Synthesis of Condensed Tannins. Part 17.† Oligomeric (2*R*,3*S*)-3,3',4',7,8-Pentahydroxyflavans: Atropisomerism and Conformation of Biphenyl and *m*-Terphenyl Analogues from *Prosopis glandulosa* ('Mesquite')

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(2*R*,3*S*)-2,3-*trans*-3',4',7,8-Tetrahydroxyflavan-3-ol [(+)-mesquitol], the predominant metabolite in the heartwood of *Prosopis glandulosa*, represents a putative precursor of a variety of oligomers, including conventional [4,6]- and [4,8]-biflavan-3-ols, a [1,6]-1,3-diarylpropylflavan-3-ol, [5,6]- and atropisomeric [5,8]-biphenyl-type biflavan-3-ols, and [5,6:5,8]-*m*-terphenyl-type triflavan-3-ols. Other participants in these condensations are mainly (+)-catechin, and also the flavan-3,4-diol analogue of (+)-mesquitol. Oligomeric structures were confirmed by biomimetic oxidative and acid-induced couplings, and by nuclear Overhauser effect difference spectroscopy. These applications enabled correction of previous structural assignments for atropisomeric [5,8]-(+)-mesquitol-(+)-catechins and [5,6:5,8]-bis-[(+)mesquitol]-(+)-catechins, and determination of their conformations.

Although oxidative coupling of flavonoids is an established natural phenomenon affecting mainly flavones and flavanones,[1] participation by flavan-3-ols in this mode of condensation is uncommon. Examples of the latter all involve 2' ⟶ 8 coupling of (+)-catechin (2,3-*trans*-3',4',5,7-tetrahydroxyflavan-3-ol) *via* the respective B- and A-ring, giving biphenyl-type 'dehydrodicatechins.'[2] They have been prepared by enzymic oxidation,[2] or isolated from black tea following fermentative peroxidation,[3] while bi- and ter-flavan-3-ol analogues, the latter based on a single biphenyl link, occur in the bark of *Quercus robur*.[4,5]

(+)-Mesquitol, the novel‡ (2*R*,3*S*)-2,3-*trans*-3',4',7,8-tetrahydroxyflavan-3-ol (**1**), which predominates in the heartwood of the mesquite (*Prosopis glandulosa*),[6] should be more susceptible to oxidative coupling than (+)-catechin, considering differences in A-ring functionality (7,8-*ortho*- *vs.* 5,7-*meta*-dihydroxy respectively). Thus, in contrast to [4,6]- and [4,8]-biflavonoids of the 'conventional' type in which (+)-mesquitol moieties among others constitute either the 'upper' (**5**) or 'lower' (**11**) units, the presence of a [5,6]-'dimer' (**16**), [5,8]-(+)-mesquitol-(+)-catechins (**19**) and (**22**), and of atropisomeric [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins (**26**) demonstrates an alternative method of tannin formation *via* oxidative phenol coupling. Yet a third method of oligomerization of the parent flavan-3-ol (**1**) is illustrated by the ring-opened [1,6]-1,3-diaryl-2-hydroxypropylflavan-3-ol metabolite (**13**), representing the first homologue of the gamberiins.[7] Nuclear Overhauser effect (n.O.e.) difference spectroscopy was used to distinguish between positional and structural alternatives for the biphenyl- and *m*-terphenyl-type oligomers, while the method of synthesis of these and other biflavanoids plausibly illustrates the final steps in their biogenesis.

The heptamethyl diacetyl derivatives of [4,6]-(−)-fisetinidol-(+)-catechin, (**10**), and [4,6]-(−)-fisetinidol-(+)-mesquitol, (**12**), both afford sharp ^{1}H n.m.r. resonances at 80 MHz in $CDCl_3$ at ambient and progressively elevated temperatures. Among compounds of this class such behaviour is indicative of 'fast' rotation about the interflavanoid bond (n.m.r. time-scale) under ambient conditions. By contrast the octamethyl ether diacetate of the biphenyl-type [5,6]-'dimer', (**17**), gives line-broadened resonances, which sharpen to a maximum at 100 °C, while at 500 MHz (20 °C) sharply defined duplicated resonances are evident in accord with its separation into two conformers on preparative layer chromatographic plates. However, after normal work-up procedures the racemate is obtained, the aforementioned phenomena indicating that in these optically labile compounds the activation energy for rotation must be considerably less than 20 kcal mol^{-1}.[8]§ Identical phenomena are associated with the corresponding derivative of the synthetic [5,5]-'dimer' (**25**). Next on the scale of stability of rotational isomers of biphenyl-type analogues are the [5,8]-(+)-mesquitol-(+)-catechin derivatives (**20**) and (**23**), to which the [5,5]-'dimeric' structure (**25**) was previously assigned[6] (see later). The conformers are readily separable giving sharply defined ^{1}H n.m.r. spectra over the range 30—60 °C, but below 100 °C slow racemization sets in and at 150 °C a *ca.* 4:3 equilibrium between *R* and *S* forms¶ is reached with evidence of exchange from partially broadened resonances.

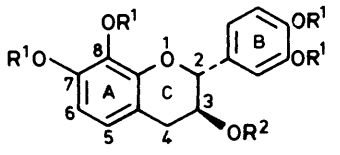
The relative stabilities of atropisomeric derivatives of [5,8]-(+)-mesquitol-(+)-catechins (**20**),(**23**) to racemization, in contrast to those of [5,6]- and [5,5]-bi-(+)-mesquitols (**17**) and (**25**), must be due to rotational restriction imposed by the rigidity of the C-4 CH_2 (C-ring) function; *ortho*-disubstitution on the D-ring relative to the bond; and also probably to the combined 'buttressing effect' of the 7,8-dimethoxy function on 6-H (A). Consideration of atropisomerism also in the free-phenolic [5,8]-(+)-mesquitol-(+)-catechins (**19**),(**22**) and [5,6]-bis-(+)-mesquitol (**16**) follows from their methylation with excess of diazomethane which gave considerable admixtures of 7-hydroxy (D-ring) heptamethyl ethers (to the resultant octamethyl ethers) identified as the respective triacetates (**21**) and (**18**). This implies the existence of strong H-bonds between 7-OH(D) and the π-system of the benzenoid A-ring in each instance, in accord with similar findings by Aulin-Erdtman and Sanden[9] for 2,2'-dihydroxybiphenyl from i.r. spectra. Contri-

† Part 16, D. A. Young, H. Kolodziej, D. Ferreira, and D. G. Doux, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2537.

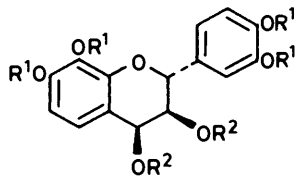
‡ Although previously isolated from *Piptadenia macrocarpa* by Miyauchi *et al.*, its structure was 'inferred' from the ^{1}H n.m.r. spectrum of its acetate without reference to configuration [Y. Miyauchi, T. Yashimoto, and K. Minami, *Mokuzai Gakkaishi*, 1976, **22**, 47 (*Chem. Abstr.*, 1976, **84**, 147704*e*)].

§ 1 kcal = 4.185 kJ.

¶ Absolute stereochemistry about the biphenyl link is defined by n.O.e. difference spectroscopy (see later).



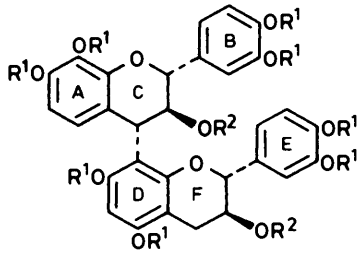
(1)



(3)

$R^1 = R^2 = H$

(2) $R^1 = Me, R^2 = Ac$ (4)



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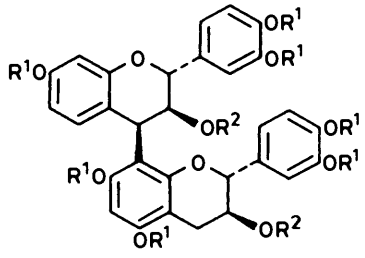
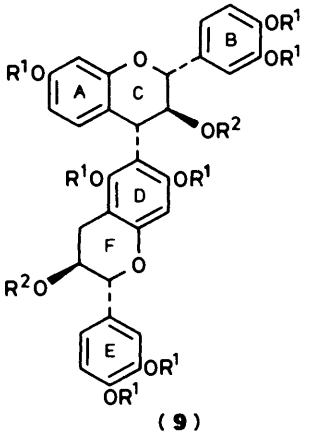


(7)

$R^1 = R^2 = H$

(6) $R^1 = Me, R^2 = Ac$ (8)



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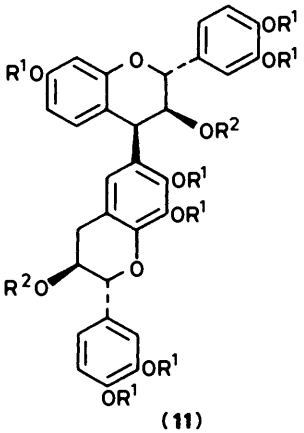


(11)

$R^1 = R^2 = H$

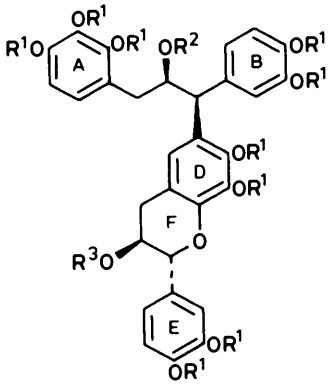
(10) $R^1 = Me, R^2 = Ac$ (12)

bution of hydrogen bonding to the stability of atropisomeric biflavanoids with functionality *ortho* to the biphenyl bond is accordingly postulated. However, no reason can be advanced for the absence of a heptamethyl ether from the products of methylation of compound (**22**), although partial separation of the [5,8]-atropisomers (**19**) and (**22**) during countercurrent distribution, consistent with their stability, is evident.

As may be expected from the aforementioned, dodecamethyl ether triactates of the *m*-terphenyl-type [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins (**26**)* were isolated as four stable atropisomers. From *ca.* 100 °C and above slow racemization sets in but appears to be incomplete even at 150 °C in $[(CD_3)_2SO]$. The increased activation energy for rotation compared with [5,8]-biphenyl analogues (**20**) and (**23**) is consistent with the increase in molecular complexity, and predictable steric effects of *ortho* functionality relative to the interflavanoid bonds.

Synthetic evidence in support of the products of phenol coupling was obtained by treatment of (+)-mesquitol (**1**) with $K_3Fe(CN)_6$ in an acetonitrile–glycine buffer[10] to give two products. Both [5,6]- and [5,5]-'dimers', obtained as methyl ethers in the ratio of 2.5:1, were identified as their octamethyl ether diacetates (**17**) and (**25**) respectively, the ^1H n.m.r. spectrum of the former being identical with that of the corresponding derivative of the natural product. However, the synthetic [5,5]-isomer (**25**) differed, on similar comparison and also in its lability of its atropisomers to racemization, from corresponding derivatives of the second natural biphenyl-type biflavan-3-ol, previously assigned[6] this structure. Subsequent examination of the conformationally stable derivatives (**20**) and (**23**) of the natural atropisomeric [5,8]-(+)-mesquitol-(+)-catechins by n.O.e. difference spectroscopy (Schemes 1 and 2) showed not only that the 'residual' D-ring proton was in each instance associated with two methoxy groups, *but also defined the bonding positions in both flavanyl units.* Substitution by (+)-mesquitol at C-8 of the 'lower' (+)-catechin (DEF) unit was supported by chemical shifts (δ 6.22, 6.16) of 6-H(D) resonances in each instance (*cf.* ref. 11). Finally, synthetic proof was available from direct oxidative phenol coupling of molar equivalents of (+)-mesquitol and (+)-catechin under conditions[10] cited above. This provided the [5,8]-atropisomers (**19**) and (**22**) as major products, identified as their respective octamethyl ether diacetates (**20**) and (**23**). They were accompanied by the novel regioisomeric [5,6]-(+)-mesquitol-(+)-catechin and [5,6]-bi-(+)-mesquitol as minor components,

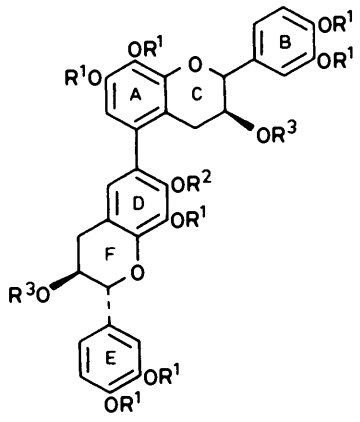
* Corrected formula (see later).



