

Dimeric naphthochromenes and other constituents from *Sinningia allagophylla* (Gesneriaceae)

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ABSTRACT

Sinningia allagophylla, found in Brazil, Paraguay and Argentina, is used by the Brazilian population as diuretic, febrifuge, depurative, and tonic. We present the isolation of nine compounds (1–9) from its tubers, four of them being new: two dimeric naphthochromenes, allagophyllidimer D (1) and allagophyllidimer E (2); a coumarin, 6,8-dimethoxybenzocoumarin (3); and a naphthoquinone-derivative, allagophyllone (4). The known compounds were identified as α -isodunnione (5), warmingiin A (6), warmingiin B (7), cleroidicin B (8), and cleroidicin C (9). All compounds were analyzed by 1D and 2D NMR, and HRMS spectra were recorded for the new compounds. Additionally, conformational analyses were carried on compounds 1 and 2. Compound 5 had been previously obtained only by synthesis, and its complete NMR data are presented here.

1. Introduction

The genus *Sinningia* (Gesneriaceae) contains about 70 species of herbs and subshrubs which are found in neotropical areas, from southern Mexico to northern Argentina (Chautems et al., 2019). The species *Sinningia allagophylla* (Mart.) Wiehler is a herb, growing to 40–80 cm in height, with perennial tubers and annual stems. Flowering during summer (January to March), it produces yellow-greenish to orange flowers, which are pollinated by hummingbirds (*Chlorostilbon lucidus*) (Bastiani et al., 2020). *S. allagophylla* is a beautiful plant that has potential for cultivation as ornamental. It is known in Brazil as “cravo-do-campo” or “batata-de-perdiz”, and in folk medicine its leaves and flowers are considered useful as febrifuge, depurative, and diuretic, while the tubers are used to make tonics and emollients (Mors et al., 2000; Ferreira et al., 2015). Previous phytochemical investigations of the tubers of *S. allagophylla* have reported the isolation of naphthochromenes, naphthoquinones and derivatives, an anthraquinone (tectoquinone), a benzocoumarin (6-methoxy-7,8-benzocoumarin), a sesquiterpene (cedrol), a triterpene (oleanolic acid), a cyclohexylethanoid (halleridone), and steroidal esters (Riva et al., 2012; Scharf et al., 2016). Among the isolated compounds, the

naphthoquinone dunnio displayed cytotoxic activity against human tumor cell lines (Riva et al., 2012), and the naphthochromene 8-methoxylapachenol showed anti-inflammatory and antinociceptive activities (Barbosa et al., 2013). In continuing our research on *S. allagophylla*, we report here the isolation of minor constituents from dichloromethane and ethyl acetate fractions of the ethanolic extract from the tubers. This phytochemical study furnished four new compounds – allagophyllidimer D (1), allagophyllidimer E (2), 6,8-dimethoxybenzocoumarin (3) and allagophyllone (4) – and five known compounds. The structures of the compounds were established by spectroscopic methods, and the data obtained were compared with literature data. For the new compounds, HRMS data were acquired, and conformational analyses were performed for compounds 1 and 2 applying the density functional theory.

2. Experimental

2.1. General experimental procedures

Optical rotations were measured in CHCl₃ on a Rudolph Research polarimeter. The UV–vis spectra were obtained on a Shimadzu UV-2401PC spectrophotometer. 1D and 2D NMR experiments were

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carried out in CDCl₃ at 295 K on a Bruker AVANCE 400 or AVANCE III 600 NMR spectrometer, observing ¹H at 400 or 600 MHz and ¹³C at 100 or 150 MHz, respectively. All ¹H and ¹³C NMR chemical shifts are given in ppm (δ), using TMS as internal reference, with coupling constants (J) in Hz. HRMS data were obtained on a Micromass ESI-Qq ToF or a Thermo Scientific LTQ-Orbitrap XL mass spectrometer, using the positive-ion mode. Geometry optimization without any constraints for compounds **1** and **2** were based on density functional theory (DFT), employing the B3LYP hybrid functional with LANL2DZ as basis set, such as implemented in the Gaussian16 suite (Frisch et al., 2016). The converged wave functions were tested to confirm that they corresponded to the ground-state potential energy surface (PES) and that the optimized molecular geometry was a global minimum.

