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1,3-Dipolar Cycloaddition Approach towards the Stereoselective Preparation of Aza-Cephalotaxine Skeleton

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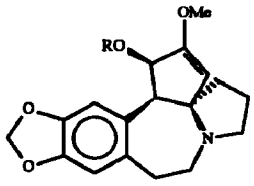
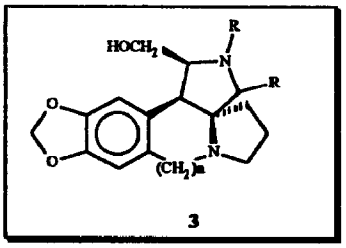
Abstract: The aza-analogue of cephalotaxine skeleton has been prepared by series of reactions which include a 1,3-dipolar cycloaddition in 100 % diastereoselectivity.

Esters of natural cephalotaxine **1**, such as antitumor alkaloid harringtonine **2** produced by *Cephalotaxus* species[1], have been the target of much synthetic interest not only due to their potential anticancer chemotherapeutic properties[2] but also because of their structural complexity. Various approaches have been devised for the skeletal construction of **1**, including six total syntheses, the most recent by Ikeda *et al.*[3] In addition considerable effort has been made to synthesize a variety of structural analogues of cephalotaxine[4].



1 R=H

2 R= COC(OH)(CH$_2$)$_2$C(OH)(CH$_3$)$_2$
CH$_2$CO$_2$CH$_3$

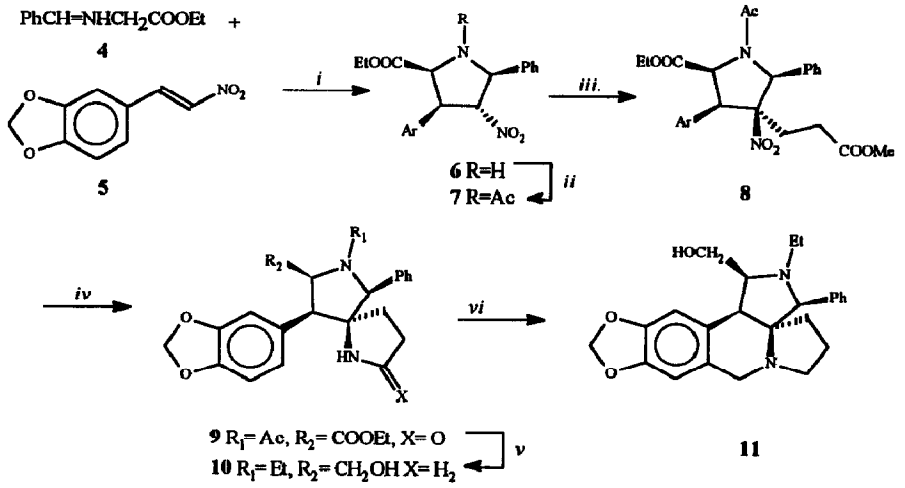


3

We wish to report our findings towards the synthesis of aza-analogues **3** of the cephalotaxine skeleton containing the requisite stereochemistry at the spiro-centre and suitable functionalities to allow introduction of aliphatic ester side chains.

Our synthetic plan was based on the stereoselective formation of the appropriate nitro-pyrrolidine by 1,3-dipolar cycloaddition, which can be converted by known methods[3,4] to the entirely new aza-cephalotaxin skeleton.

The 1,3-dipolar cycloaddition of imine **4** with nitrostyrene **5** under the conditions reported by Grigg et al.[5], in the presence of AgOAc, gave the cycloadduct **6**. Reaction of its N-acetyl derivative **7** with ethyl acrylate resulted in formation of Michael adduct **8** as a single isomer which, in a reductive cyclization process, gave exclusively the key compound **9** with the correct stereochemistry at the spiro-centre. It is important to note that the diastereoselectivity of this step was lost and an unseparable mixture of isomers was obtained if the N-methyl cycloadduct was used instead of the N-acetyl compound.



i. AgOAc, Et_3N, CH_3CN, r.t.(42 %) ii. Ac_2O, pyridine(96 %) iii. CH_2=$CHCO_2Me$, CH_3CN, Triton B, r.t. (65 %) iv. Zn, HCl, EtOH (92 %) v. $LiAlH_4$, THF reflux 3 days (98 %) vi. CH_2O ,HCl (76 %);

Compound **9** was reduced with $LiAlH_4$ to pyrrolidine **10**, which was cyclized under Pictet-Spengler conditions with aqueous formaldehyde to the corresponding isoquinoline analogue **11.** The overall yield of **11** from **5** is 18 % over the 6 steps. Further studies on preparing the seven membered ring analogues are in progress.

References and Notes

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6. All new products afforded correct elemental analysis and spectroscopic data.

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