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Studies on the Constituents of *Chloranthus* spp. III.[1] Six Sesquiterpenes from *Chloranthus japonicus*

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Six sesquiterpene lactones (I—VI) were isolated and characterized as constituents of *Chloranthus japonicus* (Chloranthaceae). The lactones chloranthalactone A—E (I—V) were found to be lindenane derivatives, and the lactone VI was identified as atractylenolide III.

The structure of chloranthalactone C (III) was determined by X-ray crystallographic analysis of a crystal of III in conjunction with the negative Cotton effect in the optical rotatory dispersion (ORD) curve and negative circular dichroism curve of the ketoalcohol (XII) prepared from III. The stereostructures of chloranthalactone A and B (I and II) were deduced from the ORD curves of the degradation products (VII and X).

The cytotoxicities of these lactones against mouse lymphosarcoma L-5178Y cells were determined in comparison with that of helenalin, and they were found to show moderate cytotoxic effects.

Keywords——*Chloranthus japonicus*; sesquiterpene lactones; lindenane derivatives; X-ray crystallographic analysis; structural elucidation; cytotoxicity; mouse lymphosarcoma L-5178Y cells

In the previous papers on the constituents of *Chloranthus* species, we reported the isolation of N-β-phenethyl-3-(3,4-methylenedioxyphenyl)-propenamide, N-β-phenethyl-3-(3,4-dimethoxy)-propenamide, and dihydropyrocurzerenone and its derivatives from *C. serratus* Roem. et Schult. (Japanese name: Futarishizuka),[1,3] isofraxidin from *C. japonicus* Sieb. (Hitorishizuka),[3] and chloranthalactone A and B from *C. glaber* Makino (Senryo).[4] In the course of our continuing investigation on the constituents of *Chloranthus* species, we isolated six sesquiterpene lactones (I—VI) including chloranthalactone A (I) and B (II) from *C. japonicus*. Five of them (I—V) were found to be tricyclic sesquiterpenes having the lindenane carbon skeleton.[5] Recently, Kawabata *et al.* reported the isolation and structural elucidation of two sesquiterpenoids, shizukanolide and its dehydro derivative.[6] The latter compound was found to be identical with chloranthalactone A by direct comparison.

Since one of the congeneric substances, chloranthalactone C (III) was obtained as colorless prisms, X-ray crystallographic analysis was carried out and the structure was elucidated as depicted in formula III. A ketone derivative (XII) was prepared from III by treatment with alkali, and was found to have a negative circular dichroism (CD) curve. Therefore, the absolute configurations of the cyclopropane ring and the ring junction of III were concluded to be identical to those of the lindenane group.[5] This result provides strong evidence for the stereostructures of compounds I and II, the plane structures of which have already been proposed.[4]

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1) Part II: T. Takemoto, M. Uchida, and G. Kusano, *Chem. Pharm. Bull.*, 24, 531 (1976).
2) Location: *a*) and *b*) *Aobayama, Sendai, Japan*; *c*) *Yamashirocho, Tokushima.*
3) T. Takemoto, M. Uchida, K. Koike, Y. Hoshina, and G. Kusano, *Chem. Pharm. Bull.*, 23, 1161 (1975).
4) M. Uchida, G. Kusano, Y. Kondo, and S. Nozoe, *Heterocycles*, 9, 139 (1978).
5) K. Takeda, H. Minato, I. Horibe, and M. Miyawaki, *J. Chem. Soc.* (*C*), 631 (1967).

Aerial parts and roots of *Chloranthus japonicus*, which were collected in mountainous areas on the outskirts of Sendai, were separately extracted with methanol at room temperature, and the extracts obtained were transferred to *n*-hexane. The final extracts were chromatographed on silica gel and eluted with mixtures of *n*-hexane, ethyl acetate and others.

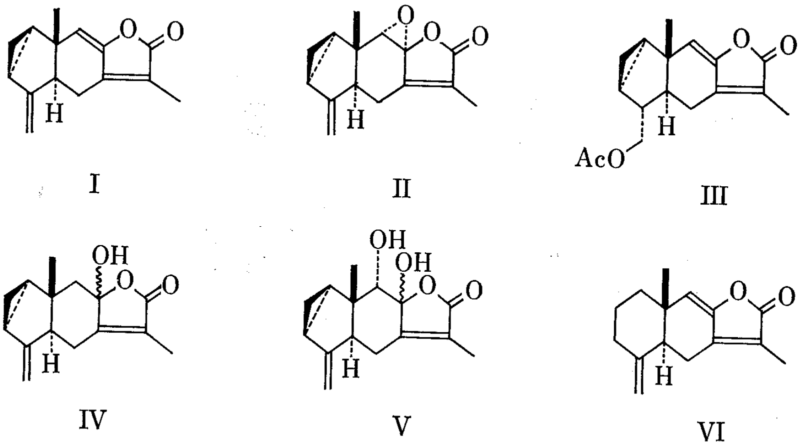

Chart 1

Chloranthalactone A (I), mp 64—65°, $[\alpha]_{340}^{27}$ −448.4°, $C_{15}H_{16}O_2$, was obtained as colorless prisms on elution with *n*-hexane–ethyl acetate (10∶1). This compound was characterized as an $\alpha,\beta,\gamma,\delta$-unsaturated-$\gamma$-lactone, the partial formula of which is depicted in **1**, by virtue of an ultraviolet (UV) maximum at 279 nm (log ε, 4.10), an infrared (IR) absorption at 1768 cm^{-1} and nuclear magnetic resonance (NMR) spectral signals at δ 1.85 ppm (3H, bs) and 6.11 ppm (1H, s). On mild treatment with dilute alkali, chloranthalactone A (I) was converted into an enol lactone hydrate (IV), mp 153—154°, $[\alpha]_{300}^{26}$ +351.4°, $C_{15}H_{18}O_3$, while on prolonged treatment with 10% potassium hydroxide in ethanol–water (1∶1), I was transformed into a ketone derivative (VII), $C_{12}H_{16}O$. These properties were similar to those observed in studies for the structural elucidation of eremolactone[7] and photooxidation products of atractylon.[8]

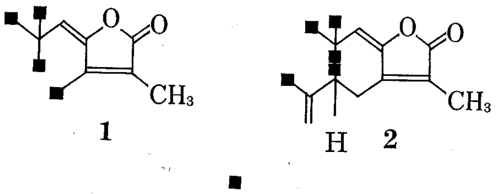

Chart 2

Treatment of the lactone hydrate (IV) with traces of *p*-toluenesulfonic acid in refluxing benzene yielded an isomer (VIII), mp (subl) 213°, $C_{15}H_{18}O_3$. In the NMR spectrum, a singlet at 1.68 ppm due to a methyl group on a double bond was found in place of the paired signals of an exocyclic methylene group and an allylic hydrogen in the spectrum of IV. Therefore, it was deduced that the 1,1-disubstituted double bond in IV had migrated to the tetrasubstituted position in VIII. In addition, a quartet at 0.29 ppm (1H, J=4,4,4 Hz, *endo* H on the cyclopropane ring) and a sextet at 0.67 ppm (1H, J=4,8,8 Hz, *exo* H on the cyclopropane ring) indicated the presence of a 1,2-disubstituted cyclopropane ring, as shown in VIII.[9] The large shielding of the *endo* hydrogen of the cyclopropanic methylene can be attributed to long-range effects arising from the diamagnetic anisotropy of the double bond.[10] Since

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[6] J. Kawabata, S. Tahara, J. Mizutani, A. Furusaki, N. Hashida, and T. Matsumoto, *Agric. Biol. Chem.*, **43**, 885 (1979).

