Synthesis of 4,8-Bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ones and Determination of their Relative Configuration *via* Long-range Proton Couplings

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A short synthesis of the furofuranoid lignan, 4-*cis*,8-*cis*-bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one (MEL), was accomplished *via* a simple regioselective hydride reduction of the dilactone parent [4-*cis*,8-*cis*-bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane-2,6-dione], followed by deoxygenation of the lactone–lactol intermediate *via* silane hydride transfer. The 4-*trans*-8-*cis*(*iso*-MEL) and the 4-*cis*-8-*trans*(*epi*-MEL) isomers, and a fourth related compound, featuring a 3-fused 5-membered ring skeleton were additionally formed. All four compounds were fully characterized by use of 1D and 2D NMR techniques. Examination of the long-range coupled proton network by delayed COSY experiments allowed determination of the relative configuration of these 4,8-diaryl-3,7-dioxabicyclo[3.3.0]octan-2-one structures. The pathways followed by these long-range proton couplings and implications of the long-range and vicinal couplings with respect to favoured conformations are discussed.

Our current research interests concern the characterization of the *p*-hydroxycinnamic acid–lignin complexes in forage plant cell walls.[1] Incorporation of feruloyl esters into coniferyl alcohol dehydrogenation polymers led to the identification of new structures which model the possible free-radical coupling products resulting from the involvement of feruloyl esters in the peroxidase-catalysed lignification processes.[2,3] Among these structures, we observed a 4,8-diaryl-3,7-dioxabicyclo-[3.3.0]octan-2-one system (Fig. 1), which arises from β–β coupling between dehydrogenated feruloyl ester and coniferyl alcohol moieties.[2] This type of γ-lactone was originally proposed as a lignin intermediate by Freudenberg and Geiger,[4,5] who obtained the dimeric phenylpropane derivative, namely pinoresinolide, from dehydrogenation of a mixture of ferulic acid and coniferyl alcohol. In order to authenticate unambiguously the structure proposed in our synthetic dehydrogenation polymer, we looked for an expedient route to this 4,8-bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo-[3.3.0]octan-2-one.[6]

The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes and a few 8-oxo derivatives, *i.e.* 4,8-diaryl-3,7-dioxabicyclo[3.3.0]octan-2-ones constitute a major group of the naturally occurring lignans.[7,8] Due to the wide range of biological activities exhibited by these furofuranoid lignans,[9,10] considerable interest has been focused on their synthesis.[11–16] Our first approach toward the synthesis of the desired racemic 4,8-diaryl-3,7-dioxabicyclo[3.3.0]octan-2-one was the mixed oxidative coupling between ferulic acid and coniferyl alcohol,[17] using silver(I) oxide as a one-electron oxidant.[3] This expedient, but low-yielding method gave the expected 4-*cis*,8-*cis*-bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one '(±)-MEL' **5**,* whose NMR spectroscopic data were in excellent agreement with those of the structure observed in the dehydrogenation polymer.[2] The sustained phytochemical interest in this lignan lactone, a natural germination inhibitor[18–21] led us to contemplate an improved synthesis of **5**. To our knowledge, besides the oxidative cross-coupling method, the only synthesis of MEL **5** that has been reported is in a recent communication by Stevens *et al.*[21] on the synthesis of furofuranoid lignans *via* an intramolecular Mukaiyama aldol condensation, a feature of which is the ability to prepare unsymmetrically substituted compounds. However, for the preparation of the symmetrical MEL **5**, we considered the dilactone **1** to be a good starting material and thought to effect selective conversion of one lactone into a cyclic ether.[22] In this paper, we report a short synthesis of (±)-MEL **5** *via* a selective two-step reduction of the parent dilactone **1**.

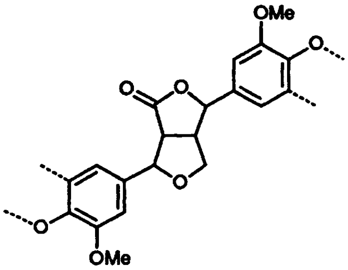

Fig. 1 4,8-Diaryl-3,7-dioxabicyclo[3.3.0]octan-2-one structure observed upon incorporation of feruloyl ester into coniferyl alcohol dehydrogenation polymer. The dotted lines indicates the possible attachment sites to the lignin polymer

Results and Discussion

The *cis*-fused dilactone **1** was prepared by oxidation of ferulic acid with aqueous iron(III) chloride and oxygen.[23,24] Vande Velde *et al.*[25] reported the successful selective reduction of the dilactone **1** into the lactol **2** using diisobutylaluminium hydride (DIBAL-H), but no yield was mentioned. Several attempts to prepare the intermediate **2** with DIBAL-H were not reproducible; varying amounts of unchanged **1** and/or dilactol compound were always observed. However, lithium borohydride ($LiBH_4$) was found to accomplish this mild regioselective reduction with remarkable efficiency. Treatment of **1** with 1.5 equiv. of $LiBH_4$ at ambient temperature in anhydrous THF (tetrahydrofuran) afforded the required hemiacetal **2**

