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LIGNANS FROM *MYRISTICA DACTYLOIDES*

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Key Word Index—*Myristica dactyloides*; Myristicaceae; lignans.

Abstract—The hexane extract from the stem bark of *Myristica dactyloides* afforded a new lignan, rel.(8*S*,8′*S*)-bis(3,4-methylenedioxy)-8,8′-neolignan and the CH_2Cl_2 extract gave two more lignans, rel.(8*S*,8′*R*)dimethyl-(7*S*,7′*R*)-bis(4-hydroxy-3-methoxyphenyl) tetrahydrofuran and rel. (8*S*,8′*S*)dimethyl-(7*S*,7′*S*)-bis(4-hydroxy-3-methoxyphenyl) tetrahydrofuran. The last compound is a new natural product. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

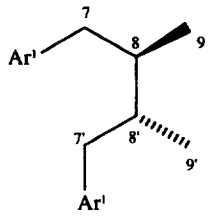
Myristica dactyloides Gaertn (local name, Malaboda) is a large tree found in the montane forests of Sri Lanka. Decoctions made out of the stem bark and leaves are widely used in the indigenous medicine of many countries. In Sri Lanka, a decoction of the bark and leaves is used as a gargle for throat ailments in Ayurvedic medicine [1] and various parts of the tree are commonly used as a medicine in the treatment of cattle. However, relatively little chemical work has been carried out on *M. dactyloides*. Myoinositol has been reported from the hot methanol extract of the stem bark [2]. In our previous studies, we reported on the isolation and characterization of eight aryl alkanones and two new lignans from hot hexane and dichloromethane extracts of the stem bark [3, 4]. In this work, we describe the isolation and structural elucidation of three lignans (**1–3**). Two of these lignans (**1** and **3**) are new natural products while the third (**2**) is new to the plant but it has been previously reported from *M. malabarica* [5]. Lignans have aroused considerable interest due to their many biological activities including antitumour activity [6]. The proposed structure for compound **1** is very closely related to the structure of the reported antitumour active lignan nordihydroguaiaretic acid (**4**) and the structure of the antimicrobially active dihydroguaiaretic acid (**5**) [6]. The structures of the other two lignans are similar to the structures of the other biological active lignans [6].

RESULTS AND DISCUSSION

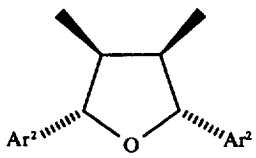
The molecular ion peak at *m/z* 326 in the mass spectrum of compound **1** suggested that the molecular formula of **1** was $C_{20}H_{22}O_4$. However, the ^{1}H NMR and ^{13}C NMR spectral data indicated the presence of only 10 carbon atoms and 11 protons. Hence each signal in the ^{1}H and ^{13}C NMR spectra had to represent two sets of identical atoms. The doublet at δ_H 6.69 (2H, J = 8.0 Hz), the broad doublet at δ_H 6.53 (2H) and the broad singlet at δ_H 6.57 (2H) indicated the presence of two 1,3,4-tribsubstituted benzene rings in the molecule (Table 1) and this was supported by the ^{13}C NMR data (Table 2). The sharp singlet at δ_H 5.90 (4H) and the triplet at δ_c 100.6 established the presence of two methylenedioxy groups attached to the benzene rings. The base peak at *m/z* 135 in the mass spectrum, which was attributed to the fragment ion formed by benzylic cleavage, provided additional support for the presence of a methylenedioxy group attached to the benzene rings. In the ^{1}H NMR spectrum of compound **1**, the benzylic protons appeared as two double doublets δ_H 2.54 (2H, J_{vic} = 14.0 Hz, J_{gem} = 6.0 Hz) and 2.33 (2H, J_{vic} = 14.0 Hz, J_{gem} = 8.0 Hz) due to the vicinal and geminal coupling. The multiplet at δ_H 1.72 (2H) and the doublet at δ_H 0.80 (6H, J = 8.0 Hz) and the signals at δ_c 38.1 (*d*), 13.8 (*q*) indicated the presence of a CH_3CH group adjacent to the benzylic group. The low intensity peak at *m/z* 163 in the mass spectrum of the compound **1** also provided additional confirmation for the presence of the $ArCH_2CH(CH_3)$-group.