(13) $R^1 = R^2 = R^3 = H$

(14) $R^1 = R^2 = Me$, $R^3 = Ac$

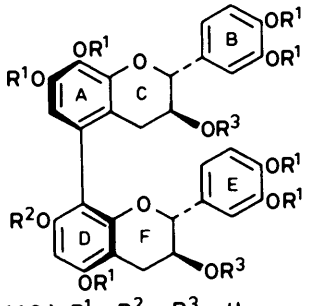
(15) $R^1 = Me$, $R^2 = R^3 = Ac$



(16)

(17)

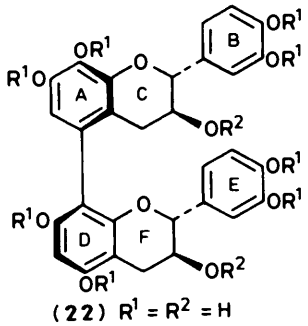
(18)



(19) $R^1 = R^2 = R^3 = H$

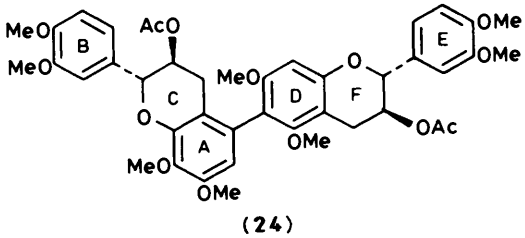
(20) $R^1 = R^2 = Me$, $R^3 = Ac$

(21) $R^1 = Me$, $R^2 = R^3 = Ac$



(22) $R^1 = R^2 = H$

(23) $R^1 = Me$, $R^2 = Ac$



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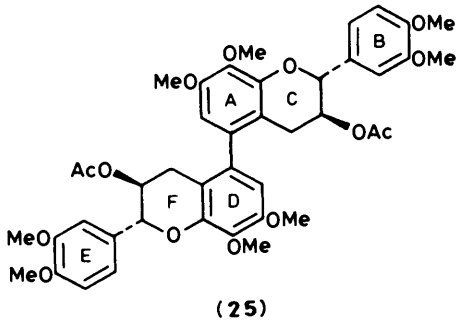

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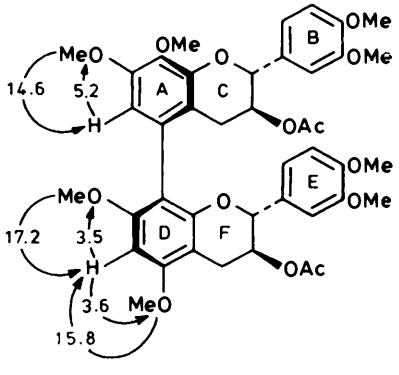

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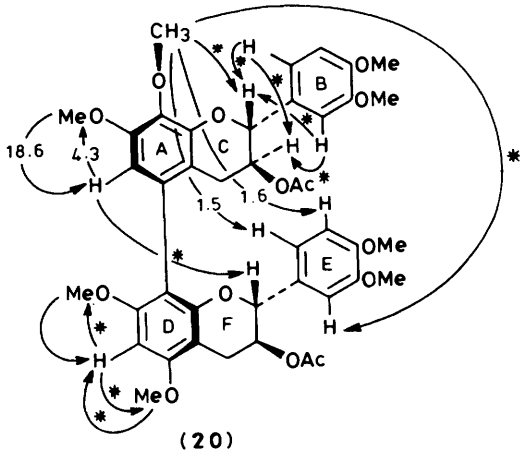
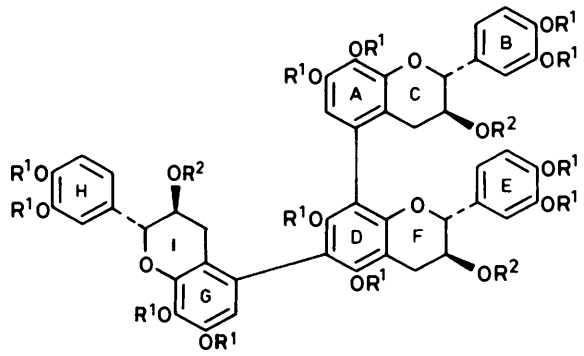


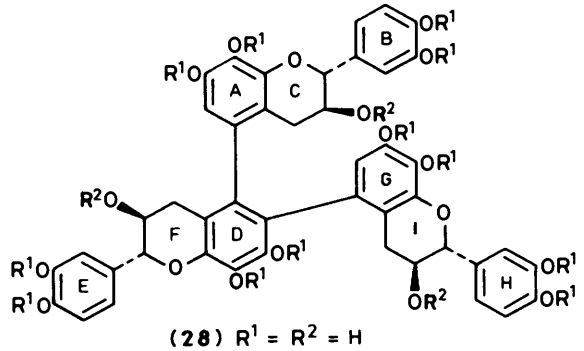
(20)

Scheme 2.

Scheme 1. Schemes 1—5 show proton associations based on nuclear Overhauser effect difference spectroscopy. Arrowheads show enhanced signals with percentage n.O.e. calculated by comparing the size ratio of the positive (enhanced) and negative (irradiated) resonances in each difference spectrum. *Indicates that signal overlap does not permit calculation



(26) $R^1 = R^2 = H$
(27) $R^1 = Me$, $R^2 = Ac$

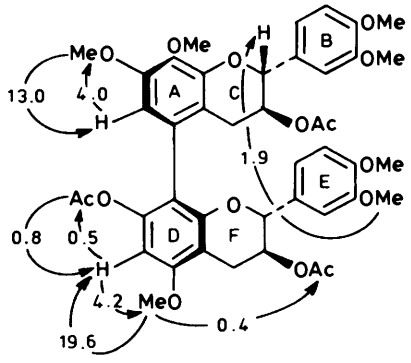


(28) $R^1 = R^2 = H$
(29) $R^1 = Me$, $R^2 = Ac$

isolated as the corresponding derivatives (**24**) and (**17**). These products were obtained in the approximate proportions 16:22:1:4, and without evidence of self-condensation of (+)-catechin under specified conditions. Thus crossed condensation proceeds at a much faster rate than the oxidative self-condensations of either (+)-mesquitol or (+)-catechin, judging also by the first appearance of products in, and optimum length of, independent reactions. Phenol couplings of this type are considered to belong to a large class of reactions which do not possess activation energy,[12] with thermodynamic rather than kinetic factors possibly dominating the course of the reaction. Those factors which may affect the stereochemistry of approach are discussed at a later stage.

The above findings, including the formation under competing conditions of the [5,6]-(+)-mesquitol-(+)-catechin,* led to the conjecture that triflavanoid analogues, previously designated as of *o*-terphenyl-type [5,5:5,6]-ter-(+)-mesquitols (**28**), did in fact have a 'central' (+)-catechin unit. Application of n.O.e. difference spectroscopy (Scheme 5) to the dodecamethyl ether triacetate of a single atropisomer, R_F 0.50, adequately supported this surmise through associations of 6-H(G) with the strongly shielded 5- and 7-OMe(D) resonances, and 6-H(A) with 7-OMe(A) and 7-OMe(D).† The first mentioned association requires a dihedral angle of *ca.* 90° between the G- and D-ring, while the abnormal shielding of 7-OMe(D) in the triflavanoids suggests a similar conformational relationship between the D- and A-ring (see later).

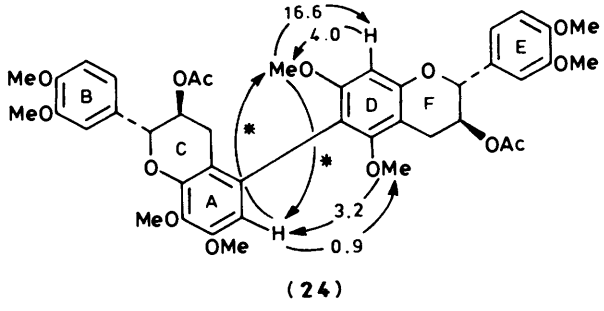
Use of conformational analysis in conjunction with n.O.e. difference spectroscopy permits assessment of the absolute configuration of the [5,8]-(+)-mesquitol-(+)-catechin derivative (**20**), R_F 0.32, about the biphenyl bond. The association of 8-OMe(A) with the *axial* 2-H(C) indicates distortion of the O–CH_3 bond to an *out-of-plane* conformation relative to the A-ring as found in 1,2,3-trimethoxybenzenes[13] (*cf.* Scheme 2). Further association of 8-OMe(A) with 2-H, 5- and 6-H(E), and of 6-H(A) with 2-H(F), establishes a [*P*]-helicity and (*S*)-conformation, and indicates a dihedral angle of *ca.* 90° between the planes of the biphenyl A- and D- ring. Similar evidence is available for its heptamethyl ether triacetate (**21**) through association of 3-OMe(E) with the *axial* 2-H(C) (Scheme 3). The



(21)

Scheme 3.

corresponding octamethoxy diacetate isomers (**23**), R_F 0.36, where interflavanyl n.O.e. associations were absent, therefore exhibits [*M*]-helicity (Scheme 1). Lack of stereochemically significant interflavanyl n.O.e. effects in the [5,6]-isomer (**24**) (Scheme 4) and the [5,6:5,8]-homologue (**27**) (Scheme 5),



(24)

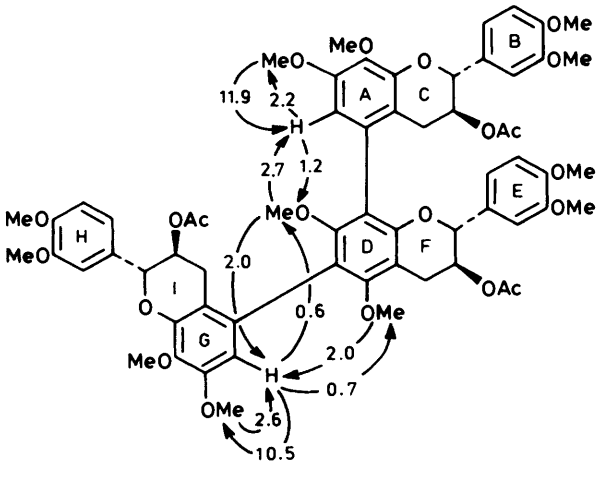
Scheme 4.

including atropisomers of the latter, precludes similar assignments.

The structure of the [1,6]-1,3-diarylpropylflavan (**13**) was substantiated by self-condensation of (+)-mesquitol (**1**) under acidic conditions developed by Freudenberg *et al.*[14] for synthesis of the homologue derived from (+)-catechin. After methylation and acetylation the condensation products gave the nonamethyl ether diacetate (**15**), in agreement with the corresponding derivative of the natural product, and also a decamethyl ether acetate (**14**). Their absolute stereochemistry was defined as (1*S*) by application of the aromatic quadrant rule to the positive Cotton effects at low wavelengths (232 nm) (*cf.* ref. 15). Considering the apparent absence of the expected

* The structure of its octamethyl ether diacetate (**24**) was substantiated by n.O.e. difference spectroscopy (Scheme 4), and by the chemical shift of 8-H(D), δ 6.36 (*cf.* ref. 11).

† Identical associations were also observed for the remaining atropisomers of R_F 0.54, 0.56, and 0.60.



(27)

Scheme 5.

(1*R*)-diastereoisomer, the natural 1,3-diarylpropylflavan appears to originate predominantly from S_N2 condensation, involving inversion of configuration at the point of junction, with ring opening.

Apart from structural proof *via* synthetic methods and n.O.e. difference spectroscopy, the aromatic bonding positions and stereochemistry of the majority of the aforementioned compounds were definable in terms of 300 MHz ^{1}H n.m.r. and mass spectroscopy supported in some instances by confirmation of absolute configurations at chiral bonding positions by c.d. spectra.[15] For example, the octa- and hepta-methyl ether diacetates of [4,8]- (**6**),(**8**) and [4,6]-linked (**10**),(**12**) biflavanoids were characterized by chemical shifts and coupling constants of heterocyclic protons (AMX and ABXY systems of 'upper' and 'lower' units respectively) in agreement with those of known analogues.[16] The aromatic bonding positions to (+)-catechin units in derivatives (**6**), (**8**), and (**10**) were determined by the chemical shifts of the remaining D-ring protons, while 6-substitution on the novel flavan-3-ol, (+)-mesquitol (**1**), as in the [4,6]-biflavanoid derivative (**12**), was established by spin-decoupling of 4-H_2(F) resonances which led to selective sharpening of the 5-H(D) singlet.

By comparison the octamethyl ether diacetate (**17**) of the [5,6]-bi-(+)-mesquitol based on a biphenyl linkage exhibits two heterocyclic ABXY systems [2-H, δ 5.11, 5.15; 3-H, δ 5.22, 5.34; 4-H_2, δ 2.38 (m, 2 × H) and 2.81 (*ax.*), 3.08 (*eq.*)], and two high-field aromatic singlets, one significantly broadened at 80 MHz (δ 6.53) and the other sharp (δ 6.47).* Irradiation of the lower-field methylene resonances led to selective sharpening of the aforementioned broadened (δ 6.53, appearing as a triplet, *J* 0.8 Hz, at 300 MHz) aromatic singlet, thus defining the singlet resonances as due to 5-H(D) and 6-H(A) respectively, and hence the interflavanoid bond as [5,6]. The presence of a biphenyl moiety is supported by mass spectrometry, the fragment ions *m/z* 331 (45%) and 330 (38%) representing the A- and D-ring biphenyl 'residue' after two reverse Diels–Alder (RDA) fragmentations with and without H-transfer, the former process being exceptionally prominent in the tetramethyl ether acetate of the parent (+)-mesquitol, compound (**2**) [*m/z* 167 (72%), 166 (8.1)]. The u.v. absorption spectrum ($\lambda_{max.}$ 230, 275 nm) of compound (**17**) exhibits a shoulder at 255 nm indicative of a degree of biphenyl conjugation,[17,18] thus contrasting with an absorption minimum at 255 nm for the [4,6]-biflavanoid derivative (**12**) ($\lambda_{max.}$ 233, 276 nm).

Identical spectral characteristics were evident for the corresponding derivative of the synthetic [5,5]-positional isomer (**25**) with the exception that both remaining [6-H(A) and 6-H(D)] resonances (δ 6.41, 6.51 in $CDCl_3$ at 300 MHz) are devoid of long-range coupling.

