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Chuktabrins A and B, Two Novel Limonoids from the Twigs and Leaves of *Chukrasia tabularis*

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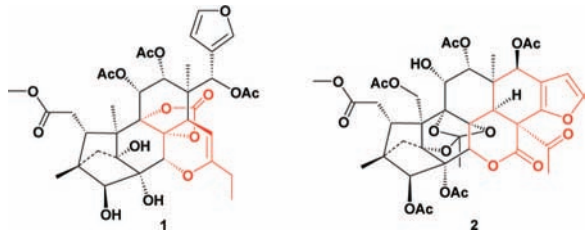
ABSTRACT



Two novel limonoids, chuktabrin A (1), featuring the unique motifs of a 1,3-dioxolan-2-one and a 3,4-dihydro-2*H*-pyran, and chuktabrin B (2), possessing an unprecedented polycyclic skeleton, were isolated from *Chukrasia tabularis*. The structures of 1 and 2 bearing a biosynthetically extended C3 and C2 unit at C-15, respectively, were elucidated on the basis of spectroscopic data, and that of 1 was confirmed by a single-crystal X-ray diffraction.

Plants of the Maliaceae family are a well-known source of structurally diverse limonoids with a wide range of bioactivities, such as insect antifeeding and antimalarial.[1] The fascinating structural features and significant biological activities of these limonoids have prompted continuous endeavors to study this plant family.[2]

Chukrasia tabularis A. Juss. (Maliaceae), a timber tree, mainly grows in the tropical areas of Asia, such as India, Malaysia, and southern China.[3] This plant has been traditionally applied for many medical purposes,[4] and demonstrated to exhibit antimicrobial activity.[5] Previous chemical studies have reported a number of phragmalin limonoids from this plant.[6] In our efforts to attain novel metabolites from *Chukrasia*

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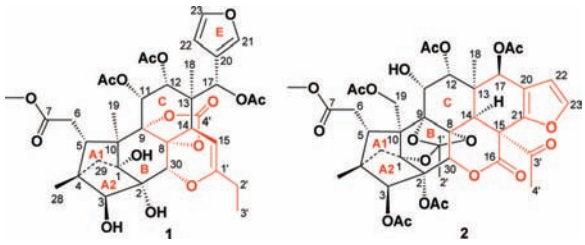
species,[7] two limonoids, chuktabrins A (**1**) and B (**2**), were further isolated from the ethanolic extract of the twigs and leaves of *C. tabularis* which were collected from Xishuangbanna of China. Chuktabrin A (**1**) featured an unprecedented 1,3-dioxolan-2-one and a 3,4-dihydro-2*H*-pyran formed via an ether bond between C-30 and C-1′ in the biosynthetically extended C3 unit at C-15. Chuktabrin B (**2**) possessed an unprecedented polycyclic skeleton with a biosynthetically extended C2 unit (acetyl) at C-15. The structures of **1** and **2** were elucidated on the basis of spectroscopic data, especially 2D NMR techniques, and that of **1** was finally confirmed by a single-crystal X-ray diffraction. The biosynthetic origin of compounds **1** and **2** was rationalized to be the phragmalin-type limonoids. We present herein the isolation and structural elucidation of two novel limonoids (**1** and **2**).



Chuktabrin A (**1**), obtained as a colorless crystal, has a molecular formula of $C_{36}H_{44}O_{16}$ as determined by the HREIMS ion at *m*/*z* 732.2608 $[M]^+$ (calcd 732.2629) with 15 degrees of unsaturation. The IR absorptions implied the presence of hydroxyl(s) (3448 cm^{-1}) and ester group(s) (1751 cm^{-1}). In accordance with the molecular formula, 36 carbon resonances were resolved in the ^{13}C NMR spectrum (Table 1), and were further classified by DEPT experiments into the categories of 8 methyls, 3 methylenes, 11 methines (5 oxygenated and 4 olefinic ones), and 14 quaternary carbons (4 ester carbonyls and 2 olefinic ones). In addition, three tertiary methyls (δ_H 1.37, 1.35, and 0.91, each 3H, s), one primary methyl (δ_H 1.12, 3H, t, $J = 7.5$ Hz), one methoxyl (δ_H 3.72, 3H, s; δ_C 52.4), three acetyls, and one β-furyl ring were distinguished by analysis of the NMR data (Table 1). Furthermore, two proton resonances at δ_H 4.41 and 3.43 (each 1H, s), which did not show any correlation with all the carbons in the HSQC spectrum, were only attributable to hydroxyls.

