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Chukvelutins A−C, 16-Norphragmalin Limonoids with Unprecedented Skeletons from *Chukrasia tabularis* var. *velutina*

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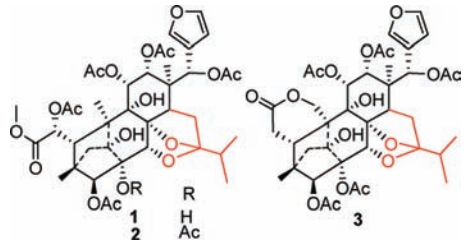
ABSTRACT



Three new 16-norphragmalin limonoids, chukvelutins A−C (1−3), were isolated from the stem bark of *Chukrasia tabularis* var. *velutina*, which possess unprecedented skeletons, featured with a characteristic ketal moiety between the phragmalin skeleton and a biosynthetically extended isobutyryl group at C-15. Their structures were elucidated by extensive spectroscopic technologies.

Limonoids from the Meliaceae family, a class of tetranortriterpenoids, are a continuing hot area of natural products research.[1] Several limonoids with novel skeletons have been isolated from some genera of Meliaceae in recent years, such as *Xylocarpus*,[2] *Chukrasia*,[3] and *Cipadessa*.[4] The structural diversity and potential biological significance have prompted us to investigate the plants of genus *Chukrasia*.

Previous chemical studies on genus *Chukrasia* focused mainly on *C. tabularis* A. Juss and afforded a series of phragmalin limonoids.[3,5] *C. tabularis* A. Juss, a timber tree, grows mainly in tropical areas of Asia. Its stem bark has been traditionally used as astringent, antidiarrheal, and anti-influenza agents in China.[6] *C. tabularis* var. *velutina* is a variety of *C. tabularis* A. Juss,[6a] from which a new class of C-15-acyl phragmalin limonoids featuring a C-16/C-30 δ-lactone ring,[5e] some phragmalin limonoids incorporating a cyclopropanyl ring,[5c] and some aliphatic compounds[7] were isolated. In our continuing study on phragmalin limonoids of this plant, three novel 16-norphragmalin limonoids,

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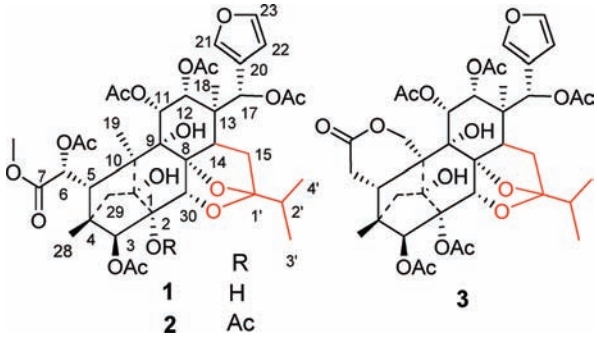
Chukvelutins A−C (**1**−**3**), were isolated from the stem bark of *C. tabularis* var. *velutina* collected in Xishuangbanna, China. These new compounds possess unprecedented 16-norphragmalin limonoid skeletons featured with a characteristic ketal moiety between the phragmalin skeleton and a biosynthetically extended isobutyryl group at C-15, forming a characteristic 2,7-dioxabicyclo[2.2.1]heptane moiety. Herein, we report the isolation and structural elucidation of these new compounds (**1**−**3**) and the plausible biosynthetic origin of them.



