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LIGNANS FROM *AEGILOPS OVATA* L.

SYNTHESIS OF A 2,4- AND A 2,6-DIARYL MONOEPOXYLIGNANOLIDE†

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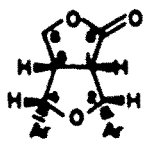
Abstract—2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octan-8-one structures are assigned to two lignans isolated from *Aegilops ovata* L. by comparing their spectroscopic data to a synthetically prepared novel 2,4- and 2,6-diaryl monoepoxylignanolide. The possibility of differentiating between these two structural types is discussed and an X-ray analysis of the 2,4-diaryl lignan is presented.

An investigation on a number of species of wild wheat growing in Israel for naturally occurring germination inhibitors led to the isolation of a lignan from *Aegilops ovata* L. possessing such activity. This lignan was originally assigned[2] a 2,4-diaryl-3,7-dioxabicyclo[3,3,0]-octan-8-one structure 1, and was the first report of a naturally occurring diaryl-substituted bicyclo[3,3,0]octane lignan containing both an ether and a lactone moiety. Subsequently, a second 2,4-diaryl lignan 2 was independently reported.[3] The main evidence favouring these 2,4-diaryl monoepoxylignanolide structures was the formation in the mass spectrum of fragments M-84 and M-85; these have been observed in the spectra of other 2,4-diaryl lignans containing a lactone ring,[4] owing to the loss of a cyclobutyrolactone moiety. Since no other bicyclo[3,3,0]octane systems containing both an ether and a lactone moiety were known at that time,[5] it was decided to study these compounds further, and we therefore decided to synthesize both a 2,4- and a 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octan-8-one.[6] Synthesis of this latter compound has led to the revised structure 13 for the naturally occurring lignan from *Aegilops ovata* L.[7] Furthermore, marked differences in the spectroscopic data for these 2,4- and 2,6-diaryl lignans were observed. Thus it is clearly possible to differentiate between these two structural types, thereby providing the basis for structural elucidation of other such monoepoxy-lignanolides. Consequently the recent suggestion[8] of degrading monoepoxylignanolides to the corresponding bis-tetrahydrofuran lignans for purposes of structure elucidation may not, therefore, appear necessary.



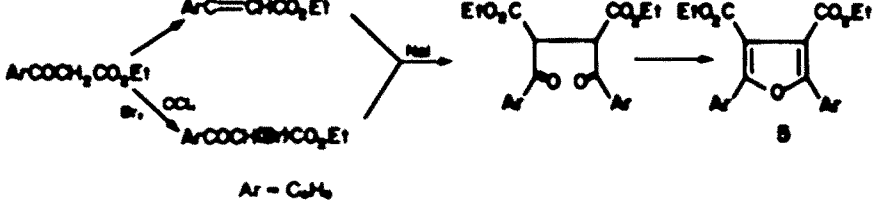
1

Ar = 3-methoxy, 4-hydroxyphenyl

2

Ar = 3,4-methylendioxyphenyl

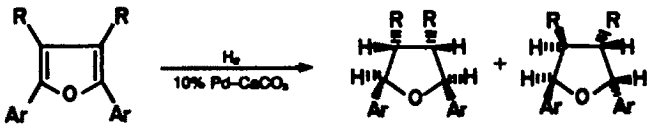
The 2,4-diaryl monoepoxylignanolide (3) was synthesized, starting from readily available ethyl benzoylacetate. Coupling of the α-bromoketoester derivative to the sodium enolate of ethyl benzoylacetate led to a 1,4-diketone which was then cyclised with polyphosphoric acid (PPA) to give the 2,5-diphenyl furan-3,4-dicarboxylic acid ethyl ester (5) (Scheme 1). Catalytic hydrogenation over 10% Pd/$CaCO_3$ led to the *trans meso*-2,5-diphenyl tetrahydrofuran-3,4-dicarboxylic acid diethyl ester (4) in a 60% conversion by a 1,4-addition. Efforts to improve the yield were unsuccessful, however.



Ar = C_6H_5

Scheme 1.

†Part III in the series of "Phenolic Constituents of the Gramineae"; for Part II see Ref. 1.



5 4 6

Ar = C_6H_5, R = $COOC_2H_5$

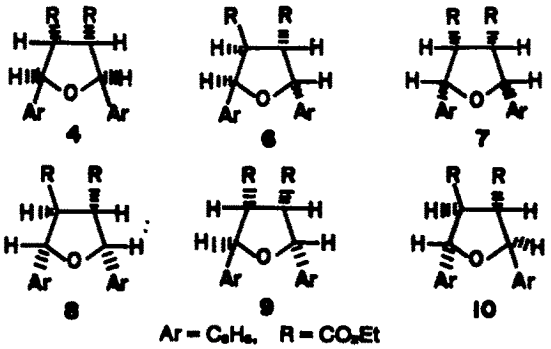
Scheme 2.

chromatographic separation led to the recovery of unreacted starting material, together with a second minor reduction product 6, being an isomer of 4, formed through a 1,2-addition reaction (Scheme 2).

It should be noted that hydrogenation, using different catalysts, of other 2,5-diphenyl furan-3,4-disubstituted derivatives [such as the diacid (5a, R = COOH), dialcohol (5b = $-CH_2OH$) and the anhydride (5c)] did not yield the desired product. Using the reported conditions (Experimental) the furan ring failed to undergo reduction (in the case of 5a, decarboxylation occurred), or the reaction took place at the C-3 substituent.

For the diester (4), ^1H and ^{13}C NMR indicated that this compound is symmetrical; one set of signals for the protons and carbons of each side of the molecule was observed. This *trans*-meso derivative may be compared to *galgravin* (4, R = Me) isolated[9] from natural sources. Out of the possible structures 6–10 which can be assigned to the isomer of 4 formed by the 1,2-addition, the r-2, 3c, 4t, 5t form, structure 6 is proposed on the following grounds. Firstly, the diester (6) was hydrolysed to a diacid which failed to give an anhydride, whereas the diacid (11), formed from the diester (4), did undergo ring closure to the anhydride (12). It is believed[10] that such ring closures can be formed if the protons H-3, H-4 are *cis* to each other, as in compound 4, but not for 6. Furthermore, two sets of signals for each side of the molecule 6 were observed (Tables 1 and 2), eliminating the possible *cis*-meso structure 7.[11,12] The comparison of benzylic proton shifts for 6 with the known compounds *veraguensin* (8, R = Me)[9,13] and *galgabin* (10, R = Me),[14] also ruled out these last two possibilities.

