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Phenylpropanoids and tetrahydrofuran lignans from *Piper solmsianum*

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Abstract

A tetrahydrofuran lignan as well as the known tetrahydrofuran lignan, (−)-grandisin, and five phenylpropanoid derivatives were isolated from *Piper solmsianum*. Their structures were determined by means of spectral analyses, including 2D NMR techniques such as NOE-DIFF and HMBC $^3J_{C-H}$. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *Piper solmsianum*; Piperaceae; Phenylpropanoids; Tetrahydrofuran lignans; (7*R*, 8*R*, 7′*S*, 8′*R*)-3′,4′-methylenedioxy-3,4,5,5′-tetramethoxy-7,7′- epoxylignan

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1. Introduction

The species *Piper solmsianum* C. DC. belongs to the Piperaceae family in which the genus *Piper* is represented by over 700 species (Parmar et al., 1997). There is an increasing number of reports on chemical constituents of this family as a result of searching for bioactive compounds (Jensen et al., 1993; Parmar et al., 1997). As part of our continuing investigation on brazilian Piperaceae species, we have investigated some species such as *P. aduncum* (Baldoqui et al., 1999) and *P. hispidum* (Alécio et al., 1998). The result of this was that prenylated benzoic acid and pyrrolidine amides were isolated, and identified as cytotoxic and antifungal compounds, respectively. The secondary metabolism in most Piperaceae species appears to be restricted to the production of only a few classes of compounds. In the case of *P. regnellii*, only benzofuran lignans are biosynthesized and accumulate, together with other phenylpropanoids (Benevides et al., 1999). In a sample of *P. solmsianum* several benzofuran lignans have been described (Moreira et al., 1995), while in *P. wightii* (Prasad et al., 1994) and *P. clarkii* (Prasad et al., 1995) a specific accumulation of tetrahydrofuran lignans was demonstrated.

In this paper, we describe a phytochemical study in which five phenylpropanoids, the lignan (−)-grandisin, and the new 7,7′-epoxylignan were isolated from leaves and stem bark of *P. solmsianum*.

2. Results and discussion

Ethyl acetate extracts from leaves and stem bark of *P. solmsianum* were submited to chromatographic procedures and resulted in the isolation of five phenylpropanoids which were identified by comparison with reported data as apiol (**1**), dillapiole (**2**), myristicin (**3**) (Benevides et al., 1999), elemicin (**4**), and isoelemicin (**5**) (Enriquez et al., 1980). All five phenylpropanoids were identified in both extracts by ^{1}H NMR spectroscopic analysis and by analytical HPLC using authentic standards.

(−)-Grandisin (**6**) was isolated as the major compound in the leaf extracts as colorless crystals [mp 118–120°, MeOH; $[\alpha]_D = -57.1°$ (c 0.35 in $CHCl_3$)] and was readily identified by analysis of its ^{1}H and ^{13}C NMR spectra. This tetrahydrofuran lignan was first isolated from *Litsea grandis* (Holloway and Scheinmann, 1974) and it has been recently described as a very active compound against the trypomastigote form of *Trypanosoma cruzi*, which is responsible for Chagas disease in the tropics (Lopes et al., 1998).

Lignan **7** was isolated as a pale yellow oil from the ethyl acetate extract obtained from stem bark, which

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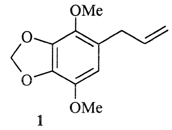

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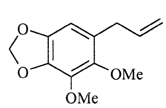

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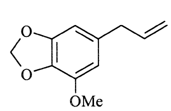

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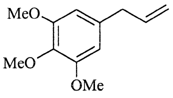

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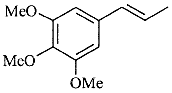

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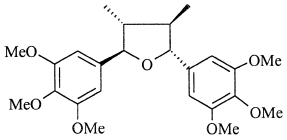

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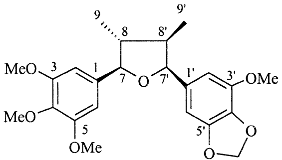

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was submitted to chromatographic steps including prep. TLC. Its molecular formula was indicated as $C_{23}H_{28}O_7$ according to the molecular ion peak observed at *m/z* 416 in its EI-mass spectrum associated with the ^1H and ^{13}C NMR spectral analysis. Its IR spectrum showed the absence of any absorptions near 3400 cm^{-1} whereas a very intense absorption band at 1129 cm^{-1} suggested C–O–C functionalities.