Comprehensive analysis of the 1D and 2D NMR spectra of **1**, especially HMBC (Figure 1), allowed the setting up of A1-, A2-, B-, C-, and E-rings, and the C-6-C-7 appendage of a phragmalin-type limonoid.[6,8] However, the NMR spectra also revealed that the characteristic D-ring of a six-membered lactone and the very common orthoacetate of a phragmalin-type limonoid were absent, but a biosynthetically extended C3 unit (C-1′ to C-3′) attached to C-15 emerged from the HMBC correlations of C-1′/H-14, H-15, H_2-2′ and Me-3′, and H-15/C-2′, suggesting that compound **1** featured a D-ring demolished 16-norphragmalin-type limonoid with a biosynthetically extended C3 unit at C-15.[7a]

In the HMBC spectrum (Figure 1), two hydroxyls resonating at δ 3.43 and 4.41 were assigned to C-1 and C-2 by the HMBC correlations from 1-O*H* to C-1 (δ 81.4) and C-10 (δ 49.5), and from 2-O*H* to C-2 (δ 73.8) and C-30 (δ 65.5), respectively; three acetoxyls were placed at C-11 (δ 68.9), C-12 (δ 71.4), and C-17 (δ 66.9) on the basis of HMBC correlations from H-11, H-12, and H-17 to each corresponding acetyl carbonyl, respectively. The only methoxyl was attached to C-7 (δ 173.0) by the HMBC correlation between O*Me* and C-7. Although no direct HMBC correlation was observed between H-30 and C-1′, the oxygenated quaternary sp^2 carbon resonance of C-1′ at δ 152.4 and the relatively upfield-resonated tertiary oxygenated C-30 at δ 65.5 implied that a 3,4-dihydro-2*H*-pyran ring was likely formed between C-30 and C-1′ via an ether bond.[9] The remaining single quaternary sp^2 carbon resonance at δ 152.4 was only attributable to the presence of a cyclic carbonate being most likely a 1,3-dioxolan-2-one[10] (for a 1,3-dioxan-2-one, the chemical shift of the carbonate carbonyl is normally around δ 149[11]). The oxygenated quaternary carbons C-8 at δ 82.3 and C-9 at δ 85.0 in an ortho-position enabled us to readily dock the 1,3-dioxolan-2-one. The only leftover hydroxyl was easily assigned to C-3 at δ 87.4 as judged from the mutual HMBC correlations of H-3/C-2 and C-5, and C-3/Me-28 and H-30. The planar structure of **1** was therefore assigned.

The relative configuration of **1** was unambiguously established by a single-crystal X-ray diffraction (Figure 1), which was consistent with that of **1** in the solution as fixed by the ROESY spectrum (see the Supporting Information, S7).

Compound **1** featured a D-ring demolished 16-norphragmalin-type limonoid with an unprecedented 1,3-dioxolan-2-one and a 3,4-dihydro-2*H*-pyran formed via an ether bond between C-30 and C-1′ in the biosynthetically extended C3 unit at C-15 (red part).

Chuktabrin B (**2**), a white amorphous powder, was assigned the molecular formula of $C_{41}H_{46}O_{20}$ on the basis of HREIMS at *m*/*z* 858.2604 $[M]^+$ (calcd 858.2582). The strong IR absorption at 1745 cm^{-1} indicated the presence of ester carbonyl groups. Besides the characteristic features of one methoxyl, five acetoxyls, an orthoacetate, a hydroxyl at δ_H 2.61 (s, by no HSQC correlation with any carbons), and an acetyl (δ_H 2.64, s, 3H; δ_C 29.0 and 203.0), one α,β-disubstituted furyl ring [δ_H 6.40 (d, $J = 1.9$ Hz) and 7.39 (d, $J = 1.9$ Hz); δ_C 118.8, 146.3, 110.7, and 144.3] was distinguished by analysis of its 1D and 2D NMR data (Table 1 and Figure 2). The remaining 22 carbons of **2** were resolved

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Table 1. ^{1}H and ^{13}C NMR Data of **1** and **2** (in $CDCl_3$)[a]

