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Synthesis of a Model of the BC Ring System of Oxygenated Angucyclines

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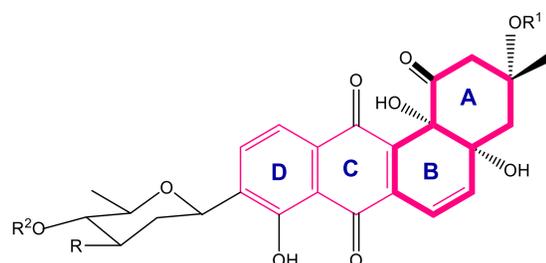


Abstract

Angucycline is a subclass of natural antibiotics, containing a characteristic tetracyclic ring structure, and featuring a wide range of biological functions, including antitumor, antiviral and antifungal properties. This extraordinarily therapeutic character has interested many chemists to develop efficient methodologies for synthesizing the tetracyclic ring system of angucycline. Construction of the BC ring configuration appears as a synthetic challenge. Successful installation of hydroxyl groups at the AB junction would pave the way for efficient syntheses. As a continuation of the previous work done on this system, our synthetic methodology focuses on the coupling of a suitably substituted Phthalide and an activated Alkyne through a tandem Michael addition/Dieckmann cyclization. The synthesis of the required phthalide and alkyne components is discussed, as well as our efforts towards the coupling components.

Introduction

As a third class of natural antibiotic, angucyclines have received much attention in recent years¹. Angucyclines contains a carbotetracyclic (ABCD ring) skeleton, which significantly contributes to a broad array of medicinal properties, such as the antitumor activity of Vineomycin¹.



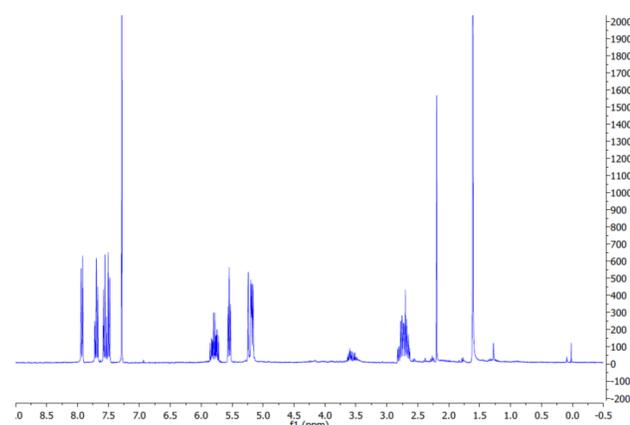
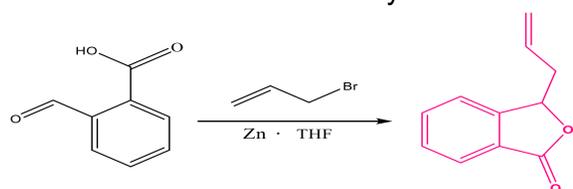
Vineomycin Structure

However, the construction of BC ring structure is still a major synthetic difficulty toward the synthesis of angucyclines. Other studies have developed methodologies in synthesizing the ring structure angucyclines, but involved many complex reagents and reaction steps³. Here we present our concise approach to construct the BC ring system.

Method and Result

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

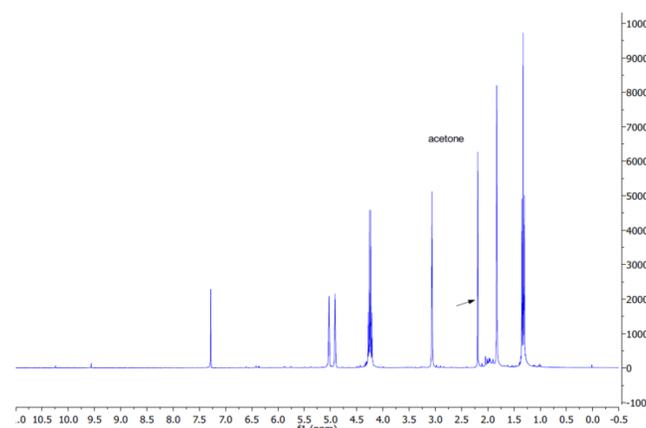
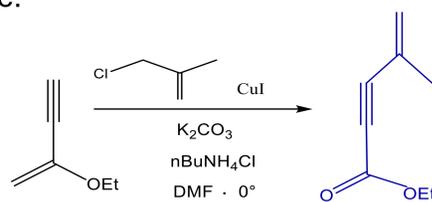
The synthesis of allyl phthalide was achieved by an allylation of 2-carboxybenzaldehyde with allyl Bromide⁴. In this approach, 478 grams of zinc was suspended in 60 mL of THF solution under N₂ gas followed by the addition of 8.1 mL of allyl bromide. Then, 4.602 g of 2-carboxybenzaldehyde suspended in 60 mL of THF solution was added to the reaction mixture⁵. The reaction was allowed to proceed at room temperature for 2hr and 50 min. The reaction was quenched with 25 mL of water and extracted 3x with 20 mL of diethyl ether.



