ORGANIC LETTERS

2007
Vol. 9, No. 17
3383−3386

Chuktabularins A–D, Four New Limonoids with Unprecedented Carbon Skeletons from the Stem Bark of *Chukrasia tabularis*

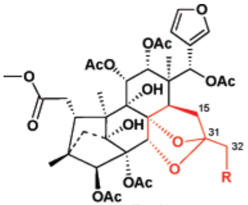
**Chuan-Rui Zhang, Sheng-Ping Yang, Shang-Gao Liao, Cheng-Qi Fan,
Yan Wu, and Jian-Min Yue***

*State Key Laboratory of Drug Research, Institute of Materia Medica, Shanghai
Institutes for Biological Sciences, Chinese Academy of Sciences, 555 Zuchongzhi Road,
Zhangjiang Hi-Tech Park, Shanghai 201203, People's Republic of China*

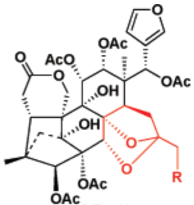
jmyue@mail.shcnc.ac.cn

Received June 19, 2007

ABSTRACT



1 R = H
3 R = CH_3



2 R = H
4 R = CH_3

Chuktabularins A–D (1–4), four novel 16-norphragmalin-type limonoids that feature unprecedented skeletons with a biosynthetically extended C2 or C3 unit at C-15 forming a unique 2,7-dioxabicyclo[2.2.1]heptane moiety, were isolated from the stem bark of *Chukrasia tabularis*. Their structures were elucidated by spectroscopic analysis and computer modeling. The biosynthetic pathway of 1–4 was postulated.

Limonoids are a class of structurally diversified nortriterpenoids with a wide range of bioactivities, such as insect antifeeding, antimalarial, and anticancer activities.[1] The attractive structures and biological significance have prompted continuous studies on these metabolites.[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] Its bark has been applied traditionally in China and India as astringent, antidiarrheal, and anti-influenza agents.[4] The extract of its leaves also showed activities against bacteria and fungi.[5] Previous chemical investigations on this plant afforded a series of phragmalin limonoids.[6] In our recent study, four limonoids were isolated from its seeds.[7] A subsequent study on its stem bark collected from Xishuangbanna of China has led to the isolation of four novel 16-norphragmalin-type limonoids, chuktabularins A−D (**1**−**4**) featuring unprecedented skeletons with a biosynthetically extended C2 or C3 unit at C-15

---

(1) (a) Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. G. E.; Towers, G. H. N. *Phytochemistry* **1992**, *31*, 377−394. (b) Roy, A.; Saraf, S. *Biol. Pharm. Bull.* **2006**, *29*, 191−201.

(2) (a) Wang, X. N.; Yin, S.; Fan, C. Q.; Wang, F. D.; Lin, L. P.; Ding, J.; Yue, J. M. *Org. Lett.* **2006**, *8*, 3845−3848. (b) Yin, S.; Fan, C. Q.; Wang, X. N.; Lin, L. P.; Ding, J.; Yue, J. M. *Org. Lett.* **2006**, *8*, 4935−4938. (c) Hay, A.-E.; Ioset, J.-R.; Ahua, K. M.; Diallo, D.; Brun, R.; Hostettmann, K. *J. Nat. Prod.* **2007**, *70*, 9−13.

(3) Chen, S. K.; Chen, B. Y.; Li, H. In *Flora Republicae Popularis Sinicae*; Zhi, Z. Z., Ed.; Science Press: Beijing, China, 1997; Vol. 43 (3), pp 47−49.

(4) Editorial Committee of the Administration Bureau of Traditional Chinese Medicine. In *Chinese Materia Medica*; Bencao, Z., Ed.; Shanghai Science and Technology Press: Shanghai, China, 1999; Vol. 5, pp 31−32.

(5) Nagalakshmi, M. A. H.; Thangadurai, D.; Muralidara Rao, D.; Pullaiah, T. *Fitoterapia* **2001**, *72*, 62−64.

(6) (a) Nakatani, M.; Abdelgaleil, S. A. M.; Saad, M. M. G.; Huang, R. C.; Doe, M.; Iwagawa, T. *Phytochemistry* **2004**, *65*, 2833−2841. (b) Connolly, J. D.; Labbé, C.; Rycroft, D. S. *J. Chem. Soc., Perkin Trans. I* **1978**, *285−288.* (c) Ragettli, T.; Tamm, C. *Helv. Chim. Acta* **1978**, *61*, 1814−1831.

