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Accurate stereochemistry for two related 22,26-epiminocholestene derivatives

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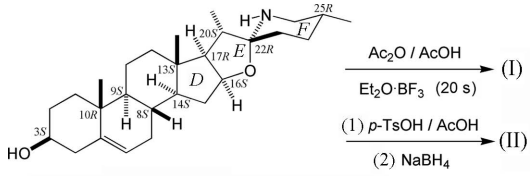
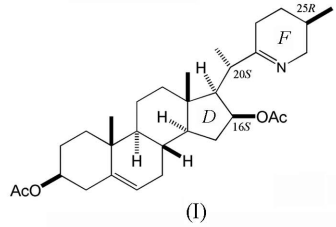
Regioselective opening of ring *E* of solasodine under various conditions afforded (25*R*)-22,26-epiminocholesta-5,22(*N*)-diene-3β,16β-diyl diacetate (previously known as 3,16-diacetyl pseudosolasodine B), $C_{31}H_{47}NO_4$, or (22*S*,25*R*)-16β-hydroxy-22,26-epiminocholesta-5-en-3β-yl acetate (a derivative of the naturally occurring alkaloid oblonginine), $C_{29}H_{47}NO_3$. In both cases, the reactions are carried out with retention of chirality at the C16, C20 and C25 stereogenic centers, which are found to be *S*, *S* and *R*, respectively. Although pseudosolasodine was synthesized 50 years ago, these accurate assignments clarify some controversial points about the actual stereochemistry for these alkaloids. This is of particular importance in the case of oblonginine, since this compound is currently under consideration for the treatment of aphasia arising from apoplexy; the present study defines a diastereoisomerically pure compound for pharmacological studies.

Comment

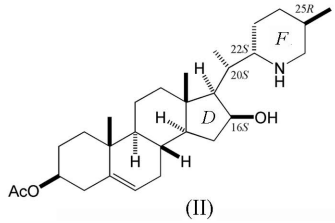
Many plants of the Solanaceae family accumulate steroidal alkaloids based on the C_{27} cholestane skeleton, *e.g.* solasodine, (1), and tomatidine, which are N-analogues of sapogenins (Friedman & McDonald, 1997). For a long time, (1) has been an essential starting material for the partial synthesis of pregnane derivatives (Sato *et al.*, 1957). 22,26-Epiminocholestenes are also accessible from (1), through a selective *E*-ring cleavage under reductive conditions (Bird *et al.*, 1979) or by acidic acetolysis. For instance, Sato *et al.* (1957) performed a selective *E*-ring opening of (1) by treatment with Ac_2O/AcOH and $ZnCl_2$ at 298 K over a long time period, affording the 22,26-epiminocholestadiene framework (I), also known as 3,16-diacetyl pseudosolasodine B.

During our work on sapogenin acetolysis, we probed a variety of Lewis acids with the hope of optimizing both the ability to regioselectively open ring *E* and the reaction rates. We have found that $Et_2O{\cdot}BF_3$ gives excellent results. In this way, (I) may be prepared starting from (1) in quantitative yield in remarkably short reaction times (see scheme). All spectroscopic and physical data for the product fit well with those of an authentic sample of pseudosolasodine B diacetate. However, an X-ray study was necessary in order to assess the absolute configuration at atom C20. This aspect should not be seen as a trivial matter, since Yang *et al.* (2004) claimed that epimerization at C20 occurs if an acid harder than $ZnCl_2$ is used. We, however, have never detected such an epimerization in the case of sapogenins treated under similar conditions (Sandoval-Ramírez *et al.*, 1999, 2003). It is also known that the reaction course may be complicated by nucleophilic attacks at atom C16 (Iglesias-Arteaga *et al.*, 2004) and epimerization at atom C25 (LaCour *et al.*, 1999).





(I)



(II)

A similar controversy about stereochemistry appeared in the case of oblonginine, a naturally occurring 22,26-epiminocholestene. The molecule was first assigned a stereochemistry of 22*R*,25*S* (Kadota *et al.*, 1995). However, a re-examination using X-ray crystallography and high-resolution NMR spectroscopy revealed that oblonginine is (22*S*,25*R*)-22,26-epiminocholest-5-en-3β-ol (Lowe *et al.*, 1998). The X-ray structure of oblonginine monohydrate reported in that paper was unfortunately not deposited with the Cambridge Structural Database (Version 5.29; Allen, 2002) (see refcode CADNIE). We can now confirm this assignment on the basis of the X-ray structure of a C16-functionalized oblonginine monoacetate, (II), synthesized from (1) following a published procedure (Kusano *et al.*, 1970; see scheme).

