

NEOLIGNANS FROM STEM BARK OF *OCOTEA VERAGUENSIS*

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Abstract—The stem bark of *Ocotea veraguensis* has yielded nine neolignans of which five appear to be novel. The new neolignans, which were identified on the basis of spectral characteristics, are* (7*S*,8*R*,1'*S*,2'*S*,3'*R*,4'*S*)- Δ^8 -2',4'-dihydroxy-3,3',5'-trimethoxy-4,5-methylenedioxy-1',2',3',4'-tetrahydro-7.3',8.1'-neolignan, (7*S*,8*R*,1'*S*,3',4'*S*)- Δ^8 -4,4'-dihydroxy-3,3',5'-trimethoxy-1',2',3',4'-tetrahydro-2'-oxo-7.3',8.1'-neolignan, (7*S*,8*S*,1'*R*)- Δ^8 -3',5'-dimethoxy-3,4-methylenedioxy-1',4'-dihydro-4'-oxo-7.0.2',8.1'-neolignan, (7*S*,8*S*,1'*R*)- Δ^8 -1'-methoxy-3,4-methylenedioxy-1',6'-dihydro-6'-oxo-7.0.4',8.3'-neolignan and (7*S*,8*S*)- Δ^8 -2',6'-dimethoxy-3,4-methylenedioxy-7.0.3',8.4',1'.0.7'-neolignan.

INTRODUCTION

Ocotea veraguensis Mez is an evergreen tree of the family Lauraceae indigenous to the forests of Central America [2]. Previous investigations by Crossley and Djerassi [3] led to the isolation of a tetrahydrofuranoid lignan, veraguensin (1), which was later synthesised [4]. As part of a continuing investigation of plants of the Santa Rosa National Park in Costa Rica [5] we have reinvestigated the stem bark of this species and have isolated nine neolignans, the structures of which are reported here.

RESULTS AND DISCUSSION

Column chromatography of a petrol extract of stem bark over silica gel followed, where necessary, by preparative centrifugal TLC gave the nine neolignans.

Five of the neolignans proved to be of the bicyclo(3.2.1) octanoid type. Two of these were identified as 2 and 3, both previously isolated from *O. catharinensis* [6] and differing from each other only in the stereochemistry of the 4'-hydroxy group, *exo* (α) in 2 and *endo* (β) in 3. ¹H NMR data for 2 and 3 had previously only been recorded at 60 MHz, complete assignments of the high-field spectra are given here (Table 1). In the course of the ¹H NMR analysis of 2 a NOE study was undertaken, the results of which are shown in Table 2. The results of the NOE were of particular value in confirming the *trans* substitution about C-7 and C-8 and the *endo* orientation of H-4' and H-7. In addition H-2' showed NOE with H-7' and H-8' but not with H-2 and H-6, indicating that H-2' must be as depicted in structure 2.

A third neolignan gave very similar spectral characteristics to 2 except for the presence of an additional methoxy substituent which was assigned to C-5 on the aromatic nucleus (¹H NMR data, Table 1 and *m/z* 151 instead of *m/z* 121) indicating the apparently novel structure 4. The absolute stereochemistry of 4 was established

from its ORD spectrum which was similar to 4'-oxo-5',6'-dihydro neolignans with identical centres of asymmetry [7, 8].

