Three New Neolignans from the Aril of *Myristica fragrans*

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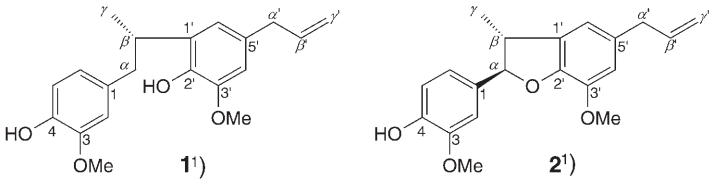
Three new neolignans, named 1-deoxycarinatone (**1**), isodihydrocarinatidin (**2**), and isolicarin A (**3**), together with the known neolignan (+)-dehydrodiisoeugenol (**4**), were isolated from mace (the aril of *Myristica fragrans* HOUTT.). Their structures were elucidated as 2-[(1*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylethyl]-6-methoxy-4-(prop-2-enyl)phenol (**1**), 4-[(2*R*,3*R*)-2,3-dihydro-7-methoxy-3-methyl-5-(prop-2-enyl)benzofuran-2-yl]-2-methoxyphenol (**2**), and 4-{(2*S*,3*R*)-2,3-dihydro-7-methoxy-3-methyl-5-[(1*E*)-prop-1-enyl]benzofuran-2-yl}-2-methoxyphenol (**3**) on the basis of spectroscopic data.

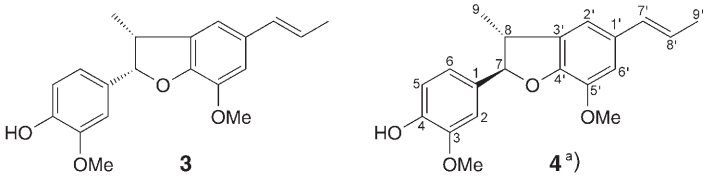
Introduction. – Mace, the aril of *Myristica fragrans* HOUTT. (Myristicaceae), is a well-known traditional Chinese medicine. It has been widely used as spice and a valuable remedy in traditional Chinese medicine for strengthening the stomach and expelling 'wind-all' [1]. Various neolignanoids from the mace have been reported [2–6]. Some of them exhibited significant dental-caries prevention against *Streptococcus mutans* [6] and antioxidation effects *in vivo* and on antilipid peroxidation in a rat-liver homogenate *in vitro* [7]. The aim of our work was to further investigate the chemical constituents of mace. Herein we describe the isolation and structural elucidation of three new neolignans, named 1-deoxycarinatone (**1**), isodihydrocarinatidin (**2**), and isolicarin A (**3**), together with one known neolignan, (+)-dehydrodiisoeugenol (**4**).

Results and Discussion. – Compound **1** was isolated as an oil. The molecular formula of **1** was determined to be $C_{20}H_{24}O_4$ by HR-ESI-MS ($[M+Na]^+$ at *m/z* 351.1566). The IR spectrum showed the presence of OH (3359 cm^{-1}), aromatic (1603, 1515, and 1463 cm^{-1}) and Me (1378 cm^{-1}) groups. The structure of **1** was deduced from its ^1H- and ^{13}C-NMR data (*Table*) and comparison of the latter with those of carinatone (=(2*S*)-1-(3,4-dimethoxyphenyl)-2-[2-hydroxy-3-methoxy-5-(prop-2-enyl)phenyl]-propan-1-one) [8] and 2-(2,6-dimethoxy-4-(prop-2-enyl)phenoxy)-1-(4-hydroxy-3-methoxyphenyl)propan-1-ol [4].

The absolute configuration of **1** was established as (*S*) on the basis of the negative *Cotton* effect at 260–285 nm in its CD spectrum and the $[\alpha_D]$ value ($[\alpha]_D^{20} = +33.3$), which were opposite to those of carinatone [8] (notice that the stereodescriptor is (*S*) in both cases). Compound **1** was named 1-deoxycarinatone (=2-[(1*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylethyl]-6-methoxy-4-(prop-2-enyl)phenol).

