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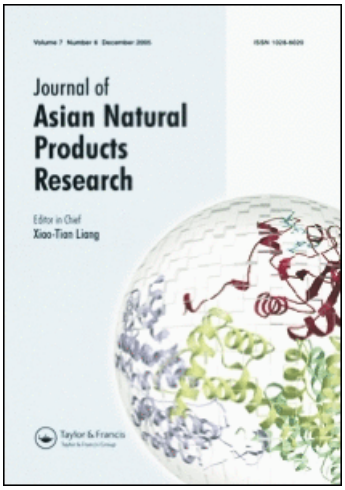

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Three new triterpenoid saponins from the leaves and stems of *Panax quinquefolium*

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Three new triterpenoid saponins from the leaves and stems of *Panax quinquefolium*

Jing Chen[a], Rui Zhao[b], Yi-Mei Zeng[a], Hei Meng[a], Wen-Jian Zuo[a], Xian Li[a] and Jin-Hui Wang[a]*

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Three new minor dammarane saponins, quinquenosides L10 (**1**), L14 (**2**), and L16 (**3**), were isolated from the leaves and stems of *Panax quinquefolium* L. By the combination of one- and two-dimensional NMR techniques and MS spectroscopic analysis, their structures were established as 20-*O*-(α-L-arabinopyranosyl-(1-6)-*O*-β-D-glucopyranosyl)-3-*O*-β-D-glucopyranosyl-dammar-24-ene-3,12, 20-triol (**1**), 20-*O*-α-L-arabinopyranosyl-3-*O*-(β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl)-dammar-24-ene-3,12,20-triol (**2**), 3-*O*-(β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl)-20-*O*-(β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl)-dammarane-3,12,20,24,25-pentaol (**3**). The content of artemisinin was significantly enhanced by 3.0 mg l^{-1} of compounds **1**, **2**, and **3** in the callus of *Artemisia annua*.

Keywords: *Panax quinquefolium* L.; leaves and stems; quinquenoside L10; quinquenoside L14; quinquenoside L16

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1. Introduction

American ginseng (roots of *Panax quinquefolium* L.) is well known for its tonic value worldwide. The leaves and stems of *P. quinquefolium* L. also show similar medical effects in recent research [1]. Chemical investigations on saponin composition of the leaves and stems of *P. quinquefolium* [2–5] have been reported by us, then in the continuation of the investigations, we report here the isolation and structural elucidation of three new minor saponins, quinquenosides L10 (**1**), L14 (**2**), and L16 (**3**).

2. Results and discussion

Quinquenoside L10 (**1**) was obtained as a white amorphous solid. Liebermann–Burchard and Molish reactions were positive. The HR-ESI-MS indicated the molecular formula of **1** to be $C_{47}H_{80}O_{17}$. The sugars were identified as D-glucose and L-arabinose by acid hydrolysis and GC compared with authentic samples. They were determined as two β-linked sugars (D-glucose) and one α-linked sugar (L-arabinose) by the coupling constants of the anomeric protons [δ 5.14 (1H, d, $J = 7.5$ Hz, H-1′), 4.98 (1H, d, $J = 7.0$ Hz, H-1‴), and 4.90 (1H, d, $J = 7.5$ Hz, H-1″)] in the ^{1}H NMR spectrum. The NMR spectra (Table 1) of **1** indicated the presence of a 20(*S*)-protopanaxadiol moiety [1]. A HSQC-TOCSY experiment on **1** showed the presence of characteristic cross-peak between H-1′ and C-6′. In the HMBC experiment, characteristic cross-peaks were observed between H-1‴ and C-6′, H-1′ and C-20, H-1″ and C-3 (Figure 1). The foregoing evidences demonstrated that β-L-arabinopyranosyl-(1-6)-β-D-glucopyranosyl moiety was located at C-20 and β-D-glucopyranosyl moiety connected with C-3. Thus, **1** was

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Table 1. ^{13}C NMR spectral data of quinquenosides L10 (**1**), L14 (**2**), and L16 (**3**).

