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Short communication

Gout prophylactic constituents from the flower buds of *Lonicera japonica*

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ABSTRACT

Two new sesquiterpene glycosides (*R*)-dehydroxyabscisic alcohol β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside (**1**) and (−)-(1*S*,2*R*,6*R*,7*R*)-1,2,6-trimethyl-8-hydroxy methyltricyclic[5.3.1.0^{2,6}]-undec-8-en-10-one β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside (**2**), were isolated from the flower buds of *Lonicera japonica*. Their structures were determined by spectroscopic and chemical methods. Compound **2** could significantly decrease monosodium urate-mediated cytokine production from activated macrophage through lowering IL-1β and TNFα.

1. Introduction

The flower buds of *Lonicera japonica* Thunb. are used to treat cold fever, influenza, and infections in traditional Chinese medicine (Tzeng et al., 2015). Many constituents such as caffeoyl quinic acids, phenolic acid, flavonoids, secoiridoids, saponins, cerebrosides and polyphenols were isolated from this plant (Bi et al., 2008; Jiang, 2015; Kakuda et al., 2000; Kumar et al., 2005; Kumar et al., 2006; Lin et al., 2008; Ni et al., 2015; Teng et al., 2000; Yu et al., 2008; Yu et al., 2015; Zheng et al., 2012). To further assess its chemical and biological diversities, we analyzed the chemical constituents from the aqueous extract of the flower buds of *L. japonica*, leading to the isolation of two new sesquiterpene glycosides (*R*)-dehydroxyabscisic alcohol β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside (**1**) and (−)-(1*S*,2*R*,6*R*,7*R*)-1,2,6-trimethyl-8-hydroxy methyltricyclic[5.3.1.0^{2,6}]-undec-8-en-10-one β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside (**2**) (Fig. 1). This study was conducted to find new agents with novel structure and biological activities from the flower buds of *L. japonica*.

2. Results

Compound **1**: $[\alpha]_D^{20}$ +26.6 (*c* 0.04, MeOH), was obtained as a white amorphous powder. The molecular formula of $C_{26}H_{40}O_{11}$ was deduced from HR-ESI-MS. The IR spectrum showed hydroxyl (3387 cm^{-1}), double bond (3022 cm^{-1}) and conjugated carbonyl (1637 cm^{-1}) groups. The ^{1}H NMR spectrum (Table 1) of **1** showed signals including two tri-substituted double bonds at δ_H 5.85 (s, H-4) and 5.66 (d, *J* = 7.0 and 6.5 Hz, H-10); a *trans*-di-substituted double bond at δ_H 5.67 (dd, *J* = 15.5 and 9.5 Hz, H-7) and 6.28 (d, *J* = 15.5 Hz, H-8); an oxygen-connecting methylene at δ_H 4.33 (dd, *J* = 12.5 and 6.5 Hz, H-11a) and 4.14 (dd, *J* = 12.5 and 7.0 Hz, H-11b); an aliphatic methylene at δ_H 2.46 (d, *J* = 16.5 Hz, H-2a) and 1.93 (d, *J* = 16.5 Hz, H-2b); an aliphatic methine at δ_H 2.62 (dd, *J* = 9.5 Hz, H-6); and four methyl groups at δ_H 1.71 (3H, s, H-12), 1.87 (3H, s, H-13), 0.92 (3H, s, H-14), and 0.85 (3H, s, H-15). Additionally, the spectrum showed two characteristic signals for glycosyl units with anomeric protons at δ_H 4.16 (d, *J* = 8.0 Hz, H-1′) and 4.82 (d, *J* = 3.0 Hz, H-1″), respectively. The ^{13}C NMR spectrum (Table 1) of **1** showed 26 carbon signals, including a carbonyl (δ 197.5, C-3) and a quaternary carbon (δ 35.2, C-1). These spectroscopic data indicates that **1** is a monocyclic sesquiterpene diglycoside.

