

CONFORMATIONAL STUDIES OF LIGNANS FROM *Durio oxleyanus* Griff. (Bombacaceae)Rudiyansyah^{1,*}, Lynette K Lambert², and Mary J Garson³¹Chemistry Department, Faculty of Mathematics and Natural Science, University of Tanjungpura, Ahmad Yani Street, Pontianak 78124, West Kalimantan, Indonesia²Centre for Magnetic Resonance, The University of Queensland, Brisbane, QLD 4072, Australia³School of Chemistry and Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072 Australia

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ABSTRACT

Searching for secondary metabolites from the wood bark of *Durio oxleyanus* has afforded two new lignans, namely threo-carolignan Y (1) and erythro-carolignan Y (2) together with three other known lignans erythro-carolignan X (3), boehmenan X (4) and boehmenan (5). The relative configurations of compounds 1 and 2 were established by J-based configurational analysis and 2D NOESY studies.

Keywords: carolignan, threo, erythro, *Durio*, Bombacaceae

INTRODUCTION

The genus *Durio* contains 28 species, of which 19 are endemic species grown in Borneo, 13 species are found in peninsular Malaysia, 6 are known in Thailand and 7 species are found in Sumatra. Of the 28 species, at least eight are notable for producing edible fruit [1]. The species *D. oxleyanus* is one of an edible fruits, found growing wild in Borneo, Sumatra and Peninsular Malaysia. Heyne states that a concoction made from the bark of *D. oxleyanus* is used to treat malaria in Sumatra and the crushed seeds of *D. oxleyanus* are used to treat sores and wounds [2].

Previous investigation on secondary metabolites from other *Durio* species, *D. zibethinus*, *D. kutejensis* and *D. carinatus*, has yielded caffeoyl triterpenes, lignans and phenolics [3-4]. As part of our concern in chemistry of *Durio* plant, in this paper we report the isolation and characterisation of lignans from *D. oxleyanus* as well as the proposed biosynthesis of isolated lignans in relation with other lignans isolated from previously reported. The relative configurations of compounds 1 and 2 were established by measuring coupling values ($^2,3J_{HC}$) using the HSQC-HECADE method [5-6] together with 2D NOESY studies. Whereas, the known compounds 3, 4 and 5 were characterized by comparison from the literature data [4,7-8].

EXPERIMENTAL SECTION

Materials

The bark of *D. oxleyanus* Griff. was collected in Bengkayang region, West Kalimantan in 2007, air dried,

and powdered. The voucher specimens were identified and stored at the Bogoriense Herbarium in Bogor as 864/IPH.1.02/lf.8/2007.

Apparatus

Optical rotations ($[\alpha]_D^{25}$) and CD spectra were measured on a Perkin-Elmer 241 MC Polarimeter and on a Jasco-J810 spectropolarimeter respectively. HRESIMS were measured using a Finnigan MAT 900 XL double focusing magnetic sector mass spectrometer in the positive ion mode. The ¹H, ¹³C, HSQC, HMBC, DQF-COSY, NOESY and HSQC-HECADE spectra were recorded either on Bruker Avance 400, Bruker Avance 500, or Bruker Avance 750 MHz spectrometers. ¹H NMR spectra were recorded relative to CDCl₃ (δ = 7.24 ppm) and MeOH-*d*₄ (δ = 3.30 ppm) respectively, whereas ¹³C NMR spectra were recorded relative to either CDCl₃ (δ = 77 ppm) or MeOH-*d*₄ (δ = 49 ppm). Vacuum liquid chromatography (VLC) was carried out on silica gel (Kieselgel 60 H) and flash column chromatography (FCC) was carried out on silica gel 60 (230-400 mesh). Thin-layer chromatography (TLC) analysis was performed on pre-coated silica gel plates (Kieselgel 60 F₂₅₄ or RP-18 F_{254s}, 20 x 20 cm, 0.25 mm thick, Merck). Spots were detected under UV light at λ 254 and λ 366 nm or by using ceric sulfate spray reagent. RP-HPLC was performed on an Agilent 1100 series instrument with a variable-wavelength UV detector. Semi-preparative separation used a μ Bondapak C₁₈ (7.8 x 300mm) 10 mm column. All solvents used were distilled prior to use.

