

Bergenin monohydrate from the
rhizomae of *Astilbe chinensis*Yi-Ping Ye,^a Hong-Xiang Sun^{b,c*} and Yuan-Jiang Pan^c

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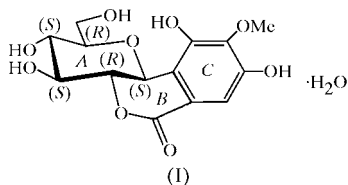
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The title compound, 4-methoxy-2-[(1*S*,2*R*,3*S*,4*S*,5*R*)-3,4,5,6-tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-2-yl]- α -resorcylic acid δ -lactone monohydrate, C₁₄H₁₆O₉·H₂O, is a *C*-glucoside of 4-*O*-methylgallic acid which has antiasthmatic, antitussive, anti-inflammatory, antifungal, anti-HIV and anti-hepatotoxic activity. The molecule is composed of three six-membered rings: an aromatic ring, a glucopyranose ring and an annellated δ -lactone ring. The glucopyranose ring exhibits only small deviations from an ideal chair conformation. The annellated δ -lactone ring possesses the expected half-chair conformation. There is one intra- and six intermolecular hydrogen bonds which form an extensive hydrogen-bonding network within the crystal.

Comment

Bergenin has been isolated from the roots of *Bergenia crassifolia* (Hua *et al.*, 1998), *B. purpurascens* and *Casalspinia digyna*, from the bark of *Corylopsis spicata* and *Mallotus japonicus* (Yoshida *et al.*, 1982), from the heartwood of *Shorea leprosula* and *Macaranga peltata*, and from the rhizome of



Astilbe chinensis (Sun *et al.*, 2002). Pharmacological experiments have indicated that it possesses significant antiasthmatic, antitussive, anti-inflammatory, antifungal (Prithiviraj *et al.*, 1997), *in vitro* anti-HIV (Piacente *et al.*, 1996) and anti-hepatotoxic activity (Kim *et al.*, 2000; Lim, Kim, Chung & Kim, 2000; Lim, Kim, Choi *et al.*, 2000). The first structures of bergenin proposed by Tschitschibabin *et al.* (1929) and Shimokoriyama (1950) were revised independently by Hay & Haynes (1958) and Posternak & Dürr (1958). The structure of bergenin, which involves an aryl β -*C*-glucoside and an aryl

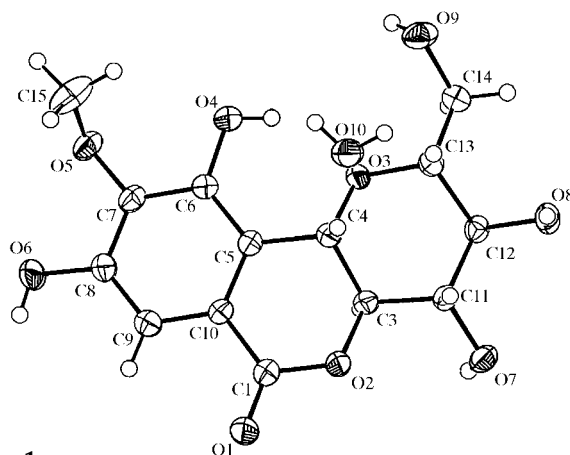


Figure 1

A view of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

δ -lactone ring, was unequivocally confirmed by synthesis of bergenin-type *C*-glucosylarenes (Frick & Schmidt, 1991) and an X-ray analysis of 3,4,8,10,11-penta-*O*-acetylbergenin (Frick *et al.*, 1991). Meanwhile, the chemical structure of the natural product bergenin from plants was determined on the basis of two-dimensional NMR data (Zhou *et al.*, 1999). The chemical structure of bergenin as the monohydrate, (I), has now been confirmed by single-crystal X-ray diffraction analysis.

The structure of (I), with the atom-numbering scheme, is shown in Fig. 1. The molecule is composed of three six-membered rings, *viz.* *A* (C5–C10, an aromatic ring), *B* (C1/O2/C3–C5/C10, an annellated δ -lactone ring) and *C* (C3–C4/C11–C13/O3, a glucopyranose ring). Ring *B* possesses the expected half-chair conformation, while ring *C* exhibits only small deviations from an ideal chair conformation. The *B/C* junction is *trans* fused. The hydroxyl and hydroxymethyl substituents at the other chiral centres (atoms C11, C12 and C13) adopt equatorial conformations with respect to the glucopyranose ring. The structure of (I) is consistent with the conformation found for 3,4,8,10,11-penta-*O*-acetylbergenin by Frick *et al.* (1991) by X-ray analysis.

All hydroxyl groups, except for C6–OH, serve as simultaneous hydrogen-bond donors and acceptors (Table 2), resulting in one intra- and six intermolecular O–H···O hydrogen bonds. The intramolecular O–H···O hydrogen bond is formed between atom H4 of the C6 hydroxyl group and the O3 ring atom of the glucopyranose moiety. The water atom, O10, acts as an acceptor, with the O6 hydroxyl atom as donor, to form O6–H6O···O10 hydrogen bonds between the solvent and bergenin.

In the solid state, screw-related molecules are linked by O7–H7O···O9ⁱⁱ, O8–H8O···O7ⁱⁱⁱ and O9–H9O···O6^{iv} hydrogen bonds, forming molecular chains along the *a* axis (see Table 2 for symmetry codes). The chain formation is further stabilized by the solvent water molecule through O10–H10B···O1^v and O10–H10A···O8ⁱⁱⁱ hydrogen bonds.

