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Conformational and Configurational Analysis of (2*R*,3*S*,5*R*)-2,5-Dimethyltetrahydropyran-3-Carboxylic Acid

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Dedicated to Prof. Pedro Joseph-Nathan on the occasion of his 65th birthday.

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Abstract. The present work describes the conformational and configurational analysis of 2,5-dimethyltetrahydropyran-3-carboxylic acid using the ALTONA software developed by the group of Joseph-Nathan. The pyrancarboxylic acid was prepared from 23-ethylidenediosgenin acetate by a sequence of reactions that involve acid catalyzed cleavage of the side chain of the sapogenin.
Keywords. NMR, sapogenins, ALTONA software, conformational analysis, configurational analysis.

Resumen. El presente trabajo describe el análisis conformacional y configuracional del ácido 2,5 dimetiltetrahidropirano-3-carboxílico empleando el programa ALTONA desarrollado por el grupo de Joseph-Nathan. El ácido piranocarboxílico fue preparado a partir del acetato de 23-etilidendiosgenina, mediante una serie de reacciones que involucran el rompimiento de la cadena lateral de la sapogenina en medio ácido.
Palabras clave. RMN, sapogeninas, programa ALTONA, análisis conformacional, análisis configuracional.

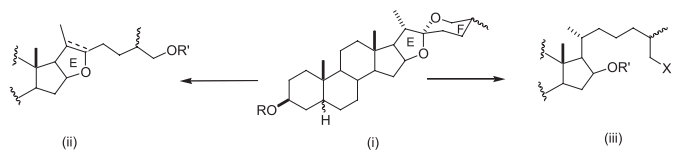
Introduction

In 1990 the group of Joseph-Nathan, Zepeda and Cerda-García-Rojas introduced the computational program ALTONA [**1**] to calculate H-C-C-H dihedral angles from experimentally determined ^{1}H-^{1}H coupling constant values using a generalized Karplus-type equation based on the protocol developed by Altona [**1**] which takes into account the electronegativity and orientation of the substituents attached to the H-C-C-H fragment under evaluation. The ALTONA protocol has been very helpful [2-14] for the assignment of the conformation and configuration of natural products by comparison of the experimental ^{1}H-^{1}H coupling constants with those obtained with a generalized Karplus type relationship using dihedral angles generated from theoretical calculations.

This paper describes the conformational and configurational analysis of 2,5-dimethyltetra-hydropyran-3-carboxylic acid using the ALTONA software. In turn, this acid was obtained from diosgenin using the acid catalyzed transformation of its spiroketal side chain reported previously, as key step [15-18]. It should be mentioned that sapogenins are precursors for biologically relevant steroids, for this reason, the spiroketal side chain has been the subject of intense efforts devoted to study its chemical reactivity. Thus, furostane/ furostene (**ii**) or cholestane (**iii**) frameworks have been obtained by selective opening of ring F or opening of both E and F rings of **i** (Scheme 1) [19,20].

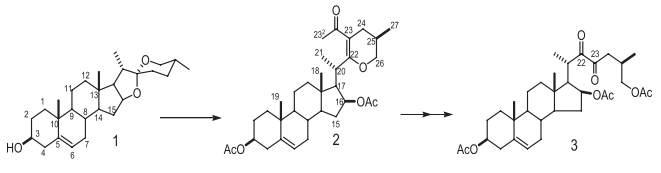
Recently, it has been shown that the regioselective opening of ring E in sapogenins produces a new skeleton, the 22,26-epoxycholestene [15-17]. From diosgenin (**1**), we have shown that the corresponding (22*E*)-(25*R*)-23-acetyl-22,26-epoxycholesta-5,22-dien-3β,16β-diol diacetate (**2**) is a very useful starting material to introduce oxygenated functions at C-22 and C-23 as in compound **3** [29] (Scheme 2).

A systematic study of the acetolysis of the side chain of sapogenins, evidenced the important role of the protons at position C-23 and the steric influence of the methyl group at C-25 on the abstraction of H_{23ax} that leads to different ratios of



Scheme 1. Structures commonly obtained by cleavage of E/F rings of sapogenins.

products from the regioselective E ring opening. Thus, a high yield (94%) of compound **2** was found in the 25*R* series [15] but it decreased to nearly 50% in the 25*S* series [16]. In continuation of our studies on the stereoselective cleavage of sapogenins, we decided to investigate the acid catalyzed spiroketal opening of a substrate with no protons at position C-23 such as [23(23^1)*E*]-23-ethylidenediosgenin acetate **7b**.

