Oligomeric Flavanoids. Part 10.† Structure and Synthesis of the First Tetrahydropyrano[3,2-*g*]chromenes Related to (4,6)-Bis-(−)-fisetinidol Profisetinidins

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The range of natural bis-fisetinidol profisetinidins is extended by identification of (+)-epifisetinidol-(4α,6)-(−)-fisetinidol (**5**), (4α,6)-bis-(+)-epifisetinidol (**7**), (4β,6′)-bis-(−)-fisetinidol (**13**), and (−)-fisetinidol-(4β,6′)-(+)-epifisetinidol (**15**). They are accompanied in the heartwood of *Colophospermum mopane* by the first tetrahydropyrano[3,2-*g*]chromenes (**17**), (**19**), (**21**), and (**23**), related to the (4,6)-bis-(−)-fisetinidol profisetinidins (**1**) and (**2**). Under mild basic conditions the latter compounds undergo pyran rearrangements affording tetrahydropyrano[3,2-*g*]chromenes (**17**), (**19**), (**21**), and (**23**) as well as two additional C-2(F) epimeric pairs (**25**), (**27**), and (**29**), (**31**). The same intermediate quinone-methide presumably leading to the C-ring-isomerized analogues may feasibly also explain the genesis of the variety of compounds in the mopane displaying a C-2 epimeric relationship to the predominant (−)-fisetinidol monomeric precursor.

We have recently[1] demonstrated the natural occurrence of the first profisetinidins and proguibourtinidins based on C-8 substituted (−)-fisetinidol [(2*R*,3*S*)-2,3-*trans*-flavan-3,3′,4′,7-tetraol] units and their related C-ring-isomerized analogues, termed[2] phlobatannins. The latter functionalized tetrahydropyrano[2,3-*h*]chromenes represented the first examples of this unique class of natural condensed tannins where the nucleophilicity of the phenolic rings effecting the pyran rearrangements is comparable to those of the rings acting as leaving groups. These observations indicate that the (4,6)-bis-fisetinidols[3,4] could similarly be susceptible to ring isomerization, thus prompting a search for such prototypes in the heartwood extract of the mopane (*Colophospermum mopane* Kirk *ex* J. Leonard), reputed for its considerable content of fisetinidol-related metabolites.[1,4] We report here our detailed results of relevance to the series of tetrahydropyrano[2,3-*g*]chromenes related to the (4α,6)-bis-fisetinidols, their characterization being facilitated by the protocol of extensive enrichment and fractionation procedures.[1,4]

Results and Discussion

The series of bis-fisetinidol profisetinidins in the methanol extract of the heartwood of the mopane, *i.e.* the (4α,6)- and (4β,6)-bis-(−)-fisetinidols (**3**) and (**2**) and the (−)-fisetinidol-(4α,6) and (4β,6)-(+)-epifisetinidols (**3**) and (**4**), is extended by the novel (+)-epifisetinidol-(4α,6)-(−)-fisetinidol (**5**) and (4α,6)-bis-(+)-epifisetinidol (**7**). The (−)-fisetinidol-(4β,6′)-(−)-fisetinidol (**13**) and (+)-epifisetinidol (**15**) similarly represent novel entries to the rare group of C ⟶ E ring-linked profisetinidins.[1,4] The (4α,6)- and (4β,6)-bis-(−)-fisetinidols (**1**) and (**2**) presumably serve as biogenetic precursors to the functionalized tetrahydropyrano[3,2-*g*]chromenes with 6,7-*cis*-7,8-*trans*-(**17**) and (**19**) and 6,7-*trans*-7,8-*trans*- (**21**) and (**23**) relative configurations. Owing to the complexity of the phenolic mixture these novel metabolites were identified as their hexamethyl ether diacetates, *e.g.* (**6**).

Comparison of the ^{1}H NMR data (Table 1) of the derivatives (**6**) and (**8**) of the (+)-epifisetinidol-(4α,6)-(−)-fisetinidol (**5**) and the (4α,6)-bis-(+)-epifisetinidol (**7**) with those of the derivatives of (**1**)—(**4**)[4] reveals their close structural resemblance. The oxygenation and spin patterns of the constituent flavanyl units are defined by decoupling and NOE experiments using the 2- and 4-heterocyclic proton and methoxy resonances as reference signals (*cf.* refs. 1 and 4). Singlets for the 5- and 8-protons [δ 6.36, 6.84, and δ 6.45, 6.73 for (**6**) and (**8**) respectively] of the D-ring establish the (4,6)-interflavanyl linkage for both compounds (**6**) and (**8**).[3] The relative configurations of these compounds are evident from the coupling constants of the heterocyclic AMX [$J_{2,3}$ *ca.* 1.0, $J_{3,4}$ *ca.* 2.0 Hz for both (**6**) and (**8**)] and AMXY [$J_{2,3}$ 7.5, *ca.* 1.0 Hz for (**6**) and (**8**) respectively] systems.[5] Confirmation of the 2,3-*cis*-3,4-*trans* configuration, unique amongst naturally occurring profisetinidins, is obtained from the pronounced NOE association of 2-H(C) with 5-H(D) and of 4-H(C) with both 2- and 6-H(B).[6]

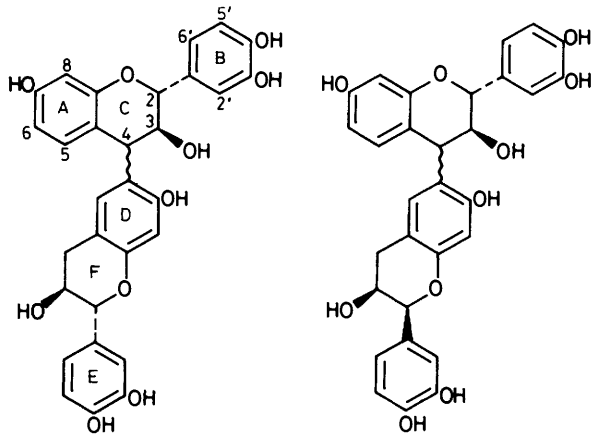
High-amplitude negative Cotton effects (CEs) at 237 and 236 nm in the CD spectra of compounds (**6**) and (**8**) respectively indicate a 4α-flavanyl substituent[7] in each instance. When taken in conjunction with ^{1}H NMR coupling constants these negative CEs indicate 2*S*,3*S*,4*R*(C):2*R*,3*S*(F) absolute configuration for (**6**) and 2*S*,3*S*,4*R*(C):2*S*,3*S*(F) for (**8**), assignments which were subsequently confirmed by synthesis (*vide infra*).

The ^{1}H NMR spectra (Table 2) of the hexamethyl ether diacetates (**14**) and (**16**) of the novel (4β,6′)-bis-(−)-fisetinidol (**13**)‡ and (−)-fisetinidol-(4β,6′)-(+)-epifisetinidol (**15**) display aromatic spin patterns characteristic of C ⟶ E-ring-linked bis-fisetinidols.[4] Substitution at C-E(E) in both (**14**) and (**16**) is confirmed by NOE association of the 'residual' E-ring singlets [δ 6.89, 7.16, 2′-H; 6.66, 6.84, 5′-H for (**14**) and (**16**) respectively] with a methoxy group [δ 3.81 (14.0%),§ 3.87 (10.9%); 3.72 (5.7%), 3.75 (6.3%) for 2′- and 5′-H in (**14**) and (**16**) respectively]. Coupling constants for the protons of the heterocyclic AMX system [$J_{2,3}$ 4.8, 3.0; $J_{3,4}$ 4.0, 4.5 Hz for (**14**) and (**16**) respectively] are abnormally small for 2,3-*trans*-3,4-*cis* relative configuration. Such an observation reflects a preferred half-

† Part 9, J. C. S. Malan, D. A. Young, J. P. Steynberg, and D. Ferreira, submitted for publication in *J. Chem. Soc., Perkin Trans. 1*, 1990, preceding paper.

