Short Communication

Shizukanolides, Two Sesquiterpenoids
from *Chloranthus japonicus*
(Chloranthaceae)Jun KAWABATA, Satoshi TAHARA, Junya
MIZUTANI,[†] Akio FURUSAKI,* Nobuhiro
HASHIBA* and Takeshi MATSUMOTO*Department of Agricultural Chemistry,
Faculty of Agriculture*Department of Chemistry, Faculty of Science
Hokkaido University, Sapporo 060, Japan

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Several plants of the genus *Chloranthus* (Chloranthaceae) are known to grow in east Asia and a few investigations of the chemical components of this genus have been performed.¹⁻⁴⁾ In this communication we wish to report the isolation and structure elucidation of two sesquiterpene lactones from *C. japonicus* Sieb. (Japanese name: Hitori-shizuka).

The ethereal extract of fresh aerial parts of *C. japonicus* (collected at Mt. Haruka-yama in the west of Sapporo in June 1977) was washed with 5% Na₂CO₃ solution and fractionated by Florisil column chromatography. The ether/pentane (1:1) eluate was rechromatographed on Florisil column to obtain colorless needles (mp 95~96.5°C, $[\alpha]_D^{20} + 200^\circ$ ($c=0.21$, CHCl₃)) named shizukanolide in about 0.02% yield.

Shizukanolide (**1**) has a molecular formula C₁₅H₁₈O₂ (M^+ 230.1308, calcd. 230.1307). The infrared absorptions at 3070, 1760, 1739, 1670, 1655 and 895 cm⁻¹ and the ultraviolet absorption at 213.5 nm ($\epsilon=17,700$) suggested the presence of an α , β -unsaturated- γ -lactone group and a terminal double bond. The NMR data were as follows: PMR (100 MHz, CDCl₃) δ 0.80 (3H, s), 0.80~0.93 (2H, m), 1.38 (1H, ddd, $J=8, 7$ and 4 Hz), 1.49 (1H, dd, $J=12$ and 10 Hz), 1.83 (3H, t, $J=1.5$ Hz), 2.00~2.20 (2H, m), 2.40~2.80 (2H, m), 2.63

(1H, dd, $J=12$ and 7 Hz), 4.76 (1H, br s), 5.01 (1H, br s), 5.01 (1H, dd, $J=10$ and 7 Hz); CMR (22 MHz, CDCl₃) δ 174.0 (s, C-12), 161.4 (s, C-7), 150.2 (s, C-4), 121.4 (s, C-11), 106.0 (t, C-15), 79.5 (d, C-8), 63.9 (d, C-5), 44.1 (t, C-9), 38.6 (s, C-10), 27.0 (d, C-1), 23.8 (t, C-6), 23.4 (d, C-3), 17.2 (q, C-14), 15.9 (t, C-2), 8.4 (q, C-13). Analysis of these data revealed that **1** contained a cyclopropane ring (PMR δ 0.80~0.93), an oxymethine carbon adjacent to a methylene carbon (PMR decoupling at δ 5.01, 1.49 and 2.63), an exocyclic double bond (two broad singlets, δ 4.76 and 5.01), a tetrasubstituted double bond (CMR) and two methyl substituents on a quaternary and olefinic carbons (PMR δ 0.80 and 1.83).

Hydrolysis of **1** with KOH/MeOH-H₂O followed by methylation gave a keto ester ($\nu_{C=O}$ 1710 and 1740 cm⁻¹) via isomerization. As a consequence of ketonization at C-8 in **1**, the C-9 methylene protons, which appear at δ 1.49 and 2.63 in **1**, were shifted to δ 2.60(s). Catalytic hydrogenation of **1** under various conditions gave a mixture of several tetrahydro- and hexahydro-compounds and the main hexahydro-product showed absorption at $\nu_{C=O}$ 1770 cm⁻¹ and as a result of saturation of double bonds, $\nu_{C=C}$ and ν_{C-H} disappeared.

FIG. 1. A Perspective View of the Shizukanolide Molecule.

[†] To whom inquiries should be addressed.