[7] A.J. Birch, J. Grimshaw, and J.P. Turnbull, *J. Chem. Soc.*, 2412 (1963).

[8] H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. Pharm. Bull.*, **12**, 755 (1964).

[9] U. Schöllkopf, G.L. Lehmann, J. Paust, and H.D. Härtl, *Chem. Ber.*, **97**, 1527 (1964).

[10] T. Nakano and S. Terao, *J. Chem. Soc.*, **1965**, 4512.

no indication of new construction of a cyclopropane ring was found in the course of the isomerization from I to compound VIII, it was suggested that I should contain a cyclopropane ring in spite of the absence of clear NMR signals due to cyclopropanic protons at high field. Furthermore, two pairs of AB quartets (1.79 ppm and 2.57 ppm, 1H, d, $J=14$ Hz; 2.83 ppm, 1H, bd, $J=15$ Hz and 3.34 ppm, 1H, d, $J=15$ Hz) in the NMR spectrum of VIII indicated the presence of two isolated methylene groups in VIII. The latter signals were attributed to a methylene group flanked by two double bonds, judging from the chemical shifts. Therefore, the partial formula **1** for chloranthalactone A (I) was developed to **2**.

Because the NMR spectrum of chloranthalactone A showed the presence of a tertiary methyl group (0.77 ppm), the partial formula **2**, a 1,2-disubstituted cyclopropane ring and the tertiary methyl group account for the entire molecular formula of chloranthalactone A, $C_{15}H_{16}O_2$. The ketone derivative (VII) showed a negative Cotton effect (trough: 311 nm, −4080°, peak: 270 nm, +3634°) in the ORD curve, which was similar to that of a ketoalcohol (XII) prepared from chloranthalactone C (III) as described later. Therefore, the compound (VII) should have a *trans* junction with a β-methyl group and α-hydrogen on an S tertiary carbon, as shown in formula VII. On the other hand, the isomeric compound (VIII) was reduced by Birch's method and a saturated acid (IX) was obtained as its methyl ester acetate (IXma), $C_{18}H_{24}O_4$. The product was ozonized, followed by treatment with potassium *t*-butoxide to yield an α,β-unsaturated ketone derivative (X), mp 206—209°, $C_{15}H_{18}O_4$. The IR bands at 1710 cm^{-1} (carboxylic acid) and 1660 cm^{-1} (ketone carbonyl), and a UV maximum at 236 nm (log ε, 4.22) indicated the structure X for the last product. Since this compound (X) showed a negative Cotton effect in the ORD curve, the cyclopropane ring should have the β-orientation,[5] and the stereostructure of chloranthalactone A (I), including the absolute configuration, was concluded to be as shown in formula I.

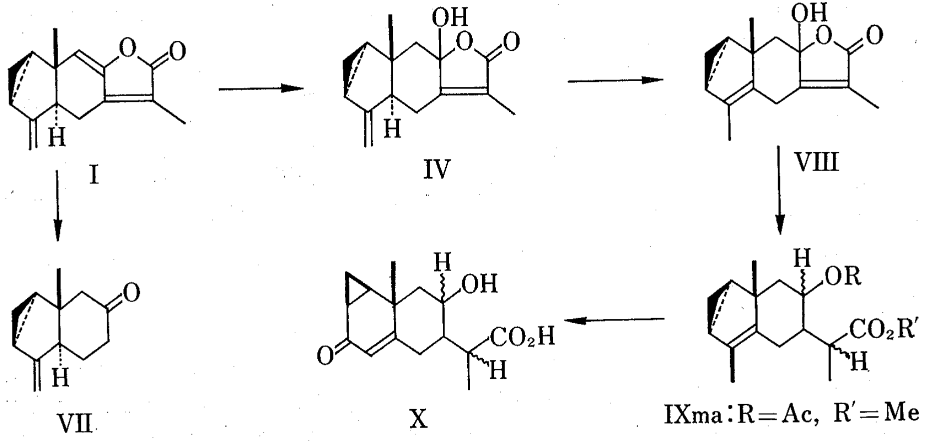


Chart 3

Chloranthalactone B (II), mp 145—146°, $[\alpha]^{27}_{340}$ −130.3°, $C_{15}H_{16}O_3$, was isolated after chloranthalactone A in the silica gel chromatography of the *n*-hexane extracts. Chloranthalactone A (I) was autooxidized to II, and chloranthalactone B (II) was thus suspected to be an artifact, but thin-layer chromatography (TLC) and gas chromatography (GLC) of extracts of fresh material of *C. glaber* showed the presence of II.

This compound (II) was characterized as an α,β-unsaturated lactone by virtue of IR bands at 1788, 1680 cm^{-1}, a UV maximum at 226 nm (log ε, 4.11) and an NMR signal at 1.87 ppm (3H, bs). The molecular formula of II, $C_{15}H_{16}O_3$, indicated addition of an oxygen atom to the molecule of I, and in the NMR spectrum of II, a singlet at 4.11 ppm (1H) was found in place of a singlet (1H) at 6.11 ppm due to δ-H on the α,β,γ,δ-unsaturated γ-lactone system of chloranthalactone A (I). Therefore, chloranthalactone B (II) should have an ethereal oxygen at the γ,δ-position in the unsaturated γ-lactone system.

The presence of the partial structure **3** in II was indicated by the results of double and triple irradiation experiments in the NMR spectrum (Fig. 1). A multiplet centered at 3.36 ppm due to an allylic hydrogen (Ha) was found to collapse to a sharp quartet upon irradiation at the pair of multiplets at 4.69 and 5.01 ppm due to exocyclic methylene hydrogens (Hb and Hc). Conversely, the latter signals collapsed to a pair of sharp singlets on irradiation at the signal due to Ha. Irradiation of the signal of Ha converted a pair of multiplets (Hd and He) at 2.25 and 2.57 ppm into a pair of broad doublets. The last signals showed a coupling constant of 16 Hz, suggesting geminal coupling between the two hydrogens (Hd and He).

