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New bisfuran derivative from sarsasapogenin An X-ray and NMR analysis

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ABSTRACT

The new bisfuran derivative, (22S,23S)-22,23-dihydroxy-23,26-epoxyfurostane (**5**), was obtained from the known oxidation of sarsasapogenin acetate with $NaNO_2/BF_3$ in 5% aqueous acetic acid. The structure of **5** was established using one and two-dimensional ^1H, ^{13}C experiments (DEPT, COSY, HETCOR and HMBC) and the configurations at the newly formed stereogenic centers were established as 22S,23S by an X-ray diffraction analysis. Addition of $TiCl_4$ to bisfuran **5** confirmed that this compound is an intermediate in the rearrangement to 22-oxo-23-spiroketals since it was transformed quantitatively into the latter product. The 23-nitroimino intermediate **2** was isolated from the same reaction and its structure established also by an X-ray diffraction analysis; this compound was further transformed into the 23-nitramine **7** which could find application in functionalization of position 24.

1. Introduction

Sapogenins are complex molecules containing a sugar bonded to a stereoidal or triterpenic nucleus, which are important sources for the syntheses of pharmacologically active steroids. Upon hydrolysis, these substances yield carbohydrates and an aglycone called sapogenin with cholestane, furostane or spirostane frameworks. Spirostane sapogenins are widely distributed in the plant kingdom and therefore are relatively cheap raw materials for the syntheses of other steroidal substances.

The main characteristic of spirostane sapogenins is a spiroketal system fused at the E/F rings of the side chain, thus spiroketal opening and functionalization constitutes one of the main strategies in the synthesis of other derivatives. Bisfuran derivatives, on the other hand, have not been isolated from plants and there are few reports concerning their synthesis, in spite of the fact that ditetrahydrofuran units are present in many natural products with remarkably diverse and important biological activity [1,2].

Suárez and co-workers in 1988 reported that treatment of steroidal spiroacetal methanesulfonate derivatives with DIBALH promotes a new rearrangement to the 2,2′-linked ditetrahydrofuran derivatives [3]. In turn, Morzycki and co-workers [4,5] described the formation of (22S,23R)-22-hydroxy-23,26-epoxyfurostanes by alkaline hydrolysis of (22S,23S)-23-bromosapogenins, as well as the reaction of (23S)-23-tosyloxyspirostanes and 23-tosylhydrazones (25R and 25S series) to give bisfuran products. In continuation of our studies on the transformation of the side chain of sapogenins [6–8] we describe herein the formation of the new bisfuran derivative **5** and 23-nitramine **7** from sarsasapogenin.

2. Experimental

2.1. General remarks

IR spectra were acquired on a FT-IR Perkin-Elmer Spectrum GX spectrophotometer using KBr pellets (υ, cm^{-1}). NMR spectra

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(^{1}H, ^{13}C, DEPT, HETCOR, COSY and HMBC) were determined with a JEOL eclipse +400, chemical shifts are stated in ppm (δ), and are referred to the residual ^{1}H signal ($\delta = 7.27$) or to the central ^{13}C triplet signal ($\delta = 77.0$) for $CDCl_3$. Mass spectra were obtained at 70 eV with a Hewlett Packard 5989A mass spectrometer. Optical rotations $[\alpha]_D^{25}$ were obtained at room temperature using chloroform solutions on a Perkin-Elmer 241 polarimeter. HRMS of **7** was obtained on a Jeol JMS-SX102A using polyethylene glycol (600) as internal reference. Elemental composition was calculated within an error of 10 ppb using the program installed in the system. Melting points were obtained on an Electrothermal 9200 apparatus and are not corrected. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 series apparatus. The products were separated by chromatography over (70–230 mesh) silica gel.

2.2. *Oxidation of sarsasapogenin acetate with $NaNO_2/BF_3{\cdot}Et_2O$*

2.2.1. *Experiment 1*

Treatment of sarsasapogenin acetate **1** with $NaNO_2/BF_3$ in glacial acetic acid, as previously described [9–13], afforded (25*S*)-3β-acetoxy-5β-spirostan-23-nitroimino (**2**), which hydrolyzes upon treatment with neutral Al_2O_3 (grade III) to give (25*S*)-3β-acetoxy-5β-spirostan-23-one (**3**) and a small quantity of (20*S*)-3β-acetoxy-5β-pregnan-20,16β-carbolactone (**4**).