(7) Fan, C. Q.; Wang, X. N.; Yin, S.; Zhang, C. R.; Wang, F. D.; Yue, J. M. *Tetrahedron* **2007**, *63*, 6741−6747.

10.1021/ol701437h CCC: $37.00

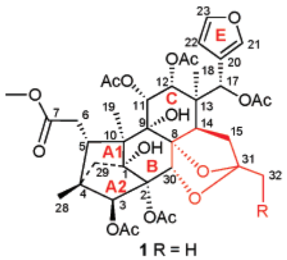
Table 1. ^{1}H and ^{13}C NMR Data of **1**−**4** (in $CDCl_3$)

	1		**2**		**3**		**4**	
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	δ_H (multi, *J* in Hz)	δ_C
1		84.4		85.5		84.5		85.6
2		82.1		81.0		82.3		81.3
3	5.22 (s)	83.4	5.34 (s)	82.8	5.22 (s)	83.5	5.35 (s)	83.0
4		45.4		45.6		45.4		45.6
5	2.57 (br d, 12.1)	41.1	2.07 (m)[a]	40.4	2.58 (br d, 11.9)	41.2	2.08 (m)[a]	40.5
6a	2.43 (br d, 16.5)	34.1	2.30 (m, 2H) [a]	31.3	2.45 (br d, 16.5)	34.1	2.31 (m, 2H) [a]	31.3
6b	2.22 (dd, 16.5, 12.1)				2.23 (dd, 16.5, 11.9)			
7		173.1		172.7		173.2		172.6
8		90.1		89.6		90.0		89.6
9		76.1		75.1		76.2		75.3
10		52.5		52.3		52.6		52.4
11	5.66 (d, 3.3)	72.4	5.63 (d, 3.6)	71.3	5.68 (d, 3.2)	72.4	5.64 (d, 3.4)	71.4
12	5.62 (d, 3.3)	73.2	5.45 (d, 3.6)	72.0	5.64 (d, 3.2)	73.2	5.46 (d, 3.4)	72.2
13		41.6		41.5		41.6		41.5
14	3.08 (dd, 11.7, 7.6)	44.8	3.27 (dd, 12.0, 7.5)	44.2	3.06 (dd, 11.8, 7.8)	44.4	3.25 (dd, 11.8, 7.6)	43.9
15β	2.53 (dd, 11.7, 7.6)	34.1	2.55 (dd, 11.7, 7.5)	35.3	2.55 (dd, 11.8, 7.8)	34.0	2.56 (dd, 11.8, 7.6)	33.9
15α	1.87 (dd, 11.7, 11.7)		1.94 (dd, 11.7, 11.7)		1.86 (dd, 11.8, 11.8)		1.90 (dd, 11.8, 11.8)	
17	6.14 (s)	71.2	6.07 (s)	71.2	6.16 (s)	71.3	6.08 (s)	71.3
18	0.90 (s, 3H)	19.0	0.89 (s, 3H)	19.0	0.91 (s, 3H)	19.0	0.90 (s, 3H)	19.1
19a	1.18 (s, 3H)	17.6	5.01 (d, 12.5)	69.3	1.19 (s, 3H)	17.7	5.03 (d, 12.4)	69.4
19b			4.18 (d, 12.5)				4.18 (d, 12.4)	
20		122.3		122.3		122.3		122.4
21	7.64 (br s)	140.5	7.48 (br s)	140.1	7.65 (br s)	140.5	7.48 (br s)	140.2
22	6.49 (br d, 1.1)	109.6	6.39 (br d, 1.0)	109.5	6.50 (dd, 1.7, 0,7)	109.6	6.40 (br d, 0.8)	109.5
23	7.36 (br t, 1.7)	143.0	7.37 (br t, 1.6)	143.2	7.37 (br t, 0.7)	143.1	7.38 (br t, 1.7)	143.2
28	0.76 (s, 3H)	16.0	0.89 (s, 3H)	15.0	0.77 (s, 3H)	16.0	0.90 (s, 3H)	15.0
29a	1.83 (d, 11.2)	40.0	2.08 (d, 11.8)[a]	38.8	1.84 (d, 11.3)	40.0	2.06 (m)[a]	38.8
29b	1.79 (d, 11.2)		2.01 (d, 11.8)		1.80 (d, 11.3)		2.03 (m)[a]	
30	4.63 (s)	71.0	4.62 (s)	71.0	4.65 (s)	70.7	4.63 (s)	70.8
31		110.2		110.9		112.6		113.3
32	1.62 (s, 3H)	18.7	1.64 (s, 3H)	18.7	1.96 (q, 7.6, 2H)	26.0	1.98 (q, 7.5, 2H)	25.9
33					1.06 (t, 7.6, 3H)	7.9	1.07 (t, 7.5, 3H)	7.8
7-OMe	3.61 (s, 3H)	51.6			3.62 (s, 3H)	51.7		
1-OH	4.63 (s)		4.86 (s)		4.64 (s)		4.89 (s)	
9-OH	3.27 (s)		3.34 (s)		3.25 (s)		3.34 (s)	
2-OAc	2.06 (s, 3H)	20.9	2.08 (s, 3H)	20.8	2.08 (s, 3H)	21.0	2.09 (s, 3H)	20.7
		169.6		169.6		169.6		169.4
3-OAc	2.47 (s, 3H)	21.0	2.48 (s, 3H)	20.9	2.48 (s, 3H)	21.1	2.48 (s, 3H)	20.9
		169.5		169.1		169.5		169.1
11-OAc	1.93 (s, 3H)	20.9	2.11 (s, 3H)	20.9	1.93 (s, 3H)	20.9	2.12 (s, 3H)	20.8
		169.5		170.9		169.5		170.9
12-OAc	2.07 (s, 3H)	20.5	2.04 (s, 3H)	20.6	2.08 (s, 3H)	20.6	2.05 (s, 3H)	20.5
		169.2		170.0		169.2		169.9
17-OAc	2.09 (s, 3H)	20.4	2.08 (s, 3H)	20.4	2.09 (s, 3H)	20.4	2.10 (s, 3H)	20.4
		168.7		168.8		168.7		168.7

