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Lignans and Neolignans[1] from Stems and Fruits of *Piper wightii*

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Abstract: Two new neolignans, (7*R*,8*R*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ-$^{1',4',8'}$-8.3'-lignan (**1**) and (7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ-$^{1',4',8'}$-8.3'-lignan (**2**) were isolated from the petroleum ether extract of stems of *Piper wightii* Miq. The structures were elucidated on the basis of their spectroscopic analysis and chemical transformation. Additionally five known neolignans, isodihydrofutoquinol A (**3**) and B (**4**), lancifolin C (**5**) and D (**6**) and wallichinine (**7**) and two known α,α'-diaryl-β,β'-dimethyltetrahydrobenzofuran lignans, calopiptin (**8**) and machilin G (**9**), were isolated for the first time from *Piper wightii*. The new neolignan **2**, isodihydrofutoquinol B (**4**), lancifolin C (**5**) and wallichinine (**7**) were also isolated from the methanolic extract of fruits of the same species alongwith gelbelgin (**10**), also a known lignan of the tetrahydrobenzofuran type.

INTRODUCTION

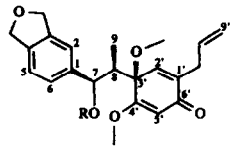
Piper species, widely distributed in the tropical and subtropical region of the world, are often used as traditional medicines and they are well known for producing a large number of physiologically active compounds.[2-5] We have isolated a variety of compounds from *Piper* species distributed in different parts of India under a project dealing with isolation of potential insecticides. These are wax esters,[6] amides,[7] alkaloids,[8] flavonoids,[7] crotepoxide,[6] lignans and neolignans.[9,10]

We now wish to report the isolation of two new neolignans, (7*R*,8*R*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ-$^{1',4',8'}$-8.3'-lignan (**1**) and (7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ-$^{1',4',8'}$-8.3'-lignan (**2**) from the petroleum ether extract of *P. wightii* Miq. stems collected from the Southern part of India. Alongwith these two new neolignans, the petroleum ether extract of *Piper wightii* has also yielded five known neolignans, isodihydrofutoquinol A (**3**)[9,13] and B (**4**),[9,13] lancifolin C (**5**)[14] and D (**6**)[14,15] and wallichinine (**7**)[16] and two known lignans, calopiptin (**8**)[9,17,18] and machilin G (**9**).[9,19] The new neolignan, *(7R,8R,3'R)*-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ$^{1',4',8'}$-8.3'-lignan (**2**), isodihydrofutoquinol

B (**4**), lancifolin C (**5**) and wallichinine (**7**) were also isolated from the methanolic extract of fruits of *Piper wightii* alongwith a lignan, gelbelgin (**10**).[18]

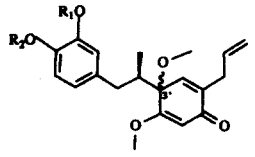
RESULTS AND DISCUSSION

The petroleum ether extract of stems of *Piper wightii* was subjected to silica gel flash column chromatography (CC) with a gradient solvent system of petroleum ether and ethyl acetate, increasing the amount of ethyl acetate stepwise. Repetitive preparative TLC of fractions collected from flash CC yielded seven neolignans (**1-7**) and two lignans (**8** and **9**). Similarly, a methanolic extract of fruits of *Piper wightii* was investigated yielding compound **10** alongwith **2, 4, 5** and **7** also isolated from petroleum ether extract of stems of *P. wightii*. Compounds **1** and **2** were found to be new natural products.



1 R = $COCH_3$

2 R = H

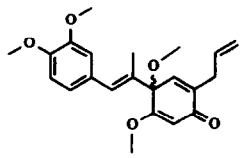


3 $R_1 = R_2 = OCH_2O$, 3'*R*

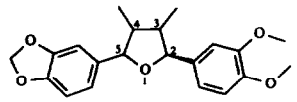
4 $R_1 = R_2 = OCH_2O$, 3'*S*

5 $R_1 = R_2 = OCH_3$, 3'*S*

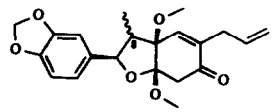
6 $R_1 = R_2 = OCH_3$, 3'*R*



7

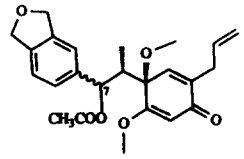


	C-3	C-4	C-5
8	*S*	*S*	*S*
9	*R*	*S*	*S*
10	*R*	*R*	*R*



11 8*R*

12 8*S*



13 7*R*

14 7*S*

Compound (**1**), $C_{23}H_{26}O_7$ (M^+ 414.1659), is a colourless viscous oil. It is optically active, $[\alpha]_D^{24}$ +43.3, and its IR and UV spectra suggest the presence of a substituted benzene ring and a conjugated ketone. A UV maximum at 246 nm suggests the presence of an α,β-α',β' unsaturated carbonyl.[11] That the substituted benzene ring is a piperonyl function is indicated by the ^{1}H NMR spectrum of **1** (δ 5.93, 2H, s and 6.75, 3H, m). The ^{1}H NMR spectrum of **1** also reveals the presence of a secondary methyl group at δ 0.70 (3H, d) , a methine proton at δ 2.39 (1H, q) and an allyl group (δ 3.12, 2H, m; 5.13, 2H, m; 5.82-5.92, 1H, m). The presence of CH_3-CH- and CH_2=CH-CH_2- is further confirmed by the ^{1}H-^{1}H COSY NMR spectrum which showed coupling of the signal at δ 0.70 with the signal at δ 2.39, and the three peaks at δ 3.12, 5.13 and 5.82-5.92 assigned