Chukvelutin A (**1**)[8] was isolated as white amorphous powder. Its molecular formula of $C_{40}H_{52}O_{18}$ was determined by the HRESIMS ion at *m*/*z* 843.3044 $[M + Na]^+$ (calcd 843.3046), which indicated 16 degrees of unsaturation. The IR absorption bands at 3450 and 1755 cm^{-1} suggested the presence of hydroxyl and ester groups. The ^1H and ^{13}C NMR data (Table 1) and the information from the subsequent 2D NMR studies (HMBC, HSQC, and NOESY) of **1** indicated the presence of a isopropyl [δ_H 2.24 (m) and 1.09 (d, J = 6.9 Hz, 2 × 3H); δ_C 31.2, 17.7, and 17.0], a β-substituted furanyl ring [δ_H 6.54, 7.39, and 7.68; δ_C 122.1, 109.5, 143.3, and 140.7], a methoxyl [δ_H 3.69; δ_C 52.5], and five acetoxyls. A singlet proton signal at δ_H 5.55 was assignable to H-6 by correlations observed in the HMBC spectrum (Figure 1) with the quaternary carbon at δ_C 45.9 (C-5), δ_C 170.4 (C-7), and an acetyl carbon at δ_C 169.9, which also suggested that C-6 had been acetoxylated.[3c] In the HMBC spectrum of **1**, the correlations between C-7 (δ_C 170.4) and H-6 (δ_H 5.55) and the ester methyl protons at δ_H 3.69 (3H, s) confirmed the characteristic C-6−C-7 appendage of phragmalin limonoids.[5b] A methylene signal at δ_C 41.0 correlating in the HSQC spectrum to two protons at δ_H 1.90 (d, J = 10.0 Hz) and 2.21 (m) were indicative of the H-29 protons of the characteristic 4, 29, 1-ring-bridge of phragmalin limonoids,[5e] which was also confirmed by HMBC correlations observed from the H-29 methylene protons to the quaternary carbons at δ_C 85.0 (C-1), 44.4 (C-4), 45.9 (C-5), and 53.7 (C-10). The analyses above and other 1D and 2D NMR spectral information suggested that **1** was a phragmalin limonoid without the characteristic C-16/C-17 δ-lactone ring (ring D) and the common *ortho*-acetate.[9]

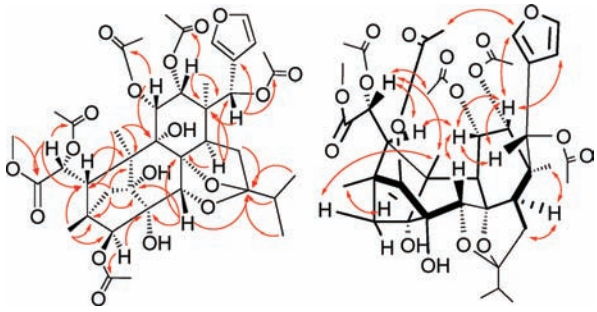


Figure 1. Key HMBC (→) and NOE (⟷) correlations of **1**.

The position of isobutyryl at C-15 was determined by the HMBC cross-peaks from H-15b (δ_H 2.49, dd, J = 11.8, 8.1 Hz) and isopropyl protons to the ketal signal at δ_C 115.2 (C-1′), which also correlated with H-30 (δ_H 4.17), suggesting the existence of an ether bridge between C-1′ and C-30. The remaining 1 degree of unsaturation suggested that an additional ring was required. On the basis of the chemical shift, C-8 also was linked with C-1′ through an ether linkage.[3a] Thus, the planar structure of **1** was demonstrated as depicted, which possessed an unprecedented skeleton with a characteristic ketal moiety between the phragmalin framework and a biosynthetically extended isobutyryl at C-15.

The relative stereochemistry of **1** was elucidated by NOESY experiment (Figure 1). Strong cross-peaks from the H-11 to H-5, H-17 and H-30, H-17 to H-12 and H-30, and H-5 to Me-28 indicated a β-orientation of these six protons. NOESY correlations of H-14 with Me-18 and of H-29 with H-3 and Me-19 revealed that these protons adopted α-orientation. The α-orientation of H-3 was also confirmed by the NOESY correlation between the 3-OAc signal and H-21 of the furan ring. The NOESY correlation of H-5 with H-6 helped to establish H-6 as β-orientation. Thus, the relative stereochemistry of **1** was demonstrated as depicted.

