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(4*R*,4a*R*,6*S*,7*S*,7a*S*)-6-Hydroxy-7-hydroxymethyl-4-methylperhydrocyclopenta[*c*]pyran-1-one chloroform solvate from *Valeriana laxiflora*

Smriti Khera,[a] Michael D. Carducci,[b] Jian-Qiao Gu[a] and Barbara N. Timmermann[a]*

[a]University of Arizona, Department of Pharmacology and Toxicology, 1703 E. Mabel St., Tucson, AZ 85721-0207, USA, and [b]University of Arizona, Department of Chemistry, 1306 E. University, Tucson, AZ 85721-0041, USA
Correspondence e-mail: btimmer@pharmacy.arizona.edu

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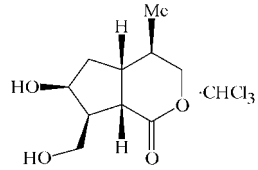
The structure of an iridolactone isolated from *Valeriana laxiflora* was established as (4*R*,4a*R*,6*S*,7*S*,7a*S*)-6-hydroxy-7-hydroxymethyl-4-methylperhydrocyclopenta[*c*]pyran-1-one chloroform solvate, $C_{10}H_{16}O_4{\cdot}CHCl_3$. The two rings are *cis*-fused. The δ-lactone ring adopts a slightly twisted half-chair conformation with approximate planarity of the lactone group and the cyclopentane ring adopts an envelope conformation. The hydroxy group, the hydroxymethyl group and the methyl group all have β orientations. The absolute configuration was determined using anomalous dispersion data enhanced by the adventitious inclusion of a chloroform solvent molecule. Hydrogen bonding, crystal packing and ring conformations are discussed in detail.

Comment

The alarming increase in the number of deaths due to tuberculosis (TB) and growing resistance to existing drugs has created an urgent need for the identification of leads for new antimycobacterial drugs. There were 8.3 million new cases of tuberculosis in the year 2000 alone, and this number is on the rise. Approximately one death every 15 s is due to TB, resulting in a total of about two million TB deaths annually (Corbett *et al.*, 2003). Strains of TB resistant to existing drugs are found in nearly every country (Cohn *et al.*, 1997), and a percentage of these strains are resistant to multiple drugs, making effective treatment extremely expensive and, in many cases, impossible. Most patients in developing countries, where TB is an even bigger problem than elsewhere in the world, cannot afford expensive drug treatments. There have been no new drugs developed for TB in over 30 years. Current TB therapy relies on drugs that are 50 years old and take six to nine months to complete, making patient compliance very difficult (World Health Organization, 2003).

As a part of the International Co-operative Biodiversity Group, our program focuses on the search for novel anti-tubercular principles of plant or microbial origins from the dry-land biodiversity of Latin America. It is in this regard that the bioassay-guided chemical investigation of the Chilean plant *Valeriana laxiflora* DC (Valerianaceae) was initiated. The methanol extract of *V. laxiflora* was found to be active against the $H_{37}Rv$ strain (ATCC 27294) of *Mycobacterium tuberculosis*, and the bioassay-directed fractionation led to the isolation of the title compound, (I), an iridolactone, as previously described (Gu *et al.*, 2004).



(I)

X-Ray crystallographic analysis of (I) was initiated to establish unequivocally its chemical structure and to determine the absolute and relative stereochemistries of all the functional groups and the ring junction at atoms C5 and C9.

The two rings are *cis*-fused, with both atom H5 and atom H9 β-oriented, as shown in Fig. 1. The δ-lactone ring adopts a slightly twisted half-chair conformation and the cyclopentane ring adopts an envelope conformation. The hydroxy group at atom C7 and the hydroxymethyl group at atom C8 both have β orientations, as does the C4 methyl group.

The unusually long bond distance of 1.572 (7) Å between the bridge atoms C5 and C9 suggests strain in the fused system. This observation has been made previously for a closely related iridolactone (Eisenbraun *et al.*, 1981). As expected in the case of δ-lactones, differences in the two C—O1 bond distances are observed, the C3—O1 bond [1.451 (7) Å] being longer than the C1—O1 bond [1.335 (6) Å] (Cheung *et al.*, 1965).

The C9—C1(O2)—O1—C3 lactone group is almost planar, with an r.m.s. deviation of 0.0208 Å and a maximum deviation of 0.352 (4) Å for atom O1. The C3—O1—C1—O2 torsion

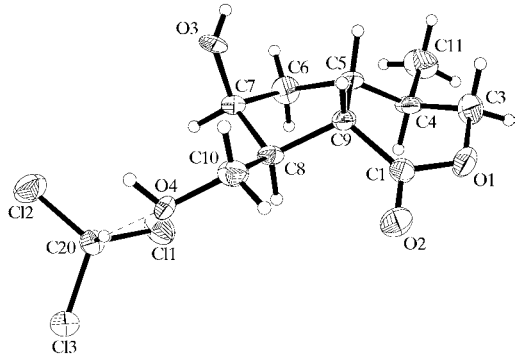


Figure 1
A view of (I), shown with 50% probability displacement ellipsoids. H atoms are shown as spheres of arbitrary radii.

