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ORIGINAL PAPER

The Crystal Structure of 3-Epismilagenin Acetate and 23-Oxo-3-epismilagenin Acetate

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Abstract The crystal structure together with unambiguous assignation of ^{1}H and ^{13}C NMR signals of 3-epismilagenin acetate **4** and 23-oxo-3-epismilagenin acetate **5** are described. Compound **4**, crystallized as orthorhombic system $a = 10.535(1)$ Å, $b = 13.775$ (1) Å, $c = 18.347$ (1) Å, $\alpha = \beta = \gamma = 90°$; with space group $P2_12_12_1$; while compound **5** crystallized as a monoclinic system $a = 10.380(1)$ Å, $b = 7.327(1)$ Å, $c = 17.881(1)$ Å, $\alpha = \gamma = 90°$, $\beta = 99.56(1)°$, with a space group $P2_1$. The presence a carbonyl group at C(23) in compound **5** produces a significant deviation from the chair conformation observed in compound **4**. The effects of the side chain modifications on the puckering parameters derived from are discussed.

Keywords Steroids · Spirostanes · 23-Oxospirostan · NMR · X-ray structure · Puckering parameters · Ring conformation

Introduction

Steroids bearing different oxygenated spiroketal side chains are wide spread in both the natural and synthetic domains. Steroid sapogenins, which particular reactivity have produced a large variety of interesting reactions and rearrangements [1–21] are characterized by the presence of a 16β,22:22,26-diepoxy moiety in side chain and can be regarded as **1**,6-dioxaspiro[4.5]decane derivatives. This kind of compounds have been subject of much research due its intrinsic biological activity [22–27] or their usefulness as staring materials for the synthesis of different bioactive compounds as sexual and adrenocortical hormones [1], ecdysteroids [28] plant growth stimulators [29–35] and cytotoxic steroids [36–41], among many others.

As a part of our project to explore the reactivity and applications of steroid bearing spiroketals side chains, we have focused our attention on different steroid sapogenins bearing intact or functionalized side chains that serve as starting materials for the synthesis of bioactive compounds. Consequently we need the detailed characterization of several compounds that are being employed as starting materials for different chemical transformations. Here in we report on the assignments of all ^{1}H and ^{13}C chemical shifts of 3-epismilagenin acetate **4** and 23-oxo-3-epismilagenin acetate **5**. The structures of compounds **4** and **5** as well as the configuration of all present chiral centers were confirmed with the aid of X-ray studies.

Experimental

General

Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY–NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. Melting points were measured on a Melt-Temp II equipment and are uncorrected. Mass spectra were registered in a thermoelectron spectrometer model DFS (double focus sector). NMR spectra were recorded in $CDCl_3$ solution in a Varian INOVA 400 spectrometer using the solvent signal

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7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C as references. NMR signals assignments were made with the aid of DEPT and a combination of 2D homonuclear (^{1}H–^{1}H) and heteronuclear (^{1}H–^{13}C) correlation techniques, which included ^{1}H–^{1}H COSY, ^{1}H–^{1}H nuclear overhauser effect (NOESY), Total correlation spectroscopy (TOCSY), heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC). All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer.

Synthesis, Characterization and Spectroscopy

(*25R*)-*5β-spirostan-3α-ol acetate*, *namely 3-epi-smilagenin acetate* (**4**) Ac_2O (20 mL) and a few crystals of DMAP were added to a solution of **3** in pyridine (40 mL) and the mixture was stirred overnight and poured into a mixture of ice and 10% HCl (300 mL). The produced solid was filtered off and dissolved in ethyl acetate (200 mL). The organic layer was washed with 10% HCl (2 × 70 mL), 10% $CuSO_4$ aqueous solution (2 × 70 mL) and water (2 × 100 mL), dried (anh. Na_2SO_4) and evaporated to afford the acetylated compound **4** (3.6 g, 7.85 mmol, 98.7%). M.p 162–163 °C from acetone (see Tables 1 and 2 for ^{1}H and ^{13}C NMR signals). MS (70 eV): 458 M^{+}, 380, 365, 329, 284, 256, 255, 254, 239, 161, 147, 139. HRMS (70 eV): *observed* 458.3391 *required for* $C_{29}H_{46}O_4$458.3396.

