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Phenylpropanoids and neolignans from *Piper regnellii*

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Abstract

Roots of *Piper regnellii* (Piperaceae) contain three phenylpropanoids: apiol, dillapiol and myristicin; seven 4′,7-epoxy-8,3′-neolignans; and three 8′,9′-*dinor*-4′,7-epoxy-8,3′-neolignans. The structures and absolute configurations of the isolates (four new neolignans including regnelline) were established based on analysis of spectroscopic data. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Piper regnellii*; Piperaceae; Phenylpropanoids; Neolignans; Regnelline; *Dinor*-neolignans

1. Introduction

Piperaceae species are mostly pioneer shrubs with economic and medicinal importance (Cronquist, 1981), and are widely spread in tropical regions. Phytochemical investigations carried out on *Piper* species have revealed the accumulation of several classes of physiologically active natural products such as alkaloids, amides, pyrones, dihydrochalcones, flavonoids, phenylpropanoids, lignans, and neolignans (Kiuchi, Nakamura, Tsuda, Kondo & Yoshimura, 1988; Orjala, Wright, Behrends, Folkers & Sticher, 1994; Ahmad, Bakar, Ibrahim & Read, 1997; Nair & Burke, 1990; Zhang et al., 1995). A comprehensive review covering the period of 1907 to 1996 on chemical composition of *Piper* species and their bioactivities was published and constitutes a rich source of information on this subject (Parmar et al., 1997). As part of our research on the chemistry of lignan/neolignans on Piperaceae species, herein we describe the first phytochemical investigation carried out on *P. regnellii*. By means of chromatographic and spectroscopic techniques we describe three phenylpropanoids, seven benzofuran neolignans, and three *dinor*-neolignans from the root extracts of *P. regnellii*.

2. Results and discussion

Ethyl acetate extracts from the roots of *P. regnellii* submitted to flash chromatography and sequential purification by preparative TLC and HPLC yielded thirteen compounds among which four are new dihydrobenzofuran neolignan derivatives. Dillapiol (**1**) (Bernhard & Thiele, 1978; Diaz, Maldonado & Ospina, 1984), apiol (**2**) (Bernhard & Thiele, 1978), and myristicin (**3**) (Diaz et al., 1984) have been previously reported in the literature, and the updated ^{1}H and ^{13}C NMR data are presented in Section 3. Compounds **5** (Hayashi & Thomson, 1975; Bernard et al., 1995), **7** (Achenbach et al., 1987), **8** and **9** (Bowden, Ritchie & Taylor, 1972; Chauret, Bernard, Arnason & Durst, 1996), **10** (Bowden et al., 1972) and **12** (Chauret et al., 1996) have also been previously isolated and were identified by comparison with reported spectroscopic data. The structures for the new compounds **4**, **6**, **11** and **13** are presented (see Scheme 1 for structures).

The molecular formula for compounds **4** was established as $C_{18}H_{18}O_2$ based on MS data (M^+ at 266), element analysis and the number of ^{1}H and ^{13}C nuclei