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Table 1. Complete NMR assignments for compound 1

#	$\delta^{13}\text{C}^a$	$\delta^1\text{H} (\text{J})^{b,c}$	HMBC ^{d,e}	COSY
1	127.2	-	3, 5, 7, 8	-
2/6	129.9	7.34, d, (8.6)	6, 2, 7	3/5
3/5	115.8	6.80, d, (8.6)	3, 5	2/6
4	157.6	-	2, 3, 5, 6	-
7	144.4	7.44, d, (15.9)	2, 6, 8	8
8	115.4	6.21, d, (15.9)	7	7
9	167.1	-	7, 8, 9a, 9b	-
1	130.1	-	2, 5, 6, 7, 8	-
2	109.9	6.91, d, (1.5)	6, 7	-
3	146.5	-	2, 5, OMe-3	-
4	145.4	-	2, 5, 6	-
5	114.0	6.86, m	-	6
6	121.0	6.87, m	2, 7	5
7	86.2	4.42, d, (6.1)	2, 8, 9a, 9b	8
8	82.5	4.47, m	7, 9a, 9b	7, 9a, 9b
9a/9b	63.7	4.51, m	7, 8	8
1''	135.9	-	2'', 5'', 6'', 7'', 8''	-
2''	112.5	6.61, d, (1.8)	6'', 7''	-
3''	150.7	-	2'', 5'', OMe-3''	-
4''	146.1	-	8'', 2'', 5'', 6''	-
5''	118.9	6.63, d, (8.0)	-	6''
6''	120.4	6.59, dd, (1.8, 8.0)	2'', 7''	5''
7''	31.8	2.60, m	2'', 6'', 8'', 9''	8''
8''	30.3	1.93, m	7'', 9''	7'', 9''
9''	63.8	4.16, t, (6.6)	7'', 8''	8''
1'''	126.9	-	2''', 5''', 7''', 8'''	-
2'''	109.4	7.01, d, (1.7)	6''', 7'''	-
3'''	146.8	-	2''', 5''', OMe-3'''	-
4'''	148.0	-	2''', 5''', 6'''	-
5'''	114.7	6.90, d, (8.2)	-	6'''
6'''	123.0	7.05, dd, (1.7, 8.2)	2''', 7'''	5'''
7'''	144.9	7.59, d, (15.9)	2''', 6''', 8'''	8'''
8'''	115.4	6.28, d, (15.9)	7'''	7'''
9'''	167.4	-	9'', 7'', 8''	-
OMe-3	55.9	3.82, s	-	-
OMe-3''	55.7	3.71, s	-	-
OMe-3'''	55.9	3.90, s	-	-
OMe-7	57.1	3.27, s	7	-

^a 750 MHz, CDCl₃ referenced to ¹³C at δ 77.0 ppm; ^b 750 MHz, CDCl₃ referenced to ¹H at δ 7.24 ppm; ^c Coupling constant in Hz; ^d HMBC connectivity from C to H; ^e Correlations observed for one bond $J_{\text{C-H}}$ of 145 Hz and long range $J_{\text{C-H}}$ of 8 Hz

Procedure

Powdered bark (7 kg) of *D. oxleyanus* Griff. was macerated with MeOH (3 x 20 L) to provide 700 g of residue (10%), which was subsequently dissolved in a mixture MeOH-H₂O (9:1) then partitioned using *n*-hexane (3 x 3 L), CHCl₃ (3 x 5 L) and EtOAc (3 x 5 L) respectively. The CHCl₃ extract (20.11 g) was fractionated by VLC using a gradient of *n*-hexane, CHCl₃ and MeOH (each collection was 250 mL) by increasing polarity to give twenty-three fractions (D1-D23) on the basis of TLC analyses. The combined fractions of D7

and D8 (1.23 g) were purified further by VLC using a gradient of *n*-hexane, EtOAc and MeOH (each collection was 100 mL) in order of increasing polarity to obtain nine fractions (D78_A - D78_I). Fraction D78_G (60 mg) was further subjected to Si gel FCC using a gradient of *n*-hexane, EtOAc and MeOH (each collection was 20 mL) in order of increasing polarity to yield three fractions (D78_GA - D78_GC). Fraction D78_GA (12 mg) was purified by C₁₈-HPLC [MeOH-H₂O (3:1, v/v) over 30 min, flow rate 1.5 mL/min, UV detection at 254 nm] to give compound 3 (5 mg). Compound 1 (3 mg) and compound 2 (5 mg) were also

