Synthesis of Condensed Tannins. Part 1. Stereoselective and Stereospecific Syntheses of Optically Pure 4-Arylflavan-3-ols, and Assessment of their Absolute Stereochemistry at C-4 by means of Circular Dichroism

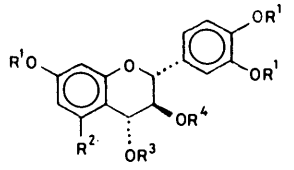
By **Jacobus J. Botha, Desmond A. Young, Daneel Ferreira,** and **David G. Roux,*** Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 Republic of South Africa

Stereoselective and also stereospecific condensation at C-4 of flavan-3,4-diols of known absolute configuration with phloroglucinol and resorcinol in acid medium proceeds at ambient temperatures with partial retention of configuration for 2,3-*trans*-isomers and with inversion for 2,3-*cis*-analogues. Circular dichroism spectra of the resultant 4-arylflavan-3-ols all exhibit multiple Cotton effects. The sign of high intensity Cotton effects to low wavelength, contributed by aryl chromophores at C-4, may almost invariably be correlated with the absolute configuration at this chiral centre of 2,3-*trans*-3,4-*trans*, 2,3-*trans*-3,4-*cis*-, and 2,3-*cis*-3,4-*trans*-isomers.

ALTHOUGH the chemistry of condensed tannins flourished in the late sixties, progress in this field was severely hampered by several factors, mainly the lack of a universal method of both synthesis and of assessing the absolute stereochemistry at C-4, *i.e.* the point of the interflavan linkage. We have recently, however, overcome these by development of a general synthetic method based upon the generation of 4-carbo-cations from flavan-3,4-diols of known absolute configuration followed by their stereoselective substitution by the strongly nucleophilic rings of phloroglucinol and resorcinol,[1] flavan-3-ols,[2] and biflavanoids,[3] to form 4-arylflavan-3-ols, biflavonoids, and triflavanoids respectively. Multiple high-intensity Cotton effects in the low wavelength region of the c.d. spectra of these 4-arylated flavan-3-ols, contributed by aryl chromophores at C-4, led to the formulation of a general chiroptical rule which permits unambiguous assignment of absolute configuration at these chiral centres for the first time.[1-3] The general applicability of this c.d. method was confirmed by Haslam and his collaborators [4] with respect to procyanidins. We now record our more detailed results of relevance to 4-arylflavan-3-ols.

RESULTS AND DISCUSSION

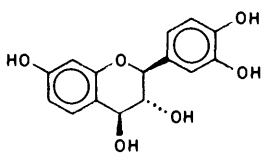
Mild acid-catalysed (0.1M HCl) stereoselective condensation [1,5] of both (+)- and (−)-leucofisetinidin (1; 2*R*,3*S*,4*R*) and (4; 2*S*,3*R*,4*S*) [6] with phloroglucinol



(1) $R^1 = R^2 = R^3 = R^4 = H$

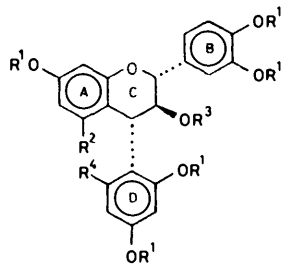
(2) $R^1 = R^3 = R^4 = H$; $R^2 = OH$

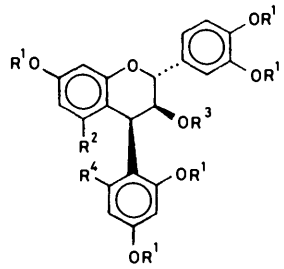
(3) $R^1 = R^3 = Me$; $R^2 = OMe$; $R^4 = Ac$



(4)

(eight-fold molar excess) at ambient temperature smoothly gave free phenolic 2,3-*trans*-3,4-*trans*-4-arylflavan-3-ols (5; 2*R*,3*S*,4*S*) and (35; 2*S*,3*R*,4*R*) and their 2,3-*trans*-3,4-*cis*-isomers (20; 2*R*,3*S*,4*R*) and (41; 2*S*,3*R*,4*S*) in *ca.* 2 : 1 ratio in each instance as sole products (*ca.* 83% overall yield). Similar reaction with resorcinol also proceeded stereoselectively affording both





(5) $R^1 = R^2 = R^3 = H$; $R^4 = OH$ (20)

(6) $R^1 = Me$; $R^2 = R^3 = H$; $R^4 = OMe$ (21)

(7) $R^1 = Me$; $R^2 = H$; $R^3 = Ac$; $R^4 = OMe$ (22)

(8) $R^1 = R^2 = R^3 = R^4 = H$ (23)

(9) $R^1 = Me$; $R^2 = R^3 = R^4 = H$ (24)

(10) $R^1 = R^3 = Me$; $R^2 = R^4 = H$ (25)

(11) $R^1 = Me$; $R^2 = R^4 = H$; $R^3 = Ac$ (26)

(12) $R^1 = R^3 = H$; $R^2 = R^4 = OH$ (27)

(13) $R^1 = R^3 = Me$; $R^2 = R^4 = OMe$ (28)

(14) $R^1 = Me$; $R^2 = R^4 = OMe$; $R^3 = H$ (29)

(15) $R^1 = Me$; $R^2 = R^4 = OMe$; $R^3 = Ac$ (30)

(16) $R^1 = R^3 = R^4 = H$; $R^2 = OH$; (31)

(17) $R^1 = R^3 = Me$; $R^2 = OMe$; $R^4 = H$ (32)

(18) $R^1 = Me$; $R^2 = OMe$; $R^3 = R^4 = H$; (33)

(19) $R^1 = Me$; $R^2 = OMe$; $R^3 = Ac$; $R^4 = H$ (34)

the 2,3-*trans*-3,4-*trans*- (8; 2*R*,3*S*,4*R*) and (38; 2*S*,3*R*,4*S*) and 2,3-*trans*-3,4-*cis*- (23; 2*R*,3*S*,4*S*) and (44; 2*S*,3*R*,4*R*) analogues in good yields (*ca.* 60%). (+)-Leucocyanidin (2; 2*R*,3*S*,4*R* or *S*) [obtained by reduction of (+)-taxifolin (55; 2*R*,3*R*) with sodium borohydride] † similarly gives the 3,4-*trans*- (12 and 16; 2*R*,3*S*,4*R*) and 3,4-*cis*- (27 and 31; 2*R*,3*S*,4*S*) analogues

† The product of $NaBH_4$ reduction of (+)-taxifolin and subsequent methylation is the 3′,4,4′,5,7-pentamethyl ether of leucocyanidin with undefined stereochemistry at C-4 (see Experimental section).

with phloroglucinol and resorcinol, respectively, albeit with greater difficulty under the same conditions [27.2, 26, and 4.8, 4% yields respectively, based on (+)-taxifolin]. The latter isomers (16) and (31) could be obtained in pure form as their hexamethyl ethers [(18) and (33)] only.

By contrast the carbo-cation formed under identical conditions from the 2,3-*cis*-3,4-*cis*-flavan-3,4-diol, (−)-teracacidin (47; 2*R*,3*R*,4*R*),[7] is captured stereospecifically by both phloroglucinol and resorcinol to form the 2,3-*cis*-3,4-*trans*-4-arylflavan-3-ol analogues (49; 2*R*,3*R*,4*R*) and (52; 2*R*,3*R*,4*S*) exclusively, and with inversion of configuration. The conditions chosen are such that these acid-catalysed couplings invariably occur without the competing anthocyanidin formation from self-condensation.