The ^1H NMR spectral data of the benzylic proton



4 6 7 8 9 10

Ar = C_6H_5, R = CO_2Et

shifts for the diesters 4 and 6 are presented in Table 1, together with related derivatives prepared from 4 and 6 respectively, and these are compared to data for known substituted tetrahydrofurans.[9,11–15] Analysis of the ^1H NMR spectra of 4 and 6 was also made using INDOR techniques[16] in C_6D_6 solutions, where differences in chemical shifts were observed in comparison to $CDCl_3$ solutions. For the diester 4 (in $CDCl_3$), H-2 and H-5* resonate at δ 5.38, and for compound 6 H-2 is assigned the signal at δ 4.98 and H-5 at δ 5.20. The mass spectra of these diesters 4 and 6 support the proposed structures, and are in accord with fragmentation pathways reported for other diaryl substituted tetrahydrofurans.[17]

Hydrolysis of the diester (4) gave diacid (11) which in refluxing Ac_2O yielded the anhydride (12). Reduction of 12 with $NaBH_4$ in isopropanol for 72 hr led to the 2,4-diaryl monoepoxylignanolide (3) (Scheme 3). This constitutes the first reported synthesis of a 2,4-diaryl-3,7-dioxabicyclo[3,3,0]octan-8-one.

From the ^1H NMR spectrum, assignment of the signals for 3 was made by decoupling all the protons in turn. Firstly, coupling between H-1 and H-2[b] (J = 5 Hz) sug-

*For tetrahydrofuran numbering see Table 2.

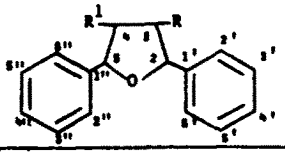
Table 1. ^1H NMR spectral data of the benzylic proton shifts for substituted tetrahydrofurans

	4			6			7			8			10		
R	H-2	H-5	J	H-2	H-5	J	H-2	H-5	J	H-2	H-5	J	H-2	H-5	J
CH_3	4.82	4.82	5-7				5.19	5.19	6.5	5.10 5.13	4.37 4.43	5-7 8	4.65	4.65	9
COOEt	5.38	5.38	7	5.20	4.98	8,8									
COOH	5.20	5.20	5	5.25	4.95	8,8									
	5.20	5.20	5												
CH_2OH	5.19	5.19	7							5.20	4.50	8-9			
CH_2OAc	5.30	5.30	7												

Values are in δ and Hz in $CDCl_3$ solutions.

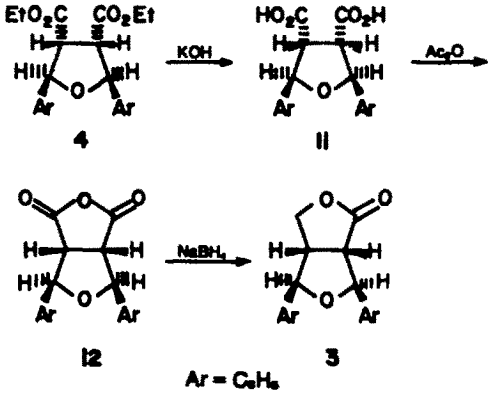
For numbering of protons see Table 2.

Table 2. ^{13}C NMR chemical shift of tetrahydrofuran derivatives of 4 and 6

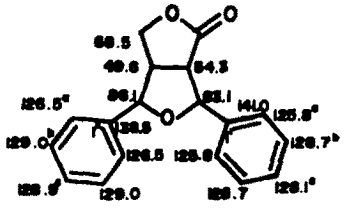


	4		6
Carbons	R=R'=CH_2OH	R=R'=CO_2Et	R=R'=CO_2Et
2,5	81.2	81.5	82.8, 83.8
3,4	48.1	52.5	54.6, 55.2
1',1''	138.9	137.6	137.4, 137.4
2',2''	126.1	127.4	126.8, 127.0
3',3''	128.4	127.8	128.4, 128.5
4',4''	127.5	127.8	128.1, 128.1
$\underline{C}O_2CH_2CH_3$		169.5	171.2, 172.1
$CO_2\underline{C}H_2CH_3$		60.3	60.8, 61.3
$CO_2CH_2\underline{C}H_3$		13.6	13.5, 14.1
$\underline{C}H_2OH$	60.8		

Chemical shifts are in ppm downfield from internal TMS, for $CDCl_3$ solutions.



Scheme 3.



a, b, c, indicate possible signal reversals.

Fig. 1. ^{13}C NMR signal assignments for 3.

gests quasi axial-equatorial coupling. This is also the case for the anhydride (12), where the observed coupling constants for the protons on both sides of the bicyclo[3,3,0]octane nucleus, are $J = 5$ Hz respectively. However, for 3, coupling of H-4 to H-5[b] ($J = 9$ Hz) is larger, and in order to accommodate such a quasi axial-axial coupling, the tetrahydrofuran ring has to be puckered, presumably to relieve steric crowding of the two benzene rings. From the ^{13}C NMR data, the carbon signals of the bicyclo[3,3,0]octane nucleus can be unambiguously assigned by relating residual coupling in the single frequency off resonance decoupled spectrum (sford) to the established ^1H NMR chemical shifts. Thus it can be seen in Fig. 1 that C(2) is shielded by 3.0 ppm relative to C(4) (γ effect), indicating that the C(2)-H(2), and the C–O bonds tend towards coplanarity. Furthermore, there is a γ effect on C(1'') from C(6), but no γ effect is felt by (C(1'), thus C(1'') resonates at a higher field than C(1') by 2.5 ppm.