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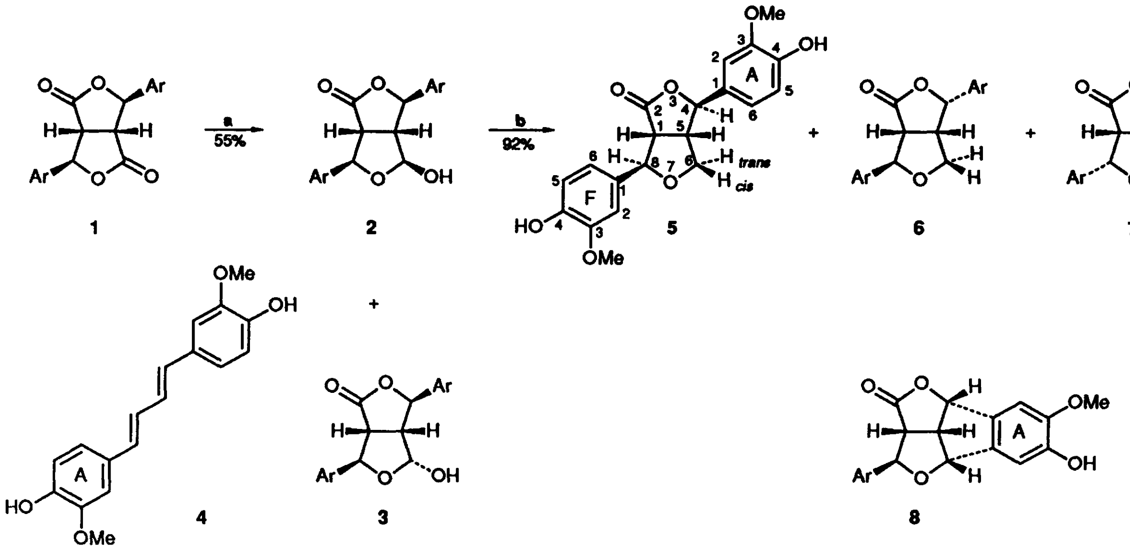
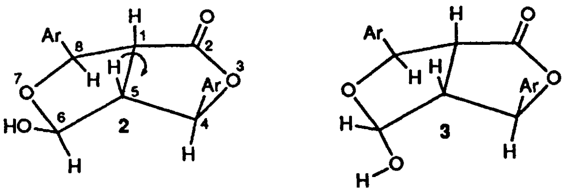
* 'MEL' Acronym commonly used as a trivial name, standing for monoepoxylignanolide according to Weinges' terminology.[6]



Scheme 1 Ar = 4-hydroxy-3-methoxyphenyl; **a**, $LiBH_4$–THF; **b**, Et_3SiH, $BF_3–Et_2O–CH_2Cl_2$. Structure **2** represents the crystalline form of the hemiacetal; in acetone solution, mutarotation gives rise to a **2**:**3** 40:60 anomeric mixture

(Scheme 1). Traces of compound **4** were discerned by ^{1}H NMR spectroscopic analysis of the chloroform extracted reaction mixture (Experimental section). This diphenylbutadiene derivative **4** may arise from the complete hydride reduction of the lactone functions of **1**, giving an acyclic tetraol by-product which, upon hydrolysis, undergoes an acid-catalysed two-fold retro-Prins reaction.[26] Crystallization from acetone afforded pure **2** in reproducible yields of 55–60%. ^{1}H NMR analysis of **2** in [$^2H_6$]-acetone revealed the presence of small amount of its anomer **3** (Scheme 1). After 24 h in the NMR tube, mutarotation gave rise to a *ca.* 40:60 anomeric mixture of the hemiacetals **2** and **3**, respectively. Their stereochemical assignment was based upon comparison of their vicinal and long-range ^{1}H–^{1}H coupling constants (Experimental section and Table 3). The fused five-membered rings in dioxabicyclo[3.3.0]octane system are presumably conformationally flexible in solution. The observed coupling constants thus reflect time-averaged couplings resulting from the distribution of solution conformations. No detailed conformational analysis was undertaken in this study. Conformational preferences, when proposed for description purposes, were estimated from experimental *J*-values and model observation. For convenience, the carbohydrate conformation terminology[27] was used to indicate the approximate conformations of the furanoid rings.

The *trans*-relationship between 6-H and 5-H in **2** was deduced from the small $J_{6,5}$ value (1.5 Hz).[25] A Karplus interpretation of this small vicinal coupling constant implicates a $H^6–C^6–C^5–H^5$ dihedral angle ($\varphi_{6,5}$) close to 90°. This φ_{trans} angle is observed in a staggered conformation of **2** obtained by rotating the molecule around the $C^1–C^5$ bond, moving 5-H clockwise away from 1-H. Upon rotation, the decrease of the dihedral angle $\varphi_{6,5}$ is accompanied by an increase of the *transoid* dihedral angles $\varphi_{1,8}$ and $\varphi_{5,4}$ (*i.e.* $\varphi_{trans} > 120°$), as reflected by the $J_{1,8}$ and $J_{5,4}$ values of 5.5 Hz and 6.6 Hz, respectively. An ^5E conformation of the lactone ring (C-5 being above the $C^1–C^2–O^3–C^4$ plane) and a $^1T_5$ conformation of the tetrahydrofuran ring (C-1 and C-5 being respectively above and below the $C^6–O^7–C^8$ plane)[27] seem to best fit the observed *J*-values. In **3**, the $J_{6,5}$ value of 5.1 Hz does not allow assignment of the C-6 configuration, but the coupling constant of 1.8 Hz between 5-H and 4-H again suggests a dihedral angle $\varphi_{5,4}$ of *ca.* 90° and a *trans* orientation for these two protons. A slight puckering of the lactone ring by rotating the molecule counterclockwise about the $C^1–C^5$ bond permits this angle. The dihedral angle between 1-H and 8-H is maintained close to 120° ($J_{1,8}$ = 4.5 Hz) in a favoured $^0T_6$ conformation of the tetrahydrofuran ring. This twist conformation would bring the *trans*-orientated hydroxy group into a *quasi*-axial position. This is confirmed by the occurrence of a long-range coupling between 5-H and the C^6-hydroxy proton ($J_{5,6\text{-OH}}$ = 1.2 Hz); the OH group having a *quasi*-axial position, an almost planar pathway is followed, favouring observation of a long-range 'W-type' coupling. The orientation of the hydroxy group also had significant effects on the ^{13}C NMR chemical shifts of anomers **2** and **3** (Experimental section). In **3**, C-6 resonates at 99.0 ppm, whereas a C-6 shift of 103.3 ppm is observed in **2**. These α-effects are in agreement with the ones observed in cyclopentanes upon hydroxy substitution.[28] An even more striking β-effect difference is observed for the C-5 resonances, as C-5 of **2** is 7.08 ppm downfield of C-5 of **3** (59.59 ppm *vs.* 52.51 ppm, respectively). The use of NOE spectroscopy did not allow unambiguous determination of the lactol configurations. For instance, in the phase sensitive NOESY spectrum of compound **2**, 4-H and 8-H gave substantial NOE cross-peaks with 5-H and 1-H, respectively, despite their *trans* relationship. 6-H Strongly correlated with 4-H, but also with 5-H. This may be explained from the proposed $^1T_5$ conformation of the tetrahydrofuran ring in which the $C^5–H^5$ and $C^6–H^6$ bonds are nearly perpendicular to each other ($\varphi_{6,5}$ ~ 90°, $J_{6,5}$ = 1.5 Hz).



