Structures of Novel Sesquiterpene Alcohols from
*Chloranthus japonicus* (Chloranthaceae)†

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Three novel sesquiterpene alcohols, shizuka-acoradienol (2), shizukafuranol (3) and shizukolidol (4), were isolated from *Chloranthus japonicus* Sieb. (Japanese name: Hitori-shizuka, Chloranthaceae). Their structures were elucidated on the basis of their physicochemical properties and some chemical reactions. Furanodienone (5), scopoletin (6a) and isoscopoletin (6b) were also isolated from this plant.

The earlier papers in this series have described the isolation of the unusual sesquiterpene lactones, shizukanolide (1) and its derivatives, from *Chloranthus japonicus* (Japanese name: Hitori-shizuka, Chloranthaceae).1~3) This paper reports the isolation and structural determination of three new sesquiterpene alcohols, shizuka-acoradienol (2), shizukafuranol (3) and shizukolidol (4), from the same source, and also mentions the identification of three additional constituents, furanodienone (5), scopoletin (6a) and isoscopoletin (6b).

Fresh leaves and roots of *C. japonicus* collected in the mountainous area of Sapporo were separately extracted with ether. Both these ethereal extracts were separated into neutral and acidic fractions. The neutral fractions were chromatographed over Florisil columns using pentane or hexane and an increasing amount of ether as eluting solvents.

Shizuka-acoradienol (2) was isolated as colorless needles (mp 128.5~130.0°C, [α]D

−203°) from ether–pentane (1:4) eluates of the neutral fraction of the roots. The molecular formula of 2 was established by HRMS as C_{15}H_{24}O (M⁺ 220.1841, calcd. for

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C_{15}H_{24}O: 220.1827), indicating four degrees of unsaturation. The $^{13}$C-NMR spectrum showed that two degrees of unsaturation came from two double bonds, with signals at $\delta$ 107.7 (t), 127.4 (d), 140.1 (d), and 146.8 (s), leaving two rings. The UV absorption maximum ($\lambda_{\text{max}}^{\text{F}}$ = 233 nm ($\epsilon$ = 18,000)) and IR absorption bands ($\nu_{\text{KBr}}$ = 1640 and 1600 cm$^{-1}$) as well as the $^1$H- and $^{13}$C-NMR spectra argued for a 1,3-disubstituted butadiene system. The $^1$H-NMR spectra (in pyridine-$d_5$) showed six low-field signals, attributable to four olefinic protons ($\delta$ 5.17, 5.32, 5.82 and 6.36) and a secondary alcohol function ($\delta$ 4.80 (OH) and 6.52 (O-CH)), and three sharp doublets, attributable to secondary methyl and isopropyl groups. Four protons at $\delta$ 1.66, 1.96, 4.80 and 5.82 are situated in the vicinity of the hydroxyl function because of their large values ($A = \delta_{\text{chloroform}-d} - \delta_{\text{pyridine}-d_5} = -0.39, -0.2, -0.30$ and $-0.63$, respectively) of the pyridine-induced solvent shift.\(^{4)}\) The carbinol proton ($\delta$ 4.80) was coupled to the methylene protons at $\delta$ 1.66 and 1.96 marked by geminal coupling. The partial structure I is therefore proposed. The residual part contains only one quater-