All HPLC separations were performed in a Waters apparatus equipped with a PDA detector and a semipreparative Nucleosil 100-5 C18 column (250 × 10 mm). Silica gel (Merck, 230–400 mesh) was used for column chromatographic (CC) separation, while silica gel 60 PF₂₅₄ (Merck) was used for analytical (0.25 mm) and preparative (1.0 mm) TLC. Compounds were visualized by exposure under UV_{254/366} light and spraying with 5% (v/v) H₂SO₄ in ethanol solution, followed by heating on a hot plate. All solvents were analytical or spectroscopic grade, and the mixtures of solvents were prepared as v/v.

2.2. Plant material

The vegetal material (tubers) was harvested in Palmeira, Paraná State, Brazil (25°26'3" S, 49°59'60" W). Clarice Bolfe Poliquesi identified the material and deposited a voucher in the herbarium of Museu Botânico Municipal de Curitiba under number MBM 313530. This species was registered on the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SISGEN) under the code AF5C97F.

2.3. Extraction and isolation

Dried and powdered tubers (166.2 g) were extracted with EtOH (3 × 1 L) at room temperature. The solvent was removed under reduced pressure, yielding the EtOH extract (27.2 g). An aliquot (2.2 g) was reserved. The remaining EtOH extract (25.0 g) was dissolved in EtOH:H₂O (1:1) (300 mL) and partitioned with hexanes (Hex, mixture of isomers), CH₂Cl₂, and EtOAc, successively (3 × 100 mL, each solvent).

The CH₂Cl₂-soluble portion (5.5 g) was subjected to silica gel CC, eluted with CH₂Cl₂, mixtures of CH₂Cl₂:acetone (95:5, 8:2, 1:1), and acetone to give 13 fractions (FD_{1–13}). Fraction FD₃ (24.7 mg) and FD₄ (16.9 mg), both eluted with CH₂Cl₂, were purified by semi-preparative HPLC (100% MeCN; 1.0 mL min⁻¹) to give **5** (retention time (Rt) 4.96 min, 1.7 mg) and **1** (Rt 11.65 min, 1.2 mg), respectively. Fraction FD₇ (20.4 mg, eluted with CH₂Cl₂) was submitted to prep. TLC in Hex:acetone (9:1) yielding **3** (1.3 mg) and a mixture (6.4 mg) that was purified by an additional prep. TLC in Hex:EtOAc (95:5), yielding **4** (1.0 mg). Fraction FD₁₀ (51.1 mg, eluted with CH₂Cl₂:acetone (8:2)) was purified by HPLC (MeCN:H₂O (80:20); 1.0 mL min⁻¹) yielding **2** (Rt 6.80 min, 2.0 mg) and a mixture of **6** + **7** (Rt 8.20 min, 7.0 mg).

The EtOAc-soluble portion (2.9 g) was submitted to silica gel CC and eluted with mixtures of CH₂Cl₂:MeOH (9:1, 8:2, 7:3, 1:1) and MeOH to give six fractions (FA_{1–6}). Fraction FA₁ (390.6 mg, eluted with CH₂Cl₂:MeOH (9:1)) was subjected to another silica gel CC, eluted with mixtures of CH₂Cl₂:MeOH (99:1, 95:5, 9:1, 1:1), and gave six subfractions (FA_{1.1–6}). Subfraction FA_{1.5} (43.7 mg, eluted with CH₂Cl₂:MeOH (9:1)) yielded **8** (4.2 mg) and **9** (5.6 mg) after repeated prep. TLC in CH₂Cl₂:MeOH (9:1).