Its ^1H NMR spectrum (Table 1) suggested **7** as an asymmetric tetrahydrofuran lignan, since signals corresponding to two oxybenzyl methines (δ5.08, *d*, 6.6 Hz; and 4.38, *d*, 6.6 Hz) and two methyl hydrogens (δ1.07, *d*, 6.6 Hz and 0.69, *d*, 6.9 Hz) could be observed. The chemical shifts observed for aromatic hydrogens at δ6.73 (*d*, 2.2, 2H), at δ6.55 (*d*, 2.1, 1H) and at δ6.60 (*d*, 2.1, 1H), associated with the presence of intense singlets corresponding to four methoxyl hydrogens [δ3.84 (3H) and 3.89 (9H)] and to a methylenedioxyphenyl hydrogens (δ5.91, *s*, 2H), respectively, indicated the substitution pattern as 3,4,5-trimethoxyphenyl and 3′-methoxy-4′,5′-methylenedioxyphenyl for the two aromatic rings. The ^{13}C NMR spectrum corroborated the assignments made for the structural determination of both aromatic rings. As expected, the symmetric 3,4,5-trimethoxyphenyl ring displayed only four different chemical shifts for the aromatic carbons (Table 1), while for the second aromatic ring bearing a methylenedioxy and a methoxyl group, the corresponding signals could be assigned. Additional evidence for the presence of both aromatic rings was also provided by analysis of its EI-MS in which fragment ions at *m/z* 196 and 179 were assigned to the trimethoxyphenyl and methoxymethylenedioxyphenyl acilium ions, respectively (Holloway and Scheinmann, 1974).

The location of each trioxygenated aromatic ring to the tetrahydrofuran ring could be determined by HMBC $^3J_{C-H}$ experiments (Table 1). Mutual cross peaks were observed between the carbinolic hydrogens H-7′ (δ5.08) and H-7 (δ4.38), respectively to C-6′ (δ106.9)/C-2′ (δ101.1) and C-6 (δ6.73)/C-2 (δ103.6).

Table 1
^1H NMR, ^{13}C NMR and HMBC $^3J_{C-H}$ spectral data for lignan **7** (*J* given in Hz in parenthesis) (500 MHz, $CDCl_3$)

C	δ^{13}C	δ^{1}H	HMBC $^3J_{C-H}$
1	135.8	–	H-8, H-2, H-6
2	103.6	6.73 (*d*, 2.2, 1H)	H-6, H-7
3	136.4	–	–
4	137.0	–	H-2, H-6
5	136.4	–	–
6	103.6	6.73 (*d*, 2.2, 1H)	H-2
7	87.4	4.38 (*d*, 6.6, 1H)	H-2, H-6, H-9
8	46.0	1.78 (*m*, 1H)	H-7′, H-9′
9	15.1	1.07 (*d*, 6.6, 3H)	H-7, H-8′
1′	134.1	–	H-8′, H-2′, H-6′
2′	101.1	6.55 (*d*, 2.1, 1H)	H-6′
3′	143.2	–	–
4′	137.3	–	H-2′, H-6′
5′	136.4	–	–
6′	106.9	6.60 (*d*, 2.1, 1H)	H-2′
7′	83.2	5.08 (*d*, 6.6, 1H)	H-2′, H-6′, H-9′
8′	47.9	2.23 (*m*, 1H)	H-7′, H-9′
9′	14.8	0.69 (*d*, 6.9, 3H)	H-7′, H-8′, H-8
O_2CH_2	101.0	5.91 (*s*, 2H)	–
OCH_3/3	56.1	3.89 (*s*, 3H)	–
OCH_3/4	60.7	3.84 (*s*, 3H)	–
OCH_3/5	56.1	3.89 (*s*, 3H)	–
OCH_3/3′	56.6	3.89 (*s*, 3H)	–

Additionally, a mutual correlation between hydrogens H-7 and H-7′ to signals corresponding to C-9 and C-9′ respectively were observed.

The relative sterochemistry at the asymmetric tetrahydrofuran ring can be proposed as *trans*(C7/C8)-*trans*(C8/C8′)-*cis*(C8′/C7′) based on the *J* of 6.6 Hz observed for both oxybenzylic hydrogens, which is compatible with a *pseudoaxial* configuration for oxybenzylic hydrogens and in agreement with the ^{13}C NMR spectral data of similar compounds (Barata et al., 1978; Úrzua et al., 1987; Shimomura et al., 1988; Silva et al., 1997). The NOE-DIFF spectra were very helpful in confirming the relative stereochemistry at the tetrahydrofuran ring. These spectra allowed the establishment of a *cis* configuration between H-7 and H-7′, since enhancement of the doublet at δ5.08 was observed after irradiation at the frequency of the other carbinolic hydrogen at δ4.38. A similar enhancement was observed between H-7′ and H-8′ which allowed the assignment of a *cis* configuration to them. Next, a *trans* configuration between H-7 and H-8 and between H-8 and H-8′ could be defined, because irradiation at the frequency of H-8 at δ1.78 caused no enhancement of the doublet corresponding to H-7 and of the multiplet at δ2.23 corresponding to H-8′. Besides, no detectable NOE effect could be observed between methyl groups at C-9 and C-9′, and thus, a *trans* configuration was established between these groups. Consequently, the relative configuration at the tetrahydrofuran ring of lignan **7** is proposed to be the same as (+)-veraguensin (Barata et al., 1978), fragransin