to CH_2=CH-CH_2- also give the expected crosspeaks. In addition, the ^{1}H NMR spectrum of **1** revealed the presence of an acetoxy group at δ 2.12 (3H, s), two methoxy groups at δ 3.16 and 3.74, two singlets at δ 5.73 and 6.38 and one triplet at δ 6.20. In the ^{1}H-^{1}H COSY spectrum, the triplet at δ 6.20 shows coupling with the signal at δ 3.12 indicating the presence of a CH=C-CH_2-CH=CH_2 moiety in **1**. On the basis of the above spectral data we propose the structure of **1** as 7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{-1',4',8'}$-8.3'-lignan and it has to be added that the absence of any observable coupling between H-8 and H-7 in **1** indicates a preferred dihedral angle close to 90°. This proposed structure is also supported by its ^{13}C NMR spectrum and EIMS fragmentation pattern.

Hydrolysis of compound **1** with alcoholic KOH gave two compounds **2** and **11**. Compound **2** was found to be the corresponding hydroxy product of **1** on the basis of its spectral data. The second reaction product **11**, $C_{21}H_{24}O_6$, is optically active, $[\alpha]_D^{24}$ +55.3 (*c* 0.06, $CHCl_3$) and has the following spectral properties: IR $\nu_{max}^{CHCl_3}$ cm^{-1}; no hydroxy absorption, 1687 (conjugated ketone), 1639, 1610, 1505, 1490, 1238, 1115, 1079 and 1034, UV $\lambda_{max}^{CHCl_3}$; 286 and 244. The ^{1}H NMR spectrum of **11** in deuteriochloroform exhibited two doublets at δ 0.88(3H, J=7.3 Hz) and 4.87(1H, J=6.3) and a double-quartet at δ 2.43, the typical AMX_3-type signal of a CH_3-CH-CH-(O)- unit; a pair of doublets at δ 2.64 and 3.30 (each 1H, J=16.4 Hz) and two sharp singlets at δ 3.43 and 3.55 (3H each) indicates the presence of an isolated methylene and two aliphatic methoxyl groups. The presence of CH_3-CH-CH-(O)- and the isolated methylene group is confirmed by the ^{1}H-^{1}H COSY spectrum which showed coupling of the signal at δ 0.88 with the signal at δ 2.43 which in turn couples with the signal at δ 4.87 and a cross peak between the signals at δ 2.64 and δ 3.30. The benzene ring, also indicated by IR and UV-spectra, was found to be a piperonyl function on the basis of its chemical shift in the ^{1}H NMR spectrum (δ 5.94, 2H, s, -OCH_2- and δ 6.63-6.78, 3H, m, Ar-H). The remaining unassigned six protons in the ^{1}H NMR spectrum of **11** were found interrelated to each other . The chemical shift value (δ 3.10, 2H, dd, J=6.7 & 1.0; 5.09-5.16, 2H, m; 5.87-6.00, 1H, m and 6.46, 1H, br s) and coupling nature of these protons reveal the presence of a CH_2=CH-CH_2-C=CH- moiety in compound **11** which is again confirmed by the ^{1}H-^{1}H-COSY spectrum. On the basis of above spectral data we propose the structure of **11** as 3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',8'}$-8.3', 7.O.4'-lignan. An NOE experiment performed on compound **11** showed strong interaction between the methyl and the aryl groups, 8-H and 7-H, but no interaction between methyl and 7-H suggesting that the aryl and the methyl groups are *cis* to each other. Further, H-8 gives good NOE effect on H-2'and the 9-CH_3 group gives effect on 3'-OCH_3 indicating that the methoxy group at 3'-position is *cis* to the 9-CH_3 group as well as to the aryl group. Since both methoxy groups are *cis* to each other (due to *cis* ring fusion) 4'-OCH_3 is also *cis* to the aryl and the methyl groups. The NOE effect of 4'-methoxy on the aryl group and *vice versa* also indicates that the aryl and the 4'-methoxy groups are *cis* to each other. Thus, the analysis of the NOE results led us to assign the relative configuration of compound **11** as rel-(7*R*,8*R*,3'*R*,4'*S*)-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',8'}$-8.3',7.O.4'-lignan. Previously , a similar compound, rel-(7*R*,8*S*,3'*R*,4'*S*)-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',8'}$-8.3',7.O.4'-lignan (kadsurin A) (**12**) has been isolated from *P. schmidtii*[9] and from *P. futokadsura*.[12] The spectral data reported for kadsurin

A and those for our compound are in close agreement except for the fact that in the ^{1}H NMR spectrum of kadsurin A 9-CH_3, 8-H and 7-H resonate at δ 0.98, 2.84 and 4.08, respectively, whereas the same protons in **11** resonate at δ 0.88, 2.43 and 4.87, respectively. The coupling constant for the doublet representing H-7 in kadsurin A is 10.8 Hz and in case of **11** 6.3 Hz. These differences in the chemical shifts of 9-CH_3, 8-H and 7-H and in the coupling constant of 7-H are due to the difference in configuration of the C-8 methyl in kadsurin A and **11**.

