Oligomeric Flavanoids. Part 8.† The First Profisetinidins and Proguibourtinidins Based on C-8 Substituted (−)-Fisetinidol Units and Related c-ring Isomerized Analogues

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Structural examination of the phenolic metabolites of *Colophospermum mopane* reveals the presence of the first profisetinidins and proguibourtinidins based on C-8 substituted (−)-fisetinidol units *i.e.* the (4α,8)-bis-(−)-fisetinidol (**1**), (+)-epifisetinidol-(4α,8)-(−)-fisetinidol (**3**), and the (+)-guibourtinidol-(4α,8)-(−)-fisetinidol (**5**). They are accompanied by the related functionalized tetrahydropyrano[2,3-*h*]chromenes (**9**), (**11**), (**13**), (**15**), and (**17**), and by a 2,4-diaryl-6-(2-benzopyranyl)chroman (**19**), the first c-ring isomerized analogue derived from a B-ring coupled profisetinidin. Efforts towards the synthesis of the (4,8)-bis-fisetinidols from 6-bromo-(−)-fisetinidol and the appropriate flavan-3,4-diol, lead to the biaryl type biflavanoids (**33**) and (**35**). Their genesis is explained in terms of an oxidative substitution reaction initiated by bromonium ion.

The natural and synthetic dimeric profisetinidins with C-D-ring linked 5-deoxyflavan-3-ol constituent units are invariably substituted at C-6 of the resorcinol type D-ring of their terminal section.[1,2] Such a conspicuous absence of (4,8)-coupled analogues among this class of oligoflavanoids contrasts with the involvement of both C-6 and C-8 in interflavanyl bonding where the A-rings of these terminal groups are of the phloroglucinol type. Our recent demonstration of a novel series of 5-deoxy (D-ring) biflavanoids in the heartwood of the mopane[2] (*Colophospermum mopane* Kirk *ex.* J. Leonard) prompted reinvestigation of the metabolites from this natural source. The methodology of extensive enrichment and fractionation procedures[2] in conjunction with our utilization of Sephadex LH-20 and Fractogel TSK HW-40 (S) as chromatographic substrates under medium pressure[3] not only revealed the presence of the first (4,8)-linked (−)-fisetinidol based profisetinidins and proguibourtinidins, but also of related C-ring isomerized analogues, termed phlobatannins,[4] in which resorcinol and pyrocatechol type rings effected these pyran rearrangements.

Results and Discussion

The biflavanoids in which both (−)-fisetinidol [(2*R*,3*S*)-2,3-*trans*-flavan-3,3′,4′,7-tetraol] and (+)-epifisetinidol [(2*S*,3*S*)-2,3-*cis*-flavan-3,3′,4′,7-tetraol] function prominently as 'terminal' moieties described in Part 1,[2] are accompanied in the heartwood of the mopane by the first (4,8)-bis(fisetinidols) (**1**) and (**3**), a (+)-guibourtinidol‡-(4,8)-(−)-fisetinidol (**5**), a series of functionalized 5-deoxytetrahydropyrano[2,3-*h*]chromenes (**9**), (**11**), (**13**), (**15**), and (**17**), a novel B-ring coupled analogue *i.e.* the proguibourtinidin (**7**),§ and the first C-ring isomerized homologue (**19**) derived from a B-ring linked profisetinidin. Owing to the complexity of the phenolic mixture the structures of these novel compounds were established from the physical data of their methyl ether diacetates, *e.g.* (**2**).

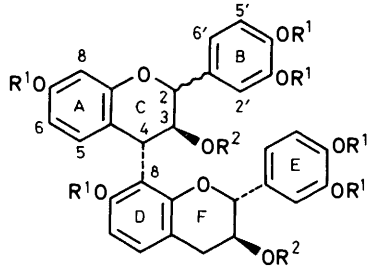
^{1}H N.m.r. data (Table 1) of the hexamethyl ether diacetate (**2**) of the (4α,8)-bis-(−)-fisetinidol (**1**), representative of the first dimeric profisetinidin with a C-8 substituted 5-deoxyflavan-3-ol terminal unit, comprise of an aromatic AB- and three ABX-systems as well as a heterocyclic AMX- and an AMXY-system. The relative configuration is evident from the ^{1}H n.m.r. coupling constants of the latter systems ($J_{2,3(C)} = J_{3,4(C)}$ 10.0 Hz, $J_{2,3(F)}$ 8.8 Hz]. These data are consistent with the presence of two (−)-fisetinidol moieties coupled *via* C-4(C) and either C-8(D) or C-2(E). The (4,8)-interflavanyl linkage is confirmed by observation of benzylic coupling of the low-field AB-doublet at δ 6.95($J_{5,6}$ 8.5 Hz) with 4-H_2(F), and by the chemical shift of 3-H(C) (δ 6.12) which indicates a 4-linked flavanyl unit which is flanked at the point of attachment to aryl rings by two *ortho* oxygen substituents.[5] A high-amplitude negative Cotton effect (C.E.) at 235 nm. in the c.d. spectrum of (**2**), when taken in conjunction with the coupling constants and the known absolute configuration of the presumed precursors of (**1**) in *C. mopane*,[2] defines the absolute configuration of this novel metabolite as 2*R*,3*S*,4*R*(C):2*R*,3*S*(F) by application of the aromatic quadrant rule.[6]

Replacement of the (−)-fisetinidol 'upper' unit in (**1**) by a (+)-epifisetinidol moiety in the (+)-epifisetinidol-(4α,8)-(−)-fisetinidol (**3**), is evident from the coupling constants (Table 1) of the heterocyclic AMX-system in the hexamethyl ether diacetate (**4**) ($J_{2,3}$ 3.0, $J_{3,4}$ 4.5 Hz). Substitution at C-8(D) is again confirmed by the chemical shift of 3-H(C) (δ 6.16) and by the benzylic coupling of the low-field AB-doublet at δ 6.77($J_{5,6}$ 8.5 Hz, 5-H(D)] and 4-H_2(F). The strong negative C.E. at 230 nm. in the c.d. spectrum of (**4**) indicates a 4α-substituent and hence an absolute configuration of 2*S*,3*S*,4*R*(C):2*R*,3*S*(F) for (**3**). Besides being only the second natural profisetinidin with a 5-deoxyflavan-3-ol terminal unit substituted at C-8, bis-fisetinidol (**3**) is the first biflavanoid with a (2*S*,3*S*)-2,3-*cis* 'upper' unit (see below).

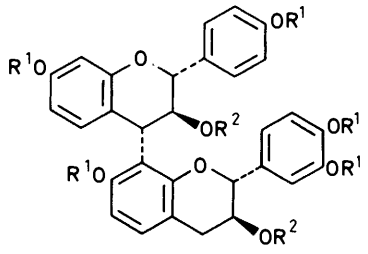
† Part 7, J. P. Steynberg, B. C. B. Bezuidenhoudt, J. F. W. Burger, D. A. Young, and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1*, 1990, preceding paper.

‡ (+)-Guibourtinidol is taken as the flavan-3-ol moiety derived from the (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,4,4′,7-tetraol, (+)-guibourtacacidin.

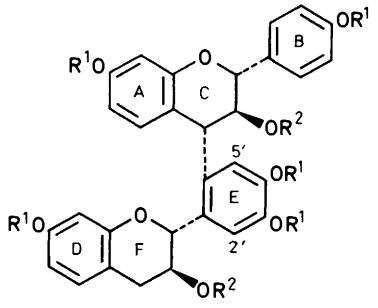
§ The position of substitution is taken as C-6′(B) of the 'lower' flavan unit to retain trivial names for the respective constituent flavanyl moieties.



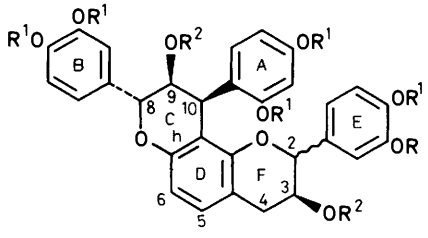
(1) ≡ ⋮, $R^1 = R^2 = H$
(2) ≡ ⋮, R^1 = Me, R^2 = Ac
(3) ≡ ▲, $R^1 = R^2 = H$
(4) ≡ ▲, R^1 = Me, R^2 = Ac



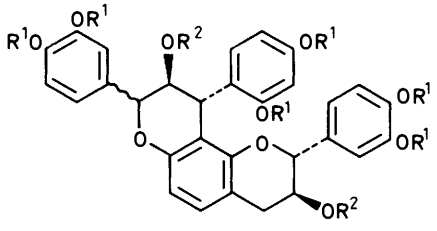
(5) $R^1 = R^2 = H$
(6) R^1 = Me, R^2 = Ac



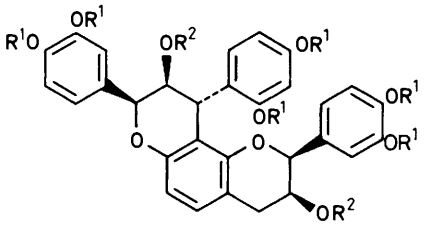
(7) $R^1 = R^2 = H$
(8) R^1 = Me, R^2 = Ac



(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 = H



(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

The series of (4,8)-coupled 5-deoxy (D-ring) biflavanoids is extended by the (+)-guibourtinidol-(4α,8)-(−)-fisetinidol (**5**). The ^{1}H n.m.r. spectral data (Table 1) of its pentamethyl ether diacetate (**6**) closely match those of the (4α,8)-bis-(−)-fisetinidol (**2**) except for the number of methoxy resonances and replacement of an aromatic ABX-system in (**2**) by an AA′BB′-pattern for (**6**). Correlation of this system with the 2-H doublet (δ 4.79) of the heterocyclic AMX-pattern and of 4-H(δ 4.94) of the latter system with 5-H(δ 6.64, dd, $J_{5,6}$ 8.5 Hz) of the highfield aromatic ABX system *via* spin-spin decoupling experiments, defines the constitution of the (+)-guibourtinidol unit. While the 2,3-*trans*-3,4-*trans*:2,3-*trans* relative configuration is evident from ^{1}H n.m.r. coupling constants of heterocyclic protons [$J_{2,3(C)} = J_{3,4(C)}$ 10.0, $J_{2,3(F)}$ 8.0 Hz], the high-amplitude negative C.E. in the 220—240 nm region of the c.d. spectrum of (**6**) facilitates definition of the absolute configuration of the novel (+)-guibourtinidol-(4α,8)-(−)-fisetinidol (**5**) as 2*R*,3*S*,4*R*(C):2*R*,3*S*(F).

