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An Exceptionally Brief Synthesis of Eupolauramine

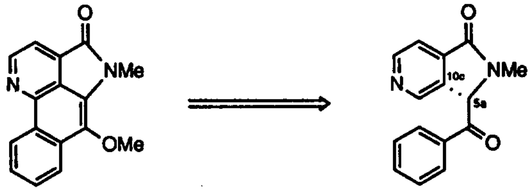
R. Richard Goehring*

Department of Chemistry
North Carolina State University, Raleigh, NC 27695-8204

Abstract: A three-step synthesis of the azaphenanthrene alkaloid eupoulauramine (1) has been achieved from 3-bromopyridine. The key step in the synthesis was a one-pot conversion of 4 to *O*-demethyleupolauramine (9) *via* an intramolecular $S_{RN}1$ reaction followed by *in situ* stilbene photocyclization. Methylation by the procedure of Weinreb gave the natural product.

Eupolauramine was isolated from *Eupomatia laurina* in 1972 by Taylor and coworkers.[1] Its structure was shown by X-ray crystallography to be that depicted by **1**,[2,3] thus identifying it as an unusual *azaphenanthrene* type alkaloid bearing a structural similarity to the aristolactams.[4] Since that time, no less than six syntheses of the molecule have appeared in print, making it a popular proving ground for new synthetic methodology.[5] Herein, we wish to report our work in this area which has led to an extremely efficient synthesis of the natural product.

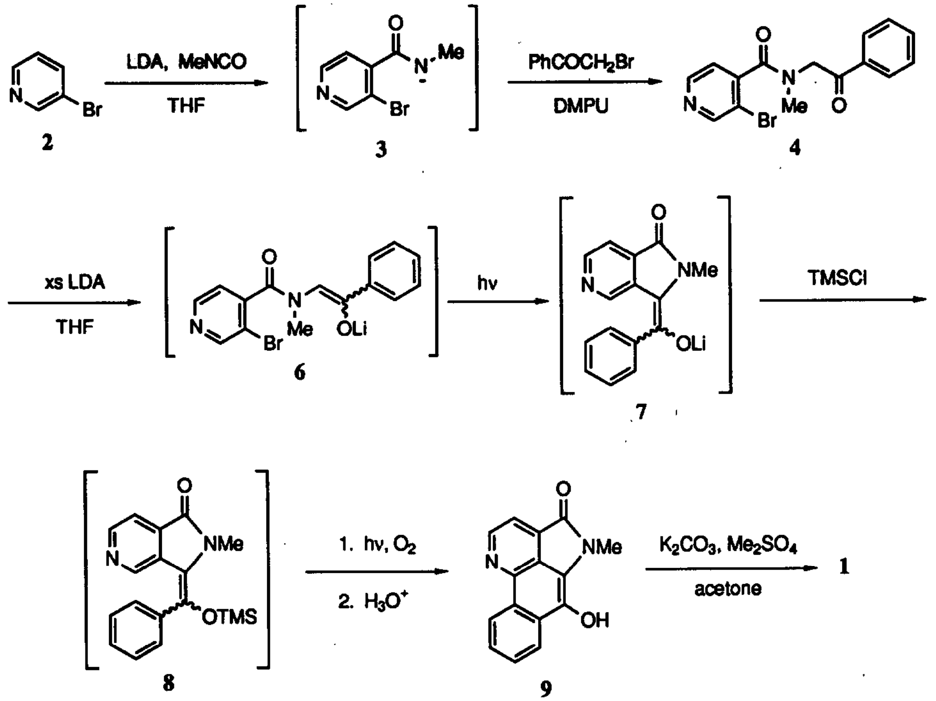
Scheme 1



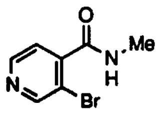
1
Eupolauramine

Our approach centered around our long-standing interest in photochemistry.[6] We reasoned that if the C_{5a}-C_{10c} bond could be formed (Scheme 1) *via* an intramolecular $S_{RN}1$ reaction,[7] such a product might be induced to undergo (perhaps in some protected form) a stilbene photocyclization[8] to afford the eupolauramine skeleton. *In actu*, ortho-metalation of 3-bromopyridine (**2**) according to the procedure of Gribble[9] afforded the 4-lithio- species that when reacted with methyl isocyanate gave, *in situ*, anion **3** (Scheme 2). When **3** was quenched with phenacyl bromide in the presence of dimethylpropyleneurea (DMPU) a 68% yield of **4** was obtained, along with 7% of **5**.[10] Thus in a single step we were able to prepare a substrate containing all but one of the carbons necessary for eupolauramine.