The above free phenolic 4-arylflavan-3-ols were characterized by methylation with diazomethane * and the resultant methyl ethers acetylated to give their 3-acetates.† ^{1}H N.m.r. coupling constants of the heterocyclic protons vary considerably (*cf.* Table) but are, with exceptions, consistent with the relative stereochemistry for 2,3-*trans*-3,4-*trans*- ($J_{2,3}$ 9.0—10.6; $J_{3,4}$ 7.5—9.4 Hz) and 2,3-*trans*-3,4-*cis*- ($J_{2,3}$ 8.0—10.0; $J_{3,4}$ 5.0—6.5 Hz) analogues (*cf.* refs. 8 and 9). The 2,3-*cis*-3,4-*trans*-isomers ($J_{2,3}$ 1.0—2.4; $J_{3,4}$ 1.9—4.0 Hz) are distinguished from their 3,4-*cis*-counterparts by extensive secondary couplings of 2-H and 4-H with aromatic protons, characteristic of 2,3-*cis*-3,4-*trans*-flavan-3,4-diols,[8,9] and by strong interaction between the 2-axial proton and 4-quasi-axial phenyl groups. The latter is reflected in the downfield position of 2-H relative to 4-H, as observed for flavan-3,4-diols.[8]

The observed orientation of the 4-aryl group in the series of 4-arylflavan-3-ols, *i.e.* reaction proceeding with partial retention of configuration at C-4 for both phloroglucinol and resorcinol in the case of the 2,3-*trans*-flavan-3,4-diols, but with selective inversion at C-4 for the 2,3-*cis*-flavan-3,4-diol, indicates that the stereochemical course of coupling is controlled primarily by the 2,3-

Correlations of coupling constants (^{1}H n.m.r.) and the sign of the low-wavelength Cotton effects (c.d.) with the relative and absolute stereochemistry, respectively, of (2*R*)- and (2*S*)-4-arylflavan-3-ols

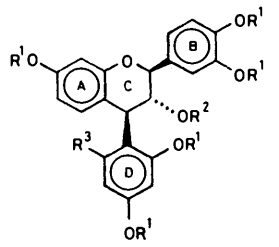
	$J_{2,3}$/Hz	$J_{3,4}$/Hz	Sign of Cotton effect at 230 nm	Position of 4-aryl function [a]
(2*R*)-4-Arylflavan-3-ols				
(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans* (5)				
3-OH-3′,4′,7;2,4,6-(OMe)$_6$ (6)	10.6	7.5	−	Below
3-OAc-3′,4′,7;2,4,6-(OMe)$_6$ (7)	10.0	9.8		
(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans* (8)				
3,3′,4′,7;2,4-(OMe)$_6$ (10)	9.4	9.4		
3-OH-3′,4′,7;2,4-(OMe)$_5$ (9)	9.4	9.4		
3-OAc-3′,4′,7;2,4-(OMe)$_5$ (11)	10.0	9.0	−	Below
(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis* (23)				
3,3′,4′,7;2,4-(OMe)$_6$ (25)	8.1	5.6		
3-OH-3′,4′,7;2,4-(OMe)$_5$ (24)	8.8	5.0		
3-OAc-3′,4′,7;2,4-(OMe)$_5$ (26)	8.0	5.0	+	Above
(2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*trans* (49)				
3-OH-4′,7,8;2,4,6-(OMe)$_6$ (50)	2.4	4.0		
3-OAc-4′,7,8;2,4,6-(OMe)$_6$ (51)	1.0	3.8	+	Above
(2*R*,3*R*,4*S*)-2,3-*cis*-3,4-*trans* (52)				
3-OH-4′,7,8;2,4-(OMe)$_5$ (53)	1.0	2.1		
3-OAc-4′,7,8;2,4-(OMe)$_5$ (54)	1.0	1.9	+	Above
(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans* (12)				
3,3′,4′,5,7;2,4,6-(OMe)$_8$ (13)	9.3	7.5		
3-OH-3′,4′,5,7;2,4,6-(OMe)$_7$ (14)	9.0	8.3		
3-OAc-3′,4′,5,7;2,4,6-(OMe)$_7$ (15)	10.0	8.5	−	Below
(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans* (16)				
3,3′,4′,5,7;2,4-(OMe)$_7$ (17)	6.8	5.5		
3-OH-3′,4′,5,7;2,4-(OMe)$_6$ (18)	9.0	7.5		
3-OAc-3′,4′,5,7;2,4-(OMe)$_6$ (19)	6.5	5.5	+	Unknown [b]
(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis* (31)				
3-OH-3′,4′,5,7;2,4-(OMe)$_6$ (33)	10.0	5.5		
3-OAc-3′,4′,5,7;2,4-(OMe)$_6$ (34)	10.0	5.8	+	Above
(2*S*)-4-Arylflavan-3-ols [c]				
(2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*trans* (35)				
3-OAc-3′,4′,7;2,4,6-(OMe)$_6$ (37)	10.0	9.8	+	Above
(2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans* (38)				
3-OAc-3′,4′,7;2,4-(OMe)$_5$ (40)	10.0	9.0	+	Above
(2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*cis* (44)				
3-OAc-3′,4′,7;2,4-(OMe)$_5$ (46)	8.0	5.0	−	Below

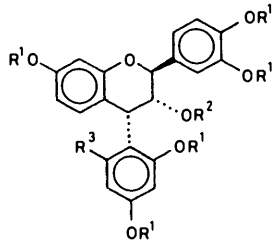
[a] Relative to the plane of ring A as in formulae (5)—(46) and (49)—(54) with the A-ring positioned to the left. [b] *Cf.* ref. 15. [c] Enantiomers of (5), (8), and (23), respectively.

* This also gave low yields of full C-3 *O*-methyl ethers [(10, (13), (17), and (25)] as side-reactions.

† Magnetic non-equivalence of H-3 and H-5 of the phloroglucinol D-rings of the 2,3-*trans*-3,4-*trans*-analogues (7) and (15) at ambient temperatures is due to chirality at C-4 coupled with restricted rotation, as evidenced by their coalescence at higher temperatures.

stereochemistry of the flavan-3,4-diol.* These phenomena may be rationalised on the plausible premise [1] that the heterocycles of the carbo-cations resulting from both (1) and (47) [(56) and (57), respectively] possess a





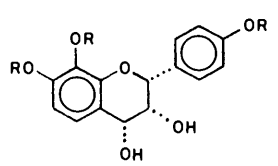
(35) $R^1=R^2=H$; $R^3=OH$
(36) $R^1=Me$; $R^2=H$; $R^3=OMe$
(37) $R^1=Me$; $R^2=Ac$; $R^3=OMe$
(38) $R^1=R^2=R^3=H$
(39) $R^1=Me$; $R^2=R^3=H$
(40) $R^1=Me$; $R^2=Ac$; $R^3=H$

(41)
(42)
(43)
(44)
(45)
(46)

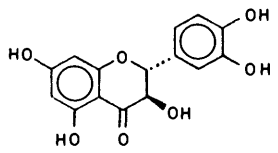
preferred sofa conformation similar to that established for 3-hydroxyflavanones.[9] Whereas nucleophilic attack on the 2,3-*cis*-carbo-cation (57; *axial* 3-OH) will occur preferentially from the less hindered ' upper ' face with contributory neighbouring group participation (inversion of configuration), the equatorial 3-OH in the 2,3-*trans*-carbo-cation (56) will exercise a limited degree of steric control. Unfavourable 1,3-diaxial interaction between the nucleophile and axial 2-H will, therefore, permit high net retention of configuration at C-4 in the latter instance.