The HMBC correlations (Fig. 1) between H-2 and C-3/C-6/C-14/C-15; between H-6 and C-1/C-2/C-4/C-13/C-14; between H-4 and C-3/C-13; between H-13 and C-5; and between H-14/H-15 and C-1/C-2/C-6; together with their chemical shifts, indicated the presence of 6-substituted 1,1,5-trimethylhex-4-en-3-one moiety. The ^{1}H – ^{1}H COSY correlations of H-6/H-7/H-8 and H-10/H-11 and the HMBC correlations between H-6 and C-8; between H-8 and C-6/C-9/C-10/C-12; between H-11 and C-9/C-10; between H-10 and C-8/C-12; and between H-12 and C-8/C-9/C-10 showed the presence of 11-oxygen substituted 9-methylpenta-7,9-dien-7-yl

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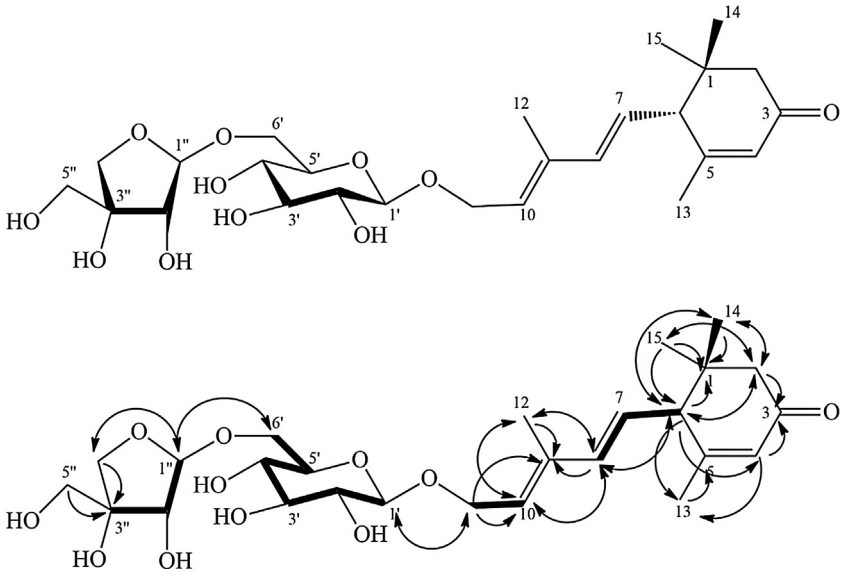

Fig. 1. Structure, key HMBC and ^{1}H–^{1}H COSY correlations of compound **1**.

side chain at C-6 of the hex-4-en-3-one moiety. Additionally, the ^{1}H–^{1}H COSY correlations of H-1′/H-2′/H-3′/H-4′/H-5′/H-6′ and their vicinal coupling constants, together with the HMBC correlations between H-1′ and C-11 and between H-11 and C-1′, indicated the connection of β-glucopyranosyloxy at C-11. The ^{1}H–^{1}H COSY correlation of H-1″/H-2″ and the HMBC correlations between H-1″ and C-4″/C-6′, between H-4″/H-5″ and C-3″, between H-6′ and C-1″, together with the quaternary nature of C-3″, suggested a β-apiofuranosyloxy at C-6′ of the β-glucopyranosyl, which was supported by NMR data comparison of the diglycosyl in **1** with structurally related compounds (Takayanagi et al., 2003; Tamaki et al., 2000) and further confirmed by enzymatic hydrolysis of **1** with snailase. In the hydrolysate of **1**, a sugar mixture of glucose and apiose was isolated by column chromatography over silica gel (CH_3CN—H_2O, 7:2, v/v) and identified by thin-layer liquid chromatography comparing with authentic sugar controls. The sugar mixture, authentic D-/L-glucose and D-/L-apiose separately reacted with L-cycteine methyl ester and arylisothiocyanate (Takana et al., 2007). The following HPLC analysis indicated that two sugar derivatives from the mixture had the same retention time (t_R) to those of D-glucose and D-apiose derivatives, which indicated that both glycosyl units in **1** were the D-configuration. The similarity of the NMR data and the circular dichroism spectra between **1** and the known acetylated β-D-glucopyranoside (Lutz and Winterhalter, 1992) indicated that **1** has the same aglycone moiety including absolute configurations. The configuration was further confirmed by comparison of the experimental CD spectra of **1** with the calculated electronic CD spectra, its aglycone, and a model compound with substitution of the diglycosyl unit by a methyl group predicted from the quantum-mechanical, time-dependent density functional theory (TDDFT) calculations (Li et al., 2010). Therefore, the structure of compound **1** was elucidated as (*R*)-dehydroxyabscisic alcohol β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside (Lutz and Winterhalter, 1993).

