Studies towards the synthesis of Aspergillitine, a unique tricyclic angular chromone from *Aspergillus versicolor*

Sebastian O. Simonetti, Enrique L. Larghi, Teodoro S. Kaufman*

Institute of Chemistry of Rosario (IQUIR, CONICET-UNR) and School of Biochemical and Pharmaceutical Sciences, National University of Rosario, Suipacha 531, S2002LRK, Rosario, Argentina

**Corresponding author*. E-mail: kaufman@iquir-conicet.gov.ar

Keywords: Aspergillitine, tricyclic angular chromone, natural product synthesis

INTRODUCTION

Aspergillus versicolor is a ubiquitous fungus. Recently, the group of Proksch studied a strain of *A. versicolor* from the marine sponge *Xestospongia exigua*,[1] isolating aspergillitine (**1**) and the aspergiones A-F (**2a-f**) as novel tricyclic angular chromones (Fig 1). Aspergillitine is unique because incorporation of a nitrogen atom in polyketides is rare, being known only few cases, such as bostricoydine (**3**). On the other side, it was demonstrated that the structures originally assigned to **2a** and **2b** correspond to **4a** and **4b**.[2] There is a distinct possibility that the structure of aspergillitine should be corrected and assigned to **5**. An unambiguous synthesis of **1** is thus required.

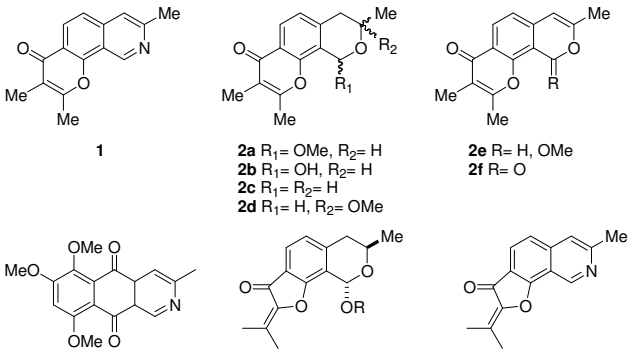
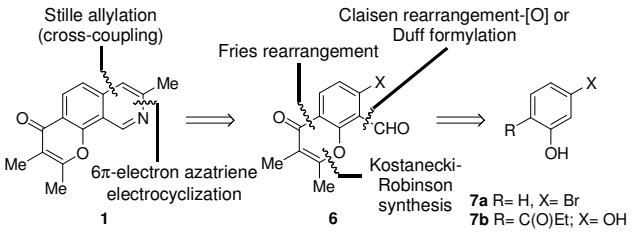


Figure 1. Chemical structures of aspergillitine (**1**), the aspergiones A-F (**2a-f**) and related natural products.

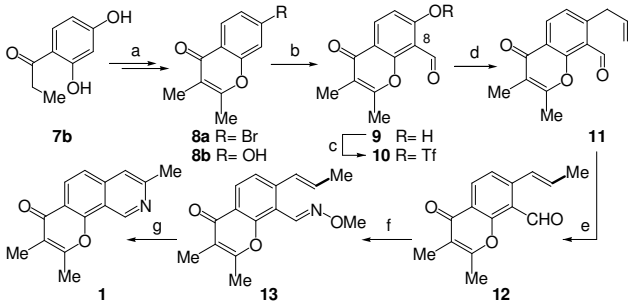
RESULTS AND DISCUSSION

The synthesis was based on the retrosynthetic analysis shown in Scheme 1.



Scheme 1. Retrosynthetic analysis of aspergillitine.

Although synthesis of the chromone intermediate **8a** could be performed from phenol **7a**, best results were achieved with **7b** (Scheme 2). This was submitted to a Kostanecki-Robinson synthesis and converted into 8-formylchromone **9** through the intermediacy of **8b**. Triflation of **9** and subsequent acetalization of **10** set the stage for a Stille allylation to **11**. Deprotection, double bond isomerization (**12**), followed by oxidation (**13**) and electrocyclization completed the synthetic sequence towards **1**.



Scheme 2. a) 1. Ac_2O, NaOAc, Δ; 2. Et_3N, Δ; 3. HCl dil. (Kostanecki-Robinson); b) 1. Urotropine, AcOH, Δ; 2. HCl (Duff formylation); c) *N*-phenyltriflimide, NaH, THF-DMF; d) 1. $HC(OMe)_3$, CSA, MeOH, 40 ºC; 2. PPh_3, LiCl, BHT, $Bu_3SnCH_2CH{=}CH_2$, $Pd(PPh_3)_2Cl_2$, DMF, Δ; 2. H^+ (work up); e) $Pd(PPh_3)_2Cl_2$, $CHCl_3$, reflux; f) $MeONH_2$.HCl, NaOAc, EtOH, reflux; h) 1,2-Cl_2-C_6H_4, MW.

CONCLUSION

We have performed a synthetic study towards the proposed structure of aspergillitine, featuring sequential Kostanecki-Robinson and 6π-electron azatriene electrocyclization reactions.

ACKNOWLEDGEMENTS

CONICET, SECyT-UNR

REFERENCES

[1] Lin, W. H.; Brauers, G.; Ebel, R.; Wray, V.; Berg, A.; Proksch, P. *J. Nat. Prod.* **2003**, *66*, 57.

[2] a) Saito, F.; Kuramochi, K.; Nakazaki, A.; Mizushina, Y.; Sugawara, F.; Kobayashi, S. *Eur. J. Org. Chem.* **2006**, 4796; b) Kuramochi, K.; Saito, F.; Nakazaki, T.; Takeuchi, T.; Tsubaki, K.; Sugawara, F.; Kobayashi, S. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 1635.