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Plumeridoid C from the Amazonian traditional medicinal plant *Himatanthus sucuuba*

Birgit Waltenberger, Judith M. Rollinger, Ulrich J. Griesser, Hermann Stuppner and Thomas Gelbrich*

Institute of Pharmacy, University of Innsbruck, Innrain 52c, 6020 Innsbruck, Austria
Correspondence e-mail: thomas.gelbrich@uibk.ac.at

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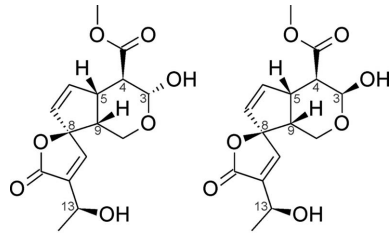
The stereochemistry of the iridoid plumeridoid C, $C_{15}H_{18}O_7$, was established by X-ray single-crystal structure analysis, giving (2′*R*,3*R*,4*R*,4a*S*,7a*R*)-methyl 3-hydroxy-4′-[(*S*)-1-hydroxyethyl]-5′-oxo-3,4,4a,7a-tetrahydro-1*H*,5′*H*-spiro[cyclopenta[*c*]pyran-7,2′-furan]-4-carboxylate. The absolute structure of the title compound was determined on the basis of the Flack *x* parameter and Bayesian statistics on Bijvoet differences. The hydrogen-bond donor and acceptor functions of the two hydroxy groups are employed in the formation of O—H···O-bonded helical chains.

Comment

As part of our search for bioactive natural products, we have investigated chemical compounds contained in the bark material of the Amazonian tree *Himatanthus sucuuba* (spruce) Woodson (Apocynaceae). In folk medicine, the bark and latex of this plant species are used for the treatment of tumours and inflammatory diseases. Pharmacological studies have shown that extracts and constituents of *Himatanthus sucuuba* possess therapeutic potential (Amaral *et al.*, 2007).

Eleven compounds, denoted (I) to (XI) (see *Supplementary materials*), were isolated and purified from the bark material (1.9 kg) of *Himatanthus sucuuba* using extraction, liquid–liquid partition, various chromatographic techniques and crystallization from solvents. The isolated compounds were identified as the iridoids plumeridoid C [(I), 60 mg] (Kuigoua *et al.*, 2010), plumericin [(II), 90 mg] (Elsässer *et al.*, 2005), plumieridin [(III), 8 mg] (Yamauchi *et al.*, 1981) and allamandicin [(IV), 7 mg] (Abe *et al.*, 1984), the flavonoids biochanin A [(V), 8 mg] (Jha *et al.*, 1980; Talukdar *et al.*, 2000), dihydrobiochanin A [(VI), 9 mg] (Osawa *et al.*, 1992), dalbergioidin [(VII), 0.3 mg] (Osawa *et al.*, 1992), naringenin [(VIII), 9 mg] (Hou *et al.*, 2001), ferreirin [(IX), 2 mg] (Osawa *et al.*, 1992) and dihydrocajanin [(X), 8 mg] (Osawa *et al.*, 1992), and the lignan pinoresinol [(XI), 9 mg] (Xie *et al.*, 2003) by means of mass spectrometry, one- and two-dimensional NMR experiments, optical rotation and comparison with data from the literature. Except for (II) and (XI), the isolation of these compounds from *Himatanthus sucuuba* is reported here for the first time.



(I) (I*a*)

A recent paper by Kuigoua *et al.* (2010) contains the first report of the existence of the iridoid plumeridoid C, (I). In order to complete the full characterization of (I) and to elucidate its absolute configuration, its crystal structure has been determined.