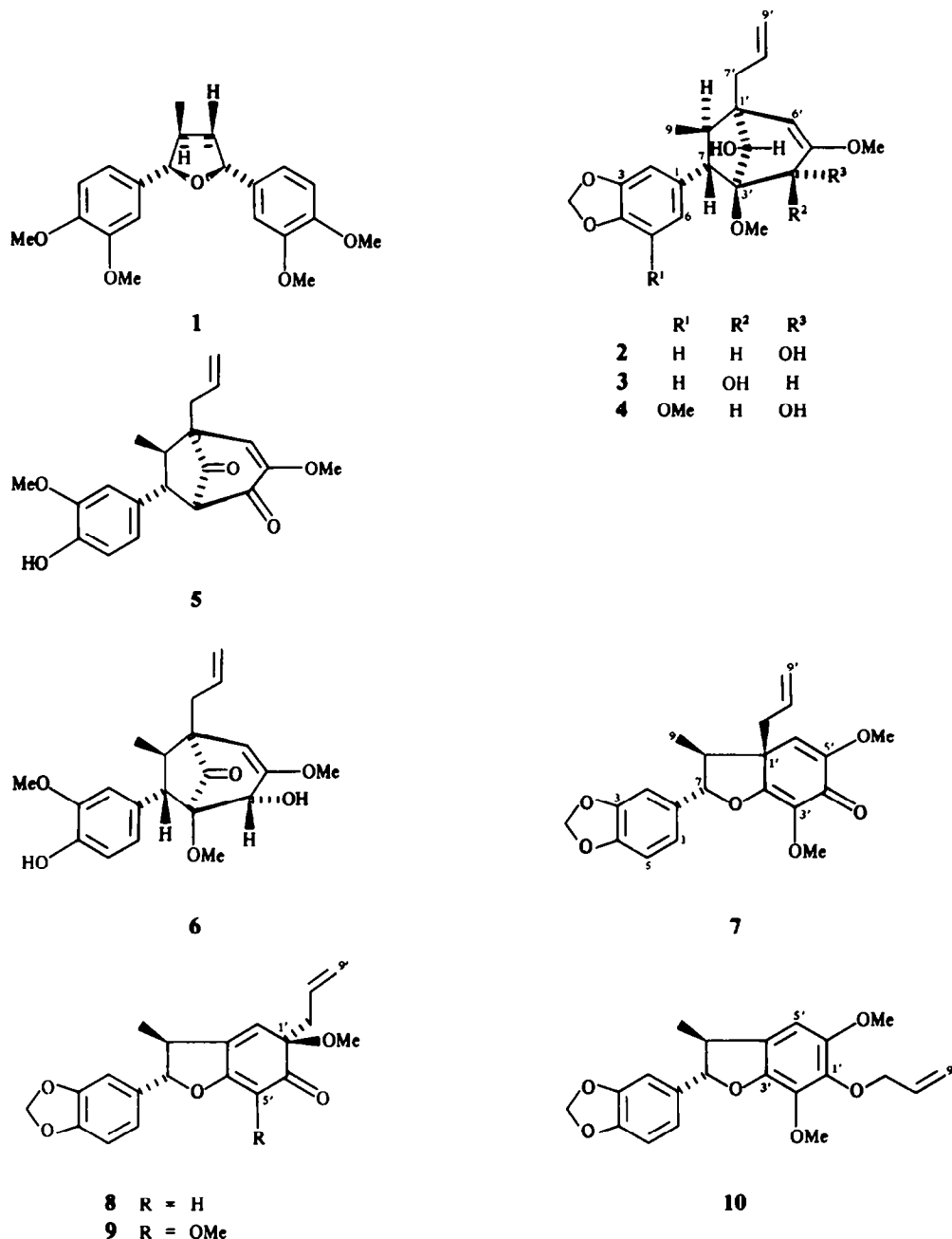
The two other neolignans of this class had carbonyl bands in their IR spectra. One, showing two carbonyls, was identified as the known compound 5 previously reported from *Aniba* sp. [9]. The second showed a single carbonyl band at 1760 cm⁻¹, indicative of a 2'-oxo rather than a 4'-oxo skeleton. A fragment at *m/z* 123 [C₇H₇O₂]⁺ in the mass spectrum indicated a guaiacyl substituent at C-7. This was confirmed by the ¹H NMR spectrum (Table 1). An NOE experiment performed on this compound (Table 2) showed a strong interaction between H-7 and H-4' comparable to 2, requiring their *endo* placement and thus the H-4' hydroxy must be *exo* orientated. On this basis the neolignan is assigned structure 6. The position of the aromatic methoxy substituent at C-3 and not C-4 was substantiated by its enhancement on irradiation of H-2. Although no direct ORD comparison was possible with compounds showing a comparable pattern of asymmetry the stereochemistry is presumed to be the same as the other four bicyclooctane lignans isolated.

The remaining four neolignans were of the benzofuranoid type. The novel compound 7 with the allyl substituent at the ring junction (C-1') was identified on the basis of its ¹H NMR spectrum which indicated the presence of a piperonyl nucleus and *trans* substitution between C-7 and C-8. The absolute stereochemistry was established as 7*S*,8*S*,1'*R* by ORD [10].

Two dihydrobenzofuranoid neolignans with geminal allyl and methoxy substituents were identified as 8 and 9; absolute stereochemistry was again established by ORD [6, 10–12]. The latter has previously been reported from *O. catharinensis* [6] but structure 8 appears to be novel. Lignans comparable to 8 but with different substitution in the aryl nucleus have been reported from *Aniba* and *Nectandra* sp. [1, 12, 13] and the C-1' epimer of 8 from both *Aniba burchellii* [11] and *A. terminalis* [14].