Scheme 2



The second step in the synthesis proved to be far more problematic than we had anticipated. Initially, we found that irradiation[11] of a THF solution of the lithium anion 6,[6a,b] either at 0°C or room temperature, gave only trace amounts (≤5% by HPLC) of the cyclized product, **10**.[12] Ultimately, it was determined that the reaction was *extremely* sensitive to traces of oxygen and other species capable of interrupting the radical-chain process. Thus, when the reaction was repeated at 0°C, under a "scrubbed" argon atmosphere,[13] with reagents and solvents that were purified[14] *immediately* before use, an 87% yield of $S_{RN}1$ product **10** was realized along with 4% of dehalogenated **11**.[15] We saw no trace of *O*-demethyleupolauramine (**9**) which could have arisen from an anionic stilbene photocyclization of anion **7**. However, when the reaction was repeated and anion **7** was reacted with an excess of trimethylsilyl chloride (TMSCl), *O*-silylated species **8** was formed *in situ* and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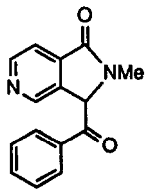
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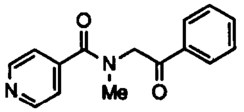
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suffered cyclization under oxidative conditions (hv, O_2) to afford, after an acidic workup, *O*-demethyleupolauramine (**9**) in 70% yield from **4**.[16, 17] This material proved to be spectroscopically identical to that reported by Weinreb.[5a] Finally, *O*-methylation by a slight variation of Weinreb's procedure completed the synthesis to give eupolauramine (**1**) in 80% yield from **9**.

In summary, we have completed a short, photochemical-based synthesis of eupolauramine. This synthesis is one of a very few examples of an intramolecular $S_{RN}1$ reaction, and, to our knowledge, is only the *second* application of such a reaction to the synthesis of a natural product.[18]

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* Present Address: Nova Pharmaceutical Corporation, 6200 Freeport Centre, Baltimore, MD 21224.

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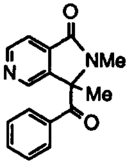
10. Compound **5** could be converted to **4** (NaH, THF, DMPU, phenacyl bromide) in 87% yield, raising the yield of **4** from 3-bromopyridine (**2**) to 74%, after this one recycle.
11. Irradiation was accomplished with a Hanovia 450-W high-pressure Hg-vapor lamp.
12. When this reaction (0°C) was performed in the dark, a comparably poor yield of **10** was obtained. This suggests that a small amount of benzyne mechanism may be operating. For an aryne approach to the aristolactams, see: Estévez, J.C.; Estévez, R.J.; Guitián, E.; Villaverde, M.C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785, and references cited therein.
13. The argon was "scrubbed" by passage through a solution of sodium-benzophenone ketyl in THF.
14. Liquids were distilled under a "scrubbed" argon atmosphere. Diisopropylamine (DIA) was distilled from CaH_2. THF was distilled from sodium-benzophenone ketyl directly into the reaction vessel. Compound **4** was recrystallized from EtOAc/hexanes (*ca* 1:3) and dried *in vacuo* (< 1mm) for 1h.
15. The radical-chain nature of this "successful" reaction was confirmed by its inhibition by a catalytic amount of di-tert-butyl nitroxide.
16. Compounds **10** and **11** were also isolated in 11% and 5% yields, respectively.
17. Attempts to prepare eupolauramine directly by *O*-methylation of anion **7**, gave what we have tentatively identified as the *C*-methylated product, **i**.



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18. For a synthesis of cephalotaxine *via* an intramolecular $S_{RN}1$ reaction, see: Semmelhack, M.F.; Chong, B.P.; Stauffer, R.D.; Rogerson, T.D.; Chong, A.; Jones, L.D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.

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