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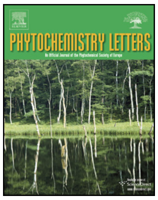

Guaianolides from *Curcuma kwangsiensis*

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ABSTRACT

Three guaianoilides, including a new compound (1R,4R,5S,8S,9Z)-4-hydroxy-1,8-epoxy-5H-guaia-7(11),9-dien-12,8-olide (**1**) and two rare ones, gweicurculactone (**2**), and 2-oxoguaia-1(10),3,5,7(11),8-pentaen-12,8-olide (**3**), together with tricosanoic acid, and β-sitosterol were isolated from the rhizomes of *Curcuma kwangsiensis* S.G. Lee and C.F. Liang (Zingiberaceae). Their structures and relative stereochemistries were determined on the basis of UV, IR, MS, and 1D NMR and 2D NMR spectroscopic methods. The absolute configurations of the new compound **1** and the previously isolated compound **2** were unambiguously determined by using CD spectroscopic data.

1. Introduction

Curcuma kwangsiensis S.G. Lee and C.F. Liang is a plant of the family Zingiberaceae, whose distribution is in China and Vietnam (Vo, 1997; Pham, 1991–1993). Results of previous chemical studies of *C. kwangsiensis* are fruitful of diarylheptanoids, some of which are potential inhibitors of nitric oxide production in lipopolysaccharide-activated macrophages (Li et al., 2010, 2011a,b) and labdanes, some of which efficiently modulates $GABA_A$ receptor (Schramm et al., 2013). Guaiane-type sesquiterpene lactone, namely gweicurculactone, was reported from *C. kawngsiensis* in the only study (Jiang et al., 1989) causing a growing interest in the search for these structurally interesting compounds. In the present paper, the extensive chromatographic isolation and structural determination of three guaianolides, including one new and two rare compounds, are reported.

2. Results and discussion

The dried and powdered rhizomes of *C. kwangsiensis* were extracted with MeOH at room temperature. The CH_2Cl_2- and EtOAc-soluble fractions were subjected to repeated silica gel and reversed-phase octadecyl silica (ODS) gel column chromatography (CC) to afford five compounds, of which compound **1** is a new guaianolide. The structures of the known compounds, tricosanoic acid, β-sitosterol (Goad and Akihisha, 1997), gweicurculactone (**2**) (Jiang et al., 1989), and 2-oxoguaia-1(10),3,5,7(11),8-pentaen-12,8-olide (**3**) (Ahmad et al., 2000), were determined on the basis of extensive spectroscopic analysis, including MS, ^1H NMR, ^{13}C NMR, $^1H–^1H$ COSY, HSQC, HMBC, and NOESY spectra. The absolute structure of gweicurculactone (**2**) was first determined by the interpretation of Cotton effects, observed in the circular dichroism (CD) spectrum.

Compound **1** was isolated as a white amorphous powder, $[\alpha]$ +55.6 ($c = 0.15$, $CHCl_3$). Its molecular formula was determined as $C_{15}H_{18}O_4$ by positive-ion high-resolution electrospray ionization MS (*m/z* 285.1097 $[M+Na]^+$, Calc. 285.1097). The UV spectrum showed an absorption maxima at 212 nm and the IR spectrum showed the absorptions of hydroxy (3465 cm^{-1}) and carbonyl (1773 cm^{-1}) groups, and double bonds (1649 cm^{-1}), indicating the presence of an α,β-unsaturated γ-lactone (Liu et al., 2013). The ^1H NMR and HSQC spectra showed the presence of a methyl group bonded to an oxygen-bearing carbon [δ_H 1.32 (3H, s)], two olefinic methyl groups [δ_H 1.80 (3H, d, $J = 2.0$ Hz) and 1.89 (3H, d, $J = 1.5$ Hz)], three sp^3 methylenes [δ_H 1.86 (1H, m), 1.90 (1H, m); 2.06 (1H, m), 2.20 (1H, m); and 2.57 (1H, ddq, $J = 17.5$ Hz, 9.5 Hz, 2.0 Hz), and 2.86 (1H, d, $J = 17.5$ Hz)], an sp^3 methine [δ_H 2.01 (1H, d, $J = 9.5$ Hz)], and an olefinic methine [δ_H 5.75 (1H, q, $J = 1.5$ Hz)]. Fifteen carbon-13 signals including three methyl groups [δ_C 7.7 (q), 12.3 (q), and 25.5 (q)], three methylenes [δ_C 19.7 (t), 28.2 (t), and 39.9 (t)], one methine [δ_C 46.7 (t)], three oxygenated carbons [δ_C 79.6 (s), 95.5 (s), and 108.5 (s)], a tetra-substituted double bond [δ_C 118.9 (s) and 155.4 (s)], a

