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Short communication

Three new monoterpene glycosides from *Sibiraea laevigata* (L.) Maxim

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ABSTRACT

Three new compounds, 3,7-dimethy-7-methoxy-3-octene-5-one-1-*O*-*β*-D-glucopyranoside (1), 3,7-dimethy-7-methoxy-3(*Z*)-octene-5-one-1-*O*-*β*-D-glucopyranoside (2) and 3,7-dimethy-3-hydroxy-6-octene-5-one-1-*O*-*β*-D-glucopyranoside (3), together with fourteen known compounds (4–17) were isolated from the leaves and shoots of *S. laevigata*. The structures of the new compounds were elucidated on the basis of extensive spectroscopic analysis, including one- and two-dimensional NMR, as well as mass spectral data. All isolates were evaluated for their α-glucosidase inhibitory and antioxidant activities. The results demonstrated that 3,7-dimethyl-3(Z),6-ocatdien-5-one-1-*O*-*β*-D-glucoside (7) and sitosteryl *β*-D-glucoside (17) exhibited α-glucosidase inhibitory effects with IC_{50} values of 220.0 and 113.0 μM, respectively.

1. Introduction

"Liucha" is used by Tibetan people to make tea as a treatment for dyspepsia and epigastric fullness after eating. Liucha is obtained from two species of *Sibiraea* (Rosaceae), *S. laevigata* and *S. angustata*, which are endemic to the plateau region between 2000 and 4000 m above sea level. *S. laevigata* and *S. angustata* mainly grow in Tibet, Qinghai and Gansu of China and *S. angustata* is also distributed in the Sichuan and Yunnan provinces (Editorial Committee of Chinese flora, 1974). The leaf shape of these two species is similar to that of a willow leaf, which is the source of the name of "Liucha" (willow tea). In addition, people have believed that drinking "Liucha" can offer health benefits. It has been commonly known that livestock such as cattle and goats have their spirits raised and their skins and hair become silky after taking "Liucha." Meanwhile, they would also lose weight, suggesting a potential anti-obesity effect of "Liucha". Thus, Liu and co-workers carried out experiments to explore the anti-obesity effect of the water extract of *S. angustata*. The results showed that the water extract of *S. angustata* can not only regulate lipid metabolism in obese rats but also inhibit the increase of rats body weight (Wang et al., 2010; Xia et al., 2011). Chemical constituent studies on *S. angustata* reveal that monoterpene glycosides are its main characteristic components, and these showed hypolipidemic and weight-loss effects (Ito et al., 2009; Wang et al., 2013; Li et al., 2010, 2015). For example, sibiskoside, a monoterpene glucoside from *S. angustata*, significantly affected the plasma levels of total cholesterol, triglycerides, and blood glucose (Ito et al., 2009). Previous bioactivity and phytochemical investigations of "Liucha" focused on *S. angustata*. Only Lai et al. reported the composition and antioxidant activity of the essential oil from aboveground parts of *S. laevigata* (Lai et al., 2016). In addition, we previously reported new monoterpenes from the EtOAc fraction of *S. laevigata* (Zhao et al., 2016). To identify the chemical constituents of "Liucha", we conducted a phytochemical study on the *n*-BuOH fraction of *S. laevigata*. Herein, we reported the separation procedure and the structural elucidation of the monoterpene glycosides and other compounds from *S. laevigata*. To explore the health benefits of "Liucha", α-glucosidase inhibitory and antioxidant activities of all of the isolates were also tested.

2. Results and discussion

Multistep column chromatography separation of the *n*-BuOH layer from the 95% ethanol extract of the young leaves and shoots of *S. leavigata* led to the isolation of seventeen compounds (**1**–**17**), including three new monoterpene glycosides (**1**–**3**) (Fig. 1).

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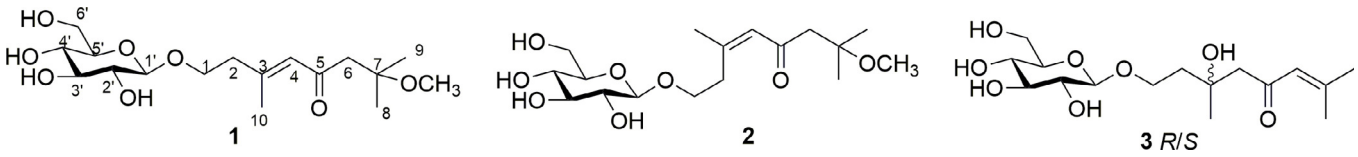

Fig. 1. Chemical structures of compounds **1**–**3**.

