

LIGNANS FROM *OCOTEA FOETENS*

H. LÓPEZ,* A. VALERA,

Centro de Productos Naturales Antonio González, Instituto Universitario de Bioorgánica,
Universidad de La Laguna, 38206 La Laguna, Tenerife, Spain

and J. TRUJILLO

Instituto de Productos Naturales y Agrobiología,
Carretera de la Esperanza, 2 C.S.I.C., 38206 La Laguna, Tenerife, Spain

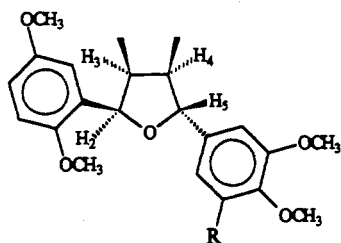
ABSTRACT.—Three novel lignans of the 2,5-diaryl-3,4-dimethyltetrahydrofuran type and two structurally related compounds were isolated from an ethanolic extract of the leaves of *Ocotea foetens*. The structures of these substances were determined by spectroscopic studies (^1H -nmr, ^{13}C -nmr, COSY, HMQC, and ROESY).

Ocotea foetens (Ait.) Benth. et Hook f.

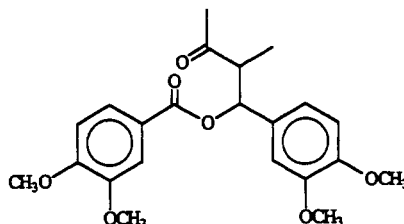
(1) (Lauraceae) which grows in the Laurisilva woods of the Canary Islands, is one of the four endemic species representing this family in Macaronesia¹ (2). This species has been identified as "Garóé," the rain tree or holy tree in El Hierro (3), one of the Canary Islands. Its wood is hard, dark, and durable, suitable for furniture making and other uses. When cut it smells unpleasant, which could be one reason why it is not commonly used in folk medicine. Many species of the family Lauraceae, and also many species of the genus *Ocotea* are important sources of lignans and neolignans (4,5). Lignans have been reported to possess several types of biological activity, including anti-feedant, antimicrobial, antineoplastic, CNS stimulant, and neuroleptic effects (6–8).

In this work we describe the isolation and structural elucidation of three lignans of the 2,5-diaryl-3,4-dimethyltetrahydrofuran type: 2-(2',5'-dimethoxyphenyl)-3,4-dimethyl-5-(3'',4'',5''-trimethoxyphenyl)-tetrahydrofuran [**1**], 2-(2',5'-dimethoxyphenyl)-3,4-dimethyl-5-(3'',4''-dimethoxyphenyl)-tetrahydrofuran [**2**], and 3',4'-dimethoxybenzoic acid-(3'',4''-dimethoxyphenyl)-2-methyl-3-oxobutyl ester [**3**], with the structurally related veraguensin and galgravin also being isolated. Compounds **1–3** have not been previously reported and the 2,5-phenyl ring disubstitution in this type of lignan is described for the first time.

From its spectral data, it was apparent that compound **1** is a 2,5-diaryl-3,4-dimethyltetrahydrofuran derivative.



1 R = OCH₃,
2 R = H



3

¹Biogeographic zone comprised of Madeira, the Canary Islands, the Cape Verde Islands, and the Azores.