No.	L10 (**1**)	L14 (**2**)	L16 (**3**)	No.	L10 (**1**)	L14 (**2**)	L16 (**3**)
1	39.5	39.6	39.2		3-glc	3-glc	3-glc
2	26.6	26.7	27.8	1′	106.0	105.0	105.1
3	88.8	88.6	89.0	2′	75.7	82.9	83.5
4	39.6	39.6	39.7	3′	79.1	77.9	78.1
5	56.4	56.4	56.4	4′	71.9	71.6	71.7
6	18.4	18.3	18.5	5′	78.2	78.0	77.2
7	35.1	35.1	35.2	6′	63.1	62.7	62.7
8	40.0	40.0	40.0		20-glc	20-ara(p)	20-glc
9	50.2	50.1	49.6	1″	98.0	98.6	98.1
10	36.9	36.8	36.9	2″	74.8	72.5	74.9
11	30.7	30.6	32.1	3″	78.2	77.9	78.3
12	70.1	69.9	71.7	4″	71.8	69.4	71.7
13	49.4	49.4	49.4	5″	76.6	66.8	78.3
14	51.3	51.3	50.3	6″	69.1		69.2
15	30.6	29.9	30.7		6′-ara(p)	2′-glc	2′-glc
16	26.7	26.5	26.8	1‴	104.5	106.0	106.1
17	51.6	51.4	51.5	2‴	72.0	77.0	77.2
18	17.3	16.1	16.3	3‴	77.8	78.3	78.2
19	16.1	15.9	16.3	4‴	68.4	71.6	71.7
20	83.0	83.5	83.5	5‴	65.4	78.1	78.0
21	22.3	22.1	28.1	6‴		62.7	62.7
22	36.1	36.8	33.6				6″-glc
23	23.1	23.1	26.3	1⁗			106.1
24	125.9	125.8	70.1	2⁗			75.3
25	131.0	131.1	72.0	3⁗			78.3
26	25.7	25.6	25.9	4⁗			71.7
27	15.9	17.3	26.1	5⁗			78.0
28	28.1	28.0	28.1	6⁗			62.8
29	16.7	16.5	16.6				
30	17.8	17.4	17.3				

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established as 20-*O*-(α-L-arabinopyranosyl-(1-6)-β-D-glucopyranosyl)-3-*O*-β-D-glucopyranosyl-dammar-24-ene-3,12,20-triol, which was shown in Figure 1, named quinquenoside L10.

Quinquenoside L14 (**2**) was obtained as a white amorphous solid, and its Liebermann–Burchard and Molish reactions were positive. The HR-ESI-MS indicated the molecular formula of **2** to be $C_{47}H_{80}O_{17}$. The sugars were identified as D-glucose and L-arabinose by acid hydrolysis and GC compared with authentic samples. The ^1H NMR spectrum of **2** showed two anomeric doublets of D-glucose at δ 4.98 (1H, d, $J = 7.5$ Hz, H-1′) and 5.37 (1H, d, $J = 7.5$ Hz, H-1‴), an anomeric doublet of a L-arabinose at δ 4.83 (1H, d, $J = 7.5$ Hz, H-1″), indicating the presence of two β-linked sugars (D-glucose) and one α-linked sugar (L-arabinose). The ^1H and ^{13}C NMR spectral data (Table 1) of **2** suggested the presence of a 20(*S*)-protopanaxadiol moiety as **1**. In the $^1H-^1H$ COSY spectrum, H-1′ (δ 4.98) showed correlation with H-2′ (δ 3.92). Together with $^1H-^{13}C$ long-range correlations between H-1′ and C-3, H-2′ and C-1′, H-1‴ and C-2′, and H-1″ and C-20, it was possible to confirm that β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl moiety was connected to C-3, and β-L-arabinosyl group was located at the C-20 (Figure 1). Thus, the structure of **2** was confirmed as 20-*O*-α-L-arabinopyranosyl-3-*O*-(β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl)-dammar-24-ene-3,12,20-triol, named quinquenoside L14 (Figure 2).