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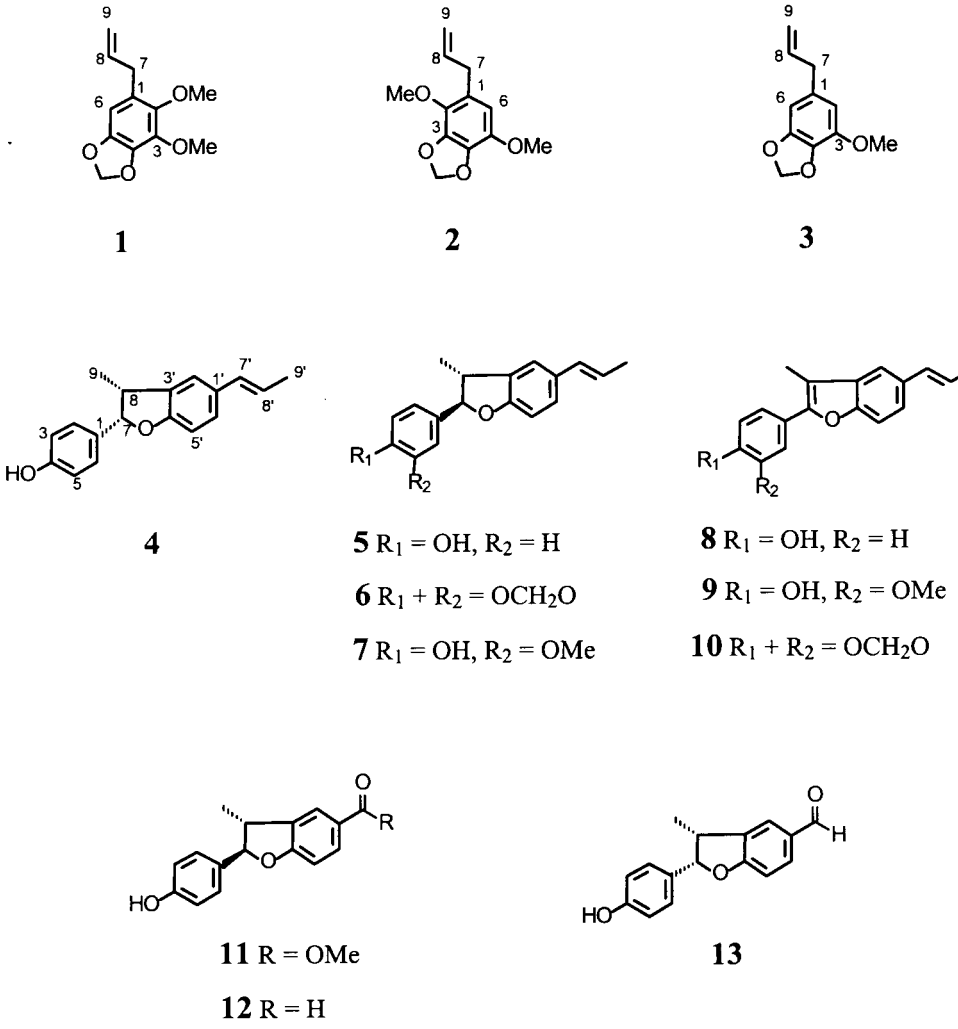

Scheme 1

in the NMR spectra. Its ^{1}H NMR spectrum revealed signals at δ 5.73 (*d*, 8.8 Hz, H-7), δ 3.61 (*dq*, 7.2, 8.8 Hz, H-8), and δ 0.82 (*d*, 7.2 Hz, H-9) which indicated the *cis*-7-aryl-8-methyl-dihydrobenzofuran system (Lima, Gottlieb & Magalhães, 1972). The *E* configuration for the propenyl group was evident from the presence of an AMX_3 spin system [δ 6.36 (*dd*, 1.4, 15.0 Hz, H-7′), 6.08 (*dq*, 6.6, 15.0 Hz, H-8′) and 1.85 (*dd*, 1.4, 6.6 Hz, H-9′)]. The *ortho* coupling constants observed between H-2/H-6 at δ 7.26 (*d*, 8.5 Hz) and H-3/H-5 at δ 6.80 (*d*, 8.5 Hz) identified the substitution pattern in the pendant aromatic ring while the remaining signals were similar to those observed for conocarpan (Hayashi & Thomson, 1975; Bernard et al., 1995). This compound was thus established as the C-7 epimer of conocarpan.

Compound **6** has the molecular formula $C_{19}H_{18}O_3$ based on MS data (M^+ at 294), elemental analysis and the number of ^{1}H and ^{13}C NMR nuclei in the NMR spectra. Analysis of its ^{1}H NMR spectrum allowed the identification of a *trans*-7-aryl-8-methyl-7,8-dihydrobenzofuran system [δ 4.98 (*d*, 8.7 Hz, H-7), 3.28 (*dq*, 6.8, 8.7 Hz, H-8) and 1.32 (*d*, 6.8 Hz, H-9)]. The methylenedioxyphenyl group was inferred by the singlet at δ 5.89 and signal at δ 101.1 in its ^{1}H NMR and ^{13}C NMR spectra, respectively, and by the fragment ion at *m/z* 135 $[C_6H_3(OCH_2O)CH_2]^+$ in its mass spectrum. As the structure for neolignan **6**, as depicted, has not been reported yet, we introduced it here as regnelline.