The final compound gave spectral characteristics for a piperonyl nucleus, *trans* substitution of aryl and methyl

*Nomenclature of neolignans follows ref. [1].



units at C-7 and C-8 (7*S*,8*S* from ORD [10]), *O*-allyl and two methoxy substituents and, from the ¹³C NMR spectrum, required placement of four adjacent oxygen substituents on an aromatic nucleus. A resonance at 57.0 ppm was indicative of the in-plane methoxy substituent at C-6'. Irradiation of the 3.81 methoxy resonance gave a 16% NOE enhancement for H-5' together with a small (*ca* 1%) enhancement for H-7'. This is in complete agreement with the dihydrobenzofuranoid neolignan type [15] and with structure 10, which again appears to be novel. Compounds 7, 9 and 10 can be regarded as forming a biosynthetic sequence in which 7 is converted to 9 by a Cope rearrangement and then 9 is converted to 10 by a *retro*-Claisen rearrangement [1].

EXPERIMENTAL

Mps uncorr. UV and ORD: MeOH. IR: KCl discs, EIMS: 70 eV, direct probe insert, 120–140°. Petrol refers to bp 60–80° fraction.

Plant material. Stem bark was collected from trees within the Santa Rosa National Park, Guanacaste Prov., Costa Rica in 1983 [2]. A voucher specimen is deposited at the Herbarium of the Missouri Botanic Gardens, St. Louis, U.S.A.

Extraction and isolation of neolignans. Powdered stem bark (600 g) was extracted with petrol, then CHCl₃ and finally with MeOH. On standing the petrol extract yielded a brown ppt which was subjected to CC over silica gel. Elution with toluene containing 15% EtOAc and a trace of HOAc gave a mixture of

Table 1. ¹H NMR spectra of neolignans isolated from *Ocotea veraguensis*. All spectra run in CDCl₃ with TMS as int. standard. Coupling constants in parentheses

Proton	2	4	3	6	5	7	8	9	10
H-2	7.09 s	6.83 d (2.2)	6.96 d (1.6)	6.66 d (2.0)	6.58 d (2.1)	6.79 d (1.4)	6.82 s	6.83 d (1.6)	6.89 d (2.2)
H-5	6.71 s	—	6.71 d (8.0)	6.81 d (8.0)	6.82 d (8.0)	6.87 d (9.1)	6.82 s	6.83 d (8.0)	6.81 d (8.5)
H-6	6.71 s	6.87 d (2.2)	6.73 dd (8.0, 1.6)	6.68 dd (8.0, 2.0)	6.59 dd (8.0, 2.1)	6.84 dd (9.1, 1.4)	6.82 s	6.86 dd (8.0, 1.6)	6.88 dd (8.5, 2.2)
O-CH ₂ -O	5.95AB q (1.4)	5.95AB q (1.4)	5.91AB q (1.6)	—	—	5.98 s	6.00 s	6.00 s	5.96 s
OMe	—	3.89 s	—	3.86 s	3.85 s	—	—	—	—
H-7	2.12 d (8.7)	2.12 d (8.9)	3.12 d (9.3)	2.52 d (8.7)	2.54 dd (7.6, 1.3)	5.18 d (9.8)	5.07 d (8.7)	5.05 d (8.6)	5.19 d (9.3)
H-8	2.30 dq (8.7, 6.6)	2.34 dq (8.9, 6.7)	2.50 dq (9.3, 6.5)	2.04 dq (8.7, 6.5)	2.14 dq (7.6, 6.5)	2.24 dq (9.8, 6.9)	3.12 dq (8.7, 6.7)	3.09 dq (8.6, 6.7)	3.33 dq (9.3, 6.7)
H-9	0.78 d (6.6)	0.80 d (6.7)	0.82 d (6.5)	0.98 d (6.5)	1.07 d (6.7)	1.15 d (6.9)	1.38 d (6.7)	1.35 d (6.7)	1.34 d (6.7)
H-2'	3.98 s	3.98 s	3.75 s	—	—	—	5.69 s	5.98 s	—
H-3'	—	—	—	—	3.56 d (1.3)	—	—	—	—
H-4'	4.28 s	4.29 s	4.72 s	4.70 d (1.6)	—	—	—	—	—
H-5'	—	—	—	—	—	—	6.20 s	—	6.42 br s
H-6'	4.56 s	4.55 s	4.46 s	4.55 s (1.6)	5.79 s	5.42 s	—	—	—
H-7'	2.46 dd (13.4, 6.5)	2.44 dd (14.0, 6.5)	2.44 dd (14.0, 7.1)	2.36 dd (14.0, 7.3)	2.58 dd (14.0, 7.1)	2.46 dd (13.5, 7.6)	2.53 dd (14.2, 7.3)	2.50 dd (14.0, 7.1)	4.53 dd (14.0, 5.8)
H-8'	5.85 ddt (16.1, 10.0, 6.6)	5.87 ddt (16.0, 10.0, 7.1)	5.86 ddt (16.0, 10.0, 7.1)	5.85 ddt (16.4, 10.4, 7.1)	5.98 ddt (16.1, 10.0, 7.1)	5.46 ddt (16.6, 9.3, 7.0)	5.72 ddt (17.0, 10.4, 7.3)	5.75 ddt (17.0, 10.2, 7.1)	6.16 ddt (16.0, 10.0, 5.8)
H-9' trans	5.15 dd (16.1, 2.2)	5.05 dd (16.0, 2.2)	5.19 dd (16.0, 2.2)	5.13 dd (16.4, 2.2)	5.25 dd (16.1, 2.2)	5.04 dd (16.6, 2.0)	5.08 dd (17.0, 2.3)	5.09 dd (17.0, 2.2)	5.32 dd (16.0, 2.2)
H-9' cis	5.09 dd (10.0, 2.2)	5.04 dd (10.0, 2.2)	5.03 dd (10.0, 2.2)	5.11 dd (10.4, 2.2)	5.16 dd (10.0, 2.2)	5.06 dd (9.3, 2.0)	5.04 dd (10.4, 2.3)	5.06 dd (10.2, 2.2)	5.24 dd (10.0, 2.2)
1'-OMe	—	—	—	—	—	—	3.14 s	3.14 s	—
2'-OMe	—	—	—	—	—	—	—	—	3.81 s
3'-OMe	2.84 s	2.86 s	3.18 s	2.82 s	—	3.82 s	—	—	—
5'-OMe	3.62 s	3.62 s	3.62 s	3.66 s	3.73 s	3.68 s	—	3.84 s	—
6'-OMe	—	—	—	—	—	—	—	—	3.98 s