The atropisomeric octamethyl ether diacetates (**20**) and (**23**) of [5,8]-(+)-mesquitol-(+)-catechin exhibited spectral characteristics [two ABXY heterocyclic systems each; *m/z* 774 (M^+, 100, 100%), 331 (67, 74), 330 (66, 74); $\lambda_{max.}$ 227, ~254sh, 273 nm each] similar to those of the [5,5]-bis-(+)-mesquitol analogue, including aromatic proton singlets (δ 6.22, 6.50 and 6.16, 6.41 respectively) devoid of long-range coupling. Significant differences were, however, the high-field positions (δ 6.22, 6.16) of their 6-H(D) resonances attributable to the enhanced mesomeric effect of the phloroglucinol D-ring (*cf.* ref. 11). The synthetic [5,6]-isomer (**24**) with aromatic singlets at δ 6.48 and 6.36 [6-H(A) and 8-H(D) respectively] is differentiated by a strongly shielded (δ 3.14) 5-OMe (D-ring) resonance, similar to conspicuous shifts which characterize spectra of [5,6:5,8]-*m*-terphenyl analogues.

Extension of the same condensation mode to the triflavanoid level in *P. glandulosa* was evident from the isolation of the four possible dodecamethyl ether triacetates (**27**) [R_F 0.60, 0.56, 0.54, and 0.50 in dichloromethane–acetone (96:4 v/v); *m/z* 1 160 (M^+, 49, 13.7, 52, and 47% respectively] of [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechin with presumed origins in both of the [5,8]-conformers (**19**) and (**22**). The four *m*-terphenyl derivatives exhibit the same spectral characteristics as their biphenyl analogues [$\lambda_{max.}$ 222, ~253sh, 274 nm]; two sharp resonances each in the high-field aromatic region (δ 6.52, 6.44; 6.56, 6.53; 6.61, 6.50; and 6.59, 6.56 respectively in $CDCl_3$) all lacking long-range coupling with their respective 4-H_2 resonances; and two exceptionally shielded methoxy-group proton resonances each (δ 3.38, 2.91; 3.20, 3.08; 3.25, 3.06; and 3.33, 3.05 respectively). The chemical shifts of the aromatic 6-H(A) and 6-H(G) singlets are in agreement with those of 5-linked (+)-mesquitol units in the [5,8]-biflavanoid analogues (**20**) and (**23**) [6-H(A), δ 6.50, 6.41] and [5,6]- and [5,5]-'dimers' [6-H(A), δ 6.47 and 6.41/6.51], indicating similar linkage by two (+)-mesquitol units to a bifuncationalized D-ring of a central flavan-3-ol unit in the triflavanoid.

In agreement with assignment based on n.O.e. difference spectroscopy, indirect evidence regarding substitution on the D-ring of the 'central' flavanyl unit may be derived from the strong shielding effects of aromatic rings on D-ring methoxy-group resonances where these are *ortho* to interflavanoid bonds. Shielded OMe resonances are, for example, absent from the ^{1}H n.m.r. spectrum ($CDCl_3$) of the synthetic [5,5]-'dimer' (**25**) due to lack of overlap, but are differentiated in the case of the [5,6]-'dimer' (**17**) (δ 3.54),† the [5,8]-atropisomers (**23**) and (**20**) (δ 3.63, 3.57 respectively), and the [5,6]-isomer (**24**) (δ 3.14). Although the degree of shielding of 7-OMe(D) resonances in the biflavanoid analogues (**20**) and (**23**) does not match those (δ 2.91—3.38) in each of the atropisomeric *m*-terphenyl derivatives (**27**), it is obvious that 7-OMe(D) groups are sandwiched between the A- and G-ring in the triflavanoids (see earlier discussion on n.O.e. difference spectroscopy) and hence are subject to enhanced shielding effects. Abnormal shielding of a single methoxy-group resonance in the case of the [5,6]-analogue (**24**) implies overlap of the A-ring by 5-OMe(D)‡

* The AB-system ($J_{5,6}$ 8.5 Hz; 5-H, δ 6.72; 6-H, δ 6.53) of (+)-mesquitol tetramethyl ether acetate (**2**) exhibits relative broadening of 5-H as the result of benzylic coupling with 4-H_2.

† Corresponding shielding is significantly absent from the spectrum of the heptamethyl triacetyl derivative (**18**) where 7-OAc(D) replaces 7-OMe(D).

‡ Identified by n.O.e. difference spectrometry.

rather than 7-OMe(D), although the enhanced effect cannot be rationalized in this instance.

The c.d. spectra of the octamethyl ether diacetates (**20**) and (**23**) of [5,8]-(+)-mesquitol-(+)-catechin atropisomers exhibit positive Cotton effects ([θ] × 10^{-4} +2.2 and +2.3 respectively) at 225—240 nm (Figure 1); absorptions which are also representative of the corresponding derivatives of the [5,6]-isomer (**24**) and the 'racemic' [5,5]- and [5,6]-'dimers' of (+)-mesquitol (**25**) and (**17**). These Cotton effects appear to be

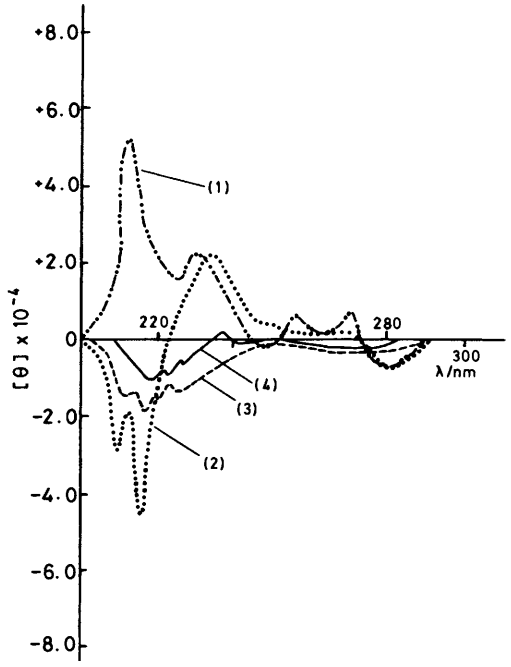


Figure 1. C.d. spectra of the octamethyl ether diacetates of atropisomeric [5,8]-(+)-mesquitol-(+)-catechins, (**20**) (1) and (**23**) (2), and of the tetramethyl ether acetates of (+)-mesquitol (**2**) (3) and (+)-catechin (4)

largely independent of differences in functionality of the diphenyl system and of atropisomerism, although falling within the conjugation band of Cotton effects attributed to simple biphenyls.[19] However, derivatives of each of the atropisomers (**20**) and (**23**) show high-amplitude negative and positive Cotton effects at lower wavelengths (205—220 nm) ([θ] × 10^{-4} −4.5 and +5.1 respectively, Figure 1), attributable to the ^1B_b transition.[20] Comparison with similar absorptions for binaphthyls[21] indicate left- and right-handed screwness respectively, namely opposite conformations to those assigned by n.O.e. difference spectroscopy. The sign of the Cotton effects in these instances may depend on the dihedral angle as in some binaphthyls, leading to reversal.[21] The [5,6:5,8]-*m*-terphenyl analogues (**27**) all exhibit the expected higher amplitude positive Cotton effects at *ca.* 230 nm, one of R_F 0.56 being of exceptional intensity (Figure 2). Two atropisomers, R_F 0.50 and 0.54, also give strongly negative effects at 200—210 nm.

The possible stereochemical mechanism of oxidative condensation of (+)-mesquitol with (+)-catechin to form [5,8]- and [5,6]-biflavanoids and also its self-condensation to give [5,6]- and [5,5]-'dimers' may be considered speculatively to involve a 'sandwich transition state' as postulated by Nonhebel and coworkers[12] for phenols. From electron spin-density considerations alone, the C-6 position (*ortho* to 7-OH) of (+)-mesquitol is less favoured for coupling than is C-5 (*para* to 8-OH), and for similar reasons C-8 of (+)-catechin (*para* to 5-OH) is favoured

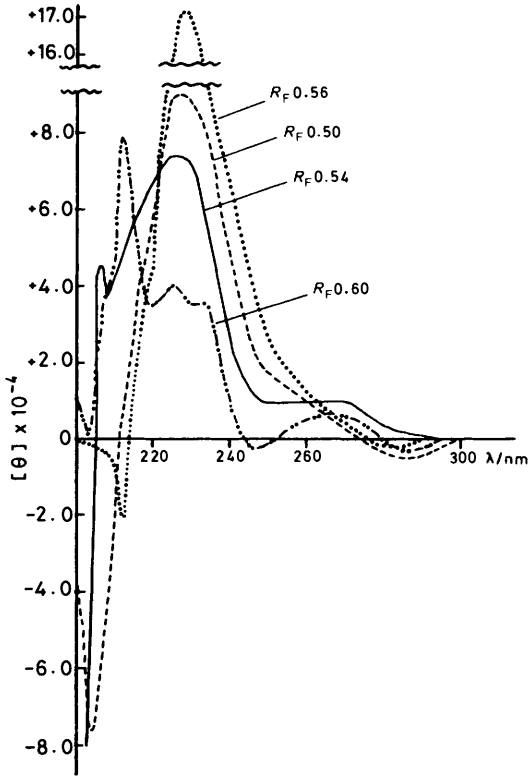


Figure 2. C.d. spectra of the dodecamethyl ether triacetates of atropisomeric [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins, (**27**)

over C-6 (*ortho* to 5-OH and 7-OH), the spin density at *para*-positions of phenoxyl radicals being twice that at *ortho*-positions.[22] As regards steric contributions, examination of Dreiding models indicates that (+)-mesquitol units may approach each other in an 'eclipsed' sandwich alignment for 6 ⟶ 6 and 5 ⟶ 5 coupling, but that electrostatic (oxygens) and steric repulsions (*axial* 2-H and 3-H, and 4-H_2 interactions) are at a maximum, rendering coupling *via* this approach unlikely (*cf.* Figure 3 and Table). However, for 5 ⟶ 5 coupling a single staggered approach with low non-bonded interaction (Table) is feasible, while for the favoured *in vitro* and *in vivo* 5 ⟶ 6 dimerization two staggered approaches are possible, each representative of a low degree of non-bonded interactions.

The speed (> ×4) of the 'mixed' (+)-mesquitol-(+)-catechin 5 ⟶ 8 oxidative coupling relative to that of self-condensation of each flavan-3-ol is of significance, being permitted by a single favourably staggered conformation combined with high electron spin-densities at the point of coupling of each unit. This could account for the natural predominance of [5,8]-(+)-mesquitol-(+)-catechin (**19**),(**22**); their preferential formation during synthesis; and the selective *in vivo* extension of condensation to [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins in spite of evidence of the transient existence of (+)-catechin in *P. glandulosa*. However, 5 ⟶ 6 coupling of (+)-mesquitol represents a minor mode under competitive conditions, due presumably to a combination of enhanced steric repulsion and less favourable electron spin-densities at the points of junction. Chromatographic evidence of *in vitro* formation of [5,6:5,8]-*m*-terphenyls (**26**) was available only when applying an initial 5:1 molar excess of (+)-mesquitol over (+)-catechin. Under these conditions* the sustained

* The reaction runs to completion during 2.5 h.

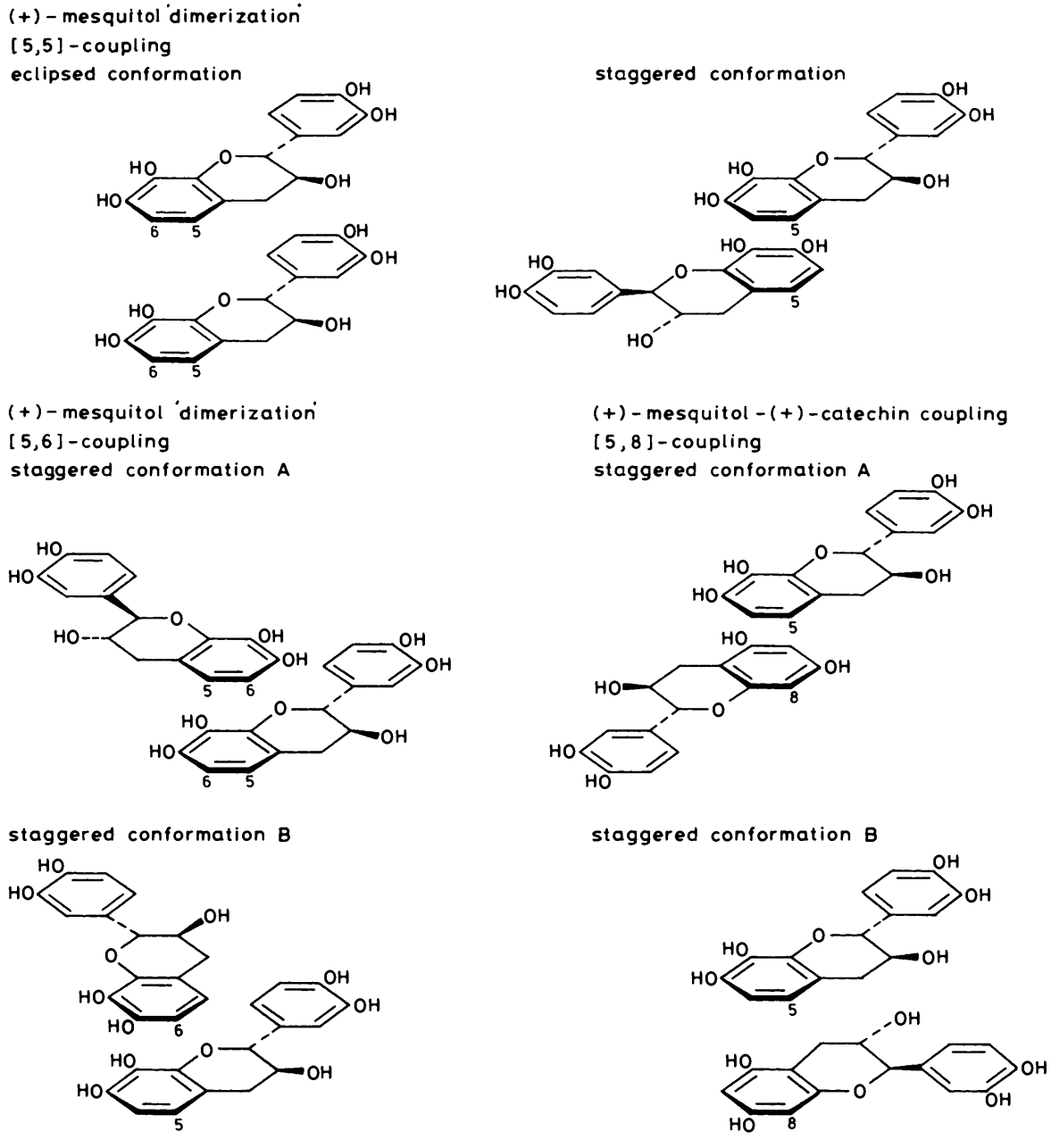


Figure 3. Stereochemistry of approach of (+)-mesquitol and (+)-catechin units.

excess of (+)-mesquitol, while permitting its [5,6]-dimerization, also allows further oxidative coupling at C-6(D) of the rapidly formed [5,8]-(+)-mesquitol-(+)-catechins. These stoicheiometric requirements are presumably those which pertain in *P. glandulosa*.

