PERGAMON

Phytochemistry 61 (2002) 427–432

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Dibenzylbutane and aryltetralone lignans from seeds of *Virola sebifera*

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Received 21 February 2002; received in revised form 14 June 2002

Abstract

Two lignans rel-(8*R*, 8′*R*)-3,4:3′,4′-bis-(methylenedioxy)-7.7′-dioxo-lignan and (7′*R*,8′*S*,8*S*)-2′-hydroxy-3,4:4′,5′-bis-(methylenedioxy)-7-oxo-2,7′-cyclolignan were isolated from seeds of *Virola sebifera*. The cyclolignan showed two atropisomers as determined by ^{1}H NMR spectroscopy at low temperature.

Keywords: Myristicaceae; *Virola sebifera*; Benzylbutane; Lignans; Aryltetralone lignans; Atropisomerism

1. Introduction

Virola sebifera (*Aublet*.) is one of the most widely spread Myristicaceae species in Brazil, occurring in "cerrados" and in moist forests as well (Rodrigues, 1980). Its seeds are the source of "ucuúba fat" which is rich in triglycerides such as trimyristin (29–38%) and laurodimyristin (30–39%) (Culp et al., 1965; Silva et al., 1997). Therefore, it also has been used as an important source of raw material for cosmetics and soaps. Previous phytochemical investigation on *V. sebifera* reported the occurrence of *N,N*-dimethyltryptamine and methyltetrahydro-β-carboline alkaloids in the bark resin as the active principle of hallucinogenic snuffs (Corothie and Nakano, 1969). Secondary metabolism in the whole fruits resulted in the accumulation of acylphloroglucinols and acylresorcinols (Kato et al., 1985; Lopes et al., 1982). In contrast, lignoids showed a specific accumulation, e.g. dibenzylbutyrolactone and furofuran lignans in pericarps (Lopes et al., 1983) and aryltetralone lignans in seeds (Lopes et al., 1982, 1984a,b). The chemical composition in leaves was very similar to that of pericarps (Fraga, 1987; Martinez et al., 1999), but hydroxy-otobain together with hydroxy-otobanone were detected as the major lignans in the leaves of seedlings (Danelutte et al., 2001).

The aim of this paper is to describe two new natural products: a dibenzylbutane (**1**) and an aryltetralone (**2**) lignans isolated from the seed extract of *Virola sebifera*. Studies involving NMR spectroscopy concerning the atropisomerism of the aryltetralone lignan are also described.

2. Results and discussion

The molecular formula of lignan **1** was established as $C_{20}H_{18}O_6$ based on the molecular ion peak at m/z 354 obtained by LRMS (30 eV) and also by elemental analysis. Characteristic features of the phenone moiety of lignan **1** was provided by ^{1}H NMR spectroscopic data which displayed a typical ABC system for the tri-substituted aromatic ring at low field indicating that the aromatic ring is conjugated to a carbonyl function (1670 cm^{-1}). The molecular symmetry was envisaged accordingly since the ^{13}C NMR spectra showed only ten signals: two signals assigned to oxygenated aromatic carbons at δ 151.6 and 148.1; one to an aromatic quaternary carbon at δ 130.7; three methine aromatic carbons at δ 124.0–107.0; one to a methylenedioxyphenyl at δ 101.7; one to carbonyl at δ 202.3; and finally, signals at δ 43.4 and 15.8 which were assigned to methine (C8/8′) and methyl carbons (C9/9′), respectively. In agreement with the structure ascribed for compound **1**, the mass spectrum showed the presence of a fragment ion peak at m/z 149, which was assigned to the

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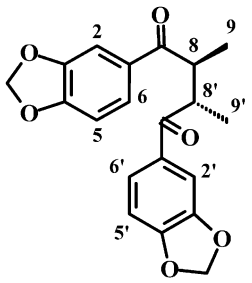
0031-9422/02/$ - see front matter
PII: S0031-9422(02)00242-X



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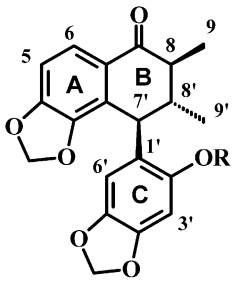

