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Diacetoxyiodobenzene-mediated synthesis of unnatural furospirostane sapogenins derived from diosgenin and tigogenin

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ABSTRACT

Two unnatural steroid sapogenins bearing a furospirostane side chain were prepared starting from the readily available spirostane sapogenins, tigogenin and diosgenin following a synthetic protocol that included: (i) introduction of a carbonyl group at position C-23, (ii) diacetoxyiodobenzene-induced F-ring contraction and (iii) $LiAlH_4$ reduction of the newly emerged methoxycarbonyl moiety. The structures of the new compounds were corroborated by NMR and X-ray studies.

1. Introduction

Spiroketals are widespread naturally occurring compounds that can be isolated from many marine and terrestrial sources that include microbes, plants, fungi and insects. The growing pharmacological importance of compounds containing spiroketal assemblies has triggered increasing interest in their synthesis and chemical reactivity [1–4].

Steroids bearing the furospirostane side chain may be considered 1,6-dioxaspiro[4.4] nonane derivatives and include naturally occurring compounds that have shown interesting antitumor activity as the ritterazines (1), cephalostatins (2) [5–9], hippuristanols (3) [10–14], as well as the antihypertensive glycosides of nuatigenin (4) [15] among others (Fig. 1).

As a part of our ongoing program on the synthesis of structurally modified steroid sapogenins we became interested in the development of synthetic protocols for the preparation of furospirostane sapogenins. Herein we describe the diacetoxyiodobenzene-mediated synthesis of two unnatural furospirostane sapogenins derived from the readily available spirostane sapogenins diosgenin and tigogenin.

2. Results and discussion

Treatment of the acetylated spirostane sapogenins 5a and 5b with $BF_3.Et_2O$ and $NaNO_2$ in acetic acid followed by hydrolysis in Al_2O_3 (Brockmann activity III) afforded the corresponding 23-oxosapogenins 6a and 6b in low yields (29–35%). As we previously discussed, the yields of the introduction of the carbonyl group at position C-23 are affected by the occurrence of a difficult to avoid side reaction that involves the cleavage of the side chain and produces variable yields of the corresponding dinorcholanic lactones [16].

Favorskii rearrangement of the obtained 23-oxo-sapogenins induced by diacetoxyiodobenzene – $C_6H_5I(OOCCH_3)_2$ – [17] produced the methyl esters of the corresponding furospirostan-23-carboxylic acids 7a and 7b. Although several reactions of hypervalent iodine compounds with double bonds have been reported [18], we have recently described that in the course of the Favorskii rearrangement of Δ^2-12-oxosteroids, the double bond in the A-ring remained unchanged [19]. Thus, in the employed reaction conditions, the double bond in the B-ring of compound 6a proved to be unreactive. Reduction of the rearranged compounds 7a and 7b with $LiAlH_4$ in refluxing THF afforded the desired furospirostane sapogenins 8a and 8b (Scheme 1).

The NMR spectra of the 23-oxosapogenins 6a-b are in good agreement with the previously reported data [20]. In addition to the signals associated to the spiroketal at C-22 (109.7–109.8 ppm) and the carbonyl function at C-23 (201.5–201.8 ppm), the NMR spectra of the 23-oxosapogenins 6a-b are characterized by the presence of the signal of C-26 (65.6 ppm) which bears the diastereotopic pair H-26 ax. (3.77–3.78 ppm) and H-26 eq. (3.57–3.59 ppm).

The conversion of tetrahydropirane F-ring into a tetrahydrofurane produces significant changes in the NMR signals of the nuclei placed in the side chain. In agreement with our previous report