Although no evidence was found of either (+)-catechin or (+)-mollisacacidin in the heartwood of *P. glandulosa*, (+)-catechin must serve as 'nucleophile' in the biogenesis of the biflavanoids (**5**), (**7**), and (**9**), and (+)-mollisacacidin as potential electrophile for (**7**), (**9**), and (**11**). Inference of their transient existence is supported by synthesis of [4,6]-2,3-*trans*-3,4-*cis*-(−)-fisetinidol-2,3-*trans*-(+)-mesquitol (**11**) by acid-induced condensation of (+)-mollisacacidin with (+)-mesquitol, which also yielded the 3,4-*trans*-isomer and a linear [4,6:4,6]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans*-bis-(−)-fisetinidol-2,3-*trans*-(+)-catechin. Similarly, [4,8]-2,3-*trans*-3,4-*trans*-(+)-mesquitol-2,3-*trans*-(+)-catechin was available synthetically as the octamethyl ether diacetate (**6**) by initial oxidative 4-methoxylation of (+)-3-*O*-acetyl-3′,4′,7,8-tetra-*O*-methylmesquitol with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in $CHCl_3$–MeOH (*cf.* ref. 23); condensation of the product with (+)-catechin; and subsequent full methylation and acetylation. The desired compound was isolated from the expected mixture of [4,6]- and [4,8]-diastereoisomers of 3,4-*trans* and 3,4-*cis* configuration which was produced.* The free phenolic [4,8]-(+)-mesquitol-(+)-catechin metabolite (**5**) plausibly results *in vivo* from a

* Mass spectrometry assists in differentiating between these configurations in terms of $M^+ - 60$:M^+ ratios of 12:1/4:1 and 1:1/1:1 respectively (*cf.* ref. 15).

Table. The stereochemistry of approach: steric interactions and electrostatic repulsions

Non-bonded interactions

[5,5]-Coupling ('dimerization' of mesquitol)

Eclipsed conformation		Staggered conformation	
Upper unit	Lower unit	Upper unit	Lower unit
C-2	2-H	7-OH	O-1
3-H	C-3	O-1	7-OH
CH_2	CH_2	8-OH	8-OH
2-Ar	2-Ar		
O-1	O-1		
3-OH	3-OH		
7-OH	7-OH		
8-OH	8-OH		

[5,6]-Coupling ('dimerization' of mesquitol)

Staggered conformation A		Staggered conformation B	
Upper unit	Lower unit	Upper unit	Lower unit
8-OH	O-1	CH_2	O-1
7-OH	CH_2	O-1	8-OH
CH_2	7-OH	8-OH	7-OH
O-1	8-OH		

[5,8]-Coupling (mesquitol-catechin)

8-OH	5-OH	8-OH	5-OH
7-OH	CH_2	O-1	CH_2
CH_2	7-OH	CH_2	O-1
		3-OH	2-Ar
		2-Ar	3-OH

condensation involving the 2,3-*trans*-3,4-*cis*-flavan-3,4-diol analogue (**3**) of (+)-mesquitol as potential electrophile.

The [5,8]-(+)-mesquitol-(+)-catechins (**19**),(**22**) and [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins (**26**) are unique in that they represent the first examples of stable atropisomeric bi- and ter-flavanoid condensed tannins.

Experimental

^{1}H N.m.r. spectra were recorded on Bruker WP-80 FT and AM-300 spectrometers, with $CDCl_3$, $(CD_3)_2CO$, and $(CD_3)_2SO$ as solvents with Me_4Si as internal standard. Tubes were firmly stoppered to avoid solvent loss where spectra were recorded above the boiling point (100 °C) of $CDCl_3$. Mass spectra were obtained with a Varian CH-5 instrument, and c.d. data in methanol on a Jasco J-20 spectropolarimeter. T.l.c. was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and were sprayed with H_2SO_4–HCHO (40:1 v/v) after development. Preparative plates (p.l.c.), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Two-way paper chromatograms on Whatman No. 1 paper (28.5 × 46 cm) were developed successively in butan-2-ol and 2% acetic acid. Preparative paper chromatography (p.p.c.) was performed on Whatman No. 3 paper (47 × 57 cm) by upward development in 2% or 20% acetic acid. After drying, component bands were located under u.v. light or with the aid of spray reagents. Separations on Sephadex LH-20 columns (2.6 × 120 cm) were in ethanol, applying 2.0 g phenol per column. Fractions (15 ml each) were collected on a rotary fraction collector, starting with introduction of the sample on the column.

Alkali fusions were performed under anhydrous conditions.[24] Methylations were with an excess of diazomethane in methanol–diethyl ether during 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at room temperature. Evaporations were done under reduced pressure at *ca.* 60 °C in a rotary evaporator. N.m.r. spectra (300 MHz) provided criteria of purity of the various atropisomers.

Isolation

Drillings (4.05 kg) from the heartwood of *Prosopis glandulosa* were exhausitively extracted with methanol (5 × 2 l) during 5 days at room temperature. The solutions were combined, and after removal of the solvent the powdered extract was dewaxed with hexane in the cold to give a pale brown amorphous powder (603 g).

The powder (20 g) was dissolved in the lower phase (200 ml) of a water–butan-2-ol–n-hexane (5:4:1 v/v) system, and subjected to countercurrent distribution (20 plates) using an equivalent volume upper phase. The content of each plate was examined by two-way chromatography and the fractions were combined as follows: upper phase plates (1—4), (5—6), (7—10), (11—13), (14—16), and (17—20), and lower phase plates (1—3), (4—5), (6—7), (8—10), (11—13), and (14—16). The liquid–liquid separation was repeated 5 times, and each of the combined fractions was separated on a Sephadex LH-20 column.

(2R,3S)-2,3-trans-3,3',4'-7,8-*Pentahydroxyflavan* (**1**).—Plates 7—10 (upper phase) contained the main component from *P. glandulosa*, but this was nevertheless subjected to column chromatography on Sephadex when tubes 41—70 were combined. After further purification by t.l.c. in benzene–acetone–methanol (6:3:1 v/v), the title compound was obtained as an amorphous solid (450 mg; R_F 0.53) which failed to crystallize from water; δ[$(CD_3)_2CO$; 80 MHz; 31 °C] 2.63 (dd, *J* 8.0 and 15.0 Hz, 4-$H_{ax.}$), 2.88 (dd, *J* 5.0 and 15.0 Hz, 4-$H_{eq.}$), 3.92 (m, 3-H), 3.92 (br s, 3-OH), 4.53 (d, *J* 7.25 Hz, 2-H), 6.25 (s, 5- + 6-H), 6.47—6.72 (m, 2'-, 5'-, and 6'-H), and 7.44 (br s, 4 × phenolic OH); alkali fusion gave pyrogallol and protocatechuic acid; c.d. $[\theta]_{300}$ 0, $[\theta]_{280}$ −1 340, $[\theta]_{255}$ −180, $[\theta]_{223}$ −16 570, and $(\theta]_{207}$ 0.

(2R,3S)-2,3-trans-3-*Hydroxy*-3',4',7,8-*tetramethoxyflavan*. Methylation of the phenol (**1**) (150 mg) followed by t.l.c. separation in benzene–acetone (8:2 v/v) gave the tetramethyl ether (R_F 0.33; 106 mg) which crystallized from ethanol as needles, m.p. 137 °C.

(2R,3S)-2,3-trans-3-*Acetoxy*-3',4',7,8-*tetramethoxyflavan* (**2**). Acetylation of the above tetramethyl ether (106 mg) gave the *monoacetate* (**2**) (96 mg), R_F 0.38 in benzene–acetone (8:2 v/v), which crystallized from ethanol as needles, m.p. 114 °C (Found: C, 64.5; H, 6.3. $C_{21}H_{21}O_7$ requires C, 64.5; H, 6.2%); δ ($CDCl_3$; 80 MHz; 31 °C) 6.75—6.50 (m, 2'-, 5'-, and 6'-H), 6.50 (br d, *J* 8.1 Hz, 5-H), 6.30 (d, *J* 8.1 Hz, 6-H), 5.16 (m, 3-H), 5.06 (d, *J* ~8.5 Hz, 2-H), 3.75, 3.70 (×2), and 3.66 (each s, 4 × OMe), 2.84 (dd, *J* ~7.5 and 15.8 Hz, 4-$H_{eq.}$), 2.64 (dd, *J* ~10.0 and 15.8 Hz, 4-$H_{ax.}$), and 1.88 (s, 3-OAc); δ (C_6D_6; 80 MHz; 31 °C) 3.81, 3.34, and 3.28 (×2) (4 × OMe); *m/z* 388 (M^+, 59%), 346 (59), 329 (56), 328 (76), 313 (43), 297 (16.8), 222 (56), 210 (30), 209 (12), 180 (100), 167 (50), 163 (18.4), and 151 (73); c.d. (Figure 1).

(2R,3S,4S)-2,3-trans-3,4-cis-3,4-*Diacetoxy*-3',4',7,8-*tetramethoxyflavan* (**4**).—The contents of plates 5—6 (upper phase) were resolved on a Sephadex column, tubes 20—37 containing a single component. Alkali fusion gave pyrogallol and protocatechuic acid only. Methylation of the free phenol (**3**) (80 mg) with diazomethane, followed by p.l.c. of the product in 1,2-dichloroethane–ethanol (8:2 v/v) gave the tetramethyl ether

(3.8 mg; R_F 0.31). Acetylation of the tetramethyl ether gave the *diacetate* (**4**) as a solid [3.0 mg; R_F 0.09 in benzene–acetone (9:1 v/v)] (Found: M^+, 446.457 93. $C_{23}H_{26}O_9$ requires M, 446.458 27); δ ($CDCl_3$; 80 MHz; 30 °C) 7.00 (br d, J 8.5 Hz, 5-H), 7.00—6.75 (m, 2′-, 5′-, and 6′-H), 6.56 (d, J 8.5 Hz, 6-H), 6.14 (dd, J 0.6 and 6.0 Hz, 4-H), 5.44 (dd, J 6.0 and 9.7 Hz, 3-H), 5.23 (d, J 9.7 Hz, 2-H), 3.89, 3.86 (×2), and 3.81 (each s, 4 × OMe), 2.11 (s, 4-OAc), and 1.84 (s, 3-OAc); m/z 446 (M^+, 52%), 387 (15.4), 386 (37), 344 (61), 328 (50), 327 (93), 326 (28), 316 (50), 301 (26), 224 (41), 222 (49), 211 (7.1), 210 (17.6), 180 (100), 165 (46), and 151 (51).

The contents of plates 4—5 (lower phase) gave an indication of a single component by two-way chromatography, but alkali fusion gave pyrogallol, resorcinol, phloroglucinol, and protocatechuic acid as degradation products, indicating complexity. Methylation of the phenolic mixture (300 mg) followed by p.l.c. separation in benzene–acetone (8:2 v/v) gave two products at R_F 0.63 (30 mg) and 0.61 (27 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* (**10**). Acetylation of the R_F 0.63 methyl ether, followed by p.l.c. separation in n-hexane–acetone–ethyl acetate (60:25:15 v/v) gave the heptamethyl ether diacetate (**10**) of [4,6]-(−)-fisetinidol-(+)-catechin (**9**) as a solid (R_F 0.27; 6.5 mg) identical with that obtained by synthesis[16] as regards ^{1}H n.m.r. (100 °C; $CDCl_3$), mass, and c.d. spectra (Found: M^+, 744.797 67. Calc. for $C_{41}H_{44}O_{13}$: M, 744.800 03).

