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Lathrophytoic acids A and B: two novel polyprenylated phloroglucinol derivatives from *Kielmeyera lathrophyton*

Miquéias F. de Almeida [a], Maria L.S. Guedes [b], Frederico G. Cruz [a,*]

[a] Gesnat, Instituto de Química, Universidade Federal da Bahia, 40170-115 Salvador, Bahia, Brazil
[b] Instituto de Biologia, Universidade Federal da Bahia, 40170-115 Salvador, Bahia, Brazil

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ABSTRACT

Two novel polyprenylated phloroglucinol derivatives were isolated from the trunk of *Kielmeyera lathrophyton* (Clusiaceae). Lathrophytoic acid A presented an unusual caged carbon skeleton with a 1,3-dione-4-cyclopentanol moiety. Lathrophytoic acid B exhibited a highly substituted bicycle[3.3.1]nonane skeleton and an isopropylfuran system which was formed by unusual cyclization of a prenyloxy side chain.

Kielmeyera is a genus of Clusiaceae, endemic of South America, which is a rich source of xanthones,[1] prenylated 4-phenyl, and 4-alkylcoumarins.[2] In a previous work, we reported the isolation of prenylated xanthones and prenylated 4-phenyl and 4-alkylcoumarins from *Kielmeyera lathrophyton*.[3] During this work were observed in the ^{1}H and ^{13}C NMR spectra of the hexane extract of the trunk, signals that indicated the presence of some substances with characteristics of carboxylic acids that had never been reported in *Kielmeyera*. The plant was collected again and re-examined aiming at the isolation and characterization of these substances. In this work, the isolation, as methyl ester, of two new polyprenylated phloroglucinyl-3-phenylpropanoic acids, lathrophytoic acids A and B, from the hexane extract of the trunk was related. The plant was harvested in campo rupestre area (rocky fields) in Chapada Diamantina, Bahia state, northeast region of Brazil.

Dried powdered trunk (2.0 kg) of *K. lathrophyton* was extracted with hexane. The extract (14.0 g) was fractionated with hexane and hexane/EtOAc mixtures in a silica gel column. Fraction 10 presented a mixture of substances that displayed chromatographic behavior characteristic of carboxylic acids. To facilitate the isolation process, this fraction was methylated with diazomethane and subsequently subjected to successive chromatography on silica gel column and preparative TLC (silica gel; hexane/EtOAc 9:1) to provide the compounds **1a** (18.3 mg) and **2a** (6.0 mg).

The methyl ester of lathrophytoic acid A, **1a**, a yellow gum, $[\alpha]_D^{25}$ +15 (*c* 0.23, MeOH), has the molecular formula $C_{30}H_{38}O_5$ deduced from DEPT, ^{13}C NMR, and HRESIMS (positive mode) on the basis of the pseudo molecular ion peak at *m*/*z* 501.2625 $[M+Na]^+$. IR absorptions (3510, 1732, 752 and 701 cm^{-1}) suggested the presence of a hydroxyl, a carbonyl, and a monosubstituted aromatic ring. Analyses of the ^{13}C and DEPT spectra (Table 1), indicated six CH_3, five CH_2, nine CH, and 10 nonhydrogenated carbons, compatible with 12 degrees of insaturation. The monodimensional NMR revealed the presence of a phenyl, a prenyl, and one terminal double bond. Additionally, three signals at δ 214.5, 214.2, and 172.1 indicated the presence of two ketone groups and one ester group, respectively. These results combined with molecular formula allowed to deduce the presence of three rings in the molecule besides the aromatic ring. The hydroxyl group suggested by IR was confirmed by the signal at δ 81.9 in the ^{13}C NMR spectrum, which is compatible with a tertiary alcohol. The backbone of molecular structure was deduced from HMBC analysis. Correlations of H-21 with C-1, C-2, C-10, C-23, C-24, and C-25; H-19 and H-20 with C-1, C-7 and C-8; H-14 with C-2, C-3, C-4, C-9, C-15, and C-16; H-5 with C-3, C-4, C-10, C-11, C-12 and C-13; H-9a and H-9b with C-2, C-3, C-7 and C-8; H-6a and H-6b with C-4, C-5, C-7, C-8, and C-9 unequivocally support to compound **1a** the structure depicted in Figure 1.