2.3.1. Allagophyllidimer D (**1**)

Amorphous red solid; [α]_D²⁰ zero (c 1.0, CHCl₃); ¹H and ¹³C, see Table 1; HRMS m/z calcd. for C₃₄H₃₇O₇ [M+H]⁺: 557.2539, found 557.2546.

Table 1

NMR Data of Compounds **1** and **2** (600 MHz, CDCl₃).

Position	1			2		
	δ_C , type	δ_H (J in Hz)	HMBC	δ_C , type	δ_H (J in Hz)	HMBC
2/2'	76.1, C			78.1, C		
3/3'	49.4, CH	2.60 d (6.3)	2, 3', 4, 4a, 12, 13	71.9, CH	3.77 d (3.7)	
4/4'	73.1, CH	4.92 d (6.3)	2, 3, 4', 4a, 5, 11	65.9, CH	4.86 d (3.7)	4a, 5
4a/4'a	113.3, C			113.0, C		
5/5'	104.6, CH	6.77 s	4, 6, 6a, 11	103.5, CH	6.92 s	4a, 6, 6a, 11,
6/6'	148.8, C			149.3, C		
6a/6'a	128.4, C			127.7, C		
7/7'	100.5, CH	7.49 d (2.7)	6, 8, 9, 10a	100.6, CH	7.48 d (2.7)	6, 8, 10a
8/8'	158.3, C			158.1, C		
9/9'	118.2, CH	7.14 dd (9.2, 2.7)	7, 8, 10a	118.4, CH	7.13 dd (9.1, 2.7)	7, 10a
10/10'	123.9, CH	8.08 d (9.2)	6a, 8, 11	123.9, CH	8.07 d (9.1)	6a, 11
10a/10'a	121.2, C			120.9, C		
11/11'	143.3, C			141.1, C		
12/12'	28.0, CH ₃	1.55 s	2, 3, 13	24.6, CH ₃	1.57 s	2, 3, 13
13/13'	24.0, CH ₃	1.45 s	2, 3, 12	23.1, CH ₃	1.33 s	2, 3, 12
OMe-6/6'	55.8, CH ₃	3.98 s	6	55.8, CH ₃	3.98 s	6
OMe-8/8'	55.3, CH ₃	3.93 s	8	55.4, CH ₃	3.93 s	8

2.3.2. Allagophyllidimer E (**2**)

Amorphous brown solid; [α]_D²⁰ zero (c 1.0, CHCl₃); ¹H and ¹³C, see Table 1; HRMS m/z calcd. for C₃₄H₃₇O₈ [M+H]⁺: 573.2488, found 573.2449.

2.3.3. 6,8-Dimethoxybenzocoumarin (**3**)

Amorphous yellow solid; UV-vis (MeOH) λ_{max}/nm (log ϵ) 215 (3.9), 245 (3.6), 276 (3.6), 286 (3.6), 372 (3.1); ¹H and ¹³C, see Table 2; HRMS m/z calcd. for C₁₅H₁₃O₄ [M+H]⁺: 257.0814, found 257.0808.

