

Oligomeric Flavanoids. Part 11.† Structure and Synthesis of the First Phlobatannins Related to (4 α ,6:4 α ,8)-Bis-(–)-fisetinidol-(+)-catechin Profisetinidin Triflavanoids

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Several members of the unique class of natural phlobatannins, representing the products of stereospecific pyran rearrangement of 2,3-*trans*-3,4-*trans*-flavan-3-ol units present in, *e.g.*, (4 α ,6:4 α ,8)-bis-(–)-fisetinidol-(+)-catechin triflavanoid profisetinidins, have been characterized. These include the functionalized 6,7-*trans*-7,8-*cis*-10,11-*trans*-11,12-*cis*-hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene (**3**) and the 10-flavanyl-6,7-*trans*-7,8-*cis*-tetrahydropyrano[2,3-*f*]chromene 'isomerization-intermediates' (**6**), (**15**), and (**17**). The proposed structures of compounds (**3**) and (**6**) were confirmed by synthesis *via* base-catalysed conversion of the 3-*O*(E)-methyl ether (**1**) of its apparent biogenetic precursor, and the relative nucleophilicity of the A- and D-ring in the 'dimeric' tetrahydropyrano[2,3-*h*]chromene (**14**) assessed by condensation with the flavan-3,4-diol, (+)-mollisacacidin.

We have recently demonstrated the natural occurrence and biomimetic synthesis of a series of functionalized tetrahydropyranochromenes, termed phlobatannins, related to (–)-fisetinidol-(4,6) and (4,8)-(+)-catechin‡ profisetinidin biflavanoids.^{1–4} The concise approach to the synthesis of these pyran-rearranged analogues based on the selective generation of B-ring quinone methides under mild basic conditions is now extended to the first formation of the naturally occurring¹ hexahydrodipyranochromene and 'isomerization-intermediates' associated with a (4 α ,6:4 α ,8)-bis-(–)-fisetinidol-(+)-catechin profisetinidin triflavanoid.

Results and Discussion

In view of the susceptibility of constituent units in oligoflavanoids to epimerization at C-2 at alkaline pH,⁵ the triflavanoid had to be selectively protected at 4-*O*(E). This was effected by using (–)-fisetinidol-(4 α ,8)-(+)-catechin 4-*O*(E)-methyl ether^{3,4} as nucleophile in the acid-catalysed⁶ condensation with (+)-mollisacacidin [(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3',4,4',7-pentaol]. Subsequent gel chromatography afforded the (4 α ,6:4 α ,8)-bis-(–)-fisetinidol-(+)-catechin 4-*O*(E)-methyl ether (**1**) and its (4 β ,6)-isomer, both of which are incapable of epimerization at C-2(F) under basic conditions. Triflavanoid (**1**) was characterized by comparison of ¹H n.m.r. and c.d. data of its nonamethyl ether triacetate with those of the permethyl ether triacetate of the corresponding phenol.⁶

Treatment of triflavanoid (**1**) with 0.025M-NaHCO₃–0.025M-Na₂CO₃ buffer (pH 10) for 5 h at 50 °C under nitrogen (Scheme), *i.e.* conditions similar to those applied by Freudenberg⁵ for epimerization at C-2 of (+)-catechin, gave complete conversion into a mixture comprising three ring-isomerized analogues. These are the hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene (**4**), the (–)-fisetinidol-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene§ (**7**), and (–)-fisetinidol-(4 α ,6)-tetrahydropyrano[2,3-*h*]chromene (**10**). Owing to difficulties in purifying these as 'free' phenols and to facilitate comparison with their natural counterparts (see below), identification was performed on the decamethyl ether triacetates, *e.g.* (**5**).

Analysis of the ¹H NMR data (300 MHz) (Table) of the dipyrano[2,3-*f*:2',3'-*h*]chromene derivative (**5**) revealed the

