Phytochemistry, Vol. 27, No. 2, pp. 563–568, 1988.
Printed in Great Britain.

0031–9422/88 \$3.00+0.00
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NEW NEOLIGNANS AND LIGNANS FROM THE ARIL OF *MYRISTICA FRAGRANS**

SUMITRA HADA, MASAO HATTORI, YASUHIRO TEZUKA, TOHRU KIKUCHI and TSUNEO NAMBA

Research Institute for Wakan-Yaku (Oriental Medicines), Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930–01, Japan

(*Revised received* 10 *July* 1987)

Key Word Index—*Myristica fragrans*; Myristicaceae; mace; neolignans; lignans.

Abstract—Eight neolignans and five lignans were isolated from mace, the aril of *Myristica fragrans*, and their structures were determined by spectroscopic methods as *erythro*-2-(4″-allyl-2″,6″-dimethoxyphenoxy)-1-(3′,4′,5′-trimethoxyphenyl)propan-1,3-diol (**1b**), *threo*-2-(4″-allyl-2″-methoxyphenoxy)-1-(4′-hydroxy-3′-methoxyphenyl) propan-1-ol (**2a**), *threo*-1-(4′-hydroxy-3′-methoxyphenyl)-2-(2″-methoxy-4″-(1‴ (*E*)-propenyl) phenoxy) propan-1-ol (**3a**), its *erythro* form (**3b**), *threo*-1-(4′-hydroxy-3′-methoxyphenyl)-1-methoxy-2-(2″-methoxy-4″-(1‴-(*E*)-propenyl)phenoxy)-propane (**4a**), its *erythro* form (**4b**), fragransol-A (**5**), fragransol-B (**6**), fragransin D_1 (**7**), fragransin D_2 (**8**), fragransin D_3 (**9**), fragransin E_1 (**10**) and the known compound austrobailignan-7 (**11**).

INTRODUCTION

In the course of isolation of antibacterial principles against a primary cariogenic bacterium, *Streptococcus mutans*, from the aril of *Myristica fragrans*, which is used as a combination of drugs for dental caries prevention in Ayurveda medical system, some lignans and neolignans have already been reported [1–3]. The major phenolic components isolated, dehydrodiisoeugenol and 5′-methoxydehydrodiisoeugenol, were demonstrated to have significant antibacterial action against *S. mutans* [1]. The present paper describes the isolation and characterization of some additional minor components.

RESULTS AND DISCUSSION

Repeated fractionation of the phenolic fraction of mace by silica gel column-chromatography and preparative HPLC led to the isolation of the following lignan and neolignan compounds, the structures of which were determined by spectroscopic methods.

Compound **1b** (**b** = *erythro*) was obtained as colourless needles, mp 104.5–105°, with the molecular formula $C_{23}H_{30}O_8$. The ^{1}H NMR spectrum showed signals for one hydroxymethyl (δ*ca* 3.9, *d*, $J = 11.5$ Hz, H-3), one benzylic methine substituted by oxygen (δ4.16, *d*, $J = 2.9$ Hz, H-1) and one methine substituted by oxygen (δ4.11, *m*, H-2) along with those for one allyl group, five methoxyls and a couple of two equivalent aromatic protons (δ6.48, H-3″ and H-5″; δ6.57, H-2′ and H-6′), revealing the presence of 3′,4′,5′-trimethoxyphenyl and 4″-allyl-2″,6″-dimethoxyphenoxyl moieties, which were also confirmed by the ^{13}C NMR spectrum (Table 1). These data and the mass fragmentation pattern showed it to be an acyclic bis-arylpropanoid type compound [2, 4]. The coupling constant between H-1 and H-2 showed a small *J* value ($J = 2.9$ Hz) indicating the presence of the *erythro* form [2, 5]. On acetylation **1b** yielded a diacetate. The ^{1}H NMR spectrum of the acetate showed two singlet peaks at δ1.99 and 2.15, ascribed to two aliphatic acetoxyls, and the H-1 and H-3 signals were shifted to the lower field, δ6.02 and 4.25/4.47 (ABX type, $J_{AB} = 12$ Hz, $J_{AX} = 3.4$ Hz and $J_{BX} = 5.9$ Hz), respectively, indicating that two hydroxyl groups are attached at the C-1 and C-3 positions in **1b**. On the basis of these data the structure of

Table 1. ^{13}C NMR spectral data for acydic bis-arylpropanids of mace

Carbon No.	**1b**	**2a**	**3a**	**3b**	**4b**
1	87.0	84.2	84.0	82.4	85.5
2	72.7	77.8	74.9	73.6	79.6
3	60.6	17.0	16.9	13.4	15.2
1′	131.0	135.2	132.6	131.8	131.3
2′	105.6	109.4	109.5	108.9	109.9
3′	153.2	146.5	146.6	146.8	146.6
4′	135.1	145.4	145.5	144.8	145.5
5′	153.2	114.0	114.1	113.9	113.8
6′	105.6	120.6	120.7	119.8	121.0
1″	135.1	146.5	146.8	140.8	141.3
2″	153.2	150.7	150.8	151.5	150.8
3″	103.1	112.4	109.5	109.5	109.9
4″	131.0	132.0	133.5	133.6	132.1
5″	103.1	120.8	119.0	119.1	120.7
6″	153.2	119.2	118.8	118.9	118.6
1‴	40.5	39.8	130.5	130.4	130.6
2‴	136.7	137.2	124.8	124.8	124.0
3‴	116.3	115.7	18.2	18.2	18.3
MeO	56.2 (x4)	55.7	55.9	55.8	55.9 (x2)
	60.7	55.9	56.1	55.9	57.2

a = *threo*; **b** = *erythro*.

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*Part 3 in the series 'Constituents of mace'. For part 2 see ref. [2].

