A Synthetic Pathway To Medicinal Natural Products

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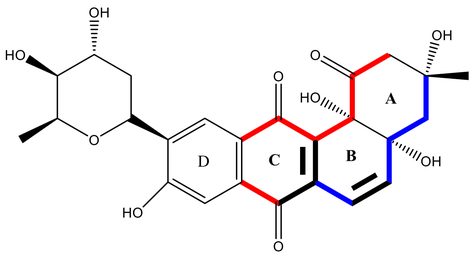
ABSTRACT

The Angucyclines constitute a large pool of natural products with a broad array of medicinal properties including antitumor and antibacterial properties. The most interesting ones such as Aquayamycin, with potential anti-HIV activity, constitutes a great synthetic challenge due to the presence of oxygen functionalities at the BC ring junction. Success in the installation of the Hydroxyl groups of the ring junction would pave the way for the synthesis of various members of the class. We have developed a concise and efficient approach to the construction of the oxygenated core of the natural products. Our synthetic approach focuses on the coupling a suitably substituted Phthalide and an activated Alkyne through a tandem Michael addition/Dieckmann cyclization. We describe the successful implementation of our synthetic strategy to generate the ABC ring system of the oxygenated natural products.

INTRODUCTION

The medicinal properties of Angucyclines stem, in part, from their unique angular unsymmetrical tetracyclic skeleton. The synthesis of the aquayamycin-type angucyclines poses considerable challenges thus limiting medicinal studies which might lead to novel therapeutics. Aquayamycin's aglycone consists in a four-ring aromatic (ABCD) system with an angular arrangement of the sensitive ABC ring.



Aquayamycn Structure

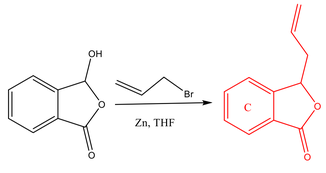
The difficulty in synthesizing Aquayamycin lies in its stereochemically complex ring system. Total syntheses have been reported which, however involve lengthy and complex reaction sequences.[3] . Here we report a concise and effective synthesis of the ABC ring framework with concomitant introduction of the oxygens and functionalities which allow for the completion of ring A

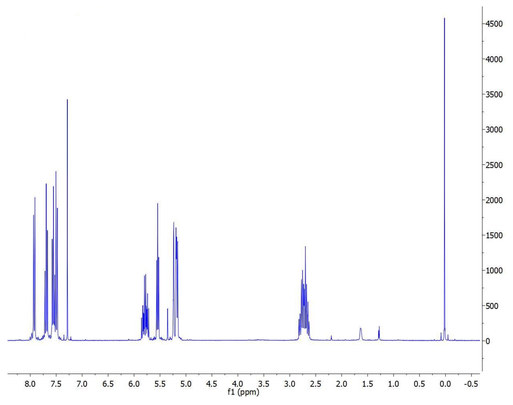
Aim: Establishing an efficient chemical synthesis approach to the construction of the ABC ring system of the oxygenated natural products.

METHODS and RESULTS (1)

Synthesis of Allyl Phthalide – Precursor of C ring- from Allyl Bromide and 2-Carboxybenzaldehyde

- The known allyl phthalide precursor of rings B and C was obtained in one step from the allylation of caboxybenzaldehyde.



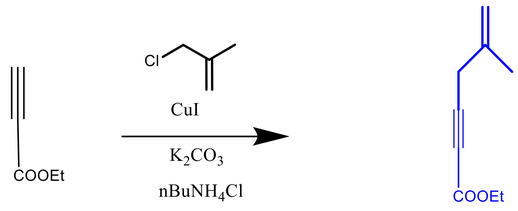


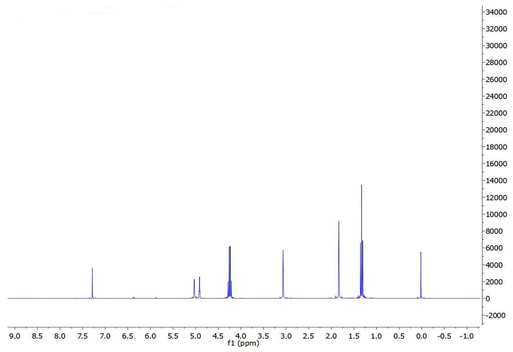
^{1}H NMR of Allyl Phthalide

Synthesis of Ethyl- 5-methylhex-5-en-2-ynoate.

