Four Phragmalin Orthoesters from the Chinese Mangrove *Xylocarpus granatum*

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Abstract
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Four new 8,9,30-phragmalin orthoesters (**1**–**4**), along with six related known compounds, namely xyloccensins O–S (**5**–**9**) and V (**10**), were isolated and characterized from the twigs and leaves of the Chinese mangrove *Xylocarpus granatum*. The structures of the new compounds were determined on the basis of extensive spectroscopic analysis and by comparison with those of related known compounds in the literature. The absolute configuration of xyloccensin Q (**7**) was revised as its enantiomer by X-ray diffraction analysis employing graphite monochromated Cu Kα radiation ($\lambda = 1.54178$ Å) with a Flack parameter of -0.04 and was further secured by a time-dependent density functional theory electronic circular dichroism (TDDFT ECD) calculation. Consequently, the absolute configurations of xyloccensins O (**5**), P (**6**), R (**8**), S (**9**), and V (**10**) were all corrected as their corresponding enantiomers, respectively. Xyloccensin S (**9**) exhibited inhibitory activity against protein tyrosine phosphatase 1B, a potential drug target for the treatment of type II diabetes and obesity, with an IC_{50} value of 8.72 μg/mL.

Supporting information available online at http://www.thieme-connect.de/products

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Introduction
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The orthoester, a functional group that features three alkoxy groups attached to a single carbon atom, has been widely discovered as a structural subunit in natural products of plant origin [1]. The orthoester-containing compounds usually show prominent pharmacological activities such as cytotoxic, antifeedant, insecticidal properties, etc. [1]. Limonoid orthoesters are characterized by the presence of a highly oxygenated limonoid skeleton containing an orthoester functionality, which exists exclusively as phragmalin orthoesters and can be classified into 1,8,9-, 8,9,11-, 8,9,12-, 8,9,14-, and 8,9,30-types according to the position of the orthoester group in the phragmalin limonoid skeleton [1]. Due to the structural complexity of phragmalin orthoesters, the structural characterization, in particular, of the absolute configuration has been a challenging task. Although, until now, about 90 phragmalin orthoesters have been reported from the plant belonging to two tribes (Swietenieae and Xylocar-

peae) of the Meliaceae family [1]. To our knowledge, only ten phragmalin orthoesters belonging to two classes, 1,8,9- and 8,9,30-phragmalin orthoesters, were isolated from the Chinese mangrove *Xylocarpus granatum* Koenig [2–6].

Mangroves of the three species in the genus *Xylocarpus* (family Meliaceae) are widely distributed in the coastal areas of Southeast Asia, Australia, East Africa, and Indian Ocean. *X. granatum* has been used as folk medicine in Southeast Asia and India for the treatment of diarrhea, cholera, and fever diseases and is a rich source of limonoids [7]. Hitherto, more than 100 limonoids have been isolated from the fruits, seeds, seed kernels, and stem bark of *X. granatum* [6–21].

We now report the chemical investigation of the twigs and leaves of the title plant, since no other phytochemical study has been conducted on these parts before. Four new 8,9,30-phragmalin orthoesters (**1**–**4**) and six related known compounds (**5**–**10**) were found (○ **Fig. 1**). This paper includes revisions of the absolute configurations of xyloccensins O–S (**5**–**9**) and V (**10**), of which the absolute configurations were previously erroneously assigned [4].

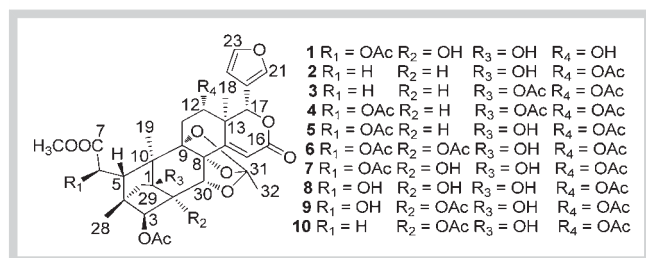* These two authors contributed equally to this work.

