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Favorskii rearrangement of 23-*oxo*-3-*epi*-smilagenin acetate induced by iodosobenzene

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Dedicated to the memory of our dearest colleague and friend Professor Amparo Tortajada López of the University of Valencia, Spain

Abstract—Treatment of (25*R*)-3α-acetoxy-5β-spirostan-23-one with diacetoxyiodobenzene in KOH/MeOH led to F-ring contraction via Favorskii rearrangement.

Steroid sapogenins are widespread in the nature and have a long history. During the mid part of the last century the particular reactivity of the spiroketal system was extensively studied.[1] Consequently, some of the members of this family have served as the starting materials for the preparation of bioactive steroids.[2] More recently, new reactions involving the spiroketal side chain have been reported.[3]

Hypervalent iodine reagents have received considerable attention.[4] Reactions of iodosobenzene with steroids bearing a carbonyl function at positions C-17 or C-20 have been reported to produce the introduction of a vicinal hydroxyl or methoxyl group,[5a,b] meanwhile the same reaction with 5α-steroids-3-ones follows different paths depending on the steric hindrance (Fig. 1).[5c,d]

After those facts, and in connection with our ongoing studies on the reactivity of steroid sapogenins functionalized at C-23 (see Refs. 3h,k), we decided to explore the reaction of iodosobenzene with (25*R*)-3α-acetoxy-5β-spirostan-23-one (23-*oxo*-3-*epi*-smilagenin acetate **1**).[3k]

When **1** was treated with KOH/MeOH and diacetoxyiodobenzene (DIB), the hereto new compound

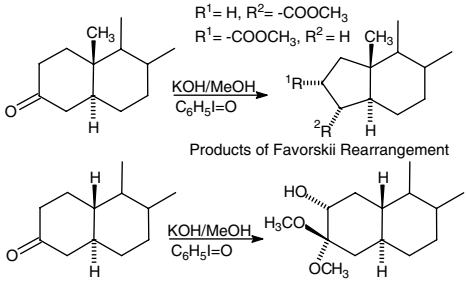
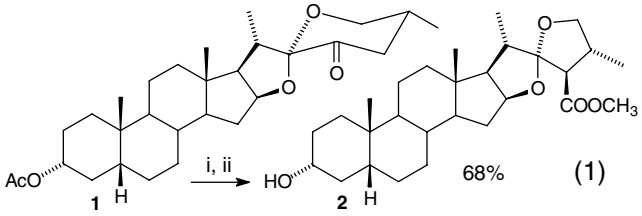


Figure 1. Reaction of iodosobenzene with 5α-steroid-3-ones.

(22*S*,23*R*,25*R*)-23-methoxycarbonyl-22,26-epoxy-24-nor-5β-furostan-3α-ol (**2**) was obtained in good yield (Eq. 1).[6]



i) KOH/MeOH reflux. ii) C_6H_5I=O, room Temp.

The ^1H and ^{13}C NMR spectra of compound **2** are in good agreement with the proposed structure and the previously reported data.[3k,7] Assignments of the ^1H

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and ^{13}C NMR signals were effected with the aid of HH-COSY, DEPT, and HETCORR experiments.

The configuration of the stereogenic center at C-23 was established with the aid of a NOESY experiment. The strong correlation between H-23 (2.85 ppm) and Me-27 (1.04 ppm) indicates their cis disposition that, taking into account the known 25*R* configuration of the starting 23-oxosapogenin **1**, suggests the *R* configuration at C-23. NOE correlations between H-23 and H-20 (2.12 ppm) also account for this assignment. Additional correlations allow the differentiation of the *pro-R* (3.48 ppm) and *pro-S* (4.04 ppm) protons attached to C-26 (Fig. 2).

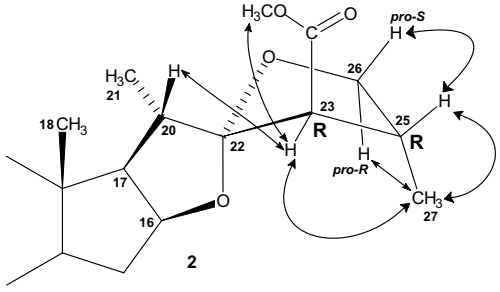
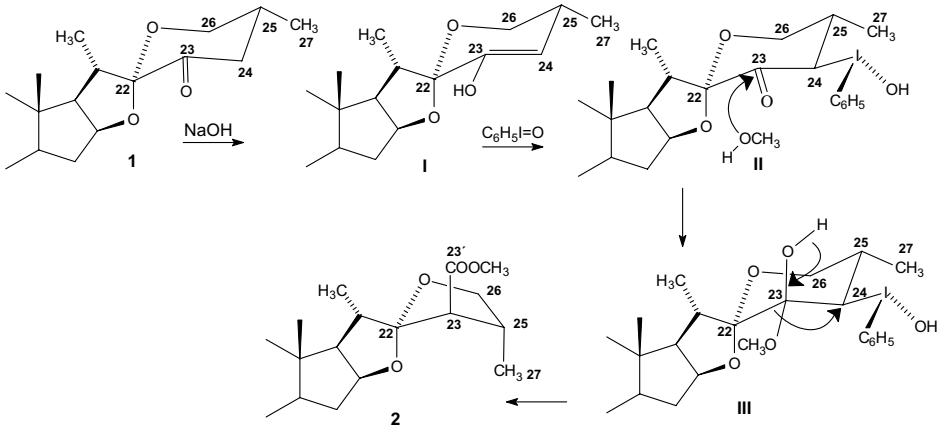


