First enantioselective total synthesis and configurational assignments of marine sesquiterpenes suberosanes as potential antitumor agents

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Introdução

Marine natural products are a rich source of innovative bioactive compounds, particularly in the filed of anticancer agents. In this context, we have undertaken the total synthesis of suberosanes, some of which, suberosanone and suberosenol A exhibiting a promising cytotoxic activity aganint solid tumor cell lines up to the picomolar level.[1] The first goal in this project was to determine the absolute configuration of these tricyclic sesquiterpenes and open a way to get reasonnable amount of material to implement biological studies. In this communication, we will describe the first asymmetric synthesis of natural suberosanone (**2**), suberosenol A (**3**) and its absolute configuration assignment.

Resultados e Discussão

Based on the first enantioselective synthesis[2] of suberosenone **1**[3] and suberosanone **2**[4], we have devised a concise asymmetric route to suberosenol A (**3**) for which several improvements of the synthesis were achieved. Key elements of the synthesis include hyperbaric asymmetric Michael addition to set up the C1 quaternary carbon center and the adjacent C8 bearing an axial methyl group, and a highly efficient silver trifluoroacetate mediated alpha-alkylation for the formation of ring A.

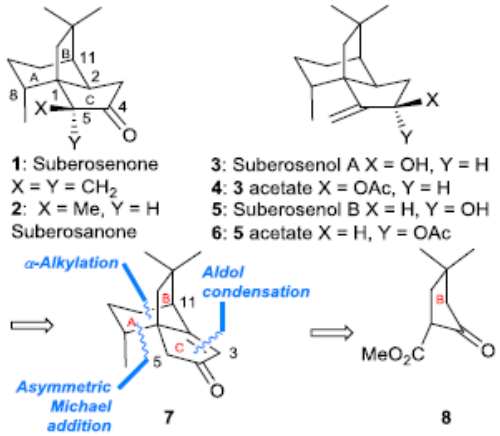

Figura 1. Retrosynthetic plan for suberosanes (**1**) to (**6**).

The common tricyclic intermediate to suberosanes **7** was obtained in 11 steps and 21.5%% overall yield from beta-ketoester **8**. Completion of the synthesis of suberosenone **1** was achieved through a three steps sequence according to Danishefski, although with a moderate 34% yield (Scheme 3).[5] Model studies were initiated to devise a short cut to the enol motive of **3** from suberosenone **1**. The results have been applied to the first asymmetric synthesis of *ent*-suberosenone **1** and suberosenol A **3**.

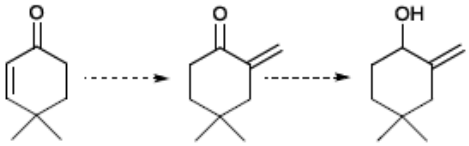

Figura 2. Model studies directed to an efficient synthesis of suberosenone (**1**) and suberosenol A (**3**).

Conclusões

We have succeeded in the first enantioselective synthesis of suberosenol A (**3**) in good overal yield and enantioselectivity, allowing the absolute configurationl assignment of the natural product. Interconverson of suberosanes (**1**), (**2**) and (**3**) will contribute to the study of these promising antitumor agents.

Agradecimentos

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