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NEOLIGNANS FROM *VIROLA CARINATA* FRUIT*

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Key Word Index—*Virola carinata*, Myristicaceae, fruits, benzodioxan neolignans, eusiderin-E, β-aryloxy-arylpropane neolignans

Abstract—The fruits of *Virola carinata* contain the lignans (−)-cubebin, (−)-hinokinin and (+)-asarinin, besides four neolignans of the β-aryloxy-arylpropane type and two neolignans of the benzodioxane (eusiderin) type

INTRODUCTION

Virola carinata is one of the most widespread and abundant Myristicaceae species in the low regions of the Amazonian valley Several of its parts have indigenous medicinal uses [2] Previous studies demonstrated the occurrence in the trunk wood of 7,4′-dimethoxyflavone besides three tetralin type neolignans (+)-guaiacin (**1a**), (−)-isootobaphenol (**1b**) and (−)-galcatin (**1c**) [3], and in the bark of tryptamines [2] besides two biphenyl type neolignans, dehydrodieugenol (**2a**) and *O*-methyl-dehydrodieugenol (**2b**) [4], of three β-aryloxy-arylpropane type neolignans, (−)-carinatone (**3a**), carinatonol (**3b**) and carinatol (**3c**), of four benzofuran type neolignans carinatine (**4a**), carinatidin (**4b**), dihydrocarinatinol (**4c**) and dihydrocarinatidin (**4d**), of a β-aryloxy-arylpropanol type neolignan carinatidiol (**5**) and of a diaryl ether type neolignan dehydrodieugenol-B (**6**) [5–7] The present study revealed the presence in the fruit kernel of three known lignans, (−)-cubebin (**7a**), (−)-hinokinin (**7b**) and (+)-asarinin (**8**), all isolated previously from *V multinervia* [8], besides the β-aryloxy-arylpropane type neolignan **9a** and the benzodioxane type neolignan eusiderin, here designated eusiderin-A (**10a**) The latter compound, isolated previously from Myristicaceae [9] and Lauraceae [10] species, together with additional β-aryloxy-arylpropane type neolignans (**11a**, **11b**, **11d**) and another benzodioxane type neolignan (**12**) was also located in the pericarp

In order to facilitate comparisons among the different compounds numbering of neolignans follow the biogenetic rules outlined in a review [10]

RESULTS

Spectral comparisons (Tables 1 and 2) classified compound **12**, $C_{18}H_{14}O_2$ $OH(OMe)_3$, into the group of benzodioxane neolignans Its major distinction from the known eusiderins A (**10a**), B (**10b**) [10], C (**10c**) and D (**10d**) [11] refers to the presence of a propenyl instead of an allyl side chain The aryl/Me substituents are *cis*-oriented in eusiderins C and D and *trans*-oriented in eusiderins A and B, as in the novel compound **12** now designated eusiderin E Besides, the ORD curves of eusiderins A and E show positive Cotton effects around 300 nm

Spectral comparisons (Tables 3–6) classified compounds **9a**, **11a**, **11b** and **11d** into the group of 8-O-4′-neolignans Compounds **9a**, $C_{18}H_{15}O(OMe)_3CH_2O_2$, **11a**, $C_{18}H_{15}O(OMe)_4OH$, and the model compound **9b**, $C_{18}H_{15}O(OMe)_5$, a constituent of *Myristica fragrans* [12], share all ^{1}H NMR features due to the basic neolignan skeleton (Table 3), including the benzylic methylene bands, with the exception of the allyl derived signals in **9a** and **9b** vs the propenyl derived signals in **11a**