The mild reaction conditions and work-up procedures are unlikely to permit conversion of the 3,4-*trans*-4-arylflavan-3-ols to the thermodynamically more stable 3,4-*cis*-analogues; a premise confirmed by the stability of the former under the appropriate reaction conditions (0.1M HCl; 20 °C; 2 h) used for condensation, and also over extended periods (48 h). The course of reaction leading to 4-arylflavan-3-ols is thus presumably kinetically controlled. This contrasts with the proposal of thermodynamic control by Haslam *et al.*[13] during synthesis of 4-arylflavan-3-ols of the cyanidin type [*e.g.* (12)] by means of acid-catalysed (HOAc) toluene-α-thiol degradation of natural procyanidins at elevated temperature (reflux) and prolonged reaction time (24 h). Since flavan-3,4-diols invariably accompany condensed tannins of the profisetinidin type, we suggest that the above mechanism also predicts the absolute stereochemistry at C-4 of those 2,3-*trans*- and 2,3-*cis*-flavan-3-ol units which constitute the natural condensed tannins.

Comparison of the c.d. spectra of the methyl ether 3-*O*-acetates of the 2,3-*trans*-3,4-*trans*- (11) and 2,3-*trans*-3,4-*cis*- (26) 4-arylflavan-3-ols (both 2*R*,3*S*) along with that of (2*R*,3*S*)-3-*O*-acetyl-3',4,7-tri-*O*-methyl-(−)-fisetinidol (58) indicates [1] that Cotton effects due to chirality at C-2 and C-3 are completely dominated by the multiple effects of the two phenyl chromophores at C-4, introduced with 4-arylation. Reversal of the sign of the high-amplitude (220—240 nm) Cotton effects occurs with inversion at C-4, a strong positive effect correlating with 4*S*, and strongly negative with 4*R*, *as defined for the* 4-(2,4-*dihydroxyphenyl*) *substituent*. This correlation, *i.e.* a positive Cotton effect indicating a quasi-axial (extending above the plane of the fused A-ring) C-4-aryl substituent and negative one indicating a



(47) R = H
(48) R = Me



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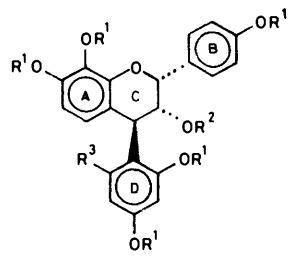
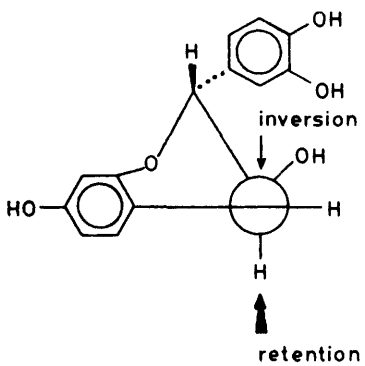


(49) $R^1=R^2=H$; $R^3=OH$
(50) $R^1=Me$; $R^2=H$; $R^3=OMe$
(51) $R^1=Me$; $R^2=Ac$; $R^3=OMe$
(52) $R^1=R^2=R^3=H$
(53) $R^1=Me$; $R^2=R^3=H$
(54) $R^1=Me$; $R^2=Ac$; $R^3=H$



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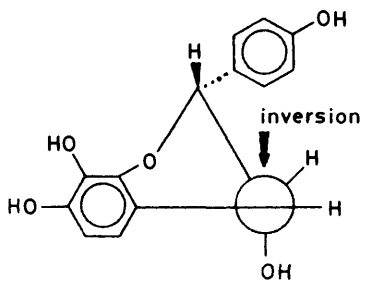
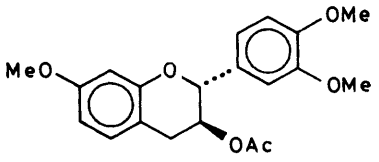


(57)

* Similar observations as regards solvolysis of 2,3-*cis*-flavan-3,4-diols *via* an S_N1 mechanism have been recorded.[10-13]

quasi-equatorial (extending below the plane of the A-ring) (*cf.* Table) C-4-aryl group also applies to the corresponding 2,3-*cis*-4-arylflavan-3-ol derivatives (51) and (54) (both 2*R*,3*R*) where the multiple high-amplitude



(58)

positive Cotton effect in the low-wavelength region is indicative of a quasi-axial orientation of the 4-aryl group. A similar relationship also exists for the 2,3-*trans*-3,4-*trans*- (7) and (15) (both 2*R*,3*S*) and (37) and (40) (both 2*S*,3*R*) and 2,3-*trans*-3,4-*cis*- (26) and (34) (both 2*R*,3*S*) and (46; 2*S*,3*R*) 4-arylflavan-3-ols. Since the sign of the Cotton effect gives a direct indication of the orientation and thus absolute stereochemistry at C-4, this chiroptical method apparently provides an unambiguous and direct criterion for determination of the absolute configuration at the point of junction of the 4-aryl and thence also flavanyl [2] and biflavanyl [3] moieties to the 'upper' unit. Our original basic findings [1-3] in this respect have been confirmed by Haslam *et al.*[4] for natural procyanidins, and is preferred to their previous indirect method based on ^{13}C n.m.r. chemical-shift differences.[14]

However, c.d. data for the methyl ether 3-*O*-acetate (19) of the 2,3-*trans*-3,4-*trans*-4-(2,4-dihydroxyphenyl)-5-hydroxyflavan-3-ol (16) where non-bonding steric interactions [8] lead to 'abnormal' coupling constants ($J_{2,3}$ 6.5 and $J_{3,4}$ 5.5 Hz) as well as for 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols, now available *via* photolysis of the 4-arylflavan-3-ols (5) and (49) (*cf.* Part 2), are not consistent with the above criteria. These discrepancies probably result from deviations from the anticipated heterocyclic half-chair conformation, as detailed in the accompanying paper.[15] Knowledge of the C-ring conformation is, therefore, a prerequisite for unequivocal assessment of absolute stereochemistry at C-4 by means of circular dichroism.

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus and are uncorrected. ^1H N.m.r. spectra were recorded on a Bruker WP-80 Fourier-transform spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard, mass spectral data on a Varian CH-5 instrument, and circular dichroism data on a Jasco J-20 spectropolarimeter. Analyses (C and H) were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, Germany. T.l.c. was performed on DC-Plastikfolin Kieselgel 60 F_{254} (0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40 : 1) after development. Preparative plates [Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether at −15 °C for 48 h, while acetylations were carried out with acetic anhydride–pyridine. Evaporations were performed under reduced pressure at 50 °C.