Anomeric lactols **2** and **3**. The arrow indicates the clockwise twisting about the $C_1–C_5$ bond (see text)

The lactol **2** was then directly de-oxygenated by triethylsilane in the presence of boron trifluoride–diethyl ether[22,29] to afford (±)-MEL **5** as the major product (47%), together with compounds **6** (14%), **7** (19%) and **8** (20%) (Scheme 1). The relative proportions were determined from ^{1}H NMR analysis of the reaction product which was subsequently purified by HPLC (Experimental section). The two diastereoisomers **6** [(±)-*iso*-MEL] and **7** [we suggest the name '(±)-*epi*-MEL' for compound **7**, by analogy with *epi*-aptosimon and *epi*-styraxin[21]] resulted from epimerization at C-4 and C-8, respectively. The

Table 1 ^{1}H NMR spectroscopic data for 3,7-dioxabicyclo[3.3.0]octan-2-one derivatives[a,b]

Proton	5 MEL	6 *iso*-MEL	7 *epi*-MEL	8
1-H	3.65 ddd (9.2, 3.7, 0.5)	3.65 dd (8.7, 2.6)	3.63 t (8.8)	3.36 dd (10.7, 6.4)
5-H	3.39 ddddd (9.2, 7.0, 4.6, 3.6, 0.6)	3.71 m	3.35 ddd (9.0, 6.6, 4.6)	4.24 dddd (10.6, 7.5, 6.9, 0.6)
8-H[c]	5.20 dquintet (3.7, 0.6)	5.16 br d (2.6)	5.05 br d (8.6)	4.72 dquintet (6.3, 0.6)
4-H[c]	5.39 br d (3.6)	5.82 br d (5.9)	5.23 br d (6.6)	5.73 br d (7.5)
6*cis*-H	4.30 ddd (9.4, 7.0, 0.5)	3.80 m	3.88 dd (9.5, 4.8)	5.60 dq (6.9, 0.6)
6*trans*-H	4.02 ddt (9.4, 4.6, 0.5)	3.47 dd (9.2, 6.7)	4.28 br d (9.5)	—

[a] Values were determined in [$^2H_6$]-acetone at 300 K with the central solvent peak as internal reference (2.04 ppm); data in parentheses are coupling constants in Hz. [b] Methoxy proton shifts, aromatic proton shifts and coupling constants are in the Experimental section. [c] In addition to ^4J couplings with aliphatic protons (Table 3), the benzylic protons are long-range coupled with the *ortho*-aromatic protons, in all compounds.

Table 2 ^{13}C NMR shifts of 3,7-dioxabicyclo[3.3.0]octan-2-one derivatives[a]

Carbon	5 MEL	6 *iso*-MEL	7 *epi*-MEL	8
1	53.71	55.35	52.43	54.58
5	50.38	46.14	52.02	51.13
8	84.43	84.56	84.43	84.18
4	85.78	81.09	86.32	84.22
6	73.44	69.98	72.08	86.62
2	177.72	177.77	174.93	177.32
A-1	132.47	129.22	132.60	133.24
A-2	110.45	109.50	110.68	108.57
A-3	148.63	148.54	148.62	150.43
A-4	147.80	147.24	147.82	150.03
A-5	115.87	115.87	115.80	112.10
A-6	119.66	118.57	120.06	135.28
OMe	56.34	56.34	56.35	56.38
F-1	133.17	133.48	129.78	132.41
F-2	110.35	110.24	111.21	110.78
F-3	148.39	148.39	147.99	148.30
F-4	147.12	147.10	147.15	147.28
F-5	115.64	115.65	115.39	115.56
F-6	119.30	119.17	120.32	119.80
OMe	56.26	56.26	56.28	56.25

[a] Values were determined in [$^2H_6$]-acetone at 300 K with the central solvent peak as internal reference (29.80 ppm).

Lewis-acid BF_3 is known to cause equilibration of the 3,7-dioxabicyclo[3.3.0]octanes.[12] Compound **8** is presumably formed *via* a competing intramolecular Friedel–Crafts alkylation reaction, again catalysed by BF_3; epimerization at C-4 places the aromatic ring A in a suitable *trans*-position for closing a five-membered ring at the electrophilic C-6 centre (Scheme 1).