All spectra run at 250 MHz except for 5 and 10 which were run at 360 MHz.

*The protons at H-7' were generally non-equivalent but showed identical coupling constants to H-8'. The chemical shift given is the mean for the two sets of signals which were never more than 0.1 ppm apart.

Table 2. Nuclear Overhauser enhancements for experiments on 2 and 6 (360 MHz)

	Proton irradiated	Enhancement (%)							
		H-2	H-6	H-7	H-8	H-4'	H-6'	H-7'	H-8'
2	9-Me	—	—	3.5	12.0	—	2.5	—	—
	H-7	3.0	3.0	—	—	9.9	—	—	—
	H-2'	—	—	—	—	—	—	1.0	4.0
6	9-Me	—	—	5.0	6.0	—	3.0	—	—
	H-2	—	—	3.5	3.0	—	—	—	1.5
	H-7	5.0	7.0	—	—	11.0	—	—	—

compounds which were sepd by centrifugal prep. TLC (silica gel), eluting with 6% EtOAc and 1% HOAc in toluene to give 5 (40 mg), and 8% EtOAc to give 8 (55 mg) followed by 9 (30 mg). Further elution of the column with 20% EtOAc yielded 2 (70 mg) followed by 3 (10 mg) and then 4 (35 mg). Elution with 22%

EtOAc gave 7 (26 mg) and then with 25% EtOAc gave 6 (35 mg). The supernatant petrol extract was concd and subjected to centrifugal prep. TLC (same system, 2% EtOAc) to give 10 (200 mg).

(7S,8R,1'S,2'S,3'R,4'S)-Δ⁸-2',4'-Dihydroxy-3',5'-dimethoxy-

3,4-methylenedioxy-1',2',3',4'-tetrahydro-7,3',8,1'-neolignan (2). Amorphous solid, $[\alpha]_D^{21} + 10^\circ$ (c 0.13, MeOH). Found: $[M]^+$ 374.1724; $C_{21}H_{26}O_6$ requires 374.1729. UV, IR, ^{13}C NMR, EIMS in agreement with published data [6]. 1H NMR, see Table 1. 2-diacetate. Found: $[M]^+$ 458.1919; $C_{25}H_{30}O_8$ requires 458.1921.