nary carbon ($\delta$ 50.9) in the $^{13}$C-NMR spectrum and the terminal carbons of the structure I are connected to the quaternary carbon, since the protons bearing these carbons showed no further coupling with any protons. The remainder of the molecule appears to be an isopropylmethylcyclopentane ring by the $^{13}$C- and $^1$H-NMR spectra. On biosynthetic grounds, the carbon skeleton of 2 is suggested to be an acorane system\(^{5)}\) and, consequently, the plain structure of 2 is deduced. Acid-catalyzed isomerization\(^{6)}\) of the allylic alcohol function of 2 gave a cyclohexenone (7) which showed an IR band ($\nu_{\text{KBr}}$ = 1670 cm$^{-1}$) and a UV maximum ($\lambda_{\text{max}}^{\text{MeOH}}$ = 242 nm). The spectroscopic properties of 7 were identical with those of acorenone (7a),\(^{7)}\) which had been isolated from Acorus calamus.\(^{8)}\) but were not consistent with those of its stereoisomers: 4-epiacorenone (7b),\(^{9)}\) acorenone B (7c)\(^{9,10)}\) and 4-epiacorenone B (7d).\(^{11)}\) The isomerization product, however, showed a specific optical rotation of $+28.8^\circ$ in contrast to the value $(-34.9^\circ)$ of the natural 7a, which indicates that 7 must be the antipode of 7a. The stereochemistry of the hydroxyl group of 2 is expected to be of $\beta$-orientation (cis to the C-14 methyl group), because the pyridine-induced solvent shift was observed on the C-14 methyl group ($A = -0.18$), but not on the C-12 (or 13) methyl group ($A > 0$). Moreover, this is also supported by the results of the NOE experiments. The NOE enhancements were clearly observed between the C-14 methyl and C-6 axial protons (11%) and between the C-12 (or 13) methyl and C-7 axial protons (6%). On the contrary, little NOE interaction was observed between the C-14 methyl and C-7 axial protons (0%) and between the C-12 (or 13) methyl and C-6 axial protons (2%). The results obtained indicate that the 7S structure (A) is preferable to the 7R type (B) and the absolute structure of 2 was thus established.

Furanodienone (5) was also obtained as colorless needles (mp 87~88°C) from ether-pentane (1 : 9) eluates of the neutral fraction of the roots. The physicochemical properties of our specimen coincided well with those of furanodienone.\(^{12)}\)

Shizukafuranol (3) was isolated as colorless needles (mp 69~70°C, $[\alpha]_D$ = -67°) from ether-hexane (1 : 1) eluates of the neutral fraction of
the leaves. The molecular formula of 3 was assigned as C_{15}H_{22}O_{2} by HRMS (M^+ 234.1640, calcd. for C_{15}H_{22}O_{2}: 234.1620). A characteristic intense ion at m/z 108 in the mass spectrum suggested 3 to be a sesquiterpene furan as shown in that of isofuranodiene (8).2) The IR absorption band at v_{Br}^{max} 3390 cm^{-1} indicated the presence of a hydroxyl function. The ^1H-NMR spectrum (in chloroform-d) showed three singlets (δ 0.88, 1.25 and 1.91, each 3H), attributable to tertiary, α-hydroxylated tertiary and allylic methyls, respectively, and a broad singlet (δ 2.36, 2H), attributable to an isolated allylic methylene group, whereas no carbinol proton was observed. The above-mentioned data and the fact that this plant contains a series of modified eudesmanes (lindenanes)1~3,13) suggest 3 to be a 4-hydroxyeudesmane derivative. This estimation was confirmed by the biogenetic preparation of 3 from isofuranodiene (8). Transannular cyclization of 8 was performed by Tsankova's method14) and gave a hydroxyfuran, which was identical with 3 in the mass, IR and ^1H-NMR spectra. The relative stereochemistry between the C-14 and C-15 methyl groups is expected to be 1,3-diaxial on the basis of the reaction mechanism; this is also supported by the facts that dehydration of 3 with phosphorus oxychloride-pyridine15) resulted in a mixture containing ca. 60% of 9 and smaller amounts of the A^1 and A^4,5 isomers16) and that little pyridine-induced solvent shift (Δ = −0.02) appeared on the C-14 methyl signal in the ^1H-NMR spectrum. The structure of shizukafuranol was thus established as shown in 3.

Shizukolidol (4) was isolated as colorless needles (mp 194~195°C, [α]_D ^{20} −64°) from ether eluates of the neutral fraction of the leaves. The mass spectrum of 4 was in agreement with the molecular formula, C_{15}H_{20}O_{3} (M^+ 248.1422, calcd. for C_{15}H_{20}O_{3}: 248.1413). The UV absorption maximum (λ_{max} ^{MeOH} 272 nm) and the IR absorption bands (v_{max} ^{KBr} 3341, 1764 and 1659 cm^{-1}) indicated the presence of a hydroxyl function and a 4-alkylidene-2-butenolide moiety. The ^1H-NMR spectrum (in chloroform-d) had three three-proton signals (δ 1.05, 1.27 and 1.90), attributable to tertiary, α-hydroxylated tertiary and allylic methyls, respectively, three one-proton signals (δ 1.80, 2.35 and 3.07) and a lowfield singlet (δ 5.52), attributable to an olefinic proton. The signal at δ 1.80 (dd, J = 14 and 3.4 Hz) was coupled to both protons at δ 2.35 (ddq, J = 17, 14 and 1.5 Hz) and 3.07 (dd, J = 17 and 3.4 Hz), which were also coupled to each other. The coupling constants of these protons indicate that two of them are axial and one is equatorial, and homoallylic coupling was observed between the axial proton at δ 3.07 and the allylic methyl protons. The above-mentioned data suggest the compound 4 to be an oxidative form of 3. Oxidation of 3 with DDQ17) yielded a corresponding butenolide, which was identical with shizukolidol in the physicochemical properties. The structure of 4 was therefore determined. Although sesquiterpene lactones having a 4-alkylidene-2-butenolide function often show antifungal2) or anti-inflammatory18) activity, shizukolidol is nearly inactive against microbial growth.

