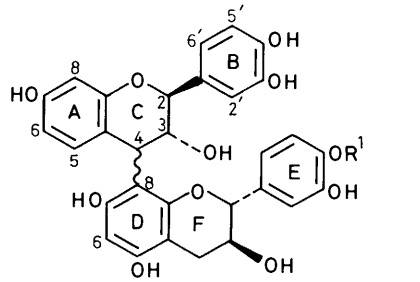
Oligomeric Flavanoids. Part 5.† Base-catalyzed C-Ring Isomerization of (+)-Fisetinidol-(+)-catechin Profisetinidins

Johann F. W. Burger, Jan P. Steynberg, Desmond A. Young, E. Vincent Brandt, and Daneel Ferreira*

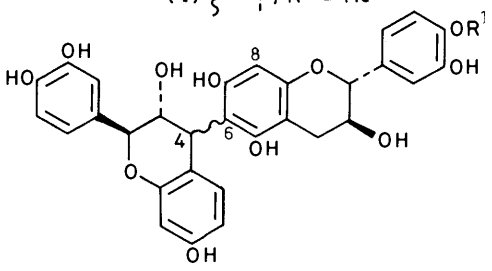
Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 South Africa

The (+)-fisetinidol-(+)-catechin profisetinidins are subject to similar base-catalyzed C-ring isomerizations to the quasi-enantiomeric (−)-fisetinidol-(+)-catechins. Whereas 'upper' 2,3-*trans*-3,4-*trans*-flavan-3-ol units are susceptible to stereospecific transformations, those species with a 2,3-*trans*-3,4-*cis*-configuration react more rapidly in a stereospecific manner and are furthermore subject to isomerization with concomitant interchange of resorcinol A- and pyrocatechol B-rings. These differences are explicable in terms of the effect of configuration at C-4 on both the rate of formation of intermediate B-ring quinone-methides and the recyclization step. This comparative study not only confirms the mechanism of A/B-ring interchange but also reveals serious shortcomings in the c.d. method for defining absolute configuration of phlobatannins with *cis*-*trans*- and all-*trans* configuration of their C-rings.

The need for synthesis of C-ring isomerized profisetinidin oligoflavanoids, termed phlobatannins,[1] in order to establish their structures unequivocally, has recently been demonstrated.[2,3] Ambiguities regarding the differentiation of these regioisomeric tetrahydropyranochromenes by physical method(s) necessitates a synthetic programme which precedes investigation of the naturally occurring analogues of this class of natural products. Our interest in the condensed tannins of *Rhus lancea* (karee)[4] and *Schinopsis balansea* (quebracho),[5] reputed for their profisetinidins with (2*S*,3*R*)-configuration of the repeating flavan-3-ol species, thus prompted investigation of base-catalysed conversions of the (+)-fisetinidol-(+)-catechin biflavanoids (**1**), (**3**), (**5**), and (**7**). Such an approach would not only serve to elaborate the structures of phlobatannins derived from these dimers but would also enable comparison with similar transformations of the diastereomerically related (−)-fisetinidol-(+)-catechins,[2,3,6] thus corroborating the proposed mechanisms associated with these conversions.



(**1**) ≡ α, R^1 = H
(**2**) ≡ α, R^1 = Me
(**3**) ≡ β, R^1 = H
(**4**) ≡ β, R^1 = Me



(**5**) ≡ α, R^1 = H
(**6**) ≡ α, R^1 = Me
(**7**) ≡ β, R^1 = H
(**8**) ≡ β R^1 = Me

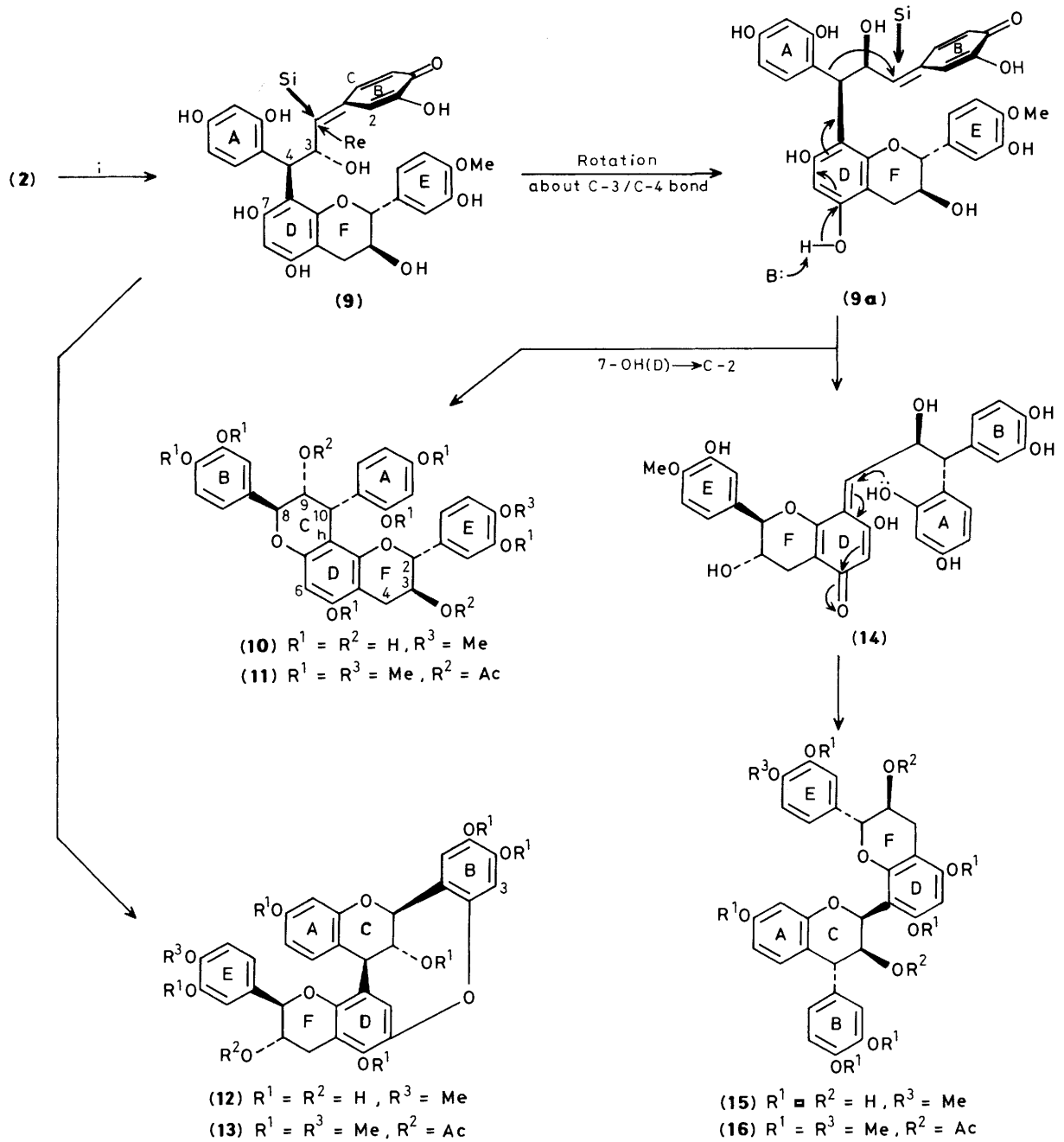
Results and Discussion

To prevent the characteristic side reactions associated with an E-ring quinone-methide,[2] the biflavanoids were used as the E-ring 4-*O*-methyl ethers (**2**), (**4**), (**6**), and (**8**). These were formed *via* acid-catalyzed condensation of (−)-leucofisetinidin-[(2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol][5] and 4′-*O*-methyl-(+)-catechin[2] and subsequent separation of the mixture using Sephadex LH–20 and Fractogel TSK HW–40(S) as chromatographic substrates.

Treatment of the (+)-fisetinidol-(4β,8)-(+)-catechin-*O*-methyl ether (**2**) with a 0.025M $NaHCO_3$–0.025M Na_2CO_3 buffer for 5 h at 50 °C under nitrogen (Scheme 1) gave partial conversion into a mixture comprised of the 8,9-*trans*-9,10-*cis*-tetrahydropyrano[2,3-*h*]chromene (**10**), the unique 4-aryl-2-flavanylbenzopyran (**15**), and a dehydro-(+)-fisetinidol-(+)-catechin (**12**). These compounds were identified by means of the spectroscopic data of their heptamethyl ether diacetates (**11**), (**16**), and (**13**).

^{1}H N.m.r. data (Table 1) of the tetrahydropyranochromene (**11**) revealed the familiar absence of the effects of dynamic rotational isomerism at ambient temperatures and n.O.e. associations of 2-OMe(A) with 3-H(A) (12.7%) and of 4-OMe(A) with both 3- and 5-H(A) (4.2 and 8.2% respectively) characteristic of a resorcinol species being 'liberated' from the C-ring in biflavanoid (**2**).[1] Coupling constants for the protons of this heterocycle ($J_{8,9}$ 10.0 and $J_{9,10}$ 6.0 Hz) in chromene (**11**) are in accord with the proposed *trans-cis* relative configuration and closely match those of the related phlobatannin with inverse stereochemistry at C-8, C-9, and C-10.[2] A strong negative Cotton effect (C.e.) in the 220—240 nm region of the c.d. spectrum of (**11**) indicates a 10α-aryl substituent thus facilitating definition of the absolute configuration as 2*R*,3*S*:8*S*,9*R*,10*R*. The relative 2,3-*cis*-3,4-*trans* configuration of the novel 4-aryl-2-flavanylbenzopyran (**16**) was

† Part 4, see ref. 3.



