



Cyclopropane- and spirolimonoids and related compounds from *Hortia oreadica*

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ABSTRACT

The dichloromethane extract from taproots of *Hortia oreadica* afforded six limonoids, these are 9,11-dehydro-12 α -acetoxyhortiolide A, hortiolide C, 11 α -acetoxy-15-deoxy-6-hydroxyhortiolide C, hortiolide D, hortiolide E, 12 β -hydroxyhortiolide E, in addition to the known limonoid, guyanin. The dichloromethane extract from stems of *H. oreadica* also afforded two limonoids 9,11-dehydro-12 α -hydroxyhortiolide A and 6-hydroxyhortiolide C. As a result of this study and literature data, *Hortia* has been shown to produce highly specialized limonoids that are similar to those from the *Flindersia* (Flindersioideae). The taxonomy of *Hortia* has been debatable, with most authors placing it in the Toddalioidae. Considering the complexity of the isolated limonoids, *Hortia* does not show any close affinity to the genera of Toddalioidae. That is, the limonoids appear to be of little value in resolving the taxonomic situation of *Hortia*.

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1. Introduction

Hortia is a Neotropical genus of the Rutaceae, traditionally included in the subfamily Toddalioidae, subtribe Toddaliinae (Engler, 1931). *Hortia* species are found from Panama to the state of São Paulo, Brazil, with most of the species occurring in the Amazonian region. Historically, De Candolle (De Candolle, 1824) described *Hortia brasiliensis* Vand., which was collected in the south-eastern part of the state of Minas Gerais and in the state of Rio de Janeiro, and Saint-Hilaire (Saint-Hilaire, 1824) described a shrub collected in Goiás and in western Minas Gerais, and also named it *H. brasiliensis*. Engler (1874) also attributed the name *H. brasiliensis* to the shrubby species of central Brazil. In the same study, he described a new arborescent species, *Hortia arborea* Engl. Recently, Groppo et al. (2005) showed that *H. brasiliensis* and *H. arborea* represent the same arborescent species, and that *H. brasiliensis* Vand. ex DC. is the correct name. Albeit well known, the shrubby species found in central Brazil remained unnamed, so Groppo et al. (2005) called it *Hortia oreadica* Groppo, Kallunki and Pirani. Our taxonomic interest in the Rutaceae motivated an investigation of the taproots and stems of *H. oreadica*, whose extracts afforded eight new limonoids (1–8, Fig. 1), in addition to the known guyanin (9). A search for previous phytochemical studies of *Hortia* species indicated that only three limonoids (Fig. 1)

have been previously reported from the genus, namely guyanin (9) (Jacobs and Ramdayal, 1986), hortiolide A (10) and B (11) (Suárez et al., 1998, 2002).

2. Results and discussion

Compound 1 showed spectroscopic characteristics close to those of hortiolide A (10) (C₂₇H₃₂O₇). HRESIMS indicated the molecular formula to be C₂₇H₃₀O₈ for compound 1, requiring the presence of additional oxygen in comparison with 10. The main changes observed in the ¹H NMR spectrum (Table 1) of compound 1 were the presence of additional signals of a hydrogen attached to a carbon adjacent to an oxygen atom (δ 4.25, d, J = 6.8 Hz) and of an olefinic hydrogen (δ 6.20, d, J = 6.8 Hz). This oxymethine hydrogen (δ 4.25) was coupled to the olefinic hydrogen at δ 6.20, and showed a one-bond correlation with the ¹³C NMR signal at δ 66.0 (HSQC) and long-range correlation with the C-14 (δ 167.3), C-17 (δ 79.8) resonances and ¹³C NMR signals at δ 153.3 and 120.7 (HMBC), indicating the presence of a hydroxyl substituent at C-12 and a double bond between C-9 (δ 153.3) and C-11 (δ 120.7). In the g-NOESY experiments, the observed NOE were similar to those found for 10. In addition, the NOE of the H-12 (δ 4.25) coming from H-17 (δ 4.91) suggested a spatial proximity of H-17 β to H-12, which requires the hydroxyl group at C-12 to be *anti* (α) to H-17 (β). The structure of the new natural product 1 was thus established as 9,11-dehydro-12 α -hydroxyhortiolide A. Its structural assignment was also supported by comparing the ¹³C NMR spectrum (Table 2) with that of hortiolide A (10) (Suárez et al., 2002).

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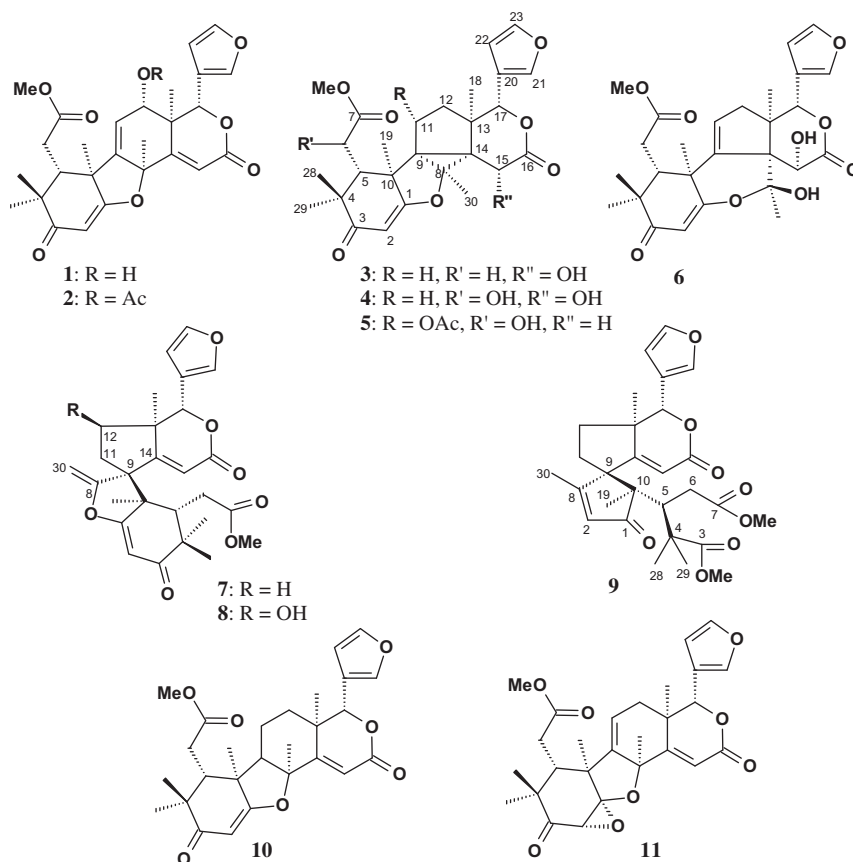


