Chlojaponilactones B – E, Four New Lindenane Sesquiterpenoid Lactones from *Chloranthus japonicus*

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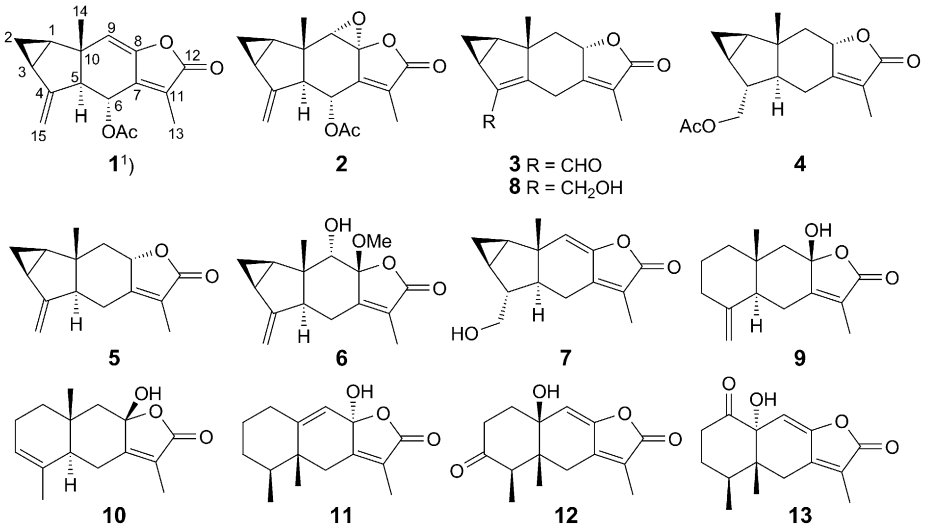
Reinvestigation of the AcOEt-soluble part of the EtOH extract of whole plants of *Chloranthus japonicus* afforded four new lindenane-type sesquiterpenoid lactones, chlojaponilactones B – E (**1** – **4**, resp.), together with nine known sesquiterpenoids. Their structures and relative configurations were established on the basis of extensive spectroscopic data and by comparison with the relevant literature.

Introduction. – *Chloranthus japonicus* (Chloranthaceae) is a perennial herb and mainly grows in the east of Asia. This herb has a long history in the traditional Chinese medicine for the treatment of traumatic injuries, rheumatic arthralgia, bone fractures, pulmonary tuberculosis, and neurasthenia [1]. Previous studies on the species led to the isolation of a variety of structurally interesting sesquiterpenoids and sesquiterpenoid dimers and trimers [2 – 15]. Recently, our group reported five lindenane disesquiterpenoids and an eudesmane sesquiterpenoid lactone isolated from the title plant and anti-HIV activity of lindenane disesquiterpenoids [16][17]. Mechanistic studies revealed that shizukaol F was a new structural type of HIV-1 RNase H inhibitor [18]. Reexamination of the AcOEt-soluble part of the EtOH extract of the species resulted in the characterization of four new lindenane-type sesquiterpenoid lactones, named chlojaponilactones B – E[1]) (**1** – **4**, resp.), together with nine known sesquiterpenoids, shizukanolide (**5**) [2], 9-hydroxyheterogorgiolide (**6**) [19], shizukanolide C (**7**) [4], chlorajapolide C (**8**) [15], atractylenolid III (**9**) [17], chlojaponilactone A (**10**) [17], tsoongianolide D (**11**) [20], tsoongianolide E (**12**) [20], and (10α)-10-hydroxy-1-oxoeremophila-7(11),8-dien-12,8-olide (**13**) [17]. Herein, we discuss the detailed structure determination of the isolates by extensive spectroscopic analysis, including 1D- and 2D-NMR and mass spectra.