A compound with structure **1** has not been previously reported. However, compounds with closely related structures (**5–9**) have been isolated from the *Virola calophylla* (Myristicaceae) [7]. Comparison of the ^{13}C NMR spectral data of the aliphatic chain with previously reported values of this type of compounds (Table 3) indicated a *threo* stereochemistry for the aliphatic chain in compound **1**. Thus compound **1** is rel.(8*S*,8′*S*)-bis(3,4-methylenedioxy)-8,8′-neolignan.

The molecular peak at *m/z* 344 in the EIMS suggested that the molecular formula of compound **2** was



1



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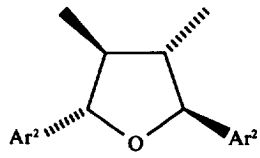

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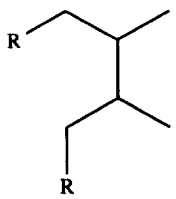
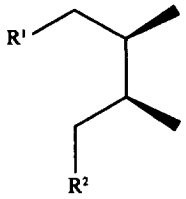
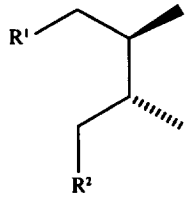


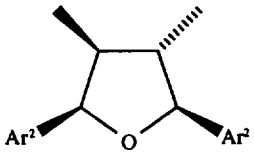
4 R = Ar^3
5 R = Ar^2



6 $R^1 = Ar^2$, $R^2 = Ar^1$
7 $R^1 = Ar^4$, $R^2 = Ar^1$

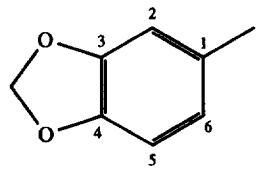


8 $R^1 = Ar^2$, $R^2 = Ar^1$
9 $R^1 = Ar^4$, $R^2 = Ar^1$



10

Ar^1 =



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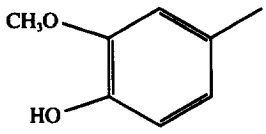

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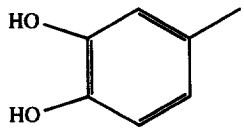

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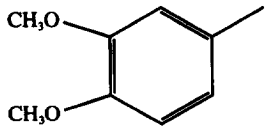

$C_{20}H_{24}O_5$. The ^1H NMR and the ^{13}C NMR data of compound **2** showed the presence of only 10 carbon atoms and 12 protons in the molecule. This suggested the symmetric nature of the molecule. Thus each signal in the ^1H NMR and ^{13}C NMR spectra must represent two identical atoms. Compound **2** showed no measurable rotation and this confirmed the symmetry of the molecule. The ^{13}C NMR spectrum of **2** indicated the presence of a trisubstituted benzene ring (Table 2). The two doubles at δ_H 6.85 (2H, J = 7.0 Hz) and 7.04 (2H, J = 1.5 Hz) and the broad doublet at δ_H 6.92 (2H, *br d*) supported 1,3,4 substitution of the benzene rings. The sharp singlet at δ_H 3.85 (6H) and δ_C 55.8 showed the presence of two methoxy groups in identical environments attached to aromatic rings. Formation of a diacetate and a dimethyl ether confirmed the presence of two phenolic hydroxyl groups in **2**. This indicated that the substituents at positions 3 and 4 of the aromatic rings were OH and OCH_3 groups. Further, the presence of a 3,4-dimethyltetrahydrofuran moiety in **2** was indicated by signals at δ_H 4.40 (2H, *d*), 1.80 (2H, *m*) and 1.05 (6H, *d*). The coupling constant J = 9.0 Hz of the doublet at δ_H 4.40 showed that the protons at 7,7′ are in *trans* configuration with the protons at 8 and 8′, respectively, as reported in previous studies [4, 8]. In addition, the ^{13}C NMR data (Table 2) also gave additional evidence for the presence of tetrasubstituted tetrahydrofuran moiety in compound **2**. Hence, it was deduced that compound **2** is rel.(8*S*,8′*R*)dimethyl-(7*S*,7′*R*)-bis (4-hydroxy-3-methoxyphenyl)tetrahydrofuran. This structure was further established by comparing its ^1H NMR data (Table 1) with those previously reported for malabaricanol A, isolated from *Myristica malabarica* [5].