The NOESY experiment (Figs. 1 and 2) allowed to establish the stereochemistry at C-5, C-21 and the right assignments of the hydrogen chemical shifts to H-9a, H-9b, H-6a, H-6b, and methyl groups H-19 and H-20 (Table 1). The NOE correlations between

* Corresponding author. Tel.: +55 071 3283 6885; fax: +55 071 3237 4117.
E-mail address: fguare@ufba.br (F.G. Cruz).

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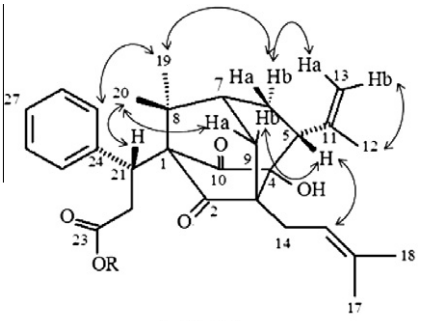
Table 1
^{1}H, ^{13}C and HMBC data for compound **1a**

No.	δ ^{1}H (mult, *J*, Hz)	δ ^{13}C	HMBC (HC)
1		75.1 (s)	
2		214.5 (s)	
3		57.2 (s)	
4		81.9 (s)	
5	2.62 (dd, 8.7, 11.7)	42.2 (d)	3, 4, 10, 11, 12, 13
6	Ha 1.65 p ov	26.8 (t)	7, 8, 9
	Hb 1,34 p ov		4, 5, 7, 8
7	1.01 p ov	42.9 (d)	
8		49.7 (s)	
9	Ha 1.99 (dd, 1.5, 13.5)	35.7 (t)	2, 3, 7, 8
	Hb 1.73 p ov		2, 3, 7, 8
10		214.2 (s)	
11		143.0 (s)	
12	1.87 s	22.9 (q)	5, 11, 13
13	Hb 4.99 s	117.0 (t)	5, 12
	Ha 5.09 s		5, 12
14	2.68 (d, 9.0)	26.9 (t)	2, 3, 4, 9, 15, 16
15	5.56 (brt, 8.0)	120.2 (d)	17, 18
16		134.3 (s)	
17	1.59 s	17.9 (q)	15, 16
18	1.71 s	26.2 (q)	15, 16
19	0.26 s	24.6 (q)	1, 7, 8
20	0.93 s	23.9 (q)	1, 7, 8
21	4.23 (dd, 4.5, 9.6)	40.8 (d)	1, 2, 10, 23, 24, 25
22	2.51 (dd, 4.5, 14.7)	40.4 (t)	1, 21, 23, 24
	2.98 (dd, 9.6, 14.7)		1, 21, 23, 24
23		172.1 (s)	
24		141.5 (s)	
25, 29	7.88 br	132.8 (d)	
26, 28	7.00 (t, 7.5)	128.5 (d)	
27	7.00 (t, 7.5)	127.2 (d)	
OMe	3.08 s	51.2 (q)	23

Measured at 300 MHz (^{1}H) and 75 MHz (^{13}C) in C_6D_6.
p ov, partial overlap.



1 R = H
1a R = Me

Figure 1. Structure and selected NOE correlations of **1a**.

H-20 and H-9a, of H-19 with H-6b and of H-5 with H-9b established the relative position of these hydrogens in the molecule. Correlations between H-20 with H-21 allowed to propose a relative configuration 21R* to C-21 in a similar approach to that used to laxifloranone.[4] Due to the steric hindrance, the group 3-phenylmethylpropanoate cannot freely rotate and assumes a conformation in which the phenyl ring is very close to methyl, H-19, one of the methylene hydrogens, H-22, would be approximately next to the plane of C-10 carbonyl and H-21 would be next to the plane of C-2 carbonyl. In this conformation the large highfield chemical shift observed to H-19 (δ 0.26) and the downfield experienced by H-22 (δ 2.98) and H-21 (δ 4.23) could be explained.

