Oligomeric Flavanoids. Part 9.† The First Biflavanoids Based on Mopanol and Peltogynol as Inceptive Electrophiles

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Continued investigation of the phenolic metabolities of *Colophospermum mopane* reveals the occurrence of the first series of biflavanoids based on mopanol and peltogynol as electrophilic species. Amongst these are the promopanidins, (+)-mopanane-(4β,6)-fisetinidols (**5**) and (**7**), the epimopanane-(4,6 and 4,8)-fisetinidols (**9**) and (**11**), and the unique oxidatively coupled epimopanone-guibourtinidol (**13**). They are accompanied by the related propeltogynidins, (+)-peltogynane-(4β,6)-fisetinidols (**15**) and (**17**), epipeltogynane-(4α,6)-(−)-fisetinidol (**19**), and (−)-fisetinidol-(4α,6')-(+)-peltogynol (**21**), the latter compound extending the rare series of biflavanoids with the equivalent of a 'terminal' flavan-3,4-diol moiety. The 2,3-*cis*-3,4-*cis*-(+)-mopanol (**23**) represents the first mopanoid/peltogynoid with (2*R*,3*R*) configuration. The structures of the (+)-mopanane-(4β,6)-fisetinidols are confirmed by synthesis, the forcing conditions of which are explained in terms of the conformational rigidity of the mopanol C-ring.

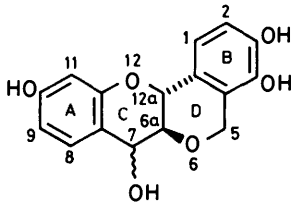
Although the peltogynols and mopanols as flavan-3,4-diol equivalents have been known since the mid-thirties,[1] the natural occurrence of flavanoid oligomers based on these inceptive electrophiles is hitherto restricted to a single promopanidin.[2] The prospects of a more general distribution have been dampened by recent observations of their formation in low concentration and under relative drastic conditions during a biomimetic synthesis[3] from (+)-peltogynol and the flavan-3-ols, (+)-catechin and (−)-fisetinidol. Continued investigation of the heartwood extract of the mopane (*Colophospermum mopane* Kirk *ex* J. Leonard), noted for its considerable content of the (+)-peltogynols and (+)-mopanols,[4,5] led to characterization of a series of novel promopanidins and the first propeltogynidins. This was accomplished using Sephadex LH-20[6] and Fractogel TSK HW-40(S)[7] as chromatographic substrates for oligoflavanoids under medium pressure.

Results and Discussion

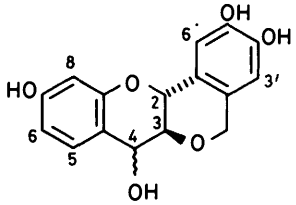
The diversity of the metabolic pool in mopane demonstrated in Parts 1[2] and 8 is extended by identification of a novel series of biflavanoids apparently arising from (+)-mopanol A ‡ or B [(**1**), (**2**)] and (+)-peltogynol A or B [(**3**), (**4**)] as potential electrophiles. These metabolites comprised of the novel (+)-mopane-(4β,6)-(−)-fisetinidol (**5**), (+)-mopanane-(4β,6)-(+)-epifisetinidol (**7**), (−)-epimopanane-(4α,6)-(+)-epifisetinidol

† Part 8, J. C. S. Malan, J. A. Steenkamp, J. P. Steynberg, D. A. Young, E. V. Brandt, and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1*. 1990, preceding paper.

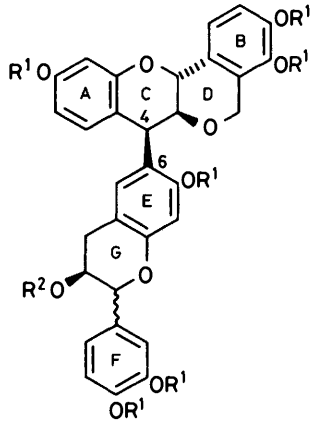
‡ (+)-Mopanol A(**1**) is (6a*S*,7*R*,12a*R*)-6a,12a-*trans*-6a,7-*trans*-3,4,7,-10-tetrahydroxy-5,6a,7,12a-tetrahydro[1]benzopyrano[3,2-*c*][2]-benzopyran. For simplicity trivial names are retained and the usual flavanoid numbering as is depicted for the peltogynols (**3**) and (**4**) is used throughout this paper.



(**1**) { ≡ ≡
(**2**) { ≡ ▲



(**3**) { ≡ ≡
(**4**) { ≡ ▲



(**5**) { ≡ ≡ , $R^1 = R^2 = H$
(**6**) { ≡ ≡ , $R^1 = Me, R^2 = Ac$
(**7**) { ≡ ▲ , $R^1 = R^2 = H$
(**8**) { ≡ ▲ , $R^1 = Me, R^2 = Ac$

Table 1. ^{1}H N.m.r. peaks (p.p.m.) of mopanoid methyl ether acetates (**6**), (**8**), (**10**), (**12**), and (**14**) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses.