Table 2. Complete NMR assignments for compound 2

#	$\delta^{13}\text{C}^a$	$\delta^1\text{H} (\text{J})^{b,c}$	HMBC ^{d,e}	COSY
1	127.2	-	3, 5, 7, 8	-
2/6	129.9	7.34, d, (8.6)	6, 2, 7	3/5
3/5	115.8	6.80, d, (8.6)	3, 5	2/6
4	157.6	-	2, 3, 5, 6	-
7	144.4	7.44, d, (15.9)	2, 6, 8	8
8	115.4	6.21, d, (15.9)	7	7
9	167.1	-	7, 8, 9a, 9b	-
1	130.1	-	2, 5, 6, 7, 8	-
2	109.9	6.91, d, (1.5)	6, 7	-
3	146.5	-	2, 5, OMe-3	-
4	145.4	-	2, 5, 6	-
5	114.0	6.86, m	-	6
6	121.0	6.87, m	2, 7	5
7	86.2	4.42, d, (6.1)	2, 8, 9a, 9b	8
8	82.5	4.47, m	7, 9a, 9b	7, 9a, 9b
9a/9b	63.7	4.51, m	7, 8	8
1"	135.9	-	2", 5", 6", 7", 8"	-
2"	112.5	6.61, d, (1.8)	6", 7"	-
3"	150.7	-	2", 5", OMe-3"	-
4"	146.1	-	8", 2", 5", 6"	-
5"	118.9	6.63, d, (8.0)	-	6"
6"	120.4	6.59, dd, (1.8, 8.0)	2", 7"	5"
7"	31.8	2.60, m	2", 6", 8", 9"	8"
8"	30.3	1.93, m	7", 9"	7", 9"
9"	63.8	4.16, t, (6.6)	7", 8"	8"
1'''	126.9	-	2''', 5''', 7''', 8'''	-
2'''	109.4	7.01, d, (1.7)	6''', 7'''	-
3'''	146.8	-	2''', 5''', OMe-3'''	-
4'''	148.0	-	2''', 5''', 6'''	-
5'''	114.7	6.90, d, (8.2)	-	6'''
6'''	123.0	7.05, dd, (1.7, 8.2)	2''', 7'''	5'''
7'''	144.9	7.59, d, (15.9)	2''', 6''', 8'''	8'''
8'''	115.4	6.28, d, (15.9)	7'''	7'''
9'''	167.4	-	9'', 7'', 8''	-
OMe-3	55.9	3.82, s	-	-
OMe-3"	55.7	3.71, s	-	-
OMe-3'''	55.9	3.90, s	-	-
OMe-7	57.1	3.27, s	7	-

^a 750 MHz, CDCl₃ referenced to ¹³C at δ 77.0 ppm; ^b 750 MHz, CDCl₃ referenced to ¹H at δ 7.24 ppm; ^c Coupling constant in Hz; ^d HMBC connectivity from C to H; ^e Correlations observed for one bond J_{C-H} of 145 Hz and long range J_{C-H} of 8 Hz

purified from fraction D78_GB (10 mg) by C₁₈-HPLC [MeOH-H₂O (3:1, v/v) over 45 min, flow rate 1.5 mL/min, UV detection at 254 nm]. Fractions D78_D and D78_E were combined and subjected to FC using *n*-hexane, EtOAc and MeOH in order of increasing polarity to give six fractions (D78_DE1 - D78_DE6). Fraction D78_DE4 was compound 5 (64 mg), and fraction D78_DE2 was fractionated by FC following purification with C₁₈-HPLC [MeOH-H₂O (3:1, v/v) over 45 min, flow rate 1.5 mL/min, UV detection at 254 nm] to obtain 4 (9 mg).

RESULT AND DISCUSSION

Establishment of the relative and absolute configurations

Purification of fraction D78_GB using MeOH-H₂O (3:1, v/v) gave 2 major peaks at 38.4 and 42.3 min that corresponded to 1 and 2, respectively. Both 1 and 2 were obtained as white amorphous solids each with molecular formula of C₄₀H₄₂O₁₂ by HRESIMS.