Compound **2**: $[\alpha]_D^{20}$ −45.9 (*c* 0.04, MeOH), was obtained as a white amorphous powder. The molecular formula $C_{26}H_{40}O_{11}$ was deduced from HR-ESI-MS. The IR spectrum of **2** showed the presence of hydroxyl (3389 cm^{-1}) and conjugated carbonyl (1738 and 1643 cm^{-1}) groups. The ^{1}H NMR spectrum (Table 1) displayed signals including three methyls (H-12, H-13, H-14), five methylenes (an oxygen-connecting) (H-3, H-4, H-5, H-11, H-15), one methane (H-7), a tri-substituted double bond (H-9). ^{13}C NMR spectrum (Table 1) showed four quaternary carbons and a carbonyl carbon (δ_C 208.6, C-10), The NMR spectrum also showed the signals ascribable to the same diglycosyl moiety in **1**. These spectroscopic data indicates that **2** is a tricyclic sesquiterpene β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside, with an aglycone moiety different from **1**. In the ^{1}H–^{1}H COSY spectrum of **2** (Fig. 2), the correlations of

Table 1
^{1}H NMR (500 MHz) and ^{13}C NMR (150 MHz) spectral data of **1** and **2** (δ in ppm, *J* in Hz, DMSO-d_6).

Nos.	1		2	
	δ_H	δ_C	δ_H	δ_C
1		35.2		61.7
2a	2.46 (1H, d, *J* = 16.5)	47.6		56.8
2b	1.93 (1H, d, *J* = 16.5)			
3a		197.5	1.32 (1H, dd, *J* = 12.0, 6.0)	38.3
3b			1.15 (1H, m)	
4a	5.85 (1H, s)	124.6	1.43 (1H, m)	27.2
4b			1.33 (1H, m)	
5a		162.4	1.67 (1H, dd, *J* = 12.0, 6.0)	40.5
5b			1.37 (1H, dd, *J* = 12.0, 6.0)	
6	2.62 (1H, d, *J* = 9.5)	55.7		57.5
7	5.67 (1H, dd, *J* = 15.5, 9.5)	126.1	2.16 (1H, d, *J* = 5.0)	50.8
8	6.28 (1H, d, *J* = 15.5)	137.6		170.2
9		135.3	6.01 (1H, d, *J* = 0.5)	123.4
10	5.66 (1H, dd, *J* = 7.0, 6.5)	127.9		208.6
11a	4.33 (1H, dd, *J* = 12.5, 6.5)	64.2	2.08 (1H, dd, *J* = 12.0, 5.0)	47.5
11b	4.14 (1H, dd, *J* = 12.5, 7.0)		1.85 (1H, d, *J* = 12.0)	
12	1.71 (3H, s)	12.2	0.95 (3H, s)	17.6
13	1.87 (3H, s)	23.5	0.93 (3H, s)	23.7
14	0.92 (3H, s)	27.8	1.11 (3H, s)	28.8
15a	0.85 (3H, s)	26.3	4.46 (1H, dd, *J* = 17.5, 2.0)	72.4
15b			4.36 (1H, dd, *J* = 17.5, 2.0)	
1′	4.16 (1H, d, *J* = 8.0)	101.4	4.22 (1H, d, *J* = 8.0)	104.7
2′	2.91 (1H, t, *J* = 8.0)	73.7	3.23 (1H, t, *J* = 8.0)	78.5
3′	3.28 (1H, dd, *J* = 9.0, 8.0)	76.1	3.12 (1H, t, *J* = 8.0)	75.4
4′	2.93 (1H, t, *J* = 9.0)	70.5	3.20 (1H, m)	71.1
5′	3.15 (1H, t, *J* = 9.0)	75.2	3.30 (1H, m)	78.8
6′a	3.80 (1H, d, *J* = 11.5)	67.3	3.95 (1H, dd, *J* = 11.5, 2.0)	68.2
6′b	3.46 (1H, dd, *J* = 11.5, 7.0)		3.51 (1H, dd, *J* = 11.5, 6.0)	
1″	4.82 (1H, d, *J* = 3.0)	109.7	4.97 (1H, d, *J* = 2.5)	111.9
2″	3.71 (1H, d, *J* = 2.0)	75.5	3.81 (1H, d, *J* = 2.5)	78.7
3″		78.5		80.2
4″a	3.88 (1H, d, *J* = 9.0)	73.7	3.83 (1H, d, *J* = 9.5)	75.6
4″b	3.52 (1H, d, *J* = 9.0)		3.63 (1H, d, *J* = 9.5)	
5″	3.36 (1H, m)	63.6	3.55 (1H, s)	65.2