Fig. 1 Structures of compounds **1**–**10**.

Results and Discussion
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The air-dried, powdered twigs and leaves (2.0 kg) of *X. granatum* were percolated exhaustively with MeOH at room temperature. The MeOH extract was partitioned between EtOAc and H_2O. The EtOAc-soluble portion was separated by Sephadex LH-20 and MCI gel column to obtain five fractions (1–5). Fraction 3 was repeatedly chromatographed over silica gel, Sephadex LH-20, and reverse-phase HPLC to afford ten phragmalin orthoesters (**1**–**10**), of which four are new compounds (**1**–**4**) and six are known ones previously isolated from the stem bark of the same plant [2, 4, 5]. The known phragmalins were identified by comparison of their spectroscopic data and $[α]_D$ values with those reported in the literature as xyloccensins Q–S (**7**–**9**) and V (**10**), respectively. However, the measured optical rotation signs of both xyloccensins O (**5**) {$[α]_D^{20}$ + 62 (*c* 0.37, acetone)} and P (**6**) {$[α]_D^{20}$ + 68 (*c* 0.13, acetone)} were the opposite from those reported by Wu et al. [2]. In order to clarify this confusion, the $[α]_D$ values of xyloccensins O (**5**) and P (**6**) provided by Wu's group were remeasured, and the similar $[α]_D$ values from Wu's samples {xyloccensin O: $[α]_D^{20}$ + 56 (*c* 0.4, acetone)}; xyloccensin P {$[α]_D^{20}$ + 49 (*c* 0.11, acetone)} confirmed the correctness of our results.

Compound **1** had the molecular formula $C_{33}H_{38}O_{15}$ as deduced from HRMS (ESI), 42 mass units less than the co-occurring compound xyloccensin Q (**7**). Its NMR data (**Table 1**) showed great similarities with those of xyloccensin Q (**7**) [4, 5]. In fact, the only difference between them was the absence of an acetyl moiety at C-12 in **1**, which was evidenced by the lack of the characteristic ^{13}C NMR peaks in its ^{13}C NMR spectrum, and the significantly upfield-shifted proton signal of H-12. Thus, the structure of **1** was determined as the 12-deacetyl derivative of xyloccensin Q (**7**).

Compound **2** had the molecular formula $C_{33}H_{38}O_{13}$. Its ^{1}H and ^{13}C NMR spectroscopic data were reminiscent of those of xyloccensin V (**10**) [4, 5]. Comparison of the ^{1}H NMR spectroscopic data of **2** and xyloccensin V (**10**) revealed that the main differences between them were the presence of a typical doublet of doublets and a pair of doublets, along with the lack of the acetoxyl group in the spectrum of **2**, suggesting that **2** was a deacetoxy derivative of xyloccensin V (**10**) at C-2, which was in good agreement with the 58 mass units difference. Thus, compound **2** was established as the 2-deacetoxy derivative of xyloccensin V (**10**).

Compound **3** had the molecular formula $C_{35}H_{40}O_{14}$. The NMR data of **3** were very similar to those of **2**, except for the presence of an acetyl moiety in **3**. Furthermore, the apparent downfield-shifted ^{13}C NMR resonance of C-1 indicated that the 1-hydroxyl group was acetylated. Compound **3** was, therefore, determined as the 1-acetyl derivative of **2**.

Compound **4** had the molecular formula $C_{37}H_{42}O_{16}$, 58 mass units more than that of **3**. The ^{1}H and ^{13}C NMR spectroscopic data

(**Table 2**) of **4** were almost identical to those of the co-occurring compound **3**; the only difference was the presence of an additional acetoxyl group in **4**. This acetoxyl was located at C-6 based on the absence of a methylene in **3** accompanying the presence of a methine in **4**. Thus, the structure of **4** was established. The singlet of H-6 required approximately 90° of the dihedral angle between H-5/H-6, indicating the stereochemistry of C-6 was the same as that of xyloccensin R (**8**) [4, 5].