(7S,8R,1'S,2'S,3'R,4'R)- Δ^8 -2',4'-Dihydroxy-3',5'-dimethoxy-3,4-methylenedioxy-1',2',3',4'-tetrahydro-7,3',8,1'-neolignan (3). Amorphous solid, $[\alpha]_D^{21} + 11^\circ$ (c 0.07, MeOH). Found: $[M]^+$ 374.1743; $C_{21}H_{26}O_6$ requires 374.1729. UV, IR and EIMS in good agreement with published data [6]. 1H NMR, see Table 1.

(7S,8R,1'S,2'S,3'R,4'S)- Δ^8 -2',4'-Dihydroxy-3,3',5'-trimethoxy-4,5-methylenedioxy-1',2',3',4'-tetrahydro-7,3',8,1'-neolignan (4). Amorphous solid, $[\alpha]_D^{21} + 8^\circ$ (c 0.18 MeOH). Found: $[M]^+$ 404.1839; $C_{22}H_{28}O_7$ requires 404.1835. UV λ_{max} nm: 235, 285. IR ν_{max} cm^{-1} : 3450, 2950, 1660, 1490, 1440, 1380. 1H NMR, see Table 1. EIMS m/z (rel. int.): 404 $[M]^+$ (100), 237 (15), 195 (25), 193 (30), 192 (30), 179 (67), 165 (31), 151 (21). ORD (c 4 mg/10 ml, MeOH): $[\phi]_{340}^{pk} + 2424$, $[\phi]_{320}^0$, $[\phi]_{310}^0 - 2222$, $[\phi]_{295}^0$, $[\phi]_{285}^{pk} + 4040$, $[\phi]_{258}^0$, $[\phi]_{252}^0 - 2020$, $[\phi]_{245}^0$.

(7R,8R,1'S,3'S)- Δ^8 -4-Hydroxy-3,5'-dimethoxy-1',2',3',4'-tetrahydro-2',4'-dioxo-7,3',8,1'-neolignan (5). Oil $[\alpha]_D^{21} - 88^\circ$ (c 0.05, MeOH). Found: $[M]^+$ 342.1418; $C_{20}H_{22}O_5$ requires 342.1467. UV, IR, EIMS, ORD in agreement with lit. [10]. 1H NMR, see Table 1.

(7S,8R,1'S,3'S,4'S)- Δ^8 -4,4'-Dihydroxy-3,3',5'-trimethoxy-1',2',3',4'-tetrahydro-2'-oxo-7,3',8,1'-neolignan (6). Oil, $[\alpha]_D^{21} + 29^\circ$ (c 0.09, MeOH). Found: $[M]^+$ 374.1726; $C_{21}H_{26}O_6$ requires 374.1729. UV λ_{max} nm: 220, 280. IR ν_{max} cm^{-1} : 3450, 2950, 1760, 1660, 1610, 1510, 1460, 1380. 1H NMR, see Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$) ppm: s at 49.2 (C-1'), 83.3 (C-3'), 130.2 (C-1), 144.9, 146.6 (C-3, C-4), 154.6 (C-5'), 210.2 (C-2'), d at 48.8 (C-8), 52.5 (C-7), 78.2 (C-4'), 100.4 (C-6'), 111.7, 114.0 (C-2, C-5), 122.4 (C-6), 133.8 (C-8'), t at 35.3 (C-7'), 118.0 (C-9'), q at 12.5 (C-9), 51.3 (3'-OMe), 55.7, 56.1 (3-OMe, 5'-OMe). EIMS m/z (rel. int.): 374 $[M]^+$ (43), 333 (35), 210 (20), 169 (100), 164 (14). ORD (c 6 mg/10 ml): $[\phi]_{360}^{pk} + 1351$, $[\phi]_{345}^0$, $[\phi]_{318}^0 - 2432$, $[\phi]_{302}^0$, $[\phi]_{292}^0 + 6756$, $[\phi]_{276}^{sh} + 8108$, $[\phi]_{250}^{pk} + 10810$.

