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2′-(4-Fluorophenyl)-[1,2,3]triazolo-[4′,5′:16,17]androst-5-en-3β-ol methanol hemisolvate

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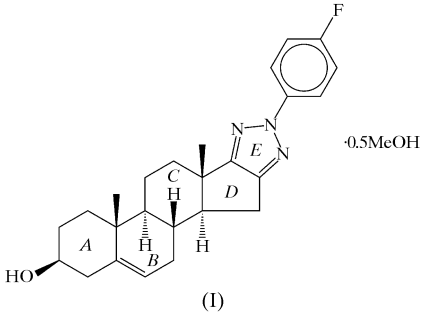
The asymmetric unit of the title compound, $C_{25}H_{30}FN_3O\cdot 0.5CH_3OH$, contains four symmetry-independent steroid and two methanol molecules. The conformations of the independent steroid molecules are very similar. Intermolecular O—H···O hydrogen bonds create two independent chains, each of which links two of the independent steroid molecules plus one methanol molecule *via* a co-operative O—H···O—H···O—H pattern. Intermolecular C—H···O and C—H···F interactions are also observed.

Comment

The present crystallographic analysis of the title compound, (I), extends our ongoing investigation of a series of androstene derivatives in order to determine the influence of different functionalities on the structure of the steroid skeleton, in particular the effect of substituents at the C3, C16 and C17 positions (Thamotharan *et al.*, 2002, and references therein; Thamotharan *et al.*, 2004).



(I)

The crystals of (I) are enantiomerically pure. However, due to the absence of any significant anomalous scatterers in (I), the absolute configuration of the molecule has not been determined by the present X-ray diffraction experiment. The enantiomer used in the refinement was assumed to correspond with the configuration of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (I).

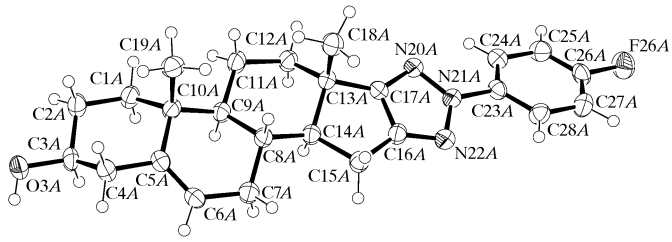


Figure 1
A view of the one of the four independent steroid molecules of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii. The other three molecules are similarly labelled (*e.g.* C1*A* = C1*B* = C1*C* = C1*D*).

The unit cell of (I), which is the asymmetric unit in this case, contains four symmetry-independent molecules, *A* to *D*, of the steroid plus two molecules of methanol. The structure was tested carefully for a relationship with a higher-symmetry space group using the program *PLATON* (Spek, 2003), but none could be found. The corresponding bond lengths and angles for the independent molecules agree well with each other. A view of the one of the four independent steroid molecules, with the atom-labelling scheme, is shown in Fig. 1.

The steroid molecules in (I) all have the same absolute configuration and longitudinally are aligned roughly parallel to one another, with adjacent molecules reversed end to end (Fig. 2). Curiously, three of the four independent steroid molecules lie with their methyl groups all pointing in roughly the same direction, while the fourth steroid molecule, *B*, is turned over, with its methyl groups pointing in the opposite direction. The core skeletons of the four independent steroid molecules have almost identical conformations, with only very minor differences in the puckering of the hydroxy-substituted cyclohexane ring (see below) or in the orientation of the plane of the *p*-fluorophenyl ring. Excluding the atoms of the *p*-fluorophenyl and hydroxy groups, the best unweighted r.m.s. fit of the corresponding remaining non-H atoms from any two molecules is 0.06 Å for molecules *B* and *C*, while the worst fit is 0.13 Å for molecules *B* and *D*. The angles between the mean planes through the *p*-fluorophenyl ring (excluding the F atom) and the adjacent five-membered ring are 18.42 (18), 19.23 (18), 2.84 (19) and 20.01 (18)° for molecules *A* to *D*, respectively, which demonstrates that the orientation of the *p*-fluorophenyl ring in molecule *C* is twisted slightly compared with its orientation in the other three molecules.

