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TWO LIGNANS AND AN ARYL ALKANONE FROM *MYRISTICA DACTYLOIDES*

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Key Word Index—*Myristica dactyloides*; Myristicaceae; stem bark; aryl alkanone; lignan; sitosterol.

Abstract—Chemical investigation of the hot hexane extract of the stem bark of *Myristica dactyloides* has resulted in the isolation of two new lignans, rel-(8*S*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran and rel-(8*R*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran, a new diaryl alkanone, 1-(2,6-dihydroxyphenyl)-9-(4-hydroxy-3-methoxyphenyl)nonan-1-one, sitosterol and six other previously reported aryl alkanones. The structures of the new compounds were deduced from their spectral data and chemical transformations.

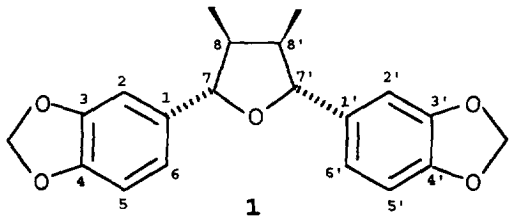
INTRODUCTION

The family Myristicaceae which consists of 18 genera and nearly 300 species is exclusively tropical and found in the lowland rain forests in the Asian tropics, tropical American (Amazonian basin), Africa and Madagascar. However, the genus *Myristica* which contains the highest number of species (*ca* 120) is found only in Asian tropics [1]. Three species of *Myristica* are found in Sri Lanka; *M. ceylanica* is endemic to Sri Lanka and both *M. dactyloides* and *M. fragrans* are also found in south India [2]. Since all three species have been used for many years in the folk medicine of several countries [3], the complete chemical investigation of these species is of great interest. Although the chemical constituents of *M. fragrans* have been studied extensively since the beginning of the 20th century due to their pharmacological properties, the other two Sri Lankan species have been relatively less explored. *M. dactyloides* is a large tree found in the mountain forests of Sri Lanka [2,3]. A decoction made out of the stem bark and leaves of this species is widely used in traditional medicine [3]. Chemical investigation of *M. dactyloides* has led to the isolation of seven aryl alkanones from the hot dichloromethane extract [4] and myoinositol from the hot methanol extract [5].

In this paper, we describe the chemical investigation of the hot hexane extract of the stem bark of *M. dactyloides* and report the isolation and structural elucidation of two new lignans, rel-(8*S*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran (**1**) and rel-(8*R*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran (**2**), a new diaryl alkanone, 1-(2,6-dihydroxyphenyl)-9-(4-hydroxy-3-methoxyphenyl)nonane-1-one (**3**). We also isolated sitosterol and six other previously reported aryl alkanones (**4–9**) from the same extract; their structures were confirmed by comparison of melting points, TLC and spectral data with previously reported values [4].

RESULTS AND DISCUSSION

Although the ^{1}H and ^{13}C NMR spectra of compound **1** showed the presence of only ten protons and ten carbon atoms, the high resolution mass spectrum confirmed its molecular formula as $C_{20}H_{20}O_5$. This suggested the symmetric nature of the molecular structure of compound **1**, with each signal in the ^{1}H and ^{13}C NMR spectra corresponding to two identical sets of protons and carbon atoms, respectively. Furthermore, the NMR spectral data (Table 1) of **1** suggested the presence of two 3,4-methylenedioxy phenyl units and a 8,8′-dimethyl-7,7′-disubstituted tetrahydrofuran moiety. The coupling constant 9.2 Hz of the doublet at δ 4.60 for H-7 and H-7′ suggested that these two protons are in a *trans*-configuration with the adjacent protons H-8 and H-8′, respectively. The symmetrical and optically inactive nature, and the *trans*-conformational arrangement of the methyl and aryl groups, suggested that the structure of compound **1** is rel (8*S*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl) tetrahydrofuran. Although this is the first report of the isolation of compound **1** as a natural product, the isolation of compound **10** which is structurally very closely related has been reported from *M. malabarica* [6]. Comparison between the spectral data of compound **1** and compound **10** provided additional evidence to confirm the symmetrical nature and the exact stereochemistry of the compound.