Figure 2 presents a stereoscopic view of a single molecule of the 2,4-diaryl monoepoxylignanolide 3 obtained by X-ray analysis. The structure was solved by direct methods,[18] and the Shelx-76 system of crystallographic programmes was incorporated for the refinement and all calculations.[19] Complex neutral atomic scattering factors were taken from the *International Tables for X-ray Crystallography* (1974).[20] Weighted full matrix least squares refinement (including isotropic H atoms) was terminated at R = 0.062 for 1521 reflections: ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$); $R_w = 0.039$ ($R_w = \Sigma(||F_o| - |F_c|| \cdot w^{1/2})/\Sigma|F_o| \cdot w^{1/2}$), $w = 2.37/\sigma^2(F_o)$. The shifts to standard deviation ratios were less than unity for all parameters.[c]

One can see that the 5-membered ring lactone is

[b]Refers to lignan numbering as shown in 1.

[c]The X-ray analysis was kindly undertaken by Dr. D. Rabinovich and F. Frolow of the Structural Chemistry Department, Weizmann Institute. Full details will be submitted for publication separately.

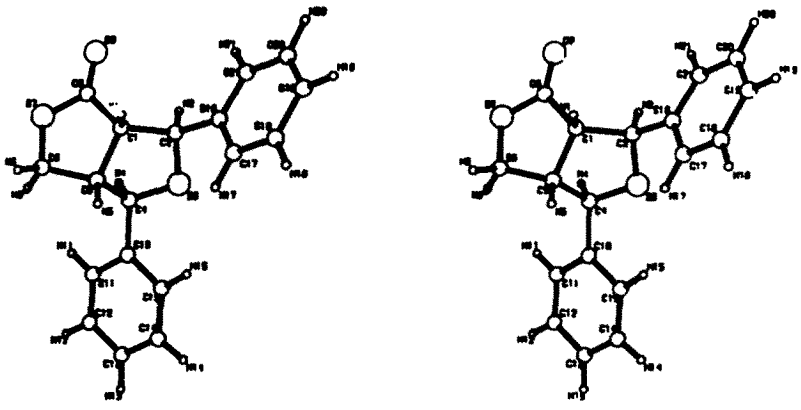
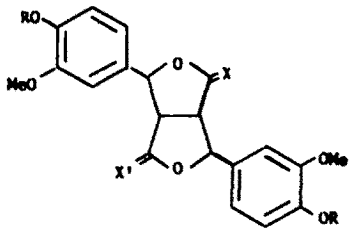


Fig. 2. Stereoscopic view of a single molecule of 3.

planar, whereas the tetrahydrofuran ring is distorted in a way that C(4) is below and out of the plane. The benzene ring attached to C(4) is orientated equatorially to the plane passing through the C(5)-C(1)-C(2)-O atoms of the tetrahydrofuran ring. The dihedral angles between H-1, H-2 and H-4, H-5 are 115° and 150° respectively, and thereby account for the observed spin-spin coupling constants between H-1, H-2 ($J = 5$ Hz) and H-4, H-5 ($J = 9$ Hz). The bridgehead hydrogens approach an eclipsed form ($\alpha = 21°$) and for H-3, H-4 $J = 9$ Hz. This then confirms the structure for this novel 2,4-diaryl monoepoxylignanolide as originally elucidated by ^1H and ^{13}C NMR data.

From the mass spectrum of 3, the highest mass peak M^+ 280 ($C_{18}H_{16}O_3$) was assigned to the molecular ion, which subsequently gave strong peaks of 236, 117 and

Table 3. ^{13}C NMR spectral data of related 2,6-diaryl lignans



13 X=O, X'=H_2, R=H

14(i) X=X'=O, R=H

14(ii) X=X'=O, R=Ac

15 X=X'=H_2, R=Ac

	13[a]	14(i)[a]	14(ii)[b]	15[c]
1	50.0	48.6	48.2	54.4
2	83.5	82.6	81.3	85.6
4	72.8	175.8	174.5	72.0
5	53.4	48.6	48.2	54.4
6	84.6	82.6	81.3	85.6
8	188.0	175.8	174.5	72.0
1',1''	131.2, 132.4	129.6	139.4	139.2
2',2''	107.9, 108.2	108.5	108.8	110.0
3',3''	146.8, 147.0	147.2	150.4	151.4
4',4''	145.5, 146.2	148.1	140.4	140.2
5',5''	114.5, 114.8	115.8	123.8	122.9
6',6''	118.1 118.5	117.6	116.5	118.0
OMe	56.1, 56.1	56.2	56.2	56.0

The chemical shifts are in ppm downfield from TMS, for $CDCl_3$ solutions.

[a] MeOH added to improve solubility; [b] δ(OAc) = 168.8, 20.6 ppm;

[c] δ(OAc) = 169.2, 20.7 ppm.

107 m.u. according to the fragmentation pattern shown in Fig. 3. Of interest, however, is the absence of a fragment peak for the loss of a cyclobutyrolactone moiety.

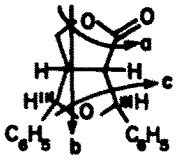
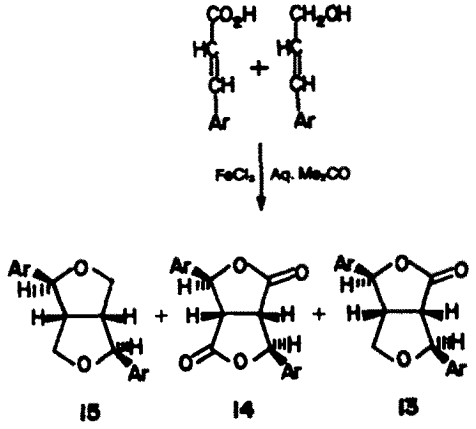


Fig. 3. Fragmentation pattern of 3 on electron impact.

Comparison of the ^{1}H NMR data of 3 to those of the naturally occurring lignan from *Aegilops ovata* L. required a revision of structure for 1. Differences in chemical shift data for their respective bicyclo[3,3,0]octane ring protons are clearly apparent as shown in Fig. 4. It was therefore considered that the naturally occurring substance may be a 2,6-diaryl substituted lignanolide, which was subsequently confirmed through an independent synthesis of a 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octan-8-one (13).[7]

A mixed oxidative phenolic coupling reaction using ferulic acid and coniferyl alcohol led to a mixture of three products which were separated by chromatography. Two of these compounds, 14 and 15, characterized from spectroscopic data are known structures.[19,21] The third compound 13 agrees in all respects with the naturally occurring lignan from *Aegilops ovata* L.