Compound **1** was obtained as light yellow gum with a chemical formula defined as $C_{17}H_{30}O_8$ according to HRESIMS. The IR spectrum of compound **1** showed absorption bands for hydroxy (3400 cm^{-1}) group, carbonyl (1679 cm^{-1}) group conjugated with double bond, and olefinic (1614 cm^{-1}) group. The ^1H NMR spectrum showed the presence of protons in the double bond [δ_H 6.32 (1H, s), H-4], methoxy [δ_H 3.25 (3H, s)] group, vinyl methyl [δ_H 2.15 (3H, s)] group, gem-dimethyl [δ_H 1.26 (6H, s)] group and an anomeric proton [δ_H 4.3 (1H, d, J = 7.8 Hz)]. The ^{13}C NMR spectrum suggested the presence of seventeen carbon signals, and these signals were further interpreted through an HSQC spectrum, indicating the presence of a carbonyl, a trisubstituted double bond, three methylene groups, including one oxygen-bearing methylene, three methyls, a methoxy group, and six carbons attributed to a sugar moiety. The proton sequence of (O)-CH_2(H-1)-CH(H-2) and the sugar unit were confirmed by the corresponding ^1H-^1H COSY cross-peaks. The sugar moiety was identified as β-D-glucopyranose by acid hydrolysis analysis, by comparison of the ^{13}C NMR data with those of β-D-glucopyranose reported in the literature (Yao et al., 2016) and by the large coupling constant of the anomeric proton. The abovementioned structural units were further constructed through inspection of the HMBC spectrum. The correlations from H-1 to C-3, from H-2 and H-6 to C-4, from H-8 and H-9 to C-6, from H-4 and H-6 to C-5, and from H-10 to C-2 were consistent with the structure of an acyclic monoterpene, as shown in Fig. 2. The HMBC correlation from H-1′ to C-1 illustrated that the β-D-glucopyranose was located at C-1, and the correlation from the methoxy protons to C-7 confirmed that the methoxy group was located at C-7. Hence, the planar structure of **1** was determined to be 3,7-dimethy-7-methoxy-3-octene-5-one-1-*O*-β-D-glucopyranoside (Fig. 1). The identification of the *Z*/*E* isomer for compound **1** was made from a NOESY experiment (Fig. 2). NOESY correlations between H-2 and H-4 confirmed the *E*-configuration of **1**.

Compound **2** showed a pseudo-molecular ion $[M+Na]^+$ at m/z 385.1872 in the HRESIMS spectrum consistent with the molecular formula $C_{17}H_{30}O_8$, which is the same as that of **1**. In addition, the UV, IR, and NMR spectral features of **2** were similar with those of **1**. Thus, **2** was identified as an isomer of **1**. Compared with the same proton in **1**, the H-2 proton in **2** was shielded. Conversely, the carbon of C-2 was deshielded in **2**, indicating that compound **2** was a *Z*-isomer of **1** (Maldonado et al., 1998). A NOESY experiment (Fig. 2) also confirmed the result through the correlations between H-4 and H-10. Thus, compound **2** was identified as 3,7-dimethy-7-methoxy-3(*Z*)-octene-5-one-1-*O*-β-D-glucopyranoside. The structures of compounds **1** and **2** showed a high resemblance to the structure of sibiraglycoside K, which was isolated from the other source of "Liucha", *S. angustata*. The only difference between the structures was an additional methoxy group in **1** and **2** (Yao et al., 2016).