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trisubstituted double bond [δ_C 123.9 (d) and 148.9 (s)], and a lactone carbonyl group [δ_C 172.5 (s)] were observed. The ^{1}H–^{1}H COSY correlations were seen for two methylenes at δ_H 1.86/2.20 (H_2-2) and 1.90/2.06 (H_2-3), and the methylene at δ_H 2.57/2.86 (H_2-6) and the *sp*^{3} methine at δ_H 2.01 (H-5), indicating the connections of CH_2-2 to CH_2-3 and CH-5 to CH_2-6. C-14 methyl group was connected to the trisubstituted double bond from the ^{1}H–^{1}H COSY correlation between the olefinic proton at δ_H 5.75 (H-9) and H_3-14 at δ_H 1.89 through an allylic coupling (J = 1.5 Hz). The planar structure of **1** could be built up by using HMBC correlations. The HMBC correlations between the methyl group at δ_H 1.32 (15-CH_3) and C-3 (δ_C 39.9)/C-4 (δ_C 79.6)/C-5 (δ_C 46.7), and between H_2-2/H_2-3 and C-4 afforded the first structural fragment. The second structural fragment was assigned from the HMBC correlations between H-5 (δ_H 2.01) and C-6 (δ_C 19.7)/C-7 (δ_C 155.4), between H_2-6 and C-1 (δ_C 95.5)/C-11 (δ_C 118.9), and between H_3-14 (δ_H 1.89) and C-1/C-9 (δ_C 123.9)/C-10 (δ_C 148.9). The degrees of unsaturation and downfield carbon-13 chemical shifts suggested an oxygen bridge between C-1 (δ_C 95.5) and C-8 (δ_C 108.5) (Matsuda et al., 2001; Liu et al., 2013; Dong et al., 2013). The second fragment was fused with the α,β-unsaturated γ-lactone moiety (δ_C 118.9, 155.4, and 172.5), since the HMBC correlations between H_2-6 and C-11, and between H_3-13 (δ_H 1.80) and C-7/C-11/C-12 (δ_C 172.5), and the presence of an acetal carbon at C-8 were observed (Ahmad et al., 2000; Liu et al., 2013; Dong et al., 2013). These fragments were assembled by using the HMBC correlations between H_3-15 and C-5, and H_2-3 and C-1, leading to the planar structure of a guaiane-type sesquiterpene lactone, 4-hydroxy-1,8-epoxy-guai-7(11),9-dien-12,8-olide. The relative stereochemistry of **1** was established by NOESY experiments. Based on the NOESY correlations, H_3-15, H-3β (δ_H 2.06), H-6β (δ_H 2.86), and H_3-13 were assigned the same orientations. H-5 gave the NOESY correlation to H_3-14, suggesting the opposite β-orientation of the oxygen bridge. The same β-orientation of C-15 methyl group was indicated since no NOESY correlation between H-5 and H_3-15 was detectable. A *Z*-geometry of the C-9/C-10 double bond was evidenced from the NOESY correlation between H_3-14 and H-9 (δ_H 5.75). The assignment of the absolute configuration of the oxygen bridge in the structure of **1** might be an issue, however, since the stereogenic C-8 was adjacent to the α,β-unsaturated γ-lactone moiety, CD could be useful as a tool of assessing its absolute configuration (Matsuda et al., 2001). Similar CD curves of **1** and phaeocaulisin A (**4**) from *C. phaeocaulis* were seen (Liu et al., 2013), namely, **1** displayed the Cotton effects at 212 nm (+3.83) and 230 nm (−5.83), determining the absolute configuration of C-8 to be *S*. Therefore, the absolute structure of **1** was determined to be (1*R*, 4*R*, 5*S*, 8*S*, 9*Z*)-4-hydroxy-1,8-epoxy-5*H*-guai-7(11),9-dien-12,8-olide.