The 'conventional' (4,8)-biflavanoids (**1**), (**3**), and (**5**) are accompanied by an additional member (**7**) of the rare series of naturally occurring B-ring coupled oligomers.[2] The ^{1}H n.m.r. spectrum (Table 1) of the pentamethyl ether diacetate (**8**) of this (+)-guibourtinidol-(4α,6′)-(−)-fisetinidol (**7**) exhibits in the heterocyclic region an AMX ($J_{2,3}$ 9.5, $J_{3,4}$ 9.8 Hz) and AMXY system ($J_{2,3}$ 6.0 Hz) characteristic of the all-*trans* configuration of both flavanyl units. Besides the AA′BB′- and two ABX-systems, the aromatic region displays two singlets (δ 6.85, 6.66) which sharpen slightly on irradiation of respectively the 4-H(C)

Table 1. ^{1}H N.m.r. (300 MHz) peaks (p.p.m.) of biflavanoids (**2**), (**4**), (**6**), and (**8**), and the dihydrochromene (**20**). Splitting patterns and *J* values (Hz) are given in parentheses

Ring	H	(2)[a]	(4)[b]	(6)[a]	(8)[c]	(20)[a]
A	5	6.64 (dd, 1.2, 8.5)	6.92 (dd, 1.5, 8.5)	6.64 (dd, 1.2, 8.5)	6.63 (dd, 1.0, 8.5)	6.30 (dd, 2.5, 8.5)
	6	6.43 (dd, 2.5, 8.5)	6.46 (dd, 2.5, 8.5)	6.42 (dd, 2.5, 8.5)	6.43 (dd, 2.5, 8.5)	6.75 (d, 8.5)
	8	6.36 (d, 2.5)	6.66 (d, 2.5)	6.31 (d, 2.5)	6.50 (d, 2.5)	6.39 (d, 2.5), 3-H
B	2	6.62 (d, 2.0)	7.15 (d, 2.0)	7.05 (d, 8.5), 2/6	7.39 (d, 8.5), 2/6	6.86 (d, 2.0)
	5	6.71 (d, 8.5)	6.64 (d, 8.5)	6.75 (d, 8.5), 3/5	6.88 (d, 8.5), 3/5	6.78 (d, 8.5)
	6	6.76 (dd, 2.0, 8.5)	7.04 (dd, 2.0, 8.5)	—	—	6.89 (dd, 2.0, 8.5)
C	2	4.83 (d, 10.0)	5.76 (d, 3.0)	4.79 (d, 10.0)	5.08 (d, 9.5)	5.34 (d, 6.0)
	3	6.12 (t, 10.0)	6.16 (dd, 3.0, 4.5)	6.02 (t, 10.0)	5.72 (dd, 9.5, 9.8)	5.52 (dd, 4.9, 6.0)
	4	4.94 (dd, 1.2, 10.0)	5.15 (d, 4.5)	4.91 (dd, 1.2, 10.0)	4.82 (d, 9.8)	4.74 (d, 4.9)
D	5	6.95 (d, 8.5)	6.77 (d, 8.5)	6.53 (d, 8.5)	6.93 (d, 9.0)	6.88 (d, 8.5)
	6	6.56 (d, 8.5)	6.38 (d, 8.5)	6.55 (d, 8.5)	6.52 (dd, 2.5, 9.0)	6.46 (dd, 2.5, 8.5)
	8	—	—	—	6.52 (d, 2.5)	6.41 (d, 2.5)
E	2	6.54 (d, 2.0)	6.78 (d, 2.0)	6.54 (d, 2.0)	6.66 (s)	6.79 (d, 1.9)
	5	6.65 (d, 8.5)	6.62 (d, 8.5)	6.67 (d, 8.5)	6.85 (s)	—
	6	6.44 (dd, 2.0, 8.5)	6.71 (dd, 2.0, 8.5)	6.41 (dd, 2.0, 8.5)	—	6.46 (d, 1.9), 7-H
F	2	4.88 (d, 8.8)	5.04 (d, 6.5)	4.88 (d, 8.0)	5.46 (d, 6.0)	4.93 (d, 6.5)
	3	4.92 (m)	5.35 (m)	5.03 (m)	5.66 (m)	5.25 (m)
	$4_{ax.}$	2.83 (dd, 9.0, 16.0)	2.75 (dd, 7.5, 16.0)	2.81 (dd, 8.5, 16.0)	2.79 (dd, 6.5, 16.0)	2.75 (dd, 7.0, 16.0)
	$4_{eq.}$	3.08 (dd, 6.0, 16.0)	2.97 (dd, 5.0, 16.0)	3.06 (dd, 6.0, 16.0)	3.03 (dd, 4.5, 16.0)	2.93 (dd, 5.0, 16.0)
OMe		3.59 (3-B), 3.71 (3-E), 3.72 (7-A), 3.82 (4-B), 3.83 (4-E), 3.85 (7-D), (each s)	3.36 (7-D), 3.38 (7-A), 3.45 (4-B), 3.46 (4-E), 3.51 (3-B), 3.55 (3-E), (each s)	3.70 (7-A), 3.74 (3-E), 3.75 (4-B), 3.84 (7-D), 3.86 (4-E) (each s)	3.69 (3-E), 3.74 (4-E), 3.75 (7-A), 3.76 (7-D), 3.80 (4-B) (each s)	3.71 (7-D), 3.74 (2-A), 3.78 (4-A), 3.81 (3-B), 3.84 (4-B), 3.86 (8-E), (each s)
OAc		1.55 (s), 1.86 (s)	1.55 (s), 1.61 (s)	1.57 (s), 1.86 (s)	1.62 (s), 1.96 (s)	1.77 (s), 1.90 (s)

[a] $CDCl_3$, 296K, [b] C_6D_6, 363K, [c] $CDCl_3$, 353K

(δ 4.82) and 2-H(F) (δ 5.46) resonances. This observation, when taken in conjunction with the n.O.e. association of the 2- and 5-H(E) singlets and a single methoxy resonance [δ 3.69 (12.2%); δ 3.74 (10.4%) respectively] in each instance, defines coupling from C-4(C) of the (+)-guibourtinidol unit to C-6(B) of the 'lower' (−)-fisetinidol moiety (*cf.* ref. 2). The c.d. spectrum of (**7**) exhibits a high-amplitude negative C.E. in the 220—240 nm region thus confirming (2*R*,3*S*,4*R*)-absolute configuration for the (+)-guibourtinidol unit. In view of the predominance of (−)-fisetinidol in the heartwood of *C. mopane*, we favour a (2*R*,3*S*)-absolute configuration for the 'terminal' flavan-3-ol moiety.

The natural occurrence of the unique class of C-ring isomerized condensed tannins is hitherto restricted to analogues derived from (−)-fisetinidol-(4,6 and 4,8)-(+)-catechins[3,4] *i.e.* compounds in which the nucleophilicity of the phenolic ring effecting the pyran rearrangement exceeds that of the ring acting as a leaving group. This series is extended by identification of the first 5-deoxytetrahydropyrano[2,3-*h*]chromenes (**9**), (**11**), (**13**), (**15**), and (**17**), and the 2,4-diaryl-6-(2-benzopyranyl)-chromane (**19**). These compounds represent the first C-ring isomerized analogues derived from precursors in which the nucleophilicities of the participating phenolic rings are of comparable magnitude.

