

Towards the Total Synthesis of Actinoranone: Unexpected Domino Retro Friedel-Crafts Acylation and Esterification.

Luiz F. T. Novaes¹ (PG), Julio C. Pastre^{1,*} (PQ).

*juliopastre@iqm.unicamp.br

1 - Universidade Estadual de Campinas (Unicamp), Lab I-224, Campinas-SP, Brazil

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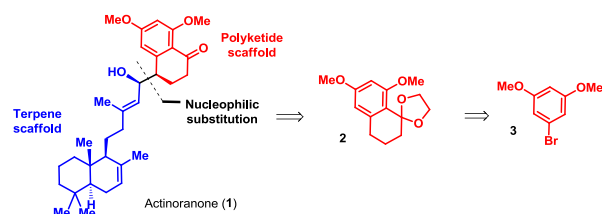
Abstract

We report herein an unprecedented domino retro Friedel Crafts (FC) acylation and esterification of electron-rich tetralones, an indanone and a benzo-suberone.

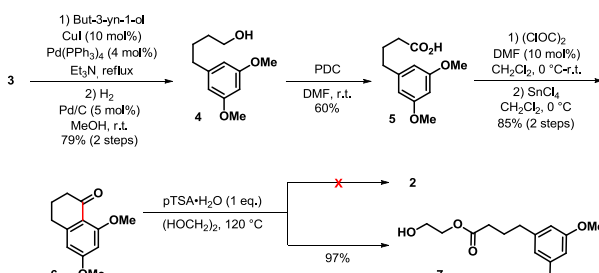
Introduction

Actinoranone (**1**) is a natural meroterpene with an unique scaffold, which displays cytotoxic activity.¹ This natural product was isolated from marine bacterium and there is no synthesis reported so far. In order to confirm the proposed structure of **1** and elucidate its stereochemistry, we designed a bioinspired retrosynthetic approach, which includes as a key fragment the ketal **2**. For our surprise, after a concise synthesis of tetralone **6** (5 steps, 40% overall yield), a conventional protocol to synthesize a dioxolane ring induced completely a domino retro FC acylation and esterification to furnish ester **8** in 97% yield, an unprecedented transformation.

A. Bioinspired disconnection



B. Synthesis of tetralone **6** and unexpected domino retro Friedel-Crafts acylation and esterification



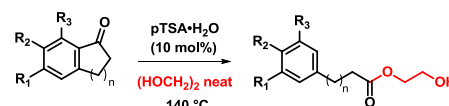
Scheme 1. Unexpected domino retro-FC acylation and esterification en route to actinoranone (**1**).

Results and Discussion

After this unexpected outcome, we decided to explore the synthetic potential of this domino reaction. Firstly, the degree of methoxylation was investigated and tetralones **8**, **10** and **12** were evaluated. Compounds **8** and **10** containing less electron-rich aromatic rings did not undergo the retro

FC reaction nor the ketalization. On the other hand, tetralone **12**, containing three methoxy groups, furnished the domino reaction product in 60% yield along 32% of the demethoxylated product **14**, which did not suffer the retro FC reaction. The size of the ring fused to the aromatic system was also evaluated: the bicycles containing a 5 and a 7 membered-ring (compounds **15** and **17**) were able to participate in a domino retro FC and esterification in high yields.

Table 1. Domino retro FC acylation and esterification.



Substrate ^a	Products	Yield ^b
8	9	N.R. ^c
10	11	N.R. ^c
6	7	99%
12	13 and 14	13 : 60% 14 : 32%
15	16	93%
17	18	89%

^aCompounds **8** and **10** were obtained from commercial source, and compounds **6**, **12**, **15** and **17** were synthesized in 4-5 steps. ^bIsolated yield. ^cNo reaction, recovery of starting material.

Conclusions

We observed a new domino reaction en route to the total synthesis of actinoranone (**1**), involving a retro FC acylation and esterification. This reaction was studied with different bicycles, and work is now in progress to evaluate different alcohols and other nucleophiles.

Acknowledgments

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¹ Fenical, W. *et al. Org. Lett.* **2013**, *15*, 5400.