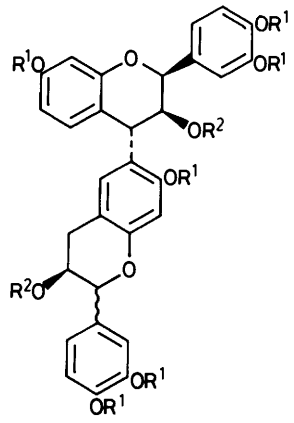
‡ The position of substitution is taken as C-6′ of ring B of the 'lower' unit in order to retain trivial names for the constituent flavanyl moieties.

§ Approximation due to signal overlap.

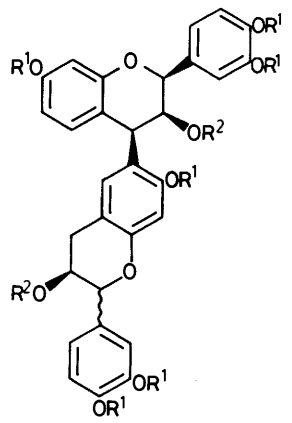


(1) ~~ = ---
(2) ~~ = ◄

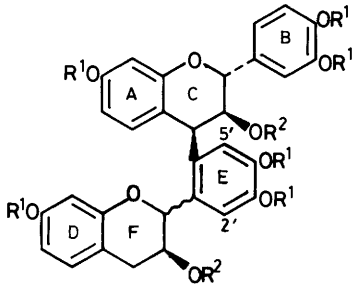
(3) ~~ = ---
(4) ~~ = ◄



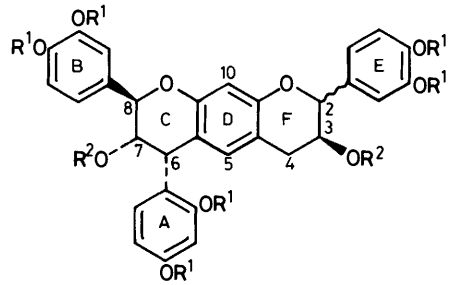
(5) ~~ = ---, $R^1 = R^2 = H$
(6) ~~ = ---, R^1 = Me, R^2=Ac
(7) ~~ = ◄, $R^1 = R^2 = H$
(8) ~~ = ◄, R^1 = Me, R^2=Ac



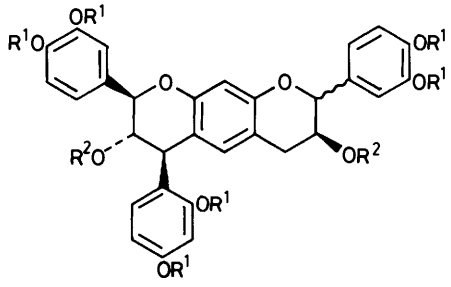
(9) ~~ = ---, $R^1 = R^2 = H$
(10) ~~ = ---, R^1 = Me, R^2=Ac
(11) ~~ = ◄, $R^1 = R^2 = H$
(12) ~~ = ◄, R^1 = Me, R^2 =Ac



(13) ~~ = ---, $R^1 = R^2 = H$
(14) ~~ = ---, R^1 = Me, R^2=Ac
(15) ~~ = ◄, $R^1 = R^2 = H$
(16) ~~ = ◄, R^1 = Me, R^2=Ac



(17) ~~ = ---, $R^1 = R^2 = H$
(18) ~~ = ---, R^1 = Me, R^2 =Ac
(19) ~~ = ◄, $R^1 = R^2 = H$
(20) ~~ = ◄, R^1 = Me, R^2=Ac



(21) ~~ = ---, $R^1 = R^2 = H$
(22) ~~ = ---, R^1 = Me, R^2 = Ac
(23) ~~ = ◄, $R^1 = R^2 = H$
(24) ~~ = ◄, R^1 = Me, R^2 = Ac

chair conformation (*A*-form)[8] for the C-ring in which the 2-aryl and 3-acetoxy functions are forced to attain axial positions by the preference of the more bulky 4-flavanyl group for an equatorial orientation. This assumption is substantiated by profound differences of the NOE association of 2-H(C) with 5-H(E) [2.3, 2.5% for (**14**) and (**16**) respectively] and of 4-H(C) with 2-H(B) [6.3, 6.8% for (**14**) and (**16**) respectively]. High-amplitude positive CEs at 237 and 235 nm in the CD spectra of compounds (**14**) and (**16**) indicate a 4β-flavanyl substituent in each instance, thus facilitating definition of the absolute configuration as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F) for (**14**) and 2*R*,3*S*,4*S*(C): 2*S*,3*S*(F) for (**16**).

The series of 5-deoxy (D-ring) tetrahydropyranochromenes[1] is extended by identification of the first analogues of this class of natural condensed tannins apparently arising from (4,6)-bis-fisetinidols of types (**1**) and (**2**). These comprise the 2,3-*trans*-6,7-*cis*-7,8-*trans*-; 2,3-*cis*-6,7-*cis*-7,8-*trans*-; 2,3-*trans*-6,7-*trans*-7,8-*trans*-; and 2,3-*cis*-6,7-*trans*-7,8-*trans*-tetrahydropyrano[3,2-*g*]chromenes (**17**), (**19**), (**21**), and (**23**). Owing to their close structural resemblance, detailed analysis of structure is given only for the hexamethyl ether diacetate (**18**) of the 6,7-*cis*-7,8-*trans* analogue. ^{1}H NMR coupling constants and chemical shifts (Table 3) of the protons of the heterocyclic AMX system ($J_{6,7}$ 5.2, $J_{7,8}$ 8.0 Hz) closely resemble those of the 5-oxygenated (D-ring) homologue[6,9] hence confirming the 6,7-*cis*-7,8-*trans* relative configuration. A 'liberated' resorcinol A-ring[2] is evident from the NOE association of 3-H(A) with 2- and 4-OMe(A) (14.7 and 2.8% respectively) and of 5-H(A) with 4-OMe(A) (5.5%). The presence of two aromatic singlets [δ 6.65, 5-H(D); 7.19, 10-H(D)] confirms a C-6 substituted DEF (−)-fisetinidol ($J_{2,3}$ 5.9 Hz) moiety and thus also the tetrahydropyrano[3,2-*g*]chromene constitution. Additional evidence for such an arrangement stems from the NOE association of 10-H with both 8-H(C) (0.9%) and 2-H(F) (1.0%). The resorcinol A- and pyrocatechol B-ring may unequivocally be located at C-6 and -8 respectively (*cf.* ref. 6) by the observed benzylic coupling of 6-H(C) with both 5-H(D) and 6-H(A) and of 8-H(C) with 2- and 6-H(B).

A similar protocol of using coupling constants (Tables 3 and 4) and appropriate decoupling and NOE experiments facilitates definition of the structures of the remaining compounds (**19**), (**21**), and (**23**). Analogues with 2,3-*cis* configuration display coupling constants of the heterocyclic AMXY system of $H_{2,3}$ *ca.* 1.0 Hz [for derivatives (**20**) and (**24**)] and those with 6,7-*trans*-7,8-*trans* configuration, $J_{6,7} = J_{7,8} = 9.5$ Hz [for derivatives (**22**) and (**24**)]. Whereas the spectra of derivatives (**18**), (**20**), (**26**), (**28**), (**30**), and (**32**) all exhibit sharp signals at ambient temperatures, those of the all-*trans* derivatives (**22**) and (**24**)

Table 1. ^{1}H NMR (300 MHz) peaks (ppm) of (4,6)-(+)-epifisetinidol-(−)-fisetinidol and bis-(+)-epifisetinidol hexamethyl ether diacetates (**6**), (**8**), (**10**), and (**12**), at 296 K. Splitting patterns and *J*-values (Hz) are given in parentheses.