Owing to the close structural resemblance of the tetrahydropyrano[2,3-*h*]chromenes, detailed structural analysis is presented for the hexamethyl ether diacetate (**10**) of the 8,9-*trans*-9,10-*cis* analogue (**9**) only. ^{1}H N.m.r. coupling constants and chemical shifts (Table 2) of the protons of the heterocyclic AMX system ($J_{8,9}$ 10.5, $J_{9,10}$ 6.0 Hz) closely resemble those of the 5-oxygenated analogue[3] thus confirming the 8,9-*trans*-9,10-*cis* relative configuration. A 'liberated' resorcinol A-ring[4] is evident from the n.O.e. associations of 3-H(A) with 2- and 4-OMe(A) (10.6 and 7.2% respectively) and of 5-H(A) with 4-OMe(A) (6.7%). Adjacency of the aromatic AB-system (*J* 8.0 Hz) to ring F is confirmed by benzylic coupling of 5-H(D) with 4-H_2(F), the XY-portion of a 2,3-*trans* heterocyclic AMXY system ($J_{2,3}$ 6.5 Hz). The n.O.e. effect of 6-H(E) with 10-H(C) (0.9%) unambiguously defines the tetrahydropyrano[2,3-*h*]chromene arrangement.[3,4] This, when taken in conjunction with the benzylic connection of 10-H(C) with 6-H(A) and of 8-H(C) with 2- and 6-H(B), also provides evidence for the location of the pyrocatechol B- and resorcinol A-rings at C-8 and -10 respectively.[7]

A similar protocol of using coupling constants (Table 2) and the relevant decoupling and n.O.e. experiments facilitates definition of the constitution and relative configuration of the remaining 5-deoxytetrahydropyrano[2,3-*h*]chromenes (**11**), (**13**), (**15**), and (**17**). Analogues with 8,9-*trans*-9,10-*trans* configuration display coupling constants of the heterocyclic AMX system of $J_{8,9}$ *ca.* 6.0, $J_{9,10}$ *ca.* 5.0 Hz [for derivative (**14**)], those with 8,9-*cis*-9,10-*trans* configuration, $J_{8,9}$ *ca.* 1.5, $J_{9,10}$ *ca.* 2.0 Hz [for derivatives (**16**) and (**18**)], and the C-2(F) epimers, $J_{2,3(F)}$ *ca.* 1.0 Hz [for derivatives (**12**) and (**18**)]. The 8,9-*cis*-9,10-*trans* relative configurations of (**16**) and (**18**) are confirmed by the n.O.e. association of 8-H(C) with 6-H(A) (*cf.* refs. 3 and 7). These novel metabolites represent the first phlobatannins where the rings involved in the pyran rearrangement are both of the resorcinol type. Their presence furthermore confirms the novel mode of coupling *via* C-8 of the terminal 5-deoxyflavan-3-ol unit.

The absolute configurations of the tetrahydropyrano[2,3-*h*]-chromenes are deduced by combination of ^{1}H n.m.r. and c.d. data of their hexamethyl ether diacetates. High-amplitude positive C.E.'s at 236 and 231 nm. for the 8,9-*trans*-9,10-*cis* derivatives (**10**) and (**12**) respectively, indicate 2*R*,3*S*:8*R*,9*S*,10*S* absolute configuration for (**9**) and 2*S*,3*S*:8*R*,9*S*,10*S* for (**11**). Negative C.E.'s in the same region for the all-*trans*-(**14**) and *cis*-*trans* (**16**) derivatives similarly defines a 2*R*,3*S*:8*R*,9*S*,10*R* configuration for (**13**) and 2*R*,3*S*:8*S*,9*S*,10*R* for (**15**). The

Table 2. ^{1}H N.m.r. (300 MHz) peaks of tetrahydropyrano[2,3-*h*]chromenes (**10**), (**12**), (**14**), (**16**), and (**18**) at 296 K. Splitting patterns and *J*-values (Hz) are given in parentheses

Ring	H	(10)[a]	(12)[b]	(14)[a]	(16)[b]	(18)[a]
A	3	6.29 (d, 2.5)	6.50 (d, 2.5)	6.19 (d, 2.5)	6.45 (d, 2.5)	6.41 (d, 2.5)
	5	6.32 (dd, 2.5, 8.0)	6.45 (dd, 2.5, 8.5)	6.11 (dd, 2.5, 8.5)	6.41 (dd, 2.5, 8.5)	6.31 (dd, 2.5, 8.5)
	6	7.17 (d, 8.0)	6.86 (d, 8.5)	6.44 (d, 8.5)	6.71 (d, 8.5)	7.04 (d, 8.5)
B	2	7.01 (d, 2.0)	6.86 (d, 2.0)	6.77 (d, 2.0)	6.90 (d, 2.0)	7.11 (d, 2.0)
	5	6.56 (d, 8.0)	6.79 (d, 8.5)	6.66 (d, 8.5)	6.76 (d, 8.5)	6.51 (d, 8.5)
	6	7.03 (dd, 2.0, 8.0)	6.91 (dd, 2.0, 8.5)	6.82 (dd, 2.0, 8.5)	6.80 (dd, 2.0, 8.5)	6.96 (dd, 2.0, 8.5)
C	8	5.46 (d, 10.5)	4.98 (d, 10.2)	5.02 (d, 7.0)	5.00 (broad s)	5.44 (broad s)
	9	6.07 (dd, 6.0, 10.5)	5.49 (dd, 6.0, 10.2)	5.64 (dd, 6.0, 7.0)	5.39 (dd, 1.5, 1.8)	5.97 (dd, 1.5, 1.9)
	10	5.77 (d, 6.0)	5.12 (d, 6.0)	4.53 (d, 6.0)	4.56 (d, 1.8)	5.34 (d, 1.9)
D	5	6.77 (d, 8.5)	6.93 (d, 8.5)	6.93 (d, 8.5)	6.97 (d, 8.5)	6.86 (d, 8.5)
	6	6.94 (d, 8.5)	6.61 (d, 8.5)	6.67 (d, 8.5)	6.69 (d, 8.5)	7.09 (d, 8.5)
E	2	6.82 (d, 2.0)	6.43 (d, 2.0	6.36 (d, 2.1)	6.41 (d, 2.0)	6.90 (d, 2.0)
	5	6.43 (d, 8.5)	6.61 (d, 8.5)	6.56 (d, 8.5)	6.59 (d, 8.2)	6.51 (d, 8.5)
	6	6.74 (dd, 2.0, 8.5)	6.23 (dd, 2.0, 8.5)	6.19 (dd, 2.1, 8.5)	6.37 (dd, 2.0, 8.2)	6.80 (dd, 2.0, 8.5)
F	2	4.88 (d, 6.5)	4.96 (broad s)	4.75 (d, 8.5)	4.86 (d, 8.0)	4.64 (s)
	3	5.39 (m)	5.21 (m)	4.94 (m)	4.97 (m)	5.54 (m)
	$4_{ax.}$	2.60 (dd, 6.9, 16.0)	2.84 (dd, 2.2, 17.0)	2.84 (dd, 9.0, 16.0)	2.88 (dd, 8.5, 16.0)	2.84 (m)
	$4_{eq.}$	2.91 (dd, 5.1, 16.0)	3.21 (dd, 4.0, 17.0)	3.04 (dd, 5.5, 16.0)	3.03 (dd, 5.5, 16.0)	2.84 (m)
OMe		3.12 (2-A), 3.26 (4-A), 3.29 (3-B), 3.31 (4-B), 3.34 (4-E), 3.49 (3-E) (each s)	3.57 (2-A), 3.66 (3-E), 3.81 (4-A), 3.83 (4-E), 3.84 (3-B), 3.85 (4-B), (each s)	3.51 (2-A), 3.60 (3-E), 3.69 (4-A), 3.77 (3-B), 3.81 (4-B), 3.82 (4-E), (each s)	3.56 (3-E), 3.73 (2-A), 3.79 (4-A), 3.81 (4-E), 3.83 (4-B), 3.84 (3-B), (each s)	3.24 (4-A), 3.28 (4-E/B), 3.30 (3-B), 3.33 (4-E/B), 3.47 (3-A), 3.55 (3-E) (each s)
OAc		1.47 (s), 1.49 (s)	1.67 (s), 1.69 (s)	1.82 (s), 1.90 (s)	1.90 (s), 1.91 (s)	1.34 (s), 1.41 (s)

[a] C_6D_6, [b] $CDCl_3$

cis-trans-derivative (**18**), however, displays a positive C.E. in the 220—240 nm. region thus apparently reflecting a 10*S* absolute configuration. Owing to the steric congestion between the 10- and 2(F)-aryl substituents, the C-ring is presumably forced into a C-3 sofa conformation with concomitant reversal of the sign of the low-wavelength C.E. In the absence of appropriate reference compounds we favour the 2*S*,3*S*:8*S*,9*S*,10*R* absolute configuration depicted in (**17**).