Compound **11b**, $C_{18}H_{14}O(OMe)_4(OH)_2$, and the model compounds **11c**, $C_{18}H_{15}O(OMe)_4OH$, a constituent of *V surinamensis* [13], and **9c**, $C_{18}H_{14}O(OMe)_5OH$, a constituent of *M fragrans* [12], share many ^{1}H NMR features due to the basic neolignan skeleton (Table 4), including the benzylic oxymethine bands The H-7, H-8 coupling constants for the *threo*-derivative **11c** (J = 8 Hz [13]) and the *erythro*-derivative **9c** (J = 3 Hz [12]), however, are diagnostically different and the novel **11b** (J = 4 Hz) must thus exist in the *erythro*-configuration Furthermore **11b** and **11c** are characterized by propenyl substituents, while **9c** is characterized by an allyl substituent

Compound **11d**, $C_{18}H_{13}O_2(OMe)_4OH$, and the synthetic model compounds **11e**, $C_{18}H_{14}O_2(OMe)_4$ [13], and **9d**, $C_{18}H_{13}O_2(OMe)_5$ [12], share many features, including the conjugated carbonyl bands (IR ν_{max} 1680 cm^{-1}) and the α-carbonylic oxymethine bands (Table 5) Here **11d** and **11e** possess propenyl substitution and **9d** allyl substitution

Comparisons with the model compounds show furthermore that all four new compounds, **9a**, **11a**, **11b**, **11d**, have identical oxygenation patterns and that, as expected, the NMR signals of H-2 and H-6 are shifted by *ca* 0 9 ppm to lower field (δ7 5) upon oxidation of the benzylic position to a ketone Thus the three OMe groups and the methylenedioxy-group of **9a** can only be located as shown

*Part XXV in the series "The Chemistry of Brazilian Myristicaceae" For Part XXIV see ref [1] Taken from part of the doctorate thesis presented by S H C to Universidade de São Paulo (1983)

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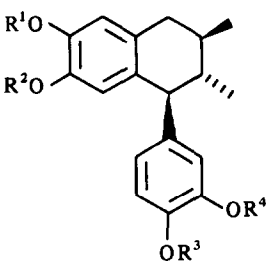
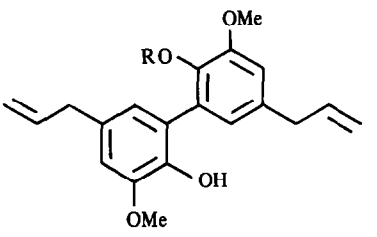


1a $R^1 = R^4 = Me, R^2 = R^3 = H$
1b $R^1 - R^2 = CH_2, R^3 = H, R^4 = Me$
1c $R^1 - R^2 = CH_2, R^3 = R^4 = Me$



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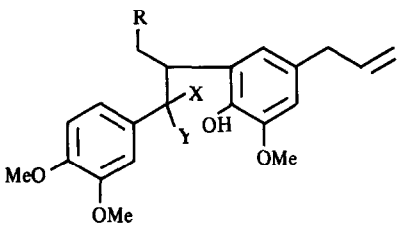
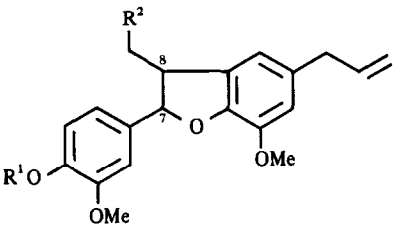
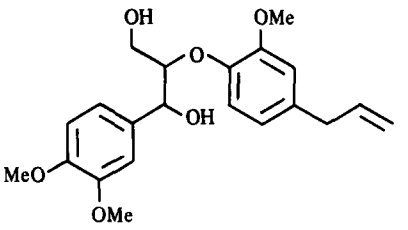
2b R = Me



3a R = H X − Y = O
3b R = OH, X − Y = O
3c R = X = H, Y = OH



4a $R^1 = Me, R^2 = H, \Delta^{7,8}$
4b $R^1 = R^2 = H, \Delta^{7,8}$
4c R = Me, R^2 = OH
4d $R^1 = R^2 = H$