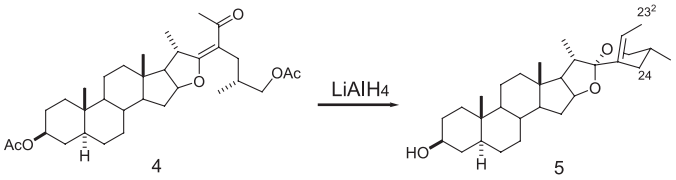


Scheme 2. Useful transformation of the 23-acetyl-22,26-epoxycholestane framework **2**.

Results and Discussion

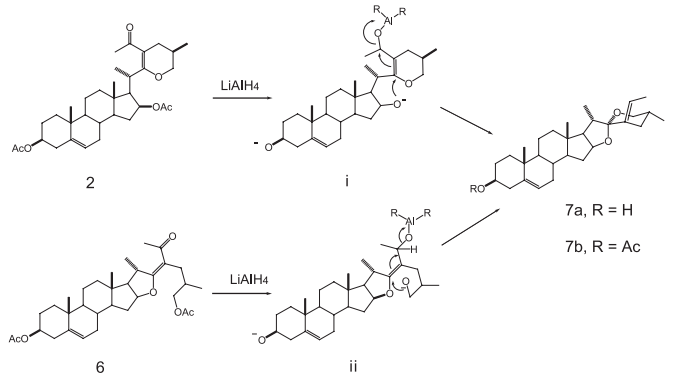
The formation of 23-ethylidenetigogenin (**5**) in about yield 70%, through the action of $LiAlH_4$ on (22*E*)-(25*R*)-23-acetyl-5α-furost-22-ene-3β,26-diol diacetate (**4**) was described by Zderic [22] (Scheme 3).

Once we were able to optimize the preparation of compounds **2** and **6**, to practically quantitative yields [17,21] we used Zderic's methodology to obtain 23-ethylidenediosgenin (**7a**) in 90% yield from (22*E*)-(25*R*)-23-acetylfurosta-5,22-diene-3β,26-diol diacetate (**6**) as well as from **2** (Scheme 4). ^{13}C NMR data of 23-ethylidenediosgenin were in agreement with those of the previously reported 23-ethylidenesarsasapogenin [23].



Scheme 3. Preparation of 23-ethylidenetigogenin (**5**) from (22*E*)-(25*R*)-23-acetyl-5a-furost-22-ene-3b,26-diol diacetate (**4**).

The formation of **7a** from **2** can be explained by initial reduction of the carbonyl groups present in the acetyl and acetates, generating the intermediate **i** (Scheme 4) followed by attack of the 16β-alkoxy group to C-22 through a *Si* side attack of the double bond. This nucleophilic attack promotes the elimination of the aluminate group at C-23^1. In the case of furostene **6**, the nucleophilic attack of 26-alkoxy group (intermediate **ii**) at C-22 occurs from the *Re* face of the double bond. In both cases the *Si* and *Re* attacks lead to the (22*S*)-spirostene **7a**, product with the natural configuration at C-22.



Scheme 4. Mechanism for the formation of [23(23^1)*E*]-ethylidenediosgenin **7a**.

Satisfactory single-crystals were obtained by slow crystallization in EtoAc. The X-ray diffraction analysis [24] of **7a** permitted to corroborate the *E* configuration at 23(23^1) position and the natural configuration at C-20, C-22 and C-25 (Figure 1).

In contrast, when the reducing agent is 9-BBN or $NaBH_4$ there is no formation of an alkoxide ion at C-16, therefore, the hydride attacks the carbonyl of the 23-acetyl group. A further participation of electrons from the furan oxygen atom leads to (25*R*)-22,26-epoxy-23-vinylcholest-22-en-3β,16b-diol diacetate (**8**) through borinate (**i**) and proton elimination (**ii**, Scheme 5) [25]. This result points out to the particular behavior of the β-alkoxy-substituted-α,β-unsaturated ketone system.

Based on these results it was envisioned that the 23-ethylidene substituted derivative **7b** could lead, under acidic conditions to a highly regioselective cleavage of ring F, as was indeed observed. The treatment of **7b** with *p*-toluenesulfonic acid, at reflux in benzene led to a single product characterized as (23*S*,23^1*R*,25*R*)-23^1,26-epoxy-23-ethylfurosta-5,20(22)-dien-3β-ol acetate (**9**). The configuration at the C-23 y C-23^1 newly formed stereogenic centers was established from the degradation products as shown in Scheme 6. Subsequent oxidation of **9** with RuO_4 afforded (2'*R*,3'*S*,5'*R*)-20-oxopregn-5-ene-3β,16β-diol 3-acetate 16-(2',5'-dimethyl)tetrahydropyran-

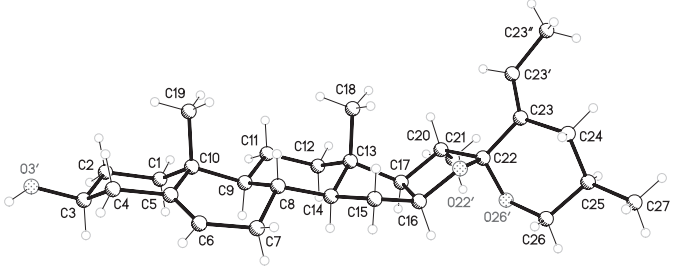


Fig. 1. Perspective view of 23-ethylidenediosgenin (**7a**).