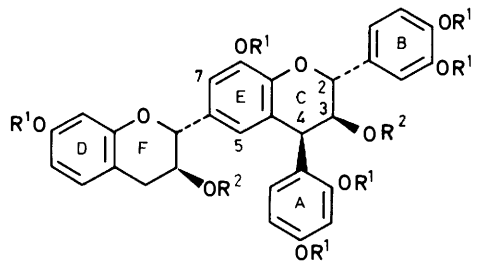
Comparison of ^{1}H n.m.r. data (Table 1) of the hexamethyl ether diacetate (**20**) of the 2,4-diaryl-6-(2-benzopyranyl)-chromane (**19**) with those of the (4α,8)-bis-(−)-fisetinidol (**2**) and the 8,9-*trans*-9,10-*cis* tetrahydropyrano[2,3-*h*]chromene (**10**) reveals replacement of the aromatic AB systems in (**2**) and (**10**) by a resorcinol type ABX pattern in (**20**), and of one of the pyrocatechol type ABX systems in (**2**) and (**10**) by two *meta*-coupled doublets (*J* 1.9 Hz) in (**20**). The doublet to lower field (δ 6.89) exhibits benzylic coupling with both 2-H(F) (δ 5.34) and 4-H(C) (δ 4.74), while that at δ 6.46 shows benzylic coupling with 2-H(F) and an n.O.e. effect (6.4%) with a single methoxy group (δ 3.86). N.O.e. and decoupling experiments establish connection of the heterocyclic AMXY system with 2,3-*trans* configuration ($J_{2,3}$ 6.5 Hz) to one of the resorcinol type ABX systems. The same methodology also facilitates identification of the substituents of the 2,3-*trans*-3,4-*cis* heterocyclic ABM system ($J_{2,3}$ 6.0, $J_{3,4}$ 4.9 Hz) using the unambiguously assigned 4-H(C) resonance (δ 4.74) as a reference signal. The n.O.e. effect of 2-H(C) (δ 5.34) with 6-H(A) (δ 6.75, 1.2%) confirms the relative 2,3-*trans*-3,4-*cis* configuration of ring C, the small $J_{2,3}$ value for such a configuration presumably reflecting a conformation in which the C-4 resorcinol moiety occupies a quasi-axial position. Its β-orientation and hence a 2*R*,3*S*(F):2*R*,3*S*,4*S*(C) absolute configuration for (**19**) is confirmed by the intense positive C.E. at 235 nm. in the c.d. spectrum of derivative (**20**).

Collectively these data indicate a C-ring isomerized structure for (**19**) which may plausibly be derived from a (4α,5′)-bis-(−)-fisetinidol (**21**) *via* an intermediate quinone-methide (**22**) (Scheme 1). Although the presumed precursor (**21**) has hitherto not been found in *C. mopane*, the occurrence of related B-ring linked fisetinidols in this natural source is now firmly established (see also ref. 2).

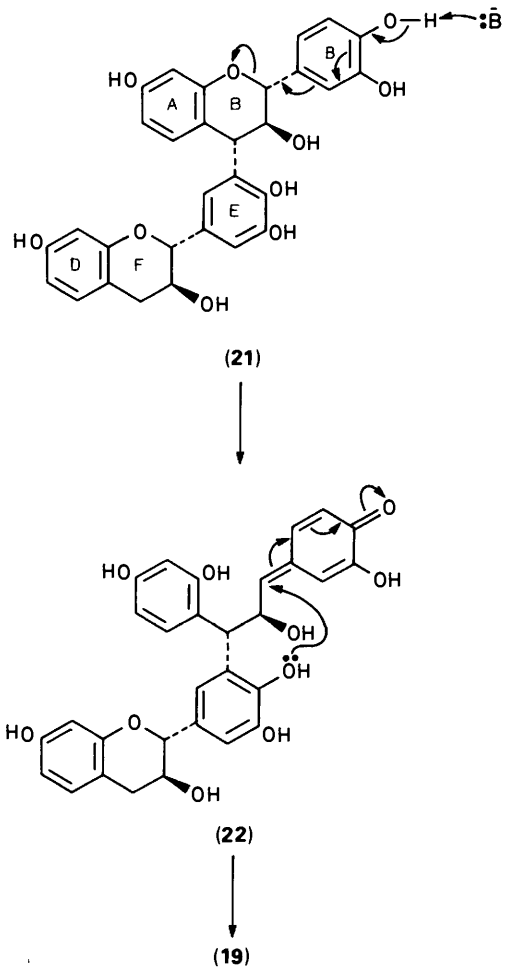
The (4α,8)-bis-(−)-fisetinidol (**1**) and its hitherto unknown (4β,8)-isomer (**23**) presumably serve as precursors to the range of tetrahydropyrano[2,3-*h*]chromenes (Scheme 2). Under base catalysis biflavanoids (**1**) and (**23**) are transformed to quinone-methides (**24**) and (**25**). Similar to the established biomimetic route to the 5-oxygenated analogues,[3,7] stereospecific pyran recyclization *via* 7-OH(D) and the *Re*-face at C-2 in the 3,4-*trans* quinone-methide (**24**) leads to the 8,9-*trans*-9,10-*cis* homologue (**9**) while the 3,4-*cis* isomer (**25**) is transformed stereoselectively to the all-*trans* and 8,9-*cis*-9,10-*trans* compounds (**13**) and (**15**). Recyclization of the 3,4-*trans* quinone-methide (**24**) involving 2-OH(A) and the *Si*-face at C-2 may explain the genesis of the (+)-epifisetinidol-(4α,8)-(−)-fisetinidol (**3**) with its unusual (2*S*,3*S*)-2,3-*cis* upper unit. Such a mechanism would eliminate speculations regarding the occurrence of a related flavan-3,4-diol in *C. mopane*. Similar epimerization at C-2(F) *via* an E-ring quinone-methide [3] may also explain formation of the (+)-epifisetinidol DEF-moiety in tetrahydropyranochromenes (**11**) and (**17**).

The ring isomerized metabolites thus originate from precursors in which the nucelophilicity of the phenolic rings effecting isomerization are of comparable [for (**1**) ⟶ (**9**)] or lower [for (**21**) ⟶ (**22**)] magnitude than those of the rings acting as leaving groups. Ring isomerization presumably leads to a decrease in conformational energy by partial removal of steric effects caused by mutual rotation of bulky groups about the interflavanyl bond of the biflavanoid precursors. Generation of the conformationally more stable product ([*e.g.* (**9**)] with its relative planar central 'core' (CDF tricyclic system) presumably provides the main impetus for these pyran rearrangements rather than the effect of different nucleophilicities of the participating phenolic rings as was initially postulated.[4]

Identification of the (4,8)-linked dimers (**1**), (**3**), and (**5**), and the related tetrahydropyrano[2,3-*h*]chromenes (**9**), (**11**), (**13**),

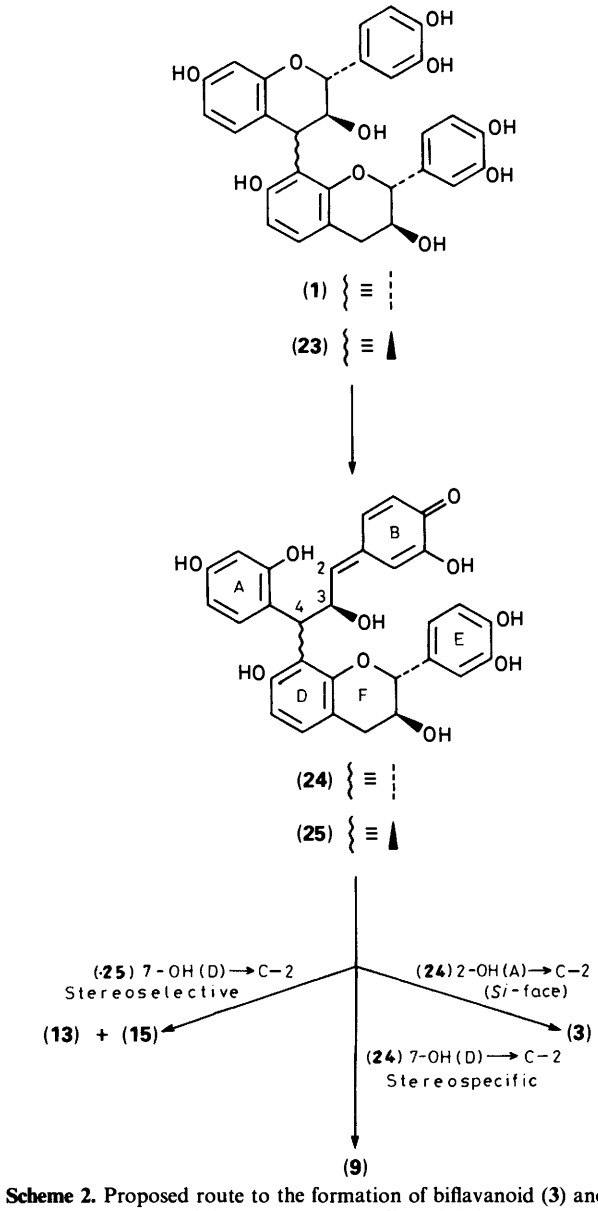


(19) $R^1 = R^2 = H$
(20) $R^1 = Me$, $R^2 = Ac$

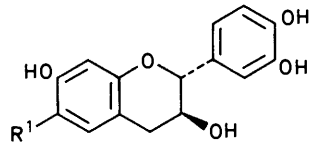


Scheme 1. Proposed route to the formation of the 2,4-diaryl-6-(2-benzopyranyl)-dihydrochromene (**19**)

(**15**), and (**17**) prompted investigation of a biomimetic sequence to these novel metabolites. Since the *in vitro* synthesis [1,2] of bis-(−)-fisetinidols leads to regiospecific substitution at C-6 of (−)-fisetinidol (**26**), this more potent nucleophilic site has to be protected prior to condensation of the flavan-3-ol and flavan-3,4-diol. Treatment of 6-bromo-(−)-fisetinidol (**27**) and (+)-mollisacacidin [(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol] with 0.1M HCl at 50 °C, however, gave none of the anticipated coupled products, *i.e.* the (−)-fisetinidol-(4,8)-6-bromo-(−)-fisetinidol or (−)-fisetinidol-(4,6′)-6-bromo-(−)-fisetinidol. The reaction mixture instead comprised of (−)-fisetinidol (**26**), the 6-bromo-dehydro-(−)-fisetinidol (**29**), 5′,6-dibromo-(−)-fisetinidol (**31**), (5′,8)-bis-6-bromo-(−)-