(7S,8S,1'R)- Δ^8 -3',5'-Dimethoxy-3,4-methylenedioxy-1',4'-dihydro-4'-oxo-7.O.4',8,3'-neolignan (7). Oil, $[\alpha]_D^{21} + 26^\circ$ (c 0.08, MeOH). Found: $[M]^+$ 370.1394; $C_{21}H_{22}O_6$ requires 370.1416. UV λ_{max} nm: 240, 270. IR ν_{max} cm^{-1} : 2850, 1650, 1610, 1500, 1450, 1350, 1240, 1100, 1040, 920. 1H NMR, see Table 1. EIMS m/z (rel. int.): 370 $[M]^+$ (87), 340 (23), 329 (100), 297 (15), 208 (92), 207 (54), 162 (30), 135 (49), 77 (23), 41 (18). ORD (c 1 mg/5 ml): $[\phi]_{321}^{pk} + 746$, $[\phi]_{315}^0$, $[\phi]_{295}^0 - 4776$, $[\phi]_{255}^{pk} + 298$.

(7S,8S,1'R)- Δ^8 -1'-Methoxy-3,4-methylenedioxy-1',6'-dihydro-6'-oxo-7.O.4',8,3'-neolignan (8). Oil, $[\alpha]_D^{21} + 60^\circ$ (c 0.05, MeOH). Found: $[M]^+$ 340.1306; $C_{20}H_{20}O_5$ requires 340.1311. UV λ_{max} nm: 239, 290, 315. IR ν_{max} cm^{-1} : 3400, 2950, 1610, 1600, 1440. 1H NMR, see Table 1. ^{13}C NMR (90.56 MHz, $CDCl_3$) ppm: s at 80.8 (C-1'), 131.7 (C-1), 140.3 (C-3'), 148.3 (C-3, C-4), 172.1 (C-4'), 199.4 (C-6'), d at 42.6 (C-8), 93.8 (C-7), 99.7 (C-5'), 106.4, 108.2 (C-2, C-5), 120.1 (C-6, C-2'), 134.2 (C-8'), t at 45.0 (C-7'), 101.3 (O-CH₂-O), 119.1 (C-9'), q at 16.2 (C-9), 53.4 (1'-OMe). EIMS m/z (rel. int.): 340 $[M]^+$ (100), 310 (22), 299 (85), 239 (22), 177 (13), 162 (27). ORD (c 4 mg/10 ml): $[\phi]_{383}^{pk} + 10256$, $[\phi]_{364}^0$, $[\phi]_{333}^{pk} - 20512$, $[\phi]_{306}^0$, $[\phi]_{285}^{pk} + 25641$, $[\phi]_{230}^0$.

(7S,8S,1'R)- Δ^8 -1',5'-Dimethoxy-3,4-methylenedioxy-1',6'-di-

hydro-6'-oxo-7.O.4',8,3'-neolignan (9). Oil $[\alpha]_D^{21} + 40^\circ$ (c 0.06, MeOH). Found: $[M]^+$ 370.1403; $C_{21}H_{22}O_6$ requires 370.1416. UV, IR, EIMS and ORD in agreement with lit. [6]. 1H NMR, see Table 1.

(7S,8S)- Δ^8 -2',6'-Dimethoxy-3,4-methylenedioxy-7.O.3',8,4',1'.O.7'-neolignan (10). Plates from petrol-EtOAc, mp 68–70°, $[\alpha]_D^{21} - 16^\circ$ (c 0.15, MeOH). Found: $[M]^+$ 370.1403; $C_{21}H_{22}O_6$ requires 370.1416. UV λ_{max} nm: 232, 288. IR ν_{max} cm^{-1} : 2900, 1600, 1460, 1350. 1H NMR, see Table 1. ^{13}C NMR (90.56 MHz, $CDCl_3$) ppm: s at 126.6 (C-4'), 134.4 (C-1), 138.2, 140.3 (C-1', C-6'), 144.5 (C-3'), 147.4, 147.8, 148.2 (C-2', C-3, C-4), d at 45.9 (C-8), 92.8 (C-7), 102.4 (C-5'), 106.4, 107.4 (C-2, C-5), 119.7 (C-6), 134.4 (C-8'), t at 74.7 (C-7'), 100.9 (O-CH₂-O), 117.2 (C-9'), q at 17.6 (C-9), 57.0 (6'-OMe), 60.5 (2'-OMe). EIMS m/z (rel. int.) 370 $[M]^+$ (100), 329 (80), 207 (12), 164 (2), 135 (12). ORD (c 0.37 mg/5 ml): $[\phi]_{305}^0 - 4000$, $[\phi]_{295}^0$, $[\phi]_{288}^{pk} + 2500$, $[\phi]_{270}^0$.

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