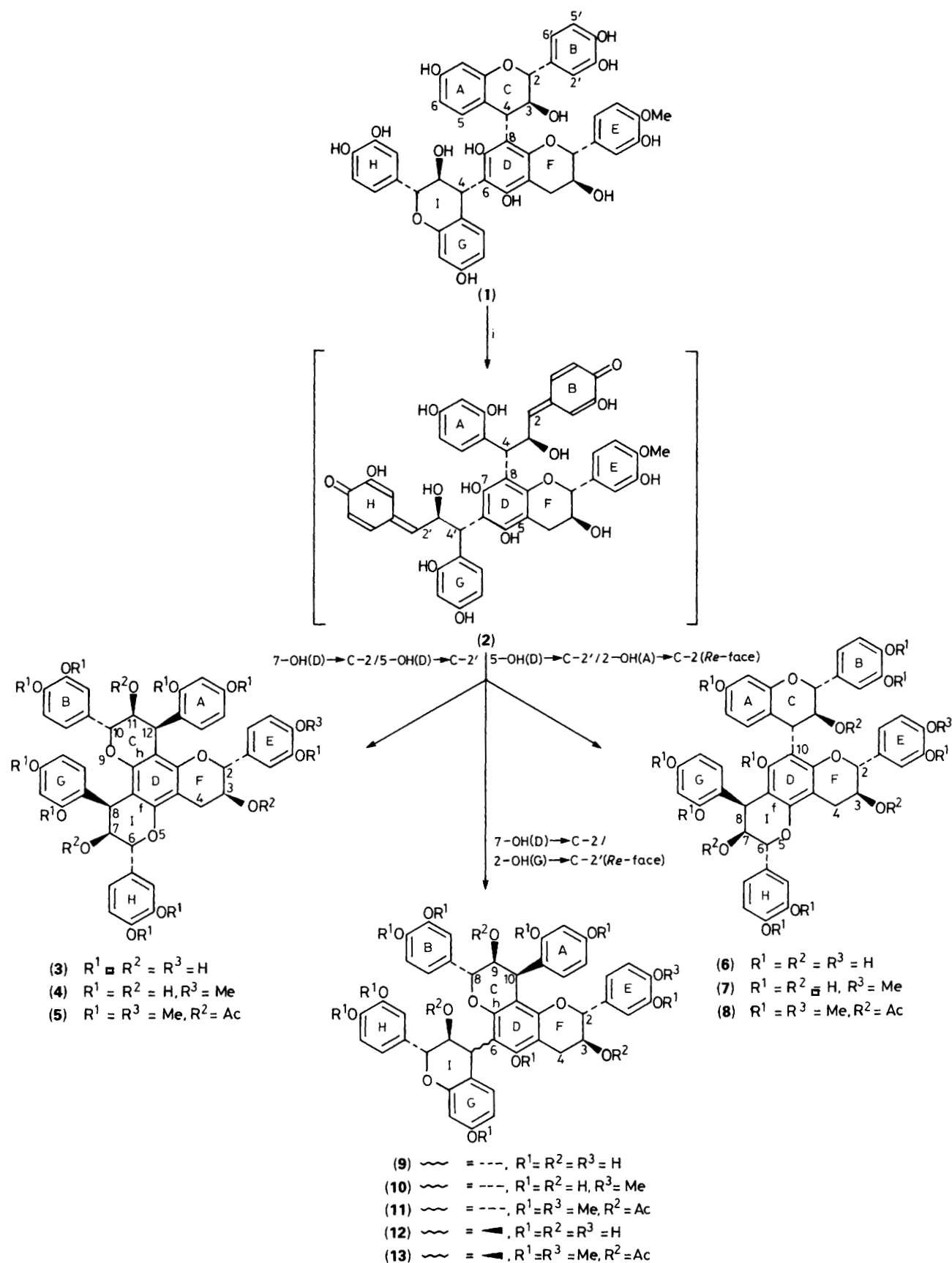
familiar absence^{1,4} of the effects of dynamic rotational isomerism at ambient temperatures⁷ and the NOE associations of 2-*OMe*(A)/2-*OMe*(G) with 3-*H*(A)/3-*H*(G) respectively and of 4-*OMe*(A)/4-*OMe*(G) with both 3- and 5-*H*(A)/3- and 5-*H*(G) respectively, characteristic of resorcinol rings being 'liberated' from the heterocyclic C- and I-ring in the triflavanoid precursor (**1**).^{1,4} These features unequivocally reflected participation of both the C- and I-ring in the pyran rearrangements and hence a dipyranochromene constitution for compound (**5**). The heterocyclic region of the spectrum revealed significant reversals of chemical shifts of benzylic C- and I-ring protons^{1,4} in comparison with those of the corresponding 2- and 4-proton resonances in bis-(–)-fisetinidol-(+)-catechin triflavanoids of both 2,3-*trans*-3,4-*trans*- and 3,4-*cis* stereochemistry.⁶ Heterocyclic coupling constants ($J_{6,7} = J_{10,11} = 10.5$, $J_{7,8} = J_{11,12} = 6.0$ Hz) are reminiscent of the 6,7-*trans*-7,8-*cis*:10,11-*trans*-11,12-*cis* relative configurations prescribed by the mechanism^{1,4} for ring isomerization and confirmed by the prominent NOE association of 6-*H*(I) with 6-*H*(G) (5.5%) and of 10-*H*(C) with 6-*H*(A) (5.0%).

NOE experiments additionally indicated association of one of the heterocyclic protons (δ 5.08) adjacent to a resorcinol unit with 2- and 6-*H*(E). Such a feature is consistent with a 10,11-*trans*-11,12-*cis*-tetrahydropyrano[2,3-*h*]chromene moiety and thus defined the hydrogen as 12-*H*(C). Subsequent decoupling experiments using the benzylic protons of rings C, E, and I as reference signals not only permitted differentiation of the very similar AMX systems of the C- and I-rings but also facilitated definition of the spin systems and positions of the pyrocatechol and resorcinol rings.^{3,4} These allocations were additionally confirmed by NOE association of 2-*OMe*(G) with 6-*H*(B) and by the weak but structurally significant effect between 8-*H*(I) and 2- and 6-*H*(B).

† Part 10, J. C. S. Malan, D. A. Young, J. P. Steynberg, and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1*, 1990, preceding paper.

‡ (–)-Fisetinidol is (2*R*,3*S*)-2,3-*trans*-flavan-3,3',4',7-tetraol and (+)-catechin its 5-oxy analogue.

§ Non-systematic name/numbering to retain the heterocyclic oxygen of the pyrano substituted flavan-3-ol entity as position 1 consistently for all products.



Scheme. Proposed route to the formation of dipyranochromene (4) and 'isomerization-intermediates' (7) and (10). Reagents and conditions: (i), $NaHCO_3$ - Na_2CO_3 , 50 °C, 5 h, N_2 . Non-systematic numbering schemes shown for (3)–(13).

Table. ^1H NMR (300 MHz) peaks (p.p.m.) of the phlobatannins (5), (8), (11), (16), and (18). Splitting patterns and J -values (Hz) are given in parentheses.