Figure 2. Selected NOE correlations.

The occurrence of **2** can be justified by a reaction path in which iodosobenzene (generated by the action of KOH over DIB) approaches the enol **I** from the β-side resulting in the iodinated ketone **II**, which adds a methoxyl group at C-23 to afford the iodinated hemiketal **III**. At this point, the cis disposition of the hydroxyl group at C-23 and the hypervalent iodine moiety at C-24 does not allow the nucleophilic attack of the C-23–OH to C-24, but the antiperiplanar disposition of the C22–C23 and C-24–iodine bonds favors the migration of C-22, producing a Favorskii rearrangement which results the contraction of the F-ring and the generation of a new stereogenic center (Scheme 1).

Interestingly, the observed reaction follows a course in which the configuration of the starting material at C-25 is transferred to the stereogenic center generated at C-23. Additional experiments directed to understand the reactivity 23-oxosapogenins through iodosobenzene-induced Favorskii rearrangement and to explore the reactivity and potential utility of such rearranged products are in the course of development.



Scheme 1.

Compound **2** presented mp 117–119 °C from EtOAc. ^1H NMR (400 MHz, $CDCl_3$): 4.43 (dt, $J = 6.0$ Hz, $J = 7.7$ Hz, 1H, H-16); 4.04 (dd, $J = 7.7$ Hz, $J = 7.7$ Hz, 1H, H-26 *pro-S*); 3.73 (s, 3H OCH_3); 3.62 (m, 1H, H-3); 3.48 (dd, 1H, $J = 8.1$ Hz, $J = 10.2$ Hz, H-26 *pro-R*); 2.85 (d, $J = 9.4$ Hz, 1H H-23); 2.66 (m, 1H H-25); 2.12 (p, $J = 6.8$ Hz, 1H H-20); 1.99 (m, 1H H-15); 1.04 (d, $J = 6.6$ Hz, 3H CH_3-27); 0.94 (d, $J = 7.34$ Hz, 3H CH_3-21) 0.93 (s, 3H CH_3-19); 0.76 (s, 3H CH_3-18). ^{13}C NMR (100 MHz): 35.3 C-1; 30.4 C-2; 71.7 C-3; 36.4 C-4; 41.9 C-5; 27.2 C-6; 26.6 C-7; 35.5 C-8; 40.4 C-9; 34.6 C-10; 20.5 C-11; 39.9 C-12; 41.1 C-13; 56.2 C-14; 31.8 C-15; 81.4 C-16; 62.7 C-17; 16.0 C-18; 23.2 C-19; 37.5 C-20; 15.5 C-21; 119.3 C-22; 59.6 C-23; 172.5 C-23′ (*C*$OOCH_3$); 37.4 C-25; 72.5 C-26; 15.4; C-27. 51.8 OCH_3. MS (70 eV): 460 M^+ 430, 402, 402, 284, 255, 229, 215, 183, 122, 83, 69, 55, 41.

In summary, we have found that the spiroketal moiety in 23-*oxo*-3-*epi*-smilagenin acetate on treatment with diacetoxyiodobenzene in KOH/MeOH undergoes F-ring contraction via Favorskii rearrangement. This reaction constitutes a new way to transform steroid sapogenins and opens a convenient pathway to new steroid diversity of potential synthetic utility.

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6. In a typical experiment, 23-*oxo*-3-*epi*-smilagenin acetate (472 mg, 1 mmol) and 0.5 g of KOH were gently refluxed in MeOH (30 ml) until no more starting material was observed in TLC (30 min). The clear solution was allowed to reach room temperature, DIB (322 mg, 1 mmol) was added and the mixture was stirred for 40 min. Ethyl acetate (60 ml) was added and the mixture was washed with concentrated solutions of NaCl (3×25 ml) and H_2O (5×15 ml), dried (anhyd Na_2SO_4), and evaporated. Chromatographic purification in silica gel (20 g) (hexane–ethyl acetate, 100/0 to 80/20 as eluent) afforded the rearranged compound **2** preceded by a small amount of the hydrolyzed 23-oxosapogenin.
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