In CDCl₃, characteristic ¹H-NMR spectroscopic details for compound 1 included three methylenes at

δ 4.18 (2H, t, $J = 6.5$ Hz, H-9"), 2.63 (2H, m, H-7") and 1.96 (2H, m, H-8"), two oxygenated methine protons at δ 4.49 (1H, m, H-8) and 4.46 (1H, d, $J = 5.8$ Hz, H-7), and geminal protons next to oxygen at δ 4.31 (1H, dd, $J = 3.8, 11.7$ Hz, H-9a) and 4.13 (1H, dd, $J = 6.0, 11.7$ Hz, H-9b). There were six methine aromatic protons at δ 6.86 (2H, m, each H-5/H-6), 6.94 (1H, br s, H-2), 6.67 (2H, m, H-2"/H-6"), 6.91 (1H, d, $J = 7.7$ Hz, H-5") and three methoxy protons at δ 3.30 (3H, s, OMe-7), 3.76 (3H, s, OMe-3") and 3.83 (3H, s, OMe-3"). DQFCOSY and HMBC data indicated the presence of a guaiacylglycerol 8-O-4" dihydroconiferyl alcohol ether derivative as the basic skeleton of the isolated compound [9-10].

The remaining proton signals were assigned by DQFCOSY and HMBC analysis to a *trans*-feruloyl group and a *trans-p*-coumaroyl group [11]. For the *trans*-feruloyl group, there were signals at δ 7.59 (1H, d, $J = 15.9$ Hz, H-7"), 6.28 (1H, d, $J = 15.9$ Hz, H-8"), 7.06 (1H, dd, $J = 1.6, 8.1$ Hz, H-6"), 7.01 (1H, d, $J = 1.6$ Hz, H-2"), 6.90 (1H, d, $J = 8.1$ Hz, H-5") and a methoxy at δ 3.91 (3H, s, OMe-3"). For the *trans-p*-coumaroyl group, there were signals at δ 7.43 (1H, d, $J = 15.9$ Hz, H-7), 6.18 (1H, d, $J = 15.9$ Hz, H-8), 7.34 (2H, d, $J = 8.6$ Hz, H-2/H-6) and 6.81 (2H, d, $J = 8.6$ Hz, H-3/H-5).

The ^{13}C NMR and HSQC data confirmed the presence of four methylenes, nineteen methines, four methoxy carbons and thirteen quaternary carbons including two carbonyls at δ 167.3 (C, C-9") and 166.8 (C, C-9). The structure of the isolated compound was constructed by long-range correlations. In the HMBC spectrum, a geminal proton at δ 4.18 showed a correlation to the carbon at δ 167.3 assigned as C-9" of the *trans*-feruloyl group. Additionally, there were three bond correlations from the two protons at δ 4.31 and 4.13 to another carbonyl at δ 166.8 assigned as C-9 and part of the *trans-p*-coumaroyl group.

The second compound **2** had almost identical ^1H -NMR spectra to **1**, except for the replacement of two doublet-doublet signals at δ 4.31 and 4.13 in compound **2** by a multiplet signal at δ 4.51 that integrated as 2 protons. The coupling constant ($J = 6.1$ Hz) of H-7 in compound **2** was slightly larger than the coupling constant ($J = 5.8$ Hz) shown in **1**. Since the J values for compounds **1** and **2** were so similar, it was important to use $^{2,3}J_{\text{HC}}$ and NOESY data to attempt to distinguish between the two stereoisomers.

Matsumori et al. [12] has developed a method to determine the relative configuration of acyclic compounds on the basis of proton-proton coupling constants together with proton-carbon coupling constants. For compounds **1** and **2** with C_7C_8 -dioxo substituents, the vicinal protons of coupling constants in an individual rotamer can be in the range 0-4 Hz (*gauche*) or 7-10 Hz (*anti*); these values are described