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angle is 177.2 (5)°, showing only a slight deviation from planarity. This configuration concurs with that reported for (+)-nepetalic acid (Eisenbraun *et al.*, 1981) and an iridane-derived lactone, boonein (Marini-Bettolo *et al.*, 1983).

The packing is dominated by hydrogen bonding, which creates an infinite tape of molecules coincident with the 2_1 axis (Table 1 and Fig. 2). The C7-hydroxy group of each molecule is hydrogen bonded through the O3—H3 group to the *b*-translated neighboring hydroxymethyl atom O4 to form a chain. Each chain faces another chain of molecules related by the 2_1 axis, so that the cyclopentane rings of the first chain are facing the cyclopentane rings of the next. Each C7-hydroxy group is then also hydrogen bonded through atom O3 to the H4—O4 hydroxymethyl group of the molecule facing it, forming a molecular tape. A solvent-accessible channel along each side of the tape allows for hydrogen bonding to the chloroform solvent (Fig. 1). Each molecule of chloroform is hydrogen bonded through atom H20 to atom O4 of the hydroxymethyl group. In addition, each carbonyl O2 atom makes short contacts with atom H5 of an adjacent molecule in the same tape, as well as to atom H9 of a molecule in an adjoining tape (see Table 1).

The inclusion of a chloroform solvent molecule in the crystal structure allowed the anomalous dispersion data to be used to arrive at the absolute configuration of (I) as 4*R*,4a*R*,6*S*,7*S*,7a*S*. The same absolute configuration has been determined by the Mosher ester procedure (Ohtani *et al.*, 1991), which also unequivocally proves enantiomeric purity (Gu *et al.*, 2004). Although, we are on the edge of full confidence in our refinement of the Flack parameter (Flack & Bernardinelli, 2000), our results are fully consistent with supporting NMR data from the synthesis of *R*- and *S*-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters.

The crystals were isolated as very thin plates, and crystal decomposition due to evaporation of solvent at room temperature posed considerable problems in the selection and mounting of a suitable crystal. Nevertheless, we were able to obtain important information on the structure, conformation and absolute configuration of (I) from this study. This information can now be used to predict the three-dimensional structures of closely related iridolactones isolated as natural products but which do not crystallize. To our knowledge, this is the first report of the absolute configuration of 1-iridolactones based on X-ray data.

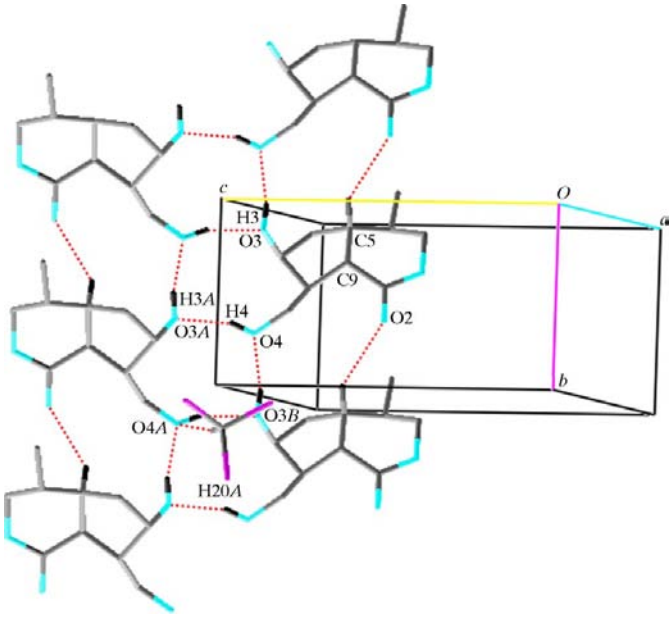

Figure 2
The packing geometry of (I), looking at the face of the hydrogen-bonded tape. Atoms labeled with the suffixes *A* and *B* are at symmetry positions $(-x, y+\frac{1}{2}, -z+2)$ and $(x, y-1, z)$, respectively.

Experimental

The dried and powdered aerial parts and roots of *V. laxiflora* (770 g) were extracted repeatedly with MeOH. This MeOH extract was filtered, the solvent was evaporated under vacuum and the resultant extract was partitioned between 90% aqueous MeOH and *n*-hexane. The 90% aqueous MeOH soluble portion was dried under vacuum and subsequently partitioned between CH_2Cl_2 and H_2O (1:1). The CH_2Cl_2 soluble extract was further fractionated by column chromatography on a silica-gel column using a step gradient of $CHCl_3$/MeOH. The fraction eluting with 20:1 $CHCl_3$/MeOH (2.2 g) was chromatographed on a silica-gel column using an *n*-hexane/*i*-PrOH/MeOH step gradient. The fraction eluting with 18:1:1 *n*-hexane/*i*-PrOH/MeOH (370 mg) was applied to a Sephadex LH-20 column, using MeOH as the mobile phase. The fraction containing (I) (60 mg) was purified by reverse-phase high-performance liquid chromatography (RP–HPLC) using CH_3CN/H_2O (1:1). Compound (I) (14 mg) was isolated at R_F = 0.62 (Gu *et al.*, 2004). Crystals were obtained as very thin colorless rectangular plates using $CHCl_3$. Crystals were removed in a drop of the mother liquor using a pipette and transferred to a drop of paratone oil to seal in the solvent and prevent evaporation. A suitable crystal was selected and transfered to a glass fiber, covered by a thin protective film of paratone, and mounted quickly to prevent solvent loss by evaporation. The paratone oil was graciously provided by Professor Marilyn Olmstead of the University of California, Davis, USA.