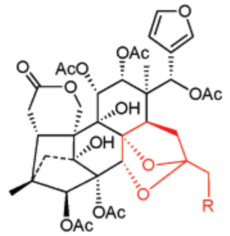
[a] Proton signals were overlapped. Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C).

forming a unique 2,7-dioxabicyclo[2.2.1]heptane system. We report herein the isolation and structural elucidation of these compounds (**1**−**4**).

The air-dried stem bark (5 kg) of *C. tabularis* was extracted with 95% ethanol at room temperature to give a crude extract (378 g), which was then partitioned between EtOAc and water to obtain the EtOAc-soluble fraction (120 g). It was fractionated via a MCI gel column eluted with MeOH−H_2O (2:8 to 9:1) in gradient to obtain five fractions. Fraction 3 (67 g) was extensively chromatographed over columns of silica gel and C-18 reversed-phase silica gel, and finally purified by semipreparative HPLC to give chuktabularins A (**1**, 8 mg), B (**2**, 15 mg), C (**3**, 12 mg), and D (**4**, 10 mg) (for details see Supporting Information).



1 R = H
3 R = CH_3



2 R = H
4 R = CH_3

Chuktabularin A (**1**)[8] was obtained as a white amorphous powder. The molecular formula $C_{38}H_{48}O_{17}$ with 15 degrees of unsaturation was determined by the HREIMS ion at *m*/*z* 776.2884 $[M]^+$ (calcd 776.2892). The IR absorption bands showed the presence of hydroxyl (3442 cm^{-1}) and ester groups (1751 cm^{-1}). In accordance with the molecular formula, 38 carbon signals were observed in the ^{13}C NMR spectrum (Table 1), and were further classified by DEPT experiments into the categories of 10 methyls, 3 methylenes, 10 methines (5 oxygenated and 3 olefinic ones), and 15 quaternary carbons (6 ester carbonyls and 1 olefinic one). In addition, four tertiary methyls (δ_H 1.62, 1.18, 0.90, and 0.76), one methoxyl (δ_H 3.61; δ_C 51.6), five acetyls, a ketal group (δ_C 110.2),[9] and a β-furyl ring were distinguished by analysis of the NMR data (Table 1). Two proton resonances at δ_H 4.63 and 3.27, which had no correlation with any carbon signals in the HSQC spectrum, were only attributable to the protons of two hydroxyls.

Comprehensive analysis of the ^1H and ^{13}C NMR data (Table 1) and 2D NMR spectra of **1**, especially HMBC (Figure 1), allowed the establishment of A1, A2, B, C, and E rings and the C-6−C-7 unit, which are the typical features of a phragmalin-type limonoid.[6,10] However, the 1D and 2D NMR spectra of **1** revealed that the characteristic D ring comprising a six-membered lactone and the common orthoacetate of a limonoid were absent. A ketal resonance at δ_C 110.2 was present, which was attached to C-15 and was assigned to the C-31 of the biosynthetically extended C2 unit (C31 and C32) on the basis of HMBC correlations of H_2-15 and Me-32 to C-31. The above analysis suggested that **1** was a 16-norphragmalin-type limonoid featuring an unprecedented skeleton with a biosynthetically extended C2 unit at C-15.