Scheme 1. Base-catalyzed conversion of (+)-fisetinidol-(+)-catechin *O*-methyl ether (**2**) and proposed route to the formation of the 4-aryl-2-flavanylbenzopyran (**15**). *Reagents and conditions:* i, $NaHCO_3$–Na_2CO_3 (pH 10), 50 °C, 5 h, N_2

evident from the coupling constants (Table 4) of the C-ring protons ($J_{2,3}$ 2.0 and $J_{3,4}$ 3.5 Hz).[3,7] Strong n.O.e. association of the D-ring proton (δ 6.04) with both methoxy groups [δ 3.63 (11.1%); δ 3.76 (12.3%)] of this ring is reminiscent of an 'intact' (+)-catechin species. The n.O.e. effect of a single methoxy function (δ 3.71) with both 6- and 8-H(A) similarly confirms the ordinary resorcinol A/C-ring arrangement of profisetinidin-type biflavanoids. Spin decoupling experiments establish a benzylic connection between 4-H(C), 5-H(A), and both 2- and 6-H of the pyrocatechol B-ring. Additional evidence for the *cis*-relationship of 2-H(C) and the C-4 pyrocatechol unit was obtained from the n.O.e. effects of 2-H(C) and 2- and 6-H(B) (1.6 and 2.8% respectively). Besides an additional but structurally insignificant n.O.e. effect of 2-H(C) with 7-OMe(D) (1.8%) this proton does not exhibit benzylic coupling thus reflecting an *o*-disubstituted phenyl residue at C-2. Collectively these features indicate an interchange of the pyrocatechol B-ring at C-2 and the C-4 (+)-catechin species in biflavanoid (**2**) thus leading to the unique 4-aryl-2-flavanylbenzopyran (**15**). The strong negative C.e. at 235 nm in the c.d. spectrum of its methyl ether diacetate (**16**) is consistent with a 4α-aryl group and hence 4*R* absolute configuration.[8–10] When the c.d. data is considered in conjunction with the ^1H n.m.r. coupling constants of the C-ring protons, the absolute configuration of this heterocycle in (**16**) may be defined as 2*S*,3*S*,4*R*. A possible mechanism explaining inversion of configuration at C-3 is discussed below.

One-proton singlets [δ 5.61, 3-H(B); δ 6.82, 6-H(B)] in the ^1H n.m.r. spectrum (Table 4) of the dehydro-(+)-fisetinidol-(+)-

Table 1. ^{1}H N.m.r. peaks (p.p.m.) of tetrahydropyrano[2,3-*h*]chromene heptamethyl ether diacetates (**11**), (**25**), (**27**), (**29**), and (**31**) in $CDCl_3$ (23 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

Ring	Proton	(11)	(25)	(27)	(29)	(31)
A	3	6.40 (d, 2.5)	6.43 (d, 2.5)	6.03 (d, 2.5)	6.31 (d, 2.5)	6.08 (d, 2.5)
	5	6.46 (dd, 2.5, 8.5)	6.33 (dd, 2.5, 8.5)	6.12 (dd, 2.5, 8.5)	6.47 (dd, 2.5, 8.5)	6.33 (dd, 2.5, 8.5)
	6	6.88 (d, 8.5)	6.68 (d, 8.5)	6.56 (d, 8.5)	7.47 (d, 8.5)	7.16 (d, 8.5)
B	2	6.86 (d, 2.0)	6.90 (d, 2.0)	6.84 (d, 2.0)	6.89 (d, 2.0)	6.54 (d, 2.0)
	5	6.79 (d, 8.0)	6.76—6.80[a]	6.73 (d, 8.5)	6.79 (d, 8.5)	6.43 (d, 8.0)
	6	6.91 (dd, 2.0, 8.0)		6.90 (dd, 2.0, 8.5)	6.65 (dd, 2.0, 8.5)	6.30 (dd, 2.0, 8.0)
C	8	5.00 (d, 10.0)	4.95 (br s, *ca.* 1.0)	4.96 (d, 8.0)	5.36 (br s, *ca.* 1.0)	5.36 (d, 5.5)
	9	5.47 (dd, 6.0, 10.0)	5.45 (dd, 1.0, 2.0)	5.56 (t, 8.0)	5.25 (dd, 1.0, 2.0)	5.93 (dd, 4.5, 5.5)
	10	5.06 (d, 6.0)	4.52 (d, 2.0)	4.59 (d, 8.0)	4.25 (d, 2.0)	4.09 (d, 4.5)
D	6	6.16 (s)	6.28 (s)	6.23 (s)	6.28 (s)	6.32 (s)
E	2	6.43 (d, 2.0)	6.65 (d, 2.5)	6.60 (d, 2.0)	6.43 (d, 2.0)	6.34 (d, 2.0)
	5	6.54 (d, 8.5)	6.73 (d, 8.5)	6.72 (d, 8.0)	6.61 (d, 8.0)	6.56 (d, 8.5)
	6	6.21 (dd, 2.0, 8.5)	6.67 (dd, 2.5, 8.5)	6.58 (dd, 2.0, 8.0)	6.42 (dd, 2.0, 8.0)	6.23 (dd, 2.0, 8.5)
F	2	4.85 (d, 7.0)	4.85 (d, 6.0)	4.29 (d, 7.5)	4.78 (d, 8.5)	4.67 (d, 9.0)
	3	5.01 (m)	5.30 (m)	5.22 (m)	4.92 (m)	4.84 (m)
	$4_{ax.}$	2.61 (dd, 6.0, 16.0)	2.67 (dd, 6.0, 17.0)	2.56 (dd, 7.0, 17.0)	2.64 (dd, 9.0, 16.0)	2.61 (dd, 9.5, 16.0)
	$4_{eq.}$	2.85 (dd, 5.5, 16.0)	2.79 (dd, 5.0, 17.0)	2.93 (dd, 6.0, 17.0)	3.12 (dd, 5.5, 16.0)	3.14 (dd, 5.5, 16.0)
	OMe	3.53 (2-A), 3.66, 3.75 (5-D), 3.80 (×2), 3.83, 3.84 (each s)	3.75 (2-A), 3.76, 3.77 (4-A), 3.81 (5-D), 3.82, 3.83, 3.85, each s	3.44 (2-A), 3.65 (4-A), 3.76 (5-D), 3.80, 3.81, 3.82, 3.85, each s	3.50 (2-A), 3.51, 3.77 (4-A), 3.80, 3.81, 3.83 (5-D), 3.86, each s	3.47, 3.62 (2-A), 3.66, 3.70, 3.74 (4-A), 3.79, 3.84 (5-D), each s
	OAc	1.66, 1.92 (each s)	1.92 (×2), s	1.75, 1.81, each s	1.87, 1.89, each s	1.85, 1.92, each s

[a] Second order.

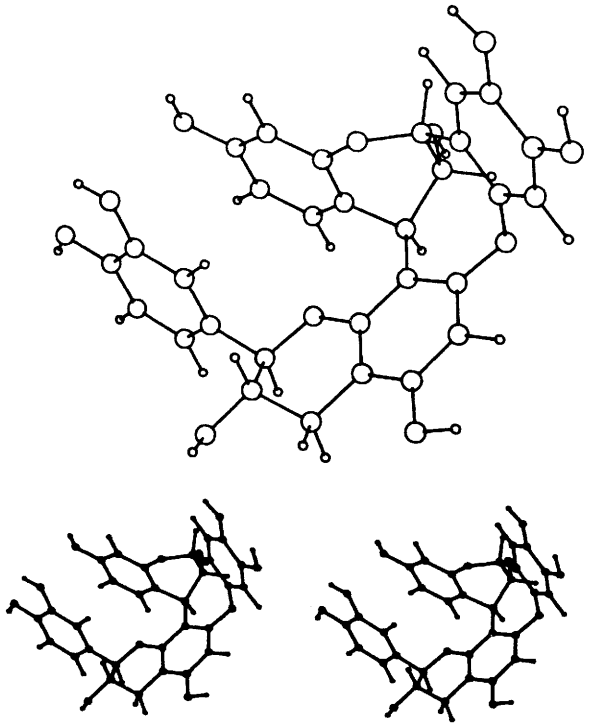
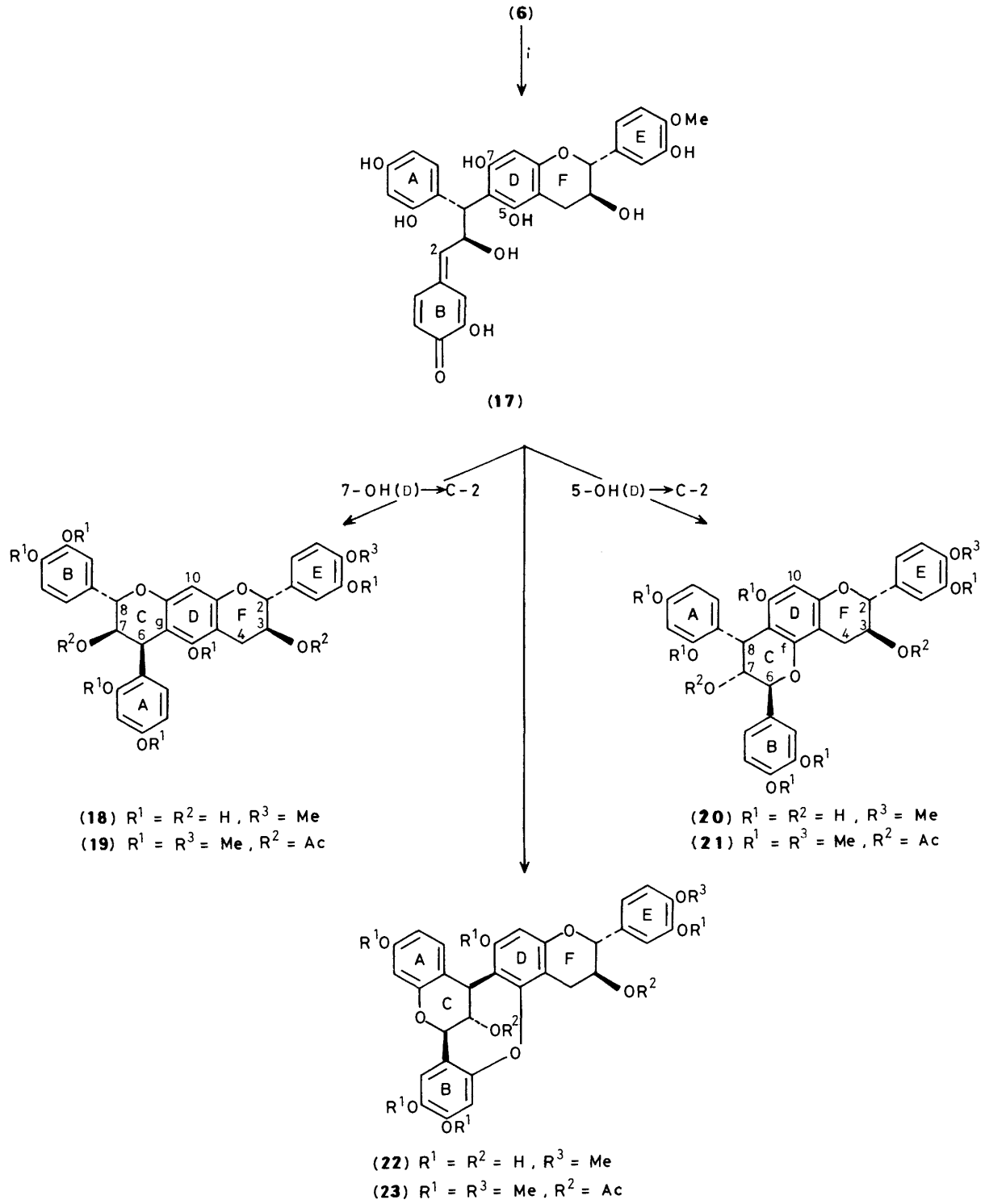