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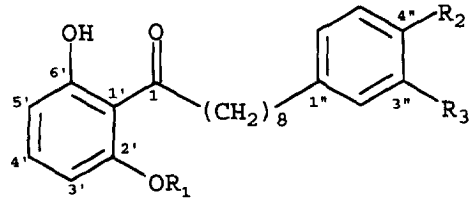
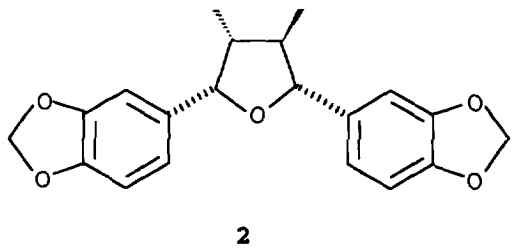


	R_1	R_2	R_3
3	H	OH	OCH_3
4	H	H	H
5	CH_3	OH	H
6	H	$O-CH_2-O$	
7	CH_3	$O-CH_2-O$	



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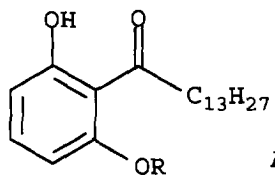
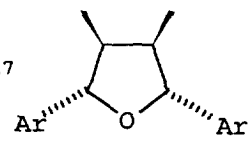


8 R = H
9 R = CH_3



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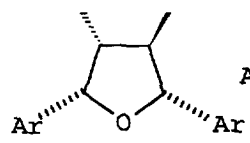

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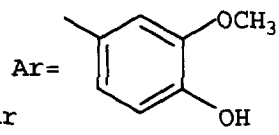

The high resolution mass spectrum of compound **2** indicated that its molecular formula was $C_{20}H_{20}O_5$. The ^1H and the ^{13}C NMR (Table 1) and the mass spectral data showed the presence of two 1,3,4-trisubstituted benzene rings. The presence of two methylenedioxy groups was established by the appearance of a sharp singlet at δ 5.93 (4H, *s*) in the ^1H NMR and two triplets at δ 100.8 and 100.7 in the ^{13}C NMR spectrum. The presence of the 8,8′-dimethyl-7,7′-disubstituted tetrahydrofuran moiety was also confirmed by the ^1H and ^{13}C spectral data (Table 1). Since the two methyl groups at the 8,8′ positions appeared at two different chemical shift values in ^1H NMR spectrum of **2**, it was deduced that the two methyls are in the *trans*-configu-

Table 1. ^1H and ^{13}C-NMR spectral data of compounds **1** and **2**

	1		**2**	
	^1H	^{13}C	^1H	^{13}C
1,1′		136.5		137.0, 134.5
2,2′	6.92(2H, *d*, *J* = 1.5 Hz)	119.8	6.9(2H, *d*, *J* = 1.4 Hz)	119.5, 119.0
3,3′		147.9		147.8, 147.4
4,4′		147.1		146.9, 146.2
5,5′	6.76(2H, *d*, *J* = 8.2 Hz)	106.7	6.77(2H, *d*, *J* = 8.2 Hz)	106.7, 106.4
6,6′	6.83(2H, *dd*, *J* = 8.2, 1.5 Hz)	108.0	6.83(2H, *dd*, *J* = 8.3, 1.4 Hz)	108.0, 107.8
7,7′	4.60(2H, *d*, *J* = 9.2 Hz)	88.4	5.39(1H, *d*, *J* = 4.0 Hz) 4.60(1H, *d*, *J* = 9.0 Hz)	85.6, 84.7
8,8′	1.75(2H, *m*)	51.1	2.40(1H, *m*) 2.02(1H, *m*)	47.5, 43.4
9,9′	1.02(6H, *d*, *J* = 6.2 Hz)	13.9	0.98(3H, *d*, *J* = 6.0 Hz) 0.61(3H, *d*, *J* = 7.0 Hz)	11.7, 9.4
$O-CH_2-O$	5.94(4H, *s*)	101.0	5.93(4H, *s*)	101.0, 100.8

ration. Unlike in compound **1**, the two benzylic protons clearly appeared as two doublets at different chemical shift values with two different coupling constants ($J_{cis} = 4.0$ Hz and $J_{trans} = 9.0$ Hz) in the ^{1}H NMR spectrum of compound **2**. This suggested that the relative configuration of the two aryl groups would be *cis*. The configurations of the two methyls and the two aryls were further confirmed by comparing the above spectral data with that of the previously isolated compound (**11**) from *Jatropa grossidentata* [7]. Hence, it was deduced that the structure of compound (**2**) is rel-(8*R*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran.