The alcoholic KOH hydrolysis of compound **1** gave only one hydroxy product **2** indicating retention of configuration at C-7. The stereochemistry at C-8 and C-3' in compound **1** and **11** will be identical. Thus, the relative configuration of **1** can be assigned as rel-(7*R*,8*R*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan. The NOE experiment performed on **1** (see Table 1) also supports the above assigned stereochemistry.

Additional evidence for the stereochemistry of compound **1** was obtained by the following reaction. Kadsurin A (**12**) when refluxed with acetic anhydride and anhydrous sodium acetate gave two α,β-α',β'-unsaturated keto acetates, **13**, $\nu_{max}^{CHCl_3}$ 1734 and 1666 cm^{-1} and **14**, $\nu_{max}^{CHCl_3}$ 1741 and 1666 cm^{-1}. Their mass spectra were similar and both giving a $[M]^+$ peak 42 mass units higher than that shown by kadsurin A. The ^{1}H NMR spectrum of **13** showed the presence of CH_3-CH-CH-(O)- (δ 0.92, 3H, d; 2.91, 1H, dq; 5.30, 1H, d), CH_2=CH-CH_2-C=CH- (δ 3.10, 2H, m; 5.09-5.16, 2H, m; 5.74-5.90, 1H, m; 6.25, 1H, br s), and a piperonyl unit (δ 5.92, 2H, s; 6.69-6.71, 3H, m). The presence of these moieties were also confirmed by the ^{1}H-^{1}H-COSY spectrum of **1**. Alongwith these moieties, the ^{1}H NMR spectrum of **1** also revealed the presence of an acetoxy group (δ1.84, 3H, s), a methoxy group attached to a sp^3-hybridised carbon atom (δ 3.03, 3H, s), another methoxy group attached to a sp^2-hybridised carbon atom (δ 3.84, 3H, s) and a singlet for one proton at δ 5.70. On the basis of these spectral data the structure of **13** is assigned as 7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan. The ^{1}H NMR spectrum of **14** is quite similar to **13** except that the chemical shifts of 9-CH_3, 8-H and 7-H which are δ 1.08 (d, J=7.2), 2.59 (dq, J=7.2 & 3.0) and 5.62 (d, J=3.0), respectively. The stereochemistry at C-8 and C-3' in **13** and **14** will be the same as in kadsurin A (**12**) because the reaction site in kadsurin A is C-7. This conclusion is also supported by the NOE results of **13** and **14**. The coupling constant obtained for the protons on C-7 and C-8 for **13** (9.5 Hz) and **14** (3.0 Hz) suggests **13** to have a *threo*- and **14** an *erythro*- configurations. This led us to assign the relative configuration of **13** and **14** as rel-(7*R*,8*S*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan and rel-(7*S*,8*S*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan, respectively. None of these two acetoxy products are identical to the isolated compound **1**. This also indicates that the stereochemistry of **1** is different to the stereochemistry of **13** and **14** with respect to the C-8 position.

Finally, the absolute stereochemistry at the C-3'carbon atom in **1** was established by comparing the Cotton effect due to the enone chromophore of **1** and lancifolin C (**5**),[14] which was found to be positive in both cases. This establishes an *R*-configuration at C-3' in **1**. Thus the absolute structure of **1** is (7*R*,8*R*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan.

Table 1. NOE Results of Compound 1.

Proton irradiated	% Enhancement										
	9-CH_3	8-H	7'-CH_2	3'-OCH_3	4'-OCH_3	9'-CH_2	8'-H	5'-H	2'-H	7-H	Ar-H
9-CH_3	-	13.3	-	-	-	-	-	1.6	2.3	-	3.0
$COCH_3$	-	-	-	-	-	1.2	2.1	-	1.7	0.6	0.8
8-H	2.2	-	-	-	-	-	-	-	-	6.7	2.3
4'-OCH_3	-	-	-	-	-	-	-	24.2	-	-	-
5'-H	-	-	-	-	3.2	-	-	-	-	-	-
2'-H	-	-	0.8	0.9	-	-	-	-	-	3.6	
7-H	-	7.4	-	-	-	-	-	-	2.0	-	3.9
Ar-H	0.9	5.5	-	-	-	-	-	-	-	9.0	-

Table 2. NOE Results of Compound 2.

Proton irradiated	% Enhancement								
	9-CH_3	8-H	7'-CH_2	3'-OCH_3	4'-OCH_3	5'-H	2'-H	7-H	Ar-H
9-CH_3	-	12.4	-	-	-	1.3	3.2	-	2.5
8-H	2.1	-	-	-	-	-	1.6	6.7	2.9
4'-OCH_3	-	-	-	-	-	22.6	-	-	-
7-H	-	7.4	-	-	-	-	7.7	-	3.6
5'-H	-	-	-	-	3.4	-	-	-	-
2'-H	-	-	2.8	0.8	-	-	-	5.7	-
Ar-H	0.64	5.8	-	-	-	-	-	6.4	-

Table 3. NOE Results of Compound 11.