The *A*–*D* steroidal nucleus of (I) exhibits the expected geometry, identical to that of solasodine (Vega-Baez *et al.*, 2006). The cleavage of the C22—O bond in ring *E* of solasodine occurs without inversion, and the stereogenic centers remain as 16*S* and 20*S*. The six-membered ring *F* includes a

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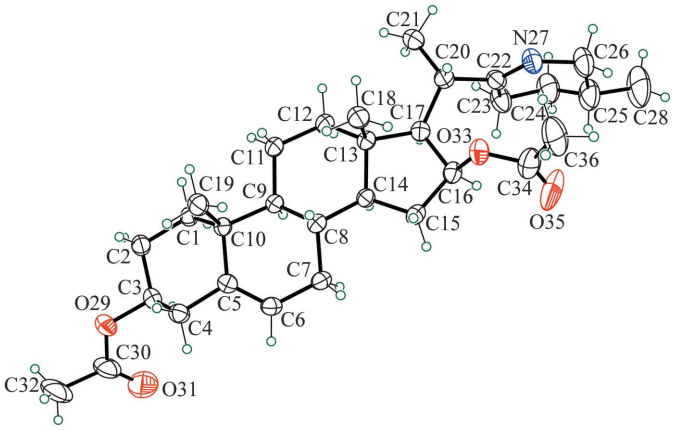

Figure 1
The structure of (I), with displacement ellipsoids at the 30% probability level for non-H atoms.

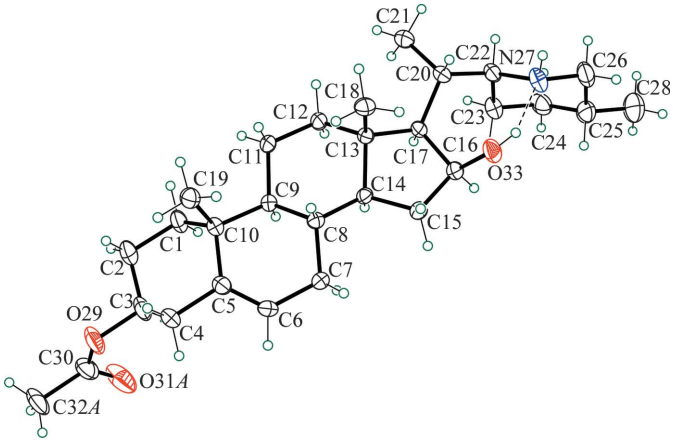

Figure 2
The structure of (II), with displacement ellipsoids at the 30% probability level for non-H atoms. Atoms O31*B* and C32*B*, disordered with O31*A* and C32*A*, have been omitted for clarity. The intramolecular hydrogen bond is shown as a dashed line.

double bond (C22═N27; Table 1) and exhibits a half-chair conformation [the puckering parameters are $\theta = 127.1\ (7)^\circ$ and $\varphi = 31.7\ (9)^\circ$; the puckering amplitude is 0.466 (6) Å; the atom sequence defining ring *F* is N27/C22–C26 (Cremer & Pople, 1975)]. As mentioned by Sato *et al.* (1957), (I) should equilibrate only under constraint to its tautomeric form including a C20═N22 double bond. In the solid state, the C20—C22 bond length clearly shows that this bond is a σ single bond without participation of tautomeric forms. The absolute configuration for atom C25 is unchanged compared with the starting material, *viz.* 25*R*, with methyl atom C28 occupying an equatorial position in ring *F* (Fig. 1).

The geometric features for the *A*–*D* nucleus in (II) are similar to those found in (I). Cleavage of the C22—O bond of solasodine occurs with retention of configuration for atoms C16, C20 and C25, as for (I). The 22*R* configuration of the spiro C atom of solasodine changes to 22*S* in (II), owing to the formation of a C—H bond at atom C22. The main difference between (I) and (II) is thus the conformation of ring *F* (Fig. 2 and Table 2), which now exhibits a chair form [the puckering parameters are $\theta = 177.6\ (4)^\circ$ and $\varphi = 93\ (8)^\circ$; atom sequence as for (I)]. The relative positions of the NH group in ring *F* and the hydroxy substituent at atom C16 in ring *D* allow the formation of a rather strong intramolecular O—H···N hydrogen bond [$D\cdots A = 2.777\ (4)$ Å, $H\cdots A = 1.93\ (4)$ Å and $D—H\cdots A = 157\ (5)^\circ$]. This stabilizing interaction explains why the OH group at atom C3 in solasodine is acetylated, while the OH group formed during *E*-ring opening is retained as a hydroxy group, at least when the conditions of Kusano *et al.* (1970) are applied. Such a protection of the C16—OH functionality is not possible for diacetate (I).