The methyl ester of lathrophytoic acid B, **2a**, a yellow gum, presented a molecular formula $C_{36}H_{46}O_5$ established from DEPT, ^{13}C NMR, and positive HRESIMS (pseudo molecular ion peak at *m*/*z* 581.3280 $[M+Na]^+$). Bands at 1750 and 1712 cm^{-1} in the IR suggested the presence of carbonyls while the absorptions at 750 and 700 cm^{-1} indicated a monosubstituted aromatic ring. Analysis of ^{1}H, ^{13}C, and DEPT (90 and 135) spectra (Table 2) showed that, similar to compound **1a**, compound **2a** also presented the 3-phenylmethylpropanoate moiety and two prenyl groups. The ^{1}H NMR also showed two doublets of methyl groups at δ 1.18 and 1.16 and a double septet of a hydrogen at δ 3.34 (0.9 and 6.6 Hz) showing coupling with the two methyl groups and an allylic coupling with a hydrogen at δ 6.64 (0.9 Hz). These signals together with the signals at δ 22.1 (CH_3), δ 22.9 (CH_3), δ 24.8 (CH), δ 139.5 (CH), δ132.2 (C), δ 166.3, and δ 125.1 in the ^{13}C NMR supported the presence of an isopropyl group linked to a trisubstituted double bond with an oxygenated olefinic CH, compatible with an isopropylfuran system. Additionally, signals of nonconjugated and conjugated carbonyls at δ 207.6 and 191.2, respectively, and an ester carbonyl at δ 171.2 were observed. Analyses of ^{13}C and DEPT (135° and 90°) spectra indicated the presences of nine CH_3, four CH_2, 11 CH, and 12 nonhydrogenated carbons. These results combined with molecular formula indicated 14 insaturation degrees and, therefore, the presence of three rings in the molecule besides the aromatic ring. The comparison of NMR data with those of the literature indicates that **2a** presents one bicyclo[3.3.1]nonane system.[5,6]

The HMBC experiments showed correlations of the methyl groups H-26 and H-25 with each other and with C-1, C-7, and C-8; of H-27 with C-1, C-2, C-9, C-28, C-29, and C-30; of H-6 with C-4, C-5, C-7, C-8, C-9, C-15, and C-20; of H-15a and H-15b with

Table 2
^{1}H, ^{13}C and HMBC data for compound **2a**

No.	δ ^{1}H (mult, *J*, Hz)	δ ^{13}C	HMBC (HC)
1		63.9* (s)	
2		166.3 (s)	
3		125.1 (s)	
4		191.2 (s)	
5		63.8* (s)	
6	2.07 (d, 4.8)	39.9 (t)	4, 5, 7, 8, 9,15,20
7	1.14 pov	49.0 (d)	20, 25
8		48.3 (s)	
9		207.6 (s)	
10	6.64 (d, 0.9)	139.5 (d)	2, 3, 11
11		132.2 (s)	
12	3.34 (dsept, 0.9, 6.9)	24.8 (d)	10, 11, 13, 14
13	1.16 (d, 6.9)	22.1 (q)	C-11
14	1.18 (d, 6.9)	22.9 (q)	C-11
15	2.85 (dd, 7.0, 14.5)	31.2 (t)	4, 5, 9, 16, 17
	2.92 (dd, 7.0, 14.5)		
16	5.60 (brt, 7.0)	120.7 (d)	1, 8, 19
17		134.2 (s)	
18	1.78 s	18.2 (q)	16, 17
19	1.65 s	26.2 (q)	16, 17, 18
20	1.44 pov	29.7 (t)	
21	4.72 (brt, 8.0)	125.6 (d)	20, 23, 24
22		131,9 (s)	
23	1.39 s	17.7 (q)	21, 22, 24
24	1.53 s	25.8 (q)	21, 22
25	1.07 s	26.2 (q)	1, 7, 8
26	0.59 s	24.9 (q)	1, 7, 8, 25
27	4.94 (dd, 3.0, 11.1)	43.5 (d)	1, 2, 9, 28, 29, 31
28	2.39 (dd, 3.0, 15.3)	40.2 (t)	27, 29, 30
	2.63 (dd, 11.1, 15.3)		27, 29, 30
29		171.2 (s)	
30		141.7 (s)	
31,35	7.89 br	131.9 (d)	
32,34	7.22 (t 7.8)	127.4 (d)	
33	7.09 (t 7.8)	127.2 (d)	
OCH_3	3.07 s	50.9 (q)	