Ring	H	(**6**), $CDCl_3$:C_6D_6 (1:1)	(**8**), C_6D_6	(**10**), $CDCl_3$	(**12**), $CDCl_3$
A	5	6.76 (d, 8.5)	6.83 (d, 8.5)	6.84 (d, 8.5)	6.88 (dd, 1.5, 8.5)
	6	6.45 (dd, 2.5, 8.5)	6.59 (dd, 2.7, 8.5)	6.49 (dd, 2.5, 8.5)	6.51 (dd, 2.5, 8.5)
	8	6.61 (d, 2.5)	6.98 (d, 2.7)	6.59 (d, 2.5)	6.60 (d, 2.5)
B	2	6.84 (d, 2.0)	7.15 (d, 2.0)	7.04 (d, 2.0)	7.00 (d, 2.0)
	5	6.54 (d, 8.5)	6.54 (d, 8.5)	6.84 (d, 8.5)	6.83 (d, 8.5)
	6	6.70 (dd, 2.0, 8.5)	7.06 (dd, 2.0, 8.5)	7.00 (dd, 2.0, 8.5)	6.90 (dd, 2.0, 8.5)
C	2	5.02 (br s, *ca.* 1.0)	5.60 (br s, *ca.* 1.0)	5.27 (br s, *ca.* 1.0)	5.06 (br s, *ca.* 1.0)
	3	5.48 (dd, 1.2, 2.1)	6.08 (dd, 1.1, 2.0)	5.54 (dd, 1.0, 4.5)	5.56 (dd, 1.0, 4.5)
	4	4.44 (d, 2.1)	4.90 (d, 2.0)	5.08 (d, 4.5)	5.09 (d, 4.5)
D	5	6.36 (s)	6.84 (s)	6.59 (s)	6.59 (s)
	8	6.45 (s)	6.73 (s)	6.47 (s)	6.50 (s)
E	2	6.73 (d, 2.0)	7.08 (d, 2.0)	6.86 (d, 2.0)	7.04 (d, 2.0)
	5	6.56 (d, 8.5)	6.61 (d, 8.2)	6.84 (d, 8.5)	6.84 (d, 8.5)
	6	6.76 (dd, 2.0, 8.5)	6.91 (dd, 2.0, 8.2)	6.90 (dd, 2.0, 8.5)	7.00 (dd, 2.0, 8.5)
F	2	4.82 (d, 7.5)	4.63 (br s, *ca.* 1.0)	5.00 (d, 6.5)	5.26 (br s, *ca.* 1.0)
	3	5.18 (m)	5.36 (m)	5.30 (m)	5.32 (m)
	4_{ax}	2.45 (dd, 7.5, 16.0)	2.60 (dd, 2.0, 17. 5)	2.57 (dd, 7.5, 16.0)	2.65 (dd, 2.5, 17.5)
	4_{eq}	2.70 (dd, 5.5, 16.0)	2.73 (dd, 4.5, 17.5)	2.91 (dd, 5.0, 16.0)	3.16 (dd, 4.5, 17.5)
OMe		3.51 (7-A), 3.52 (4-B), 3.54 (4-E), 3.56 (3-B), 3.57 (3-E), 3.62 (7-D) (each s)	3.27 (4-B), 3.32 (3-B), 3.33 (7-A), 3.35 (4-E), 3.56 (3-E), 3.52 (7-D) (each s)	3.79 (7-A), 3.83 (7-D), 3.85—3.86 (3-E, 4-E, 4-B), 3.88 (3-B) (each s)	3.80 (7-A), 3.85 (7-D), 3.86 (4-E), 3.87 (4-B), 3.88 (3-B), 3.90 (3-E) (each s)
OAc		1.60, 1.68 (each s)	1.43, 1.57 (each s)	1.68, 1.90 (each s)	1.58, 1.82 (each s)

Table 2. ^{1}H NMR (300 MHz) peaks (ppm) of the (4β,6′)-bis-(−)-fisetinidol and (−)-fisetinidol-(4β,6)-(+)-epifisetinidol hexamethyl ether diacetates (**14**) and (**16**). Splitting patterns and *J*-values (Hz) are given in parentheses.

Ring	H	(**14**), C_6D_6, 296 K	(**16**), $CDCl_3$, 353 K
A	5	6.74 (dd, 1.0, 8.5)	6.63 (dd, 1.5, 8.5)
	6	6.45 (dd, 2.5, 8.5)	6.41 (dd, 2.5, 8.5)
	8	6.63 (d, 2.5)	6.62 (d, 2.5)
B	2	6.79 (d, 2.1)	6.95 (d, 8.0)
	5	6.54 (d, 8.5)	6.77 (d, 8.0)
	6	6.78 (dd, 2.1, 8.5)	6.90 (dd, 2.0, 8.0)
C	2	5.43 (d, 4.8)	5.57 (br d, 3.0)
	3	5.48 (dd, 4.0, 4.8)	5.47 (dd, 3.0, 4.5)
	4	4.52 (br d, 4.0)	4.20 (dd, 1.5, 4.5)
D	5	6.92 (d, 8.5)	6.85 (d, 8.5)
	6	6.50 (dd, 2.5, 8.5)	6.47 (dd, 2.5, 8.5)
	8	6.36 (br d, 2.5)	6.41 (d, 2.5)
E	2	6.89 (s)	7.16 (s)
	5	6.66 (s)	6.84 (s)
F	2	4.77 (d, 9.0)	4.88 (br s, *ca.* 1.0)
	3	5.05 (m)	4.95 (m)
	4_{ax}	2.51 (dd, 9.0, 16.2)	2.55 (br d, 5.0)
	4_{eq}	3.03 (dd, 5.9, 16.2)	2.61 (br s, *ca.* 1.0)
OMe		3.64 (3-B), 3.72 (4-E), 3.74 (7-D, 4-B), 3.81 (7-A, 3-E) (each s)	3.74 (7-D), 3.75 (4-E), 3.81 (7-A), 3.82 (4-B), 3.83 (3-B), 3.87 (3-E) (each s)
OAc		1.50, 1.58 (each s)	1.81, 2.03 (each s)

show the characteristic effects of dynamic rotational isomerism. We cannot explain this unexpected spectral behaviour at present. These novel metabolites extend the series of C-ring-isomerized compounds where the nucleophilicity of the rings involved in the pyran rearrangement is of comparable magnitude.[1]

The absolute configurations of the tetrahydropyrano[3,2-*g*]chromenes are deduced by combination of ^{1}H NMR and CD data of their hexamethyl ether diacetates. High-amplitude positive CEs at 236 and 238 nm for the 6,7-*cis*-7,8-*trans* derivatives (**18**) and (**20**), respectively, indicate 2*R*,3*S*:6*S*,7*S*,8*R* absolute configuration for (**17**) and 2*S*,3*S*:6*S*,7*S*,8*R* for (**19**). A negative CE at 236 nm for the 6,7-*trans*-7,8-*trans* derivative (**24**) similarly defines the 2*S*,3*S*:6*R*,7*S*,8*R* configuration for (**23**). The all-*trans* derivative (**22**), however, displays a positive CE at 238 nm which presumably reflects an α orientation of the 6-aryl group. The same derivative of a synthetic sample of compound (**21**) (*vide infra*) exhibits identical chiroptical properties to those of the natural product, hence indicating a 6β substituent and 2*R*,3*S*:6*R*,7*S*,8*R* absolute configuration for compound (**21**). Such an inversion of the sign of the low-wavelength CE resembles similar observations for some of the 5-oxygenated (D-ring) analogues[6] and cannot be satisfactorily explained at present.

The structures of these novel tetrahydropyrano[3,2-*g*]chromenes were confirmed by the synthetic protocol applicable to the (−)-fisetinidol-(+)-catechin-derived analogues.[6,9] Thus, treatment of the (4α,6)-bis-(−)-fisetinidol (**1**)[3,4] at pH 10 (0.025M-Na_2CO_3–0.25M-$NaHCO_3$ buffer) for 7 h at 50 °C gave conversion into a mixture of starting material, the (4α,6)-bis-fisetinidols (**5**) and (**7**), and the functionalized tetrahydropyrano[3,2-*g*]chromenes (**17**), (**19**), (**29**), and (**31**) (Scheme). Amongst these the (4α,6)-bis-fisetinidols (**5**) and (**7**) and the 6,7-*cis*-7,8-*trans*-tetrahydropyrano[3,2-*g*]chromenes (**17**) and (**19**) are identical with the natural products by comparison of the physical data of their hexamethyl ether diacetates. The all-*cis* configuration of the C-ring of the remaining C-ring-isomerized homologues (**29**) and (**31**) is evident from the ^{1}H NMR coupling constants[5] ($J_{6,7}$ *ca.* 4.5, $J_{7,8}$ *ca.* 1.0 Hz) (Tables 3 and 4) of the heterocyclic AMX systems in their hexamethyl ether diacetates (**30**) and (**32**). Their C-2(F) epimeric relationship is similarly confirmed by *J*-values [$J_{2,3}$ 6.1, *ca.* 1.0 Hz for (**30**) and (**32**) respectively] of the heterocyclic AMXY systems. Notable for

Table 3. ^{1}H NMR (300 MHz) peaks (ppm) of the tetrahydropyrano[3,2-*g*]chromene hexamethyl ether diacetates (**18**), (**22**), (**26**), and (**30**) with 2,3-*trans* (F-ring) configurations. Splitting patterns and *J*-values (Hz) are given in parentheses.