TABLE 1. ¹H-Nmr Data of Compounds 1-3.^a

Proton	Compound		
	1	2	3
H-1			5.95 (d, 10.0)
H-2	5.48 (d, 4.4)	5.48 (d, 4.4)	3.22 (m)
H-3	2.46 (m)	2.46 (m)	
H-4	2.46 (m)	2.46 (m)	2.25 (s)
H-5	4.66 (d, 9.2)	4.67 (d, 9.2)	
H-2'			7.49 (d, 2.0)
H-3'	6.86 (s)	6.86 (s)	
H-4'	6.86 (s)	6.86 (s)	
H-5'			6.86 (d, 8.4)
H-6'	6.92 (s)	6.93 (s)	7.64 (dd, 8.4, 2.0)
H-2''	6.63 (s)	6.96 (d, 1.8)	6.93 (d, 1.6)
H-5''		6.85 (d, 9.2)	6.85 (d, 8.4)
H-6''	6.63 (s)	6.92 (dd, 9.2, 1.8)	7.00 (dd, 8.4, 1.6)
Me-2			0.98 (d, 7.2)
Me-3	1.02 (d, 6.8)	1.02 (d, 6.4)	
Me-4	0.63 (d, 6.4)	0.63 (d, 7.2)	
MeO-	3.82 (s)	3.85 (s)	3.86 (s)
	3.84 (s)	3.88 (s)	3.89 (s)
	3.88 (s)	3.89 (s)	3.90 (s)
	3.90 (s)	3.90 (s)	3.93 (s)

^aChemical shifts are expressed in δ values, with multiplicities and J values (Hz) in parentheses.

From the ¹H-nmr (Table 1) and ¹³C-nmr (Table 2) data, the magnetic equivalence of the H-3 and H-4 protons and the lack of equivalence of the H-2 and H-5 benzylic protons suggested that one of the aryl groups is *trans* to the other three substituents of the tetrahydrofuran ring. 2D ROESY nmr data (9) showed correlations between the two methyl doublets (δ 0.63 and 1.02) and H-5 (δ 4.66), H-5 with H-2'', H-6'' (δ 6.63), and H-2 with signals at δ 6.86 and 6.92. Thus, it was apparent that the *trans* aryl group is tri-substituted and was affixed to C-5. The signals at δ 6.86 (2H) and 6.91 (1H) clearly belonged to the two-substituted aryl rings. However, the splitting patterns and chemical shifts of these signals differed from the usual veratric system in related lignans and pointed to a 2,5-substitution model found in a few natural products (10-13), which clearly does not follow the established biogenetic route for lignans and neolignans (14-17). 2,5-Dimethoxybenzyl alcohol was used as a

model compound for comparison with **1** and their ¹H-nmr data were almost superimposable as far as the aromatic system is concerned.

The ¹H-nmr data of **2** showed the characteristic features of a 2,5-diaryl-3,4-dimethyltetrahydrofuran lignan. From the 2D ROESY data and the coupling constants of H-2, H-3 and H-4, H-5 (Table 1) were apparent, and therefore the relative stereochemistry is as depicted in **2**. This structure coincides with that of ganschisandrin, isolated by Yue *et al.* from *Schisandra sphenantera* (18). However, significant differences in optical activity, ¹³C-nmr data, and the aromatic region of the ¹H-nmr spectrum were observed. A careful study of the ¹H-nmr spectrum of **2** led us to the conclusion that one of the aromatic rings of **2** has two methoxy groups at C-3, C-4, and a veratric system, while in the other aryl group 2,5-disubstitution was apparent.

The 2D COSY nmr spectrum of **2** showed a multiplet (δ 3.22, 1H) couple

TABLE 2. ¹³C-Nmr Data for Compounds 1-3.^a

Carbon	Compound		
	1	2	3
C-1			78.05
C-2	84.87	84.77	33.05
C-3	43.48	43.46	209.78
C-4	47.53	47.55	29.69
C-5	85.97	85.69	
C-1'	137.35	135.70	122.53
C-2'	148.74	147.79	112.17
C-3'	110.89	110.86	
C-4'	118.06	118.09	
C-5'	145.35	148.49	111.07
C-6'	109.37	109.41	123.45
C-1''	134.25	133.26	130.73
C-2''	102.96	109.11	110.26
C-3''	142.40	148.71	
C-4''	139.35	149.14	
C-5''	140.00	118.50	111.07
C-6''	102.96	110.97	119.96
Me-2			13.65
Me-3	12.05	11.88	
Me-4	9.45	9.45	
MeO	55.92	55.89	55.88
	56.14	55.95	55.97
	60.83		56.03