The asymmetric unit of (I) consists of one formula unit (Fig. 1). As the compound consists only of O, C and H atoms, Cu $K\alpha$ radiation was used to enable the determination of the absolute configuration, and 1210 Friedel pairs were measured. This yielded a refined Flack (1983) *x* parameter and standard uncertainty (s.u.) of −0.01 (13). We note that the obtained s.u. value is slightly above the suggested upper confidence limit of 0.10 for the determination of the absolute structure of an enantiopure compound (Flack & Bernardinelli, 2000). However, additional confirmation was obtained from the examination of Bayesian statistics on 1210 Bijvoet pairs (Hooft *et al.*, 2008) carried out using the program *PLATON* (Spek, 2009). The calculated Hooft *y* parameter was 0.07 (6)

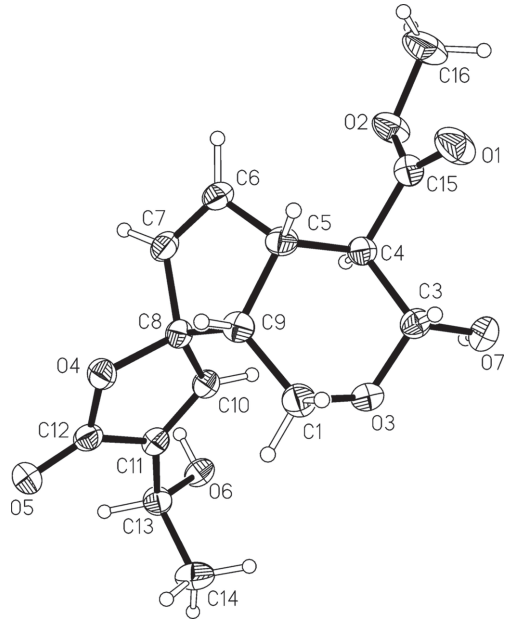


Figure 1
The molecular structure of (I), with displacement ellipsoids drawn at the 50% probability level.

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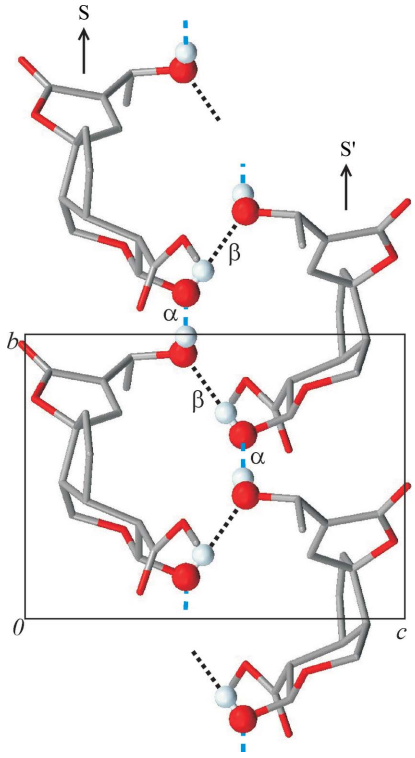

Figure 2
A single O—H···O-bonded helical chain in the crystal structure of (I), viewed along [100]. The two strands of the chain are denoted S and S′, with the hydrogen bonds α = O6—H6O···O7(x, $y+1$, z) and β = O7—H7O···O6($-x+2$, $y-\frac{1}{2}$, $-z+1$).

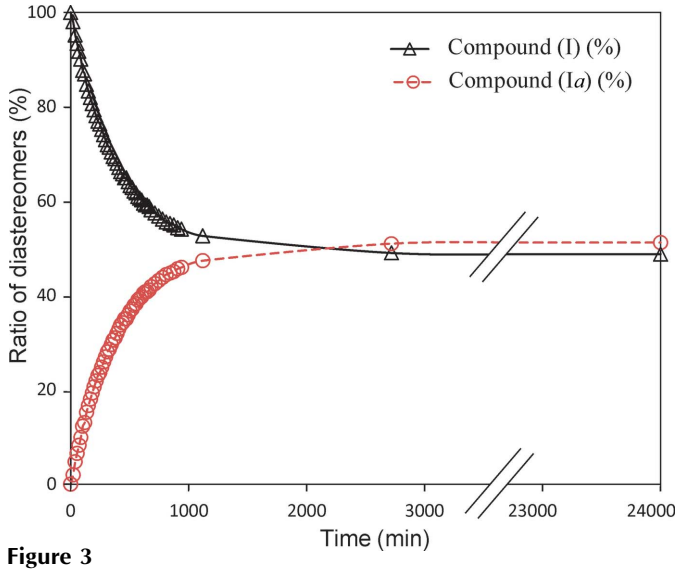

Figure 3
Time-dependent ratio of diastereomers (I) and (I*a*) in a CD_3OD solution, analysed by ^{1}H NMR. Compound (I) was dissolved in CD_3OD at zero time.

with G = 0.9 (1). The calculated probability values $P3$(true), $P3$(twin) and $P3$(wrong) were 1.000, 0.000 and 0.000, respectively. This confirmed the absolute configuration of the six stereocentres as 3*R*, 4*R*, 5*S*, 8*R*, 9*R* and 13*S* (see Scheme). Moreover, these results are consistent with the relative configuration of (I) that was proposed by Kuigoua *et al.* (2010) on the basis of NMR data.