^{13}C NMR for these compounds (Table 3) are in accord with the proposed 2,6-diaryl structures. It is noteworthy that in the assignment of the carbon spectrum of 13, it was possible to compare the signals of one side of the bicyclo[3,3,0]octane nucleus, namely the carbon atoms 1,2 and 8 to those of 14, seen as a symmetrical dilactone. Furthermore, the other side of the nucleus (carbons 4, 5 and 6) compare well to those of compound 15, which is a symmetrical bis-tetrahydrofuran.

^{1}H NMR decoupling studies on 13 and the naturally occurring lignanolide were made, using selective decoupling and INDOR techniques giving exact measurements of the chemical shift and spin-spin coupling constants for the bicyclo[3,3,0]octane ring protons. These results, together with mass spectral data for 13 are in good agreement with those reported for 2,6-diaryl lignans, recently isolated[22] having a similar stereochemistry.

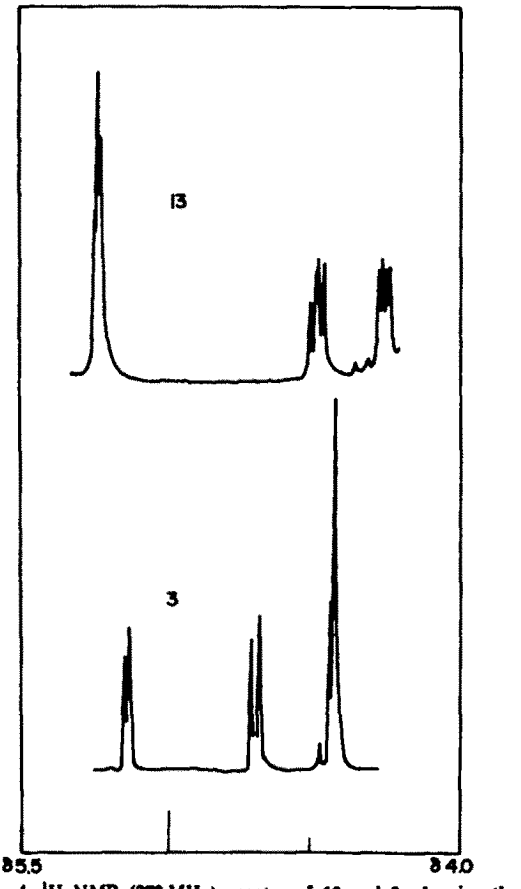
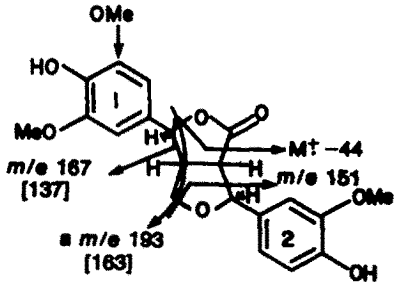


Fig. 4. ^{1}H NMR (270 MHz) spectra of 13 and 3, showing the benzylic and oxymethylene protons of the bicyclo[3,3,0]octane ring.

It therefore appears that in the 2,6-diaryl monoepoxylignanolide series, there is a consistency in the values for the spin-spin coupling constants of the benzylic protons in relation to their stereochemistry. The small J values indicate *trans*, i.e. (axial-equatorial) coupling to the bridgehead hydrogens. However, for the 2,4-diaryl monoepoxylignanolide series, this may not always be the case, owing to the distortion of the tetrahydrofuran ring, and more caution must be taken over the stereochemical assignments of the benzylic hydrogens.

Together with 13 a second lignan (16) has been isolated from *Aegilops ovata* L. Immediate comparison of the ^{1}H NMR spectrum of 16 to 13 showed a difference in the aromatic ring substitution and a third aromatic methoxy



16, M⁺ 402; 13 [M⁺ 372]

Fig. 5. Fragmentation patterns of 13 and 16 upon electron impact: values in brackets refer to 13.

group was observed. However, the substitution of the bicyclo[3,3,0]octane ring is the same as that of 13, therefore this lignan forms the second naturally occurring 2,6-diaryl monoepoxylignanolide of this new series. In order to locate the position of the third methoxy group, ^{1}H NMR decoupling studies were made and have been previously communicated.[7] The fragmentation patterns upon electron impact of 13 and 16 are similar. However, for 16 the fragment peak of 193 m.u. arises by pathway a, shown in Fig. 5, and is only possible when the third methoxy group is in Ar-1. This is supported by the absence of a peak of 163 m.u. for 16 but seen in the fragmentation of 13. A similar argument may be made for the appearance of the peak of 167 m.u. for 16, absent for 13.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer, and UV spectra were taken on a Cary-14 spectrophotometer. Mass spectra were obtained on a Varian MAT 731 High Resolution Mass Spectrometer under the supervision of Dr. Z. V. Zaretskii. All peaks are accurately mass measured and the molecular weight determinations are in excellent agreement with results of elemental analyses. The % values given in parentheses are based on values of base peak = 100%. ^{1}H NMR were recorded at 60 MHz on a Varian A-60, at 90 MHz on a Bruker HFX-10 and at 270 MHz on a Bruker WH-270 instrument. ^{13}C NMR were recorded at 22.6 MHz on a Bruker-WH90 spectrometer operating in the Fourier transform mode. X-ray single crystal analysis was made using three-dimensional intensity data (two quadrants) collected at room temp. on an Enraf-Nonius CAD-4 diffractometer, with graphite monochromatized MoKα radiation, using a spherical specimen of 0.15 mm radius. 1521 independent reflections with $F_o > 3\sigma(F_o)$ were used for structure analysis.

Tlc data refer to silica gel F, and the eluent stated, and for column chromatography, silica gel 60 (E. Merck) was used. Acetylation reactions were carried out using Ac_2O/pyridine at room temp. for 16 hr.