Ring	Proton	(6)[a]	(8)[a]	(10)[a]	(12)[c]	(14)[b]
A	5	6.95 (d, 8.5)	7.00 (d, 8.5)	6.90 (d, 8.5)	6.63 (d, 8.0)	7.79 (d, 8.5)
	6	6.55 (dd, 2.5, 8.5)	6.59 (dd, 2.5, 8.5)	6.49 (dd, 2.5, 8.5)	6.36 (dd, 2.5, 8.0)	7.04 (d, 8.5)
	8	6.96 (d, 2.5)	6.96 (d, 8.5)	6.46 (d, 2.5)	6.39 (d, 8.0)	—
B	5	6.63 (d, 8.5)	6.59 (d, 8.5)	6.86 (d, 8.5)	6.81 (d, 8.5)	6.46 (d, 8.5)
	6	7.70 (dd, 1.0, 8.5)	7.66 (dd, 1.2, 8.5)	7.13 (br, d, 8.5)	6.97 (br, d, 8.5)	6.74 (br, d, 8.5)
C	2	5.54 (d, 9.9)	5.51 (d, 9.9)	4.66 (br, s, *ca.* 1.0)	4.89 (d, 2.9)	4.65 (d, 3.9)
	3	4.03 (dd, 6.3, 9.9)	4.03 (dd, 6.5, 9.9)	overlapped by OMe	4.16 (dd, 2.9, 3.5)	4.16 (d, 3.9)
	4	5.36 (d, 6.3)	5.35 (d, 6.5)	4.56 (d, 2.0)	4.81 (dd, 1.5, 3.5)	—
D		4.92 (d, 16.0)	4.87 (d, 16.0)	5.12 (d, 16.0)	5.06 (d, 16.0)	5.07 (d, 16.0)
		4.75 (d, 16.0)	4.73 (d, 16.0)	4.85 (d, 16.0)	4.64 (d, 16.0)	4.85 (d, 16.0)
E	5	6.86 (br, s)	6.93 (br, s)	6.36 (br, s)	6.94 (d, 8.5)	7.17 (d, 8.5)
	6/8	6.73 (s), (6-H)	6.77 (s) (6-H)	6.53 (s) (6-H)	6.58 (d, 8.5) (8-H)	6.36 (dd, 2.5, 8.5)
						6.51 (d, 8.5) (8-H)
F	2	6.93 (d, 2.0)	7.04 (d, 2.0)	6.99 (d, 2.0)	6.69 (d, 2.0)	6.82 (d, 2.0)
	5	6.44 (d, 8.5)	6.57 (d, 8.0)	6.84 (d, 8.5)	6.75 (d, 8.5)	6.84 (d, 8.0)
	6	6.96 (dd, 2.0, 8.5)	6.90 (dd, 2.0, 8.0)	6.93 (dd, 2.0, 8.5)	6.63 (dd, 2.0, 8.5)	6.90 (dd, 2.0, 8.0)
G	2	5.02 (d, 6.9)	4.74 (br, s, *ca.* 1.0)	5.01 (br, s, *ca.* 1.0)	4.91 (d, 7.0)	5.16 (d, 7.8)
	3	5.40 (m)	5.30 (m)	5.35 (m)	5.19 (m)	5.28 (m)
	$4_{ax.}$	2.35 (dd, 7.3, 16.5)	2.60 (m)	2.73 (dd, 2.2, 16.5)	2.85 (dd, 7.5, 15.5)	2.81 (dd, 7.5. 15.5)
	$4_{eq.}$	2.57 (dd, 5.2, 16.5)	2.60 (m)	3.15 (dd, 4.0, 16.5)	3.06 (dd, 5.1, 15.5)	2.96 (dd, 5.3, 15.5)
	OMe	3.26 (4-B), 3.33 (4-F), 3.34 (7-A), 3.37 (3-F), 3.53 (7-E/3-B), each s	3.26 (4-B), 3.34 (4-F), 3.35 (7-A), 3.48 (3-F), 3.50 (7-E), 3.54 (3-B), each s	3.74 (7-A), 3.79 (3-B), 3.85 (4-F/7-E), 3.87 (4-B), 3.88 (3-F), each s	3.71 (7-A), 3.73 (7-E/3-F), 3.79 (3-B), 3.84 (4-B), 3.86 (4-F), each s	3.71 (7-E/3-B), 3.80 (8-A), 3.89 (4-F), 3.90 (7-A), each s
	OAc	1.14 (s)	1.12 (s)	1.92 (s)	1.90 (s)	1.98 (s)

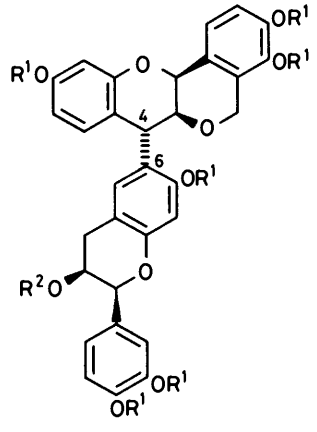
[a] C_6D_6, 296 K. [b] $CDCl_3$, 296 K. [c] $CDCl_3$, 353 K.

(**9**), (−)-epimopanane-(4α,8)-(−)-fisetinidol (**11**), and the first propeltogynidins, (+)-peltogynane-(4β,6)-(−)-fisetinidol (**15**),* (+)-peltogynane-(4β,6)-(+)-epifisetinidol (**17**), (−)-epipeltogynane-(4α,6)-(−)-fisetinidol (**19**), and (−)-fisetinidol-(4α,6′)-(+)-peltogynol (**21**).† They are accompanied by the C–O linked (+)-guibourtinidol (3′,4″-*O*)-epimopanone (**13**) and 2,3-*cis*-3,4-*cis*-(+)-mopanol (**23**), the first peltogynoid/mopanoid with a 2*R*,3*R*,4*R* absolute configuration. Owing to the complexity of the phenolic mixture all compounds were identified as methyl ether acetates *eg.* (**6**).

The ^{1}H n.m.r. spectral data (Table 1) at 300 MHz of the hexamethyl ether acetates (**6**) in $CDCl_3$ and (**8**) in C_6D_6 of the (+)-mopanane-(4β,6)-(−)-fisetinidol-(**5**) and (+)-epifisetinidol (**7**) closely resemble those of the (4β,6)-bis-fisetinidols.[2,8] The key features of the spectra of (**6**) and (**8**) are the presence of a single acetoxy resonance in each instance, the characteristic isolated heterocyclic AB system of the D-ring[5] [δ 4.92, 4.75; 4.87, 4.73, *J* 16.0 Hz for (**6**) and (**8**) respectively], and the aromatic AB pattern of ring B.[2] Involvement of the 3-hydroxyl group in an ether linkage is confirmed by the chemical shifts of 3-H(C) [δ 4.03 for both (**6**) and (**8**)]. Coupling constants of the heterocyclic AMX system [$J_{2,3}$ 9.9, $J_{3,4}$ 6.3 Hz; 9.9, 6.5 Hz for (**6**) and (**8**)

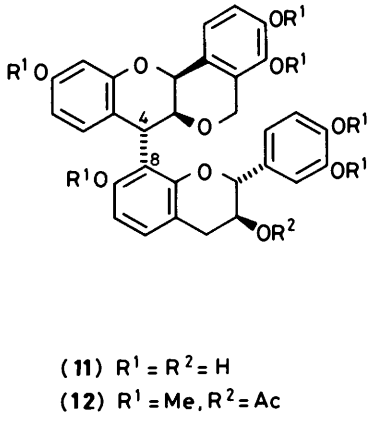
* The trivial names mopanane and peltogynane are proposed for the 4-deoxy mopanoid and peltogynoid moieties and will be used throughout this paper.

† The position of substitution is taken C-6′ (E) in order to retain trivial names for the consistent flavanyl moieties.