The molecular formula of Chukvelutin B (**2**),[10] $C_{42}H_{54}O_{19}$, was determined by the HRESIMS ion at *m*/*z* 885.3145 [M

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(8) Chukvelutin A (**1**): white amorphous power; $[\alpha]^{25}_D$ +26 (*c* 0.080, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 211 (3.72) nm; IR (KBr) ν_{max} 3450, 2975, 1755, 1634, 1373, 1220, 1031, 928, 899, 603 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1; negative ESIMS *m*/*z* (rel int) 855.5 $[M + Cl]^-$ (100); positive ESIMS *m*/*z* (rel int) 838.4 $[M + NH_4]^+$ (100); HRESIMS *m*/*z* 843.3044 $[M + Na]^+$ (calcd $C_{40}H_{52}O_{18}Na$, 843.3046).

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(10) Chukvelutin B (**2**): white amorphous power; $[\alpha]^{25}_D$ +32 (*c* 0.065, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 211 (3.79) nm; IR (KBr) ν_{max} 3441, 2973, 1758, 1631, 1372, 1239, 1220, 1037, 932, 905, 603 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1; negative ESIMS *m*/*z* (rel int) 897.8 $[M + Cl]^-$ (100); positive ESIMS *m*/*z* (rel int) 880.4 $[M + NH_4]^+$ (100); HRESIMS *m*/*z* 885.3145 $[M + Na]^+$ (calcd $C_{42}H_{54}O_{19}Na$, 885.3152).

(11) Chukvelutin C (**3**): white amorphous power; $[\alpha]^{25}_D$ +17 (*c* 0.085, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 211 (3.62) nm; IR (KBr) ν_{max} 3429, 2978, 1751, 1633, 1373, 1227, 1040, 925, 602 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1; negative ESIMS *m*/*z* (rel int) 823.8 $[M + Cl]^-$ (100); positive ESIMS *m*/*z* (rel int) 806.3 $[M + NH_4]^+$ (100); HRESIMS *m*/*z* 811.2783 $[M + Na]^+$ (calcd $C_{39}H_{48}O_{17}Na$, 811.2784).

Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Data of **1**−**3** (in $CDCl_3$)