(*25R*)-*3α-acetoxy-5β-spirostan-23-one*, *namely 23-oxo-3-epi-smilagenin acetate* (**5**) $BF_3{\cdot}Et_2O$ (8 mL, 64.8 mmol) was added to a solution of **4** (8 g, 17.44 mmol) in glacial acetic acid (200 mL). To the stirred mixture $NaNO_2$ (1.4 g, 19.7 mmol) was added over 20 min. The additions of $BF_3{\cdot}Et_2O$ and $NaNO_2$ were repeated, the reaction mixture was poured into ice-water (1 L). The separated solid was filtered off and, washed with water (4 L), dissolved in CH_2Cl_2 (200 mL), dried (anh. Na_2SO_4) and evaporated. The produced residue was dissolved in the minimum amount of 1/1 hexane/benzene mixture applied to a chromatographic column packed with Al_2O_3 (Brockmann activity III), and eluted with 10/1 hexane/ethyl acetate

Table 2 ^{13}C chemical shifts of compounds **4** and **5**

C (Number)	4	5	C (Number)	4	5 (Δ ppm)
1	35.0	35.0	**16**	80.9	83.4 (+2.5)
2	26.6	26.6	**17**	62.3	61.8 (−0.5)
3	74.3	74.2	**18**	16.4	16.1 (−0.3)
4	32.2	32.2	**19**	23.3	23.3
5	41.8	41.8	**20**	41.6	34.7 (−6.9)
6	26.9	26.9	**21**	14.5	14.4 (−0.1)
7	26.6	26.5	**22**	109.2	109.8 (+0.6)
8	35.4	35.4	**23**	31.4	201.8 (+170.4)
9	40.5	40.5	**24**	28.8	45.2 (+16.4)
10	34.7	34.7	**25**	30.3	35.8 (+5.5)
11	20.6	20.5	**26**	66.8	65.6 (−1.2)
12	40.2	40.0	**27**	17.1	17.1 (0)
13	40.6	41.1	**CH_3COO-3**	170.6	170.5
14	56.3	56.4	**CH_3COO-3**	21.4	21.4
15	31.8	31.7			

Δ ppm associated to the changes in the side chain are given in *parentheses* and were calculated using the previous compound as reference

Table 1 ^{1}H chemical shifts of steroid sapogenins **4** and **5**

H	4	5	H	4	5
1α	1.80	1.80	**12β**	**1.70**	**1.74**
1β	1.01	1.02	**14α**	1.19 (m)	1.15
2α	1.40	1.38	**15α**	1.97 (m)	1.98 (m)
2β	1.67	1.67	**15β**	1.20 (m)	1.27
3β	4.71 (m)	4.71 (m)	**16α**	**4.38 (m)**	**4.59 (m)**
4α	1.81 (m)	1.80	**17α**	1.75	1.74
4β	1.53	1.53	**18 (CH_3)**	0.74 (s)	0.74 (s)
5β	1.44	1.44	**19 (CH_3)**	0.93 (s)	0.93 (s)
6α	1.24	1.23	**20β**	1.85	2.86 (m)
6β	1.85	1.85	**21 (CH_3)**	0.95 (d, $J = 6.9$)	0.92 (d, $J = 7.0$)
7α	1.08	1.07	**23 *a***	1.67	–
7β	1.36	1.38	**23 *b***	1.59	–
8β	1.57	1.57	**24 *Pro-S* (ax.)**	1.62	2.42 (m)
9α	1.42	1.40	**24 *Pro-R* (eq.)**	1.45 (m)	2.47 (dd, $J = 10.7, 10.7$)
11α	1.38	1.38	**25**	1.61 (m)	2.27 (m)
11β	1.24 (m)	1.23	**26 *Pro-S* (eq.)**	3.46 (ddd, $J = 10.7, 4.4, 1.6$)	3.57 (ddd, $J = 11.2, 4.6, 1.4$)
12α	1.17	1.13	**26 *Pro-R* (ax.)**	3.36 (dd, $J = 10.9, 10.9$)	3.77 (dd, $J = 11.3, 11.3$)

mixture. The collected fractions were evaporated to afford the ketone **5** (4.5 g, 9.52 mmol, 54.6%). M.p 184–186 °C *from ethyl acetate/hexane* (see Tables 1 and 2 for ^{1}H and ^{13}C NMR signals). MS (FAB): 473 MH^{+}, 444, 389, 329, 255. HRMS (FAB) *observed* 473.3260 *required for* $C_{29}H_{45}O_5$473.3267.