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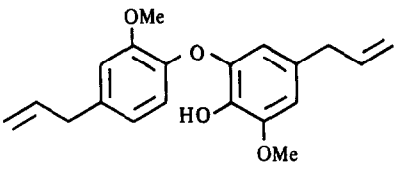

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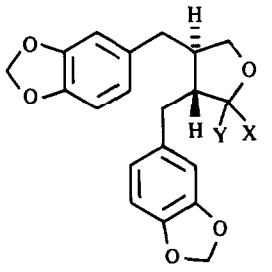
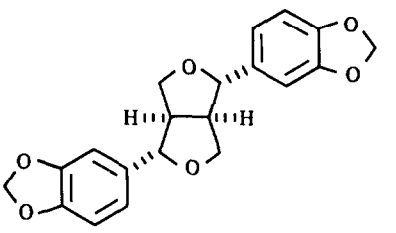


7a X = H, Y = OH
7b X − Y = O



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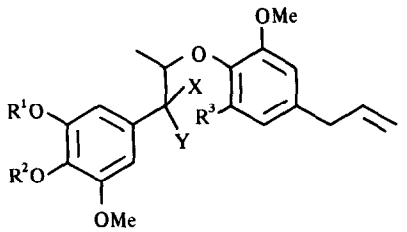
in the formula The ^{13}C NMR spectra (Table 6) demonstrate that the pairs of aromatic rings in **11a**, **11b** and **11d** are symmetrically substituted, a fact which defines the substitution of each pair by four OMe groups and one OH group as shown in the formulae

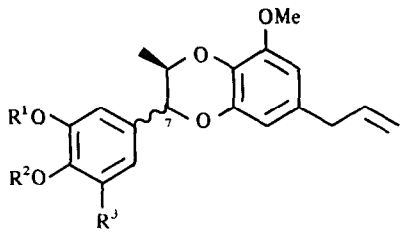
In accordance with these deductions, all mass spectra show intense peaks at *m/z* 194 and 193 assigned to ions derived from the oxydimethoxy-allyl (**9a**) and propenyl (**11a**, **11b**, **11d**) parts of the molecules An additional strong peak appears in this region (*m/z* 192) only in the case of the allyl-derivative (**9a** → **13**) Peaks at *m/z* 165 and 167 are assigned to tropylium ions *ex* **9a** and **11a**, while peaks at *m/z* 181 are caused by arylacylium ions *ex* **11b** and **11d**

DISCUSSION

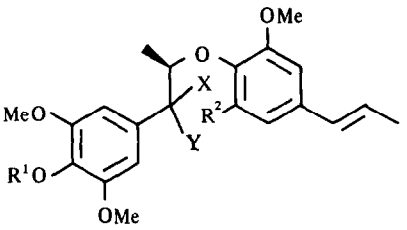
The data obtained so far indicate a differential distribution to exist for lignoids of different parts of *V carinata*



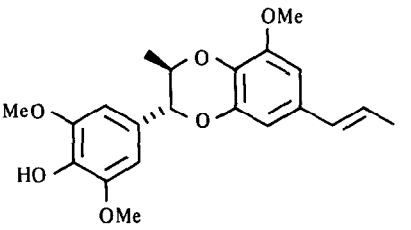
9a $R^1-R^2=CH_2$ $R^3=OMe$, X = Y = H
9b $R^1=R^2=Me$ $R^3=OMe$ X = Y = H
9c $R^1=R^2=Me$ $R^3=OMe$, X = H, Y = OH (*erythro*)
9d $R^1=R^2=Me$ $R^3=OMe$, X − Y = O



10a $R^1=R^2=Me$ $R^3=OMe$, 7-αAr
10b $R^1-R^2=CH_2$, $R^3=H$, 7-αAr
10c $R^1=R^2=Me$, $R^3=OMe$, 7-βAr
10d $R^1=R^2=Me$, $R^3=H$ 7-βAr