The spectral data (see Experimental) suggested that the basic structure of compound **3** was very similar to that of the previously reported diaryl alkanones **4–7** [4] and Malabaricone-C [6]. The presence of additional methoxyl group was indicated by the ^{1}H NMR signal at δ 3.85 (3H, *s*) and the signal at δ 56.1 (*q*) in the ^{13}C NMR spectrum. Potassium permanganate oxidation of compound **3** to vanillic acid confirmed the positions of the methoxyl and hydroxyl group of the second benzene ring.

Methylation of **3** with Mel-anhydrous K_2CO_3 in acetone giving dimethylated (**12**) and trimethylated (**13**) derivatives of **3** also provided extra evidence for the presence of three hydroxyl groups (see Experimental). Hence, the spectral data, as well as the degradation and the methylation studies, indicated that compound **3** had the structure, 1-(2′,6′-dihydroxyphenyl)-9-(4″-hydroxy-3″-methoxyphenyl)nonan-1-one.

EXPERIMENTAL

Mps are uncorr. Identities of compounds were established by mmp, co-TLC, IR, NMR and MS comparisons. ^{1}H and ^{13}C NMR were recorded at 200 MHz and 50 MHz, respectively, at the Institute of Pharmaceutical Chemistry, University of Münster, Germany. IR spectra were recorded in KBr discs unless otherwise stated and MS were recorded at the Institute of Fundamental Studies, Kandy, Sri Lanka. Prep. TLC was carried out on Merck Kieselgel 60 F_{254}. Flash and medium pressure CC was carried out on Merck Kieselgel 60 (230–400 mesh ASTM).

Plant material. M. dactyloides Gaertn 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 21 August 1984) at the National Herbarium, Royal Botanic Gardens, Peradeniya, Sri Lanka.

Extraction and isolation. Dried and powdered stem bark (1 kg) was extracted successively with hot hexane, hot CH_2Cl_2 and hot MeOH. The hot hexane extract (9 g) was flash chromatographed over silica gel and eluted with a gradient of hexane–EtOAc.

Compound **1**. The column fr. eluted with EtOAc–hexane (2:25) was further purified by prep. TLC to give rel-(8*S*,8′*R*)-dimethyl-(7*S*,7′*R*)-bis(3,4-methylenedioxyphenyl)tetrahydrofuran (**1**) as an oil (47 mg). $[\alpha]_D$ 0 (CH_2Cl_2, *c* 0.01). IR ν_{max} (film): 2860, 1600, 1485, 1440, 1370, 1260, 980, 720 cm^{-1}. ^{1}H and ^{13}C NMR in $CDCl_3$: Table 1. EIMS *m/z* (rel. int.): 340 (37) $[M]^+$, 190 (100), 175 (55), 162 (39), 149 (33), 145 (85), 135 (20), 117 (36), 91 (32), 77 (26) and 65 (32); HR-MS *m/z* 340.1301 ($[M]^+$, calcd for $C_{20}H_{20}O_5$: 340.1310).

Compound **2**. Elution with EtOAc–hexane (1:10) gave a pale yellow oily mixt. which was sepd by prep. TLC to give the colourless oil rel-(8*R*,8′*R*)-dimethyl-(7*S*,7′*R*) - bis(3,4 - methylenedioxyphenyl)tetrahydrofuran (**2**) (62 mg). $[\alpha]_D$ −20, (CH_2Cl_2, *c* 0.2). IR ν_{max} (film): 3440, 2912, 1648, 1625, 1558, 1539, 1520, 1507, 1491, 1472, 1456, 1433, 1421, 1302, 1187, 1110, 976 cm^{-1}. ^{1}H and ^{13}C NMR in $CDCl_3$: Table 1. EIMS *m/z* (rel. int.): 340 (39) $[M]^+$, 190 (100), 175 (99), 162 (78), 149 (60), 145 (99), 135 (39), 117 (60); HR-MS *m/z* 340.1314 ($[M]^+$, calcd for $C_{20}H_{20}O_5$: 340.1310).

