

Structure and absolute configuration of a secolignan from *Peperomia blanda*

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ABSTRACT

A secolignan, (–)-2-methyl-3-[bis(3',4'-methylenedioxy-5'-methoxyphenyl) methyl]butyrolactone (**1**), with a rare *cis* configuration was isolated from the aerial parts of *Peperomia blanda* (Piperaceae). The structure of this compound was elucidated by a combination of spectroscopic methods, including ultraviolet, infrared, 1D- and 2D- nuclear magnetic resonance as well as high resolution mass spectrometry data. The absolute configuration of (–)-**1** was determined as (2*R*,3*S*) by the comparison of experimental electronic circular dichroism (ECD) spectroscopy and time-dependent density functional theory (TDDFT) calculations.

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1. Introduction

Peperomia blanda (Jacq.) H.B. & K., a perennial herb that typically grows in wet rock crevices, is found from northeast to the south of Brazil (Guimarães and Giordano, 2004). Chemical studies of the aerial parts of *P. blanda* showed the presence of two chromenes (Velozo et al., 2006), two C-glycosylflavones with antioxidant activity (Velozo et al., 2009), and five tetrahydrofuran lignans with trypanocidal activity (Felippe et al., 2008).

Species of *Peperomia* have revealed the presence of a special class of secolignans known as peperomins, which showed important biological activities, such as antifeedant (Govindachari et al., 1998), cytotoxic (Cheng et al., 2003; Wu et al., 2006; Xu et al., 2006), anti-HIV (Zhang et al., 2007), and anti-inflammatory (Tsutsui et al., 2009). It is also noteworthy that these secolignans show structural features similar to the podophyllotoxin skeleton (Sibi et al., 2001) used for the clinical treatment of warts and malign neoplasms (Castro et al., 2003). In this work we report the structure elucidation and absolute configuration of a new secolignan, the (–)-2-methyl-3-[bis(3',4'-methylenedioxy-5'-methoxyphenyl) methyl]butyrolactone (**1**),

with a rare *cis* configuration at the γ -butyrolactone ring, isolated from the aerial parts of *P. blanda*. A racemic mixture of this compound was synthesized by Zee and Chou (1990), however this is the first time that this isomer is reported as a natural product.

Although three levorotatory secolignans with *cis* configuration at the γ -butyrolactone ring have been described from *P. dindygulensis* (Wu et al., 2006) their absolute configuration remained undetermined. Herein, a combination of electronic circular dichroism (ECD) spectroscopy and time-dependent density functional theory (TDDFT) calculations was successfully used to determine the absolute configuration of (–)-**1** as (2*R*,3*S*).

2. Results and discussion

Compound **1** (Fig. 1) was isolated from the CH₂Cl₂ soluble portion of the EtOAc extract of the aerial parts of *P. blanda*. Its molecular formula was established as C₂₂H₂₂O₈ by HRMS ([M + Na]⁺ obsd *m/z* 437.1209, calcd 437.1212) in combination with extensive NMR analysis. The ¹H NMR spectrum exhibited resonances of four meta-coupled aromatic hydrogens at δ 6.28 (H-2', *J* = 1.5 Hz), 6.31 (H-6', *J* = 1.5 Hz), 6.35 (H-2'', *J* = 1.5 Hz) and 6.41 (H-6'', *J* = 1.5 Hz), two methylenedioxy groups at δ 5.83 (d, *J* = 1.5 Hz), 5.85 (d, *J* = 1.5 Hz), 5.86 (d, *J* = 1.5 Hz), and 5.87 (d, *J* = 1.5 Hz), and two O-methyl singlets at δ 3.82 and 3.83. This set of signals characterized two 3,4-methylenedioxy-5-methoxy-

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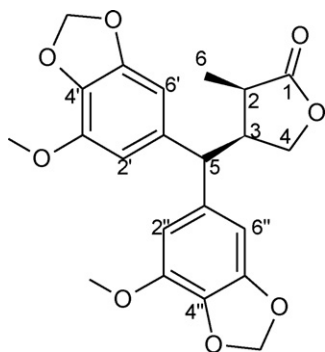


Fig. 1. Structure of (2*R*,3*S*)-secolignan from the aerial parts of *Peperomia blanda*.

phenyl rings with magnetically non-equivalent methylenedioxy protons resulting from the anisotropy of the aromatic ring (Rezende and Kato, 2002). A doublet at δ 1.04 (H-6, d, J = 8.0 Hz) was assigned to the methyl group, multiplets at δ 3.96 (H-4a) and 3.84 (H-4b) due to the methylene group of the butyrolactone moiety, and resonances at δ 2.63 (H-2, dq, J = 7.5, 8.0 Hz), 3.25 (H-3, m), and 3.59 (H-5, d, J = 12.0 Hz), due to three methine groups, were observed. A γ -butyrolactone ring was confirmed by the HMBC and HMQC cross-peaks between H-2, H-4, and H-6 and the lactone carbonyl carbon [δ 179.9 (C-1)]. The ^{13}C NMR data corroborated the presence of the butyrolactone system, and all signals were accordingly assigned based on the HMBC data (Table 1). The *cis* configuration at the γ -butyrolactone ring was established by 1D NOESY experiments. Upon irradiation of H-2 an NOE enhancement was observed for H-3. Based on the relative configuration assigned to **1**, there were only two possible absolute configuration, namely (2*S*,3*R*) or (2*R*,3*S*).