3'-carboxylate (**10**), which was submitted to basic hydrolysis to give 16,17-didehydropregnenolone (**11**) and (2*R*,3*S*,5*R*)-2,5-dimethyltetra-hydropyran-3-carboxylic (**12**).

The 400 MHz ^{1}H NMR spectrum of **9** showed two close multiplets at δ 4.66 and δ 4.53, for H-16 and H-3, respectively. The signals at δ 3.75 and δ 2.93 were assigned to the 26*eq* (ddd, $J_{26eq,26ax}$ = 11.0 Hz, $J_{26eq,25}$ = 3.4 Hz and $J_{26eq,24eq}$ = 1.4 Hz) and 26*ax* (t, $J_{26ax,26eq} = J_{26ax,25}$ = 11.0 Hz) diastereotopic protons. The doublet at δ 2.37 corresponds to the allylic proton H-17 showing $J_{17,16}$ = 10.0 Hz while the singlets at δ 1.57 and δ 2.00 fit with Me-21 and 3-OAc. The secondary methyl groups gave signals at δ 1.09 (Me-23^2) and δ 0.75 (Me-27).

The APT spectrum showed the carbonyl signal at δ 170.4, and two new sp^2 carbons at δ 104.6 (C-20) and 152.1 (C-22), characteristic for the vinyl carbons in the dihydrofuran moiety of pseudosapogenins; the C-5 and C-6 double bond signals appeared in 139.7 and 122.4 ppm while C-16, C-23^1, C-26 and C-3 were at δ 84.4, 75.1, 74.4 and 73.8, respectively.

The mechanism for the formation of **9** is shown in Scheme 7. Cleavage of the F ring leads to a positively activated α,β-unsaturated system **(i)** and an alcohol at C-26. The hydroxy group then attacks the double bond from the *Re* side at C-23^1, in a Michael type nucleophilic attack. Subsequent protonation of Δ^{22} at C-23 from the *Re* face is promoted by the furanic oxygen atom. The methyl groups at C-23^1 and C-25 if placed equatorially, anchor the 6-membered furan ring, would direct the protonation only by the *Re* face. As a result, all substituents of the pyran ring would be placed equatorially.

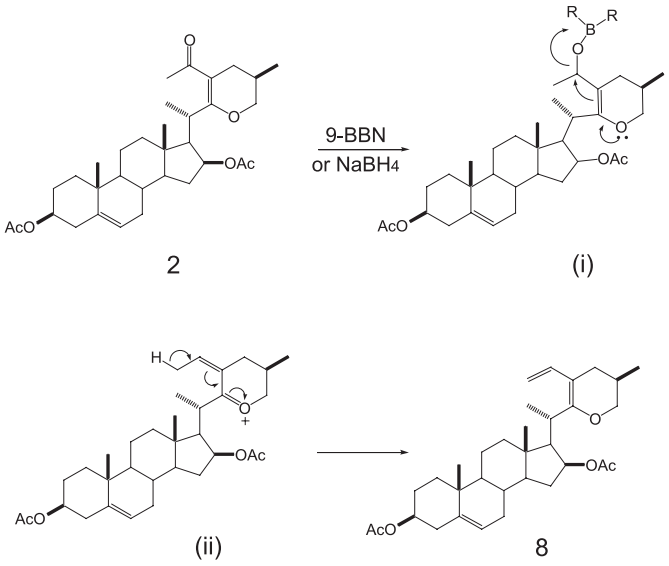
It should be noted that isopseudosapogenins having an *exo*-furan double bond (as **ii**) have not been reported in the literature because the pseudosapogenin structure (as **9**) is thermodynamically more stable (a difference of 6.5 kcal/mole has been obtained from calculations using HyperChem 7.0 software).