Ring	H	(5), CDCl_3 , 298 K	(8), CDCl_3 , 298 K	(11), $(\text{CD}_3)_2\text{CO}$, 297 K	(16), $\text{CDCl}_3\text{-C}_6\text{D}_6$ (3:2) 298 K	(18), C_6D_6 , 298 K
A	3/8	6.28 (d, 2.5)	6.38 (d, 2.5)	6.37 (d, 2.5)	6.52 (d, 8.5)	6.59 (d, 8.5)
	5/6	6.33 (dd, 2.5, 8.5)	6.48 (dd, 2.5, 8.5)	6.37 (dd, 2.5, 8.0)	6.50 (dd, 2.5, 8.5)	6.58 (dd, 2.5, 8.5)
	6/5	6.58 (d, 8.5)	6.81 (d, 8.5)	6.92 (d, 8.0)	6.96 (dd, 1.1, 8.5)	7.13 (dd, 1.1, 8.5)
B	2	6.69 (d, 2.0)	6.63–6.68, 6.46–6.55	6.43 (d, 2.5)	6.79 (d, 2.5)	7.24 (d, 8.5):2/6
	5	6.70 (d, 8.5)		6.68 (d, 8.0)	6.55 (d, 8.5)	6.73 (d, 8.5):3/5
	6	6.69 (dd, 2.0, 8.5)		6.21 (dd, 2.5, 8.0)	6.75 (dd, 2.5, 8.5)	
C	10/8/2	4.59 (d, 10.5)	4.78 (d, 10.0)	5.08 (d, 10.0)	4.78 (d, 10.0)	4.82 (d, 10.0)
	11/9/3	5.29 (dd, 6.0, 10.5)	6.01 (t, 10.0)	4.97 (dd, 10.0, 6.0)	6.22 (t, 10.0)	6.51 (t, 10.0)
	12/10/4	5.08 (d, 6.0)	4.54 (d, 10.0)	5.07 (d, 6.0)	4.73 (dd, 1.0, 10.0)	4.84 (dd, 1.1, 10.0)
E	2	6.76 (d, 2.0)	6.63–6.68, 6.46–6.65	6.91 (d, 2.0)	6.90 (d, 2.0)	6.81 (d, 2.5)
	5	6.76 (d, 8.5)		6.90 (d, 8.5)	6.59 (d, 8.5)	6.64 (d, 8.0)
	6	6.71 (dd, 2.0, 8.5)		6.79 (dd, 2.0, 8.5)	6.85 (dd, 2.0, 8.5)	6.74 (dd, 2.5, 8.0)
F	2	4.57 (d, 7.5)	4.78 (d, 9.0)	4.63 (d, 8.0)	5.09 (d, 9.0)	5.35 (d, 9.5)
	3	5.23 (m)	4.92 (m)	5.15 (m)	5.16 (m)	5.53 (m)
	4 _{ax}	2.64 (dd, 8.0, 17.0)	2.68 (dd, 9.5, 17.0)	2.83 (dd, 8.0, 16.0)	2.88 (dd, 8.5, 17.0)	3.11 (dd, 9.0, 17.0)
	4 _{eq}	3.04 (dd, 5.5, 17.0)	3.15 (dd, 6.5, 17.0)	3.15 (dd, 5.5, 16.0)	overlapped by OMe	overlapped by OMe
G	3/8	6.34 (d, 2.5)	6.47 (d, 2.5)	6.33 (d, 2.5)	6.42 (d, 2.5)	6.44 (d, 2.5)
	5/6	6.52 (dd, 2.5, 8.5)	6.34 (dd, 2.5, 8.5)	6.53 (dd, 2.5, 8.5)	6.24 (dd, 2.5, 8.5)	6.11 (dd, 2.5, 8.5)
	6/5	7.01 (d, 8.5)	6.72 (d, 8.5)	6.75 (dd, 1.1, 8.5)	6.91 (d, 8.5)	7.02 (d, 8.5)
H	2	6.83 (d, 2.0)	6.83 (d, 2.0)	6.84–6.86	6.89 (d, 8.5):2/6 6.69 (d, 8.5):3/5	6.95 (d, 2.0)
	5	6.79 (d, 8.5)	6.79 (d, 8.5)	6.75		6.52 (d, 8.5)
	6	6.89 (dd, 2.0, 8.5)	6.89 (dd, 2.0, 8.5)	6.84–6.86		6.94 (dd, 2.0, 8.5)
I	6/2	5.01 (d, 10.5)	4.97 (d, 10.5)	4.94 (d, 10.0)	5.22 (d, 10.0)	5.43 (d, 10.0)
	7/3	5.41 (dd, 6.0, 10.5)	5.42 (dd, 6.0, 10.5)	6.29 (t, 10.0)	5.72 (dd, 5.5, 10.0)	5.95 (dd, 5.5, 10.0)
	8/4	5.12 (d, 6.0)	5.17 (d, 6.0)	4.75 (d, 10.0)	5.47 (d, 5.5)	5.76 (d, 5.5)
	OMe	3.42 (2-G), 3.47 (2-A), 3.75, 3.81, 3.82 ($\times 3$), 3.84, 3.85, 3.86 (each s)	3.51, 3.55 (9-D), 3.69 3.74 (7-A), 3.75 (4-G), 3.80, 3.82 (2-G), 3.84 ($\times 2$), 3.85 (4-H) (each s)	3.52 (2-A), 3.32 (4-H), 3.61 (3-B), 3.75 (4-A), 3.76 (4-B), 3.77 (3-H), 3.78 (4-E), 3.79 (7-G), 3.80 (3-E), 3.83 (5-D) (each s)	3.29, 3.30, 3.36, 3.37, 3.38, 3.39, 3.41, 3.44, 3.56 (9-D) (each s)	3.19 (4-B), 3.23 (4-G), 3.31, 3.32, 3.33 ($\times 2$), 3.36, 3.51, 3.61 (9-D) (each s)
	OAc	1.87, 1.67 ($\times 2$) (each s)	1.42, 1.74, 1.81 (each s)	1.66, 1.69, 1.86 (each s)	1.54, 1.51, 1.34 (each s)	1.55, 1.49, 1.38 (each s)

* Second order.