Cyclohexane ring *A* of the steroid nucleus adopts a slightly distorted chair conformation in each of the four independent molecules, with the degree of distortion being molecule *A* $\simeq$ *B* > *C* > *D*. The key puckering parameter (Cremer & Pople, 1975) for a chair conformation is θ, which should be 0° for an ideal chair. The values of θ are 10.0 (4), 9.8 (4), 6.6 (4) and 5.0 (4)° for molecules *A* to *D*, respectively, for the generic atom sequence C1—C2—C3—C4—C5—C10. Thus, the pre-

‡ Deceased.

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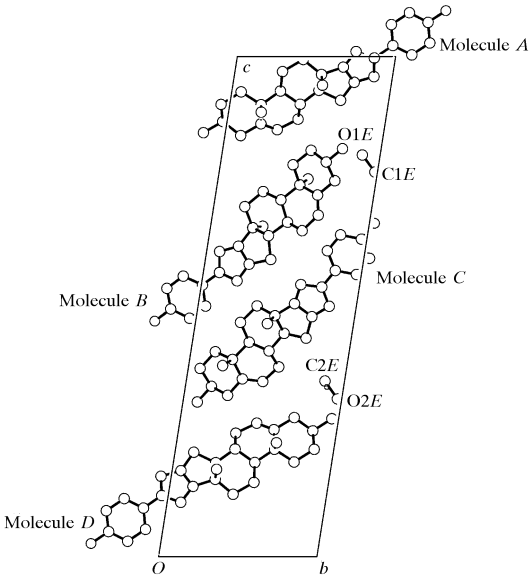

Figure 2
A view of the unique molecules of (I) in the unit cell, projected down the *a* axis. All H atoms have been omitted for clarity.

sence of a hydroxy group at C3 has slightly disturbed the usual chair conformation of ring *A* of the steroid nucleus in the molecules, although least of all in molecule *D*. The C3—O3 bond is oriented equatorially in all four molecules and is (+)synclinal to the C3—C4 bond in molecules *B*, *C* and *D*, while it is (−)synclinal to the C3—C4 bond in molecule *A*.

In cyclohexene ring *B*, the C5═C6 (Csp^2—Csp^2) distances of 1.327 (4), 1.322 (4), 1.324 (5) and 1.326 (5) Å in molecules *A* to *D*, respectively, confirm the localization of the double bond at this position. This double bond imposes an almost perfect 8β,9α-half-chair conformation on ring *B* in all four independent molecules. The ideal half-chair puckering parameters are $\theta = 50.8^\circ$ and $\varphi_2 = (60n + 30)^\circ$ (Cremer & Pople, 1975), and for the generic atom sequence C5—C6—C7—C8—C9—C10 of ring *B*, the experimental puckering parameters are $\theta = 51.5\ (4)^\circ$ and $\varphi_2 = 211.5\ (5)^\circ$ for molecule *A*, $\theta = 49.9\ (4)^\circ$ and $\varphi_2 = 212.1\ (6)^\circ$ for molecule *B*, $\theta = 52.3\ (4)^\circ$ and $\varphi_2 = 211.3\ (5)^\circ$ for molecule *C*, and $\theta = 51.7\ (4)^\circ$ and $\varphi_2 = 212.9\ (5)^\circ$ for molecule *D*.

Ring *C* assumes a distorted chair conformation in all four independent molecules, with the degree of distortion being molecule *D* $\simeq$ *A* > *C* > *B*. The values of the puckering parameter θ are 17.1 (4), 11.4 (4), 13.1 (4) and 17.1 (4)° for molecules *A* to *D*, respectively, for the generic atom sequence C8—C9—C11—C12—C13—C14.

The five-membered ring *D* of the steroid nucleus adopts a conformation approximately halfway between that of a 13β,14α-half-chair and a 14α-envelope conformation in all four independent molecules. The critical puckering parameter is φ_2 (Cremer & Pople, 1975), which has values of 206.9 (6), 207.8 (6), 209.3 (6) and 208.3 (6)° for molecules *A* to *D*, respectively, for the generic atom sequence C13—C14—C15—C16—C17. The nearest φ_2 values for ideal half-chair and envelope conformations are 198 and 216°, respectively, so the experimental values are very close to the halfway point between the ideal extremes. The pseudorotation and maximum torsion angles (Rao *et al.*, 1981) are 8.1 (4) and 35.2 (2)°, respectively, for molecule *A*, 9.1 (4) and 36.3 (2)° for molecule *B*, 10.7 (4) and 37.5 (2)° for molecule *C*, and 9.4 (4) and 36.7 (2)° for molecule *D*.