A selective oxidation of $\Delta^{20(22)}$ using RuO_4 was successfully carried out leading to pregnanic ester **10** (Scheme 6). The ^{1}H NMR of **10** showed a multiplet at δ 5.48 for H-16, which is shifted to high frequencies, as expected for a proton at position *gem* to an ester. The multiplet at δ 4.57 was assigned to H-3 and the diastereotopic protons at position 6' appear at δ 3.80 and 2.97. The doublet of quartets ($J_{2',3'}$ = 9.6 Hz and $J_{2',2''}$ = 6.1 Hz) at δ 3.42 was assigned to H-2′. The Me-21 and acetate groups appear at δ 2.06 and 2.00 respectively, while the doublet at δ 1.15 was assigned to Me-2′′.

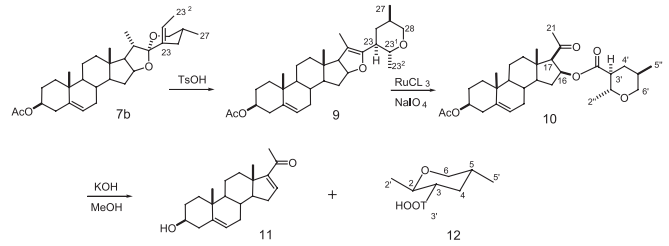
The correlation between the diastereotopic protons at position 6' and the signal at δ 0.78, in the COSY spectrum, allowed to confirm the assignment for 5′. Similarly, a correlation with the signal at δ 1.15 (Me-2′′) allowed assignment of H-2′.

The APT spectrum of **10** at 100 MHz shows a new signal at δ 205.3 due to the carbonyl at position 20 and another one at δ 173.4 for the carbonyl of the ester group at C-16 position. C-16 was shifted from δ 84.4 to δ 74.6, compared to the starting material **9**.

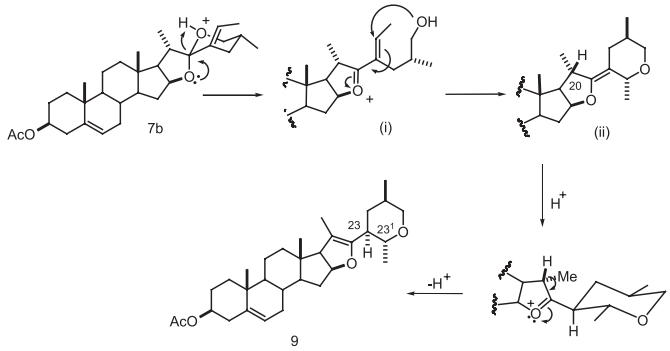
In order to confirm the assignment of the newly formed stereogenic centers in the pyran ring, the pregnane **10** was



Scheme 5. Mechanism for the formation of (25*R*)-22,26-epoxy-23-vinylcholest-22-en-3β,16β-diol diacetate (**8**).



Scheme 6. Oxidative degradation of furostene **9** to afford the pyran **12**.



Scheme 7. Proposed mechanism for the formation of furostadiene **9**.

hydrolyzed with KOH/MeOH to give **11** and **12** (Scheme 6). In turn, **11** was characterized by comparison with an authentic sample.

The stereochemistry at positions 2 and 3 of compound **12** was established from the coupling constants in the ^{1}H NMR spectrum using the ALTONA software [1a] in combination with AM1 calculations (HyperChem 7.0).

Taking as reference the *R* configuration at C-5, the pyran signals at δ 3.85 and 3.03 (which show the same coupling patterns as the methylene protons at C-26 in the epoxycholestene derivative **2**), were assigned to the diastereotopic protons H-6*ax* and H-6*eq*, respectively. The signal corresponding to the new stereogenic center (C-2) appeared as a doublet of quartets ($J_{2ax,3ax}$ = 9.9 Hz, $J_{2ax,2'}$ = 6.2 Hz) at δ 3.48; showing a characteristic *trans* diaxial coupling with H-3. The ddd at δ 2.30 ($J_{3ax,4ax}$ = 12.5 Hz, $J_{3ax,2ax}$ = 9.9 Hz, $J_{3ax,4eq}$ = 3.7 Hz) was assigned to H-3; the first two coupling constants are characteristic for *trans* diaxial couplings with H-2*ax* y H-4*ax* and confirm the *S* configuration for C-3. These results allow to determine that the stereochemistry at C-5 is retained therefore it can used to obtain the relative configuration at C-2 and C-3.

The assignments were confirmed by a COSY experiment that shows that the signal at δ 3.48 (H-2) correlates with those at δ 2.30 (H-3) and δ 1.23 (Me-2').

