IPAP18 Innovations in Pharmacy ADVANCES & PERSPECTIVES

Salamanca Congress 24-28 Sept.

#IPAP18 Posters

Departamento de Medicina Física y Farmacología
Universidad de La Laguna

CSIC Consejo Superior de Investigaciones Científicas

SUSTAINABLE SYNTHESIS IN THE SYNTHESIS OF HETEROCYCLES OF DIFFERENT SIZES CONTAINED IN MARINE TOXINS

Alejandro RODRÍGUEZ RODRÍGUEZ[1]*, Juan Ignacio PADRÓN PEÑA[2], Juan Miguel LÓPEZ SORIA[2], Susana ABDALA KURI[1] and Sandra DÉVORA GUTIÉRREZ[1].

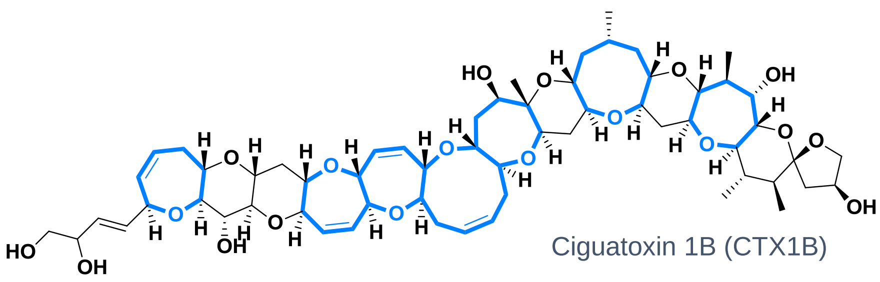
[1] Department of Physical Medicine and Pharmacology, Section of Pharmacy, Universidad de La Laguna. Tenerife. Spain. *alu0100850222@ull.edu.es

[2] Institute of Natural Products and Agrobiology, CSIC. La Laguna. Tenerife. Spain.

Introduction

For some years now, within organic chemistry, sustainable metal catalysis has been emerging as one of the most promising candidates to replace traditional metal catalysis, which is much more expensive and polluting (1). The main objective of this work is to synthesize medium sized oxacycles by means of iron (III) salt catalysis. Iron has all the ideal characteristics as it is one of the most powerful Lewis acids and has catalytic and oxophilic properties that facilitate the synthesis of these oxacicles.

These heterocycles are known structural reasons for many natural products. For example, ciguatoxins, which are marine toxins composed exclusively of polyoxacyclic structures. They cause an intoxication known as ciguatera, of which 20,000 to 50,000 cases are registered annually and which can lead to neurological disorders (2). These marine toxins have so many heterocycles in their molecular composition that it is clear that their toxic properties lie in the synergy of this combination or in some of them in particular. In this paper we will show the methodology used to obtain medium sized oxacycles using iron(III) salts as sustainable metal catalysts.



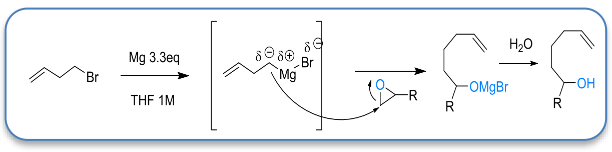
Ciguatoxin 1B (CTX1B)

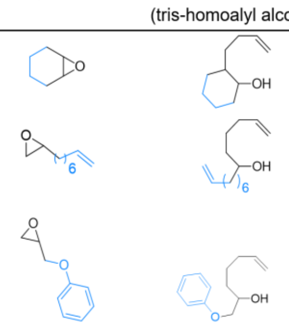
Results and discussion

The use of this methodology based on Fe(III)-salts as catalysts has allowed us to synthesize six oxacycle with a total of seven members, counting chloro-oxepanes (three) and dehalogenated oxepanes (three). These products are the result of a short and effective combination that, in three reaction steps, allows to obtain products with a high added value. The reaction steps involved are: Grignard reaction, tandem 1.5-hydride migration-double Prins cycling and dehalogenation.