The ^{1}H NMR spectroscopic data for compounds **5**–**8** are summarized in Table 1, with ^{13}C NMR chemical shifts given in Table 2. The aromatic ring carbon shifts were unambiguously assigned from proton-detected short- and long-range ^{13}C–^{1}H correlation spectra.[30,31] Configurational determinations were supported by analysis of the proton vicinal coupling constants and further studied by NOE spectroscopy. The 2D phase-sensitive NOESY experiment was particularly helpful for rapidly determining through-space connectivities. In compound **5** (Fig. 2a), strong correlations were observed between 1-H and 5-H, and between 5-H and 6*cis*-H. 6*trans*-H Gave a strong response with 4-H, proving the *trans*-orientation of the latter. However, weaker but still substantial NOE cross-peaks were observed for 5-H/6*trans*-H, 5-H/4-H and 1-H/8-H. Although these NOE

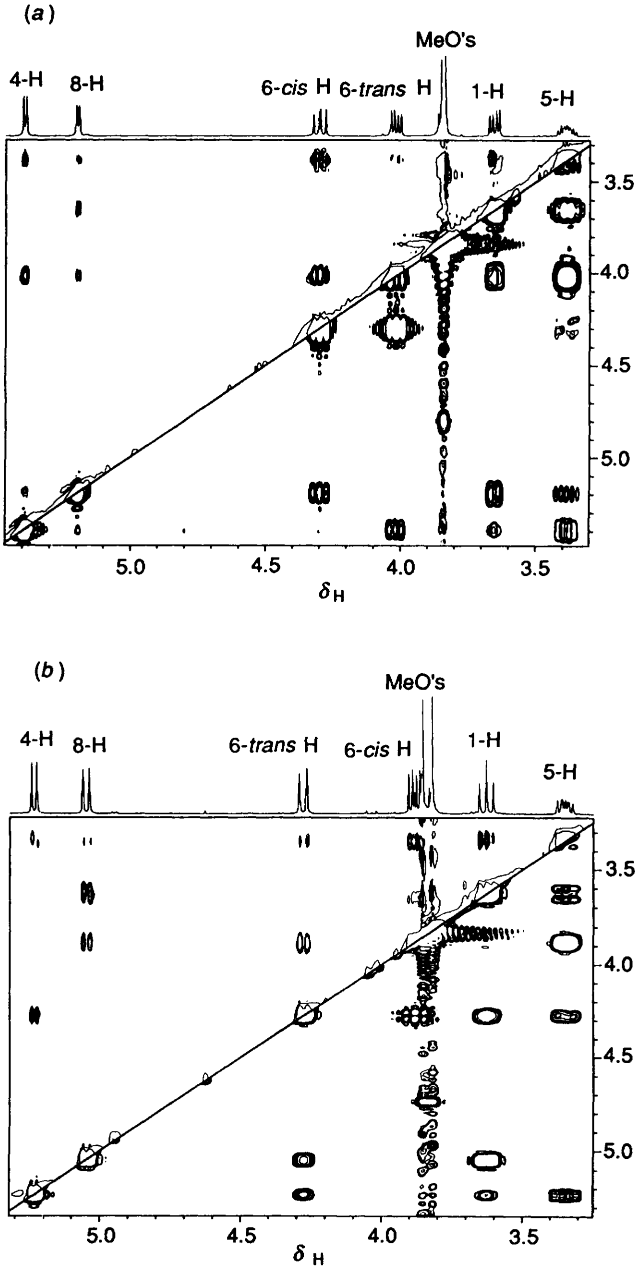
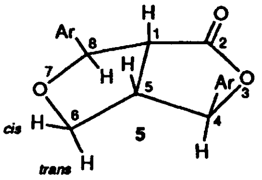
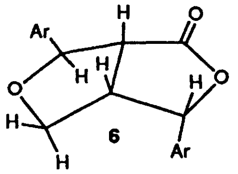


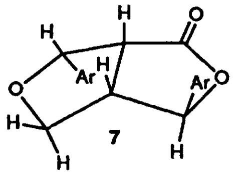
Fig. 2 Aliphatic regions of the phase sensitive NOESY (top left) and delayed COSY (bottom right) spectra of (*a*) **5** (MEL); (*b*) **7** (*epi*-MEL)

data are to be carefully interpreted for configurational determination purposes, they are in agreement with an almost eclipsed conformation of the molecule ($\varphi_{1,5}$ ~ 0° and φ_{trans} ~ 120°). In such a conformation, the *trans* and bridgehead protons are spatially close enough to lead to NOE responses. Computer molecular modelling using 'SYBYL' (version 5.4, Tripos Associates) have shown that these protons are within 3.1 Å. The establishment of the configuration at C-8 relied on the observation of a weak cross-peak for 8-H/6*trans*-H.

Compound **7** differs from **5** only in the configuration at C-8 and its structure is firmly supported by analysis of the NOESY spectrum (Fig. 2b). Intense crosspeaks for 8-H/1-H and 8-H/6*cis*-H established the *cis* relationship between these protons and the *trans*-orientation of the aryl group at C-8. A strong correlation between 6*trans*-H and 4-H also confirmed the *cis*-orientation of the aryl group at C-4. The *trans*-orientation of the C-8 aryl group causes the tetrahydrofuran ring to adopt a different favoured conformation with respect to **5**. 6*trans*-H Appeared as a slightly broadened doublet (J_{gem} = 9.5 Hz, Table 1) in the 1D spectrum of **7**. The small vicinal coupling with 5-H was not resolved, again implicating a dihedral angle $\varphi_{6,5}$ close to 90°, observed in a proposed $^{1}T_{5}$ conformation of the tetrahydrofuran ring. In this puckered conformation, the C-8 aryl group takes a pseudo-axial orientation, decreasing a possible steric interaction with the C-2 carbonyl. The 0.5 ppm upfield shift of 6*cis*-H in **7** is explained by the relief of the deshielding effect of the C-8 aryl group experienced by 6*cis*-H in **5**. 6*cis*-H Is upfield of 6*trans*-H in **7**, whereas the reverse is observed in **5** (Table 1). The C-6 methylene proton assignments deduced here for **7** are opposite to those made by Stevens *et al.*[21] for related furofuranoid lignans of the *epi*-series.







