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Pyridine-3,4-dicarboximide as starting material for the total synthesis of the natural product eupolauramine and its isomer *iso*-eupolauramine endowed with *anti*-tubercular activities

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ABSTRACT

A direct and convenient synthetic pathway for preparation of the key intermediate aza-isoindolinone **4a**/**4b**, which could be ready obtained from pyridine-3,4-dicarboximide was described. This approach was valorized in the total synthesis of the natural product eupolauramine **7b** and in the first synthesis of the position analog *iso*-eupolauramine **7a**, which was obtained after 6 steps in an overall yield of 13%. The developed strategy represents the first synthetic approach employing a starting material already embedding the pyridine and the lactam cycles (cycles D and C, respectively) of the azaphenanthrene lactam framework. These compounds, mainly the new non-natural product, showed a good inhibitory activity against *Mycobacterium tuberculosis* growth.

1. Introduction

Eupolauramine (Fig. 1), an unusual azaphenanthrene alkaloid, was first isolated in 1972 by Bowden et al.[1] from the bark of an Australian tree named *Eupomatia laurina*. Its chemical structure was first elucidated by X-ray crystallography (1976)[2] because only small amounts of this compound were available, preventing chemical or spectral experiments. Recently (2011), eupolauramine was also isolated from the bark of the Brazilian *Anaxagorea dolichocarpa* and exhibited in vitro antitumor properties (K562 leukemic cells: $IC_{50} \sim 70$ μM).[3]

The first total synthesis of eupolauramine was reported by Levin *et al*[4] only eleven years after its discovery, in which a hetero Diels–Alder approach was employed to construct the pyridine ring. The original structure of this compound, its rare natural occurrence and the little information about its potential biological activities have attracted continuous synthetic efforts contributing to the report of eight total and three formal syntheses. Including all disclosed routes, many different approaches could be identified with regard to the order of construction of the four cycles of the azaphenanthrene lactam core: *i*) starting from naphthalene derivatives corresponding to the rings *A* and *B* of the natural product eupolauramine[5] ii) starting from simple phenyl derivatives (cycle *A*) followed by the subsequent formation of rings D, B and C[4,6] *iii*) employing pyridine compounds (cycle *D*) as starting materials followed by the introduction of ring A, then preparation of the lactam ring and finally formation of cycle[7] or followed by creation of the azaphenanthrene framework and then lactam formation,[8] *iv*) starting from pyrrole-2-carboxylate via the benz[*f*]indole moiety (A-B-C rings).[9] It is interesting to note that among all the routes reported in the literature, none employed, as starting material, a structure already embedding the lactam ring (cycle *C*) as a preformed cycle. In most of the approaches, the lactam ring formation occurs in the final steps of the synthesis.

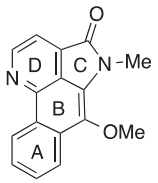

Fig. 1. Structure of the natural product Eupolauramine.

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One of the most recent synthesis of eupolauramine, disclosed by Hoarau et al.,[10] explored an interesting approach in which the aza-isoindolinone **4b** (*Z*=I) is employed as a key intermediate, starting from the 3-chloro-4-pyridinecarboxylic acid (Scheme 1). However, in the first two steps of the synthesis of **4b**, the loss of atoms is very extensive, leading to a non atom-economic synthesis of eupolauramine uniquely.

Based on our longstanding experiences in the synthesis of aza-isoindolinones as antitubercular agents[11] from pyridine-3,4-dicarboximide (**1**), we describe herein a convenient approach for the synthesis of the natural product eupolauramine and its non-precedent isomer *iso*-eupolauramine, employing for the first time a starting material embedding the 'lactam ring' as a preformed cycle (Scheme 1). The antitubercular activities of eupolauramine and *iso*-eupolauramine were also evaluated towards inhibition of *Mycobacterium tuberculosis* growth.

2. Results and discussion

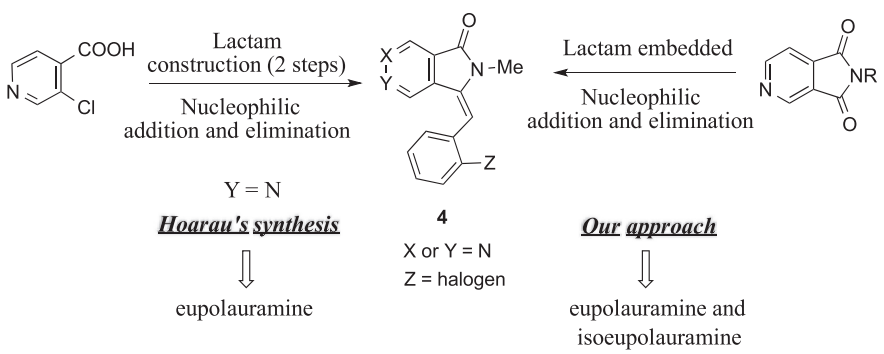
The first step of the synthesis of (*iso*)-eupolauramine consisted in the N-methylation of pyridine-3,4-dicarboximide (**1**), which was treated with MeI and K_2CO_3 in acetone at 50 °C to afford **2** with a good chemoselectivity, methylation in favor of the imide nitrogen rather than the pyridine nitrogen, and in a good yield (75%) (Scheme 2).

