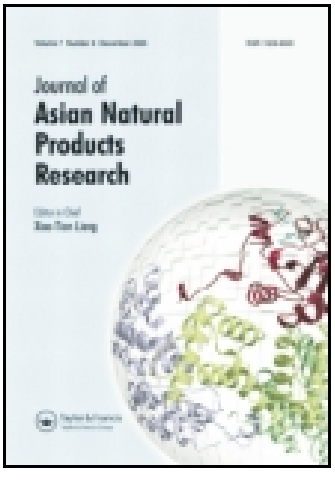

Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

Three new compounds from the leaves of Liquidambar formosana

Rui-Jian Zhong[a], Hui Yuan[ab], Hui-Zheng Fu[a], Guo-Ping Zhou[a], Xin Wu[a], Chun-Hua Zhang[a] & Ming-Ming Yuan[ab]

[a] Jiangxi Provincial Institute for Drug and Food Control, Nanchang, 330029, China

[b] Pharmaceutical Department, Nanchang University, Nanchang, 330006, China

Published online: 11 Nov 2013.

To cite this article: Rui-Jian Zhong, Hui Yuan, Hui-Zheng Fu, Guo-Ping Zhou, Xin Wu, Chun-Hua Zhang & Ming-Ming Yuan (2013) Three new compounds from the leaves of Liquidambar formosana, Journal of Asian Natural Products Research, 15:12, 1249-1255, DOI: 10.1080/10286020.2013.837456

To link to this article: http://dx.doi.org/10.1080/10286020.2013.837456

Journal of Asian Natural Products Research, 2013
Vol. 15, No. 12, 1249–1255, http://dx.doi.org/10.1080/10286020.2013.837456

Three new compounds from the leaves of *Liquidambar formosana*

Rui-Jian Zhong[a], Hui Yuan[a,b], Hui-Zheng Fu[a]*, Guo-Ping Zhou[a]*, Xin Wu[a], Chun-Hua Zhang[a] and Ming-Ming Yuan[a,b]

[a]*Jiangxi Provincial Institute for Drug and Food Control, Nanchang 330029, China;* [b]*Pharmaceutical Department, Nanchang University, Nanchang 330006, China*

(*Received 14 May 2013; final version received 20 August 2013*)

Two new flavan glycosides, (2*S*)-5,7,4′-trihydroxyflavan-7-*O*-β-D-glucopyranoside (**1**) and (2*S*)-5,7,4′-trihydroxyflavan-5-*O*-β-D-glucopyranoside (**2**), and a new neolignan, (7*S*,8*S*)-3-methoxyl-3′-*O*-β-D-glucopyrannosyl-4′:8,5′:7-diepoxyneolignan-4,9′-diol (**3**), were isolated from the leaves of *Liquidambar formosana* Hance. Their structures were elucidated on the basis of spectroscopic data and chemical evidence.

Keywords: *Liquidambar formosana*; flavan glycosides; neolignan

1. Introduction

Liquidambar formosana Hance, belonging to the family Hamamelidaceae, is widely distributed in China, Laos, North Korea, Vietnam, and Japan, and it is known for its resins [1]. Its leaves are used in folk medicine for treating dysentery, diarrhea, hemostasis, and detoxification [2]. Previous phytochemical studies on this plant have led to the isolation and identification of several flavonoids, triterpenoids, and tannins [1,3–8]. Up to date, there are few reports on the chemical constituents or bioactive compounds from the leaves of *L. formosana*. In our preliminary screening, the EtOAc part of the H_2O extract from the leaves of *L. formosana* showed antimicrobial activity. As part of a program to discover significant antimicrobical properties from plant resources has led to the isolation of three new compounds, (2*S*)-5,7,4′-trihydroxyflavan-7-*O*-β-D-glucopyranoside (**1**), (2*S*)-5,7,4′-trihydroxyflavan-5-*O*-β-D-glucopyranoside (**2**), and (7*S*,8*S*)-3-methoxyl-3′-*O*-β-D-glucopyrannosyl-4′:8,5′:7-diepoxyneolignan-4,9′-diol (**3**), from the leaves of *L. formosana* (Figure 1). We report herein the isolation and elucidation of three new compounds.