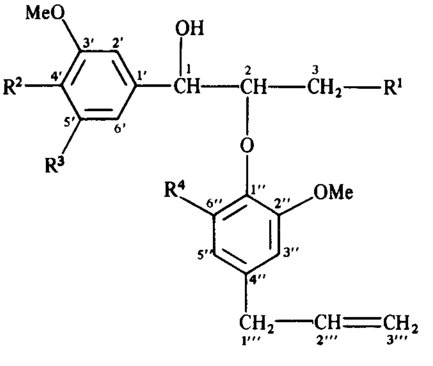
1b was concluded to be *erythro*-2-(4″-allyl-2″,6″-dimethoxyphenoxy)-1-(3′,4′,5′-trimethoxyphenyl) propan-1,3-diol, a new natural product.

Compound **2a** (**a** = *threo*), $C_{20}H_{24}O_5$, an oil, showed very similar ^{1}H NMR and mass spectra to those of previously isolated *erythro*-2-(4″-allyl-2″-methoxyphenoxy)-1-(4′-hydroxy-3′-methoxyphenyl)propan-1-ol (**2b**) [2], but the coupling constant between H-1 and H-2 was larger (J = 8.3 Hz) and the ^{13}C chemical shift of the *sec*-methyl (C-3) was in lower field, δ17.0 [2, 6], than in **2b** (J = 3.4 Hz and δ13.4, respectively), which reveals it to be a *threo* form of **2b**, a new natural product.

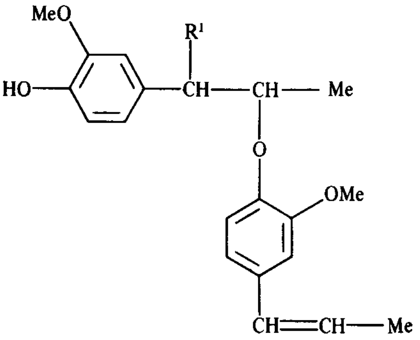
Compound **3a** was obtained as an oil. The ^{1}H NMR spectrum showed characteristic signal pattern for acyclic bis-arylpropanoids, but with a 1‴-(*E*)-propenyl side-chain. The ^{13}C NMR showed the presence of 4′-hydroxy-3′-methoxypenyl and 2″-methoxy-4″-(1‴-(*E*)-propenyl)-phenoxyl moieties, which were also confirmed by mass spectrometry. The larger coupling constant between H-1 and H-2 (J = 8.4 Hz) and the low-field chemical shift (δ 16.9) for the *sec*-methyl (C-3) in the ^{13}C NMR spectrum, indicate it to be a *threo* form [2, 6]. These findings consequently led us to characterize the structure of **3a** as *threo*-1-(4′-hydroxy-3′-methoxyphenyl)-2-(2″-methoxy-4″-(1‴ (*E*)-propenyl) phenoxy) propan-1-ol, a new natural product.

Compound **3b**, $C_{20}H_{24}O_5$, an oil, showed very similar ^{1}H NMR and mass spectral patterns to those of **3a**, but with a smaller coupling constant between H-1 and H-2 (J = 2.9 Hz), and the high-field chemical shift for the *sec*-methyl (C-3) (δ13.4) in the ^{13}C NMR spectrum. This indicates it to be an *erythro* form of **3a**, a new natural product. However, both **3a** and **3b** have been previously synthesized by Ag_2O or hydrogen peroxide-peroxidase oxidation of (*E*)-isoeugenol [7, 8] but have been isolated as diacetates or a mixture of *threo* and *erythro* forms, respectively. The spectral data of the diacetate of **3a** agreed well with the published data [7].

Compound **4a** and **4b**, colourless oils, showed mixed spectroscopic data for *threo* and *erythro* forms of the acyclic bis-arylpropanoids; the two doublet signals for *threo* and *erythro* isomers showed $J_{1,2}$ values of 8.5 and 4.9 Hz in ^{1}H NMR (CD_3COOD) and the *sec*-methyl (C-3) signals at δ16.4 and 15.2, respectively, in the ^{13}C NMR ($CDCl_3$). In addition, the ^{1}H NMR spectrum was quite similar to the reported data for 1-(4′-hydroxy-3′-methoxyphenyl)-1-methoxy-2-(2″-methoxy-4″-(1‴-propenyl)-phenoxy) propane derivatives synthesized by dye-sensitized photooxidation, free radical-mediated oxidation and anodic oxidation [9–11], but the propenyl side-chain was determined as an *E*-form on the criterion of the large coupling constant between the vicinal vinyl-protons (J = 16 Hz). On the basis of the above evidence, the structures of **4a** and **4b** were concluded to be *threo*- and *erythro*-1-(4′-hydroxy-3′-methoxyphenyl)-1-methoxy-2-(2″-methoxy-4″-(1‴-(*E*)-propenyl)-phenoxy) propane. The ratio of the *threo* and *erythro* isomers was found to be 3:7 by ^{1}H NMR, but its further separation could not be done because of the little amount of the compounds. This is the first report of these compounds as natural products.



1b R^1 = OH, R^2 = R^3 = R^4 = OMe
2a R^1 = R^3 = R^4 = H, R^2 = OH
a = *threo*, b = *erythro*