Compound **3** was also obtained as light yellow gum and was assigned a molecular formula of $C_{16}H_{28}O_8$, which was determined through HRESIMS to be the same as sibiraglycosides I (**4**) and J (**5**). The IR spectrum of **3** also showed presence of a hydroxy (3408 cm^{-1}) group, conjugated carbonyl (1672 cm^{-1}) group, and olefinic (1613 cm^{-1}) group. Inspection of the ^{13}C NMR spectrum of **3** revealed the presence of a carbonyl group (δ_C 202.4), a double bond (δ_C 157.3 and 126.4), an oxygen-bearing quaternary carbon (δ_C 72.5), an oxymethylene (δ_C 67.0), and carbon signals due to a sugar unit. In addition, the NMR spectrum of **3** closely resembled those of sibiraglycoside I (**4**) and J (**5**), indicating that **3** was an isomeride of **4** and **5** (Yao et al., 2016). The structure of **3** was deduced through 2D NMR correlations. The hydroxyl group was attached at C-3, which was supported by HMBC correlations from H-1 to C-3 and C-1′. HMBC correlations from the methyls (δ_H 2.12 and 1.91) and H-4 to the tertiary carbon (δ_C 126.4) of the double bond, and from the olefinic proton and H-4 to the carbonyl supported the presence of an isobutenyl group that was connected with the carbonyl. Using this data, along with the correlations from the singlet methyl to C-2 and C-4, the planar structure of **3** was established as 3,7-dimethy-3-hydroxy-6-octene-5-one-1-*O*-β-D-glucopyranoside. It was noted that the ^{13}C NMR spectra of compound **3** recorded at room temperature exhibited the doubling of some signals. This observation could result from the *R*/*S* configuration of the hydroxyl group at C-3. Because there was no large, sterically hindering group on the hydroxyl, the molecular could be very flexible and thus we could not separate the two enantiomorphs. Thus, the structure of compound **3** could be only elucidated as a planar structure.

The other known compounds were identified as sibiraglycoside I (**4**) (Yao et al., 2016), sibiraglycoside J (**5**) (Yao et al., 2016),

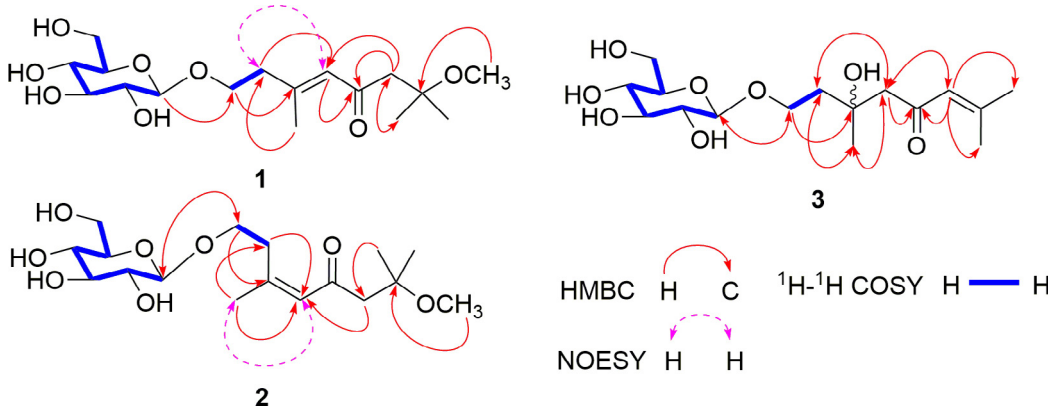

Fig. 2. Key HMBC, NOESY, and ^1H-^1H COSY correlations of compounds **1**–**3**.

3,7-dimethyl-3(*E*),6-ocatdien-5-one-1-*O*-*β*-D-glucoside (**6**) (Takeda et al., 1990), 3,7-dimethyl-3(*Z*),6-ocatdien-5-one-1-*O*-*β*-D-glucoside (**7**) (Takeda et al., 1990), 3,7-dimethyl-2(*E*),6-ocatdien-5-one-1-*O*-*β*-D-glucoside (**8**) (Takeda et al., 1990), sibiraglucoside G (**9**) (Wang et al., 2013), sibiraglucoside H (**10**) (Wang et al., 2013), sibiskoside (**11**) (Ito et al., 2009), kodemarioside A (**12**) (Yoshida et al., 2010), kodemarioside E (**13**) (Yoshida et al., 2010), cimicifugolide A (**14**) (Ma et al., 2013), (3*S*)-4-α-hydroxy-3-(2-hydroxyethyl-idene)-5-*β*-(2-methyl-prop-1-enyl)-dihydrofuran-2-one (**15**) (Ma et al., 2013), 4-(*β*-D-glucopyranosyloxy)-3-(3-methyl-2-butenyl) benzoic acid (**16**) (Bilia et al., 1993), and sitosteryl *β*-D-glucoside (**17**) (Sakakibara et al., 1983) through comparison of NMR data with those reported in the literature.