Proton irradiated	9-CH_3	8-H	5'-H_a	7'-CH_2	5'-H_b	3'-OCH_3	4'-OCH_3	8'-H	2'-H	7-H	Ar-H
9-CH_3	-	13.2	-	-	-	0.7	0.4	-	1.0	-	3.0
8-H	0.7	-	-	-	-	-	-	-	10.9	6.7	-
3'-OCH_3	-	-	5.6	-	-	-	-	-	3.7	-	0.7
4'-OCH_3	-	-	1.4	-	4.6	-	-	-	-	-	1.8
7-H	-	12.4	-	-	-	-	-	-	1.9	-	3.5
2'-H	-	12.7	-	1.7	-	1.3	-	-	-	-	-
Ar-H	0.6	-	-	-	-	-	1.2	-	-	8.0	-

Compound 2, $C_{21}H_{24}O_6$ (M^+ 372.1601), is a pale yellow viscous oil. It is optically active, $[\alpha]_D^{24}$ + 89.0 and its IR spectrum shows the presence of a hydroxy group (3436 cm^{-1}) and an α,β-unsaturated ketone (1666 cm^{-1}). Its UV-, ^1H NMR-, ^1H-^1H COSY-, NOE (see Table 2), ^{13}C NMR- and Mass spectra show the presence of

piperonyl, CH_3-CH-, and CH=C-CH_2-CH=CH_2 moieties in the molecule and these spectral data are almost similar to those of compound **1** except for the absence of a signal corresponding to an acetoxy group. Its ^{1}H NMR spectrum showed additionally a signal for a hydroxyl group at δ 1.75 (br s). On the basis of the above spectral data the structure of **2** is proposed as rel-(7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ-$^{1',4',8'}$-8.3'-lignan. The hydroxy product obtained during alcoholic-KOH hydrolysis of compound **1** was found identical in all respect to the isolated compound **2**. This indicates that the relative configuration of the isolated compound **2** is the same as for **1**. The absolute stereochemistry of **2** was established as identical to that of **1** by comparing the CD data of **2** with those of lancifolin C (**5**).[14] Thus the absolute stereochemistry of **2** is (7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan.

EXPERIMENTAL

Melting points were determined on a Büchi 535 hot oil apparatus and are uncorrected. IR spectra were recorded (KBr pellet or a film) on a Perkin-Elmer 1720 infrared FT spectrophotometer and UV spectra on a Shimadzu UV 160 A spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 or AC-500 at 250 or 500 and 62.9 or 125 MHz, respectively. Chemical shifts are reported in δ units with TMS as internal standard. The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dq = double-quartet, m = multiplet and br = broad are used throughout. Coupling constants (J) are reported in Hz. EIMS were recorded on a Varian MAT 311A mass spectrometer at 70 ev. Optical rotations and circular dichroism spectrum (CD) were recorded on a Perkin-Elmer 141 polarimeter and custom built spectrometer, respectively. Silica-gel 60 (230-400 mesh, art 9385, Merck) was used for flash CC and TLC was performed on Merck silica gel 60 F_{254} plates. The spots were visualised under UV light or by spraying with 10% aq. H_2SO_4 followed by heating at around 120°C for few minutes. Preparative TLC was performed either on silica gel 60 $PF_{254+366}$, Merck preparative kieselgel 60 F_{254} or Merck preparative aluminiumoxide 60 F_{254} plates. Compounds **8**, **9** and **10** turned pink when heated after H_2SO_4 spraying.

Plant material. Leaves and stems, and fruits of the plant *Piper wightii* Miq. were collected from Doddabetta, Ooty (Tamil Nadu, India) in November 1990 and January 1992, respectively.The voucher specimens have been deposited in the herbarium of Botanical Survey of India (BSI), Southern Circle, TNAU campus, Coimbatore (Tamil Nadu, India).

Extraction and isolation. Crushed and dried stems (1.35 Kg) were extracted successively with petroleum ether, dichloromethane and methanol. Fruits (0.82 Kg) were extracted only with petroleum ether and methanol. Both extracts were concentrated *in vacuo*. The petroleum ether extract of stems of *P. wightii* was flash column chromatographed with a gradient solvent system of petroleum ether and ethyl acetate, increasing the concentration of ethyl acetate stepwise and forty seven different fractions were collected. Seven neolignans, (7*R*,8*R*,3'*R*)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan (**1**), (7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan (**2**), isodihydrofutoqinol A (**3**), isodi-

hydrofutoqinol B (4), lancifolin C (5), lancifolin D (6), wallichinine (7) and two α,α'-diaryl-β,β'-dimethyltetrahydrobenzofuran lignans, calopiptin (8) and machilin G (9) were isolated from different fractions by repetitive preparative TLC or by crystallisation. Similarly, the methanolic extract of fruits of *P. wightii* was fractionated on a silica gel column with a gradient solvent system of petroleum ether- chloroform and finally with chloroform and methanol. The 10g fraction eluted with 90% chloroform in petroleum ether was found to be a complex mixture on its TLC-examination. It was again subjected to flash CC on a silica gel column and fifteen fractions were collected. Four neolignans, (7*R*,8*R*,3'*R*)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'-lignan (2), isodihydrofutoqinol B (4), lancifolin C (5) and wallichinine (7), also isolated from petroleum ether extract of stems and one lignan of the above type, gelbelgin (10) were purified from different fractions by repetitive preparative TLC or by crystallisation.

