New Aza-pterocarpan Analogues by Intramolecular 1,3-Dipolar Cycloaddition in *in situ* generated nitroneolefins

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INTRODUCTION

As part of a program aiming the synthesis of new compounds with anticancer and antiparasitic action, we recently synthesized aza-pterocarpans such as **1** and **2** (Figure 1).[1,2] Compound **1** showed significant activity against cancer cell lines and Leshimania.[1] In order to have more information on the structure-activity relationship in this new class of prototypes, we decided to prepare compounds type **3**.

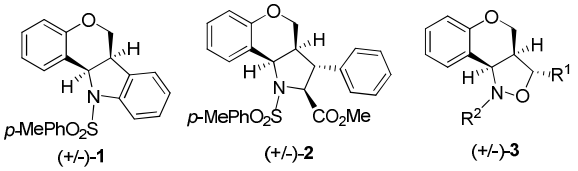
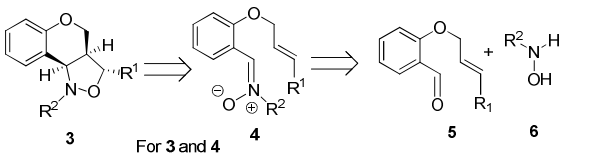


Figure 1. Aza-pterocarpan **1** and analogs (**2** and **3**).

In this communication we describe the stereoselective synthesis of these analogues *via* intramolecular 1.3-dipolar cycloaddition (1,3DCI) in nitrones (**4**) prepared from salicylaldehyde derivatives (**5**) and hydroxiamines (**6**). These precursors can be prepared and isolated or, more conveniently, generated *in situ*.



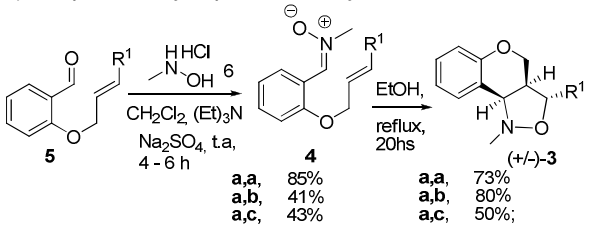
a,**a**; R^1=H, R^2=Me
a,**b**; R^1=CO_2Me, R^2=Me
a,**c**; R^1=Ph, R^2=Me
b,**a**; R^1=H, R^2=Bn
b,**b**; R^1=CO_2Me, R^{32}=Bn
b,**c**; R^1=Ph, R^2=Bn
a; R^1=H
b; R^1=CO_2Me
c; R^1=Ph
a; R^2=Me
b; R^2=Bn

Scheme 1. Retrosynthesis for **3** through [3+2] intramolecular in nitroneolefins.

RESULTS AND DISCUSSION

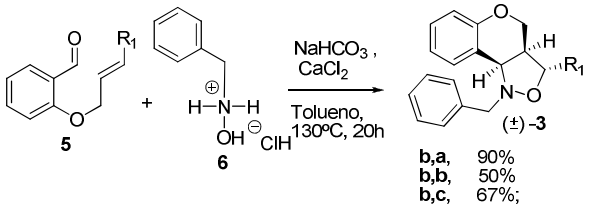
Our first results are shown in Scheme 2 involving the use of *N*-methyl hydroxylamine **6a** as source of nitrones.

N-methyl nitrones (**4a**,**a** to **4a**,**c**) were synthesized for testing the stepwise intramolecular cycloaddition (Scheme 2). These cyclo-additions were accomplished in ethanol over reflux,[3] leading to the stereoselective formation of **3a**,**a** to **3a**,**c** (Scheme 2), as previously reported the synthesis of **3a**,**a**.[4]



Scheme 2. Synthesis of **3a,a** to **3a-c.**

Our next step was the reaction with benzylhydroxylamine (**6b**),[4] Our interest was focused on the possibility of subsequent removal of the benzyl group by hydrogenolysis, allowing the preparation of nitrones not substituted at the *N* atom for subsequent functionalizion. In this case, the nitrones were generated *in situ*[4], leading stereoselectively to the target molecules in reasonable to good yields (Scheme 3).



Scheme 3. Synthesis of **3b**,a to **3b-c**.

CONCLUSION

The one pot stereoselective synthesis of *N*-benzyl isoxazolidines **3b**,**a** to **3b**,**c** could be accomplished in reasonable to good yields. Efforts for the removal of the *N*-benzyl group are underway.

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