New Phragmalin-Type Limonoid Orthoesters from the Bark of *Chukrasia tabularis* var. *velutina*

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Three new phragmalin-type limonoid orthoesters, velutabularins K – M (**1** – **3**) and seven structurally related known compounds were isolated from the bark of *Chukrasia tabularis* var. *velutina*. The structures of these compounds were elucidated by spectroscopic analysis. The structure of **1** was confirmed by single crystal X-ray diffraction. In addition, the brine shrimp lethality of compounds **1**, **3**, and the known compounds was evaluated.

Introduction. – Limonoids are well known for their structural diversity and extensive bio-activities [1]. Phragmalin-type limonoids are characterized by *A* and *B* rings consisting of tricyclo[3.3.$1^{2,10}$.$1^{1,4}$]decane or tricyclo[4.2.$1^{10,30}$.$1^{1,4}$]decane [2] and the presence of ester groups generally located at C(1), C(8), C(9), or C(8), C(9), C(11), or C(8), C(9), C(14), or C(8), C(9), C(30) [3]. This type of limonoids is only found in the Meliaceae family [1][4][5]. *Chukrasia tabularis* A. JUSS. var. *velutina* (WALL.) KING is a timber tree that is distributed mainly in tropical areas of Asia, including India and southern China [6]. The stem bark of this plant has been applied as traditional astringent, anti-influenza, and antidiarrheal agents [6]. Previous research on this plant mainly reported numerous phragmalin limonoids with different skeletons including 16-norphragmalins, phragmalin orthoesters with appendages at C(15), normal phragmalins, and their orthoester derivatives [2][7][8]. In the present investigation on this plant, three new phragmalin-type limonoid orthoesters, velutabularins K – M (**1** – **3**; *Fig. 1*) and seven known compounds (tabularisins A and B [2], tabularisin E [8], tabularisin H [8], chuktabularin A [9], chuktabularin F [10], and chuktabularin G [10]) were isolated from the bark of *C. tabularis* var. *velutina*. The structures of the new compounds were established on the basis of HR-ESI-MS, IR, and NMR (^{1}H-NMR, ^{13}C-NMR, HSQC, HMBC, COSY, and ROESY) spectra. Furthermore, the structure of compound **1** was confirmed by single crystal X-ray diffraction analysis. The brine shrimp lethality of compounds **1**, **3**, and the known compounds was also evaluated.

Results and Discussion. – Velutabularin K (**1**) was isolated as colorless powder. The molecular formula was established by positive HR-ESI-MS at *m*/*z* 811.2633 [M + Na]$^+$ as $C_{38}H_{44}O_{18}$ (calc. 811.2425, $C_{38}H_{44}NaO_{18}^+$), indicating 17 degrees of unsaturation. The IR absorption bands at 1758 and 3434 cm^{-1} suggested the presence of CO and OH groups. The ^{1}H- and ^{13}C-NMR (with DEPT) spectra of **1** obviously suggested the