with both a doublet (δ 0.98, 3H) and a second doublet (δ 5.95, 1H), all of which could be assigned to a sequence $-O-CH(Ar)-CH-CH_3$, similar to **1** and **2**. In the ¹H-nmr spectrum, a singlet (δ 2.25, 3H) of a methyl ketone and four singlets assignable to four methoxy groups were observed. Between δ 7.64 and 6.85 signals appeared for six aromatic protons, in good agreement with the occurrence of two 3,4-disubstituted aryl groups, although a withdrawing group attached to the aromatic ring was considered likely to be responsible for the downfield-shifted signals at δ 7.64 (1H, dd, $J_1=8.4$ Hz, $J_2=2.0$ Hz) and δ 7.49 (1H, d, $J=2.0$ Hz). Signals at δ 109.78 and 165.25 ppm in the ¹³C-nmr spectrum were assigned to ester and ketone carbonyl groups, respectively. These data are in good accordance with structure **1**, a compound which may derive from a tetrahydrofuran lignan by oxidative cleavage. A similar oxidation was postulated to explain the structure of magnostellin B, isolated from *Magnolia stellata* (19).

In addition to these three new products, two lignans of the same type were isolated and their spectroscopic data were closely comparable with those of the previously reported veraguensin (20) and galgravin (21).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—¹H- and ¹³C-nmr spectra were taken on a Bruker AMX-400 using TMS as internal standard. Ms were obtained on a VG Micromass ZAB-2F spectrometer. Hplc were run in a Shimadzu LC-9A instrument. Si gel (Kieselgel 60, Merck) and Sephadex LH-20 were used for cc, and Kieselgel 60F₂₅₄ (Merck) was employed for tlc. Anhydrous Na₂SO₄ was used for drying solvents, and all solvents were evaporated under reduced pressure.

PLANT MATERIAL.—*Ocotea foetens* (Ait.) Benth. et Hook f. was collected from Las Mercedes Forest in Tenerife, Canary Islands, authenticated by Dr. Pedro Pérez de Paz, Faculty of Pharmacy, University of La Laguna, Spain, and a voucher specimen deposited in the Department of Biology of the University of La Laguna.

EXTRACTION AND ISOLATION.—The air-dried powdered leaves were extracted with EtOH, and the raw extract was successively chromatographed with *n*-C₆H₁₄ and increasing amounts of EtOAc mixtures and finally with pure EtOAc. The *n*-C₆H₁₄-EtOAc (7:3) extract was chromatographed on Sephadex LH-20 and eluted with MeOH. From one fraction of this last column a compound was isolated which seemed to be pure on tlc but on hplc gave five products: **1** (2.2 mg), **2** (2.5 mg), **3** (3.2 mg), veraguensin (4.8 mg), and galgravin (3.4 mg).

2-(2',5'-Dimethoxyphenyl)-3,4-dimethyl-5-(3'',4'',5''-trimethoxyphenyl)-tetrahydrofuran [1].— $[\alpha]_D^{20} = -18.97^\circ$ ($c=1.6$, CHCl₃); cims (C₂H₅), m/z 431 [M+29]⁺ (7), 403 [M+1]⁺ (100), 385 (12), 265 (27), 236 (19), 235 (19), 208 (10); C₂₃H₃₀O₆, hrms, m/z (found 402.2039, requires 402.2042); ¹H- and ¹³C-nmr data (400 MHz, CDCl₃), see Tables 1 and 2, respectively.

2-(2',5'-Dimethoxyphenyl)-3,4-dimethyl-5-(3'',4''-dimethoxyphenyl)-tetrahydrofuran [2].— $[\alpha]_D^{20} = +73.7^\circ$ ($c=1.9$, CHCl₃); cims (C₂H₅), m/z 401 [M+29]⁺ (18), 373 [M+1]⁺ (100), 236 (14), 235 (98), 217 (10), 206 (31), 167 (18); C₂₂H₂₈O₆, hrms, m/z (found 372.1936, requires 372.1939); ¹H- and ¹³C-nmr data, see Tables 1 and 2, respectively.