Results and Discussion. – Chlojaponilactone B (**1**) was obtained as a white, amorphous powder. Based on HR-ESI-MS (*m*/*z* 309.1099 ([M + Na]$^+$)), the molecular formula was established as $C_{17}H_{18}O_4$ requiring nine degrees of unsaturation. The absorption bands in the IR spectrum at 1787, 1737, and 1639 cm^{-1}, and the UV maximum at 284 nm (log ε 4.09) indicated the presence of an α,β-unsaturated γ-lactone moiety in **1**, similar to chloranthalactone A (=(4a*S*,5a*S*,6a*R*,6b*S*)-4a,5,5a,6,6a,6b-

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*



hexahydro-3,6b-dimethyl-5-methylenecycloprop[2,3]indeno[5,6-*b*]furan-2(4*H*)-one) [2][3]. The ^{1}H-NMR spectrum of **1** (*Table 1*) showed four upfield signals at δ(H) 0.89–0.92, 0.95–0.97, 1.66–1.69, and 1.96–2.01 (4*m*, 4 H), characteristic of the cyclopropane ring of lindenane sesquiterpenoids [3–5], two Me *s* at δ(H) 1.86 and 0.88 (Me (13) and Me (14), resp.), one olefinic H-atom at δ(H) 6.28 (*s*, H–C(9)), and two broad *s* at δ(H) 5.09 and 4.76 for an exocyclic terminal C=C bond (CH_2(15)). All 17 C-atoms were resolved in the ^{13}C-NMR spectrum (*Table 2*) and were categorized by DEPT experiments as three Me, two CH_2 (one olefinic), and five CH groups (one O-bearing and one olefinic), and seven quaternary C-atoms (four olefinic and two ester CO). The NMR data (*Tables 1* and *2*) of **1** were similar to those of chloranthalactone A apart from the presence of an AcO group (δ(H) 6.11 (*d*, J = 12.0 Hz, H–C(6)) and 2.18 (*s*, Ac); δ(C) 65.6 (*d*, C(6)), 20.5 (*q*, *Me*CO), and 170.5 (*s*, Me*C*O)) instead of the CH_2(6) group in the latter. This was confirmed by the ^{1}H,^{1}H-COSY cross-peak of H–C(6) (δ(H) 6.11, *d*, J = 12.0 Hz) with H–C(5) (δ(H) 3.26, *d*, J = 12.0 Hz) and the HMBCs H–C(6)/AcO, C(4), C(5), C(8), C(9), and C(11) (*Fig.*). The relative configuration of **1** was established by a ROESY experiment (*Fig.*), in which correlations including Me(14)/H$_\beta$–C(2) and Me(14)/H–C(6) indicated that H–C(6), the cyclopropane ring and Me(14) were cofacial, and they were arbitrarily assigned as being β-oriented. Other correlations, *i.e.* H–C(1)/H$_\alpha$–C(2), H–C(1)/H–C(3), and H–C(5)/H–C(3) revealed that these H-atoms should adopt α-orientation. Therefore, the structure of **1** was determined as (1α,3α,5α,6α)-6-(acetyloxy)lindena-4(15),7(11),8-trieno-12,8-lactone[1]).

Chlojaponilactone C (**2**) had the molecular formula $C_{17}H_{18}O_5$, as deduced by HR-ESI-MS (*m*/*z* 325.1046 ([M + Na]$^+$)). The ^{1}H-NMR spectrum of **2** also showed several features of a lindenane sesquiterpenoid with a three-membered ring. Comparison of NMR data of **2** (*Tables 1* and *2*) with those of chloranthalactone B (=(1a*S*,5a*S*,6a*S*,7a*R*,7b*S*,7c*S*)-5,5a,6,6a,7,7a,7b,7c-octahydro-4,7b-dimethyl-6-methylene-3*H*-cycloprop[2,3]oxireno[4,5]indeno[5,6-*b*]furan-3-one) [3] exhibited that the major difference

Table 1. *^{1}H-NMR Data* ($CDCl_3$) *of Compounds* **1**–**4**[1]). δ in ppm, J in Hz.

