Oligomeric flavanoids. Part 26.† Structure and synthesis of the first profisetinidins with epifisetinidol constituent units

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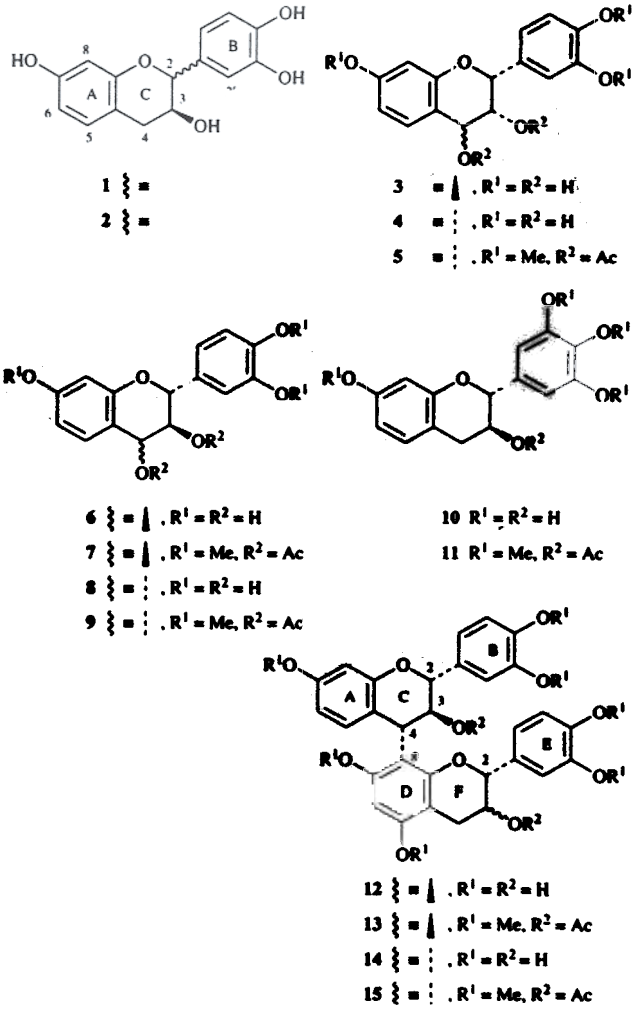
The natural occurrence of the first oligomeric profisetinidins with (2*R*,3*R*)-2,3-*cis*-epifisetinidol chain extender units is demonstrated in the bark of *Pithecellobium dulce* (Guamúchil). Semi-synthesis using the appropriate flavan-3-ol and flavan-3,4-diol precursors permits unequivocal structural and stereochemical assignment of the novel dimeric epifisetinidol-(4β,8)-catechin and epicatechins 16 and 18, the trimeric bis-epifisetinidol-(4β,6:4β,8)-catechin and epicatechins 33 and 35, the fisetinidol-(4α,8)-catechin-(6,4β)-epifisetinidol 37 and fisetinidol-(4α,8)-epicatechin-(6,4β)-epifisetinidol 39.

The profisetinidins, with their 3′,4′,7-trihydroxyflavan-3-ol extender units, are the most important polyflavanoids of commerce, forming the major constituents of wattle and quebracho tannins.[1–7] Their genesis presumably involves coupling of the flavan-3,4-diols, fisetinidol-4α-ol and *ent*-fisetinidol-4β-ol as incipient electrophiles, to a variety of nucleophilic flavan-3-ols and related compounds.[8] Naturally occurring oligomers exhibit predominantly 2,3-*trans* relative stereochemistry and possess either 2*R*,3*S* (*Acacia mearnsii*[1–5,7,9] and *Colophospermum mopane*[10–13]) or 2*S*,3*R* (*Schinopsis* spp. or *Rhus lancea*[6,9]) absolute configurations. 5-Deoxy (A-ring) analogues exhibiting a 2,3-*cis* relative configuration of the chain extender moieties are extremely rare and are hitherto restricted to two tentative (4,6)-bis-fisetinidols which occur in very low concentrations in the heartwood of *C. mopane*,[13] a promelacacinidin[14] from *Acacia melanoxylon*, and four proteracacinidins[15] from *A. galpinii* and *A. caffra*. Results relevant to the abundant occurrence of mono-, di- and tri-meric profisetinidins with a 2,3-*cis* relative stereochemistry of extender units from the bark of *Pithecellobium dulce* (Roxb.) Benth (Guamúchil, Madras thorn), a member of the Leguminosae (Mimosoideae) reputed for its effectiveness as a leather tannage,[16] are discussed here.