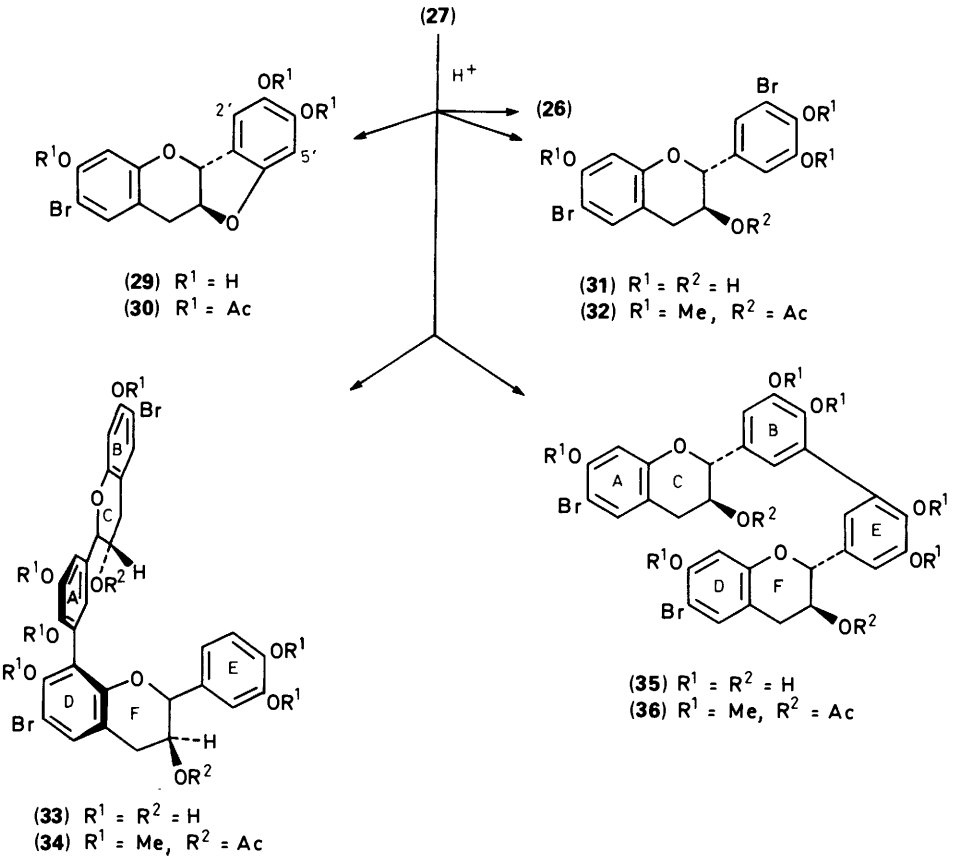
Scheme 2. Proposed route to the formation of biflavanoid (**3**) and the tetrahydropyrano[2,3-*h*]chromenes (**9**), (**13**), and (**15**)



(**26**) $R^1 = H$
(**27**) $R^1 = Br$
(**28**) $R^1 = PhSe$

fisetinidol (**33**), and the (5′,5′)-bis-6-bromo-(−)-fisetinidol (**35**) (Scheme 3).

The 6-bromo-dehydro-(−)-*fisetinidol* (**29**) was identified as the peracetate (**30**). Its ^1H n.m.r. spectrum (Table 3) exhibits three aromatic acetoxy resonances, two sharp and two broadened one-proton singlets in the aromatic region, and a heterocyclic AMXY-system. The chemical shift of 3-H(C) (δ 3.95), the M-portion of the latter spin pattern, indicates involvement of 3-OH in an ether linkage and thus a dihydrobenzofuran arrangement for (**30**). Besides the sharp (δ 6.51) and broadened (δ 7.17) one-proton singlets of 8- and



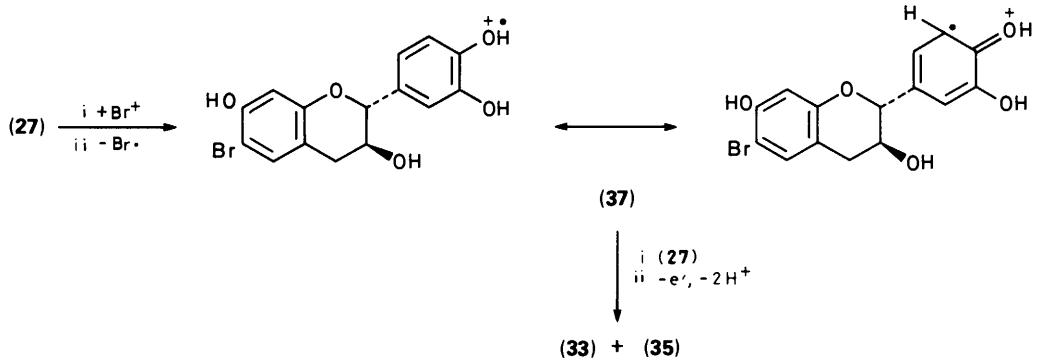
Scheme 3. Acid-catalysed conversion of 6-bromo-(−)-fisetinidol (**27**)

Table 3. ^{1}H N.m.r. (300 MHz) peaks of brominated (−)-fisetinidols (**27**), (**30**), (**32**), (**34**), and (**36**) at 296 K. Splitting patterns and *J*-values (Hz) are given in parentheses

Ring	H	(27)[a]	(30)[b]	(32)[b]	(34)[b]	(36)[b]
A	5	7.16 (s)	7.34 (s)	7.17 (s)	7.13 (s)	7.08, 7.23 (s)
	8	6.46 (s)	6.76 (s)	6.51 (s)	6.47 (s)	6.50, 6.74 (s)
B	2	6.85 (d, 2.0)	7.45 (d, 1.0)	6.75 (d, 2.0)	6.87 (d, 2.0)	6.67, 6.75 (d, 2.5)
	5	6.78 (d, 8.5)	6.71 (s)			
	6	6.71 (dd, 2.0, 8.5)		6.87 (d, 2.0)	6.79 (d, 2.0)	6.85, 6.79 (d, 2.5)
C	2	4.68 (d, 7.5)	4.65 (dd, 1.0, 9.5)	5.13 (d, 6.0)	5.11, (d, 5.8)	5.12 (d, 5.5)
	3	4.04 (m)	3.95 (m)	5.33 (m)	5.31 (m)	5.28 (m)
	$4_{ax.}$	2.71 (dd, 8.3, 16.2)	2.90 (dd, 10.5, 16.0)	2.75 (dd, 6.0, 16.2)	2.66, 2.85 (m)	2.01 (dd, 6.0, 16.5)
	$4_{eq.}$	2.89 (dd, 5.1, 16.2)	3.05 (dd, 6.0, 16.0)	2.96 (dd, 5.0, 16.2)	4-CH_2 (C + F)	2.81 (m)
D	5				7.21 (s)	7.08, 7.23 (s)
	8					6.50, 6.74 (s)
E	2				6.65 (d, 2.0)	6.67, 6.75 (d, 2.5)
	5				6.77 (d, 8.5)	
	6				6.70 (dd, 2.0, 8.5)	6.85, 6.79 (d, 2.5)
F	2				5.14 (d, 4.8)	4.88 (d, 6.5)
	3				5.31 (m)	5.15 (m)
	$4_{ax.}$					2.81 (m)
	$4_{eq.}$					3.00 (dd, 5.2, 16.5)
OMe				3.55 (3-B), 3.85 (4-B/7-A) (each s)	3.44 (7-D), 3.72 (4-B), 3.77 (3-E), 3.81 (7-A, 3-B), 3.83 (4-E) (each s)	3.51, 3.69, 3.80 (x2), 3.82, 3.83 (each s)
OAc			2.28 (s), 2.30 (s), 2.31 (s)	1.98 (s)	1.80 (s), 1.99 (s)	1.93 (s), 1.96 (s)

[a] $(CD_3)_2CO$, [b] $CDCl_3$

5-H(A) respectively, the ^{1}H n.m.r. spectrum (Table 3) of the trimethyl ether acetate (**32**) of the 5′,6-dibromo-(−)-fisetinidol (**31**) displays in the aromatic region two one-proton *m*-coupled doublets indicative of substitution at C-5(B). The presence of



Scheme 4. Proposed mechanism for the formation of biaryl type biflavanoids (**33**) and (**35**)

two bromine substituents is confirmed by mass spectrometry which shows M^+, 518, 516, 514.