Ring	H	(**18**), C_6D_6, 296 K	(**22**), $CDCl_3$, 353 K	(**26**), C_6D_6, 296 K	(**30**), $CDCl_3$—C_6D_6 (1:1), 296 K
A	3	6.44 (d, 2.5)	6.45 (d, 2.5)	6.51 (d, 2.5)	6.35 (d, 2.5)
	5	6.30 (dd, 2.5, 8.5)	6.40 (dd, 2.5, 8.5)	6.25 (dd, 2.5, 8.5)	6.24 (dd, 2.5, 8.5)
	6	7.21 (d, 8.5)	6.95 (d, 8.5)	6.96 (d, 8.5)	6.90 (d, 8.5)
B	2	6.99 (d, 2.0)	6.99 (d, 2.0)	7.06 (d, 2.0)	6.91 (d, 2.0)
	5	6.50 (d, 8.1)	6.81 (d, 8.5)*	6.51 (d, 8.5)	6.52 (d, 8.0)
	6	7.02 (dd, 2.0, 8.1)	6.98 (dd, 2.0, 8.5)	6.90 (dd, 2.0, 8.5)	6.84 (dd, 2.0, 8.0)
C	6	5.27 (d, 5.2)	4.58 (dd, 1.5, 9.5)	4.89 (d, 2.5)	5.10 (d, 4.2)
	7	5.97 (dd, 5.2, 8.0)	5.70 (t, 9.5)	5.95 (dd, 1.0, 2.5)	5.59 (dd, 1.0, 4.2)
	8	5.54 (d, 8.0)	4.97 (d, 9.5)	5.44 (br s, *ca.* 1.0)	5.06 (br s, *ca.* 1.0)
D	5	6.65 (br s)	6.39 (d, 1.5)	6.62 (s)	6.64 (s)
	10	7.19 (s)	6.55 (s)	7.25 (s)	6.81 (s)
E	2	6.91 (d, 2.0)	6.90 (d, 2.0)	6.91 (d, 2.5)	6.76 (d, 2.0)
	5	6.47 (d, 8.0)	6.82 (d, 8.5)*	6.42 (d, 8.0)	6.47 (d, 8.1)
	6	6.96 (dd, 2.0, 8.0)	6.89 (dd, 2.0, 8.5)	6.93 (dd, 2.5, 8.0)	6.80 (dd, 2.0, 8.1)
F	2	5.21 (d, 5.9)	5.01 (d, 6.5)	5.20 (d, 6.5)	4.94 (d, 6.1)
	3	5.49 (m)	5.27 (m)	5.49 (m)	5.26 (m)
	4_{ax}	2.59 (dd, 6.5, 16.5)	2.66 (dd, 7.0, 16.2)	2.15 (dd, 7.0, 16.5)	2.54 (dd, 7.5, 16.5)
	4_{eq}	2.80 (dd, 5.0, 16.5)	2.87 (dd, 5.0, 16.2)	2.86 (dd, 5.0, 16.5)	2.77 (dd, 5.5, 16.5)
OMe		3.21 (2-A), 3.30 (4-A), 3.32 (3-B, 4-B), 3.34 (4-E), 3.36 (3-E) (each s)	3.75 (2-A), 3.77 (4-A), 3.82 (3-E), 3.83 (4-B)*, 3.84 (4-E)*, 3.85 (3-B) (each s)	3.30 (4-B), 3.31 (3-B), 3.35 (4-A), 3.37 (4-E), 3.39 (3-E), 3.52 (2-A) (each s)	3.45 (4-A), 3.49 (4-E, 4-B), 3.52 (3-E), 3.55 (3-B), 3.56 (2-A) (each s)
OAc		1.52, 1.53 (each s)	1.63, 1.91 (each s)	1.50, 1.60 (each s)	1.45, 1.62 (each s)

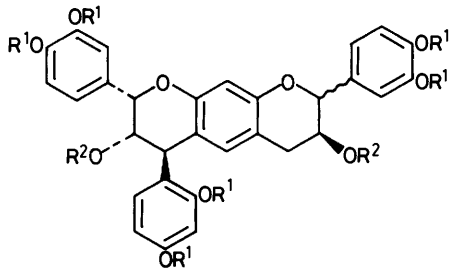
* Peaks may be interchanged.

Table 4. ^{1}H NMR (300 MHz) peaks (ppm) of the tetrahydropyrano[3,2-*g*]chromene hexamethylether diacetates (**20**), (**24**), (**28**), and (**32**) with 2,3-*cis* (F-ring) configurations. Splitting patterns and *J*-values (Hz) are given in parentheses.

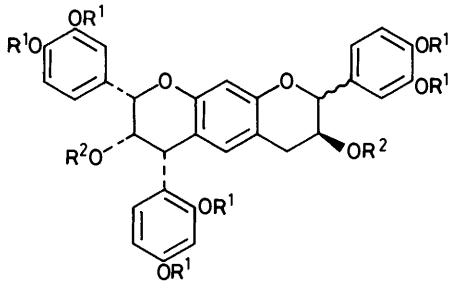
Ring	H	(**20**), $CDCl_3$, 296 K	(**24**), $CDCl_3$, 353 K	(**28**), $CDCl_3$, 296 K	(**32**), $(CD_3)_2CO$, 296 K
A	3	6.45 (d, 2.5)	6.46 (d, 2.5)	6.50 (d, 2.5)	6.55 (d, 2.5)
	5	6.44 (dd, 2.5, 8.5)	6.41 (dd, 2.5, 8.5)	6.39 (dd, 2.5, 8.5)	6.44 (dd, 2.5, 8.5)
	6	6.86 (d, 8.5)	6.97 (d, 8.5)	6.66 (d, 8.5)	6.97 (d, 8.5)
B	2	6.86 (d, 2.0)	6.96 (d, 2.0)	6.89 (d, 2.0)	7.12 (d, 2.0)
	5	6.80 (d, 8.5)	6.82 (d, 8.5)	6.77*	6.94 (d, 8.2)
	6	6.91 (dd, 2.0, 8.5)	7.00*		7.05 (dd, 2.0, 8.5)
C	6	4.85 (d, 5.5)	4.58 (dd, 1.5, 9.5)	4.42 (d, 2.5)	5.14 (br d, 4.5)
	7	5.47 (dd, 5.5, 8.5)	5.69 (t, 9.5)	5.36 (dd, 1.5, 2.5)	5.49 (dd, 1.0, 4.5)
	8	5.10 (d, 8.5)	4.97 (d, 9.5)	5.01 (br s, *ca.* 1.0)	5.43 (br s, *ca.* 1.0)
D	5	6.62 (br s)	6.41 (d, 1.5)	6.69 (s)	6.60 (br s)
	10	6.64 (s)	6.59 (s)	6.72 (s)	6.51 (s)
E	2	7.01 (d, 2.0)	7.01 (d, 2.0)	7.04 (d, 2.0)	7.12 (d, 2.0)
	5	6.84 (d, 8.5)	6.84 (d, 8.5)	6.85 (d, 8.5)	6.93 (d, 8.5)
	6	6.95 (dd, 2.0, 8.5)	6.92 (dd, 2.0, 8.5)	6.95 (dd, 2.0, 8.5)	7.04 (dd, 2.0, 8.5)
F	2	5.06 (br s, *ca.* 1.0)	5.03 (br s, *ca.* 1.0)	5.09 (br s, *ca.* 1.0)	5.23 (br s, *ca.* 1.0)
	3	5.35 (m)	5.36 (m)	5.38 (m)	5.41 (m)
	4_{ax}	2.80 (dd, 2.5, 17.5)	2.74 (dd, 3.0, 17.0)	2.84 (dd, 2.5, 17.5)	2.75 (dd, 2.0, 17.5)
	4_{eq}	3.13 (dd, 4.3, 17.5)	3.08 (dd, 4.5, 17.0)	3.20 (dd, 4.5, 17.5)	3.22 (dd, 4.5, 17.5)
OMe		3.75 (2-A), 3.80 (4-A), 3.84 (3-B), 3.85 (4-B), 3.88 (4-E), 3.89 (3-E) (each s)	3.75 (2-A), 3.78 (4-A), 3.85 (4-B), 3.86 (3-E, 4-E), 3.87 (3-B) (each s)	3.79 (4-A), 3.83 (4-B), 3.84 (3-B), 3.87 (2-A), 3.88 (4-E), 3.89 (3-E) (each s)	3.77 (4-A), 3.78 (4-E), 3.80 (4-B, 3-E or -B), 3.81 (3-B or -E), 3.88 (2-A) (each s)
OAc		1.75, 1.90 (each s)	1.63, 1.86 (each s)	1.90, 1.95 (each s)	1.63, 1.80 (each s)