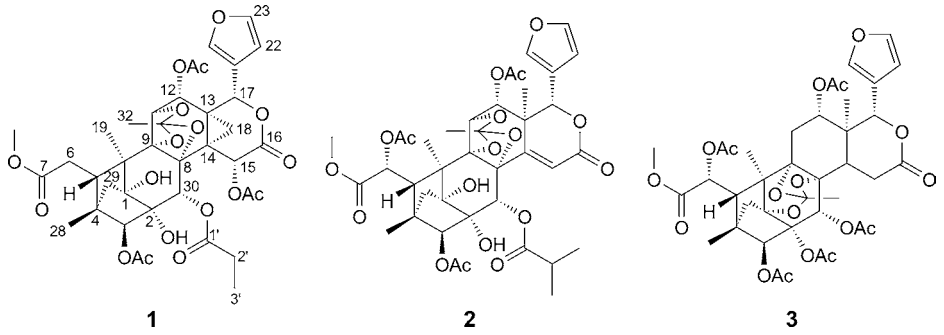

Fig. 1. *Chemical structures of compounds* **1**–**3**

presence of a β-substituted furyl ring (δ(H) 7.47 (*s*), 6.49 (*d*, $J = 1.5$), 7.39 (*t*, $J = 1.5$); δ(C) 121.9, 142.0, 109.6, 143.3) [1], a characteristic orthoacetate (δ(H) 1.65 (*s*, 3 H); δ(C) 16.2, 119.7) [1], and two OH groups (δ(H) 2.83 (*s*), 3.39 (*s*)). Extensive analysis of the NMR spectra data (*Table*) of **1** indicated the presence of a propionyl group, a MeO, three AcO, two Me, three CH_2, seven CH (six of them were O-bearing) groups, eight quaternary C-atoms (four of them were O-bearing), as well as two ester CO groups. The aforementioned data suggested that **1** is a phragmalin-type limonoid [2]. Comparison of NMR data of **1** with those of tabularisin A [2] showed high similarity. The differences between the two compounds were that there was a propionyl group located at C(30) and no substitution at C(6) in **1**, instead of isobutyryl and AcO at C(30) and C(6) in tabularisin A, respectively. These conclusions were supported by the ^{1}H,^{1}H-COSY correlations between H_a–C(6) (δ(H) 2.65 (*m*)), H_b–C(6) (δ(H) 2.45 (*d*, $J = 12.2$)), and H–C(5) (δ(H) 2.57 (*d*, $J = 12.2$)), and between Me(3′) (δ(H) 1.15 (*t*, $J = 7.5$, 3 H)) and H_a–C(2′) (δ(H) 2.34 (*m*)), and HMB correlations from H–C(30) (δ(H) 5.39 (*s*)), H_b–C(2′) (δ(H) 1.15 (*t*, $J = 7.5$)), and H–C(3′) to C(1′) (δ(C) 170.9). Nevertheless, there was no HMB correlations from H–C(11) to C(31) to support the presence of a C(8),C(9),C(11)-orthoacetate (*Fig. 2*). The full structure of **1** was definitively established by a single-crystal X-ray diffraction experiment (*Fig. 3*). Finally, the structure of compound **1** was established as depicted.