The ^1H- and ^{13}C-NMR data of **1** indicated the presence of two MeO (δ(H) 3.81 (*s*) and 3.87 (*s*); δ(C) 55.8 and 56.0), a Me (δ(H) 1.18 (*d*, J = 7.0 Hz); δ(C) 19.3), and a prop-2-enyl group. In addition, the





[a]) 8,3'-Neolignane atom numbering.

signals of five aromatic protons were observed and distributed to two aromatic rings on the basis of the coupling constants in the ^{1}H-NMR spectrum, where two *m*-positioned protons of one aromatic ring appeared at δ(H) 6.55 (*d*, J = 2.0 Hz) and 6.60 (*d*, J = 2.0 Hz), and three protons of the other aromatic ring appeared at δ(H) 6.62 (*d*, J = 2.0 Hz), 6.66 (*dd*, J = 2.0, 8.0 Hz), and 6.78 (*d*, J = 8.0 Hz) as an *ABX* system. Comparison with ^{13}C-NMR data of carinatone [8] and 2-[(2,6-dimethoxy-4-(prop-2-enyl)phenoxy]-1-(4-hydroxy-3-methoxyphenyl)propan-1-ol [4] led to the conclusion that a 2-hydroxy-3-methoxy-5-(prop-2-enyl)phenyl and a 4-hydroxy-3-methoxyphenyl groups existed in **1**. Further, two *dd* at δ(H) 2.65 (*dd*, J = 8.5, 13.5 Hz, 1 H) and 2.94 (*dd*, J = 6.0, 13.5 Hz, 1 H), a Me group at δ(H) 1.18 (*d*, J = 7.0 Hz), and a CH group at δ(H) 3.37 (*ddt*, J = 6.0, 7.0, 8.5 Hz) in the ^{1}H-NMR spectrum of **1** suggested a partial structure Ph–CH_2–CH(R)–Me in the molecule [3]. In the EI-MS of **1**, the molecular ion at *m*/*z* 328 (M^+) and fragment ions at *m*/*z* 191 ([2-hydroxy-3-methoxy-5-(prop-2-enyl)phenylethane]$^+$, base peak) and 137 [4-hydroxy-3-methoxyphenylmethylene]$^+$), and their corresponding dehydroxyl fragment ions at *m*/*z* 175 and 121 supported also the structure of **1**.

Compound **2** was isolated as an oil with the molecular formula $C_{20}H_{22}O_4$, which was consistent with the analysis of the HR-EI-MS (M^+) at *m*/*z* 326.1515).

The ^{1}H- and ^{13}C-NMR data of **2** (*Table*) and comparison with those of dihydrocarinatidin (=4-[(2*S*,3*S*)-2,3-dihydro-7-methoxy-3-methyl-5-(prop-2-enyl)-benzofuran-2-yl]-2-methoxyphenol) [9–12] suggested that **2** was the enantiomer of dihydrocarinatidin [13]. By comparison of the optical rotation ($[\alpha]_D^{20} = +15.0$) of **2** with that of dihydrocarinatidin ($[\alpha]_D^{20} = -12.7$), the absolute configuration of **2** was determined to be (2*R*,3*R*) (systematic atom numbering). The positive *Cotton* effect at 260–285 nm in the CD spectrum of **2** further supported the above inference [14]. Therefore, the structure of **2** was concluded to be 4-[(2*R*,3*R*)-2,3-dihydro-7-methoxy-3-methyl-5-(prop-2-enyl)benzofuran-2-yl]-2-methoxyphenol and named isodihydrocarinatidin.

The ^{1}H-NMR data of **2** were similar to those of dihydrocarinatidin with a *trans*-2-aryl-2,3-dihydro-3-methylbenzofuran moiety, which showed characteristic signals at δ 5.08 (*d*, J = 9.5 Hz) for H–C(α) and 1.37 (*d*, J = 7.0 Hz) for Me(γ) [9–12][1]). The ^{13}C-NMR data indicated the presence of a 3-methoxy-5-

[1]) Arbitrary atom numbering; for systematic names, see, *e.g.*, *Exper. Part.*

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1**–**4**. At 500 and 125 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz.

