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An alternative reduction course of the spiroketal side chain of steroid sapogenins induced by the presence of a 23*E*-benzylidene moiety

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ABSTRACT

Treatment of 25*R* and 25*S*-23*E*-benzylidenespirostanes with $NaBH_3CN$ in acetic acid produced the hydride addition at either C-23 (normal course) or C-23′ (abnormal course) leading to 23*E*-benzylidenefurostanes and 23*R*-benzylspirostanes. In the case of the 25*S*-23*E*-benzylidenespirostane a minor amount of a 23*R*-benzylfurostane produced by the over-reduction of the side chain was isolated.

Introduction

Steroid sapogenins (SE) occupy a paramount place as starting materials for the synthesis of a wide variety of bioactive steroids that include sexual and adrenocortical hormones,[1] plant growth promoting substances,[2] and the potent antitumor agents ritterazines and chephalostatines,[3] among many others. For nearly 70 years the synthesis of such bioactive compounds has prompted an intensive search for new ways for the modification or degradation of the side chain of SE.[4] In particular, the reductive opening of the spiroketal side chain to produce dihydrosapogenins has been achieved by treatment with different reducing reagents under both, Bronsted or Lewis catalysis (Scheme 1).[5]

Additionally, the functionalization at C-23 has recently focused increased attention because the presence of a substituent at this position produces changes in the reactivity profile of the spiroketal moiety and also triggers interesting rearrangements that are not observed in the non-fuctionalized SE.[6]

We have recently described that treatment of different SE with benzaldehyde and $BF_3{\cdot}Et_2O$ produces moderate to good yields of the corresponding 23*E*-benzylidenespirostanes.[7] This has prompted us to study the influence of the 23*E*-benzylidene moiety in the course of the reduction of the spiroketal moiety. Herein we report on the reduction 23*E*-benzylidenespirostanes with $NaBH_3CN$ in acetic acid.

Results and discussion

Treatment of 23*E*-benzylidene tigogenin acetate **(1a)** with $NaBH_3CN$ in acetic acid/CH_2Cl_2 afforded a 2/1 mixture of the 23*E*-benzylidenfurostane **2a** and the 23*R*-benzylspirostane **3a**. Almost similar results were obtained when 23*E*-benzylidene sarsasapogenin acetate **(1b)** was submitted to the same procedure. Meanwhile reduction of **1b** also afforded a minor amount of the over-reduced derivative **4b**, all attempts at production and isolation of the over-reduced derivative **4a** were unsuccessful (Scheme 2 and Table 1).

The reductive opening of the F ring can be corroborated by upfield shift of the signal of C-22 and the presence of a new ^1H signal corresponding to H-22 (See Supplementary data file for comparative NMR tables). The configuration at C-22 in the (22*S*, 23*E*)-benzylidenfurostanes **2a** and **2b** was verified by the observation of the H-21 ↔ H-22 NOE effect that indicates their spatial proximity and, as a consequence, the *S* configuration at C-22 (Fig. 1). The additional NOE and HMBC correlations indicate the integrity of the tetrahydrofuran ring and the benzylidene moiety (Fig. 1).

In the 23*S*-benzylspirostanes **3a** and **3b**, the reduction of the double bond between C-23 and C-23′ can be corroborated by the upfield shifts of the NMR signals associated to C-23, C-23′, and H-23 (See Supplementary information file for comparative NMR tables). The additional NOE and HMBC correlations indicate the integrity of the spiroketal moiety and the phenyl group. The *S* configuration at C-23 in compounds **3a** and **3b** can be determined by observation of the H-23 ↔ H-20 NOE effect that indicates the axial orientation of H-23. In addition, the strong H-23 ↔ H-27 NOE