2.3.4. Allagophyllone (**4**)

Amorphous white solid; [α]_D²⁰ zero (c 1.0, CHCl₃); ¹H and ¹³C, see

Table 2

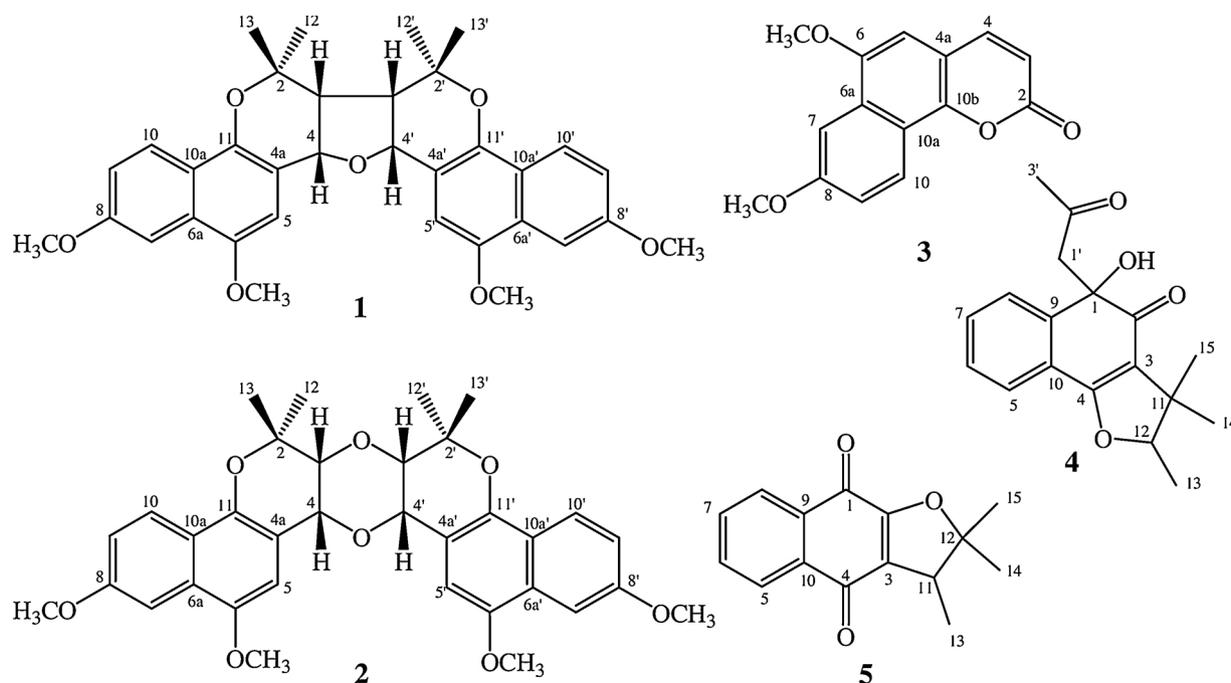
NMR Data (400 MHz, CDCl₃) of Compound **3**.

Position	δ_C , type	δ_H (J in Hz)	HMBC
2	161.2, C		
3	114.9, CH	6.47 d (9.4)	2, 4a
4	144.5, CH	7.74 d (9.4)	2, 5, 10b
4a	112.4, C		
5	100.5, CH	6.69 s	4, 6, 6a, 10b
6	151.2, C		
6a	129.2, C		
7	101.6, CH	7.57 d (2.6)	6, 10a
8	159.9, C		
9	119.9, CH	7.30 dd (9.2, 2.6)	10a
10	124.2, CH	8.42 d (9.2)	6a, 8, 10b
10a	118.8, C		
10b	146.5, C		
OMe-6	55.8, CH ₃	4.04 s	6
OMe-8	55.5, CH ₃	3.97 s	8

Table 3
NMR Data of Compounds **4** and **5** (400^a and 600^b MHz, CDCl₃).

Position	4 ^a			5 ^b		
	δ _C , type	δ _H (J in Hz)	HMBC	δ _C , type	δ _H (J in Hz)	HMBC
1	77.5, C			178.8, C		
2	196.5, C			158.1, C		
3	117.4, C			127.7, C		
4	168.9, C			182.7, C		
5	124.3, CH	7.65 dd (7.7, 1.4)*	4, 7, 9	126.1, CH	8.06 dd (7.3, 1.1)*	4, 9
6	128.1, CH	7.38 ddd (7.7, 7.7, 1.1)	8, 10	134.1, CH	7.71 ddd (7.6, 7.3, 1.4)	5, 10
7	131.4, CH	7.50 ddd (7.7, 7.7, 1.4)	5, 9	132.9, CH	7.66 ddd (7.6, 7.5, 1.1)	5, 9
8	126.0, CH	7.66 dd (7.7, 1.1)*	10, 6	126.1, CH	8.08 dd (7.5, 1.4)*	1
9	144.1, C			132.0, C		
10	122.8, C			133.3, C		
11	44.1, C			44.5, C		
12	92.5, CH	4.63 q (6.6)	14, 15	93.9, CH	3.26 q (7.2)	13, 14, 15, 2
13	14.0, CH ₃	1.46 d (6.6)	11, 12	14.3, CH ₃	1.32 d (7.2)	3, 12
14	24.6, CH ₃	1.42 s	3, 11, 12, 15	28.8, CH ₃	1.51 s	11, 12, 15
15	20.6, CH ₃	1.17 s	3, 11, 12, 14	22.2, CH ₃	1.49 s	11, 12, 14
1'	58.0, CH ₂	2.84 bs	1, 2, 2', 9			
2'	205.6, C					
3'	32.2, CH ₃	2.10 s	2'			