Because the main differences between the new compounds **1**–**4** and the co-occurring known phragmalin limonoids, xyloccensins O–S (**5**–**9**) and V (**10**), were the different positions of acetylation and deacetylation, the absolute configurations of these new compounds are likely to be the same. The absolute configurations of xyloccensins O–S (**5**–**9**) and V (**10**) have been determined by the modified Mosher's method in combination with ECD analysis [4]. Since xyloccensin Q (**7**) could be easily crystallized, to secure the correctness of the previously assigned absolute configuration mentioned above, the compound was submitted for X-ray diffraction analysis with a mirror Cu Kα radiation (λ = 1.54178 Å) (**Fig. 2**). The absolute configuration of xyloccensin Q (**7**) was unambiguously assigned as 1*R*,2*R*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*,10*R*,12*S*,13*S*, 17*R*,30*R*,31*S*, opposite to that reported by Wu et al. [4].

To further support the configurational assignment of **7**, we applied the solid-state TDDFT ECD method, which has been recently developed for the configurational assignment of natural products, since the conformational analysis step can be skipped [22–25]. Both the solid-state and solution ECD spectra of **7** showed similar profiles with positive Cotton effects at 219 and 261 nm, respectively. Four computed TDDFT ECD spectra, calculated for the DFT optimized X-ray geometry of (1*R*,2*R*,3*S*,4*R*,5*S*,6*R*,8*R*, 9*S*,10*R*,12*S*,13*S*,17*R*,30*R*,31*S*)-**7** with four different functions (B3LYP, BH&HLYP, CAM- B3LYP, PBE0) and the TZVP basis set, reproduced the experimental solid-state ECD spectrum well (Supporting Information), confirming the absolute configuration of **7**. In light of these observations, the absolute configuration of xyloccensin Q (**7**) should be revised as its corresponding enantiomer. Accordingly, the absolute configurations of xyloccensins O (**5**), P (**6**), R (**8**), S (**9**), and V (**10**) should be corrected as their corresponding enantiomers since their configurations were also determined by application of the same method used for xyloccensin Q (**7**) [4]. Therefore, the ECD spectra of xyloccensins O (**5**), P (**6**), R (**8**), S (**9**), and V (**10**) were measured again. The similar ECD spectra of xyloccensins O–S (**5**–**9**) and V (**10**) (Supporting Information) clearly indicate that they are homochiral and, thus, their absolute configurations were revised as their corresponding enantiomers.

The absolute configurations of new compounds **2** and **3** were determined by comparing their ECD spectra with the related known compounds **5**–**10** since they bear the same chromophores, unsaturated δ-lactone, and furan ring. Although the intensities and maxima were slightly different, the similar ECD pattern for compounds **2** and **3**, which were governed by the C-13 and C-17 chirality centers, suggested an *R, R* configuration for C-13 and C-17. The absolute configurations of compounds **1** and **4** were not determined directly because of the scarcity of material, but are assumed to be in the same series.

Although many phytochemical investigations have been reported on the fruits, seeds, seed kernels, and stem bark of *X. granatum*, this is the first report on the chemical constituents of the twigs and leaves of the Chinese mangrove *X. granatum*. It is interesting to note that the different parts of the plant can produce different metabolites. Specifically, the twigs and leaves of *X. granatum*

Table 1 NMR data for compounds **1** and **2**.