Measured at 300 MHz (^{1}H) and 75 MHz (^{13}C) in C_6D_6.
p ov, partial overlap.
* This signals may be changed.

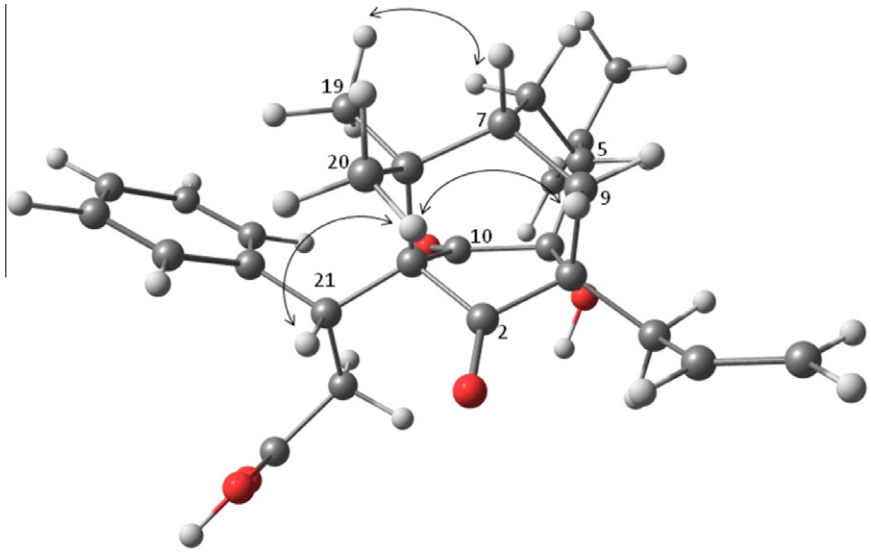


Figure 2. Structure of **1a** optimized with AM1 Hamiltonian showing some NOE key correlations.

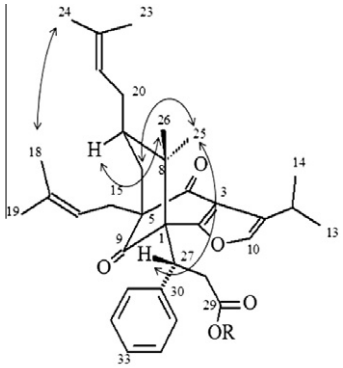


Figure 3. Structure and selected NOE correlation of **2a**.

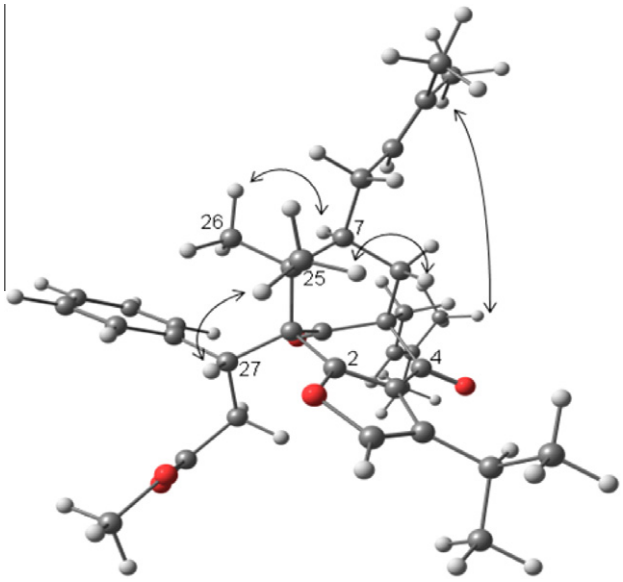


Figure 4. Structure of **2a** optimized with AM1 Hamiltonian showing some NOE key correlations.