All compounds isolated from *S. laevigata* were evaluated for their α-glucosidase inhibitory effect and antioxidant activity using ABTS and DPPH radical scavenging assays. The results showed that compounds **9**, **10**, **12**, and **13** displayed radical scavenging effect against ABTS radical with SC_{50} values of 25.3, 27.3, 39.3 and 31.6 μM, respectively. They also showed potent radical scavenging effect against DPPH radical with SC_{50} values of 28.3, 25.1, 31.6, and 30.8 μM, respectively. Compounds **7** and **17** exhibited α-glucosidase inhibitory effects with IC_{50} values of 220.0 and 113.0 μM, respectively. Acarbose was used as positive control with the IC_{50} values of 182.9 μM.

3. Materials and methods

3.1. General experimental procedures

IR spectra were recorded on a Bruker Tensor-27 FT-IR spectrometer (Bruker Corporation, Germany) with KBr pellets. Optical rotations were acquired on Jasco P-1020 automatic polarimeter (Jasco Inc, Easton, MD, USA). UV spectra were measured on a Shimadzu UV2401A ultraviolet-visible spectrophotometer (Shimadzu Corporation, Kyoto, Japan). HRESIMS were recorded on an API Qstar Pulsa LC/TOF spectrometer. NMR spectra were obtained on a Bruker Avance III-600 spectrometer, using TMS as an internal standard. Chemical shifts were reported in units of *δ* (ppm), and coupling constants (*J*) were expressed in Hz. Column chromatography (CC) was carried out over silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Qingdao, China) and MCI gel CHP 20P (75–150 μm, Tokyo, Japan). Pre-coated silica gel plates (Qingdao Haiyang Chemical Co., Qingdao, China) were used for TLC. TLC detection was done under UV light (254 nm and 365 nm) and by spraying the plates with a 10% sulfuric acid ethanol solution followed by heating. An Agilent series 1200 (Agilent Technologies) was used for analytical HPLC. Preparative HPLC (prep-HPLC) was done on a Hanbon liquid chromatograph (Hanbon Sci & Tech, Jiangsu, China). Prep-HPLC columns DAC-HB50, XAqua C-18 and XAmide (10 μm, 100 Å, 250 mm × 20 mm, Acchrom, Beijing, China) were used in for compound separation. 1,1-Diphenyl-2-picrylhydrazyl free radical (DPPH, purity >97%), 2,2′-Azinobis-(3-ethylbenzthiazoline-6-sulfonate) (ABTS, purity >98%) and *p*-nitrophenyl α-D-glucopyranoside (pNPG, purity ≥98%) were obtained from Sigma (St. Louis, MO, USA).

3.2. Plant material

The young leaves and shoots of *S. leavigata* were collected in Huzhu City, Qinghai Province, China in August 2011 and were identified by Professor Lijuan Mei. A voucher specimen (No. 0317608) was deposited in the Key Laboratory of Tibetan Medicine Research (Northwest Institute of Plateau Biology, Chinese Academy of Science).

3.3. Extraction and isolation

The air-dried and powdered young leaves and shoots of *S. leavigata* (9.5 kg) were extracted with 95% ethanol under reflux. After removal of the organic solvent, the ethanol extract was suspended in water and then extracted successively with EtOAc and *n*-BuOH. The *n*-BuOH fraction (300 g) was subjected to a silica gel CC, eluting with a $CHCl_3$-MeOH-H_2O gradient system (9:1:0.1–6:4:1, v/v/v), to give four fractions (Fr. 1–4). Fr. 1 (80 g) was separated by MCI gel CHP 20P CC, eluting with a gradient of aqueous MeOH (elution with 10%-90% of methanol) to yield fractions 1a–1c. Fraction 1a was subjected to a silica gel CC, eluting with an isocratic system of $CHCl_3$-MeOH-H_2O (9:1:0.1) to yield compounds **16** (6 mg) and **17** (51 mg). Fraction 1b was further subjected to prep-HPLC using column DAC-HB50 to obtain fractions 1b-1 and 1b-2. Compounds **1** (22 mg) and **2** (51 mg) were obtained from fraction 1b-1 through purification on an XCharge C18 column (elution with 14% MeCN with 0.2% FA for 20 min, with a flow rate of 15 mL/min). Using the same purification method, compound **8** (33 mg) was obtained from fraction 1b-2. Fraction 1c was purified on an XCharge C18 column (elution with 10–40% MeCN with 0.2% FA for 60 min with a flow rate of 15 mL/min) to yield compounds **14** (11 mg) and **15** (7 mg). Fr. 2 (54 g) was separated by MCI gel CHP 20P CC, eluting with 90% aqueous MeOH to give Fr. 21 (27 g), followed by preparative HPLC on a DAC-HB50 column (elution with 30–50% MeOH with 0.2% FA for 60 min with a flow rate of 60 mL/min) to yield fractions 2a and 2b. Fraction 2b was further purified on an XCharge C18 column (elution with 10–30% MeCN with 0.2% FA for 60 min with a flow rate of 15 mL/min) to yield compounds **4** (22 mg) and **5** (51 mg). Fr. 3 (37 g) was purified by prep-HPLC using a DAC-HB50 column (elution with 30–60% MeOH with 0.2% FA for 60 min with a flow rate of 60 mL/min) to give nine fractions (Fr. 3a-3i). Fraction 3b was purified on an XAqua C-18 column (elution with 10–30% MeCN with 0.2% FA for 50 min with a flow rate of 15 mL/min) to get compounds **3** (22 mg), **6** (13 mg), and **7** (15 mg). Using the same purification method, compounds **11** (37 mg) and **13** (17 mg) were obtained from fractions 3d and 3f, respectively. Fraction 3 h was purified on an XAqua C-18 column (elution with 23% MeCN with 0.2% FA with a flow rate of 15 mL/min) to yield compound **12** (25 mg). Compounds **9** (13 mg) and **10** (21 mg) were obtained from the purification of fraction 3i on an XCharge C-18 column (elution with 10–30% MeCN with 0.2% FA for 40 min with a flow rate of 15 mL/min).