Compound **3**. Elution with EtOAc–hexane (1:4) gave a pale yellow gummy mixt. (126 mg) which on sepn by medium pressure CC followed by prep. TLC gave 1-(2′,6′-dihydroxyphenyl)-9-(4″-hydroxy-3″-methoxyphenyl)nonan-1-one (**3**) (61 mg) as an amorphous powder. IR ν_{max}: 3600–3100, 2900, 2850, 1630, 1600, 1510, 1460, 1245, 1090, 830, 780, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.10 (2H, *br s*, D_2O-exchangeable), 7.19 (1H, *t*, *J* = 8.2 Hz), 6.78 (1H, *d*, *J* = 2.0 Hz), 6.76 (1H, *d*, *J* = 8.2 Hz), 6.65 (1H, *dd*, *J* = 8.1 & 2.0 Hz), 6.38 (2H, *d*, *J* = 8.2 Hz), 5.75 (1H, *br s*), 3.85 (3H, *s*), 3.12 (2H, *t*, *J* = 7.5 Hz), 2.49 (2H, *t*, *J* = 7.5 Hz), 1.69 (2H, *m*), 1.55 (2H, *m*) and 1.31 (8H, *br s*). ^{13}C NMR ($CDCl_3$): δ 208.3 (*s*), 161.4 (2C, *s*), 145.1 (*s*), 144.6 (*s*), 136.4 (*s*), 135.8 (*d*), 120.0 (*d*), 114.7 (*d*), 110.8 (*d*), 110.2 (*s*), 108.4 (2C, *d*), 56.1 (*q*), 44.8 (*t*), 35.2 (*t*), 31.4 (*t*), 29.3 (*t*), 29.2 (2C, *t*), 29.9 (*t*), 24.5 (*t*). EIMS *m/z* (rel. int.): 372 (10) $[M]^+$, 328 (15), 271 (10), 255 (13), 241 (23), 165 (17), 151 (13), 149 (38), 137 (100), 122 (14), 91 (19), 81 (21), 77 (20), 71 (24) and 69 (24); HR-MS *m/z* 327.1928 ($[M]^+$, calcd for $C_{22}H_{28}O_5$: 327.1936).

Methylation of **3**. A mixt. of compound (**3**) (18 mg) and anhydrous K_2CO_3 (23 mg) in dried Me_2CO was treated at reflux temp. for 6 hr. The mixt. was allowed to cool, MeI (1 ml) added and stirring continued for another 2 hr; the two major reaction products formed were sepd by prep. TLC. The less polar oily compound was identified as 1-(6-hydroxy-2-methoxyphenyl)-9-(3,4-dimethoxyphenyl)nonane-1-one (**12**), (8 mg). IR ν_{max} (film): 2928, 1619, 1590, 1507, 1456, 1257, 1235, 1088, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 12.35 (1H, *s*), 7.32 (1H, *t*, *J* = 8.0 Hz), 6.79 (1H, *d*, *J* = 8.2 Hz), 6.71 (2H, *m*), 6.67 (1H, *dd*, *J* = 8.0, 1.5 Hz), 6.39 (1H, *dd*, *J* = 8.0, 1.4 Hz), 3.89 (3H, *s*), 3.87 (3H, *s*), 3.85 (3H, *s*), 3.04 (2H, *t*, *J* = 7.2 Hz), 2.54 (2H, *t*, *J* = 7.1 Hz), 1.55 (12H, *br s*). EIMS *m/z* (rel. Int.): 400 (28) $[M]^+$, 150 (100), 137 (35), 99 (20), 97 (18), 85 (40), 83 (28), 71 (67). The other product was identified as 1-(2, 6-dimethoxyphenyl)-9-(3,4-dimethoxyphenyl)nonane-1-one (**13**), (6 mg). IR ν_{max} (film): 2928, 1702, 1587,

1507, 1459, 1257, 1110, 1027 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25 (1H, *t*, $J = 8.0$ Hz), 6.79 (1H, *d*, $J = 8.5$ Hz), 6.72 (2H, *m*), 6.54 (2H, *d*, $J = 8.0$ Hz), 3.87 (3H, *s*), 3.85 (3H, *s*), 3.78 (6H, *s*), 2.73 (2H, *t*, $J = 7.2$ Hz), 2.54 (2H, *t*, $J = 7.5$ Hz), 1.58 (12H, *br s*). EIMS *m/z* (rel. int.): 414 (27), 400 (18), 234 (11), 193 (15), 165 (100), 151 (82), 137 (12), 107 (15).

Oxidation of **3**. Compound **3** (10 mg) was treated with acidic $KMnO_4$ soln (2 ml) at 70° for 30 min. The reaction mixt. was dild with H_2O (10 ml) and extracted with $CHCl_3$ (2 × 5 ml). The organic phase was evapd to dryness and purified by prep. TLC to give vanillic acid.

Compound **4–9**. Compounds **4** (30 mg), **5** (180 mg), **6** (200 mg), **7** (50 mg), **8** (120 mg) and **9** (40 mg) were isolated from the column frs eluted with EtOAc–hexane (3:20), (1:5), (3:20), (1:20), (3:25) and (1:25), respectively. They were identified by comparison of their spectral data with lit. [4].

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