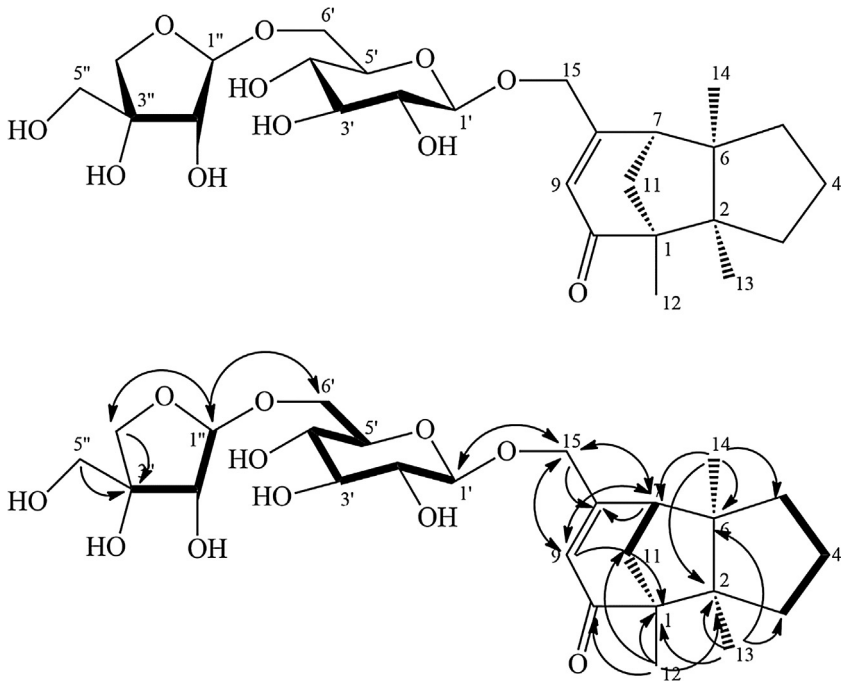

Fig. 2. Structure, key HMBC and ^{1}H–^{1}H COSY correlations of compound **2**.