Position	1 δ_H (J in Hz)[a]	δ_H (J in Hz)[b]	δ_C[b]	2 δ_H (J in Hz)[a]	δ_H (J in Hz)[b]	δ_C[b]
1			83.5, qC			81.7, qC
2			76.7, qC	3.09, dd (12.0, 4.0)	3.15, dd (12.0, 3.7)	44.6, CH
3	4.78, s	4.52, s	85.6, CH	5.36, d (12.0)	5.29, d (12.0)	77.7, CH
4			44.9, qC			46.1, qC
5	2.53, s	2.41, s	44.9, qC	2.33, d (12.0)	2.30, d (12.3)	40.8, CH
6a	5.51, s	5.42, s	71.2, CH	3.17, d (17.0)	2.23, d (17.5)	32.4, CH$_2$
6b				2.48, dd (17.0, 12.0)	1.99, d (17.5, 12.3)	
7			171.3, qC			174.5, qC
8			84.1, qC			82.0, qC
9			87.4, qC			86.7, qC
10			48.2, qC			47.7, qC
11a	2.29, dd (13.7, 4.0)	2.29, dd (12.3, 3.6)	34.2, CH$_2$	2.25, m	2.25, dd (15.0, 3.8)	33.0, CH$_2$
11b	2.06[c]	1.98, d (14.6)		2.04[c]	2.04[c]	
12	4.04, dd (13.7, 4.0)	3.98, d (12.3)	66.5, CH	4.82, dd (13.6, 4.2)	4.79, dd (13.3, 4.2)	68.7, CH
13			44.2, qC			42.9, qC
14			154.1, qC			153.9, qC
15	6.82, s	6.41, s	123.4, CH	6.71, s	6.55, s	123.0, CH
16			163.4, qC			163.6, qC
17	5.88, s	5.90, s	78.9, CH	5.98, s	5.98, s	78.8, CH
18	1.45, s	1.48, s	13.1, CH$_3$	1.52, s	1.52, s	14.4, CH$_3$
19	1.26, s	1.30, s	16.3, CH$_3$	1.24, s	1.25, s	14.6, CH$_3$
20			121.2, qC			121.1, qC
21	7.62, s	7.65, s	142.4, CH	7.48, s	7.41, s	142.0, CH
22	6.61, s	6.61, s	109.6, CH	6.64, s	6.34, s	110.2, CH
23	7.52, d (1.5)	7.54, t (1.5)	144.9, CH	7.62, s	7.41, s	143.0, CH
28	0.88, s	0.92, s	15.5, CH$_3$	0.74, s	0.76, s	15.3, CH$_3$
29a	2.11, d (10.2)	2.10, d (10.5)	40.3, CH$_2$	2.16, d (11.0)	1.98, d (11.3)	42.6, CH$_2$
29b	1.69, d (10.2)	1.83, d (10.5)		1.45, d (11.0)	1.46, d (11.3)	
30	5.09, s	5.14, s	77.9, CH	4.98, d, (4.0)	4.65, d (3.7)	74.7, CH
31			119.3, qC			119.8, qC
32	1.68, s	1.70, s	16.4, CH$_3$	1.68, s	1.68, s	16.6, CH$_3$
2-OAc						
3-OAc	2.00, s	2.04, s	21.7, CH$_3$	1.97, s	2.05, s	21.8, CH$_3$
			169.6, qC			170.7, qC
6-OAc	2.24, s	2.22, s	21.0, CH$_3$			
			169.5, qC			
12-OAc				1.59, s	1.60, s	19.9, CH$_3$
						170.5, qC
30-OAc						
7-OMe	3.83, s	3.76, s	53.5, CH$_3$	3.74, s	3.71, s	52.1, CH$_3$
1-OH		3.50, s				
2-OH		3.54, s				

[a] Measured in acetone-d_6, [b] measured in CDCl$_3$, and [c] overlapped signals without designating multiplicity

contained a high content of 8,9,30-orthoesters, xyloccensins Q–S (**7–9**). A systematic literature check revealed that the 8,9,30-orthoesters were mainly distributed in the stem bark [2, 4, 5], whereas the 1,8,9-orthoesters were found in the fruit, including the fruit rind and seeds [3, 6]. In general, the stems and leaves of *X. granatum* are probably the main source of 8,9,30-orthoesters. Our research result was consistent with the conclusion that a high concentration of phragmalin orthoesters in the stem bark of *Xylocarpus* plants may serve as an important chemical defense against ecological invasion [3].