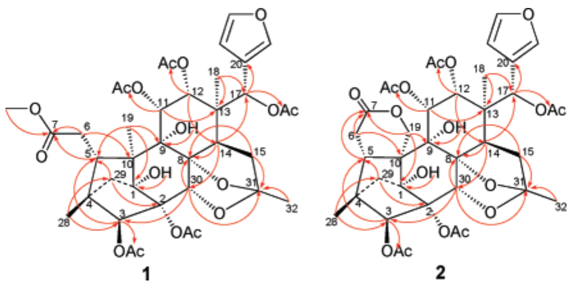


Figure 1. Key HMBC (H→C) correlations of **1** and **2**

In the HMBC spectrum (Figure 1), two hydroxyls resonating at δ 4.63 and 3.27 were assigned to C-1 and C-9 by the HMBC correlations from 1-OH to C-1 and 9-OH to C-9, respectively; four acetoxyls were placed at C-3, C-11, C-12, and C-17 on the basis of HMBC correlations from the H-3, H-11, H-12, and H-17 to each corresponding carbonyl of the acetyls, respectively. The remaining one acetoxyl was subsequently assigned to C-2 on the basis of its downfield shifted carbon resonance at δ 82.1 (for the case of 2-OH, the C-2 carbon resonance normally appeared at ca. δ_C 78.0),[6,10] and this was confirmed by the ROESY correlation of Me-32/2-OAc (Figure 2). The last two oxygenated carbons at δ 90.1 and δ 71.0 were respectively assigned to C-8 and C-30 as judged by the mutual HMBC correlations of H-14, H_2-15 and H-30/C-8, H-14/C-30, and H-30/C-3 and C-14. Both C-8 and C-30 were linked with C-31 via oxygen atoms to form the ketal group on the basis of their chemical shifts and key HMBC correlation between H-30 and C-31. The only methoxyl was attached to C-7 by the HMBC correlation between OMe and C-7. The planar structure of **1** was thus assigned as a 16-norphragmalin-type limonoid featuring an unprecedented skeleton with a biosynthetically extended C2 unit at C-15 forming a unique 2,7-dioxabicyclo[2.2.1]heptane moiety (red part).

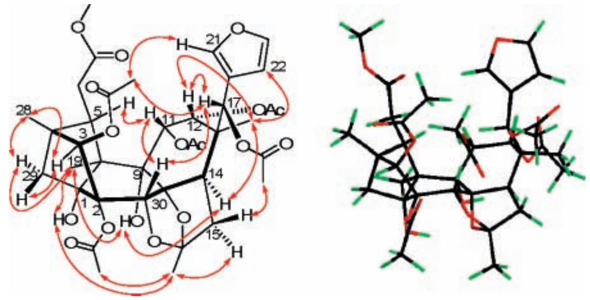


Figure 2. ROESY (↔) correlations and the 3D computer modeling of **1**.

The relative stereochemistry of **1** was fixed by a ROESY experiment (Figure 2), in which the correlations of H-5/H-11, H-11/H-30, H-12/H-17, 3-OAc/H-17, 3-OAc/H-21, and H-17/H-30 indicated that 3-OAc, H-5, H-11, H-12, H-17, and H-30 were cofacial, and were arbitrarily assigned as the β-configuration. In consequence, the ROESY cross-peaks of Me-18/H-22, Me-18/H-14, H-14/9-OH, 9-OH/Me-19, Me-19/1-OH, 1-OH/Me-32, and Me-32/2-OAc revealed that H-14, Me-18, Me-19, Me-32, 1-OH, 9-OH, and 2-OAc were α-oriented. Thereby, two ether bonds forming the five-membered ketal system were α-directed. Subsequently, the CH_2-29 group was assigned to the α-position on the basis of ROESY correlations of Me-19/H-29a and H-3/H-29b. Steric bulk reduced free rotation around the C-13/C-17 bond, and allowed the observation of ROESY correlations of H-17/

---

[8] **Chuktabularin A (1):** White amorphous powder $[\alpha]^{20}_D$ +20 (*c* 0.135, $CHCl_3$); IR (KBr) ν_{max} 3442, 2983, 1751, 1632, 1371, 1225, 1045, 875, 602 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; ESIMS *m*/*z* 799 $[M + Na]^+$; EIMS *m*/*z* 776 (4) $[M]^+$, 758 (5), 716 (27), 656 (42), 554 (48), 536 (54), 494 (72), 440 (54), 398 (55), 221 (65), 179 (100), 149 (44), 95 (62), 81 (33); HREIMS *m*/*z* 776.2884 $[M]^+$ (calcd for $C_{38}H_{48}O_{17}$ 776.2892).