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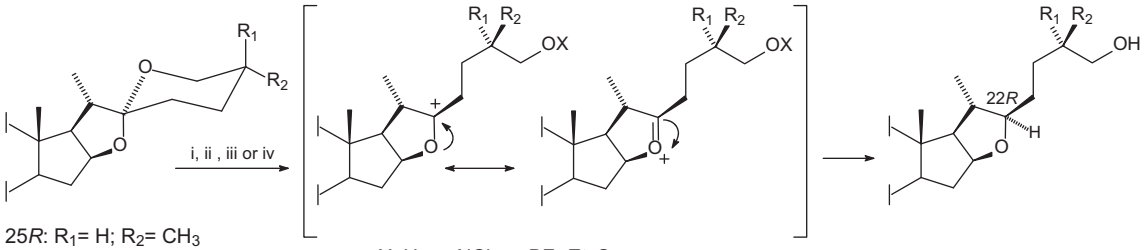
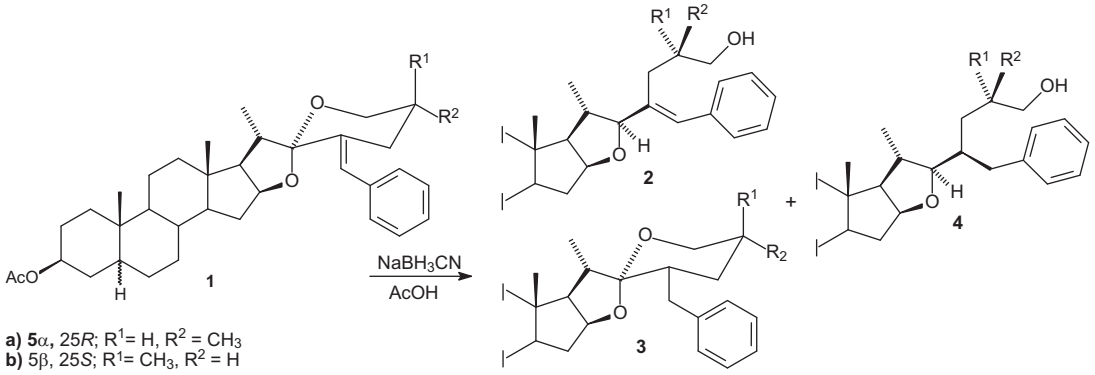


Scheme 1. Reductive F ring opening in SE.



Scheme 2. Reduction of **1a** and **1b**.

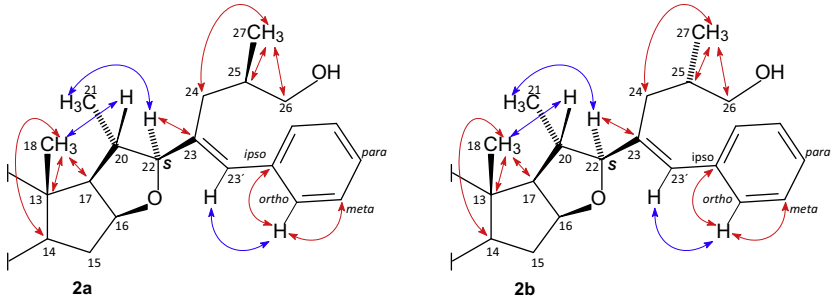


Figure 1. Selected NOE y HMBC correlations in the side chains of the (22*S*,23*E*)-benzylidenfurostanes **2a** and **2b**.

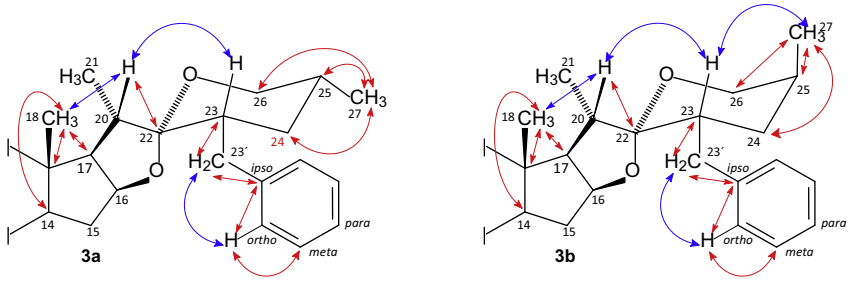


Figure 2. Selected NOE y HMBC correlations in the side chains of the 23*R*-benzylspirostanes **3a** and **3b**.