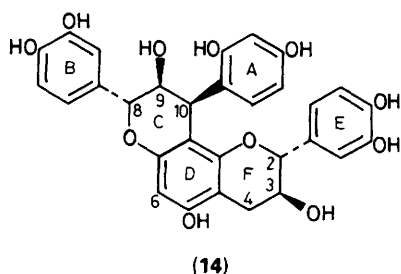
The above heterocyclic coupling constants in conjunction with the known absolute configuration of triflavanoid (1)⁶ indicated a 2*R*,3*S*:6*R*, 7*S*, 8*S*:10*R*, 11*S*, 12*S* configuration for compound (4). A high-amplitude positive Cotton effect at 240 nm in the CD spectrum of compound (5) confirmed the 8 β , 12 β orientation of resorcinol units.⁸ Since the DEF-(+)-catechin moiety possesses (2*R*,3*S*) absolute configuration and hence a 2 α pyrocatechol E-ring, the aforementioned NOE association of 12 α -H(c) with 2- and 6-H(e) unequivocally confirmed the 12 β -aryl group. The NOE effect of 10-H(c) with 6-H(a) then indicates a 10 α -pyrocatechol moiety and similarly 8-H(i) with 2- and 6-H(b), and 6-H(i) with 6-H(g) reminiscent of 8 β - and 6 α -aryl substituents. Owing to the unreliability of the chiroptical method at this level⁹ these NOE features may usefully complement existing methods towards definition of absolute configuration amongst this class of condensed tannins.

Involvement of a single heterocycle in the pyran rearrangement leading to the 'isomerization-intermediates' (7) and (10) was evident from the heterocyclic AMX system in each of the ^1H NMR spectra (Table) of the decamethyl ether triacetates (8) and (11), similarly free of dynamic rotational isomerism, which corresponds to an 'intact' 2,3-*trans*-3,4-*trans* [$J_{2,3(\text{C/I})} = J_{3,4(\text{C/I})} = 10.0$ Hz] C-4-substituted (–)-fisetinidol moiety. A single intact flavanyl unit and hence a 10- or 6-(–)-fisetinidol-tetrahydropyranochromene-type structure for compounds (8) and (11) was confirmed by NOE experiments which indicated the 'release' of a single resorcinol moiety in each instance (see above) with the involvement of the remaining resorcinol unit in

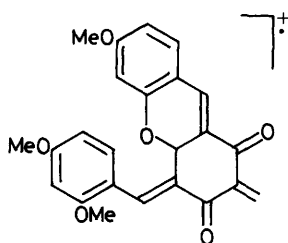
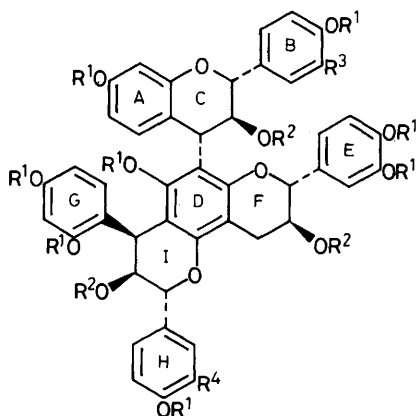
the A/C-ring system of, e.g., (8) being evident from the NOE association of only 7-OMe(A) with 8-H(A). Differentiation of these closely related analogues as a (–)-fisetinidol-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene (8) and a (–)-fisetinidol-(4 α ,6)-tetrahydropyrano[2,3-*h*]chromene (11) was effected by the NOE association of 9-OMe(D) with both 4-H(c) and 8-H(i) for (8) and of 5-OMe(D) with both 4-H(i) and 5-H(g) for (11). The 6-flavanyltetrahydropyrano[2,3-*h*]chromene arrangement for compound (11) was additionally confirmed by the typical^{1,4} NOE effect of 10-H(c) with 2- and 6-H(e).

The absolute configurations depicted in structures (8) and (11) are based on ^1H NMR data, the known absolute configuration of triflavanoid (1), and the mechanism of their genesis from (1) (*vide infra*). Both tetrahydropyrano[2,3-*f*]- and [2,3-*h*]-chromenes (8) and (11) gave clear, high-amplitude Cotton effects [positive for (8), negative for (11)] in the 220–240 nm region of their CD spectra. Although not permitting stereochemical assignment to compounds (8) and (11), the CD features were employed comparatively to assess the absolute configuration of related natural products (*vide infra*).