Crystallography

Suitable crystals for X-ray diffraction studies were obtained from the analytical samples as follows: crystals of **4** on cooling from a warm acetone solution; crystals of **5** on overnight cooling from a warm ethyl acetate solution. Compound **5** crystallized as a monoclinic system with a space group $P2_1$; while compound **4,** crystallized as orthorhombic systems with space group $P2_12_12_1$. X-ray diffraction measurements were performed on an oxford diffraction atlas (Gemini) diffractometer with Mo K_α radiation $\lambda = 0.71073$ Å. Data collection routine and data reduction were carried out with the CrysAlisPro, Oxford Diffraction Ltd., Oxford Diffraction [42]. The structures of all molecules were solved using SIR2004 [43] and refined using SHELXL-97 [44]. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were found in difference Fourier maps, placed at geometrically calculated positions and refined using the riding model. The obtained bond lengths and angles of each compound are normal and are available from the electronic supporting information (CIF file) for the structure. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center as supplementary material numbers CCDC 773327 **4**, CCDC 773329 **5**. 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.

Results and Discussion

3-Epismilagenin acetate **4** was obtained by acetylation of 3-epismilagenin **3** following the standard Ac_2O/pyridine procedure. Treatment of 3-epismilagenin acetate **4** with $NaNO_2$ and $BF_3{\cdot}Et_2O$ in acetic acid followed by column chromatography in Al_2O_3 (Brockman Activity III) afforded the ketone **5** (Scheme 1).

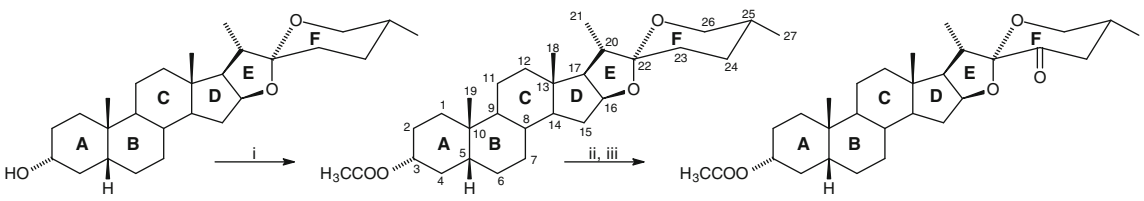
Crystallographic Studies

The absolute configuration of the studied compound **5** was considered and corroborated as that from the starting material **4**. Both studied compounds contain the steroid ABCD fused framework with the axial methyl groups attached to C(10) and C(13). All compounds show cis A/B, trans B/C and trans C/D ring junctions. Compounds **4** and **5** bear the 16β,22:22,26-diepoxy moiety characteristic of the spirostanic side chain. Puckering parameters for compounds **4**, and **5**, were calculated as described by Cremer and Pople [45] (Table 3).

In compound **4** the equatorial acetoxy group bonded to C(3) is arranged in such a way that the carbonyl O atom is close to eclipse the axial H atom attached to C(3) and does not disturb A ring, which presents a conformation very similar to a chair. B ring assumes an almost perfect chair conformation while C ring assumes a perfect chair conformation. D ring can be described as cyclopentane twisted on C(13)–C(14). E Ring is an envelope in O(3)-exo with absolute L configuration. The tetrahydrofuran E ring is cis-fused to the cyclopentane D ring. Finally F ring assumes a conformation very similar to a chair, (see Table 4; Fig. 1). The crystal structure of compound **4** is shown in Fig. 2, with the ellipsoid drawn at the 50% of probability [46].

The molecules in the unit cell of **4** show no classic hydrogen bonds and all are linked via short contacts at C–H···O hydrogen bonds, C(18)–H(18B)···O(3) (2.56 H···O, 3.267(3) C···O). The packing of the crystal is assumed to be dictated by van der Waals interactions and intermolecular C–H···O hydrogen bonds. In Fig. 3 two view of the cell packing of this compound is shown. Where it can be observed less symmetrical arrangement than in **5**.