11a $R^1=X=Y=H$, $R^2=OMe$
11b $R^1=X=H$, $R^2=OMe$, Y = OH (*erythro*)
11c $R^1=Me$, $R^2=Y=H$, X = OH (*threo*)
11d $R^1=H$ $R^2=OMe$ X − Y = O
11e $R^1=Me$ $R^2=H$, X − Y = O



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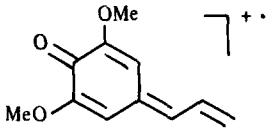

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Table 1 ^{1}H NMR chemical shifts (δ) of benzodioxane neolignans **10a**, **10b**, **12** (60 MHz, $CDCl_3$), **10c** and **10d** (270 MHz, $CDCl_3$)

	10a,b [11]		**10c,d** [9]		**12**	
H	δ	J	δ	J	δ	J
9	1 30*d*	6	1 15*d*	6 5	1 25*d*	6
8	3 9–4		4 60*dq*	2 5, 6 5	4 05–4 25	
7	4 58*d*	8	5 1*d*	2 5	4 55*d*	8
9′	4 9–5 3		5 1–5 2		1 85*d*	6
8′	5 6–6 3		5 98*ddt*	6 5, 10 6, 17	5 8–6 2	
7′	3 31*d*	7	3 31*d*	7	6 45–6 75	

Coupling constants (J) in Hz

Table 2 ^{13}C NMR chemical shifts (δ) of benzodioxane neolignans (20 MHz, $CDCl_3$)

C	**10a,b** [11] δ	**10c,d** [9] δ	**12** δ
9	17 2±0 1	12 6	17 3
8	74 1	73 2	74 3
7	81 4±0 2	77 1	81 1
9′	115 7±0 1	115 9	18 2
8′	137 3±0 1	137 5	124 3
7′	40 0	40 0	130 7

Trunk wood and bark contain derivatives of *dioxy*-allyl and propenylphenols The compounds from wood belong to the 2,7′,8,8′-neolignan type (**1**), while the compounds from bark belong to the 3,3′- (**2**), 8,3′- (**3**), 7-O-4′,8,3′- (**4**), 8-O-4′- (**5**) and 3-O-4′- (**6**) neolignan types The fruit-kernels contain lignans of identical oxygenation pattern (**7**, **8**) All other constituents of the fruit, however, are derivatives of *trioxy*-allyl and propenylphenols belonging to 8-O-4′- (**9**, **11**) and 7-O-3′,8-O-4′- (**10**, **12**) neolignan types Kernels seem to accumulate preferentially neolignans formed by the oxidative coupling of propenyl- and

Table 3 ^{1}H NMR chemical shifts (δ) of β-aryloxy-arylpropane neolignans (80 MHz, $CDCl_3$)

	9b[12]		**9a**		**11a**	
H	δ	J	δ	J	δ	J
9	1 23 *d*		1 25 *d*	6	1 25 *d*	6
8	3 82 *m*		4 1–4 5		4 1–4 5	
7	3 10 *dd*	5 5, 7 7	3 05 *dd*	6, 14	3 10 *dd*	6, 14
			2 70 *dd*	8, 14	2 70 *dd*	8, 14
9′	5 06 *m*		4 9–5 2		1 85 *d*	
8′	5 90 *m*		6 6–6 25		6 1–6 3	
7′	3 33 *br d*		3 30 *d*	7	6 5–6 75	

Coupling constants (J) in Hz

Table 4 ^{1}H NMR chemical shifts (δ) of *erythro* (**9c**, **11b**) and *threo* (**11c**) β-aryloxy-α-hydroxy-arylpropane neolignans (60, 80, 100 MHz, respectively, in $CDCl_3$)