Position	**1**		**2**		**3**		**4**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
C(1)		132.2		132.2		130.9		132.1
H–C(2)	6.62 (*d*, *J* = 2.0)	111.7	6.98 (*d*, *J* = 1.5)	108.9	6.87 (*d*, *J* = 2.0)	109.0	6.97 (*d*, *J* = 1.5)	108.8
C(3)		146.1		146.6		146.2		146.6
C(4)		143.5		145.7		144.9		145.7
H–C(5)	6.78 (*d*, *J* = 8.0)	113.8	6.88 (*d*, *J* = 7.5)	114.0	6.88 (*d*, *J* = 8.0)	114.1	6.88 (*d*, *J* = 8.0)	114.0
H–C(6)	6.66 (*dd*, *J* = 2.0, 8.0)	121.9	6.91 (*dd*, *J* = 1.5, 7.5)	119.9	6.79 (*dd*, *J* = 2.0, 8.0)	119.5	6.91 (*dd*, *J* = 1.5, 8.0)	119.8
C(1′)		133.3		133.2		134.3		133.2
C(2′)		146.0		145.7		146.2		146.5
C(3′)		141.2		144.0		144.0		144.0
H–C(4′)	6.60 (*d*, *J* = 2.0)	108.5	6.63 (br. *s*)	109.1	6.80 (br. *s*)	109.1	6.79 (br. *s*)	109.3
C(5′)		130.9		133.5		132.2		132.0
H–C(6′)	6.55 (*d*, *J* = 2.0)	121.9	6.60 (br. *s*)	111.8	6.78 (br. *s*)	113.9	6.76 (br. *s*)	113.2
$CH_2(\alpha)$ or H–C(α)	2.65 (*dd*, *J* = 8.5, 13.5), 2.94 (*dd*, *J* = 6.0, 13.5)	50.4	5.08 (*d*, *J* = 9.5)	93.7	5.77 (*d*, *J* = 8.5)	88.7	5.10 (*d*, *J* = 9.0)	93.6
H–C(β)	3.37 (*ddt*, *J* = 6.0, 7.0, 8.5)	42.7	3.45 (*dq*, *J* = 7.0, 10.0)	45.7	3.59 (*dq*, *J* = 7.0, 8.5)	41.5	3.45 (*dq*, *J* = 7.0, 9.5)	45.5
Me(γ)	1.18 (*d*, *J* = 7.0)	19.3	1.37 (*d*, *J* = 7.0)	17.4	0.83 (*d*, *J* = 7.0)	17.0	1.38 (*d*, *J* = 6.5)	17.4
$CH_2(\alpha')$ or H–C(α')	3.30 (*d*, *J* = 6.5)	40.1	3.36 (*d*, *J* = 6.5)	40.2	6.35 (*dd*, *J* = 1.5, 15.5)	130.9	6.36 (*dd*, *J* = 1.5, 15.5)	130.8
H–C(β')	5.95 (*ddt*, *J* = 6.5, 8.2, 13.5)	137.9	6.00 (*ddt*, *J* = 6.5, 8.2, 13.5)	137.9	6.10 (*dq*, *J* = 6.5, 15.5)	123.4	6.10 (*dq*, *J* = 6.5, 15.5)	123.3
$CH_2(\gamma')$ or Me(γ')	5.03 (*ddt*, *J* = 1.5, 4.3, 8.2), 5.05 (*ddt*, *J* = 1.5, 4.3, 13.5)	115.4	5.06 (*ddt*, *J* = 1.5, 3.0, 8.2), 5.13 (*ddt*, *J* = 1.5, 3.0, 13.5)	115.6	1.86 (*dd*, *J* = 1.5, 6.5)	18.3	1.87 (*dd*, *J* = 1.5, 6.5)	18.2
MeO	3.81 (*s*)	55.8	3.87 (*s*)	56.0	3.87 (*s*)	55.9	3.88 (*s*)	55.8
MeO	3.87 (*s*)	56.0	3.88 (*s*)	56.0	3.92 (*s*)	55.9	3.89 (*s*)	55.8
OH	5.59 (*s*)		5.63 (*s*)		5.57 (*s*)		5.62 (*s*)	

(prop-2-enyl) phenyl and a 4-hydroxy-3-methoxyphenyl moiety in the molecule, which were in agreement with fragmentation ions at *m/z* 147 ([3-methoxy-5-(prop-2-enyl)phenyl]$^+$) and 123 ([4-hydroxy-3-methoxyphenylmethylene]$^+$) in the EI-MS.

The molecular formula for compound **3** was established as $C_{20}H_{22}O_4$ on the basis of HR-EI-MS data (M^+ at *m/z* 326.1516) and the total number of C- and H-atoms was estimated from the NMR (*Table*) spectra. The ^{1}H-NMR data indicated the presence of a *cis*-2-aryl-2,3-dihydro-3-methylbenzofuran moiety [14][15] in **3**, and further data suggested that **3** was a diastereoisomer of dehydrodiisoeugnol (=4-{(2*R*,3*R*)-2,3-dihydro-7-methoxy-3-methyl-5-[(1*E*)-prop-1-enyl]benzofuran-2-yl}-2-methoxyphenol; **4**. The absolute configuration of **3** was established as (2*S*,3*R*) (systematic atom numbering) on the basis of the positive *Cotton* effect at 260–285 nm in its CD spectrum and the $[\alpha_D]$ value ($[\alpha]_D^{20} = -24.2$), which were compared with those of (−)-7-epiconocarpan (=(7*S*,7′*E*,8*R*)-4′,7-epoxy-8,3′-neolignan-7′-ene-4-ol = 4-{(2*S*,3*R*)-2,3-dihydro-3-methyl-5-[(1*E*)-prop-1-enyl]benzofuran-2-yl}phenol) [14]. Therefore, the structure of **3** was determined to be 4-{(2*S*,3*R*)-2,3-dihydro-7-methoxy-3-methyl-5-[(1*E*)-prop-1-enyl]benzofuran-2-yl}-2-methoxyphenol and named isolicarin A.

