Structures of Novel Sesquiterpene Ketones from *Chloranthus serratus* (Chloranthaceae)†

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Two naturally occurring new sesquiterpene ketones, neoacolamone (1) and 7a-hydroxy-neoacolmone (2), were isolated from the roots of *Chloranthus serratus* (Thunb.) Roem. et Schult. (Japanese name: Futari-shizuka, Chloranthaceae). The structures were elucidated on the basis of their physicochemical properties and chemical reactions. Three sesquiterpene ketones, acoragermacrone (3), acolamone (4) and zederone (5), and four additional sesquiterpenes including lindenanolides were also found in the same source. The relationships of these isolates to the constituents of *C. japonicus* and to the sesquiterpene biogenesis in the *Chloranthus* species are discussed.

The chemical constituents of *Chloranthus serratus* (Thunb.) Roem. et Schult. (Japanese name: Futari-shizuka, Chloranthaceae) have been investigated by Takemoto et al. Two amides, two amides, and two sesquiterpenes, were identified. Our reinvestigation in connection with the chemical constituents of *Chloranthaceae* plants from a chemotaxonomic interest gave four germacranes, three eudesmanones and two lindenanolides.

The root extract of *C. serratus* was fractionated by column chromatography with Florisil or silica gel and by preparative TLC (PTLC) on silica gel. The less polar fractions gave four sesquiterpenes, while the more polar fractions yielded five sesquiterpenes, 2, 5, 7, 8 and 9. The physicochemical properties of 6, 7, 8 and 9 agreed with those of isofuranodiene, furanodienone, chloranthalactone C and shizukanolide C (revised name of desacetylchloranthalactone C), respectively, which have already been confirmed as constituents of *C. japonicus* (Japanese name: Hitori-shizuka). The structures of 3, 4 and 5 were deduced from analyses of their MS, IR and 1H-NMR data, and they were identified by comparing the spectral properties with those of the known compounds, acoragermacrone, acolamone and zederone, respectively. The structure of 5 was also confirmed by its direct conversion from furanodienone (7). Epoxidation of 7 with alkaline hydrogen peroxide yielded an a,β-epoxyketone. The physicochemical properties of the product were identical with those of 5 and with the reported data for zederone. The compounds 1 and 2 were naturally occurring new sesquiterpenes and are named neoacolamone and 7a-hydroxyneoacolmone, respectively. Their structures were established through chemical and spectroscopic procedures.

Neoacolamone (1): The structure of 1 was

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† Studies on the Chemical Constituents of Chloranthaceae Plants. Part IV. For Part III, see ref. 1.

* In a similar manner, we wish to give the revised name "shizukanolide A" to "shizukanolide" and "shizukanolide B" to "dehydroshizukanolide."

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established to be \((7S,10R)\)-eudesm-4-en-6-one by direct comparison with a reductive dehydroxylation product (10) of 2 (see the following part). Although the compound 1 was chemically prepared from acolamone (4) by Niwa et al., the isolation of 1 from a natural source is the first example.

\[2\]: The molecular ion at \(m/z\) 236 of 2 in the mass spectrum suggested the molecular formula to be \(C_{15}H_{24}O_2\), indicating four degrees of unsaturation. The IR spectrum showed absorptions at 3450, 1670 and 1610 cm\(^{-1}\), attributable to hydroxyl and \(\alpha,\beta\)-unsaturated carbonyl functions. The \(^{13}\)C-NMR absorptions at \(\delta\) 203.4 (s), 137.6 (s) and 142.9 (s) also showed a carbonyl group and a tetrasubstituted double bond. Two other quarternary carbons appeared at \(\delta\) 37.2 and 78.7, and the latter was expected to be attached to a hydroxyl function. The relatively low intensity (\(e=4200\)) of a UV absorption at 256 nm is characteristic of a heteroannular cisoid enone. Two degrees of unsaturation are thus attributed to the enone function, leaving two rings. The \(^1\)H-NMR spectrum had a set of signals, \(\delta 0.93\) (3H, d, \(J=6.8\) Hz), 0.98 (3H, d, \(J=6.8\) Hz) and 2.28 (1H, septet, \(J=6.8\) Hz), attributable to an isopropyl group bearing a quarternary carbon, two three-proton singlets at \(\delta 0.99\) and 1.78, attributable to tertiary and allylic methyls, respectively, and a two-proton triplet at \(\delta 2.11\), attributable to an allylic methylene. The residual eight protons, attributable to four methylene groups by the \(^{13}\)C-NMR spectrum, were found at \(\delta 1.4\sim2.0\) (complex), and there was neither a methylene group adjacent to the carbonyl group, nor an isolated one. The isopropyl group needs to be attached to the quarternary carbon bearing the hydroxyl group, because the methine proton of the isopropyl group showed a large pyridine-induced solvent shift.

\[\delta_{\text{chloroform-d}} - \delta_{\text{pyridine-d$_5$}} = -0.51,\]
in the NMR spectrum. On biogenetic grounds, the possible structure 2 is presented, for eudesmane-type sesquiterpenes have been found in Chloranthaceae plants major constituents. The proposed structure of 2 and its stereochemistry was established through chemical transformation reactions.

