Structures of Shikodomedin (*X*-Ray Analysis) and Shikokiamedin: New Cytotoxic 8,9-Seco-*ent*-kaurenoids from *Rabdosia shikokiana* var. *intermedia*

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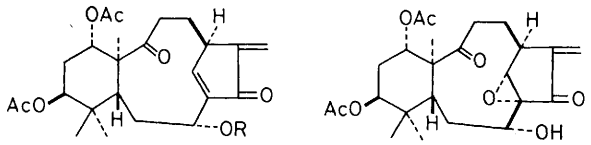
The structure and absolute configuration of shikodomedin, a major diterpenoid of *Rabdosia shikokiana* var. *intermedia*, has been shown to be that in structure (**1**) on the basis of *X*-ray analysis of the monobromoacetate (**3**); shikokiamedin, a minor diterpenoid, was deduced to have structure (**2**) by spectroscopic comparison with shikodomedin (**1**).

Previously, we isolated the new diterpenoids shikodomedin (**1**) and shikokiamedin (**2**)[1] from the aerial part of *Rabdosia shikokiana* (Makino) Hara var. *intermedia* (Kudo) Hara.[2] Both compounds exhibited cytotoxic activity against cultured rat mammary cancer cells FM 3A/B.† We now report the determination of the structure of these new compounds.

Shikodomedin (**1**), $C_{24}H_{32}O_7$, m.p. 193—194 °C, $[\alpha]_D^{20}$ −67.0° (*c* 0.46, $CHCl_3$), showed the following spectral data: λ_{max} (MeOH) 245 nm (ε 7887); ν_{max} ($CHCl_3$) 3600, 1730, 1700, 1650, and 1620 cm^{-1}; ^{13}C n.m.r.‡ δ 64.0 (d), 71.0 (d), 76.9 (d), 116.8 (t), 145.7 (s), 148.6 (s), 159.3 (d), 170.3 (s), 170.7 (s), 194.7 (s), and 212.2 (s) p.p.m.; ^1H n.m.r.‡ δ 1.02 (9H, s), 1.89 and 2.12 (each 3H, s), 4.56 (1H, dd, *J* 12 and 6 Hz), 4.78 (1H, t, *J* 4 Hz), 5.49 (1H, dd, *J* 10 and 6 Hz), 5.38 and 6.02 (each 1H, br s), and 7.24 (1H, d, *J* 4 Hz). These data suggest that shikodomedin has the structure (**1**) which corresponds to the 1α-acetoxy derivative of shikoccin.[3] The detailed structure was established by *X*-ray analysis of the monobromoacetate (**3**), m.p. 165—167 °C, which was obtained by treatment of (**1**) with bromoacetyl bromide in methylene dichloride in the presence of α-pinene; suitable crystals were obtained from propan-2-ol.

Crystal data: $C_{26}H_{33}BrO_8$, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 9.760(3)$, $b = 15.299(5)$, $c = 18.305(5)$ Å, $U = 2733.4$ Å^3, $D_m = 1.34$ g/cm^3, μ(Mo-K_α) = 16.4 cm^{-1}. The cell dimensions and intensities were measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo-K_α radiation in the ω-scan mode for $2\theta < 60°$. 1409 independent reflections [$I > 1.96\sigma(I)$] were used for the structure analysis. The structure was solved by the direct method using MULTAN on a Syntex XTL computer. Refinement by block-diagonal least-squares led to a final *R* value of 0.088. The absolute configuration of the molecule was determined by Bijvoet's anomalous-dispersion method based on the observed and calculated structure factors of 30 Friedel pairs. The molecular structure of (**3**) is illustrated in Figure 1. This is the first report of the crystal structure of a compound having the novel 8,9-seco-*ent*-kaurene skeleton.§

Shikokiamedin (**2**), $C_{24}H_{32}O_8$, $[\alpha]_D^{20}$ −42.5° (*c* 0.26, $CHCl_3$), was obtained as an amorphous powder and showed the following physical data: λ_{max} (MeOH) 232.5 nm (ε 5972);



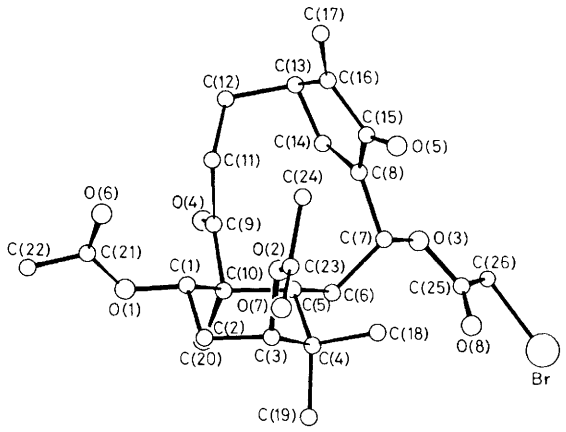


Figure 1. Molecular structure of compound (**3**). Hydrogen atoms are omitted for clarity.

ν_{max} ($CHCl_3$) 3590 (OH), 1730 (OAc), and 1700 and 1640 (five membered ketone conjugated with an exo-CH_2 group) cm^{-1}. The ^1H and ^{13}C n.m.r. spectra of (**2**) are very similar to those of shikodomedin (**1**) except that signals [^1H n.m.r.: δ 3.68 (1H, s); ^{13}C n.m.r.: δ 60.6 (d) and 64.4 p.p.m. (s)] due to a trisubstituted epoxide unit adjacent to a carbonyl group were observed instead of those due to the trisubstituted double bond in (**1**). Jones oxidation[4] of shikodomedin (**1**) gave shikokiamedin (**2**). These facts indicate that shikokiamedin has the 8,14-epoxyshikodomedin structure (**2**). From a consideration of Dreiding models, the oxiran ring was assigned the (8*R*, 14*R*)-configuration, since the proton attached to the oxiran ring gave a singlet. Accordingly, shikokiamedin has structure (**2**).

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† 10 μg ml^{-1} of shikodomedin (**1**) and shikokiamedin (**2**) exhibited inhibitory activities (63.3 and 62.0%, respectively) on the growth of cultured rat mammary cancer FM 3A/B cells. The detailed study will be published elsewhere.

‡ All ^1H and ^{13}C n.m.r. spectra were measured in $CDCl_3$ using tetramethylsilane as internal standard.

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

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