The availability of the tetrahydropyrano[2,3-*h*]chromene (14)^{1,4} not only offered opportunity to establish unequivocally the structure of the 6-flavanyltetrahydropyrano[2,3-*h*]chromene (10) *via* synthesis but also of the assessment of the relative nucleophilicity of the A- and D-rings. Acid-catalysed coupling of molar equivalents of (+)-mollisacacidin and compound (14) resulted in two products (9) and (12) only. The decamethyl ether triacetate (11) exhibited identical ^1H NMR



Non-systematic numbering scheme.



and CD spectral properties with those outlined above, hence confirming the identity of the products. The 1H NMR spectrum of the 3,4-*cis*(1) derivative (13) is, however, subject to severe line-broadening and signal duplication at ambient temperatures. At 453 K in $(CD_3)_2SO$ the spectrum is still plagued by the adverse effects of dynamic rotational isomerism, but we were still able to define the 2,3-*trans*-3,4-*cis*(1) relative configuration ($J_{2,3}$ 8.0, $J_{3,4}$ 7.0 Hz). Coupling, therefore, occurs preferentially in each instance at C-6(D), the remaining nucleophilic site on the phloroglucinol ring system of the (+)-catechin moiety of compound (14), despite involvement of two of its three functional groups as heteroatoms in pyran ring systems. From this result we venture the prediction that, barring steric inhibition of condensation with ring A, bifunctionality of the ring-isomerized products in adhesive applications involving formaldehyde is ensured by potent nucleophilicity at both C-

5(A) and C-6(D) in (14) and at C-5 of both the A- and G-ring in, e.g., compound (3).

Additional structural information was sought *via* the mass spectral fragmentation data of compounds (5), (8), (11), and (13). Besides confirmation of the molecular ion (M^+ , m/z 1 100) in each instance, the spectra of all isomers were dominated by three successive retro-Diels-Alder (RDA) fragmentations and concomitant loss of a methoxyl radical¹⁰ leading to the m/z 403 ion (19) which is subsequently transformed to a m/z 287 fragment by loss of the 2,4-dimethoxybenzyl group with hydrogen transfer. Although the spectra of all four isomers also exhibited m/z 1 040 and 980 ions resulting from loss of acetic acid *via* McLafferty fragmentation, the extensive coincidence of fragments greatly reduces the utility of mass spectrometry as a probe for differentiation of compounds (5), (8), (11), and (13).

Under basic conditions the bis-(−)-fisetinidol-(+)-catechin (1) is presumably transformed to quinone methide¹¹ (2) involving both the B- and H-ring. The stereospecific pyran recyclization *via* 7-OH(D) and 5-OH(D) and the *Re*-faces at C-2 and -2' respectively, encountered for biflavonoids with 2,3-*trans*-3,4-*trans* constituent units,^{1,4} may feasibly rationalize the genesis of the dipyranochromene (4) as a product of dual isomerization. The (−)-fisetinidol-(4 α ,10)- and (4 α ,6)-tetrahydropyrano[2,3-*f*]- and [2,3-*h*]-chromene (7) and (10) presumably also have a common origin in quinone methide (2) by the stereochemical pathways indicated in the Scheme. Although these might have been overlooked as a result of minor concentrations, we could not find evidence for the C-2(c) and C-2(i) epimers of compounds (7) and (10) respectively. Notable also is the conspicuous absence of a 10-(−)-fisetinidol-tetrahydropyrano[2,3-*g*]chromene originating *via* pyran recyclization involving 7-OH(D) and C-2'. This may reflect preferred conformations about the interflavanyl bonds in compounds (1) and (2) favouring attack of 7-OH(D) at C-2 and of 5-OH(D) at C-2'.

Amongst the phlobatannins in the Scheme, the dipyrano[2,3-*f*:2',3'-*h*]chromene (3) and the (−)-fisetinidol-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene (6) coexist with (4 α ,6:4 α ,8)-bis-(−)-fisetinidol-(+)-catechin in the heartwood of both *Colophospermum mopane*¹² (mopane) and *Guibourtia coleosperma*¹² (false mopane). Their identity were assessed by comparison of 1H NMR and CD data of the decamethyl ether triacetates (5) and (8) with those of the synthetic counterparts. In *C. mopane* the dipyranochromene (3) is accompanied by two closely related 'isomerization-intermediates,' i.e. the (−)-fisetinidol-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene (15) with a 3-deoxy H-ring and also the (+)-guibourtinidol*-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene (17). The structures of these novel metabolites were defined by application of the 1H NMR protocol outlined above to their phenolic methyl ether triacetates (16) and (18) (1H NMR data—see table). Comparison of the CD data of compounds (16) and (18) with that of the synthetic (−)-fisetinidol-(4 α ,10)-tetrahydropyrano[2,3-*f*]chromene reveals striking resemblance in the 220–280 nm regions, thus presumably reflecting the same 2*R*,3*S*:6*R*,7*S*,8*S*:2*R*,3*S*,4*S*(c) absolute configuration for both structures (15) and (17). In the absence of synthetic evidence these allocations are, however, tentative.

Our recent demonstration of the diversity amongst the 'dimeric' analogues of this class of condensed tannins^{3,4,13} in conjunction with the results in this paper presumably indicate ubiquity similar to those of their 'conventional' bi- and tri-flavanoid precursors. The apparent conformational stability of the pyran-rearranged compounds and the relative planarity of the central 'core' after dual isomerization [e.g. the CDF1 tetracyclic system of compound (3)] will possibly contribute to reduced solubility in aqueous media and thus enhancement of their affinity for collagen substrates.

* (+)-Guibourtinidol is the (2*R*,3*S*)-2,3-*trans*-flavan-3,4',7-triol ABC-moiety.