Dehydroxylation of 2 with zinc-acetic acid-hydrochloric acid\(^{13}\) yielded two reaction products, 10 and 11, which showed molecular ions at \(m/z\) 220 in the mass spectra. The IR and \(^1\)H-NMR spectra of the major product, 10, completely coincided with those of \((7S,10R)\)-eudesm-4-en-6-one.\(^{6}\) The optical property of 10, \([\alpha]_D+105^\circ\), indicates that 10 had the same stereochemistry as that of the \((7S,10R)\)-isomer (lit., \([\alpha]_D+72^\circ\)). The eudesmane ring system of 2 was thus confirmed, and consequently 2 inevitably has an \(R\) configuration at C-10. The results of CD analysis of 10 also support this stereochemistry, because the positive Cotton effect in the 230\sim260 nm region of the heteroannular cisoid enone indicates that 10 must have the same stereochemistry, concerned with C-10 bearing a methyl group as not that of cholest-5-en-4-one (105) but of cholest-4-en-6-
one (10R). On the other hand, the structure of the minor product, 11, was expected to be an epimer of 10 at C-7, i.e., (7R,10R)-eudesm-4-en-6-one, by the similarity of the mass spectrum to that of 10. Since the dehydroxylation reaction was non-stereospecific, the configuration at C-7 of 2 remained to be determined. Dehydration of 2 with thionyl chloride-pyridine resulted in a mixture of 12 and 13 in the ratio of 9:1. Both of them showed M+ 218 (GC-MS), corresponding to the molecule of 2-H2O. The structure of the major product (12) was induced by 1H-NMR spectroscopy as follows. Two methyls at δ 1.02 and 1.05 (each d, J = 6.8 Hz) and a methine at δ 2.94 (doublet of septet, J = 6.8 (d) and 1.0 (sep) Hz) showed an isopropyl group. The methine proton showed an allylic coupling with a newly appeared olefinic proton at δ 6.48 (ddd, J = 5.7, 2.9 and 1.0 Hz). On the other hand, the minor product was estimated to have an isopropylidene group as shown in 13. A dehydration reaction of alcohol with thionyl chloride-pyridine can be expected to be a concerted trans elimination. The predominancy of 12 therefore indicates the configuration of C-7 in 2 to be S (axial OH on C-7), while the exo-olefin product (13) should be mainly formed if the C-7 hydroxyl group is equatorial. This estimation was also supported by the results of a hydride reduction of 2. Reduction of 2 with lithium aluminum hydride yielded a mixture of three dihydro-products, 14, 15 and 16, in the ratio of 23:21:1. One of the main products, 14, showed its molecular ion at m/z 238 by mass spectrometry, and the carbonyl absorption in the IR spectrum of 2 disappeared, with the hydroxyl absorption strengthening and branching. The 1H-NMR spectrum (in pyridine) showed that new hydroxyl (δ 5.65) and carbinol (δ 4.95) protons appeared, whereas no other practical change of the spectrum was observed. The large value (−0.31) of the pyridine-induced solvent shift of the angular methyl on C-10 in the NMR spectrum shows that the new hydroxyl group occupies a position 1,3-diaxial to the methyl, and the coupling constant (2.2 Hz) between the hydroxyl and carbinol protons also suggests the hydroxyl group on C-6 to be axial. The structure 14 was thus deduced. Another major product, 15, showed an IR absorption band at 1706 cm−1 assignable to a non-conjugated carbonyl group. The structure of 15 should thus be 7-hydroxyeudesman-6-one. Although both cis- and trans-decalone-type structures are possible, analysis of the CD spectrum ([θ]215,217 +2570) of 15 according to the octant rule suggests that the configuration of a trans-decalone-type is favorably acceptable. Furthermore, the ORD values of 15, [θ]215 +1920° and [θ]233 +830°, agreed approximately with those of a trans-decalone. A new C-5 proton introduced through reduction was detected at δ 2.80 in the NMR spectrum and the coupling constant (3.9 Hz) of this proton with 4-H suggests an axial-equatorial spin coupling system. The structure of 15 was thus determined. The large value (−0.40) of the pyridine-induced solvent shift of 5-H in the NMR spectrum showed that the C-5 proton occupied a position 1,3-diaxial to the C-7 hydroxyl function. The stereochemistry at C-7 (R) thus concluded is well compatible with that deduced from the dehydration mechanism of 2. The minor product, 16, was estimated to be an epimer of 14 at C-6 by the fact that it showed a quite similar mass spectrum to that of 14, in addition to lacking a carbonyl absorption in the IR spectrum. The reduction mechanism of α-hydroxyketone with hydride reagents is well understood, in that the reductant initially intercalates between the carbonyl and hydroxyl groups, followed by the attack of a hydride onto the carbonyl (or β-olefinic) carbon from the less hindered side. If the starting material has an axial C-7-OH like 2a, both a ketol and diol are expected to be produced as major products. On the contrary, 2b with an equatorial C-7-OH seems to be hardly attacked on the carbonyl carbon by a
hydride because of the large steric hindrance at the β-face by the angular methyl and at the α-face by the axial isopropyl group. Thus, 2b can be expected to give the ketol as a major reduction product. In fact, reduction of 2 afforded the products expected in the former case. Therefore, the results give more evidence to deduce the stereochemistry at C-7 in 2 as R by the chemical reactivity. The absolute structure of 2 was thus established as (1R,10R)-1-hydroxyeudesm-4-en-6-one. The characterized compounds were related to each other on a biogenetic basis and are depicted in Fig. 1.