	1		**2**		**3**	
no.	δ_H (multi, J in Hz)	δ_C	δ_H (multi, J in Hz)	δ_C	δ_H (multi, J in Hz)	δ_C
1		85.0		84.4		85.5
2		74.0		82.4		81.4
3	5.08 (s)	86.3	5.17 (s)	84.0	5.35 (s)	83.1
4		44.4		45.2		45.7
5	2.85 (br s)	45.9	2.84 (br s)	45.5	2.08 (m)[a]	40.6
6a	5.55 (d, 1.2)	71.8	5.56 (d, 1.2)	71.7	2.23 (dd, 6.4, 13.2)	31.5
6b					2.30 (m)[a]	
7		170.4		170.2		172.6
8		90.2		90.1		89.6
9		76.2		76.4		75.3
10		53.7		54.3		52.4
11	5.58 (d, 3.2)	72.7	5.62 (d, 3.2)	72.7	5.63 (d, 3.5)	71.4
12	5.73 (d, 3.2)	72.8	5.73 (d, 3.2)	73.0	5.46 (d, 3.5)	72.1
13		41.6		41.6		41.5
14	3.04 (dd, 11.8, 8.1)	44.2	3.06 (dd, 11.9, 7.7)	44.3	3.22 (dd, 12.0, 7.6)	43.8
15a	1.93 (dd, 11.8, 11.8)	31.6	1.85 (dd, 11.9, 11.5)	32.1	1.90 (dd, 12.0, 11.6)	32.1
15b	2.49 (dd, 11.8, 8.1)		2.56 (dd, 11.5, 7.7)		2.58 (dd, 11.6, 7.6)	
17	6.20 (s)	71.1	6.12 (s)	71.4	6.08 (s)	71.4
18	0.94 (s, 3H)	18.7	0.91 (s, 3H)	19.1	0.92 (s, 3H)	19.1
19a	1.25 (s, 3H)	16.8	1.25 (s, 3H)	17.0	4.17 (d, 12.5)	69.4
19b					5.04 (d, 12.5)	
20		122.1		122.4		122.4
21	7.68 (br s)	140.7	7.65 (br s)	140.4	7.48 (br s)	140.2
22	6.54 (d, 1.1)	109.5	6.50 (d, 1.1)	109.6	6.40 (d 1.1)	109.5
23	7.39 (t-like, 1.5)	143.3	7.38 (t-like, 1.5)	143.2	7.38 (t-like, 1.5)	143.2
28	0.93 (s, 3H)	16.6	0.91 (s, 3H)	16.7	0.90 (s, 3H)	15.1
$29_{pro\text{-}R}$	1.90 (d, 10.0)	41.0	1.83 (d, 10.0)	41.4	2.02 (d, 11.6)	38.8
$29_{pro\text{-}S}$	2.21 (m)[a]		2.19 (m)[a]		2.06 (m)[a]	
30	4.17 (s)	71.6	4.60 (s)	70.5	4.62 (s)	70.5
1′		115.2		114.8		115.3
2′	2.24 (m)[a]	31.2	2.22 (m)[a]	31.5	2.32 (m)[a]	31.4
3′	1.09 (d, 6.9, 3H)	17.7	1.06 (d, 7.0, 3H)	17.8	1.07 (d, 6.9, 3H)	17.8
4′	1.09 (d, 6.9, 3H)	17.0	1.09 (d, 6.8, 3H)	16.8	1.09 (d, 7.1, 3H)	16.7
7-OCH_3	3.69 (s, 3H)	52.5	3.68 (s, 3H)	52.5		
1-OH			4.73 (s)		4.87 (s)	
2-OAc			2.08 (s, 3H)	169.6, 20.4	2.11 (s, 3H)	170.9, 20.6
3-OAc		169.7		169.2		169.1
	2.38 (s, 3H)	21.1	2.45 (s, 3H)	21.0	2.48 (s, 3H)	20.9
6-OAc		169.9		169.8		
	2.19 (s, 3H)	21.1	2.21 (s, 3H)	21.1		
11-OAc		169.8		169.6		169.9
	2.02 (s, 3H)	21.4	2.02 (s, 3H)	21.5	2.05 (s, 3H)	20.6
12-OAc		169.3		169.3		169.3
	2.09 (s, 3H)	20.5	2.09 (s, 3H)	20.5	2.12 (s, 3H)	21.0
17-OAc		168.9		168.7		168.6
	2.11 (s, 3H)	20.7	2.10 (s, 3H)	21.0	2.07 (s, 3H)	20.6

[a] Signal pattern unclear due to overlapping.

+ Na]$^+$ (calcd 885.3152). Analysis of the ^{1}H and ^{13}C NMR data of **2** showed that it was likely to be an acetyl derivative of **1**. The only difference was the C-2 signal (δ_C 74.0) and H-3 (δ_H 5.08) of **1** downfield shifted severely to δ_C 82.4 and δ_H 5.17 of **2** (Table 1), which suggested the substitution of a 2-OAc in **2**. The relative configuration was determined to be the same as **1** by the NOESY spectrum.