3.4. α-Glucosidase assay

The α-glucosidase inhibition assay was adapted from Yilmazer-Musa et al. (Yilmazer-Musa et al., 2012). 0.26 U of α-glucosidase from *Saccharomyces cerevisiae* were diluted with 0.1 M phosphate buffer consisting of Na_2HPO_4 and KH_2PO_4 (pH 6.5). The 25 μL test compound and 25 μL α-glucosidase were preincubated in 96-well plates at 37 °C for 15 min. The reaction was initiated by adding 50 μL of 0.3125 mM pNPG as substrate. The plate was incubated for an additional 15 min at 37 °C, followed by the reaction being stopped by adding 50 μL of 0.2 M Na_2CO_3. All test compounds were dissolved in DMSO, then diluted with buffer. The reaction was monitored by the change of absorbance at 405 nm using a Dimension RxL Max clinical chemistry system Enspire MP150 (Siemens Healthineers).

3.5. DPPH radical scavenging assay

The DPPH assay was performed as described in previous paper (Gao et al., 2010), and ascorbic acid was used as the positive control. Reaction mixtures containing an ethanol solution of 200 μM DPPH (100 μL) and 2-fold serial dilutions of the sample

Table 1
^{1}H NMR and ^{13}C NMR spectroscopic data of compounds **1–3** (CD_3OD).

Pos.	1		2		3	
	δ_H ppm, mult. (*J* in Hz)	δ_C	δ_H ppm, mult. (*J* in Hz)	δ_C	δ_H ppm, mult. (*J* in Hz)	δ_C
1	3.75, m 4.08, dd (9.8, 6.5)	68.3	3.71, m 4.00, dd (16.5, 7.1)	69.2	3.69, m 4.06, ddt (13.8. 9.9, 6.8)	67.0
2	2.50, t (6.5)	41.9	2.91, td (7.1, 1.8)	35.3	1.89, m	41.9
3		156.4		157.4		72.52/72.49
4	6.32, s	127.4	6.29, s	127.8	2.66, dd (15.0, 7.1) 2.68, dd (15.0, 3.1)	50.02/50.14
5		201.8		201.4		202.4
6	2.64, s	54.2	2.62, s	54.1	6.23, s	126.4
7		76.2		76.1		157.30/157.26
8	1.26, s	25.9	1.26, s	25.7	2.12, s	20.8
9	1.26, s	25.9	1.26, s	25.7	1.91, s	27.7
10	2.15, s	19.8	1.99, s	26.5	1.25/1.26, s	27.75/27.62
1′	4.30, d (7.8)	104.4	4.31, d (7.8)	104.3	4.30, d (7.8)	104.1
2′	3.18, t (8.2)	75.1	3.18, t (8.4)	75.1	3.15, m	75.1
3′	3.37, dd (12.1, 5.6)	78.1	3.38, m	78.3	3.35, m	78.1
4′	3.29, overlapped	71.7	3.30, overlapped	71.8	3.26, overlapped	71.6
5′	3.30, overlapped	78.0	3.29, overlapped	78.0	3.26, over;apped	77.9
6′	3.69, dd (11.5, 2.7) 3.89, d (11.5)	62.8	3.69, dd (12.3, 2.7) 3.88, d (12.3)	62.9	3.66, m 3.86, d (13.9)	62.7
OCH_3	3.25, s	49.9	3.24, s	49.8		

solutions were placed in a 96 well microplate and incubated at room temperature for 30 min. After incubation, the absorbance was read at 517 nm and the scavenging activity was determined by following equation: % scavenging activity = $[A_{blank} - A_{sample}]/A_{blank} \times 100$. The SC_{50} value was obtained and was defined as the concentration of sample required to scavenge 50% of DPPH radicals.