Precursor of B ring

- The require ynoate was synthesized in one step from the copper-mediated coupling of ethylpropiolate with methallyl chloride



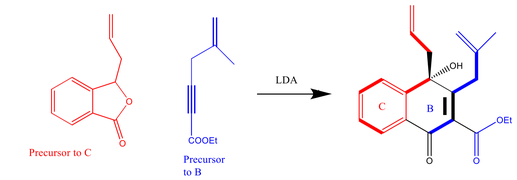


^{1}H NMR of Ynoate

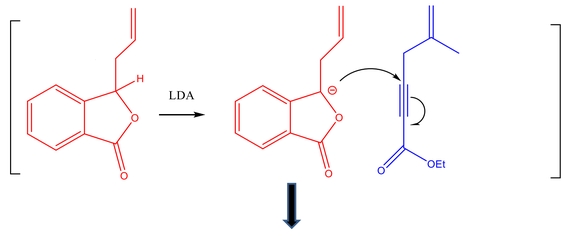
METHODS and RESULTS (2)

Coupling of Allyl Phthalide and Ethyl 5-methylhex-5-en-2-ynoate.

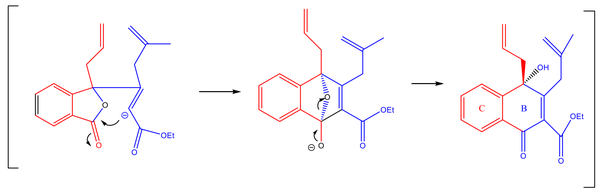
- The Allyl phthalide and ynoate underwent a smooth tandem Michael5-Dieckman coupling upon deprotonation of the phthalide with lithium diisopropylamide (LDA).



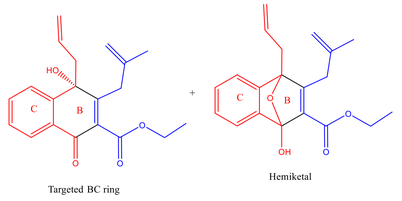
Deprotonation followed by Michael Addition



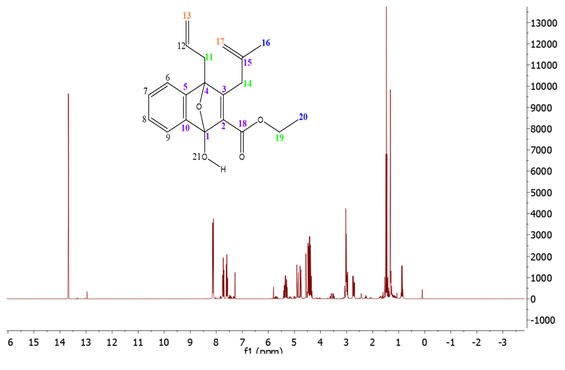
Dieckmann Condensation



The expected BC ring was accompanied by the corresponding hemiketal.

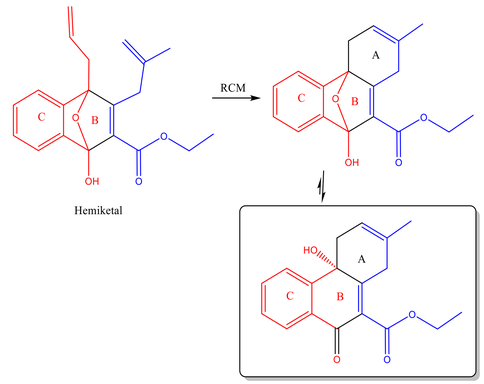


Targeted BC ring Hemiketal



NMR of the target BC ring as the hemiketal tautomer

Preliminary experiments using the hemiketal indicate that the ring-closing metathesis reaction has proceeded according to our projection and resulted in the synthesis of the ABC ring system of the angucyclines.



Hemiketal

CONCLUSION

We have achieved a remarkably concise and efficient four-step approach to the synthesis of the ABC ring of the medicinally relevant angucyclines. The devised route establishes the carbon framework as well as functionalities amenable to further modifications and paves the way for future medicinal studies.

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