Pergamon

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An Expedient Synthesis of *epi*-Eburnamenine via an Intramolecular 1,4-Dipolar Cycloaddition Reaction

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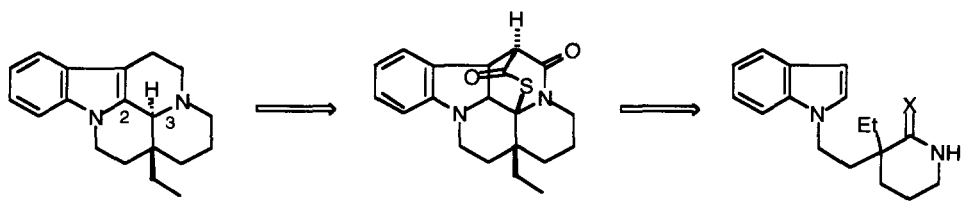
Abstract: The intramolecular 1,4-dipolar cycloaddition of an anhydro-4-hydroxy-2-oxo-1,3-thiazium hydroxide across a tethered indole π-bond has been used for the construction of the pentacyclic skeleton of *epi*-16,17-dihydroeburnamenine.

The pentacyclic skeleton common to the eburnamenine alkaloids is widely represented in various plant families and provides a challenging target for synthesis.[1,2] The great majority of the published syntheses construct the C_2-C_3 carbon carbon bond *via* either a Pictet-Spengler or a Bischler-Napieralski cyclization.[3] In conjunction with our continuing interest in stereocontrolled approaches to complex aza polycyclic ring systems,[4,5] we have developed a fundamentally different approach to the construction of the pentacyclic skeleton of *epi*-eburnamenine which is based on an intramolecular 1,4-dipolar cycloaddition of an anhydro-4-hydroxy-2-oxo-1,3-thiazium hydroxide across a tethered indole π-bond.

Our strategy is shown in antithetic format in Scheme I and is centered on the construction of the key cycloadduct **2**. We reasoned that *epi*-16,17-dihydroeburnamenine (**1**)[6] should be accessible from **2**, which, by analogy with our previous work, should be available by an intramolecular 1,4-dipolar cycloaddition of thiazinium betaine **6** (*vide infra*). Cycloaddition of betaine **6** across the pendant indole π-system would be expected to lead to the pentacyclic skeleton found in **1**. In this communication we describe our initial experiments that verify the underlying viability of this approach to the eburnamenine family of alkaloids.

Scheme I

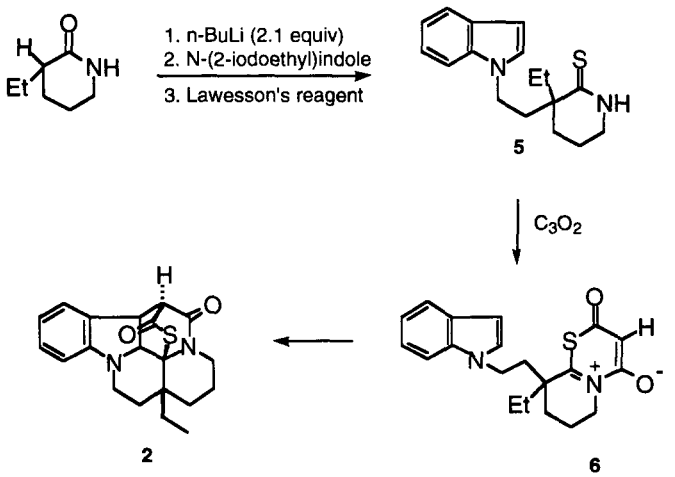


1; *epi*-16,17-dihydroeburnamenine

2

3; X=O
5; X=S

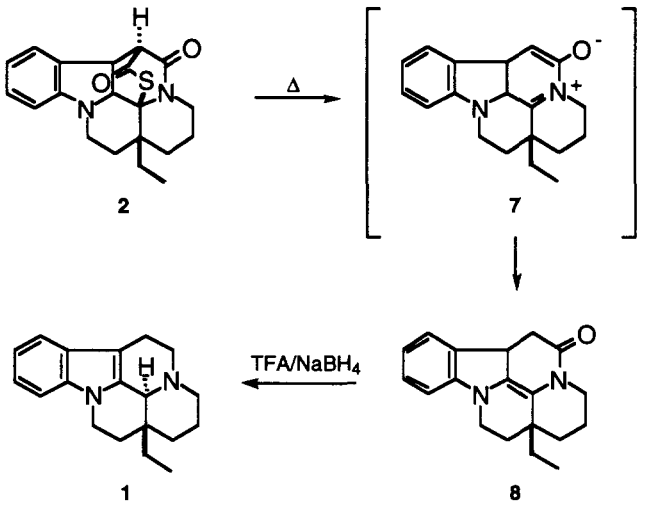
The synthesis of cycloadduct **2** commences with the easily available lactam **3**. Treatment of 3-ethyl-2-piperidone (**4**)[7] in THF with 2.1 equiv of n-butyllithium at 0°C followed by the addition of N-(2-iodoethyl)indole[8] afforded **3** in 80% overall yield. In this case, reaction of the amide dianion proceeded smoothly with no need for any additional cosolvents (*i.e.*, HMPA, DMPA) which are often necessary in order to facilitate C-alkylation.[9] The resultant 3,3-disubstituted lactam **3** was converted into the corresponding thiolactam **5** by sulfuration with Lawesson's reagent.[10] Generation of the bright yellow betaine **6** as a transient intermediate was accomplished by the reaction of **5** with carbon suboxide[11] at 25°C for 12 h which afforded the desired 1,4-dipolar cycloadduct **2** as a single diastereomer in 95% yield.



2 **5** **6**

It should be noted that indoles generally participate in cycloaddition chemistry as $4_\pi s$ components[12] and very few examples exist where this heteroaromatic ring has been utilized as a dipolarophile.[13] The conversion of **6→2** represents one of those rare examples in the literature involving dipolar cycloaddition across an indolyl π-bond and opens up this approach as a potentially general strategy for the synthesis of a variety of indolyl alkaloids.

Efforts were next focused on the conversion of cycloadduct **2** to *epi*-16,17-dihydroeburnameine **1**. Heating a sample of **2** neat at 210°C for 10 min resulted in the facile loss of COS[14] and the concomitant formation of the pentacyclic enamide **8** in quantitative yield. This reaction presumably involves the initial formation of 1,4-dipole **7** which undergoes a subsequent proton shift to generate **8**. Reduction of **8** using an excess of trifluoroacetic acid/$NaBH_4$ in refluxing dioxane[15] for 8 h afforded **1** in 90% yield. The stereochemistry of the ring junction was confirmed by single X-ray crystallography.[16] A likely scenario



for the one-pot reduction of **8→1** involves protonation of the enamide, aromatization to generate the indole followed by amide reduction. The *trans*-stereochemistry can be rationalized as being the consequence of a steric effect of the angular ethyl group which directs protonation to the less hindered face of the molecule.[2]

In conclusion, the successful preparation of *epi*-16,17-dihydroeburnamenine *via* an intramolecular 1,4-dipolar cycloaddition of a thiazinium betaine establishes the merit of our method as outlined in Scheme I. Further work to extend this strategy toward other indole alkaloids is in progress and the results of these investigations will be reported in due course.

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