Two of the nine sesquiterpenes, 1 and 2, were isolated from a natural source for the first time. The compounds 3 and 4 were originally isolated from *Acorus calamus* (Araceae) and 6 from *Stenocylax michelii* (Myrtaceae), probably the same compound from *Curcuma zedoaria* (Zingiberaceae). The compound 7 was also found in *C. zedoaria* and *Commiphora erythreae* (Burseraceae). The compounds 8 and 9 were also found in *Chloranthus japonicus*. The amount of the sesquiterpenes in *C. serratus* may reflect two biosynthetic flows both predominant in this plant, one being 6→7→5 and the other, 3→4→1→2. The biosynthesis of lindenanolides (8 and 9) does not seem as active in *C. serratus* as in *C. japonicus*. The latter plant produces several lindenanolides as major sesquiterpenes in addition to such germacrane as 6. Furanodienone (7) was once isolated as a miticide ingredient. It has been known that roots of *C. serratus* contain insecticidal substances. We found about 0.1% of 7 in fresh roots of this herb, therefore this compound may be partially responsible for the insecticidal activity of this plant.

The Chloranthaceae belonging to Polycarpiidae were thought to be a family of primitive angiosperms, and monocotyledonae plants are phylogenically related to Polycarpiidae. The similarity of sesquiterpene contents in *C. serratus* to that in monocotyledonae plants (Araceae and Zingiberaceae) may, therefore, not be so surprising. The distribution of sesquiterpenes containing the lindenane skeleton is taxonomically very limited and compounds in this class have been found so far only in Lauraceae (*Lindera strychnifolia* and *Neolisea sericea*), Chloranthaceae (*C. japonicus*, *C. serratus* and *Sarcandra glabra*) and Compositae (*Onoseris albican* and *Wunderlichia mirabilis*).

**EXPERIMENTAL**

Melting points were determined on a hot plate and were uncorrected. Optical rotations and CD-ORD spectra were measured on JASCO DIP-4 and J-20 instruments, respectively. Mass spectrometry was carried out on a JEOL JMS-D300 instrument. IR and UV spectra were recorded on Hitachi 285 and EPS-3T instruments, respectively. NMR spectra were determined on JEOL FX-200 and FX-100 instruments.

