Low Temperature Crystal Structure of Natural Diosgenone

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The molecular structure of diosgenone, a natural steroidal sapogenin, closely related to diosgenin and isolated from *Solanum nudum*, was solved by single crystal X-ray diffractometry at 120 K and refined by full-matrix least-squares to an agreement factor, R1 = 0.054. It crystallizes in the monoclinic space group P2$_1$, with a = 15.1870(4) Å, b = 7.2710(2) Å, c = 21.2840(6) Å, β = 99.251(1) °, and four molecules in the unit cell (Z = 4). The results constitute the first structural report on a steroidal sapogenin from the diosgenin group.

Introduction

Solanum nudum (Solanaceae), a shrub growing in different regions of South America, is used in the Pacific area of Colombia, under the names *zapata* or *zapatico*, for treatment of fevers associated with malaria. Its activity was confirmed by *in vitro* screening of ethanol extracts of the plant that showed promising antimalarial potency (Saez *et al.*, 1998). Some years ago, a steroidal alkaloid, *solanudine*, was found in the fruits of this plant (Usubillaga, 1988) and, recently, a number of steroids have been isolated from methanolic extracts of its aerial parts (Saez *et al.*, 1998).

Diosgenone, the major component of these extracts, was now isolated for the first time in a pure form from a natural source although it has been known ever since Marker *et al.* (1940) obtained it by oxidation of diosgenin and reported some of its properties and reactions. It is closely related to diosgenin and to tigogenin (Fieser and Fieser, 1949), steroids that have been used as starting points for the synthesis of sex hormones. In the present communication we report the crystal structure of this interesting natural product, which so far was only investigated by spectroscopic methods. The present study constitutes also the first structural report on a steroidal sapogenin from the diosgenin group.

Crystal data, collection procedures and refinement results are summarized in Table I. All hydrogen atoms but one of a methyl group were found among the first 90 peaks of a difference Fourier map. However, they were positioned on a stereochemical basis and refined with the riding model. The methyl H-atoms were treated in the refinement as rigid bodies and allowed to rotate around the corresponding C-C bond, such as to maximize the sum of the observed electron density at the three calculated H-positions. As expected, these refined positions converged to staggered methyl configurations.

Figure 1 is an ORTEP drawing (Johnson, 1976) showing one of the molecules present in the asymmetric unit cell. A set of selected bond distances and angles is given in Table II. There are two molecules per asymmetric unit with a quite similar conformation. The root mean squares deviation between homologous atoms for the best least-squares superposition of the two molecules performed by the algorithm of Kabsch (1976), is 0.256 Å.

As it can be seen the compound has the skeleton which is typical of steroid sapogenins (Fieser and Fieser, 1949). Because of the negligible small atomic anomalous dispersion for the radiation employed in our experiments (the molybdenum Kα-line), a reliable crystallographic determination of the absolute molecular configuration was not possible. But, the right-handed *R* chirality is supported by the presence of the cyclopentanephenanthrene molecular fragment with the same stereo conformation reported for two related natural products, namely guggulsterol-1 (Bajaj *et al.*, 1981) and 16β-methylprogesterone (Weeks *et al.*, 1976).

Empirical formula	$C_{27}H_{40}O_3$
Formula weight	412.59
Crystal system, space group	monoclinic, $P2_1$
Unit cell dimensions	$a = 15.1870(4)$ Å
	$b = 7.2710(2)$ Å
	$c = 21.2840(6)$ Å
	$\beta = 99.251(1)$ °
Volume	2319.7(1) Å^3
Z; calculated density	4; 1.181 g/mL
Absorption coefficient (μ)	0.075 mm^{-1} (Mo-Kα)
F(000)	904 electrons
Scattering θ-range for data collection	1.54 to 25.00 °
Independent reflections	7707 [R(int)] = 0.075
Observed reflections [$I > 2\sigma(I)$]	6245
Data/restraints/parameters	7707/1/549
Goodness-of-fit on F^2	1.056
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0537, wR2 = 0.1196
R indices (all data)	R1 = 0.0739, wR2 = 0.1320
Largest diff. peak and hole	0.273 and −0.262 e.Å^{-3}

Table I. Crystal data, diffraction data collection procedures and refinement results for diosgenone.

R indices defined as: $R1 = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$; $wR2 = [\Sigma w (Fo^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

The short C(14)-C(15) bond distance of 1.345(4) Å clearly confirms the location of a double bond between these two carbon atoms. The double C = O bond, at the C(13) carbon, is of 1.230(3) Å, whereas the other C-O bonds, involving the O(11) and O(12) oxygen atoms, ranged between 1.428(3) and 1.447(3) Å. The O(12)–C(122)–O(11) angle (109.8(2)°) is practically at the expected tetrahedral value.

All C-C bond distances not included explicitly in Table II ranged between 1.516 and 1.565 Å, whereas the values for the C–C–C angles not included in the Table are between 107.7 and 115.8 °.

Experimental

Isolation of diosgenone

Solanum nudum was collected in the coastal area of the department of Nariño, Colombia. A voucher sample is stored under registration number 554 in the Herbarium of the University of Antioquia (Medellín). Diosgenone was extracted from the stems and leaves of the plant as previously described (Saez *et al.*, 1998). In order to obtain single crystals adequate for a structural analysis, the product was dissolved in absolute ethanol and maintained at room temperature. After a few weeks, crystal deposition was observed.