Figure. 3D Perspective and stereo-pair of the dehydro-(+)-fisetinidol-(+)-catechin (**12**)

catechin derivative (**13**) indicated substitution at C-6(B) in the parent biflavanoid (**2**). The small coupling constants of the C-ring protons ($J_{2,3}$ 2.5 and $J_{3,4}$ 3.5 Hz) are compatable with dihedral angles approaching 90° as a result of conformational restrictions imposed on this ring by the 8-membered oxygen heterocycle. The abnormal shielding of 4-H(C) (δ 3.39), 3-H(B) (δ 5.61), and 2- and 6-H(E) (δ 5.86 and 6.13 respectively) relative to the chemical shifts of these protons in the parent biflavanoid (**2**) is explicable in terms of anisotropy of proximal functionalities, *e.g.* 2- and 6-H(E) by the A-ring. Similar deshielding of 3-H(C) (δ 6.02) results from its close proximity to the oxygen of the 8-membered ring. The Figure represents a computer simulated 3D perspective demonstrating the cup-like conformation involving the A-, B-, C-, D-, and 8-membered rings. Such a conformation resembles those of the calixarenes which were recently established by *X*-ray analysis.[11]

The C-ring quinone-methide (**9**) apparently served as common precursor to the tetrahydropyrano[2,3-*h*]chromene (**10**), the 4-aryl-2-flavanylbenzopyran (**15**), and the dehydro analogue (**12**). Stereospecific cyclization involving 7-OH(D) and the *Si*-face at C-2 in the quinone-methide, *i.e.* with retention of configuration of C-2 in biflavanoid (**2**), affords the 8,9-*trans*-9,10-*cis*-phlobatannin (**10**) (*cf.* ref. 2). Formation of the dehydro-(+)-fisetinidol-(+)-catechin (**12**) represents the alternative mode of cyclization of 7-OH(D) with 6-C(B) followed by oxidative removal of hydride ion during work-up. Initial 1,3-aryl migration of the resorcinol unit to the *Si*-face at C-2 in the quinone-methide (**9a**) and subsequent cyclization involving 2-OH of the resorcinol species and the *Si*-face in quinone-methide (**14**) could feasibly explain the formation of the novel 4-aryl-2-flavanylbenzopyran (**15**) with inversed stereochemistry at C-3(C). Such a migration of the resorcinol unit contrasts with observations of a preferential shift of the (+)-catechin species in profisetinidins with 3,4-*cis*-configuration (C-ring) owing to the enhanced migratory aptitude of its phloroglucinol-type D-ring.[3,6]

Base treatment of the (+)-fisetinidol-(4β,6)-(+)-catechin-*O*-methyl ether (**6**) as above led to conversion into a mixture comprised of the 7,8-*trans*-6,7-*cis*-tetrahydropyrano[2,3-*g*]-chromene (**18**), 6,7-*trans*-7,8-*cis*-tetrahydropyrano[2,3-*f*]-chromene (**20**), and the dehydro-(+)-fisetinidol-(+)-catechin (**22**) (Scheme 2). These were again characterized by means of the physical data of their permethyl ether diacetates (**19**), (**21**), and (**23**). ^{1}H N.m.r. data (Tables 2 and 3) of the tetrahydropyrano-chromenes (**19**) and (**21**) confirm the *trans-cis* configurations [$J_{7,8}$ 10.5 and $J_{6,7}$ 5.5 Hz for (**19**); $J_{6,7}$ 10.5 and $J_{7,8}$ 5.5 Hz for (**21**)] for their C-rings. These regioisomers are differentiated by means of n.O.e. experiments which indicate selective association (14.5%) between the D-ring singlet (δ 6.12) and the methoxy



Scheme 2. Base-catalyzed conversion of (+)-fisetinidol-4β,6)-(+)-catechin *O*-methyl ether (**6**). *Reagents and conditions:* i, $NaHCO_3$–Na_3CO_3 (pH 10), 50 °C, 5 h, N_2

group (δ 3.55) of this ring in the case of the [2,3-*f*]-isomer (**21**) only. The n.O.e. effect (1.2%) of 9-OMe(D) with 8-H(C) for the [2,3-*f*]-isomer (**21**) but absence of similar associations for [2,3-*h*]-analogues, *e.g.* (**11**), may serve as useful parameters in the differentiation of these classes of phlobatannins. Similar effects were also observed for the (−)-fisetinidol-(+)-catechin derived tetrahydropyrano[2,3-*h*]- and [2,3-*f*]chromenes.[2] Associations between 5-OMe(D) and the methylene protons of ring F ($H_{4ax.}$ 0.8% and $H_{4eq.}$ 0.5%) for the tetrahydropyrano-[2,3-*h*]chromene (**11**) are, however, inconsistent for analogues of this series and thus less reliable as a probe for differentiation. Assignment of *R* absolute configuration to C-6 and C-8 in the [2,3-*g*]-(**19**) and [2,3-*f*]-(**21**) regioisomers respectively was effected by the high-amplitude negative C.E.s in the 220—240 nm regions of their c.d. spectra.

The ratio (*ca.* 2:1) of the [2,3-*f*]- and [2,3-*g*]-phlobatannins

Table 2. ^{1}H N.m.r. peaks (p.p.m.) of tetrahydropyrano[2,3-*g*]chromene heptamethyl ether diacetates (**19**), (**35**), and (**37**) in $CDCl_3$ (23 °C) at 300 MHz. Splitting patterns and *J*-values are given in parentheses

Ring	Proton	(19)	(35)	(37)
A	3	6.47 (d, 2.5)	6.51 (d, 2.5)	6.30 (d, 2.5)
	5	6.44 (dd, 2.5, 8.5)	6.36 (dd, 2.5, 8.5)	6.47 (dd, 2.5, 8.5)
	6	6.87 (d, 8.5)	6.65 (d, 8.5)	7.43 (d, 8.5)
B	2	6.84 (d, 2.0) } *a*	6.87 (d, 2.0)	6.90 (d, 2.0)
	5	6.78 (d, 8.0) } *a*	} 6.75—6.77 [b]	6.81 (d, 8.0)
	6	6.88 (dd, 2.0, 8.0) } *a*	} 6.75—6.77 [b]	6.70 (dd, 2.0, 8.0)
C	6	5.15 (d, 5.5)	5.03 (br s, *ca.* 1.0)	5.44 (br s, *ca.* 1.0)
	7	5.41 (dd, 5.5, 10.5)	5.37 (dd, 1.0, 2.0)	5.34 (dd, 1.0, 2.0)
	8	4.98 (d, 10.5)	4.62 (d, 2.0)	4.38 (d, 2.0)
D	10	6.43 (s)	6.55 (s)	6.51 (s)
E	2	6.88 (d, 2.0) } *a*	6.91 (d, 2.0)	6.93 (d, 2.0)
	5	6.83 (d, 8.0) } *a*	6.85 (d, 8.0)	6.85 (d, 8.0)
	6	6.91 (dd, 2.0, 8.0) } *a*	6.93 (dd, 2.0, 8.0)	6.96 (dd, 2.0, 8.0)
F	2	4.97 (d, 8.0)	5.07 (d, 6.5)	4.97 (d, 8.0)
	3	5.30 (m)	5.36 (m)	5.30 (m)
	$4_{ax.}$	2.70 (dd, 7.5, 16.5)	2.76 (dd, 8.0, 16.5)	2.75 (dd, 8.5, 16.5)
	$4_{eq.}$	2.97 (dd, 5.0, 16.5)	2.93 (dd, 5.0, 16.5)	3.10 (dd, 5.5, 16.5)
	OMe	3.28 (5-D), 3.79 (4-A), 3.81 (2-A), 3.83, 3.84, 3.86 (× 2), each s	3.33 (5-D), 3.78 (4-A), 3.83 (× 2), 3.85, 3.87, 3.88 (2-A), each s	3.30 (5-D), 3.50 (2-A), 3.76 (4-A), 3.86, 3.87, 3.88 (× 2), each s
	OAc	1.71, 1.90, each s	1.90, 1.95, each s	1.86, 1.90, each s

[a] May be interchanged. [b] Second order.