Structural elucidation of the 6-bromo-bis-(−)-fisetinidols (**33**) and (**35**) was done on their hexamethyl ether diacetates (**34**) and (**36**). Their 'dimeric' nature is evident from the two heterocyclic AMXY systems in the ^{1}H n.m.r. spectra (Table 3). In addition the spectrum of (**34**) exhibits in the aromatic region a sharp one-proton singlet (δ 6.47), two broadened one-proton singlets (δ 7.13, 7.21), two *m*-coupled doublets (δ 6.87, 6.75, *J* 2.0 Hz), and an ABX-pattern, the chemical shifts of which are compatible with an 'intact' pyrocatechol moiety. The high-field aromatic singlet and one of the *m*-doublets exhibit strong n.O.e. association with the overlapping 7-(A) and 3-(B) methoxy resonances (δ 3.81). Allocation of spin systems to constituent flavanyl units was performed *via* decoupling experiments using the 2-H(C- and F-rings) resonances, broadened aromatic singlets, and *m*-doublets as reference signals. Comparison of the ^{1}H n.m.r. spectral data (Table 3) of analogue (**36**) with that of (**34**) indicates replacement of the pyrocatechol ABX-system in (**34**) with two *m*-doublets in (**36**) as well as the presence of an additional sharp one-proton singlet exhibiting a strong n.O.e. effect with a single methoxy resonance, in the high-field aromatic region. As a result of the identical substituted flavanyl units and thus the absence of reference signals in the spectrum of (**36**), the spin systems of the constituent moieties could not be differentiated. The ^{1}H n.m.r. data when taken in conjunction with mass spectrometric evidence for the presence of two bromine substituents in each of (**34**) (M^+ 874, 872, 870) and (**36**) (M^+ 874, 872, 870) establish B-D and B-E-ring linkages for (**34**) and (**36**) respectively and hence the structures as (5′,8)- and (5′,5′)-bis-6-bromo-(−)-fisetinidols (**33**) and (**35**).

The sharp signals in the ^{1}H n.m.r. spectra of the derivatives of the biaryl type flavanoids (**34**) and (**36**) at ambient temperatures indicates the presence of single atropisomers in each instance. Conformational analysis (Dreiding models) in conjunction with n.O.e. difference spectroscopy permits assessment of the absolute configuration[8–10] about the biphenyl bond for the (5′,8)-bis-6-bromo-(−)-fisetinidol derivative (**34**). The association of 4-OMe(B) (δ 3.72) with 2-H(F) (δ 5.14, 1.4%) establishes [*P*]-helicity and an [*S*]-configuration and indicates a dihedral angle of *ca.* 90° between the planes of the biphenyl B- and D-rings. The aforementioned absence of reference signals in the spectrum of (**36**) precludes assignment of absolute configuration about the biphenyl bond for this regiomer. Steric factors similar to those advanced for the B-D-ring linked bis-(+)-catechin atropisomers[9] also govern the stabilities of derivatives (**34**) and (**36**). For both (**34**) and (**36**) racemization sets in at *ca.* 70 °C reaching an approximate 1:1 equilibrium at 100 °C in $CDCl_3$ with evidence of exchange from duplicated resonances.

The formation of (−)-fisetinidol (**26**) in the above reaction indicates that the 5′,6-dibromo-(−)-fisetinidol (**31**) originates from the 6-bromo analogue (**27**) *via* an intermolecular acid-catalysed debromination at C-6 and re-bromination at C-5(B) as was demonstrated for the C-6 ⟶ C-8 'bromine dance'[11] in 6-bromo-tetra-*O*-methyl-(+)-catechin. Similar to the formation of dehydro-dicatechin A in the enzymic[12] or ferricyanide[9] oxidation of (+)-catechin, the 6-bromo-dehydro-(−)-fisetinidol (**29**) presumably forms *via* oxidation of (**27**) to a B-ring *o*-quinone followed by 1,4-Michael addition of 3-OH(C) and subsequent aromatization by proton transfer.

The same species effecting oxidation of the *o*-dihydroxy functionality in (**27**) presumably also gives rise to the formation of the biaryl type biflavanoids (**33**) and (**35**). Although the *o*-quinone may originate from aerial oxidation of 6-bromo-(−)-fisetinidol (**27**) under acidic conditions,[13] the absence of $C(sp^2)$–$C(sp^2)$ products of type (**33**) in reactions of (−)-fisetinidol (**26**) and (+)-mollisacacidin under acid catalysis[1,2] discriminates against air/H^+ as oxidizing agent. Considering the role of the nitrosonium ion[14,15] in the formation of biaryls in electrophilic aromatic nitration it appears more reasonable that the observed dimerization is initiated by bromonium ion (Scheme 4). Initial electron transfer, preferentially from the electron rich *o*-dihydroxy functionality, presumably leads to a radical cation of type (**37**) which dimerizes to biflavanoids (**33**) and (**35**) by oxidative substitution at respectively C-8(A) and C-5(B) of the 6-bromo-(−)-fisetinidol (**27**). These reactions are presumably promoted by oxygen (*c.f.* ref. 15 for the role of oxygen in the nitrosonium ion mediated formation of biaryls) since the yields of products (**29**), (**33**), and (**35**) were considerably reduced when the reaction was performed under nitrogen.* Under neutral conditions, however, none of products (**29**), (**31**), (**33**) or (**35**) is formed thus presumably reflecting the necessity of H^+ in the generation of bromonium ion. We could, however, find no literature precedent supporting the role of Br^+ in effecting oxidative substitution type reactions.

Finally, we used the 6-phenylselenyl-(−)-fisetinidol (**28**) as a nucleophile in the acid-catalysed condensation with (+)-mollisacacidin. Under these mild conditions the phenylseleno group is rapidly lost to generate (−)-fisetinidol which then condenses *via* C-6(A) with the flavan-3,4-diol as was previously reported.[1,5] We are presently investigating the utilization of the 8-lithio derivative of tri-*O*-methyl-(−)-fisetinidol as a possible route to the novel (4,8)-bis-fisetinidols and related ring isomerized analogues. These results will be dealt with elsewhere.

Identification of the first naturally occurring profisetinidins and proguibourtinidins based on a C-8 substituted (−)-fisetinidol unit and the difficulties associated with the *in vitro*

* The same product distribution was also observed when 6-bromo-(−)-fisetinidol was treated with 0.1M HCl in the absence of (+)-mollisacacidin.

synthesis of these analogues, presumably reflects the presence of an enzyme in *C. mopane* capable of effecting coupling at the less reactive and more hindered 8-position compared to C-6.

Experimental

^{1}H N.m.r. spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$, C_6D_6, and $(CD_3)_2CO$ with Me_4Si as internal standard. Mass spectra were obtained with a Kratos MS80 instrument and c.d. data in methanol on a Jasco J-20 spectropolarimeter. T.l.c. was performed on precoated Merck plastic sheets (DC-Plastikfolien Kieselgel 60 F_{254}, (0.25 mm) and compounds were located by H_2SO_4–HCHO (40:1 v/v) spray reagent. Preparative plates (p.l.c.), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm), were air-dried and used without prior activation. Column chromatography was carried out in ethanol on Sephadex LH-20 and Fractogel TSK HW-40(S) under m.p.l.c. conditions (column size, flow rate, and pressure to be specified in each instance). Fractions were collected starting with the appearance of the first phenolic material (u.v.-detector). Methylations were performed with an excess of diazomethane in methanol-diethyl ether over 48 h at −15 °C, while acetylations were carried out in acetic anhydride–pyridine at ambient temperatures. Evaporations were done under reduced pressures at *ca.* 60 °C in a rotary evaporator.

Fractionation of the Heartwood Extract of Colophospermum mopane

The enriched methanol extract[2] (6 × 20 g) was subjected to column chromatography on Sephadex LH-20 (5 × 105 cm column, flow rate: 9 ml/min, 0.8 bar pressure) to give four fractions: A [Relative retention time (RR_t), 0—0.5 h] (7.5 g), B(RR_t, 0.5—1.2 h) (4.5 g), C(RR_t, 1.2—4 h) (7.5 g), and D(RR_t 4.0—8.6 h) (13.9 g). The 'dimeric' flavanoids described here were found in fraction C. Column chromatography on Sephadex LH-20 was repeated on a portion (7 g) of this fraction as above to afford four fractions: 1(RR_t, 0—1.8 h) (0.618 g), 2(RR_t, 1.8—3.6 h) (1.952 g), 3(RR_t 3.6—4.6 h) (0.771 g), and 4(RR_t, 4.6—8.8 h) (1.707 g).

Novel 'Dimeric' Metabolites from Fractions 1—4. *Fraction* 1.—This fraction was resolved on Fractogel (3.5 × 45 cm column, flow rate: 4 ml/min, 0.3—6.0 bar pressure) into subfractions 1.1(RR_t, 0—1.3 h) (0.102 g) and 1.2(RR_t 1.3—3.1 h) (91 mg). Methylation of fraction 1.1 followed by p.l.c. [(benzene–acetone, 9:1) × 2] afforded two bands, 1.1.1 * (R_F 0.21, 14.3 mg) and 1.1.2 (R_F 0.17, 8.7 mg). Fractions marked with an asterisk throughout the experimental section comprised of novel proguibourtinidins and/or propeltogynidins and/or profisetinidins and related C-ring isomerized analogues. Their structural elucidation and biomimetic syntheses will be published elsewhere. Acetylation of band 1.1.2 and purification by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) ×2] gave two fractions, 1.1.2.1 (R_F 0.36, 1.9 mg) and 1.1.2.2 * (R_F 0.29, 2.1 mg). The former fraction afforded the (+)-*guibourtinidol*-(4α,8)-(−)-*fisetinidol pentamethyl ether diacetate* (**6**) as a white amorphous solid (Found: M^+, 684.2589 $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H (Table 1); c.d. $[\theta]_{293}$ 0, $[\theta]_{284}$ -3.7×10^4, $[\theta]_{279}$ 0, $[\theta]_{267}$ 5.9×10^4, $[\theta]_{251}$ 0, $[\theta]_{232}$ -48.2×10^4, $[\theta]_{227}$ -16.8×10^4, and $[\theta]_{202}$ 0.