2. Results and discussion

The leaves of *L. formosana* were collected from Yiyang, Jiangxi Province, China and identified by Prof. Guiping Yuan, Jiangxi Provincial Institute for Drug and Food Control. The H_2O extract of the leaves of *L. formosana* was fractionated by different solvents, among which the EtOAc fraction displayed significant antimicrobial activity at a concentration of 10 μg/ml. The EtOAc fraction was subjected to separation using various column chromatography (CC) techniques to afford three new compounds (**1**–**3**).

Compound **1** was obtained as a white amorphous powder. The molecular formula $C_{21}H_{24}O_9$ was determined by HR-TOF-MS (*m/z* 421.1496 $[M + H]^+$, calcd for 421.1493) and supported by NMR spectroscopic data. The UV spectrum showed absorption maxima at 271 nm. The ^1H NMR spectrum of **1** in CD_3OD exhibited a set of AA′BB′ system at δ_H 7.21 (2H, d, $J = 8.4$ Hz) and 6.77 (2H, d,

*Corresponding authors. Email: fhzfhz620@sohu.com

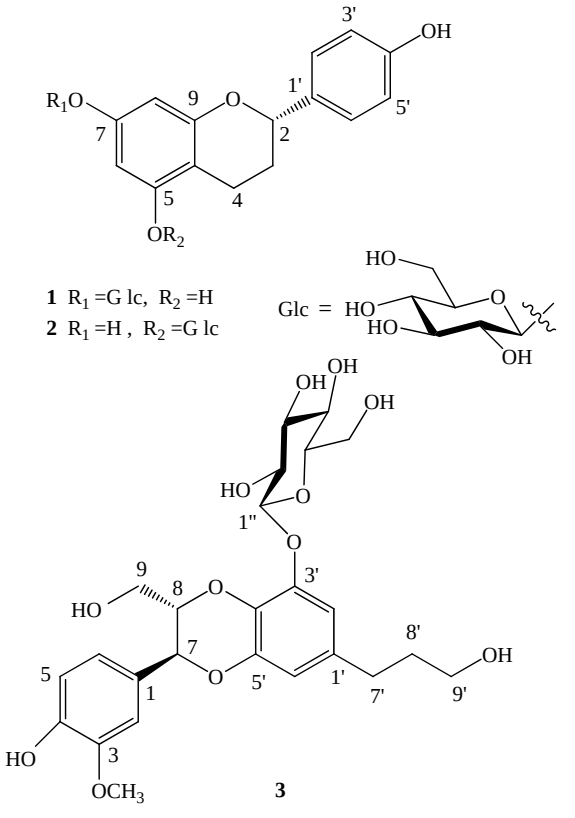

Figure 1. Chemical structures of compounds **1**–**3**.

$J = 8.4$ Hz), two *meta*-coupled aromatic protons at δ_H 6.23 (1H, d, $J = 2.0$ Hz) and 5.99 (1H, d, $J = 2.0$ Hz), and an anomeric proton at δ_H 4.86 (1H, overlap) correlated with one anomeric carbon at δ_C 102.8 in the HSQC spectrum. The ^{13}C NMR spectrum of **1** displayed 21 carbon signals, of which 6 were assigned to the sugar moiety. Comparison of its ^{1}H and ^{13}C NMR spectral data with those of 5,7,4′-trihydroxyflavan suggested that they have the same framework [9]. The structural difference is that there is an additional sugar unit in compound **1**. Acid hydrolysis of **1** with 2 M HCl afforded D-glucose, which was identified by GC analysis of their trimethylsilyl L-cysteine derivatives [10]. In the HMBC spectrum, the presence of correlation from Glc-H-1″ (δ_H 4.86) to C-7 (δ_C 158.1) confirmed that the glucose unit is located at C-7. In the NOESY spectrum, Glc-H-1″ (δ_H 4.86) showed correlations with H-6 (δ_H 6.23) and H-8 (δ_H 5.99), further indicating that the glucose unit is attached to C-7. Based on the known 2*S* absolute configuration of *S*-3,4-dihydro-2-phenyl-2H-1-benzopyran [11–13], and the same fact that a negative Cotton effect ascribed to the ^1L_b transition at 277 nm was observed in the CD spectrum of **1**, the absolute configuration at C-2 was assigned as *S*. Thus, compound **1** was elucidated as (2*S*)-5,7,4′-trihydroxyflavan-7-*O*-β-D-glucopyranoside.

