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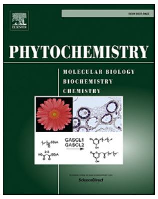

Guaianolide sesquiterpene lactones and aporphine alkaloids from the stem bark of *Guatteria friesiana*

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ABSTRACT

Three guaianolide sesquiterpenes, denoted guatterfriesols A-C, and four aporphine alkaloid derivatives were isolated from the stem bark of the Amazonian plant *Guatteria friesiana*. Thus far, sesquiterpene lactones have not been described in Annonaceae. Structures of the previously undescribed compounds were established by using 1D and 2D NMR spectroscopy in combination with MS. The absolute stereochemistry was assigned via NOE NMR experiments, ECD spectroscopy, and theoretical calculations using the TDDFT approach. Among the isolated compounds, the alkaloid guatterfriesidine showed anti-glycation activity by inhibiting the formation of advanced glycation end-products (AGEs) through the prevention of oxidation in both BSA/methylglyoxal and BSA/fructose systems.

1. Introduction

Guatteria Ruiz & Pav, the largest and oldest genus of the Annonaceae family, comprises 177 species, 25 of which have been recently described. Its distribution occurs through neotropical regions, from southeastern Mexico to southern Brazil. In Brazil, 15 species are described from the southeastern, eastern, and northeastern regions. Most of the species are popularly known as “envireiras” due to the presence of long tough fibers in the bark (Maas et al., 2015). Some *Guatteria* species are used in folk medicine to treat dyspepsia, stomachache, and fever (Maia et al., 2005; Andreazza et al., 2016). Previous pharmacological investigations revealed that some species have cytotoxic (Brito et al., 2012), antimicrobial (Costa et al., 2008), antioxidant (Mahiou et al., 2000), and antiparasitic activities (Mahiou et al., 2000; Montenegro et al., 2003). In general, these properties have been attributed to the presence of a large diversity of alkaloids (mainly aporphinoids), terpenoids (mono- and sesquiterpenes), and phenolic compounds (Costa et al., 2016).

Guatteria friesiana (W.A. Rodrigues) Erkens & Maas (synonym: *Guatteriopsis friesiana*) is a small tree (3–10 m) distributed exclusively in the Brazilian Amazon region (Maas et al., 2015). Previous phytochemical investigations on this species described terpenoids (in the essential oils) and a rich alkaloid content (Brito et al., 2012; Costa et al., 2008, 2009, 2016). In our continuing search for bioactive compounds derived from endemic Amazon plants, we reinvestigated the chemical content of the stem bark from *G. friesiana*. Three guaianolide sesquiterpenes and four aporphine alkaloids were isolated, all previously undescribed compounds. Moreover, the anti-glycation potential of the isolated compounds was also evaluated.

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2. Results and discussion

2.1. Chemical investigation

The *n*-hexane extract from the stem bark of *G. friesiana* after fractionation afforded two compounds, **1** and **2**. The MeOH extract from the same tissues, when subjected to an acid-base extraction, silica gel column chromatography, and preparative-TLC, afforded five compounds (**3**–**7**) (Fig. 1).

Compound **1** was obtained as white crystal needles. The exact mass recorded by using HRESIMS (*m/z* 265.1486 $[M+H]^+$, calcd 265.1434) yielded the molecular formula $C_{15}H_{21}O_4$, in corroboration with ^{13}C NMR data (Table 1). The ^1H NMR spectrum showed only shielded signals (<3.00 ppm) corresponding to methine, methylene, and methyl hydrogens. ^{13}C NMR and DEPT spectra indicated 15 carbon atoms, of which six were quaternary, three methyl, four methylene, and two methines. A guaianolide sesquiterpene skeleton was assumed based on comparison with reported data (Fang et al., 2017; Maas et al., 2011). A slightly unshielded signal at δ 1.85 (s) suggested a methyl group connected to an olefinic carbon. HMBC correlations for this hydrogen resonance (CH_3-13) with δ 161.0 (C-7), 124.8 (C-11), and 172.4 (C-12) confirmed a methylfuran-2(5*H*)-one moiety (lactone ring) in **1** (Fig. 2).

A seven-membered carbon ring was found to be linked to the lactone portion. This proposal was based on the observed HMBC correlations of methylene hydrogens at 2.59 (m, H-8) with δ 103.8 (C-6), 161.0 (C-7), 36.0 (C-9), 33.5 (C-10), and C-11 and of H-9 hydrogens (δ 1.58 m and 1.94 m) with δ 45.9 (C-1), C-7, C-8, C-10, and 13.3 (CH_3-14) (Fig. 2). COSY correlations of δ 2.00 (H-10) with 1.08 (H-14) and H-8 with H-9 confirmed the proposal. Further COSY correlations of H-1 (δ 2.08) with H-2 (δ 1.33 and 1.52) and of H-2 with H-1 and H-3 (δ 1.70 and 1.92) indicated a cyclopentane moiety in **1**. A C-4/C-5 epoxide was found to be linked to the cyclopentane ring. This proposal was further confirmed via HMBC correlations between δ 1.63 (H-15) and typical carbinolic quaternary carbons at δ 72.8 (C-4) and 72.0 (C-5). Furthermore, correlations of H-2 with C-4 and of H-3 with C-4 and C-5 reinforced this idea. A C-6-hydroxy substituent was deduced based on the signal at δ 4.82 (s), which showed no correlation in the HSQC experiment. However, HMBC correlations with C-5, C-6, and C-7 were observed.

