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On the reactivity of 23-methoxycarbonyl furospirostanes

Mariana Macías-Alonso, Marcos Flores-Álamo, Martin A. Iglesias-Arteaga*

Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 Mexico, D.F., Mexico

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ABSTRACT

Brønsted and Lewis acid-catalysed reactions of the 23-methoxycarbonyl furospirostanic side chain are described. While bromination, deuteration and $BF_3{\cdot}Et_2O$/AcOH treatment involve regioselective F-ring opening with exclusive participation of Δ^{22}-furostenic intermediates, $BF_3{\cdot}Et_2O/Ac_2O$ treatment leads to irreversible E- or F-ring cleavage.

1. Introduction

Spiroketals constitute a large family of naturally occurring compounds that have been isolated from both terrestrial and marine organisms. In general the spiroketal moiety is a prevalent structure in a large number of important natural products that have attracted much interest, not only for their wide spectrum of biological activity, but also for their interesting reactivity and usefulness in the preparation of other bioactive compounds [1–3].

Steroids bearing spiroketal side chains are widespread in both the natural and synthetic domains. Spirostanic sapogenins (see Fig. 1) the reactivity of which has produced a wide variety of interesting reactions [4–24] are characterized by the presence of a 16β,22:22,26-diepoxy moiety in the side chain, being 1,6-dioxaspiro[4.5] decane derivatives. Such compounds have been subject of much research due to their intrinsic biological activity [25–30] as well as their usefulness as starting materials for the synthesis of bioactive compounds such as sex and adrenocortical hormones, [4] ecdysteroids, [31] plant growth stimulators, [32–38] and cytotoxic steroids, [39–45] among many others.

It is well known that, in acid media, spirostanic sapogenins present an equilibrium in which the spiroketalic side chain is opened to the oxacarbenium ion **I** that may lose a proton from either C-20 or C-23 to produce Δ^{20} or Δ^{22} enol ethers (see Scheme 1) [4]. Most of the reactivity of the spirostanic side chain can be justified on the basis of these two enolic forms and the oxacarbenium ion **I**.

Furospirostanes, a smaller and somewhat less known family of steroids bearing a 16β,22:22,25-diepoxy moiety in the chain, may be considered 1,6-dioxaspiro[4.4]nonane derivatives, and includes compounds with antitumor activity as the ritterazines **(4),** cephalostatines **(5)** [41–45], or hippuristanols **(6–8)** [46–49], among others (see Fig. 2).

Fuchs and coworkers correlated the cytotoxicity of cephalostatins and their synthetic analogues with that of the potent anti-tumor steroid OSW-1 and hypothesized that the cytotoxic activity of such compounds may be connected with the possibility of the generation of oxacarbenium ions around C-22 [50–52]. In the light of this hypothesis, the fact that other furospirostanes with different 16β,22:22,25-diepoxy side chains (i.e. hippuristanols **6–8**, Fig. 2) and even steroid sapogenins (**1–3**, Fig. 1) with the 16β,22:22,26-diepoxy side chain, (*all theoretically able to produce oxacarbeniums ions around C-22*), have shown toxic activity against different cancer cell lines, should not be considered a mere coincidence. On the contrary, this fact supports Fuchsĭs hypothesis, and constitute an invitation to the study of the biological activity and reactivity of other compounds bearing slightly or even drastically modified side chains that still are able to generate oxacarbeniums ions around C-22.

As a part of our project to explore the reactivity of steroid bearing spiroketals side chains, we have found that treatment of 23-oxo-spirostanes with diacetoxyiodobenzene (DIB) and KOH in methanol produces a *quasi*-Favorskii F-ring contraction that leads to 23-methoxycarbonyl-furospirostanes (see Scheme 2) [10].

This has led us to initiate a program to study the reactivity of the derived compounds as well as their usefulness as starting materials for the synthesis of other potentially bioactive steroids bearing

* Corresponding author. Tel.: +52 55 56223803; fax: +52 55 56223803.
E-mail address: martin.iglesias@servidor.unam.mx (M.A. Iglesias-Arteaga).

