Velutinalide C, a New Polycyclic Phragmalin Limonoid from the Leaves of *Chukrasia tabularis* var. *velutina*

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Velutinalide C (**4**), a new polycyclic phragmalin limonoid featuring a C(15) – C(21) linkage and a C_4 unit at C(15), together with two known related compounds, chukfuransins C and D (**2** and **3**, resp.), was isolated from the leaves of *Chukrasia tabularis* var. *velutina*. The structure of the new compound **4** was elucidated on the basis of extensive spectroscopic analyses and comparison with literature data.

Introduction. – Phragmalin limonoids, exemplified by phragmalin (**1**; *Fig. 1*) [1], are a type of ring *B*,*D*-seco-limonoids with characteristic tricyclo [3.3.$1^{2,10}$.$1^{1,4}$]decane or tricyclo [4.2.$1^{10,30}$.$1^{1,4}$]decane (rearranged phragmalin limonoids) *A*- and *B*-ring systems, most of which bear orthoester groups at positions 1,8,9 or 8,9,14 or 8,9,30 or 8,9,11, and C(16)/C(17) δ-lactone ring (ring *D*) [2 – 5]. In few cases, ring *D* was cleaved, leading to C(16)/C(17) δ-seco-lactone [6], C(16)/C(8) δ-lactone [7], and C(16)/C(30) δ-lactone derivatives [8]. Many phragmalin limonoids showed biological properties, such as antifeedant [9], anti-inflammatory [10], K^+ channel blocking [11], and antibacterial [12] activities, which attracted great interest from synthetic organic chemists as challenging targets for total synthesis [13]. Genus *Chukrasia* (Meliaceae), comprising only two species *Chukrasia tabularis* and *Chukrasia tabularis* var. *velutina*, is a primary source of phragmalin limonoids [14]. So far, more than 140 naturally occurring phragmalin limonoids have been found in genus *Chukrasia*, and some of them possess novel C-atom skeletons, including 16-nor type [15][16], 15-enolic-acyl-16-nor type [17], 15-enolic-acyl type with C(16)/C(30) δ-lactone ring [8], 13/14/18-cyclopropanyl type [5][18], and 19-nor-type [11][19] phragmalin limonoids. Recently, five unprecedented polycyclic phragmalin limonoids, namely chuktabrin B [17], chukfuransins A and B [20], chukfuransins C and D (**2** and **3**, resp.) [20], featuring a common ring *E* (furan ring), formally involved in skeleton reconstruction (C(15)–C(21) linkage for chuktabrin B, **2** and **3**; and C(15)–C(20) linkage for chukfuransins A and B), were isolated from *C. tabularis* collected from Yunnan and Guangdong Province, P. R. China, respectively. Furthermore, among those with C(15)–C(21) linkage, chuktabrin B possessed an extended C_2 unit at C(15), while **2** and **3** had extended C_4 units at C(15), indicating that the genus *Chukrasia* can contiguously provide structurally intriguing phragmalin limonoids.

In the course of our ongoing search for bioactive metabolites from Chinese medicinal plants [21 – 25], the leaves of *C. tabularis* var. *velutina* were collected from

Zhanjiang, Guangdong Province, P. R. China. A preliminary chemical investigation of the AcOEt extract of *C. tabularis* var. *velutina* resulted in the discovery of two new *C(15)*-acyl-phragmalin limonoids, velutinalides A and B [26]. Our investigation on the minor constituents of the same collection led to the isolation of one additional new polycyclic phragmalin limonoid, named velutinalide C (**4**), together with two known related compounds, **2** and **3** (*Fig. 1*). Herein, we report the isolation and structure elucidation of the new compound **4**.

Results and Discussion. – Routine workup [26] of the AcOEt-soluble portions of the MeOH extract of the leaves of *C. tabularis* var. *velutina* afforded one new compound, named velutinalide C (**4**), together with two known related compounds, chukfuransins C and D (**2** and **3**, resp.) [20] (*Fig. 1*). The structures of the known compounds were readily assigned by comparison of their spectral data with those reported in [20]. Furthermore, comparison of the $[\alpha]_D$ values recorded for **2** and **3** with those reported in [20] allowed an unambiguous assignment of the absolute configuration for these two polycyclic phragmalin limonoids.