2.2.2. *Experiment 2*

Treatment of sarsasapogenin acetate **1** (10.00 g, 21.83 mmol) with $NaNO_2/BF_3$ in acetic acid (100 ml, 5% aqueous solution) provided a mixture of compounds **3**–**5**. The products were chromatographed over silica gel with mixtures of hexane/EtOAc of increasing solvent polarity to give: 2.80 g (27% yield) of (25*S*)-3β-acetoxy-5β-spirostan-23-one (**3**), mp = 171–172 °C (literature [13], 171–173 °C) (hexane/EtOAc, 9:1); 3.10 g (37% yield) of (20*S*)-3β-acetoxy-5β-pregnan-20,16β-carbolactone (**4**), mp = 188 °C (literature [14], 184.5–185.5 °C) (hexane/EtOAc, 8:2); 0.70 g (7% yield) (rf = 1.3 hexane/EtOAc, 7:3) of (22*S*,23*S*)-22,23-dihydroxy-23,26-epoxyfurostane (**5**), mp = 178–179 °C (hexane/EtOAc, 7:3).

2.2.3. *Experiment 3*

Treatment of sarsasapogenin acetate **1** (8.00 g, 17.46 mmol) with $NaNO_2/BF_3$ in 80 ml glacial acetic acid provided **2** and **4**. The products were chromatographed over silica gel to give 3.30 g (37% yield) of (25*S*)-3β-acetoxy-5β-spirostan-23-nitroimino intermediate (**2**) [11,13] (hexane/EtOAc, 9:1) and 2.20 g (32% yield) of (20*S*)-3β-acetoxy-5β-pregnan-20,16β-carbolactone (**4**), mp = 188 °C (literature [14], 184.5–185.5 °C) (hexane/EtOAc, 8:2).

2.2.4. *(22S,23S)-22,23-Dihydroxy-23,26-epoxy-furostane (5)*

Compound **5**: white crystals, mp 178–179 °C (hexane/AcOEt); $[\alpha]_D^{25}$ −60° (c, 1.0, $CHCl_3$); IR_{max}: 3538 (OH), 3475 (OH), 2950 (CH), 1727 (OAc), 1452, 1377, 1252, 1145 cm^{-1}; MS, *m*/*z* (%): 490 (M^+, 1), 472 ($M^+ - 18$, 4), 444 (4), 389 (37), 329 (100), 315 (26), 255 (85), 130 (43); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.03 (1H, br, H-3), 4.60 (1H, td, $J = 7.7$ and 7.3 Hz, H-16), 4.18 (1H, t, $J = 8.2$ Hz, H-26), 3.39 (1H, br, OH), 3.35 (1H, t, $J = 8.2$, H-26), 3.13 (1H, br, OH), 2.65 (1H, m, H-20), 2.37 (1H, m, H-25), 2.01 (3H, s, 3-$OCOCH_3$), 1.04 (3H, d, $J = 7.0$ Hz, CH_3-27), 1.02 (3H, d, $J = 6.2$ Hz, CH_3-21), 0.95 (3H, s, CH_3-19), 0.76 (3H, s, CH_3-18); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8 (3-$OCOCH_3$), 109.5 (C-22), 107.1 (C-23), 82.1 (C-16), 75.5 (C-26), 70.8 (C-3), 63.6 (C-17), 56.4 (C-14), 41.3 (C-13), 40.3 (C-12), 40.1 (C-15), 40.0 (C-9), 37.3 (C-5), 36.3 (C-25), 35.3 (C-8), 35.1 (C-10), 32.5 (C-20), 31.9 (C-4), 30.8 and 30.7 (C-1, C-2), 26.5 (C-6, C-7), 25.0 (C-24), 23.9 (C-19), 21.6 (3-$OCOCH_3$), 20.9 (C-11), 17.1 (C-21), 16.5 (C-18), 16.0 (C-27). Anal. calcd. for $C_{29}H_{46}O_6$: C 70.99, H 9.45, O 19.56; found: C 70.71, H 9.81, O 19.48.