[9] (a) Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D. *J. Org. Chem.* **1997**, *62*, 3902−3909. (b) He, J.; Feng, X. Z.; Zhao, B. *J. Nat. Prod.* **2003**, *66*, 1249−1251. (c) Manfrotto, C.; Mella, M.; Freccero, M.; Fegnoni, M.; Albini, A. *J. Org. Chem.* **1999**, *64*, 5024−5028.

[10] (a) Saad, M. M. G.; Iwagawa, T.; Doe, M.; Nakatani, M. *Tetrahedron* **2003**, *59*, 8027−8033. (b) Wu, J.; Xiao, Q.; Huang, J. S.; Xiao, Z. H.; Qi, S. H.; Li, Q. X.; Zhang, S. *Org. Lett.* **2004**, *6*, 1841−1844. (c) Wu, J.; Zhang, S.; Xiao, Q.; Li, Q. X.; Huang, J. S.; Long, L. J.; Huang, L. M. *Tetrahedron Lett.* **2004**, *45*, 591−593.

H-30, H-17/H-12, H-22/Me-18, 3-OAc/H-21, and H-15β/17-OAc, which demonstrated the stereochemistry at C-17 as depicted.

A computer modeled 3D structure (Figure 2) of **1** was generated by using MM2 force field calculations for energy minimization with the molecular modeling program Chem3D Ultra 9.0. The relative stereochemistry and the conformation of **1** assigned by ROESY spectrum were compatible with those of **1** offered by computer modeling, in which the close contacts of atoms calculated in space were consistent with the ROESY correlations (Figure 2, Supporting Information).

Chuktabularin B (**2**)[11] showed the HREIMS ion at *m/z* 760.2541 $[M]^+$ corresponding to the molecular formula of $C_{37}H_{44}O_{17}$ (calcd 760.2578) requiring 16 double bond equivalents. The ^1H and ^{13}C NMR data (Table 1) of **2** showed high similarity to those of **1**, except for the presence of an oxygenated C-19 methylene (δ_H 5.01 and 4.18, δ_C 69.3) in **2** instead of the Me-19 of **1**, and the absence of the methoxyl at C-7, suggesting that a six-membered 7,19-lactone was likely formed in **2**. This was confirmed by the key HMBC correlation (Figure 1) between H_2-19 and C-7. The ROESY correlations of H-19a/1α-OH and H-19b/H-29a revealed that the six-membered 7,19-lactone ring was α-directed. The comprehensive interpretation of 2D NMR spectra (Supporting Information), in particular, HMBC and ROESY (Figures 1 and 3), verified the structure of **2**. A computer modeled 3D structure (Figure 3) was also supportive evidence for the structure of **2**.

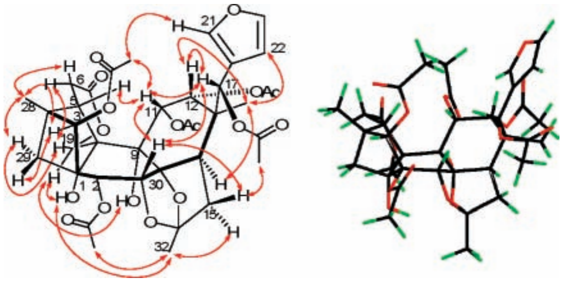
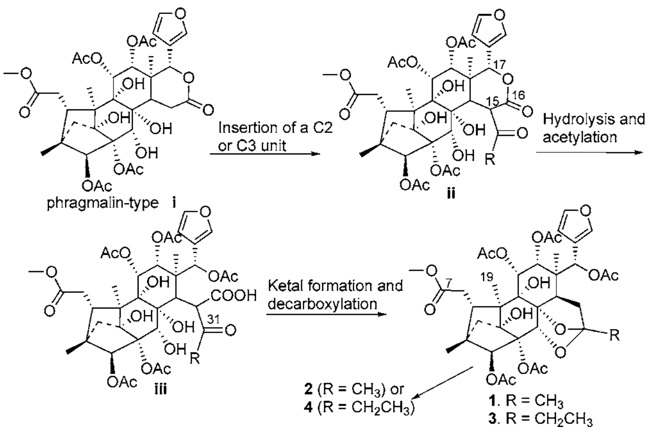


Figure 3. ROESY (↔) correlations and the 3D computer modeling of **2**.