(7R,8R,3'R)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ*-*$^{1',4',8'}$*-8.3'-lignan* (1). Colourless viscous oil (15mg); $C_{23}H_{26}O_7$ (M^+ 414.1659, Calcd. 414.1679); $[\alpha]_D^{24}$ +43.3 (c 0.20, $CHCl_3$); IR (KBr) cm^{-1}. 1746, 1667, 1638, 1611, 1504, 1492, 1444, 1386, 1368, 1330, 1314, 1232, 1162, 1145 and 1079; UV ($CHCl_3$) nm. 246 and 286; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.70(3H, d, J=7.1, CH_3-9), 2.12(3H, s, $COCH_3$), 2.39(1H, q, J=7.1, H-8), 3.12(2H, m, CH_2-7'), 3.16(3H, s, CH_3O-3'), 3.74(3H, s, CH_3O-4'), 5.13(2H, m, CH_2-9'), 5.73(1H, s, H-5'), 5.82-5.92(1H, m, H-8'), 5.93(2H, s, -OCH_2O-), 6.20(1H, t, J=1.5, H-2'), 6.38(1H, s, H-7) and 6.75(3H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.6(C-9), 21.2($COCH_3$), 32.9(C-7'), 47.5(C-8), 52.6(CH_3O-3'), 55.8(CH_3O-4'), 72.2(C-7), 79.6(C-3'), 100.9(-OCH_2O-), 105.5, 106.1(C-5',C-2), 108.1(C-5), 117.1(C-9'), 118.6(C-6), 131.9(C-1), 134.9(C-2'), 138.9(C-8'), 140.5(C-1'), 146.7, 147.6(C-4, C-3), 169.6($COCH_3$), 172.4(C-4') and 186.2(C-6'); EIMS, m/z (% rel. int.): 414(M^+, 10.8), 233(24), 194(100), 179(23), 162(13), 151(24), 149(21), 43(69) and 18(10.5); CD (5.7 mg/100 ml MeOH, 226-400 nm): $[\Theta]_{226}^{min}$ -700920, $[\Theta]_{239}$ 0, $[\Theta]_{241}$ +320796, $[\Theta]_{252}^{max}$ +1145700, $[\Theta]_{268}$ +320796, $[\Theta]_{277}$ 0, $[\Theta]_{290}^{min}$ -126027, $[\Theta]_{295}^{max}$ -80199, $[\Theta]_{306}^{min}$ -148941, $[\Theta]_{316}$ -68742, $[\Theta]_{330}$ 0 and $[\Theta]_{400}$ 0.

(7R,8R,3'R)-7-hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-Δ*-*$^{1',4',8'}$*-8.3'-lignan* (2). Pale yellow viscous oil (11 mg from stems and 50 mg from fruits); $C_{21}H_{24}O_6$ (M^+ 372.1601, Calcd. 372.1593); $[\alpha]_D^{24}$ +89.0 (c 0.37, $CHCl_3$); IR(KBr)cm^{-1}. 3436, 1666, 1609, 1504, 1489, 1441, 1402, 1230, 1116, 1039, 1003 and 929; UV($CHCl_3$)nm. 246 and 286; ^1H NMR(250 MHz, $CHCl_3$) δ: 0.62(3H, d, J=7.3, CH_3-9), 1.75(1H, br s, -OH), 2.31(1H, q, J=7.3, H-8), 3.13(2H, dd, J=6.7, 1.0, CH_2-7'), 3.18(3H, s, CH_3O-3'), 3.75(3H, s, CH_3O-4'), 5.07-5.15(2H, m, CH_2-9'), 5.42(1H, s, H-7), 5.72(1H, s, H-5'), 5.80-5.98(1H, m, H-8'), 5.93(2H, s, -OCH_2O-), 6.70(1H, t, J=1.1, H-2') and 6.74-6.86(3H, m, Ar-H); ^{13}C NMR(62.8 MHz, $CDCl_3$) δ: 6.7(C-9), 32.9(C-7'), 48.2(C-8), 52.6(CH_3O-3'), 55.8(CH_3O-4'), 70.6(C-7), 80.3(C-3'), 100.9(-OCH_2O-), 105.4, 106.4, 107.9(C-5', C-2, C-5), 116.7(C-9'), 118.6(C-6), 135.3(C-2'), 138.4(C-1), 139.7(C-1'), 140.8(C-8'), 146.4, 147.6(C-4, C-3), 172.8(C-4') and 186.6(C-6'); EIMS, m/z (% rel. int.): 372 (M^+ 15.4), 340(19), 194(100), 179(40), 175(55), 163(39), 162 (28.7), 151(68), 105(30), 93(45), 65(45.4), 43(60), 29(15) and 18(20); CD (3.7 mg/100 ml MeOH,

225-400 nm): $[\Theta]_{225}^{min}$ -272229, $[\Theta]_{234}$ 0, $[\Theta]_{241}$ +494962, $[\Theta]_{252}^{max}$ +1047670, $[\Theta]_{264}$ +494962, $[\Theta]_{279}$ 0, $[\Theta]_{292}^{min}$ -107241, $[\Theta]_{298}^{max}$ -90743, $[\Theta]_{305}^{min}$ -107241, $[\Theta]_{314}$ -57745, $[\Theta]_{340}$ 0 and $[\Theta]_{400}$ 0.