Velutinalide C (**4**), optically active white amorphous powder ($[\alpha]_D^{18} = +99.1^\circ$ ($c = 0.45$, $CHCl_3$)), had the molecular formula of $C_{36}H_{44}O_{13}$, as determined by HR-ESI-MS (*m/z* 707.2679 ($[M+Na]^+$; calc. 707.2680), which indicated 15 degrees of unsaturation. The IR spectrum showed the absorptions indicating the presence of OH (3440 cm^{-1}) and ester C=O (1733 cm^{-1}) functionalities. The ^{13}C-NMR spectrum displayed 36 C-atom resonances (*Table*) including those of eight Me, five CH_2, and eight CH groups (two olefinic and three O-bearing), and 15 quaternary C-atoms (two olefinic, four ester C=O, and four O-bearing). Besides the characteristic features, of three tertiary Me groups (δ(H) 1.17 (*s*), 0.99 (*s*), and 0.99 (*s*); δ(C) 15.8, 14.5, and

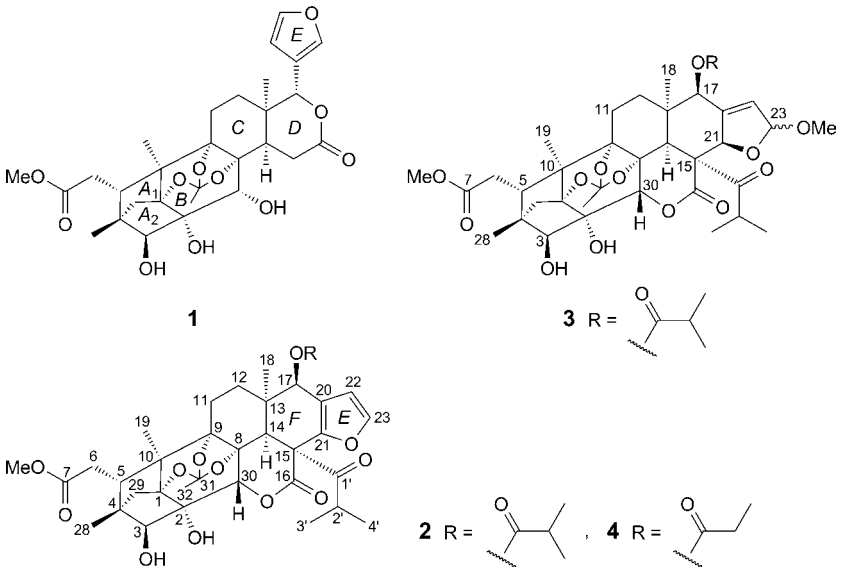

Fig. 1. *Structures of* **1**–**4**

28.6), a MeO group (δ(H) 3.66 (*s*); δ(C) 52.0), an orthoacetate group (δ(H) 1.56 (*s*); δ(C) 118.7 and 21.1), and an isobutanoyl group (δ(H) 3.36–3.40 (*m*, 1 H), 1.29 (*d*, J = 6.6, 3 H), and 1.12 (*d*, J = 6.6, 3 H); δ(C) 208.4, 38.6, 20.0, and 19.8), one α,β-disubstituted furyl ring (δ(H) 6.46 (*d*, J = 1.8, 1 H) and 7.34 (*d*, J = 1.8, 1 H); δ(C) 118.7, 148.8, 110.5, and 143.1), and a propanoyloxy group (δ(H) 2.44–2.48 (*m*, 2 H) and 1.03 (*t*, J = 7.8, 3 H); δ(C) 174.4, 26.6, and 8.7) were distinguished by analysis of the ^{1}H- and ^{13}C-NMR data (*Table*). There were 15 degrees of unsaturation in the molecule of **4**, of which nine were comprised by four ester C=O groups, an orthoacetate group, and the α,β-disubstituted furyl ring, and the remaining six degrees of unsaturation required **4** to possess six further rings at the central core. The aforementioned spectroscopic features strongly suggested that **4** is a polycyclic phragmalin limonoid with a common furan ring involved in skeleton reconstruction. Comparison of the ^{1}H- and ^{13}C-NMR data of **4** with those of co-occurring chukfuransin