General Condensation and Work-up Procedures.—The flavan-3,4-diol (*ca.* 0.002 mol) and phenolic unit (*ca.* 0.016 mol) were dissolved in 0.1M HCl (250 ml) and the mixture stirred at room temperature (20—25 °C). After addition of water (250 ml) the mixture was extracted with ethyl acetate (4 × 150 ml) and the combined extracts dried (Na_2SO_4). Evaporation of the solvent followed by p.l.c. separation [benzene–acetone–methanol (6 : 3 : 1)] afforded the free phenolic 4-arylflavan-3-ols.

(2R,3S,4R)-*Flavan*-3,3′,4,4′,7-*pentaol–Phloroglucinol Condensation.*—Coupling of compound (1) (435 mg) with phloroglucinol (1.512 g) for 2 h gave (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-4-(2,4,6-trihydroxyphenyl)flavan-3,3′,4′,7-*tetraol* (5) [321 mg (53%), R_F 0.42] as a light-brown amorphous solid, in addition to the (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*cis*-isomer (20) (R_F 0.48) mixed with unchanged compound (1).

Methylation of the 4-arylflavan-3-ol (5) (100 mg) followed by p.l.c. separation [hexane–benzene–acetone (5 : 4 : 1)] gave the *hexamethyl ether* (6) (70 mg, R_F 0.21) as a colourless solid (Found: M^+, 482.533. $C_{27}H_{30}O_8$ requires M, 482.535); δ 7.19—6.12 (m, 8 H, aromatic), 4.81 (d, 2-H, $J_{2,3}$ 10.6 Hz), 4.80 (d, 4-H, $J_{3,4}$ 7.5 Hz), 4.45 (dd, 3-H, J 7.5 and 10.6 Hz), 3.93, 3.90, 3.82, 3.75, and 3.50 (all s, 6 × OMe), and 1.70 (s, 3-OH).

(2R,3S,4S)-2,3-trans-3,4-trans-3-*Acetoxy*-3′,4′,7-*trimethoxy*-4-(2,4,6-*trimethoxyphenyl*)*flavan* (7).—Acetylation of the hexamethyl ether (6) (50 mg) afforded the *monoacetate* (48 mg) as a white amorphous solid (Found: C, 66.4; H, 6.2. $C_{29}H_{32}O_9$ requires C, 66.4; H, 6.1%); *m/e* 464 (M^+ − 60, 100%), 449 (15.4), 434 (17.0), 433 (52), 327 (13.9), 315 (16.0), 297 (20), 287 (11.9), 272 (15.1), 271 (72), 256 (11.8), 232 (17.4), 180 (17.6), 167 (12.1), 165 (17.7), 151 (49), 137 (14.1), and 121 (16.1); δ 7.09—6.25 [m, 2- + 5- + 6-H (B), 5- + 6- + 8-H (A)], 6.07 [s, 3- + 5-H (D)], 6.02 (t, 3-H, J 9.8 and 10.0 Hz), 4.90 (d, 2-H, J 10.0 Hz), 4.85 (d, 4-H, $J_{3,4}$ 9.8 Hz), 3.86, 3.84, 3.74, 3.69, and 3.60 (all s, 6 × OMe), and 1.57 (s, 3-OAc); c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{282}$ −1 758, $[\theta]_{277}$ 0, $[\theta]_{265}$ +9 090, $[\theta]_{248}$ 0, $[\theta]_{231}$ −46 667, $[\theta]_{218}$ 0.

(2R,3S,4R)-2,3-trans-3,4-cis-3-*Acetoxy*-3′,4′,7-*trimethoxy*-4-(2,4,6-*trimethoxyphenyl*)*flavan* (20).—Methylation of the R_F 0.48 band followed by p.l.c. separation [benzene–acetone (8 : 2)] gave the hexamethyl ether (21) (R_F 0.58]), and hence the acetate (22) [24 mg, R_F 0.32 in benzene–acetone (19 : 1)], identical to the synthetic isomer derived from condensation [15] of (+)-3′,4′,7-tri-*O*-methylleucofisetinidin with tri-*O*-methylphloroglucinol and subsequent acetylation (*cf.* Part 2).[15]

(2S,3R,4S)-*Flavan*-3,3′,4,4′,7-*pentaol–Phloroglucinol Condensation.*—Coupling of phloroglucinol to compound (4) as described above afforded the (2S,3R,4R)-2,3-*trans*-3,4-*trans*-4-(2,4,6-trihydroxyphenyl)flavan-3,3′,4′,7-tetraol (35) (55%) as a light-brown solid. Its methyl ether (36), a colourless solid, and the *methyl ether* 3-O-*acetate* (37), a white solid (Found: C, 66.3; H, 6.2. $C_{29}H_{32}O_9$ requires C, 66.4; H, 6.1%), display identical m.s.-fragmentation and n.m.r. spectra to those observed for the (2*R*,3*S*,4*R*)-flavan-3,3′,4,4′,7-pentaol analogues, while the c.d. spectrum (in MeOH) of the monoacetate (37), $[\theta]_{293}$ 0, $[\theta]_{280}$ +3 526, $[\theta]_{276}$ 0, $[\theta]_{265}$ −7 053, $[\theta]_{249}$ 0, $[\theta]_{233}$ +44 842, and $[\theta]_{223}$ 0, shows the anticipated mirror-image relationship relative to the enantiomer (7).

The 2,3-*trans*-3,4-*cis*-isomer (41) or its derivatives (42) and (43) were not isolated.

(2R,3S,4R)-*Flavan*-3,3',4,4',7-*pentaol–Resorcinol Condensation*.—Reaction of compound (1) (300 mg) with resorcinol (912 mg) for 2 h afforded two bands, R_F 0.35 (87 mg, 22%) and 0.27 (153 mg, 38%).

(*a*) The R_F 0.35 band gave (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4-dihydroxyphenyl)flavan-3,3',4',7-tetraol (23) as a light-brown solid. Methylation of the 4-arylflavan-3-ol (23) (50 mg) followed by p.l.c. separation [hexane–benzene–acetone (5 : 4 : 1)] afforded two bands, R_F 0.26 (4 mg), and 0.19 (24 mg). The former fraction gave the *hexamethyl ether* (25) as a colourless amorphous solid (Found: M^+, 466.535. $C_{27}H_{30}O_7$ requires M, 466.536); δ 6.73—6.26 (m, 9 H, aromatic), 4.99 (d, 2-H, $J_{2,3}$ 8.1 Hz), 4.73 (d, 4-H, $J_{3,4}$ 5.6 Hz), and 3.11 (s, 3-OH).