Hydrolysis of 7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',8'}$*-8.3'-lignan* (**1**). To a solution of **1** (4.5 mg) in ethanol (2 ml) was added 4N aq KOH (0.2 ml) and the solution was stirred at RT for 40 min. Then the solution was diluted with water and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4) and evaporated to a gummy residue (3.8 mg) which on purification by preparative TLC yielded two compounds, **2** (1.5 mg) and **11** (1.5 mg), as oils. Compound **11** was identified on the basis of its spectral data as rel-*(7R,8R,3'R,4'S)*-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',8'}$-8.3',7.O.4'-neolignan, $[\alpha]_D^{24}$ +55.3 (c 0.06, $CHCl_3$); IR ($CHCl_3$)cm^{-1}. 1687, 1639, 1610, 1505, 1490, 1238, 1115, 1079 and 1034; UV ($CHCl_3$)nm. 286 and 244. ^1H NMR(250 MHz, $CHCl_3$) δ: 0.88(3H, d, J=7.3, CH_3-9), 2.43(1H, dq, J=7.3 & 6.3, H-8), 2.64(1H, d, J=16.4, H_a-5'), 3.10(2H, dd, J=6.7 and 1.0, CH_2-7'), 3.30(1H, d, J=16.4, H_b-5'), 3.43(3H, s, CH_3O-3'), 3.55(3H, s, CH_3O-4'), 4.87(1H, d, J=6.3, H-7), 5.09-5.16(2H, m, CH_2-9'), 5.87-6.00(1H, m, H-8'), 5.94(2H, s, -OCH_2O-), 6.46(1H, br s, H-2') and 6.63-6.78(3H, m, Ar-H); ^{13}C NMR(125 MHz, $CHCl_3$) δ:10.5(C-9), 33.1(C-7'), 43.3(C-5'), 48.7, 49.8, 52.5(C-8, CH_3O-3', CH_3O-4'), 82.1(C-7), 82.2(C-3'), 100.8(-OCH_2O-), 101.1(C-4'), 106.8(C-2), 107.9(C-5), 117.4(C-9'), 119.2(C-6), 133.1(C-1), 134.5(C-8'), 141.9(C-1'), 143.3(C-2'), 146.6, 147.5(C-4, C-3) and 194.5(C-6'); EIMS, m/z(% rel. int.): 372(M^+ 6), 340(1.5), 298(1.5), 271(9), 257(2), 230(4), 211(12.3), 210(100), 191(9), 179(8), 162(41), 151(91), 149(21), 135(12), 103(8), 91(15.4), 77(11), 57(9), 43(10) and 39(4).

Treatment of kadsurin A (**12**) *with acetic anhydride and anhydrous NaOAc.* A mixture of kadsurin A (**12**, 60 mg) and anhydrous NaOAc (60 mg) in acetic anhydride (8ml) was refluxed for 12 hr.The mixture was cooled, poured into ice-cold water and extracted with ether. The ether extracts were washed with wather, dried and evaporated *in vacuo*. The residue (63 mg) was purified by preparative TLC (solvent system- 7% ethyl acetate in benzene) yielding three compounds, **13, 14** and the starting compound **12**. The polar compound **13** (25 mg) was identified as rel-*(7R,8S,3'R)*-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-$\Delta^{1',4',8'}$-8.3'lignan, $[\alpha]_D^{24}$ -75.2 (c 1.09, $CHCl_3$); IR($CHCl_3$)cm^{-1}. 1734, 1666, 1636, 1610, 1505, 1490, 1446, 1369, 1329, 1230, 1166, 1127, 1071, 1040 and 992; UV($CHCl_3$)nm. 287 and 245; ^1H NMR(250 MHz, $CDCl_3$)δ: 0.92(3H, d, J=7.1, CH_3-9), 1.84(3H, s, $COCH_3$), 2.91(1H, dq, J=7.1 & 9.5, H-8), 3.03(3H, s, CH_3O-3'), 3.10(2H, m, CH_2-7'), 3.84(3H, s, CH_3O-4'), 5.09-5.16(2H, m, CH_2-9'), 5.30(1H, d, J=9.5, H-7), 5.70(1H, s, H-5'), 5.74-5.90(1H, m, H-8'), 5.92(2H, s, -OCH_2O-), 6.25(1H, br s, H-2') and 6.69-6.71(3H, m, Ar-H); ^{13}C NMR(62.9 MHz, $CDCl_3$)δ: 11.3(C-9), 21.2($COCH_3$), 33.0(C-7'), 44.2(C-8), 51.2(CH_3O-3'), 55.8(CH_3O-4'), 76.7, 77.2(C-7, C-3'), 101.1(-OCH_2O-), 104.2(C-5'), 107.7, 107.9(C-2, C-5), 117.2(C-9'), 121.7(C-6), 133.0(C-1), 135.0, 136.1(C-2', C-8'), 141.9(C-1'), 147.4, 147.7(C-3, C-4), 169.1($COCH_3$), 173.6(C-4') and 186.0(C-6'); EIMS, m/z(% rel. int.): 414(58), 383(18), 354(3), 340(5), 236(8), 207(10), 194(100), 193(22), 191(25), 179(34), 151(42), 149(13), 131(4), 93(8), 43(25).