* Second order.

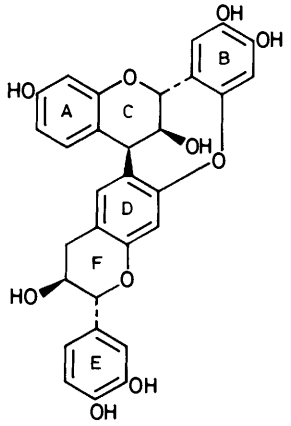
both compounds (**30**) and (**32**) is the conspicuous absence of NOE association of 6-H(C) with 2- and 6-H(B) and of 8-H(C) with 6-H(A), in contrast to the profound NOE effects of these protons in derivatives with *cis-trans* configuration (see ref. 6 and also below). This observation thus provides a powerful probe for differentiation between these classes of compounds which was hitherto based on small differences in coupling constants. Derivatives (**18**), (**20**), (**30**), and (**32**) all exhibit high-amplitude positive CEs in the 235—240 nm region of their CD spectra, which indicates a 6α-aryl group. When taken in conjunction with the known absolute configuration of the starting material,[3] the signs of these CEs confirm the absolute configuration of the



(25) ~~ = ---, $R^1 = R^2 = H$
(26) ~~ = ---, R^1 = Me, R^2 = Ac
(27) ~~ = ◄, $R^1 = R^2 = H$
(28) ~~ = ◄, R^1 = Me, R^2 = Ac



(29) ~~ = ---, $R^1 = R^2 = H$
(30) ~~ = ---, R^1 = Me, R^2 = Ac
(31) ~~ = ◄, $R^1 = R^2 = H$
(32) ~~ = ◄, R^1 = Me, R^2 = Ac



(33)

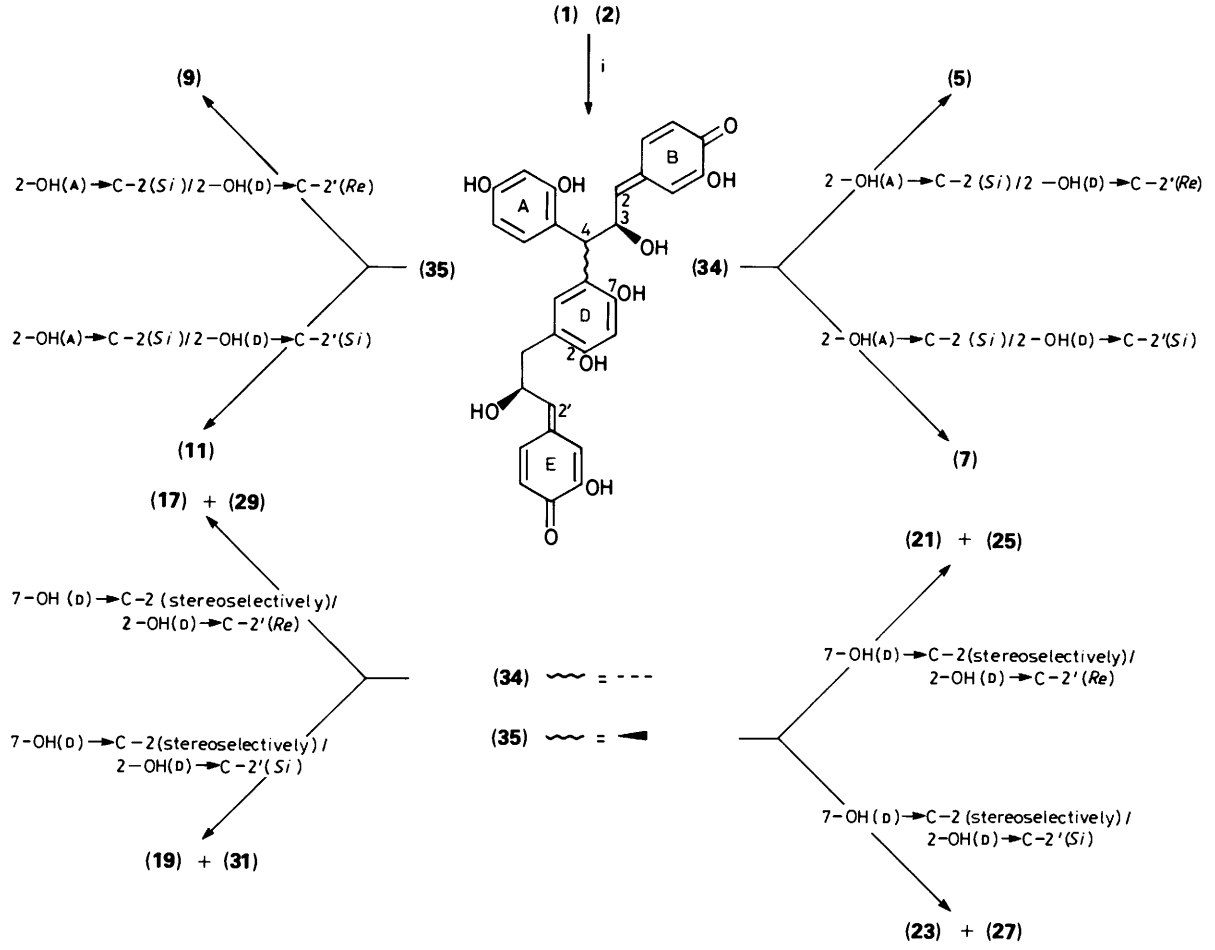
products from Nature, *i.e.* (**5**), (**7**), (**17**), and (**19**) (*vide supra*) and indicate a 2*R*,3*S*:6*S*,7*S*,8*S* configuration for compound (**29**) and 2*S*,3*S*:6*S*,7*S*,8*S* for compound (**31**).