The compound **11** has the molecular formula $C_{17}H_{16}O_4$ determined as mentioned above. Its ^{1}H NMR spectrum was quite similar to that of conocarpan, except that the signals corresponding to propenyl moiety had been replaced by the singlet corresponding to methyl ester. This functional group was confirmed by ^{13}C NMR spectrum in which signals corresponding to a carbonyl ester at δ 190.9 and to an aliphatic meth-

oxyl at δ 50.5 were observed. The ester was defined at the C-7′ position based on the similarities of chemical shifts corresponding to the dihydrobenzofuran system and by the deshielding effect caused by carbonyl in the protons H-2′ (δ 7.75) and H-6′ (δ 7.74) in the ^{1}H NMR spectrum. Thus, the structure of **11** was established as methyl (7*R*,8*R*)-4-hydroxy-8′,9′-*dinor*-4′,7-epoxy-8,3′-neolignan-7′-ate. A *dinor*-dihydrobenzofuran-neolignan aldehyde of this type has already been described (Chauret et al., 1996) but the *dinor*-dihydrobenzofuran neolignan ester **11** is a novel compound.

The compound **13**, molecular formula $C_{16}H_{14}O_3$, had its structure identified as the C-7 epimer of decurrenal (**12**), which was first described in *P. decurrens* (Chauret et al., 1996) and also isolated in this work. The presence of the aldehyde group was established based on the characteristic signal at δ 9.86 in its ^{1}H NMR spectrum. The assignment of the *cis* configuration between methyl and *p*-hydroxyphenyl groups was based on the chemical shift corresponding to the oxybenzylic, methinic and methyl protons as observed to C-7 *epi* conocarpan.

The absolute configurations for the new compounds **4**, **6**, **11** and **13** could be established by comparison of the CD curves with those model compounds which were analysed by ORD and R-X crystallographic studies (Gottlieb et al., 1977; Aiba et al., 1977). The positive Cotton effect at 260 to 285 nm observed for compounds **6** and **11** can be associated to the β-configuration for the aryl group. Considering the *trans* configuration between aryl/methyl, as defined by ^{1}H NMR data, the absolute configurations were established as 7*R* and 8*R*. In the case of neolignans **4** and **13**, the negative signals, observed in the same range of the CD curve, indicated the α-configuration for the aryl groups. This assignment is in agreement with the ^{1}H NMR data which showed the *cis* configuration between aryl/methyl and, therefore, the absolute configurations were defined as 7*S* and 8*R* (Gottlieb et al., 1977; Aiba et al., 1977).

In summary, *P. regnellii* is a source of highly oxygenated phenylpropanoids (**1**–**3**, 1.5% of crude extracts) and a series of benzofuran derivatives which are supposedly produced by oxidative coupling of mono-(**4**, **5**, **8**, **11**–**13**, 1.0%) or dioxygenated propenylphenols (**6**, **7**, **9** and **10**, 0.6%). The profile of neolignans is similar in roots, stems and leaves of *P. regnellii* according to HPLC analysis (see Section 3).

3. Experimental

3.1. General

The ^{1}H NMR (300 MHz) spectra were recorded on a Brüker DPX-300 spectrometer, using TMS as an int. standard. The ^{13}C NMR (50 MHz) spectra were recorded on a Brüker AC-200 spectrometer. EIMS were measured at 70 eV on a HP 5990/5988 A spectrometer. IR: KBr, $[\alpha]_D$ measured at $\lambda = 589$ nm. The CD curves were recorded on an ISA Jobin-Yvon CD-6 spectropolarimeter. Elemental analyses were performed on a Perkin-Elmer CHN Elemental Analyser 2400.

3.2. Plant material

The specimens of *P. regnellii* collected at the Campus of Universidade de São Paulo (Brazil) in August 1996 was identified by Dr Antônio Salatino (Departamento de Botânica of the Instituto de Biociências of the Universidade de São Paulo). A voucher specimen is deposited at the Herbarium (Benevides S/n.SPF112.6.84) of the Instituto de Biociências of the Universidade de São Paulo.