Table 3. ^{1}H N.m.r. peaks (p.p.m.) of tetrahydropyrano[2,3-*f*]chromene heptamethyl ether diacetates (**21**), (**39**), (**41**), and (**43**) in $CDCl_3$ (23 °C) at 300 MHz. Splitting patterns and coupling constants (Hz) are given in parentheses

Ring	Proton	(21)	(39)	(41)	(43)
A	3	6.46 (d, 2.5)	6.51 (d, 2.5)	6.30 (d, 2.5)	6.30 (d, 2.5)
	5	6.40 (dd, 2.5, 8.5)	6.35 (dd, 2.5, 8.5)	6.02 (dd, 2.5, 8.5)	6.47 (dd, 2.5, 8.5)
	6	6.76 (d, 8.5)	6.65 (d, 8.5)	6.32 (d, 8.5)	7.42 (d, 8.5)
B	2	6.81 (d, 2.0)	6.83 (d, 2.0)	6.67 (d, 2.0)	6.87 (d, 2.0)
	5	6.77 (d, 8.5)	6.74—6.79 [a]	6.63 (d, 8.0)	6.77 (d, 8.5)
	6	6.87 (dd, 2.0, 8.5)		6.75 (dd, 2.0, 8.0)	6.61 (dd, 2.0, 8.5)
C	6	4.92 (d, 10.5)	4.95 (br s, *ca.* 1.0)	5.07 (d, 6.0)	5.25 (br s, *ca.* 1.0)
	7	5.38 (dd, 5.5, 10.5)	5.40 (dd, 1.0, 2.0)	5.67 (dd, 5.0, 6.0)	5.31 (dd, 1.0, 2.0)
	8	5.08 (d, 5.5)	4.50 (d, 2.0)	4.48 (d, 5.0)	4.30 (d, 2.0)
D	10	6.12 (s)	6.17 (s)	6.13 (s)	6.19 (s)
E	2	6.90 (d, 2.0)	6.95 (d, 2.0)	6.92 (d, 2.0)	6.95 (d, 2.0)
	5	6.83 (d, 8.0)	6.86 (d, 8.0)	6.84 (d, 8.0)	6.84 (d, 8.0)
	6	6.93 (dd, 2.0, 8.0)	6.99 (dd, 2.0, 8.0)	6.96 (dd, 2.0, 8.0)	6.96 (dd, 2.0, 8.0)
F	2	4.98 (d, 7.5)	4.96 (d, 8.0)	4.98 (d, 8.0)	5.00 (d, 8.0)
	3	5.35 (m)	5.42 (m)	5.38 (m)	5.41 (m)
	$4_{ax.}$	2.66 (dd, 7.5, 16.5)	2.76 (dd, 8.5, 16.5)	2.78 (dd, 8.0, 16.5)	2.82 (dd, 8.0, 16.5)
	$4_{eq.}$	3.02 (dd, 4.5, 16.5)	3.21 (dd, 5.5, 16.5)	3.16 (dd, 5.5, 16.5)	3.16 (dd, 5.5, 16.5)
	OMe	3.55 (9-D), 3.78 (2-A), 3.79 (4-A), 3.82, 3.83 (× 2), 3.86, each s	3.57 (9-D), 3.79 (4-A), 3.82, 3.83, 3.87, 3.88, 3.89 (2-A), each s	3.42 (9-D), 3.67 (4-A), 3.75, 3.79, 3.80 (2-A), 3.86, 3.87, each s	3.49 (2-A), 3.59 (9-D), 3.76 (4-A), 3.86 (× 2), 3.87 (× 2), each s
	OAc	1.70, 1.91, each s	1.89, 1.91, each s	1.90, 1.92, each s	1.88, 1.93, each s

[a] Second order.

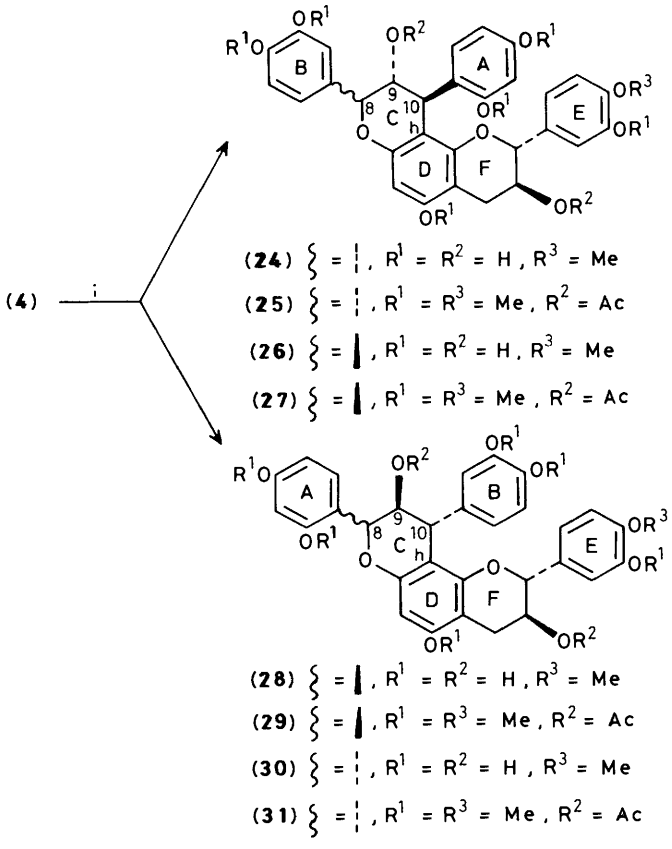
(**20**) and (**18**) reflects a similar preference for ring isomerization of biflavanoid (**6**) involving 5-OH(D) and C-2 of quinone-methide (**17**) as that encountered for the (−)-fisetinidol-(4α,8)-(+)-catechin.[2] Since it has been shown that the two rotational isomers at the interflavan bond are not evenly populated in the procyanidins,[12] the aforementioned observation presumably results from a preferred interflavanyl conformation favouring participation of 5-OH(D) in the cyclization step. MM2 Calculations to confirm such an assumption are presently being undertaken. ^{1}H N.m.r. data (Table 4) of the dehydro-(+)-fisetinidol-(+)-catechin derivative (**23**) again displayed two one-proton singlets [δ 5.43, 3-H(B); δ 6.92, 6-H(B)] indicative of substitution at C-6(B) in the biflavanoid precursor (**6**). The chemical shifts of these signals are confirmed by appropriate n.O.e. and decoupling experiments using the B-ring methoxy- and 2-H(C) resonances as reference signals. Involvement of 5-OH(D) in cyclization is confirmed by strong n.O.e. association (12.6%) of 7-OMe(D) (δ 3.71) with 8-H(D) (δ 6.04). The conspicuous shielding of 3-H(B) (δ 5.43) and 4-H(C) (δ 3.47) is explicable on the same basis as regioisomer (**13**) (see above). Owing to removal of ring E from the anisotropic shielding zone of the A-ring as compared to its position in (**13**), the protons of the former ring in (**23**) resonate in the anticipated low-field aromatic region. Coupling constants for the C-ring protons ($J_{2,3}$ 2.0 and $J_{3,4}$ 3.0 Hz) reflect a similar cup-like conformation involving the A-, B-, C-, D-, and 8-membered oxygen heterocycle as that proposed for the (4,8)-coupled analogue (**13**). A common feature of the dehydro-(+)-fisetinidol-(+)-catechin derivatives (**13**) and (**23**) and the diastereoisomer derived from the (−)-fisetinidol-(4α,8)-(+)-catechin [2] is the large coupling constant of

Table 4. ^{1}H N.m.r. peaks (p.p.m.) of the 4-aryl-2-flavanylbenzopyran and dehydro-(+)-fisetinidol-(+)-catechin methyl ether acetates (**16**), (**13**), and (**23**) in $CDCl_3$ (23 °C) at 30 MHz. Splitting patterns and J values (Hz) are given in parentheses

Ring	Proton	(16)	(13)	(23)
A	5	6.78 (d, 8.0)	6.74 (d, 8.5)	6.81 (d, 8.0)
	6	6.41 (dd, 2.5, 8.0)	6.44 (dd, 2.5, 8.5)	6.36 (dd, 2.5, 8.0)
	8	6.44 (d, 2.5)	5.90 (d, 2.5)	6.34 (d, 2.5)
B	2	6.73 (d, 2.0)		
	3/5	6.66 (d, 8.0)	5.61 (s)	5.43 (s)
	6	6.58 (dd, 2.0, 8.0)	6.82 (s)	6.92 (s)
C	2	5.75 (d, 2.0)	5.15 (t, 2.5)	5.29 (t, 2.0)
	3	5.31 (dd, 2.0, 3.5)	6.02 (dd, 2.5, 3.5)	5.80 (t, 3.0)
	4	4.11 (d, 3.5)	3.39 (dd, 2.0, 3.5)	3.47 (dd, 2.0, 3.0)
D	6/8	6.04 (s)	6.37 (s)	6.04 (s)
E	2	6.83 (d, 2.0)	5.86 (d, 2.0)	6.90 (d, 2.0)
	5	6.73 (d, 8.5)	6.51 (d, 8.0)	6.87 (d, 8.0)
	6	6.75 (dd, 2.0, 8.5)	6.13 (dd, 2.0, 8.0)	6.95 (dd, 2.0, 8.0)
F	2	4.86 (d, 6.0)	3.65 (d, 10.0)	5.08 (d, 8.0)
	3	5.22 (m)	4.55 (m)	5.32 (m)
	$4_{ax.}$	2.65 (dd, 6.5, 17.0)	2.35 (dd, 6.0, 16.5)	2.48 (dd, 8.5, 16.5)
	$4_{eq.}$	2.78 (dd, 5.5, 17.0)	3.03 (dd, 6.0, 16.5)	2.95 (dd, 5.5, 16.5)
	OMe	3.63 (5-D), 3.71 (7-A), 3.72, 3.76 (7-D), 3.77, 3.79, 3.86, each s	3.50 (7-A), 3.51, 3.73 (4-B), 3.75, 3.77 (5-D), 3.88 (5-B), each s	3.15 (4-B), 3.70 (7-A), 3.71 (7-D), 3.89, 3.90 (5-B) each s
	OAc	1.87, 1.83, each s	1.76, 1.92, each s	1.90, 1.95, each s

2- and 3-H(F) ($J_{2,3}$ 8.5—10.0 Hz). This indicates a predominance of E-forms towards the F-ring conformation[13] since an axial E-ring would lead to severe repulsive interactions with rings A and B and thus contribute less prominently.

Treatment of the (+)-fisetinidol-(4α,8)-(+)-catechin *O*-methyl ether (**4**) at pH 10 for 3 h at 50 °C under nitrogen led to complete conversion to a mixture from which four ring-isomerized products were obtained (Scheme 3). These include the 8,9-*cis*-9,10-*trans*- and 8,9-*trans*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromenes (**24**) and (**26**) [$J_{8,9}$ *ca.* 1.0 and 8.0; $J_{9,10}$ 2.0 and 8.0 Hz for their heptamethyl ether diacetates (**25**) and (**27**) respectively] and the pair of *cis-trans*- and all-*trans* analogues (**28**) and (**30**) [$J_{8,9}$ *ca.* 1.0 and 5.5; $J_{9,10}$ 2.0 and 4.5 Hz for (**29**) and (**31**) respectively] with interchanged resorcinol A- and pyrocatechol B-rings (*cf.* Table 1 for ^{1}H n.m.r. data).

