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Structure and Stereochemistry of Radermasinin, a Novel Cytotoxic Triterpene Lactone from *Radermachia sinica*. *X*-Ray Crystal Structure of Radermasinin Monohydrate

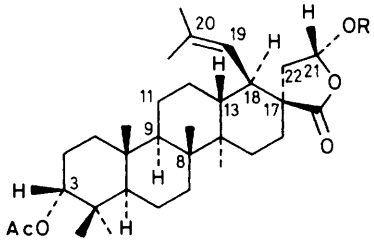
Gregory K. Rice,[a] Toshio Yokoi,[a] Toshimitsu Hayashi,[a] Hideyo Suzuki,[a] Kuo-Hsiung Lee,*[a] and Andrew T. McPhail*[b]

[a] *Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514, U.S.A.*
[b] *Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.*

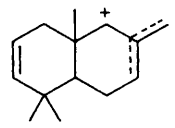
The structure and stereochemistry of radermasinin, a novel cytotoxic triterpene lactone isolated from *Radermachia sinica*, have been established from spectral data and single-crystal *X*-ray analysis of its monohydrate.

In the course of our continuing search among Formosan plants for novel potential antitumour agents,[1] the methanolic extract of the leaves and twigs of *Radermachia sinica* (Hemsl.)† (Bignoniaceae), a hitherto uninvestigated species, was found to show significant inhibitory activity *in vivo* against P-388 lymphocytic leukaemia.‡ We report herein on the isolation and structural characterization of a novel triterpene, radermasinin (**1**),§ which is the major active principle from *R. sinica*.

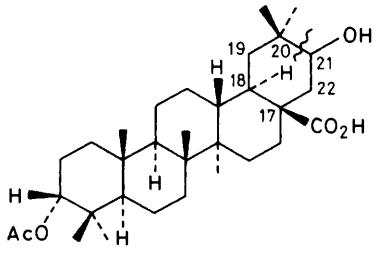
Radermasinin was isolated in 0.0007% yield from the active chloroform extract of *R. sinica* by silica gel column chromatography and preparative t.l.c. guided by an *in vitro* KB cell culture assay. Radermasinin (**1**) {$C_{32}H_{50}O_5$, *m/z* 514.3646 (M^+), m.p. 239—242 °C, $[\alpha]_D^{20}$ −27.0° (*c* 0.58, $CHCl_3$)} showed i.r. bands (Nujol) at 3380 (OH), 1760 (γ-lactone), 1735 and 1245 cm^{-1} (acetyl). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) indicated the presence of seven methyl groups (δ 0.84—1.78), an acetyl group [δ 2.08 (3H, s, 3-OAc)], and



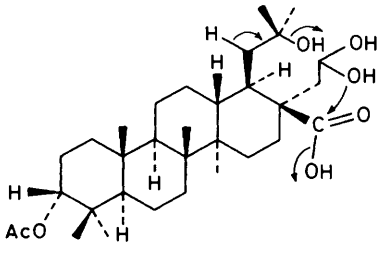
(**1**) R = H
(**2**) R = Ac



(**3**)



(**4**)



(**5**)

† This plant, which is also known as 'Shan Tsai Duo' in Taiwan, was collected in the spring of 1979 in Chia-Hsien, Kaohsiung-Shen, Taiwan. Plant material was procured and identified by Professor Huan-Chang Huang of the School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan.

‡ *In vivo* and *in vitro* activities were assayed by Dr. I. H. Hall, Division of Medicinal Chemistry and Natural Products, and by Dr. Y. C. Cheng and Mr. M. Fisher, Cancer Reseach Centre, UNC-CH, respectively, according to a literature method (R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 1972, **3**, 1). The methanolic extract of *R. sinica* showed significant ($T/C \geq 120\%$) antileukaemic activity in P-388 leukaemia (T/C = 148%) at the 50 mg kg^{-1} day^{-1} level. Radermasinin (**1**) and its acetate (**2**) demonstrated significant (ED_{50} <4.0 μg ml^{-1}) cytotoxicity (ED_{50} = 3.3 μg ml^{-1} and 3.5 μg ml^{-1}, respectively) in the KB cell culture *in vitro* (assayed by Y. C. C. and M. F.).

§ It is of interest to note that radermasinin is a 3α-acetoxy terpenoid. This is most unusual as triterpenoids are almost universally 3β-alcohols unless oxidised to the corresponding ketone.

two low-field protons attached to carbon atoms bearing oxygen functions [δ 4.62 (1H, t, *J* 2.6 Hz, 3-H) and 5.60 (1H, m, 21-H)]. Assignment of the acetyl group at C(3) was based on the observation of a diagnostically important mass peak at *m/z* 189 [(**3**), base peak] associated with cleavage of C(9)–C(11) and C(8)–C(14) bonds followed by the loss of acetic acid, as seen in a typical fragmentation pattern of saturated oleananes[2] such as dihydromachaerinic acid lactone.[3]

The complete structure and stereochemistry of (**1**) were established unequivocally by *X*-ray analysis of crystals of the monohydrate.¶ A view of the structure of (**1**) is provided in Figure 1. The crystals comprise extended chains of head-to-tail hydrogen-bonded [O(37) · · · O(34) 2.786 Å] radermasinin molecules related by the 2_1 screw axis along *b*, an arrangement which generates channels in the vicinity of 2_1 screw axes along *c* wherein lie disordered water molecules which form a hydrogen-bonded chain along *c*.

The presence of a *gem*-dimethylvinyl group at C(18) in addition to a spiro γ-hydroxy-γ-lactone moiety at C(17) is suggestive of a possible biosynthetic pathway involving (**4**) as

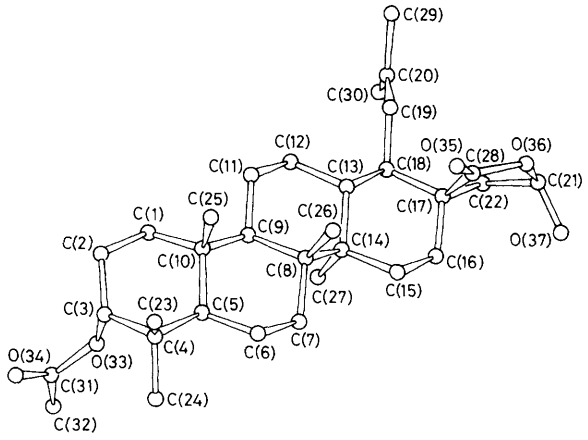


Figure 1. Structure and solid-state conformation of radermasinin (**1**); hydrogen atoms have been omitted for clarity.

precursor, followed by oxidative cleavage of the C(20)–C(21) bond and subsequent dehydration and ring closure of (**5**) to yield (**1**).

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¶ *Crystal data:* $C_{32}H_{50}O_5 \cdot H_2O$, M = 532.77, orthorhombic, space group $P2_12_12_1$, a = 13.847(3), b = 31.614(5), c = 7.484(1) Å, U = 3276.2 Å^3, Z = 4, D_c = 1.080 g cm^{-3}. From a total of 3345 non-equivalent forms recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-K_α radiation, incident-beam graphite monochromator; ω—2θ scans, θ = 4—67°), only those 1479 reflections with $I > 3.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. The structure was solved by direct methods. Full-matrix least-squares adjustment of atomic positional and thermal parameters (anisotropic C, O; fixed H contributions) converged to R = 0.061 (R_w = 0.089). Calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programs. The direct methods program MULTAN11/82 was employed. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.