Conformational and Configurational Analysis of (2R,3S,5R)-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 pyracarboxylic acid was prepared from 23-ethylidene-diosgenin 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.

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 H-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 H-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-dimethyltetrahydropyran-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-epoxycholestenone [15-17]. From diosgenin (1), we have shown that the corresponding (22E)-(25R)-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 H23ax that leads to different ratios of

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 como paso clave de una serie de reacciones que involucran el rompimiento de la cadena lateral del sapogeno en medio ácido.

Palabras clave. RMN, sapogeninas, programa ALTONA, análisis conformacional, análisis configuracional.

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 25R series [15] but it decreased to nearly 50% in the 25S 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')E]-23-ethylidendiosgenin acetate 7b.

Results and Discussion

The formation of 23-ethylidenetigogenin (5) in about 70% yield, through the action of LiAlH₄ on (22E)-(25R)-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-ethylidendiosgenin (7a) in 90% yield from (22E)-(25R)-23-acetyl-5α-furosta-5,22-diene-3β,26-diol diacetate (6) as well as from 2 (Scheme 4).

13C NMR data of 23-ethylidenediosgenin were in agreement with those of the previously reported 23-ethylidenesarsasapogenin [23].

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'. 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 (25R)-spirostene 7a, product with the natural configuration at C-22.

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') 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 NaBH₄, 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 (25R)-22,26-epoxy-23-vinylcholest-22-en-3β,16β-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 (23S,23'R,25R)-23,26-epoxy-23-ethylfurosta-5,20(22)dien-3β-ol acetate (9). The configuration at the C-23 y C-23' newly formed stereogenic centers was established from the degradation products as shown in Scheme 6. Subsequent oxidation of 9 with RuO₄ afforded (2'R,3'S,5'R)-20-oxopregn-5-ene-3β,16β-diol 3-acetate 16-(2',5'-dimethyl)tetrahydropyran-
Conformational and Configurational Analysis of (2R,3S,5R)-2,5-Dimethyltetrahydropyran-3-Carboxylic acid

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

The 400 MHz 1H 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-232) 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 at 139.7 and 122.4 ppm while C-16, C-23, 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, in a Michael type nucleophilic attack. Subsequent protonation of Δ22 at C-23 from the Re face is promoted by the furanic oxygen atom. The methyl groups at C-23 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 Δ20(22) using RuO4 was successfully carried out leading to pregnane ester 10 (Scheme 6). The 1H 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
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 1H 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 epoxysterone derivative 2), were assigned to the diastereotopic protons H-6ax and H-6eq, respectively. The signal corresponding to the new stereogenic center (C-2) appeared as a doublet of quartets (J_{2ax,2ax} = 9.9 Hz, J_{2ax,2'ax} = 6.2 Hz) at δ 3.48; showing a characteristic trans diaxial coupling with H-3. The ddd at δ 2.30 (J_{2ax,4eq} = 12.5 Hz, J_{2ax,2ax} = 9.9 Hz, J_{2ax,3ax} = 3.7 Hz) was assigned to H-3; the first two coupling constants are characteristic for trans diaxial couplings with H-2ax y H-4ax and confirm the S configuration for C-3. These results allow to determine that the stereochemistry at C-5 is retained therefore it can be 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_{exp}) by means of the ALTONA software [1a]. On the basis of J_{exp} and f_{exp} values Molecular Mechanics (AM1) and Density Functional Theory (DFT) were used to optimize the configuration 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_{H3ax-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 5S-isomer).

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

The 13C-NMR spectrum of (2R,3S,5R)-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 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_3), since these signals have a chemical shift difference of only δ 0.2.

**Conclusions**

The 23-ethylidene derivative 7b was successfully transformed into the epoxycarboxylic 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 2R,3S. Therefore, the configurations at C-23 and C-23' in 23-ethyl-23,26-epoxyfurost-5,22-diene (9) must be 23R,23'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 (1H) and 100 MHz (13C) 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

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

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<td>12.2</td>
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<td>11.6</td>
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Perkin Elmer 241 polarimeter in CHCl₃ 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.

Calculations 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 B3LYP/6-31G* level of theory. Molecular modeling was realized using AM1 calculations (HyperChem 7.0).

1H NMR (400 MHz, CDCl₃) δ: 5.56 (1H, m, H-233), 5.28 (1H, m, H-6), 4.66 (1H, m, H-16), 4.35 (1H, m, H-3), 3.75 (1H, ddd, J₂0,21 = 5.5 Hz, J₂0,21 = 11.0 Hz, J₂0,21 = 3.4 Hz, J₂0,21 = 1.4 Hz, H-26eq), 3.39 (1H, d, J₂0,21 = 9.54 Hz y J₂0,21 = 6.2 Hz, H-233), 2.93 (1H, d, J₂0,21 = 11.0 Hz, H-6ax), 2.37 (1H, d, J₂0,21 = 10.0 Hz, H-17), 2.00 (3H, s, 3-OCCOCH₃), 1.57 (3H, s, CH₃-19), 0.99 (3H, s, CH₃-18). 13C NMR (100 MHz, CDCl₃) δ: 170.4 (3-OCO), 152.1 (C-22), 139.7 (C-5), 122.4 (C-6), 104.6 (C-20), 84.4 (C-16), 75.1 (C-23), 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-OCCOCH₃), 20.1 (C-11), 19.8 (CH₂-23), 19.4 (CH₃-19), 17.1 (CH₂-27), 13.9 (CH₂-18), 11.6 (CH₃-21).