Fig. 1. Structure of isolated compounds (1–9) and reported limonoids (10–11) in literature.

Compound **2** exhibited similar NMR spectra to **1** (Tables 1 and 2) except for the presence of a secondary acetoxy group (^{13}C NMR signals δ 169.4, 20.8, ^1H NMR signal OCOMe δ 2.02). A significant downfield shift for H-12 (δ 5.28), when compared with **1**, determined the position of the acetoxy at C-12. The ^1H NMR resonance at δ 5.28 and a methyl ^1H NMR signal at δ 2.02 showed long-range correlation with the ^{13}C NMR resonances at δ 169.4 (HMBC), confirming an acetoxy group at C-12. In the g-NOESY experiments, the observed NOE were similar to those found for **1**. Thus, the structure of the new limonoid was characterized as 9,11-dehydro-12 α -acetoxyhortiolidide A (**2**).

The structure of compound **3** is more complex than those of **1** and **2**. The NMR spectra (Tables 1 and 2) and extensive analysis of 2D NMR spectra confirmed the hortiolidide-type (**10**, **11**) framework for **3**. One of the changes observed in the ^1H and ^{13}C NMR spectra was the replacement of the resonances for an α,β -unsaturated δ -lactone D-ring by signals for a 15-hydroxy- δ -lactone. The ^1H NMR signal for H-15 at δ 4.40 (d, J = 1.8 Hz) showed one-bond correlation with the ^{13}C NMR resonance at δ 64.1 (HSCQ) and H-15 was coupled only to the hydrogen of a hydroxyl group (δ 3.03, d, J = 1.8 Hz). Moreover, the existence of correlations between the ^1H NMR signal for H-15 and the ^{13}C NMR resonances at δ 45.5 (quaternary), 48.2 (quaternary), and 171.5 led to their assignments as C-13, C-14 and C-16, respectively. The COSY experiments showed correlation of the signals for H-11a and H-11b only with the resonances for H-12a and H-12b. The ^1H NMR signals for H-11a and H-11b showed a long-range correlations with the ^{13}C NMR resonances of C-10 (δ 47.6, quaternary) and C-14 (δ 48.2, quaternary). The methyl ^1H NMR signal at δ 1.42, assigned to Me-19, showed cross-peaks with the ^{13}C NMR signals for C-1, C-5, C-10 and at δ 46.8 (quaternary), allowing the assignment of the

resonance at δ 46.8 to C-9, since it was the only carbon left in the skeleton for a 3J correlation. The ^{13}C NMR spectrum (Table 2) for **3** exhibited resonances in close agreement with those for the corresponding carbons in hortiolidide A (**10**) (Suárez et al., 1998, 2002). However, the quaternary carbons C-9 and C-14 could not be explained by the presence of a normal C-ring as in hortiolidide A (**10**). The formation of a cyclopropane ring involving C-9, C-8 and C-14 in a 9,11-dehydrohortiolidide A precursor may have occurred, resulting in a hortiolidide-A-bicyclo-[5 $^{11-14}$,1 8,9,14]-hexane system, whose spectroscopic properties were in accord with the above data. HREIMS showed the molecular formula $\text{C}_{27}\text{H}_{32}\text{O}_8$ and confirmed the structure **3** for this compound.

The relative stereochemistry of compound **3** was determined from g-NOESY experiments. The NOEs of the H-5 (δ 2.52) and H-17 (δ 5.35) coming from H-15 (δ 4.40) suggested a spatial proximity of H-5 β and H-17 β to H-15, which requires the hydroxyl group at C-15 to be *anti* (α) to H-5 and H-17. In the same way, the NOEs of the H₃-19 (δ 1.42) and H₃-18 (δ 1.18) coming from H₃-30 (δ 1.87), required the Me-30 to be *syn* (α) to Me-18 and Me-19. All these NOEs require rings A and D nearer to boat conformations and cyclopropane ring on the α -side of the molecule. The structural assignment was also supported by comparing the ^{13}C NMR spectrum with that of hortiolidide A (**10**) (Suárez et al., 2002).

The final confirmation of the structure of **3**, named hortiolidide C, came from a single-crystal X-ray diffraction analysis (Fig. 2). The low temperature crystal structure of hortiolidide C (**3**) shows the presence of two hortiolidide molecules, one CH_3OH and one water molecule per asymmetric unit (Tables S1 and S2). *Ortep*⁴ type view of both hortiolidide C conformers showing selected atoms labeling and the 50% probability ellipsoids are presented in Fig. 2a and b, respectively.

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