Quinquenoside L16 (**3**) was obtained as a white amorphous solid. Its Liebermann–Burchard and Molish reactions were positive.

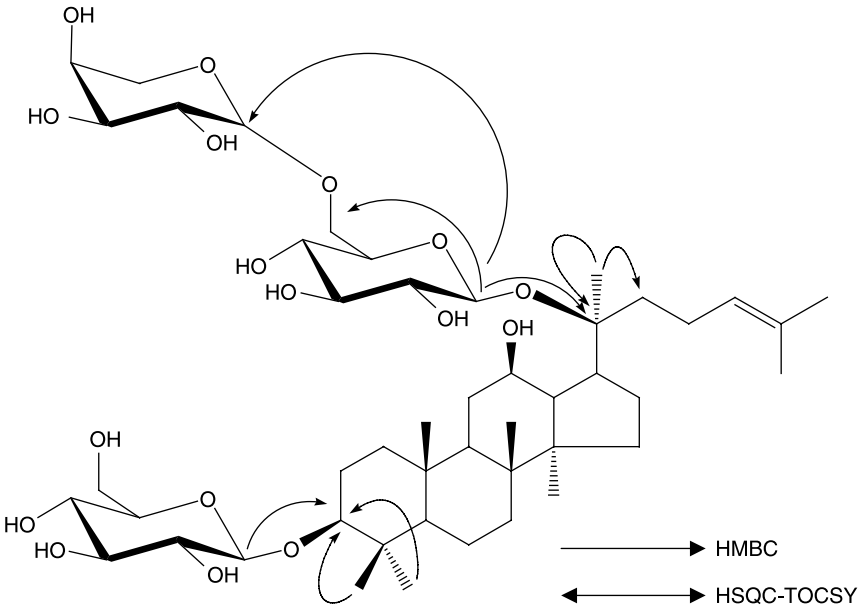

Figure 1. Key HSQC-TOCSY and HMBC correlations of quinquenosides L10 (**1**).

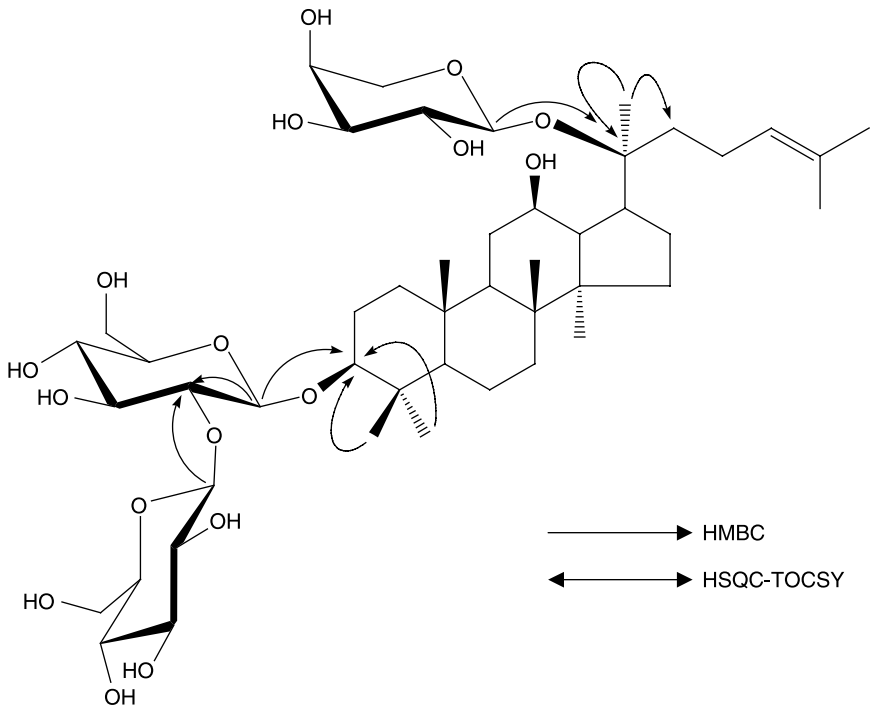

Figure 2. Key HMBC correlations of quinquenosides L14 (**2**).