Inspection of a plot of the Bijvoet pairs $\delta(F_o^2)$ against $\delta(F_c^2)$ generated with *PLATON* (Spek, 2009) does not reveal a clear trend. All quadrants of the plot are populated by a significant number of points. This contrasts with the observation that all of the numerical indicators (x, y, $P2$, $P3$) give a very clear indication of the absolute structure and are consistent between themselves. We note that the error bars on the plot indicate that many of the Bijvoet differences are small compared with experimental error. However, even with this limitation, the data give clear indications in terms of the numerical parameters that have been developed to distinguish absolute structures.

The cyclopentene ring of (I) displays a C9 envelope conformation, with atom C9 displaced by 0.420 (2) Å from the plane defined by atoms C5/C6/C7/C8. As indicated by its Cremer–Pople ring-puckering parameters [Q = 0.544 (2) Å, θ = 163.4 (2)° and φ = 139.7 (6)°; Cremer & Pople, 1975], the geometry of the tetrahydropyran ring (O3/C1/C9/C5/C4/C3) is best described as a slightly distorted chair. The mean plane of the furan ring and the plane defined by atoms C7/C8/C9 form an angle of 88.11 (8)°. The mean plane of the –CC(=O)OC fragment C4/C15/O1/O2/C16 is almost perpendicular to the plane defined by atoms C3/C4/C5, with which it forms an angle of 81.27 (10)°.

The molecule of (I) contains two OH groups, O6 in the hydroxyethyl fragment and the O7 group on the tetrahydropyran ring. The hydrogen-bond donor and acceptor functions of both are utilized to give a one-dimensional helical chain that propagates along [010] (Table 1 and Fig. 2). This hydrogen-bonded chain consists of two strands of O6—H6O···O7(x, $y+1$, z)-bonded molecules, neighbouring molecules of which are related to one another by translational symmetry. The two strands of a chain are related by a 2_1 screw axis and linked to one another *via* O7—H7O···O6($-x+2$, $y-\frac{1}{2}$, $-z+1$) interactions. Hence, every molecule of (I) is O—H···O-bonded to four neighbouring molecules. Using the graph-set notation proposed by Etter *et al.* (1990) and Bernstein *et al.* (1995), the hydrogen-bonded molecules of (I) are linked together *via* fused $R_3^3(15)$ rings. The crystal packing of these O—H···O-bonded chains generates two notable short inter-chain contacts, *viz.* C1—H1*B*···O5($-x+2$, $y-\frac{1}{2}$, $-z$) and C5—H5···O4($-x+1$, $y-\frac{1}{2}$, $-z$), with H···O distances of 2.37 and 2.47 Å, respectively (Table 1). The first interchain contact is observed between the CH_2 group of the tetrahydropyran ring and the carbonyl group on the furan ring of a neighbouring molecule, while the second contact involves the chiral centre C5 of the fused cyclopentene and tetrahydropyran rings of one molecule and the furan O atom of another.

We have found that, in methanol solution, diastereomerization of (I) occurs at position 3, yielding the epiplumeridoid C [(I*a*); Kuigoua *et al.*, 2010]. This phenomenon was studied in a time-dependent ^{1}H NMR experiment. Compound (I) (1 mg) was dissolved in CD_3OD and isochronous ^{1}H NMR measurements of the (I):(I*a*) ratio were started instantaneously. This experiment confirmed the diastereomerization at position 3, giving a chemical equilibrium of 1:1.05 between (I)

and (I*a*) [(I): 3*R*, 4*R*, 5*S*, 8*R*, 9*R*, 13*S*; (I*a*): 3*S*, 4*R*, 5*S*, 8*R*, 9*R*, 13*S*] after approximately two days (Fig. 3). These results suggest that crystallization from a methanol solution yields compound (I) exclusively, even though diastereomerization takes place in a methanol solution so that the epimers (I) and (I*a*) are both present. Moreover, NMR experiments have shown that both (I) and (I*a*) are also contained in a deuterated pyridine solution.