The ^{13}C NMR chemical shifts of the three isomeric 4,8-bis-(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ones **5**, **6** and **7** (Table 2) provide additional evidence of the proposed stereochemical assignments. In particular, the aromatic ring A-1 and F-1 shifts (see Scheme 1 for ring designations) were found to be sensitive to configurational changes at the benzylic positions. The A-1 and F-1 signals of *cis*-orientated aryl groups appeared at 132.5–133.5 ppm, whereas in *iso*-MEL **6** A-1 resonates at 129.2 ppm, and in *epi*-MEL **7**, F-1 resonates at 129.8 ppm. Such a relation between the aromatic ring carbon-1 shifts and the benzylic configuration was first observed in 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes by Pelter *et al.*[32]

The three-fused five-membered ring skeleton of compound **8** was deduced from its ^{1}H NMR and ^{1}H–^{13}C chemical shift correlation spectra. A quaternary aromatic carbon at 133.2 ppm exhibited strong three-bond coupling responses with 6-H and 5-H, and a weaker two-bond response for coupling with 4-H. This carbon was assigned to the A-1 carbon of the indane moiety of the molecule. On the other hand, 4-H and 5-H strongly correlated *via* three bonds with the quaternary aromatic carbon at 135.3 ppm, assigned to A-6, while 6-H exhibited an expected weaker two-bond response. Three-bond responses correlating A-2 with 4-H and A-5 with 6-H were also observed. The *cis* interaction between 4-H, 5-H and 6-H was confirmed from intense NOE cross-peaks in the NOESY spectrum of **8**. A less intense NOE peak was observed for 8-H/1-H, suggesting a *trans* relationship. In addition, the $J_{1,8}$ value of 6.4 Hz is in agreement with a *transoid* dihedral angle $\varphi_{1,8}$ > 120°, observed in a °*E* conformation of the tetrahydrofuran ring. The F-1 signal at 132.4 ppm seems to confirm the *cis*-orientation of the C-8 aryl group (Table 2).

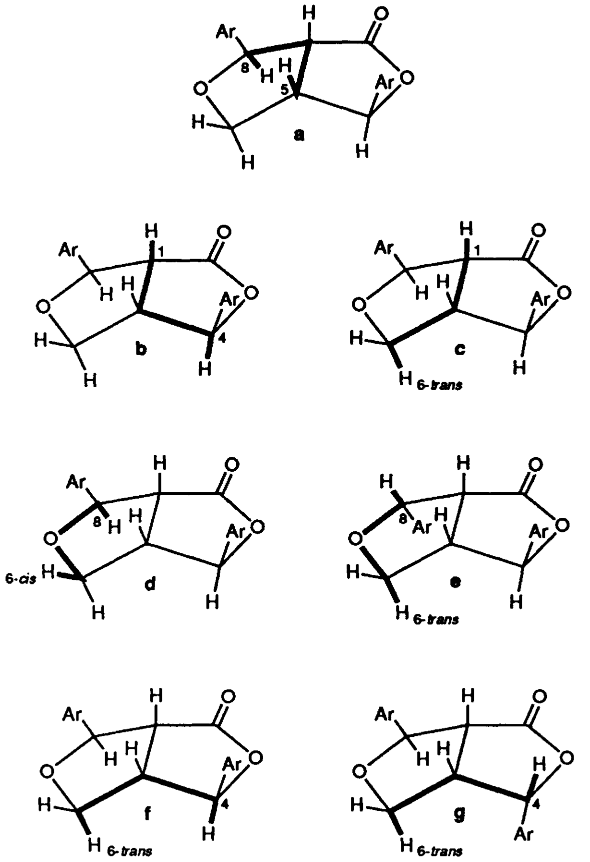


Fig. 3 Typical long-range ^{1}H-^{1}H coupling pathways followed in 3,7-dioxabicyclo[3.3.0]octan-2-one derivatives (see text for discussion)

Long-range ^{1}H–^{1}H Couplings.—The ^{1}H NMR spectra of the compounds investigated clearly revealed small couplings whose detection was improved by resolution enhancement. These long-range couplings could be assigned from interpretation of double quantum filtered COSY spectra. However, additional couplings, not resolved in the 1D spectrum were also observed, and the use of the delayed COSY experiment[33] (250 ms delay) allowed better resolution and detection of these, as well as additional couplings. The results are summarized in Table 3. Examination of the pathways followed by these long-range couplings, essentially ^{4}J, was used for determining the relative configuration of the 4,8-diaryl-3,7-dioxabicyclo[3.3.0]octan-2-one compounds. In the case of **5**, the bridgehead 5-H signal appeared as a 32 peak pattern in the 1D spectrum. The delayed COSY experiment revealed a four-bond coupling with the 8*trans*-H (Fig. 2a). 8-H Was coupled with 6*cis*-H, but no coupling was observed with 6*trans*-H. Similarly, 1-H correlated with 6*trans*-H, but not with 6*cis*-H. A weaker cross-peak was observed for 1-H/4-H. These ^{4}J couplings follow the same type of *transoid* pathway in which a *trans* proton is coupled with a

Table 3 Long-range ^1H–^1H couplings in 3,7-dioxabicyclo[3.3.0]octan-2-one derivatives as observed by delayed COSY experiments[a]