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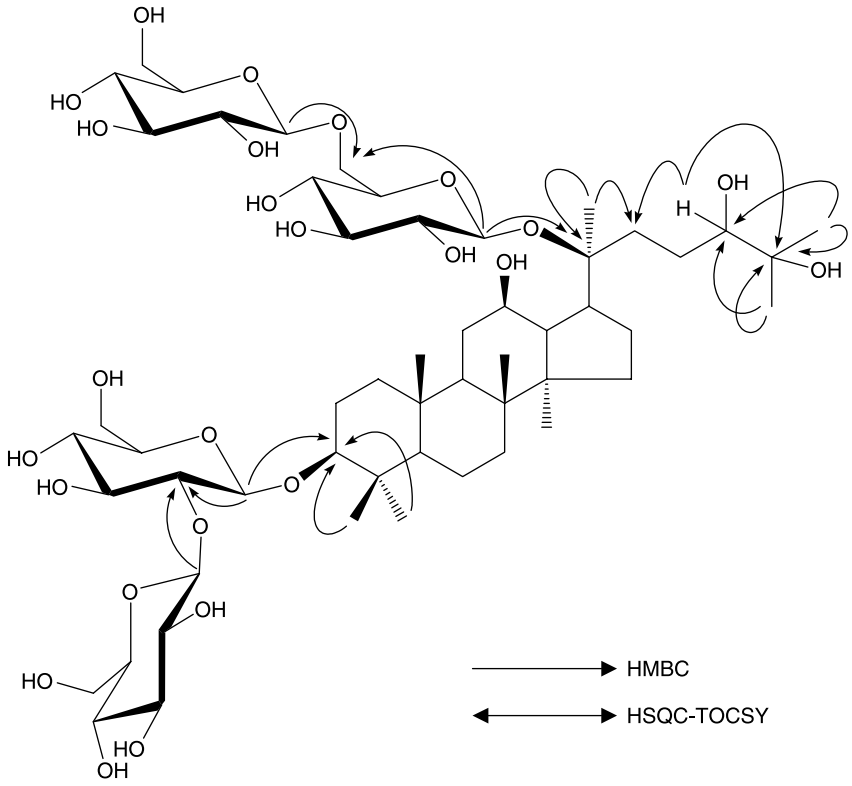

Figure 3. Key HSQC-TOCSY and HMBC correlations of quinquenosides L16 (**3**).

The HR-ESI-MS indicated the molecular formula of **3** to be $C_{54}H_{94}O_{25}$. The sugars were identified as D-glucose and L-arabinose by acid hydrolysis and GC compared with authentic samples. The ^{1}H NMR spectrum of **3** showed four anomeric doublets of D-glucose at δ 4.92 (1H, d, $J = 7.5$ Hz, H-1′), 5.10 (1H, d, $J = 7.5$ Hz, H-1″), 5.37 (1H, d, $J = 7.5$ Hz, H-1‴), and 5.13 (1H, d, $J = 7.5$ Hz, H-1⁗), indicating the presence of β-linked D-glucose. The ^{1}H and ^{13}C NMR spectral data (Table 1) of **3** suggested the presence of a 20(*S*)-dammarane-3,12,20-triol moiety as **1**. But there was no olefinic signal of H-24 in the ^{1}H and ^{13}C NMR spectrum of **3**, indicating that there was no 24-ene moiety in **3**. In the HMBC spectrum, H-26, 27 showed long-range correlations to C-24 and C-25, together with ^{1}H–^{13}C long-range correlations between H-24 and C-22, C-25. Thus, it was possible to confirm that **3** has a 24,25-diol moiety, as quinquenoside L9 [6].