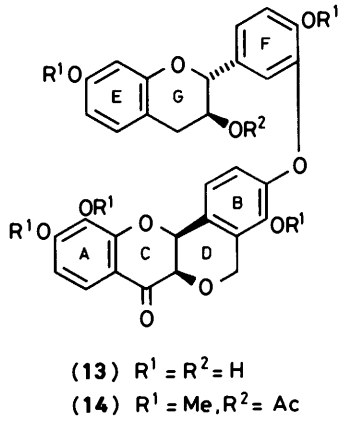
(**9**) $R^1 = R^2 = H$

(**10**) $R^1 = Me, R^2 = Ac$



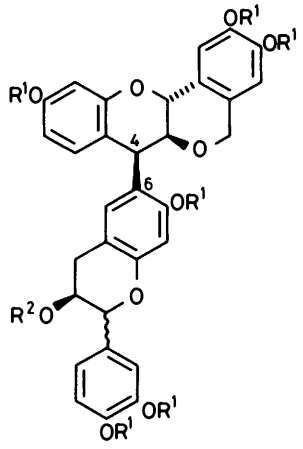
(**11**) $R^1 = R^2 = H$

(**12**) $R^1 = Me, R^2 = Ac$



(**13**) $R^1 = R^2 = H$

(**14**) $R^1 = Me, R^2 = Ac$

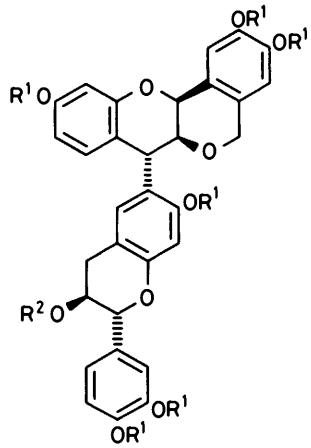


(15) { ≡ ≡ , $R^1 = R^2 = H$

(16) { ≡ ≡ , R^1 = Me, R^2 = Ac

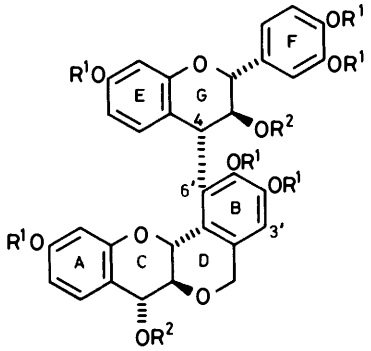
(17) { ≡ ▲ , $R^1 = R^2 = H$

(18) { ≡ ▲ , R^1 = Me, R^2 = Ac



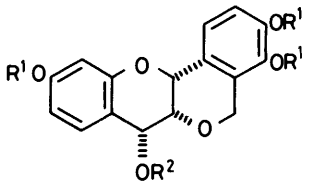
(19) $R^1 = R^2 = H$

(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

resp.] confirm the 2,3-*trans*-3,4-*cis* relative configurations of the (+)-mopanane moieties. The 2,3-*trans* and 2,3-*cis* configurations of the (−)-fisetinidol and (+)-epifisetinidol units similarly follow from the respective *J*-values [6.9 (**6**), *ca.* 1.0 Hz (**8**)] while the (4,6)-bonding is confirmed by the sharp 8-H(E) and broadened 6-H(E) resonances.[8] Connectivities of the different spin systems were established by decoupling experiments using the heterocyclic 2- and 4-H resonances as reference signals. This protocol and the appropriate n.O.e. experiments to define the aromatic substitution pattern and the position of interflavanyl bonding have been amply demonstrated in earlier papers of this series and will not be repeated here. The 2*R*,3*S*,4*S*(C):2*R*,3*S*(G) and 2*R*,3*S*,4*S*(C):2*S*,3*S*(G) absolute configurations for (**5**) and (**7**) implicated by positive Cotton effects (C.E.'s) in the 225—240 nm region in the c.d. spectra of (**6**) and (**8**) were confirmed by synthesis (see below).

^{1}H N.m.r. coupling constants (Table 1) of the heterocyclic AMX-($J_{2,3}$ *ca.* 1.0, $J_{3,4}$ 2.0 Hz) and AMXY-($J_{2,3}$ *ca.* 1.0 Hz) systems for the hexamethyl ether acetate (**10**) of the (−)-epimopanane-(4α,6)-(+)-epifisetinidol (**9**) confirm the relative 2,3- *cis*-3,4-*trans*-(C) and 2,3-*cis*-(G) configurations of the constituent flavanyl units. These coupling constants in conjunction with the negative C.E. at 237 nm in the c.d. spectrum of (**10**) indicate a 2*S*,3*S*,4*R*(C):2*S*,3*S*(G) absolute configuration for this novel metabolite (**9**). Inspection of the ^{1}H n.m.r. data (Table 2) of the (−)-epimopanane-(4α,8)-(−)-fisetinidol hexamethyl ether acetate (**12**) indicates the characteristic spin patterns of the 2,3-*cis*-3,4-*trans*-($J_{2,3}$ 2.9, $J_{3,4}$ 3.5 Hz) mopanoid moiety.[2] Coupling at C-8 of the (−)-fisetinidol unit ($J_{2,3}$ 7.0 Hz) is confirmed by the AB system of ring E[δ 6.94, 6.58; 5- and 6-H(E) resp., *J* 8.5 Hz] which was correlated with respectively 4-H_2(G) and 7-OMe(E) by decoupling and n.O.e. experiments (*cf.* Part 8). Evidence for a 4α-flavanyl substituent and hence 2*S*,3*S*,4*S*(C):2*R*,3*S*(G) absolute configuration for (**11**) is obtained from the high-amplitude negative C.E. at 230 nm in the c.d. spectrum of (**12**). This novel metabolite complements the rare group of biflavanoids with a C-8 substituted 5-deoxy flavan-3-ol terminal unit (*cf.* Part 8). The ^{1}H n.m.r. spectrum (Table 1) of the (+)-guibourtinidol-(3′,4″-*O*)-epimopanone pentamethyl ether acetate* (**14**) exhibits two aromatic ABX systems which were correlated with the 2,3-*trans* heterocyclic AMXY system of ring G *via* the appropriate decoupling experiments. N.O.e experiments, however, indicate that only the *o*-proton (δ 6.84, *J* 8.0 Hz) of the ABX system of the F-ring shows association with a methoxy resonance (δ 3.89). Such an observation demonstrates a deviation from the usual pyrocatechol nature of this ring and reflects interflavanyl bonding *via* C-3(F) of a (+)-guibourtinidol (3′,4′,7-trihydroxy substitution pattern) moiety. The spin patterns of the remaining flavanyl unit comprised of an aromatic AB-[δ 6.46, 6.74, *J* 8.5 Hz, 5- and 6-H(B) resp.] and a heterocyclic AB system (δ 5.07, 4.85, *J* 16.0 Hz) indicative of the B/D-ring nature of the mopanoids. Additional heterocyclic AB-[δ 4.65, 4.16, *J* 3.9 Hz, 2- and 3-H(C) resp.] and aromatic AB systems [δ 7.79, 7.04, *J* 8.5 Hz, 5- and 6-H(A) resp.] in conjunction with the presence of five methoxy resonances in the spectrum of (**14**) are reminiscent of a C-8(A) hydroxylated mopanone ABCD-moiety for (**13**). Proof for the interflavanyl linkage *via* 4-OH(B) and for the aromatic oxygenation pattern of this unit is obtained by n.O.e. experiments which indicate association of a single proton [6-H(A)] of this moiety with a methoxy resonance [δ 3.80, 7-OMe(A)]. In the absence of suitable reference compounds the absolute configurations for both the C-(2*S*,3*R*) and G-rings (2*R*,3*S*) indicated in (**13**) are tentative. This novel metabolite apparently arises *via* phenol oxidative coupling, initiated by generation of an oxygen radical at 4-OH(B), of the constituent monomeric units. Its identification thus represents a rare exception in a metabolic pool where $C_{(sp^3)}$–$C_{(sp^2)}$ coupled analogues, originating from a two-electron process, predominate.