H-3/H-4/H-5 and H-7/H-11, together with their chemical shifts and coupling patterns, indicated that there were two vicinal coupling aliphatic units in the aglycone moiety. In the HMBC spectrum, correlations between H-13 and C-1/C-2/C-3/C-6 and between H-14 and C-2/C-5/C-6/C-7 showed connections of the C-2 with C-1/C-3/C-6/C-13 and C-6 with C-2/C-5/C-7/C-14, which formed a 2,6-disubstituted 2,6-dimethyl five-membered ring. The HMBC correlations between H-12 and C-1/C-2/C-10/C-11 indicated linkages between the C-1 with C-10/C-11/C-12, and further confirmed the connection between the C-1 and C-2. In addition, the HMBC correlations between H-7 and C-8/C-9/C-15; between H-9 and C-1/C-7/C-15; between H-15 and C-8/C-9; together with the chemical shifts, showed that both the methine (C-7) and the oxymethylene (C-15) were connected to one end (C-8) of the tri-substituted double bond and that C-1 was connected *via* the carbonyl (C-10) to the other end (C-9), which constructed the 8-oxymethylene cyclohexene ring fused with the latter five-membered ring to give the tricyclic bridged structure of the aglycone in **2**. The presence of β-apiofuranosyl-(1″ → 6′)-β-glucopyranosyl was deduced by the similar ^{1}H–^{1}H COSY and HMBC correlations to **1**. Additionally, the HMBC correlations between H-15 and C-1′ and between H-1′ and C-15 indicated the diglycosyl at C-15 of the aglycone. In the NOE spectrum, irradiation of H-11a enhanced H-13 and H-14, indicating that the bridge methylene (C-11) and the two methyl groups were oriented in the same direction. The D-configuration was assigned for the two glycosyl units in **2** according to the same method described in **1**. The CD spectrum of **2** displayed a negative cotton effect at 335 nm ($\Delta\varepsilon - 2.36$) for the $n \rightarrow p^{*}$ transition of cyclohexanone chromophore, suggesting **2** possesses 1*S*,7*R* configuration according to the octant rule for cyclohexenones (Snatzke, 1965), which was further confirmed by comparison of the experimental CD spectrum of **2** with the calculated ECD spectra and the aglycone methyl ether (model compound). Thus, the structure of compound **2** was elucidated as (−)-(1*S*,2*R*,6*R*,7*R*)-1,2,6-trimethyl-8-hydroxy methyltricyclic [5.3.1.$0^{2,6}$]-undec-8-en-10-oneβ-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside.

3. Conclusions

We isolated and identified two new sesquiterpene glycosides (*R*)-dehydroxyabscisic alcohol β-D-apiofuranosyl-(1″ → 6′)-β-D-glucopyranoside (**1**) and (−)-(1*S*,2*R*,6*R*,7*R*)-1,2,6-trimethyl-8-hydroxy methyltricyclic[5.3.1.$0^{2,6}$]-undec-8-en-10-one β-D-apiofuranosyl-(1″ → 6′)-β-D-glucopyranoside (**2**), from the flower buds of *L. japonica*. Compound **2** could significantly decrease monosodium urate-mediated cytokine production from activated macrophage through lowering IL-1β and TNFα (Fig. 3). These results provided scientific clues to identify compound **2** as a potential new gout prophylactic agent.

4. Experimental

4.1. General experimental procedure

Optical rotations were measured on P-2000 polarimeter (JASCO, Tokyo, Japan). The UV spectrum was obtained using a Shimadzu UV-2401-A spectrophotometer with PhotoMultiplier Tube. IR spectra were recorded on a Nicolet 5700 FT-IR microscope instrument (FT-IR microscope transmission) (Thermo Electron Corporation, Madison, USA). The NMR spectra were recorded on a Bruker AV-500 spectrometer, using TMS as an internal standard. HR-ESI-MS spectra were measured on a Bruker UHR-TOF maXis spectrometer. Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Inc., Qingdao, China), Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden), CHP 20P (Mitsubishi Chemical Inc., Tokyo, Japan). HPLC was performed on an Agilent 1100 apparatus equipped with a UV detector and an YMC-Pack ODS-A (YMC, 1 × 15 cm) column (Agilent, USA).

4.2. Plant material

The flower buds of *L. japonica* were collected in May 2014 from Shangqiu, Henan Province, China, and authenticated by Prof. Li Ma from Institute of Materia Medica. A voucher specimen (No.