H-Atom	**1**[a])	**2**[a])	**3**[b])	**4**[a])
H–C(1)	1.66–1.69 (*m*)	1.71–1.76 (*m*)	1.58–1.62(*m*)	1.18–1.22 (*m*)
H_α–C(2)	0.89–0.92 (*m*)	0.91–0.95 (*m*)	0.93 (*td*, *J* = 8.0, 5.0)	0.71–0.77 (*m*)
H_β–C(2)	0.95–0.97 (*m*)	0.86–0.90 (*m*)	0.26 (*dd*, *J* = 8.0, 4.5)	0.88–0.89 (*m*)
H–C(3)	1.96–2.01 (*m*)	1.97–2.05 (*m*)	2.26 (*td*, *J* = 8.0, 3.0)	1.23–1.25 (*m*)
H–C(4)	–	–	–	1.64–1.67 (*m*)
H–C(5)	3.26 (*d*, *J* = 12.0)	3.63 (*d*, *J* = 11.2)	–	1.68–1.69 (*m*)
H_α–C(6)	–	–	2.93 (*d*, *J* = 15.0)	2.58–2.59 (*m*)
H_β–C(6)	6.11 (*d*, *J* = 12.0)	5.84 (*d*, *J* = 11.2)	4.17 (*d*, *J* = 15.0)	2.60–2.61 (*m*)
H–C(8)	–	–	5.02–5.05 (*m*)	4.97 (*t*, *J* = 8.6)
H_α–C(9)	6.28 (*s*)	–	1.46 (*t*, *J* = 11.5)	1.41 (*t*, *J* = 11.2)
H_β–C(9)	–	4.18 (*s*)	2.50 (*dd*, *J* = 11.5, 6.0)	2.55–2.56 (*m*)
Me(13)	1.86 (*s*)	1.89 (*s*)	1.84 (*s*)	1.77 (*s*)
Me(14)	0.88 (*s*)	0.74 (*s*)	1.37 (*s*)	0.86 (*s*)
H_a–C(15)	4.76 (br. *s*)	4.75 (*s*)	9.92 (*s*)	4.10–4.14 (*m*)
H_b–C(15)	5.09 (br. *s*)	5.05 (*s*)	–	4.15–4.19 (*m*)
Ac	2.18 (*s*)	2.13 (*s*)	–	2.07 (*s*)

[a]) Recorded at 400 MHz. [b]) Recorded at 500 MHz.

Table 2. *^{13}C-NMR Data* ($CDCl_3$, 100 MHz) *of Compounds* **1**–**4**[1]). δ in ppm.

C-Atom	**1**	**2**	**3**	**4**
C(1)	26.3 (*d*)	23.8 (*d*)	27.5 (*d*)	27.5 (*d*)
C(2)	17.3 (*t*)	17.0 (*t*)	15.3 (*t*)	15.9 (*t*)
C(3)	22.4 (*d*)	22.6 (*d*)	21.0 (*d*)	22.9 (*d*)
C(4)	147.0 (*s*)	146.8 (*s*)	141.6 (*s*)	42.7 (*d*)
C(5)	65.7 (*d*)	55.6 (*d*)	161.1 (*s*)	62.2 (*d*)
C(6)	65.6 (*d*)	62.4 (*d*)	25.0 (*t*)	25.1 (*t*)
C(7)	146.1 (*s*)	148.8 (*s*)	159.2 (*s*)	161.8 (*s*)
C(8)	148.5 (*s*)	88.0 (*s*)	77.4 (*d*)	79.5 (*d*)
C(9)	119.6 (*d*)	64.0 (*d*)	46.8 (*t*)	44.7 (*t*)
C(10)	41.1 (*s*)	41.7 (*s*)	51.0 (*s*)	40.4 (*s*)
C(11)	124.3 (*s*)	134.2 (*s*)	122.2 (*s*)	121.1 (*s*)
C(12)	170.4 (*s*)	169.3 (*s*)	176.0 (*s*)	174.6 (*s*)
C(13)	8.8 (*q*)	9.5 (*q*)	8.8 (*q*)	8.3 (*q*)
C(14)	23.4 (*q*)	17.8 (*q*)	21.7 (*q*)	16.6 (*q*)
C(15)	108.8 (*t*)	108.8 (*t*)	187.0 (*d*)	65.9 (*t*)
Ac	170.5 (*s*)	170.2 (*s*)		171.1 (*s*)
	20.5 (*q*)	20.6 (*q*)		20.9 (*q*)