3.6. $ABTS^{+}$ radical scavenging assay

The ABTS radical cation decolorization assay was carried out as previously reported (Re et al., 1999). ABTS was dissolved in water to make a 7 mM solution. The ABTS radical cation ($ABTS^{\bullet}+$) was produced by reacting ABTS stock solution with 2.45 mM potassium persulfate (final concentration) and allowing the mixture to stand in the dark at room temperature for 12–16 h before use. The $ABTS^{\bullet}+$ solution was diluted with ethanol to give an absorbance of 0.700 ± 0.020 at 734 nm. Aliquots of the solutions containing the test compounds (20 μL) were added into each well of 96-well cell culture plates. And then 180 μL of the diluted $ABTS^{\bullet}+$ solution ($A_{734nm} = 0.700 \pm 0.020$) was added to the plates. The absorbance reading was taken after mixing for 5 min. The optical density was measured at 734 nm on a microplate reader. All determinations were carried out in triplicate. The percentage inhibition of absorbance at 734 nm is calculated, and the IC_{50} value was calculated.

3.7. Acid hydrolysis of compounds *1–3*

The acid hydrolysis of compounds **1–3** was performed as described previously (Zhao et al., 2013). Compound **1–3** (5 mg) in 2 M HCl (2 mL) were heated at 80° C using a water bath for 8 h. The reaction mixture was partitioned between $CHCl_3$ and H_2O three times. The aqueous layer was neutralized by base and then concentrated to dryness to give a saccharide residue. The solution of the sugar residue together with the standard, D/L glucose, in 1.5 mL pyridine was added to L-cysteine methyl ester hydrochloride and kept at 60° C for 1 h. Trimethylsilylimidazole was added to the reaction mixture, which was kept again at 60° C for 30 min. The supernatants (4 μL) were then analysed by GC. The monosaccharides of compounds **1–3** were determined to be D-glucose by comparing of the retention times of their corresponding derivatives with those of standard D/L glucose.

3.8. Spectroscopic data

3,7-dimethy-7-methoxy-3(*E*)-octene-5-one-1-*O*-β-D-glucopyranoside (**1**), Light yellow gum; [α]25.7 D: −25.14 (*c* 0.012, CH_3OH); IR (KBr) ν_{max} (cm^{-1}): 3400, 2973, 2933, 1679, 1614, 1380 and 1077; UV (MeOH) λ_{max} nm (log ε): 195 (3.60), 242 (3.96), 387 (1.47); ^{1}H NMR and ^{13}C NMR data see Table 1; HRESIMS: *m*/*z* 385.1825 $[M+Na]^{+}$ (calcd. 385.1833).

3,7-dimethy-7-methoxy-3(*Z*)-octene-5-one-1-*O*-β-D-glucopyranoside (**2**), Light yellow gum; [α]25.7 D: −47.00 (*c* 0.02, CH_3OH); IR (KBr) ν_{max} (cm^{-1}): 3420, 2972, 2931, 1679, 1611, 1379 and 1075; UV (MeOH) λ_{max} nm (log ε): 203 (3.79), 240 (3.87), 323 (2.34); ^{1}H NMR and ^{13}C NMR data see Table 1; HRESIMS: *m*/*z* 385.1827 $[M+Na]^{+}$ (calcd. 385.1833).

3,7-dimethy-3-hydroxy-6-octene-5-one-1-*O*-β-D-glucopyranoside (**3**), Light yellow gum; IR (KBr) ν_{max} (cm^{-1}): 3408, 2971, 2927, 2721, 1672, 1631, 1379 and 1078; UV (MeOH) λ_{max} nm (log ε): 195 (3.67), 240 (3.98), 323 (2.50); ^{1}H NMR and ^{13}C NMR data see Table 1; HRESIMS: *m*/*z* 371.1653 $[M+Na]^{+}$ (calcd. 371.1676).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2017.01.002.

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