Crystallographic study

Intensity data were collected with a colorless crystal fragment of dimensions 0.28 × 0.24 × 0.18 mm, at 120 (2) *K*, using a Kappa CCD diffrac-
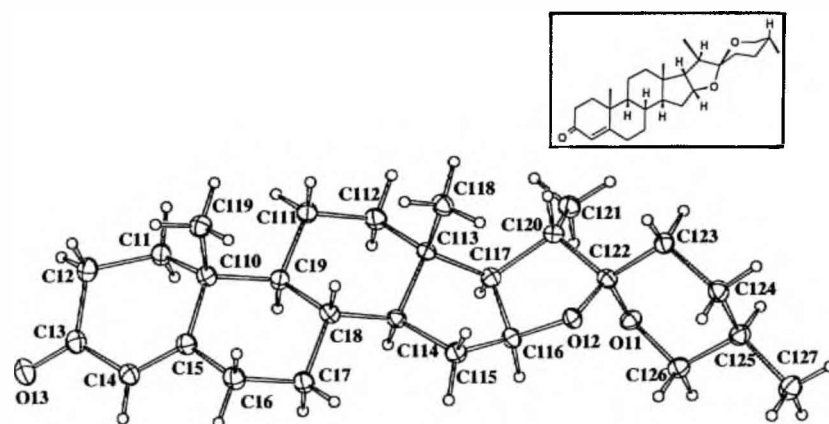

Fig. 1. Plot of one of the diosgenone molecules in the asymmetric unit showing the labeling of the non-H atoms and their displacement ellipsoids (Inset: conventional drawing of the structure).

Bond distances

C(122)–O(11)	1.428(3)	C(126)–O(11)	1.433(3)
C(122)–O(12)	1.427(3)	C(116)–O(12)	1.447(3)
C(13)–O(13)	1.230(3)	C(11)–C(12)	1.524(4)
C(11)–C(110)	1.541(4)	C(12)–C(13)	1.496(4)
C(13)–C(14)	1.467(4)	C(14)–C(15)	1.345(4)
C(15)–C(16)	1.505(4)	C(15)–C(110)	1.517(4)
C(110)–C(119)	1.543(4)	C(113)–C(118)	1.534(4)
C(116)–C(117)	1.543(4)	C(117)–C(120)	1.545(4)
C(120)–C(121)	1.519(4)	C(120)–C(122)	1.535(4)
C(122)–C(123)	1.517(4)	C(123)–C(124)	1.527(4)
C(124)–C–(125)	1.522(4)	C(125)–C(126)	1.516(4)
C(125)–C(127)	1.532(4)		

Bond angles

C(122)–O(11)–C(126)	112.7(2)	C(122)–O(12)–C(116)	105.41(18)
C(12)–C(11)–C(110)	113.4(2)	C(13)–C(12)–C(11)	111.6(2)
O(13)–C(13)–C(14)	121.2(3)	O(13)–C(13)–C(12)	123.0(3)
C(14)–C(13)–C(12)	115.7(2)	C(14)–C(15)–C(16)	119.8(3)
C(14)–C(15)–C(110)	123.7(3)	C(16)–C(15)–C(110)	116.5(2)
C(15)–C(16)–C(17)	111.8(2)	C(16)–C(17)–C(18)	111.1(3)
C(114)–C(18)–C(17)	110.8(2)	C(114)–C(18)–C(19)	108.0(2)
C(114)–C(113)–C(117)	99.3(2)	C(18)–C(114)–C(115)	120.4(2)
C(115)–C(114)–C(113)	103.1(2)	C(116)–C(115)–C(114)	101.2(2)
O(12)–C(116)–C(115)	112.6(2)	O(12)–C(116)–C(117)	105.2(2)
C(116)–C(117)–C(120)	104.5(2)	C(116)–C(117)–C(113)	104.7(2)
C(120)–C(117)–C(113)	120.9(2)	C(122)–C(120)–C(117)	102.9(2)
O(11)–C(122)–O(12)	109.8(2)	O(11)–C(122)–C(123)	111.1(2)
O(12)–C(122)–C(123)	108.5(2)	O(11)–C(122)–C(120)	106.7(2)
O(12)–C(122)–C(120)	104.6(2)	C(125)–C(124)–C(123)	110.2(2)
O(11)–C(126)–C(125)	112.2(2)	C(122)–C(123)–C(124)	112.3(2)

Table II. Selected bond distances (Å) and angles (°) for diosgenone.

tometer provided with a low-temperature device (Oxford Cryosystems, Oxford/England) and using graphite monochromated Mo-Kα radiation (λ = 0.71070 Å). The data were corrected for Lorentz and polarization effects. Absorption correction was not applied as the linear absorption coefficient (μ) is very low. The unit cell dimensions were obtained by least-squares refinement of the angular settings for 4390 reflections in the 1.00 < θ < 26.02 ° range and the structure was solved by direct and Fourier methods. The final molecular model was obtained by anisotropic full-matrix least-squares refinement of non-hydrogen atoms. Programs used were DENZO and SCALEPACK (Otwinowski and Minor, 1997) for data reduction and correction, and SHELXS-97 and SHELXL-97 (Sheldrick, 1997a,b) for structure solution and refinement, respectively.

Supplementary crystallographic data

Atomic coordinates and equivalent isotropic displacement parameters, full bond distances and angles for the two molecules in the asymmetric unit cell, anisotropic displacement parameters and hydrogen coordinates and isotropic displacement parameters can be obtained from the authors and have been deposited with the Cambridge Crystallographic Centre under the deposition number CCDC 187489.

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