¹H NMR Spectrum of Allyl Phthalide

Precursor of B ring: Synthesis of Ethyl-5-methylhex-5-en-2-ynoate

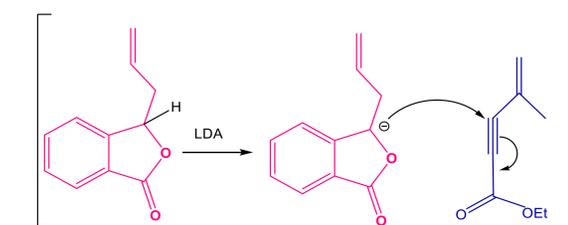
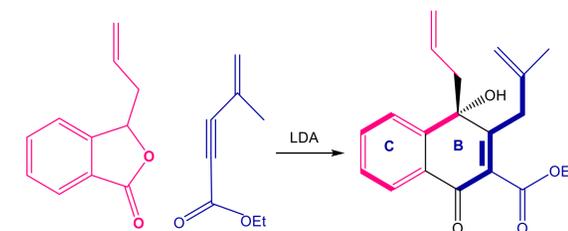
Our approach involves the allylic substitution of an alkyl halide by an acetylenic nucleophile⁶. 9.1 mL of methyl chloride was dissolved in 100 mL of DMF solution followed by the addition of 0.9061 g copper iodide along with 19.077 g of potassium carbonate and 2.633 g of n-butyl ammonium chloride. After the solution was cooled to 0°C, the reaction mixture was extracted with diethyl ether. The organic extract was dried over sodium sulfate.



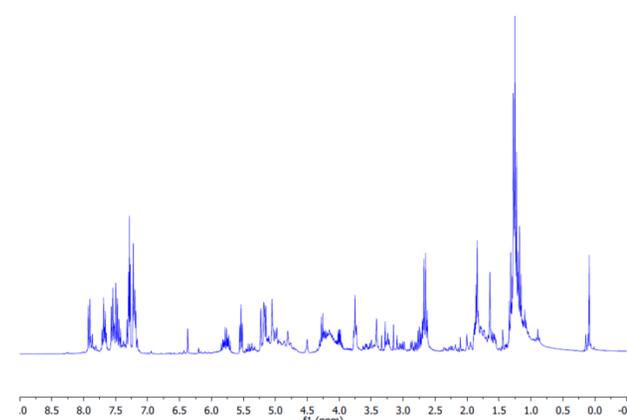
¹H NMR Spectrum of Ynoate

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

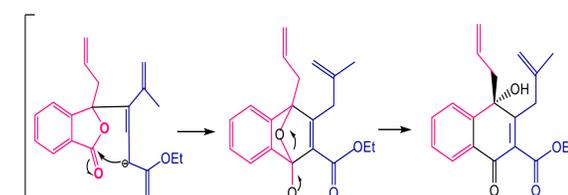
Elaboration of the coupling reaction was performed by Michael addition followed by Dieckmann condensation. Based on our synthetic methodology, a suspension of 1.46mmol of allyl phthalide in 3 mL of THF was prepared and further added into 1.76mmol of LDA solution under N₂ gas at -78°C. After stirring at -78°C for 15 minutes, the temperature was raised to -40°C. Then, 1.46mmol of Ethyl-5-methylhex-5-en-2-ynoate was introduced to the solution under -78°C. After stirring overnight, the reaction was quenched with ammonium chloride and extracted with diethyl ether. The resulting orange organic layer was dried over sodium sulfate.



Deprotonation followed Michael Addition



¹H NMR Spectrum of Crude Product



Dieckmann Condensation

Conclusion

In summary, we developed a concise synthetic approach of a model of the BC Ring system of oxygenated angucycline by employing a tandem Michael addition/Dieckmann cyclization as the key reaction. We successfully synthesized the allyl phthalide by allylation, and ynoate by allylic substitution. Additionally, the synthesis of ally phthalide and Ethyl-5-methylhex-5-en-2-ynoate has been partially accomplished. However, the construction of the BC ring system is a synthetic challenge. Future experiments will focus on establishing better coupling conditions for components, which will undergo Michael addition and Dieckmann condensation.

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Acknowledgements

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