The novel series of promopanidins is accompanied by the first naturally occurring propeltogynidins (**15**), (**17**), (**19**), and (**21**). Amongst these the (+)-peltogynane-(4β,6)-(−)-fisetinidol (**15**) and (+)-peltogynane-(4β,6)-(+)-epifisetinidol (**17**) have previously been synthesized.[3] They were thus identified by comparison of the physical data of their hexamethyl ether acetates (**16**) and (**18**) with those of the synthetic counterparts. Noteworthy, however, is the characteristic replacement of the

* The ABCD designation for the rings of the *lower* mopanoid unit is retained to facilitate comparison of ^{1}H n.m.r. data with those of the promopanidins.

Table 2. ^{1}H N.m.r. peaks (p.p.m.) of peltogynoid methyl ether acetates (**16**), (**18**), (**20**), and (**22**) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses.

Ring	Proton	(16)[a]	(18)[a]	(20)[a]	(22)[a]
A	5	6.83 (d, 8.5)	6.85 (d, 8.5)	6.90 (d, 8.5)	7.12 (dd, 1.0, 8.5)
	6	6.49 (dd, 2.2, 8.5)	6.49 (dd, 2.5, 8.5)	6.48 (dd, 2.5, 8.5)	6.57 (dd, 2.5, 8.5)
	8	6.58 (d, 8.5)	6.59 (d, 2.5)	6.46 (d, 2.5)	6.15 (d, 2.5)
B	3	6.44 (s)	6.44 (s)	6.53 (s)	6.59 (s)
	6	7.23 (s)	7.26 (s)	6.91 (s)	
C	2	5.07 (d, 9.8)	5.07 (d, 9.7)	4.60 (br, s, *ca.* 1.0)	5.22 (d, 9.9)
	3	4.05 (dd, 6.3, 9.8)	4.06 (dd, 6.3, 9.7)	3.94 (dd, 1.0, 2.1)	3.94 (dd, 9.0, 9.9)
	4	4.96 (d, 6.3)	4.96 (d, 6.3)	4.56 (d, 2.1)	6.37 (d, 9.0)
D		4.88 (d, 14.5)	4.88 (d, 14.7)	4.94 (d, 15.0)	5.02 (d, 15.8)
		4.68 (d, 14.5)	4.68 (d, 14.7)	4.88 (d, 15.0)	4.80 (d, 15.8)
E	5	6.49 (br, s)	6.52 (br, s)	6.33 (br, s)	7.00 (d, 8.5)
	8	6.53 (s)	6.56 (s)	6.45 (s)	6.53 (d, 2.5)
	6	—	—	—	6.51 (dd, 2.5, 8.5)
F	2	6.87 (d, 2.0)	6.97 (d, 2.0)	6.85 (d, 2.0)	6.95 (d, 2.0)
	5	6.82 (d, 8.0)	6.82 (d, 8.2)	6.81 (d, 8.0)	6.82 (d, 8.5)
	6	6.83 (dd, 2.0, 8.0)	6.90 (dd, 2.0, 8.2)	6.87 (dd, 2.0, 8.0)	7.00 (dd, 2.0, 8.5)
G	2	4.90 (d, 7.5)	4.98 (br, s, *ca.* 1.0)	4.95 (d, 7.5)	4.91 (d, 9.9)
	3	5.24 (m)	5.28 (m)	5.25 (m)	5.54 (dd, 9.9, 10.5)
	$4_{ax.}$	2.72 (dd, 8.3, 15.5)	2.77 (dd, 2.5, 17.5)	2.70 (dd, 7.0, 16.5)	4.96 (dd, 1.5, 10.5)
	$4_{eq.}$	2.90 (dd, 5.4, 15.5)	3.09 (dd, 4.0, 17.5)	2.95 (dd, 5.0, 16.5)	
OMe		3.79 (7-A), 3.82 (4-B), 3.83 (3-F), 3.85 (7-E), 3.86 (4-F), 3.96 (5-B), each s	3.80 (7-A), 3.83 (4-B), 3.84 (3-F), 3.86 (4-F/7-E), 3.96 (5-B), each s	3.73 (7-A), 3.83 (3-F/7-E), 3.84 (4-B), 3.85 (4-F), 3.90 (5-B), each s	3.69 (7-A), 3.72 (4-B), 3.78 (7-E/4-B), 3.85 (4-F), 3.86 (3-F), each s
OAc		1.85 (s)	1.86 (s)	1.93 (s)	2.24 (s), 1.54 (s)

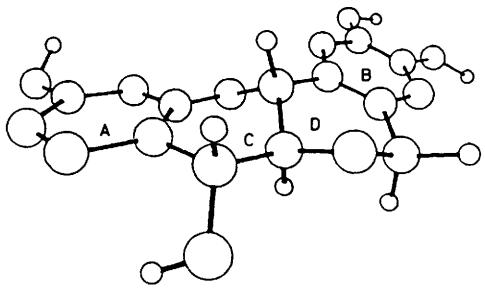
[a] $CDCl_3$, 296 K.

aromatic AB system of ring-B in the ^{1}H n.m.r. spectra of the promopanidins by *p*-coupled singlets for the propeltogynidins. Attention is also drawn to the incorrect assignment of *R*-absolute configuration at C-4(C) [C-7(C) in ref. 3] for both (**15**) and (**17**) by Roux and co-workers.[3]

Comparison of ^{1}H n.m.r. data (Table 2) of the (−)-epi-peltogynane-(4β,6)-(−)-fisetinidol hexamethyl ether acetate (**20**) with those of the mopanoid analogue (**10**) reveals their close structural resemblance. Coupling constants ($J_{2,3}$ *ca.* 1.0, $J_{3,4}$ 2.1 Hz) of the heterocyclic AMX system, the isolated D-ring methylene doublet of doublets (δ 4.94, 4.88, *J* 15.0 Hz), and the ABX pattern and *p*-coupled singlets (δ 6.53 and 6.91) in the aromatic region, unambiguously establishes the 'upper' 2,3-*cis*-3,4-*trans* peltogynoid unit. The 'terminal' moiety is similarly defined as a C-6 substituted (−)-fisetinidol by the ABX system, one broadened (δ 6.33) and one sharp (δ 6.45) singlet in the aromatic region, and the coupling constant ($J_{2,3}$ 7.5 Hz) of the heterocyclic AMXY system. Notable in the spectra of both the mopanoid- and peltogynoid-derivatives (**10**) and (**20**) is the appearance of the 5-H(E) resonances at higher field compared to the chemical shifts of the 8-H(E) signals. This presumably reflects a preferred conformation about the interflavanyl bond in which the quasi-axial 3-O(C) function exercises anisotropic shielding of 5-H(E). The 2*S*,3*S*,4*R*(C):2*R*,3*S*(G) absolute configuration of (**19**) is again derived from proton coupling constants and the high amplitude negative C.E. at 232 nm in the c.d. spectrum of the methyl ether acetate (**20**).