C (**2**) revealed that they share the same structure of rings *A*–*C* and *E*, a C(16)/C(30) δ-lactone ring, and a biosynthetically extended C_4 unit (isobutanoyl) at C(15), with the only difference occurring at the substitutent at C(17) in ring *F*, where the isobutanoyloxy group (δ(H) 2.74–2.78 (*m*, 1 H), 1.14 (*d*, J = 6.9, 3 H), and 0.95 (*d*, J = 6.9, 3 H); δ(C) 177.5, 33.1, 18.8, and 19.2) of **2** was replaced by a propanoyloxy group (δ(H) 2.44–2.48 (*m*, 2 H) and 1.03 (*t*, J = 7.8, 3 H); δ(C) 174.4, 26.6, and 8.7) in **4**, which was in good accordance with the molecular weight for **4** that was 14 mass units less than that of **2**. Furthermore, the slightly upfield shifted ^{13}C-NMR signals at C(18) (δ(C) 28.6 for **4**; 28.9 for **2**), and C(20) (118.7 for **4**; 119.8 for **2**), and the diagnostic HMBC (*Fig. 2*) between H–C(17) and the corresponding C=O C-atom (δ(C) 174.4) of the propanoyloxy group in **4** further confirmed the assignment. Finally, a comprehensive analysis of the ^{1}H,^{1}H-COSY, HSQC, and HMBC spectra allowed assignment of all chemical shifts in ^{1}H- and ^{13}C-NMR spectra (*Table*) of **4**.

The relative configurations for ring-junction atoms of **4** were suggested to be the same as those of the co-occurring **2**, based on almost identical ^{1}H- and ^{13}C-NMR chemical shifts and biogenetic considerations. Furthermore, the relative configuration at C(17), identical with that of **2**, was determined by ROESY experiment (*Fig. 2*). Thus, the ROESY correlations Me(32)/H–C(14), Me(18)/H–C(17), Me(18)/H–C(14), and H–C(14)/H–C(17) indicated that H–C(17) is α-oriented, consequently establishing the β-orientation of the propanoyloxy group at C(17). In addition, the

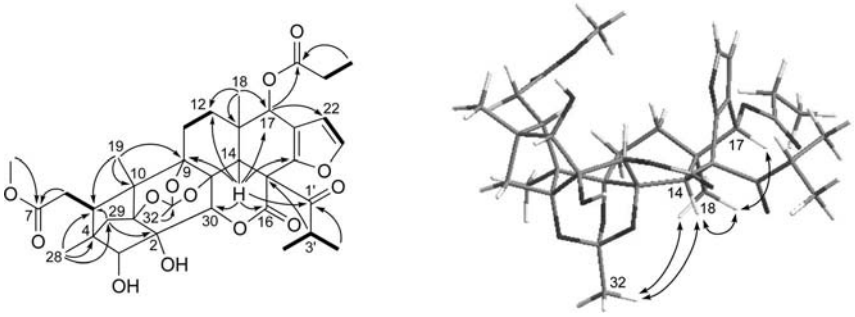

Fig. 2. *Selected ^{1}H,^{1}H-COSY* (—), *HMB* (H → C), *and NOESY* (H ↔ H) *correlations of* **4**

Table. *^{1}H- and ^{13}C-NMR Data of* **4**, *and ^{13}C-NMR Data of* **2** (in $CDCl_3$; δ in ppm, J in Hz)[a])