The other less polar compound **14** (10 mg) was identified as rel-*(7S,8S,3'R)-7-acetoxy-3',4'-dimethoxy-3,4-methylenedioxy-6'-oxo-*$\Delta^{1',4',8'}$*-8.3'-lignan*, $[\alpha]_D^{24}$ -21.2 (c 0.47, $CHCl_3$); IR($CHCl_3$)cm^{-1}. 1741, 1666, 1635,

1612, 1505, 1492, 1446, 1379, 1235, 1217, 1212, 1192, 1168, 1072, 1043, 1022 and 991; UV($CHCl_3$)nm. 287 and 246; ^{1}H NMR(250 MHz, $CDCl_3$)δ: 1.08(3H, d, J=7.2, CH_3-9), 1.96(3H, s, $COCH_3$), 2.59(1H, dq, J=7.2 & 3.0, H-8), 3.07(1H, dd, J=6.7 & 1.1, H_a-7'), 3.05(3H, s, CH_3O-3'), 3.19(1H, dd, J=6.7 & 1.1, H_b-7'), 3.78(3H, s, CH_3O-4'), 5.11-5.18(2H, m, CH_2-9'), 5.62(1H, d, J=3.0, H-7), 5.68(1H, s, H-5'), 5.80-5.98(1H, m, H-8'), 5,91(2H, s, -OCH_2O-), 6.32(1H, br s, H-2'), 6.53-6.59(2H, m, H-2 & H-6) and 6.70(1H, d, J=7.9, H-5); ^{13}C NMR(62.8 MHz, $CHCl_3$)δ: 7.7(C-9), 20.8($COCH_3$), 33.0(C-7'), 46.8(C-8), 51.7(CH_3O-3'), 55.7(CH_3O-4'), 73.1, 73.7(C-7, C-3'), 100.9(-OCH_2O-), 106.0, 106.2, 107.9(C-5', C-2, C-5), 117.3(C-9'), 119.0(C-6), 134.1(C-1), 134.8(C-2'), 138.2(C-8'), 140.0(C-1'), 146.8, 147.5(C-3, C-4), 169.8($COCH_3$), 171.5(C-4') and 186.5(C-6'); EIMS, m/z(% rel. int.): 414(M^+, 53), 383(10), 340(9), 236(8), 233(10), 207(5), 194(100), 191(22), 179(29), 151(29), 131(4), 123(4), 93(6), 69(3) and 43(24).

Isodihydrofutoquinol A (**3**). Colouless oil (21.7 mg); $[\alpha]_D^{24}$ -7.1 (c 0.84, MeOH) (lit[9] $[\alpha]_D^{25}$ -5.9; c 0.08, MeOH); IR, UV, ^{1}H and ^{13}C NMR and EIMS as previously reported.[9,13]

Isodihydrofutoquinol B (**4**). Pale yellow viscous oil (800 mg from stems and 300 mg from fruits); $[\alpha]_D^{24}$ +105.4 (c 2.6, MeOH) (lit[9] $[\alpha]_D^{22}$ +108.5; c 0.15, MeOH); IR, UV, ^{1}H and ^{13}C NMR and EIMS as previously reported.[9,13]

(+)-Lancifolin C (**5**). Pale yellow viscous oil (25 mg from stems and 20 mg from fruits); $[\alpha]_D^{24}$ +77.7 (c 1.06, $CHCl_3$); CD (3.5 mg/100 ml MeOH, 226-400 nm): $[\Theta]_{226}^{min}$ -80288, $[\Theta]_{237}$ 0, $[\Theta]_{242}$ +110743, $[\Theta]_{251}^{max}$ +260245, $[\Theta]_{268}$ +110743, $[\Theta]_{286}$ 0, $[\Theta]_{301}^{min}$ -24917, $[\Theta]_{316}$ -8306, $[\Theta]_{330}$ 0, $[\Theta]_{400}$ 0 (lit[14] CD, 5.0 mg/100 ml MeOH, 240-400 nm: $[\Theta]_{253}^{max}$ +15650, $[\Theta]_{278}$ 0, $[\Theta]_{290}^{max}$ -8550, $[\Theta]_{302}^{max}$ -9650); IR, UV, ^{1}H NMR and EIMS as previously reported.[14]