The hexamethyl ether diacetate (**22**) of the (−)-fisetinidol-(4α,6)-(+)-peltogynol (**21**) exhibits ^{1}H n.m.r. spectral features (Table 2) conspicuously different from those of the above promopanidins and propeltogynidins. The methylenic AB system (δ 4.80, 5.02, *J* 15.8 Hz) and chemical shift (δ 3.94) of the 3-proton of a heterocyclic 2,3-*trans*-3,4-*trans* AMX system are, however, reminiscent of the C/D-ring system in mopanoids and peltogynoids. A 4α-substituted (−)-fisetinidol 'upper' unit is evident from the coupling constants ($J_{2,3}$ = $J_{3,4}$ 9.9 Hz) of the heterocyclic AMX system and the two aromatic ABX patterns associated with the resorcinol A- and pyrocatechol B-rings. The chemical shift of 5-H(A) (δ 5.12, dd, *J* 1.0, 8.5 Hz) of the remaining aromatic ABX system and of one of the acetoxy resonances (δ 2.24) correspond with the adjacency of 5-H(A) to an *O*-acetyl substituted benzylic carbon.[9] When taken in conjunction with the aromatic singlet at δ 6.57 and the coupling constants ($J_{2,3}$ 9.9, $J_{3,4}$ 9.0 Hz) of the tetracyclic AMX system, these features are compatible with a B-ring substituted (+)-mopanol A or (+)-peltogynol A terminal unit. Decoupling experiments using the 4-H(G), 2- and 4-H(C), and methylene (D) resonances as reference signals, indicate selective benzylic coupling of the proton at δ 6.57 and the D-ring methylene protons, thus unequivocally establishing bonding at C-6(B) of a (+)-peltogynol moiety. The proposed 2*R*,3*S*,4*R*(G):2*R*,3*S*,4*R*(C) absolute configuration for (**21**) is based on coupling constants and the high-amplitude negative C.E. at 232 nm in the c.d. spectrum of hexamethyl ether diacetate (**22**), and its presumed biogenetic formation from (+)-mollisacacidin [(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*- flavan-3,3′,4,4′,7-pentaol] and (+)-peltogynol A (**3**). The novel metabolite (**21**), being both a profisetinidin and a propeltogynidin, does not only complement the rare group of B-ring linked oligoflavanoids[2] but also of the class of oligoflavanoids with the equivalent of a 'terminal' flavan-3,4-diol unit.[3,9,10]

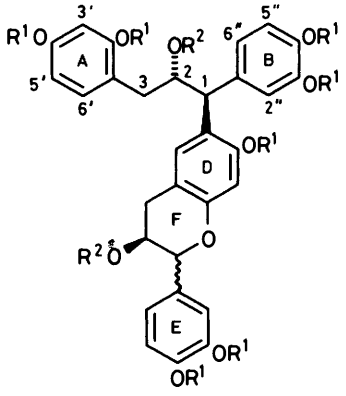
The ^{1}H n.m.r. spectrum of the novel 2,3-*cis*-3,4-*cis*-(+)-mopanol trimethyl ether acetate (**24**) exhibits the characteristic aromatic and D-ring methylene spin patterns of the mopanoid skeleton. Coupling constants ($J_{2,3}$ *ca.* 1.0, $J_{3,4}$ 4.5 Hz) of the heterocyclic AMX system confirms the all-*cis* relative



(25)

configuration.[11] The α-orientation of the 4-*O*-acetyl group and hence 2*R*,3*R*,4*R* absolute configuration of (**23**) is evident from comparison of the c.d. data (negative C.E. at 229 nm) of methyl ether diacetate (**24**) with those of the corresponding derivatives of authentic samples of (+)-mollisacacidin and its C-4 epimer, (+)-gleditsin. Identification of the mopanol analogue (**23**) with its unique (2*R*,3*R*)-2,3-*cis* configuration from the diverse metabolic pool of *C. mopane* demonstrates the extreme care to be exercised in allocation of the absolute configuration of promopanidins and propeltogynidins with 2,3-*cis* configuration of their C-rings *eg.* (**9**), (**11**), and (**19**). Thus re-assessment of the chiroptical properties (positive C.E. at 237 nm) of the first promopanidin,[2] mopanane-(4α,6)-(−)-fisetinidol, to which a 2*S*,3*S*,4*R* (C-ring) absolute configuration has tentatively been assigned, necessitates alteration of configuration to 2*R*,3*R*,4*S*. Such a change is substantiated by our experience with the extended number of reference compounds (**9**), (**11**), and (**19**).

The structures of the (+)-mopanol-(4β,6)-fisetinidols (**5**) and (**7**) were proved unequivocally by synthesis from (+)-mopanol A (**1**) and the readily available (−)-fisetinidol.[2] Adoption of the conditions established for the formation of the analogous peltogynoid pair[3] (**15**) and (**17**) affords the promopanidins (**5**) and (**7**) and the 1,3-diaryl-1-flavanyl-propan-2-ols (**26**) and (**28**). Notable is the exclusive formation of products with 3,4-*cis* configuration (**5**) and (**7**) at the point of interflavanyl linkage which has previously[3] been attributed to a reaction under thermodynamic control. The synthetic process thus apparently closely resembles the biogenesis of (**5**) and (**7**). The more severe conditions required for condensation of (+)-peltogynol (**3**) with (+)-catechin and (−)-fisetinidol compared to those for flavan-

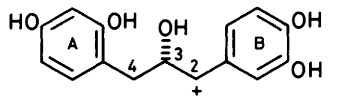


(**26**) { ≡ ≡ , $R^1 = R^2 = H$

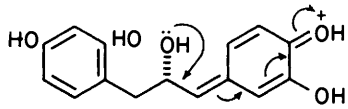
(**27**) { ≡ ≡ , $R^1 = Me, R^2 = Ac$

(**28**) { ≡ , $R^1 = R^2 = H$

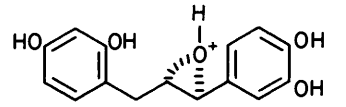
(**29**) { ≡ , $R^1 = Me, R^2 = Ac$



(**30**)



(**31**)



(**32**)

3,4-diols with the same nucleophiles were explained in terms of differences in the activation energy leading to the intermediate C-4 carbocations.[3] The ease of formation of 4-carbocations from flavan-3,4-diols has been ascribed to contributions of the boat and inverted half-chair conformations in which the 3-hydroxy group is favourably aligned to anchimerically assist formation of the benzylic carbocation. Owing to the high energy requirements[12,13] involvement of a boat conformation must, however, be rejected. The increased energy requirements for the condensation reactions of (+)-mopanol A (**1**) and (+)-peltogynol A (**3**) therefore result from the C-ring of these compounds being restricted to an (E) C-3 sofa conformation (**25**) (3D perspective) hence eliminating contributions by an A-conformer towards a decrease in the activation energy.