2a R=H
2b R=Ac

methylenedioxyphenyl acylium ion. The multiplicities for all carbons given by analysis of DEPT 135° corroborated with the assignments obtained by HETCOR spectra to indicate structure **1**. This is the first description of this lignan as a natural product. Nevertheless, the racemate has previously been obtained by synthesis (Biftu et al., 1978). The specific rotation $\alpha_D = -125.0°$ ($c = 0.1$, CH_3OH, 25 °C) observed in **1** indicated that the configurations at carbons 8/8′ should be *R,R* or *S,S* since no optical rotation should be expected for *meso* compounds (*S*/*R* or *R*/*S*).

The lignan **2a** gave a molecular ion peak (70 eV) at *m*/*z* 354 in the EI-MS spectrum and is in accordance with the molecular formula $C_{20}H_{18}O_6$ and the results of elemental analysis. Its IR spectra showed characteristic absorptions for hydroxyl and carbonyl functions at 3393 and 1670 cm^{-1}, respectively. The ^1H NMR spectrum was very similar to that of oxo-otobanone, a previously isolated lignan from *V. sebifera* (Lopes et al., 1982) and also from *V. elongata* (Kato et al., 1990). The major differences were observed for signals corresponding to the aromatic and methylenedioxyphenyl protons of ring C (δ 5.8–6.3) (Table 1). The ^1H NMR spectrum (200 MHz, $CDCl_3$) showed aromatic protons as two singlets at δ 6.33 (1H) and 6.34 (1H) and the methylenedioxyphenyl protons as a broad singlet at δ 5.84. At 300 MHz ($CDCl_3$), the methylenedioxyphenyl protons split into two singlets at δ 5.82 (*s*, 1H) and 5.81 (*s*, 1H). The spectrum taken in acetone-d_6 displayed singlets at δ 5.85 (3H) and 5.75 (1H) and also showed better differentiation for the aromatic protons of ring C at δ 6.46 (*s*, 1H) and 6.37 (*s*, 1H), although the signal of one methylenedioxyphenyl hydrogen overlapped with the methylenedioxyphenyl signal of ring A (δ 5.85). Such a substitution pattern of a 2-hydroxy-4,5-methylenedioxyphenyl group observed for this new lignan **2a** has been previously described for an aryltetralone lignan isolated from *Virola elongata* (Kato et al. 1990); and in the antioxidant lignan isolated as a derivative from *Sesamum indicum* (Fukuda et al., 1986) and *Saururus chinensis* (Ahn et al., 2001).

In order to investigate atropisomerism in lignan **2a**, an acetate derivative **2b** was prepared (see Experimental), where NMR spectra were analysed. The acetate derivative (**2b**) showed absorption of an acetoxyl carbonyl group at 1760 cm^{-1} in its IR spectrum; a molecular ion peak at *m*/*z* 396 in its MS spectrum. The ^1H and ^{13}C NMR spectroscopic data corroborated this conversion showing a singlet at δ 1.80 (*s*, $C\underline{H}_3CO$) and signals at δ 169.2 ($CH_3\underline{C}O$) and at 20.5 ($\underline{C}H_3CO$). Furthermore, the ^1H NMR spectrum showed absorptions of aromatic protons H6′ and H3′ deshielded by δ +0.19 and +0.20 respectively, as compared to the **2a**, in agreement with the expected substitution pattern for a 2-hydroxy-4,5-methylenedioxyphenyl group. The expanded signals in the range of δ 5.6–7.8 of ^1H NMR spectrum (300 MHz) taken in acetone-d_6 showed four doublets completely differentiated at δ 6.01 and 6.02 (2*d*, 0.95 Hz) and δ 5.67 and 5.87 (2*d*, 1.4 Hz). In addition to these data, the ^{13}C NMR spectra (50 MHz, acetone-d_6) showed a very broad peak at δ 42.6 assigned to C7′, indicating that the rotation of aromatic ring C is strongly hindered.