The R_F 0.19 fraction afforded the *pentamethyl ether* (24) as a white solid (Found: M^+, 452.510. $C_{26}H_{28}O_7$ requires M, 452.509); δ 7.01—6.33 (m, 9 H, aromatic), 4.89 (d, 2-H, $J_{2,3}$ 8.8 Hz), 4.75 (d, 4-H, $J_{3,4}$ 5.0 Hz), 4.35 (dd, 3-H, J 5.0 and 8.8 Hz), 3.84 (9 H), 3.78, and 3.76 (all s, 5 × OMe), and 3.01 (s, 3-OH). Acetylation of the pentamethyl ether (24) (20 mg) gave (2R,3S,4S)-2,3-trans-3,4-cis-3-*acetoxy*-3',4',7-*trimethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan* (26) (18 mg) as a colourless solid (Found: C, 67.8; H, 6.0. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%); *m/e* 494 (M^+, 26%), 435 (22), 434 (75), 403 (11.8), 297 (21), 287 (38), 286 (12.6), 285 (34), 273 (6.7), 272 (2.5), 271 (8.1), 257 (10.7), 242 (32), 241 (100), 222 (9.0), 180 (55), 165 (13.1), 151 (42), 137 (14.8), and 121 (10.9); δ 6.94—6.28 (m, 9 H, aromatic), 5.53 (dd, 3-H, J 8.0 and 5.0 Hz), 5.13 (d, 2-H, $J_{2,3}$ 8.0 Hz), 4.82 (d, 4-H, $J_{3,4}$ 5.0 Hz), 3.82, 3.81, 3.77 (6 H), and 3.73 (all s, 5 × OMe), and 1.64 (s, 3-OAc); c.d. (MeOH) $[\theta]_{300}$ 0, $[\theta]_{287}$ −3 030, $[\theta]_{280}$ −1 151, $[\theta]_{267}$ −3 333, $[\theta]_{249}$ 0, $[\theta]_{232}$ +49 769, and $[\theta]_{217}$ +7 373.

(*b*) The R_F 0.27 band afforded (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-(2,4-dihydroxyphenyl)flavan-3,3',4',7-tetraol (8) as a light-brown solid.

Methylation of this 4-arylflavan-3-ol (50 mg) followed by p.l.c. separation [hexane–benzene–acetone (5 : 4 : 1)] gave two bands, R_F 0.23 (3 mg) and 0.17 (25 mg). The R_F 0.23 fraction gave the *hexamethyl ether* (10) as a colourless solid (Found: M^+, 466.537. $C_{27}H_{30}O_7$ requires M, 466.536); δ 7.19—6.25 (m, 9 H, aromatic), 4.85 (d, 2-H, $J_{2,3}$ 9.4 Hz), 4.49 (d, 4-H, $J_{3,4}$ 9.4 Hz), 3.90, 3.88, 3.79, 3.76, and 3.73 (all s, 5 × OMe), 3.84—3.61 (t, 3-H, J 9.4 Hz), and 2.71 s, 3-OMe).

The R_F 0.17 fraction afforded the *pentamethyl ether* (9) as a white amorphous solid (Found: M^+, 452.509. $C_{26}H_{28}O_7$ requires M, 452.509); δ 7.10—6.17 (m, 9 H, aromatic), 4.77 (d, 2-H, $J_{2,3}$ 9.4 Hz), 4.55 (d, 4-H, $J_{3,4}$ 9.4 Hz), 4.08 (t, 3-H, J 9.4 Hz), 3.83, 3.81, and 3.74 (6 H), 3.68 (all s, 5 × OMe), and 2.20 (s, 3-OH).

(2R,3S,4R)-2,3-trans-3,4-trans-3-*Acetoxy*-3',4',7-*trimethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan* (11).—Acetylation of the pentamethyl ether (9) (20 mg) followed by crystallization from ethanol gave the 3-O-*acetate* (18 mg) as fine white needles, m.p. 135—136 °C (Found: C, 68.0; H, 6.2. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%); *m/e* 494 (M^+, 0%), 434 (100), 419 (11.8), 404 (16.2), 403 (57), 297 (39), 273 (2.5), 242 (10.9), 241 (58), 217 (10.5), 180 (34), 165 (14.5), 151 (36), 137 (13.8), and 121 (12); δ 7.03—6.28 (m, 9 H, aromatic), 5.77 (t, 3-H, J 10.0 and 9.0 Hz), 5.0 (d, 2-H, $J_{2,3}$ 10.0 Hz), 4.62 (d, 4-H, $J_{3,4}$ 9.0 Hz), 3.85, 3.83, 3.73 (6 H), and 3.71 (all s, 5 × OMe), and 1.58 (s, 3-OAc); c.d. (MeOH) $[\theta]_{300}$ 0, $[\theta]_{288}$ +909, $[\theta]_{283}$ +606, $[\theta]_{267}$ +5 151, $[\theta]_{243}$ 0, $[\theta]_{232}$ −39 696, and $[\theta]_{218}$ −6 667.

(2S,3R,4S)-*Flavan*-3,3',4,4',7-*pentaol–Resorcinol Condensation*.—Coupling of resorcinol to compound (4) as described for compound (1) also gave both the (2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*-4-arylflavan-3-ol (38) as a light brown solid and (2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*cis*-4-arylflavan-3-ol (44) as a light brown solid. Their methyl ethers [(39) and (45), respectively, both white solids] and *methyl ether* 3-O-*acetates* [(40), a white solid and (46), fine white needles (from ethanol), m.p. 135—136 °C, respectively] (Found: C, 67.9, 67.8; H, 6.2, 6.3, respectively. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%) displays m.s. and n.m.r. data identical to those indicated for the (2*R*,3*S*,4*R*)-flavan-3,3',4,4',7-pentaol analogues, while the c.d. spectra (MeOH) of the monoacetates (40) {$[\theta]_{297}$ 0, $[\theta]_{288}$ −713, $[\theta]_{282}$ −475, $[\theta]_{267}$ −2 850, $[\theta]_{254}$ 0, $[\theta]_{248}$ +2 137, $[\theta]_{244}$ 0, $[\theta]_{232}$ +35 150, and $[\theta]_{222}$ 0} and (46) {$[\theta]_{295}$ 0, $[\theta]_{288}$ +1 403, $[\theta]_{281}$ +673, $[\theta]_{268}$ +2 245, $[\theta]_{252}$ 0, $[\theta]_{232}$ −32 559, and $[\theta]_{217}$ 0}, show the anticipated mirror-image relationship relative to their enantiomers (11) and (26).

(2*R*,3*R*,4*R*)-*Flavan*-3,4,4',7,8-*pentaol–Phloroglucinol Condensation*.—Reaction of compound (47) (435 mg) with phloroglucinol (1.512 g) for 3.5 h gave (2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*trans*-4-(2,4,6-trihydroxyphenyl)flavan-3,4',7,8-tetraol (49) (210 mg, 51%), R_F 0.24, as a light brown solid.

Methylation of the 4-arylflavan-3-ol (49) (200 mg) followed by p.l.c. separation [hexane–benzene–acetone (5 : 4 : 1), twice] afforded the *hexamethyl ether* (50) (58 mg), R_F 0.18, as a white amorphous solid (Found: M^+, 482.533. $C_{27}H_{30}O_8$ requires M, 482.535); δ 7.34, 6.85 (2 × d, aromatic AA'BB' system, J 8.5 Hz), 6.50 (d, 5-H, J 8.5 Hz), 6.35 (d, 6-H, J 8.5 Hz), 6.11 [s, 3- and 5-H (ring D)], 5.40 (d, 2-H, $J_{2,3}$ 2.4 Hz), 4.52 (d, 4-H, $J_{3,4}$ 4.6 Hz), 4.40—4.05 (m, 3-H), and 3.91, 3.80, 3.77 (6 H), and 3.57 (6 H) (all s, 6 × OMe).