The ^{1}H n.m.r. spectra (Table 3) of the phenolic methyl ether acetates (**27**) and (**29**) of the 1-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,7-tetrahydroxyflavan-6-yl]-3-(2,4-dihydroxyphenyl)-1-(3,4-dihydroxyphenyl)-propan-2-ol (**26**) and the 1-[(2*S*,3*S*)-2,3-*cis*-3,3′,4′,7-tetrahydroxyflavan-6-yl]-3-(2,4-dihydroxyphenyl)-1-(3,4-dihydroxyphenyl)-propan-2-ol (**28**) each exhibits three aromatic ABX systems, two aromatic singlets, and two AMXY systems in the heterocyclic region. When taken in conjunction with the presence of seven methoxy resonances these spin patterns indicate a 1,3-diarylpropan-2-ol arrangement substituted at C-1 by a (−)-fisetinidol-($J_{2,3}$ 7.5 Hz) and a (+)-epifisetinidol moiety ($J_{2,3}$ *ca.* 1.0 Hz) for (**27**) and (**29**) respectively. Cleavage of the heterocycle of a (−)-fisetinidol unit with concomitant 'liberation' of a resorcinol unit from the A/C-ring junction is substantiated by the n.O.e. association of 2′-OMe(A) with 3′-H(A) [14.6, 12.5% for (**27**) and (**29**) resp.] and of 4′-OMe(A) with both 3′- and 5′-H(A) [9.3, 7.5% for (**27**), 8.1, 7.5%* for (**29**)]. The chemical shifts of the aromatic singlets establish linkage of the propan-2-ol moiety to C-6 of the (−)-fisetinidol and (+)-epifisetinidol units (see above). The relatively severe reaction conditions (1M HCl, 60 °C, 9.5 h) required for inducing formation of a mopanoid C-4 carbocationic intermediate presumably also leads to protonation of the heterocyclic oxygen of (−)-fisetinidol. Formation of a single diastereomer (**26**) then results from intermolecular coupling at C-2 *via* a predominantly S_N2cA mechanism.

* Approximated values due to overlap of OMe resonances.

Table 3. ^{1}H N.m.r. peaks (p.p.m.) of the 1,3-biaryl-1-flavanylpropan-2-ol methyl ether acetates (**27**) and (**29**) in $CDCl_3$ at 296 K (300 MHz). Splitting patterns and *J*-values (Hz) are given in parenthesis

Ring	Proton	(27)	(29)
A	3	6.36 (d, 2.5)	6.36 (d, 2.5)
	5	6.32 (dd, 2.5, 8.5)	6.31 (dd, 2.5, 8.2)
	6	6.87 (d, 8.5)	6.87 (d, 8.2)
	1	4.47 (d, 9.5)	4.50 (d, 9.5)
	2	5.92 (m)	5.94 (m)
	3-CH_2	2.50 (dd, 9.5, 14.3)	2.50 (dd, 8.2, 14.0)
		2.96 (dd, 3.5, 14.3)	2.97 (dd, 3.5, 14.0)
B	2	6.86 (d, 2.0)	6.98 (d, 2.0)
	5	6.79 (d, 8.0)	6.83 (d, 8.5)
	6	6.89 (dd, 2.0, 8.0)	6.92 (dd, 2.0, 8.5)
D	5	7.06 (br, s)	7.09 (br, s)
	8	6.41 (s)	6.45 (s)
E	2	6.84 (d, 2.0)	6.89 (d, 2.0)
	5	6.76 (d, 8.0)	6.78 (d, 8.5)
	6	6.87 (dd, 2.0, 8.0)	6.91 (dd, 2.0, 8.5)
F	2	4.97 (d, 7.5)	5.00 (br, s, *ca.* 1.0)
	3	5.28 (m)	5.38 (m)
	4_{ax}	2.79 (dd, 8.0, 16.0)	2.85 (dd, 2.5, 17.5)
	$4_{eq.}$	2.97 (dd, 5.2, 16.0)	3.19 (dd, 4.9, 17.5)
OMe		3.72 (7-D), 3.75 (4-A), 3.76 (2-A), 3.81 (3-B), 3.83 (4-E), 3.84 (4-B), 3.85 (3-E), each s	3.74 (4-A/7-D), 3.77 (2-A), 3.83 (4-E), 3.85 (4-B), 3.87 (3-B/3-E), each s
OAc		1.65 (s), 1.90 (s)	1.63 (s), 1.89 (s)

Alternatively a formal C-2 carbocation (**30**) may intramolecularly be stabilized as a protonated oxirane (**32**) *via* a B-ring quinone-methide of type (**31**). The 1-flavanylpropan-2-ol (**26**) subsequently forms by stereospecific *trans*-diaxial opening of the strained oxirane (**32**). Similar protonation of the heterocyclic oxygen of the (−)-fisetinidol moiety in (**26**) also explains formation of the epimeric C-1 (+)-epifisetinidol-propan-2-ol (**28**) by recyclization *via* 2-OH(A) and the *Si*-face at C-2 in quinone-methide (**31**). These results complement the extensive investigations of the acid-catalyzed reactions of flavan-3-ols with phloroglucinol and resorcinol[14–17] and of the self-condensation of (+)-catechin under similar conditions.[18]

Experimental

^{1}H N.m.r. spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ or C_6D_6 with Me_4Si as internal standard. Accurate mass estimations 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 pre-coated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40:1) after development. Preparative plates (p.l.c.), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether over 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at ambient temperatures. Evaporations were performed under reduced pressure at *ca.* 60 °C in a rotary evaporator.