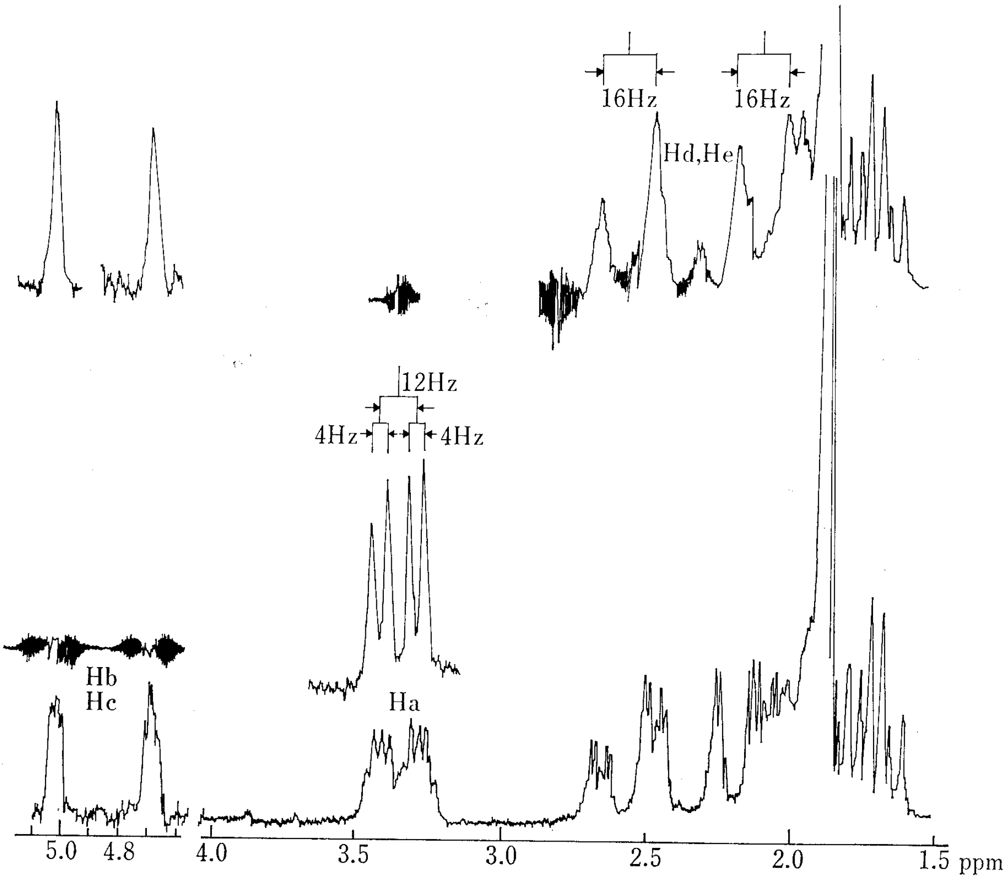
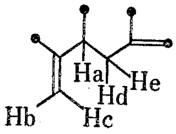


Fig. 1. NMR Spectrum of Chloranthalactone B (II)



3

Every signal of the ^{13}C–NMR spectrum of chloranthalactone B (II) could be assigned resonably to a carbon in the structure II, as shown in Chart 4. These results were similar to those for lindenane derivatives.[11] When chloranthalactone A (I) was treated in refluxing xylene bubbled through with oxygen gas for 4 hr, II was obtained quantitatively. Therefore, the formula II was proposed for the structure of chloranthalactone B on the basis of the results of photooxidation of I to II and the properties of II. The large deshielding of the allylic hydrogen (Ha in formula **3**, 3.36 ppm) was attributed to long-range effects arising

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11) K. Tori, M. Ueyama, I. Horibe, Y. Tamura, and K. Takeda, *Tetrahedron Lett.*, **1975**, 4583.

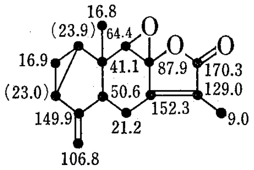
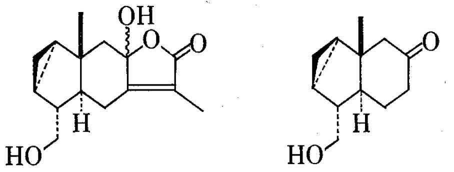


Chart 4



XI XII

Chart 5

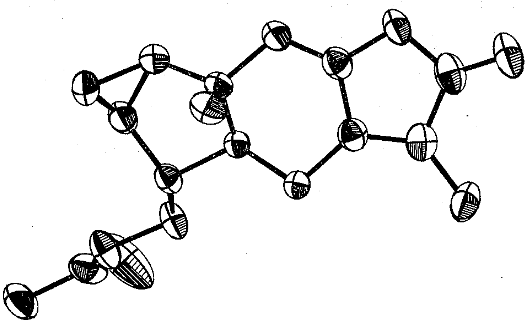


Fig. 2. Perspective View of the Chloranthalactone C Molecule

from the paramagnetic anisotropy of the epoxide ring in II. In the light of the NMR data, the orientation of the epoxide ring was considered to be α.

The third compound (III), named chloranthalactone C, mp 159—160°, $C_{17}H_{20}O_4$, was obtained as colorless prisms on elution with *n*-hexane–ethyl acetate (5: 1), next to phytosterols in silica gel chromatography of the *n*-hexane extracts. The compound (III) was characterized as an $\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone having an acetoxy methyl group on the basis of a UV maximum at 281.5 nm (log ε, 4.30), IR absorption bands at 1770, 1730 cm^{-1}, and NMR signals at 1.90 ppm (3H, s, 13-CH_3), 2.10 ppm (3H, s, $COCH_3$), 4.23 ppm (2H, d, J=6 Hz, CH–$C\underline{H}_2$–OAc), 6.24 ppm (1H, s, 9-H). On mild treatment with alkali, III afforded a desacetyl enol lactone hydrate (XI), mp 221—222°, $C_{15}H_{20}O_4$, while on prolonged treatment III provided a ketoalcohol (XII), $C_{12}H_{18}O_2$.

Because several attempts to correlate this compound to other substances with established structures were unsuccessful, X-ray crystallographic analysis of III was carried out. A colorless crystal with dimentions of about $0.25 \times 0.15 \times 0.3$ mm^3 was used for intensity data collection, and for determination of the precise cell dimensions. The structure was solved by the direct method and refined to give an R factor of 0.093. A computer-generated drawing of the structure is shown in Fig. 2. The relative sterostructure of chloranthalactone C (III) was thus clarified. Furthermore, the ketoalcohol (XII) showed a negative Cotton effect in the ORD curve and a negative CD curve. Therefore, the carbon at C_5 in XII was elucidated to have S-configuration, and the stereostructure III of chloranthalactone C was found to correspond to the absolute structure.

The fourth compound (IV), named chloranthalactone D, mp 153—154°, $C_{15}H_{18}O_3$, was obtained as colorless needles on elution with *n*-hexane–ethyl acetate (5: 1) and the fifth compound (V), named chloranthalactone E, mp 162—163°, $C_{15}H_{18}O_4$, was obtained as colorless prisms on elution with *n*-hexane–ethyl acetate (2: 1) in silica gel chromatography of the *n*-hexane extracts. Compound IV was identical with the enol lactone hydrate (IV), which was prepared from chloranthalactone A (I) by mild treatment with alkali, and compound V was identical with the diol (V), which was prepared from chloranthalactone B (II) by treatment with acid (comparisons of the *Rf* value on TLC and the spectroscopic data).

The sixth compound (VI), mp 192—193°, $C_{15}H_{20}O_3$, was obtained as colorless needles and was identified as atractylenolide III[12] by comparison of the *Rf* value on TLC and the spectroscopic data with those of an authentic specimen.