Experimental

¹H NMR spectra were recorded on a Bruker AM-300 spectrometer for CDCl₃, C₆D₆, (CD₃)₂CO, or (CD₃)₂SO solutions with Me₄Si as internal standard. Mass spectral data were obtained with a Kratos MS80 instrument, and CD data in methanol on a Jasco J-20 spectropolarimeter. Preparative plates (PLC) (20 × 20 cm) Kieselgel PF₂₅₄ (1.0 mm) were air-dried and used without prior activation. Column chromatography was on Sephadex LH-20 in ethanol or mixtures of methanol and ethanol. Methylations were performed with an excess of diazomethane in methanol–diethyl ether at –15 °C for 48 h, while acetylations were in acetic anhydride–pyridine at ambient temperatures. Evaporations were done under reduced pressure at ca. 60 °C in a rotary evaporator.

Phlobatannin (6) from Guibourtia coleosperma.—The extraction of the heartwood with moist ethyl acetate and the fractionation of the extract by a Craig countercurrent procedure and gel chromatography (Sephadex LH-20/ethanol) were fully described in Part 3⁴ and will not be repeated here. Appropriate bands were selected according to the characteristic purple-red colouration on TLC with the spray reagent. The methyl ether fraction 2F₅ (886 mg) was resolved by PLC in hexane–acetone–ethyl acetate (5:3:2 v/v, × 4) to five bands, 2F₅A (R_F 0.60, 39 mg), 2F₅B (R_F 0.54, 79 mg), 2F₅C (R_F 0.50, 100 mg), 2F₅D (R_F 0.48, 160 mg), and 2F₅E (R_F 0.45, 185 mg). The 2F₅D band was further purified by PLC in chloroform–hexane–acetone (85:8:7 v/v, × 3) to give a main band at R_F 0.36 (50 mg). This was acetylated and resolved by PLC in benzene–acetone (9:1 v/v) to give (2R,3S:6R,7S,8S)-2,3-trans-6,7-trans-7,8-cis-3,7-diacetoxy-10-[(2R,3S,4S)-2,3-trans-3,4-trans-3-acetoxy-3',4',7-trimethoxyflavan-4-yl]-8-(2,4-dimethoxyphenyl)-2,6-bis-(3,4-dimethoxyphenyl)-9-methoxy-3,4,7,8-tetrahydro-2H,6H-pyrano[2,3-f]chromene* (8) as a white solid (15 mg), R_F 0.50 (Found: C, 66.5, H, 5.8. C₆₁H₆₄O₁₉ requires C, 66.54; H, 5.86%); ¹H NMR data (Table); CD [θ]₂₈₈ 0, [θ]₂₇₅ 0.6 × 10⁵, [θ]₂₅₃ 0.23 × 10⁵, [θ]₂₃₆ 2.8 × 10⁵, [θ]₂₃₂ 0, [θ]₂₂₇ –1.9 × 10⁵, and [θ]₂₁₇ –0.7 × 10⁵. Fraction 2F₅E comprised dipyrano[2,3-f:2',3'-h]chromenes related to a (4α,6:4β,8)-bis-(–)-fisetinidol-(+)-catechin and a (4α,6:4α,8)-bis-(–)-fisetinidol-(–)-epicatechin and will be dealt with elsewhere.

Phlobatannins (3), (15), and (17) from Colophospermum mopane.—Following the extraction and fractionation procedures of the methanol extract in Part 1¹⁴ of this series, PLC separation in benzene–acetone–methanol (6:3:1, v/v) of the residue (46 g) of the Soxhlet extraction afforded three crude fractions, at R_F 0.61 (13.2 g), 0.44 (3.7 g), and 0.28 (8.7 g). The R_F 0.61 and 0.44 fractions have been dealt with in Part 1.¹⁴ Gel chromatography (Sephadex LH-20/ethanol–methanol, 9:1 v/v) of the R_F 0.28 fractions subsequently gave nine sub-fractions.¹⁴ Sub-fraction 3 (*t*_{RR1} 71–88 h, 1.08 g) was methylated and the mixture was resolved by PLC in benzene–acetone (8:2 v/v, × 3) to two bands, at R_F 0.47 (84 mg) and 0.39 (134 mg).

The R_F 0.47 band was acetylated and successively purified by PLC in hexane–ethyl acetate–acetone (60:25:15 v/v, × 4) (R_F 0.31, 20 mg) and 1,2-dichloroethane–hexane–acetone (6:3:1 v/v, × 4) to give two bands, at R_F 0.48 (4 mg) and 0.46 (3 mg). The R_F 0.48 band gave (2R,3S:6R,7S,8S)-2,3-trans-6,7-trans-7,8-cis-3,7-diacetoxy-10-[(2R,3S,4S)-2,3-trans-3,4-trans-3-acetoxy-3',4',7-trimethoxyflavan-4-yl]-8-(2,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-9-methoxy-6-(4-methoxyphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrano[2,3-f]chromene* (16) as a white solid (Found: M⁺, 1 070.3951. C₆₀H₆₂O₁₈ requires M, 1 070.3940); ¹H NMR data (Table); *m/z* 1 070 (M⁺, 2.5%), 1 010 (7.0), 979

(6.0), 950 (4.0), 818 (4.0), 402 (6.0), 297 (9.0), 287 (28.0), 267 (10.0), 180 (100), and 191 (20); CD [θ]₂₈₇ 0, [θ]₂₇₅ 0.3 × 10⁵, [θ]₂₆₇ 0, [θ]₂₄₈ 0, [θ]₂₄₂ 0.2 × 10⁵, [θ]₂₃₉ 0, [θ]₂₃₀ –2.7 × 10⁵, [θ]₂₂₀ –5.8 × 10⁵, [θ]₂₁₀ –8.0 × 10⁵, and [θ]₂₀₁ 0.