Since all these data were consistent with hindered rotation around the C1′–C7′ bond the dynamic nuclear magnetic resonance (DNMR) was applied to further investigate this phenomena as described herein. A set of spectra was recorded at 25°,−20°,−30°,−40°,−50° and −60° (500 MHz, $CDCl_3$). A broadening of all signals was observed as the temperature was lowered to −20 °C and then it was followed by a duplication for all signals at −60 °C, clearly indicating the existence of two atropisomers (Table 2; Fig. 2). Such isomerism has already been demonstrated for arylnaphthalene lignans (Charlton et al., 1996; Wolf et al., 1997), but not fully investigated. The interconversion between these atropisomers was hindered by the acetoxyl group (aromatic ring C) close to the methylenedioxyphenyl group vicinity (ring A), as represented in Fig. 1. The two sets of signals were assigned to atropisomers **I** and **II** and in both cases (Table 3), the acetoxyl group assumed the orthogonal position with respect to the tetrahydronaphtalene system in the twisted chair conformation as indicated by J*ax-ax* of 9.8 Hz observed for coupling between H7′ and H8′. A

Table 1
^1H NMR spectral data for lignan **2a** (ring C) in different conditions

Solvents	Conditions	Ar-H3′ (δ)	Ar-H6′	CH_2O_2 (ring A and C)
$CDCl_3$	25 °C 200 MHz	6.33 (*s*, 1H)	6.34 (*s*, 1H)	5.67 (1H, *d*, *J* = 1.3 Hz, A) 5.77 (1H, *d*, *J* = 1.3 Hz, A) 5.84 (2H, *brs*, C)
	25 °C 300 MHz	6.30 (*s*, 1H)	6.32 (*s*, 1H)	5.67 (1H, *d*, *J* = 1.3 Hz, A) 5.77 (1H, *d*, *J* = 1.3 Hz, A) 5.81 (1H, *s*, C) 5.82 (1H, *s*, C)
Acetone –D_6	25 °C 300 MHz	6.46 (*s*, 1H)	6.37 (*s*, 1H)	5.85 (3H, *s*, A/C) 5.75 (1H, *s*, A/C)

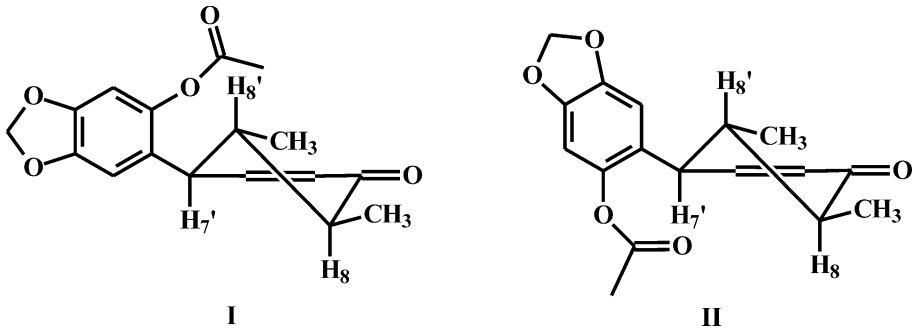

Fig. 1. Atropisomers of lignan **2b**.

Table 2
^{1}H NMR spectral data for lignan **2b** at 25 °C

Hydrogens	$T = 25$ °C		
	δ (Hz)	$\Delta\delta_I$[a]	$\Delta\delta_{II}$[a]
9	1.17 (*d*, 6.5)	−0.03	
9′	0.93 (*d*, 6.7)	−0.08	0.00
8	2.28–2.41 (*m*)	+ 0.07	−0.12
8′	2.01–2.10 (*m*)	−0.19	
7′	3.82 (*brs*)	+ 0.20	−0.23
6	7.59 (*d*. 8.2)	+ 0.01	−0.04
5	6.71 (*d*, 8.2)	+ 0.02	−0.02
6′	6.49 (*brs*)	+ 0.08	−0.22
3′	6.52 (*brs*)	+ 0.29	−0.11
CH_2O_2 (ring C)	5.91 (*s*)	+ 0.03 −0.01	−0.13 −0.19
CH_2O_2 (ring A)	5.63 (*d*, 1.2) 5.75 (*d*, 1.2)	+ 0.38 + 0.23	−0.13 −0.10
CH_3–CO	1.50 (*brs*)	−0.03	+ 0.83

[a] $\Delta\delta_I$: (δ-δ_I) and $\Delta\delta_{II}$: (δ-δ_{II}): chemical shifts differences between **2b** at 25 °C and conformer I at −60 °C, and between **2b** at 25 °C and conformer II at −60 °C, respectively.