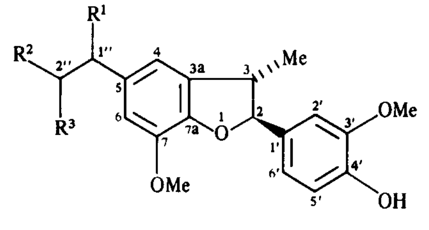


3a, **3b** R^1 = OH
4a, **4b** R^1 = OMe
a = *threo*, b = *erythro*

Compound **5** was obtained as an oil. The ^{1}H NMR spectrum showed a characteristic signal pattern of dihydrobenzofuran type neolignans but with signals at δ4.0 (1H, *d*, J = 5.5 Hz, H-1″), 3.9 (1H, *m*, H-2″), 1.19 (3H, *d*, J = 6.2 Hz, H-3″) and 3.31 (*s*, aliphatic MeO) ascribed to the presence of a –CH(OR^2)–CH(OR^1)–Me group (R^1 = H, R^2 = Me or R^1 = Me, R^2 = H) in place of a common 1‴-(*E*)-propenyl side-chain present in a series of dihydrobenzofuran derivatives from mace and nutmeg [1, 4, 12–15]. Furthermore, double resonance experiments supported the presence of this functional group as well as a 2,3-dihydro-2-aryl-3-methylbenzofuran system. The ^{1}H NMR spectrum of the acetate showed two singlet peaks for aliphatic and aromatic acetoxyls (δ2.01 and 2.31, respectively). The multiplet signal for H-2″ in **5** was shifted from δ3.90 to 5.03 on acetylation, indicating that the aliphatic hyrdoxyl group is attached to C-2″. Accordingly the aliphatic methoxyl group was considered to be attached to C-1″. The double-resonance experiments on the acetate showed that on irradiation at δ5.03 (H-2″), the doublet at δ4.20 (H-1″) and also the doublet at δ1.22 (H-3″), each became a singlet. Appreciable NOE between Me-3 and H-2 protons indicate that the adjacent 2-aryl and 3-methyl substituents are oriented with a *trans* relationship. Furthermore, the broad singlet signals at δ6.72 and 6.78 could be assigned to H-4 and H-6 by signal enhancements on irradiation at δ1.40 (Me-3) and 3.90 (MeO-7), respectively. These findings along with its ^{13}C NMR data led us to characterize the structure of **5** as 2,3-dihydro-5-(2″-hydroxy-1″-methoxypropyl)-2-(4′-hydroxy-3′-methoxyphenyl)-7-methoxy-3-methylbenzofuran, a new natural product, which is named fragransol-A.

Compound **6**, $C_{19}H_{22}O_5$, an oil, also showed characteristic signals for 2-aryl-3-methyl-2,3-dihydrobenzofurans in its ^{1}H NMR spectrum; δ1.38 (*d*, Me-3), 3.45 (*m*, H-3) and 5.10 (*d*, H-2). The spectrum further showed signals for one benzylic methine (δ2.84, *t*, H-1″), one hydroxymethyl (δ*ca* 3.9, H-2″), two methoxyls and five aromatic protons. The ^{1}H NMR spectrum of the acetate showed two singlets at δ2.06 and 2.31 for aliphatic and aromatic acetoxyls, respectively, and the signal for H-2″ in **6** was shifted from δ *ca* 3.9 to 4.26 on acetylation. The double resonance experiments for the acetate showed that on irradiation at δ4.26 (H-2″), the triplet at δ2.90 (H-1″) became a singlet. The NOE experiments showed the relative configuration of the acetate is identical with that of **5**. These findings and the ^{13}C NMR data led us to determine the structure of **6** as 2,3-dihydro-5-(2″-hydroxyethyl)-2-(4′-hydroxy-3′-methoxyphenyl)-7-methoxy-3-methylbenzofuran, a new natural product, which is named fragransol B.

Compound **7**, $C_{22}H_{28}O_6$, an oil, showed characteristic ^{1}H NMR signals for tetrahydrofuran type lignans. The chemical shifts of two *sec*-methyls (δ1.03 and 1.08, Me-3 and Me-4), two methines (δ2.34, *m*, H-3 and H-4) and two benzylic methines substituted by oxygen (δ4.52, *d*, $J = 6.1$ Hz, H-2 and H-5) was very similar to those of fragransin C_1 having a relative configuration of 2,3-*trans*/3,4-*cis*/4,5-*trans*, which has been previously isolated from mace [3]. However, the ^{13}C NMR spectrum showed the presence of 3″,4″,5″-trimethoxyphenyl and 4′-hydroxy-3′-methoxyphenyl moieties, which were also supported by the intense fragment ions at *m/z* 236 and 192 ascribed to (Ar–CH–CH(Me)–CH(Me)]$^+$ but with Ar = 3,4,5-trimethoxyphenyl and Ar = 4-hydroxy-3-methoxyphenyl, respectively (Table 2). These findings led us to conclude the structure of **7** as *r*-2-(4′-hydroxy-3′-methoxyphenyl)-*c*-5-(3″,4″,5″-trimethoxyphenyl)-*t*-3,*t*-4-dimethyltetrahydrofuran, a new natural product, which is named fragransin D_1.



5 R¹ = OMe, R² = OH, R³ = Me
6 R¹ = R² = H, R³ = OH

Compound **8**, $C_{22}H_{28}O_6$, an oil, had the same [M]$^+$ and mass fragmentation pattern as **7** (Table 2), revealing them to be isomers. However, the multiplet signal for two methines (H-3 and H-4) were observed in higher field, δ1.78 and the doublet signal ($J = 9$ Hz) for two methine substituted by oxygen (H-2 and H-5) in lower field, δ4.64, which was very similar to those of fragransin C_2 (2,3 *trans*/3,4 *trans*/4,5 *trans*) from mace [3]. These findings led us to conclude the structure of **8** as *r*-2-(4′-hydroxy-3′-methoxyphenyl)-*t*-5-(3″,4″,5″-trimethoxyphenyl)-*t*-3,*c*-4-dimethyltetrahydrofuran, a new natural product, which is named fragransin D_2.

Compound **9**, $C_{22}H_{28}O_6$, an oil, had the same [M]$^+$ and mass fragmentation pattern as **7** and **8**, that revealed them to be isomeric. But the ^{1}H NMR spectrum showed the signals for two *sec*-methyls (δ0.70 and 1.07, Me-4 and Me-3), two methines (δ1.81 and 2.26, each *ddq*, H-3 and H-4) and two benzylic methines substituted by oxygen (δ4.43 and 5.10, each *d*, $J = 9.2$ and 8.5 Hz, H-2 and H-5, respectively), which were very similar to those of fragransin C_{3b} (2,3-*trans*/3,4-*trans*/4,5-*cis*) from mace [3]. The two dimensional ^{1}H–^{1}H COSY experiment showed that the aromatic H-2″ and H-6″ at δ6.55 were correlated with H-5 and also with the three methoxyls (MeO-3″, MeO-4″ and MeO-5″), indicating a 3″, 4″,5″-trimethoxyphenyl substituent to be attached at the C-5 position. Similarly the aromatic H-2′ and H-6′ at δ7.0 and 7.04, respectively, were correlated with H-2 and also with MeO-3′ at δ3.91, indicating a 4′-hydroxy-3′-methoxyphenyl substituent to be attached at the C-2 position. The stereochemistry of **9** was further confirmed by ^{1}H–^{13}C COSY and NOE experiments. On the basis of these data, the structure of **9** was concluded to be *r*-2-(4′-hydroxy-3′-methoxyphenyl)-*c*-5-(3″,4″,5″-trimethoxyphenyl)-*t*-3,*c*-4-dimethyltetrahydrofuran, a new natural product, which is named fragransin D_3.