3',4'-Dimethoxybenzoic acid-(3'',4''-dimethoxyphenyl)-2-methyl-3-oxobutyl ester [3].—Eims, m/z 402 [M]⁺ (9), 257 (6), 237 (8), 220 (13), 179 (22), 167 (100), 149 (36); C₂₂H₂₆O₇, hrms, m/z (found

402.2043, requires 402.2042); ^1H - and ^{13}C -nmr data, see Tables 1 and 2, respectively.

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LITERATURE CITED

1. O. Eriksson, A. Hansen, and P. Sundin, "Flora of Macaronesia. Checklist of Vascular Plants." Botanical Garden and Museum, University of Oslo, Oslo, 1979, 2nd Ed., p. 66.
2. D. Bramwell and Z. Bramwell, "Flora Silvestre de Las Islas Canarias," Editorial Rueda, Madrid, 1990, p. 104.
3. L. Ceballos Fernández de Córdoba and F. Ortuño Medina, "Vegetación y Flora Forestal de las Canarias Occidentales," Excmo, Cabildo Insular de Tenerife, Tenerife, 1976, p. 325.
4. D.A. Whiting, *Nat. Prod. Rep.*, **2**, 191 (1985).
5. R.S. Ward, *Nat. Prod. Rep.*, **7**, 1 (1993).
6. O.R. Gottlieb, in: "Proceedings of the First International Congress on Medical Plant Research, Section A, the University of Munich, Sept. 1976." Ed. by H. Wagner and P. Wolff, Springer-Verlag, New York, 1977, p. 227.
7. V.R. Koppaka and F.M. Alvarez, *Tetrahedron Lett.*, **24**, 4947 (1983).

8. F. El-Feraly, S. Cheatham, and R.L. Breedlove, *J. Nat. Prod.*, **46**, 493 (1983).
9. A. Estévez-Braun, R. Estévez-Reyes, and A.G. González, *Tetrahedron*, **50**, 5203 (1994).
10. F. Cullmann, F.K. Adam, and H. Becker, *Phytochemistry*, **34**, 831 (1993).
11. J.N. Roitman and E. Wollenweber, *Phytochemistry*, **33**, 936 (1993).
12. M. Iinuma, J. Yokoyama, M. Ohyama, M. Mizuno, and N. Ruangrunsi, *Phytochemistry*, **33**, 203 (1993).
13. N.C. Barnah, R.P. Sharma, G. Thyagarajan, W. Herz, and S.V. Govindan, *Phytochemistry*, **18**, 2003 (1979).
14. D.A. Whiting, *Nat. Prod. Rep.*, **2**, 204 (1985).
15. I. Frias, J.M. Siverio, C. González, J.M. Trujillo, and J.A. Pérez, *Biochem. J.*, **273**, 109 (1991).
16. N.G. Lewis and E. Yamamoto, *Ann. Rev. Plant Physiol., Plant Mol. Biol.*, **41**, 455 (1990).
17. L.B. Davin and N.G. Lewis, *Rec. Adv. Phytochemistry*, **26**, 325 (1992).
18. Y.-M. Yeu, Y.-Z. Chen, S.-M. Hua, Y.-L. Cheng, and Y.-X. Cui, *Phytochemistry*, **28**, 1774 (1989).
19. T. Iida, Y. Noro, and K. Ito, *Phytochemistry*, **22**, 211 (1983).
20. N.S. Crossley and C. Djerassi, *J. Chem. Soc.*, 1459 (1962).
21. G.H. Hughes and E. Ritchie, *Aust. J. Chem.*, **7**, 104 (1954).

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