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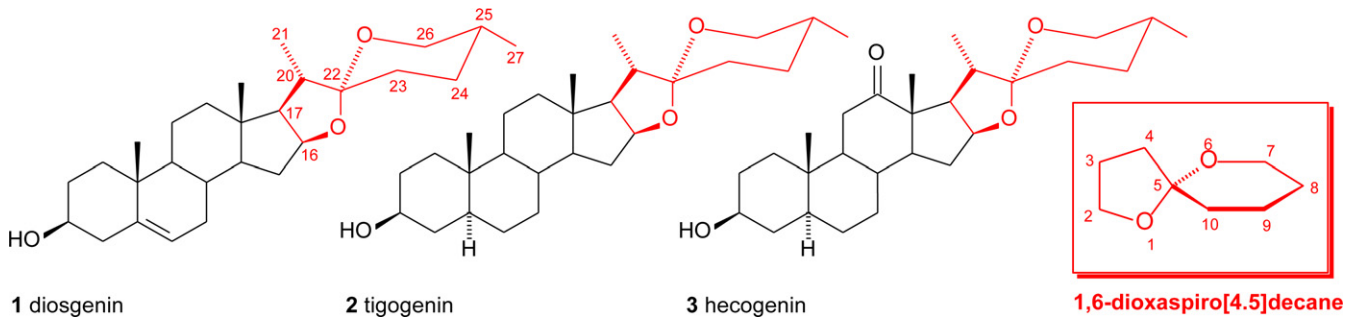
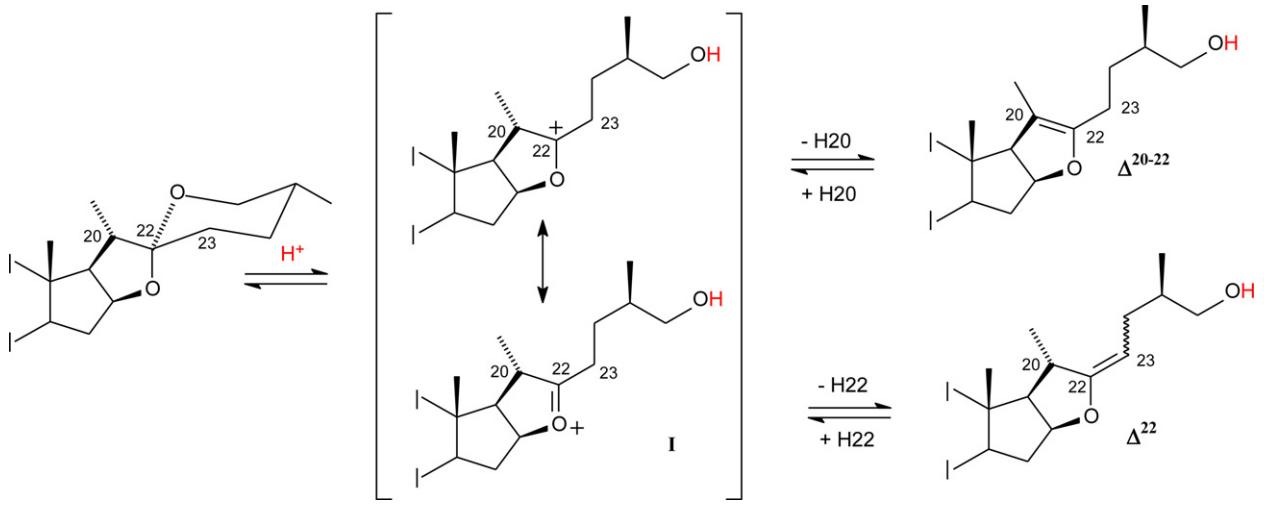


Fig. 1. Some naturally occurring spirostanic sapogenins.



Scheme 1.

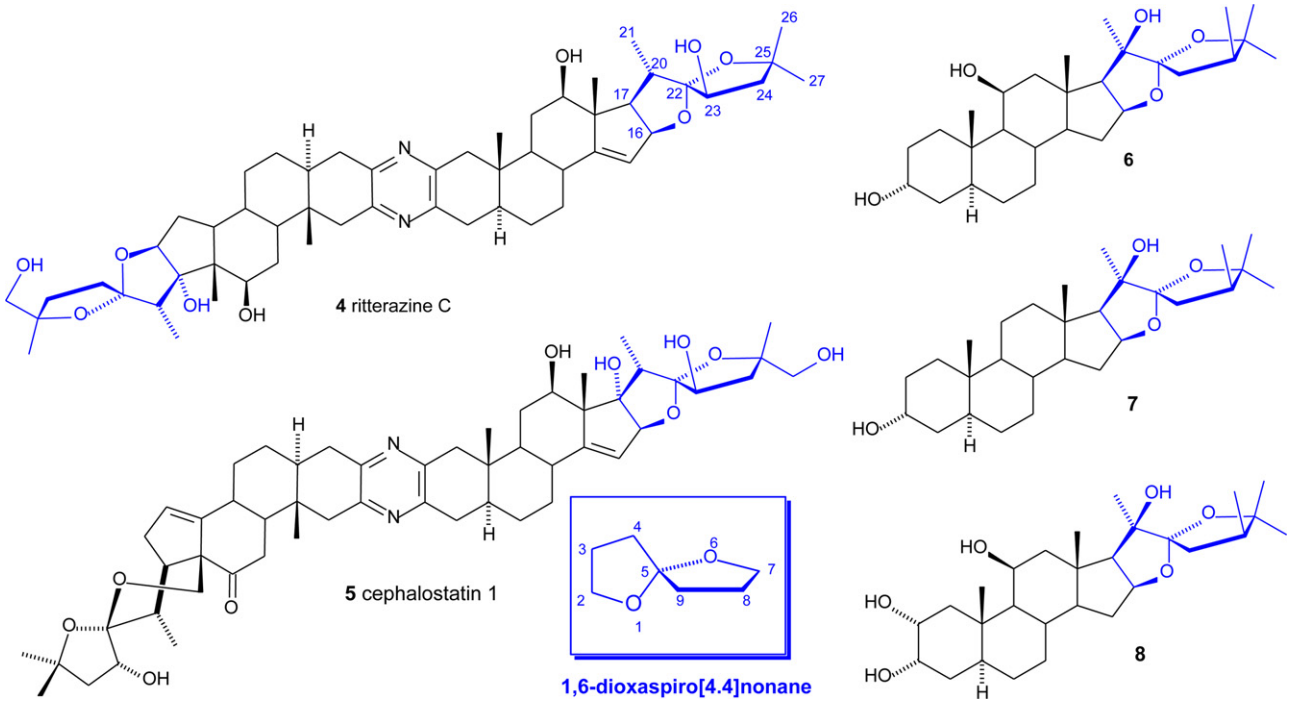


Fig. 2. Some furospirostanes with cytotoxic activity against cancer cells.