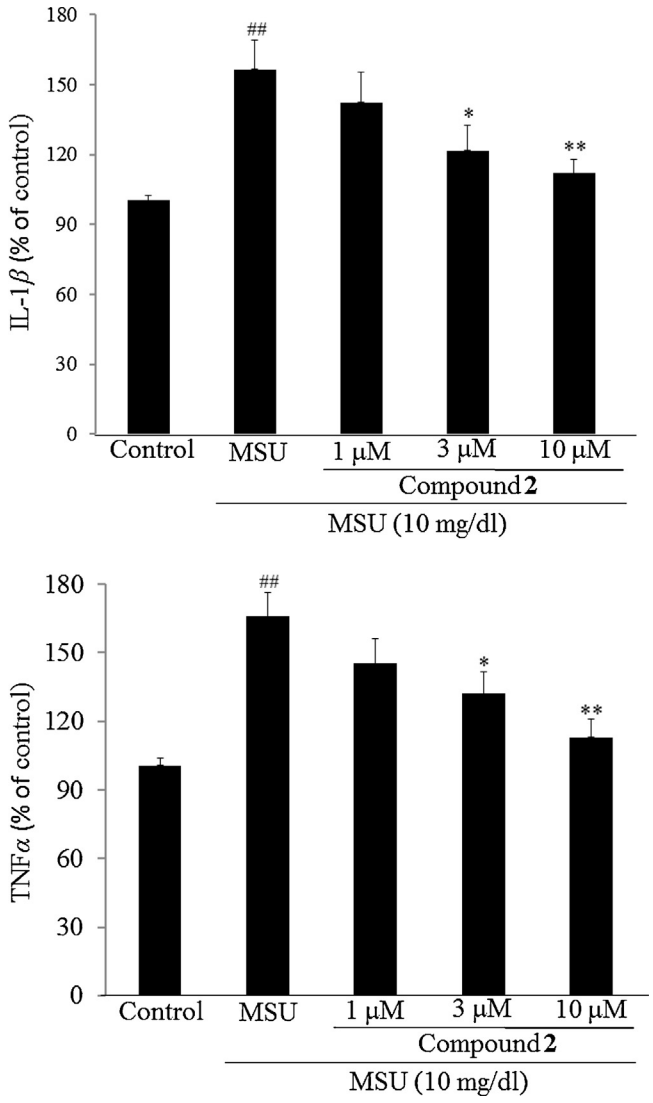

Fig. 3. Compound **2** inhibited MSU induced cytokine production. THP-1 macrophages were pretreated with different concentrations of compounds for 4 h followed by stimulation with MSU (10 mg/dL) for 24 h. Media were analyzed for IL-1β and TNFα production by ELISA. Values were expressed as mean ± SD ($n = 3$). $^{\#\#}P < 0.01$ *vs* Control group; $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* MSU group.

20140522) was deposited at the Department of Rheumatology and Immunology, Shanghai East Hospital, Tongji University School of Medicine (Shanghai, China).