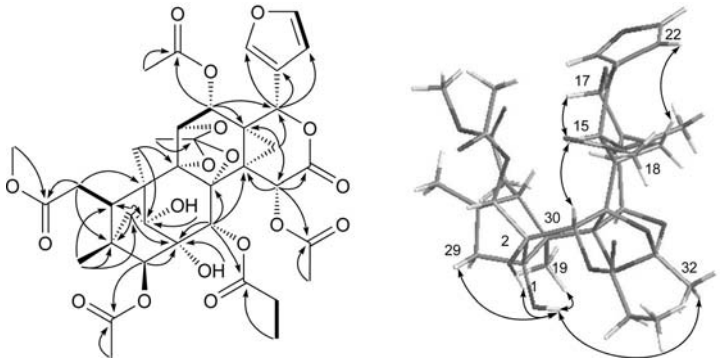

Fig. 2. *HMBC* (→), *COSY* (▬), *and ROESY* (↔) *correlations of* **1**

Table. *[1]H- and [13]C-NMR Data of Compounds* **1**–**3**

Position	**1**		**2**		**3**	
	δ(H)[a])	δ(C)[b])	δ(H)[c])	δ(C)[d])	δ(H)[a])	δ(C)[b])
1		82.8		83.2		86.2
2		76.3		75.8		86.0
3	5.51 (*s*)	85.6	5.17 (*s*)	85.5	5.08 (*s*)	81.7
4		43.9		44.5		46.5
5	2.57 (*d*, *J* = 12.2)	38.0	2.63 (*s*)	43.9	3.33 (*m*)	39.6
6	2.65 (*m*, H_a[e])), 2.45 (*d*, *J* = 12.2, H_b)	32.9	6.13 (*s*)	70.8	6.10 (*s*)	71.7
7		173.7		171.6		170.0
8		78.2		77.1		84.9
9		90.4		90.7		85.3
10		44.7		44.6		47.0
11	4.17 (*d*, *J* = 3.6)	74.8	4.40 (*d*, *J* = 1.9)	75.7	2.39 (*dd*, *J* = 3.4, 13.8, H_a), 1.80 (*t*, *J* = 13.8, H_b)	32.0
12	5.14 (*d*-like, *J* = 3.6)	66.4	4.96 (*d*, *J* = 1.9)	68.3	4.58 (*d*, *J* = 12.7)	69.2
13		30.9		42.2		39.0
14		30.6		155.9	2.25 (*d*, *J* = 10.5)	44.4
15	7.22 (*s*)	69.6	6.77 (*s*)	123.0	3.33 (*m*, H_a), 2.80 (*dd*, *J* = 10.7, 20.3, H_b)	27.2
16		166.9		163.9		170.1
17	6.43 (*s*)	71.3	5.81 (*s*)	78.7	5.56 (*s*)	77.2
18	2.65 (*m*, , H_a[e])), 1.44 (*d*, *J* = 5.9, H_b)	18.5	1.80 (*s*)	18.0	1.20 (*s*)	14.3
19	1.31 (*s*)	14.5	1.38 (*s*)	14.7	1.22 (*s*)	14.4
20		121.9		120.8		121.1
21	7.47 (*s*)	142.0	7.51 (br.*s*)	142.4	7.47 (*s*)	141.3
22	6.49 (*d*, *J* = 1.5)	109.6	6.62 (*d*, *J* = 1.2)	110.5	6.43 (*s*)	110.1
23	7.39 (*t*, *J* = 1.5)	143.3	7.43 (*t*, *J* = 1.6)	143.2	7.39 (*s*)	143.5
28	0.82 (*s*)	14.1	1.00 (*s*)	15.4	1.09 (*s*)	16.0
29	1.91 (*d*, *J* = 1.3, H_a), 2.29 (*d*, *J* = 1.3, H_b)	38.7	1.96 (*d*, *J* = 11.2, H_a), 2.18 (*d*, *J* = 11.2, H_b)	40.2	2.13 (*d*, *J* = 11.3, H_a), 1.71 (*d*, *J* = 11.3, H_b)	41.0

Table (cont.)

Position	**1**		**2**		**3**	
	δ(H)[a])	δ(C)[b])	δ(H)[c])	δ(C)[d])	δ(H)[a])	δ(C)[b])
30	5.39 (*s*)	70.5	5.69 (*s*)	67.1	6.31 (*s*)	69.3
31		119.7		119.7		119.5
32	1.65 (*s*)	16.2	1.72 (*s*)	16.1	1.66 (*s*)	21.3
1′		170.9		175.1		
2′	2.34 (*m*), 1.15 (*t*, *J* = 7.5)	27.2	2.61 (*dd*, *J* = 6.9, 13.6)	34.1		
3′	1.15 (*t*, *J* = 7.5)	9.0	1.28 (*d*, *J* = 6.9)	19.8		
4′			1.25 (*d*, *J* = 6.9)	18.8		
7-MeO	3.76 (*s*)	52.4	3.79 (*s*)	53.7	3.78 (*s*)	53.5
2-AcO					1.62 (*s*)	169.7, 20.5
3-AcO	2.20 (*s*)	169.1, 21.0	2.06 (*s*)	169.8, 21.8	2.28 (*s*)	170.6, 21.6
6-AcO			2.24 (*s*)	169.4, 21.1	2.17 (*s*)	170.1, 21.5
12-AcO	1.66 (*s*)	170.6, 19.7	1.66 (*s*)	171.1, 20.0	2.16 (*s*)	170.7, 22.1
15-AcO	2.36 (*s*)	172.2, 21.4				
30-AcO					1.94 (*s*)	169.0, 21.9
1-OH	2.83 (*s*)		2.87 (*s*)			
2-OH	3.39 (*s*)		3.34 (*s*)			

[a]) Recorded at 400 MHz in $CDCl_3$. [b]) Recorded at 100 MHz in $CDCl_3$. [c]) Recorded at 600 MHz in $CDCl_3$. [d]) Recorded at 125 MHz in $CDCl_3$. [e]) Signal pattern unclear due to overlapping.