*Isolation of furanodienone (7).* Fresh roots (1.93 kg) of *C. serratus* collected at Mt. Sankaku-yama in Sapporo in June 1981 were extracted twice with ether at room temperature. The ether extracts were combined, concentrated, washed with 5% NaHCO₃ and sat. NaCl, and dried over MgSO₄. After removal of the solvent, the residue was loaded on a Florisol column and eluted with a hexane–ether gradient. Compound 7 was isolated from the hexane–ether (19:1) eluates. Recrystallization from hexane yielded 7 as colorless prisms (1.45 g). The physicochemical properties of 7 agreed well with those of furanodienone.
Isolation of 7α-hydroxyneoacolamone (2). Successive elution of the column with hexane-ether (9:1 and 7:1) followed by crystallization from hexane gave 2 as colorless needles (430 mg). mp 77~154°C; [α]_D^20 +212° (c=0.57, CHCl₃); MS m/z: 236 (M⁺, 2%), 218 (11), 138 (82), 137 (37), 109 (100), 43 (19); IR ν_C=CH cm⁻¹: 3440, 1670, 1610, 1015; UV λ_max nm (ε): 240 (240); ORD (c=0.0058, EtOH) [α]_D^24 (nm): +517° (320), -136° (280); 1H-NMR δ_H (ppm): 0.97 (3H, d, J=6.8Hz, 12-13-H), 1.14 (3H, s, 14-H), 1.4~1.9 (7H, m), 1.7 (1H, s, OH), 1.78 (3H, s, 15-H), 1.95 (1H, dd, J=15 and 4.0Hz, 8α-H), 2.11 (2H, t, J=6.0Hz, 8β-H); 13C-NMR δ_C (ppm): 16.0 (q), 18.1 (q), 23.7 (1H, d, J=1.0Hz, 11-H), 2.32 (1H, d, J=1.0Hz, 15-H), 2.78 (1H, septet, J=6.8Hz, 11-H); ν_C=CH cm⁻¹: 1710, 1640; ORD (c=0.078, MeOH) [α]_D^23 (nm): +259° (320), -136° (280); 1H-NMR δ_H (ppm): 0.97 (3H, d, J=6.8Hz, 12-13-H), 1.23 (3H, s, 15-H), 1.58 (3H, s, 14-H), 1.78 (3H, s, 15-H), 1.95 (1H, dd, J=15 and 4.0Hz, 8α-H), 2.11 (2H, t, J=6.0Hz, 8β-H); 13C-NMR δ_C (ppm): 17.5 (q), 24.0 (q), 29.3 (s), 37.2 (s), 38.3 (t), 78.7 (s), 137.6 (s), 142.9 (s), 203.4 (s).

Isolation of zederone (5). Successive elution of the column with hexane-ether (1:1) followed by crystallization from hexane-ether afforded 5 as colorless plates (15 mg): mp 153~154°C; [α]_D^20 +220° (c=0.10, CHCl₃); MS m/z: 220 (M⁺, 70%), 205 (100), 178 (86), 177 (55), 149 (48), 107 (50), 93 (53), 81 (54); IR ν_C=CH cm⁻¹: 1677, 1618; UV λ_max nm (ε): 249 (5600); 1H-NMR δ_H (ppm): 0.89 (3H, d, J=6.6Hz, 9-H), 0.94 (3H, d, J=6.8Hz, 9-H), 0.94 (3H, s, 14-H), 0.84 (3H, s, 15-H), 1.68 (3H, s); 13C-NMR δ_C (ppm): 0.89 (3H, d, J=6.6Hz, 12-13-H), 1.07 (3H, s, 14-H), 1.4~1.8 (7H, m), 1.7 (1H, s, OH), 1.76 (3H, s, 15-H), 1.88 (3H, s, 14-H), 2.14 (3H, s, 15-H), 2.35 (3H, s, 15-H), 2.91 (1H, brs), 5.01 (1H, brs), 5.94 (1H, brs). 3: [α]_D^24 +7.0° (c=1.33, CHCl₃); MS m/z: 220 (M⁺, 0.6%), 205 (2), 177 (2), 150 (2), 81 (100); IR ν_C=CH cm⁻¹: 1675, 1603, 1570, 1087; UV λ_max nm (ε): 243.5 (5500); 1H-NMR δ_H (ppm): 0.91 (3H, s, 6-H), 0.97 (3H, d, J=6.3Hz, 6-H), 1.23 (3H, brs), 2.02 (3H, d, J=1.0Hz, 10-H), 4.90 (1H, m), 5.64 (1H, brs). The physicochemical properties of 1, 4 and 3 agreed with those of (7S,10R)-eudes-4-en-6-one,6,11 acolamone6 and acorgermacrone,6,7 respectively.