Isolation of 2,6-diaryl lignanolides 13 *and* 16 *from* Aegilops ovata L., (for details of basic extraction procedure, see ref. 23). The benzene-$CHCl_3$ fraction (1 g) was chromatographed over silica gel, and on eluting with benzene-EtOAc (4:1) gave a fraction containing a mixture of 13 and 16. These lignans were separated on thick layer chromatoplates (silica gel 1 mm) developed with benzene-EtOAc-MeOH (55:50:5), yielding 80 mg and 5 mg respectively.

2,6 - Bis - (3 - methoxy - 4 - hydroxyphenyl) - 3,7 - dioxabicyclo[3,3,0]octan - 8 - one, 13 $[\alpha]_D^{20}$ -46°, m.p. 122–123° with dec. ($CHCl_3$-Et_2O): UV (MeOH) λ_{max} 236 (ε 967) and 287 (ε 521) nm.: IR (KBr) $\nu_{C=O}$ 1775 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ 3.18 m, partially resolved by decoupling $J_{3,4}$ = 3.5 Hz (1, H-5), 3.40 dd, J = 9 and 3.5 Hz (1, H-1), 3.78 s (6, OMe), 4.15 dd J = 10 and 4 Hz (1, H-4), 4.30 dd J = 10 and 6 Hz (1, H-4), 5.27 d J = 3.5 Hz (2, H-2, -6), 5.80 s disappearing on exchange with D_2O (2, OH), 6.8–6.9 br (6, Ar-H); M.S. *m/e* M$^+$ 372 ($C_{20}H_{20}O_7$, 26%), 328 ($C_{19}H_{20}O_5$, 10%), 287 ($C_{16}H_{15}O_5$, 3%), 286 ($C_{16}H_{14}O_5$, 3%), 163 ($C_{10}H_{11}O_3$, 40%), 151 ($C_8H_7O_3$, 100%), 137 ($C_8H_6O_2$, 40%). This compound was acetylated.

2,6 - Bis - (3 - methoxy - 4 - acetoxyphenyl - 3,7 - dioxabicyclo[3,3,0]octan - 8 - one, m.p. 166–168°. ^{1}H NMR ($CDCl_3$) δ 2.24 s (6, OAc), 3.15 m (1, H-5), 3.42 dd J = 9 and 3.5 Hz (1, H-1), 3.74 s (6, OMe), 4.15 dd J = 10 dd 4 Hz (1, H-4), 4.30 dd J = 10 and 6 Hz (1, H-4), 5.26 d J = 3.5 Hz (2, H-2, -6), 6.9–7.1 br (6, Ar-H); M.S. *m/e* M$^+$ 456 ($C_{24}H_{24}O_9$, 5%), 414 ($C_{22}H_{22}O_8$, 15%), 372 ($C_{20}H_{20}O_7$, 100%), 286 ($C_{16}H_{14}O_5$, 5%), 163 ($C_{10}H_{11}O_3$, 35%), 151 ($C_8H_7O_3$, 80%), 137 ($C_8H_6O_2$, 40%).

2 - (3 - Methoxy - 4 - hydroxyphenyl), 6 - (3', - 5' - dimethoxy - 4' - hydroxyphenyl) - 3,7 - dioxabicyclo[3.3.0]octan - 8 - one, 16, oil: UV λ_{max} (MeOH) 236 (ε 967) and 290 (ε 521) nm: IR (KBr) $\nu_{C=O}$ 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.27 m, partially resolved by decoupling $J_{3,4}$ = 3.5 Hz (1, H-5), 3.47 dd J = 9 and 3.5 Hz (1, H-1), 3.82 s (6, OMe), 3.84 s (3, OMe), 4.15 dd J = 10 and 4 Hz (1, H-4), 4.32 dd J = 10 and 4 Hz (1, H-4), 5.27 d J = 3.5 Hz (1, H-6), 5.29 d J = 3.5 Hz (1, H-2), 6.48 s (2, Ar^1-H), 6.96 br (3, Ar^2-H); M.S. *m/e* M$^+$ 402 ($C_{21}H_{22}O_8$, 20%), 358 ($C_{20}H_{22}O_6$, 10%), 317 ($C_{17}H_{17}O_6$, 5%), 193 ($C_{11}H_{13}O_3$, 40%), 167 ($C_9H_{11}O_3$, 100%), 151 ($C_8H_7O_3$, 40%). This compound was acetylated.

2 - (3 - Methoxy - 4 - acetoxyphenyl), 6 - (3',5' - dimethoxy - 4' - acetoxyphenyl) - 3,7 - dioxabicyclo[3,3,0]octan - 8 - one, m.p. 154–155°; ^{1}H NMR ($CDCl_3$) 2.23 s (3, OAc), 2.26 s (3, OAc), 3.27 m (1, H-5), 3.59 dd J = 9 and 3.5 Hz (1, H-1), 3.76 s (6, OMe), 3.78 s (3, OMe), 4.15 dd J = 10 and 4 Hz (1, H-4), 4.32 dd J = 10 and 6 Hz (1, H-4), 5.27 d, J = 3.5 Hz (1, H-6), 5.29 d J = 3.5 Hz (1, H-2), 6.41 s (2, Ar^1-H), 6.93 br (3, Ar^2-H); M.S. *m/e* M$^+$ 486 ($C_{25}H_{26}O_{10}$, 5%), 444 ($C_{23}H_{24}O_9$, 30%), 402 ($C_{21}H_{22}O_8$, 100%), 358 ($C_{20}H_{22}O_6$, 7%), 318 ($C_{17}H_{18}O_6$, 3%), 317 ($C_{17}H_{17}O_6$, 5%), 193 ($C_{11}H_{13}O_3$, 13%), 167 ($C_9H_{11}O_3$, 11%), 151 ($C_8H_7O_3$, 20%), 137 ($C_8H_6O_2$, 8%).