All isolated phragmalin orthoesters were subjected to the bioassay of inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), a potential drug target for the treatment of type II diabetes and obesity [26]. Of them, only xyloccensin S (**9**) showed in-

hibitory activity with an IC$_{50}$ value of 8.72 µg/mL. Although limonoids were reported to possess various bioactivities [27], to the best of our knowledge, this is the first report of PTP1B inhibitory activities in limonoids.

Materials and Methods
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Plant material
The twigs and leaves of *X. granatum* (2.0 kg) were collected in December 2009 from Dongzhai Harbor, Hainan Province, China, and identified by Professor Guo-Rong Xin of the Institute of Biological Science, Sun Yat-Sen University. A voucher specimen (NO. 09-

Table 2 NMR data for compounds **3** and **4**.

Position	**3** δ_H (J in Hz)[a]	δ_H (J in Hz)[b]	δ_C[b]	**4** δ_H (J in Hz)[a]	δ_H (J in Hz)[b]	δ_C[b]
1			85.5, qC			85.4, qC
2	4.08, dd (12.0, 4.0)	4.11, dd (12.0, 4.1)	34.5, CH	4.10, dd (12.0, 4.4)	4.14, dd (4.1, 12.0)	37.3, CH
3	5.30, d (12.0)	5.32, d (12.0)	77.0, CH	5.26, d (12.0)	5.27, d (12.0)	77.4, CH
4			46.0, qC			45.7, qC
5	2.37, d (12.0)	2.23, m[c]	39.1, CH	2.54, brs	2.51, s	43.7, CH
6a	3.18, d (17.0)	3.16, d (16.5)	32.9, CH₂	6.26, s	6.36, s	71.2, CH
6b	2.47, dd (17.0, 12.0)	2.23, d (16.5)				
7			174.4, qC			171.7, qC
8			81.1, qC			84.2, qC
9			84.1, qC			81.0, qC
10			49.3, qC			50.2, qC
11a	2.26, m	2.23, m[c]	32.7, CH₂	2.31, dd (14.0, 4.4)	2.34, dd (13.6, 4.3)	32.5, CH₂
11b	2.04[c]	1.98, m		2.04[c]	2.00, m	
12	4.84, dd (13.9, 4.0)	4.82, dd (13.5, 4.1)	68.9, CH	5.04, dd (13.5, 4.5)	4.98, dd (13.6, 4.2)	68.7, CH
13			42.9, qC			42.9, qC
14			154.5, qC			154.4, qC
15	6.67, s	6.33, s	122.9, CH	6.66, s	6.30, s	123.0, CH
16			163.6, qC			163.6, qC
17	5.95, s	5.95, s	78.8, CH	5.89, s	5.94, s	78.9, CH
18	1.58, s	1.62, s	14.5, CH₃	1.58, s	1.60, s	14.4, CH₃
19	1.30, s	1.26, s	15.3, CH₃	1.29, s	1.27, s	16.2, CH₃
20			121.2, qC			121.1, qC
21	7.49, s	7.42, s	142.0, CH	7.54, brs	7.45, s	142.0, CH
22	6.63, d (1.7)	6.55, d (1.3)	110.2, CH	6.65, brs	6.56, d (1.5)	110.2, CH
23	7.61, brs	7.40, d (1.6)	143.0, CH	7.62, t (1.7)	7.40, d (1.5)	143.0, CH
28	0.76, s	0.77, s	14.4, CH₃	0.96, s	0.95, s	15.5, CH₃
29a	2.26, m	2.46, d (11.6)	39.0, CH₂	2.41, dd (10.0, 1.3)	2.49, d (10.5)	40.2, CH₂
29b	1.55, m	1.82, d (11.6)		1.40, d (10.0)	2.11, d (10.5)	
30	4.82, d (4.0)	4.49, d (4.0)	73.4, CH	4.83, d (4.4)	4.48, d (4.1)	73.2, CH
31			119.9, qC			119.7, qC
32	1.59, s	1.60, s	16.7, CH₃	1.59, s	1.62, s	16.7, CH₃
1-OAc	1.94, s	1.99, s	22.2, CH₃	1.94, s	2.00, s	22.2, CH₃
			170.2, qC			170.2, qC
3-OAc	1.97, s	2.05, s	21.8, CH₃	1.95, s	2.03, s	21.8, CH₃
			170.6, qC			170.4, qC
6-OAc				2.21, s	2.20, s	21.0, CH₃
						169.2, qC
12-OAc	1.51, s	1.52, s	19.9, CH₃	1.51, s	1.55, s	19.9, CH₃
			170.6, qC			170.5, qC
30-OAc						
7-OMe	3.75, s	3.72, s	52.2, CH₃	3.81, s	3.76, s	53.3, CH₃