The R_F 0.46 band gave (2R,3S:6R,7S,8S)-2,3-trans-6,7-trans-7,8-cis-3,7-diacetoxy-10-[(2R,3S,4S)-2,3-trans-3,4-trans-3-acetoxy-4',7-dimethoxyflavan-4-yl]-8-(2,4-dimethoxyphenyl)-2,6-bis-(3,4-dimethoxyphenyl)-9-methoxy-3,4,7,8-tetrahydro-2H,6H-pyrano[2,3-f]chromene* (18) as a white solid (Found: M⁺, 1 070.3927); ¹H NMR data (Table); *m/z* 1 070 (M⁺, 2.7%), 1 010 (9.0), 979 (8.0), 950 (3.0), 818 (2.0), 402 (34.0), 297 (6.0), 287 (59.0), 267 (39.0), 180 (100), and 191 (35.0); CD [θ]₂₉₀ 0, [θ]₂₇₈ 0.8 × 10⁵, [θ]₂₆₄ 0, [θ]₂₅₁ 0, [θ]₂₄₁ 1.2 × 10⁵, [θ]₂₃₇ 1.7 × 10⁵, [θ]₂₃₅ 0, [θ]₂₃₀ –3.9 × 10⁵, and [θ]₂₂₈ 0.

Acetylation of the R_F 0.39 methyl ether band (130 mg) and successive purification by PLC in hexane–ethyl acetate–acetone (60:25:15 v/v, × 2) (R_F 0.29, 62 mg) and in benzene–acetone (9:1 v/v, × 2) gave two bands, at R_F 0.37 (18 mg) and 0.28 (15 mg). The former band consisted of the heptamethyl ether diacetate of the known¹⁵ (–)-fisetinidol-(4α,8)-(+)-catechin. The R_F 0.28 band afforded (2R,3S:6R,7S,8S:10R,11S,12S)-2,3-trans-6,7-trans-7,8-cis-10,11-trans-11,12-cis-3,7,11-triacetoxy-8,12-bis-(2,4-dimethoxyphenyl)-2,6,10-tris-(3,4-dimethoxy-3,4,7,8,11,12-hexahydro-2H,6H,10H-dipyrano[2,3-f:2',3'-h]-chromene* (5) as a white solid (Found: C, 66.7; H, 5.8. C₆₁H₆₄O₁₉ requires C, 66.54; H, 5.86%); ¹H NMR data (Table); *m/z* 1 100 (M⁺, 4.5%), 1 040 (5.0), 980 (3.0), 847 (2.0), 685 (4.0), 596 (2.0), 403 (14.0), 298 (11.0), 287 (47.0), 267 (12.0), 180 (100), and 194 (37.0); CD [θ]₂₇₀ 0, [θ]₂₆₀ –0.7 × 10⁴, [θ]₂₅₀ 0, [θ]₂₃₅ 2.6 × 10⁴, [θ]₂₂₀ 0.6 × 10⁴, and [θ]₂₀₀ 0.

The (4α,6:4α,8)-bis-(–)-fisetinidol-(+)-catechin triflavanoid which apparently serves as biogenetic precursor to compounds (3) and (6) was present in several fractions of both *G. coleosperma* and *C. mopane*. Such detail will be presented elsewhere.

Synthesis of Triflavanoid (1).—(–)-Fisetinidol-(4α,8)-(+)-catechin 4-*O*(E)-methyl ether^{3,4} (2 g) was dissolved in 0.1M-HCl (250 ml) containing ethanol (10 ml). The mixture was stirred at room temperature and a solution of (+)-mollisacacidin (1 g) in 0.1M-HCl (50 ml) was added dropwise during 1 h. The mixture was stirred at room temperature for 15 h, then extracted with ethyl acetate (4 × 150 ml), and the extract was dried (Na₂SO₄) and evaporated to dryness. The light-brown residue (2.8 g) was subjected to column chromatography (Sephadex LH-20/ethanol, 3 × 150 cm column; 1.5 ml min^{–1} flow rate; 24-ml fractions; first litre of eluant discarded) to give four fractions, 1 (tubes 67–114, 677 mg), 2 (220–290, 580 mg), 3 (291–310, 270 mg), and 4 (310–376, 736 mg). Fraction 1 consisted of starting biflavanoid, fraction 2 of the (4β,6:4α,8)-bis-(–)-fisetinidol-(+)-catechin 4-*O*(E)-methyl ether, fraction 4 of its (4α,6)-isomer (1), and fraction 3 of a mixture of the two triflavanoids. Identification was effected by comparison of ¹H NMR data of the permethyl ether triacetates with those of authentic samples.⁶

Base-catalysed Conversion of Triflavanoid (1).—The mono-*O*-methyl ether (1) (500 mg) was dissolved in a 0.025M-NaHCO₃–0.025M-Na₂CO₃ buffer solution (200 ml) (pH 10) under nitrogen and the mixture was stirred at 50 °C for 5 h. Chilling to 0 °C followed by acidification with 0.1M-HCl, extraction with ethyl acetate (4 × 250 ml), drying (Na₂SO₄) of the extract, and evaporation to dryness, afforded a light-brown residue (439 mg). This was subjected to column chromatography (Sephadex LH-20/ethanol, 3 × 90 cm column; 1 ml min^{–1}, flow rate; 16-ml fractions; first 800 ml of eluant discarded) to give fractions 1 (tubes 17–52, 195 mg) and 2 (53–75, 87 mg).