Grignard's reaction

This reaction causes that the carbon attached to the magnesium (Mg) manifests a high nucleophilia facilitating the attack to electrophilic centers. These attacks have been carried out on a series of epoxies that have resulted in a secondary alcohol as the final product. These secondary alcohols will be used as a starting product in the Prins reaction

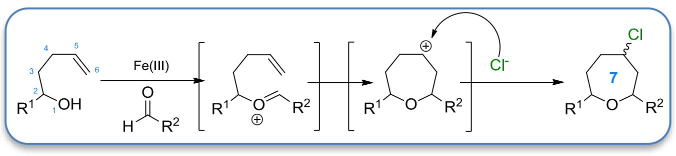




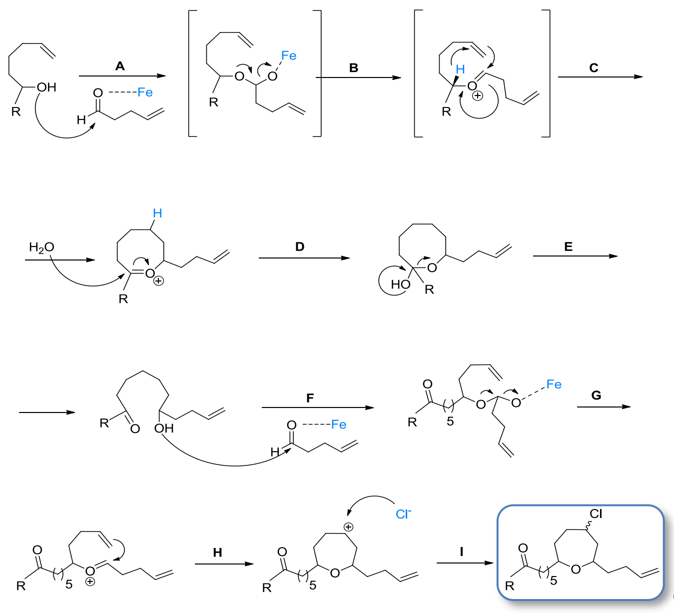
Entrance	Epoxide	Product (tris-homoalyl alcohol)	t (h)	Eff. (%)
1			2	30%
2			2	59%
3			2	27%

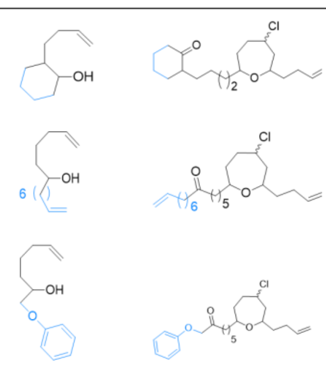
Prins' reaction.

Originally, this reaction consists of the nucleophilic attack of a double terminal bond to an aldehyde/ketone, resulting in the formation of a carbon-carbon bond and the production of a secondary β-carbocation to the generated hydroxyl. In this work, the attack of the double terminal link was directed to other electrophilic centers, specifically to oxocarbocations (3). Prins' reaction has allowed us to synthesize medium-sized heterocycles thanks to the catalytic and oxophilic action of iron.



The proposed mechanism that justifies obtaining these heterocycles is shown below:



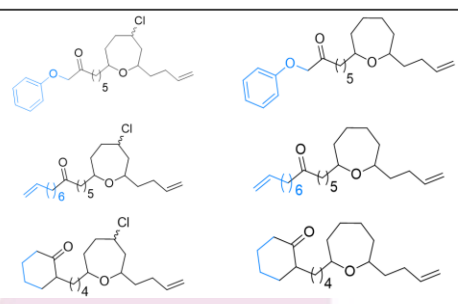


Entrance	Alcohol	Oxepane	t(h)	Overall Eff. (%)	Reaction Eff. (%)	Chemical event Eff. (%)
1			24	37	61	78
2			24	51	71	84
3			24	48	69	83

These results have been produced thanks to the action of the catalytic system Fe(III)/TMSCl, in the framework of sustainable metal catalysis, which demonstrates that it can be a good substitute for synthesis with organometallic catalysts predominant in the current panorama of synthetic organic chemistry.

Radical dehalogenation.

It is performed as a last step because none of the heterocycles that make up ciguatoxin are halogenated.



Entrance	Chlorine-oxepane	Final Product	t (h)	Eff. (%)
1			2	83
2			2	35
3			2	81

The Fe(III) catalytic system makes it possible to efficiently obtain the oxygen rings present in ciguatoxins (CTX). In only three reaction steps, complex and functionalized molecules have been obtained in a sustainable environment, with economy of atoms and a clear orientation towards green chemistry.

Acknowledgements: This research was supported by the Department of Pharmacology of the Universidad de la Laguna and by the Centro Superior de Investigaciones científicas (CSIC). A.R.R. appreciates the opportunity to develop this end-of-career project oriented to chemical research. The authors thank also APROFARCA for the Congress financial support provided.

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