Compound	$J_{8,5}$	$J_{8,6trans}$	$J_{8,6cis}$	$J_{4,1}$	$J_{4,6trans}$	$J_{4,6cis}$	$J_{1,6trans}$	$J_{1,6cis}$
2	++	+		++	++		++	
3	+		++	+		−		+
5	++	−	++	+	++	−	++	−
6	++	−	++	−	++	−	++	+
7	−	++	−	+	++	−	++	−
8	++		++	−		−		−

[a] ++: intense cross-peak, +: less intense cross-peak, −: weak or no cross-peak.

bridgehead proton (Fig. 3**a**, **b** and **c**) and/or with a *cis* proton (Fig. 3**d**). The *only cis* interaction that gives rise to an observable ^4J coupling in **5** was the 1,3-diaxial interaction between 6*trans*-H and 4-H, which follows an almost planar pathway (Fig. 3**f**). These observations were confirmed upon examination of the long-range COSY spectrum of **7** (Fig. 2b). If the prominent coupling pathway observed in **5** is general, 8*cis*-H should be coupled with 6*trans*-H, but not with 6*cis*-H in **7**, the reverse being observed in **5** (Fig. 3e and **d**, respectively). Indeed, 6*trans*-H gave coupling responses with all protons of the dioxabicyclo[3.3.0] system. As in **5**, 1-H correlated with 6*trans*-H and 4-H, but not with 6*cis*-H. No coupling was observed between 5-H and the *cis*-orientated 8-H, although a weak correlation could be discerned between these two protons by increasing the delay to 300 ms. Of particular note is the fact that no ^4J coupling occurred between 4*trans*-H and 6*cis*-H in **5** and **7**.

Due to congestion in the 3.6–3.8 ppm range of the spectrum of **6**, a detailed first order analysis was not possible. However, the configuration at C-8 was readily confirmed from observation of cross-peaks for 8-H/6*cis*-H and 8-H/5-H. 4-H Was not coupled with either of its *cis* four-bond neighbours, 1-H and 6*cis*-H, proving the *trans*-orientation of the C-4 aryl group. The *cis*-orientated 4-H was unexpectedly coupled to 6*trans*-H (Table 3) by following a pathway structurally related to the unobserved 4*trans*-H/6*cis*-H interaction of **5** and **7**. Analysis of the vicinal coupling constant values in **6** (in particular, $J_{1,8}$ = 2.6 Hz) suggested a slight puckering of the molecule with the tetrahydrofuran ring in a ^5E form. This puckered conformation appeared sufficient to place the bonds between 4-H and 6*trans*-H in an almost coplanar 'dipper' arrangement (Fig. 3**g**),[34] and between 1-H and 6*cis*-H in a *quasi* W-shape, both interactions giving rise to observable cross-peaks. A similar conformational change occurred in the lactol **3** where a W-type coupling also occurred between 1-H and 6*cis*-H (Table 3).

In compound **8**, the fused indane moiety increased the rigidity of the basic dioxabicyclo[3.3.0] system which is forced into an eclipsed conformation. Again, the delayed COSY data was expected to help elucidate the configuration at the benzylic positions, especially at C-8, whose substituent orientation could not be unambiguously determined by NOE spectroscopy. Intense crosspeaks were observed for 8-H/5-H and for 8-H/6-H, proving the *cis*-orientation of the C-8 aryl group. The lactols **2** and **3** also exhibited the same array of long-range couplings and their configuration was confirmed from the results given in Table 3. A strong 1,3-diaxial coupling between 4-H and 6*trans*-H in **2** suggested the *cis*-orientation of the C-6 hydroxy group. Comparison of the responses exhibited for 8-H/6-H and for 1-H/6-H in both compounds confirmed their configuration at C-6; the strong correlations between 1-H and 6*trans*-H in **2**, and between 8-H and 6*cis*-H in **3** occurring across the usual *transoid* four-bond arrangement.

Conclusions.—4,8-Bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ones, including the germination inhibitor (±)-MEL, have been synthesized *via* selective two-step hydride-silane reduction procedure. The long-range proton coupling network of these 4,8-diaryl-3,7-dioxabicyclo[3.3.0]octan-2-one structures was examined by application of the delayed COSY experiment. The most prominent long-range couplings occurred between *trans*-interacting protons, *e.g.* a benzylic proton having a *trans* orientation exhibits a readily detectable ^4J coupling with a bridgehead proton. These observations allowed determination of the relative configuration of the prepared compounds, making the delayed COSY experiment an efficient alternative to the use of NOE spectroscopy, while providing conformational insights.

Experimental

Melting points are uncorrected. Evaporations were conducted under reduced pressure at temperatures less than 42 °C unless otherwise noted. Further elimination of organic solvents, as well as drying of the residues, was accomplished under high vacuum (90–120 mTorr) at room temperature. Column chromatography was performed on silica gel 60 (230–400 mesh) and TLCs were performed with Alugram Sil-G/UV$_{254}$ plates (Macherey-Nagel), with visualization by UV light. HPLC separation of furofuranoid products was carried out on a dual pump system (Gilson) using a C_{18} column (Whatman Partisil-10 ODS-2, 9.4 × 250 mm). The mobile phase was H_2O–MeOH and gradient elution (0–2 min: 40% MeOH, 2–40 min: 50% MeOH, 40–2 min: 100% MeOH, multiple injections) was applied at a flow rate of 3 cm^3 min^{-1}. Column effluent was monitored by UV detection (Gilson model 116) at 295 nm (AUFS 2.000). Eluted fractions were concentrated under reduced pressure and then freeze-dried. NMR spectra of samples in [$^2H_6$]-acetone were run at 300 K on a Bruker AMX-360 360 MHz narrow-bore instrument fitted with a 5 mm 4-nucleus (QNP) probe with normal geometry (proton coil further from the sample). The central solvent signals were used as internal reference (^{1}H, 2.04 ppm; ^{13}C, 29.8 ppm). One- and two-dimensional NMR spectra were obtained using standard pulse sequence programs. The delayed COSY[33] spectra in Fig. 2 were run, using 5 mg of sample in *ca.* 0.3 cm^3 of solvent, with Bruker's cosylr pulse program, using 90° pulses of 10.7 μs and a delay of 250 ms. 1K data points were recorded in t_2 and 256 increments of 16 transients in t_1. The data matrix was zero-filled to 1K(t_2) × 512(t_1) real points and sine-bell apodization was applied in both dimensions prior Fourier transformation. The phase sensitive NOESY spectra in Fig. 2 were run by using Bruker's standard noesytp pulse program with a mixing time of 1s and a relaxation delay of 4s. A 2K × 256 data matrix was acquired using 16 transients per t_1 increment. Squared cosine-bell apodization was applied in both dimensions, the matrix zero-filled and Fourier transformed to a final size of 2K × 1K real points.

