Structure of Neoliacinic Acid, a New Highly Oxidized Sesquiterpene from *Neolitsea acciculata* Koidz

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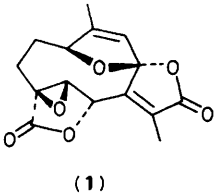
A new labile highly oxygenated sesquiterpene has been isolated from *Neolitsea acciculata* Koidz (*Lauraceae, Inugashi* in Japanese), and its structure determined by *X*-ray diffraction analysis.

In our previous paper,[1] we reported the isolation and structural characterization of neoliacine (**1**), a new germacranolide sesquiterpene dilactone with moderate cytotoxicity in Hella cell culture *in vitro*, from the fresh leaves of *N. acciculata*. We further examined chemical components of the same plant, and have isolated the sesquiterpene acid (**2**), which is expected to have antitumour activity.

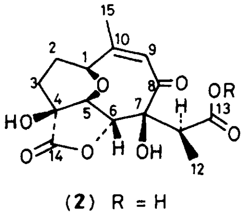
The acidic fraction obtained from the acetone extract of the fresh leaves (10 kg) was treated with diazomethane in ethereal solution to give the corresponding methyl carboxylate derivatives. After purification by column chromatography on silica gel, recrystallization from an ethyl acetate solution afforded neoliacinic acid (**2**) as its methyl ester, methyl neoliacinate (**2a**). $C_{16}H_{20}O_8$; *m/z* 340 (electron impact) from molecular ion and elemental analysis; colourless plates; m.p. 214.5—215.5 °C (decomp.); $[\alpha]_D$ −108° (*c* 0.3, EtOAc).

The i.r. spectrum of (**2a**) showed that it contained an α,β-unsaturated ketone (ν 1645 and 1690 cm^{-1}), a γ-lactone (ν 1795 cm^{-1}), and hydroxy groups (ν 3425 and 3480 cm^{-1}), in addition to the methyl ester group (ν 1719 cm^{-1}).

In the ^1H n.m.r. spectrum a narrowly split doublet at δ 1.61 (3H, *J* 1.2 Hz) and a multiplet at δ 5.80 (1H, m) revealed the presence of an allylic methyl group and an olefinic proton bonded to β- and α-carbon atoms, respectively, of an α,β-unsaturated ketone. A doublet at δ 1.22 (3H, *J* 7 Hz) and a quartet at δ 2.88 (1H, *J* 7 Hz) were also assigned to the methyl and methine protons, respectively, on the carbon adjacent to the carbonyl carbon of the ester group [δ 3.47 (3H, s)] and, therefore, the atom adjacent to this tertiary carbon should be quaternary. These assignments were further corroborated by its ^{13}C n.m.r. spectrum in CD_3SOCD_3: δ 10.9 (q, C-12), 18.0 (q, C-15), 43.9 (d, C-11), 51.3 (q, C-16), 123.1 (d, C-9), 144.9 (s, C-10), 171.6 (s, C-13), 175.1 (s, C-14), and 206.0 (s, C-8).



(1)



(2) R = H
(2a)R = Me

Compound (**2a**) could not be esterified with acetic anhydride–pyridine under mild conditions, and its ^1H n.m.r. spectrum showed no peaks corresponding to protons on carbon atoms [δ 72.6 (s, C-4) and 79.6 (s, C-7)] bearing hydroxy groups. Two sharp singlets at δ 4.97 and 6.49 disappeared on addition of D_2O. Based on these facts, the two hydroxy groups were concluded to be at tertiary positions.

Furthermore, the ^{13}C n.m.r. spectrum showed signals corresponding to two methylene (δ 21.8 and 24.4) and three methine groups (δ 71.5, 77.1, and 83.3) attached to secondary carbon atoms also bounded to an oxygen atom. One of these methine protons [δ 4.62 (d, *J* 4 Hz)] was attributed to the γ-proton (H-6) spin-coupled to the β-proton [H-5, δ 4.24 (d, *J* 4 Hz)] in the γ-lactone. These two protons (H-5 and H-6) appeared as signals of an AB system, indicating them to be adjacent to a quaternary carbon atom. Since (**2a**) contains seven degrees of unsaturation, five units of which can be accounted for by the partial structures described above, the

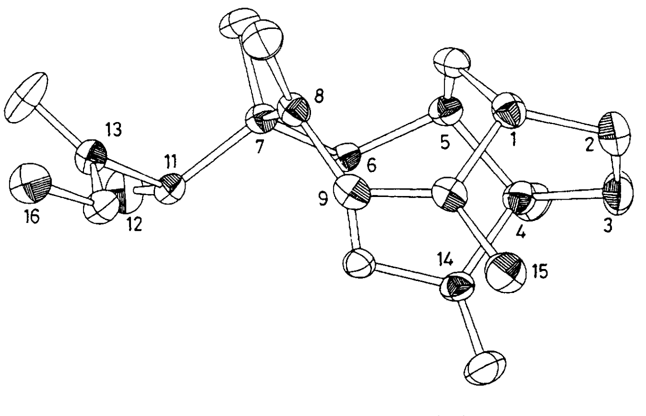


Figure 1. The structure of methyl neoliacinate (**2a**). Hydrogen atoms have been omitted for clarity.

remaining portion might possess an ether ring system, the signals at δ 4.24 (1H, d, J 4 Hz) and 4.44 (1H, m) corresponding to the protons at ether-bearing C-5 and C-1, respectively.

The spectral properties detailed above, together with consideration of the structures of neoliacine (**1**) and other sesquiterpenes isolated from same plant,[2] indicated that (**2a**) is a germacranolide-type sesquiterpene bearing an unique ether linkage and a γ-lactone group. In order to confirm the molecular structure, a single crystal X-ray analysis was carried out.†

Figure 1 shows a perspective drawing of the X-ray structure, and neoliacinic acid should thus be represented by the relative stereostructure (**2**) consisting of a ten-membered skeleton with an ether linkage between C-1 and C-5. Neoliacinic acid (**2**) may be biosynthesized *via* re-etherification followed by cleavage of the α-methyl-α,β-unsaturated-γ-lactone in neoliacine (**1**).

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† *Crystal data* for (**2a**): orthorhombic, space group $P2_1$, $a = 6.655\,(1)$, $b = 16.823(2)$, $c = 7.366(1)$ Å, $\beta = 109.70(1)°$. All unique diffraction intensities with $2\theta < 50.0°$ were collected in the variable speed ω-scan mode on a Syntex R3 four-circle diffractometer with graphite monochromated Mo-K_α radiation (λ 0.7107 Å). A total of 1596 reflections were judged to be observed after correction for Lorentz, polarization, and background effects. A phasing model obtained by MULTAN 78[3] was refined using the UNICS program system.[4] Block-diagonal least-squares refinement with anisotropic thermal parameters for the hydrogen atoms converged to a final $R = 0.038$. 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.

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