Compound **10**, $C_{20}H_{22}O_5$, an oil, also showed characteristic signals for 2,5-bis-aryl-3,4-dimethyltetrahydrofuran having a symmetrical 2,3 *trans*/3,4 *cis*/4,5 *trans* configuration in the ^{1}H NMR spectrum; δ1.02 (6H, *d*, Me-3 and Me-4), 2.28 (2H, *m*, H-3 and H-4), 4.46 (2H, *d*, $J = 6.8$ Hz, H-2 and H-5). In addition, the signals for one

Table 2. Mass spectral data for tetrahydrofuran lignans of mace

Compound	[M]†	[Ar–CH=CH–Me]†	[Ar–CO–CH$_2$–Me]†	$\left[\begin{matrix}\text{CH–Me}\\ \text{Ar–CH–CH–Me}\end{matrix}\right]^{\dagger}$	$\left[\begin{matrix}\text{CH}\\ \text{Ar–CH–CH–Me}\end{matrix}\right]^{\dagger}$	[ArCO]†
7	388 (70)	164 (20)	224 (10)	192 (100)	177 (45)	195 (10)
		208 (70)	180 (10)	236 (80)	221 (50)	151 (40)
8	388 (50)	164 (15)	224 (15)	192 (75)	177 (40)	195 (10)
		208 (100)	180 (15)	236 (60)	221 (50)	151 (40)
9	388 (50)	164 (10)	224 (8)	192 (100)	177 (40)	196 (10)
		208 (10)	180 (3)	236 (40)	221 (20)	151 (10)
10	342 (35)	164 (18)	178 (8)	192 (80)	177 (30)	149 (15)
		162 (16)	180 (10)	190 (80)	175 (30)	151 (20)
11	342 (30)	164 (15)	178 (8)	192 (50)	177 (20)	149 (18)
		162 (15)	180 (10)	190 (100)	175 (52)	151 (16)

methylenedioxyl (δ5.96), one methoxyl (δ3.91), one hydroxyl (δ5.56) groups and six aromatic protons, revealed the presence of 3′,4′-methylenedioxyphenyl and 4″-hydroxy-3″-methoxyphenyl moieties, which were also confirmed by the observation of mass fragment ions at *m/z* 190 and 192, ascribed to $[\text{Ar-}\dot{\text{C}}\text{H-CH(Me)-}\dot{\text{C}}\text{H(Me)}]^+$ (Ar = 3,4-methylenedioxyphenyl and Ar = 4-hydroxy-3-methoxyphenyl, respectively, Table 2). On the basis of these findings, the structure of **10** was concluded to be *r*-5-(4″-hydroxy-3″-methoxyphenyl)-*c*-2-(3′,4′-methylenedioxyphenyl)-*t*-3,*t*-4-dimethyltetrahydrofuran, a new natural product, which is named fragransin E_1.

Compound **11**, $C_{20}H_{22}O_5$, an oil, was isomeric with **10** and was found to be austrobailignan-7, isolated previously from *Austrobaileya scandens* [16], by comparing with the published spectral data and also by 2D ^{1}H–^{1}H NMR and NOE experiments. It is the first report of this compound in mace.

In conclusion, eight neolignans and five lignans including *threo* and *erythro* acyclic bis-arylpropanoids (**1b**, **2a**, **3a**, **3b**, **4a**, **4b**) and 2,3-dihydro-2-aryl-3-methylbenzofurans (**5** and **6**) and 2,5-bis-aryl-3,4-dimethyltetrahydrofurans (**7**, **8**, **9**, **10** and **11**) were isolated from mace. These compounds except **11** were all new natural products although some of them (**3a**, **3b**, **4a** and **4b**) have been already synthesized by oxidative coupling of (*E*)-isoeugenol.

EXPERIMENTAL

General. Mps: uncorr. ^{1}H NMR and ^{13}C NMR spectra were measured with TMS as int. std. MS were measured at 70 eV (EIMS probe).

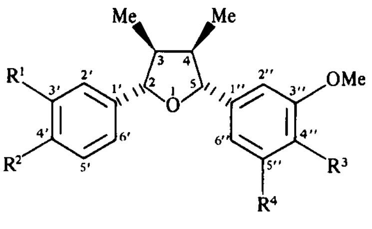
Mace was purchased from W. Wilbert and Co., Colombo, Sri Lanka in 1983 and the botanical source was identified by one of the authors (T.N).

Isolation. The phenolic fraction (31.5 g) of mace was chromatographed on a silica gel column with benzene and EtOAc (0–50%), which gave various lignans and neolignans as have been reported [1–3] along with a mixt. of unidentified compounds. This mixt. was further purified to give the following compounds, **1b** (5 mg as a pure form), **2a** (5 mg), **3a** (25 mg), **3b** (20 mg), **4a** (*ca* 3 mg), **5** (*ca* 3 mg), **6** (*ca* 3 mg), **7** (*ca* 3 mg), **8** (*ca* 3 mg), **9** (3.5 mg), **10** (*ca* 3 mg) and **11** (*ca* 3 mg), by prep. TLC (Merck Kieselgel 60 F_{254} or Merck PSC 60 F_{254} plate) and prep. HPLC (Chemosorb 5 Si, column size, 10 mm i.d. × 500 mm, Chemco Co., solvent system, hexane–dichloroethane–EtOH, 19:4:2).