Experimental

The general experimental conditions used for the isolation and identification of compounds (I) to (XI), including the detailed isolation protocols and chemical structures, the characteristic UV–Vis and FT–IR data for (I) and the NMR spectroscopic data for (I) and (I*a*), are available in the *Supplementary materials*.

^{1}H NMR experiments for the evaluation of the diastereomerization were carried out on a Bruker TXI600 at 298 K in CD_3OD (referenced to the residual nondeuterated solvent signals). The $[\alpha]_D^{20}$ values for (I) and for the 1:1.05 mixture of (I) and (I*a*) were determined as +70.5 and +82.0, respectively (c = 0.97, methanol).

Simultaneous melting and decomposition of (I) were observed above 454 K. The colourless prisms of (I) used for this study were obtained by crystallization from a saturated methanol solution. The unit-cell parameters of six different crystals were determined and found to be consistent with (I). There was no indication of the presence of crystals of (I*a*) in the investigated batch.

Crystal data

$C_{15}H_{18}O_7$
M_r = 310.29
Monoclinic, $P2_1$
a = 9.6736 (2) Å
b = 7.6203 (1) Å
c = 10.6303 (2) Å
β = 107.142 (2)°
V = 748.81 (2) Å^3
Z = 2
Cu $K\alpha$ radiation
μ = 0.93 mm^{-1}
T = 173 K
0.20 × 0.20 × 0.15 mm

Data collection

Oxford Xcalibur Ruby Gemini Ultra diffractometer
Absorption correction: multi-scan [*CrysAlis PRO* (Oxford Diffraction, 2003); multi-scan absorption correction using spherical harmonics, implemented in *SCALE3 ABSPACK* scaling algorithm]
T_{min} = 0.766, T_{max} = 1.000
7011 measured reflections
2651 independent reflections
2615 reflections with $I > 2\sigma(I)$
R_{int} = 0.029

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.081
S = 1.09
2651 reflections
225 parameters
3 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Absolute structure: Flack (1983), with 1210 Friedel pairs
Flack parameter: −0.01 (13)

All H atoms were identified in a difference map. Methyl H atoms were idealized and included as rigid groups that were allowed to rotate but not tip (C—H = 0.98 Å). H atoms bonded to tertiary (C—H = 1.00 Å), secondary (C—H = 0.99 Å) and aromatic C atoms (C—H = 0.95 Å) were positioned geometrically. H atoms attached to O atoms were refined with restrained distances [O—H = 0.82 (2) Å]. The U_{iso} parameters of all H atoms were refined freely.

Table 1
Geometry of hydrogen bonds and other contacts (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6O···O7^{i}	0.83 (2)	1.99 (2)	2.8153 (15)	174 (2)
O7—H7O···O6^{ii}	0.80 (2)	1.92 (2)	2.7218 (15)	176 (2)
C1—H1B···O5^{iii}	0.99	2.37	3.2969 (18)	156
C5—H5···O4^{iv}	1.00	2.47	3.3243 (16)	143

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

The absolute configuration of this structure was confirmed by the Flack (1983) parameter and Bayesian statistics on 1210 Bijvoet pairs (Hooft *et al.*, 2008). The Flack parameter is −0.01 (13) for the reported structure and 0.99 (13) for the inverted structure. Friedif, R_A and R_D values (Flack & Shmueli, 2007; Flack *et al.*, 2011) were calculated using *PLATON* (Spek, 2009). Friedif reflects the ability to determine the absolute structure, and Friedif_{stat} = 36 has a low value as only C, H and O atoms are present, while Friedif_{obs} is 1286. The R_A and R_D values are 0.050 and 0.989, respectively, for the reported structure, and 0.050 and 1.022, respectively, for the inverted structure.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2003); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2003); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3259). Services for accessing these data are described at the back of the journal.

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