(2R,3R,4R)-2,3-cis-3,4-trans-3-*Acetoxy*-4',7,8-*trimethoxy*-4-(2,4,6-*trimethoxyphenyl*)*flavan* (51).—Acetylation of the hexamethyl ether (50 mg) and crystallization from ethanol gave the *monoacetate* (48 mg) as colourless needles, m.p. 193—194 °C (Found: C, 66.3; H, 6.3. $C_{29}H_{32}O_9$ requires C, 66.4; H, 6.2%); *m/e* 524 (M^+, 2.5%), 464 (100), 450 (10.7), 449 (31), 433 (29), 357 (4.5), 345 (12.1), 333 (1.6), 302 (13.9), 301 (78), 297 (11.5), 181 (6.0), 167 (14.8), 166 (13.9), 151 (12), 150 (8.7), 137 (8.5), and 121 (39); δ 7.25, 6.78 (2 d, aromatic AA'BB' system, J 8.5 Hz), 6.47 (d, 5-H, J 8.5 Hz), 6.33 (d, 6-H, J 8.5 Hz), 6.18 [s, 3- and 5-H (ring D)], 5.47 (s, 3-H, J < 1 Hz), 5.44 (s, 2-H, $J_{2,3}$ < 1 Hz), 4.53 (d, 4-H, $J_{3,4}$ 3.8 Hz), 3.90, 3.78, 3.75, 3.73, and 3.57 (6 H) (all s, 6 × OMe), and 1.81 (s, 3-OAc); c.d. (MeOH) $[\theta]_{292}$ 0, $[\theta]_{267}$ −4 242, $[\theta]_{253}$ 0, $[\theta]_{232}$ +43 939, $[\theta]_{229}$ +36 363, $[\theta]_{225}$ +50 000, and $[\theta]_{209}$ 0.

(2R,3R,4R)-*Flavan*-3,4,4',7,8-*pentaol–Resorcinol Condensation*.—Reaction of compound (47) (500 mg) with resorcinol (1.52 g) for 3.5 h gave a single product, R_F 0.28, which overlaps unchanged compound (47), R_F 0.27.

Methylation of this mixture followed by p.l.c. separation [benzene–acetone (9 : 1)] afforded two bands, R_F 0.10 (58 mg), and 0.33 (56 mg). Crystallization of the former fraction from ethanol gave (2*R*,3*R*,4*R*)-4',7,8-trimethoxyflavan-3,4-diol (48) as small white needles, m.p. 158—159 °C (lit.,[7] 159 °C).

The R_F 0.33 fraction afforded (2R,3R,4S)-2,3-cis-3,4-trans-4',7,8-*trimethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan*-3-*ol* (53) as a colourless amorphous solid (Found: M^+, 452.507.

$C_{26}H_{28}O_7$ requires M, 452.509); δ 7.30 and 6.84 (2 d, aromatic AA'BB' system, J 8.5 Hz), 6.67 (d, 5-H, J 8.5 Hz), 6.58 [d, 6-H (ring D), J 8.5 Hz], 6.51 (d, 6-H, J 8.5 Hz), 6.47 [d, 3-H (ring D), J 2.5 Hz], 6.32 [dd, 5-H (ring D), J 8.5 and 2.5 Hz], 4.97 (s, 2-H, $J_{2,3}$ <1 Hz), 4.50 (d, 4-H, $J_{3,4}$ 2.1 Hz), 4.06 (d, 3-H, J 4.9 Hz), and 3.94, 3.84 (6H), and 3.77 (6H) (all s, 5 × OMe).

(2R,3R,4S)-2,3-cis-3,4-trans-3-*Acetoxy*-4',7,8-*trimethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan* (54).—Acetylation of the pentamethyl ether (40 mg) and crystallization from ethanol gave the *monoacetate* (38 mg) as white needles, m.p. 156—157 °C (Found: C, 68.0; H, 6.1. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%); *m/e* 494 (M^+, 2.5%), 435 (33), 434 (100), 420 (5.3), 419 (17), 403 (22), 327 (3.2), 303 (3), 302 (1.2), 297 (8.1), 288 (1.2), 272 (13.2), 271 (73), 151 (8.5), 150 (10.2), 137 (7.1), and 121 (24); δ 7.19 and 6.73 (2 d, aromatic AA'BB' system, J 8.5 Hz), 6.62—6.22 [m, 5- and 6-H (ring A) and 3-, 5-, and 6-H (ring D)], 5.37 (s, 3-H, J 1 Hz), 5.02 (s, 2-H, $J_{2,3}$ <1 Hz), 4.41 (d, 4-H, $J_{3,4}$ 1.9 Hz), 3.92, 3.84 (6 H), 3.73, and 3.72 (all s, 5 × OMe), and 1.84 (s, 3-OAc); c.d. (MeOH) $[\theta]_{292}$ 0, $[\theta]_{268}$ − 12 121, $[\theta]_{237}$ 0, $[\theta]_{231}$ +18 484, $[\theta]_{223}$ +6 060, $[\theta]_{219}$ +21 363, and $[\theta]_{209}$ 0.

(+)-*Leucocyanidin–Phloroglucinol Condensation*

(2R,3S)-2,3-trans-3-*Hydroxy*-3',4,4',5,7-*pentamethoxy*-*flavan*.*—(+)-Taxifolin (55) (500 mg) (Senn Chemicals, Cat. No. 2226) and sodium borohydride (250 mg) were dissolved in ethanol (100 ml) and the mixture stirred at room temperature for 1 h. After addition of 0.1M HCl (10 ml) and water 1 l), the mixture was extracted with ethyl acetate (4 × 50 ml), the combined extracts dried (Na_2SO_4), and the solvent concentrated to *ca.* 10 ml under reduced pressure at 40 °C. The mixture was diluted with MeOH (90 ml) and methylated with diazomethane. P.l.c. separation [benzene–acetone (8 : 2)] gave (2*R*,3*S*)-2,3-*trans*-3',4,4',5,7-pentamethoxyflavan-3-ol (144 mg), R_F 0.44, as a colourless solid (Found: M^+, 376.411. $C_{22}H_{26}O_8$ requires M, 376.410); δ 6.94—6.82 (m, 2'- and 6'-H), 6.42 (d, 5-H, J 8.5 Hz), 6.03 (s, 6- and 8-H), 4.65 (d, 2-H, $J_{2,3}$ 8.5 Hz), 4.51 (d, 4-H, $J_{3,4}$ 5.8 Hz), 4.14 (dd, 3-H, J 8.5 and 5.8 Hz), 3.81 (6 H), 3.77, and 3.69 (all s, 4 × OMe), and 3.41 (s, 3-OMe).

Acetylation of the pentamethyl ether (100 mg) gave the *monoacetate* (3), (4*R* or 4*S*) (99 mg) as a white amorphous solid (Found: C, 63.1; H, 6.3. $C_{22}H_{26}O_8$ requires C, 63.2; H, 6.3%); *m/e* 418 (M^+, 15.5%); δ 6.88—6.76 (m, 2'- and 6'-H), 6.67 (d, 5'-H, J 8.5 Hz), 6.10 and 6.02 (2 d, 6- and 8-H, J 2.5 Hz), 5.54 (dd, 3-H, J 5.0 and 4.0 Hz), 5.09 (d, 2-H, $J_{2,3}$ 5.0 Hz), 4.44 (d, 4-H, $J_{3,4}$ 4.0 Hz), 3.77 (6 H), 3.73, and 3.71 (all s, 4 × OMe), 3.18 (s, 4-OMe), and 1.96 (s, 3-OAc).

