Total Synthesis of Four Stereoisomers of Acaterin through a Te/Li Exchange Protocol

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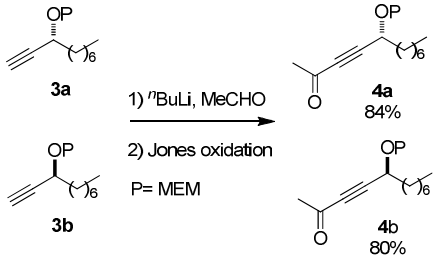
INTRODUCTION

Acaterin[1] **(1)** is an inhibitor of Acyl-coenzyme A cholesterol acyl transferase (ACAT). It was first isolated from a culture of *Pseudomonas sp*. This type of inhibitor has a promising role in the treatment of atherosclerosis. The butenolide skeleton with an α-alkyl chain, can be obtained from γ-butyl-telluro-allylic alcohols by Te/Li exchange reaction and capture with CO_2 according to a methodology recently established in our group.[2]

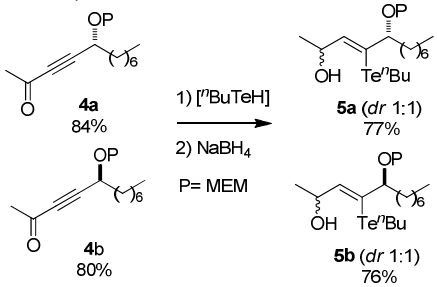
RESULTS AND DISCUSSION

Initially, the alkynones **4a** and **4b** were prepared from enantiopure OMEM-3-decinols **3a** and **3b**, respectively by deprotonation of the acetylene portion, addition to acetaldehyde and Jones oxidation of the intermediate alcohols (Scheme 1).



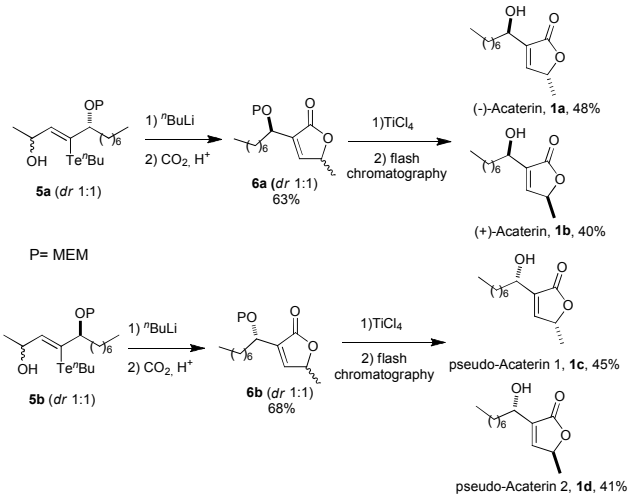
Scheme 1. Preparation of alkynones **4a** and **4b**.

The alkynones **4a** and **4b** were submitted to a hydrotelluration reaction and the products were reduced with $NaBH_4$, providing the diastereoisomeric mixtures (1:1) of γ-butyl-telluro-allyl alcohols **5a** and **5b** (Scheme 2).



Scheme 2. Preparation of organotellurides **5a** and **5b.**

The γ-butyl-telluro-allyl alcohols **5a** and **5b** were submitted to a Te/Li exchange reaction, generating a 1,4-C,O lithium dianionic intermediates, which on reaction with CO_2 and subsequent acid hydrolysis yielded the diastereoisomeric mixtures **6a** and **6b**. In the next step, the MEM group was removed[3], yielding the enantiopure forms of four stereoisomers of Acaterin after purification by flash chromatography (Scheme 3)



Scheme 3. Preparation of four stereoisomers of Acaterin (**1a-d**)

CONCLUSION

The four stereoisomers of Acaterin were prepared and isolated in a few synthetic steps, using a Te/Li exchange reaction as the key step.

ACKNOWLEDGEMENTS

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