(-)-Lancifolin D (**6**). Pale yellow viscous oil (42 mg); $[\alpha]_D^{24}$ -26.8 (c 1.47, Me_2CO) (lit[15] $[\alpha]_D^{18}$ +28.57; c 0.21, Me_2CO); CD (4.2 mg/100 ml MeOH, 226-400 nm): $[\Theta]_{226}^{max}$ +54293, $[\Theta]_{239}$ 0, $[\Theta]_{251}^{min}$ -153437, $[\Theta]_{270}$ 0, $[\Theta]_{275}$ +35409, $[\Theta]_{288}^{max}$ +76718, $[\Theta]_{302}$ +35409, $[\Theta]_{314}$ 0, $[\Theta]_{318}$ -11803, $[\Theta]_{335}^{min}$ -23606, $[\Theta]_{356}$ -11803, $[\Theta]_{380}$ 0, $[\Theta]_{400}$ 0 (lit[15] CD, MeOH, nm: $[\Theta]_{210}$ 0, $[\Theta]_{223}$ +4092, $[\Theta]_{240}$ 0, $[\Theta]_{247}$ -1302, $[\Theta]_{252}$ 0, $[\Theta]_{281}$ +7068, $[\Theta]_{342}$ 0, $[\Theta]_{365}$ +614); IR, UV, ^{1}H NMR and EIMS as previously reported.[14,15]

Wallichinine (**7**). Colourless oil (32 mg from stems and 43 mg from fruits). $[\alpha]_D^{24}$ -21.0 (c 0.712, $CHCl_3$) (lit[16] $[\alpha]_D^{30}$ 0.0; c 0.86, $CHCl_3$); IR, UV, ^{1}H and ^{13}C NMR as reported previously.[16]

Calopiptin (**8**). Colourless solid (35 mg), mp. 88-90° (lit[9] mp 79-83°); $[\alpha]_D^{24}$ +23.6 (c 0.87, $CHCl_3$) (lit[9] $[\alpha]_D^{22}$ +30.0; c 0.10, $CHCl_3$); IR, UV, ^{1}H and ^{13}C NMR and EIMS were similar to literature values.[9,17,18]

Machilin G (**9**). Colourless oil (76 mg); $[\alpha]_D^{24}$ -10.4 (c 1.38, $CHCl_3$) (lit[9] $[\alpha]_D^{22}$ -12.8; c 0.123, $CHCl_3$); its spectral data (IR, ^1H and ^{13}C NMR and EIMS) were found identical in all respects with published data.[9,19]

Gelbelgin (**10**). Colourless solid (5.3 mg), mp. 141-42 (lit[18] mp. 142-43); $[\alpha]_D^{22}$ -140.5 (c 0.31, $CHCl_3$) (lit[18] $[\alpha]_D^{25}$ -135.5 (c 0.2, $CHCl_3$) identified by comparison of its mp, IR, ^1H NMR and mass spectra with literature data.[18]

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REFERENCES AND NOTES

1. Nomenclature follows Gottlieb, O. R. *Prog. Chem. Org. Nat. Prod.* **1978,** *35,* 1.
2. Kirtikar, K. R.; Basu, B. D. *Indian Med. Plants* **1933,** *3,* 2131.
3. Gervan, R. I.; Greenberg, N. H.; Macdonald, M. M. ; Schumacher, A. M; Affott B. J. *Cancer Chemother. Rep.* **1972,** *3,* 1.
4. Dominguez, X. A; Alcorn, J. *J. Ethnopharmacol.* **1985,** *13,* 139.
5. Loder, J. W.; Moorhouse, A.; Russell, G. B. *Aust. J. Chem.* **1969,** *22,* 1531.
6. Boll, P. M.; Hald, M.; Parmar, V. S.; Tyagi, O. D.; Bisht, K. S.; Sharma, N. K; Hansen, S. *Phytochemistry* **1992,** *31,* 1035.
7. Parmar, V. S.; Sinha, R; Shakil, N. A.; Tyagi, O. D.; Boll, P. M. *Indian J. Chem.* **1993,** *32B,* 392.
8. Olsen, C. E.; Tyagi, O. D.; Boll, P. M.; Hussaini, F. A.; Parmar, V. S.; Sharma, N. K.; Taneja, P; Jain, S. C. *Phytochemistry* **1993** *33,* 518.
9. Tyagi, O. D.; Jensen, S.; Boll, P. M.; Sharma, N. K.; Bisht, K. S.; Parmar, V. S. *Phytochemistry* **1993,** *32,* 445.
10. Jensen, S.; Olsen, C. E.; Tyagi, O. D.; Boll, P. M.; Hussaini, F. A.; Parmar, V. S. *Phytochemistry,* in press.
11. Caine, D.; Dowson, J. B. *Chem. Commun.* **1970,** 1232.
12. Chang, M. N.; Han, Gui-Qiu.; Arison, B. H.; Springer, J. P.; Hwang, San-Bao; Shen, T. Y. *Phytochemistry* **1985,** *24,* 2079.
13. Matsui, K; Munakata, K. *Tetrahedron Lett.* **1976,** 4371.
14. Diaz P. P.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry 1980, 19,* 285.
15. Arison, B. H.; Hwang, S. B. *Acta. Pharma. Sinica* **1991,** *26,* 345.
16. Han, G. Q.; Wei, L. H.; Li, C. L.; Qiao, L.; Jia, Y. Z.; Zheng, Q. T. *Acta Pharm. Sinica* **1989,** *24,* 438.
17. Riggs, N. V.; Stevens, J. D. *Aust. J. Chem.* **1962,** *15,* 305.
18. Takaoka, D.; Watanabe, K.; Hiroi, M. *Bull. Chem.Soc., Japan* **1976,** *49,* 3564.
19. Shimomura, H.; Sashida, Y.; Oohara, M. *Phytochemistry* **1988,** *27,* 634.

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