(+)-Taxifolin (55) (1 g) and sodium borohydride (500 mg) were stirred in ethanol (200 ml) for 1 h at room temperature. Phloroglucinol (3.5 g) and 0.1M HCl (200 ml) were added and stirring was continued for 30 min. After addition of water (1 l) the mixture was extracted with ethyl acetate (4 × 100 ml), the combined extracts dried (Na_2SO_4), and the solvent evaporated to leave a solid (3.8 g). P.l.c. separation [benzene–acetone–methanol (6 : 3 : 1)] afforded an isomeric mixture of (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*- and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4,6-trihydroxyphenyl)flavan-3,3',4',5,7-pentaol [(12) and (27) respectively], 400 mg (32%), R_F 0.34] as a colourless solid.

Methylation of the 4-arylflavan-3-ols (400 mg) followed by p.l.c. separation [benzene–acetone (9 : 1)] gave three bands, R_F 0.53 (32 mg), 0.41 (18 mg), and 0.32 (70 mg).

The R_F 0.53 fraction afforded the 2,3-trans-3,4-trans-*octamethyl ether* (13) as a colourless solid (Found: M^+, 526.590. $C_{29}H_{34}O_9$ requires M, 526.589); δ 7.02 [dd, 6-H (ring B), J 8.5 and 2.5 Hz], 6.97 [d, 2-H (ring B), J 2.5 Hz], 6.79 [d, 5-H (ring B), J 8.5 Hz], 6.07 and 5.89 (2 d, 6- and 8-H, J 2.5 Hz), 6.04 [s, 3- and 5-H (ring D)], 4.59 (d, 4-H, $J_{3,4}$ 7.5 Hz), 4.49 (d, 2-H, $J_{2,3}$ 9.3 Hz), 3.94—3.72 (m, 3-H), 3.85—3.34 (all s, 7 × OMe), and 2.75 (s, 3-OMe). No evidence of the 3,4-*cis*-analogue (28) was obtained.

Crystallization of the R_F 0.32 fraction from ethanol gave the heptamethyl ether (14) as colourless needles, m.p. 195—196 °C (lit.,[16] 204 °C); † *m/e* 512 (M^+, 24%); δ 4.58 (d, 4-H, $J_{3,4}$ 8.3 Hz), 4.52 (d, 2-H, $J_{2,3}$ 9.0 Hz), and 4.20 (dd, 3-H, J 9.0 and 8.3 Hz).

(2R,3S,4R)-2,3-trans-3,4-trans-3-*Acetoxy*-3',4',5,7-*tetramethoxy*-4-(2,4,6-*trimethoxyphenyl*)*flavan* (15).—Acetylation of the heptamethyl ether (70 mg) and crystallization from ethanol afforded the monoacetate (80 mg) as white needles, m.p. 160—161 °C (lit.,[16] 165 °C); † *m/e* 494 M^+ −60, 100%); δ 5.73 (dd, 3-H, J 10.0 and 8.5 Hz), 4.69 (d, 4-H, $J_{3,4}$ 8.5 Hz), and 4.68 (d, 2-H, $J_{2,3}$ 10.0 Hz); c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{280}$ −7 575, $[\theta]_{276}$ 0, $[\theta]_{265}$ +18 181, $[\theta]_{256}$ 0, $[\theta]_{234}$ −47 878, $[\theta]_{218}$ 0.

(2R,3S,4S)-2,3-trans-3,4-cis-3-*Acetoxy*-3',4',5,7-*tetramethoxy*-4-(2,4,6-*trimethoxyphenyl*)*flavan* (27).—Acetylation of the 2,3-*trans*-3,4-*cis* methyl ether (29), (R_F 0.41 fraction) gave the *acetate* (30) [9 mg, R_F 0.49 in benzene–acetone (19 : 1 v/v)] as a colourless amorphous solid (Found: M^+, 554.600. $C_{30}H_{34}O_{10}$ requires M, 554.599); δ (305 K) 6.85—6.70 (m, 2'- and 6'-H), 6.63 (d, 5'-H, J 8.0 Hz), 6.05 and 5.84 (dd, 3''- and 5''-H, J 3 Hz), 6.05 and 5.87 (dd, 6- and 8-H, J 3 Hz), 5.32 (dd, 3-H, ΣJ_S 16 Hz), 5.08 (d, 2-H, $J_{2,5}$ 10.0 Hz), 4.95 (d, 4-H, J 6.0 Hz), 3.80 (6H), 3.73, 3.72, 3.69, 3.50, and 3.28 (all s, 7 × OMe), 1.66 (s, OAc); at 373 K the 3''-H and 5''-H resonances merged into a sharp singlet (δ 6.00) with coincidental merging of the δ 3.72 and 3.28 resonances into a broadened singlet at δ 3.50; c.d. (MeOH) $[\theta]_{280}$ 0, $[\theta]_{270}$ +1 065, $[\theta]_{260}$ +532, $[\theta]_{237}$ +22 905, $[\theta]_{220}$ +17 845, $[\theta]_{216}$ +46 344, $[\theta]_{209}$ +8 256, $[\theta]_{205}$ +18 644, and $[\theta]_{200}$ 0.

(+)-*Leucocyanidin–Resorcinol Condensation*.—Reduction of (+)-taxifolin (55) (1 g) with sodium borohydride (500 mg), and coupling with resorcinol (3.08 g) followed by work-up as described for the (+)-taxifolin–phloroglucinol condensation afforded a single fraction, R_F 0.39 (52 mg).

Methylation followed by p.l.c. separation [benzene–acetone (9 : 1)] of the product gave three bands, R_F 0.56 (4 mg), 0.47 (8 mg), and 0.39 (26 mg).

The R_F 0.56 fraction gave (2R,3S,4R)-2,3-trans-3,4-trans-3,3',4',5,7-*pentamethoxy*-4-(2,4-*dimethoxyphenyl*)-*flavan* (17) as a colourless solid (Found: M^+, 496.560. $C_{28}H_{32}O_8$ requires M, 496.562); δ 6.80 [dd, 6-H, (ring B), J 8.5 and 2.5 Hz], 6.74 [d, 2-H (ring B), J 2.5 Hz], 6.63 [d, 5-H (ring B), J 8.5 Hz], 6.41 [d, 6-H (ring D), J 8.5 Hz], 6.31 and 6.19 (2 d, 6- and 8-H, J 2.5 Hz), 6.04 [dd, 5-H (ring D), J 8.5 and 2.5 Hz], 5.97 [d, 3-H, (ring D), J 2.5 Hz], 4.87 (d, 2-H, $J_{2,3}$ 6.8 Hz), 4.46 (d, 4-H, $J_{3,4}$ 5.5 Hz), 3.89—3.73

* Direct comparison of coupling constants and chemical-shift parameters of the derivatives with those of their 5-deoxy-analogues (2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-3-hydroxy-4-methoxyflavans [12]) is inconclusive as regards the 3,4-stereochemistry of the new compound.

† The stereochemistry and optical purity of these derivatives were not specified previously.[16]

(m, 3-H), 3.77, 3.73 (9 H), 3.67, and 3.41 (all s, 6 × OMe), and 3.07 (s, 3-OMe).