The stereochemistry of **1** was assigned via circular dichroism with the aid of NOESY experiments. Irradiation at the H-1 frequency caused an NOE increase of H-2α and H-3α proton signals, suggesting its α-orientation. In addition, NOE correlation between H-10 and H-2β allowed the proposal of the methyl group at C-14 being in the α-orientation. The C-6-hydroxy substituent displayed NOE correlation with the H-15 methyl protons, indicating that both were in the same direction (β-orientation). Thus, the C-4/C-5 epoxide group was found to be on the opposite side (α-orientation) (Fig. 2). The absolute stereochemistry of **1** was assessed using ECD, which gave a positive Cotton effect at λ 221 nm ($\Delta\varepsilon$ +30.3) and a negative Cotton effect at λ 249 nm ($\Delta\varepsilon$ −108.7) (Fig. 3A). The observed data are in accordance with the empirical rule for the α,β-unsaturated γ-lactones (Uchida and Kuriyama, 1974), and the spectrum profile was similar to that of previously reported sesquiterpene lactones (Du et al., 2017). Because ECD data for guaianolide lactones are still scarce, a screening of several structural combinations was performed via the TDDFT approach using the triple-zeta Pople basis set [6−311++g(d,p)] (Lynch et al., 2003). The agreement between the experimental and calculated spectra in MeOH led to the assignment of the absolute configuration of **1** as 1*S*,4*S*,5*R*,6*S*,10*R*. Therefore, compound **1** was assigned as a previously undescribed guaianolide sesquiterpene named guatterfriesol A.

Compound **2** was obtained as a colorless oil. Its molecular formula was determined to be $C_{15}H_{21}O_4$ from the ^{13}C NMR and HRESIMS data (*m/z* 265.1422 $[M+H]^+$, calcd 265.1434). A comparative analysis of the NMR data (Table 1) for compounds **1** and **2** indicated the same structure. Once they were separated via TLC, it was assumed that **2** was a diastereomer of **1**. The ^1H NMR spectrum indicated the absence of the C-6-hydroxy substituent singlet signal, which could be indicative of a hindered region caused by the same orientation of the C-4/C-5 epoxide.

The relative stereochemistry of **2** was established using NOESY. Similar to compound **1**, irradiation at the H-1 frequency caused an NOE increase of the H-2α signal, indicating its α-orientation. NOE correlations of H-10 with H-2α and H-2β with a methyl group at C-14 allowed the proposal of β-orientation of the methyl group. In addition, H-2β correlated with H-3β, reinforcing this proposal. The orientation of the C-15-methyl was proposed as α based on the NOE correlations between H-3α and H-15 (Fig. 2). The ECD spectrum of **2** showed a positive Cotton effect at λ 222 nm ($\Delta\varepsilon$ +30.3) and a

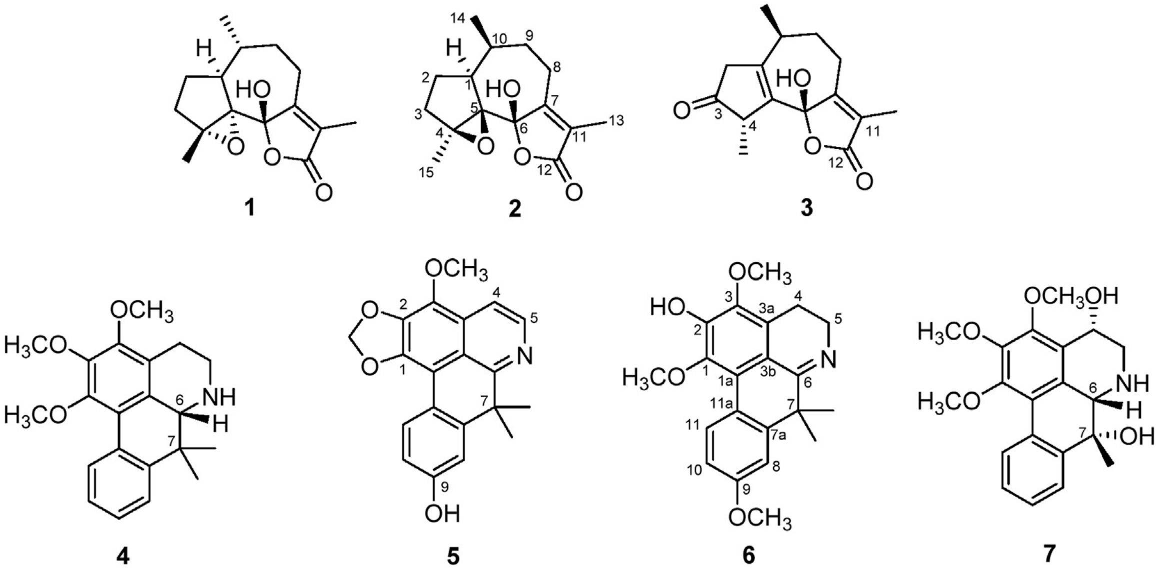

Fig. 1. Structures of compounds **1**–**7** isolated from *Guatteria friesiana*.