Compound **2** was obtained as a white amorphous powder, It had the same molecular formula as **1**, namely $C_{21}H_{24}O_9$, as deduced by HR-TOF-MS (*m/z* 419.1311 $[M-H]^-$, calcd for 419.1323). The NMR spectroscopic data

of **2** were almost identical with those of **1**. The only difference between **2** and **1** is the linkage position of glucose. In the HMBC spectrum of **2**, a long-range correlation from Glc-H-1″ (δ_H 4.84) to C-5 (δ_C 157.8) confirmed that the glucose unit is located at C-5. In the NOESY spectrum, Glc-H-1″ (δ_H 4.84) exhibited a clear correlation with H-6 (δ_H 6.24), while no NOE correlation of Glc-H-1″/H-8 was observed, further suggesting that the glucose unit is attached to C-5. The CD spectrum of **2** displayed a negative Cotton effect at 276 nm, similar to compound **1**, and the absolute configuration of C-2 in compound **2** was determined to be *S*. Thus, compound **2** was determined as (2*S*)-5,7,4′-trihydroxyflavan-5-*O*-β-D-glucopyranoside.

Compound **3** was obtained as a white amorphous powder, and its positive-ion HR-TOF-MS gave a quasi-molecular ion peak at *m/z* 525.1973 $[M + H]^+$, which indicated the molecular formula to be $C_{25}H_{32}O_{12}$. The UV spectrum showed an absorption maximum at 278 nm. The ^{1}H NMR spectrum of **3** in DMSO-d_6 exhibited the following proton signals: ABX-type aromatic protons at δ_H 6.98 (1H, d, $J = 3.6$ Hz), 6.82 (1H, dd, $J = 7.8$, 3.6 Hz), and 6.79 (1H, d, $J = 7.8$ Hz); two *meta*-coupled aromatic protons at δ_H 6.55 (1H, d, $J = 1.8$ Hz) and 6.39 (1H, d, $J = 1.8$ Hz); a hydroxypropyl group at δ_H 2.45–2.48 (2H, m), 1.65–1.68 (2H, m), 3.47 (1H, dd, $J = 12.0$, 6.6 Hz), and 3.65 (1H, d, $J = 12.0$ Hz); a moiety of (ph) **CH**(O)—**CH**(O)—**CH$_2$**O— [δ_H 4.87 (1H, d, $J = 7.2$ Hz), 4.04–4.07 (1H, m), 3.39 (1H, t, $J = 6.6$ Hz), 3.33 (1H, dd, $J = 12.0$, 4.2 Hz)]; a methoxyl singlet at δ 3.77 (3H, s); and an anomeric signal of a sugar unit at δ_H 4.94 (1H, d, $J = 7.2$ Hz). The carbon signals in the ^{13}C NMR spectrum of **3** further confirmed the above units. Comparison of the NMR spectroscopic data of **3** with those of (7*R*,8*R*)-3-methoxyl-9-*O*-β-D-xylopyranosyl-4′:7,5′:8-diepoxyneodiepoxyneolignan-4,9′-diol [14] demonstrated that the aglycone part of **3** was likely to be a dihydrobenzofuran skeleton. Significant HMBC correlations were observed between H-6/C-7, H-7/C-6, H-8/C-7, H-8/C-9, H-8/C-4′, and OCH$_3$/C-3 (Figure 2). From the foregoing pieces of evidence, the skeleton of **3** could be concluded as 3-methoxyl-4′:8,5′:7-diepoxyneolignan-4,9′-diol.