2.3. *(23R,25S)-3β-Acetoxy-16β,23:23,26-diepoxy-5β-cholestan-22-one (6)*

To a solution of (22*S*,23*S*)-22,23-dihydroxy-23,26-epoxyfurostane (**5**) (13 mg, 0.03 mmol) in dry dichlorometane (4 ml), $TiCl_4$ was added (0.02 ml, 8 eq.). The reaction was stirred at room temperature overnight, poured over water and the organic layer extracted with dichlorometane (2 × 5 ml), dried over anhydrous $MgSO_4$ and evaporated under vacuum. The 22-oxo-23-spiroketal was obtained in quantitative yield (rf = 2.2, hexane/EtOAc, 7:3), mp = 168 °C (literature [19], 169–171 °C).

2.4. *(25S)-3β-Hydroxy-5β-spirostan-23-ene-23-nitramine (7)*

To a solution of (25*S*)-3β-acetoxy-5β-spirostan-23-nitroimino (**2**) (562 mg, 1.08 mmol) in ethylene glycol were added 17 ml of a 10% aqueous solution of NaOH. The reaction mixture was heated 22 h under reflux at 110–120 °C, cooled to room temperature and poured over water. The organic layer extracted with ethyl acetate (3 × 10 ml), dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude reaction product (0.56 g) was chromatographed over silica gel (hexane/EtOAc, 8:2) to give 350 mg (68% yield) (rf = 0.9, hexane/EtOAc, 7:3) of **7**.

Compound **7**: white powder, mp 154–156 °C; $[\alpha]_D^{25}$ −30° (c, 1.0, $CHCl_3$); IR_{max}: 3561, 2929 (CH), 1584, 1314 (NNO_2), 910 (N–O) cm^{-1}; MS, *m*/*z* (%): 474 (M^+, 3), 443 (6), 429 (28), 388 (6), 347 (41), 329 (40), 287 (42), 273 (84), 215 (15), 147 (46), 107 (61), 41 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.26 (1H, br, NH), 6.44 (1H, d, $J = 7.0$ Hz, H-24), 4.53 (1H, q, $J = 8.0$ Hz, H-16), 4.11 (1H, br, H-3), 3.91 (1H, dd, $J = 3.3$ and 11.4 Hz, H-26), 3.51 (1H, d, $J = 11.4$ Hz, H-26), 2.27 (1H, m, H-25), 2.10 (1H, m, H-20), 1.20 (3H, d, $J = 7.0$ Hz, CH_3-27), 0.98 (3H, d, $J = 6.2$ Hz, CH_3-21), 0.97 (3H, s, CH_3-19), 0.82 (3H, s, CH_3-18); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.9 (C-24), 129.5 (C-23), 107.8 (C-22), 82.5 (C-16), 67.2 (C-3), 63.8 (C-26), 61.4 (C-17). 56.5 (C-14), 41.2 (C-13), 40.1 (C-12), 39.9 (C-9), 38.5 (C-20), 36.6 (C-5), 35.4 (C-10), 35.3 (C-8), 33.6 (C-4), 31.7 (C-15), 30.0 (C-1), 29.9 (C-25), 27.9 (C-2), 26.6 (C-6, C-7), 23.9 (C-19), 20.9 (C-11), 17.5 (C-27), 16.5 (C-18), 14.5 (C-21). HRMS calcd. *m*/*z* for $C_{27}H_{43}O_5N_2$ ($M^+ + 1$): 475.3172; found: 475.3159 error 2.6 ppm.

2.5. *Crystal structure determination*

Crystals of **2** and **5** suitable for X-ray analysis were obtained from a mixture of hexane–ethyl acetate (9:1) and (7:3), respectively, by slow evaporation of the solvent at room temperature. The X-ray measurement of (25*S*)-3β-acetoxy-5β-