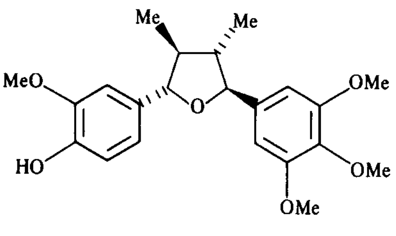
erythro-2-(4″-*Allyl*-2″,6″-*dimethoxyphenoxy*)-1-(3′,4′,5′-*trimethoxyphenyl*)*propan*-1,3-*diol* (**1b**). Colourless needles, mp 104.5–105°; high resolution MS: Found, *m/z* 434.1970, Calcd for $C_{23}H_{30}O_8$, *m/z* 434.1941 (M^+); EIMS (rel. int.) *m/z*: 434 (20, M^+), 240 (15), 220 (100), 197 (15), 194 (85); ^{1}H NMR (270 MHz; $CDCl_3$), δ: 3.38 (2H, *d*, J = 6.6 Hz, 2x H-1‴), 3.82 (3H, *s*, MeO), 3.85 (6H, *s*, 2x MeO), 3.88(6H, *s*, 2x MeO), 3.90 (2H, overlapped with methoxyl signals, *d*, J = 11.5 Hz, 2x H-3), 4.11 (1H, *m*, H-2), 4.16 (1H, *d*, J = 2.9 Hz, H-1), 5.10–5.20 (2H, *m*, 2x H-3‴), 5.90–6.05 (1H, *m*, H-2‴), 6.48 (2H, *s*, H-3″ and H-5″), 6.57 (2H, *s*, H-2′ and H-6′); IR ν_{max} cm^{-1}: 3450 (OH), 1595, 1505, 1460, 1422, 1130.

Acetate of **1b**. Colourless oil; high resolution MS: Found. *m/z*: 518.2161, Calcd for $C_{27}H_{34}O_{10}$, *m/z*: 518.2150 (M^+); EIMS (rel. int.) *m/z*: 518 (10, M^+), 458 (3), 371 (20), 265 (50), 223 (100), 194 (90); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.99 (3H, *s*, AcO-3), 2.15 (3H, *s*, AcO-1), 3.31 (2H, *d*, J = 6.8 Hz, 2x H-1‴), 3.73 (3H, *s*, MeO), 3.82 (6H, *s*, 2x MeO), 3.83 (6H, *s*, 2x MeO), 4.25 (1H, *dd*, J = 3.4, 12.0 Hz, Ha-3), 4.47 (1H, *dd*, J = 5.9, 12.0 Hz, Hb-3), 4.61 (1H, *m*, H-2), 5.05–5.13 (2H, *m*, H-3‴), 5.93–6.00 (1H, *m*, H-2‴), 6.02 (1H, *d*, J = 4.9 Hz, H-1), 6.36 (2H, *s*, H-2′ and H-6′), 6.60 (2H, *s*, H-3″ and H-5″).

threo-2-(4″-*Allyl*-2″-*methoxyphenoxy*)-1-(4′-*hydroxy*-3′-*methoxyphenyl*)*propan*-1-*ol* (**2a**). Colourless oil; high resolution MS: Found, *m/z*: 344.1579, Calcd for $C_{20}H_{24}O_5$, *m/z* 344.1622 (M^+), EIMS (rel. int.) *m/z*: 344 (40, M^+), 326 (80, $M^+ - H_2O$), 192 (80), 180 (15), 164 (100), 153 (100); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.16 (3H, *d*, J = 6.1 Hz, 3xH-3), 3.36 (2H, *d*, J = 6.8 Hz, H-1‴), 3.89 (3H, *s*, MeO), 3.90 (3H, *s*, MeO), 4.04 (1H, m, H-2), 4.61 (1H, *d*, J = 8.3 Hz, H-1), 5.05-5.15 (2H, *m*, H-3‴), 5.60 (1H, *s*, OH), 5.90–6.05 (1H, m, H-2‴), 6.71-6.95 (6H, *m*, H-Ar).



7 $R^1 = R^3 = R^4 = OMe$, $R^2 = OH$
10 $R^1, R^2 = O\text{—}CH_2\text{—}O$, $R^3 = OH$, $R^4 = H$



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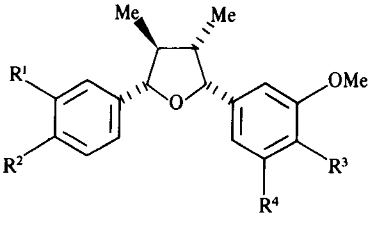

9 $R^1 = R^3 = R^4 = OMe$, $R^2 = OH$
11 $R^1, R^2 = O\text{—}CH_2\text{—}O$, $R^3 = OH$, $R^4 = H$

threo-1-(4′-*Hydroxy*-3′-*methoxyphenyl*)-2-(2″-*methoxy*-4″-(1‴-(*E*)-*propenyl*)*phenoxy*)*propan*-1-*ol* (**3a**). Colourless oil; high resolution MS: Found, *m/z* 344.1693, Calcd for $C_{20}H_{24}O_5$, *m/z* 344.1622 (M^+); EIMS (rel. int.) *m/z*: 344 (20, M^+), 192 (100), 180 (10), 164 (100), 153 (40); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.16 (3H, *d*, *J* = 6.2 Hz, 3x H-3), 1.88 (3H, *dd*, *J* = 6.6, 1.5 Hz, 3x H-3‴), 3.83 (3H, *s*, MeO), 3.91 (3H, *s*, MeO), 4.1 (1H, *m*, H-2), 4.62 (1H, *d*, *J* = 8.4 Hz, H-1), 5.63 (1H, *s*, OH), 6.15 (1H, *m*, H-2‴), 6.35 (1H, *dd*, *J* = 15.8, 1.5 Hz, H-1‴), 6.87–6.92 (6H, *m*, H-Ar).