Acid hydrolysis of **3** with 2 M HCl afforded D-glucose, which was identified by GC analysis of their trimethylsilyl L-cysteine derivatives [10]. On the basis of the coupling constant of anomeric proton and the chemical shift of the anomeric carbon, the anomeric configuration of the glucose moiety was determined as β [15]. The proton and protonated carbon signals in the NMR spectra of **3** were assigned unequivocally on the basis of ^{1}H–^{1}H COSY and HSQC spectroscopic analyses. In the HMBC spectrum of **3**, a long-range correlation from Glc-H-1″ (δ_H 4.94) to C-3′ (δ_C 144.4) confirmed that the glucose unit is attached to C-3′ (Figure 2). The relative configuration of H-7 and H-8 was *trans* from the $J_{7,8}$ value of 7.2 Hz in the ^{1}H NMR spectrum. The absolute configurations of C-7 and C-8 were determined as 7*S*,8*S* on the basis of the positive Cotton effect at 238 nm in the CD spectrum [16–19]. Therefore, compound **3** was characterized as (7*S*,8*S*)-3-methoxyl-3′-*O*-β-D-glucopyrannosyl-4′:8,5′:7-diepoxyneolignan-4,9′-diol.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on an Autopol IV-T/V (Rudolph Research Analytical, New Jersey, NJ, USA). UV spectra were recorded in MeOH on a Jasco V650 spectrophotometer (JASCO, Inc., Easton, Maryland, USA). CD spectra were measured on a MOS-450/AF-CD (Bio-Logic, Claix, France). The ^{1}H (600 MHz), ^{13}C (150 MHz) and 2D NMR spectra were recorded on a Bruker AVANCE III 600 instrument using tetramethylsilane as an internal reference (Bruker Company, Billerica, MA, USA). ESI-MS data were

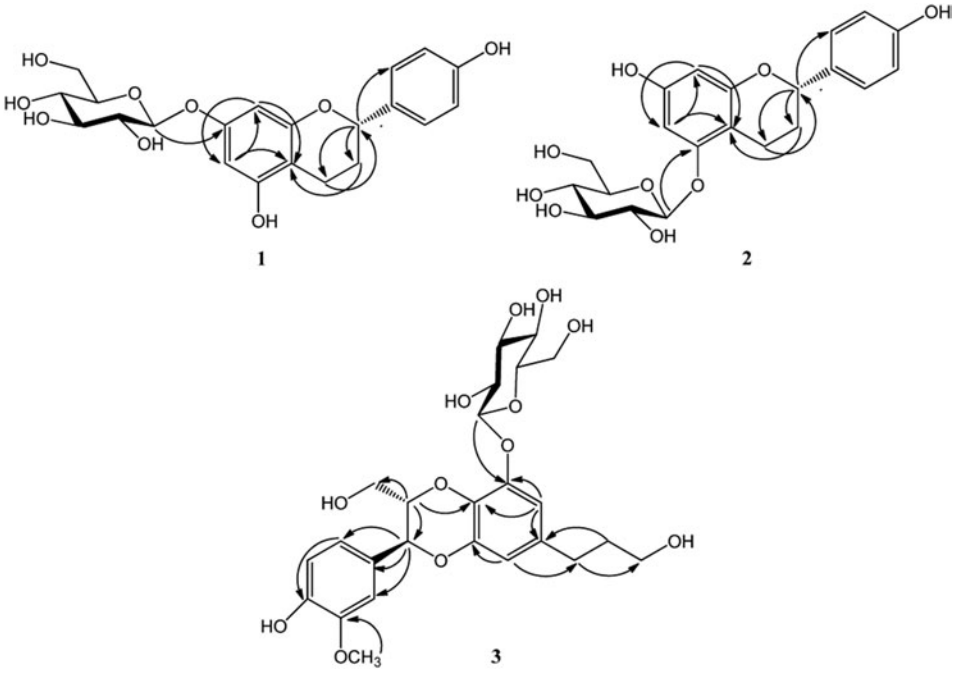

Figure 2. Key HMBC (H → C) correlations of compounds **1**–**3**.

collected on a HPLC-MS ZQ4000/2695 instrument (Waters Company, Milford, MA, USA). HR-TOF-MS data were obtained on an Agilent 7890-7000A mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Preparative HPLC was conducted with an Agilent Technologies 1200 series instrument with an multiple wavelength detector using a YMC-pack ODS (Octadecylsilyl)-A column (10 μm, 250 × 20 mm). CC was carried out with silica gel (200–300 mesh, Qingdao Marine Chemical Ltd, Qingdao, China), Develosil ODS (50 μm, Nomura Chemical Co. Ltd, Osaka, Japan), Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden). TLC (thin-layer chromatography) was carried out with glass precoated with silica gel GF_{254}. Spots were visualized under UV light or by spraying with 10% sulfuric acid in EtOH followed by heating.