Experimental

The rhizomes of *Astilbe chinensis* were collected in Anji county, Zhejiang Province, China, in August 2001. The plants were identified

as *A. chinensis* (Maxim.) Franch. et Savat. by Professor Xiang-Ji Xue, College of Pharmaceutical Science, Zhejiang University. A voucher specimen (No. 200120) was deposited with the Laboratory of Nature and Biochemistry, Zhejiang University. The rhizomes of *A. Chinensis* were dried in the dark in a ventilated hood and then ground. The material (5.0 kg) was extracted with MeOH (3 × 25 l) at room temperature to give 366 g of extract. The MeOH extract was suspended in H₂O and sequentially partitioned with petroleum ether and EtOAc. The EtOAc extract (90.9 g) was absorbed onto silica gel and chromatographed on a silica-gel column, eluting successively with CHCl₃, CHCl₃/MeOH (9:1), CHCl₃/MeOH (4:1) and CHCl₃/MeOH (1:1), which yielded five fractions. The third fraction was subjected to column chromatography on Sephadex LH-20, eluting with MeOH, which afforded 15.342 g of the pure title compound, (I). Crystals suitable for X-ray structure analysis were obtained by slow evaporation from an MeOH/H₂O (1:1) solution at room temperature (m.p. 412–413 K). Spectroscopic analysis, ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 163.3 (C1), 150.9 (C6), 148.1 (C7), 140.8 (C8), 118.1 (C5), 116.1 (C10), 109.7 (C9), 81.9 (C13), 80.0 (C3), 74.0 (C11), 72.4 (C4), 71.0 (C12), 61.3 (C14), 60.0 (C15).

Crystal data

C ₁₄ H ₁₆ O ₉ ·H ₂ O	Mo Kα radiation
M _r = 346.28	Cell parameters from 34 reflections
Orthorhombic, P2 ₁ 2 ₁ 2 ₁	θ = 3.2–14.7°
a = 7.497 (1) Å	μ = 0.13 mm ⁻¹
b = 13.930 (2) Å	T = 288 (2) K
c = 14.282 (2) Å	Prism, colourless
V = 1491.5 (4) Å ³	0.56 × 0.52 × 0.50 mm
Z = 4	
D _x = 1.542 Mg m ⁻³	

Data collection

Siemens P4 diffractometer	h = 0 → 10
ω scans	k = 0 → 19
2523 measured reflections	l = -1 → 19
2330 independent reflections	3 standard reflections
1787 reflections with I > 2σ(I)	every 97 reflections
R _{int} = 0.010	intensity decay: 3.5%
θ _{max} = 29.2°	

Table 1 Selected geometric parameters (Å, °).

O1—C1	1.219 (3)	O2—C1	1.351 (3)
C3—O2—C1—O1	166.0 (2)	O4—C6—C7—O5	3.9 (3)
C3—O2—C1—C10	-15.0 (3)	O5—C7—C8—O6	-2.3 (3)
C1—O2—C3—C4	50.0 (3)		

Table 2 Hydrogen-bonding geometry (Å, °).

D—H...A	D—H	H...A	D...A	D—H...A
O4—H4O...O3	0.82	1.96	2.668 (2)	144
O6—H6O...O10 ⁱ	0.82	1.81	2.625 (2)	169
O7—H7O...O9 ⁱⁱ	0.82	1.93	2.737 (2)	167
O8—H8O...O7 ⁱⁱⁱ	0.82	1.92	2.733 (2)	171
O9—H9O...O6 ^{iv}	0.82	2.04	2.823 (2)	159
O10—H10B...O1 ^v	0.83 (2)	2.03 (2)	2.860 (3)	179 (4)
O10—H10A...O8 ⁱⁱⁱ	0.83 (2)	1.96 (2)	2.768 (2)	171 (3)

Symmetry codes: (i) 1 - x, 1/2 + y, 3/2 - z; (ii) x - 1, y, z; (iii) 1/2 + x, 1/2 - y, 1 - z; (iv) 1/2 + x, 3/2 - y, 1 - z; (v) 1 + x, y, z.

Refinement

Refinement on F ²	w = 1/[σ ² (F _o ²) + (0.049P) ²]
R[F ² > 2σ(F ²)] = 0.036	where P = (F _o ² + 2F _c ²)/3
wR(F ²) = 0.088	(Δ/σ) _{max} < 0.001
S = 0.96	Δρ _{max} = 0.27 e Å ⁻³
2330 reflections	Δρ _{min} = -0.19 e Å ⁻³
232 parameters	Extinction correction: SHELXL97
H atoms treated by a mixture of constrained and independent refinement	(Sheldrick, 1997)
	Extinction coefficient: 0.0135 (19)

After location of the H atoms in difference density maps, all H atoms of the bergenin molecule were positioned using SHELXL97 HFIX instructions (Sheldrick, 1977) and treated as riding atoms with C—H distances in the range 0.93–0.98 Å. Water H atoms (H10A and H10B) were refined with O—H distance restraints (Table 2). The structure was refined using the absolute stereochemistry established through chemical synthesis (Frick & Schmidt, 1991).

Data collection: XSCANS (Siemens, 1994); cell refinement: XSCANS; data reduction: SHELXTL/PC (Siemens, 1991); program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: SHELXTL/PC; software used to prepare material for publication: SHELXTL/PC.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1134). Services for accessing these data are described at the back of the journal.

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