	9c[12]		**11b**		**11c**[13]	
H	δ	J	δ	J	δ	J
9	1 13 *d*		1 15 *d*	6	1 19 *d*	6
8	4 35 *dq*		4 3–4 5		4 14 *m*	
7	4 80 *d*	3	4 75 *d*	4	4 62 *d*	8
9′	5 11 *m*		1 85 *d*	6	1 87 *d*	5 5
8′	5 99 *m*		6 1–6 4		6–6 3	
7′	3 38 *br d*		6 8–6 9		6 37 *d*	16

Coupling constants (J) in Hz

Table 5 ^{1}H NMR chemical shifts (δ) of β-aryloxy-α-oxo-arylpropane neolignans **9d**, **11e**, **11d** (resp 60, 100, 80 MHz, $CDCl_3$)

	9d[12]		**11e**[13]		**11d**	
H	δ	J	δ	J	δ	J
9	1 57 *d*	6 8	1 71 *d*	7	1 55 *d*	7
8	5 30 *q*	6 8	5 33 *q*	7	5 25 *q*	7
9′	5 06 *m*		1 83 *d*	6	1 87 *d*	6
8′	5 90 *m*	}	6–6 4		5 8–6 3	
7′	3 30 *br d*	}			6 5–6 8	

Coupling constants (J) in Hz

allylphenols (**9a**, **10a**), while in the pericarp one sole such derivative (**10a**) is accompanied by four neolignans formed by the oxidative coupling of two propenyl derivatives (**11a**, **11b**, **11d**, **12**)

EXPERIMENTAL

Isolation of constituents Unripe fruits of *V carinata* (Benth) Warb were collected by Hipólito F Paulino Fo on Feb 2, 1981, near km 126 of the Santarém–Cuiabá road, Municipality of Santarém, Pará State The fruits were separated into kernels, pericarps, arils and teguments Kernels (150 g) and pericarps (75 g) were percolated with $CHCl_3$ The extracts (86 g and 38 g, respectively) were crystallized from MeOH to glycerides (71 g and 28 g, respectively) The mother-liquors were evapd The residue from the kernels (15 g) was partioned between petrol and MeOH–H_2O (9 1) The petrol soln was evapd and the residue (11 5 g) was submitted to CC (150 g silica gel) Elution with petrol–EtOAc (9 1) gave in order six fractions Fr 1 (3 5 g) was composed of aliphatic material Frs 2 (1 1 g) and 3 (3 2 g) were crystallized from C_6H_{14}–$CHCl_3$ to glycerides (0 4 g and 1 7 g, respectively) The mother-liquors were evapd The residue of Fr 2 (0 6 g) was separated by prep TLC (silica gel, C_6H_6–EtOAc 9 1) into **8** (14 mg) and **9a** (14 mg) The residue of Fr 3 was composed of **10a** (1 5 g) Fr 4 (2 g) and 5 (1 4 g) were separated by prep TLC (silica gel, C_6H_6–EtOAc 9 1 and 19 1, respectively) into **7b** (0 5 g) and **7a** (0 1 g), respectively The residue from the pericarps (10 g) was submitted to CC (100 g silica gel) Elution with C_6H_6–EtOAc (4 1) gave in order five fractions Fr 1 (3 1 g) was composed of aliphatic material Frs 2 (1 5 g), 3 (0 8 g), 4 (1 4 g) and 5 (0 5 g) were separated by prep TLC (silica gel, C_6H_6–EtOAc 9 1) into **10a** (26 mg) and **11a** (26 mg), **11a** (88 mg) and **12** (48 mg), **11b** (140 mg) and **11c** (140 mg), **11b** (100 mg) and **11c** (30 mg), respectively