Table 1
Products and yields of the reduction of **1a** and **1b**

Starting material	Products (Yield%)		
(1a) 5α, 25*R*; R^1= H, R^2 = CH_3	**2a** (64)	**3a** (32)	-
(1b) 5β, 25*S*; R^1= CH_3, R^2 = H	**2b** (52)	**3b** (18)	**4b** (4)

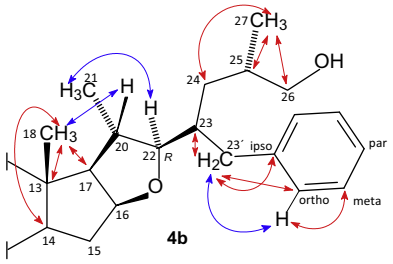


Figure 3. Selected NOE y HMBC correlations in the side chain of the (22*R*,23*S*)-benzylfurostane **4b**.

effect observed in compound **3b** provides further evidence on the *S* configuration at C-23 (Fig. 2).

In compound **4b**, the reductive opening of the F ring can be corroborated by the upfield shift of the signal of C-22 and the presence of a new ^{1}H signal corresponding to H-22. The upfield shifts of the NMR signals associated to C-23, C-23′, and H-23 indicate the reduction of the double bond between C-23–C-23′ (See Supplementary data file for comparative NMR tables). The observed H-22 ↔ H-21 NOE effect indicates the alpha orientation of H-22 and consequently the *R* configuration at C-22. The NMR spectra do not provide conclusive evidence on the configuration at C-23, but it can be inferred by mechanistic considerations *(vide infra)*.