3.3. Isolation

Dried roots of *P. regnellii* (50 g) were milled and extracted with EtOAc yielding 4.0 g of extract. This extract was submitted to CC (silica gel 200 g) eluted with a gradient of hexane:EtOAc, followed by prep. TLC and HPLC using normal phase (hexane:CH_2Cl_2:EtOAc-25:24:1) yielding **1** (25.3 mg), **2** (24.4 mg), **3** (12.0 mg), **4** (10.0 mg), **5** (25.1 mg), **6** (8.3 mg), **7** (6.0 mg), **8** (5.0 mg), **9** (9.5 mg), **10** (4.3 mg), **11** (3.3 mg), **12** (7.3 mg) and **13** (3.0 mg).

3.4. 2,3-Dimethoxy-4,5-methylenedioxy-allylbenzene (dillapiol) (*1*)

$C_{12}H_{14}O$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (2H, *dd, J* = 1.5; 6.6 Hz, H-7), 3.78, 3.80 (6H, *s*, OMe-2, OMe-3), 4.96 (1H, *dd, J* = 1.5; 9.0 Hz, H-9a), 4.97 (1H, *dd, J* = 1.5; 15.4 Hz, H-9b), 5.81 (1H, *m*, H-8), 5.88 (2H, *s*, OCH_2O), 6.23 (1H, *s*, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 126.0 (C-1), 135.1 (C-2), 137.6 (C-3), 144.6 (C-4), 144.3 (C-5), 102.7 (C-6), 33.9 (C-7), 137.4 (C-8), 115.5 (C-9), 61.3 (OMe-2), 50.9 (OMe-3), 101.1 (OCH_2O).

3.5. 3,6-Dimethoxy-4,5-methylenedioxy-allylbenzene (apiol) (*2*)

$C_{12}H_{14}O_4$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (2H, *dd, J* = 1.5; 6.6 Hz, H-7), 3.68 (3H, *s*, OMe-2), 3.94 (3H, *s*, OMe-5), 4.96 (1H, *dd, J* = 1.5; 9.0 Hz, H-9a), 4.97 (1H, *dd, J* = 1.5; 15.4 Hz, H-9b), 5.79 (1H, *m*, H-8), 5.86 (2H, *s*, OCH_2O), 6.28 (1H, *s*, H-2).

3.6. 3-Methoxy-4,5-methylenedioxy-allylbenzene (myristicin) (**3**)

$C_{11}H_{12}O_3$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (2H, *d*, J = 6.7 Hz, H-7), 3.81 (3H, *s*, OMe), 4.99 (1H, *dd*, J = 1.7; 8.0 Hz, H-9a), 5.01 (1H, *dd*, J = 1.7; 17.1 Hz, H-9b), 5.85 (1H, *m*, H-8), 5.86 (2H, *s*, OCH_2O), 6.28 (1H, *d*, J = 1.4 Hz, H-6), 6.32 (1H, *d*, J = 1.4 Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 126.0 (C-1), 104.9 (C-2), 137.6 (C-3), 144.5 (C-4), 144.3 (C-5), 102.7 (C-6), 33.8 (C-7), 137.3 (C-8), 115.5 (C-9), 51.0 (OMe-3), 101.0 (OCH_2O).

3.7. (7S,8R)-4-Hydroxy-4′,7-epoxy-8,3′-neolignan-7′[E]-ene (**4**)