rel-(7R,8R)-Δ^7-4-*Hydroxy*-3,5,5′-*trimethoxy*-7-*O*-3′,8-*O*-4′-*neolignan* (*eusiderin-E*, **12**) Oil, UV λ_{max}^{MeOH} nm 210, 275 (ε11 100, 2150) IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3500, 1610, 1590, 1505, 1460, 1330, 1270, 1220, 1150, 1100, 1040, 990, 960, 915 ^{1}H NMR (δ) Table 1 and 6 6 (*br s*, H-2, H-6, H-2′, H-6′), 3 85 (*s*, 3 MeO) ^{13}C NMR δ Table 2 and 132 2 (C-1), 104 5 (C-2), 147 4 (C-3), 135 6 (C-4), 147 4 (C-5), 104 5 (C-6), 132 4 (C-1′), 107 4 (C-2′), 144 6 (C-3′), 131 9 (C-4′), 148 7 (C-5′), 102 2 (C-6′), 56 6 (MeO-3, MeO-5), 56 2 (MeO-5′) MS *m/z* (rel int) 372 ([M]$^+$, 20), 256 (30), 194 (46), 193 (7), 192 (2), 191 (8), 181 (3), 165 (3), 164 (2), 163 (3), 135 (5), 74 (100)

Table 6 ^{13}C NMR chemical shifts (δ) of β-aryloxy-arylpropane neolignans (20 MHz, $CDCl_3$)

C	**9a**	**11a**	**11b**	**11d**	**11c**[13]
9	19 6	19 6	12 8	17 6	17 0
8	79 5	79 9	73 3	80 2	78 5
7	43 3	43 4	82 6	196 5	83 6
9′	115 8	18 2	18 2	17 9	18 2
8′	137 4	124 9	125 5	124 9	124 6
7′	40 5	130 0	130 0	130 5	130 2
1	133 5	131 1	131 1	126 3	137 6
2	109 2	103 3	103 1	106 8	104 2
3	148 7	147 0	147 1	146 3	152 9
4	135 4	133 3	134 1	139 6	135 5
5	143 4	147 0	147 1	146 3	152 9
6	105 8	103 3	103 1	106 8	104 2
1′	133 6	131 1	134 0	134 4	133 3
2′	103 3	106 5	104 5	102 6	109 1
3′	153 9	153 8	153 7	152 9	150 5
4′	134 5	133 5	134 1	133 6	146 4
5′	153 7	153 8	153 7	152 9	118 6
6′	103 7	106 5	104 5	102 6	118 7
MeO-3	—	} 56 0	} 56 1	} 55 0	} 56 0
MeO-5	56 6				
MeO-4	—	—	—	—	60 6
MeO-3′	} 56 0	} 56 3	} 56 3	} 56 0	55 6
MeO-5′					—
CH_2O_2-3,4	101 1	—	—	—	—

ORD (MeOH) $[\phi]^{pk}_{318} -5100$, $[\phi]^{tr}_{282} -9050$, $[\phi]^{pk}_{230} -4650$ (for ORD of eusiderin-A (**10a**) see ref [9])

Δ^8-3,4-*Methylenedioxy*-5,3′,5′-*trimethoxy*-8-O-4′-*neolignan* (**9a**) Oil, UV λ^{MeOH}_{max} nm 240, 267 (ε16 850, 12 700) IR $\nu^{CHCl_3}_{max}$ cm^{-1} 1630, 1590, 1500, 1450, 1430, 1240, 1225, 1190, 1120, 1090, 1040, 920 ^{1}H NMR δ Table 3 and 6 50 (*br s*, H-2), 6 35 (*br s*, H-6, H-2′, H-6′), 3 85 (*s*, MeO-5), 3 80 (MeO-3′, MeO-5′), 5 85 (*s*, CH_2O_2) ^{13}C NMR (Table 6) MS *m/z* (rel int) 386 ([M]$^+$, 23), 221 (3), 194 (78), 193 (100), 192 (40), 165 (17), 135 (14), 107 (4) ORD (MeOH) $[\phi]^{tr}_{278} -4550$, $[\phi]^{pk}_{266} -1950$, $[\phi]^{tr}_{258} -2400$, $[\phi]_{250}$ 0, $[\phi]^{pk}_{242} +8950$, $[\phi]^{tr}_{234} +5300$