For compound **1**, the configuration (2*R*,3*S*) was arbitrarily chosen, and after conformational analysis and geometry optimi-

zation, the seven lowest-energy conformers were identified. The main conformational changes were related to rotations about the C-5–C-1', C-5–C-1'', C-3'–O and C-3''–O single bonds (Fig. 2). Owing to the symmetrical pattern of the substituents linked to C-5 the effects of rotation about the C-3–C-5 bond could not be probed.

The overall patterns of the gas phase calculated weighted ECD spectra were consistent with those of the experimental one, i.e., a negative Cotton effect (CE) near 275 nm, a positive CE near 260 nm, and a negative CE near 230 nm (Fig. 3). The experimentally observed negative CE around 275 nm may result from two high-amplitude negative rotational strengths common to the seven conformers considered, while the positive CE around 260 nm is contributed by three positive rotational strengths at around 250, 255, and 260 nm. The negative CE near 230 nm may arise from a series of predominantly negative low-amplitude rotational strengths since the two high-amplitude ones predicted at around 233 and 237 nm are expected to cancel each other. Additionally, the presence of a negative bisignate CD couplet at around 265 nm is suggestive of exciton coupling (Berova et al., 2007) between the two identical chromophores, e.g. 3,4-methylenedioxy-5-methoxyphenyl rings, which are located near in space and have their transition moments oriented with a negative angle. The negative CE near 230 nm is due to electronic transitions of the asymmetric lactone system. Thus, by comparing ECD measurements with the results of TDDFT calculations carried out at the B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d) level, the absolute configuration of (–)-**1** was unambiguously determined as (2*R*,3*S*). Also, as the experimental measurements were carried out in polar solvents, the self-consistent reaction field (SCRF) with polarizable continuum model (PCM) was employed to simulate solution-state ECD spectra of **1** in acetonitrile at the B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d) level. However, the calculated ECD spectra of each conformer were largely similar to the ones obtained by B3LYP/6-311++G(2d,2p) in the gas phase. The suitability of B3LYP/6-31G(d) for the optimization of geometry as well as B3LYP/6-311++G(2d,2p) for ECD calculations

Table 1
NMR data of compound **1** (CDCl₃, 11.7T).

Position	^1H (δ) ^a	^{13}C (δ)	HMBC ^b
1		179.9 (q) ^c	
2	2.63 dq (7.5, 8.0)	43.0 (t)	1, 4, 6
3	3.25 m	37.2 (t)	
4a, 4b	3.96 m, 3.84 ov ^d	70.3 (s)	1, 3, 2
5	3.59 d (12.0)	50.2 (t)	2, 4, 1', 1'', 2', 2'', 6', 6''
6	1.04 d (8.0)	10.4 (p)	3, 2
1'		136.3 (q)	
2'	6.28 d (1.5)	107.4 (t)	5, 4', 6'
3'		149.5 (q)	
4'		134.3 (q)	
5'		143.6 (q)	
6'	6.31 d (1.5)	101.0 (t)	5, 2', 4'
1''		136.5 (q)	
2''	6.35 d (1.5)	107.4 (t)	5, 4'', 6''
3''		149.5 (q)	
4''		134.3 (q)	
5''		143.7 (q)	
6''	6.41 d (1.5)	101.1 (t)	5, 2'', 4''
OCH ₂ O	5.87 d (1.5)	101.4 (s)	3', 4'
	5.86 d (1.5)	101.4 (s)	3'', 4''
	5.85 d (1.5)	101.4 (s)	3'', 4''
	5.83 d (1.5)	101.4 (s)	3'', 4''
5'-OCH ₃	3.82 s	56.9 (p)	5'
5''-OCH ₃	3.83 s	57.0 (p)	5''

^a Multiplicities were determined with the assistance of ^1H – ^1H COSY experiments, J in Hz.

^b HMBC correlations from H to C.

^c Letters, p, s, t and q, in parentheses indicate, respectively, the primary, secondary, tertiary and quaternary carbons, assigned by DEPT.

^d Overlapped.

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