Reductive dehydroxylation of 7α-hydroxyneoacolamone (2). To a mixture of coarse zinc powder (70 mg) and acetic acid (0.7 ml) was added 2 (50 mg) with stirring at 50°C. Conc. HCl (0.1 ml) was then added to the mixture over 2 min, followed by another addition of conc. HCl (0.1 ml) after 30 min. The reaction mixture was stirred for another 30 min, poured into sat. NaCl and extracted with ether. The ether extract was washed successively with 5% NaHCO₃ and sat. NaCl, and dried over MgSO₄. Removal of the solvent resulted in a mixture of two products, which were separated by PTLC (SiO₂/benzene) to give 10 (25 mg) and 11 (1 mg) as colorless oils. The physicochemical properties of 10 coincided well with those of neoacolamone (1). 11: MS m/z: 220 (M⁺, 70%), 205 (100), 178 (89), 149 (58), 137 (45), 107 (43).

Dehydration of 7α-hydroxyneoacolamone (2). To a solution of 2 (24 mg) in dry pyridine (1 ml) was added SOCl₂ (0.2 ml) at -5°C. The reaction mixture was left overnight, poured into ice-cooled water and extracted with ether. The ether extract was washed successively with dil. HCl, 5% NaHCO₃ and sat. NaCl, and dried over MgSO₄. Removal of the solvent resulted in a mixture of two products, 13 and 14. The major product, 13, was isolated by PTLC (SiO₂/hexane-benzene (1:1)) to give a colorless oil (15 mg). 13: [α]_D^20 +79° (c=0.01, CHCl₃); GC-MS m/z: 218 (M⁺, 49%), 203 (70), 175 (61), 161 (100), 147 (20), 133 (3); IR ν_C=CH cm⁻¹: 1652, 1600; UV λ_max nm (ε): 247.5 (9650); 1H-NMR δ_H (ppm): 1.02 (3H, d, J=6.8Hz, 12-13-H), 1.05 (3H, d, J=6.8Hz, 12-13-H), 1.07 (3H, s, 14-H), 1.4~1.8 (4H, m, 1-2-H), 1.94 (3H, s, 15-H), 2.0~2.4 (4H, m, 3- and 9-H), 2.94 (1H, doublet of septet, J=6.8 (sep) and 1.0 (d) Hz, 11-H), 6.46 (1H, ddd, J=5.7, 2.9 and 1.0 Hz, 8-H). 14: GC-MS m/z: 219 (M⁺ +1, 23%), 218 (M⁺, 100), 204 (22), 203 (94), 190 (11), 189 (15), 176 (17), 175 (54), 161 (19), 147 (22), 133 (18), 119 (17), 105 (18).

Reduction of 7α-hydroxyneoacolamone (2). To a stirred...
solution of LiAlH₄ (47 mg) in dry ether (10 ml) was added dropwise a solution of 2 (105 mg) in dry ether (0.2 ml) over 5 min at −20°C under N₂. The reaction mixture was stirred continuously for 10 min at −20°C and then for 15 min at room temperature. To the mixture was added EtOAc (2 ml) and ether (20 ml). The ether solution was washed with sat. NaCl and dried over MgSO₄. Removal of the solvent yielded a mixture of three products, which were separated by PTLC (SiO₂-hexane-ether (3:1)) to give 14 (46 mg), 15 (42 mg), each as colorless needles. 14: mp 103–105°C; [α]D = 108° (c=0.13, CHCl₃). MS m/z: 238 (M⁺, 1%), 220 (1), 177 (2), 139 (100), 121 (93); IR νmax/cm⁻¹: 3580, 3450, 2950, 2925, 990; 1H-NMR δ(CDCl₃): 0.96 (3H, d, J=6.8Hz, 12(13)-H), 1.02 (3H, d, J=2.2Hz, 6-OH). 15: mp 93–95°C; [α]D +65.2° (c=0.23, MeOH); MS m/z: 238 (M⁺, 1%), 220 (1), 177 (12), 139 (100), 121 (93); IR νmax/cm⁻¹: 3115, 3045, 2925, 2850, 990. 1H-NMR δ(CDCl₃): 1.09 (3H, s, 14-H), 1.75 (3H, s, 15-H), 2.55 (1H, septet, J=7=7.0Hz, 11-H), 4.39 (1H, brs, 7-OH), 4.95 (6a-H), 5.65 (1H, d, J=1.5Hz, 6a-H); δ(CDCl₃): 1.23 (12(13)-H), 1.42 (12(13)-H), 1.53 (14-H), 1.71 (15-H), 2.55 (1H, septet, J=7=6.8Hz, 11-H), 4.39 (1H, brs, 7-OH), 4.95 (6a-H), 5.65 (1H, d, J=2.2Hz, 6-OH). 16: mp 135–137°C; MS m/z: 238 (M⁺, 1%), 220 (1), 177 (12), 139 (100), 121 (93), 43 (63); IR νmax/cm⁻¹: 3425, 3340, 785.

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