A HSQC-TOCSY experiment of **3** showed the presence of characteristic cross-peak between H-1″ and C-6″. In the HMBC spectrum, characteristic correlations were observed between H-1⁗ and C-6″, H-1″ and C-20, H-1′ and C-3, and H-1⁗ and C-2′ (Figure 3), which suggested that β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl moiety was located at C-20 and β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl moiety was connected to C-3. Thus, the structure of **3** was established as 3-*O*-(β-D-glucopyranosyl-(1-2)-*O*-β-D-glucopyranosyl)-20-*O*-(β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl)-dammarane-3,12,20,24,25-pentaol, named quinquenoside L16.

Calli induced from *Artemisia annua* L. leaf on MS mediums (1962) [7] supplemented with sucrose (3%, w/v), agar (0.7%, w/v), 0.5 mg l^{-1} of 2,4-D, and 1.0 mg l^{-1} of 6-BA were chosen as experimental materials. The materials were subcultured on MS

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Table 2. Contents of artemisinin in the callus subcultured on MS mediums supplemented with different saponins after 42 days cultivation.

Group	Mean ± SD (mg g^{-1})	RSD% ($n = 6$)
1	0.98 ± 0.24*	8.5
2	0.64 ± 0.17*	9.8
3	0.58 ± 0.13*	7.6
Control	0.00	–

*$P < 0.01$; SD, standard deviation; RSD, relative SD of six replicates.

mediums supplemented with sucrose (3%, w/v), agar (0.7%, w/v), 0.5 mg l^{-1} of 6-BA, and 4 mg l^{-1} of IAA. Except for the control, 3 mg l^{-1} of compounds **1**, **2**, and **3** were also added into the above MS mediums, respectively. All the materials belonged to homogeneous callus, which was derived from the same leaf to ensure homologue and comparability. Callus was cultured at 25 ± 2°C under 16/8 h photoperiod. After 42 days of subculture, the calli were separately harvested and dried at room temperature. Six replicates were selected randomly from each group and treated as above. The dried solid calli were crushed in a mortar and about 100 mg were extracted with a total of 2 ml petroleum ether and acetone (1:1, v/v) as extraction solvent for 20 min in an ultrasonic bath. Organic solvent fractions were evaporated and the residue was dissolved in 200 μl MeOH accurately. Determination of artemisinin was performed on the HPLC-ELSD system equipped with a Venusil XBP-C_{18} column (C_{18}, 200 mm × 4.6 mm, 5 μm) as the literature reported [8].

Statistic analysis data (by Student's *t*-test) of artemisinin content between ginsenoside-treated groups and control group were shown in Table 2. The content of artemisinin was significantly enhanced by 3.0 mg ml^{-1} of compounds **1**, **2**, and **3**, up to 0.98 ± 0.24 mg g^{-1}, 0.64 ± 0.17 mg g^{-1}, and 0.58 ± 0.13 mg g^{-1} ($P < 0.05$, $n = 6$), respectively. No artemisinin was detected in the control group free of saponins. The results showed that the three new ginsenoside could remarkably promote the biosynthesis of artemisinin in the callus. It might be relevant to the positive effects of ginsenosides on the redifferentiation of callus as the study reported [9].