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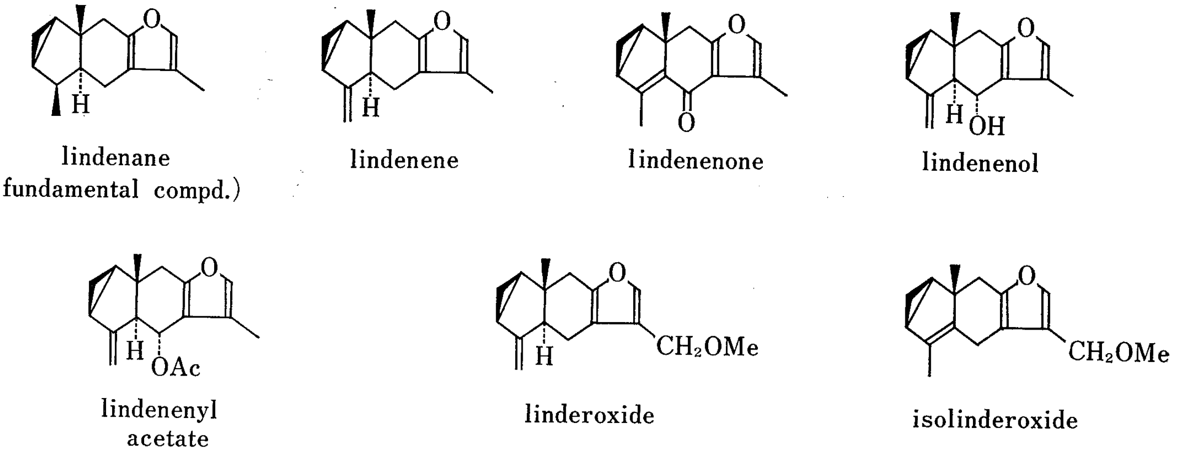
[12] K. Endo, T. Taguchi, F. Taguchi, H. Hikino, J. Yamahara, and H. Fujimura, *Chem. Pharm. Bull.*, 27, 2954 (1979).

Thus, six sesquiterpene lactones (I—VI) were isolated and characterized as constituents of *Chloranthus japonicus.* Five of them (I—V) were found to be lindenane derivatives. Lindenene,[13] lindenenone,[14] lindenenol, lindenenyl acetate,[15] linderoxide,[16] and isolinderoxide[5] have been obtained as lindenane-type constituents specific to *Lindera strychnifolia* Vill. (Lauraceae). The compounds I, II, IV, V seem to correspond to oxidation products of lindenene, which have never been isolated. It is interesting that *Chloranthus japonicus* (Chloranthaceae) contains compounds related to lindenane derivatives, which are characteristic of a taxonomically very different species, *Lindera strychnifolia* (Lauraceae). In addition atractylenolide III (VI), which is a constituent of *Atractylodes* species (Compositae), was isolated from another species for the first time.



lindenane (fundamental compd.)

lindenene

lindenenone

lindenenol

lindenenyl acetate

linderoxide

isolinderoxide

Chart 6

The study of chemical agents involved in the adaptation of species and organization of communities is a part of the field of chemical ecology.[17] Herbs of *Chloranthus* species grow in shady ground, where many kinds of microorganisms flourish. Therefore, the herbs might produce chemical agents (allelochemics) which provide defense against attack or infection by microorganisms. Moreover, some of these allelochemics might show important biological activities.[18] The fact that roots of *Chloranthus japonicus* (called *Kyui*) are used as antifungal and antiinflamatory agents in Chinese medicine,[19] suggests the presence of such allelochemics in this herb.

Table I. Cytotoxitities of Some Sesquiterpene Lactones in Mouse Lymphosarcima L-5178Y Cells

Compounds	ID_{50} (μg/ml)
Chloranthalactone A (I)	2.5
Chloranthalactone B (II)	1.0—2.5
Chloranthalactone C (III)	20
Chloranthalactone D (IV)	50
Chloranthalactone C epoxide (XIII)	20
Atractylenolide I (XIV)	80
Atractylenolide III (VI)	100
Helenalin	0.01

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13) K. Takeda, H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.* (*C*), **1969**, 1920.
14) K. Takeda, I. Horibe, M. Teraoka, and H. Minato, *J. Chem. Soc.* (*C*), **1969**, 2786.
15) K. Takeda, M. Ikuta, and M. Miyawaki, *Tetrahedron*, **20**, 2991 (1964).
16) H. Ishii, T. Tozyo, M. Nakamura, and K. Takeda, *Tetrahedron*, **24**, 625 (1968).
17) E. Sondheimer and J. Simeone, "Chemical Ecology," Academic Press, New York, London, 1970.
18) R.H. Whittaker and P.P. Feeny, *Science*, **171**, 757 (1971).

We therefore investigated biological activities, especially the cell grow-inhibitory effects, of the constituents of this plant. The cytotoxicities of chloranthalactone A—D (I—IV), chloranthalactone C epoxide (XIII), atractylenolide I (XIV) and III (VI) against mouse lymphosarcoma L-5178Y cells were examined in comparison with that of helenalin, which is known to have high cytotoxicity. Table I lists the ID_{50} values for cytoxicity; chloranthalactone A, which is a major constituent of this plant, and chloranthalactone B were found to be cytotoxic to L-5178Y cells to some degree.

Atractylenolide III (VI) was reported to show an antiinflamatory effect,12) and chloranthalactone A (I) was reported to show remarkable activity as an antifungal agent rather than as an antibacterial one.6) In view of the moderate cytotoxicities of these compounds (I—VI), other biological activities, such as possible selective inhibitory effects against some cell lines, should be examined.

Experimental20)

Isolation of Chloranthalactone A (I)——Roots of *C. japonicus* were washed with water and dried for three days. The partially dried roots (1.8 kg) were extracted with MeOH (10 l) three times at room temperature. MeOH was evaporated off *in vacuo* and the concentrate was extracted with *n*-hexane. The *n*-hexane extract (30 g) was chromatographed on SiO_2. Elution with *n*-hexane–AcOEt (10: 1) gave oily constituents. After distillation *in vacuo*, an oily substance (3 g), bp 3 mmHg 143—144°, was obtained. GLC (t_R 2.34 min, 1.5% SE-30, 4 mm × 1.5 m, column temperature, 121°, carrier gas, N_2). $[\alpha]^{27}_{340}$ $-448.4°$ (c=0.1, MeOH). *Anal.* Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.71; H, 6.97. MS *m/e*: 228 (10%, M^+), 213 (22, M^+-CH_3), 91 (100). UV λ^{MeOH}_{max} nm (log ε): 279 (4.10). IR $\nu^{CS_2}_{max}$ cm^{-1}: 1768 ($\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone), 1660, 882 (=CH_2). NMR ($CDCl_3$) δ: 0.77 (3H, s, C_{15}–3H), 1.85 (3H, bs, C_{13}–3H), 4.75 (1H, m, C_{14}–H), 4.95 (1H, m, C_{14}–H), 6.11 (1H, s, C_9–H). This compound (140 mg) was also obtained from the aerial parts (3.2 kg) of this herb. An authentic specimen of crystalline 8,9-dehydro-shizukanolide was kindly provided by Prof. Mizutani, and on direct comparison of *Rf* values on TLC and NMR spectra, it proved to be identical with our chloranthalactone A. A small portion of colorless prisms of the former was added to an *n*-hexane solution of our oily compound and colorless prisms of mp 64—65° were obtained.