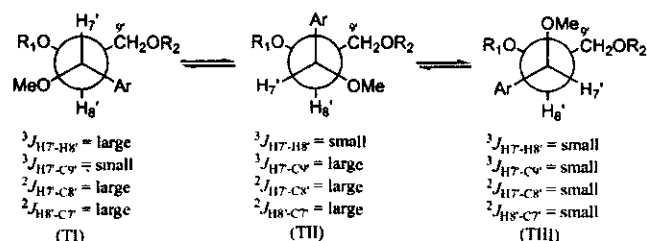


Fig 1. The three possible staggered conformers of compound **1**

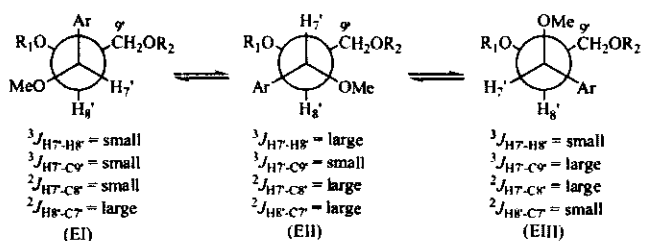


Fig 2. The three possible staggered conformers of compound **2**

as small or large, respectively. For heteronuclear coupling constants, the $^3J_{\text{HC}}$ value range from 1-3 Hz (*gauche*) or from 5-7 (*anti*), described as small or large, while $^2J_{\text{HC}}$ values can be 0-2 (small) or -4 to -6 Hz (large). The information from $^{2,3}J_{\text{HC}}$ can thus provide useful additional information about conformational preferences. In an individual compound, the coupling constant values are observed as a weighted average of the values of each rotamer that contributes to the conformational equilibrium [12]. Fig. 1 and 2 show three possible staggered conformers that can be drawn for each diastereoisomer and below each rotamer is listed the approximate magnitude of the $^3J_{\text{HH}}$ or $^{2,3}J_{\text{HC}}$ that would be expected for this conformation.

Since there is no hydrogen bonding involved, there will be a preference for conformer **TI** (Fig. 1) in compound **1** and conformer **EII** (Fig. 2) in compound **2**. In both of these rotamers, H-7 and H-8 are diaxial, leading to a prediction of the largest coupling constants, as was observed.

Next, NOESY data were used to attempt and provide additional support for the proposed stereochemistry. The NOESY data for compounds **1** and **2** are given in Tables 3 and 4, respectively. These tables describe the anticipated correlations for all the conformers shown in Fig. 1 and Fig. 2 then documents those that were observed. Both compounds showed similar NOESY correlations between H-2/H-8, H-6/H-8 and H-7/H-9. In compound **1**, the geminal protons H-9a and H-9b showed correlations to the methine aromatic protons H-2 and H-6, consistent with the major conformer **TI**. In contrast, the NOESY spectrum of compound **2** showed correlations between the

Table 3. NOESY data for three possible staggered conformers for compound 1 in CDCl₃

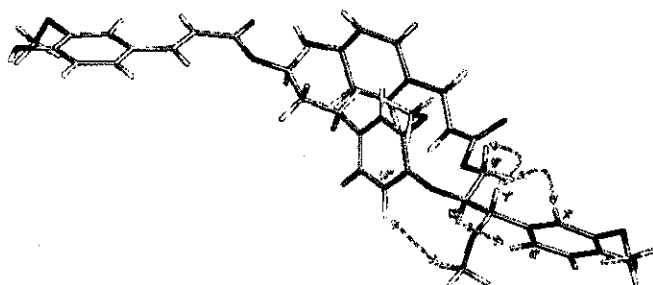
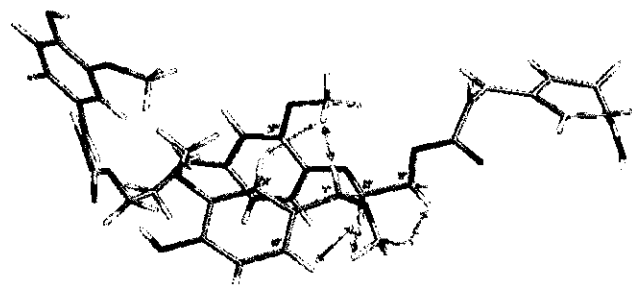
Conformer TI		Conformer TII		Conformer TIII	
Expected H – H correlations	Observed correlation	Expected H – H correlations	Observed correlation	Expected H – H correlations	Observed correlation
OMe - H-8	-	H-7 - H-8	-	H-2 - H-8	+
OMe - H-5"	+	H-7 - H-5"	-	H-2 - H-5"	-
OMe - OMe-3"	-	H-7 - OMe-3"	-	H-2 - OMe-3"	-
H-2 - H-9	+	OMe - H-8	-	H-6 - H-8	+
H-2 - H-8	+	OMe - H-9	-	H-6 - H-5"	-
H-6 - H-9	+	H-2 - H-9	+	H-6 - OMe-3"	-
H-6 - H-8	+	H-2 - OMe-3"	-	H-7 - H-9	+
H-7 - H-9	+	H-2 - H-5"	-	H-7 - H-8	-
H-7 - OMe-3"	-	H-6 - H-9	+	OMe - 9	-
H-7 - H-5"	-	H-6 - OMe-3"	-	OMe - OMe-3"	-
		H-6 - H-5"	-	OMe - H-5"	+

(+) = expected nOe correlation was observed; (-) = expected nOe correlation not observed.