(1S,2R)-2-*Acetoxy*-1-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-6-*yl*]-1-(3,4-*dimethoxyphenyl*)-3-(2,3,4-*trimethyoxyphenyl*)*propane** (**15**). Acetylation of the methyl ether, R_F 0.61, followed by p.l.c. separation in n-hexane–acetone–ethyl acetate (60:25:15 v/v) gave the *title nonamethyl ether diacetate* as a solid, R_F 0.22 (7.3 mg); (Found: M^+, 790.316 38. $C_{43}H_{50}O_{14}$ requires M, 790.320 06); δ ($CDCl_3$; 300 MHz; 24 °C) 6.96 [dd, J 2.5 and 8.5 Hz, 6-H(B)], 6.89 [d, J 1.9 Hz, 2-H(B)], 6.86 [dd, J 1.9 and 8.0 Hz, 6-H(E)], 6.825 [s, 5-H(D)], 6.82 [d, J 8.0 Hz, 2-H(E)], 6.805 [d, J 8.0 Hz, 5-H(B)], 6.78 [d, J 8.1 Hz, 5-H(E)], 6.71 [d, J 8.5 Hz, 6-H(A)], 6.50 [d, J 8.5 Hz, 5-H(A)], 5.80 (m, 2-H), 5.25 [m, 3-H(F)], 5.10 [d, J 6.0 Hz, 2-H(F)], 4.51 (d, J 10.0 Hz, 1-H), 3.88, 3.835 (×3), 3.82, 3.80, 3.797, 3.785, and 3.787 (each s, 9 × OMe), 2.98 (dd, J 3.0 and 14.0 Hz, 3-H), 2.87 [dd, J 4.5 and 16.0 Hz, 4-$H_{eq.}$(F)], 2.725 [dd, J 7.0 and 16.0 Hz, 4-$H_{ax.}$(F)], 2.49 [dd, J 9.0 and 14.0 Hz, 3-H], 1.91 [s, 3-OAc(F)], and 1.62 (s, 2-OAc); m/z 790 (M^+, 2.5%), 730 (12.8), 670 (2.8), 537 (100), 495 (19.7), 477 (5.3), 343 (2.8), 329 (2.8), 327 (4.4), 300 (1.8), 253 (2.2), 222 (2.0), 193 (2.8), 181 (30), 180 (25), 179 (4.2), 167 (10.7), 166 (8.8), 151 (72), and 149 (7.4); c.d. $[\theta]_{290}$ 0, $[\theta]_{270}$ −1 250, $[\theta]_{258}$ 0, $[\theta]_{232}$ +10 000, $[\theta]_{218}$ +4 500, $[\theta]_{214}$ +39 000, $[\theta]_{211}$ +21 000, $[\theta]_{210}$ +25 000, and $[\theta]_{200}$ 0.

(2R,3S)-2,3-trans-3-*Acetoxy*-8-[(2R,3S,4R)-2,3-trans-3,4-cis-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* (**8**).—The contents of plates 14—16 (lower phase) appeared to consist of a single component after purification on a Sephadex column (tubes 64—131), R_F 0.48, 0.36 (two-way paper chromatography). Alkali fusion gave resorcinol, phloroglucinol, and protocatechuic acid. Methylation with diazomethane, followed by purification by p.l.c. in benzene–acetone (8:2 v/v), gave a major product, R_F 0.39 (22.8 mg). Acetylation of the heptamethyl ether followed by p.l.c. in benzene–acetone (9:1 v/v) gave the heptamethyl ether diacetate (**8**) as a solid, R_F 0.62 (21.9 mg) (Found: M^+, 744.799 38. Calc. for $C_{41}H_{44}O_{13}$: M, 744.800 03); ^{1}H n.m.r. [150 °C; $(CD_3)_2SO$], mass fragmentation, and c.d. spectra were in agreement with those of the synthetic product.[16]

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S,4R)-2,3-trans-3,4-cis-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,7,8-*tetramethoxyflavan* (**12**).—The contents of plates 5—6 (upper phase) appeared to consist of a single component, R_F 0.47, 0.36, by two-way paper chromatography, after separation on a Sephadex column (tubes 120—130). Alkali fusion gave resorcinol, pyrogallol, and protocatechuic acid. Methylation with diazoacetone (60 mg) followed by p.l.c. in 1,2-dichloroethane–acetone (9:1 v/v) gave a single product, R_F 0.86 (28.3 mg). Acetylation of the heptamethyl ether followed by p.l.c. in benzene–acetone (8:2 v/v) gave the *diacetate* (**12**) as a solid, R_F 0.52 (17.9 mg) (Found: C, 66.1; H, 6.0. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 5.8%); δ ($CDCl_3$; 80 MHz; 30 °C) 7.03—6.70 (m, 7 × ArH), 6.59 [d, J 2.0 Hz, 8-H(A)], 6.47 [dd, J 2.0 and 8.1 Hz, 6-H(A)], 6.39 (br s, 5-H(D)], 5.52 [dd, J 4.8 and 7.0 Hz, 3-H(C)], 5.31 [m, 3-H(F)], 5.20 [d, J 7.0 Hz, 2-H(C)], 5.11 [d, J 6.5 Hz, 2-H(F)],4.66 [d, J 4.8 Hz, 4-H(C)], 3.89, 3.88 (×2), 3.84 (×2), 3.80, and 3.78 (each s, 7 × OMe), 2.98 [dd, 4($H_{eq.}$(F)], 2.69 [dd, 4-$H_{ax.}$(F)], 1.94 [s, 3-OAc(F)], and 1.84 [s, 3-OAc(C)]; m/z 744 (M^+, 42%), 685 (23), 684 (48), 626 (3.6), 625 (9.2), 624 (7.1), 522 (0.8), 492 (19.5), 491 (69), 463 (7.5), 462 (10.1), 450 (7.2), 449 (26), 443 (3.6), 432 (3.6), 431 (10.5), 387 (1.2), 357 (1.2), 300 (2.2), 269 (15.1), 222 (14.8), 180 (100), and 151 (90).

The contents of plates 1—3 (lower phase) gave the appearance of a single component by two-way paper chromatography, R_F 0.44, 0.42, after separation on a Sephadex column (tubes 37—75). Methylation of the purified phenol (475 mg) with diazomethane gave a mixture of methyl ethers which were resolved by p.l.c. in 1,2-dichloroethane–acetone (85:15 v/v) to afford compounds with R_F 0.18 (30 mg) and 0.24 (71 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-8-[(2R,3S,4S)-2,3-trans-3,4-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* (**6**). Acetylation of the octamethyl ether, R_F 0.18, gave the *octamethyl ether diacetate* (**6**) as a solid (28.7 mg), R_F 0.52 in benzene–acetone (8:2 v/v) (Found: C, 65.1; H, 6.0. $C_{42}H_{46}O_{14}$ requires C, 65.0; H, 6.0%); δ ($CDCl_3$; 80 MHz; 100 °C) 7.00—6.56 (m, 6 × ArH), 6.39 [s, 5-H(A) + 6-H(A)], 6.16 [br s, 5-H(D)], 5.95 [t, J 9.9 Hz, 3-H(C)], 5.03 [m, 3-H(F)], 4.88 [d, J 9.9 Hz, 2-H(C)], 4.84 [d, J 7.8 Hz, 2-H(F)], 4.80 [d, J 9.9 Hz, 4-H(C)], 3.78 (×5), 3.72, 3.67, and 3.66 (each s, 8 × OMe), 3.03 [dd, J 5.0 and 16.0 Hz, 4-$H_{eq.}$(F)], 2.63 [dd, J 8.0 and 16.0 Hz, 4-$H_{ax.}$(F)], 1.84 [s, 3-OAc(F)], and 1.56 [s, 3-OAc(C)]; m/z 774 (M^+, 10.6%), 714 (58), 683 (5.8), 672 (2.1), 654 (25), 537 (2.2), 521 (32), 492 (25), 461 (10.4), 344 (17.6), 343 (67), 330 (3.1), 329 (0.9), 327 (13.3), 300 (13.6), 299 (63), 222 (2.8), 180 (48), and 151 (100).

(S)-{(2R,3S)-2,3-trans-3-*Acetoxy*-8-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,5,7-*tetramethyoxyflavan*} (**20**). Acetylation of the octamethyl ether, R_F 0.24, gave the *octamethyl ether diacetate* (**20**) as a solid (70 mg), R_F 0.46, in 1,2-dichloroethane–acetone (9:1 v/v) and R_F 0.32 in n-hexane–acetone–ethyl acetate (60:25:15 v/v, ×3) (Found: M^+, 774.286 58. $C_{42}H_{46}O_{14}$ requires M, 774.288 46); δ ($CDCl_3$; 80 MHz; 100 °C) 7.25—6.66 (m, 6 × ArH), 6.41 [s, 6-H(A)], 6.16 [s, 6-H(D)], 5.25 [m, 3-H (C and F)], 4.97 [d, J 6.25 Hz, 2-H(C and F)], 3.84, 3.81 (×2), 3.78 (×2), 3.75 (×2), and 3.57 (each s, 8 × OMe), 3.16—2.50 [m, 4-H_2 (C and F)], 1.94 [s, 3-OAc(C or F)], and 1.78 [s, 3-OAc(F or C)]; c.d. (Figure 1).

(R)-{(2R,3S)-2,3-trans-3-*Acetoxy*-8-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,5,7-*tetramethoxyflavan*} (**23**).—Plates 5—6 (upper phase) gave a single product, R_F 0.25, 0.47, on two-way paper chromatograms after resolution on a Sephadex column (tubes 52—60). The

* (2*R*,3*S*)-2,3-*trans*-3-Acetoxy-6-[(1*S*,2*R*)-2-acetoxy-1-(3,4-dimethoxyphenyl)-3-(2,3,4-trimethoxyphenyl)propyl]-3′,4′,7,8-tetramethoxyflavan.

proanthocyanidin test[25] was negative. Methylation of the phenol (148 mg) followed by purification by p.l.c. in benzene–acetone (6:4 v/v) gave an octamethyl ether, R_F 0.55 (47 mg) and a heptamethyl ether, R_F 0.44 (18 mg). Acetylation of the octamethyl ether followed by p.l.c. in n-hexane–acetone–ethyl acetate (60:25:15 v/v, × 3) gave the *octamethyl ether diacetate* (**23**) as a pale yellow solid, R_F 0.36 (17.1 mg) (Found: C, 65.7; H, 6.1%; M^+, 774.287 35. $C_{42}H_{46}O_{14}$ requires C, 65.1; H, 6.0%; *M*, 774.288 46); δ ($CDCl_3$; 80 MHz; 100 °C) 6.97—6.69 [m, 6 × ArH(B and E)], 6.50 [s, 6-H(A)], 6.22 [s, 6-H(D)], 5.34—4.97 [m, 3-H(C and F)], 5.25 [d, *J* 5.25 Hz, 2-H(C or F)], 4.91 [d, *J* 5.25 Hz, 2-H (F or C)], 3.86, 3.80 (× 4), 3.75, 3.69, and 3.63 (each s, 8 × OMe), 3.97—2.47 [m, 4-H_2 (C and F)], 1.86 [s, 3-(OAc (C or F)], and 1.81 [s, 3-OAc (F or C)]; c.d. (Figure 1).

The mass fragmentation spectra of the pair of [5,8]-linked atropisomers (**23**) and (**20**) are respectively as follows: *m/z* 774 (M^+, 100, 100%), 732 (12.6, 18.2), 715 (42, 46), 714 (61, 50), 683 (46, 47), 672 (13.3, 14), 656 (33, 43), 655 (61, 48), 654 (43, 46), 553 (38, 4.4), 552 (7.2, 7.6), 522 (5.2, 5.8), 521 (12.2, 10.7), 510 (14.6, 15.6), 493 (59, 47), 492 (61, 49), 479 (50, 46), 478 (24, 19.7), 477 (56, 46), 463 (12.5, 17), 462 (23, 29), 461 (59, 45), 374 (12.3, 13.6), 373 (46, 44), 359 (58, 47), 344 (57, 48), 343 (78, 68), 342 (23, 24), 333 (13.2, 17.9), 332 (49, 46), 331 (74, 67), 330 (74, 66), 301 (3.2, 49), 300 (7.4, 49), 270 (11.2, 11.4), 222 (10.6, 13.6), 180 (65, 57), and 151 (89, 90).

(R)-{(2R,3S)-2,3-trans-3,7-*Diacetoxy*-8-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,5-*trimethoxyflavan*} (**21**). Acetylation of the heptamethyl ether, R_F 0.44, obtained during separation of the above compound gave the *heptamethyl ether triacetate* (**21**), R_F 0.29 in n-hexane–acetone–EtOAc (60:25:15 v/v; × 3), as a solid (20 mg) (Found: M^+, 802.280 13. $C_{43}H_{46}O_{15}$ requires *M*, 802.283 67); δ ($CDCl_3$; 300 MHz; 25 °C) 6.84 [d, *J* 2.0 Hz, 2-H(B)], 6.83 [dd, *J* 2.0 and 8.0 Hz, 6-H(B)], 6.77 [d, *J* 8.0 Hz, 5-H(E)], 6.74 [dd, *J* 2.0 and 8.0 Hz, 6-H(E)], 6.69 [d, *J* 2.0 Hz, 2-H(E)], 6.68 [d, *J* 8.0 Hz, 5-H(B)], 6.50 [s, 5-H(A)], 6.40 [s, 6-H(D)], 5.20 [m, 2-H (C)] and 3-H(C and F)], 4.95 [d, *J* 4.8 Hz, 2-H(F)], 3.88, 3.85, 3.845, 3.81, 3.79, 3.755, and 3.65 (each s, 7 × OMe), 2.78—2.40 [m, 2 × 4-H_2 (C and F)], 2.29 [s, 7-OAc(D)], 1.95 and 1.86 [each s, 3-OAc(C and F)]; *m/z* 802 (M^+, 72%), 742 (32), 683 (20), 682 (10.2), 531 (14.2), 503 (12.4), 371 (17.1), 359 (24), 358 (29), 345 (10.2), 329 (23), 328 (10.3), 317 (29), 316 (28), 315 (12.9), 301 (33.6), 285 (11.0), 273 (10.6), 193 (17.4), 180 (53), 175 (15.6), 167 (26), 165 (29), and 151 (100); c.d. $[\theta]_{300}$ 0, $[\theta]_{290}$ −1 100, $[\theta]_{280}$ 0, $[\theta]_{250}$ +4 600, $[\theta]_{227}$ +56 100, and $[\theta]_{200}$ 0.