Compound **2** was isolated as a red amorphous powder and its elemental composition was determined to be $C_{15}H_{16}O_2$. The NMR spectroscopic data showed good coincidence with those of gweicurculactone (**2a**), isolated from the same plant (Jiang et al., 1989). The structure of **2a** was previously assigned by the single-crystal X-ray diffraction experiment and the chiral center at the 4-position was determined to have *R* configuration (Jiang et al., 1989). However, X-ray analysis was performed by the direct method and the computer generated drawing must have ambiguously depicted one of the enantiomers. The absolute configuration at the 4-position of **2** was confirmed in this study by comparing its CD data with the reported values of (4*S*)-4-hydroxy-gweicurculactone (**5**) (Yin et al., 2013). Since the sign of optical rotation and CD data of **2a** were not reported, at this moment, it is uncertain that compounds **2** and **2a** are identical compounds or not, although they were isolated from the same plant. Since the NMR data of **2a** are not easily accessible, those of **2** are compiled on the basis of careful inspection of 1D and 2D NMR spectral data and included in the Experimental of this paper.

Some ^{13}C NMR signals of compound **3** were also reassigned in comparison with the literature values (Ahmad et al., 2000) after examining its two-dimensional NMR spectra (Figs. 1–3). Q2

3. Experimental

3.1. General procedures

Optical rotations were determined using a JASCO P-1030 digital polarimeter. IR spectrum was obtained on a Horiba FT-710 Fourier transform spectrophotometer. UV spectra were recorded on a JASCO V-520 spectrophotometer. CD spectra were obtained on a JASCO J-720 spectropolarimeter. HRESIMS spectra were measured on a Applied Biosystems QSTAR XL mass spectrometer. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), DEPT, ^{1}H–^{1}H COSY, HSQC, HMBC, and NOESY spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. Merck silica gel and RP-18 (Merck, Darmstadt, Germany) were used for column chromatography (CC). Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC aluminum sheets.

3.2. Plant material

The rhizomes of *C. kwangsiensis* were collected in Dak Glei, Kontum province, Viet Nam, in August 2008. The plant sample was identified by Dr. Nguyen Quoc Binh, Institute of Ecology and Biological Resources, Vietnam National Academy of Science and

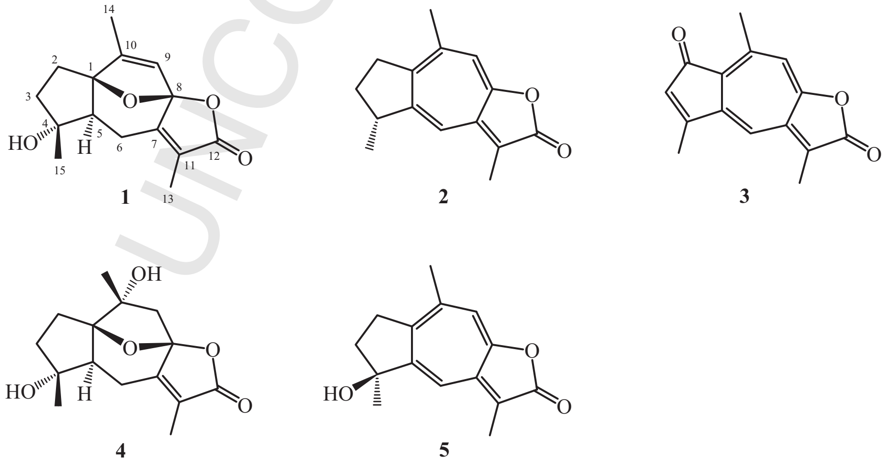

Fig. 1. Chemical structures of compounds **1–5**.

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