was the appearance of the resonances for an AcO group at δ(H) 5.84 (*d*, *J* = 11.2 Hz, H–C(6)) and 2.13 (*s,* Ac) and δ(C) 62.4 (*d,* C(6)), 20.6 (*q, Me*CO), and 170.2 (*s,* Me*C*O). The key correlations from the H-atom at δ(H) 5.84 (*d*) to Ac (δ(C) 170.2), C(5), C(7), C(8), and C(11) in the HMBC spectrum placed the AcO group at C(6), which was also confirmed by the ^{1}H,^{1}H-COSY cross-peak of δ(H) 3.63 (H–C(5))/δ(H) 5.84 (H–C(6)). The relative configuration of **2** was deduced from a ROESY

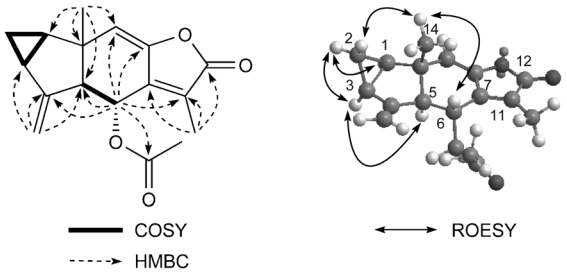


Figure. *Key 2D-NMR correlations observed for chlojaponilactone B* (**1**)

experiment. The ROESY correlations Me(14)/H_β–C(2), Me(14)/H–C(6), and Me(14)/H–C(9) suggested that H–C(6), H–C(9), and the cyclopropane ring were β-oriented. Thus, the structure of **2** was elucidated as (1α,3α,5α,6α,8β)-6-(acetyloxy)-8,9-epoxylindena-4(15),7(11)-dieno-12,8-lactone[1]).

Chlojaponilactone D (**3**) showed a molecular formula $C_{15}H_{16}O_3$ by HR-ESI-MS (*m*/*z* 267.0989 ([M + Na]$^+$)). The ^{1}H-NMR spectrum of **3** (*Table 1*) displayed a H-atom signal of an aldehyde group at δ(H) 9.92 (*s*), as well as a 1,2-disubstituted cyclopropane ring at δ(H) 0.26 (*dd*, J = 8.0, 4.5 Hz, H_β–C(2)), 0.93 (*td*, J = 8.0, 5.0 Hz, H_α–C(2)), 1.58–1.62 (*m*, H–C(1)), and 2.26 (*td*, J = 8.0, 3.0 Hz, H–C(3)). Comparison of the ^{13}C-NMR data (*Table 2*) of **3** with those of chlorajapolide A (=(4*R*,5a*S*,6a*R*,6b*S*,7a*S*)-2,4,5a,6,6a,6b,7,7a-octahydro-4-hydroxy-3,6b-dimethyl-2-oxocycloprop[2,3]indeno[5,6-*b*]furan-5-carboxaldehyde) [15] showed a strong resemblance, with the exception of the chemical shift of C(6) at δ(C) 25.0 (*t*) clearly showing that C(6) of **3** was not substituted by an OH group. The ROESY correlations Me(14)/H_β–C(2) and Me(14)/H–C(8) suggested that H–C(8) was β-oriented. Consequently, the structure of **3** was assigned as (1α,3α,8α)-15-oxolindena-4,7(11)-dieno-12,8-lactone[1]).