4-cis,8-cis-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)-3,7-*dioxabicyclo*[3.3.0]*octane*-2,6-*dione* **1**.—Ferulic acid (10.19 g, 0.052 mol) was oxidized into the dilactone **1** with $FeCl_3$·$6H_2O$ (28.00 g, 0.103 mol) in the presence of an oxygen stream, according to the usual procedure.[23] Crystallization from acetone afforded **1** (2.25

g, 22%) as white plates, m.p. 213.8–214.7 °C (lit.,[23] 208–209 °C); 1H NMR spectroscopic data were in agreement with lit. values;[25] δ_C 49.11 (1/5), 56.39 (OMe's), 83.22 (4/8), 110.40 (F-2's) 116.00 (F-5's), 119.57 (F-6's), 130.82 (F-1's), 148.17 (F-4's), 148.72 (F-3's) and 175.99 (2/6).

4-cis,8-cis-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)-6-cis-*hydroxy*-3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* **2**.—The dilactone **1** (507 mg, 1.31 mmol) was dissolved in anhydrous THF (10 cm^3) and cooled to 0 °C. $LiBH_4$ (10 cm^3 of 0.18 mol dm^{-3} solution, 1.80 mmol) in anhydrous THF was slowly added with stirring *via* a pipette. The mixture became yellowish milky and was then stirred at ambient temperature for 20 h after which time TLC ($CHCl_3$–EtOAc, 1 : 1) indicated good conversion into a slower moving material. Additional $LiBH_4$ (4 mg) was then added as a solid and the mixture was allowed to react until TLC showed complete conversion (*ca.* 2–3 h). The reaction mixture was cooled to 0 °C and hydrolysed with 0.1 mol dm^{-3} HCl (10 cm^3) to give a clear solution which was extracted three times with $CHCl_3$ (3 × 10 cm^3). The organic layer was washed with water and satd. aq. NaCl, dried over $MgSO_4$ and evaporated to leave an off-white solid (498 mg). TLC revealed the presence of traces of compound **4** (see below) as a fast moving spot which turned bright red upon UV exposure. Pure **2** (297 mg, 58%) was obtained by crystallization from acetone as white fine crystals, m.p. 195.6–196.6 °C (lit.,[25] 194–195 °C) (Found: M$^+$, 388.1167. $C_{20}H_{20}O_8$ requires *M*, 388.1158); δ_H 3.31 (1 H, dddd, *J* 8.7, 6.6, 1.5, 0.7, 5-H), 3.54 (1 H, dd, *J* 8.7, 5.5, 1-H), 3.82 (3 H, s, F3-OMe), 3.87 (3 H, s, A3-OMe), 5.32 (1 H, br d, *J* 5.4, 8-H), 5.38 (1 H, br d, *J* 6.7, 4-H), 5.68 (1 H, dd, *J* 4.4, 1.5, 6-H), 5.93 (1 H, d, *J* 4.5, 6-OH), 6.79 (1 H, d, *J* 8.1, F-5), 6.86 (1 H, d, *J* 8.1, A-5), 6.94 (1 H, ddd, *J* 8.1, 2.0, 0.5, A-6), 6.96 (1 H, ddd, *J* 8.1, 2.0, 0.6, F-6), 7.12 (1 H, d, *J* 2.0, A-2), 7.21 (1 H, d, *J* 2.0, F-2) and 7.51, 7.76 (each 1 H, s, 2 × ArOH); δ_C 54.28 (1), 56.18 (F-3-OMe), 56.35 (A3-OMe), 59.59 (5), 83.87 (4), 84.98 (8), 103.27 (6), 110.73 (F-2 and A-2), 115.39 (F-5), 115.85 (A-5), 119.70 (F-6), 120.30 (A-6), 131.46 (A-1), 135.06 (F-1), 146.95 (F-4), 148.10 (F-3), 148.21 (A-4), 148.74 (A-3) and 176.76 (2).

Mutarotation occurred in [$^2H_6$]-acetone to give rise to a 60 : 40 **3** : **2** anomeric mixture.

4-cis,8-cis-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)-6-trans-*hydroxy*-3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* **3**; δ_H 3.36 (1 H, dddd, *J* 10.4, 5.1, 1.8, 1.2, 5-H), 3.52 (1 H, dd, *J* 10.4, 4.5, 1-H), 5.27 (1 H, br d, *J* 4.5, 8-H), 5.70 (1 H, br d, *J* 1.8, 4-H), 5.88 (1 H, dd, *J* 5.1, 3.3, 6-H) and 5.96 (1 H, dd, *J* 3.3, 1.2, 6-OH); δ_C 54.18 (1), 52.51 (5), 81.00 (4), 81.53 (8), 99.04 (6), 133.03 (A-1), 133.89 (F-1) and 177.84 (2).