	1		**2**	
no.	δ_C	δ_H (multi, J in Hz)	δ_C	δ_H (multi, J in Hz)
1	81.4		84.5	
2	73.8		83.2	
3	87.4	3.67 (s)	81.9	5.44 (s)
4	43.4		46.0	
5	37.9	2.53 (br d,11.6)	35.6	2.95 (br d,10.9)
6a	32.4	2.36(dd,17.1,11.6)	32.6	2.68 (br d,17.4)
6b		2.00 (br d,17.1)		2.50 (dd,17.4,10.9)
7	173.0		171.8	
8	82.3		81.2	
9	85.0		83.5	
10	49.5		47.9	
11	68.9	5.16 (d, 3.3)	70.3	5.00 (dd, 2.1, 0.7)
12	71.4	4.89 (d, 3.3)	69.3	5.12(brs)
13	43.6		40.4	
14	44.3	2.77 (d, 4.6)	47.9	3.32 (s)
15	92.3	4.72 (d, 4.6)	56.8	
16			165.5	
17	66.9	6.09 (s)	67.6	5.66 (s)
18	17.8	1.35 (s, 3H)	25.4	1.41 (s, 3H)
19	13.8	1.37 (s, 3H)	66.3	a 4.58 (d,11.6)
				b 4.21 (d,11.6)
20	118.9		118.8	
21	144.2	7.90 (br s)	146.3	
22	109.0	6.42 (br t, 0.8)	110.7	6.40 (d, 1.9)
23	143.4	7.39 (br t, 1.7)	144.3	7.39 (d, 1.9)
28	14.6	0.91 (s, 3H)	14.2	0.96 (s, 3H)
29a	43.0	2.09 (d,11.1)	40.0	1.86 (d,11.9)
29b		1.47 (d,11.1)		1.82 (d,11.9)
30	65.5	4.87 (s)	75.3	5.83 (s)
1′	152.4		119.5	
2′	26.3	2.20 (q, 7.5, 2H)	20.5	1.69 (s, 3H)
3′	10.8	1.12 (t, 7.5, 3H)	203.0	
4′	152.4		29.0	2.64 (s, 3H)
7-OMe	52.4	3.72 (s, 3H)	51.8	3.68 (s, 3H)
hydroxyl	1-OH: 3.43 (s)		11-OH: 2.61 (s)	
	2-OH: 4.41 (s)			
	3-OH: not obsd			
acetoxyl	11-OAc: δ_H 1.96 (s, 3H), δ_C 21.1, 169.1		2-OAc: δ_H 2.12 (s, 3H), δ_C 21.0, 169.8	
	12-OAc: δ_H 2.10 (s, 3H), δ_C 20.6, 170.2		3-OAc: δ_H 2.19 (s, 3H), δ_C 21.7, 170.2	
	17-OAc: δ_H 1.99 (s, 3H), δ_C 20.8, 169.1		12-OAc: δ_H 2.13 (s, 3H), δ_C 20.9, 170.5	
			17-OAc: δ_H 2.29 (s, 3H), δ_C 21.7, 170.5	
			19-OAc: δ_H 2.14 (s, 3H), δ_C 21.7, 169.7	

[a] Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C).

in the ^{1}H and ^{13}C NMR spectra (with DEPT) as two ester carbonyls (δ_C 165.5 and 171.8), eight quaternary carbons (four oxygenated), seven methines (five oxygenated), three methylenes (one oxygenated), and two tertiary methyls [δ_H 1.41 (s) and 0.96 (s); δ_C 25.4 and 14.2]. Thirteen out of the 19 double bond equivalents were occupied by the aforesaid functionalities, and the remaining ones required compound **2** possessing six other rings in the core.

The 1D and 2D NMR spectra of **2** revealed that it also shared the typical skeleton of A1-, A2-, B-, and C-rings, and the C-6-C-7 side chain of phragmalin-type limonoids. Two methyls were assigned to Me-18 and Me-28 by the HMBC correlations of Me-18/C-12, C-13 and C-17, and Me-28/C-3, C-4 and C-29, respectively. An acetoxyl group was attached to C-19 by the HMBC correlation of H_2-19/C-10, C-1 and C-9, and H_2-19/19-OAc. A key methine proton signal at δ_H 3.32 (s) correlating with C-8, C-13, C-17, and C-30 was recognized to be H-14. In consequence, the C-15 quaternary carbon at δ_C 56.8 was fixed by the correlation of H-14/C-15, and the C-16, C-21, and C-3′ were then attached to C-15 by the HMBC correlations of H-14/C-16, C-21 and C-3′, and Me-4′/C-15. In addition, a unique linkage between C-16 and C-30 via an ester bond to form a δ-lactone ring was constructed by the key HMBC correlation of H-30/C-16. The only hydroxyl was attached to C-11 by the HMBC correlations of 11-OH/C-11 and C-12. Furthermore, the

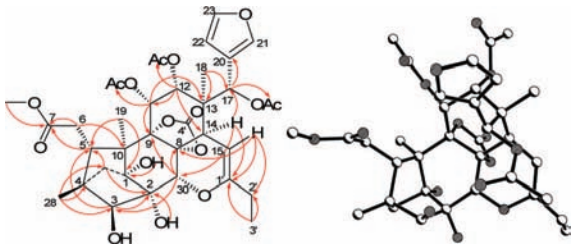


Figure 1. Key HMBC correlations (red arrows) and X-ray structure of **1**.

methoxyl at C-7 and the three acetoxyls at C-3, C-12, and C-17 were also assignable by HMBC correlations (Figure 2). Although there were no direct HMBC correlations available, an acetoxyl at C-2 and one 1,8,9-orthoacetate were tentatively assigned in comparison with the same substituted pattern of this type of limonoid reported,[6c,8d] which was supported by the ROESY correlations from 2-OAc to H_2-29 and Me-2′, and from Me-2′ to H-14 and Me-4′ (Figure 2).