The structure was unambiguously established by X-ray crystallography. The crystal data of **1** were as follows: orthorhombic; space group $P2_12_12_1$; $a=11.121(3)$, $b=33.299(7)$, $c=6.951(2)$ Å; $Z=8$, $D_c=1.188$ gcm $^{-3}$. Intensity data with 2θ -values up to 140° were collected on a Rigaku four-circle diffractometer using $\text{CuK}\alpha$ radiation monochromatized with an LiF crystal. 2537 independent structure factor magnitudes greater than their estimated standard deviations were selected for the structural study. The structure was elucidated by the Monte Carlo direct method⁽⁵⁾ on the basis of 570 E -values above 1.30. The starting set was composed of the 20 strongest reflections. Tentative phase values for the starting reflections were derived from successively generated random numbers. In order to extend this tentative phase set, 12 cycles of the tangent procedure⁽⁶⁾ were carried out. The 52nd phase set which showed a low R_K -value⁽⁷⁾ of 30.3% led to the correct solution; an E -map calculated with 535 phases yielded all 34 independent non-hydrogen atoms. The structure thus obtained was refined by the block-diagonal-matrix least-squares method with anisotropic temperature factors. After all 36 hydrogen atoms had been located in a difference Fourier map, the least-squares refinement was repeated including these hydrogen atoms. The final R -value is 5.6%. Thus, the structure has been established as shown in Fig. 1 except for the absolute configuration.

The geometries of the two independent molecules are almost identical. The six-membered ring takes a somewhat distorted chair form, and the cyclopentane ring adopts an envelope form in which the C-5 atom deviates remarkably from the mean plane for the other four atoms. The γ -lactone ring is nearly planar owing to the existence of the C-7=C-11 double bond.

The absolute structure of **1** was deduced by correlation between **1** and lindenene, which was found in the root of *Lindera strychnifolia* and the absolute configuration of which was determined by Takeda *et al.*⁽⁸⁾ **1** was reduced by DIBAH^9 to give a furano-derivative (**2**).

The physicochemical properties of **2**, IR $\nu_{\text{max}}^{\text{liquid film}}$ cm $^{-1}$: 3070, 1660, 1625, 1560, 880; GC-MS $m/e(\%)$: 214(M^+ , 75), 199(12), 185(10), 172(32), 109(100), 108(68), 106(37), 91(39); $[\alpha]_D^{25} -51.4^\circ$ ($c=0.11$, CHCl_3), agreed with those of lindenene ($[\alpha]_D -50.1^\circ$, CHCl_3).

On the other hand, the ethereal extract of fresh roots of *C. japonicus* was similarly fractionated to give a second sesquiterpene lactone (**3**) as colorless prisms (mp $64\sim65.5^\circ\text{C}$, $[\alpha]_D^{25} +59.8^\circ$ ($c=1.02$, CHCl_3)) in 0.017% yield. **3** showed a molecular ion peak at 228.1166 ($\text{C}_{15}\text{H}_{16}\text{O}_2$) and had an intense ultraviolet absorption at 282.5 nm ($\epsilon=20,400$). The infrared spectrum of **3** showed absorptions at 1775, 1660, 1650, 1639 and 883 cm $^{-1}$. The PMR spectrum of **3** was quite similar to that of **1** except that signals of C-9 methylene and C-8 oxymethine protons disappeared and that a new peak of vinylic proton (δ 6.25(s)) appeared. Alkaline NaBH_4 reduction of **3** yielded a mixture of saturated γ -lactones. The main product **4** (GLC *ca.* 70% yield) was isolated as crystals, GC-MS $m/e(\%)$: 232 (M^+ , 8.9); IR $\nu_{\text{max}}^{\text{KBr}}$ cm $^{-1}$: 1759, 1170, 964. Equally alkaline NaBH_4 reduction of **1** gave **4** as a main product. Thus, we determined **3** to be 8, 9-dehydro-shizukanolide. Recently, Uchida *et al.*⁽⁴⁾ isolated chloranthalactone A (**3'**), colorless oil bp $143\sim144^\circ\text{C}/3$ mmHg, from *Chloranthus glaber* (*Sarcandra glabra*) and proposed the plane structure, which was identical to that of **3**. Since the physicochemical properties of **3'** reported were slightly different from those of **3**, precise comparison between **3'** and **3** should be required.

Although shizukanolide (**1**) is antimicrobial-ly inactive, dehydro-compound (**3**) shows remarkable activity as an antifungal agent rather than antibacterial one.

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