The pseudo-torsion angles C19*A*—C10*A*···C13*A*—C18*A* = 8.4 (3)° in molecule *A*, C19*B*—C10*B*···C13*B*—C18*B* = 10.7 (3)° in molecule *B*, C19*C*—C10*C*···C13*C*—C18*C* = 6.8 (3)° in molecule *C* and C19*D*—C10*D*···C13*D*—C18*D* = 8.2 (3)° in molecule *D* provide a quantitative measure of the twist about the length of the molecule, and show that the molecules in (I) are not twisted to any significant degree and that the entire molecule is quite flat, rather than being folded.

In (I), the hydroxy substituent O3*B*—H of molecule *B* acts as a donor for an intermolecular hydrogen bond with the hydroxy atom O3*A* of a neighbouring molecule *A* (Table 1), and simultaneously acts as an acceptor for an intermolecular hydrogen bond from the hydroxy group O1*E*—H of one of the methanol molecules. In turn, atom O1*E* of this methanol molecule acts as an acceptor for an intermolecular hydrogen bond from the hydroxy group O3*A*—H of a second molecule *A*. This sequence links steroid molecules *B* and *A*, plus one of the independent methanol molecules, in that order, into a co-operative O—H···O—H···O—H pattern, thus producing a chain which runs parallel to the [100] direction and has a graph-set motif of $C_3^3(6)$ (Bernstein *et al.*, 1995). The two steroid molecules extend outwards perpendicular to the direction of this chain and almost diametrically opposed to each other. An identical pattern of intermolecular hydrogen bonds links steroid molecules *C* and *D*, plus the second independent methanol molecule, in that order, into chains which run parallel to the [$\bar{1}$00] direction. Thus, the structure contains two symmetry-independent hydrogen-bonded chain motifs, which lie parallel to each other but run in opposite directions (Fig. 3).

Atoms C18*A* and C18*D* participate in weak intermolecular C—H···F interactions with atoms F26*D* and F26*A*, respec-

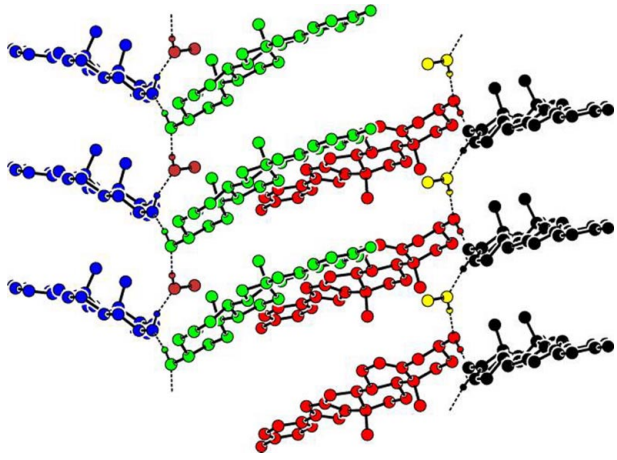

Figure 3
Two symmetry-independent hydrogen-bonded chain motifs in (I), showing the O—H···O—H···O—H pattern.

tively, of different neighbouring steroid molecules. These interactions serve to link steroid molecule *A* to molecule *D*, then to another molecule *A*, thus creating a chain with a graph-set motif of $C_2^2(22)$ running parallel to the [111] direction. Atom C14*C* has a similar interaction with atom F26*B*, thus linking steroid molecule *C* to *D*, but there is no reciprocal interaction to complete a chain or ring motif. However, all C—H···F interactions act to crosslink the two symmetry-independent O—H···O hydrogen-bonded chains. A weak intermolecular C—H···O interaction also exists between atoms C15*A* and O15*A* of two adjacent steroid molecules of type *A*, thus building a chain parallel to the *y* axis with a graph-set motif of *C*(10). Atom C15*D* of molecule *D* interacts with atom O3*C* of molecule *C*, but there is no further interaction emanating from molecule *C*.