* overlapping.

**Fig. 1.** Chemical structures of the new (**1** – **4**) identified compounds in *Sinningia allagophylla*. Compound **5** was isolated for the first time from a natural source.**Table 3;** HRMS m/z calcd. for C₁₈H₂₁O₄ [M+H]⁺: 301.1439, found 301.1435.**2.3.5. α -Isodunnione (5)**Amorphous yellow solid; [α]_D²⁰ zero (c 1.0, CHCl₃); ¹H and ¹³C, see **Table 3**; HRMS m/z calcd. for C₁₅H₁₅O₃ [M+H]⁺: 243.10212, found 243.09682.**3. Results and discussion**

Compound **1** (Fig. 1) was isolated as an amorphous red solid. Its positive HRMS showed an ion at m/z 557.2546 [M+H]⁺, indicating the molecular formula C₃₄H₃₆O₇, with 17 indices of hydrogen deficiency. In the ¹H NMR, we observed signals for three hydrogens (δ_H 7.14–8.08) in a spin system of a 1,2,4-trisubstituted benzene (H-7, H-9, H-10) and one isolated aromatic hydrogen (δ_H 6.77, H-5), along with two methoxy groups (δ_H 3.93, 3.98), one oxymethinic hydrogen (δ_H 4.92, H-4) coupled with one methinic hydrogen (δ_H 2.60, H-3), and two methyl groups (δ_H 1.45, 1.55) (**Table 1**). These data resembled those of the naphthochromane 8-methoxylapachenol, previously isolated from this plant (Riva et al., 2012). From HSQC and HMBC data, the presence of 17 different carbons and 18 hydrogens was deduced. Considering the molecular formula, compound **1** must have a symmetrical dimeric structure, which was determined from correlations observed in the HSQC and HMBC spectra (Supplementary material). The methoxy groups were located at C-6 and C-8 due to the correlations among H-7 (δ_H 7.49) and the singlet at δ_H 3.98 with C-6 (δ_C 148.8), and H-10 (δ_H 8.08) and the singlet at δ_H 3.93 with C-8 (δ_C 158.3) in the HMBC spectrum. Also, the methyl groups (δ_H 1.45 and 1.55) showed cross-peaks with an oxygenated quaternary carbon at δ_C 76.1 (C-2) and a methinic carbon at δ_C 49.4 (C-3). Cross-peaks were also observed between C-3 and the hydrogen at δ_H 2.60 (H-3) in the HSQC spectrum. In the HMBC spectrum, H-3 showed cross-peaks with C-3' (δ_C 49.4), C-4 (δ_C 73.1), and C-4a (δ_C 113.3). Contrastingly, the hydrogen at δ_H 4.92 (H-4) showed cross-peaks with C-4 in the HSQC, and also with C-4' (δ_C 73.1), C-5 (δ_C 104.6), and C-11 (δ_C 143.3) in the HMBC spectrum (**Table 1**). Therefore, the two halves of **1** are linked by C-3/C-3' and C-4/C-4' through a tetrahydrofuran ring. The conformational analysis done by DFT calculations showed that, in the condition of minimum energy, the tetrahydrofuran