Fractionation of the Heartwood Extract of Colophospermum mopane.—The fractionation procedure for the methanol extract of the heartwood using Sephadex LH-20 and Fractogel TSK HW-40(S) as chromatographic substrates in ethanol under atmospheric- and medium pressure-conditions, was fully described in Part 8 and will not be repeated here. Details of the steps leading to the fractions indicated in the following headings *i.e.* 1 · 1 · 1, 2 · 2 · 1, and 4 will thus also be found in Part 8. Those sub-fractions marked with an asterisk comprised of novel proguibourtinidins and/or profisetinidins and related C-ring isomerized analogues, details of which will be published elsewhere.

Fraction 1 · 1 · 1. Acetylation of the methyl ether fraction 1 · 1 · 1 followed by p.l.c. [(benzene–hexane–acetone, 6:3:1) × 2] afforded two bands, 1 · 1 · 1 · 1 (R_F 0.54, 4.7 mg) and 1 · 1 · 1 · 2* (R_F 0.31, 6.4 mg). The R_F 0.54 band gave (2R,-3S,4R)-2,3-cis,3,4-cis-3′,4′,7-*tri*-O-*methyl*-4-O-*acetyl*-(+)-*mopanol* (**24**) as a white solid (Found: M^+, 386.1365. $C_{21}H_{22}O_7$ requires *M*, 386.1366); δ_H ($CDCl_3$, 300 MHz, 296 K) 7.17 [d, *J* 8.5 Hz, 6-H(B)], 7.11 [dd, *J* 0.9 and 8.5 Hz, 5-H(A)],6.90 [d, *J* 8.5 Hz, 5-H(B)], 6.51 [dd, *J* 2.5 and 8.5 Hz, 6-H(A)], 6.36 [d, *J* 2.5 Hz, 8-H(A)], 6.14 [dd, *J* 1.0 and 4.5 Hz, 4-H(C)], 5.13 [d, *J* 16.5 Hz, -CH_2(D)], 4.94 (br s, *ca.* 1.0 Hz, 2-H(C)], 4.78 [d, *J* 16.5 Hz, -CH_2(D)], 4.25 [dd, *J* 1.0 and 4.5 Hz, 3-H(C)], 3.70 [s, 7-OMe(A)], 3.80 [s, 3-OMe(B)], 3.87 [s, 4-OMe(B)], and 2.26 [s, 4-OAc(C)]; c.d. $[\theta]_{278}$ O, $[\theta]_{267}$ 0.4 × 10^4, $[\theta]_{251}$ O, $[\theta]_{229}$ −13.3 × 10^4, $[\theta]_{223}$ −15.2 × 10^4, and $[\theta]_{204}$ O; $[\alpha]_D^{21}$ +85 ° (*c* 0.0047 in MeOH).

Fraction 2 · 2 · 1. This fraction was acetylated and subsequently purified by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) ×4] to give the *epimopanane*-(4α,8)-(−)-*fisetinidol hexamethyl ether acetate* (**12**) as a white amorphous solid (R_F 0.51, 17.6 mg) (Found: M^+, 684.2571. $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H(Table 1); c.d. $[\theta]_{295}$ O, $[\theta]_{282}$ −1.5 × 10^4, $[\theta]_{274}$ O, $[\theta]_{265}$ 0.7 × 10^4, $[\theta]_{256}$ O, $[\theta]_{236}$ −14.0 × 10^4, $[\theta]_{230}$ −24.2 × 10^4, and $[\theta]_{213}$ O.

Fraction 4. This fraction (1.707 g) was further resolved by Fractogel TSK HW-40(S) (3.5 × 45 cm. column, flow rate: 4.0 ml/min, 0.3—6.0 bar pressure) in ethanol to give sub-fractions 4.1 [relative retention time (RR_t)0—2.4 h, 424 mg], 4.2 (RR_t 2.45—4.20 h, 360 mg), and 4.3* (RR_t 4.25—6.93 h, 417 mg), fraction collection starting at appearance of the first phenolic compounds (u.v.-detector). Methylation of 4.1 followed by p.l.c. [(benzene–acetone–methanol, 90:9:1) ×3] afforded seven bands, 4 · 1 · 1 (R_F 0.49, 23.6 mg), 4 · 1 · 2 (R_F 0.45, 18.2 mg), 4 · 1 · 3 (R_F 0.41, 31.9 mg), 4 · 1 · 4 (R_F 0.37, 31.9 mg), 4 · 1 · 5* (R_F 0.31, 111 mg), 4 · 1 · 6 (R_F 0.24, 35.1 mg), and 4 · 1 · 7* (R_F 0.20, 61.8 mg). Fraction 4 · 1 · 1 was acetylated and the mixture resolved by p.l.c. [(hexane–acetone–ethyl acetate, 7:2:1) ×3] into three bands at R_F 0.34 (10.9 mg), 0.29 (6.4 mg), and 0.25 (1.8 mg). The R_F 0.34 band gave the (+)-*mopanane*-(4β,6)-(−)-*fisetinidol hexamethyl ether acetate* (**6**) as a white solid (Found: M^+, 684.2583. $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H (Table 1); c.d. $[\theta]_{298}$ O, $[\theta]_{282}$ −9.1 × 10^4, $[\theta]_{256}$ O, $[\theta]_{234}$ 46.0 × 10^4, $[\theta]_{232}$ 48.1 × 10^4, $[\theta]_{226}$ 41.9 × 10^4, $[\theta]_{220}$ 47.7 × 10^4, and $[\theta]_{205}$ 7.5 × 10^4. The R_F 0.29 band afforded the (+)-*mopanane*-(4β,6)-(+)-*epifisetinidol hexamethyl ether acetate* (**8**) as a white solid (Found: M^+, 684.2589. $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H (Table 1); c.d. $[\theta]_{300}$ O, $[\theta]_{290}$ −1.7 × 10^4, $[\theta]_{277}$ O, $[\theta]_{234}$ 9.3 × 10^4, $[\theta]_{227}$ 10.8 × 10^4, and $[\theta]_{203}$ O. The R_F 0.25 band gave the *epimopanane*-(4α,6)-(+)-*epifisetinidol hexamethyl ether acetate* (**10**) as a white solid (Found: M^+, 684.2598. $C_{39}H_{40}O_{11}$ requires *M*, 684.2571); δ_H (Table 1); c.d. $[\theta]_{292}$ O, $[\theta]_{284}$ 0.3 × 10^4, $[\theta]_{276}$ O, $[\theta]_{267}$ −0.5 × 10^4, $[\theta]_{257}$ −0.6 × 10^4, $[\theta]_{240}$ −3.4 × 10^4, $[\theta]_{237}$ −3.3 × 10^4, and $[\theta]_{232}$ O.

Acetylation of fraction 4 · 1 · 2 followed by p.l.c. [(hexane–acetone–ethyl acetate, 65:20:15) ×3] gave the known[2] epimopanane-(4β,6)-(−)-fisetinidol, R_F 0.43, as a white solid (4.9 mg).