Position	**4**		**2**
	δ(H)	δ(C)[b])	δ(C)[b])
1	–	85.4 (*s*)	85.4 (*q*)
2	–	77.9 (*s*)	78.1 (*q*)
3	3.68 (*s*)	83.2 (*d*)	83.0 (*d*)
4	–	45.8 (*s*)	45.8 (*s*)
5	2.85–2.89 (*m*)	35.2 (*d*)	35.3 (*d*)
6	2.45–2.49 (*m*), 2.27–2.31 (*m*)	34.0 (*t*)	34.1 (*t*)
7	–	172.9 (*s*)	172.9 (*s*)
8	–	81.6 (*s*)	81.7 (*s*)
9	–	84.9 (*s*)	85.0 (*s*)
10	–	45.8 (*s*)	45.8 (*s*)
11	1.81–1.85 (*m*), 2.18 (br. *d*, J = 11.7)	26.0 (*t*)	25.9 (*t*)
12	1.39–1.43 (*m*), 1.99–2.03 (*m*)	27.9 (*t*)	27.8 (*t*)
13	–	39.6 (*s*)	39.5 (*s*)
14	2.85 (*s*)	48.3 (*d*)	48.4 (*d*)
15	–	57.6 (*s*)	57.5 (*s*)
16	–	167.4 (*s*)	167.2 (*s*)
17	5.33 (*s*)	71.8 (*d*)	71.7 (*d*)
18	0.99 (*s*)	28.6 (*q*)	28.9 (*q*)
19	1.17 (*s*)	15.8 (*q*)	15.7 (*q*)
20	–	118.7 (*s*)	119.8 (*s*)
21	–	148.8 (*s*)	148.7 (*s*)
22	6.46 (*d*, J = 1.8)	110.5 (*d*)	110.5 (*d*)
23	7.34 (*d*, J = 1.8)	143.1 (*d*)	143.1 (*d*)
28	0.99 (*s*)	14.5 (*q*)	14.5 (*q*)
29	1.86 (*d*, J = 10.5), 1.64 (*d*, J = 10.5)	39.8 (*t*)	39.6 (*t*)
30	5.74 (*s*)	75.6 (*d*)	75.6 (*d*)
31	–	118.7 (*s*)	118.7 (*s*)
32	1.56 (*s*)	21.1 (*q*)	21.1 (*q*)
1′	–	208.4 (*s*)	208.5 (*s*)
2′	3.36–3.40 (*m*)	38.6 (*d*)	38.6 (*d*)
3′	1.12 (*d*, J = 6.6)	19.8 (*q*)	19.8 (*q*)
4′	1.29 (*d*, J = 6.6)	20.0 (*q*)	20.0 (*q*)
2-OH	not observed	–	–
3-OH	3.29 (br. *s*)	–	–
7-MeO	3.66 (*s*)	52.0 (*q*)	51.9 (*q*)
$MeCH_2$*C*OO–C(17)	–	174.4 (*s*)	
Me*C*H_2COO–C(17)	2.44–2.48 (*m*)	26.6 (*t*)	
MeCH_2COO–C(17)	1.03 (*t*, J = 7.8)	8.7 (*q*)	
Me$_2$*C*HCOO–C(17)			177.5 (*s*)
			33.1 (*d*)
			18.8 (*q*)
			19.2 (*q*)

[a]) Assignments were achieded by DEPT, ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments. [b]) Multiplicities from DEPT sequence.

absolute configuration of **4** was assigned as the same as that of **2**, by comparison of the CD data of **4** with those of **2**, of which the absolute configuration was recently determined by X-ray diffraction analysis [20]. Therefore, the structure of **4** was elucidated as 17-propanoyloxy derivative of **2**.

A literature survey revealed that almost all reported phragmalin limonoids with various different C-atom skeletons [16][18][19] were isolated from Yunnan *C. tabularis* var. *velutina*. To the best of our knowledge, this is the second report of the phragmalin limonoids from *C. tabularis* var. *velutina* collected from Zhanjiang, Guangdong Province, P. R. China. It may be worth pointing out, although velutinalides A and B, previously reported by our group, belong to the common *C(15)*-acyl-type phragmalins, the skeleton of the newly discovered polycyclic phragmalin limonoid, velutinalide C (**4**), characterized by C(15) – C(21) linkage and a biosynthetically extended C_4 unit at C(15), is relatively rare.