Scopoletin (6a) and isoscopoletin (6b) were also isolated from the acidic fraction of the leaves and identified by a direct comparison with authentic specimens.

So far, about twenty acoranes have been isolated from plants, but compounds which have a cis configuration between the C-1 iso-propyl and C-4 methyl groups as shown in shizuka-acoradienol (2) are very rare. Among them, the compound 2 is the first entry to the (1R,4R)-acorane system. Furthermore, most of the natural acoranes are distributed in the plants of Gymnospermae (Cupressaceae)19) and Monocotyledoneae (Gramineae20) and Araceae21)), whereas only a few reports on the identification of the acoranes from the plants of Dicotyledoneae (Umbelliferae)22) have been published. It is interesting that an acorane was isolated from the Chloranthus sp. belonging to Polycarpiidae, the lowest infraclass of Dicotyledoneae, which can be regarded as a phylogenetic junction from Gymnospermae to Monocotyledoneae and to the other Di-
cotyledoneae.

**EXPERIMENTAL**

*General.* Melting points were determined on a hot plate and were uncorrected. Optical rotations and CD spectra were measured on JASCO DIP-4 and J-20 instruments, respectively. Mass spectrometry was carried out on a JOEL JMS-D300 instrument. IR and UV spectra were recorded on Hitachi 285 and EPS-3T instruments, respectively. Most 1H-NMR spectra were determined on a JOEL FX-400, FX-100 and PS-100 instruments. Some 1H- and 13C-NMR spectra were obtained on a JEOL FX-200 instrument.

**Isolation of shizuka-acoradienol (2) and furanodienone (5).** Fresh roots (3.5 kg) of *C. japonicus* collected at Mt. Sankaku-yama in Sapporo in June 1979 were extracted thrice with ether at room temperature. The ether extracts were combined, concentrated, washed with 5% NaHCO3 and dried over Na2SO4. After removal of the solvent, the residue was charged on a Florisil column and eluted with a pentane-ether gradient. Compound 2 was isolated from the pentane-ether (8:2) eluates. Recrystallization from hexane gave colorless needles (98 mg): mp 128.5 ~ 130.0 °C; [α]D + 67° (c=0.06, CHC13); MS m/z: 248.1422 (M+, C15H20O3, 32%), 177 (26), 175 (100), 163 (52), 43 (33); IR νmax cm⁻¹: 3341, 1764, 1659, 1006; UV λmax nm (ε): 272 (27,500); 1H-NMR δMeCl: 0.73 (12-H), 0.12 (14-H), 1.27 (3-H, s, 12-H), 1.43 (15-H), 1.88 (13-H), 2.40 (9-H), 3.10 (6α-H), 5.17 (15-H), 5.32 (10-H), 6.53 (9-H), 6.52 (1-H, d, J=6.3 Hz, 10-H); δMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 0.73 (12-H), 0.76 (13-H), 0.92 (14-H), 1.66 (6β-H), 1.96 (1H, br s, 15-H), 5.19 (1H, br d, J=1.4 Hz, 15-H), 5.32 (1-H, d, J=9.8 Hz, 15-H), 6.15 (1-H, d, J=9.8 Hz, 10-H); δδMeCl: 3.71 (24.0 Hz), 3.76 (24.0 Hz), 0.93 (14-H), 1.56 (15-H), 1.88 (13-H), 2.36 (9-H), 3.10 (6α-H), 5.17 (15-H), 5.32 (10-H), 6.53 (9-H), 6.52 (1-H, d, J=6.3 Hz, OH); 13C-NMR δMeCl: 13.7 (q, 14-C), 22.9 (q, 12-C), 23.4 (q, 13-C), 27.3 (t, 2 or 3-C), 29.3 (t, 3 or 2-C), 30.4 (d, 11-C), 31.5 (t, 6-C), 47.3 (d, 4-C), 50.9 (s, 5-C), 57.9 (d, 1-C), 67.8 (d, 7-C), 107.7 (t, 15-C), 127.4 (d, 9-C), 140.1 (d, 10-C), 146.8 (s, 8-C).