The R_F 0.47 fraction afforded (2R,3S,4S)-2,3-trans-3,4-cis-3′,4′,5,7-*tetramethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan*-3-*ol* (33) as a colourless solid (Found: M^+, 482.533. $C_{27}H_{30}O_8$ requires M, 482.535); δ 6.92 [d, 2-H (ring B), J 2.5 Hz], 6.92 [dd, 6-H (ring B), J 8.5 and 2.5 Hz], 6.81 [d, 5-H (ring B), J 8.5 Hz], 6.74 [d, 6-H (ring D), J 8.5 Hz], 6.51 [d, 3-H (ring D), J 2.5 Hz], 6.40 [dd, 5-H (ring D), J 8.5 and 2.5 Hz], 6.18 and 6.06 (2 d, 6- and 8-H, J 2.5 Hz), 4.96 (d, 4-H, $J_{3,4}$ 5.5 Hz), 4.67 (d, 2-H, $J_{2,3}$ 10.0 Hz), 4.29 (dd, 3-H, J 10.0 and 5.5 Hz), 3.86, 3.84, 3.83, 3.77, 3.76, and 3.59 (all s, 6 × OMe).

(2R,3S,4S)-2,3-trans-3,4-cis-3-*Acetoxy*-3′,4′,5,7-*tetramethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan* (34).—Acetylation of the hexamethyl ether (8 mg) gave the *monoacetate* (7 mg) as a colourless solid (Found: C, 66.3; H, 6.3. $C_{29}H_{32}O_9$ requires C, 66.4; H, 6.2%); *m/e* 524 (M^+, 21%); δ 6.91—6.79 [m, 6-H (ring D) and 2-, 5-, and 6-H (ring B)], 6.41 [d, 3-H (ring D), J 2.5 Hz], 6.36 [dd, 5-H (ring D), J 8.5 and 2.5 Hz], 6.14 and 6.02 (2 d, 6- and 8-H, J 2.5 Hz), 5.45 (dd, 3-H, J 10.0 and 5.8 Hz), 5.04 (d, 4-H, $J_{3,4}$ 5.8 Hz), 4.94 (d, 2-H, $J_{2,3}$ 10.0 Hz), 3.82 (6-H), 3.77 (6 H), 3.74, and 3.55 (all s, 6 × OMe), and 1.68 (s, 3-OAc); c.d. (MeOH) $[\theta]_{300}$ 0, $[\theta]_{276}$ +7 878, $[\theta]_{268}$ 0, $[\theta]_{260}$ −6 060, $[\theta]_{248}$ 0, $[\theta]_{235}$ +21 818, $[\theta]_{230}$ +5 454.

The R_F 0.39 fraction gave (2R,3S,4R)-2,3-trans-3,4-trans-3′,4′,5,7-*tetramethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan*-3-*ol* (18) as a colourless solid (Found: M^+, 482.536. $C_{27}H_{30}O_8$ requires M, 482.536); δ 6.95 [dd, 6-H, (ring B), J 8.5 and 2.5 Hz], 6.89 [d, 2-H (ring B), J 2.5 Hz], 6.77 [d, 5-H (ring B), J 8.5 Hz], 6.60 [d, 6-H (ring D), J 8.5 Hz], 6.35 [dd, 5-H (ring D), J 8.5 and 2.5 Hz], 6.20 [d, 3-H (ring D), J 2.5 Hz], 6.15 and 6.00 (2 × d, 6- and 8-H, J 2.5 Hz), 4.62 (d, 2-H, $J_{2,3}$ 9.0 Hz), 4.46 (d, 4-H, $J_{3,4}$ 7.5 Hz), 3.98 (dd, 3-H, J 9.0 and 7.5 Hz), and 3.82, 3.81, 3.80, 3.71 (6 H), and 3.37 (all s, 6 × OMe).

(2R,3S,4R)-2,3-trans-3,4-trans-3-*Acetoxy*-3′,4′,5,7-*tetramethoxy*-4-(2,4-*dimethoxyphenyl*)*flavan* (19).—Acetylation of the hexamethyl ether (24 mg) afforded the *monoacetate* (24 mg) as a white amorphous solid (Found: C, 66.4; H, 6.3. $C_{29}H_{32}O_9$ requires C, 66.4; H, 6.2%); *m/e* 524 (M^+, 0%), 493 (3.9), 480 (14.8), 478 (51), 466 (20), 465 (82), 464 (100), 449 (33), 434 (26), 433 (82), 341 (18.4), 328 (55), 327 (85), 325 (18.7), 315 (13.8), 313 (24), 311 (32), 303 (3.2), 302 (2.4), 301 (16.4), 300 (19.8), 297 (22), 287 (20), 285 (23), 272 (18.8), 271 (81), 256 (22), 232 (22), 225 (13.4), 222 (4.3), 194 (8.8), 181 (13.2), 180 (68), 179 (18.7), 167 (41), 165 (35), 152 (18.2), 151 (85), 149 (29), 137 (21), and 121 (30); δ 6.91—5.92 (m, 8 H, aromatic), 5.62 (dd, 3-H, J 7.5 and 5.5 Hz), 5.00 (d, 2-H, $J_{2,3}$ 6.5 Hz), 4.42 (d, 4-H, $J_{3,4}$ 5.5 Hz), 3.75 (9 H), 3.72, 3.65, and 3.41 (all s, 6 × OMe), and 1.87 (s, 3-OAc); c.d. (MeOH) $[\theta]_{305}$ 0, $[\theta]_{286}$ +8 787, $[\theta]_{273}$ +3 030, $[\theta]_{260}$ +3 030, $[\theta]_{242}$ +22 424, and $[\theta]_{232}$ 0.

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REFERENCES

[1] J. J. Botha, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1978, 698.
[2] J. J. Botha, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1978, 700.
[3] J. J. Botha, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1979, 510.
[4] M. W. Barrett, W. Klyne, P. M. Scopes, A. C. Fletcher, L. J. Porter, and E. Haslam, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2375.
[5] J. J. Botha, Ph.D. Thesis, University of the Orange Free State, Bloemfontein, December 1978.
[6] J. W. Clark-Lewis and D. G. Roux, *J. Chem. Soc.*, 1959, 1402; J. W. Clark-Lewis and G. F. Katekar, *J. Chem. Soc.*, 1962, 4502.
[7] J. W. Clark-Lewis, G. F. Katekar, and P. I. Mortimer, *J. Chem. Soc.*, 1961, 499.
[8] M. I. Baig, J. W. Clark-Lewis, and M. J. Thompson, *Aust. J. Chem.*, 1969, **22**, 2645; M. I. Baig, J. W. Clark-Lewis, R. W. Jemison, and M. J. Thompson, *Chem. Commun.*, 1969, 820.
[9] J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Aust. J. Chem.*, 1964, **17**, 632.
[10] M. J. Betts, B. R. Brown, and M. R. Shaw, *J. Chem. Soc. C*, 1969, 1178.
[11] J. W. Clark-Lewis and L. R. Williams, *Aust. J. Chem.*, 1967, **20**, 2151.
[12] I. C. du Preez, D. Ferreira, and D. G. Roux, *J. Chem. Soc. C*, 1971, 336.
[13] R. S. Thompson, D. Jacques, E. Haslam, and R. J. N. Tanner, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1387.
[14] A. C. Fletcher, L. J. Porter, E. Haslam, and R. K. Gupta, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1628.
[15] J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, following paper.
[16] K. Weinges, H-D. Marx, and K. Göritz, *Chem. Ber.*, 1970, **103**, 2336.