Crystal data

$C_{10}H_{16}O_4{\cdot}CHCl_3$
M_r = 319.60
Monoclinic, $P2_1$
a = 10.523 (3) Å
b = 6.0404 (15) Å
c = 11.231 (3) Å
β = 94.478 (5)°
V = 711.7 (3) Å^3
Z = 2
D_x = 1.491 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 794 reflections
θ = 2.6–18.8°
μ = 0.65 mm^{-1}
T = 173 (2) K
Parallelepiped, colorless
0.78 × 0.09 × 0.02 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.268, T_{max} = 0.987
6446 measured reflections
2420 independent reflections
1504 reflections with $I > 2\sigma(I)$
R_{int} = 0.088
θ_{max} = 25.0°
$h = -12 \rightarrow 12$
$k = -7 \rightarrow 7$
$l = -13 \rightarrow 13$
58 standard reflections
frequency: 1200 min
intensity decay: 0.2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.062$
$wR(F^2) = 0.104$
$S = 0.98$
2420 reflections
161 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0327P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}
Absolute structure: Flack (1983), 1038 Friedel pairs
Flack parameter = 0.11 (12)

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

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O4^{i}	0.84	1.88	2.651 (5)	152
O4—H4···O3^{ii}	0.84	1.87	2.654 (4)	156
C20—H20···O4	1.00	2.42	3.402 (6)	166
C5—H5···O2^{i}	1.00	2.70	3.575 (7)	146
C9—H9···O2^{iii}	1.00	2.49	3.188 (6)	127

Symmetry codes: (i) $x, y-1, z$; (ii) $-x, \frac{1}{2}+y, 2-z$; (iii) $-x, y-\frac{1}{2}, 1-z$.

The best available crystal, which was larger than the beam in one dimension, was used in order to enhance diffraction (Görbitz, 1999). Nevertheless, the observed diffraction pattern was weak. H atoms were easily visible in difference Fourier maps, but all H atoms were placed at ideal positions and constrained to ride on the atoms to which they were bonded (C—H = 0.98–1.00 Å), except for the hydroxy H atoms, which were constrained to an O—H distance of 0.84 Å and a C—O—H angle of 109.5°. As a result of the fortuitous inclusion of a heavy-atom solvent molecule ($CHCl_3$) in the crystal structure, we were able to use the anomalous dispersion data to arrive at the absolute configuration of (I).

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

The structure of the title compound was determined in the Molecular Structure Laboratory of the Department of Chemistry, University of Arizona. The diffractometer was obtained with funds provided by the NSF (grant No. CHE9610374). This study was supported by NIH grant No. 5U01TW00316-10 awarded to BNT.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1145). Services for accessing these data are described at the back of the journal.

References

Bruker (1997). *SAINT*, *SHELXTL* and *SMART*. Versions 5.0. Bruker AXS Inc., Madison, Wisconsin, USA.
Cheung, K. K., Overton, K. H. & Sim, G. A. (1965). *Chem. Commun.* **24**, 634–635.
Cohn, D. L., Bustreo, F. & Raviglione, M. C. (1997). *Clin. Infect. Dis.* **24** (Suppl. 1), S121–130.
Corbett, E., Watt, C., Walker, N., Maher, D., Williams, B., Raviglione, M. & Dye C. (2003). *Arch. Intern. Med.* **163**, 1009–1021.
Eisenbraun, E. J., Browne, C. E., Eliel, E. L., Harris, D. L., Rahman, A. & van der Helme, D. (1981). *J. Org. Chem.* **46**, 3302–3305.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Görbitz, C. H. (1999). *Acta Cryst.* B**55**, 1090–1098.
Gu, J.-Q., Wang, Y., Franzblau, S. G., Montenegro, G., Yang, D. & Timmermann, B. N. (2004). *Planta Med.* **70**, 509–514.
Marini-Bettolo, G. B., Nicoletti, M., Messana, I. & Patamia, M. (1983). *Tetrahedron*, **39**, 323–329.
Ohtani, I., Kusumi, T., Kashman, Y. & Kakisawa, H. (1991). *J. Am. Chem. Soc.* **113**, 4092–4096.
Sheldrick, G. M. (1997). *SHELXL*97 and *SHELXS*97. University of Göttingen, Germany.
Sheldrick, G. M. (2003). *SADABS*. Version 2.03. Bruker AXS Inc., Madison, Wisconsin, USA.
World Health Organization (2003). Background Document Prepared for the Second *Ad hoc* Committee on the TB Epidemic, 18–19 September 2003, Montreux, Switzerland.