Isolation of Chloranthalactone B (II)——The eluates following the fractions containing chloranthalactone A were rechromatographed on SiO_2, and elution with *n*-hexane–acetone (100: 3) followed by recrystallization of the product from acetone provided colorless prisms (360 mg), mp 145—146°, $[\alpha]^{27}_{340}$ $-1303.3°$ (c=0.1, MeOH). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 74.08; H, 6.68. MS *m/e*: 244 (0.4%, M^+), 105 (100), 91 (64). UV λ^{MeOH}_{max} nm (log ε): 226 (4.11). IR ν^{KBr}_{max} cm^{-1}: 1788, 1680 (α,β-unsaturated γ-lactone), 1660, 919, 818 (=CH_2). NMR ($CDCl_3$) δ: 0.64 ppm (3H, s, C_{15}–3H), 1.87 (3H, bs, C_{13}–3H), 3.36 (1H, m, C_5–H), 4.11 (1H, s, C_9–H), 4.69 (1H, m, C_{14}–H), 5.01 (1H, m, C_{14}–H). ^{13}C-NMR ($CDCl_3$) δ: 9.0 ppm (1C, q, C-13), 16.8 (1C, q, C-15), 16.9 (1C, t, C-2), 21.2 (1C, t, C-6), 21.0 (1C, d, C-3 or C-1), 23.9 (1C, d, C-1 or C-3), 41.1 (1C, s, C-10), 50.6 (1C, d, C-5), 64.4 (1C, d, C-9), 87.9 (1C, s, C-8), 106.8 (1C, t, C-14), 129 (1C, s, C-11), 149.9 (1C, s, C-4), 152.3 (1C, s, C-7), 170.3 (1C, s, C-12).

Isolation of Chloranthalactone C (III)——The aerial parts (32 kg) of *C. japonicus* were extracted with MeOH (30 l) at room temperature three times, and the extracts were concentrated to 5 l. The concentrate was extracted with *n*-hexane and the extract (280 g) was chromatographed on SiO_2. Elution with benzene–AcOEt (9: 1) followed by recrystallization of the product from acetone gave colorless prisms (III, 2.8 g), mp 159—160°. *Anal.* Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.54; H, 6.92. MS *m/e*: 288 (M^+). UV λ^{MeOH}_{max} nm (log ε): 281.5 (4.30). IR ν^{KBr}_{max} cm^{-1}: 1770, 1235 ($\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone), 1730, 1225 (acetate), 1640 (double bond). NMR ($CDCl_3$) δ: 0.90 ppm (3H, s, C_{15}–3H), 1.90 (3H, bs, C_{13}–3H), 2.10 (3H, s, $OCOCH_3$), 4.23 (2H, d, J=6 Hz, C_{11}–2H), 6.24 (1H, s, C_9–H). The same compound (75 mg) was obtained from the roots (1.8 kg) of this herb. After extraction with MeOH at room temperature, the extract was shaken with *n*-hexane and AcOEt. Both extracts were chromatographed on SiO_2. Elution with *n*-hexane–AcOEt (2: 1) provided colorless prisms (35 mg) from the *n*-hexane extract and (40 mg) from the AcOEt extract.

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19) K. Kimura, "Kokuyaku-Honzokomoku," IV, Shunyodo, Tokyo, 1974, p. 368.

20) Melting points were determined on a Yanagimoto hot stage and are uncorrected. Microanalysis, NMR and mass spectrometry were performed by the Analysis Center of this institute. IR spectra were obtained with a Shimadzu IR-27G photometer. ^{1}H-NMR spectra were determined on Hitachi Perkin-Elmer R-20 and JEOL PS-100 spectrometers using tetramethylsilane as an internal standard. ^{13}C-NMR spectra were determined on a JEOL 100 NMR spectrometer, equipped with a PFT-100 pulsed-Fourier transform spectrometer with ^{13}C-accessories, in combination with a JEC-60 spectrum computer.

Isolation of Chloranthalactone D (IV)——After the isolation of chloranthalactone C (III), elution with *n*-hexane–acetone (4: 1) followed by recrystallization of the product from AcOEt gave colorless needles (22 mg), mp 153—154°, $[\alpha]^{26}_{300}$ +351.4° (*c*=0.1, MeOH). *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 3.37. Found: C, 77.17; H, 7.35. MS *m/e*: 246 (33%, M^+), 228 (70, M^+-H_2O), 121 (40), 93 (100). UV λ^{MeOH}_{max} nm (log ε): 208 (4.24). UV $\lambda^{MeOH+NaOH}_{max}$ nm (log ε): 264 (3.97). IR ν^{KBr}_{max} cm^{-1}: 3360 (OH), 1736, 1689 (α,β-unsaturated γ-lactone), 1663, 909, 893 ($=CH_2$). NMR ($CDCl_3$) δ: 0.94 ppm (3H, s, C_{15}–3H), 1.82 (3H, bs, C_{13}–3H), 3.49 (1H, m, C_5–H), 4.79 (1H, m, C_{14}–H), 5.01 (1H, m, C_{14}–H). NMR (pyr-d_5) δ: 1.11 ppm (3H, s, C_{15}–3H), 1.79 (3H, s, C_{13}–3H), 3.78 (1H, m, C_5–H), 4.85 (1H, m, C_{14}–H), 5.07 (1H, m, C_{14}–H).

Isolation of Chloranthalactone E (V)——After the isolation of chloranthalactone D, elution was carried out with *n*-hexane–AcOEt (3: 2) and the resulting material was rechromatographed on Al_2O_3. Elution with *n*-hexane–AcOEt (1: 1) followed by recrystallization from AcOEt gave colorless needles, mp 162—163°. *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.42; H, 7.01. MS *m/e*: 262 (M^+). IR ν^{KBr}_{max} cm^{-1}: 3520, 3390 (OH), 1740, 1682 (α,β-unsaturated γ-lactone), 1660, 860 ($=CH_2$). NMR ($CDCl_3$) δ: 0.55 (3H, s, C_{15}–3H), 1.81 (3H, bs, C_{13}–3H), 3.35 (1H, m, C_5–H), 3.95 (1H, s, C_9–H), 4.70 (1H, d, *J*=3 Hz, C_{14}–H), 4.93 (1H, d, *J*=3 Hz, C_{14}–H), 5.8 (1H, bs, OH; this signal disappeared on addition of D_2O.).

Acetylation of Chloranthalactone E (V)——Chloranthalactone E (V, 18.8 mg) was acetylated in pyridine (2 ml) and Ac_2O (1 ml) at room temperature. After treatment, an oily product (15 mg) was obtained. IR $\nu^{CHCl_3}_{max}$ cm^{-1}: 1775, 1750, 1660, 1190, 880. NMR ($CDCl_3$) δ: 0.88 (3H, s, C_{15}–3H), 1.87 (3H, bs, C_{13}–3H), 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 4.74 (1H, m, C_{14}–H), 4.99 (1H, m, C_{14}–H), 5.64 (1H, s, C_9–H).