White amorphous. ($C_{18}H_{18}O_2$ requires 81.20% C, 6.77% H; found 81.43% C, 6.72% H). $[\alpha]_D^{21}$ −33.3° (MeOH, *c* 0.03). RR_t = 8.91 min in HPLC (C-18 Econosil column, 5 μm, 250 × 4 mm i.d., with gradient from MeCN–H_2O 7:3 (7 min) changing to 85:15 (15 min); flow rate 1 ml min^{-1}, detection at 280 nm) (condition A). UV λ_{max}^{MeOH} nm (ϵ): 220 (12,750), 275 (6380). CD (MeOH, *c* 0.003): $[\theta]_{211}$ −4649, $[\theta]_{218}$ 0, $[\theta]_{229}^{max}$ +14,390, $[\theta]_{235}$ 0, $[\theta]_{243}^{max}$ −9923, $[\theta]_{275}$ 0, $[\theta]_{282}$ +2658. IR ν_{max}^{film} cm^{-1}: 3542, 2964, 1614, 1015. MS *m*/*z* (rel. int.): 266 $[M]^+$ (100), 251 (31), 223 (17), 171 (12), 131 (26), 91 (20), 77 (17). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (3H, *d*, J = 7.2 Hz, H-9), 1.85 (3H, *dd*, J = 1.4; 6.6 Hz, H-9′), 3.61 (1H, *dq*, J = 7.2, 8.8 Hz, H-8), 5.73 (1H, *d*, J= 8.8 Hz, H-7), 6.08 (1H, *dq*, J = 6.6; 15.0 Hz, H-8′), 6.36 (1H, *dd*, J = 1.4; 15.0 Hz, H-7′), 6.75 (1H, *d*, J = 7.4 Hz, H-5′), 6.80 (2H, *d*, J = 8.5 Hz, H-3/H-5), 7.12 (1H, *d*, J = 7.4 Hz, H-6′), 7.14 (1H, *d*, J = 1.8 Hz, H-2′), 7.26 (2H, *d*, J = 8.5 Hz, H-2/H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.3 (C-1), 127.7, 127.8 (C-2, C-6), 115.0, 115.4 (C-3, C-5), 155.6 (C-4), 92.6 (C-7), 40.7 (C-8), 16.7 (C-9), 131.2 (C-1′), 120.6 (C-2′), 132.6 (C-3′), 158.0 (C-4′), 109.2 (C-5′), 126.3 (C-6′), 130.7 (C-7′), 123.0 (C-8′), 18.4 (C-9′).

3.8. (7R,8R)-3,4-Methylenedioxy-4′,7-epoxy-8,3′-neolignan-7′[E]-ene (**6**)

White amorphous. ($C_{19}H_{18}O_3$ requires 77.55% C, 6.12% H; found 77.63% C, 6.32% H). $[\alpha]_D^{21}$ +85.5° (MeOH, *c* 0.06). RR_t = 17.33 min in HPLC (condition A). UV λ_{max}^{MeOH} nm (ϵ): 232 (11,250), 265 (8750), 290 (7500). CD (MeOH, *c* 0.003): $[\theta]_{214}$ +6270, $[\theta]_{215}$ 0, $[\theta]_{219}^{max}$ −7667, $[\theta]_{229}$ 0, $[\theta]_{260}^{max}$ +15,770, $[\theta]_{294}^{sh}$ +3760. IR ν_{max}^{film} cm^{-1}: 3445, 1488, 1122. MS *m*/*z* (rel. int.): 294 $[M]^+$ (90), 282 (100), 265 (11), 147 (20), 135 (55), 103 (10), 77 (18). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, *d*, J = 6.8 Hz, H-9), 1.79 (1H, *dd*, J = 1.6; 6.6 Hz, H-9′), 3.28 (1H, *dq*, J = 6.8; 8.7 Hz, H-8), 4.98 (1H, *d*, J = 8.7 Hz, H-7), 5.89 (2H, *s*, OCH_2O), 6.01 (1H, *dq*, J = 6.6; 15.0 Hz, H-8′), 6.29 (1H, *dd*, J = 1.5; 15.0 Hz, H-7′), 6.67 (1H, *d*, J = 1.7 Hz, H-2), 6.70 (1H, *dd*, J = 1.7; 7.5 Hz, H-6), 6.72 (1H, *d*, J = 7.5 Hz, H-5), 6.80 (1H, *dd*, J = 1.6; 7.4 Hz, H-6′), 6.84 (1H, *d*, J = 1.5 Hz, H-2′), 7.04 (1H, *d*, J = 7.4 Hz, H-5′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 131.3 (C-1), 106.5 (C-2), 147.6, 147.9 (C-3, C-4), 108.2 (C-5), 119.9 (C-6), 92.7 (C-7), 45.3 (C-8), 17.9 (C-9), 134.5 (C-1′), 120.7 (C-2′), 132.1 (C-3′), 158.2 (C-4′), 109.3 (C-5′), 126.3 (C-6′), 130.7 (C-7′), 123.0 (C-8′), 18.4 (C-9′), 101.1 (OCH_2O).