ring adopts a slightly bent conformation, where one atom of the ring is out of its molecular plane. At the same time, the two halves are extended far from the tetrahydrofuran ring (Fig. 2). The coupling constant between H-3/H-4 ($J = 6.3$ Hz) suggests that they are on a *cis*-relationship. Considering the least energetic conformation of the molecule obtained by the DFT calculations, the dihedral angle between H-3 and H-4 is 25.7° ; therefore, the hydrogens are closely aligned (close to 0°) confirming that they are at the same side of the ring or in a *cis*-relationship. Accordingly, the specific rotation of **1** was zero, indicating a *meso* compound. Compound **1** is the fourth dimer isolated from *S. allagophylla*, and following the nomenclature, it was named allagophyllidimer D.

Compound **2**, named allagophyllidimer E, was isolated as an amorphous brown solid. Its molecular formula was determined as $C_{34}H_{36}O_8$, with 17 indices of hydrogen deficiency, from the ion at m/z 573.2449 $[M+H]^+$ in positive HRMS. As in **1**, the NMR data (Table 1) showed only 17 different carbons, indicating again a symmetrical dimeric compound. The NMR data of **2** were remarkably close to those of **1**, revealing a similar structure. Accordingly, in the 1H NMR, we observed three hydrogens (δ_H 7.13–8.07) with multiplicities and coupling constants typical of a 1,2,4-trisubstituted aromatic ring (H-7, H-9 and H-10), one isolated aromatic hydrogen (δ_H 6.92, H-5), two methoxy groups (δ_H 3.93, 3.98), and two methyl groups (δ_H 1.33, 1.57). Two oxymethinic hydrogens in a spin system, at δ_H 3.77 (H-3) and 4.86 (H-4), showing cross-peaks with carbons at δ_C 71.9 and 65.9, respectively, were also observed in the HSQC spectrum. The location of these oxygenated carbons at C-3 and C-4 was deduced from the correlations in the HMBC spectrum. The most important were: H-12 (δ_H 1.57) and H-13 (δ_H 1.33) with the carbon at δ_C 71.9 (C-3); the hydrogen at δ_H 4.86 (H-4) with C-4a (δ_C 113.0) and C-5 (δ_C 103.5); and H-5 (δ_H 6.92) with C-4a and C-11 (δ_C 141.1) (Table 1). The small coupling constant between H-3/H-4 ($J = 3.7$ Hz) indicates a *cis*-relationship. The conformational analysis showed that the dioxane ring adopts a chair-like geometry, where hydrogens H-3, H-3', H-4, H-4' occupy a *pseudo*-axial position, while the two halves stay in the *pseudo*-equatorial places, giving the molecule the overall shape of an “L” (Fig. 3). The dihedral angle obtained by DFT between H-3 and H-4 is 32.7° ; as in the case of compound **1**, H-3 and H-4 are close to each other, at the same side of the ring, confirming their relationship as *cis*. In agreement, the optical rotation of **2** was found to be zero.

Compound **3** was isolated as a yellow solid that displayed fluorescence under irradiation with UV light (λ 365 nm). Its HRMS spectrum in positive mode showed an ion at m/z 257.0808 $[M+H]^+$, compatible with the molecular formula $C_{15}H_{12}O_4$, consistent with ten indices of