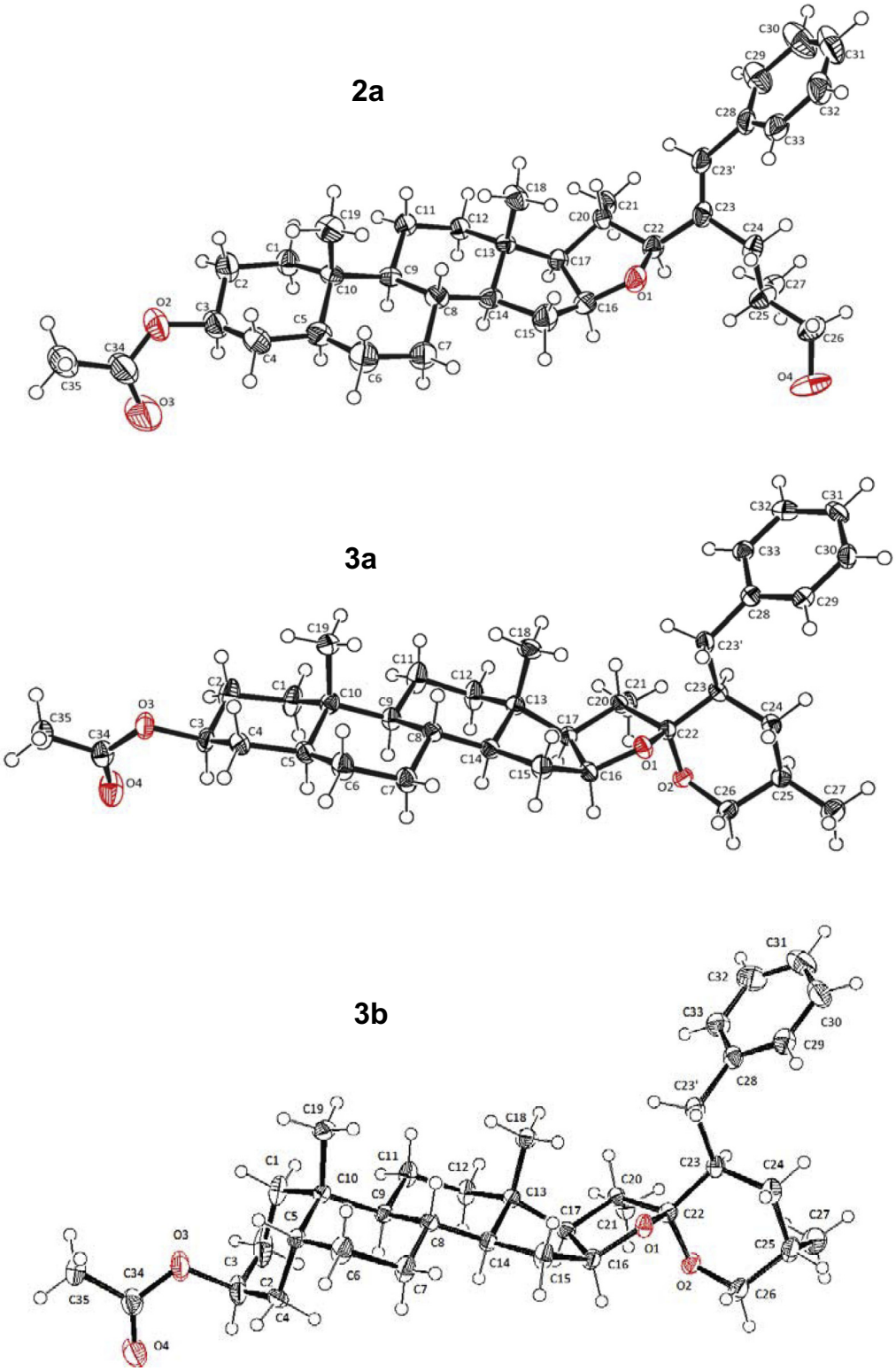
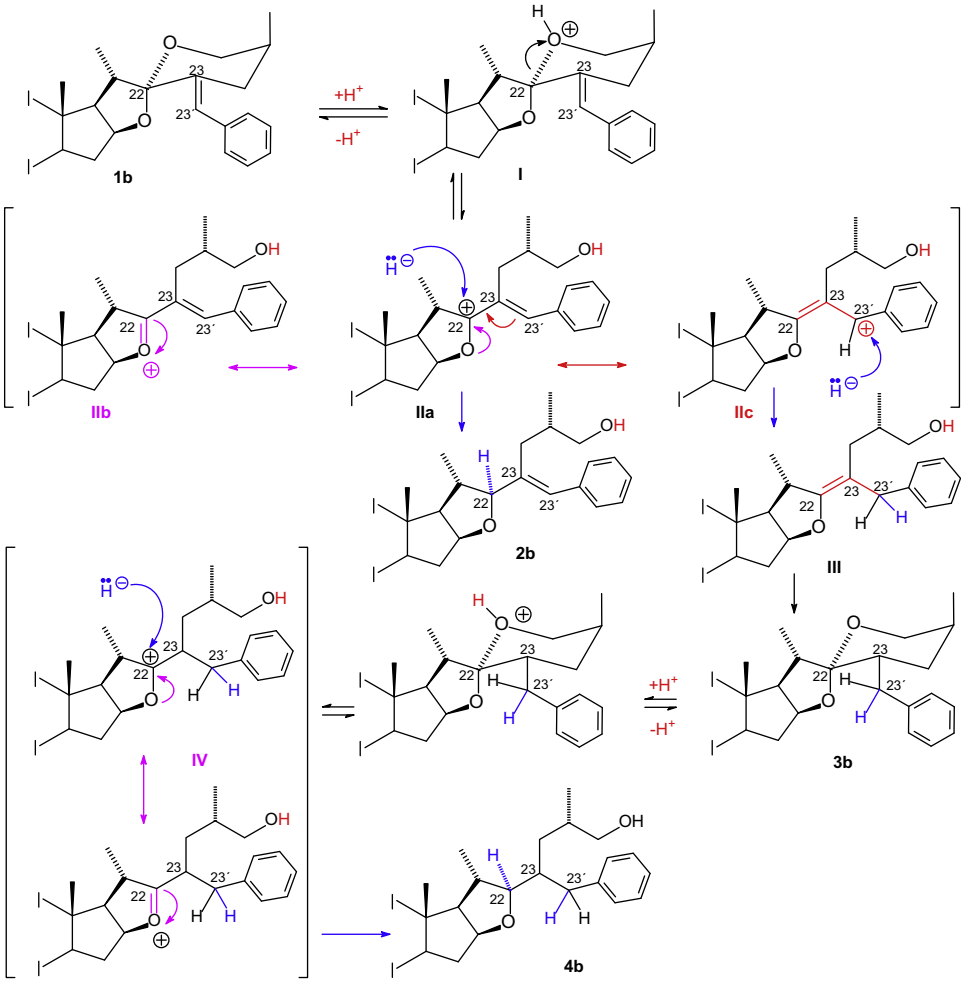