3. Experimental

3.1 General experimental procedures

The melting points were determined on Yamaco MP-S3 Micro-hot stage and are uncorrected. ESI-MS was performed on Finnigan LCQ mass spectrometer. HR-ESI-MS was performed on QSTAR LCQ mass spectrometer. A model CD-2095 Chiral Detector (Jasco, Tokyo, Japan) was used for CD analysis. The IR spectra were recorded on Bruker IR S-55 spectrometer. The NMR spectra were recorded in pyridine-d_5 on a Bruker AV-600 spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz), using TMS as the internal standard. For HMQC-TOCSY, data matrix is 384 × 1024 points, applying a zero filling in the F1, F2 dimension and a 90° shifted qsine window function in both dimensions, consisting of 1024 × 1024 points, going along FT transform. Preparative HPLC was carried out on a Hitachi L-7420 UV–vis spectrophotometric detector at 210 nm and TEDAchrom YWG C18 reversed phase column (250 mm × 20 mm, i.d. 10 μm). Silica gel for chromatography was produced by Qingdao Ocean Chemical Group Co. of China.

3.2 Plant material

The leaves and stems of *P. quinquefolium* L. were collected from Canada by Dalian Tianma Pharmacy Co. Ltd, and was identified by Prof. Tiande Qing. A voucher specimen (No. 20061009) has been deposited in the School of Chinese medicine, Shenyang Pharmaceutical University in China.

3.3 Extraction and isolation

Dried leaves and stems of *P. quinquefolium* L. (2.0 kg) were extracted with hot water (3 × 20 l) and the water soluble fraction was extracted with $CHCl_3$ and *n*-BuOH.

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The *n*-BuOH extract was subjected to column chromatography on reversed-phase highly porous polymer column D101, and was eluted with H_2O (40 l) and 95% EtOH (40 l), and then afforded the EtOH fraction (312 g). A part of the EtOH fraction (100 g) was chromatographed over a silica gel column (400 g) to yield fraction A ($CHCl_3$–CH_3OH 100:15) and fraction B ($CHCl_3$–CH_3OH 100:30). Fraction A was rechromatographed over an ODS column eluting with 60% MeOH to give fraction A-1 and 70% MeOH to give fraction A-2, and fraction A-2 was then subjected to preparative RP-HPLC (75% MeOH) to yield **1** (15 mg, $t_R = 54$ min) and **2** (10 mg, $t_R = 43$ min). Fraction B was rechromatographed over an ODS column eluting with 70% MeOH to give fraction B-1 and 80% MeOH to give fraction B-2. Fraction B-2 was then subjected to preparative RP-HPLC (45% CH_3CN) to yield **3** (13 mg, $t_R = 62$ min).

3.3.1 *Compound **1***

White amorphous solid; IR(KBr) ν_{max} (cm^{-1}): 3420 (νOH), 2925 (νCH), 1652 (νC═C), 1384, 1078, 1040, and 624. ^{1}H NMR (600 MHz, Pry-d_5) δ: 5.26 (1H, brs, H-24), 5.14 (1H, d, $J = 7.5$ Hz, H-1′), 4.98 (1H, d, $J = 7.0$ Hz, H-1‴), 4.90 (1H, d, $J = 7.5$ Hz, H-1″), 3.18 (1H, dd, $J = 8.0$, 2.8 Hz, H-3), 1.61 (3H, s, 27-CH_3), 1.61 (3H, s, 21-CH_3), 1.60 (3H, s, 26-CH_3), 1.28 (3H, s, 28-CH_3), 0.98 (3H, s, 29-CH_3), 0.95 (3H, s, 30-CH_3), 0.92 (3H, s, 18-CH_3), and 0.77 (3H, s, 19-CH_3); ^{13}C NMR spectral data, see Table 1. HR-ESI-MS *m/z*: 917.5453 $[M + H]^+$ (calcd for $C_{47}H_{81}O_{17}$, 917.5474) and 939.5309 $[M + Na]^+$ (calcd for $C_{47}H_{80}O_{17}Na$, 939.5293). CD (MeOH) $\Delta\varepsilon_{220\,nm}$ +4.78, $\Delta\varepsilon_{337\,nm}$ −0.52, and $\Delta\varepsilon_{350\,nm}$ +0.33.

