Área: Org

Three one-pot subsequent reactions to achieve artemisinin analogues

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Highlights

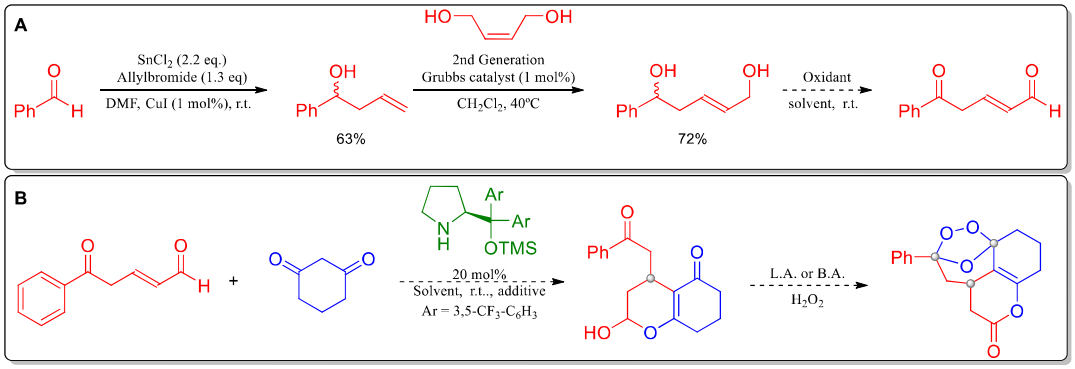
Organocatalysed synthesis of Artemiscinin analogues connecting three individual processes

Resumo/Abstract

Artemisinin (ART) was the first drug used against malaria. However, numerous strains of *Plasmodium falciparum* resistant to various drugs, including ART itself, were observed. This highlights the need for the discovery and development of new antimalarial drugs. In this context, there is precedent that the 1,2,4-trioxolane (ozonide) endoperoxide system exhibits good anti-malarial activity, as seen with arterolane and artefenomel, which have already been approved for clinical trials in some countries.

In this work, it is proposed that an analogue of ART containing the 1,2,4-trioxolanes can be synthetized in three subsequencial one-pot synthetic steps: **1 –** The oxidation of a 1,5-diol to the corresponding α,β-unsaturated dicarbonyl using oxidants that are in current optimization; **2 –** The asymmetric Michael addition with Jørgensen-Hayashi catalyst, followed by an cyclic hemiketal formation using 1,3-cyclohexadione and the α,β-unsaturated 1,5-dicarbonylic compound generated in the previous step[1]; **3 -**The third step consists in concomitantly performing the lactol oxidation providing the δ-lactone and converting the 1,5-dicarbonyl system to a 1,2,4-trioxolane (ozonide) using hydrogen peroxide and Lewis or Brønsted acid[2]. In each step, the reaction progress will be monitored via TLC using the appropriated revelation solutions. Due to the expected instability of intermediates only the ozonide generated in the third step, will be isolated by column chromatography and characterized with ^{1}H and ^{13}C NMR. To obtain the desired Michael acceptor, the sequence of reactions described in the first scheme was followed.

Besides, the three individual reactions are already well established, the present work aims to intertwine the transformations in a logical way that allows for the obtention of a biologically relevant product using inexpensive and easily synthesized precursors.



Scheme 1A - General methods to synthetize the desired Michael acceptor; **1B –** General proposal to synthetize the ART analogue.

References:

[1] Franke, P. T.; *et. al.* Chem. Eur. J. 2008, 14, 6317. [2] Gomes, G. P. *et. al.* Angew. Chem. Int. Ed. **2017**, *56*, 4955.

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