Z*-configuration. The O-Piv functionality could be also straightforwardly converted into the required methoxy group. The oxanion **9** was thus quenched in situ with pivaloyl chloride and the whole operation delivered the rather congested adduct **10**. The use of the pivaloyl group in conjunction with the choice of the temporary auxiliary was rewarded here: treatment of the adduct **10** with *p*TSA afforded the enol lactam derivative **3** according to the mechanistic pathway portrayed in the Scheme 2. The key model, compound **3**, was obtained as a mixture of separable *Z*- and *E*-isomers with the required *Z*-isomer predominant by a large margin (*Z*:*E* 80:20). The oxidative free radical cyclization reaction (AIBN, Bu_3SnH) of the major stereoisomer proceeded uneventfully to furnish the fused (aza)aristolactam **11**. The ultimate replacement of the pivaloyloxy group by the methoxy functionality was inspired by Nicolaou's mild process for the transesterification of aromatic pivaloates into phenols.[16] Thus, removal of the pivaloate group by exposure to Cs_2CO_3–18-crown-6 in methanol followed by in situ trapping of the phenoxide anion with a methylating agent delivered straightforwardly the target natural product eupolauramine (**1**) with 11.5% yield over the six steps.[17] The spectral data of **1** were identical to those reported for the natural product eupolauramine.[2]



Scheme 2 a) (i) BuLi (2.2 equiv), THF, –78 °C, 30 min, then 0 °C, 15 min; (ii) DMF, –78 °C, 1 h, then r.t., 2 h; b) *p*TSA, BtH, toluene, reflux, 3 h; c) (i) BuLi, THF, –78 °C, 20 min; (ii) 2-BrC_6H_4CHO, THF, –78 °C to –40 °C, 30 min; d) –78 °C, PivCl, –78 °C to r.t., 1 h; e) *p*TSA, toluene, reflux, 1 h; f) (i) Separate *Z*-**3** and *E*-**3**, flash column chromatography, SiO_2, EtOAc–hexanes (40:60); (ii) *Z*-**3**, AIBN (1 equiv), Bu_3SnH (1.5 equiv), benzene, reflux 5 h; g) Cs_2CO_3 (2 equiv), 18-crown-6 (0.6 equiv), Me_2SO_4 (2.2 equiv), MeOH, reflux, 24 h.

In summary, we have completed a concise synthesis of eupolauramine. The advantage of this synthesis lies in the ease of elaboration of the intermediates involved in the assembly of this alkaloid and the reported synthetic tactics emphasize the high versatility and potential of the benzotriazole as a temporary auxiliary for synthetic purposes.

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(17) All new compounds have been fully characterized. ^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR and APT spectral data (75 MHz, $CDCl_3$) and elemental analysis of the key intermediates for Compound **10**: white solid, mp 176–177 °C. ^{1}H NMR: δ = 1.12 (s, 9 H, 3 CH_3), 2.83 (s, 3 H, NCH_3), 5.89 (d, *J* = 8.3 Hz, 1 H, ArH), 6.15 (d, *J* = 7.8 Hz, 1 H, ArH), 6.81 (t, *J* = 7.8 Hz, 1 H, ArH), 7.06 (t, *J* = 6.8 Hz, 1 H, ArH), 7.17 (t, *J* = 7.8 Hz, 1 H, ArH), 7.24–7.36 (m, 2 H, ArH + CHOC=O), 7.55 (d, *J* = 8.3 Hz, 1 H, ArH), 7.76 (d, *J* = 4.8 Hz, 1 H, ArH), 8.11–8.14 (m, 1 H, ArH), 9.05 (d, *J* = 4.8 Hz, 1 H, ArH), 9.17 (s, 1 H, ArH). ^{13}C NMR: δ = 27.0 (3 CH_3), 27.9 (CH_3), 38.6 (C), 74.4 (CH), 83.4 (C), 109.9 (CH), 117.7 (CH), 122.0 (CH), 124.8 (CH), 125.6 (C), 126.8 (CH), 128.6 (CH), 128.7 (CH), 130.8 (CH), 131.4 (C), 132.5 (C), 133.8 (CH), 135.6 (C), 140.7 (C), 145.6 (CH), 146.6 (C), 151.1 (CH), 165.1 (C), 175.7 (C). Anal. Calcd for $C_{26}H_{24}BrN_5O_3$ (534.42): C, 58.44; H 4.53; N, 13.10. Found: C, 58.79; H, 4.84; N, 13.37. Compound ***Z*-3**: white solid, mp 169–170 °C. ^{1}H NMR: δ = 1.25 (s, 9 H, 3 CH_3), 3.55 (s, 3 H, NCH_3), 7.25–7.47 (m, 3 H, ArH), 7.64–7.76 (m, 3 H, ArH), 8.64 (d, *J* = 4.9 Hz, 1 H, ArH). ^{13}C NMR: δ = 26.8 (3 CH_3), 29.4 (CH_3), 39.3 (C), 116.8 (CH), 124.5 (C), 127.4 (C), 127.9 (CH), 130.0 (C), 131.8 (C), 132.0 (CH), 133.7 (CH), 134.3 (C), 134.4 (CH), 135.8 (C), 143.9 (CH), 149.3 (CH), 165.4 (C), 176.4 (C). Anal. Calcd for $C_{20}H_{19}BrN_2O_3$ (415.29): C, 57.84; H, 4.61; N, 6.75. Found: C, 57.61; H, 4.54; N, 6.47.