Isolation of Atractylenolide III (VI)——In the chromatography of the *n*-hexane extract, the eluates with benzene–AcOEt (9: 1) were rechromatographed on SiO_2; elution with benzene–$CHCl_3$ (100: 1) followed by recrystallization from acetone gave atractylenolide III (VI) (120 mg), as colorless needles, mp 192—193°. *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.63, H, 7.87. MS *m/e*: 248 (M^+). UV λ^{MeOH}_{max} nm (log ε): 218 (4.04). IR ν^{KBr}_{max} cm^{-1}: 3350 (OH), 1740, 1700 (α,β-unsaturated γ-lactone), 1640, 895 ($=CH_2$). Comparison of TLC, and IR and NMR spectra showed this compound to be identical with an authentic specimen of atractylenolide III. NMR ($CDCl_3$) δ: 1.02 ppm (3H, s, C_{15}–3H), 1.78 (3H, bs, C_{13}–3H), 4.14 (1H, bs, OH, disappeared on addition of D_2O), 4.55 (1H, bs, C_{14}–H), 4.80 (1H, bs, C_{14}–H).

Conversion of Chloranthalactone A (I) into B (II)——i) Chloranthalactone A (I, 85 mg) was dissolved in MeOH (10 ml) and left to stand at room temperature for 10 days. The residue after removal of the solvent was chromatographed on TLC (Kiesel gel HF_{254}, solvent: *n*-hexane–acetone (9: 1)). Colorless prisms (41.8 mg) were obtained after recrystallization from acetone. The NMR and IR spectra were superimposable on those of chloranthalactone B (II).

ii) Chloranthalactone A (1.7 mg) was treated in refluxing xylene (1 ml) bubbled through with oxygen gas for 4.4 hr. The resulting solution was analyzed by GLC. Analysis of a 5 μl aliquot of the solution according to a calibration curve gave a value of 9.9 μg/5 μl, corresponding to a yield of 1.98 mg/ml (Calcd: 1.82 mg/ml). Therefore, this reaction was deduced to be quantitative.

Conversion of Chloranthalactone A (I) to Chloranthalactone D (IV)——Chloranthalactone A (I, 1.25 g) was dissolved in pyridine (100 ml) and water (25 ml) containing KOH (1.2 g) and the reaction mixture was stirred at room temperature under N_2 for 5 hr. The solution was thus poured into dil. HCl (100 ml) containing ice and after standing at room temperature for 30 min extraction was carried out. The ether layer was washed with water, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on SiO_2. Elution with *n*-hexane–acetone (4: 1) followed by recrystallization of the product from acetone gave colorless plates (928 mg), mp 153—154°. Comparison of TLC, mp and spectroscopic data with those of an authentic specimen showed this product to be identical with chloranthalactone D (IV).

Conversion of Chloranthalactone A (I) to a Ketone Derivative (VII)——Chloranthalactone A (I, 300 mg) was dissolved in a mixture of EtOH (8 ml) and water (8 ml), and potassium hydroxide (1.6 g) was added. The alkaline solution was refluxed for 9 hr on a boiling water bath. After cooling, water was added and the mixture was extracted with ether. The residue, after usual treatment, was chromatographed on SiO_2. Elution with *n*-hexane–ether (96: 4) provided a colorless oily product (VII, 29.3 mg). t_R 2.25 min in GLC (1.5% OV-17, 4 mm × 1.5 m, column temperature, 155°, carrier gas, N_2). ORD (*c*=0.1, MeOH): $[\phi]_{311}$ −4080 (trough), $[\phi]_{270}$ +3634° (peak). MS *m/e*: 176 (37%, M^+), 161 (27, M^+-CH_3), 119 (82), 105 (90), 91 (100). IR $\nu^{CS_2}_{max}$ cm^{-1}: 1708 (carbonyl group on a six-membered ring), 1660, 880 (exocyclic methylene). NMR ($CDCl_3$) δ: 0.47 ppm (3H, s, C_{15}–3H), 2.53 (2H, s, C_9–2H), 2.98 (1H, bd, *J*=13 Hz, C_6–H), 4.68 (1H, bs, C_{14}–H), 4.97 (1H, bs, C_{14}–H).

Preparation of an Allylic Alcohol Derivative from Chloranthalactone A (I)——Chloranthalactone A (I, 528 mg) in dioxane (5 ml) was added to clear solution of SeO_2 (400 mg) in dioxane (20 ml) and water (1 ml). The reaction solution was refluxed on a boiling water bath for 45 min. After cooling to room temperature, the products were extracted with an excess of ether. The residue after usual treatment was dissolved in ether, and metallic mercury (0.5 g) was added with stirring. After removal of the inorganic material and of the solvent, the residue was chromatographed on silicic acid (Mallinkrodt). Elution with *n*-hexane–acetone (30: 1) followed by recrystallization of the product from acetone gave colorless prisms (126.6 mg). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 74.01; H, 6.75. MS *m/e*: 244 (50%, M^+), 226 (45, M^+-H_2O), 91 (100). UV λ^{MeOH}_{max} nm (log ε): 273 (4.26). IR ν^{KBr}_{max} cm^{-1}: 3440 (OH), 1730 ($\alpha,\beta,\gamma,\delta$-unsaturated

γ-lactone), 1650, 880 (exocyclic methylene). NMR ($CDCl_3$) δ: 0.76 (1H, sextet, $J=4$, 8, 8 Hz, C_{2exo}–H), 1.32 (3H, s, C_{15}–3H), 1.90 (3H, d, $J=2$ Hz, C_{13}–3H), 2.60 (1H, bd, $J=16.5$ Hz, C_6–H), 3.12 (1H, d, $J=16.5$ Hz, C_6–H), 4.93 (1H, s, C_{14}–H), 5.07 (1H, s, C_{14}–H), 5.45 (1H, s, C_9–H).

Recovery of Chloranthalactone A (I) from Chloranthalactone D (IV)——Chloranthalactone D (IV, 200 mg) was dissolved in pyridine (5 ml), and $POCl_3$ (0.5 ml) was added dropwise under N_2 while cooling with ice-water. After leaving the mixture overnight at room temperature, the reaction solution was poured into ice-water and extracted with ether. The residue after usual treatment yielded an oily product (154.2 mg). The IR and NMR spectra were superimposable on those of I.

Isomerization of Chloranthalactone D (IV)——Chloranthalactone D (IV, 94 mg) was dissolved in benzene (5 ml) and *p*-TsOH (2 mg) was added. The mixture was refluxed for 5 hr. After cooling, the reaction solution was washed with water and dried over Na_2SO_4. The residue, after usual treatment, was recrystallized from acetone to give colorless prisms (50 mg), mp (subl) 213°, $[\alpha]_{340}^{20}$ $-263.6°$ ($c=0.1$, MeOH). *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.93; H, 7.33. MS *m/e*: 246 (45%, M^+), 231 (23, M^+-CH_3), 228 (65, M^+-H_2O), 213 (100), 185 (70). IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 1738, 1694 (α,β-unsaturated γ-lactone). NMR (pyr-d_5) δ: 0.29 (1H, q, $J=4$, 4, 4 Hz, C_{2endo}–H), 0.67 (1H, sextet, $J=4$, 8, 8 Hz, C_{2exo}–H), 1.53 (1H, s, C_{15}–3H), 1.63 (3H, s, C_{14}–3H), 1.73 (3H, s, C_{13}–3H), 1.79 (1H, d, $J=14$ Hz, C_9–H), 2.57 (1H, d, $J=14$ Hz, C_9–H), 2.83 (1H, bd, $J=15$ Hz, C_6–H), 3.34 (1H, bd, $J=15$ Hz, C_6–H).