Synthesis of 13, 14, 15. $FeCl_3$ (2 g) was dissolved in H_2O (40 ml), filtered, a further 40 ml H_2O added, and left stirring at room temp. whilst bubbling O_2 through the soln. A mixture of ferulic acid (300 mg) and coniferyl alcohol (prepared as reported[24]) (340 mg) in acetone (25 ml) was added dropwise over 10 mins, the soln stirred for a further 10 min, passage of O_2 stopped, and the soln left at room temp. overnight. The red-brown ppt was filtered off and suspended in 10% H_2SO_4 warmed to 60° for 10 min, cooled and extracted into Et_2O which was combined with the Et_2O extract of the aqueous filtrate, washed with H_2O and dried over Na_2SO_4. Filtration and removal of solvent gave a yellow oil chromatographed over silica gel eluting with $CHCl_3$ to give firstly 14 (30 mg) then 13 (40 mg) and finally 15 together with unreacted coniferyl alcohol. Compound 15 was purified and identified as its diacetate derivative.

2,6 - Bis - (3 - methoxy - 4 - hydroxyphenyl) - 3,7 - dioxabicyclo[3,3,0]octan - 8 - one, 13, (*synthetic*), m.p. 190–192°, with spectroscopic data in excellent agreement with that found for the naturally occurring lignan.

2,6 - Bis(3 - methoxy - 4 - hydroxyphenyl) - 3,7 - dioxabicyclo[3,3,0] - octane - 4,8 - dione 14(*i*), m.p. 206–208° (lit.[25] m.p. 208–209°); IR (KBr) $\nu_{C=O}$ 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 3.61 dd, J = 2 and 9 Hz (2, H-1, 5), 3.89 s (6, OMe), 5.90 d J = 2 Hz (2, H-2, 6), 6.82–7.20 br (6, Ar-H); M.S. *m/e* M$^+$ 386 ($C_{20}H_{18}O_8$, 60%), 151 ($C_8H_7O_3$, 100%).

2,6 - Bis(3 - methoxy - 4 - acetoxyphenyl) - 3,7 - dioxabicyclo[3,3,0]octane - 4,8 - dione 14 (*ii*), prepared by acetylation of 14(i), m.p. 210–212°. ^{1}H NMR ($CDCl_3$) δ 2.30 s (6, OAc), 3.61 dd J = 9 and 2 Hz (2, H-1, -5), 3.84 s (6, OMe), 5.90 d J = 2 Hz (2, H-2, -6), 6.8–7.0 br (6, Ar-H): M.S. *m/e* M$^+$ 470 ($C_{24}H_{22}O_{10}$, 2%), 428 (30%), 356 (100%), 151 (75%).

2,6 - Bis - (3 - methoxy - 4 - acetoxyphenyl) - 3,7 - dioxabicyclo[3,3,0]octane 15, m.p. 153–155° (30 mg): ^{1}H NMR ($CDCl_3$) δ 2.30 s (6, OAc), 2.9–3.1 m (2, H-1, -5), 3.84 s (6, OMe), 3.8–4.0 m (2, H-4, -8), 4.2–4.4 m (2, H-4, -8), 4.75 d J = 4 Hz (2, H-2, -6), 6.9–7.2 br (6, Ar-H): M.S. *m/e* M$^+$ 442 ($C_{24}H_{26}O_8$, 12%), 400 (50%), 358 (57%), 163 ($C_{10}H_{11}O_3$, 45%), 151 ($C_8H_7O_3$, 100%).

Synthesis of the 2,4-diaryl lignan (3). Ethyl benzoylacetate (50 ml) in CCl_4 (200 ml) was stirred at −5° and Br_2 (17 ml) in CCl_4 (85 ml) added dropwise over 15 min. The reaction was maintained for 1 hr at 0° and 3 hr at room temp. On warming the reaction vessel to 60°, HBr was evolved and the solvent was then distilled off under reduced pressure leaving a yellow oil. Passage through a silica column eluting with benzene gave the α-ketobromoester m.p. 58–60°: ^{1}H NMR ($CDCl_3$) δ 1.20 t J = 7 Hz (3, CH_3), 4.25 q J = 7 Hz (2, CH_2), 5.95 s (1-C*H*Br), 7.5–8.2 br (5, Ar-H): M.S. *m/e* M$^+$ 271 ($C_{11}H_{11}O_3Br$).

Ethyl benzoylacetate (50 ml) was added to a stirred mixture of dry THF (200 ml) and Na wire (6 g). The soln immediately turned yellow, dissipating heat, and was left overnight then refluxed for a further hr. The orange soln was cooled and the *sodium enolate* derivative precipitated out as a white solid, and immediately added to dry THF (50 ml) and NaI (1 g). The mixture was stirred during the slow addition of the α-ketobromoester in THF (50 ml) while maintaining the temp. below 30°. The mixture was stirred at room temp. for 8 hr, at 40° for 16 hr, cooled to 0° and ice-water added until the soln became clear and then extracted into Et_2O, which was washed with 5% HCl soln, H_2O and

dried over $CaCl_2$. Filtration and removal of solvent left a red oil which upon trituration with MeOH and on standing several days at 0° gave white crystals (30 g) of the *1,4-diketone*, m.p. 117–119°; ^1H NMR ($CDCl_3$) δ 1.0 *t* J = 7 Hz (6, $-CH_3$), 4.0 q J = 7 Hz (4, OCH_2-), 5.7 s (2, -CH-), 7.5–8.2 br (10, Ar-H); M.S. M^+ 382 ($C_{22}H_{22}O_6$, 5%), M^+-H_2O, 364 ($C_{22}H_{20}O_5$, 10%), 189 (87%), 144 (100%), 105 (100%).

2,5-Diphenyl-furan-3,4-dicarboxylic acid diethyl ester, 5. The 1, 4-diketone (5 g) was added to polyphosphoric acid (30 g) at 60°. The mixture was maintained for 1 hr at 75°–85° with stirring, cooled and poured over crushed ice. The brown soln slowly gave way to a white milky suspension, extracted into Et_2O washed (2 × H_2O) and dried over $CaCl_2$. On filtering and removal of solvent, a white solid (5) crystallised out (4.2 g), recrystallised from Et_2O-hexane, m.p. 79–80°. ^1H NMR ($CDCl_3$) δ 1.2 t J = 7 Hz (6, $-CH_3$), 4.4 q J = 7 Hz (4, OCH_2-), 7.5–8.2 br (10, Ar-H); M.S. *m/e* M^+ 364 ($C_{22}H_{20}O_5$, 10%), 105 (100%).