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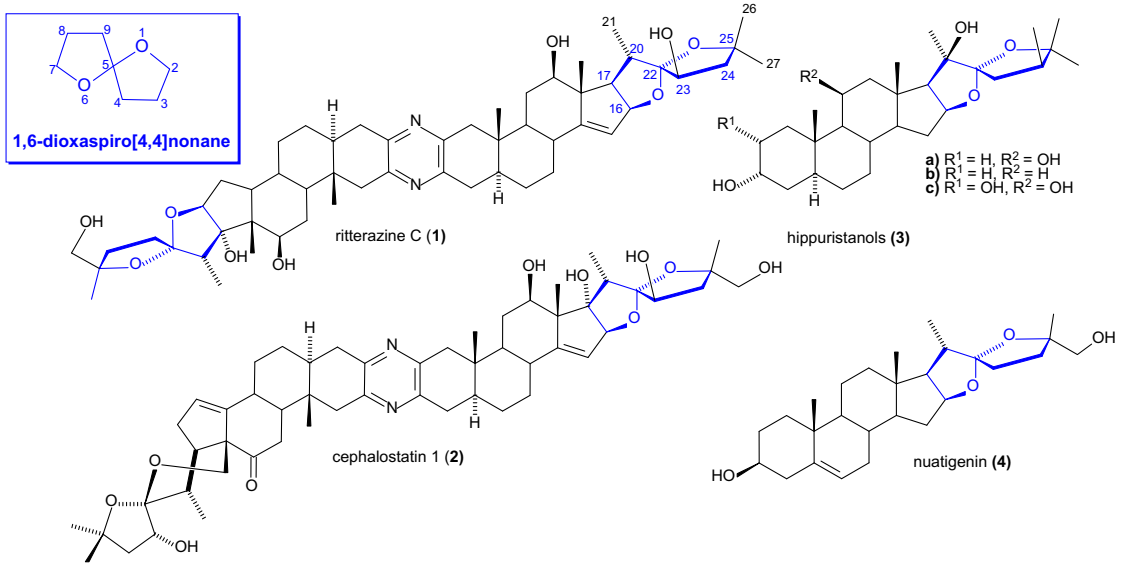
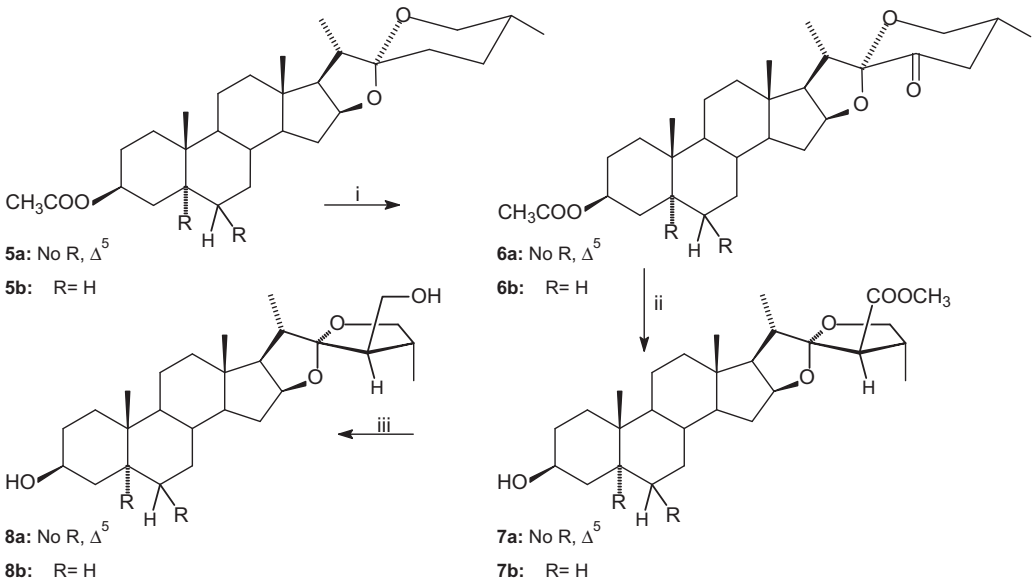


Fig. 1. Some naturally occurring bioactive steroids bearing the furospirostane side chain.



Scheme 1. Synthesis of furospirostane sapogenins 8a and 8b.

[17], the NMR spectra of the rearranged compounds 7a-b show the ^{1}H and ^{13}C NMR signals corresponding to the CH_3O group at 3.71–3.72 and 51.8 ppm, respectively. In addition, the ^{13}C signal of the spiroketal at C-22 (119.3 ppm) and the carboxyl at C-23^{1} (172.50 ppm) as well as the signal of C-25 (72.4–72.5) which bears the diastereotopic pair H-25 *pro-S* (4.01–4.02 ppm) and H-25 *pro-R* (3.46–3.48 ppm) characterize the NMR spectra of the rearranged compounds 7a-b.

The ^{1}H and ^{13}C NMR spectra of the reduced derivatives 8a-b are characterized by the presence of the signals of the diastereotopic protons H-23^{1}a (3.79–3.74 ppm) and H-23^{1}b (3.72 ppm) which are attached to C-23^{1} (62.4–62.5 ppm). Additionally, the NMR spectra show the signal of the spiroketal at C-22 (120.2 ppm) as well as that of the diastereotopic pair H-25 *pro-S* (3.95–3.96 ppm) and 25 *pro-R* (3.43 ppm) attached to C-25 (72.2 ppm).

In the rearranged compounds 7a-b and 8a-b, the respective *R* and *S* configurations of the stereogenic centers generated at C-23 can be determined by observation of the NOE correlations of H-23 with the 24^{1}-methyl group both in the α-side of the F-ring. Additional NOE correlations corroborated the integrity of the side chain (Fig. 2).

Finally, X-ray studies carried out with compound 8b corroborated the *trans* array of the C-23^{1} hydroxymethyl moiety and the C-24^{1} methyl group (Fig. 3) and as a consequence, the *S* configuration of the new stereogenic center at C-23 in the target furospirostane sapogenins 8a and 8b.