3.3.2 *Compound **2***

White amorphous solid; IR(KBr) ν_{max} (cm^{-1}): 3420 (νOH), 2932 (νCH), 1384, 1078, 1050, 1030, and 620. ^{1}H NMR (600 MHz, Pry-d_5) δ: 5.26 (1H, t, $J = 7.0$ Hz, H-24), 4.98 (1H, d, $J = 7.5$ Hz, H-1′), 5.37 (1H, d, $J = 7.5$ Hz, H-1″), 4.83 (1H, d, $J = 7.5$ Hz, H-1‴), 3.22 (1H, m, H-3), 1.60 (3H, s, 27-CH_3), 1.60 (3H, s, 21-CH_3), 1.55 (3H, s, 26-CH_3), 1.27 (3H, s, 28-CH_3), 1.10 (3H, s, 29-CH_3), 0.94 (3H, s, 30-CH_3), 0.94 (3H, s, 18-CH_3), and 0.79 (3H, s, 19-CH_3); ^{13}C NMR spectral data, see Table 1. HR-ESI-MS *m/z*: 917.5463 $[M + H]^+$ (calcd for $C_{47}H_{81}O_{17}$, 917.5474). CD (MeOH) $\Delta\varepsilon_{220\,nm}$ +0.74 and $\Delta\varepsilon_{336\,nm}$ −0.17.

3.3.3 *Compound **3***

White amorphous solid; IR(KBr) ν_{max} (cm^{-1}): 3420 (νOH), 2925 (νCH), 1384, 1076, 1030, and 584. ^{1}H NMR (600 MHz, Pry-d_5) δ: 4.92 (1H, d, $J = 7.5$ Hz, H-1′), 5.10 (1H, d, $J = 7.5$ Hz, H-1″), 5.37 (1H, d, $J = 7.5$ Hz, H-1″) and 5.13 (1H, d, $J = 7.5$ Hz, H-1″), 3.24 (1H, m, 3H), 1.60 (3H, s, 21-CH_3), 1.28 (3H, s, 29-CH_3), 1.27 (3H, s, 28-CH_3), 1.35 (3H, s, 26-CH_3), 1.20 (3H, s, 27-CH_3), 1.10 (3H, s, 30-CH_3), 0.96 (3H, s, 18-CH_3), and 0.80 (3H, s, 19-CH_3); ^{13}C NMR spectral data, see Table 1. HR-ESI-MS *m/z*: 1143.6175 $[M + H]^+$ (calcd for $C_{54}H_{95}O_{25}$, 1143.6162). CD (MeOH) $\Delta\varepsilon_{220\,nm}$ +2.84 and $\Delta\varepsilon_{337\,nm}$ −0.38.

3.4 *Acid hydrolysis*

A solution of compounds **1**, **2**, or **3** (3.0 mg each) in 2 M trifluoroacetic acid (1 ml) was heated at 110°C for 2 h, and then dried by N_2 gas. After cooling, the reaction mixture was neutralized with Amberlite IRA-400 resin (OH^- form) and the resin was filtered. After removal of the solvent under pressure from the filtrate, the residue was passed through a Sep-Pak C18 cartridge with H_2O and MeOH. The H_2O eluate was concentrated and the residue was treated with L-cysteine methyl ester hydrochloride (2.0 mg) in pyridine (1.0 ml) at 60°C for 2 h. After dried by N_2 gas, the residue was treated with *N*-(trimethylsilyl)imidazol (0.2 ml) at 60°C for 1 h. The reaction was ended by adding water (1.0 ml), and extracted with cyclohexane (1.0 ml, three times). The cyclohexane layer

was collected and concentrated to 1.0 ml for GC analysis to identify the derivatives of D-glucose (**4**), L-arabinose (**5**) from compounds **1**, **2**, and **3**.

GC analysis was performed with an OV-17 column and an H_2 flame ionization detector at a column temperature of 220°C, vaporizer temperature of 280°C, and detector temperature of 280°C. The R_t of **4** and **5** are 14.0 and 7.3 min, respectively.

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