Many phragmalin limonoids exhibited broad bioactivities as mentioned above. To explore their possible bioactivities, all isolates, **2** – **4**, were evaluated for their tumor cell growth inhibition and antibacterial activities. Unfortunately, **2** – **4** were found to be inactive against the growth of tumor cell lines human lung adenocarcinoma A-549 and human lymphocytic leukemia HL-60 at a concentration of 20 μg ml^{-1}. In addition, **2** – **4** showed no efficient inhibition effect on microbial growth, with an *MIC* (minimum inhibitory concentration) value of higher than 0.5 mg ml^{-1} against *Staphylococcus aureus* NEWMAN and *Pseudomonas aeruginosa* MPAO1, respectively. Further studies should be conducted to understand the true biological/ecological role of these metabolites in the life cycle of the plant of the Meliaceae family.

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Experimental Part

General. TLC: Precoated silica-gel plates (SiO_2; *G60*, F_{254}; *Yan Tai Zi Fu Chemical Group Co.*). Column chromatography (CC): commercial SiO_2 (200 – 300 and 300 – 400 mesh; *Qing Dao Hai Yang Chemical Group Co.*) or *Sephadex LH-20* (*General Electric Company*). Reversed-phase (RP) HPLC: *Agilent 1100* series liquid chromatography equipped with a *VWD G1314A* detector at 210 nm and a semi-prep. *ZORBAX ODS* column (250 mm × 9.4 mm i.d., 5 μm particle size). Optical rotations: *PerkinElmer 341* polarimeter at the Na D-line; cell length 10 cm. UV Spectra: *756 CRT* spectrophotometer; λ_{max} (log ε) in nm. CD Spectra: *JASCO 810* spectrometer; λ_{max} ($\Delta\varepsilon$) in nm. IR Spectra: *Nicolet Magna FT-IR 750* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian Mercury-300* (300 MHz for ^{1}H) and *Varian Mercury-400* (100 MHz for ^{13}C) spectrometers; assignments supported by ^{1}H,^{1}H-COSY, HSQC, HMBC, and ROESY experiments; δ in ppm rel. to residual $CDCl_3$ (δ(H) 7.26, δ(C) 77.0) as internal standard, *J* in Hz. ESI-MS and HR-ESI-MS: *Q-TOF-Micro-LC-MS/MS* spectrometer; in *m*/*z*.

Plant Material. The leaves of *C. tabularis* var. *velutina* were collected from Zhanjiang, Guangdong Province, P. R. China, in July 2009 and identified by Assoc. Professor *J.-G. Shen* of Shanghai Institute of Material Medica, Chinese Academy of Sciences. A voucher sample (No. 09-P-49) is available for inspection at the Herbarium of SIMM-CAS.

Extraction and Isolation. The chipped leaves of *C. tabularis* var. *velutina* (1 kg) were extracted exhaustively with MeOH (3 × 5 l) at r.t. The MeOH extract was concentrated *in vacuo* to give a residue, which was suspended in H_2O, and partitioned successively with AcOEt and BuOH. The AcOEt-soluble

extract was evaporated *in vacuo* to give a residue (27 g), which was subjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1) to afford three fractions, *Frs. 1–3*. *Fr. 2* (8 g) was subjected to CC (SiO_2; petroleum ether/AcOEt 90:10, 70:30, 50:50), followed by a gradient of $CHCl_3$/MeOH (90:10, 80:20, 70:30, 60:40), to give five subfractions, *Frs. 2.1–2.5*. *Fr. 2.3* (1.6 g) was subjected to CC (SiO_2; $CHCl_3$/MeOH 99:1, 98:2, 95:5) to give four subfractions, *Fr. 2.3.1–2.3.4*; then *Fr. 2.3.3* was separated by semi-prep. HPLC (MeCN/H_2O 80:20; 2.0 ml min^{-1}) to yield pure **2** (t_R 19.3 min; 10.8 mg), **3** (t_R 18.1 min; 4.7 mg), and **4** (t_R 16.2 min; 5.7 mg).

