Notes

5-Methoxyjusticidin A, a New Arylnaphthalene Lignan from *Protium unifoliolatum*

Antonio C. Siani,*,† M. das G. B. Zoghbi,‡ Esther L. A. Wolter,§ and Ivo Vencato⊥

LQPN, Far-Manguinhos, FIOCRUZ, R. Sizenando Nabuco 100, 21041-250, Rio de Janeiro, RJ, Brazil, Departamento de Botânica, Museu Paraense Emílio Goeldi, C.P. 399, 66040-170, Belém, PA, Brazil, CPPN, Instituto Nacional de Pesquisas da Amazônia, C.P. 478, 69011-970, Manaus, AM, Brazil, and Departamento de Química, Universidade Federal de Santa Catarina, C.P. 88040-400, Florianópolis, SC, Brazil

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A new arylnaphthalene lignan, 9-(1,3-benzodioxol-5-yl)-4,5,6,7-tetramethoxynaphtho[2,3-*C*]-furan-1(3*H*)-one (5-methoxyjusticidin A, **1**), was isolated from a Et_2O extract of the wood of *Protium unifoliolatum*. The structure of **1** was determined by both spectroscopic and X-ray crystallographic methods.

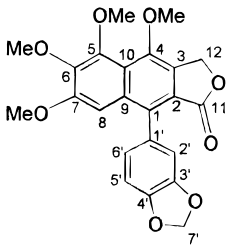
The occurrence of lignans in the family Burseraceae is documented for only a few genera. Dibenzylbutyrolactone lignans occur in the genus *Protium*,[1,2] whereas lignans of the dihydronaphthalene and tetrahydronaphthalene types have been found so far only in the genus *Bursera*, and sesamin (2,6-diaryl-3,7-dioxabicyclo[3.3.0]-octane) has been recorded in species of the genus *Commiphora*.[3]

Semisynthetic derivatives of the aryltetralin lignan podophyllotoxin are used clinically for their anticancer activity,[4] while arylnaphthalene lignans have been isolated from plants used traditionally against several diseases. The cytotoxicity of such compounds is reported,[5] as well as their antidepressant,[6] contraceptive,[7] antitumor,[8] and antiviral[9] activities.

A new lignan, 5-methoxyjusticidin A (**1**), was isolated from the wood of *Protium unifoliolatum* Engl. (Burseraceae), and its structure determination is the subject of this paper. This represents the first fully aromatic arylnaphthalene lignan isolated from a species in the family Burseraceae.

Chromatographic separation of the Et_2O extract of the wood of *P. unifoliolatum* resulted in the isolation of compound **1** as colorless flakes, mp 193 °C. The UV spectrum was typical for an arylnaphthalene system, and IR absorption bands at 1765 and 926 cm^{-1} suggested the presence of γ-lactone and methylenedioxy groups, respectively. Additionally, the carbonyl absorption in association with the deshielded singlet signal at 5.42 ppm in the ^1H NMR spectrum for the lactone methylene protons suggested that the carbonyl group was vicinal to the 1-aryl functionality. The ^1H NMR spectrum also confirmed the presence of a methylenedioxy group, which exhibited two characteristic protons at δ 6.07 (1H) and 6.03 (1H), respectively. Among the four aromatic protons that appeared in the ^1H NMR spectrum, the well-defined singlet at 6.97 ppm corresponded to H-8 and showed that the C-4 position was substituted. Two protons were ortho-coupled (2 × d, J = 9.6 Hz) and the fourth was meta-coupled to the more shielded doublet (J = 1.7 Hz). These data were consistent with the 1,3,4-trisubstitution pattern of the phenyl group. The lack of any signal around 7.5 ppm (H-5) suggested that this position was substituted.

The EIMS of **1** exhibited a molecular ion peak at m/z 424, which corresponded to a molecular formula of $C_{23}H_{20}O_8$. The mass spectrum showed little fragmentation and followed a pattern similar to that displayed by justicidin A.[10] The more significant peaks corresponded to aromatic methyl ester cleavage to produce losses of m/z 30 (H_2CO) and m/z 43 (CH_3 + CO).



The number of carbons in the molecule of **1** was corroborated by the ^{13}C NMR and DEPT NMR data. The HETCOR spectrum permitted the confirmation of the proposed assignments for the protonated carbons in the molecule. The signals at 169.5 and 66.5 ppm of the lactone carbonyl and methylenedioxy group of the lactone were characteristic of an arylnaphthalene lignan, and the chemical shifts of the aryl methoxy groups (62.4, 62.0, 61.4, and 55.8 ppm) indicated that only one of these (55.8 ppm) did not have O-disubstitution.

The structure of **1** as 9-(1,3-benzodioxol-5-yl)-4,5,6,7-

* To whom correspondence should be addressed. Fax: 55-21-2703912. E-mail: siani@far.fiocruz.br.
† FIOCRUZ.
‡ Departamento de Botânica.
§ Instituto Nacional de Pesquisas da Amazônia.
⊥ Universidade Federal de Santa Catarina.