3.2 Plant material

The leaves of *L. formosana* were collected from Yiyang, Jiangxi Province, China, in May 2012 and were identified by Prof. Guiping Yuan at Jiangxi Provincial Institute for Drug and Food Control, China. A voucher specimen (No. 20120516) has been deposited in the Herbarium of Jiangxi Provincial Institute for Drug and Food Control.

3.3 Extraction and isolation

The powdered dried leaves of *L. formosana* (12.0 kg) were extracted with H_2O at reflux for 3 × 3 h. The extracted solution was evaporated under reduced pressure to yield a dark residue (2.1 kg), which was suspended in H_2O (16 liters) and then partitioned with $CHCl_3$ (3 × 16 liters), EtOAc (3 × 16 liters), and *n*-BuOH (3 × 16 liters), successively. After removing the solvent, the EtOAc-soluble portion

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectral data of compounds **1** and **2** in CD_3OD (δ in ppm, J in Hz).

	1			**2**	
Position	δ_H	δ_C	Position	δ_H	δ_C
2	4.88 (1H, overlap)	78.3	2	4.82 (1H, overlap)	77.4
3	2.71–2.73 (2H, m)	20.5	3	1.88–1.93 (1H, m) 2.87–2.92 (1H, m)	20.6
4	1.91–1.95 (1H, m) 2.09–2.11 (1H, m)	30.7	4	2.08–2.11 (1H, m) 2.60–2.65 (1H, m)	30.8
5		158.0	5		157.8
6	6.23 (1H, d, 2.0 Hz)	96.8	6	6.24 (1H, d, 2.4 Hz)	96.7
7		158.1	7		157.9
8	5.99 (1H, d, 2.0 Hz)	99.0	8	5.85 (1H, d, 2.4 Hz)	98.7
9		157.9	9		158.0
10		105.7	10		105.2
1′		133.5	1′		134.4
2′	7.21 (1H, d, 8.4 Hz)	128.6	2′	7.22 (1H, d, 7.8 Hz)	128.6
3′	6.77 (1H, d, 8.4 Hz)	116.3	3′	6.77 (1H, d, 7.8 Hz)	116.2
4′		158.4	4′		158.3
5′	6.77 (1H, d, 8.4 Hz)	116.3	5′	6.77 (1H, d, 8.4 Hz)	116.2
6′	7.21 (1H, d, 8.4 Hz)	128.6	6′	7.22 (1H, d, 8.4 Hz)	128.6
Glc-1″	4.86 (1H, overlap)	102.8	Glc-1″	4.84 (1H, d, 7.8 Hz)	102.7
2″	3.45–3.46 (1H, m)	75.1	2″	3.45–3.46 (1H, m)	75.1
3″	3.43–3.45 (1H, m)	78.4	3″	3.43–3.44 (1H, m)	79.1
4″	3.40–3.42 (1H, m)	71.6	4″	3.40–3.42 (1H, m)	71.6
5″	3.38–3.40 (1H, m)	79.0	5″	3.43–3.44 (1H, m)	77.3
6″	3.71 (1H, dd, 12.0, 5.0 Hz) 3.89 (1H, d, 12.0 Hz)	63.1	6″	3.73 (1H, dd, 11.0, 4.8 Hz) 3.91 (1H, d, 11.0 Hz)	62.7

(232 g) was fractionated via silica gel CC, eluting with $CHCl_3$:MeOH (3:1, v/v), to give 19 major fractions A_1–A_{19} on the basis of TLC analysis. Fraction A_{11} (16.6 g) was subjected to silica gel CC and eluted with $CHCl_3$:MeOH (15:1 to 1:1, v/v) to afford 12 fractions ($A_{11\text{-}1}$–$A_{11\text{-}12}$). Fraction $A_{11\text{-}8}$ (2 g) was separated by ODS CC (50 μM, 10–100% MeOH–H_2O) to give 20 subfractions. Subfraction 12 (184 mg) was further separated by preparative HPLC (YMC-ODS-A 5 μM, 250 mm × 20 mm, detection at 210 nm) using 13% CH_3CN–H_2O (7 ml/min) as mobile phase to yield **1** (5.4 mg, t_R 111 min) and **2** (6.2 mg, t_R 121 min). Fraction A_{14} (6 g) was separated by ODS CC (50 μM, 10–100%, MeOH–H_2O) to afford 10 subfractions. Subfraction $A_{14\text{-}4}$ (120 mg) was further separated by preparative HPLC (YMC-ODS-A 5 μM, 250 mm × 20 mm, detection at 210 nm) using 15% CH_3CN–H_2O (7 ml/min) as mobile phase to yield **3** (6.7 mg, t_R 102 min).