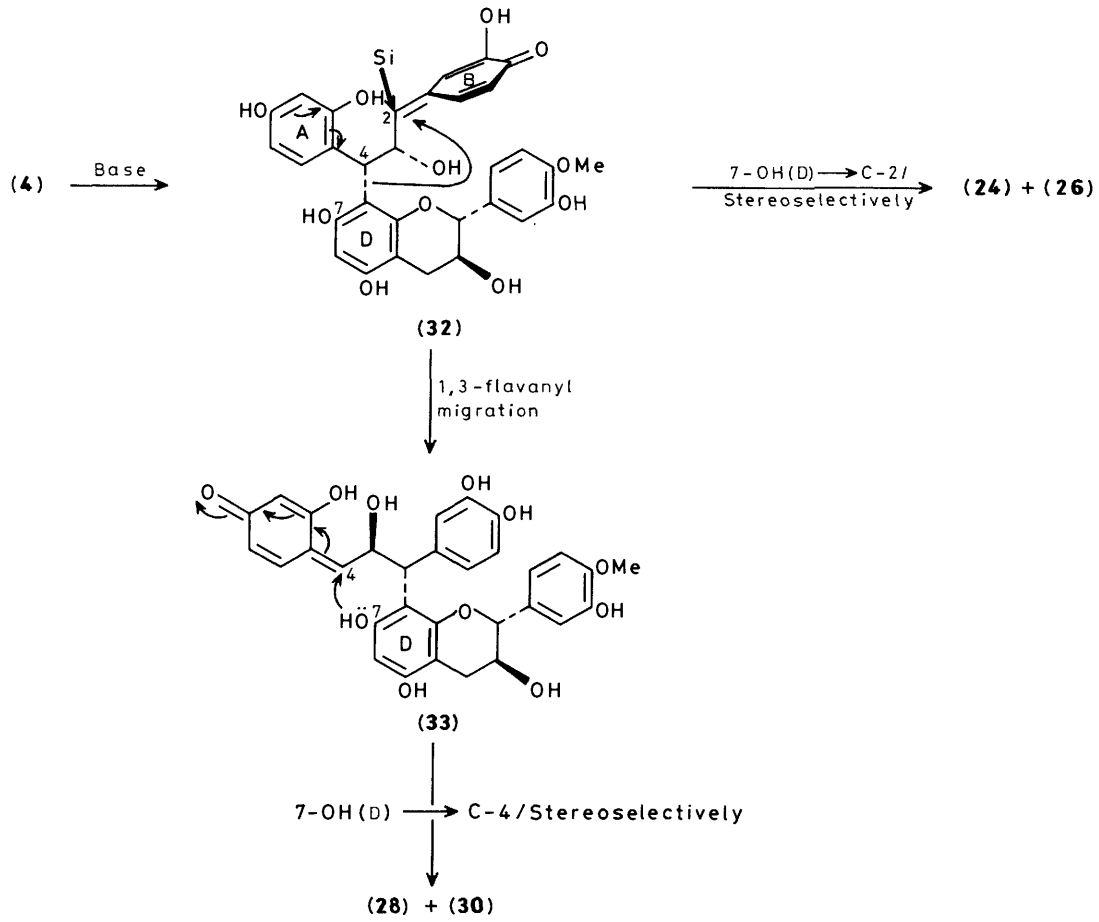


Scheme 3. Base-catalyzed conversion of (+)-fisetinidol-(4α,8)-(+)-catechin *O*-methyl ether (**4**). *Reagents and conditions:* i, $NaHCO_3$–Na_2CO_3 (pH 10), 50 °C, 3 h, N_2

Differentiation of the groups (**25**), (**27**) and (**29**), (**31**) was effected by comparison of the chemical shifts of their 6-H(A) and 8-H(C) resonances. In the latter pair these protons exhibit the conspicuous deshielding [δ −0.79 and −0.70, 6-H(A); −0.41 and −0.40, 8-H(C) for (**29**) and (**31**) respectively] associated with such a ring interchange.[3] The chemical shifts of 8- and 10-H(C), and thus proof for an A-/B-ring interchange in the *cis-trans* analogue (**29**), are confirmed by 2D-heteronuclear correlation of these protons with C-8 and C-10 respectively (δ 67.79 and 41.19). Owing to insufficient quantities a similar approach could not be adopted for the all-*trans* isomer (**31**). When taken in conjunction with spin decoupling results, *i.e.* benzylic coupling between 8-H(C) and 2- and 6-H(B) in (**25**) and (**27**) but with 6-H(A) in (**29**) and (**31**) and between 10-H(C) and 6-H(A) in (**25**) and (**27**) but with 2- and 6-H(B) in (**29**) and (**31**), the above deshielding phenomena are sufficient to differentiate these classes of phlobatannins (see also below).

Prominent n.O.e associations between 8-H(C) (δ 4.95) and 6-H (δ 6.68, 2.5%) in (**25**) and between 8-H(C) (δ 5.36) and 2- (δ 6.90, 1.4%) and 6-H(B) (δ 6.78, *ca.* 3.0%*) in (**29**) confirm their *cis-trans* configurations. These furthermore indicate preferred sofa conformations (C-ring) in which the C-10 aryl substituent approaches a near-axial [β for (**25**), α for (**29**)] orientation. In the all-*trans* analogues (**27**) and (**31**) the above associations are conspicuously absent. The sequence of formation of the tetrahydropyrano[2,3-*h*]chromenes (**24**), (**26**), (**28**), and (**30**) was determined by analysis of samples taken at regular intervals by column chromatography using Sephadex LH-20 and ethanol as eluant. When taken in conjunction with observations of the stability of these compounds under conditions similar to those

* Approximation due to signal overlap.



Scheme 4. Proposed mechanism of formation of the A-/B-ring interchanged phlobatannins (**28**) and (**30**)

of their formation, these results indicate the simultaneous genesis of the phlobatannins from biflavanoid (**4**).[3,6] The pair (**24**) and (**26**) thus originates by stereoselective recyclization involving 7-OH(D) and both *Re*- and *Si*-faces* in quinone-methide (**32**) (Scheme 4). The unique conversion (**4**)→(**28**) + (**30**) is explicable in terms of migration of the (+)-catechin species at C-4 to the *Si*-face at C-2 in quinone-methide (**32**). Stereoselective pyran recyclization of (**33**) *via* 7-OH(D) generates the tetrahydropyrano[2,3-*h*]chromenes (**28**) and (**30**). The latter mechanism prescribes inversion of the absolute configuration at the chiral centres of ring C in the ring-interchanged analogues (**28**) and (**30**) when compared to those of the 'normal' isomers (**24**) and (**26**). Such an inversion at C-10 should lead to reversal of the sign of the low wavelength C.e.s in the c.d. spectra of groups (**24**), (**26**) and (**28**), (**30**). The heptamethyl ether diacetates (**25**), (**27**) and (**29**), (**31**), however, all exhibit intense negative C.e.s in the 220—240 nm region of their c.d. spectra, indicating a 10-aryl substituent below the plane of the C/D-ring system by application of the aromatic quadrant rule.[10] These negative C.e.s are consistent with the 10*R* absolute configuration proposed for both (**29**) and (**31**) but atypical of the anticipated 10*S* configuration for (**25**) and (**27**). Since a similar discrepancy was also observed for those (−)-fisetinidol-(4β,8)-(+)-catechin derived 8,9-*cis*-9,10-*trans*- and all-*trans*-tetrahydropyrano[2,3-*h*]chromenes† with 10β-aryl substituents,[3,6] the sign of the low wavelength C.e. is obviously not a reliable parameter for the determination of absolute configuration at C-10 in [2,3-*h*]-phlobatannins with these configurations. Comparison of the coupling constants of 2-H(F) (Table 5) in the series of [2,3-*h*]-isomers derived from the 3,4-*cis*-(−)- and -(+)-fisetinidol-(+)-catechins indicates that in each of the groups of four, one pair of compounds exhibits *J*-values of 6.0—7.5 Hz and the remaining pair 8.5—9.0 Hz. Owing to the fact that the magnitude of the coupling constant of 2-H of flavan-3-ols is determined by the ratio of A- and E-conformers[13] (C-ring), *i.e.* small *J*-values (*ca.* 7.0 Hz) reflecting significant contributions of A-forms, the aforementioned variation of $J_{2,3(F)}$ may be attributed to similar phenomena operating in the (+)-catechin species of the [2,3-*h*]-phlobatannins. Conformational analysis (Dreiding models) indicates that 10α-aryl substituents should inhibit the existence of A-conformers (F) thus resulting in larger coupling constants of 2-H while 10β-groups would readily

Table 5. 2-H(F) Coupling constants (Hz) of 8,9-*cis*-9,10-*trans*- and all-*trans*-[2,3-*h*]-phlobatannins derived from (+)- and (−)-fisetinidol-(+)-catechins (2*S*- and 2*R*-series respectively)

	2*S*	2*R*
cis-trans	6.0	8.5
cis-trans (RIC)[a]	8.5	6.0
trans-trans	7.5	8.5
trans-trans (RIC)[a]	9.0	7.0

[a] RIC Denotes ring-interchanged products.