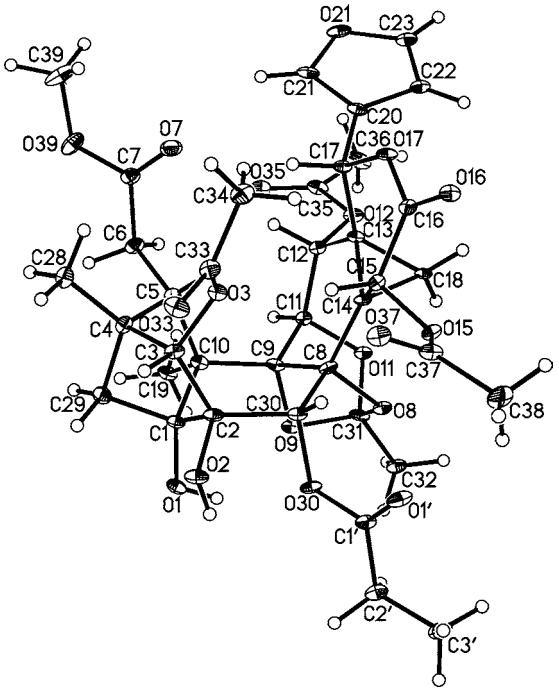

Fig. 3. *ORTEP Diagram of the X-ray crystallographic structure of* **1**

Velutabularin L (**2**), obtained as colorless powder, has the molecular formula $C_{39}H_{46}O_{18}$ which was determined by HR-ESI-MS *m*/*z* 825.2573 $[M+Na]^+$ (calc. 825.2582, $C_{39}H_{46}NaO_{18}^+$). The IR absorption bands at 3436, 1746, and 1629 cm^{-1} indicated the presence of OH, CO, and α,β-unsaturated ester CO groups, respectively. The NMR spectra of **2** revealed the presence of a β-substituted furyl ring (δ(H) 7.51 (br. *s*), 6.62 (*d*, $J=1.2$), 7.43 (*t*, $J=1.6$); δ(C) 120.8, 142.4, 110.5, 143.2), a typical orthoacetate (δ(H) 1.72 (*s*, 3 H); δ(C) 16.1, 119.7), an isobutyryl, a MeO, three AcO, and two OH groups. These signals suggested that compound **2** is a limonoid. Comparing the NMR data of **2** with those of tabularisin A [2] indicated that these two compound shared a similar structure skeleton. However, compound **2** possessed a Me group at C(18) and an α,β-unsaturated δ-lactone ring. In addition, there was no substitution at C(15) in **2**. These assignments were verified by the HMB correlations from H–C(15) (δ(H) 6.77 (*s*)) to C(13) (δ(C) 42.2), C(14) (δ(C) 155.9), and C(16) (δ(C) 163.9), H–C(17) (δ(H) 5.81 (*s*)) to C(14), and Me(18) (δ(H) 1.80 (*s*, 3 H)) to C(12) (δ(C) 68.3), C(13), C(14), and C(17) (δ(C) 78.7), Therefore, the structure of **2** was elucidated.

Velutabularin M (**3**) was obtained as colorless, amorphous powder. The molecular formula $C_{39}H_{46}O_{18}$ was established by HR-ESI-MS (*m*/*z* 825.2573 $[M+Na]^+$, calc. 825.2582, $C_{39}H_{46}NaO_{18}^+$). Analysis of the NMR spectra indicated that **3** is also a limonoid with a similar structure to tabularisin N [1]; compound **3** differs from tabularisin N mainly by the presence of each an AcO group at C(2) and C(6), as well as no substitution at C(11) and C(19). This was confirmed by the HMB correlations from

H–C(6) (δ(H) 6.10 (*s*)) to δ(C) 170.1, ^{1}H,^{1}H-COSY correlations between H–C(12) (δ(H) 4.58 (*d*, $J = 12.7$)) and CH_2(11) (δ(H) 2.39 (*dd*, $J = 13.8, 3.4$)), 1.80 (*t*, $J = 13.8$), each 1 H). According to the NMR data, compound **3** bears five AcO groups. Besides the AcO group at C(6), AcO groups at C(3), C(12), and C(30) could be established by the HMB correlations from H–C(3) (δ(H) 5.08 (*s*)) to δ(C) 170.6, H–C(12) to δ(C) 170.7, and H–C(30) (δ(H) 6.31 (*s*)) to δ(C) 169.0, respectively. In comparison with the NMR data of similar compounds, C(2) was obviously shifted downfield to δ(C) 86.0 [4]. In addition, a ROESY correlation was observed between δ(H) 1.62 (*s*, Me(2-AcO), 3 H) and Me(19) (δ(H) 1.22 (*s*, 3 H)). This confirmed that the remaining AcO group was located at C(2) and indicated its α orientation [4][9]. Consequently, the structure of **3** was assigned.