Methylation of fraction 1 and PLC separation in benzene–

* Non-systematic numbering scheme used (see Scheme).

acetone (8:2 v/v, $\times 2$) afforded a band at R_F 0.37 (34 mg), which was acetylated to give the dipyrano[2,3-*f*:2',3'-*h*]chromene derivative (5) as a white solid (36 mg) with ^1H NMR and CD data identical with those of the corresponding derivative of metabolite (3) from *C. mopane*.

Fraction 2 was methylated and the mixture was resolved by PLC in benzene–acetone–methanol (85:13:2 v/v, $\times 3$) to two bands, at R_F 0.34 (14 mg) and 0.31 (9 mg). Acetylation of the R_F 0.34 band gave the 10-(–)-fisetinidoltetrahydropyrano[2,3-*f*]chromene derivative (8) (15 mg) with ^1H NMR and CD data identical with those of the corresponding derivative of compound (6) from *G. colesperma*. The R_F 0.31 band was acetylated to give (2R,3S:8R,9S,10S)-2,3-trans-8,9-trans-9,10-cis-3,9-diacetoxy-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3-acetoxy-3',4',7-trimethoxyflavan-4-yl]-10-(2,4-dimethoxyphenyl)-2,8-bis-(3,4-dimethoxyphenyl)-3,4,9,10-tetrahydro-2H,8H-pyrano (2,3-*h*]chromene* (11) as a white solid (10 mg) (Found: C, 66.6; H, 5.8. $\text{C}_{61}\text{H}_{64}\text{O}_{19}$ requires C, 66.54; H, 5.86%). ^1H NMR data (Table); CD $[\theta]_{290}^{\text{DMSO}}$ 0, $[\theta]_{283}^{\text{DMSO}}$ 0.5×10^5 , $[\theta]_{277}^{\text{DMSO}}$ 0, $[\theta]_{265}^{\text{DMSO}}$ -1.0×10^5 , $[\theta]_{252}^{\text{DMSO}}$ -0.7×10^5 , $[\theta]_{241}^{\text{DMSO}}$ -3.5×10^5 , $[\theta]_{239}^{\text{DMSO}}$ -3.1×10^5 , $[\theta]_{235}^{\text{DMSO}}$ -4.7×10^5 , $[\theta]_{233}^{\text{DMSO}}$ -1.2×10^5 , $[\theta]_{229}^{\text{DMSO}}$ -2.8×10^5 , $[\theta]_{226}^{\text{DMSO}}$ -1.9×10^5 , and $[\theta]_{220}^{\text{DMSO}}$ 0.

Synthesis of 6-(–)-Fisetinidoltetrahydropyrano[2,3-*h*]chromenes (9) and (12).—A mixture of the 8,9-trans-9,10-cis-tetrahydropyrano[2,3-*h*]chromene* (14)^{1,4} (204 mg) and (+)-mollisacacidin (49.7 mg) was dissolved in 0.1M-HCl (70 ml) and the solution was stirred at room temperature for 22.5 h. Extraction with ethyl acetate (10 \times 150 ml), drying (Na_2SO_4) of the extract, and evaporation of the solvent afforded a light-brown powder (210 mg). Column chromatography (Sephadex LH-20/ethanol, 3.2 \times 45 cm column; 0.3 ml min^{–1}, flow rate; 10-ml fractions; first 500 ml of eluant discarded) gave three fractions, 1 (tubes 60–97, 78 mg), 2 (103–125, 15 mg), and 3 (140–175, 66 mg). The first fraction consisted of starting phlobatannin (14). Fractions 2 and 3 were methylated separately and the products were resolved by PLC in benzene–acetone (8:2 v/v) to give methyl ether bands 2.1 (R_F 0.12, 8 mg) and 3.1 (R_F 0.12, 31 mg). Acetylation of band 3.1 and subsequent PLC in benzene–acetone (8:2 v/v) gave a band at R_F 0.45 (14 mg) comprising the (–)-fisetinidol-(4 α ,6)-tetrahydropyrano[2,3-*h*]chromene derivative (11) with physical data identical with those of the corresponding derivative of compound (10). Band 2.1 was acetylated and the product purified by PLC in benzene–acetone (8:2 v/v) to give the (–)-fisetinidol-(4 β ,6)-tetrahydropyrano[2,3-*h*]chromene derivative (13) as an amorphous solid, R_F 0.45 (5 mg) (Found: M^+ , 1 100.4058. $\text{C}_{61}\text{H}_{64}\text{O}_{19}$

requires M , 1 100.4041); ^1H NMR [$(\text{CD}_3)_2\text{SO}$; 453 K] δ 5.41 (9-H, dd, $J_{8,9}$ 10.0, $J_{9,10}$ 6.5 Hz) and 5.54 [3-H(i), dd, $J_{2,3}$ 8.3, $J_{3,4}$ 7.0 Hz]; CD $[\theta]_{290}^{\text{DMSO}}$ 0, $[\theta]_{285}^{\text{DMSO}}$ 0.4×10^5 , $[\theta]_{263}^{\text{DMSO}}$ 0, $[\theta]_{236}^{\text{DMSO}}$ 3.1×10^5 , $[\theta]_{231}^{\text{DMSO}}$ 5.8×10^5 , $[\theta]_{228}^{\text{DMSO}}$ 3.4×10^5 , and $[\theta]_{200}^{\text{DMSO}}$ 0.

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* Non-systematic numbering scheme used (see Scheme).