hydrogen deficiency. The 1H NMR data (Table 2) showed signals of four aromatic hydrogens, one being isolated (δ_H 6.69, H-5) and three (δ_H 7.30–8.42) being in a spin system characteristic of a 1,2,4-trisubstituted aromatic system (H-7, H-9, H-10), besides signals for two olefinic hydrogens (δ_H 6.47, H-3; 7.74, H-4) and two methoxy groups (δ_H 3.97, 4.04). From HSQC and HMBC data, the presence of 15 different carbons, including a carbonyl lactone (δ_C 161.2), was deduced. All data pointed to a benzocoumarin with two methoxy groups. The structure was determined by the correlations in the HSQC and HMBC spectra (Table 2). The most important cross-peaks were the following: H-4 (δ_H 7.74) with C-2 (δ_C 161.2), C-5 (δ_C 100.5), and C-10b (δ_C 146.5); H-10 (δ_H 8.42) and the signal at δ_H 3.97 (OMe-8) with C-8 (δ_C 159.9); and H-7 (δ_H 7.57) and the signal at δ_H 4.04 (OMe-6) with C-6 (δ_C 151.2). These and remaining correlations (Table 2) led to the identification of **3** as 6,8-dimethoxybenzocoumarin, a new compound similar to another one previously isolated from *S. allagophylla*, but with an additional methoxy group (Scharf et al., 2016).

Compound **4**, named allagophyllone, was isolated as an amorphous white solid. Its molecular formula was deduced as $C_{18}H_{20}O_4$, with nine indices of hydrogen deficiency, from NMR data and an ion at m/z 301.1435 $[M+H]^+$ in the positive HRMS. The 1H NMR of **4** showed signals of four aromatic hydrogens (δ_H 7.38–7.66) in a spin system typical of a 1,2-disubstituted benzene, besides the signals for a 2,3-dihydro-2,3,3-trimethylhydrofuran group (quartet at δ_H 4.63, two singlets at δ_H 1.17 and 1.42, and a doublet at δ_H 1.46). These signals resembled those of the naphthoquinones dunnione or α -dunnione, previously isolated from this plant (Scharf et al., 2016), but the presence of signals for a methylene group (δ_H 2.84) and an acetyl group (δ_H 2.10) pointed to a derivative. In the HMBC spectrum, the hydrogen at δ_H 7.65 (H-5) showed cross-peaks with a carbon at δ_C 168.9, which is typical of C-4 in the framework of dunnione (Inoue et al., 1983). However, it was lacking the signals at δ_C 181 and 175, which are expected for C-1 and C-2 in dunniones. Instead, signals for a ketocarbonyl (δ_C 205.6, C-2'), an α,β -unsaturated ketocarbonyl (δ_C 196.5, C-2), and a quaternary oxygenated carbon (δ_C 77.5, C-1) were observed. These data suggested that one carbonyl group of the quinone system in the dunnione framework had been replaced by a hydroxy group and an aliphatic group. From HSQC and HMBC data, a 2-oxopropyl group was defined by singlets at δ_H 2.84 (H-1') and 2.10 (H-3'), and by the carbons at δ_C 32.2 (C-3'), 58.0 (C-1'), and 205.6 (C-2'). The position of this group in C-1 was deduced from correlations in HMBC among H-1' and carbons at δ_C 77.5 (C-1), 144.1 (C-9), and 196.5 (C-2). These and the remaining correlations (Table 3) led to structure **4**. However, it was not possible to assign