Brine Shrimp Lethality. Compounds **1**, **3**, and the seven known compounds were tested for their brine shrimp lethality [11] at the concentrations of 100, 50, and 10 ppm in DMSO. Toosendanin [12] was used as positive control and showed 100% lethality at the concentrations of 10 ppm, and a LC_{50} value of 4.03 μM. All tested compounds were inactive toward brine shrimp at the concentrations of 10 and 50 ppm, while they showed brine shrimp lethality at the concentration of 100 ppm. The percentages of lethality of **1**, **3**, tabularisin A, tabularisin B, tabularisin E, tabularisin H, chuktabularin A, chuktabularin F, and chuktabularin G were 47, 16, 24, 33, 20, 18, 25, 19, and 61%, respectively.

Cytotoxicity Assay. The *in vitro* cytotoxicity of the seven known compounds against HL-60, SMMC-7721, A-549, MCF-7, and SW480 cell lines was determined through the MTT method [13]. None of these compounds showed obvious cytotoxicity.

Experimental Part

General. TLC plates were precoated with silica gel GF_{254} and HF_{254} (*Qingdao Haiyang Chemical Plant*, Qingdao, P. R. China). Semi-prep. HPLC was performed on an *Agilent* column (5 μm, i.d. 9.4 × 250 mm, *XDB-C8*, *Agilent*, USA), eluted with MeOH/H_2O or MeCN/H_2O (flow rate: 6.0 or 5.0 ml/min, detection: UV 230 nm or 210 nm) at 25°. Column chromatography was performed over silica gel (90–150 μm; *Qingdao Marine Chemical Inc.*), *MCI* gel (*CHP20P*, 75–150 μm, *Mitsubishi Chemical Industries Ltd.*), C_{18} reversed-phase silica gel (20–45 μm; *Merck*, Darmstadt, Germany), and *Sephadex LH-20* (40–70 μm; *Amersham Pharmacia Biotech AB*, Uppsala, Sweden). Optical rotations were determined with a *PerkinElmer 241* polarimeter. IR Spectra were recorded on a *Bio-Rad FTS-135* spectrometer with a KBr disk. NMR Spectra were recorded on a *Bruker AM-400* or *Bruker Avance III 600* spectrometer (^{1}H-NMR: 400 or 600 MHz, ^{13}C-NMR: 100 or 150 MHz). EI-MS/ESI-MS and HR-EI-MS/HR-ESI-MS spectra were measured with a *Finnigan MAT 90* instrument and *VG Auto Spec-3000* spectrometer, resp. Single-crystal data were measured on a *Bruker APEX DUO* diffractometer.

Plant Material. The air-dried stem bark of *C. tabularis* var. *velutina* was collected in Xishuangbanna, Yunnan Province, P. R. China, in September, 2010, and identified by Prof. *Xun Gong* of Kunming Institute of Botany, Chinese Academy of Sciences (CAS). A voucher specimen (No. H20101105) was deposited with the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, CAS, Kunming, P. R. China.

Extraction and Purification. The air-dried stem bark of *C. tabularis* var. *velutina* (3.5 kg) was extracted by 95% MeOH three times (4 l × 3, 3 h for each extraction, 45°), and then partitioned by petroleum ether (2.0 l × 3), AcOEt (2.0 l × 3), and BuOH (2.0 l × 3) at 20° resp., to give the AcOEt-soluble fraction *AS* (84.0 g). *AS* was subjected to a SiO_2 column (10 × 30 cm) eluted with $CHCl_3$/AcOEt (9 : 1 (7.5 l), 7 : 3 (7.5 l), 5 : 5 (7.5 l), 1 : 2 (7.5 l)) and MeOH (8.0 l) to afford five fractions (*Frs. 1–5*). *Fr. 3* (25.0 g) was further chromatographed over reversed-phase C_{18} silica gel (3 × 40 cm) eluted with MeOH/