Birch Reduction of the Isomerized Enol Lactone Hydrate (VIII)——Lithium metal (0.5 g) was added to liquid ammonia at $-70°$ in a CryoCool apparatus (Neslab Instruments, Inc., Portsmouth, N.H., U.S.A.). Isomerized lactol (VIII, 106 mg) in THF (4 ml) was added dropwise to blue lithium radical solution in liquid ammonia. After stirring at $-70°$ for 10 min, MeOH (3 ml) was added. The reaction solution was left at this temperature for 1 hr, then the ammonia was allowed to evaporate. The reaction solution was acidified with dil. H_2SO_4 and extracted with AcOEt. The AcOEt layer was washed with water 5 times and dried over Na_2SO_4. The residue, after removal of the drying agent and the solvent, was methylated with CH_2N_2. The products were chromatographed on SiO_2 and elution with *n*-hexane–AcOEt (5: 1) provided a major product. After examination of the NMR spectrum [$CDCl_3$: 0.08 ppm (1H, q, $J=4$, 4, 4 Hz, C_{2endo}–H), 0.70 (1H, sextet, $J=4$, 8, 8 Hz, C_{2exo}–H), 1.02 (3H, s, C_{15}–3H), 1.22 (3H, d, $J=7$ Hz, C_{13}–3H), 3.4 (1H, m, C_8–H), 3.68 (3H, s, OCH_3)], this product was acetylated. The product was purified by silica gel chromatography and elution with *n*-hexane–AcOEt (20: 1) provided the major product (IXma, 32 mg) as an oil. MS *m/e*: 304 (15%, M^+, $C_{18}H_{24}O_4$), 244 (100, M^+-AcOH). NMR ($CDCl_3$) δ: 0.07 ppm (1H, q, $J=4$, 4, 4 Hz, C_{2endo}–H), 0.63 (1H, sextet, $J=4$, 8, 8 Hz, C_{2exo}–H), 1.08 (3H, s, C_{15}–3H), 1.15 (3H, d, $J=7$ Hz, C_{13}–3H), 1.64 (3H, bs, C_{14}–3H), 1.99 (3H, s, OAc), 3.67 (3H, s, OCH_3), 5.05 (1H, m, C_8–H).

Preparation of α,β-Unsaturated Ketone (X)——The methyl ester acetate (IXma, 25 mg) was dissolved in $CHCl_3$ (3 ml) and ozone was introduced into the solution for 10 min at $-70°$ in the CryoCool apparatus. Zinc powder (*ca.* 1 g pretreated with dil. HCl) and 10% AcOH were added and the mixture was heated on a boiling water bath. After extraction with AcOEt, the products were treated with potassium *t*-butoxide in *t*-butyl alcohol on a boiling water bath for 1 hr. Water was added and, after cooling to room temperature, the mixture was acidified with dil. H_2SO_4. The acidified mixture was extracted with AcOEt and the extract was chromatographed on SiO_2. Elution with AcOEt followed by recrystallization of the product from acetone provided colorless needles, mp 206—209°. MS *m/e*: 262 (M^+, $C_{15}H_{18}O_4$). IR ν_{max}^{KBr} cm^{-1}: 1710 (COOH), 1660 (α,β-unsaturated ketone). UV λ_{max}^{MeOH} (log ε): 236 (4.11). NMR ($CDCl_3$) δ: 0.04 (1H, q, $J=4$, 4, 4 Hz C_{2endo}–H), 0.80 (1H, sextet, $J=4$, 8, 8 Hz, C_{2exo}–H), 1.23 (3H, d, $J=6$ Hz, C_{13}–3H), 1.31 (3H, s, C_{15}–3H), 4.0 (1H, m, C_8–H), 5.62 (1H, s, C_{14}–H=H on α carbon in α,β-unsaturated ketone system). ORD ($c=0.15$, dioxane): $[\phi]_{350}$ $-12200°$ (trough), $[\phi]_{308}$ $+2096°$ (peak).

Preparation of a Desacetyl Enol Lactone Hydrate (XI) from Chloranthalactone C (III)——Chloranthalactone C (III, 100 mg) was dissolved in MeOH (12 ml), and NaOH (180 mg) was added. The mixture was refluxed for 1 hr. After cooling to room temperature, the reaction mixture was neutralized with dil. HCl and extracted with AcOEt. The residue after usual treatment was chromatographed on SiO_2 and elution with *n*-hexane–AcOEt (2: 1) followed by recrystallization of the product from MeOH gave colorless needles (XI, 38.6 mg), 221—222°. *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.77; H, 7.63. MS *m/e*: 264 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3455, 3200 (OH), 1725, 1680 (unsaturated lactone). NMR (pyr-d_5) δ: 1.06 (3H, s, C_{15}–3H), 1.72 (3H, s, C_{13}–3H), 3.97 (2H, d, $J=6$ Hz, C_{14}–2H).

Preparation of a Ketoalcohol (XII) from Chloranthalactone C (III)——Chloranthalactone C (III, 500 mg) was refluxed for 2 hr in a mixture (40 ml) of EtOH and water (1: 1) containing 6 g of KOH. After cooling to room temperature, water was added and the mixture was extracted with AcOEt. The residue, after usual treatment, was chromatographed on Al_2O_3 and SiO_2. Elution with *n*-hexane–acetone (20: 1) gave an oily product (XII, 57.6 mg). MS *m/e*: 195 (5%, M^++1), 194 (5, M^+), 164 (85), 123 (100). IR $\nu_{max}^{CS_2}$ cm^{-1}: 3450, 3200 (OH), 1710 (C=O). NMR ($CDCl_3$) δ: 0.67 ppm (3H, s, C_{10}–CH_3), 2.53 (2H, s, C_9–2H), 3.77 (2H, m, CH_2OH). ORD ($c=0.1$, MeOH): $[\phi]_{307}$ $-5044°$ (trough), $[\phi]_{264}$ $+6790$ (peak). CD ($c=0.1$, MeOH): $[\phi]_{288}$ -1350.

X-Ray Analysis of Chloranthalactone C (III)——Crystal data: $C_{17}H_{20}O_4$, mol wt.=288.33, orthorhombic space group $P2_12_12_1$, $a=6.928(1)$, $b=31.456(4)$, $c=6.764(1)$ Å, $V=1474.01$ Å^3, $Z=4$, $\rho_{calcd}=1.30$ g cm^{-3}.

A total of 1578 independent reflections within $2\theta < 140°$ was collected using a $\theta-2\theta$ scan method with a 2θ scan rate of 2° min^{-1}. The background was measured at each end of the scan for 10 sec. The intensities were corrected for Lorenz and polarization factors but not for absorption factors.