The ^{1}H-NMR spectrum of **3** revealed signals at δ(H) 5.77 (*d*, *J* = 8.5 Hz, H(α)), 3.59 (*dq*, *J* = 7.0, 8.5 Hz, H(β)), and 0.83 (*d*, *J* = 7.0 Hz, Me(γ))[1]), typical for a *cis*-2-aryl-2,3-dihydro-3-methylbenzofuran moiety [14][15]. The (1*E*)-prop-1-enyl group was evident from the presence of an *AMX*$_3$ spin system at δ(H) 6.35 (*dd*, *J* = 1.5, 15.5 Hz, H(α')), 6.10 (*dq*, *J* = 6.5, 15.5 Hz, H(β')), and 1.86 (*dd*, *J* = 1.5, 6.5 Hz, Me(γ'))[1]). The five aromatic protons of **3** appeared as an *ABX*-type pattern (δ(H) 6.79 (*dd*, *J* = 2.0, 8.0 Hz), 6.87 (*d*, *J* = 2.0 Hz), and 6.88 (*d*, *J* = 8.0 Hz)), and as that of two *m*-positioned protons (δ(H) 6.78 (br. *s*) and 6.80 (br. *s*)). Their substitution patterns agreed with those of dehydrodiisoeugnol (=(+)-licarin A; **4**) [16][17]. The EI-MS showed the molecular-ion peak at *m/z* 326 (base peak) and fragment ions at *m/z* 309 ([*M* − OH]$^+$), 295 ([*M* − MeO]$^+$), 264 ([*M* − 2 MeO]$^+$), 147 ([3-methoxy-5-(prop-1-enyl)phenyl]$^+$), and 137 ([4-hydroxy-3-methoxyphenylmethylene]$^+$), which were consistent with a dehydrodiisoeugnol structure [16].

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Experimental Part

General. Column chromatography (CC): neutral aluminium oxide (activated, 150 mesh; *Merck*). TLC: silica gel GF_{254} plates (*Merck*). Semi-prep. HPLC: *P680* chromatograph (*Dionex Co.*, CA); *UVD170U* detector; *Phenomenex-Luna-10-C18-(2)* column (250 mm × 21.2 mm (i.d.), 10 μm); flow rate 9.9 ml/min, eluting with MeOH/H_2O. Optical rotations: *Perkin-Elmer 243B* polarimeter; in $CHCl_3$. UV Spectra: *Varian Cary-300-UV-VIS* spectrometer; in MeOH; λ_{max} (log ε) in nm. CD Spectra: *Jasco J-810* spectropolarimeter; in MeOH. IR Spectra: *Thermo-Nicolet Nexus-470-FT-IR* spectrometer; KBr pellets; in cm^{-1}. NMR Spectra: *Varian INOVA-500* spectrometer; at 500 (^{1}H) and 125 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to $SiMe_4$, *J* in Hz. MS: *Finnigan Trace-2000-GC-MS* spectrometer for EI and a *Bruker Daltonics-Apex-IV Fourier*-transform *ICR* high-resolution spectrometer for HR-ESI and HR-EI; in *m/z*.

Plant Material. The aril of *M. fragrans* (mace) was purchased from *W. Wilbert Co.*, Colombo, Sri Lanka.

Extraction and Isolation. The powdered mace (936 g) was extracted with MeOH (3 × 3000 ml) at r.t., 4 h each. After solvent evaporation, 209.5 g of the residue was obtained, which was dissolved in 95% aq. MeOH and extracted with hexane to afford a hexane (113 g) and a 95% aq. MeOH (176.5 g) extract, resp. The 95% MeOH extract (84.5 g) was dissolved in Et_2O (1.0 l), and extracted with 5% HCl soln.

(3 × 150 ml). The residual org. layer was neutralized and extracted with 5% $NaHCO_3$ soln. (3 × 150 ml). The 5% $NaHCO_3$ soln. was acidified to pH 4 and extracted with Et_2O (3 × 150 ml). The Et_2O soln. was concentrated to afford an acidic fraction (1.0 g). The 5% $NaHCO_3$-treated org. layer was washed with 5% NaOH soln. (3 × 150 ml) and then concentrated to afford a neutral fraction (30 g). The neutral fraction (9.3 g) was subjected to CC (neutral alumina 80 cm × 7 cm (i.d.) column, benzene/AcOEt (0–100%): *Fractions 1–20* (*ca.* 1000 ml each). *Fr. 8* (600 mg) was purified by semi-prep. reversed-phase HPLC ($MeOH/H_2O$ 65:35): **1** (1.2 mg), **2** (1.5 mg), **3** (1.7 mg), and **4** (500 mg).