H_2O (5:5 (2.0 l), 6:4 (5.0 l), 6.5:3.5 (4.0 l), 7:3 (3.0 l), 8:2 (2.0 l), 9:1 (2.0 l), 10:0 (2.0 l)) to give three fractions (*A1–A3*). *A2* (20.0 g) was subjected to a SiO_2 column (4 × 30 cm) with $CHCl_3$/acetone (50: 1 (1.5 l), 40:1 (2.5 l), 35:1 (2.5 l), 25:1 (1.0 l)) to give seven fractions (*B1–B7*). *B2* (250 mg) was separated over a SiO_2 column (2 × 20 cm) with $CHCl_3$/acetone (40:1, 350 ml) to give three fractions (*I1–I3*). *I2* (55.0 mg) was separated by semi-prep. HPLC with MeOH/H_2O (6:4; 5 ml/min) to afford tabularisin H (32.0 mg; t_R 23.8 min). *B3* (1.3 g) was subjected by SiO_2 column (3 × 16 cm) with $CHCl_3$/AcOEt (25:1, 600 ml) to give four fractions (*J1–J4*). *J2* (1.04 g) was then chromatographed over *Sephadex LH-20* CC (2 × 100 cm) with MeOH (1.2 l) to afford fractions *K1–K4*. *K2* (150 mg) and *K3* (170 mg) were separated by semi-prep. HPLC with MeOH/H_2O (5 ml/min) to afford tabularisin A (30.8 mg; MeOH/H_2O 6:4, t_R 20.5 min) and tabularisin E (42.0 mg; MeOH/H_2O 7:3, t_R 12.7 min), resp. *J3* (200 mg) was separated by semi-prep. HPLC with MeOH/H_2O (6:4; 5 ml/min) to afford tabularisin B (30.0 mg; t_R 18.3 min) and chuktabularin F (12.0 mg; t_R 26.0 min). *B4* (800 mg) was separated over a SiO_2 column (2 × 20 cm) eluted with $CHCl_3$/AcOEt (8:1, 1.5 l) to give four fractions (*C1–C4*). *C2* (220 mg) was then subjected to *Sephadex LH-20* CC (1.0 × 100 cm) with MeOH (450 ml) to afford four fractions (*D1–D4*). *D2* (25.0 mg) was further purified by semi-prep. HPLC with MeOH/H_2O (6:4; 6 ml/min) to yield compound **1** (8.4 mg; t_R 19.1 min). *B6* (3.4 g) was separated over a SiO_2 column (5 × 33 cm) with $CHCl_3$/AcOEt (5:1 (1.8 l), 4:1 (3.0 l), 3:1 (2.5 l)) to give four fractions (*E1–E4*). *E2* (1.1 g) was further subjected to SiO_2 CC (4 × 25 cm) with $CHCl_3$/acetone (35:1, 1.8 l) to give three fractions (*F1–F3*). *F1* (141.0 mg) was then separated by semi-prep. HPLC with MeOH/H_2O (6:4; 5 ml/min) to give three fractions (*G1–G3*). *G2* (21.7 mg; t_R 11.0 min) was further purified by semi-prep. HPLC with MeCN/H_2O (3.5:6.5; 6 ml/min) to yield compounds **2** (2.4 mg; t_R 45.0 min) and **3** (7.0 mg; t_R 40.0 min). *Fr. 4* (10.0 g) was separated over a SiO_2 column (4 × 30 cm) with $CHCl_3$/MeOH (100:1 (1.2 l), 80:1 (1.4 l), 65:1 (1.4 l), 40:1 (1.5 l)) to give four fractions (*G1–G4*). *G3* (2.6 g) was subjected to *Sephadex LH-20* CC (2 × 150 cm) with $CHCl_3$/MeOH (1:1, 2.5 l) to afford five fractions (*H1–H5*). *H3* (850 mg) was separated over a SiO_2 column (3 × 18 cm) eluted with $CHCl_3$/AcOEt (6:1, 650 ml) to give three fractions (*L1* (20.1 mg, chuktabularin A), *L2* (68.8 mg), and *L3*). *L2* was separated over a SiO_2 column (1 × 16 cm) with $CHCl_3$/AcOEt (6:1, 450 ml) to yield chuktabularin G (7.8 mg).