The structure was solved by the direct method using the MULTAN program and was refined by the block-diagonal least-squares method. Several cycles of refinements involving all non-hydrogen atoms with anisotropic temperature factors led to an R factor $[R=\sum||F_0|-|Fc||/\sum|F_0|]$ of 0.093. No attempt was made to locate the hydrogen atoms, since the bond lengths and angles obtained were the expected ones for the structure III.

The final positional parameters are shown in Table II. A list of the observed and calculated structure factors, and other results, is available from the authors on request.

Table II. Final Positional Parameters for the Chloranthalactone C Crystal

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C (1)	0.5599(12)	0.1720(2)	0.6662(11)	264(21)	738(0)	157(17)	−004(6)	−060(37)	000 (6)
C (2)	0.4961(15)	0.2119(2)	0.5522(12)	373(26)	617(0)	213(19)	−004(8)	104(51)	008 (6)
C (3)	0.6708(12)	0.1860(2)	0.4837(11)	223(18)	750(0)	178(17)	−012(6)	−040(36)	015 (6)
C (4)	0.6400(10)	0.1517(2)	0.3252(10)	152(15)	671(0)	156(15)	−010(5)	−005(30)	015 (5)
C (6)	0.5227(10)	0.0708(2)	0.3636(10)	212(17)	569(0)	145(15)	−012(5)	−017(34)	001 (5)
C (7)	0.5024(10)	0.0409(2)	0.5355(10)	151(15)	750(0)	194(17)	−009(6)	−006(35)	005 (5)
C (11)	0.5045(10)	−0.0025(2)	0.5440(12)	133(14)	825(0)	251(20)	−005(6)	009(37)	006 (6)
C (12)	0.4868(12)	−0.0139(2)	0.7549(12)	153(15)	897(0)	284(21)	−008(6)	071(38)	028 (7)
C (8)	0.4785(11)	0.0573(2)	0.7363(11)	167(16)	802(0)	180(17)	−011(6)	−016(33)	011 (6)
C (9)	0.4602(11)	0.0979(2)	0.7883(10)	194(17)	723(0)	154(16)	−007(6)	−017(33)	008 (5)
C (10)	0.4605(10)	0.1293(2)	0.6201 (9)	178(16)	673(0)	117(14)	−001(5)	−072(30)	006 (5)
C (5)	0.5975(10)	0.1123(2)	0.4562(10)	159(15)	556(0)	131(14)	−008(5)	−014(29)	003 (5)
C (14)	0.2468(11)	0.1337(2)	0.5496(12)	153(16)	1141(0)	188(18)	009(6)	−031(35)	010 (7)
C (13)	0.5261(13)	−0.0357(2)	0.3875(13)	270(21)	0651(0)	303(23)	−010(7)	029(49)	−013 (7)
C (15)	0.8174(11)	0.1443(2)	0.2044(12)	162(17)	0734(0)	229(19)	003(6)	052(35)	034 (6)
C (16)	1.0253(13)	0.1929(2)	0.0246(11)	223(20)	1268(0)	157(17)	−016(8)	−061(38)	008 (7)
C (17)	1.0311(14)	0.2319(2)	−0.1007(12)	284(23)	1095(0)	215(20)	−021(8)	056(44)	032 (7)
O (1)	0.4692 (8)	0.0235(1)	0.8664 (7)	225(13)	0725(0)	212(12)	−001(4)	037(27)	028 (4)
O (12)	0.4829 (9)	−0.0487(1)	0.8331 (9)	283(15)	0871(0)	339(17)	004(5)	096(37)	046 (5)
O (15)	0.8470 (7)	0.1842(1)	0.0878 (8)	163(11)	0908(0)	246(14)	−012(4)	005(25)	038 (5)
O (16)	1.1646(10)	0.1705(2)	0.0631(12)	199(16)	3153(1)	465(26)	008(8)	119(40)	144(10)

Most of the calculations were carried out on an ACOS-60 machine at the University of Tohoku using a program modified by the authors.

Epoxidation of Chloranthalactone C (III)——III (100 mg) was dissolved in $CHCl_3$ (5 ml) and *m*-chloroperbenzoic acid (66 mg) was added while cooling with ice-water. After addition of the oxidation agent, the reaction flask was to warm to room temperature and left to stand for 8 hr. The reaction solution was washed with 1% KOH and water, then dried over Na_2SO_4. After removal of the solvent and drying agent, the residue was recrystallized from acetone to yield colorless needles, mp 158—159°, $C_{17}H_{20}O_5$. MS *m/e*: 304 (M^+). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1790, 1725, 1670, 1240. NMR ($CDCl_3$): 0.74 ppm (3H, s, C_{15}–3H), 1.82 (3H, bs, C_{13}–3H), 2.07 (3H, s, OAc), 4.08 (1H, s, C_9–H), 4.26 (2H, d, $J=6$ Hz, C_{14}–2H).

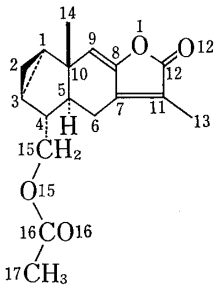

Chart 7. Numbering of Chloranthalactone C (see Table II)

Preparation of Chloranthalactone E (V) from Chloranthalactone B (II)——Chloranthalactone B (II, 44 mg) was dissolved in EtOH (20 ml) and 1% H_2SO_4 (10 ml) was added with stirring. After stirring for 30 min, the reaction solution was neutralized with saturated $NaHCO_3$ and extracted with AcOEt. The residue, after usual treatment, was chromatographed on SiO_2, and elution with *n*-hexane–acetone (100: 7) followed by recrystallization of the product from MeOH gave colorless needles (25.2 mg), mp 163—164°. The IR and NMR spectra were superimposable on those of the isolated diol (V).

Dehydration of Atractylenolide III (VI)——Atractylenolide III (VI, 15.8 mg) was dissolved in pyridine (2.5 ml) and $POCl_3$ was added while cooling with ice-water. The reaction solution was left at room temperature overnight, and was then poured into ice-water and extracted with ether. The ether solution was washed with dil. HCl and then water, and dried over Na_2SO_4. The residue after usual treatment was chromatographed on SiO_2, and elution with *n*-hexane–AcOEt (20 : 1) followed by recrystallization from AcOEt provided colorless prisms (XIV, 10.7 mg), mp 109—110°. The IR and NMR spectra were superimposable on those of an authentic specimen of atractylenolide I.

Cytotoxicity——Cytotoxicity of the sesquiterpene lactone was evaluated by the trypan blue dye exclusion method. Mouse lymphosarcome L-5178Y cells were cultured with 200 μl of RPMI 1640 culture medium supplemented with penicillin, streptomycin and 10% calf serum, on microplates. After culture for 24 hr, various concentrations of the sesquiterpenes were added to the wells and the cultures were incubated for a further 72 hr. The viable cell number was determined at 24, 48 and 72 hr. One-tenth ml of the cell suspension was mixed with 0.9 ml of Türk solution, composed of 1% gentian violet and 1% acetic acid in water, and the stained cells were counted in a hemocytometer. The methods and materials used have been described in detail elsewhere.[21]

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[21] H. Hemmi, H. Kitame, N. Ishida, G. Kusano, Y. Kondo, S. Nozoe, *J. Pharmacol. Dyn.*, **2**, 339 (1979).