4.3. Extraction and isolation

The dried flower buds of *L. japonica* (45 kg) were extracted with H_2O (120 L, 3 × 1 h). The aqueous extracts were evaporated under reduced pressure to yield a brown residue (22 kg). The residue was then dissolved in H_2O (100 L), loaded on a macroporous adsorbent resin (HPD-110, 20 L) column (20 cm × 200 cm), and eluted successively with H_2O (50 L), 60% EtOH (100 L), and 95% EtOH (80 L) to yield three fractions (Fr. 1–Fr. 3). Fr. 2 (280 g) was chromatographed over MCI gel CHP 20P, eluting successively with H_2O (20 L), 40% EtOH (30 L), 60% EtOH (30 L), and 95% EtOH (10 L), to give five fractions (Fr. 2.1–Fr. 2.5). Fr. 2.3 (26 g) was subjected to CC over silica gel, with elution by a gradient of increasing acetone (0–100%) in petroleum ether, to yield subfractions Fr. 2.3.1–Fr. 2.3.5. Fr. 2.3.2 (4.1 g) was separated by CC over Sephadex LH-20, eluted with petroleum ether–$CHCl_3$–MeOH (5:5:2, *v*/*v*/*v*), to give Fr. 2.3.2.1–Fr. 2.3.2.6. Fr. 2.3.2.4 (75 mg) was separated by reversed-phase semi-preparative HPLC, using MeOH–H_2O (40:60, *v*/*v*) as the mobile phase (1.5 mL/min, UV 254 nm), to yield **1** (1.2 mg, $t_R = 25$ min). Fr. 2.3.4 (3.5 g) was separated by CC over Sephadex LH-20, eluted with petroleum ether–$CHCl_3$–MeOH (5:5:1, *v*/*v*/*v*), to give Fr. 2.3.4.1–Fr. 2.3.4.5. Fr. 2.3.4.4 (85 mg) was separated by reversed-phase (C18) semi-preparative HPLC, using MeOH–H_2O (60:40, *v*/*v*) as the mobile phase (1.5 mL/min, UV 220 nm), to yield **2** (1.8 mg, $t_R = 26$ min).

4.4. (R)-dehydroxyabscisic alcohol β-D-apiofuranosyl-(1″ → 6′)-β-D-glucopyranoside (*1*)

White amorphous powder; $[\alpha]_D^{20}$ +26.6 (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ε) 239 (5.68), 341 (4.73) nm; CD (MeOH) 225 (Δε − 25.5), 262 (Δε + 40.6), 328 (Δε − 2.81) nm; IR ν_{max} 3387, 3022, 2845, 1637, 1425, 1369, 1252, 1049, 825, 652 cm^{-1}; ^1H and ^{13}C NMR data see Table 1. HR-ESI-MS *m*/*z*: 551.2469 $[M + Na]^+$ (Calcd. for $C_{26}H_{40}O_{11}Na$, 551.2461).

4.5. (−)-(1S,2R,6R,7R)-1,2,6-trimethyl-8-hydroxy methyltricyclic [5.3.1.$0^{2,6}$]-undec-8-en-10-one β-D-apiofuranosyl-(1″ → 6′)-β-D-glucopyranoside (*2*)

White amorphous powder; $[\alpha]_D^{20}$ −45.9 (*c* 0.04, MeOH); UV (MeOH) λ_{max}(log ε) 209 (4.73), 231 (4.52) nm; CD (MeOH) 231 (Δε + 0.65), 335 (Δε − 2.36) nm; IR ν_{max} 3389, 3015, 2917, 1738, 1643, 1473, 1335, 1172, 923, 825, 552 cm^{-1}; ^1H and ^{13}C NMR data see Table 1. HR-ESI-MS *m*/*z*: 529.2631 $[M + H]^+$ (Calcd. for $C_{26}H_{41}O_{11}$, 529.2640).

4.6. Cell culture and treatment

Human monocytic cell line, THP-1 (ATCC TIB-202), purchased from Shanghai Cell Bank (Shanghai, China), was grown in RPMI 1640 with HEPES, supplemented with 10% FBS and penicillin/streptomycin. Cells were induced to differentiate into mature macrophages using 12-*O*-tetradecanoylphorbol-13-acetate (Enzo Life Sciences) at a concentration of 0.5 μM for 3 h. After induction, cells were washed with PBS and then plated into 12-well tissue culture plates at a density of 6×10^5 cells/well and incubated overnight. Prior to any activation studies, cells were washed with PBS followed by the addition of 0.5 mL of serum-free Opti-MEM per well (Orlowsky et al., 2014).

4.7. Inhibition studies

To test for anti-inflammatory effects of compounds, macrophages were pretreated with different concentrations of compounds for 4 h prior to the addition of monosodium urate (MSU) crystals (10 mg/dL). Culture media were collected at 24 h and IL-1β and TNFα concentrations were analyzed by ELISA. The IL-1β and TNFα data were from 4 separate experiments (Orlowsky et al., 2014).

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