The conversion of **2** into **3** was achieved by metal mediated addition reaction. When 2-bromobenzylmagnesium bromide was reacted with **2** under argon at −78 °C, a mixture of **3a** and **3b** (2:1, respectively) was formed in 70% yield. Indeed, the addition of the nucleophilic organometallic agent occurs upon *para*[12] or *meta*-carbonyl group but never to both carbonyl groups simultaneously. These compounds were purified and separated by flash column chromatography. The prompt formation of the two regioisomers, in the course of this step, offers a new possibility of synthesis for the natural product eupolauramine (**7b**) and for its novel position analog *iso*-eupolauramine (**7a**): whereas the *meta* compound (**3b**) leads to eupolauramine synthesis, the *para* isomer (**3a**) is used to prepare *iso*-eupolauramine. Interestingly, this step allows the introduction of all carbons necessary to the (*iso*)eupolauramine framework.

To further explore the reaction selectivity, we also examined the reaction of **2** with other organometallic reagents (Table 1). When 2-bromobenzylzinc bromide was employed at 0 °C to react with **2**, the selectivity in favor of the *para* compound was better than with the Grignard's reagent and can even be improved when the same reaction was performed at −40 °C (Table 1). This result is not so evident however, it could be attributed to a stronger coordination of Zn^{2+} to the most soft oxygen carbonyl when compared to Mg^{2+}, facilitating a 6-membered intermediate state formation and hence a nucleophic attack upon the other carbonyl group.[13] Attempts to use an organosamarium derivative led to a very poor conversion yield.

To achieve the key intermediate **5** from **3** two strategies are possible: i) cyclisation followed by elimination or ii) elimination then cyclisation. The advantage of the first strategy is that only one dehydrated product is formed whereas two geometric isomers *Z*/*E* can be generated in the second one. Cyclisation attempts of **3a** (X=CH, Y=N, Z=Br) by action of tributyltin hydride (*n*-Bu_3SnH) in the presence of 2,2′-azobisisobutyronitrile (AIBN) were not successful. In contrast, treatment of **3** with methanesulfonylchloride (MsCl) in the presence of TEA in CH_2Cl_2 at room temperature afforded directly the dehydrated compound **4** as a mixture of two non-separable (*E*/*Z*) isomers, but with a good diastereoselectivity in favor of the *E*-isomer (in a 85:15 ratio) as deduced from ^{1}H NMR analysis of the crude mixture (based on the integration of the ethylenic protons at 6.68 ppm (*E*) and 6.89 ppm (*Z*) for **4a** and at 6.59 ppm (*E*) and 6.85 ppm (*Z*) for **4b**). Then **4** was submitted to radical cyclization conditions by the use of *n*-Bu_3SnH, in the presence of a stoichiometric amount of AIBN in toluene. In this reaction only the (*E*)-**4** compound underwent the oxidative radical cyclization, furnishing the desired fused azaphenanthrene lactam framework with a satisfactory yield. The remaining (*Z*)-**4** compound was then readily eliminated by flash column chromatography in this step. The next regioselective bromination of **5** allowed functionalization to further introduce the methoxy group present in the *iso*-eupolauramine skeleton. Treatment of **5b** with Br_2 and sodium acetate in $CHCl_3$ led indeed to the 6-bromo azaphenanthrene lactam **6b**[10] in 88% yield. The bromination of **5a** in the same conditions but with a large excess of bromine also allowed the selective introduction of the bromine atom at the 5-position (compound **6a**), as could be evidenced by the disappearance of the singlet at 7.25 ppm in the ^{1}H NMR spectrum. Final substitution of the bromine by a methoxy group (conversion of **6b** into **7b**) was first studied by using the Hoarau's method.[10] This methodology is based on halogen-metal exchange between **6b** and PhLi, followed by a reaction with bis-(trimethylsilyl)peroxide $(Me_3SiO)_2$ as an electrophile to form the phenolic hydroxyl. Then reaction of the phenol with dimethyl sulfate lead to the expected compound **7b** (eupolauramine).

However, when Hoarau's method was tried upon **6a**, this step proved to be much more challenging than we had expected and we were not able to get **7a**. Moreover, all attempts to use *t*-BuLi in the place of PhLi to achieve **7a** also failed. In both cases, only the products resulting from dehalogenation or direct substitution of Br by the phenyl or *t*-butyl group were isolated. Taking into account that the by-products formed in this step arise from a nucleophilic attack upon **6a** where the halogen at C5 serve as a leaving group, we tried a more classic method, i.e. nucleophilic aromatic reaction, to



Scheme 1. Synthetic approaches for the synthesis of compound **4**.

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