Table 3
^{1}H NMR spectral data for conformers **I** and **II** of lignan **2b** at −60 °C

Hydrogens	$T = -60$ °C				δ_{II-1}[a]
	I		II		
	(δ_I, Hz)	Integral	(δ_{II}, Hz)	Integral	
9	1.13–1.15 (*brs*)	6.76	1.13–1.15 (*brs*)	nd[b]	0.00
9′	0.85 (*d*, 5.4)	2.74	0.93 (*d*, 5.4)	2.42	+ 0.08
8	2.35–2.47 (*m*)	1.64	2.21–2.25 (*m*)	nd[b]	−0.12
8′	1.87 (*m*)	1.92	1.87 (*m*)	1.92	0.00
7′	4.02 (*d*, 10.0)	0.98	3.59 (*d*,10.4)	0.93	−0.43
6	7.60 (*d*, 8.2)	1.00	7.55 (*d,* 8.2)	0.77	−0.05
5	6.73 (*d*, 8.2)	1.00	6.69 (*d,* 8.2)	0.84	−0.04
6′	6.57 (*s*)	0.92	6.27 (*s*)	0.89	−0.30
3′	6.78 (*s*)	0.84	6.38 (*s*)	0.77	−0.40
CH_2O_2 (ring C)	5.94 (*s*) 5.90 (*s*)	1.10 1.10	5.78 (*s*) 5.72 (*s*)	0.92 0.94	−0.16 −0.18
CH_2O_2 (ring A)	6.01 (*s*) 5.98 (*s*)	0.78 0.79	5.76 (*s*) 5.65 (*s*) 0.78 0.73	−0.25 −0.33	
CH_3-Acet	1.47 (*sl*)	3.64	2.33 (*sl*)	3.29	+ 0.86

[a] $\delta_{II–I}$: chemical shifts differences between both conformers.
[b] Not determined due to overlapping with signal of water.

clear shielding effect (δ −0.30) could be seen for aromatic proton H6′ of atropisomer **II** due to the effect of the closer aromatic ring A (Table 3). Consistently, the acetoxyl protons in this conformer were deshielded from δ 1.47 (**I**) to 2.33 (**II**). The doublets at δ 4.02 and 3.59 could be assigned as dibenzylic proton H7′ of atropisomers **I** and **II,** respectively. In case of **II**, the dibenzylic proton H7′ was shielded by anisotropy of the acetoxyl carbonyl (Fig. 1). The relative composition between the two atropisomers was determined as 53 (**I**) and 47 (**II**),