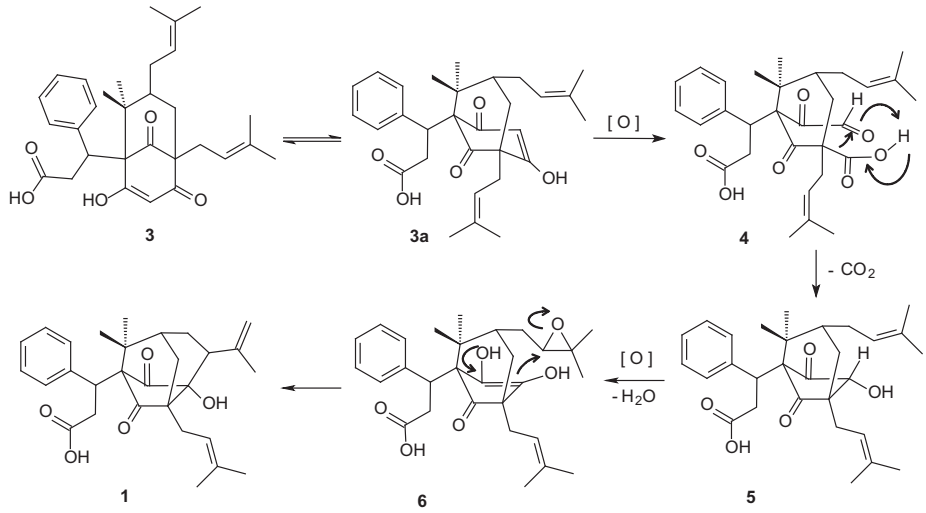
C-4, C-5, and C-9 that along with the correlations of H-7 with C-20 and C-25 and the correlations of H-10 with C-2 and C-3 indubitably, assure to this compound the structure **2a** (Fig. 3).

The NOESY experiment provides valuable information about the relative stereochemistry at C-7 and C-27. Both NOE correlations of H-25 with H-6 and of H-7 with H-26 suggested that the molecule has a configuration as depicted in Figures 3 and 4. The cyclohexanone ring formed by C-1, C-8, C-7, C-6, C-5, and C-9, adopts a boat conformation in order to minimize the strong 1,3-diaxial repulsions that it would have in the chair form. This assumption is reinforced by the fact that the chemical shift of C-7 (δ 49.0) and the difference in the chemical shifts of H-6a and H-6b (zero in this case) were in compliance with those of benzophenones and acylphloroglucinols with similar bicyclo[3.3.1]nonane system with a boat conformation of the cyclohexanone ring.[5–7] Additional observed NOE between H-18 and H-24 corroborated this proposition since this correlation would not be possible with the inverse stereochemistry or with the cyclohexanone ring in the chair conformation. Further NOE correlations between H-25 with H-27 and H-31 allowed to propose a relative configuration 27R* to C-27 in a similar approach to those that were used in compound **1a** and laxifloranone.[4] The 3-phenylmethylpropanoate moiety in compound **2a** adopted a conformation in which H-27 was in the plane of furan ring, one of the methylene hydrogens, H-28, would be approximately next to the plane of C-9 carbonyl and the phenyl group was close to C-26 (Fig. 4).