The molecular ion peak at *m/z* 344 in the mass spectrum of compound **3** suggested that its molecular formula was $C_{20}H_{24}O_5$. The aromatic region in the ^1H NMR spectrum of compound **3** is almost identical with that of compound **2** suggesting the presence of a

Table 1. ^{1}H NMR spectral data of compounds **1–3** and some related lignans

H	**1**	**2**	Malbaricanol A*	**3**	**10**†
2,2′	6.57 (2H, *br. s*)	7.04 (2H, *d*, J = 1.5 Hz)		6.99 (2H, *br. s*)	6.85 (1H, *d*) 7.04 (1H, *d*)
5,5′	6.69 (2H, *d*, J = 8.0 Hz)	6.85 (2H, *d*, J = 7.0 Hz)	6.75 (4H, *s*) 6.85 (2H, *s*)	6.88 (2H, *d*, J = 7.2 Hz)	6.88 (1H, *d*) 6.92 (1H, *d*)
6,6′	6.53 (2H, *br. d*, J = 8.0 Hz)	6.92 (2H, *br. d*)		6.92 (2H, *br. d*)	6.82 (1H, *dd*) 6.99 (1H, *dd*)
7,7′	2.33 (2H, *dd*, J = 14.0 & 8.0 Hz) 2.54 (2H, *dd*, J = 14.0 & 6.0 Hz)	4.40 (2H, *d*, J = 9.0 Hz)	4.43 (2H, *d*, J = 8.0 Hz)	4.04 (1H, *d*, J = 9.0 Hz) 5.11 (1H, *d*, J = 9.0 Hz)	4.40 (1H, *d*) 5.11 (1H, *d*)
8,8′	1.72 (2H, *m*)	1.80 (2H, *m*)	2.25 (2H, *m*)	1.80 (1H, *m*) 2.25 (1H, *m*)	1.78 (1H, *ddq*) 2.23 (1H, *ddq*)
9,9′	0.80 (6H, *d*, J = 8.0 Hz)	1.05 (6H, *d*, J = 7.0 Hz)	1.02 (3H, *d*, J = 8.0 Hz)	0.66 (3H, *d*, J = 7.5 Hz) 1.05 (3H, *d*, J = 7.5 Hz)	0.66 (3H, *d*) 1.06 (3H, *d*)
O-CH_2-O	5.90 (4H, *s*)				
O-CH_3		3.85 (6H, *s*)	3.80 (6H, *s*)	3.85 (3H *s*) 3.90 (3H, *s*)	3.86 (3H, *s*) 3.91 (3H, *s*)
OH		5.85 (1H, *br. s*)		5.65 (2H, *br. s*)	5.60 (1H, *br. s*)
config at 7,7′		7*S*,7′*R*	7*S*,7′*R*	7*S*,7′*S*	7*R*,7′*S*
config at 8,8′		8*S*,8′*R*	8*S*,8′*R*	8*S*,8′*S*	8*S*,8′*S*

* Reported in ref. [5].
† Reported in ref. [9].

Table 2. ^{13}C NMR spectral data of compounds **1**–**3** and **10***

C	1	2	3	10*
1,1′	135.4	134.2	133.2, 132.7	133.2, 132.8
2,2′	109.2	108.5	108.5	109.7, 109.4
3,3′	147.3	146.5	146.4, 146.1	146.5, 146.2
4,4′	145.4	145.1	144.9, 144.5	145.2, 144.6
5,5′	107.9	109.7	109.4, 109.1	114.2, 113.9
6,6′	121.7	119.9	119.3, 119.2	119.9, 119.3
7,7′	41.1	88.3	87.3, 83.1	87.3, 83.1
8,8′	38.1	47.7	45.9, 44.3	47.8, 46.0
9,9′	13.8	14.9	13.8, 12.9	15.0, 15.0
O-CH_2-O	100.6	—	—	
OCH_3		55.8	55.8	55.8

* Reported in ref. [9].