Δ^7-4-*Hydroxy*-3,5,3′,5′-*tetramethoxy*-8-O-4′-*neolignan* (**11a**) Oil, UV λ^{MeOH}_{max} nm 233, 267 (ε16 500, 14 850) IR $\nu^{CHCl_3}_{max}$ cm^{-1} 3500, 1610, 1580, 1500, 1460, 1330, 1270, 1240, 1220, 1140, 1120, 1040, 960, 920 ^{1}H NMR δ Table 3 and 6 45 (*s*, H-2, H-6), 6 55 (*s*, H-2′, H-6′), 3 80 (*s*, MeO-3, MeO-5), 3 85 (*s*, MeO-3′, MeO-5′) ^{13}C NMR (Table 6) MS *m/z* (rel int) 388 (M$^+$, 8), 372 (2), 221 (5), 195 (61), 194 (70), 193 (8), 192 (3), 191 (7), 167 (17), 165 (8), 164 (7), 163 (14), 135 (15) ORD (MeOH) $[\phi]^{pk}_{350} -750$, $[\phi]^{tr}_{272} -6300$, $[\phi]_{263}$ 0, $[\phi]^{pk}_{258} +500$, $[\phi]^{tr}_{254} +250$, $[\phi]^{pk}_{236} +7000$, $[\phi]_{230}$ 0, $[\phi]^{tr}_{220} -8950$

rel-(7S,8R)-Δ^7-4,7-*Dihydroxy*-3,5,3′,5′-*tetramethoxy*-8-O-4′-*neolignan* (**11b**) Oil, UV λ^{MeOH}_{max} nm 225, 267 (ε15 150, 9700) IR $\nu^{CHCl_3}_{max}$ cm^{-1} 3500, 1610, 1580, 1500, 1460, 1330, 1270, 1240, 1220, 1140, 1120, 1050, 960, 900 ^{1}H NMR δ Table 4 and 6 60 (*s*, H-2, H-6), 6 55 (*s*, H-2′, H-6′), 3 80 (*s*, MeO-3, MeO-5), 3 85 (*s*, MeO-3′, MeO-5′) ^{13}C NMR (Table 6) MS *m/z* (rel int) 404 ([M]$^+$, 10), 402 (5), 386 (3), 211 (4), 194 (20), 193 (60), 192 (8), 181 (15), 165 (4), 164 (10), 163 (38), 153 (10), 135 (8) ORD (MeOH) $[\phi]^{pk}_{350} -100$, $[\phi]^{tr}_{286} -5300$, $[\phi]^{pk}_{256} -250$, $[\phi]^{tr}_{236} -750$, $[\phi]_{220}$ 0

Δ^7-4-*Hydroxy*-3,5,3′,5′-*tetramethoxy*-7-*oxo*-8-O-4′-*neolignan* (**11d**) Oil, UV λ^{MeOH}_{max} nm 225, 273, 295 (ε15 450, 7300, 6750) IR $\nu^{CHCl_3}_{max}$ cm^{-1} 3400, 1680, 1590, 1520, 1510, 1460, 1420, 1330, 1275, 1240, 1220, 1150, 1125, 1050, 960, 910 ^{1}H NMR δ Table 5 and 7 55 (*s*, H-2, H-6), 6 50 (*br s*, H-2′, H-6′), 3 80 (*s*, MeO-3, MeO-5), 3 85 (*s*, MeO-3′, MeO-5′) ^{13}C NMR (Table 6) MS *m/z* (rel int) 402 ([M]$^+$, 26), 372 (3), 221 (16), 209 (3), 208 (3), 194 (45), 193 (100), 181 (45), 165 (7) ORD (MeOH) $[\phi]_{350}$ 0, $[\phi]^{tr}_{286} -5300$, $[\phi]^{pk}_{256} -250$, $[\phi]^{tr}_{236} -750$, $[\phi]_{220}$ 0

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