[a] Measured in acetone-d_6, [b] measured in CDCl₃, and [c] overlapped signals without designating multiplicity

P-69) is available for inspection at the Herbarium of the Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and isolation

The air-dried, powdered twigs and leaves of *X. granatum* (2.0 kg) were percolated with MeOH (10 L × 3) at room temperature. The extract was evaporated to dryness under reduced pressure to give 154.0 g of residue. The residue was partitioned with EtOAc to afford 29.7 g of EtOAc extract. The EtOAc extract was separated by Sephadex LH-20 (4 × 100 cm, CHCl₃/MeOH 1 : 1) and MCI gel column (4 × 40 cm, MeOH/H₂O 30 : 70, 50 : 50, 80 : 20, 100 : 0, each 2 L) to obtain five fractions (Fr. 1–5). Fr. 3 (7.9 g) was subjected to silica gel vacuum liquid chromatography (4 × 100 cm, 800 g), eluting with CHCl₃/MeOH (100 : 1, 50 : 1, 20 : 1, 8 : 2, each 3 L), to obtain 15 fractions. Fraction 4 (150.3 mg) was chromatographed on silica gel (3.5 × 30 cm, 12 g) with petroleum ether/acetone (95 : 5,

8 : 2, 7 : 3, each 250 mL) to yield **5** (> 95 %, 4.6 mg), **6** (> 95 %, 10.0 mg), and three subfractions, 4a–c. Fraction 4a was separated by Agilent semipreparative HPLC, eluting with MeOH/H₂O (73 : 27), to afford **3** (> 98 %, 2.8 mg, t_R 31.5 min), while compound **2** (> 98 %, 2.4 mg, t_R 38.5 min) was prepared in the same manner using MeOH/H₂O (70 : 30) from 4b. Fraction 4c was purified by reversed-phase HPLC, eluted with MeOH/H₂O (67 : 33), to yield **4** (> 98 %, 1.3 mg, t_R 42.9 min). Fraction 5 (2.17 g) was subjected to column chromatography on silica gel (6 × 30 cm, 160 g) eluted with a gradient of petroleum ether/acetone (9 : 1, 8 : 2, 7 : 3, 1 : 1, each 600 mL) to give four major fractions, 5a–5 d. Fraction 5c was chromatographed over Sephadex LH-20 (3 × 120 cm), eluting with CHCl₃/MeOH (1 : 1), and subsequently purified by HPLC (CH₃CN/H₂O, 67 : 33) to give **10** (> 98 %, 4.0 mg, t_R 31.5 min). Fraction 5 d (0.51 g) was subjected to column chromatography on silica gel (3 × 30 cm, 40 g), eluted with petroleum ether/acetone
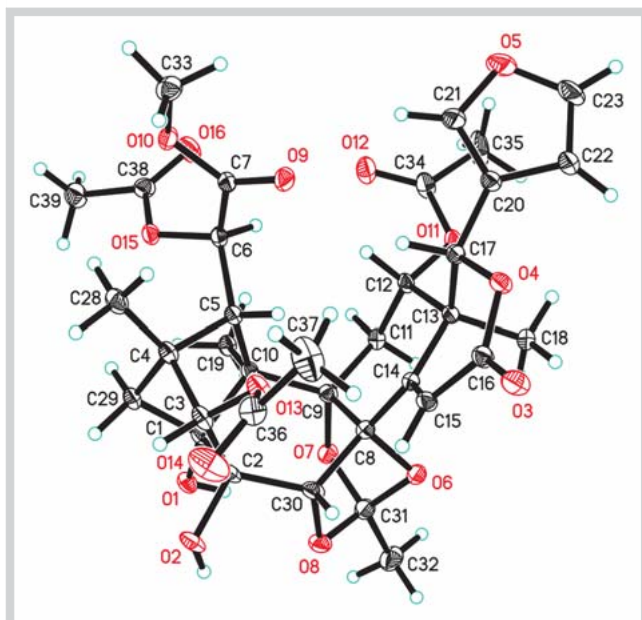
Fig. 2 X-ray crystal structure of **7**. (Color figure available online only.)