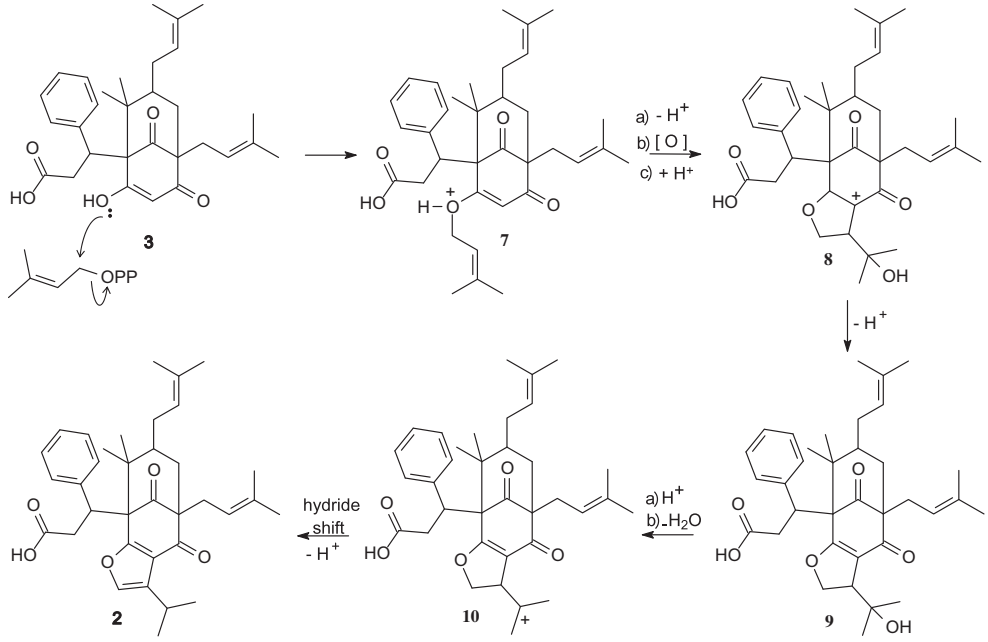
Latrophytoic acid A presented an unusual caged carbon skeleton with a 1,3-dione-4-cyclopentanol moiety probably formed by ring contraction via decarboxylation, of a precursor presenting a six-membered ring trione system which originated from phloroglucinol (Scheme 1).

Lathrophytoic acid B exhibited a highly substituted bicyclo[3.3.1]nonane skeleton, widely found in benzophenones[5] and polyprenylated acylphloroglucinols[6] isolated from Clusiaceae species. This compound presented an isopropylfuran system arising from an unprecedented cyclization of a prenyloxy side chain (Scheme 2).

This class of substances along with polyprenylated benzophenones,[5] polyprenylated acylphloroglucinols,[6] and neoflavonoids,[2]



Scheme 1. Proposed biogenetic pathway for compound **1**.



Scheme 2. Proposed biogenetic pathway for compound **2**.

widely found in Clusiaceae species, keep between them a very close biogenetic relationship.[8]

By analogy with hyperforin biosynthesis[8b] it is reasonable to propose a polyketide-type pathway for the generation of the phloroglucinol moiety of compounds **1** and **2**. The β-condensation of cinnamic acid with three molecules of malonyl-CoA produces the 3-phloroglucinyl-3-phenylpropanoic acid moiety that undergoes three prenylations to give a precursor as **3** (Scheme 1). This precursor is analogous to a possible intermediary in the biosynthesis of polyprenylated benzophenone derivatives from Clusiaceae species.[9] The β-condensation of the cinnamic acid with three molecules of malonyl-CoA is a pathway usually accepted to explain the biosynthesis of neoflavonoids which are compounds that have been isolated from this species[3] and from other species of the genus *Kielmeyera*.[2] The formation of the unusual cyclo-1,3-dione-4-pentanol moiety in **1** could be explained by an oxidative cleavage of the intermediary **3a**, with **s**ubsequent decarboxylation followed by an intramolecular aldol condensation forming **5**. Selective epoxydation of one prenyl lateral chain and epoxide ring opening by the attack of enol with subsequent dehydration would produce **1** (Scheme 1).

In order to explain the formation of the unprecedented isopropylfuran ring system in compound **2** (Scheme 2) was postulated a nucleophilic substitution reaction between an enol and isopentenylpyrophosphate to form the prenyloxy side chain. There are several reports of prenyloxy group presence in species of Clusiaceae.[10] After a sequence of reactions as delineated in Scheme 2, compound **2** would be formed.

Although more than 20 *Kielmeyera* species already had been examined, this is the first time that this class of substance is related in the genus.

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