Acetate of **3a**. Colourless oil; EIMS (rel. int.), *m/z*: 428 (100, M^+), 265 (90), 223 (100), 191 (50), 181 (90), 164 (100); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.19 (3H, *d*, *J* = 6.2 Hz, 3x H-3), 1.87 (3H, *dd*, *J* = 6.6, 1.5 Hz, 3x H-3‴), 2.03 (3H, *s*, AcO-1), 2.31 (3H, *s*, AcO-4′), 3.829 (3H, *s*, MeO), 3.832 (3H, *s*, MeO), 4.54 (1H, *dq*, *J* = 6.2, 6.8 Hz, H-2), 5.95 (1H, *d*, *J* = 6.8 Hz, H-1), 6.13 (1H, *m*, H-2‴), 6.34 (1H, *dd*, *J* = 15.8, 1.5 Hz, H-1‴), 6.72–7.01 (6H, *m*, H-Ar).

erythro-1-(4′-*Hydroxy*-3′-*methoxyphenyl*)-2-(2″-*methoxy*-4″-(1‴(E)-*propenyl*)*phenoxy*)*propan*-1-*ol* (**3b**). Colourless oil; high resolution MS: Found, *m/z* 344.1668, Calcd for $C_{20}H_{24}O_5$, *m/z* 344.1622 (M^+); EIMS *m/z*: 344 (50, M^+), 326 (40, $M^+ - H_2O$), 192 (40), 180 (20), 164 (100), 153 (90); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.17 (3H, *d*, *J* = 6.4 Hz, 3x H-3), 1.88 (3H, *dd*, *J* = 6.6, 1.5 Hz, 3x H-3‴), 3.90 (6H, *s*, 2x MeO), 4.33 (1H, *dq*, *J* = 6.4, 2.9 Hz, H-2), 4.82 (1H, *d*, *J* = 2.9 Hz, H-1), 5.56 (1H, *s*, OH), 6.16 (1H, *m*, H-2‴), 6.36 (1H, *dd*, *J* = 17.3, 1.5 Hz, H-1‴), 6.72–6.97 (6H, *m*, H-Ar).

erythro-1-(4′-*Hydroxy*-3′-*methoxyphenyl*)-1-*methoxy*-2-(2″-*methoxy*-4″-(1‴-(E)-*propenyl*)*phenoxy*)*propane* (**4b**). Colourless oil; high resolution MS: Found, *m/z* 358.1769, Calcd for $C_{21}H_{26}O_5$, *m/z* 357.9488 (M^+); EIMS (rel. int.) *m/z*: 358 (10, M^+), 194 (50), 192 (5), 167 (100), 164 (15); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.31 (3H, *d*, *J* = 6.1 Hz, 3x H-3), 1.85 (3H, *dd*, *J* = 6.6, 1.5 Hz, 3x H-3‴), 3.32 (3H, *s*, MeO-1), 3.80 (3H, *s*, MeO), 3.88 (3H, *s*, MeO), 4.29 (1H, *d*, *J* = 4.6 Hz, H-1), 4.35 (1H, *m*, H-2), 5.56 (1H, *s*, HO), 6.1 (1H, *m*, H-2‴), 6.3 (1H, *dd*, *J* = 16.0, 1.5 Hz, H-1‴), 6.6-6.94 (6H, *m*, H-Ar). ^{1}H NMR (270 MHz, CD_3COOD) δ: 1.28 (3H, *d*, *J* = 6.4 Hz, 3x H-3), 1.83 (3H, *dd*, *J* = 4.9, 1.5 Hz, 3x H-3‴), 3.30 (3H, *s*, MeO-1), 3.86 (3H, *s*, MeO), 3.87 (3H, *s*, MeO), 4.31 (1H, *d*, *J* = 4.9 Hz, H-1), 4.57 (1H, *m*, H-2), 6.1 (1H, *m*, H-2‴), 6.28 (1H, *dd*, *J* = 14.3, 1.5 Hz, H-1‴), 6.64–7.04 (6H, *m*, H-Ar).

2,3-*Dihydro*-5-(2″-*hydroxy*-1″-*methoxypropyl*)-2-(4′-*hydroxy*-3′-*methoxyphenyl*)-7-*methoxy*-3-*methylbenzofuran*, (*fragransol-A*) (**5**). Colourless oil; EIMS (rel. int.) *m/z*: 374 (100, M^+), 329 (100), 193 (45), 179 (35), 165 (90), 137 (98); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.19 (3H, *d*, *J* = 6.2 Hz, 3x H-3″), 1.39 (3H, *d*, *J* = 7.0 Hz, Me-3), 3.31 (3H, *s*, MeO-1″), 3.50 (1H, *m*, H-3), 3.90 (6H, *s*, MeO-7 and MeO-3′) 3.90 (1H, *m*, H-2″), 4.0 (1H, *d*, *J* = 5.5 Hz, H-1″), 5.12 (1H, *d*, *J* = 9.5 Hz, H-2), 5.65 (1H, *s*, HO-4′), 6.71 (1H, *br s*, H-4), 6.77 (1H, *br s*, H-6), 6.91–7.0 (3H, *m*, H-2′, H-5′ and H-6′); ^{13}C NMR ($CDCl_3$) δ: 93.8 (C-2), 45.6 (C-3), 133.2 (C-3a), 115.1 (C-4), 131.6 (C-5), 111.0 (C-6), 144.2 (C-7), 147.3 (C-7a), 131.9 (C-1′), 109.0 (C-2′), 146.7 (C-3′), 145.8 (C-4′), 114.1 (C-5′), 119.9 (C-6′), 88.0 (C-1″), 70.8 (C-2″), 18.3 (C-3″), 17.4 (Me-3), 56.0 (2x MeO), 57.0 (MeO).

Acetate of **5**. Colourless oil; high resolution MS: Found, *m/z* 458.1951, Calcd for $C_{25}H_{30}O_8$, *m/z* 458.1939 (M^+), EIMS (rel. int.) *m/z*: 458 (18, M^+), 426 (8), 371 (100), 329 (50), 299 (10), 205 (20), 193 (22), 137 (20); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.22 (3H, *d*, *J* = 6.4 Hz, 3x H-3″), 1.42 (3H, *d*, *J* = 6.7 Hz, Me-3), 2.01 (3H, *s*, AcO-2″), 2.31 (3H, *s*, AcO-4′), 3.33 (3H, *s*, MeO-1″), 3.46 (1H, *m*, H-3), 3.83 (3H, *s*, MeO-3′), 3.90 (3H, *s*, MeO-7), 4.20 (1H, *d*, *J* = 4.5 Hz, H-1″), 5.03 (1H, *dq*, *J* = 6.7, 4.5 Hz, H-2″), 5.18 (1H, *d*, *J* = 9.1 Hz, H-2), 6.72 (1H, *br s*, H-4), 6.78 (1H, *br s*, H-6), 6.98 (1H, *dd*, *J* = 1.4, 7.9 Hz, H-6′), 7.02 (1H, *d*, *J* = 7.9 Hz, H-5′), 7.07 (1H, *d*, *J* = 1.4 Hz, H-2′).