In compound **5**, the equatorial acetoxy group bonded to C(3) is arranged in such a way that the carbonylic oxygen nearly eclipses the axial H atom attached to C(3) and does not disturb A ring, which present a chair conformation. While B ring assumes a perfect chair conformation, C ring is very similar to a chair. D ring can be described as cyclopentane twisted on C(13)–C(14). Finally E ring



i) Ac_2O/pyr, RT, overnigth; ii) $BF_3{\cdot}Et_2O/NaNO_2/H_3CCOOH$; iii) Al_2O_3

Scheme 1 Synthetic approach, carbon numbering and ring designation of studied compounds

Table 3 Crystal data and structure refinement for **4** and **5**

Identification code	**4**	**5**
Empirical formula	$C_{29}H_{46}O_4$	$C_{29}H_{44}O_5$
Formula weight	458.66	472.64
Temperature (K)	298(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Unit cell dimensions	$a = 10.5350(4)$ (Å), $\alpha = 90°$	$a = 10.3800(5)$ (Å), $\alpha = 90°$
	$b = 13.7750(6)$ (Å), $\beta = 90°$	$b = 7.3270(3)$ (Å), $\beta = 99.56(1)°$
	$c = 18.3470(7)$ (Å), $\gamma = 90°$	$c = 17.8810(8)$ (Å), $\gamma = 90°$
Volume (Å^3)	2662.51(18)	1341.02(10)
Z	4	2
Density (calculated) (Mg/m^3)	1.144	1.171
Absorption coefficient (/mm)	0.074	0.078
Diffractometer/scan	Oxford diffraction atlas (Gemini)	Oxford diffraction atlas (Gemini)
Radiation/wavelength (Å)	Mo K_α/0.71073	Mo K_α/0.71073
F(000)	1008	516
θ range for data collection (°)	3.16–26.06	3.29–26.05
Index ranges	$-12 \le h \le 13$, $-17 \le k \le 16$, $-17 \le l \le 22$	$-12 \le h \le 12$, $-9 \le k \le 6$, $-22 \le l \le 18$
Reflections collected	9313	7025
Independent reflections	2960 [R(int) = 0.0310]	2857 [R(int) = 0.0242]
Completeness to theta = 26.06°, 26.05°	99.7%	99.8%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2960/0/304	2857/1/312
Goodness-of-fit on F^2	0.972	0.962
Final R indices [I > 2σ(I)]	$R1 = 0.0363$, w$R2 = 0.0876$	$R1 = 0.0358$, w$R2 = 0.0837$
R indices (all data)	$R1 = 0.0503$, w$R2 = 0.0920$	$R1 = 0.0495$, w$R2 = 0.0869$
Absolute structure parameter	−0.006(13)	−0.006(13)
Extinction coefficient	0.0104(13)	None
Largest diff. peak and hole (e/Å^3)	0.137 and −0.110	0.125 and −0.147

Table 4 Calculated puckering parameters for compound **4**

Ring	Q (Å)	θ (°)	φ (°)	Order and direction of the calculation
A	0.552(2)	177.0(2)	213(5)	From C(1) to C(10), counterclockwise
B	0.563(2)	3.5(2)	271(3)	From C(5) to C(10), counterclockwise
C	0.564(2)	3.0(2)	226(5)	From C(8) to C(14), clockwise
F	0.533(2)	171.5 (2)	170(2)	From O(4) to C(26), clockwise
Ring	Q(2) (Å)	φ (°)		Order and direction of the calculation
D	0.488(2)	197.9(2)		From C(13) to C(17), counterclockwise
E	0.368(2)	182.1(3)		In this order; O(3), C(22) C(20), C(17), C(16)

presents an envelope O(3)-exo with absolute L configuration. The tetrahydrofuranic E ring is cis-fused to the cyclopentane D ring. The F ring assumes a conformation close to a chair that is somewhat distorted due to the presence of carbonyl function at C(23) (see Table 5). The crystal structure of compound **5** is shown in Fig. 4, with the ellipsoid drawn at the 50% of probability [46].

The two molecules in the unit cell of **5** show no classic hydrogen bonds and they are linked via short contacts at: C(8)–H(8)···O(5) (2.686 Å H···O, 3.606(2) Å C···O) and