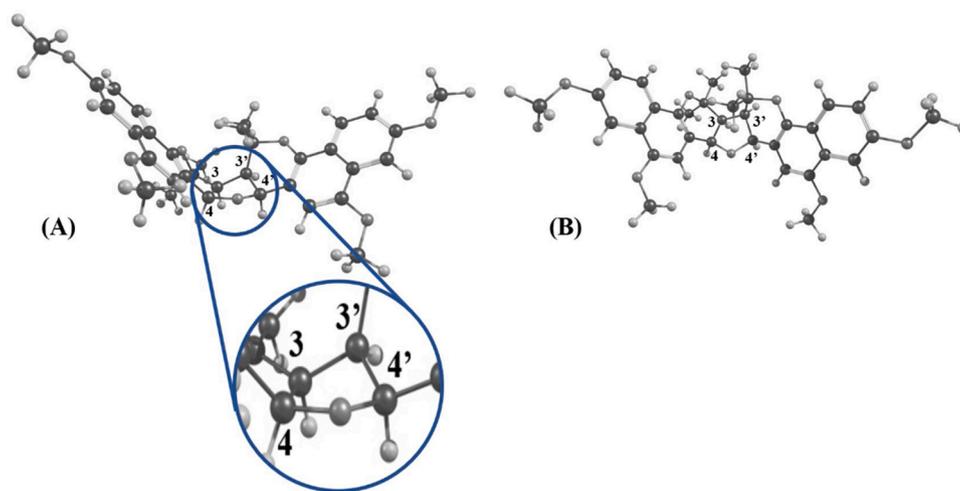


Fig. 2. Two views of the more stable conformation calculated for allagophyllidimer D (**1**). (A) shows a view where it is possible to see the tetrahydrofuran ring slightly twisted, and (B) shows a model of the molecule in another twisted view of the minimal energy conformation, uncovering the highest number of atoms. Carbons of the tetrahydrofuran ring are numbered for clarity.

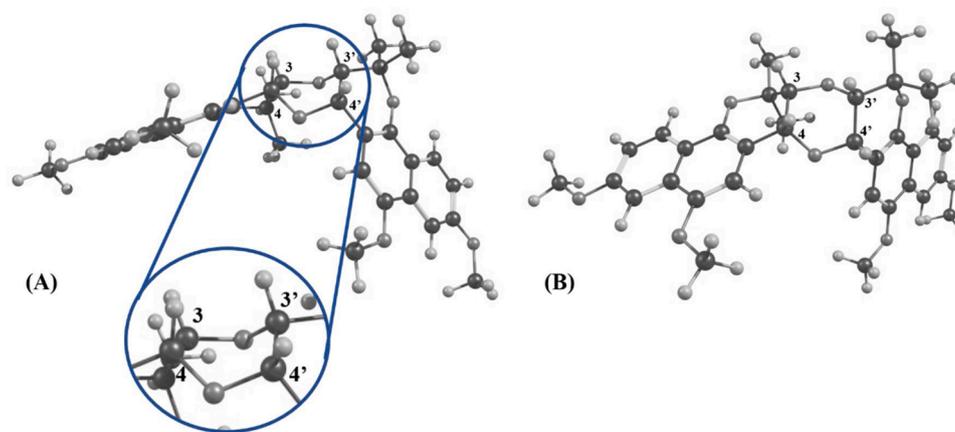


Fig. 3. Two views of the least energetic conformation calculated for allagophylldimer E (2). (A) shows a better view of the chair-like conformation of the dioxane ring, and (B) shows a view uncovering all the atoms in the molecule at the minimal energy conformation. Carbons of the dioxane ring are numbered for clarity.

the relative configuration between C-1 and C-12 since the optical rotation of **4** was zero, indicating a racemic mixture.

The known compounds were identified as α -isodunnione (**5**) (Kobayashi et al., 1991), warmingiin A (**6**), warmingiin B (**7**) (Winiewski et al., 2017), cleroidicin B (**8**) (Tian et al., 1997), and cleroidicin C (**9**) (Inoue et al., 1983). Compound **5** had previously been synthesized, but this is the first report of it obtained from a natural source. Its ^{13}C NMR data were lacking, and therefore, complete NMR data are presented in Table 3. Compounds **6–9** are being reported for the first time in *S. allagophylla*.

4. Conclusions

In this study, we present the isolation and identification of nine compounds from *Sinningia allagophylla*. The results add to the chemical diversity of the genus *Sinningia*. Dimers of naphthochromenes are thus far restricted to *Sinningia allagophylla*, and here we present the isolation of two new compounds belonging to this class, allagophylldimer D (**1**) and allagophylldimer E (**2**). Besides that, a cyclohexylethanoid, a coumarin, a naphthoquinone derivative, and dimeric naphthoquinones derivatives were shown to be present at the tubers of *S. allagophylla*. DFT studies proved to be able to infer the relative stereochemistry of the compounds when allied to comparison with data of previously isolated compounds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

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