2,5-Diphenyl furan-3,4-dicarboxylic acid (5a), m.p. 235–237° (lit. m.p.[25] 235–237°) and *2,5-diphenylfuran-3,4-dicarboxylic acid anhydride* (5c), m.p. 259–260° (lit. m.p.[25] 254–255°) were prepared as reported.[25]

2,5 - Diphenyl - 3 - hydroxymethylfuran - 4 - carboxylic acid (5d). Compound 5c (280 mg) in THF (25 ml) was added slowly to a stirred mixture of $NaBH_4$ (40 mg) in THF (2 ml) at 0°, then allowed to warm to room temp. and left stirring for a further 2 hr, 6N HCl (2 ml) was added, THF distilled off under reduced pressure and H_2O (20 ml) added, before extracting the soln into Et_2O. The organic layer was extracted with 5% $NaHCO_3$ soln which was then acidified and re-extracted into Et_2O, the organic layer washed with H_2O(2x) and dried over Na_2SO_4. On filtering and removal of solvent, a white solid (5d) remained (200 mg), recrystallised from acetone-petroleum ether, m.p. 206–208°; IR (KBr), 3500–3000 (O–H), $\nu_{C=O}$ 1730, 1675 cm^{-1}; M.S. *m/e* M^+ 294 ($C_{18}H_{14}O_4$, 20%), 105 (100%).

2,5-Diphenyl-3,4-di(hydroxymethyl)furan 5b. Compound 5c added to a stirred suspension of LAH (500 mg) and $AlCl_3$ (500 mg) in dry THF (50 ml) at 0°. The mixture was allowed to warm to room temp. over 2 hr with stirring then refluxed for a further 24 hr, cooled, EtOAc added followed by a saturated soln of Na_2SO_4 until a white gelatinous mass formed. The mixture was filtered, the ppt washed with acetone and 10% H_2SO_4, and all the washings added to the filtrate, the organic solvents distilled off under reduced pressure and extracted into Et_2O (2 × 100 ml). The Et_2O soln was washed with H_2O(2x), dried over $NaSO_4$ and on filtering and removal of solvent a white crystalline solid (5b) precipitated out (350 mg) m.p. 169–170°. IR (KBr), 3400–3300, 1010 cm^{-1}; M.S. *m/e* M^+ 280 ($C_{18}H_{16}O_3$, 20%), 105 (100%).

Hydrogenations of substituted furans (5, 5b, 5c)

General procedure. A mixture of the compound to be reduced (50–100 mg), catalyst usually (20–50 mg) and solvent (50–100 ml) was maintained with shaking under an atmosphere of H_2 at the desired temp. and pressure. After filtration of the spent catalyst, the filtrate was examined by tlc. For isolation of products, the solvents were removed and the products separated by chromatography, and analysed by tlc, IR and ^1H NMR spectroscopy.

Compound 5b (80 mg) in EtOH (50 ml) was hydrogenated over 10% Pd-$CaCO_3$ (20 mg) at room temp. for 5 hr at 50 atm. Tlc indicated the presence of one reaction product, which chromatographic separation over Alumina (grade III) eluting with benzene gave *trans - meso - 2,5 - diphenyltetrahydrofuran - 3 - hydroxymethyl - 4 - methyl* (15 mg) as an oil. ^1H NMR ($CDCl_3$) δ 1.25 d J = 5 Hz (3, $-CH_3$), 2.80 s disappearing upon exchange with D_2O (1-OH), 2.6–3.3 m (2, H-3, -4), 4.75 d J = 4 Hz (2, $-CH_2O$), 5.15 m, resolved by decoupling, J = 8 Hz (2, H-2, 5), 7.4–7.9 br (10, Ar-H); M.S. *m/e* M^+ 272 ($C_{18}H_{20}O_3$, 20%), 105 (100%).

Compound 5c (80 mg) in AcOH-MeOH (1:1, 50 ml) was hydrogenated over 5% Pd-charcoal (20 mg) at room temp. for 5 hr at 30 atm. Tlc indicated the presence of 5d confirmed by isolation (20 mg) and comparison with the reaction product of the anhydride (5c) reduction using $NaBH_4$.

Using 5% Pd-$CaCO_3$ (20 mg) in EtOH (80 ml), 5c (50 mg) gave also 5d (20 mg) as the only reduction product of reaction.

Hydrogenation of 5 (100 mg) over 10% Pd-$CaCO_3$ catalyst (100 mg) in abs. EtOH (200 ml) at 100° under 100 atm pressure for 3 hr followed by filtration and removal of solvent gave an oil. Chromatography over Alumina (grade III) eluting firstly with hexane gave unreacted starting material. Hexane-benzene (30%) eluted 6 (10 mg) and with hexane-benzene (50%), the diester (4) (60 mg) was separated.

trans - *Meso* - 2,5 - *diphenyltetrahydrofuran* - 3,4 - *dicarboxylic acid diethyl ester*, 4, m.p. 62–63°, ^1H NMR ($CDCl_3$) δ 0.78 t J = 7 Hz (6, CH_3), 3.6–3.8 m (6, CH_2 + H-3, -4), 5.38 d J = 7 Hz (2, H-2, -5), 7.2–7.8 br (10, Ar-H); C_6D_6 δ 0.70 t J = 7 Hz (6, CH_3), 3.4 d, J = 8 Hz (2, H-3, -4), 3.7 q J = 7 Hz (4-CH_2), 5.15 d, J = 7 Hz (2, H-2, -5), 7.2–7.6 br (10, Ar-H); M.S. *m/e* M^+ 368 ($C_{22}H_{24}O_5$, 5%), 299 (5%), 262 (36%), 217 (15%), 189 (100%), 115 (57%), 105 (28%).