3.9. Methyl-(7R,8R)-4-hydroxy-8′,9′-dinor-4′,7-epoxy-8,3′-neolignan-7′-ate (**11**)

Yellow oil. ($C_{17}H_{16}O_4$ requires 71.83% C, 5.63% H; found 71.78% C, 5.67% H). $[\alpha]_D^{21}$ +30.1° (MeOH, *c* 0.08). RR_t = 3.59 min in HPLC (condition A). UV λ_{max}^{MeOH} nm (ϵ) 225 (18,000), 280 (7710). CD (MeOH, *c* 0.003): $[\theta]_{214}$ +3824, $[\theta]_{217}$ 0, $[\theta]_{222}^{max}$ −2754, $[\theta]_{229}$ 0, $[\theta]_{242}^{max}$ +9582, $[\theta]_{263}^{sh}$ +2600. IR ν_{max}^{film} cm^{-1}: 3562, 2873, 1720, 1519. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, *d*, J = 7.0 Hz, H-9), 3.40 (1H, *dq*, J = 7.0, 8.5 Hz, H-8), 5.20 (1H, *d*, J = 8.5 Hz, H-7), 3.50 (3H, *s*, OMe) 6.83 (2H, *dd*, J = 1.8; 6.8 Hz, H-3/H-5), 6.90 (1H, *d*, J = 9.0 Hz, H-5′), 7.30 (2H, *dd*, J = 1.8; 6.8 Hz, H-2/H-6), 7.74 (1H, *dd*, J = 1.7; 9.0 Hz, H-6′), 7.75 (1H, *d*, J = 1.7 Hz, H-2′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 129.3 (C-1), 127.8 (C-2, C-6), 115.4 (C-3, C-5), 156 (C-4), 92.6 (C-7), 45.2 (C-8), 17.6 (C-9), 133.6 (C-1′), 124.5 (C-2′), 133.5 (C-3′), 164.7 (C-4′), 109.5 (C-5′), 132.7 (C-6′), 190.9 (C-7′), 50.5 (OMe).

3.10. (7S,8R)-4-Hydroxy-8′,9′-dinor-4′,7-epoxy-8,3′-neolignan-7′-aldehyde (**13**)

Yellow oil. ($C_{16}H_{14}O_3$ requires 70.50% C, 5.51% H; found 7.25% C, 5.42% H). $[\alpha]_D^{21}$ −29.1° (MeOH, *c* 0.10). RR_t = 4.42 min in HPLC (condition A). UV λ_{max}^{MeOH} nm (ϵ): 230 (5940), 285 (3330). CD (MeOH, *c* 0.003) $[\theta]_{220}$ −10,458, $[\theta]_{228}$ 0, $[\theta]_{234}^{max}$ +29,099, $[\theta]_{250}$ 0, $[\theta]_{275}$ −18,553, $[\theta]_{296}^{sh}$ −11,096. IR ν_{max}^{film} cm^{-1}: 3410, 2950, 1690, 1594, 1251, 1120. MS *m*/*z* (rel. int.): 254 ($[M]^+$, 45), 239 (10), 225 (11), 149 (100), 107 (47). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, *d*, J = 6.8 Hz, H-9), 3.64 (1H, *dq*, J = 6.8; 9.0 Hz, H-8), 5.89 (1H, *d*, J = 9.0 Hz, H-7), 6.86 (2H, *dd*, J = 2.0; 6.6 Hz, H-3/H-5), 6.94 (1H, *d*, J = 8.7 Hz, H-5′), 7.29 (2H, *dd*, J = 1.9; 6.6 Hz, H-2/H-6), 7.72 (1H, *dd*, J = 1.7; 8.7 Hz, H-6′), 7.73 (1H, *d*, J = 1.7 Hz, H-2′), 9.86 (1H, *s*, H-CO). ^{13}C NMR (50 MHz, $CDCl_3$): δ 130.6 (C-1), 127.7, 127.8 (C-2, C-6), 115.6, 115.7 (C-3, C-5), 156.1 (C-4), 93.7 (C-7), 44.5 (C-8), 16.8 (C-9), 133.5 (C-1′), 124.5 (C-2′), 134.4 (C-3′), 164.7 (C-4′), 109.8 (C-5′), 133.6 (C-6′), 190.8 (C-7′).

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