Similar treatment of the (4β,6)-bis-(−)-fisetinidol (**2**) affords a mixture comprising the (4β,6)-bis-fisetinidols (**9**) and (**11**), and the tetrahydropyrano[3,2-*g*]chromenes (**21**), (**23**), (**25**), and (**27**) (Scheme). These compounds are accompanied by at least four dehydrobis-fisetinidols of type (**33**) (*cf.* ref. 9), details of which will be published elsewhere. The structures of the novel (+)-epifisetinidol-(4β,6)-(−)-fisetinidol (**9**) and (4β,6)-bis-(+)-epifisetinidol (**11**) are evident from comparison of the ^{1}H NMR data (Table 1) of their hexamethyl ether diacetates (**10**) and (**12**) with those of derivatives (**6**) and (**8**). Coupling constants of the heterocyclic AMX [$J_{2,3(C)}$ *ca.* 1.0, $J_{3,4(C)}$ 4.5 Hz for both (**10**) and (**12**)] and AMXY [$J_{2,3(F)}$ 6.5, *ca.* 1.0 Hz for (**10**) and (**12**) respectively] systems confirm the relative all-*cis* configuration for the C-ring of both isomers and the 2,3-*trans* and 2,3-*cis* arrangement of the F-rings of both compounds (**10**) and (**12**). Retention of the 4β orientation of the flavanyl group in compounds (**9**) and (**11**) is confirmed by the high-amplitude positive CEs at 233 and 236 nm in the CD spectra of derivatives (**10**) and (**12**) respectively. The hexamethyl ether diacetates (**22**) and (**24**) of the all-*trans*- and 2,3-*cis*-6,7-*trans*-7,8-*trans*-tetrahydropyrano[3,2-*g*]chromenes (**21**) and (**23**) exhibit ^{1}H NMR (Tables 3 and 4) and CD properties identical with those of the corresponding derivatives of the natural products. The synthetic all-*trans*- and 2,3-*trans*-6,7-*trans*-7,8-*cis*-isomer (**22**) and (**26**) conspicuously also show positive CEs at 235 and 238 nm respectively in their CD spectra, which may indicate a 6α-aryl substituent and hence inversion of the absolute configuration at the chiral centres of ring C. Such an inversion is usually associated with an interchange of the resorcinol A- and pyrocatechol B-rings.[6] The location of these rings at C-6 and -8 respectively by means of decoupling experiments for both compounds (**22**) and (**26**) is confirmed for the natural product (**22**), by 2D-heteronuclear correlation of 8-H with C-8 (δ 80.5), thus reflecting the same absolute configuration as was proposed above. Although insufficient sample quantities did not permit similar confirmation for compound (**26**), the available evidence supports the 2*R*,3*S*:6*R*,7*S*,8*S* absolute configuration for compound (**25**). ^{1}H NMR coupling constants (Tables 3 and 4) of the heterocyclic AMX [$J_{6,7}$ *ca.* 1.0, $J_{7,8}$ 2.5 Hz for both (**26**) and (**28**)] and AMXY [$J_{2,3}$ 6.5, *ca.* 1.0 Hz for (**26**) and (**28**) respectively] systems of the hexamethyl ether diacetates (**26**) and (**28**) of the remaining C-2(F) epimeric pair of tetrahydropyrano[3,2-*g*]chromenes (**25**) and (**27**) are in agreement with the 2,3-*trans*-6,7-*trans*-7,8-*cis*- and 2,3-*cis*-6,7-*trans*-7,8-*cis* relative configurations[6] for compounds (**26**) and (**28**) respectively. A strong negative CE at 237 nm in the CD spectrum of derivative (**28**) indicates a 6β-aryl substituent, thus confirming the 2*S*,3*S*:6*R*,7*S*,8*S* absolute configuration of compound (**27**) implied by the mechanism for these conversions.[6,9]

Under the mild basic conditions the (4,6)-bis-(−)-fisetinidols (**1**) and (**2**) are presumably converted into quinone methides (**34**)* and (**35**)* involving both the B- and E-ring (Scheme). Reversal of this process by stereoselective recyclization[10–12] *via* 2-OH of both the A- and D-ring and the quinone methide faces at C-2 and -2′ as indicated may feasibly explain the genesis of the natural (+)-epifisetinidol-(4α,6)-(−)-fisetinidol (**5**), (4α,6)-bis-(+)-epifisetinidol (**7**), the (+)-epifisetinidol-(4β,6)-(−)-fisetinidol (**9**), and of the (4β,6)-bis-(+)-epifisetinidol (**11**). The latter two compounds will, no doubt, eventually also be found in Nature. These observations when taken in conjunction with the readily occurring epimerization of (+)-catechin and (−)-epicatechin under mild basic or neutral conditions,[12–14] may well indicate that the natural (+)-epifisetinidol-(4α,6)-(−)-fisetinidol (**5**) and the (4α,6)-bis-(+)-epifisetinidol (**7**) are 'biosynthetic artefacts' hence eliminating the necessity to invoke the occurrence of flavan-3-ol and flavan-3, 4-diol precursors with 'out of line' C-ring configurations in *C. mopane*.

Quinone methides (**34**) and (**35**) presumably also serve as precursors to the tetrahydropyrano[3,2-*g*]chromenes, *i.e.* (**34**) ⟶ (**17**), (**19**), (**29**), and (**31**), and (**35**) ⟶ (**21**), (**23**), and (**27**) *via* the stereochemical pathways indicated in the Scheme (*cf.* ref. 9). The stereoselectivity of the pyran recyclization

* Quinone methides (**34**) and (**35**) are postulated and have not been isolated.



Scheme. Proposed route to the formation of tetrahydropyrano[3,2-*g*]chromenes (**17**), (**19**), (**21**), (**23**), (**25**), (**27**), (**29**), and (**31**), the (4,6)-bis-(+)-epifisetinidols (**7**) and (**11**) and (+)-epifisetinidol-(4,6)-(−)-fisetinidols (**5**) and (**9**) with unusual heterocyclic configurations; *Reagents and conditions:* i, $NaHCO_3$–Na_2CO_3, 50 °C, 7 h, N_2.

involving the (4α, 6) quinone methide (**34**) contrasts with the observed stereospecificity for similar conversions of quinone methides derives from (−)-fisetinidol-(4α,6 and 8)-(+)-catechins.[2,9] It may be attributed to reduced nucleophilicity of the resorcinol-type D-ring in compound (**34**) with that of the phloroglucinol moiety in the corresponding intermediate of the (−)-fisetinidol-(+)-catechins, hence allowing sufficient time for rotation about the C^2–C^3 bond and attack of 7-OH(D) to both faces at C-2.

Despite the fact that the tetrahydropyrano[3,2-*g*]chromenes (**25**), (**27**), (**29**), and (**31**) have hitherto not been found in the mopane, the conspicuous similarities between the *in vivo* and *in vitro* processes are clear. The mild basic conditions effecting the transformations in the Scheme thus presumably closely match those prevailing in Nature. These conditions may then also explain the vast number of compounds in the metabolic pool of *C. mopane* exhibiting a C-2 epimeric relationship to the predominant (−)-fisetinidol monomer.[1,4]

Experimental

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer, in $CDCl_3$, C_6D_6, or $(CD_3)_2CO$ solutions with Me_4Si as internal standard. Accurate mass estimates were obtained with a Kratos MS80 instrument, and c.d. data on a Jasco J-20 spectropolarimeter for methanol solutions. TLC was performed on pre-coated Merck plastic sheets (silica gel $60PF_{254}$, 0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40:1 v/v) after development. Preparative plates (PLC), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Separations on Sephadex LH-20 were in a column (3.2 × 95 cm) in ethanol. Methylations were performed with an excess of diazomethane in methanol–diethyl ether during 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at ambient temperatures. Evaporations were performed under reduced pressure at *ca.* 70 °C in a rotary evaporator.

Bis-fisetinidols and Tetrahydropyrano[3,2-g]*chromenes from* C. mopane.—The fractionation procedure for the methanol extract of the heartwood was fully described in Parts 8 and 9. Details of the steps leading to the fractions indicated in the following headings, *i.e.* 2·2·3, 2·2·5, 2·2·7, 3·2·1, 4·1·5, 4·2·2, and 4·3, will thus also be found in these papers.

Fraction 2·2·3. Acetylation of the methyl ether fraction 2·2·3 (Part 8)[1] followed by preparative liquid chromatography (PLC) (benzene–hexane–acetone, 6:3:1 v/v, × 3) afforded a main band at R_F 0.52 (12.1 mg). Deacetylation with 1% methanolic KOH and subsequent separation by PLC (hexane–acetone–ethyl acetate–methanol, 65:15:15:5 v/v, × 2) gave a main band at R_F 0.17 (2.0 mg). Acetylation afforded the (+)-*epifisetinidol*-(4α,6)-(−)-*fisetinidol hexamethyl ether diacetate* (**6**) as a white solid (2.1 mg) (Found: M^+, 714.2681. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); ^1H NMR data (Table 1); CD $[\theta]_{297}$ 0, $[\theta]_{283}$ −5.3 × 10^4, $[\theta]_{273}$ 0, $[\theta]_{263}$ 2.1 × 10^4, $[\theta]_{254}$ 1.6 × 10^4, $[\theta]_{243}$ 5.2 × 10^4, $[\theta]_{239}$ 0, $[\theta]_{237}$ −5.0 × 10^4, and $[\theta]_{232}$ 0.