*3.3.1 (2S)-5,7,4′-Trihydroxyflavan-7-O-β-D-glucopyranoside (**1**)*

$C_{21}H_{24}O_9$, white amorphous powder; $[\alpha]_D^{20}$ −50.0 (*c* 0.04, MeOH); UV (MeOH) λ_{max}: 271 nm; CD (MeOH) $\Delta\varepsilon_{277\,nm}$ −0.552; for ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) spectral data, see Table 1; positive ESI-MS *m/z*: 421 $[M + H]^+$; negative ESI-MS *m/z*: 419 $[M - H]^-$; HR-TOF-MS *m/z*: 421.1496 $[M + H]^+$ (calcd for $C_{21}H_{25}O_9$, 421.1493).

*3.3.2 (2S)-5,7,4′-Trihydroxyflavan-5-O-β-D-glucopyranoside (**2**)*

$C_{21}H_{24}O_9$, white amorphous powder; $[\alpha]_D^{20}$ −23.0 (*c* 0.1, MeOH); UV (MeOH) λ_{max}: 272 nm; CD (MeOH) $\Delta\varepsilon_{276\,nm}$ −1.69; for ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) spectral data, see Table 1; positive ESI-MS *m/z*: 421 $[M + Na]^+$; negative ESI-MS *m/z*: 419 $[M - H]^-$; HR-TOF-MS *m/z*: 419.1311 $[M - H]^-$ (calcd for $C_{21}H_{23}O_9$, 419.1323).

*3.3.3 (7S,8S)-3-Methoxyl-3′-O-β-D-glucopyrannosyl-4′:8,5′:7-diepoxyneolignan-4,9′-diol (**3**)*

$C_{25}H_{32}O_{12}$, white amorphous powder; $[\alpha]_D^{20}$ −28.6 (*c* 0.22, MeOH); UV (MeOH) λ_{max}: 278 nm; CD (MeOH) $\Delta\varepsilon_{238\,nm}$ −0.369; ^{1}H NMR (600 MHz, DMSO) δ_H: 1.65–1.68 (2H, m, H-8′), 2.45–2.48 (2H, m, H-7′), 3.16–3.19 (1H, m, H-4″), 3.24–3.26 (2H, m, H-2″, H-5″), 3.27–3.30 (1H, m, H-3″), 3.33 (1H, dd, J = 12.0, 4.2 Hz, H-9a), 3.39 (2H, t, J = 6.6 Hz, H-9′a, H-9′b), 3.47 (1H, dd, J = 12.0, 6.6 Hz, H-6″a), 3.54 (1H, dd, J = 12.0, 4.2 Hz, H-9b), 3.65 (1H, d, J = 12.0 Hz, H-6″b), 3.77 (3H, s, 3-OCH_3), 4.04–4.07 (1H, m, H-8), 4.87 (1H, d, J = 7.2 Hz, H-7), 4.94 (1H, d, J = 7.2 Hz, H-1″), 6.39 (1H, d, J = 1.8 Hz, H-6′), 6.55 (1H, d, J = 1.8 Hz, H-2′), 6.79 (1H, d, J = 7.8 Hz, H-5), 6.82 (1H, dd, J = 7.8, 3.6 Hz, H-6), 6.98 (1H, d, J = 3.6 Hz, H-2); ^{13}C NMR (150 MHz, DMSO) δ_C: 128.2 (C-1), 112.2 (C-6), 148.0 (C-3), 148.0 (C-4), 120.8 (C-5), 115.8 (C-2), 77.5 (C-7), 78.1 (C-8), 60.5 (C-9), 134.2 (C-1′), 110.2 (C-2′), 144.4 (C-3′), 131.9 (C-4′), 146.3 (C-5′), 108.9 (C-6′), 31.8 (C-7′), 34.6 (C-8′), 60.5 (C-9′), 100.7 (C-1″), 73.8 (C-2″), 75.9 (C-3″), 70.1 (C-4″), 76.0 (C-5″), 61.1 (C-6″), 56.2 (3-OCH_3); positive ESI-MS *m/z*: 525 $[M + H]^+$; negative ESI-MS *m/z*: 523 $[M - H]^-$; HR-TOF-MS *m/z*: 525.1973 $[M + H]^+$ (calcd for $C_{25}H_{33}O_{12}$, 525.1967).