Methylation of fraction 1.2 followed by p.l.c. (benzene–ethyl acetate–acetone, 7:2:1) afforded a single band at R_F 0.36 (14.1 mg). Acetylation and subsequent purification by p.l.c. [(hexane–ethyl acetate–acetone, 7:2:1) × 3] gave three fractions, 1.2.1 (R_F 0.42, 2.4 mg), 1.2.2 * (R_F 0.38, 1.8 mg), and 1.2.3 (R_F 0.19. 4.8 mg). The R_F 0.42 band gave an additional sample of (**6**) while the R_F 0.19 band afforded (2R,3S:8S,9S,10R)-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* (**16**) as a white amorphous solid (Found: M^+, 714.2692. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); δ_H (Table 2); c.d. $[\theta]_{295}$ 0, $[\theta]_{283}$ -3.6×10^4, $[\theta]_{276}$ 0, $[\theta]_{265}$ 4.1×10^4, $[\theta]_{263}$ 0, $[\theta]_{236}$ -4.5×10^4, $[\theta]_{233}$ -10.7×10^4, $[\theta]_{230}$ -19.8×10^4, and $[\theta]_{228}$ 0.

Fraction 2.—This fraction was similarly resolved on Fractogel to give sub-fractions 2.1 (RR_t 0—28 h) (0.39 g) and 2.2 (RR_t 2.8—5.9 h) (0.903 g). Methylation of 2.1 and p.l.c. separation [(benzene–acetone–methanol, 90:9:1) ×2] afforded four bands, 2.1.1 (R_F 0.42, 52.8 mg), 2.1.2 (R_F 0.32, 81.5 mg), 2.1.3 * (R_F 0.22, 31.4 mg), and 2.1.4 (R_F 0.18, 17.9 mg). The R_F 0.42 band was acetylated and the mixture resolved by p.l.c. [(hexane–benzene–acetone, 6:3:1) ×7] into two fractions at R_F 0.66 (8.9 mg) and 0.58 (1.5 mg). The R_F 0.66 fraction consisted of the (+)-*guibourtinidol*-(4α,6′)-(−)-*fisetinidol pentamethyl ether diacetate* (**8**) as a white amorphous solid (Found: M^+, 684.2563. $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H (Table 1); c.d. $[\theta]_{294}$ 0, $[\theta]_{287}$ 2.8×10^4, $[\theta]_{281}$ 0, $[\theta]_{267}$ -17.8×10^4, $[\theta]_{245}$ 0, $[\theta]_{238}$ -37.8×10^4, and $[\theta]_{230}$ 0.

The R_F 0.58 band afforded the (+)-*epifisetinidol*-(4α,8)-(−)-*fisetinidol hexamethyl ether diacetate* (**4**) as a white amorphous solid (Found: M^+, 714.2677. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); δ_H (Table 1); c.d. $[\theta]_{292}$ 0, $[\theta]_{285}$ -0.3×10^4, $[\theta]_{278}$ 0, $[\theta]_{268}$ 0.4×10^4, $[\theta]_{260}$ 0, $[\theta]_{230}$ -12.6×10^4, and $[\theta]_{223}$ -11.7×10^4. Acetylation of fraction 2.1.2 and purification by p.l.c. [(benzene–hexane–acetone, 6:3:1) ×2] gave (2*R*,3*S*:8*R*,9*S*,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* (**10**) as a white amorphous solid, R_F 0.33 (18 mg) (Found: M^+, 714.2693. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); δ_H (Table 2); c.d. $[\theta]_{291}$ 0, $[\theta]_{288}$ -0.1×10^4, $[\theta]_{286}$ 0, $[\theta]_{282}$ 0.4×10^4, $[\theta]_{279}$ 0, $[\theta]_{266}$ 3.4×10^4, $[\theta]_{243}$ 0, $[\theta]_{236}$ 3.0×10^4, $[\theta]_{233}$ 0, $[\theta]_{220}$ -16.7×10^4, and $[\theta]_{216}$ 0. Fraction 2.1.4 was acetylated and the mixture separated by p.l.c. [(benzene–acetone–methanol, 90:9:1) ×2] to give a main band at R_F 0.69 (8.2 mg). This was further resolved by p.l.c. [(hexane–acetone–ethyl acetate 7:2:1) ×8] into two bands at R_F 0.66 (2.4 mg) and 0.58 (3.2 mg). The former fraction gave 6-[(2*R*,3*S*)-2,3-trans-3-*acetoxy*-7-*methoxybenzopyran*-6-*yl*]-2-(3,4-*dimethoxyphenyl*)-4-(2,4-*dimethoxyphenyl*)-3-*acetoxy*-8-*methoxy*-(2*R*,3*S*,4*S*)-2,3-trans-3,4-cis-3,4-*dihydro*-2*H*-*chromene* (**20**) as a white amorphous solid (Found: M^+, 714.2688. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); δ_H (Table 2); c.d. $[\theta]_{320}$ 0, $[\theta]_{302}$ 0.3×10^4, $[\theta]_{294}$ 0, $[\theta]_{287}$ -0.7×10^4, $[\theta]_{281}$ -0.6×10^4, $[\theta]_{267}$ -1.6×10^4, $[\theta]_{244}$ 0, $[\theta]_{235}$ 6.3×10^4, and $[\theta]_{228}$ 0. The R_F 0.58 band consisted of the known[2] (4β,6)-bis-(−)-fisetinidol hexamethyl ether diacetate.

Methylation of sub-fraction 2.2 and subsequent separation by p.l.c. [(benzene–acetone–methanol, 90:9:1) ×4] gave eight bands, 2.2.1 * (R_F 0.44, 75.4 mg), 2.2.2 (R_F 0.40, 66.1 mg), 2.2.3 * (R_F 0.39, 54.1 mg), 2.2.4 * (R_F 0.31, 75.3 mg), 2.2.5 * (R_F 0.25, 124 mg), 2.2.6 (R_F 0.19, 96.9 mg), 2.2.7 (R_F 0.14, 40.1 mg), and 2.2.8 (R_F 0.09, 22.9 mg). Fraction 2.2.2 was acetylated and the mixture purified by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) ×4] to give (2*S*,3*S*:8*R*, 9*S*,10*S*)-3,9-*diacetoxy*-2,8-*bis*(3,4-*dimethoxyphenyl*)-10-(2,4-*dimethoxyphenyl*)-2,3-cis-8,9-trans-9,10-cis-3,4,9,10-*tetrahydro*-2*H*,8*H*-*pyrano*[2,3-h]chromene (**12**) as a white amorphous solid, R_F 0.41 (8.2 mg) (Found: M^+, 714.2689. $C_{40}H_{42}O_{12}$ requires *M*, 714.2676); δ_H (Table 2); c.d. $[\theta]_{291}$ 0, $[\theta]_{280}$ 4.1×10^4, $[\theta]_{272}$ 0, $[\theta]_{261}$ 1.7×10^4, $[\theta]_{250}$ 0, $[\theta]_{234}$ 21.3×10^4, $[\theta]_{231}$ 34.0×10^4, $[\theta]_{224}$ 17.3×10^4, and $[\theta]_{205}$ 0. Fraction 2.2.5 was de-acetylated by treatment with methanolic KOH solution (5 ml; 1% w/v) for 12 h at 45 °C. The mixture was acidified (0.1M HCl), extracted with ethyl acetate (3 × 50 ml), the extract dried (Na_2SO_4) and

evaporated to dryness. P.l.c. separation [(hexane–benzene–acetone, 5:4:1) × 2] afforded three bands at R_F 0.43* (21 mg), 0.39 (40.1 mg) and 0.28 (3.8 mg). Acetylation of the R_F 0.39 band and subsequent purification by p.l.c. [(hexane–acetone–ethyl acetate, 7:2:1) × 10] gave the known[2] hexamethyl ether diacetates of (4α,6)-bis-(−)-fisetinidol and (−)-fisetinidol-(4α,8)-(+)-afzelechin. The R_F 0.28 band was acetylated to give the (4α,8)-*bis*-(−)-*fisetinidol hexamethyl ether diacetate* (**2**) as a white amorphous solid (4.2 mg) (Found: M^+, 714.2687. $C_{40}H_{42}O_{12}$ requires M, 714.2676); δ_H (Table 1); c.d. $[\theta]_{293}$ 0, $[\theta]_{283}$ −3.9 × 10^4, $[\theta]_{276}$ 0, $[\theta]_{265}$ 3.0 × 10^4, $[\theta]_{251}$ 0, $[\theta]_{235}$ −33.7 × 10^4, and $[\theta]_{230}$ 0. Fraction 2.2.6 was acetylated and resolved by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) × 4] into two bands at R_F 0.39 (51.3 mg) and 0.34 (4.5 mg). The former band consisted of the (4α,8)-bis-(−)-fisetinidol derivative (**2**) and the latter of the same derivative of the known[2] (−)-fisetinidol-(4β,6)-(+)-epifisetinidol. Acetylation of fraction 2.2.7 followed by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) × 3] gave two bands at R_F 0.44* (5.7 mg) and 0.38 (4.6 mg). The latter fraction afforded a further portion of (**2**). Fraction 2.2.8 was acetylated and subsequently purified by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) × 10] to give (2S,3S:8S,9S,10R)-3,9-*diacetoxy*-2,8-*bis*(3,4-*dimethoxyphenyl*)-10-(2,4-*dimethoxyphenyl*)-2,3-cis-8,9-cis-9,10-trans-3,4,9,10-*tetrahydro*-2*H*,8*H*-*pyrano*[2,3-h]*chromene* (**18**) as a white amorphous solid, R_F 0.37 (9.8 mg) (Found: M^+, 714.2692. $C_{40}H_{42}O_{12}$ requires M, 714.2676); δ_H (Table 2); c.d. $[\theta]_{292}$ 0, $[\theta]_{285}$ −2.5 × 10^4, $[\theta]_{279}$ 0, $[\theta]_{265}$ 5.6 × 10^4, $[\theta]_{242}$ 1.0 × 10^4, $[\theta]_{237}$ 3.6 × 10^4, $[\theta]_{230}$ 17.0 × 10^4, $[\theta]_{227}$ 31.2 × 10^4, and $[\theta]_{218}$ 0.