4-hydroxy-3-methoxyphenyl moiety in compound **3**. Two sharp singlets at δ_H 3.85 and 3.90 (3H each) provided evidence for the presence of two methoxyl groups in different environments attached to the benzene rings. The two doublets at δ_H 0.66 and 1.05, two multiplets at δ_H 1.80 and 2.25 and two *trans* doublets at δ_H 4.40 and 5.11 indicated the presence of a 3,4-dimethyl-2,5-disubstituted tetrahydrofuran moiety. The *trans* coupling constant (J = 9.0 Hz) of the 7 and 7′ protons due to the coupling with 8 and 8′ protons, respectively, indicated that the aryl and the methyl groups attached to the tetrahydrofuran moiety were in the *trans* configuration (see refs [4, 8]). The ^1H NMR signals due to the methine and methyl protons in the tetrahydrofuran moiety showed that **3**, unlike **2**, was not symmetric. Thus the methyl groups of the tetrahydrofuran moiety of compound **3** should be in the *trans* configuration. Hence compound **3** is rel.(8*S*,8′*S*)dimethyl-(7*S*,7′*S*)-bis(4-hydroxy-3-methoxyphenyl) tetrahydrofuran. The spectral data of compound **10** reported earlier from the root bark of *Jatropa grossidentata* [9] and of various types of previously reported lignans [10–12] gave additional support to the structure proposed for compound **3**.

EXPERIMENTAL

Mps: uncorr.; Identities of compounds were established by mmp, co-TLC, IR, NMR and MS comparison; ^1H and ^{13}C NMR: 200 and 50 MHz; Prep. TLC; Merck Kieselgel 60 F_{254}; Flash and medium pressure CC: Merck Kieselgel 60 (230–300 mesh ASTM).

Plant material. Myristica dactyloides was collected from the Kandy district in the Central Province of Sri Lanka and identified by comparison with the Herbarium specimen (2852, collected by Jayasooriya, Balasubramanium & Greller on 21st August 1984) at the National Herbarium, Royal Botanic Gardens, Peradeniya, Sri Lanka.

The hot hexane extract (9 g) was chromatographed on silica gel and the column was eluted with hexane containing increasing amounts of EtOAc. The fractions eluted with 2% EtOAc–hexane (1:49) gave compound **1** (35 mg) after further purification by flash CC and prep. TLC.

The hot CH_2Cl_2 extract (20 g) was chromatographed on silica gel and eluted with hexane-CH_2Cl_2 gradients. The column fractions eluted with CH_2Cl_2–hexane (1:9–3:22) gave both compounds **2** (120 mg) and **3** (130 mg) after further purification by CC and prep. TLC.

Rel.(8R,8′S)-*bis*(3,4-*methylenedioxy*)-8,8′-*neolignan* (**1**). Oily compound, $[\alpha]_D^{25}$ 0 (*c* 0.10, $CHCl_3$); IR ν_{max} cm^{-1}: 2900, 1600, 1480, 1430, 1375, 1240, 1185, 1095, 1030, 925, 865, 805, 770; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 326 (100) $[M]^+$, 325 (99), 190 (14), 189 (13), 163 (19), 162 (17), 149 (17), 135 (98), 105 (45), 91 (16), 79 (36).

Rel.(8R,8′S)-dimethyl-(7R,7′S)-*bis*(4-*hydroxy*-3-*methoxyphenyl*) *tetrahydrofuran* (**2**) (*Malabaricanol—A*). Pale yellow oily compound; IR ν_{max} cm^{-1}: 2950, 1710, 1600, 1505, 1450, 1370, 1270, 1240, 1160, 1110, 1030, 940, 860, 810, 750; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 334 (40) $[M]^+$, 192 (58), 177 (100), 164 (40), 161 (59), 160 (39), 145 (85), 124 (42), 117 (33).

Rel.(8R,8′R)-*dimethyl*-(7R,7′S)-*bis*-(4-*hydroxy*-3-*methoxyphenyl*) *tetrahydrofuran* (**3**). Yellow oil; IR ν_{max} cm^{-1}: 2950, 1715, 1600, 1510, 1450, 1360, 1270, 1170, 1110, 1040, 940, 860, 820, 760; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 334 (40) $[M]^+$, 192 (56), 177 (100), 164 (37), 161 (56), 145 (83), 124 (42), 117 (33).

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Table 3. ^{13}C NMR spectral data of alkyl carbons of some of the reported lignans*

C	5	6	7	8	9	10
9,9′	16.05	15.86, 16.04	16.06, 16.17	13.61, 13.70	13.75, 13.81	13.76
8,8′	38.75	37.71	37.68	37.52	37.85	38.12
7,7′	39.02	38.92	39.04	40.76	41.05	41.06
Configuration	meso	erythro	erythro	threo	threo	threo

* Spectral data of compounds **5**–**9** were reported in ref. [8].

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