3.4 Determination of absolute configurations of the sugar moieties in 1–3

Based on the reported procedure [10], each 2 mg of compounds **1**–**3** was dissolved in 2 M HCl (dioxane:H_2O, 1:1 v/v) and refluxed for 10 h. After removal of the HCl by evaporation and extraction with EtOAc, the H_2O extract was again evaporated and dried *in vacuo* to furnish a monosaccharide residue. The residue was dissolved in pyridine (1 ml) to which 2 mg of L-cysteine methyl ester hydrochloride was added. The mixture was kept at 60°C for 2 h, evaporated under an N_2 stream, and dried *in vacuo*, then trimethylsilylated with *N*-trimethylsilylimidazole (0.2 ml) for 2 h. The mixture was partitioned between *n*-hexane and H_2O (2 ml each), and the *n*-hexane extract was analyzed by GC. In the acid hydrolysate of **1**–**3**, D-glucose was verified by comparison with retention times of its derivatives and with those of corresponding control samples prepared in the same way.

Acknowledgments

We thank Prof. A.H. Liu at Center of Analysis and Testing Nanchang University for NMR measurements.

References

[1] J. Yu, S.S. Liu, and L.J. Xuan, *Nat. Prod. Res.* **26**, 630 (2012).
[2] Jiangsu New Medical College, *Dictionary of Traditional Chinese Medicine* (Shanghai Science and Technology Press, Shanghai, 1977), Vol. 1, p. 1261.
[3] Y.M. Liu, Y.M. Liu, and M. Ma, *Food Sci.* **31**, 35 (2010).
[4] N.Y. Yang, J.H. Chen, and G.S. Zhou, *Fitoterapia* **82**, 927 (2011).
[5] M.R. Chen, H. Wang, and H.M. Yuan, *Chin. J. Mod. Appl. Pharm.* **27**, 840 (2010).
[6] T. Hatano, R. Kira, M. Yoshizaki, and T. Okuda, *Phytochemistry* **25**, 2787 (1986).
[7] T. Okuda, T. Hatano, T. Kaneda, M. Yoshizaki, and T. Shingu, *Phytochemistry* **26**, 2053 (1987).

[8] P.C. Jiang, *Guangxi Med. J.* **20**, 240 (1998).
[9] M. Sauvain, J.P. Dedet, N. Kunesch, and J. Poisson, *J. Nat. Prod.* **57**, 403 (1994).
[10] D.M. Zhang, I. Miyase, M. Kuroyanagi, K. Umehara, and A. Ueno, *Chem. Pharm. Bull.* **44**, 810 (1996).
[11] Y. Yang, T. Zhang, and L. Xiao, *J. Asian Nat. Prod. Res.* **12**, 194 (2010).
[12] S. Antus, T. Kurtan, L. Juhasz, L. Kiss, M. Hollosi, and Z.S. Majer, *Chirality* **13**, 493 (2001).
[13] K. Baba, K. Takeuchi, M. Doi, M. Inoue, and M. Kozawa, *Chem. Pharm. Bull.* **34**, 1540 (1986).
[14] W.J. Xiang, L. Ma, and L.H. Hu, *Fitoterapia* **81**, 1228 (2010).
[15] T. Miyase, H. Noguchi, and X.M. Chen, *J. Nat. Prod.* **62**, 993 (1999).
[16] N.C. Kim, T.N. Graf, C.M. Sparacino, M. C. Wani, and M.E. Wall, *Org. Biomol. Chem.* **1**, 1684 (2003).
[17] A. Sy-Cordero, T.N. Graf, Y. Nakanishi, M.C. Wani, R. Agarwal, D.J. Kroll, and N.H. Oberlies, *Planta Med.* **76**, 644 (2010).
[18] T.C. Lin, J.M. Fang, and Y.S. Cheng, *Phytochemistry* **51**, 793 (1999).
[19] M.S. Silva, J.M. Barbosa-Filho, M. Yoshida, and O.R. Gottlieb, *Phytochemistry* **28**, 3477 (1989).