Fraction 4 · 1 · 3 was acetylated and the mixture resolved by p.l.c. [(hexane–benzene–acetone, 5:4:1) ×11] to give two bands at R_F 0.37 (12.9 mg) and 0.31 (4.3 mg). The former band gave the *epimopanane*-(4α,6)-(−)-*fisetinidol hexamethyl ether acetate* (**20**) as a white amorphous solid (Found: M^+, 684.2543.

$C_{39}H_{40}O_{11}$ requires M, 684.2571); δ_H (Table 2); c.d. $[\theta]_{300}$ O, $[\theta]_{285}$ -2.1×10^4, $[\theta]_{275}$ O, $[\theta]_{250}$ 1.5×10^4, $[\theta]_{236}$ O, $[\theta]_{232}$ -4.5×10^4, $[\theta]_{229}$ -4.8×10^4, and $[\theta]_{226}$ O. The R_F 0.31 band gave the known[3] (+)-peltogynane-(4β,6)-(−)-fisetinidol hexamethyl ether acetate (**16**) as a white solid. To facilitate comparison, its ^1H n.m.r. data is also presented in Table 2.

Acetylation of fraction 4 · 1 · 4 and subsequent p.l.c. [(hexane–benzene–acetone, 6:3:1) ×12] afforded the known[3] (+)-peltogynane-(4β,6)-(+)-epifisetinidol hexamethyl ether acetate (**18**) as an amorphous white solid (16.9 mg), δ_H (Table 2).

Fraction 4 · 1 · 6 was acetylated and the mixture resolved by p.l.c. [(benzene–ethyl acetate–acetone, 80:15:5) ×2] to give three bands 4 · 1 · 6 · 1 (R_F 0.67, 10.0 mg). 4 · 1 · 6 · 2* (R_F 0.61, 8.6 mg), and 4 · 1 · 6 · 3* (R_F 0.51, 8.5 mg). The R_F 0.67 band afforded the *(−)-fisetinidol-(4α,6′)-(+)-peltogynol hexamethyl ether diacetate* (**22**) as a white solid (Found: M^+, 742.2649. $C_{41}H_{42}O_{13}$ requires M, 742.2626); δ_H (Table 2); c.d. $[\theta]_{290}$ O, $[\theta]_{281}$ 1.9×10^4, $[\theta]_{264}$ 1.5×10^4, $[\theta]_{244}$ 5.2×10^4, $[\theta]_{237}$ O, $[\theta]_{232}$ -9.3×10^4, $[\theta]_{228}$ O, $[\theta]_{224}$ 5.9×10^4, and $[\theta]_{215}$ O.

Methylation of fraction 4 · 2 followed by p.l.c. [(benzene–acetone–methanol, 90:9:1) ×3] gave four bands 4 · 2 · 1 (R_F 0.42, 16.1 mg), 4 · 2 · 2* (R_F 0.26, 38.3 mg), 4 · 2 · 3* (R_F 0.22, 38.1 mg), and 4 · 2 · 4* (R_F 0.18, 47.2 mg). The R_F 0.42 band was acetylated and the mixture purified by p.l.c. [(hexane–benzene–acetone, 5:4:1) ×10] to give the *(+)-guibourtinidol-(3′,4″-0)-7-hydroxy-epimopanone pentamethyl ether acetate* (**14**) as a white solid, R_F 0.47 (0.7 mg) (Found: M^+, 684.2231. $C_{38}H_{36}O_{12}$ requires M, 684.2207); δ_H (Table 1).

Acid-catalyzed condensation of (+)-mopanol A(1) *and (−)-fisetinidol.*—A mixture of (+)-mopanol A(**1**) (450 mg) and (−)-fisetinidol (857 mg) was stirred in 1M HCl (25 ml) for 9.5 h at 60 °C. The mixture was cooled to 25 °C and extracted with ethyl acetate (4 × 100 ml). Drying (Na_2SO_4) of the combined extract and evaporation of the solvent gave a purple solid (1.24 g) which was resolved by column chromatography, using Sephadex LH-20/ethanol (3.2 × 92 cm column, flow rate: 4.0 ml/min, atmospheric pressure), into four fractions, 1 (RR_f 0—6.0 h, 12.1 mg), 2 (RR_f 6.5—16.0 h, 32 mg), 3 (RR_f 30.5—41 h, 73.1 mg), and 4 (RR_f 41.5—56.0 h, 185.5 mg). Fraction 1 and 2 consisted of mopanol A and (−)-fisetinidol.

Methylation of fraction 3 followed by p.l.c. [(benzene–acetone–methanol, 90:9:1) ×2] afforded a single band at R_F 0.13 (22.4 mg). This was acetylated and the mixture resolved by p.l.c. [(benzene–hexane–acetone, 6:3:1) ×4] into two bands at R_F 0.25 (9.8 mg) and 0.17 (7.6 mg). The former band gave 1-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-6-*yl*]-3-(2,4-*dimethoxyphenyl*)-1-(3,4-*dimethoxyphenyl*)-2-*acetoxypropane* (**32**) as a white solid (Found: M^+, 730.3001. $C_{41}H_{46}O_{12}$ requires M, 730.2989); δ_H (Table 3); c.d. $[\theta]_{300}$ O, $[\theta]_{290}$ -1.7×10^4, $[\theta]_{277}$ O, $[\theta]_{234}$ 9.3×10^4, $[\theta]_{227}$ 10.8×10^4, and $[\theta]_{203}$ O. The R_F 0.17 band afforded 1-[(2S,3S)-2,3-trans-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-6-*yl*]-3-(2,4-*dimethoxyphenyl*-1-(3,4)-*dimethoxyphenyl*)-2-*acetoxypropane* (**34**) as a white amorphous solid (Found: M^+, 730.2997. $C_{41}H_{46}O_{12}$ requires M, 730.2989); δ_H (Table 3); c.d. $[\theta]_{298}$ O, $[\theta]_{287}$ 1.1×10^4, $[\theta]_{280}$ O, $[\theta]_{269}$ -1.8×10^4, $[\theta]_{246}$ O, $[\theta]_{236}$ -8.7×10^4, $[\theta]_{225}$ -9.5×10^4, and $[\theta]_{213}$ O.

Methylation of fraction 4 followed by p.l.c. [(benzene–acetone, 85:15) ×2] afforded a main band at R_F 0.52 (120.2 mg). This was acetylated and subsequently resolved by p.l.c. [(benzene–hexane–acetone, 5:4:1) ×2] to give two bands at R_F 0.39 (71 mg) and 0.34 (22.7 mg). The former consisted of the (+)-mopanane-(4β,6)-(−)-fisetinidol hexamethyl ether acetate (**6**) and the latter of the (+)-epifisetinidol analogue (**8**) with ^1H n.m.r. and c.d. data identical to those of the corresponding derivatives of the natural products.

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