1-Deoxycarinatone (=*2-[(1S)-2-(4-Hydroxy-3-methoxyphenyl)-1-methylethyl]-6-methoxy-4-(prop-2-enyl)phenol*; **1**): Oil. $[\alpha]_D^{20} = +33.3$ ($c = 0.6$, $CHCl_3$). CD (MeOH): 225 (neg.), 240 (pos.), 252 (neg.), 291 (neg.). UV (MeOH): 230 (3.94), 280 (3.49). IR (KBr): 3359, 2924, 2854, 1603, 1515, 1463, 1378, 1316, 1272, 1123, 1042, 929, 862. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 328 (M^+), 191 (100, [2-hydroxy-3-methoxy-5-(prop-2-enyl)phenylethane]$^+$), 175 [3-methoxy-5-(prop-2-enyl)phenylethane]$^+$), 137 ([4-hydroxy-3-methoxyphenylmethylene]$^+$), 121 ([3-methoxyphenylmethylene]$^+$). HR-ESI-MS: 351.1566 ([M + Na]$^+$, $C_{20}H_{24}NaO_4^+$; calc. 351.1567).

Isodihydrocarinatidin (=*4-[(2R,3R)-2,3-Dihydro-7-methoxy-3-methyl-5-(prop-2-enyl)benzofuran-2-yl]-2-methoxyphenol*; **2**): Oil. $[\alpha]_D^{20} = +15.0$ ($c = 0.6$, $CHCl_3$). CD (MeOH): 225 (neg.), 240 (pos.), 261 (pos.). UV (MeOH): 238 (4.13), 282 (3.81). IR (KBr): 3449, 2960, 2929, 1606, 1516, 1495, 1453, 1328, 1270, 1205, 1139, 1032, 952, 852, 820. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 326 (100, M^+), 311 ([M – Me]$^+$), 295 [M – MeO]$^+$), 147 ([3-methoxy-5-(prop-2-enyl)phenyl]$^+$), 137 ([4-hydroxy-3-methoxyphenylmethylene]$^+$). HR-EI-MS: 326.1515 (M^+), $C_{20}H_{22}O_4^+$; calc. 326.1518).

Isolicarin A (=*4-{(2S,3R)-2,3-Dihydro-7-methoxy-3-methyl-5-[(1E)-prop-1-enyl]benzofuran-2-yl}-2-methoxyphenol*; **3**): Oil. $[\alpha]_D^{20} = -24.2$ ($c = 1.1$, $CHCl_3$). CD (MeOH): 220 (neg.), 243 (pos.), 289 (neg.). UV (MeOH): 221 (3.94), 272 (3.67). IR (KBr): 3420, 2924, 2853, 1608, 1518, 1500, 1453, 1339, 1270, 1217, 1143, 1031, 966, 862, 818. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 326 (100, M^+), 311 ([M – Me]$^+$), 309 ([M – OH]$^+$), 295 ([M – MeO]$^+$), 264 ([M – 2 MeO]$^+$), 147 ([3-methoxy-5-(prop-1-enyl)phenyl]$^+$), 137 ([4-hydroxy-3-methoxyphenylmethylene]$^+$). HR-EI-MS: 326.1516 (M^+, $C_{20}H_{22}O_4^+$; calc. 326.1518).

(+)-Dehydrodiisoeugenol (**4**): White amorphous powder. $[\alpha]_D^{20} = +18.0$ ($c = 1.0$, $CHCl_3$). CD (MeOH): 225 (neg.), 266 (pos.), 307 (neg.). UV (MeOH): 218 (4.06), 274 (3.82). IR (KBr): 3419, 2951, 2925, 1610, 1518, 1496, 1453, 1336, 1274, 1220, 1144, 1030, 954, 861, 810. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 326 (100, M^+), 311 ([M – Me]$^+$), 309 ([M – OH]$^+$), 295 ([M – MeO]$^+$), 264 ([M – 2 MeO]$^+$), 147 ([3-methoxy-5-(prop-1-enyl)phenyl]$^+$), 137 ([4-hydroxy-3-methoxyphenylmethylene]$^+$). The above NMR and MS data were in agreement with those of dehydrodiisoeugenol [14].

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