In order to confirm the supposed configuration/conformation of **12**, theoretical studies were undertaken. Firstly, experimental coupling constants (J_{EXP}) were used to calculate the dihedral angle (f_{ALTONA}) by means of the ALTONA software [1a]. On the basis of J_{EXP} and f_{ALTONA} values Molecular Mechanics (AM1) and Density Functional Theory (DFT) were used to optimize the conformation of minimum energy of **12**. These values permitted to obtain theoretical coupling constants from the ALTONA software (Table 1). The calculated coupling constants give excellent agreement with the experimental values, except for $J_{H5ax\text{-}H6eq}$ where the experimental value is smaller. On the basis of these results, we conclude that the pyrancarboxylic acid presents a chair conformation in which all substituents are in equatorial positions. Very different values were obtained from other configurational alternatives (v.g. the 5*S*-isomer).

The minimum energy conformation for pyran **12** calculated using an AM1 semiempirical approach (HyperChem 7.0) is shown in Figure 2.

Table 1. Experimental and calculated coupling constants (J) and dihedral angles (f) for pyran 12.

	H_{2ax} -H_{3ax}	H_{3ax} -H_{4ax}	H_{3ax} -H_{4eq}	H_{4ax} -H_{5ax}	H_{4eq} -H_{5ax}	H_{5ax} -H_{6ax}	H_{5ax} -H_{6eq}
J_{EXP}	9.9	12.5	3.7	12.5	3.7	11.0	3.9
ϕ_{ALTONA}	-165	179	57	-179	-55	158	62
ϕ_{AM1}	-176	173	55	-175	-56	176	54
ϕ_{DFT}	-177	173	56	-175	-57	176	57
J_{ALTONA}	10.8	12.2	4.0	12.2	3.5	11.6	5.0

The ^{13}C-NMR spectrum of (2*R*,3*S*,5*R*)-2,5-dimethyltetrahydropyran-3-carboxylic acid (**12**) at 100 MHz shows signals at δ 179.8 the carboxylic acid, δ 74.2 and 74.0 for C-6 and C-2, δ 40.3 for C-3, δ 35.9 for C-4, δ 29.9 for C-5 and δ 20.0 and δ 16.9 for the 2′ and 5′ methyl signals. It is worth mentioning that the APT was very informative for the assignment of C-2(CH) and C-6 (CH_2), since these signals have a chemical shift difference of only δ 0.2.

Conclusions

The 23-ethylidene derivative **7b** was successfully transformed into the epoxycompund **9** in acidic medium, through the cleavage of the spirostane F ring. The driving force for the cleavage of ring F is the formation of a positively-activated planar α,β-unsaturated ketone intermediate with a maximum of orbital conjugation. In contrast, cleavage of the E ring in **7b** would lead to a conjugated system with a twisted 6-membered ring which is higher in energy.

Subsequent oxidation of **9** afforded the pregnanic ester **10** which after hydrolysis gave 16,17-didehydropregnenolone **11** and the chiral pyrancarboxylic acid **12**. Detailed NMR analysis of **12** allowed, with the help of ALTONA software, to establish unambiguously the configuration at the newly formed stereogenic centers which were found to be 2*R*,3*S*. Therefore, the configurations at C-23 and C-23^1 in 23-ethyl-23^1,26-epoxyfurost-5,22-diene 3β-ol acetate (**9**) must be 23*R*, 23^1*S*. The highly stereospecific formation of **9** is attributed to a protonation-deprotonation sequence from **7** (Scheme 7).

Experimental Part

Melting points were determined on a Melt-temp apparatus and were not corrected. NMR spectra were measured at 400 MHz (^{1}H) and 100 MHz (^{13}C) with a JEOL Eclipse spectrometer, using $CDCl_3$ as the solvent and TMS as internal reference. Optical rotations were measured at room temperature on a

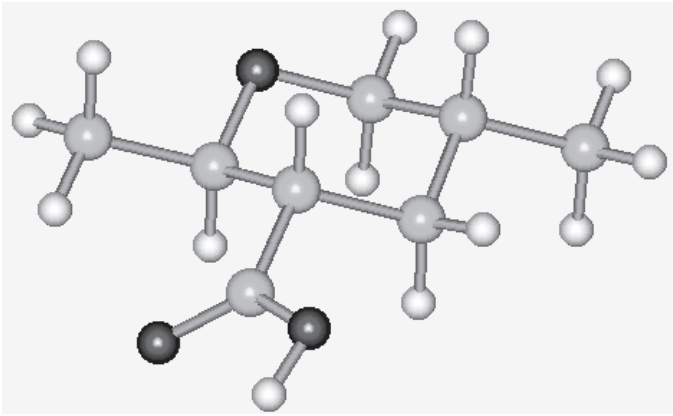


Fig. 2. The minimum energy conformation for pyran **12**

Perkin Elmer 241 polarimeter in $CHCl_3$ solutions using a 10 cm cell. The infrared spectra were determined using KBr pellets on a Perkin Elmer FT-IR One. Mass spectra were obtained on a HP 5989A. X-ray diffraction data were collected in a Bruker P4 diffractometer.