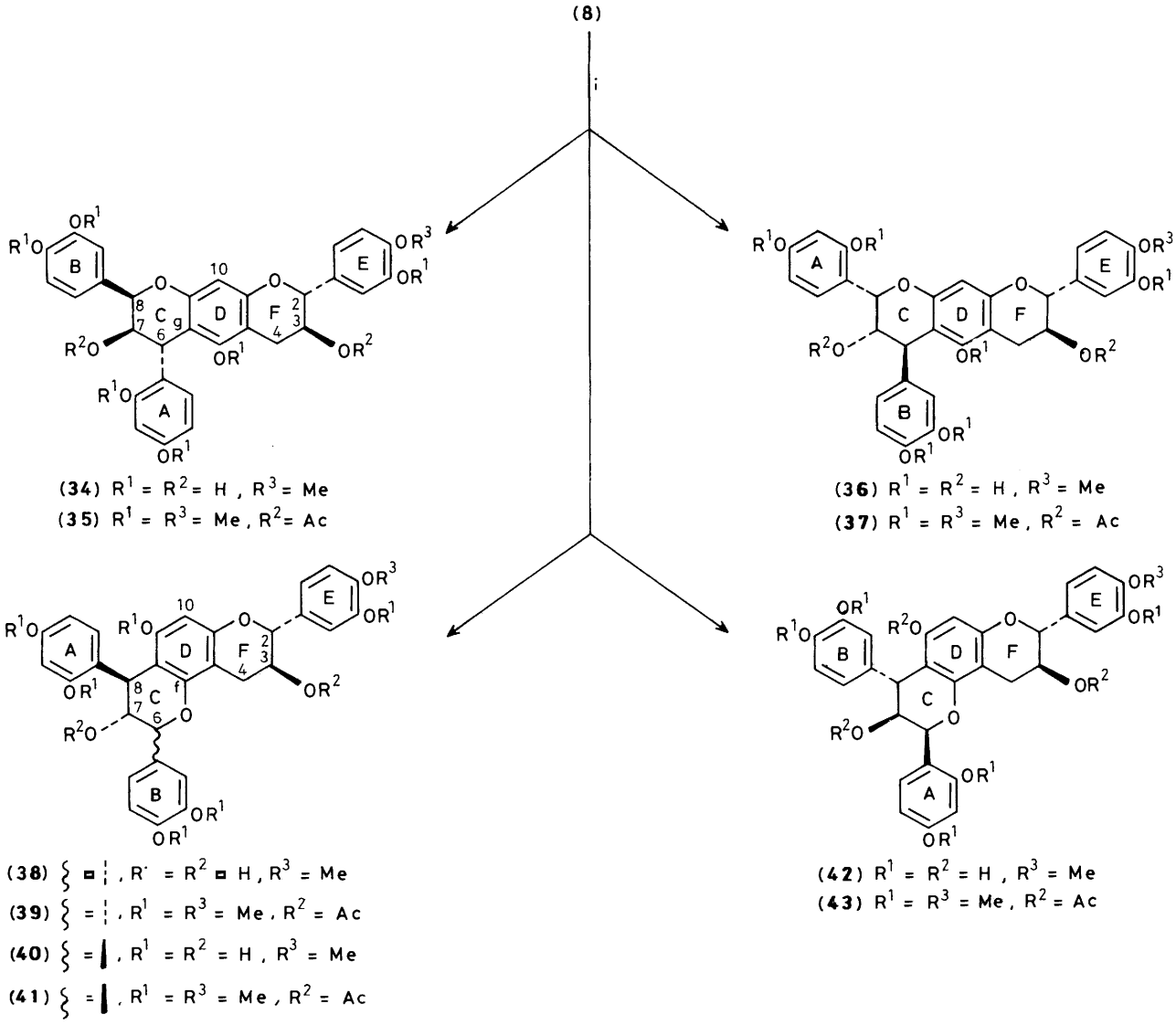
* The equivalent of, respectively, inversion and retention of absolute configuration at C-2 in biflavanoid (**4**).

† Possessing an enantiomeric relationship to (**25**), (**27**), (**29**), and (**31**) with regard to their C-rings.

'allow' these A-forms with concomitant decrease in *J*-values. Based on these fundamentals the 'normal' 8,9-*cis*-9,10-*trans*- and all-*trans*-tetrahydropyrano[2,3-*h*]chromenes (**25**) and (**27**) [$J_{2,3(F)}$ 6.0—7.5 Hz] and the ring-interchanged analogues (**29**) and (**31**) [$J_{2,3(F)}$ 8.5—9.0 Hz] possess β- and α-orientated aryl species at C-10 respectively. Consideration of these features in conjunction with the ^{1}H n.m.r. coupling constants of C-ring protons and the known absolute configuration of biflavanoid (**4**) hence enables definition of the absolute configuration of these analogues as 2*R*,3*S*:8*R*,9*R*,10*S* for (**25**); 2*R*,3*S*:8*S*,9*R*,10*S* for (**27**); 2*R*,3*S*:8*S*,9*S*,10*R* for (**29**) and 2*R*,3*S*:8*R*,9*S*,10*R* for (**31**). The phenomenon of ring interchange being associated with inversion of absolute configuration at C-3 of the biflavanoid precursor is thus firmly established (*cf.* refs. 3 and 6).

Base treatment of the (+)-fisetinidol-(4α,6)-(+)-catechin methyl ether (**8**) afforded a mixture consisting of five ring-isomerized products (**34**), (**36**), (**38**), (**40**), and (**42**) which were characterized as heptamethyl ether diacetates (**35**), (**37**), (**39**), (**41**), and (**43**) (Scheme 5; ^{1}H n.m.r. data, Tables 2 and 3). Amongst these the anticipated 7,8-*cis*-6,7-*trans*-tetrahydropyrano[2,3-*g*]chromene (**35**) ($J_{7,8}$ *ca.* 1.0 and $J_{6,7}$ 2.0 Hz) and the predominant, 6,7-*cis*-7,8-*trans*-[2,3-*f*]-regioisomer (**39**) ($J_{6,7}$ *ca.* 1.0 and $J_{7,8}$ 2.0 Hz) are differentiated by the selective n.O.e association of 10-H(D) (δ 6.17) with 9-OMe (δ 3.57, 14.5%) in the latter instance only. The n.O.e. effect of 8-H(C) [for (**35**)] or 6-H(C) [for (**39**)] with 6-H(A), characteristic of tetrahydropyranochromenes with *cis*-*trans*-configurations of C-ring heterocycles,[3] is observed for both (**35**) and (**39**). Similar n.O.e. association of 10-H(D) (δ 6.13) with 9-OMe(D) (δ 3.42, 15.1%) and coupling constants of C-ring protons ($J_{6,7}$ 6.0 and $J_{7,8}$ 5.0 Hz) enables definition of the structure of the all-*trans* tetrahydropyrano[2,3-*f*]chromene derivative (**41**).

The remaining pair of *cis*-*trans* tetrahydropyrano[2,3-*g*]- (**36**) [$J_{7,8}$ *ca.* 1.0 and $J_{6,7}$ 2.0 Hz for (**37**)] and [2,3-*f*]-chromenes (**42**) [$J_{6,7}$ *ca.* 1.0 and $J_{7,8}$ 2.0 Hz for (**43**)] was again differentiated by appropriate n.O.e. effects of 10-H(D). Their ^{1}H n.m.r. spectral data furthermore reveal the characteristic deshielding of 6-H(A) [δ −0.78 and −0.77 for (**37**) and (**43**) respectively] and 6/8-H(C) [δ −0.41 for 8-H(C) of (**37**); −0.30 for 6-H(C) of (**43**)] relative to those of the 'normal' *cis*-*trans* analogues (**35**) and (**39**), associated with those phlobatannins possessing interchanged resorcinol A- and pyrocatechol B-rings.



Scheme 5. Base-catalyzed conversion of (+)-fisetinidol-(4α,6)-(+)-catechin *O*-methyl ether (**8**). *Reagents and conditions:* i, $NaHCO_3$–Na_2CO_3 (pH 10), 50 °C, 3 h, N_2

Owing to the small quantities of biflavanoid (**8**) the anticipated all-*trans* isomers of (**34**), (**36**), and (**42**) were presumably overlooked in preliminary separation of the phenolic mixture.

The above series of phlobatannins (**34**), (**36**), (**38**), (**40**), and (**42**) derived from the (+)-fisetinidol-(4α,6)-(+)-catechin (**8**) presumably originate *via* a quinone-methide of type (**17**) (Scheme 2) by mechanisms similar to those in Scheme 4. High-amplitude positive C.e.s in the 220-240 nm region of their c.d. spectra confirm 8*S* absolute configuration for the 6,7-*cis*-7,8-*trans*- and all-*trans* tetrahydropyrano[2,3-*f*]chromenes (**39**) and (**41**). The ring-interchanged analogue (**43**) exhibits an intense negative C.e. at 232 nm indicative of the C-8 aryl group below the plane of the C/D-ring system. When the c.d. data are interpreted in conjunction with ^{1}H n.m.r. coupling constants, the absolute configuration of these analogues may be defined as 2*R*,3*S*:6*R*,7*R*,8*S* for (**39**), 2*R*,3*S*:6*S*,7*R*,8*S* for (**41**), and 2*R*,3*S*:6*R*,7*S*,8*R* (**43**). C.d. curves of the *same sample* of both (**35**) and (**37**) are, however, non-repetitive thus rendering the absolute configurations 2*R*,3*S*:6*S*,7*R*,8*R* for (**35**) and 2*R*,3*S*:6*R*,7*S*,8*S* for (**37**) speculative. At present we cannot explain these peculiar chiroptical properties.

The (+)- and (−)-fisetinidol-(+)-catechin profisetinidins thus exhibit similar behaviour under basic conditions. Whereas 'upper' 2,3-*trans*-3,4-*trans*-flavan-3-ol units are susceptible to slower but stereospecific C-ring isomerization, those species with 2,3-*trans*-3,4-*cis* configuration react stereoselectively and are furthermore subject to interchange of resorcinol A- and pyrocatechol B-rings. It seems reasonable to suggest that the rate-determining step in these C-ring isomerizations involves reversible generation of the quinone-methide, *e.g.* (**9**) (Scheme 1). In 3,4-*cis*-biflavanoids, *e.g.* (**4**), 7-OH(D) is favourably orientated to anchimerically assist cleavage of the O–C-2 bond thus enhancing both the rate of quinone-methide formation and C-ring isomerization of 3,4-*cis*-flavan-3-ol units. Once formed, quinone-methides derived from 3,4-*trans*-(−)- and -(+)-fisetinidol units are favourably aligned for rapid and stereospecific recyclization *via* 7-OH(D). The near-axial (+)-catechin species in 3,4-*cis*-quinone-methides, *e.g.* (**32**) (Scheme 4), would 'ease' to a more equatorial position thus facilitating stereoselective pyran recyclization with preference for attack of 7-OH(D) at the *Si*- and *Re*-faces in the 2*R*- and 2*S*-series of profisetinidins respectively. This would presumably result in sufficient lifetimes to allow for secondary rearrangements to the A/B-ring interchanged products.

Experimental

^{1}H N.m.r. and ^{13}C n.m.r. spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were obtained with a Kratos MS80 instrument and c.d. data on a Jasco J-20 spectropolarimeter in methanol. T.l.c. was performed on pre-coated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates 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. Separations on Sephadex LH-20 and Fractogel TSK HW-40(S) were on various column sizes and at differing flow rates (to be specified in each instance) in ethanol. Methylations were performed with an excess of diazomethane in methanol–diethyl ether over 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at ambient temperatures. Evaporations were performed under reduced pressure at *ca.* 60 °C in a rotary evaporator.