Chuktabularins C (**3**)[12] and D (**4**)[13] with molecular formulas of $C_{39}H_{50}O_{17}$ (at *m/z* 790.3037 $[M^+]$) and $C_{38}H_{46}O_{17}$ (at *m/z* 774.2762 $[M]^+$) as determined by HREIMS showed the presence of one more CH_2 unit than those of **1** and **2**, respectively. Analyses of ^1H and ^{13}C NMR data (Table 1) of **3** and **4** indicated that they are the respective analogues of **1** and **2** by incorporating a biosynthetically extended C3 unit into C-15 instead of a C2 one. Thus, the structures of chuktabularins C (**3**) and D (**4**) were established, and verified by 2D NMR spectra (Supporting Information).

Scheme 1. The Plausible Biogenetic Origin of **1**−**4**



The origin of **1**−**4** (Scheme 1) was proposed to be the phragmalin-type limonoid **i**. Insertion of a C2 or a C3 unit, e.g., via acetyl-CoA or propionyl-CoA, into the intermediate **i** by a Claisen reaction[14] would produce a key intermediate **ii**, which could undergo a hydrolysis and acetylation to yield **iii**. Ketal formation and decarboxylation would form chuktabularin A (**1**) or C (**3**). Compounds **1** or **3** could finally be transformed into **2** or **4** via oxidation and intramolecular esterification.

Acknowledgment. Financial support from the Key Project of National Natural Science Foundation (Grant No. 30630072) is gratefully acknowledged. We thank Prof. You-Kai Xu of Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences for the collection and identification of the plant material.

Supporting Information Available: Experimental procedures; key HMBC and NOESY (**3**)/ROESY (**4**) correlations of **3** and **4**; IR, EIMS, and 1D and 2D NMR spectra of chuktabularins A−D (**1**−**4**); and the close contacts of atoms in space for compounds **1**−**4** calculated by computer modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701437H

---

[11] **Chuktabularin B (2):** White amorphous powder $[\alpha]^{20}_D$ +16 (*c* 0.160, $CHCl_3$); IR (KBr) ν_{max} 3431, 2956, 1751, 1633, 1373, 1227, 1041, 924, 602 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; ESIMS *m/z* 783 $[M + Na]^+$; EIMS *m/z* 760 (7) $[M]^+$, 742 (10), 718 (26), 700 (24), 658 (36), 466 (38), 424 (61), 382 (100), 364 (28), 149 (30), 95 (32), 81 (18); HREIMS *m/z* 760.2541 $[M]^+$ (calcd for $C_{37}H_{44}O_{17}$ 760.2578).

[12] **Chuktabularin C (3):** White amorphous powder $[\alpha]^{20}_D$ +27 (*c* 0.110, $CHCl_3$); IR (KBr) ν_{max} 3442, 2956, 2921, 2850, 1755, 1630, 1461, 1373, 1242, 1034, 602 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; ESIMS *m/z* 813 $[M + Na]^+$; EIMS *m/z* 790 (1) $[M]^+$, 772 (5), 730 (22), 712 (8), 670 (27), 494 (40), 182 (46), 95 (42), 57 (100); HREIMS *m/z* 790.3037 $[M]^+$ (calcd for $C_{39}H_{50}O_{17}$ 790.3048).

[13] **Chuktabularin D (4):** White amorphous powder $[\alpha]^{20}_D$ +25 (*c* 0.120, $CHCl_3$); IR (KBr) ν_{max} 3431, 2958, 1751, 1373, 1225, 1040, 602 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; ESIMS *m/z* 797 $[M + Na]^+$; EIMS *m/z* 774 (3) $[M]^+$, 756 (5), 732 (13), 714 (16), 672 (27), 480 (37), 438 (53), 396 (70), 149 (77), 95 (41), 57 (100); HREIMS *m/z* 774.2762 $[M]^+$ (calcd for $C_{38}H_{46}O_{17}$ 774.2735).

[14] Dewick, P. M. *Medicinal Natural Products*: *A Biosynthetic Approach*, 2nd ed.; John Wiley & Sons Ltd.: Chichester, England, 2004; pp 15−17.