(7 : 3, 6 : 4), to afford the major fraction 5d1, which was further purified by HPLC (MeOH/H$_2$O, 70 : 30) to yield **7** (> 98 %, 10.0 mg, t_R 12.8 min), **8** (> 98 %, 4.4 mg, t_R 11.4 min), **9** (> 98 %, 6.5 mg, t_R 14.2 min), and **1** (> 98 %, 1.5 mg, t_R 8.6 min).

(1): White amorphous powder; $[\alpha]_D^{20}$ + 48.0 (c 0.13, MeOH); IR (KBr) v_{max} 3389, 2954, 2929, 1731, 1643, 1421, 1370, 1237, 1165, 1091, 1026 cm^{-1}; ^{1}H and ^{13}C NMR data, see ○ **Table 1**; HRE-SIMS m/z 697.2105 [M + Na]$^+$ (calcd. for C$_{33}$H$_{38}$O$_{15}$Na, 697.2108).

(2): White amorphous powder; $[\alpha]_D^{20}$ + 53.3 (c 0.05, CH$_3$CN); ECD (MeCN, λ_{max} [nm] ($\Delta\varepsilon$), c = 7.91 × 10^{-4}): 266 (3.16), 214 (15.42). IR (KBr) v_{max} 3410, 2920, 1735, 1605, 1422, 1385, 1239, 1037 cm^{-1}; ^{1}H and ^{13}C NMR data, see ○ **Table 1**; HRESIMS m/z 655.2190 [M + Na]$^+$ (calcd. for C$_{33}$H$_{38}$O$_{13}$Na, 655.2210).

(3): Colorless gum; $[\alpha]_D^{20}$ + 94.7 (c 0.025, CH$_3$CN); ECD (MeCN, λ_{max} [nm] ($\Delta\varepsilon$), c = 1.46 × 10^{-4}): 286 (3.34), 260 (1.71), 211 (5.38). IR (KBr) v_{max} 2985, 1740, 1610, 1422, 1400, 1240, 1035 cm^{-1}; ^{1}H and ^{13}C NMR data, see ○ **Table 2**; HRESIMS m/z 707.2319 [M + Na]$^+$ (calcd. for C$_{35}$H$_{40}$O$_{14}$Na, 707.2316).

(4): Colorless gum; $[\alpha]_D^{20}$ + 40 (c 0.03, CH$_3$CN); IR (KBr) v_{max} 2900, 1735, 1600, 1412, 1375, 1240, 1027 cm^{-1}; ^{1}H and ^{13}C NMR data, see ○ **Table 2**; HRESIMS m/z 765.2362 [M + Na]$^+$ (calcd. for C$_{37}$H$_{42}$O$_{16}$Na, 765.2371).

Supporting information

Original spectra for compounds **1**–**4**, the CD spectra, details regarding the experimental protocols, and crystal data for xyloc-censin Q (**7**) are available as Supporting Information.

Acknowledgements
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Conflict of Interest
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The authors declare no conflict of interest.

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