**(2R,23R,25R)-23,26-epoxy-23-ethylidenediosgenin-5α,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 CH₂Cl₂, washed with H₂O, dried over Na₂SO₄ 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: νₘₐₓ cm⁻¹ 1736 (AcO), 1629 (C=O). 1H NMR (400 MHz, CDCl₃) 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, J₂0,21 = 5.5 Hz, J₂0,21 = 11.0 Hz, J₂0,21 = 3.4 Hz, J₂0,21 = 1.4 Hz, H-26eq), 3.39 (1H, d, J₂0,21 = 9.54 Hz y J₂0,21 = 6.2 Hz, H-233), 2.93 (1H, d, J₂0,21 = 11.0 Hz, H-6ax), 2.37 (1H, d, J₂0,21 = 10.0 Hz, H-17), 2.00 (3H, s, 3-OCCOCH₃), 1.57 (3H, s, CH₃-19), 0.99 (3H, s, CH₃-18). 13C NMR (100 MHz, CDCl₃) δ: 170.4 (3-OCO), 152.1 (C-22), 139.7 (C-5), 122.4 (C-6), 104.6 (C-20), 84.4 (C-16), 75.1 (C-23), 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-OCCOCH₃), 20.1 (C-11), 19.8 (CH₂-23), 19.4 (CH₃-19), 17.1 (CH₂-27), 13.9 (CH₂-18), 11.6 (CH₃-21).

**(2R,33S,53R)-20-oxopregn-5-ene-3b,16b-diol 3-acetate (25)**. A solution of 270 mg (0.56 mmol) of 9, in 2 mL of CH₂CN and 4 mL of de CH₂Cl₂, were added 400 mg (1.9 mmol) of NaIO₄ (dissolved in 1 mL of H₂O) and a catalytic quantity of RuCl₃. The reaction mixture was vigorously stirred at room temperature for 2 h, filtered over silica gel and washed with CH₂Cl₂. 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: νₘₐₓ cm⁻¹ 1736 (AcO), 1200 (C=O). 1H NMR (400 MHz, CDCl₃) 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, J₂0,21 = 11.0 Hz, J₂0,21 = 3.4 Hz, J₂0,21 = 1.4 Hz, H-26eq), 3.42 (1H, d, J₂0,21 = 9.8 Hz y J₂0,21 = 6.1 Hz, H-2), 2.97 (1H, dd, J₂0,21 = 3.11 Hz, H-2), 2.37 (1H, d, J₂0,21 = 10.0 Hz, H-17), 2.06 (3H, s, 3-OCCOCH₃), 2.00 (3H, s, CH₃-21), 1.15 (3H, d, J₂0,21 = 6.5 Hz, CH₃-21), 1.05 (3H, s, CH₃-19), 1.01 (3H, s, CH₃-18), 0.78 (3H, d, J₂0,21 = 7.0 Hz, CH₃-5β). 13C NMR (100 MHz, CDCl₃) δ:
205.3 (C-20), 173.4 (C-3’’’), 170.7 (3-OCOCH3) 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-OCOCH3), 20.3 (C-11), 20.1 (CH2-2’’’’), 19.4 (CH3-18), 16.8 (CH3-5’’’), 13.5 (CH3-19).

(2R,3S,5R)-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 H2O. The reaction mixture was refluxed for 30 min, then extracted with CH2Cl2 (2x30 mL). The organic phase was dried over Na2SO4 to give 3b-hydroxypregnan-5,16-dien-20-one (11). The aqueous phase was neutralized with HCl and extracted with CH2Cl2. The organic phase was dried over Na2SO4 and evaporated to dryness. The residue was submitted to chromatography over silica gel to give 29 mg (97% yield) of (2R,3S,5R)-2,5-dimethyltetrahydropyran-3-carboxylic acid (12).

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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.ac.uk or http://www.ccdc.cam.ac.uk).

Acknowledgements

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References


24. Crystal data for: $\text{C}_{29}\text{H}_{44}\text{O}_3$, $M = 440.64$, crystal system: orthorhombic, colorless plate, $0.70 \times 0.44 \times 0.16 \text{mm}^3$, space group $P 2_1 2_1 2_1$, unit cell dimensions $a = 7.3789(6)$ $b = 17.4492(12)$ $c = 19.9518(17)$ Å, 6428 reflections collected on a Bruker P4 diffractometer at room temperature, with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 4.66 - 56.00$ °, independent reflections (II): 5612 ($R_{int} = 0.031$), Parameters refined: 290: Final $R$ indices [$I > 2\sigma(I)$], $R_I = 0.0456$, $wR_2 = 0.1015$, Final $R$ indices [all data] $R_F = 0.0775$, $wR_2 = 0.1185$.