Fraction 2 · 2 · 5. The methyl ether fraction 2 · 2 · 5 was further resolved by PLC (hexane–benzene–acetone, 5:4:1, v/v, × 2), to give two bands at R_F 0.43 (21 mg) and 0.39 (40.1 mg). Acetylation of the R_F 0.39 band followed by PLC (hexane–acetone–ethyl acetate, 7:2:1, v/v, × 10) afforded the known (4α,6)-bis-(−)-fisetinidol and (−)-fisetinidol-(4α,8)-(+)-afzelechin hexamethyl ether diacetates.[1] The R_F 0.43 band was acetylated and subsequently purified by PLC (hexane–acetone–ethyl acetate, 7:2:1 v/v, × 10) to give the (4β,6′)-*bis*-(−)-*fisetinidol hexamethyl ether diacetate* (**14**) as a white solid, R_F 0.41 (7.4 mg) (Found: M^+, 714.2689); ^{1}H NMR data (Table 2); CD $[\theta]_{295}$ 0, $[\theta]_{282}$ -4.9×10^4, $[\theta]_{264}$ 0, $[\theta]_{253}$ 0, $[\theta]_{237}$ 4.3×10^4, and $[\theta]_{232}$ 0.

Fraction 2 · 2 · 7. The R_F 0.44 band obtained by acetylation and PLC separation of fraction 2 · 2 · 7 (Part 8)[1] afforded the (−)-*fisetinidol*-(4β,6′)-(+)-*epifisetinidol hexamethyl ether diacetate* (**16**) as a white solid (5.7 mg) (Found: M^+, 714.2682); ^{1}H NMR data (Table 2); CD $[\theta]_{300}$ 0, $[\theta]_{280}$ -5.5×10^4, $[\theta]_{260}$ -1.0×10^4, $[\theta]_{249}$ 0, $[\theta]_{235}$ 16.4×10^4, and $[\theta]_{225}$ 0.

Fraction 3 · 2 · 1. Acetylation of fraction 3 · 2 · 1 (Part 8)[1] gave (2*R*,3*S*:6*S*,7*S*,8*R*)-2,3-trans-6,7-cis-7,8-trans-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**18**) as a white solid (27.7 mg) (Found: M^+, 714.2684); ^{1}H NMR data (Table 3); CD $[\theta]_{304}$ 0, $[\theta]_{294}$ -8.4×10^4, $[\theta]_{262}$ 0, $[\theta]_{238}$ 15.6×10^4, $[\theta]_{235}$ 22.7×10^4, $[\theta]_{230}$ 7.8×10^4, $[\theta]_{227}$ 11.7×10^4, and $[\theta]_{223}$ 0.

Fraction 4 · 1 · 5. This fraction (111 mg) (Part 9) was further resolved by PLC (benzene–acetone–methanol, 90:9:1 v/v, × 3) into two bands, at R_F 0.29 (73.1 mg) and 0.23 (17.6 mg). The R_F 0.29 band was acetylated and the mixture separated by PLC (hexane–acetone–ethyl acetate, 65:20:15 v/v, × 3) to give three fractions, at R_F 0.53 (33.9 mg), 0.49 (17.7 mg), and 0.43 (12.8 mg). The R_F 0.53 fraction gave the known[4] (4α,6′)-bis-(−)-fisetinidol hexamethyl ether diacetate, and the R_F 0.49 fraction an additional portion of the (+)-epifisetinidol-(4α,6)-(−)-fisetinidol derivative (**6**). The R_F 0.43 fraction afforded the (4α,6)-*bis*-(+)-*epifisetinidol hexamethyl ether diacetate* (**8**) as a white solid (Found: M^+, 714.2670); ^{1}H NMR. data (Table 1); CD $[\theta]_{289}$ 0, $[\theta]_{283}$ -1.0×10^4, $[\theta]_{250}$ -1.0×10^4, $[\theta]_{236}$ -24.6×10^4, $[\theta]_{232}$ -28.9×10^4, and $[\theta]_{220}$ 0.

The R_F 0.23 band from the initial separation of fraction 4 · 1 · 5 was acetylated and the mixture resolved by PLC (hexane–acetone–ethyl acetate, 65:20:15 v/v, × 3) to two fractions, at R_F 0.49 (3.4 mg) and 0.37 (6.9 mg). The former fraction gave the known[4] (4α,6′)-bis-(−)-fisetinidol hexamethyl ether diacetate and the latter an additional portion of the tetrahydropyrano[3,2-*g*]chromene derivative (**18**).

Fraction 4 · 2 · 2. Acetylation of this fraction (38.3 mg) (Part 9) followed by PLC (benzene–ethyl acetate-acetone, 7:2:1 v/v, × 4) afforded two bands, at R_F 0.65 (12.2 mg) and 0.61 (7.6 mg). The former band gave (2R,3S:6R,7S,8R)-2,3-trans-6,7-trans-7,8-trans-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**22**) as a white solid (Found: M^+, 714.2683); ^{1}H NMR data (Table 3); CD $[\theta]_{302}$ 0, $[\theta]_{286}$ -2.3×10^4, $[\theta]_{278}$ 0, $[\theta]_{268}$ 3.0×10^4, $[\theta]_{255}$ 2.5×10^4, $[\theta]_{240}$ 5.7×10^4, $[\theta]_{235}$ 2.7×10^4, and $[\theta]_{231}$ 0. The R_F 0.61 band afforded (2S,3S:6S,7S,8R)-2,3-cis-6,7-cis-7,8-trans-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*-[3,2-g]*chromene* (**20**) as a white solid (Found: M^+, 714.2677); ^{1}H NMR data (Table 4); CD $[\theta]_{303}$ 0, $[\theta]_{294}$ -3.6×10^4, $[\theta]_{261}$ 0, $[\theta]_{237}$ 11.4×10^4, and $[\theta]_{230}$ 0.

Fraction 4 · 3. Methylation of fraction 4 · 3 (417 mg) (Part 9) and subsequent PLC separation (benzene–acetone–methanol, 90:9:1, v/v, × 3) afforded two bands, at R_F 0.17 (23.8 mg) and 0.09 (145.8 mg). The latter fraction consisted of known[3] profisetinidins based on (−)-fisetinidol and (+)-catechin and (−)-epicatechin 'terminal' units. Acetylation of the R_F 0.17 band followed by PLC (hexane–acetone–ethyl acetate, 7:2:1 v/v, × 9) gave (2S,3S:6R,7S,8R)-2,3-cis-6,7-trans-7,8-trans-3,7-diacetoxy-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**24**) as a white solid (R_F 0.27, 6.4 mg) (Found: M^+, 714.2688); ^{1}H NMR data (Table 4); CD $[\theta]_{300}$ 0, $[\theta]_{270}$ 2.1×10^4, $[\theta]_{244}$ 0, $[\theta]_{236}$ -9.9×10^4, $[\theta]_{234}$ -13.3×10^4, $[\theta]_{230}$ -20.2×10^4, and $[\theta]_{220}$ 0.