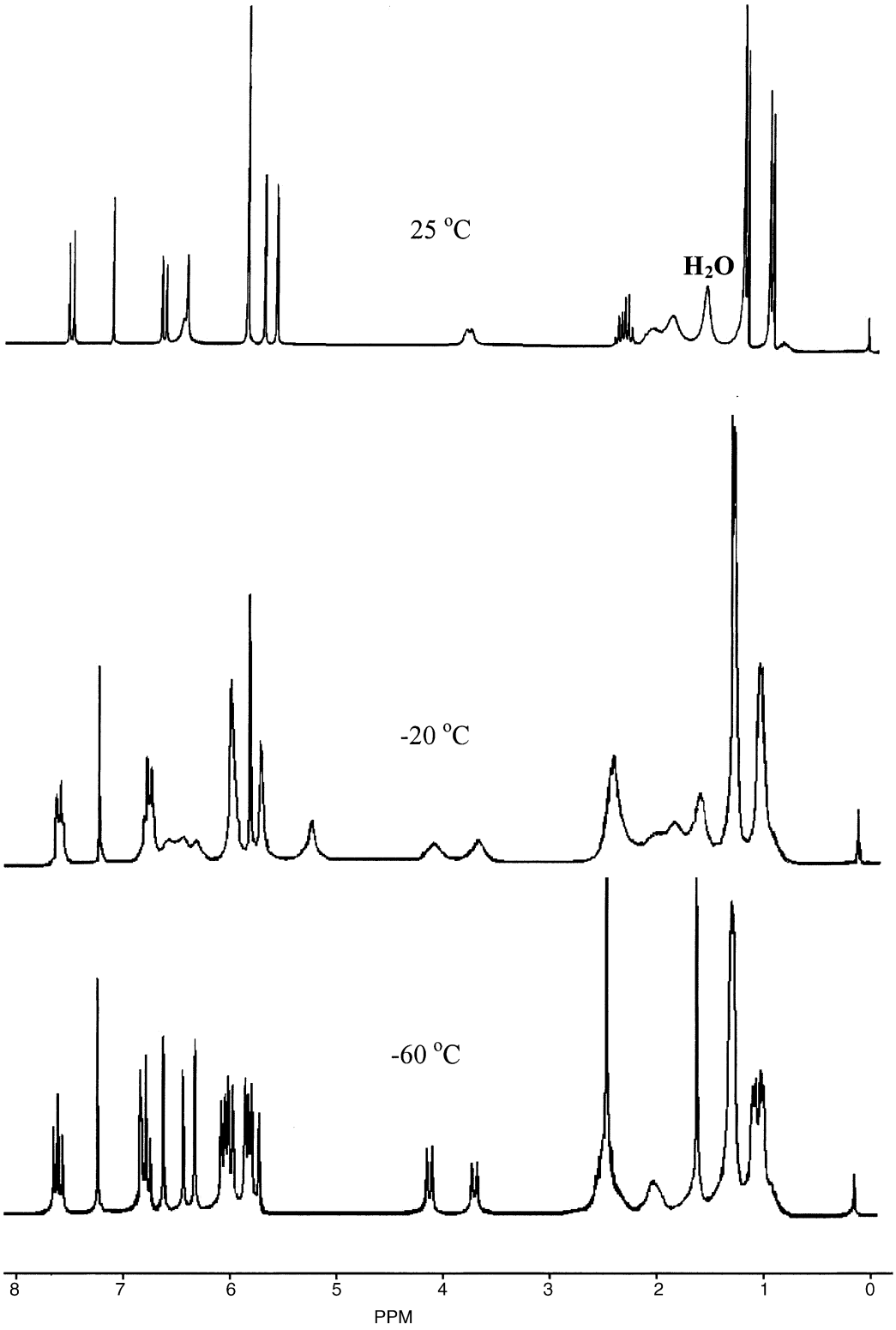

Fig. 2. ^{1}H NMR spectra ($CDCl_3$, 300 MHz) for lignan **2b**, recorded at different temperatures.

respectively, by calculating the average integration observed for all signals.

The absolute configuration for lignan **2a** could be assigned accordingly as described for all aryltetralone lignans having a β configuration for ring C. Such a determination was based on the chemical conversion to aryltetralin analogs in which there was solid evidence based on circular dichroism and optical rotation data (Kato et al., 1990). In the case of **2a** a negative optical rotation ($[\alpha]_D$ −29.5°) could be tentatively correlated to a β configuration for ring C. The *trans* equatorial configuration between methine protons was determined based on comparison of ^{1}H NMR spectral data with a similar compound in which coupling constants in the range of 9.0–9.5 Hz was assigned to a *trans* diaxial relationship between H-7′/H-8′ (Kuo et al., 1976; Fernandes et al., 1993). For a *cis* diequatorial configuration a much smaller coupling constant (4.3 Hz) would be expected (Joshi et al., 1979; Urzúa and Shamma, 1988).