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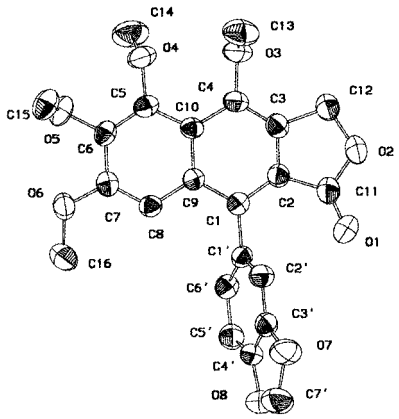

Figure 1. ORTEP drawing of **1** at 50% probability level.

tetramethoxynaphtho[2,3-*C*]furan-1(3*H*)-one (5-methoxyjusticidin A) was confirmed by single-crystal X-ray crystallography. (See Figure 1.)

Experimental Section

General Experimental Procedures. UV and FT-IR spectra were recorded on a Beckman DB-65 and a Nicolet 205 spectrophotometer, respectively. NMR spectra were obtained on a Bruker AC 200-A spectrometer operating at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C and were measured using TMS as internal standard. Mass spectra were recorded on an HP 6890 GC coupled to an MS spectrometer, operating at 70 eV. X-ray analysis was performed with a Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation and ω-2θ scan.

Plant Material. The wood of *P. unifoliolatum* was collected at Vivenda Verde, situated on the Manaus−Itacoatiara road, State of Amazonas, Brazil, in April 1991. A voucher specimen (no. 162 628) has been deposited at the Herbarium of the Instituto Nacional de Pesquisas da Amazônia (INPA), Manaus, AM, Brazil.

Extraction and Isolation. The wood (5.3 kg) was ground and extracted at room temperature with Et_2O. The solvent was evaporated to give 19.2 g of extract. This was subjected to column chromatography on Si gel and eluted with *n*-hexane, *n*-hexane−CH_2Cl_2 mixtures, CH_2Cl_2, and CH_2Cl_2−MeOH mixtures (100 mL each fraction). A fraction eluted with pure CH_2Cl_2 (4.37 g) was rechromatographed (*n*-hexane−EtOAc gradient) over silica gel to give 53 mg of **1**.

5-Methoxyjusticidin A (1): obtained as colorless flakes (MeOH); mp 193 °C; UV (EtOH) λ_{max} (log ϵ) 236 (5.02), 264 (5.28), 368 (4.31) nm; IR (KBr) ν_{max} 2940, 1765, 1599, 1473, 1458, 1437, 1419, 1358, 1340, 1227, 1294, 1158, 1107, 1063, 1028, 929 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.97 (1H, s, H-8), 6.95 (1H, d, J = 9.6, H-5′), 6.79 (1H, d, J = 1.7, H-2′), 6.78 (1H, dd, J = 9.6, 1.7 Hz, H-6′), 6.03 and 6.08 (2H, 2 × d, J = 1.3 Hz, O−CH_2−O), 5.42 (2H, s, H-12), 4.03 (3H, s, OCH_3-4), 3.99 (3H, s, OCH_3-5 or -6), 3.97 (3H, s, OCH_3-6 or -5), 3.76 (3H, s, OCH_3-7); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169.5 (C=O), 153.2 (C-6), 149.2 (C-7), 148.2 (C-4′) 147.7 (C-5 or C-3′) 147.6 (C-3′ or C-5) 145.0 (C-4), 135.6 (C-8), 133.6 (C-1′), 130.0 (C-1), 128.6 (C-3), 123.7 (C-6′), 122.3 (C-10), 120.8 (C-1), 110.7 (C-2′), 108.3 (C-5′), 103.9 (C-8), 101.3 (O−CH_2−O), 66.5 (C-12), 62,4 (OCH_3-6 or -5), 62,0 (OCH_3-5 or -6), 61.4 (OCH_3-4), 55.8 (OCH_3-7); EIMS *m*/*z* 426 (4), 425 (22), 424 [M]$^+$ (100), 394 (9), 379 (12), 366 (3), 365 (3), 351 (4), 323 (4).

X-ray Crystallographic Analysis of 1.[11] The compound crystallizes in the monoclinic space group $P2_1/n$, a = 8.987(2), b = 21.446(4), c = 10.392(2) Å, β = 90.03(3)°, V = 200.9(7) Å^3, Z = 4 and with a calculated density of 1.407 mg·m^{-3}. The structure was solved by direct methods and refined by full-matrix least-squares with 1809 observed [$I > 2\sigma(I)$] reflections, 281 parameters, anisotropic nonhydrogen atoms, and isotropic hydrogens in calculated positions. The final *R*-factor is 5.1%, and the weight for a reflection was calculated using SHELXL-93 scheme.

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