Dihydro-5-(2″-*hydroxyethyl*)-2-(4′-*hydroxy*-3′-*methoxyphenyl*)-7-*methoxy*-3-*methylbenzofuran*, (*fragransol*-B), (**6**). Colourless oil; high resolution MS: Found, *m/z* 330.1435, Calcd for $C_{19}H_{22}O_5$, *m/z* 330.1466 (M^+); EIMS (rel. int.) *m/z*: 330 (100, M^+), 290 (50), 179 (5), 165 (5), 150 (8), 137 (20); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.38 (3H, *d*, *J* = 6.8 Hz, Me-3), 2.84 (2H, *t*, *J* = 6.5 Hz, 2x H-1″), 3.45 (1H, *m*, H-3), 3.88 (6H, *s*, MeO-7 and MeO-3′), 3.90(2H, *t*, 2x H-2″), 5.10 (1H, *d*, *J* = 9.8 Hz, H-2), 5.62 (1H, *s*, HO-4′), 6.64 (1H, *br s*, H-4), 6.67 (1H, *br s*, H-6), 6.90–6.98 (3H, *m*, H-2′, H-5′ and H-6′); ^{13}C NMR ($CDCl_3$) δ: 93.6 (C-2), 45.6 (C-3), 135.0 (C-3a), 116.1 (C-4), 132.1 (C-5), 112.7 (C-6), 144.2 (C-7), 146.7 (C-7a), 132.1 (C-1′), 109.0 (C-2′), 146.7 (C-3′), 145.8 (C-4′), 114.1 (C-5′), 119.8 (C-6′), 39.1 (C-1″), 63.8 (C-2″), 17.5 (Me-3), 56.0 (2x MeO).

Acetate of **6**. Colourless oil; EIMS (rel. int.) *m/z*: 414 (100, M^+), 372 (100), 354 (90), 312 (100), 297 (70), 188 (50), 175 (40); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.40 (3H, *d*, *J* = 6.7 Hz, Me-3), 2.06 (3H, *s*, AcO-2″), 2.31 (3H, *s*, AcO-4′), 2.90 (2H, *t*, *J* = 7.3 Hz, 2x H-1″), 3.48 (1H, *dq*, *J* = 6.8, 9.2 Hz, H-3), 3.83 (3H, *s*, MeO-3′), 3.90 (3H, *s*, MeO-7), 4.26 (2H, *t*, *J* = 7.3 Hz, 2x H-2″), 5.15 (1H, *d*, *J* = 9.2 Hz, H-2), 6.61 (1H, *br s*, H-4), 6.66 (1H, *br s*, H-6), 6.97 (1H, *dd*, *J* = 1.5, 8.2 Hz, H-6′), 7.01 (1H, *d*, *J* = 8.2 Hz, H-5′), 7.06 (1H, *d*, *J* = 1.5 Hz, H-2′).

r-2-(4′-*Hydroxy*-3′-*methoxyphenyl*)-c-5-(3″,4″,5″-*trimethoxyphenyl*)-t-3, t-4-*dimethyltetrahydrofuran*, (*fragransin*-D_1), (**7**). An oil; high resolution MS: Found, *m/z* 388.1908, Calcd for $C_{22}H_{28}O_6$, *m/z* 388.1884 (M^+); $[\alpha]_D = +18.38$ ($CHCl_3$, *c*0.136); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.03 (3H, *d*, *J* = 6.8 Hz, Me-4), 1.08 (3H, *d*, *J* = 6.6 Hz, Me-3), 2.34 (2H, *m*, H-3 and H-4), 3.837 (3H, *s*, MeO), 3.842 (6H, *s*, 2x MeO), 3.89 (3H, *s*, MeO), 4.52 (2H, *d*, *J* = 6.1 Hz, H-2 and H-5), 5.57 (1H, *s*, HO-4′), 6.65 (2H, *s*, H-2″ and H-6″), 6.85–6.96 (3H, *m*, H-2′, H-5′ and H-6′); ^{13}C NMR($CDCl_3$) δ: 131.5 (C-1′), 103.5 (C-2′), 153.2 (C-3′), 138.0 (C-4′), 153.2 (C-5′), 103.5 (C-6′), 87.4 (C-2), 44.5 (C-3), 44.5 (C-4), 87.4 (C-5), 13.2 (Me-3), 12.6 (Me-4), 134.2 (C-1″), 109.3 (C-2″), 146.5 (C-3″), 145.1 (C-4″), 113.9 (C-5″), 119.3 (C-6″), 55.9 (MeO-3′), 56.1 (MeO-3″ and MeO-5″), 60.7 (MeO-4″).

r-2-(4′-*Hydroxy*-3′-*methoxyphenyl*)-t-5-(3″,4″,5″-*trimethoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (*fragransin* D_2), (**8**). An oil; high resolution MS: Found, *m/z* 388.1874, Calcd for $C_{22}H_{28}O_6$, *m/z* 388.1884 (M^+); $[\alpha]_D = +30.49$ ($CHCl_3$; *c* 0.106), ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.05 (3H, *d*, *J* = 5.9 Hz, Me), 1.08 (3H, *d*, *J* = 6.1 Hz, Me), 1.78 (2H, *m*, H-3 and H-4), 3.83 (3H, *s*, MeO), 3.89 (6H, *s*, 2x MeO), 3.92 (3H, *s*, MeO), 4.64 (2H, *d*, *J* = 9.0 Hz, H-2 and H-5), 5.57 (1H, *s*, HO-4′), 6.62 (2H, *s*, H-2″ and H-6″), 6.83-6.94 (3H, *m*, H-2′, H-5′ and H-6′); ^{13}CNMR ($CDCl_3$) δ: 131.5 (C-1′), 103.2 (C-2′), 153.2 (C-3′), 138.0 (C-4′), 153.2 (C-5′), 103.2 (C-6′), 88.3 (C-2), 51.0 (C-3), 51.0 (C-4), 88.3 (C-5), 14.0 (Me-3), 14.0 (Me-4), 134.2 (C-1″), 109.3 (C-2″), 146.5 (C-3″), 145.1 (C-4″), 113.9 (C-5″), 119.3 (C-6″), 55.9 (MeO-3′), 56.1 (MeO-3″ and MeO-5″), 60.7 (MeO-4″).