Fraction 3.—This fraction was resolved on Fractogel as above into two sub-fractions 3.1* (RR_t 0.0—0.9 h) (0.156 g) and 3.2 (RR_t 1.0—1.9 h) (0.181 g). Fraction 3.2 was methylated and the mixture resolved by p.l.c. [(benzene–ethyl acetate–acetone, 7:2:1) × 2) to give four bands, 3.2.1* (R_F 0.50, 27.1 mg), 3.2.2. (R_F 0.39, 28.8 mg), 3.2.3* (R_F 0.33, 23.0 mg), and 3.2.4 (R_F 0.28, 13.3 mg). Acetylation of band 3.2.2 followed by p.l.c. [(benzene–hexane–acetone, 6:3:1) × 6] afforded four bands at R_F 0.38 (3.4 mg), 0.33 (2.3 mg), 0.27 (5.1 mg), and 0.22 (4.3 mg)*. The R_F 0.38 band consisted of the known[1] (4α,6)-bis-(−)-fisetinidol hexamethyl ether diacetate. The R_F 0.33 band afforded the tetrahydropyrano[2,3-*h*]chromene derivative (**16**). The R_F 0.27 band gave (2R,3S:8R,9S,10R)-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* (**14**) as a white amorphous solid (Found: M^+, 714.2687. $C_{40}H_{42}O_{12}$ requires M, 714.2676); δ_H (Table 2); c.d. $[\theta]_{298}$ 0, $[\theta]_{289}$ 0.9 × 10^4, $[\theta]_{283}$ 0.8 × 10^4, $[\theta]_{270}$ 2.4 × 10^4, $[\theta]_{255}$ 1.5 × 10^4, $[\theta]_{243}$ 4.9 × 10^4, $[\theta]_{237}$ 0, $[\theta]_{233}$ −7.7 × 10^4, $[\theta]_{230}$ −8.2 × 10^4, $[\theta]_{227}$ −11.3 × 10^4, $[\theta]_{225}$ − 14.3 × 10^4, and $[\theta]_{221}$ 0. Acetylation of fraction 3.2.4 afforded the (4α,8)-bis-(−)-fisetinidol hexamethyl ether diacetate (**2**) (14.1 mg).

Fraction 4.—This fraction consists of novel propeltogynidins and C-ring isomerized (4,6)-bis-fisetinidols, details of which will be published elsewhere.

Synthesis of C-6 protected (−)-Fisetinidols. 6-Bromo-(−)-fisetinidol (**27**).—(−)-Fisetinidol (250 mg) was dissolved in acetone (25 ml) and a solution of freshly crystallized *N*-bromosuccinimide (NBS) (162.5 mg) in acetone (15 ml) slowly added over 2 h with stirring at room temperature. After 7 h a portion of NBS (25 mg) was added and stirring continued for 33 h. The mixture was taken up in ethyl acetate (100 ml), washed with water (3 × 100 ml), the extract dried (Na_2SO_4) and evaporated to dryness. Purification by p.l.c. [(benzene–acetone–methanol, 15:4:1) × 2] afforded 6-bromo-(−)-fisetinidol (**27**) as a brown amorphous powder, R_F 0.52 (225 mg); δ_H (Table 3).

6-Phenylselenyl-(−)-fisetinidol (**28**).—(−)-Fisetinidol (650 mg) was dissolved in tetrahydrofuran (THF) (10 ml) and a solution of phenylselenylbromide[16] (1.4 g) in THF (5 ml) slowly added over 1 h with stirring at room temperature. After 170 h at room temperature the solvent was removed with nitrogen and the mixture separated on Sephadex LH-20 (3 × 45 cm column, flow rate −4.0 ml/min, atmospheric pressure). Diphenyl diselenide migrated with the solvent front, (−)-fisetinidol had RR_t 6.0—8.0 h, and the *6-phenylselenyl-(−)-fisetinidol* (**28**) RR_t 8.5—13 h (200 mg). The latter compound was obtained as a brown amorphous powder (Found: M^+, 429.0769. $C_{21}H_{18}O_5Se$ requires M, 429.0754); δ_H [300 MHz, $(CD_3)_2CO$] 7.20—7.35 (5 H,m,Ph), 6.87 [d, J 2.0 Hz, 2-H(B)], 6.80 [d, J 8.5 Hz, 5-H(B)], 6.74 [dd, J 2.0 and 8.5 Hz, 6-H(B), 6.47 [s, 8-H(A)], 5-H(A), overlapped by ArH resonances, 4.70 [d, J 7.5 Hz, 2-H(C)], 4.05 [m, 3-H(C)], 2.90 [dd, J 5.2 and 16.2 Hz, 4-$H_{eq.}$(C)], and 2.72 [dd, J 8.5 and 16.2 Hz, 4-H_{ax}·(C)].

Acid Treatment of 6-Bromo-(−)-fisetinidol (**27**) *and (+)-Mollisacacidin.*—6-Bromo-(−)-fisetinidol (**27**) (192 mg) and (+)-mollisacacidin (158 mg) were dissolved in 0.1M HCl (100 ml) at 50 °C and the mixture was stirred at this temperature for 14 h. The solution was chilled with ice, extracted with ethyl acetate (4 × 100 ml) and the combined solvents dried (Na_2SO_4) and evaporated to dryness. The brown residue (320 mg) was resolved on Sephadex LH-20 (2.5 × 65 cm column, flow rate –4.0 ml/min, atmospheric pressure) to give fractions 1(RR_t 0—4 h) (70 mg) and 2(RR_t 23—30 h) (110 mg). Acetylation of fraction 1 and purification by p.l.c. [(hexane–benzene–acetone, 5:4:1) × 2] afforded tetra-*O*-acetyl-(−)-fisetinidol (3.1 mg), 6-bromo-tetra-*O*-acetyl-(−)-fisetinidol (25.7 mg) penta-*O*-acetyl-(+)-mollisacacidin (8.4 mg) and the *tri-O-acetyl-6-bromo-dehydro-(−)-fisetinidol* (**30**) (9.3 mg) as a white amorphous powder (Found: M^+, 478.0061. $C_{21}H_{17}O_8Br$ requires M, 478.0088†); δ_H (Table 3).

Fraction 2 was methylated and the mixture resolved by p.l.c. [(benzene–acetone, 8:2) × 2] into two bands at R_F 0.51 (45.3 mg) and 0.47 (28.5 mg). Acetylation of the R_F 0.51 band and purification by p.l.c. [(benzene–hexane–acetone, 6:3:1) × 3] afforded two fractions at R_F 0.45 (15.4 mg) and 0.41 (11.5 mg). The former band gave the (5′,8)-*bis*-6-*bromo-(−)-fisetinidol hexamethyl ether diacetate* (**34**) as a white amorphous solid (Found: M^+, 874.0861. $C_{40}H_{40}O_{12}Br_2$ requires M, 874.0848†) δ_H (Table 3). The R_F 0.41 band afforded the (5′,5′)-*bis*-6-*bromo-(−)-fisetinidol hexamethyl ether diacetate* (**36**) as a white amorphous solid (Found: M^+, 874.0859. $C_{40}H_{40}O_{12}Br_2$ requires M, 874.0848†); acetylation of the R_F 0.47 band gave the 5′,6-*dibromo-(−)-fisetinidol trimethyl ether acetate* (**32**) as a white amorphous solid (30.8 mg) (Found: M^+, 517.9597 $C_{20}H_{20}O_6Br_2$ requires M, 517.9588†); δ_H (Table 3).

Repetition of the reaction but in a nitrogen atmosphere led to a similar product distribution at much lower yields *e.g.* (**30**) (4.3 mg), (**32**) (3.2 mg), (**34**) (3.1 mg), and (**36**) (2.9 mg) and after increased reaction time (30 h). The disappearance of (+)-mollisacacidin in both reactions may be ascribed to acid-catalyzed polymerization[17] as is evidenced by the high concentration of polar condensed tannin analogues on t.l.c.

Acid Treatment of 6-Bromo-(−)-fisetinidol (**27**).—Treatment of 6-bromo-(−)-fisetinidol (**27**) (25 mg) with 0.1M HCl (12 ml) for 24 h at 50 °C followed by work-up, separation, and

† Based on the ^{81}Br isotope, mass 80.9164.

derivatization as above afforded an identical distribution of (−)-fisetinidol and the 6-bromo-(−)-fisetinidol analogues (**30**), (**32**), (**34**), and (**36**) as was described in the preceding paragraph.

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