Compound 5 was obtained from the pentane-ether (8:2) eluates. Recrystallization from hexane gave colorless needles (38 mg): mp 87 ~ 88°C; MS m/z: 230 (M+, 47%), 215 (22), 150 (50), 122 (100), 94 (26), 81 (48); IR νmax cm⁻¹: 1644, 1608, 1231, 1013, 755; UV λmax nm (ε): 241 (9150), 269 (sh, 8800); 1H-NMR δMeCl: 1.30 (3H, s), 1.99 (3H, s), 2.13 (3H, s), 3.69 (2H, s), 5.16 (1H, m), 5.80 (1H, s), 7.05 (1H, s). All analytical data were in good agreement with those of furanodienone.

**Isolation of shizukafurananol (3) and shizukolidol (4).** Fresh leaves (3.3 kg) of *C. japonicus* collected at Mt. Sankaku-yama in Sapporo in July 1980 were extracted...
Identification of scopoletin (6a) and isoscopoletin (6h).

There were methyl signals at δ 0.76, 0.84 and 1.05 ppm, corresponding to the C-10 methyl of the A15 (9), A4 and A4,5 isomers, respectively, exomethylene protons at δ 4.69 and 4.84, corresponding to the 15-H of 9, and an olefinic proton at δ 5.33, corresponding to the 3-H of the A4 isomer. The intensity of these signals indicated a composition of ca. 60% 9, 25% A4 and 15% A4,5 isomers.

Transannular cyclization of 8. Preparation of (±)-3. To a stirred solution of Hg(OAc)2 (64 mg) in 2 ml of aqueous THF (1:1) was added dropwise a solution of 8 (42 mg) in THF (1 ml). After stirring for 5 min, 3 m-NaOH (1 ml) and 0.5 m-NaBH4 (in 3 m-NaOH, 1.5 ml) were added to the mixture. The resulting black suspension was stirred for a further 20 min, poured into sat. NaCl and extracted with ether. The ether extract was chromatographed over Florisil, and elution with ether–hexane (1:1) afforded a hydration product, (+)-3, as colorless powders (31 mg). The physicochemical properties of the product were coincident with those of shizukolidol.

DDQ oxidation of 3. Preparation of 4. To a solution of 3 (4 mg) in dry dioxane (0.2 ml) was added DDQ (15 mg). After shaking for 5 min at 45°C, the mixture was diluted with an excess amount of ether and filtered. The filtrate was washed with 5% Na2CO3, dried, concentrated and fractionated by PTLC (SiO2/benzene–ethyl acetate (1:1)) to give an unsaturated lactone (4) as colorless needles (1 mg), which was identical with shizukafuranol in the physicochemical properties.

Identification of scopoletin (6a) and isoscopoletin (6h). The acidic fraction of the leaves was chromatographed over SiO2 with a hexane-acetone gradient. The crude systems of ether and benzene-ether-acetic acid (30:20:5) were purified by repeated PTLC (SiO2) with solvent to afford 6a (5 mg) and 6b (1 mg). 6a: mp 201°C; MS m/z: 192 (M+, 100%), 177 (5), 164 (12), 149 (28), 69 (22); IR ν cm⁻¹: 3330, 1705, 1563, 1286, 1136; 1H-NMR δ ppm: 3.98 (3H, s), 5.57 (1H, brs), 6.12 (1H, s), 6.27 (1H, d, J=9.5Hz), 6.84 (1H, d, J=9.5Hz), 6.92 (1H, s), 7.60 (1H, d, J=9.3Hz), 6.29 (1H, d, J=9.5Hz), 6.83 (1H, s), 6.97 (1H, s), 7.59 (1H, d, J=9.5Hz). All analytical data of 6a and 6b were agreeable with those of authentic scopoletin and isoscopoletin, respectively.

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