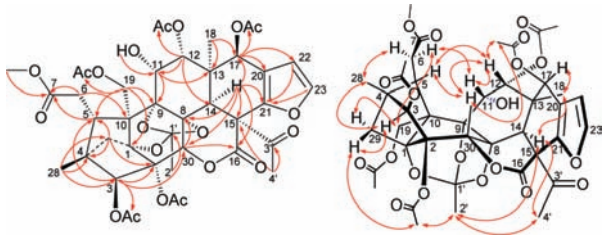
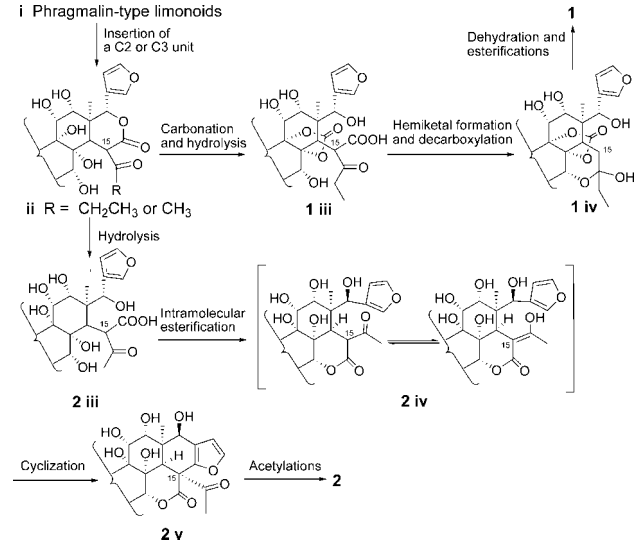


Figure 2. Key HMBC (red arrows) and ROESY (red double-headed arrows) correlations of **2**.

The relative configuration of **2** was established by the ROESY spectrum (Figure 2). The correlations of Me-2′/H-14, Me-2′/Me-4′, and Me-2′/2-OAc indicated that they were cofacial, and were randomly assigned as the α-configuration. In consequence, the Me-18 and H-17 were α-oriented as deduced from the correlations of H-14/Me-18 and H-17/Me-18. Furthermore, the ROESY correlations of H-30/17-OAc and H-5, and H-12/H-5 and 17-OAc, especially the significant correlation of H-12/H-30, revealed that they were *β*-oriented, and also indicated that the C-ring took a boat-conformation. The H-11 correlated with both H-12 and H-6a was then fixed as the *β*-configuration. The ROESY correlations of H-3/H-29b, H-29a/H_2-19, and H-19b/H-6b indicated that H-3, CH_2-29, CH_2-19, and CH_2-6 were in the α-orientation. The relative configuration of **2** assigned by the ROESY spectrum was biosynthetically consistent with those of phragmalin-type analogues.

Compound **2** possessed an unprecedented polycyclic skeleton featuring the structural merits of a 4,5,6,7-tetrahydrobenzofuran formed via a cyclization reaction between C-15 and C-21,[12] a *δ*-lactone furnished between C-16 and C-30, and a biosynthetically extended C2 unit at C-15 (red part).

Scheme 1. The Plausible Biosynthetic Origin of **1** and **2**



The biosynthetic origin of **1** and **2** (Scheme 1) was proposed to be the phragmalin-type limonoid (**i**).[1c,8b] Insertion of a C2 or C3 unit, e.g., via acetyl-CoA or propionyl-CoA through a Claisen reaction,[13] would produce a common intermediate **ii** for **1** and **2**. The intermediate **ii** when undergoing the hydrolysis and carbonation processes would yield **1iii**, which then would be transformed into **1iv** via a hemiketal formation and decarboxylation. The intermediate **1iv** would be finally converted into **1** by dehydration and esterifications. Simple hydrolysis of the key intermediate **ii** would give **2iii**, which would undergo an intramolecular esterification to produce **2iv**. The C-15 position of **2iv** is highly activated by two adjacent carbonyl groups, and an enol-form of **2iv** would be easily produced in equilibrium. The enolate of **2iv** would be further transformed to the crucial intermediate **2v** via a cyclization reaction as reported.[12] Acetylations of **2v** would finally yield **2**.

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Supporting Information Available: Experimental procedures and physical and spectroscopic data of chuktabrins A (**1**) and B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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