The content of plates 1—3 (lower phase) gave a single compound, R_F 0.46, 0.32, on two-way chromatograms after fractionation on a Sephadex column (tubes 98—118). The proanthocyanidin test was negative. Methylation of the phenol (140 mg) with diazomethane, followed by separation by p.l.c. in benzene–acetone (7:3 v/v), gave two products, an octamethyl ether at R_F 0.40 (64.3 mg) and a heptamethyl ether, R_F 0.33 (32.3 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,7,8-*tetramethoxyflavan* (**17**). Acetylation of the octamethyl ether, R_F 0.40, followed by further purification by p.l.c. in benzene–acetone (8:2 v/v) gave the *title diacetate* (**17**) as a solid, R_F 0.47 (34.5 mg) [Found: M^+, 774.285 81. $C_{42}H_{46}O_{14}$ requires *M*, 774.288 46]; δ ($CDCl_3$; 80 MHz; 100 °C) 7.06—6.73 [m, 6 × ArH(B and E)], 6.53 [br s, 5-H(D)], 6.47 [s, 6-H(A)], 5.34 [m, 3-H (C and F)], 5.16 [d, *J* 5.25 Hz, 2-H(C)], 5.09 [d, *J* 5.75 Hz, 2-H(F)], 3.91, 3.89, 3.82 (× 2), 3.81, 3.78 (× 2), and 3.54 (each s, 8 × OMe), 3.06 [dd, *J* ~5.0 and ~16.0 Hz, 4-$H_{eq.}$(F)], 2.81 [dd, *J* ~8.0 and ~16.0 Hz, 4-$H_{ax.}$(F)], 2.67 [m, 4-H_2(C)], 1.92 [s, 3-OAc(C or F)], and 1.88 [s, 3-OAc(F or C)]; *m/z* 774 (M^+, 81%), 732 (18.2), 715 (40), 714 (48), 683 (32), 672 (28), 656 (7.6), 655 (13.5), 654 (27), 553 (7.5), 552 (10.2), 551 (5.4), 510 (12.4), 493 (29), 492 (37), 479 (15.9), 478 (13.3), 477 (33), 463 (10.5), 462 (13.9), 461 (26), 374 (2.0), 373 (10.1), 359 (9.3), 344 (18.9), 343 (46), 342 (12.7), 333 (4.9), 332 (46), 331 (45), 330 (38), 301 (26), 300 (8.0), 270 (7.1), 222 (24), 180 (65), and 151 (100); c.d. $[\theta]_{294}$ 0, $[\theta]_{290}$ −670, $[\theta]_{283}$ 0, $[\theta]_{250}$ +11 400, $[\theta]_{233}$ +32 900, and $[\theta]_{200}$ +3 350.

(2R,3S)-2,3-trans-3,7-*Diacetoxy*-6-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,8-*trimethoxyflavan* (**18**). Acetylation of the heptamethyl ether, R_F 0.33, followed by p.l.c. of the product in benzene–acetone (8:2 v/v) gave the *heptamethyl ether triacetate* (**18**) as a solid, R_F 0.47 (24.1 mg) (Found: C, 64.3; H, 5.7. $C_{43}H_{46}O_{15}$ requires C, 64.3; H, 5.8%); δ ($CDCl_3$; 80 MHz; 100 °C) 7.02—6.72 [m, 6 × ArH (B and E)], 6.55 [br s, 5-H(D)], 6.38 [s, 6-H(A)], 5.38—5.06 [m, 2-H and 3-H (C and F)], 3.89, 3.81 (× 2), 3.80, and 3.78 (× 3) (each s, 7 × OMe), 3.09 [dd, 4-$H_{eq.}$(F)], 2.81 [dd, 4-$H_{ax.}$(F)], 2.70 [dd, 4-$H_{eq.}$(C)], 2.51 [dd, 4-$H_{ax.}$(C)], and 1.59, and 1.57 (× 2) [each s, OAc (C, D, and F)]; *m/z* 802 (M^+, 31%), 760 (6.4), 741 (10.1), 682 (15.5), 538 (2.1), 520 (1.9), 478 (15.6), 359 (2.7), 358 (1.3), 317 (15.1), 316 (10.3), 222 (5.3), 180 (63), and 151 (100).

Atropisomeric (2R,3S)-2,3-trans-3-*Acetoxy*-6,8-*bis*[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′-7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,5,7-*tetramethoxyflavans* (**27**).—The content of plates 1—3 (lower phase) gave indication of the presence of two components, of R_F 0.21, 0.51 and 0.13, 0.46 by two-way paper chromatography, after column chromatographic separation on Sephadex (tubes 126—170). Proanthocyanidins were shown to be absent. Methylation of the free phenolic fraction (278 mg) followed by p.l.c. in dichloromethane–acetone (8:2 v/v) gave three products, at R_F 0.50 (63.3 mg), 0.42 (29.3 mg), and 0.27 (30.6 mg).

Acetylation of the dodecamethyl ether, R_F 0.50, followed by p.l.c. in dichloromethane–acetone (96:4 v/v), gave the *triacetate* (**27**) as a pale yellow solid, R_F 0.56 (50.3 mg) (Found: C, 65.0: H, 6.0. $C_{63}H_{68}O_{21}$ requires C, 65.2; H, 5.9%); δ ($CDCl_3$; 80 MHz; 100 °C) 7.00—6.63 [m, 9 × ArH(B, E, and H)], 6.56 [s, 6-H(C or G)], 6.53 [s, 6-H(G or C)], 5.39—5.08 (m, 5 × heterocyclic H), 4.89 [d, *J* 6.5 Hz, 2-H (C, F, or I)], 3.94, 3.86 (× 2), 3.84, 3.78 (× 3), 3.77, 3.72, 3.63, 3.20, and 3.08 (each s, 12 × OMe), 2.91—2.55 [m, 3 × 4-H_2(C, F, and I)], and 1.88, 1.85, and 1.83 [each s, 3 × 3-OAc(C, F, and I)]; c.d. (Figure 2).

Acetylation of the dodecamethyl ethers, R_F 0.42, followed by p.l.c. in dichloromethane–acetone (96:4 v/v) gave two dodecamethyl ether triacetates, at R_F 0.60 (29.2 mg) and 0.54 (18.8 mg).

The R_F 0.60 dodecamethyl ether triacetate (**27**) was isolated as a colourless solid; δ ($CDCl_3$; 80 MHz; 100 °C) 7.05—6.72 [m, 9 × ArH(B, E, and H)], 6.52 [s, 6-H(A or G)], 6.44 [s, 6-H(G or H)], 5.44—5.13 (m, 4 × heterocyclic H), 4.97 (d, *J* 7.0 Hz, 2-H), 4.94 (d, *J* 7.0 Hz, 2-H), 3.94, 3.86 (× 3), 3.84 (× 3), 3.81, 3.78, 3.75, 3.38, and 2.91 (each s, 12 × OMe), 3.38—2.69 (m, 3 × 4-H_2), and 1.94, 1.91, and 1.81 (each s, 3 × 3-OAc); c.d. (Figure 2).

The R_F 0.54 dodecamethyl ether triacetate (**27**) was isolated as a colourless solid; δ ($CDCl_3$; 80 MHz; 100 °C) 7.06—6.67 [m, 9 × ArH(B, E, and H)], 6.61 [s, 6-H(A or G)], 6.50 [s, 6-H(G or A)], 5.42—5.13 (m, 4 × heterocyclic H), 5.03 (d, *J* 6.5 Hz, 2 × 2-H), 3.95, 3.86 (× 4), 3.83 (× 3), 3.80, 3.66, 3.25, and 3.06 (each s, 12 × OMe), 3.06—2.19 (m, 3 × 4-H_2), and 2.00, 1.80, and 1.78 (each s, 3 × 3-OAc); c.d. (Figure 2).

Acetylation of the dodecamethyl ether, R_F 0.27, followed by p.l.c. in dichloromethane–acetone (96:4 v/v) gave another dodecamethyl ether triacetate (**27**) as a pale yellow solid, R_F 0.50 (31 mg); δ ($CDCl_3$; 80 MHz; 100 °C) 7.30—6.63 (m, 9 × ArH), 6.59 [s, 6-H(G or A)], 6.56 [s, 6-H(G or A)], 5.41—5.00 (m, 4 × heterocyclic H), 4.91 (d, *J* 6.5 Hz, 2 × 2-H), 3.92, 3.89, 3.84, 3.80 (× 4), 3.77 (× 2), 3.64, 3.33, and 3.05 (each s, 12 × OMe), 3.13—2.38 (m, 3 × 4-H_2), and 1.84, 1.83, and 1.67 (each s, 3 × 3-OAc); c.d. (Figure 2).

Mass fragmentation spectra of the dodecamethyl ether triacetates (**27**) of R_F 0.56, 0.60, 0.54, and 0.50 were respectively: *m/z* 1 160 (M^+, 13.7, 49, 52. 47), 1 141 (13.5, 9.5, 13.0, −), 1 140 (−, 2.3, −, 40), 1 101 (−, 5.6, 5.0, 7.1), 1 100 (9.9, 18.0, 18.2, 42), 982 (2.9, −, −, 9.6), 939 (1.1 −, −, 2.3), 938 (−, −, −, 4.1), 879 (2.0, 2.8, 2.7, 6.3), 878 (4,5, 2.8, 3.7, 11.9), 847 (6.7, 3.8, 2.6, 18.9), 820 (2.4, 2.3, 1.9, 9.4), 819 (4.8, 3.2, 3.9, 15.9), 818 (2.1, 1.7, 1.5, 5.9), 773 (1.6, 1.6, −, 4.0), 718 (3.0, 2.1, 2.8, 10.4), 717 (9.0, 6.0, 5.1, 32), 716 (7.5, 4.3, 57, 24), 658 (8.4, 17.3, 28, 10), 657 (5.8, 3.9, 6.4, 20), 656 (4.0, 3.2, 3.7, 9.0), 653 (2.9, 3.4, 2.3, 2.8), 552 (1.3, 18.7, 14.3, 1.7), 551 (2.2, 13.8, 12.1, 2.5), 497 (23, 70, 18.3, 26), 496 (2.1, 4.1, 36, 3.8), 495 (5.1, 6.2, 72, 9.4), 494 (3.1, 2.6, 5.9, 4.5), 437 (2.5, −, 1.6, 4.4), 436 (2.2, −, −, 2.8), 435 (4.4, 3.3, 2.5, 4.9), 434 (3.9, 1.9, 1.5, 4.9), 431 (3.7, 4.0, 5.5, 3.8), 389 (2.3, 2.6, 2.8, 3.5), 387 (2.6, 6.1, 10.8, 3.8), 331 (2.7, 1.8, 3.3, 2.6), 330 (3.0, 2.3, 2.1, 4.0), 329 (2.8, 4.8, 6.4, 12.7), 327 (11.9, 12.7, 10.1, 15.2), 267 (2.7, 38, 27.4, 3.7), 266 (1.4, 11.3, 8.9, 1.4), 222 (17.6, 7.9, 11.3, 16.3), 180 (52, 53, 66, 48), 166 (16.6, 18.1, 16.7, 13.3), 165 (47, 56, 59, 40), and 151 (100, 78, 82, 100).

Synthesis of Biflavanoids with 2,3-trans-3,3′,4′,7,8-*Pentahydroxyflavans as Constituent Units*

(+)-Mollisacacidin (580 mg) and (+)-2,3-*trans*-3′,4′,7,8-tetrahydroxyflavan-3-ol (**1**) (1.74 g) were dissolved in 0.1M-HCl (50 ml) and the solution was stirred for 24 h at ambient temperatures. The course of the reaction was monitored by t.l.c. in benzene–acetone–methanol (6:3:1 v/v). After consumption of most of the (+)-mollisacacidin, the reaction mixture was extracted with ethyl acetate (5 × 25 ml), the extract was dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure. The products were resolved by p.l.c. in benzene–acetone–methanol (6:3:1 v/v) to give two compounds, at R_F 0.34 (341 mg) and 0.25 (1.99 mg).

Methylation of the former (R_F 0.34) with diazomethane, followed by p.l.c. in benzene–acetone (7:3 v/v), gave a single product at R_F 0.46 (174 mg). Acetylation of the heptamethyl ethers, followed by p.l.c. in dichloromethane–acetone (98:2 v/v), provided two heptamethyl ether diacetate derivatives, at R_F 0.47 (74.6 mg) and 0.39 (11.7 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S,4R)-2,3-trans-3,4-cis-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,7,8-*tetramethoxyflavan* (**12**). The heptamethyl ether diacetate R_F 0.47, was isolated as a solid, with ^{1}H n.m.r., mass, and c.d. spectra identical with the derivative of the natural product.