The molecular formula of chlojaponilactone E (**4**) was determined as $C_{17}H_{22}O_4$ by HR-ESI-MS (M^+ at *m*/*z* 290.1510). Compound **4** was also recognized as a lindenane sesquiterpenoid from its NMR data (*Tables 1* and *2*), which were quite similar with those of chloranthalactone C (=(4a*S*,5*R*,5a*S*,6a*R*,6b*S*)-5-[(acetyloxy)methyl]-4a,5,5a,6,6a,6b-hexahydro-3,6b-dimethylcycloprop[2,3]indeno[5,6-*b*]furan-2(4*H*)-one) [5]. The major difference was the absence of the trisubstituted C=CH group between C(8) and C(9), which was compensated by the presence of one oxymethine resonance at (δ(H) 4.97 (*t*, J = 8.6 Hz) and δ(C) 79.5, and of a CH_2 resonance at δ(H) 1.41 (*t*, J = 11.2 Hz) and 2.55–2.56 (*m*) and δ(C) 44.7. The oxymethine group was inferred to be located at C(8) from the HMBCs δ(H) 4.97/C(7), C(9), and C(11) and the ^{1}H,^{1}H-COSY cross-peaks δ(H) 4.97/CH_2(9). The ROESY correlations Me(14)/H_β–C(2), Me(14)/H–C(4), and Me(14)/H–C(8) indicated that H–C(4) and H–C(8) were β-oriented. Hence, the structure of **4** was determined as (1α,3α,4α,5α,8α)-15-(acetyloxy)-linden-7(11)-eno-12,8-lactone[1]).

The stimulatory effects of compounds **1**–**3** and **8** on GLUT4 translocation were measured as described in [21]. The results showed that none of the tested compounds had any discernible stimulatory activity at a concentration of 10 μM.

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Experimental Part

General. Semi-prep. HPLC: *Agilent-1100* apparatus; *Zorbax SB-C-18* column (9.4 mm × 25 cm, 5 μm; *Agilent*). Column chromatography (CC): silica gel (SiO_2; 200–300 mesh; *Qingdao Marine Chemical Inc.*, P. R. China) or SiO_2 *H* (10–40 μm; *Qingdao Marine Chemical Inc.*), *MCI* gel *CHP20P* (75–150 μm, *Mitsubishi Chemical Co.*), and *Sephadex LH-20* (*GE Healthcare*); TLC: SiO_2 plates; detection with a UV254 lamp or by heating the plates sprayed with 10% H_2SO_4 in EtOH. Optical rotations: *Jasco-P-1020* digital polarimeter. UV Spectra: *Shimadzu-UV-2401-PC* spectrophotometer; λ_{max} (log ε) in nm IR Spectra: *Bruker-Tensor-27* spectrophotometer; KBr pellets; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AM-400* (400 and 100 MHz) and *-DRX-500* (500 and 125 MHz) instruments; δ in ppm rel. to SiMe as internal standard, *J* in Hz. ESI-MS: *Bruker-HTC/Esquire* spectrometer; in *m*/*z*. HR-ESI-MS: *API-Qstar-Pulsar* instrument.

Plant Material. Whole plants of *C. japonicus* were collected from Panshi City, Jilin Province, China, in June 2010 and identified by Dr. *En-De Liu* of the Kunming Institute of Botany. A voucher specimen (No. HY0003) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China.

Extraction and Isolation. The dried and powered material (10 kg) was extracted three times with 95% EtOH (3 × 40 l) under reflux. The filtrate was concentrated to give a residue (740 g), which was dissolved in H_2O and extracted with AcOEt and then BuOH. The AcOEt extract (380 g) was subjected to CC (*MCI* gel, MeOH/H_2O 3:7 → 9:1): *Fractions A–C*). *Fr. B* (185 g) was subjected to CC (SiO_2, petroleum ether/acetone 20:1 → 1:5): *Frs. B$_1$–B$_9$*. *Frs. B$_1$–B$_4$* were repeatedly subjected to CC (SiO_2, petroleum ether/acetone 50:1 → 1:1; SiO_2, $CHCl_3$/MeOH 0:1 → 25:1; *Sephadex LH-20*, MeOH) and semiprep. HPLC (MeCN/H_2O 30 → 55%): **1** (9 mg), **2** (9 mg), **3** (8 mg), **4** (22 mg), shizukanolide (**5**; 20 mg), 9-hydroxyheterogorgiolide (**6**; 10 mg), shizukanolide C (**7**; 12 mg), chlorajapolide C (**8**; 11 mg), atractylenolid III (**9**; 11 mg), chlojaponilactone A (**10**; 12 mg), tsoongianolide D (**11**; 7 mg), tsoongianolide E (**12**; 8 mg), and (10α)-10-hydroxy-1-oxoeremophila-7(11),8-dieno-12,8-lactone (**13**; 10 mg).