r - 2,3c,4t,5t - 2,5 - Diphenyltetrahydrofuran - 3,4 - dicarboxylic acid diethyl ester, 6, oil; ^1H NMR ($CDCl_3$) δ 0.80 t J = 7 Hz (3, $-CH_3$), 1.0 t J = 7 Hz (3, $-CH_3$), 3.3–3.8 m (4, $-CH_2$ + H-3, -4), 4.0 q J = 7 Hz (2, $-CH_2$), 4.98 d J = 8 Hz (1, H-5), 5.20 d J = 8 Hz (1, H-2), 7.0–7.5 br (10, Ar-H); (C_6D_6) δ 0.55 t J = 7 Hz (3, $-CH_3$), 0.8 t J = 7 Hz (3, $-CH_3$), 3.4 d J = 7 Hz (2, H-3, -4), 3.9 q, J = 7 Hz (2, CH_2), 3.95 q J = 7 Hz (2, CH_2), 5.1 d J = 8 Hz (1, H-5), 5.2 d J = 8 Hz (1, H-2), 7.0–7.5 br (10, Ar-H); M.S. *m/e* M^+ 368 ($C_{22}H_{24}O_5$, 5%), 299 (7%), 262 (36%), 217 (12%), 189 (100%), 115 (60%), 105 (30%).

trans - *Meso* - 2,5 - *diphenyl* - 3,4 - *dihydroxymethyltetrahydrofuran*, (4, R = CH_2OH); obtained by reduction of 4 using LAH/THF, as an oil. ^1H NMR ($CDCl_3$) δ 2.5 br disappearing upon exchange with D_2O (2, OH), 2.9–3.3 m (2, H-3, -4), 3.4–3.6 m (4, $-CH_2O$), 5.19 d J = 7 Hz (2, H-2, -5), 7.3–7.9 br (10, Ar-H); M.S. *m/e* M^+ 284 ($C_{18}H_{20}O_3$, 30%), 105 (100%).

trans - *Meso* 2,5 - *diphenyl* - 3,4 - *diacetoxymethyltetrahydrofuran* (4, R = CH_2OAc); obtained as an oil by acetylation of the above diol. ^{1} H NMR ($CDCl_3$) δ 1.8 s (6, OAc), 2.8–3.2 m (2, H-3, -4), 3.6–4.1 m (4, $-CH_2O$), 5.30 d J = 7 Hz (2, H-2, -5), 7.3–7.7 br (10, Ar-H); M.S. *m/e* M^+ 368 ($C_{22}H_{24}O_5$, 10%), 284 (100%).

trans - *Meso* - 2,5 - *diphenyltetrahydrofuran* - 3,4 - *dicarboxylic acid*, 11. Compound 4 (60 mg) was dissolved in EtOH (1 ml), added to 10% aq. (25% alc.) KOH (10 ml) and the mixture refluxed for 2 hr. The soln was cooled and poured onto crushed ice, extracted into Et_2O, which was dried over Na_2SO_4 and after filtration and removal of solvent a white solid (11) (48 mg) remained, recrystallised from $CHCl_3$, m.p. 197–199°. ^1H NMR ($CDCl_3$) δ 3.6 m (2, H-3, -4), 5.20 d J = 5 Hz (2, H-2, -5), 7.4–7.8 br (10, Ar-H); M.S. *m/e* M^+ 312 ($C_{18}H_{16}O_5$, 5%), 206 (12%), 188 (20%), 164 (100%), 146 (15%), 115 (45%), 105 (75%).

The *diester* 6 (10 mg) was converted into the corresponding r-2, 3c, 4t, 5t-*2,5-diphenyltetrahydrofuran-3,4-dicarboxylic acid*, by the same procedure, m.p. 220–221° (dec.); ^1H NMR ($CDCl_3$) δ 3.6 m (2, H-3, -4), 4.95 d J = 8 Hz (1, H-5), 5.25 d J = 8 Hz, (1, H-2), 7.5–7.9 br (10, Ar-H).

trans - *Meso* - 2,5 - *diphenyltetrahydrofuran* - 3,4 - *dicarboxylic acid anhydride*, 12. Compound 11 (90 mg) was dissolved in Ac_2O (15 ml) and brought to reflux for 2 hr, the solvent was removed by distillation under reduced pressure leaving a white solid (80 mg) m.p. 225–226°. IR (KBr) $\nu_{C=O}$ 1860, 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–3.6 m (2, H-3, -4), 5.20 d J = 5 Hz (2, H-2, -5), 7.2–7.6 br (10, Ar-H); M.S. *m/e* M^+ 294 ($C_{18}H_{14}O_4$, 2%), 206 (13%), 189 (40%), 164 (60%), 146 (73%), 115 (90%), 105 (100%).

2,4 - Diphenyl - 3,7 - dioxabicyclo[3,3,0]*octan - 8 - one*, 3. Compound 12 (60 mg) was suspended in iso-propanol (10 ml), $NaBH_4$ (15 mg) added slowly, and the mixture left stirring for 72 hr. Water was added, overlayered with Et_2O and the aq. layer brought to pH 6 with 5% HCl with vigorous stirring. The organic layer was removed, washed with H_2O (3x), dried over Na_2SO_4, filtered and the solvent removed. Chromatography over silica eluting with benzene-$CHCl_3$ (9:1) gave 3 (30 mg) recrystallised from $CHCl_3$-hexane, m.p. 95–96°. UV (MeOH) λ_{max} 258 (ϵ 600) nm; I.R. (KBr) $\nu_{C=O}$ 1760 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 3.15 tdd J = 9, 5.5 and 2.5 Hz [1, H-5 (lignan numbering)], 3.38 dd J = 9 and 5 Hz (1, H-1), 4.40 m (2, $-CH_2O$), 4.71 d J = 9 Hz (1, H-4), 5.25 d J = 5 Hz (1, H-2), 7.3–7.6 br (10, Ar-H); M.S. *m/e* M^+ 280 ($C_{18}H_{16}O_3$, 38%), 235 (4%), 174 ($C_{11}H_{10}O_2$, 38%), 129 ($C_{10}H_9$, 100%), 117 (C_9H_9, 75%), 115 (C_9H_7, 55%), 105 (C_7H_5O, 34%). Crystal data: orthorhombic, Pbca; *a* = 8.377 (1),

$b = 10.985$ (1), $c = 31.250$ (1): $V = 2900.5$ Å, $z = 8$, $Dc = 1.30\ g\ cm^{-3}$, $F(000) = 1200.00$, $\mu = 0.43\ cm^{-1}$.

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