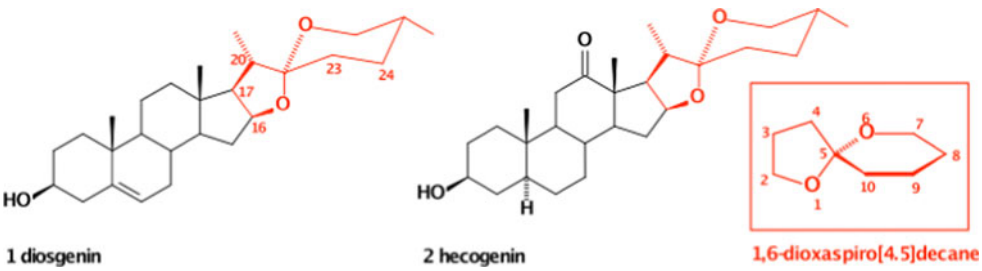


Fig. 1 Some naturally occurring steroid sapogenins

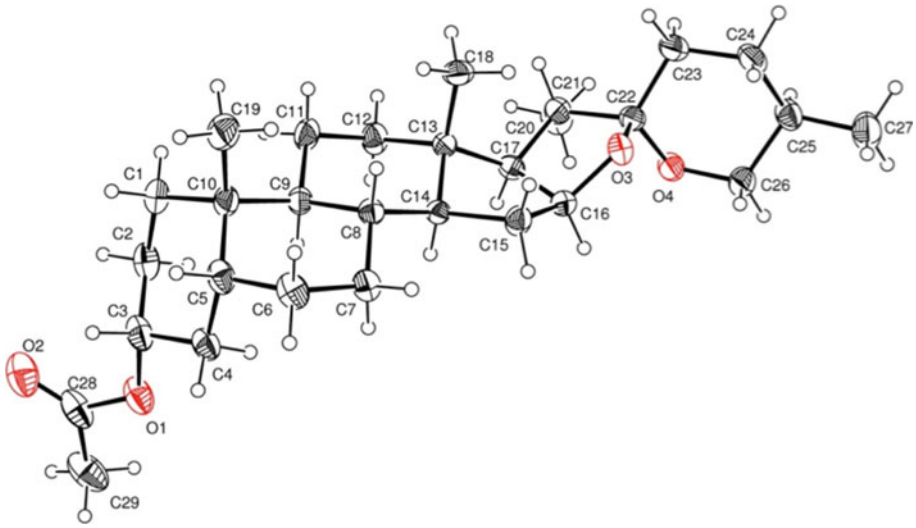


Fig. 2 Crystal structure of compound **4** with the thermal ellipsoids drawn at the 50% of probability

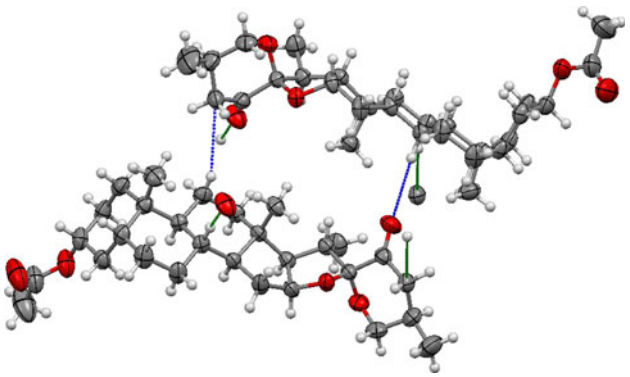


Fig. 3 View of the intermolecular interactions in compound **4**

C(11)–H(11B)···C(24) (2.870 Å H···C, 3.635(2) C···C). Each molecule has four of these short contacts and the crystal grows along the *b* axe. The packing of the crystal is assumed to be dictated by van der Waals interactions and intermolecular C–H···O hydrogen bonds. In Fig. 5 the cell packing of this compound is shown.

In order to establish quantitative differences among the studied compounds, a least-squares overlay analysis of the structures by pairs is performed. Table 6 shows the results of least-squares overlay analysis obtained with the program Mercury [47]. From the obtained data it is clear that, as expected, the modifications introduced in the side chain do not produce significant conformational changes in the

Table 5 Calculated puckering parameters for compound **5**

Ring	Q (Å)	θ (°)	φ (°)	Order and direction of the calculation
A	0.550(2)	175.9(2)	234(3)	From C(1) to C(10), counterclockwise
B	0.564(2)	0.0(2)	264(7)	From C(5) to C(10), counterclockwise
C	0.570(2)	3.1(2)	259(3)	From C(8) to C(14), clockwise
F	0.551(2)	176.7(2)	188(1)	From O(4) to C(26), clockwise
Ring	Q(2) (Å)	φ (°)		Order and direction of the calculation
D	0.474(2)	201(1)		From C(13) to C(17), counterclockwise
E	0.373(2)	110(4)		In this order; O(3), C(22), C(20), C(17), C(16)