Calcultations were carried out using a Pentium IV-based PC. For molecular mechanics calculations the PCMODEL program (Serena Software, Bloomington, IN, USA) was used. DFT calculations were performed using Spartan at the B3LPY/6-31G* level of theory. Molecular modeling was realized using AM1 calculations (HyperChem 7.0).

[23(23¹)*E*]-23-ethylidenediosgenin (7a). $LiAlH_4$ (186 mg, 4.9 mmol) was slowly added to a solution of 500 mg (0.925 mmol) of (25*R*)-23-acetyl-22,26-epoxycholesta-5,22-diene-3β,16β-diol diacetate (**2**) in 30 mL of anhydrous THF. The reaction mixture was refluxed for 2 h and cooled to room temperature. Excess $LiAlH_4$ was destroyed with EtOAc, MeOH and water; the precipitate was filtered and the solvent evaporated under vacuum. The organic phase was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated to dryness to give 380 mg of crude, which was purified over silica gel, eluted with petroleum ether/AcOEt (95:5) to give 360 mg of **7a** (88% yield) which was crystallized with EtOAc (mp 233-234 °C).

Note: The same product was obtained from (25*R*)-23-acetylfurosta-5,22-diene-3β,26-diol diacetate (**6**) under similar reaction conditions in approximately the same yield.

MS (70 eV): *m/z* (int. rel.): 440 $[M]^+$ (80), 425(100), 381(52), 165(67), 141(95). $[\alpha]_D$ = -67.7° ($CHCl_3$, c = 0.1). IR: ν_{max} cm^{-1} 3493 (OH), 2930 (C-H), 1625 (C=C). ^1H NMR (400 MHz, $CDCl_3$) δ : 5.56 (1H, m, H-23¹), 5.28 (1H, m, H-6), 4.35 (1H, m, H-16), 3.49 (3H, m, H-26*eq*, H-26*ax* y H-3), 2.43 (1H, m, H-20), 1.61 (3H, d, *J* = 6.5 Hz, CH_3-23²), 0.99 (3H, s, CH_3-19), 0.97 (3H, d, $J_{20,21}$ = 6.0 Hz, CH_3-21), 0.82 (3H, d, $J_{25,27}$ = 6.5 Hz, CH_3-27), 0.79 (3H, s, CH_3-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9 (C-5), 134.9 (C-23), 121.4 (C-6), 117.5 (C-23¹), 110.9 (C-22), 80.3 (C-16), 71.8 (C-3), 66.2 (C-26), 61.0 (C-17), 56.5 (C-14), 50.1 (C-9), 42.3 (C-4), 40.5 (C-10), 40.1 (C-20), 37.3 (C-1), 37.1 (C-12), 36.7 (C-13), 32.7 (C-7), 32.1 (C-15), 31.8 (C-8), 31.7 (C-2), 31.6 (C-24), 31.4 (C-25), 21.0 (C-11), 19.5 (C-19), 17.4 (C-27), 16.5 (C-18), 14.8 (C-21), 12.7 (C-23²). Anal. Calc for $C_{29}H_{44}O_3$: C 79.04%; H 10.06%; O 10.89% Found: C 78.95%; H 10.11%, O 10.89%.

[23(23¹)*E*]-23-ethylidenediosgenin acetate 7b. A solution of 1 mL de pyridine, 2 mL de CH_2Cl_2 and 200 mg (0.45 mmol) of 23-ethylidenediosgenin **7a** was added by 2 mL (21 mmol) of acetic anhydride and the reaction mixture was stirred at room temperature for 5 hr. The reaction mixture was poured over iced water and extracted with CH_2Cl_2/H_2O, the organic phase was washed with 5% HCl, neutralized with $NaHCO_3$ and dried over Na_2SO_4.The solution was evaporated to dryness to give 180 mg (83% yield) of **7b**.