r-2-(4′-*Hydroxy*-3′-*methoxyphenyl*)-c-5-(3″,4″,5″-*trimethoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (*fragransin* D_3), (**9**). An oil; high resolution MS: Found, *m/z* 388.1895, Calcd for $C_{22}H_{28}O_6$, *m/z* 388.1884 (M^+); $[\alpha]_D = +11.45$ ($CHCl_3$; *c*0.262); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.7 (3H, *d*, *J* = 7.0 Hz, Me-4), 1.07 (3H, *d*, *J* = 6.4 Hz, Me-3), 1.81 (1H, *ddq*, H-3), 2.26 (1H, *m*, H-4), 3.83 (9H, *s*, 3x MeO), 3.91 (3H, *s*, MeO), 4.43 (1H, *d*, *J* = 9.2 Hz, H-2), 5.10 (1H, *d*, *J* = 8.5 Hz, H-5), 5.60 (1H, *s*, HO-4′), 6.55 (2H, *s*, H-2″ and H-6″), 6.93 (1H, *d*, *J* = 7.9 Hz, H-5′), 7.00 (1H, *dd*, *J* = 7.9, 1.8 Hz, H-6′), 7.04 (1H, *d*, *J* = 1.8 Hz, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.8 (C-1′), 109.6 (C-2′), 146.6 (C-3′), 145.3 (C-4′), 114.3 (C-5′), 119.3 (C-6′), 87.4 (C-2), 47.5 (C-3), 46.1 (C-4), 83.3 (C-5), 15.1 (Me-3), 14.9 (Me-4), 132.8 (C-1″), 104.3 (C-2″), 153.0 (C-3″), 136.9 (C-4″), 153.0 (C-5″), 104.3 (C-6″), 55.9 (MeO-3′), 56.1 (MeO-3″ and MeO-5″), 60.9 (MeO-4″). The assignments of ^{1}H and ^{13}C signals were done on the basis of ^{13}C–^{1}H COSY, ^{1}H–^{1}H COSY and NOE expts.

Acetate of **9**. An oil, EIMS: (rel. int.) m/z: 430 (45, M^+), 388 (8), 303 (10), 236 (20), 208 (22), 192 (100), 177 (18), 145 (18); ^{1}H NMR (270 MHz, $CDCl_3$), δ: 0.69 (3H, *d*, $J = 6.8$ Hz, Me-4), 1.13 (3H, *d*, $J = 6.6$ Hz, Me-3), 1.8 (1H, *m*, H-3), 2.25 (1H, m, H-4), 2.32 (3H, *s*, AcO-4′), 3.82 (6H, *s*, 2x MeO), 3.84 (3H, *s*, MeO), 3.85 (3H, *s*, MeO), 4.49 (1H, *d*, $J = 9.5$ Hz, H-2), 5.12 (1H, *d*, $J = 8.1$ Hz, H-5), 6.54 (2H, *s*, H-2″ and H-6″), 7.05–7.15 (3H, *m*, H-2′, H-5′ and H-6′).

r-5-(4″-*Hydroxy*-3″-*methoxyphenyl*)-c-2-(3′,4′-*methylenedioxyphenyl*)-t-3,t-4-*dimethyltetrahydrofuran* (*fragransin* E_1), (**10**). An oil; high resolution MS: Found, m/z 342.1513, Calcd for $C_{20}H_{22}O_5$, m/z 342.1675 (M^+); $[\alpha]_D = 0$, ($CHCl_3$; *c*0.11), ^{1}H NMR (270 MHz, $CDCl_3$), δ: 1.02 (6H, *d*, $J = 6.8$ Hz, Me-3 and Me-4), 2.28 (2H, *m*, H-3 and H-4), 3.91 (3H, *s*, MeO-3″), 4.46 (2H, *d*, $J = 6.8$ Hz, H-2 and H-5), 5.56 (1H, *s*, HO-4″), 5.96 (2H, *s*, -O-CH_2-O-), 6.77-6.97 (6H, *m*, H-Ar).

r-5-(4″-*Hydroxy*-3″-*methoxyphenyl*)-c-2-(3′,4′-*methylenedioxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (*austrobailignan*-7), (**11**). An oil; high resolution MS: Found, m/z 342.1449, Calcd for $C_{20}H_{22}O_5$, m/z 342.1675 (M^+); $[\alpha]_D = +16.67$ ($CHCl_3$; *c*0.090); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.65 (3H, *d*, $J = 7.0$ Hz, Me-4), 1.04 (3H, *d*, $J = 6.7$ Hz, Me-3), 1.74 (1H, *ddq*, H-3), 2.22 (1H, *ddq*, H-4), 3.89 (3H, *s*, MeO-3″), 4.36 (1H, *d*, $J = 9.5$ Hz, H-2), 5.10 (1H, *d*, $J = 8.5$ Hz, H-5), 5.53 (1H, *s*, HO-4″), 5.97 (2H, *s*, –O–CH_2–O–), 6.81 (1H, *d*, $J = 7.9$ Hz, H-5′), 6.81 (1H, *dd*, $J = 1.5$, 8.2 Hz, H-6″), 6.86 (1H, *d*, $J = 1.5$ Hz, H-2″), 6.89 (1H, *d*, $J = 8.2$ Hz, H-5″), 6.93 (1H, *dd*, $J = 7.9$, 1.5 Hz, H-6′), 7.03 (1H, *d*, $J = 1.5$ Hz, H-2′). All assignments were done on the basis of ^{1}H–^{1}H COSY and NOE expts.

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