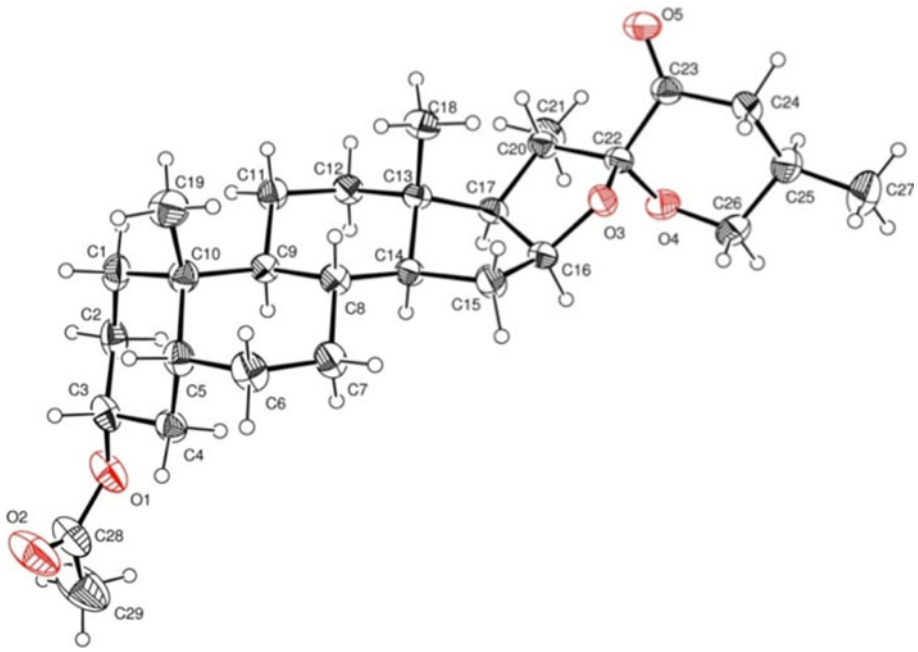


Fig. 4 Crystal structure of compound **5** with the thermal ellipsoids drawn at the 50% of probability

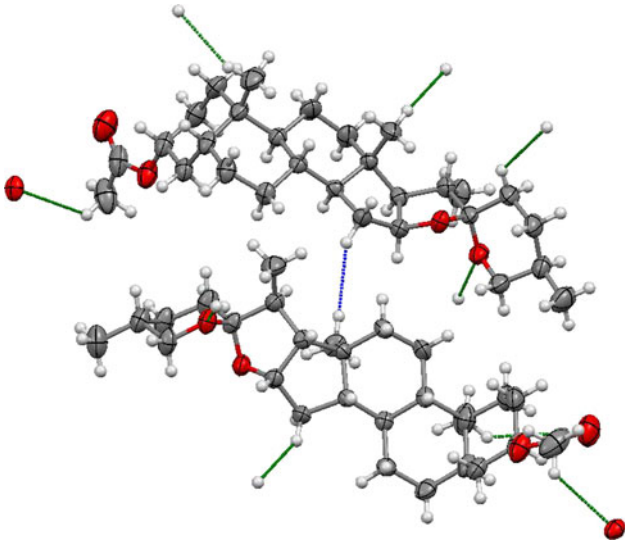


Fig. 5 View of the intermolecular interactions in compound **5**

Table 6 Least-squares overlay analysis of the rings, performed by each pair of structures

Rings	**5** vs **4**
A	0.0143
B	0.0105
C	0.0095
D	0.0158
E	0.0203
F	0.0322

Table 7 Puckering descriptors of compound **4** and **5** obtained using the PLATON program

Rings	**4**	**5**
A	Very similar to a C-form	Very similar to a C-form
B	Very similar to a C-form	C-form
C	C-form	Very similar to a C-form
D	Twisted on C(13)–C(14)	Twisted on C(13)–C(14)
E	Envelope O(3)-exo	Envelope O(3)-exo
F	Very similar to a C-form	Close to a C-form

steroid framework at least qualitatively, (notice that the observed deviation in rings A to D are less than 0.016).

While a small deviation is observed when E ring of compounds **4** and **5** are compared, introduction of the carbonyl group at C(23) in compound **5**, that implies the introduction of a sp [2] atom in the F ring results on a significant deviation from the chair conformation observed in compound **4** (*compare the puckering parameters of **4** and **5***). Table 7 shows the puckering descriptors as defined by Cremer and Pople [45] and calculated using the PLATON program [48, 49]. The minor differences observed amongst rings A to D across all compounds may be attributed to the different intermolecular interactions that are, of course, influenced by the changes introduced in the side chain.

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