IR (KBr): ν_{max} cm^{-1} 1740 (AcO), 1629 (C=C), 1200 (C-O). ^1H NMR (400 MHz, $CDCl_3$) δ : 5.55 (1H, q, $J_{23^1,23^2}$ = 6.2 Hz, H-23¹), 5.33 (1H, d, *J* = 4.8 Hz, H-6), 4.57 (1H, m, H-16), 3.46 (2H, m, H-26*eq*, H-26*ax*), 2.43 (1H, m, H-20), 1.99 (3H, s, 3-OCOCH_3), 1.60 (3H, d, *J* = 6.5 Hz, CH_3-23²), 1.00 (3H, s, CH_3-19), 0.96 (3H, d, $J_{20,21}$ = 6.0 Hz, CH_3-21), 0.80 (3H, d, $J_{25,27}$ = 6.5 Hz, CH_3-27), 0.79 (3H, s,CH_3-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6 (3-O*CO*CH_3), 139.7 (C-5), 134.9 (C-23), 122.4 (C-6) 117.5 (C-23¹), 110.9 (C-22), 80.3 (C-16), 73.9 (C-3), 66.1 (C-26), 61.5 (C-17), 56.4 (C-14), 50.0 (C-9), 40.4 (C-4), 40.0 (C-10), 38.1 (C-1), 37.1 (C-20), 37.0 (C-12), 36.8 (C-13), 32.7 (C-8), 32.1 (C-15), 31.8 (C-7), 31.7 (C-2), 31.4 (C-25), 27.8 (C- 24), 21.5 (3-OCOCH_3), 20.9 (C-11), 19.4 (C-19), 17.4 (C-27), 16.5 (C-18), 14.8 (C-21), 12.7 (C-23²).

(23*S*,23¹*R*,25*R*)-23¹,26-epoxy-23-ethylfurosta-5,20(22)-dien-3β-ol acetate (9). A solution of 300 mg (0.62 mmol) of **7b** and 150 mg of *p*-TsOH, in 5 mL of benzene, was refluxed for 30 min. The solvent was evaporated and the residue dissolved in CH_2Cl_2, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was submitted to chromatography over silica gel and eluted with petroleum ether/AcOEt (4:1) to give 270 mg (90%) of **9**. IR: ν_{max} cm^{-1} 1736 (AcO), 1629 (C=C). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.33 (1H, d, *J* = 4.8 Hz, H-6), 4.66 (1H, m, H-16), 4.53 (1H, m, H-3), 3.75 (1H, ddd, $J_{26eq,26ax}$ = 11.0 Hz, $J_{26eq,25}$ = 3.4 Hz, $J_{26eq,24eq}$ = 1.4 Hz, H-26*eq*), 3.39 (1H, dq, $J_{23,23}{}^1$ = 9.54 Hz y $J_{23^1,23^2}$ = 6.2 Hz, H-23¹), 2.93 (1H, dd, $J_{26ax,26eq}$ = $J_{26ax,25}$ = 11.0 Hz, H-26*ax*), 2.37 (1H, d, $J_{17,16}$ = 10.0 Hz, H-17), 2.00 (3H, s, 3-OCOCH_3), 1.57 (3H, s, CH_3-21), 1.09 (3H, d, $J_{23^2,23^1}$ = 6.5 Hz, C-23²), 0.99 (3H, s, CH_3-19), 0.75 (3H, d, $J_{25,27}$ = 7.0 Hz, CH_3-27), 0.63 (3H, s, CH_3-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 170.4 (3-O*C*OCH$_3$), 152.1 (C-22), 139.7 (C-5), 122.4 (C-6), 104.6 (C-20), 84.4 (C-16), 75.1 (C-23¹), 74.4 (C-26), 73.8 (C-3), 64.0 (C-17), 55.0 (C-14), 50.0 (C-9), 43.3 (C-10), 41.1 (C-23), 39.5 (C-4), 38.2 (C-15), 37.3 (C-1), 36.2 (C-12), 36.0 (C-2), 34.2 (C-13), 32.2 (C-7), 31.2 (C-8), 31.0 (C-25), 27.8 (C-24), 21.5 (3-OCO***C***H_3), 21.0 (C-11), 19.8 (CH_3-23²), 19.4 (CH_3-19), 17.1 (CH_3-27), 13.9 (CH_3-18), 11.6 (CH_3-21).

(2'*R*,3'*S*,5'*R*)-20-oxopregn-5-ene-3b,16b-diol 3-acetate 16-(2',5'-dimethyl)tetrahydro-pyran-3'-carboxylate (10). To a solution of 270 mg (0.56 mmol) of **9**, in 2 mL de CH_3CN and 4 mL de CH_2Cl_2, were added 400 mg (1.9 mmol) of $NaIO_4$ (dissolved in 1 mL de H_2O) and a catalytic quantity of $RuCl_3$. The reaction mixture was vigorously stirred at room temperature for 2 h, filtered over silica gel and washed with CH_2Cl_2. The product was evaporated to dryness and the residue purified by chromatography over silica gel. The fractions eluted with petroleum ether/EtOAc (9:1) gave 150 mg (52%) of **10**. IR: ν_{max} cm^{-1} 1736 (AcO), 1200 (C-O). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.48 (1H, m, H-16), 5.33 (1H, d, *J* = 4.8 Hz, H-6), 4.57 (1H, m, H-3), 3.80 (1H, ddd, $J_{6'eq,6'ax}$ = 11.0 Hz, $J_{6'ax,5'}$ = 3.4 Hz, $J_{6'eq,4'eq}$ = 1.8 Hz, H-6'*eq*), 3.42 (1H, dq, $J_{2',3'}$ = 9.8 Hz y $J_{2',2''}$ = 6.1 Hz, H-2'), 2.97 (1H, dd, $J_{6'ax,6'eq}$ = $J_{26ax,25}$ = 11.0 Hz, H-6'*ax*), 2.37 (1H, d, $J_{17,16}$ = 10.0 Hz, H-17), 2.06 (3H, s, 3-OCOCH_3), 2.00 (3H, s, CH_3-21), 1.15 (3H, d, $J_{2'',2'}$ = 6.5 Hz, CH_3-2''), 1.05 (3H, s, CH_3-19) 1.01 (3H, s, CH_3-18), 0.78 (3H, d, $J_{5',5''}$ = 7.0 Hz, CH_3-5''). ^{13}C NMR (100 MHz, $CDCl_3$) d:

205.3 (C-20), 173.4 (C-3''), 170.7 (3-O*C*OCH$_3$) 140.0 (C-5), 122.0 (C-6), 74.6 (C-16), 74.2 (C-2′), 73.9 (C-6'), 73.7 (C-3), 66.7 (C-17), 54.3 (C-14), 50.0 (C-9), 49.5 (C-3'), 42.1 (C-10), 38.1 (C-15), 37.9 (C-1), 37.0 (C-12), 36.7 (C-4), 35.9 (C-13), 35.4 (C-2), 31.6 (C-7), 30.8 (C-8), 30.4 (C-21), 30.0 (C-5'), 27.8 (C-4'), 21.5 (3-OCO*CH$_3$*), 20.3 (C-11), 20.1 (CH$_3$-2′′), 19.4 (CH$_3$-18), 16.8 (CH$_3$-5′′), 13.5 (CH$_3$-19).

(2*R*,3*S*,5*R*)-2,5-dimethyltetrahydropyran-3-carboxylic acid (12). To a solution of 100 mg (0.19 mmol) of **10** in 5 mL of MeOH, was added 100 mg (1.78 mmol) of KOH in 0.5 mL of H_2O. The reaction mixture was refluxed for 30 min, then extracted with CH_2Cl_2 (2x30 mL). The organic phase was dried over Na_2SO_4 to give 3b-hydroxypregnan-5,16-dien-20-one (**11**). The aqueous phase was neutralized with HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was submitted to chromatography over silica gel to give 29 mg (97% yield) of **(2*R*,3*S*,5*R*)-2,5-dimethyltetrahydropyran-3-carboxylic** (**12**). IR: ν_{max} cm^{-1} 3176 (OH), 1700 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.85 (1H, ddd, $J_{6eq,6ax}$ = 11.0 Hz, $J_{6eq,5ax}$ = 3.8 Hz, $J_{6eq,4eq}$ = 2 Hz, H-6*eq*), 3.48 (1H, dq, $J_{2ax,3ax}$ = 9.9 Hz, $J_{2ax,2'}$ = 6.2 Hz, H-2), 3.03 (1H, t, $J_{6ax,6eq}$ = $J_{6ax,5ax}$ = 11.0 Hz, H-6*ax*), 2.30 (1H, ddd, $J_{3ax,4ax}$ = 12.5 Hz, $J_{3ax,2ax}$ = 9.9 Hz, $J_{3ax,4eq}$ = 3.7 Hz, H-3*ax*), 2.06 (1H, dtd, $J_{4eq,4ax}$ = 12.5 Hz, $J_{4eq,5ax}$ = $J_{4eq,3ax}$ = 3.7 Hz, $J_{4eq,2eq}$ = 2.0 Hz, H-4*eq*), 1.72 (1H, m, H-5), 1.37 (1H, q, $J_{4ax,4eq}$ = $J_{4ax,5ax}$ = $J_{4ax,3ax}$ = 12.5 Hz, H-4*ax*), 1.23 (3H, d, $J_{2ax,2'}$ = 6.2 Hz, Me-2), 0.82 (3H, d, $J_{5ax,5'}$ = 6.6, Me-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.8 (COOH), 74.2 (C-6), 74.0 (C-2), 40.3 (C-3), 35.9 (C-4), 29.9 (C-5), 20.0 (*C*H$_3$-2′), 16.8 (*C*H$_3$-5′).

Supplementary Data

Crystallographic data have been deposited at the Cambridge Crystallographic Data Center with deposition number CCDC 603727 for compound **7a**. Copies of the information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB1EZ, UK (fax:+44 1223 336; e-mail deposit@ccdc.cam.uk or http://www.ccdc.cam.ac.uk).

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