X-Ray Crystallographic Analysis of **1**. $C_{38}H_{44}O_{18}$, $M_r = 788.73$, crystal size: 0.22 × 0.15 × 0.13 mm, monoclinic, $a = 10.412(6)$ Å, $b = 16.334(10)$ Å, $c = 11.394(7)$ Å, $\alpha = 90.00°$, $\beta = 93.248(9)°$, $\gamma = 90.00°$, $V = 1935(2)$ Å^3, $T = 100(2)$ K, space group *P*21, $Z = 2$, $\mu(\text{Mo}K_\alpha) = 0.108$ mm^{-1}, 19556 reflections measured, 9942 independent reflections ($R_{int} = 0.1602$). The final R_1 values were 0.0922 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2069 ($I > 2\sigma(I)$). The final R_1 values were 0.2375 (all data). The final $wR(F^2)$ values were 0.2846 (all data). The goodness of fit on F^2 was 0.922. *Flack* parameter = 2.3(19).

A colorless crystal of **1** was obtained in MeOH, the intensity data were collected on a *Bruker APEX DUO* diffractometer with MoK_α radiation. The crystal structure of **1** was solved by direct methods (SHLXS-97), expanded using difference *Fourier* technique, and refined by the program and the full-matrix least-squares calculations. The non-H-atoms were refined anisotropically, H-atoms were fixed at calculated positions.

CCDC-1015870 contains the supplementary crystallographic data for this work. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Velutabularin K (= rel-*(2*R,*3*S,*3a*R,*3b*R,*6a*R,*7R*,*7a*R,*8*S,*11*R,*11a*S,*11b*R,*12*R,*13*S,*13a*R,*14*S)-*8-(Furan-3-yl)dodecahydro-13,13a-dihydroxy-3-(2-methoxy-2-oxoethyl)-2,3a,5-trimethyl-10-oxo-12-(propionyloxy)-5,11b-epoxy-2,13:7a,11a-dimethano[1,3]dioxolo[4,5-*g*]indeno[5,4-*f*]isochromene-7,11,14-triyl Triacetate*; rel-*(1*R,*2*S,*3*R,*6*S,*7*R,*8*R,*9*R,*13*R,*14*R,*15*R,*18*S,*19*S,*20*R,*22*S)-3,8,18-Tris(acetyloxy)-6-(furan-3-yl)-15,19-dihydroxy-22-(2-methoxy-2-oxoethyl)-11,14,17-trimethyl-4-oxo-5,10,12,21-tetraoxaoctacyclo[9.9.1.1^{2,7}.1^{14,17}.0^{1,13}.0^{2,7}.0^{9,13}.0^{15,19}]tricos-20-yl Propanoate*; **1**). Colorless, amorphous powder. $[\alpha]_D^{21} = +8.5$ ($c = 0.11$, $CHCl_3$). IR (KBr): 3434, 1758, 1212, 1024. ^{1}H- and ^{13}C-NMR: see *Table*. HR-ESI-MS: 811.2633 ($[M + \text{Na}]^+$, $C_{38}H_{44}NaO_{18}^+$; calc. 811.2425).

Velutabularin L (= rel-*(2*R,*3*S,*3a*R,*3b*R,*6a*R,*7*R,*7a*R,*8*S,*11b*R,*12*R,*13*S,*13a*R,*14*S)-*3-((*R)-1-Acetoxy-2-methoxy-2-oxoethyl)-8-(furan-3-yl)-1,2,3,3a,6a,7,7a,8,10,12,13,13a-dodecahydro-13,13a-dihydroxy-12-(isobutyryloxy)-2,3a,5,7a-tetramethyl-10-oxo-5,11b-epoxy-2,13-methano[1,3]dioxolo[4,5-*g*]indeno[5,4-*f*]isochromene-7,14-diyl Diacetate*; rel-*(3*R,*3a*S,*3b*S,*6a*S,*7*S,*7a*S,*8*R,*11b*S,*12*S,*13*R,*13a*S,*14*R)-7,14-Bis(acetyloxy)-3-[(1*S*)-1-(acetyloxy)-2-methoxy-2-oxoethyl]-8-(furan-3-yl)-2,3,3a,6a,7,7a,10,12,13,13a-decahy-

*dro-13,13a-dihydroxy-2,3a,5,7a-tetramethyl-10-oxo-1*H,*8*H-*5,11b-epoxy-2,13-methano[1,3]dioxolo[4,5-*g*]indeno[5,4-f]isochromen-12-yl 2-Methylpropanoate*; **2**). White, amorphous powder. $[\alpha]_D^{21} = +0.6$ ($c =$ 0.11, $CHCl_3$). IR (KBr): 3436, 1746, 1629, 1215, 1027. ^{1}H- and ^{13}C-NMR, see *Table*. HR-ESI-MS: 825.2573 ($[M + Na]^+$, $C_{39}H_{46}NaO_D^{18}$; calc. 825.2582).