Chukvelutin C (**3**)[11] was isolated as white amorphous powder with the molecular formula $C_{39}H_{48}O_{17}$ as determined by the HRESIMS ion at *m*/*z* 811.2783 [M + Na]$^+$ (calcd 811.2784). The IR absorption bands at 3429 and 1751 cm^{-1} suggested the presence of hydroxyl and ester groups. The ^{1}H and ^{13}C NMR data (Table 1) and the information from the subsequent 2D NMR studies (HMBC, HSQC, and NOESY) of **3** indicated the presence of an isopropyl, a β-substituted furanyl ring, and five acetoxyls. The data from decouplings and the subsequent 2D NMR suggested that **3** was also a 16-norphragmalin limonoid with the same basic skeleton as **1**. The obvious difference was the presence of two oxygenated methylene protons at δ_H 4.17 and 5.04 (each

d, $J = 12.5$ Hz) corresponding to a carbon at δ_C 69.4 (C-19) in HSQC. They showed HMBC correlations (Figure 2)

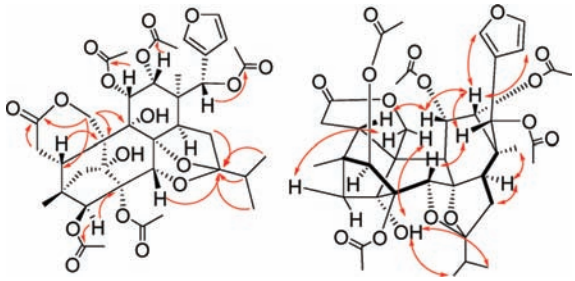

Figure 2. Selected HMBC (→) and NOE (⟷) correlations of **3**.

with carbons at δ_C 52.4 (C-10), 75.3 (C-9), 40.6 (C-5), and 172.6 (C-7), which suggested that the 19-methyl had been oxygenated, forming a six-membered lactone ring with a carbonyl (C-7).[5b,12] The stereochemistry of **3** was elucidated by the NOESY correlations (Figure 2) and indicated that all of the asymmetric carbons had configurations the same as those of **1**. Thus, the structure of **3** was established as shown.

The biosynthetic origin of **1**−**3** (Scheme 1) was proposed to be the phragmalin-type limonoid (**a**) with a 1,8,9-*ortho*-acetate and an isobutyryl at C-30.[1a] The important intermediate (**b**) was produced by insertion of an isobutyryl group to C-15 from C-30 through a Claisen reaction and the cleavage of C-16/C-17 δ-lactone.[1a,3a] Decarboxylation and de-ortho-acetation of it yielded another intermediate (**c**), which, after a series of ketal formation and esterification, gave **1**−**3**, respectively.

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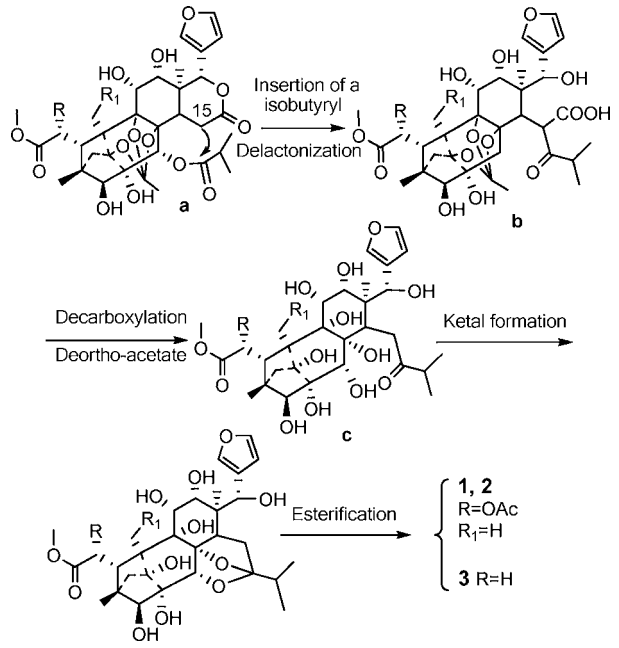
Scheme 1. Plausible Biosynthetic Origin of **1**−**3**



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Supporting Information Available: Experimental procedures; IR, ESIMS, HRESIMS, and 1D and 2D NMR spectra of Chukvelutins A−C (**1**−**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

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