The isolation of these two lignans from seeds of *V. sebifera* suggests a biosynthetic sequence in which a hydroxylation step would be expected after the formation of aryltetralone **2a** since its precursor had already been previously described (Lopes et al., 1984a). The evaluation of antioxidant activity for **2a** should be further performed.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded in a Bruker AC 200, DPX 300 and DRX 500 MHz spectrometers with $CDCl_3$ or acetone-d_6 as solvent. Chemical shifts are reported relative to TMS as internal standard.

3.2. Plant material

Fruits of *Virola sebifera* collected, in August 1994 from specimens near km 74 of the Araraquara-Bauru road at São Paulo State. A voucher specimen (Kato-0191) deposited at the herbarium of Instituto de Botânica (Secretaria do Meio Ambiente do Estado de São Paulo) was identified by Dr. William A. Rodrigues (Universidade Federal do Paraná- Curitiba).

3.3. Isolation of constituents

Seeds were dried, milled (212 g) and extracted (3 l×6, 2 days each) suspended in hot acetone (48°, 2 l) hexane-EtOAc (9:1–1:1), ether:hexane (1:6), which after concentration under vacuum yielded 112 g of crude extract. The extract was suspended in hot acetone and kept in the refrigerator for 24 h. The fat material (66 g) which solidfied after refrigeration was separated by filtration, and the acetone fraction was concentrated under vacuum to yield a solid (55 g). This was submitted to chromatography under vacuum with silica gel 60 H (63–210 μm), column 18.5 cm (d) × 6.5 (h) using a gradient of hexane–EtOAc affording fractions. Fraction 3 (9.2 g) was recrystalized in ether/hexane to yield lignan **1** (881 mg). Fraction 7 (6.5 g) was submitted to CC on silica (32.5 × 4.0 cm) eluted with isocratic hexane/CH_2Cl_2/$(CH_3)_2CO$ (8.3:82.5:9.2). Fraction 4 was recrystallized in ether/hexane yielding lignan **2a** (274 mg).

3.4. Rel-(8R, 8′R or 8S, 8′S)-3,4:3′,4′-bis(methylenedioxy)-7.7′-dioxo-lignan (**1**)

Colourless solid, mp 210–212°. $[\alpha]_D = -125.0°$ (*c* 0.1, CH_3OH). IR υ^{film} cm^{-1}: 1670 (CO), 1611, 1504, 1463 and 1440. MS 30 eV, *m*/*z* (rel. int.): 354 ($M^{+\bullet}$), 336 (12), 207 (27), 205 (5), 149 (100), 122 (2), 91 (2). Chemical analysis. Found C, 67.80; H, 5,11; O, 27.09. $C_{20}H_{18}O_6$ requires C 67.78; H, 5.12; O, 27.10%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (*d*, *J* = 7.0 Hz, 6H-9/9′), 3.77 (*m*, 2H-8/8′), 7.56 (*dd*, *J* = 8.2 and 1.7 Hz, 2H-6/6′), 6.79 (*d*, *J* = 8.2Hz, 2H-5/5′), 7.35 (*d*, *J* = 1.7 Hz, 2H-2/2′), 5.95 (*s*, 2 CH_2O_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 130.7 (C1/1′), 108.27 (C2/2′), 148.1 (C3/3′), 151.6 (C4/4′), 107.9 (C5/5′), 124.6 (C6/6′), 202.3 (C7/7′), 43.4 (C8/8′), 15.8 (C9/9′) and 101.7 (CH_2O_2)

3.5. (7′R,8′S,8S)-2′-hydroxy-3,4:4′,5′-bis(methylenedioxy)-7-oxo-2,7′-cyclolignan (**2a**)