Figure 4. Crystal structures of compound **2a**, **3a** and **3b** with the thermal ellipsoids drawn at 50% of probability.



Scheme 3. Possible reaction mechanism.

The integrity of the tetrahydrofuran ring can be verified by the additional NOE and HMBC correlations (Fig. 3).

X-ray studies carried out in monocrystals of compounds **2a**, **3a**, and **3b** confirmed the proposed structures (Fig. 4), (See supplementary data file for X-ray refinement data).[8]

Possible reaction mechanism

The occurrence of the isolated compounds can be rationalized by a pathway that initiates with the acid catalyzed F ring opening to produce the intermediate **II**. At this point addition of the hydride at C-22 leads to the observed 23*E*-benzylidenespirostane **2a** and **2b**. The occurrence of the 23-benzylspirostanes **3a** and **3b** evidences the addition of the hydride to C-23′ and suggests the significant contribution of the allylic-benzylic carbocation **IIc** to the actual structure of the intermediate (Scheme 3).

The occurrence of the over-reduced compound **4b** can be explained by acid catalyzed F ring opening of **3b** leading to the intermediate **IV** that undergoes hydride addition to C-22. Considering a fast hydride addition to C-22 in the intermediate **IV**, it can be assumed that compound **4b** retains the *S*-configuration of **3b** at C-23.

Attempts at production and isolation of the over-reduced compound **4a** derived from reduction of **3a** included scaling up the reaction or increase of the amount of $NaBH_3CN$ added, and were all unsuccessful. This indicates the resistance of the 23*S*,25*R*-23-benzyl side chain of **3a** to the F ring opening. The slightly increased reactivity shown by **3b** may be explained considering that the F ring opening in the 23*S*,25*S*-23-benzyl side chain of **3b**, produces the release of tensions associated with the presence of the axial methyl group at C-25, favoring the F ring opening.

Conclusions

We have found that 23*E*-benzylidenespirostanes undergo hydride addition at either C-23 (normal course) or C-23′ (abnormal course). This finding indicates that the presence of the benzylidene moiety at C-23 produces a deviation of the normal course of the reductive F ring opening followed by the non-functionalized SE. The hereto unknown compounds may constitute useful synthetic intermediates in the preparation of potentially bioactive steroids. Further experiments directed to study the reactivity of the 23*E*-benzylidenespirostane side chain are on development.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.011.

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8. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as Supplementary material numbers CCDC 939827 (**2a**), 939828 (**3a**) and 939829 (**3b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail:deposit@ccdc.cam.ac.uk.