

Structures of Shikoccin, a Unique 8,9-Seco-*ent*-kaurene Diterpenoid, and Shikoccidin (X-Ray Crystallography), a New Penta-oxygenated *ent*-Kaurene Diterpenoid

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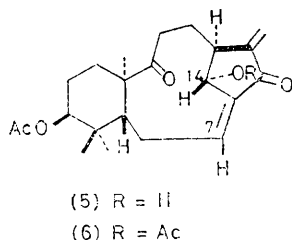
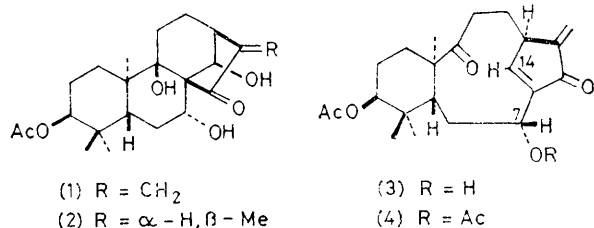
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Summary The structure of shikoccidin, a minor diterpenoid of *Rabdosia shikokiana* var. *occidentalis*, was determined by X-ray analysis to be as shown in (1), from which the structure of the main diterpenoid shikoccin was deduced to be (3).

OUR recent investigation of ether extracts of the dry aerial parts of *Rabdosia shikokiana* (Makino) Hara var. *occidentalis* (Murata) Hara¹ (Labiatae) resulted in the isolation of two new diterpenoids. The major diterpenoid, shikoccin (m.p. 150–152 °C, $[\alpha]_D^{24} + 47^\circ$ (CHCl₃), u.v. (MeOH) 246 nm (ϵ 7460)) has been shown to possess marginal *in vivo* anti-tumour activity against P 388 lymphocytic leukaemia in mice.



The detailed structure and relative stereochemistry of shikoccidin (1), C₂₂H₃₂O₆, m.p. 181–182 °C, $[\alpha]_D^{22} + 7.2^\circ$ (EtOH) were established by X-ray diffraction. (1) was crystallised from ethyl acetate, orthorhombic, space group *P*₂₁₂₁₂₁, *a* = 19.76(2), *b* = 15.81(4), *c* = 7.207(5) Å, *Z* = 4. Intensity data were collected using a densitometer from Weissenberg films taken using Cu-*K*_α radiation. The structure was solved by the direct method and refined by block-diagonal least-squares calculations. The crystal includes one disordered ethanol molecule in the unit cell. The most probable position of the solvent molecule was estimated from the difference Fourier map. The final *R*-value is 0.137 for 1499 reflections.† A perspective drawing of the

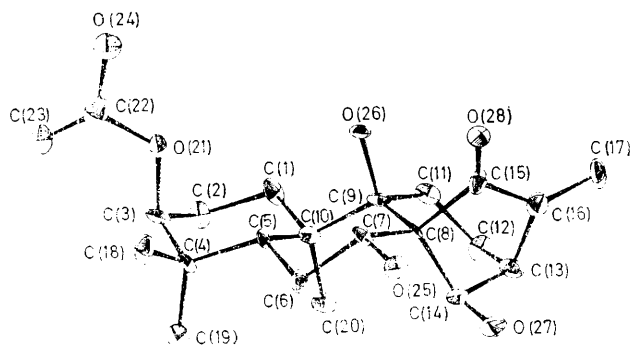


FIGURE. A perspective drawing of shikoccidin (1).

shikoccidin molecule is shown in the Figure. The structure has an intramolecular hydrogen-bond between the C-9 axial OH and the C-15 ketone O (O...O distance 2.85 Å). All computations for the X-ray analysis were performed on a FACOM M-190 in the Data Processing Centre of Kyoto University, using the program system KPAX which included the UNICS program.

Shikoccidin (1) on catalytic hydrogenation (Pd-C) gave only the dihydro-derivative (2), m.p. 172–174 °C, whose c.d. spectrum showed a -Cotton effect at 325 nm and a +Cotton effect at 298 nm.² These data suggested the absolute configuration to be as represented in (1).

Shikoccidin (1) on treatment with acetic anhydride in pyridine gave an acetate, m.p. 183–185 °C, which was shown to have no hydroxy group but two acetoxy groups [i.r. (KBr) 1736 cm⁻¹, n.m.r. (CDCl₃) δ 2.02, 2.15 (each 3H, s), 4.78 (1H, m), and 5.50 (1H, dd, *J* 5 and 11 Hz)], two ketone groups [i.r. (KBr) 1740 and 1702 cm⁻¹], an exocyclic methylene group [i.r. (KBr) 1654 cm⁻¹, n.m.r. (CDCl₃) δ 6.19 and 5.45 (each 1H)], and a trisubstituted double bond [i.r. (KBr) 1623 cm⁻¹, n.m.r. (CDCl₃) δ 7.20 (1H, d, *J* 2 Hz)]. It was shown to be identical with shikoccin monoacetate (4) derived from shikoccin by acetylation with acetic anhydride in pyridine.

This led to the assignment of structure (3) to shikoccin. Thus the structure of shikoccin corresponds to that of a retroaldol reaction product from shikoccidin. The alternative double bond isomeric structure (5) is excluded by the following facts. (i) The n.m.r. signal δ 4.45 in shikoccin and at δ 5.50 in shikoccin monoacetate (dd, *J* 5 and 11 Hz) may be assigned to C-7-H in (3) and (4), but not to C-14-H in (5) and (6). (ii) A doublet (*J* 2 Hz) at δ 7.26 in shikoccin and at

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

δ 7.20 in its monoacetate may be assigned to C-14-H in (3) and (4), but not to C-7-H in (5) and (6). (iii) Strain of the ten-membered ring system in (3) and (4) is less than that in (5) and (6).

Finally, shikoccidin (1) was treated as in the extraction procedure, but no transformation into shikoccin (3) was observed, thus confirming that shikoccin is a natural product.

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¹ H. Hara, *J. Japan Bot. (Shokubutsu Kenkyu Zasshi)*, 1972, **47**, 193. (Cf. *Isodon shikokianus* var. *occidentalis* Murata). For the diterpenoids of *Isodon shikokianus* see: T. Kubota and I. Kubo, *Bull. Chem. Soc. Japan*, 1969, **42**, 1778; T. Isobe, T. Kamikawa, I. Kubo, and T. Kubota, *ibid.*, 1973, **46**, 583; and I. Kubo, M. J. Pettei, K. Hirotsu, H. Tsuji, and T. Kubota, *J. Amer. Chem. Soc.*, 1978, **100**, 628.

² J. MacMillan and E. R. H. Walker, *J. C. S. Perkin I*, 1972, 986.