Chlojaponilactone B (= *(1α,3α,5α,6α)-6-(Acetyloxy)lindena-4(15),7(11),8-trieno-12,8-lactone* = rel-*(4*R*,4a*S*,5a*S*,6a*R*,6b*S*)-4-(Acetyloxy)-4a,5,5a,6,6a,6b-hexahydro-3,6b-dimethyl-5-methylenecyclopro-p[2,3]indeno[5,6-b]furan-2-(4*H*)-one*; **1**). White amorphous powder. $[\alpha]_D^{14} = +2.75$ ($c = 0.08$, MeOH). UV (MeOH): 284 (4.09). IR (KBr): 3433, 1787, 1737, 1639, 1227. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 309 ($[M+Na]^+$). HR-ESI-MS: 309.1099 ($[M+Na]^+$, $C_{17}H_{18}NaO_4^+$; calc. 309.1103).

Chlojaponilactone C (= *(1α,3α,5α,6α,8β)-6-(Acetyloxy)-8,9-epoxy-lindena-4(15),7(11)-dieno-12,8-lactone* = rel-*(1a*R*,5*S*,5a*R*,6a*R*,6b*R*,7a*S*,7b*R*,7c*R*)-5-(Acetyloxy)-5,5a,6,6a,7,7a,7b,7c-octahydro-4,7b-dimethyl-6-methylene-3*H*-cycloprop[2,3]oxireno[4,5]indeno[5,6-*b*]furan-3-one*; **2**): White amorphous powder. $[\alpha]_D^{15} = -54.7$ ($c = 0.13$, MeOH). UV (MeOH): 224 (3.92). IR (KBr): 3443, 1787, 1731, 1639, 1232. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 325 ($[M+Na]^+$). HR-ESI-MS: 325.1046 ($[M+Na]^+$, $C_{17}H_{18}NaO_5^+$; calc. 325.1051).

Chlojaponilactone D (= *(1α,3α,8α)-15-Oxo-lindena-4,7(11)-dieno-12,8-lactone* = rel-*(5a*R*,6a-*S*,6b*R*,7a*R*)-2,4,5a,6,6a,7,7a-Octahydro-3,6b-dimethyl-2-oxocycloprop[2,3]indeno[5,6-*b*]furan-5-carbox-aldehyde*; **3**). White amorphous powder. $[\alpha]_D^{21} = -128.9$ ($c = 0.12$, MeOH). UV (MeOH): 206 (4.17). IR (KBr): 1748, 1663, 1228, 1037. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 267 ($[M+Na]^+$). HR-ESI-MS: 267.0989 ($[M+Na]^+$, $C_{15}H_{16}NaO_3^+$; calc. 267.0997).

Chlojaponilactone E (= *(1α,3α,4α,5α,8α)-15-(Acetyloxy)linden-7(11)-eno-12,8-lactone* = rel-*(4a*R*,5-S*,5a*R*,6a*S*,6b*R*,7a*R*)-5-[(Acetyloxy)methyl]-4a,5,5a,6,6a,7,7a-octahydro-3,6b-dimethylcloprop[2,3]inde-no[5,6-*b*]furan-2(4*H*)-one*; **4**). White amorphous powder. $[\alpha]_D^{24} = +3.6$ ($c = 0.09$, MeOH). UV (MeOH): 217 (4.17). IR (KBr): 1735, 1681, 1242, 1036. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 313 ($[M+Na]^+$). HR-ESI-MS: 290.1510 (M^+, $C_{17}H_{22}O_4^+$; calc. 290.1518).

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