Table 4. NOESY data for three possible staggered conformers for compound 2 in CDCl₃

Conformer E1		Conformer EII		Conformer EIII	
Expected H – H correlations	Observed correlation	Expected H – H correlations	Observed correlation	Expected H – H correlations	Observed correlation
OMe - H-8	+	H-2 - H-8	+	H-7 - H-8	-
OMe - H-5"	-	H-2 - H-5"	-	H-7 - H-5"	-
OMe - OMe-3"	-	H-2 - OMe-3"	+	H-7 - OMe-3"	+
H-2 - H-9	+	H-6 - H-8	+	H-2 - H-8	+
H-2 - OMe-3"	+	H-6 - H-5"	-	H-2 - H-9	+
H-2 - H-5"	-	H-6 - OMe-5"	-	H-6 - H-8	+
H-6 - H-9	+	OMe - H-8	+	H-6 - H-9	+
H-6 - OMe-3"	-	OMe - H-9	+	OMe - H-9	+
H-6 - H-5"	-	H-7 - H-9	+	OMe - OMe-3"	-
H-7 - H-8	-	H-7 - H-5"	-	OMe - H-5"	-
H-7 - H-9	+	H-7 - OMe-3"	+		

(+) = expected nOe correlation was observed; (-) = expected nOe correlation not observed.

**Fig 3.** Three dimension model of conformer TI and some NOESY correlations for compound 1 in CDCl₃**Fig 4.** Three dimension model of conformer EII and some NOESY correlations for compound 2 in CDCl₃

geminal protons H-9 a and H-9 b to the -OMe protons, as expected for the major conformer EII. Even though NOESY correlations from the geminal protons H-9 to H-2 and H-6 were observed in compound 2 (Table 4), these were interpreted as contributions from minor conformers EI and EIII. Fig. 3 and 4 show the three dimension model of conformers TI and EII respectively.

Finally, the inspection of $^{2,3}J_{HC}$ values confirms the

correctness of the configurational assignments. Analysis of the HSQC-HECADE [5-6] spectra in CDCl₃ indicated that compound 1 had a *gauche* relationship between H-7 and C-9 since the $^3J_{H7-C9}$ was +1.0 Hz, $^2J_{H7-C8}$ was -4.5 Hz and $^2J_{H8-C7}$ was -3.9 Hz, with each value conveniently described as small, large and large. Similarly compound 2 showed $^3J_{H7-C9}$ of +2.4, $^2J_{H7-C8}$ of -5.3 Hz and $^2J_{H8-C7}$ of -3.6 Hz, each value described as

small, large and large. These data confirmed that the conformer TI and the conformer EII were the major contributors to the conformational situation for compounds 1 and 2 respectively. With all of these data, it was apparent that the two methoxy compounds 1 and 2 had *threo* and *erythro* configurations, respectively.

The analysis of circular dichroism (CD) spectra allowed the absolute configuration for both 1 and 2 to be established. According to some literature [13-18], the lignan compounds all show a trend in which the Cotton effect in the 230 – 240 nm range is positive when the C-8 configuration is *S*. It was also apparent from the published CD data that the *erythro* isomers show a red shifted maxima compared to the *threo* isomers. Owing to solubility issues, the spectra of 1 and 2 were recorded in acetonitrile and as a result, compound 1 showed positive Cotton effects at 238.9 nm while compound 2 was red shifted to 240 nm. Hence, compound 1 may have 7*S*,8*S* configuration while 2 may have 7*R*,8*S* configuration. The $[\alpha]_D$ values of the two methoxy compounds 1 and 2 were -16.0 (c 0.2, MeOH) and -2.6 (c 0.2, MeOH) respectively.

CONCLUSION

Two new lignans 1 and 2 have been isolated and characterized by chemical studies. The intensive studies of conformational preferences, 2D NMR experiments including HSQC-HECADE and NOESY and the CD spectroscopy were very useful for assignment of the configuration of the lignans that showed multi-conformer equilibria. This study showed that NMR-based methods in combination with chiroptical approaches were able to confirm the relative and absolute configurations of complex lignans despite the presence of multiple conformers.

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