Experimental

For the synthesis of (I), a mixture of solasodine (300 mg, 0.72 mmol), Ac_2O (3.0 ml, 32 mmol), AcOH (1.0 ml, 17 mmol) and $Et_2O{\cdot}BF_3$ (0.7 ml, 5.5 mmol) was stirred for 20 s at 298 K. The reaction mixture was poured into iced water and shaken vigorously. Concentrated NH_4OH was added until a basic pH was obtained, and the product was extracted with CH_2Cl_2 (3 × 10 ml), washed with brine and water, dried over anhydrous Mg_2SO_4, and finally concentrated to dryness under reduced pressure. The crude product was chromatographed over silica gel using hexane/EtOAc (7:3), affording (I) in quantitative yield. Suitable single crystals were obtained by slow evaporation of an AcOEt solution. Spectroscopic data are in full agreement with the crystal structure (see archived CIF). Compound (II) was prepared following a literature procedure (Kusano *et al.*, 1970). Suitable single crystals of (II) were obtained by slow evaporation of an AcOEt solution. Spectroscopic data are in full agreement with the crystal structure (see archived CIF).

Compound (I)

Crystal data

$C_{31}H_{47}NO_4$
$M_r = 497.70$
Orthorhombic, $P2_12_12_1$
$a = 6.1137\ (16)$ Å
$b = 11.6779\ (14)$ Å
$c = 41.330\ (5)$ Å
$V = 2950.8\ (9)$ Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.07$ mm^{-1}
$T = 296\ (1)$ K
0.60 × 0.26 × 0.16 mm

Data collection

Bruker *P*4 diffractometer
3812 measured reflections
3026 independent reflections
1931 reflections with $I > 2\sigma(I)$
$R_{int} = 0.028$
3 standard reflections every 97 reflections intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.154$
$S = 1.03$
3026 reflections
332 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}

Compound (II)

Crystal data

$C_{29}H_{47}NO_3$
$M_r = 457.68$
Monoclinic, *C*2
$a = 10.026\ (2)$ Å
$b = 7.4403\ (14)$ Å
$c = 35.508\ (6)$ Å
$\beta = 95.512\ (18)^\circ$
$V = 2636.4\ (9)$ Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.07$ mm^{-1}
$T = 296\ (1)$ K
0.60 × 0.40 × 0.18 mm

Table 1
Selected geometric parameters (Å, °) for (I).

C5—C6	1.329 (5)	C20—C22	1.527 (5)
C16—O33	1.455 (5)	C22—N27	1.282 (5)
C20—C21	1.523 (6)	C26—N27	1.484 (6)
C5—C6—C7	125.7 (4)	C22—N27—C26	118.9 (4)

Table 2
Selected geometric parameters (Å, °) for (II).

C5—C6	1.313 (5)	C20—C22	1.557 (4)
C16—O33	1.435 (4)	C22—N27	1.483 (5)
C20—C21	1.536 (5)	C26—N27	1.466 (4)
C5—C6—C7	124.9 (3)	C22—N27—C26	112.7 (3)

Data collection

Bruker *P*4 diffractometer
4449 measured reflections
2526 independent reflections
2236 reflections with $I > 2\sigma(I)$
$R_{int} = 0.043$
3 standard reflections every 97 reflections intensity decay: 2%

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$
$wR(F^2) = 0.135$
$S = 1.04$
2526 reflections
322 parameters
5 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}

Carbonyl atom O31 and methyl group C32 in (II) are disordered over two sites, for which occupancies were refined and converged to 0.47 (4) and 0.53 (4) for O31*A*/C32*A* and O31*B*/C32*B*, respectively. In order to obtain a sensible geometry for this acetate group, bond lengths involving disordered sites were restrained [C30—O31 = 1.20 (1) Å (two restraints) and C30—C32 = 1.53 (1) Å (two restraints)]. All C-bonded H atoms in (II) were placed in idealized positions and constrained to ride on their parent atoms, with C—H bond lengths fixed at 0.93 (H6*A*), 0.96 (methyl CH_3), 0.97 (methylene CH_2) and 0.98 Å (methine CH). U_{iso}(H) values were calculated at $1.3U_{eq}$(C) for methyl groups and $1.2U_{eq}$(C) otherwise. Rigid methyl groups were allowed to rotate about their C—C bonds in order to obtain accurate torsion angles. H atoms bonded to heteroatoms N27 and O33 were found in a difference map and refined with free coordinates [U_{iso}(H) = $1.3U_{eq}$(N,O)]. For (I), the acetate group at atom C3 is almost certainly disordered as in (II), as reflected in the displacement parameters for atoms O31 and C32. However, we were unable to model disordered sites satisfactorily. H atoms were placed in idealized positions, with C—H bond lengths fixed as for (II) and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl groups and $1.2U_{eq}$(C) otherwise. In both structures, Friedel pairs [663 for (I) and 394 for (II)] were merged and the stereochemistry assumed from the synthesis.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL-Plus* (Release 5.10; Sheldrick, 2008); program(s) used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELXTL-Plus* and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3197). Services for accessing these data are described at the back of the journal.

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