B_3, verrucosin, fragransin C_{3a} and fragransin C_{3b} (Hattori et al., 1987). These set of data allowed the establishment of the structure of the new tetrahydrofuran lignan as (7*R*, 8*R*, 7′*S*, 8′*R*)-3′,4′-methylenedioxy-3,4,5,5′-tetramethoxy-7,7′-epoxylignan.

In a previous study, the occurrence of a benzofuran neolignan eupomatenoid-6 of a specimen of *P. solmsianum* was reported (Moreira et al., 1995). In our case, we detected the presence of several phenylpropanoids and (−)-grandisin, together with a new tetrahydrofuran lignan.

3. Experimental

3.1. General

IR spectra were measured in KBr. EIMS were measured at 70 eV on a HP 5990/5988 A spectrometer. ^1H NMR (300 and 500 MHz), ^{13}C NMR (75 and 125 MHz), NOE and HMBC spectra ($^3J_{C-H}$ optimized to 8.0 Hz) were recorded on VARIAN DPX-300 and DPX-500 spectrometers using $CDCl_3$ (Aldrich) as solvent and TMS as int. standard. Chemical shifts were reported in δ units (ppm) and coupling constants (J) in Hz. Silica gel (Merck, 70-230 mesh) was used for CC and silica gel 60 PF_{254} Merck (0.50 mm and 1 mm) for anal. and prep. TLC. Spots on chromatograms were detected under UV light (254 and 365 nm) and by spraying ceric sulphate followed by heating. HPLC analyses were performed in a Shimadzu LC-10 instrument equipped with a C-18 Econosil column, (5 μ, 250×4 mm). $[\alpha]_D$ was measured at $\lambda = 589$ nm in a digital polarimeter JASCO model DIP-370.

3.2. Plant material

Specimens of *P. solmsianum* were collected at the campus of Universidade de São Paulo (Brazil) in June, 1998 and in Ubatuba, São Paulo, Brazil in October, 1998 and were identified by Dr Elsie Franklin Guimarães (Jardim Botânico do Rio de Janeiro, Brazil). A voucher specimen (329676) is deposited at the Herbarium of Jardim Botânico do Rio de Janeiro.

3.3. Isolation

Dried leaves (578 g) and stem bark (6.7 g) of *P. solmsianum* were milled and extracted with EtOAc which after conc. in vacuo yielded 42.0 g and 0.54 g of crude extracts, respectively. These extracts were submitted to CC and eluted with a gradient of hex:EtOAc, followed by prep. TLC to afford apiol (**1**), dillapiole (**2**), myristicin (**3**), elemicin (**4**), isoelemicin (**5**) and (−)-grandisin (**6**). Fraction 29 (56.0 mg) obtained from extracts of stem bark was further submitted to prep. TLC using hexane–EtOAc 7:3, to afford the lignan **7** (37.5 mg).

3.4. HPLC analysis

Crude extracts were filtered on a Sep-Pak column using MeOH as eluent. A sample containing 1 μl of each extract and pure samples of apiol, dillapiole, myristicin, elemicin, isoelemicin and grandisin were analysed by HPLC using a C-18 Econosil column (5 μm, 250×4 mm), with a gradient (Condition A) from MeCN–H_2O 85:15 (20 min) to MeCN 100% (10 min), flow rate 0.9 ml min^{-1}, and detection at 280 nm.

3.5. (7R, 8R, 7′S, 8′R)-3′,4′-Methylenedioxy-3,4,5,5′-tetra-methoxy-7,7′-epoxylignan (7)

Pale yellow oil; ($C_{23}H_{28}O_7$); *RRt* = 19.1 min in condition A; $[\alpha]_D^{21}$ −12.1 (c 0.33.); IR ν_{max}^{film} cm^{-1}: 2956, 1634, 1591, 1507, 1458, 1235, 1129, 1036; UV λ_{max}^{MeOH} nm (ϵ): 270 (92300); 246 (14950), 207 (2366); ^1H NMR; ^{13}C NMR and HMBC $^3J_{C-H}$ see Table 1.

Acknowledgements

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