Synthesis of Biflavanoids (**2**), (**4**), (**6**), *and* (**8**).—4-*O*-Methyl-(+)-catechin[2] (10 g) and (−)-leucofisetinidin (5.2 g) were dissolved in HCl (0.1M; 500 ml) and the mixture was stirred for 12 h at 20 °C. An additional portion of (−)-leucofisetinidin (2.5 g) was added and stirring was continued for 6 h. The mixture was extracted with ethyl acetate (6 × 200 ml) and the extract was dried (Na_2SO_4) and evaporated to dryness. The light-brown residue (14.5 g) was subjected to column chromatography (4.5 × 120 cm column, flow rate 1.2 ml min^{-1}, 30 ml eluant/tube) using Sephadex LH-20 to give the following fractions: 1[tubes 100—137 (3.31 g)], 2[181—265 (4.79 g)], 3[287—379 (5.3 g)], 4[431—500 (0.32 g)], and 5[821—1 050 (1.3 g)]. Fraction 1 consisted of 4′-*O*-methyl-(+)-catechin, fraction 2 of the (+)-fisetinidol-(4α,8)-(+)-catechin *O*-methyl ether (**4**), fraction 3 of the (4β,8)-dimer (**2**), fraction 4 of the (4α,6)-biflavanoid (**8**), and fraction 5 of a mixture of the (4β,6)-analogue (**6**) and small quantities of a 'trimeric' species. The latter mixture was resolved by column chromatography on Fractogel TSK HW-40(S) (ethanol) under M.P.L.C. conditions (4.9 × 46 cm column, 3 bar, flow rate 5 ml min^{-1}) to give the (+)-fisetinidol-(4β,6)-(+)-catechin *O*-methyl ether (**6**) [tubes 81—140 (501 mg)] and a trimeric fraction [tubes 141—180 (200 mg)] which was not further investigated. The 'protected' biflavanoids (**2**), (**4**), (**6**), and (**8**) were identified by comparison of ^{1}H n.m.r. data of their heptamethyl ether diacetates with those of the corresponding derivatives of authentic samples.[5]

Base-catalyzed Conversions

(+)-*Fisetinidol*-(4β,8)-(+)-*catechin* O-*Methyl Ether* (**2**).—Biflavanoid (**2**) (577 mg) was dissolved in 150 ml of a 0.025M Na_2CO_3–0.025M $NaHCO_3$ buffer (pH 10) and the mixture stirred under nitrogen for 5 h at 50 °C. The mixture was cooled to 0 °C, acidified with 1M HCl, and extracted with ethyl acetate (5 × 200 ml). The organic extracts were dried (Na_2SO_4) and evaporated to afford a light-brown powder (560 mg) which was chromatographed on Sephadex LH-20 (3.5 × 50 cm column, flow rate 1.2 ml min^{-1}, 30 ml eluant/tube, first 200 ml of eluant discarded) to give three fractions: 1[tubes 4—14 (66 mg)], 2[35—43 (37.5 mg)], and 3[47—68 (280 mg)].

Methylation of fraction 1 and subsequent purification by p.l.c. [1,2-dichloroethane–acetone–methanol (90:9:1 v/v); × 2] afforded a single band at R_F 0.17 (31 mg). Acetylation gave the dehydro-(+)-fisetinidol-(+)-catechin (**13**) as a *white amorphous solid* (36 mg) (Found: M^+, 728.2435. $C_{40}H_{40}O_{13}$ requires M, 728.2469); ^{1}H n.m.r. see Table 4; c.d. $[\theta]_{358}$ 0, $[\theta]_{343}$ 2.8 × 10^4, $[\theta]_{310}$ 2.7 × 10^5, $[\theta]_{305}$ 2.7 × 10^5, $[\theta]_{273}$ 0, $[\theta]_{265}$ −3.5 × 10^4, $[\theta]_{254}$ −1.4 × 10^4, $[\theta]_{238}$ −2.7 × 10^5, $[\theta]_{226}$ −9.8 × 10^4, $[\theta]_{223}$ −1.2 × 10^5, $[\theta]_{221}$ −4.8 × 10^4, and $[\theta]_{218}$ 0.

Fraction 2 was further purified to a single band R_F 0.56, (9 mg) by p.l.c. [benzene–acetone–methanol (6:3:1 v/v); × 2]. Methylation followed by p.l.c. [chloroform–hexane–acetone (90:6:4 v/v); × 2] afforded a band at R_F 0.32 (5 mg). Acetylation gave (2*S*,3*S*,4*R*)-2,3-*cis*-3,4-*trans*-3-acetoxy-2-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,5,7-tetramethoxyflavan-8-yl]-4-(3,4-dimethoxyphenyl)-7-methoxy-3,4-dihydro-2*H*-benzopyran (**16**) as a *white amorphous solid* (4 mg) (Found: M^+, 744.2794. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 4; c.d. $[\theta]_{289}$ 0, $[\theta]_{270}$ −1.2 × 10^5, $[\theta]_{252}$ −7.4 × 10^4, $[\theta]_{235}$ −5.3 × 10^5, and $[\theta]_{230}$ −7.4 × 10^4. Fraction 3 was resolved by p.l.c. [benzene–acetone–methanol (6:3:1 v/v)] into two bands, R_F 0.37 (53 mg) and R_F 0.31 (64 mg). The band at R_F 0.37 was methylated and the mixture separated by p.l.c. [chloroform–ethyl acetate (9:1 v/v); × 2] to give a single band at R_F 0.37 (28 mg). Acetylation afforded (2*R*,3*S*:8*S*,9*R*,10*R*)-3,9-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]-chromene (**11**) as a *white amorphous solid* (30 mg) (Found: M^+, 744.2796. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 1; c.d. $[\theta]_{286}$ 0, $[\theta]_{280}$ −5.4 × 10^4, $[\theta]_{267}$ 0, $[\theta]_{260}$ 2.0 × 10^4, $[\theta]_{250}$ 0, $[\theta]_{240}$ −3.7 × 10^5, $[\theta]_{227}$ −7.5 × 10^5, and $[\theta]_{218}$ −6.3 × 10^5. The band at R_F 0.31 was resolved by

p.l.c. [chloroform–hexane–acetone (90:6:4 v/v); ×2] to give a main band at R_F 0.24 (33 mg). Acetylation afforded the hexamethyl ether diacetate of starting biflavanoid (**2**).[5]

(+)-Fisetinidol-(4β,6)-(+)-catechin O-*Methyl Ether* (**6**).—Biflavanoid (**6**) (500 mg) was treated in buffer solution (200 ml) under nitrogen for 5 h at 50 °C and worked up as above. Column chromatography on Sephadex LH-20 (3.5 × 50 cm column, flow rate 1.6 ml min^{-1}, 20 ml eluant/tube, first 200 ml of eluant discarded) afforded the following fractions: 1[tubes 1—6 (1 mg)], 2[12—30 (38 mg)], 3[37—91 (305 mg)], and 4[121—157 (63 mg)]. Fraction 1 consisted of 4′-*O*-methyl-(+)-catechin.

Fraction 2 was methylated and the mixture resolved by p.l.c. [hexane–benzene–acetone–methanol (40:40:15:5, v/v); ×2] to give a single discrete band at R_F 0.14 (5 mg). Acetylation afforded the dehydro-(+)-fisetinidol-(+)-catechin (**23**) as a *white amorphous solid* (6 mg) (Found: M^+, 728.2443. $C_{40}H_{40}O_{13}$ requires M, 728.2469); ^{1}H n.m.r. see Table 4; c.d. $[\theta]_{400}$ 2.6 × 10^4, $[\theta]_{350}$ 9.4 × 10^4, $[\theta]_{320}$ 3.8 × 10^4, $[\theta]_{284}$ 1.8 × 10^5, $[\theta]_{247}$ 0, $[\theta]_{240}$ −6.3 × 10^4, $[\theta]_{238}$ 0, $[\theta]_{233}$ −2.2 × 10^5, and $[\theta]_{221}$ 0.

Methylation of fraction 3 and subsequent separation by p.l.c. [benzene–acetone (9:1 v/v)] afforded three bands at R_F 0.29 (12 mg), 0.23 (55 mg), and 0.15 (23 mg). Acetylation of the band at R_F 0.29 gave a mixture comprising compounds where the secondary hydroxy functions had been partially methylated (^{1}H n.m.r.). This mixture was thus not further investigated. Acetylation of the R_F 0.23 band afforded (2*R*,3*S*:6*S*,7*R*,8*R*)-3,7-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene (**21**) as a *white amorphous solid* (62 mg) (Found: M^+, 744.2758. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 3; c.d. $[\theta]_{293}$ 0, $[\theta]_{280}$ −4.8 × 10^4, $[\theta]_{271}$ 0, $[\theta]_{258}$ 3.9 × 10^4, $[\theta]_{247}$ 0, $[\theta]_{231}$ −3.6 × 10^5, and $[\theta]_{224}$ 0. Acetylation of the band at R_F 0.15 gave (2*R*,3*S*:6*R*,7*R*,8*S*)-3,7-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-3,4,6,7-tetrahydro-2*H*,8*H*-pyrano[2,3-*g*]chromene (**19**) as a *white amorphous solid* (27 mg) (Found: M^+, 744.2751. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 2; c.d. $[\theta]_{295}$ 0, $[\theta]_{279}$ −1.0 × 10^5, $[\theta]_{255}$ 0, $[\theta]_{235}$ −1.1 × 10^5, $[\theta]_{277}$ −1.9 × 10^5, $[\theta]_{225}$ −1.8 × 10^5, $[\theta]_{220}$ −2.2 × 10^5, and $[\theta]_{216}$ −1.1 × 10^5. Fraction 4 was methylated and the mixture resolved by p.l.c. [chloroform–ethyl acetate (9:1 v/v); ×2] to give a single band at R_F 0.20 (9 mg). Subsequent acetylation afforded the hexamethyl ether diacetate of the starting biflavanoid (**6**).[5]

(+)-Fisetinidol-(4α,8)-(+)-catechin O-*Methyl Ether* (**4**).—Treatment of biflavanoid (**4**) (288 mg) in buffer solution (150 ml) under nitrogen for 3 h at 50 °C and work-up as above afforded a light-brown residue (223 mg). Column chromatography on Sephadex LH-20 (3.5 × 50 cm column, flow rate 0.6 ml min^{-1}, 15 ml eluant/tube, first 150 ml of eluant discarded) gave four fractions: 1[tubes 10—15 (2 mg)], 2[16—27 (18 mg)], 3[30—40 (19 mg)], 4[41—58 (137 mg)], and 5[65—80 (18 mg)]. Fraction 1 consisted of 4′-*O*-methyl-(+)-catechin.