Colourless solid. mp 167–168°. $[\alpha]_D$ −29.5° (*c* 0.1, CH_3OH). IR υ^{film} cm^{-1}: 3393, 1670 (CO), 1619, 1586 and 1503. MS 70 eV, *m*/*z* (rel. int.): 354 ($M^{+\bullet}$, 100), 337 (9), 307 (15), 298 (15), 297 (41), 279 (9), 271 (71), 165 (13), 149 (20). Chemical analyses. Found C, 67.81; H, 5.10; O, 27.09. $C_{20}H_{18}O_6$ requires C 67.78; H, 5.12; O, 27.10%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (*d*, *J* = 6.5 Hz, 3H-9′), 1.17, (*d*, *J* = 6.5 Hz, 3H-9), 1.99 (*ddq*, *J* = 6.5; 9.8; 12.4 Hz, 1H-8′), 2.36 (*dq*, 6.5 and 12.4 Hz, 1H-8), 4.12 (*d*, *J* = 9.8 Hz, 1H-7′), 6.33 (*s*, 1H-6′), 7.62 (*d*, *J* = 8.2 Hz, 1H-6), 6.73 (*d*, 8.2 Hz, 1H-5), 6.34 (*s*, 1H-3′), 5.84 (*d*, *J* = 1.0 Hz, 2H-CH_2O_2, 5.67 (*d*, *J* = 1.3 Hz, 1H-CH_2O_2), 5.77 (*d*, 1.3 Hz, 1H-CH_2O_2). ^{13}C NMR (50 MHz, acetone-d_6): δ 13.1 (C9), 17.9 (C9′), 48.3 (C8), 43.2 (C8′), 198.5 (C7), 42.6 (C7′), 123.1(C6), 150.8 (C6′), 107.7 (C5), 98.1 (C5′), 152.5 (C4), 145.9 (C4′), 147.8 (C3), 141.5 (C3′), 129.0 (C2), 109.0 (C2′), 129.0 (C1), 122.7 (C1′), 101.7 (CH_2O_2), 101.0 (CH_2O_2).

3.6. Acetylation of **2a**

The lignan **2a** (12 mg) was acetylated for 24 h with acetic anhydride (1 ml)/pyridine (0.05 ml). After work-up, the organic phase was dried over anhydrous Na_2SO_4, evaporated and purified by prep-TLC with hexane: CH_2Cl_2:AcOH: *i*-PrOH (23.1:75.4:0.8:0.8) yielding 8.0 mg of **2b** (59%).

3.7. (7′R,8′S,8S)-2′-Acetoxy-3,4:4′,5′-bis(methylenedioxy)-7-oxo-2,7′-cyclolignan (**2b**)

Colourless oil. IR ν^{film} cm^{-1}: 1760 (CO), 1682, 1622, 1589 and 1503. MS 70 eV, *m/z* (rel. int.): $M^{+\bullet}$ 396 (15), 355 (21), 354 (100), 339, (13), 336 (14), 297 (39), 271 (61), 165 (19), 149 (10), 115 (19). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (*d*, $J=6.5$ Hz, 3H-9′), 1.17 (*d*, $J=6.5$ Hz, 3H-9), 1.98–2.06 (*m,* 1H-8′), 2.25–2.38 (*m*, 1H-8), 3.80 (*d,* $J=9.8$ Hz, 1H-7′), 6.49 (*s,* 1H-6′), 7.59 (*d*, $J=8.2$ Hz, 1H-6), 6.71 (*d*, $J=8.2$ Hz, 1H-5), 6.52 (*s*, 1H-3′), 5.92 (*s*, 2H–CH_2O_2), 5.75 (*d*, $J=1.5$ Hz, 1H–CH_2O_2), 5.63 (*d*, $J=1.5$ Hz, 1H–CH_2O_2), 1.80 (*s,* CH_3–CO). ^{13}C NMR (50 MHz, acetone-d_6): δ 12.5 (9), 14.3 (9′), 48.1(8), 42.4 (8′), 198.6 (7), 42.4 (7′), 123.0 (6), 145.9 (6′), 107.8 (5), 105.3 (5′), 152.7 (4), 145.8 (4′), 143.9 (3), 147.1 (3′), 128.7 (2), 113.2 (2′), 128.2 (1), 127.1 (1′), 102.6 (CH_2O_2), 102.7 (CH_2O_2), 169.2 (CH_3CO), 20.5 (CH_3CO).

Acknowledgements

This work was supported by grants and fellowships provided by FAPESP, PADCT and CNPq.

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