Experimental

A solution of 3β-acetoxy-2′-*p*-fluorophenyl-5-androsteno[16,17-*d*]-triazole (0.2 g, 0.45 mmol) in methanol (30 ml) and potassium hydroxide (0.2 g) was refluxed for 30 min. The reaction mixture was poured into ice-cold water and neutralized with glacial acetic acid. The product obtained was filtered off, washed, dried and crystallized from methanol to afford (I) (institution code DPJ-258; yield 0.18 g, 99.28%; m.p. 487–489 K).

Crystal data

$C_{25}H_{30}FN_3O\cdot0.5CH_4O$	$Z = 4$
$M_r = 423.54$	$D_x = 1.266$ Mg m^{-3}
Triclinic, *P*1	Mo $K\alpha$ radiation
$a = 6.8086$ (1) Å	Cell parameters from 7675 reflections
$b = 10.5682$ (3) Å	$\theta = 2.0$–$25.0°$
$c = 32.5223$ (7) Å	$\mu = 0.09$ mm^{-1}
$\alpha = 80.7761$ (9)°	$T = 160$ (2) K
$\beta = 87.7492$ (13)°	Prism, pale yellow
$\gamma = 74.1122$ (11)°	0.35 × 0.10 × 0.08 mm
$V = 2221.61$ (9) Å^3	

Data collection

Nonius KappaCCD area-detector diffractometer	$R_{int} = 0.055$
φ and ω scans with κ offsets	$\theta_{max} = 25.1°$
30 909 measured reflections	$h = -8 \rightarrow 8$
7832 independent reflections	$k = -11 \rightarrow 12$
6305 reflections with $I > 2\sigma(I)$	$l = -38 \rightarrow 38$

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*E*—H1···O3*B*^{i}	0.92 (5)	1.78 (5)	2.697 (4)	176 (5)
O3*A*—H3*A*···O1*E*^{ii}	0.85 (5)	1.87 (5)	2.721 (4)	175 (5)
O3*B*—H3*B*···O3*A*^{iii}	0.90 (4)	1.79 (5)	2.687 (4)	175 (4)
O2*E*—H2···O3*C*^{iv}	0.83 (5)	1.89 (5)	2.715 (4)	171 (5)
O3*C*—H3*C*···O3*D*^{ii}	0.98 (7)	1.77 (6)	2.714 (4)	161 (6)
O3*D*—H3*D*···O2*E*	0.98 (6)	1.80 (6)	2.740 (4)	161 (4)
C18*D*—H18*C*···F26*A*^{v}	0.98	2.43	3.400 (4)	170
C14*C*—H143···F26*B*^{vi}	1.00	2.45	3.307 (4)	144
C15*A*—H151···O3*A*^{iii}	0.99	2.51	3.434 (4)	154
C15*D*—H157···O3*C*^{vii}	0.99	2.52	3.369 (4)	144
C18*A*—H183···F26*D*^{viii}	0.98	2.48	3.417 (4)	161

Symmetry codes: (i) $x-1, y, z$; (ii) $x, y-1, z$; (iii) $x, 1+y, z$; (iv) $1+x, 1+y, z$; (v) $1+x, y-1, z-1$; (vi) $x-1, 1+y, z$; (vii) $1+x, y, z$; (viii) $x, 1+y, 1+z$.

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0402P)^2 + 0.1129P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.093$	$\Delta\rho_{max} = 0.17$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.18$ e Å^{-3}
7832 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
1152 parameters	Extinction coefficient: 0.0138 (16)
H atoms treated by a mixture of independent and constrained refinement	

The positions of the hydroxy H atoms were determined from a difference Fourier map and refined freely along with their isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with $U_{iso}(H) = 1.5U_{eq}(C)$, but were allowed to rotate freely about the C—C bonds. All remaining H atoms were placed in geometrically idealized positions (C—H = 0.95–1.00 Å) and were constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$. Due to the absence of any significant anomalous scatterers in (I), attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 6782 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of 0.1 (4). Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond with that of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (I). Reflections $01\bar{2}$, $01\bar{1}$, 012, 004, 010, 011, $11\bar{3}$, $0\bar{1}2$, $0\bar{1}1$ and $\bar{1}\bar{1}3$ were partially obscured by the beam stop and were omitted.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SnB* (Miller *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1714). Services for accessing these data are described at the back of the journal.

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