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,7,8-*tetra methoxyflavan*. The *heptamethyl ether diacetate*, R_F 0.39, was isolated as a solid (Found: M^+, 744.276 97. $C_{41}H_{44}O_{13}$ requires *M*, 744.277 91); δ ($CDCl_3$; 80 MHz; 100 °C) 7.09—6.33 (m, 8 × ArH), 6.44 [br s, 5-H(D)], 5.63 [t, $J_{2,3} = J_{3,4} = 9.2$ Hz, 3-H(C)], 5.30 [m, 3-H(F)], 5.02 [d, *J* 6.0 Hz, 2-H(F)], 4.95 [d, *J* 9.2 Hz, 2-H(C)], 4.53 [d, *J* 9.2 Hz, 4-H(C)], 3.86, 3.81 (× 3), 3.78, 3.75, and 3.72 (each s, 7 × OMe), 3.00 [dd, 4-$H_{eq.}$(F)], 2.67 [dd, 4-$H_{ax.}$(F)], 1.88 [s, 3-OAc(F)], and 1.63 [s, 3-OAc(C)]; *m/z* 744 (M^+, 8.8%).

(2R,3S,4S)-2,3-trans-3,4-trans-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-6-*yl*]-6-[(2R,3S,4R)-2,3-trans-3,4-cis-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-3′,4′,7-*trimethoxyflavan*. Methylation of the phenolic product, R_F 0.25, from the condensation, followed by p.l.c. in 1,2-dichloroethane–acetone (8:2 v/v) gave a main product, R_F 0.37 (39.3 mg). Acetylation of the decamethyl ether gave the title *decamethyl ether triacetate* as a solid (39 mg), R_F 0.19 in 1,2-dichloroethane–acetone (95:5 v/v) (Found: C, 66.4; H, 6.0. $C_{61}H_{64}O_{19}$ requires C, 66.5; H, 5.9%); δ ($CDCl_3$; 80 MHz; 100 °C) 7.11—6.22 (m, 12 × ArH), 6.47 [s, 5-H(D)], 6.34 [s, 8-H(D)], 6.28 [br s, 5-H(G)], 5.62 [t, Σ*J* 19.0 Hz, 3-H(F)], 5.48 [dd, *J* 4.75 and 6.5 Hz, 3-H(C)], 5.23 [m, 3-H(I)], 5.09 [d, *J* 6.5 Hz, 2-H(C)], 5.00 [d, *J* 9.5 Hz, 2-H(F)], 4.94 [d, *J* 7.75 Hz, 2-H(I)], 4.67 [d, *J* ~4.75 Hz, 4-H(C)], 4.56 [d, *J* ~9.5 Hz, 4-H(F)], 3.84, 3.83, 3.81, 3.80 (× 2), 3.78, 3.71, 3.70, and 3.66 (× 2) (each s, 10 × OMe), 3.00 [dd, 4-$H_{eq.}$(I)], 2.66 [dd, 4-$H_{ax.}$(I)], and 1.86, 1.75, and 1.61 [each s, 3 × 3-OAc(C, F, and I)]; *m/z* 1 041 (M^+ − 59, 42%), 1 040 (M^+ − 60, 67), 744 (6.2), 714 (7.1), 713 (1.5), 684 (11.4), 657 (3.5), 656 (5.6), 629 (3.7), 628 (5.1), 492 (5.7), 491 (6.5), 463 (3.5), 449 (3.9), 431 (4.6), 387 (1.3), 357 (2.1), 327 (6.1), 269 (3.2), 222 (5.8), 180 (44), and 151 (100).

Oxidative Dimerization of (+)-*Mesquitol*

(+)-2,3-*trans*-3,3′,4′,7,8-Pentahydroxyflavan (**1**) (1.16 g) was dissolved in a solution of acetonitrile–glycine buffer[11] (3 ml) (1:3 v/v; pH 9) under N_2. A solution of $K_3Fe(CN)_6$ (2.634 g) dissolved in the same buffer (6 ml) at 0 °C was added dropwise during 0.5 h and the mixture was kept under N_2 at ambient temperature for 48 h. After acidification the solution was extracted with EtOAc, and solids recovered from the extract were subjected to column chromatography on Sephadex LH-20 with ethanol as eluant. The fractions were grouped as follows: 1 (tubes 26—30), 2 (31—36), 3 (60—75), 4 (80—94), 5 (95—115), 6 (116—135), 7 (136—150), and 8 (165—225).

Fraction 1 (100.8 mg) consisted of the unchanged flavan-3-ol; fraction 2 (10.1 mg) gave (+)-2,3-*trans*-3′,4′,7,8-tetramethoxydihydroflavonol after methylation; fraction 5 gave a mixture of methyl ethers (110 mg) after methylation. Resolution by p.l.c. in dichloromethane–acetone (87:13 v/v) gave three fractions, at R_F 0.37 (55.4 mg), 0.28 (17.8 mg), and 0.19 (10.3 mg). The products of acetylation of each of the R_F 0.28 and 0.19 methyl ethers gave two products, at R_F 0.33 and 0.27 in benzene–acetone (9:1 v/v).

(2R,3S)-2,3-trans-3-*Acetoxy*-5-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,7,8-*tetramethoxyflavan* (**25**). The octamethyl ether diacetates, R_F 0.33 and 0.27, were interconvertible, giving a single ^{1}H n.m.r. spectrum which differed from those of the [5,8]-biphenyl-type atropisomers (**20**) and (**23**) derived from *P. glandulosa*. The *title compound* was isolated as a solid (Found: M^+, 774.282 72. $C_{42}H_{46}O_{14}$ requires *M*, 774.288 46); δ ($CDCl_3$; 300 MHz; 24 °C) 6.40 [s, 6-H(A or D), 6.29 [s, 6-H(D or A)], 3.905 (× 2), 3.85, 3.845, 3.823, 3.82, 3.797, and 3.767 (each s, 8 × OMe), and 1.95 and 1.96 [each s, 2 × 3-OAc(C and F)]; δ (C_6D_6; 300 MHz; 25 °C)* 7.003 [dd, *J* 2.0 and 8.0 Hz, 6-H(B)], 6.98 [d, *J* 2.0 Hz, 2-H(B)], 6.935 [d, *J* 2.0 Hz, 2-H(E)], 6.87 [dd, *J* 2.0 and 8.5 Hz, 6-H(E)], 6.525 [d, *J* ~8.5 Hz, 5-H(E)], 6.51 [s, 6-H(D or A)], 6.48 [d, *J* 8.0 Hz, 5-H(B)], 6.41 [s, 6-H(A or D)], 5.685 [m, 3-H(C)], 5.48 [m, 3-H(F)], 5.37 [d, *J* 5.5 Hz, 2-H(C)], 5.33 [d, *J* 5.5 Hz, 2-H(F)], 4.00, 3.99, 3.45, 3.42, 3.365, 3.355, 3.32, and 3.31 (each s, 8 × OMe), 2.92 [dd, *J* 4.0 and 16.0 Hz, 4-$H_{eq.}$(C)], 2.75 [dd, *J* 6.2 and 16.0 Hz, 4-$H_{ax.}$(C)], 2.59 [dd, *J* 5.8 and 16.5 Hz, 4-$H_{ax.}$(F)], 2.45 [dd, *J* 4.8 and 16.5 Hz, 4-$H_{eq.}$(F)], 1.615 [s, 3-OAc-(C or F)], and 1.51 [s, 3-OAc(F or C)]; *m/z* 774 (M^+, 29%), 714 (18.7), 655 (10.0), 654 (9.9), 505 (7.0), 503 (5.4), 492 (6.1), 479 (7.0), 343 (4.0), 331 (5.4), 330 (3.8), 301 (4.5), 246 (3.4), 193 (21), 180 (22), 167 (15.7), and 151 (100); c.d. $[\theta]_{200}$ +2 000, $[\theta]_{220}$ +18 800, $[\theta]_{227}$ +28 000, $[\theta]_{240}$ +10 300, $[\theta]_{250}$ +2 300, $[\theta]_{260}$ +2 300, $[\theta]_{270}$ +2 300, $[\theta]_{280}$ 0, $[\theta]_{290}$ −700, and $[\theta]_{300}$ 0.

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,7,8-*tetramethoxyflavan* (**17**). Fraction 7 gave a solid (89.8 mg) after methylation. P.l.c. of the product in n-hexane–acetone–ethyl acetate (50:35:15 v/v)

* The allocations ABC and DEF are obviously interchangeable, but nevertheless indicate intraflavanyl associations of resonances attributable to each unit.

gave two octamethyl ethers, at R_F 0.40 and 0.48. These were acetylated independently and the octamethyl ether diacetates were each separated by p.l.c. in 1,2-dichloroethane–acetone (95:5 v/v) into two products, at R_F 0.31 (1.9 mg) and 0.25 (27.3 mg). In solution they gave identical ^1H n.m.r. spectra, in complete agreement with that of the derivative of the [5,6]-linked natural compound isolated from *P. glandulosa*.

Mutual Condensation of (+)-Mesquitol and (+)-Catechin

(+)-Mesquitol (**1**) (1.16 g) and (+)-catechin (1.16 g) were dissolved in a 1:3 (v/v) acetonitrile–glycine buffer (60 ml) (pH 9) under N_2 as before. A solution of $K_3Fe(CN)_6$ (13.92 g) in the same buffer (80 ml) was added, and the reaction was allowed to proceed at ambient temperature for 2 h, after which the mixture was acidified and extracted with EtOAc (5 × 200 ml). The extractives were resolved on a Sephadex LH-20 column (3.5 × 36.5 cm) with ethanol as eluant. Fractions (15 ml each) were collected and grouped as follows: 6—11 (229 mg), 17—36 (281), 37—45 (194), 46—72 (218), 73—86 (33.7), 87—104 (66.3), 105—147 (177), and 148—187 (237).

Fractions 17—45 were combined and methylated with diazomethane. The methyl ethers (476 mg) were separated by p.l.c. in dichloromethane–acetone–methanol (95:4:1 v/v, × 5) to give two products, at R_F 0.32 (57.1 mg) and 0.28 (75.4 mg). Each methyl ether was acetylated and the products were separated by p.l.c. in n-hexane–acetone–EtOAc (60:25:15 v/v, × 3). The octamethyl ether diacetate, R_F 0.36 (53.3 mg), derived from the former proved to be identical with derivative (**23**) of (*R*)-[5,8]-(+)-mesquitol-(+)-catechin from *P. glandulosa*. the corresponding (*S*)-conformer, R_F 0.32 (75.6 mg) was derived from the latter and proved to be identical with compound (**20**).

Combination of fractions 73—104, followed by methylation, gave a mixture of octamethyl ethers (117.4 mg). These were resolved by p.l.c. in dichloromethane–acetone (8:2 v/v) into two products, at R_F 0.51 (3.4 mg) and 0.40 (13.9 mg). Acetylation of each gave octamethyl ether diacetates, at R_F 0.42 (3.5 mg) and 0.48 (14.1 mg) respectively. The latter proved to be identical with the [5,6]-bi-(+)-mesquitol derivative (**17**).

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-5-*yl*]-3′,4′,5,7-*tetramethoxyflavan* (**24**). The *title compound*, R_F 0.42, was isolated as a solid (Found: M^+, 774.282 72. $C_{43}H_{46}O_{14}$ requires *M*, 774.288 46); δ ($CDCl_3$; 300 MHz; 25 °C) 6.93 [dd, *J* 2.0 and 8.0 Hz, 6-H(B)], 6.89 [d, *J* 2.0 Hz, 2-H(B)], 6.875 [dd, *J* 2.0 and 8.0 Hz, 6-H(E)], 6.855 [d, *J* 2.0 Hz, 2-H(E)], 6.84 [d, *J* 8.0 Hz, 5-H(E)], 6.77 [d, *J* 8.0 Hz, 5-H(B)], 6.475 [s, 6-H(A)], 6.365 [s, 8-H(D)], 5.32 [m, 3-H(F)], 5.26 [quartet, *J* 5.5 Hz, 3-H(C)], 5.23 [d, *J* 5.5 Hz, 2-H(C)], 4.955 [d, *J* 7.8 Hz, 2-H(F)], 3.94, 3.87*, 3.83 (× 2), 3.80, 3.70, and 3.145 (each s, 8 × OMe), 3.00 [dd, *J* 5.5 and 16.0 Hz, 4-$H_{eq.}$(F)], 2.73 [dd, *J* 8.0 and 16.0 Hz, 4-$H_{ax.}$(F)], 2.567 and 2.563 [each d, *J* 5.5 Hz, 4-H_2(C)], and 1.955 and 1.925 [each s, 2 × 3-OAc(C and F)]; *m/z* 774 (M^+, 39%), 714 (25), 552 (5.8), 492 (5.1), 387 (1.3), 330 (2.5), 327 (6.7), 222 (3.6), 180 (38), and 151 (100).

Biflavanoid Synthesis Using 4-Functionalized (+)-Mesquitol Tetramethyl Ether Acetate as Electrophile

A stirred solution of (+)-mesquitol tetramethyl ether (1.038 g, 3 mmol) in pure anhydrous $CHCl_3$ (100 ml) was treated dropwise under N_2 with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.362 g, 6 mmol) in methanol (20 ml). The mixture was stirred for a further 5 h after which time the DDQ was destroyed with $NaBH_4$ (*cf.* ref. 23). Water (200 ml) was added and the solution was extracted with $CHCl_3$ (3 × 50 ml). The solid extractives were acetylated, and the acetates were separated by p.l.c. on 160 plates in n-hexane–acetone–EtOAc (60:25:15 v/v) to give two fractions, at R_F 0.48 (461 mg), 3-*O*-acetyl-3′,4′,7,8-tetra-*O*-methylmesquitol (**2**), and 0.42 (224 mg).