Fraction 2 comprised a mixture of unidentified compounds in which recyclization of an intermediate quinone-methide did not involve 7-OH(D) (*cf.* ref. 3). Details of these will be published elsewhere.

Fraction 3 was methylated and the mixture separated by p.l.c. [benzene–acetone (8:2 v/v); ×2] to give a methyl ether band at R_F 0.44 (2 mg). Acetylation afforded (2*R*,3*S*:8*S*,9*S*,10*R*)-3,9-diacetoxy-2,10-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*cis*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**29**) as a *white amorphous solid* (2.5 mg) (Found: M^+, 744.2808, $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 1; c.d. $[\theta]_{250}$ 0, $[\theta]_{240}$ −1.6 × 10^5, $[\theta]_{233}$ −3.6 × 10^5, $[\theta]_{219}$ −1.4 × 10^5, and $[\theta]_{216}$ 0.

Methylation of fraction 4 and p.l.c. separation [chloroform–hexane–acetone (90:6:4 v/v); ×2] gave two bands at R_F 0.36 (4.5 mg) and 0.30 (52 mg). Acetylation of the band at R_F 0.36 afforded (2*R*,3*S*:8*S*,9*R*,10*S*)-3,9-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]-chromene (**27**) as a *white amorphous solid* (5 mg) (Found: M^+, 744.2801. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 1; c.d. $[\theta]_{320}$ 0, $[\theta]_{285}$ −8.8 × 10^4, $[\theta]_{270}$ −9.8 × 10^4, $[\theta]_{255}$ −9.3 × 10^4, $[\theta]_{242}$ −2.2 × 10^5, $[\theta]_{239}$ −1.6 × 10^5, $[\theta]_{235}$ −5.3 × 10^5, $[\theta]_{232}$ −2.5 × 10^5, $[\theta]_{223}$ −8.8 × 10^4, and $[\theta]_{218}$ 2.7 × 10^4. The band at R_F 0.30 was further resolved by p.l.c. [1,2-dichloroethane–ethyl methyl ketone–methanol (85:13:2 v/v); ×2] into two fractions at R_F 0.59 (6 mg) and 0.54 (9 mg). Acetylation of the former fraction gave (2*R*,3*S*:8*R*,9*R*,10*S*)-3,9-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*cis*-9,10-*trans*-3,4,9,10-*tetrahydro*-2*H*,8*H*-pyrano[2,3-*h*]chromene (**25**) as a *white amorphous solid* (8 mg) (Found: M^+, 744.2786. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 1; c.d. $[\theta]_{290}$ 0, $[\theta]_{265}$ −4.7 × 10^4, $[\theta]_{250}$ −2.4 × 10^4, $[\theta]_{242}$ −1.4 × 10^4, $[\theta]_{228}$ −2.8 × 10^5, $[\theta]_{224}$ −2.0 × 10^5, $[\theta]_{215}$ −4.9 × 10^5, and $[\theta]_{205}$ 0. Acetylation of the R_F 0.54 fraction afforded the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene (**29**) with interchanged resorcinol A- and pyrocatechol B-rings. Its physical data were identical with those of the corresponding derivative from fraction 3 described above.

Fraction 5 was methylated and subsequently purified by p.l.c. [benzene–acetone (8:2 v/v); ×2] to give a single band at R_F 0.39 (4 mg). Acetylation afforded (2*R*,3*S*:8*R*,9*S*,10*R*)-3,9-diacetoxy-2,10-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano-[2,3-*h*]chromene (**31**) as a *white amorphous solid* (5 mg) (Found: M^+, 744.2808. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 1; c.d. $[\theta]_{300}$ 0, $[\theta]_{280}$ −9.3 × 10^4, $[\theta]_{267}$ −1.9 × 10^5, $[\theta]_{247}$ 0, $[\theta]_{241}$ −1.3 × 10^5, $[\theta]_{239}$ −3.5 × 10^5, and $[\theta]_{236}$ 0.

(+)-Fisetinidol-(4α,6)-(+)-catechin O-*Methyl Ether* (**8**).—Biflavanoid (**8**) (290 mg) was treated with buffer solution (150 ml) under nitrogen for 3 h at 50 °C. Work-up as before gave a light-brown residue (240 mg) which was chromatographed on Sephadex LH-20 (3.5 × 50 cm column, flow rate 0.6 ml min^{-1}, 15 ml of eluant/tube, first 150 ml of eluant discarded) to give the following fractions: 1[tubes 38—42 (1 mg)], 2[62—69 (8 mg)], 3[74—97 (163 mg)], and 4[98—107 (15 mg)]. Fraction 1 consisted of 4′-*O*-methyl-(+)-catechin. Methylation of fraction 2 followed by p.l.c. [chloroform–ethyl acetate (9:1 v/v)] gave two bands at R_F 0.54 (≪1 mg) and 0.39 (≪1 mg) which were not further investigated.

Fraction 3 was methylated and the mixture resolved by p.l.c. [chloroform–ethyl acetate (9:1 v/v)] into three bands at R_F 0.56 (1 mg), 0.49 (33 mg), and 0.39 (11 mg). Acetylation of the R_F 0.56 band gave (2*R*,3*S*:6*S*,7*R*,8*S*)-3,7-diacetoxy-2,6-bis-(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*trans*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]-chromene (**41**) as a *white amorphous solid* (1.5 mg) (Found: M^+ − HOAc, 684.2559. $C_{41}H_{44}O_{13}$ − HOAc requires M, 684.2571); ^{1}H n.m.r. see Table 3; c.d. $[\theta]_{302}$ 0, $[\theta]_{283}$ −4.3 × 10^5, $[\theta]_{260}$ −1.6 × 10^5, $[\theta]_{239}$ −6.6 × 10^5, $[\theta]_{236}$ 0, $[\theta]_{234}$ 2.8 × 10^5, $[\theta]_{233}$ 0, $[\theta]_{231}$ −4.0 × 10^5, and $[\theta]_{221}$ 0. The R_F 0.49 band was acetylated and the mixture resolved by p.l.c. [chloroform–hexane–acetone (90:6:4 v/v)] into two fractions at R_F 0.57 (13 mg) and 0.50 (7 mg). The R_F 0.57 fraction afforded (2*R*,3*S*:6*S*,7*S*,8*R*)-3,7-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene

(**43**) as a *white amorphous solid* (Found: M^+, 744.2813. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 3; c.d. $[\theta]_{272}$ 0, $[\theta]_{260}$ 3.1×10^3, $[\theta]_{250}$ 6.2×10^3, $[\theta]_{237}$ -1.1×10^5, $[\theta]_{232}$ -2.4×10^5, $[\theta]_{225}$ -5.8×10^4, $[\theta]_{223}$ 0, $[\theta]_{211}$ 4.7×10^5, and $[\theta]_{205}$ 1.4×10^5. The R_F 0.50 fraction gave (2*R*,3*S*:6*R*,7*R*,8*S*)-3,7-diacetoxy-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene (**39**) as a *white amorphous solid* (Found: M^+, 744.2765. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 3; c.d. $[\theta]_{290}$ 0, $[\theta]_{266}$ -1.4×10^5, $[\theta]_{254}$ 0, $[\theta]_{236}$ 8.1×10^{10}, and $[\theta]_{230}$ 0. Acetylation of the R_F 0.39 band followed by p.l.c. [hexane–chloroform–ethyl acetate (1:8:1 v/v)] afforded a fraction at R_F 0.53 (2 mg) which comprised of (2*R*,3*S*:6*R*,7*S*,8*S*)-3,7-diacetoxy-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-3,4,7,8-tetrahydro-2*H*,8*H*-pyrano[2,3-*g*]chromene (**37**) as a *white amorphous solid* (Found: M^+, 744.2759. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 2; c.d. $[\theta]_{295}$ 0, $[\theta]_{284}$ -7.4×10^4, $[\theta]_{278}$ -7.9×10^4, $[\theta]_{270}$ -1.1×10^5, $[\theta]_{260}$ -7.4×10^4, $[\theta]_{248}$ 0, $[\theta]_{239}$ -1.3×10^5, $[\theta]_{238}$ 0, $[\theta]_{235}$ -6.9×10^4, and $[\theta]_{234}$ 0.

Fraction 4 was methylated and the mixture resolved by p.l.c. [chloroform–ethyl acetate (9:1 v/v)] into two bands at R_F 0.28 (1 mg) and 0.24 (1 mg). Acetylation of the band at R_F 0.28 afforded 1 mg of (**37**) with physical data identical to those of the same compound described in the preceding paragraph. Acetylation of the R_F 0.24 band gave (2*R*,3*S*:6*S*,7*R*,8*R*)-3,7-diacetoxy-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-3,4,6,7-tetrahydro-2*H*,8*H*-pyrano[2,3-*g*]chromene (**35**) as a *white amorphous solid* (1 mg) (Found: M^+, 744.2757. $C_{41}H_{44}O_{13}$ requires M, 744.2782); ^{1}H n.m.r. see Table 2; c.d. $[\theta]_{295}$ 0, $[\theta]_{284}$ -7.4×10^4, $[\theta]_{276}$ -6.3×10^4, $[\theta]_{270}$ -1.0×10^5, $[\theta]_{246}$ 0, $[\theta]_{241}$ 8.2×10^4, $[\theta]_{238}$ 2.7×10^4, $[\theta]_{237}$ 1.5×10^5, $[\theta]_{235}$ 0, $[\theta]_{228}$ -3.6×10^5, and $[\theta]_{223}$ 0.

The sequence of formation of the phlobatannins (**24**), (**26**), (**28**), and (**30**) derived from the (+)-fisetinidol-(4α,8)-(+)-catechin *O*-methyl ether (**4**) and the stability of the *cis-trans*-analogues (**25**) and (**28**) under conditions similar to those for their formation, were performed in a manner identical with that described for the (−)-fisetinidol-(4β,8)-(+)-catechin (*cf.* ref. 3) and will not be repeated here.

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