Velutabularin M (= rel-*(4*R,*4a*R,*5*R,*6a*R,*9a*S,*11*S,*12*R,*12a*R,*13*R,*13a*S,*15*R,*16*R)*-15-((*S)*-1-Acetoxy-2-methoxy-2-oxoethyl)-4-(furan-3-yl)dodecahydro-4a,8,11,16-tetramethyl-2-oxo-6a,9a,11-(epiethane-[1,1,2]triyl)-8,13a-epoxycyclopenta[7,8][1,3]dioxocino[5,4-f]isochromene-5,12,12a,13-tetrayl Tetraacetate*; *Methyl* rel-*(2*R*)-(Acetyloxy)[(1*R,*6*S,*7*S,*8*S,*10*S,*14*R,*15*S,*16*S,*18*S,*19*S,*20*S*)-8,18,19,20-tetrakis(acetyloxy)-6-(furan-3-yl)-7,12,15,17-tetramethyl-4-oxo-5,11,13,21-tetraoxaheptacyclo[10.8.1.1^{14,17}.0^{1,10}.0^{2,7}.0^{10,15}.0^{14,19}]docos-16-yl]acetate*; **3**). White, amorphous powder. $[\alpha]_D^{22} = -71.7$ ($c = 0.12$, $CHCl_3$). IR (KBr): 3438, 1746, 1233, 1027. ^{1}H- and ^{13}C-NMR, see *Table*. HR-ESI-MS: 825.2573 ($[M + Na]^+$, $C_{39}H_{46}NaO_{18}^+$; calc. 825.2582).

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REFERENCES

[1] C.-R. Zhang, S.-P. Yang, X.-Q. Chen, Y. Wu, X.-C. Zhen, J.-M. Yue, *Helv. Chim. Acta* **2008**, *91*, 2338.
[2] C.-Q. Fan, X.-N. Wang, S. Yin, C.-R. Zhang, F.-D. Wang, J.-M. Yue, *Tetrahedron* **2007**, *63*, 6741.
[3] J. Luo, J.-S. Wang, X.-B. Wang, X.-F. Huang, J.-G. Luo, L.-Y. Kong, *Tetrahedron* **2009**, *65*, 3425.
[4] J. Luo, J.-S. Wang, X.-B. Wang, J.-G. Luo, L.-Y. Kong, *Chem. Pharm. Bull.* **2011**, *59*, 225.
[5] S.-G. Liao, H.-D. Chen, J.-M. Yue, *Chem. Rev.* **2009**, *109*, 1092.
[6] J. Luo, Y. Li, J.-S. Wang, J. Lu, X.-B. Wang, J.-G. Luo, L.-Y. Kong, *Chem. Pharm. Bull.* **2012**, *60*, 195.
[7] Y. Li, J Luo, H. Li, L.-Y. Kong, *Molecules* **2013**, *18*, 373.
[8] C.-R. Zhang, S.-P. Yang, Q. Zhu, S.-G. Liao, Y. Wu, J.-M. Yue, *J. Nat. Prod.* **2007**, *70*, 1616.
[9] C.-R. Zhang, S.-P. Yang, S.-G. Liao, C.-Q. Fan, Y. Wu, J.-M. Yue, *Org. Lett.* **2007**, *9*, 3383.
[10] J. Luo, J.-S. Wang, X.-B. Wang, J.-G. Luo, L.-Y. Kong, *J. Nat. Prod.* **2010**, *73*, 835.
[11] E.-J. Kim, F. Tian, M.-H. Woo, *J. Nat. Prod.* **2000**, *63*, 1503.
[12] Y. S. Xie, P. G. Fields, M. B. Isman, W. K. Chen, X. Zhang, *J. Stored Prod. Res.* **1995**, *31*, 259.
[13] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, *J. Natl. Cancer Inst.* **1991**, *83*, 757.

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