(2R,3S,4S)-3-*Acetoxy*-3′,4,4′,7,8-*pentamethoxyflavan*. The *title product*, R_F 0.42, of 2,3-*trans*-3,4-*cis* configuration, was isolated as a solid, R_F 0.42 (Found: M^+, 418.165 87. $C_{22}H_{26}O_8$ requires M, 418.168 36); δ ($CDCl_3$; 80 MHz; 30 °C) 7.00 [dd, *J* 2.0 and 8.0 Hz, 6-H(B)], 6.94 [overlap, 2-H(B)], 6.91 [d, *J* 8.5 Hz, 5-H(A)], 6.81 [d, *J* 8.5 Hz, 5-H(B)], 6.53 [d, *J* 8.5 Hz, 6-H(A)], 5.37 [s, *J* < 1 Hz, 2-H(C)], 5.34 [d, *J* 2.5 Hz, 3-H(C)], 4.34 [d, *J* 2.5 Hz, 4-H(C)], 3.84 (× 2), 3.81, and 3.79 (each s, 4 × ArO*Me*), 3.42 [s, 4-OMe(C)], and 1.94 [s, 3-OAc(C)].

A solution of the aforementioned 3-acetoxy-3′,4,4′,7,8-pentamethoxyflavan (224 mg, 0.54 mmol) and (+)-catechin (280 mg, 1 mmol) in methanol (10 ml) was treated with M-HCl and the mixture was kept at 45 °C for 5 days. The solution was filtered through Celite, and concentrated, water (100 ml) was added, and the mixture was extracted with EtOAc. After recovery the extractives were methylated and the octamethyl ethers were purified by p.l.c. in 1,2-dichloroethane–acetone (85:15 v/v) to give a single fraction at R_F 0.23 (105.8 mg). After acetylation the octamethyl ether diacetates were separated by p.l.c. in benzene–acetone (9:1 v/v) into two fractions, at R_F 0.24 (69.7 mg) and 0.32 (16.1 mg).

Re-separation of the R_F 0.24 fraction (35 mg) on 20 Merck DC-Fertigplatten Kieselgel 60 F_{254} in benzene–1,2-dichloroethane–acetone (40:55:5 v/v, × 4) gave two compounds, at R_F 0.26 (16.2 mg) and 0.21 (7 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-8-[(2R,3S,4S)-2,3-trans-3,4-trans-3-*acetoxy*-3′,4′,7,8-*tetramethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* (**6**). The octamethyl ether diacetate, R_F 0.26, was isolated as a solid (Found: M^+, 774.282 72. Calc. for $C_{42}H_{46}O_{14}$: *M*, 774.288 46), which proved to be identical with the corresponding derivative of the natural product.

[4,8]-2,3-trans-3,4-cis:2,3-trans *Isomer*. The *isomeric octamethyl ether diacetate*, R_F 0.21, was isolated as a solid (Found: M^+, 774.282 72. $C_{42}H_{46}O_{14}$ requires *M*, 774.288 46); δ ($CDCl_3$; 80 MHz; 95°C) 7.09—6.63 (m, 6 × ArH), 6.50 [br d, *J* 8.5 Hz, 5-H(A)], 6.34 [d, *J* 8.5 Hz, 6-H(A)], 6.19 [s, 6-H(D)], 5.58 [dd, *J* 6.0 and 9.0 Hz, 3-H(C)], 5.33 [d, *J* 9.0 Hz, 2-H(C)], 3.84 (× 4), 3.79 (× 3), and 3.78 (each s, 8 × OMe), 1.91 [s, 3-OAc(F)], and 1.78 [s, 3-OAc(C)] (other resonances could not be distinguished due to base-line noise).

Re-separation of the R_F 0.32 fraction on 8 Merck DC-Fertigplatten Kieselgel 60 F_{254} in benzene–acetone–methanol (84:14:2 v/v, × 3) gave two products, at R_F 0.31 (4 mg) and 0.28 (7.1 mg).

[4,6]-2,3-trans-3,4-trans:2,3-trans *Isomer*. The *octamethyl ether diacetate*, R_F 0.28, was isolated as a solid (Found: M^+, 774.282 72); δ ($CDCl_3$; 80 MHz; 95°C) 7.19—6.81 (m, 6 × ArH), 6.44 [s, 5-H(A) + 6-H(A)], 6.33 [s, 8-H(D)], 5.99 [t, Σ*J* 19.0 Hz, 3-H(C)], 5.37 [m, 3-H(F)], 4.98 [d, *J* 7.25 Hz, 2-H(F)], 4.94 [d, *J* 9.5 Hz, 2-H(C)], 4.83 [d, *J* 9.5 Hz, 4-(H(C)], 4.03 (× 2), 3.84 (× 2), 3.83, 3.80 (× 2), and 3.61 (each s, 8 × OMe), 3.19 [dd, *J* 5.25 and 16.0 Hz, 4-$H_{eq.}$(F)], 2.80 [dd, *J* 7.8 and 16.0 Hz, 4-$H_{ax.}$(F)], 1.93 [s, 3-OAc(F)], and 1.66 [s, 3-OAc(C)].

[4,6]-2,3-trans-3,4-cis:2,3-trans *Isomer*. The octamethyl ether diacetate, R_F 0.31, was isolated as a solid (Found: M^+, 774.282 72); δ ($CDCl_3$; 80 MHz; 95 °C) 7.09—6.75 (m, 6 × ArH), 6.59 [br d, *J* 8.0 Hz, 5-H(A)], 6.44 [d, *J* 8.0 Hz, 6-H(A)], 6.34 [s, 8-H(D)], 5.56 [dd, Σ*J* 15.0 Hz, 3-H(C)], 5.41 [m, 3-H(F)], 5.35 [d, *J* ~6.25 Hz, 2-H(F)], 5.32 [d, *J* 8.5 Hz, 2-H(C)], 5.08 [br d, *J* 6.25 Hz, 4-H(C)], 3.94, 3.87 (× 3), and 3.84 (× 4) (each s, 8 × OMe), 3.22—2.72 [m, 4-H_2(F)], 2.00 [s, 3-OAc(F)], and 1.75 [s, 3-OAc(C)].

Mass fragmentation spectra of the above compounds in the sequence [4,8]-3,4-*trans*, [4,8]-3,4-*cis*, [4,6]-3,4-*trans*, and [4,6]-3,4-*cis* are: *m/z* 774 (M^+, 24, 40, 7.9, 32%), 715 (42, 12.3, 60, 18.9), 714 (100, 35, 100, 34), 655 (19.4, 9.2, 4.1, 0.9), 654 (42, 12.4, 11.9,

* Two signals are observed.

3.0), 623 (21, 5.2, 4.8, 1.6), 552 (1.7, 8.7, 1.3, 1.9), 537 (5.3, 52, 4.5, 58), 521 (39, 85, 40, 100), 493 (21, 24, 7.5, 5.2), 492 (35, 48, 6.0, 4.4), 477 (23, 11.9, 40, 4.9), 461 (13.4, 6.3, 14.2, 5.7), 387 (0.7, 3.0, 1.5, 2.6), 343 (8.9, 89, 16.3, 17.1), 331 (5.5, 6.7, 0.9, 4.0), 330 (3.2, 1.8, 1.1, 1.7), 328 (4.9, 9.2, 5.7, 7.4), 327 (23, 20, 21, 16.9), 301 (12.6, 16.6, 5.4, 9.4), 300 (17.3, 19.6, 12.8, 11.3), 299 (85, 88, 60, 76), 222 (5.5, 4.2, 2.1, 6.3), 180 (42, 44, 54, 51), and 151 (99, 100, 96, 99).

Self-Condensation of 3,3′,4′,7,8-Pentahydroxyflavan with Ring Fission

The flavan-3-ol (**1**) (1.16 g) was dissolved in dioxane–2M-HCl (3 ml) 1 : 4 v/v) and the solution was kept at ambient temperature under N_2 for 24 h (*cf.* ref. 13). The acidic solution was neutralized with excess of aqueous sodium hydrogencarbonate, and was then repeatedly extracted with EtOAc (3 × 100 ml). The extracted product was methylated, and the tetramethyl ether of the unchanged flavan (874 mg) was partly removed by crystallization from ethanol. The remainder was resolved by p.l.c. in n-hexane–acetone–EtOAc (50:35:15 v/v, ×3) to give two products of condensation, at R_F 0.33 (15.8 mg) and 0.22 (33.8 mg). Independent acetylation followed by p.l.c. in n-hexane–acetone–EtOAc (60:20:15 v/v, ×2) gave the respective methyl ether acetates, at R_F 0.31 (5.9 mg) and 0.24 (20.3 mg).

(2R,3S)-2,3-trans-3-*Acetoxy*-6-[(1S,2R)-2-*acetoxy*-1-(3,4-*dimethoxyphenyl*)-3-(2,3,4-*trimethoxyphenyl*)*propyl*]-3′,4′,7,8-*tetramethoxyflavan* (**15**). This compound, R_F 0.24, isolated as a solid, gave ^{1}H n.m.r. (300 MHz; $CDCl_3$; 25 °C) and mass fragmentation spectra identical with those of its natural counterpart (**15**).

The R_F 0.31 methyl ether acetate proved to be the decamethyl ether acetate (**14**) of the same condensation product in which 3-OMe replaced 3-OAc, δ ($CDCl_3$; 300 MHz; 25 °C) 7.02 [br s, 5-H(D)], 6.91—6.84 [m, 4 × H, 2-H and 6-H (B and E)], 6.82 [d, *J* 8.5 Hz, 5-H(A)], 6.79, 6.76 [each d, *J* 8.0 Hz, 5-H (B and E)], 6.545 [d, *J* 8.5 Hz, 6-H(A)], 5.29 [m, 3-H(F)], 5.10 [d, *J* 6.5 Hz, 2-H(F)], 4.34 [d, *J* 7.8 Hz, 1-H], 3.995 (m, 2-H), 3.855, 3.845 (×3), 3.820, 3.805, 3.780 (×2), and 3.700 (each s, 9 × ArO*Me*), 3.01, 2,.85, 2.77, 2,.58 [each dd, 3-H_2 and 4-H_2 (F)], 2.930 (s, 3-OMe), and 1.930 [s, 3-OAc(F)].

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References

1 H. D. Locksley, *Fortschr. Chem. Org. Naturst.*, 1973, **30**, 207.
2 K. Weinges, W. Bähr, W. Ebert, K. Göritz, and H.-D. Marx, *Fortschr. Chem. Org. Naturst.*, 1969, **27**, 158.
3 L. Vuatez and H. Brandenberger, *J. Chromatogr.*, 1961, **5**, 17.
4 B.-Z. Ahn and F. G. Stirner, *Arch. Pharm. (Weinheim, Ger.)*, 1971, **304**, 666.
5 B.-Z. Ahn, *Arch. Pharm. (Weinheim, Ger.)*, 1974, **307**, 186.
6 E. Jacobs, D. Ferreira, and D. G. Roux, *Tetrahedron Lett.*, 1983, **24**, 4627.
7 G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.*, 1981, **28**, 3145.
8 E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 177.
9 G. Aulin-Erdtman and R. Sanden, *Acta Chem. Scand.*, 1963, **17**, 1991.
10 P. L. Sorensen, *Biochem. Z.*, 1909, **21**, 131; 1909, **22**, 352.
11 H. K. L. Hundt and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1227.
12 D. R. Armstrong, C. Cameron, D. C. Nonhebel, and P. G. Perkins, *J. Chem. Soc., Perkin Trans. 2*, 1983, 563, 575, 581.
13 A. Makriyannis and S. Fesik, *J. Am. Chem. Soc.*, 1982, **104**, 6462.
14 K. Freudenberg and K. Weinges, *Justus Liebigs Ann. Chem.*, 1963, **668**, 92; K. Freudenberg and J. M. Alonso de Lama, *ibid.*, 1958, **612**, 78.
15 J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1220.
16 J. J. Botha, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1235.
17 J. Dale, *Acta Chem. Scand.*, 1957, **11**, 650.
18 D. Buza and W. Polaczkowa, *Tetrahedron*, 1965, **21**, 3407.
19 K. Mislow, E. Brunnenberg, K. Records, K. Wellman, and C. Djerassi, *J. Am. Chem. Soc.*, 1963, **85**, 1342.
20 J. R. Platt, *J. Chem. Phys.*, 1949, **17**, 484.
21 N. Harada and K. Nakanishi, 'Circular Dichroic Spectroscopy. Exciton Coupling in Organic Chemistry,' Oxford University Press, Oxford, 1983, pp. 195—200.
22 T. G. Stone and W. A. Waters, *J. Chem. Soc.*, 1964, 213.
23 J. A. Steenkamp, D. Ferreira, and D. G. Roux, *Tetrahedron Lett.*, 1985, **26**, 3045.
24 D. G. Roux, *J. Am. Leather Chem. Assoc.*, 1958, **53**, 384.
25 W. Pigman, E. Anderson, R. Fischer, M. A. Buchanan, and B. L. Browning, *Trans. Paper Pulp Inst.*, 1953, **36**, 4 (*Chem. Abstr.* 1953, **47**, 108446).

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