Chukfuransin C (= *(1*R,*5*R,*6*S,*7*S,*9*S,*10*R,*11*S,*14*R,*15*R,*21*S,*24*R,*25*S*)-6,7-Dihydroxy-9-(2-methoxy-2-oxoethyl)-3,8,10,14-tetramethyl-21-(2-methylpropanoyl)-22-oxo-2,4,19,23,26-pentaoxanonacyclo[12.10.1.1^{3,11}.1^{5,8}.0^{1,11}.0^{5,10}.0^{6,24}.0^{16,20}.0^{21,25}]heptacosa-16(20),17-dien-15-yl 2-Methylpropanoate*; **2**). White amorphous powder. $C_{37}H_{46}O_{13}$. $[\alpha]_D^{18} = +88.7$ ($c = 1.02$, $CHCl_3$). CD ($c = 1.0 \cdot 10^{-3}$ M, MeOH): 213 (−6.23), 236 (+5.87).

Chukfuransin D (= *(1*R,*5*R,*6*S,*7*S,*9*S,*10*R,*11*S,*14*R,*15*R,*18*ξ,*20*R,*21*S,*24*R,*25*S*)-6,7-Dihydroxy-18-methoxy-9-(2-methoxy-2-oxoethyl)-3,8,10,14-tetramethyl-21-(2-methylpropanoyl)-22-oxo-2,4,19,23,26-pentaoxanonacyclo[12.10.1.1^{3,11}.1^{5,8}.0^{1,11}.0^{5,10}.0^{6,24}.0^{16,20}.0^{21,25}]heptacos-16-en-15-yl 2-Methylpropanoate*; **3**). White amorphous powder. $C_{38}H_{50}O_{14}$. $[\alpha]_D^{18} = +31.0$ ($c = 0.39$, $CHCl_3$). CD ($c = 9.59 \cdot 10^{-4}$ M, MeOH): 192 (+34.6), 288 (−3.06).

Velutinalide C (= *(1*R,*5*R,*6*S,*7*S,*9*S,*10*R,*11*S,*14*R,*15*R,*21*S,*24*R,*25*S*)-6,7-Dihydroxy-9-(2-methoxy-2-oxoethyl)-3,8,10,14-tetramethyl-21-(2-methylpropanoyl)-22-oxo-2,4,19,23,26-pentaoxanonacyclo-[12.10.1.1^{3,11}.1^{5,8}.0^{1,11}.0^{5,10}.0^{6,24}.0^{16,20}.0^{21,25}]heptacosa-16(20),17-dien-15-yl Propanoate*; **4**). White amorphous powder. $[\alpha]_D^{18} = +99.1$ ($c = 0.45$, $CHCl_3$). UV (MeOH): 239 (4.77). CD ($c = 7.31 \cdot 10^{-4}$ M, MeOH): 213 (−8.02), 237 (+9.75). IR (KBr): 3440, 2965, 1733, 1140. ^{1}H- and ^{13}C-NMR: see *Table*. ESI-MS: 707 ($[M+Na]^+$). HR-ESI-MS: 707.2679 ($[M+Na]^+$, $C_{36}H_{44}O_{13}Na^+$; calc. 707.2680).

Cytotoxicity Assays. The cytotoxicities of **2**–**4** against A-549 and HL-60 cell lines were evaluated by using sulforhodamine B (SRB) [27] and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) [28] method. Etoposide phosphate was used as positive control, with IC_{50} values of 0.5 μg ml^{-1} for A-549 and 5.4 μg ml^{-1} for HL-60 cell lines, resp.

Antibacterial Test. The antimicrobial activities of **2**–**4** against *S. aureus* NEWMAN and *P. aeruginosa* MPAO1 strains were tested by paper disk diffusion antimicrobial susceptibility test [29] and *MIC* method, resp., zones of inhibition were measured after 24 h of incubation at 37°. For the *MIC* method, all isolates were dissolved in DMSO and diluted with culture broth to a concentration of 0.5 mg ml^{-1}. Further, 1:2 serial dilutions were performed by addition of culture broth to reach concentrations ranging from 0.5 to 0.0156 mg ml^{-1}; 100 μl of each dilution were distributed in 96-well plates, as well as a sterility control and a growth control (containing culture broth plus DMSO, without isolates). Each test and growth control well was inoculated with 5 μl of a bacterial suspension (10^5 CFU/well). The 96-well plates were incubated at 37° for 24 h. *MIC* Values of the compounds against *S. aureus* NEWMAN and *P. aeruginosa* MPAO1 strains were defined as the lowest concentration of each compound, which completely inhibited bacterial growth.

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