Base-catalysed Transformations of (4,6)-*Bis*-(−)-*fisetinidols* (**1**) *and* (**2**)

(4α,6)-*Bis*-(−)-*fisetinidol* (**1**).—The (4α,6)-bis-fisetinidol (1) (500 mg) was dissolved in a 0.025M-Na_2CO_3–0.025M-$NaHCO_3$ buffer (pH 10) (100 ml) and the mixture was stirred under N_2 at 50 °C for 7 h. The mixture was chilled on ice, acidified with 0.1M-HCl, and extracted with ethyl acetate (4 × 250 ml). Drying (Na_2SO_4) of the extract followed by evaporation of solvent afforded a light-brown powder (479 mg), which was subjected to column chromatography (3.2 × 95 cm column; flow rate 4.0 ml min^{-1}; atmospheric pressure) on Sephadex LH-20/ethanol. Two fractions, 1 (RR_t 0—16 h, 21.1 mg) and 2 (RR_t 18—50 h, 390 mg) were obtained starting with appearance of the first phenolic substances (UV monitor). Fraction 1 comprised a complex mixture in which the concentrations of the constituents did not merit further investigation. Fraction 2 was methylated and the mixture was separated by PLC (benzene–acetone–methanol, 90:9:1 v/v, × 3) to give four bands, at R_F 0.29 (25.3 mg), 0.23 (37.8 mg), 0.19 (44.2 mg), and 0.14 (164.6 mg).

Acetylation of the R_F 0.29 band followed by PLC (hexane–acetone–ethyl acetate–methanol, 65:15:15:5 v/v, × 2) afforded 2S,3S:6S,7S,8S)-2,3-cis-6,7-cis-7,8-cis-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**32**) as a white solid (R_F 0.33, 2.9 mg) (Found: M^+, 714.2681); ^{1}H NMR data (Table 4); CD $[\theta]_{303}$ 0, $[\theta]_{274}$ 12.7×10^4, $[\theta]_{250}$ 0, $[\theta]_{239}$ 14.3×10^4, $[\theta]_{237}$ 19.8×10^4, and $[\theta]_{233}$ 0.

The R_F 0.23 band was further resolved by PLC (benzene–hexane–acetone, 6:3:1 v/v, × 7) to two fractions, at R_F 0.42 (24.6 mg) and 0.37 (6.2 mg). Acetylation of the former followed by PLC (hexane–benzene–acetone, 6:3:1 v/v, × 14) afforded the (+)-epifisetinidol-(4α,6)-(−)-fisetinidol hexamethyl ether diacetate (**6**) (R_F 0.27, 15 mg), and the (4α,6)-bis-(+)-epifisetinidol (**8**) (R_F 0.23, 6.1 mg) with spectral properties identical with those of the corresponding derivatives of the natural products. Acetylation of the R_F 0.37 band gave (2R,3S:6S,7S,8S)-2,3-trans-6,7-cis-7,8-cis-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**30**) as a white solid (16.5 mg) (Found: M^+, 714.2685); ^{1}H NMR data (Table 3); CD $[\theta]_{304}$ 0, $[\theta]_{284}$ -15.9×10^4, $[\theta]_{247}$ 0, $[\theta]_{238}$ 11.8×10^4, and $[\theta]_{234}$ 0.

Acetylation of the R_F 0.19 band and subsequent purification by PLC (benzene–hexane–acetone, 6:3:1 v/v, × 2) gave the 2,3-*trans*-6,7-*cis*-7,8-*trans*-tetrahydropyrano[3,2-*g*]chromene hexamethyl ether diacetate (**18**) (R_F 0.39, 22.4 mg) and the 2,3-*cis* epimeric derivative (**20**) with physical data identical with those of the natural product derivatives.

The R_F 0.14 band consisted of the starting biflavanoid (**1**).

(4β,6)-*Bis*-(−)-*fisetinidol* (**2**).—The (4β,6)bis-(−)-fisetinidol (**2**) (850 mg) was treated with base and the resulting mixture was resolved by column chromatography as was described above for compound (**1**). Three fractions, 1(RR_t 0—19.5 h, 198.5 mg), 2(RR_t 20—43 h, 221.8 mg), and 3(RR_t 43.5—67 h, 403.9 mg) were obtained. Fraction 1 comprised at least four dehydrobisfisetinidols of type (**33**). Their details will be presented elsewhere.

Methylation of fraction 2 followed by PLC (benzene–acetone–

methanol, 90:9:1 v/v, ×4) afforded two bands, at R_F 0.22 (77.1 mg) and 0.14 (47.4 mg). Acetylation and PLC separation (benzene–hexane–acetone, 6:3:1 v/v, ×4) of the R_F 0.22 band gave the hexamethyl ether diacetate[3] of the (4α,6)-bis-(−)-fisetinidol (**2**) (R_F 0.47, 69 mg). The R_F 0.14 band was similarly acetylated and purified by PLC (benzene–hexane–acetone, 6:3:1 v/v, ×3) to give the hexamethyl ether diacetate[4] of the (−)-fisetinidol-(4β,6)-(+)-epifisetinidol (**4**) (R_F 0.31, 60.7 mg).

Fraction 3 was methylated and the mixture was resolved by PLC (benzene–ethyl acetate–acetone, 7:2:1 v/v, ×3) to five bands, at R_F 0.50 (46.9 mg), 0.47 (61.8 mg), 0.43 (100 mg), 0.40 (58.3 mg), and 0.34 (34.7 mg). The R_F 0.50 band was acetylated and subsequently separated by PLC (benzene–hexane–acetone, 6:3:1 v/v, ×2) to give (2R,3S:6R,7S,8S)-2,3-cis-6,7-trans-7,8-cis-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**26**) as a white solid (R_F 0.32, 19.1 mg) (Found: M^+, 714.2688); ^{1}H NMR data (Table 3); CD $[\theta]_{300}$ 0, $[\theta]_{286}$ -5.4×10^4, $[\theta]_{275}$ 0, $[\theta]_{265}$ 3.6×10^4, $[\theta]_{250}$ 1.8×10^4, $[\theta]_{238}$ 6.4×10^4, and $[\theta]_{234}$ 0. Acetylation of the R_F 0.47 band and purification by PLC (benzene–hexane–acetone, 6:3:1 v/v, ×2) afforded the all-*trans* (R_F 0.34, 14.6 mg) and 2,3-*cis*-6,7-*trans*-7,8-*trans* (R_F 0.26, 31.1 mg) tetrahydropyrano[3,2-*g*]chromene hexamethyl ether diacetates (**22**) and (**24**) with spectral data identical with those of the natural product derivatives. Acetylation of the R_F 0.43 band followed by PLC (benzene–hexane–acetone, 6:3:1 v/v, ×2) gave an additional sample of the all-*trans* derivative (**22**), R_F 0.38 (76.0 mg). The R_F 0.40 band was similarly acetylated to give (2S,3S:6R,7S,8S)-2,3-cis-6,7-trans-7,8-cis-3,7-*diacetoxy*-6-(2,4-*dimethoxyphenyl*)-2,8-*bis*-(3,4-*dimethoxyphenyl*)-3,4,7,8-*tetrahydro*-2H,6H-*pyrano*[3,2-g]*chromene* (**28**) (61.5 mg) as a white solid (Found: M^+, 714.2691); ^{1}H NMR data (Table 4); CD $[\theta]_{300}$ 0, $[\theta]_{270}$ 6.9×10^4, $[\theta]_{243}$ 0, $[\theta]_{237}$ -5.2×10^4, and $[\theta]_{233}$ 0. Acetylation of the R_F 0.34 band and PLC separation (benzene–hexane–acetone, 5:4:1 v/v, ×3) afforded two fractions, at R_F 0.21 (19.0 mg) and 0.17 (8.4 mg). The former fraction gave the (+)-epifisetinidol-(4β,6)-(−)-*fisetinidol hexamethyl ether diacetate* (**10**) as a white solid (Found: M^+, 714.2674); ^{1}H NMR data (Table 1); CD $[\theta]_{297}$ 0, $[\theta]_{283}$ -2.8×10^4, $[\theta]_{253}$ 0, $[\theta]_{233}$ 16.8×10^4, and $[\theta]_{218}$ 0. The R_F 0.17 fraction afforded the (4β,6)-*bis*-(+)-*epifisetinidol hexamethyl ether diacetate* (**12**) as a white solid (Found: M^+. 714.2681); ^{1}H NMR data (Table 1); CD $[\theta]_{306}$ 0, $[\theta]_{280}$ -9.2×10^4, $[\theta]_{248}$ 0, $[\theta]_{236}$ 18.1×10^4, $[\theta]_{233}$ 14.3×10^4, and $[\theta]_{227}$ 0.

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