1,4-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)*butadiene* **4** (from several runs), pink crystals from acetone–light petroleum (b.p. 40–60 °C), m.p. 218.5–219.1 °C (Found: M$^+$, 298.1214. $C_{18}H_{18}O_4$ requires *M*, 298.1205); δ_H 3.87 (6 H, s, 2 × OMe), 6.56 (2 H, m, 1-H/4-H), 6.78 (2 H, d, *J* 8.1, 2 × A-5), 6.85–6.92 (4 H, m, 2-H/3-H and 2 × A-6), 7.12 (2 H, d, *J* 1.9, 2 × A-2) and 7.71 (2 H, s, 2 × ArOH); δ_C 56.21 (OMe), 109.76 (A-2), 115.96 (A-5), 120.95 (A-6), 128.07 (2/3), 130.81 (A-1), 132.49 (1/4), 147.41 (A-4) and 148.60 (A-3).

Synthesis of Compounds **5**, **6**, **7** *and* **8**.—Triethylsilane (131 mg, 1.127 mmol) and boron trifluoride–diethyl ether (92.3 mg, 0.648 mmol) were slowly added *via* syringe to a suspension of the hemiacetal **2** (125 mg, 0.324 mmol) in CH_2Cl_2 (passed through alumina) cooled to 0 °C, under nitrogen. The cooling bath was removed and the reaction mixture stirred at ambient temperature overnight (*ca.* 10–15 h). After this time, TLC ($CHCl_3$–EtOAC, 1 : 1) showed complete disappearance of **2**. The reaction was quenched with satd. aq. $NaHCO_3$ and the mixture extracted with CH_2Cl_2. The organic layer was washed with satd. aq. NaCl, dried over Na_2SO_4 and evaporated to leave a white solid (109 mg), whose ^1H NMR spectroscopic analysis indicated that four products were present: **5** (MEL, 47%), **6** (*iso*-MEL, 14%), **7** (*epi*-MEL, 19%) and **8** (20%). This product mixture was then submitted to silica gel chromatography ($CHCl_3$) to yield **7** (16.8 mg, 14.0%) as a white solid and a less polar fraction (85 mg) which contained **5**, **6** and **8**. This fraction was separated by HPLC to afford **8** (17.6 mg, 14.8%), **5** (35.3 mg, 29.4%) and **6** as a 5 : 1 **6** : **5** mixture (5.1 mg).

4-cis,8-cis-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)-3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* **5**, white–yellow amorphous solid; δ_H see Table 1 and 3.84 (3 H, s, A3-OMe), 3.85 (3 H, s, F3-OMe), 6.80 (1 H, d, *J* 8.1, F-5), 6.83 (1 H, d, *J* 8.1, A-5), 6.86 (1 H, ddd, *J* 8.1, 2.0, 0.7, F-6), 6.88 (1 H, ddd, *J* 8.1, 2.0, 0.7, A-6), 7.00 (1 H, br d, *J* 2.0, F-2), 7.04 (1 H, br d, *J* 2.0, A-2) and 7.63, 7.78 (each 1 H, s, 2 × ArOH); δ_C see Table 2.

4-trans,8-cis-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* **6**, δ_H see Table 1 and 3.84 (3 H, s, F3-OMe), 3.87 (3 H, s, A3-OMe), 6.80 (1 H, d, *J* 8.1, F-5), 6.83–6.86 (2 H, m, A-6 and F-6), 6.86 (1 H, d, *J* 8.1, A-5), 6.97 (1 H, br d, *J* 2.0, F-2), 6.98 (1 H, br d, *J* 2.0, A-2) and 7.57, 7.67 (each 1 H, s, 2 × ArOH); δ_C see Table 2.

4-cis,8-trans-*Bis*(4-*hydroxy*-3-*methoxyphenyl*)-3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* **7**, white solid (Found: M$^+$, 372.1203. $C_{20}H_{20}O_7$ requires *M*, 372.1209); δ_H see Table 1 and 3.82 (3 H, s, F3-OMe), 3.85 (3 H, s, A3-OMe), 6.78 (1 H, d, *J* 8.1, F-5), 6.84 (1 H, d, *J* 8.1, A-5), 6.87 (1 H, ddd, *J* 8.1, 2.0, 0.6, F-6), 6.91 (1 H, ddd, *J* 8.1, 2.0, 0.5, A-6), 6.98 (1 H, br d, *J* 2.0, F-2), 7.08 (1 H, br d, *J* 2.0, A-2) and 7.47, 7.70 (each 1 H, s, 2 × ArOH); δ_C see Table 2.

11-*Hydroxy*-6-(4-*hydroxy*-3-*methoxyphenyl*)-10-*methoxy*-3a,4,6,6a-*tetrahydro*-3*H*-3,4-*benzenofuro*[3,4-c]*furan*-1-*one* **8**, off-white fine crystals from CH_2Cl_2–light petroleum (b.p. 40–60 °C), m.p. 220.8–221.5 °C (Found: M$^+$ 370.1053. $C_{20}H_{18}O_7$ requires *M*, 370.1052); δ_H see Table 1 and 3.81 (3 H, s, F3-OMe), 3.87 (3 H, s, A3-OMe), 6.78 (1 H, d, *J* 8.1, F-5), 6.84 (1 H, ddd, *J* 8.1, 2.0, 0.6, F-6), 6.89 (1 H, br s, A-5), 6.99 (1 H, br d, *J* 2.0, F-2), 7.00 (1 H, br s, A-2) and 7.57, 7.96 (each 1 H, s, 2 × ArOH); δ_C see Table 2.

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