Results and discussion

The two fisetinidols **1** and **2** were named (−)-fisetinidol[17] and (+)-epifisetinidol[18] respectively, some thirty years ago. In order to be consistent with the latest nomenclature proposals,[19] compound **2** should be designated *ent*-epifisetinidol (see also ref. 8). The natural products from Guamúchil with (2*R*,3*R*)-2,3-*cis* fisetinidol constituent units will thus accordingly be named as epifisetinidol-derived profisetinidins in this paper.

The methanol extract of Guamúchil bark afforded a series of mono-, di- and tri-meric profisetinidins exhibiting both 2,3-*trans* and 2,3-*cis* relative configurations of the constituent fisetinidol moieties. The monomeric compounds comprised of the 3′,4′,7-trihydroxy-flavan-3,4-diols, epifisetinidol-4β-ol **3**,[20] epifisetinidol-4α-ol **4**,[20] the fisetinidol-4β- and 4α-ols **6** and **8**[20] and the 3′,4′,5′,7-tetrahydroxyflavan-3-ol, robinetinidol **10**.[21] These compounds were identified by comparison of their ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) and CD data (see Experimental section) with those of authentic samples,[20–22] either as free phenol **3**, or as permethylaryl ether acetates **5**, **7**, **9** and **11**. ^{1}H NMR and CD data of the derivatives **13** and **15** of the known fisetinidol-(4α,8)-catechin and -epicatechin dimers **12**[1] and **14**[11] similarly permitted definition of their structures.



† For Part 25, see P. J. Steynberg, A. Cronjé, J. P. Steynberg, B. C. B. Bezvidenhoudt, E. V. Brandt and D. Ferreira, *Tetrahedron*, 1997, **53**, 2591.

Table 1 ^{1}H NMR peaks (δ_H, 300 MHz) of flavan-3,4-diols and derivatives at 296 K. Splitting patterns and J values (Hz) are given in square brackets.

Proton	3[a,b]	4[a](5)[b]	6[a](7)[b]	8[a](9)[b]
5-H(A)	7.12 [d, 8.5]	7.27 (7.10) [d, 8.5]	7.12 (7.18) [d, 8.5]	7.27 (7.05) [d, 8.5]
6-H(A)	6.41 [dd, 2.5, 8.8]	6.41 (6.58) [dd, 2.5, 8.5]	6.42 (6.54) [dd, 2.5, 8.5]	6.43 (6.56) [dd, 2.5, 8.5]
8-H(A)	6.32 [d, 2.5]	6.25 (6.54) [d, 2.5]	6.25 (6.46) [d, 2.5]	6.19 (6.46) [d, 2.5]
2-H(B)	7.05 [d, 2.0]	7.07 (6.99) [d, 2.0]	6.92 (6.94) [d, 2.0]	6.93 (6.94) [d, 2.0]
5-H(B)	6.79 [d, 8.0]	6.78 (6.84) [d, 8.5]	6.80 (6.85) [d, 8.5]	6.79 (6.84) [d, 8.5]
6-H(B)	6.84 [dd, 2.0, 8.00]	6.48 (6.97) [dd, 2.0, 8.5]	6.75 (6.99) [dd, 2.0, 8.5]	6.75 (6.95) [dd, 2.0, 8.5]
2-H(C)	5.05 [d, 1.0]	5.0 (5.26) [br s]	4.86 (5.19) [d, 9.0, 10.5]	4.60 (5.02) [d, 10.0, 9.5]
3-H(C)	3.86 [dd, 1.0, 3.0]	3.97 (5.62) [dd, 1.0, 4.5]	3.91 (5.47) [dd, 3.5, 9.0, 10.5]	3.75 (5.54) [dd, 8.0, 10.0; 7.5, 9.5]
4-H(C)	4.45 [d, 3.0]	4.90 (6.28) [d, 4.5]	4.48 (6.15) [d, 3.5]	4.66 (6.24) [d, 8.0, 7.5]
OMe[c]		3.79 (7-A), 3.86 (3-B), 3.88 (4-B), each s	3.75 (7-A), 3.87 (3-B), (4-B), each s	3.75 (7-A), 3.87 (3-B), (4-B), each s
OAc[c]		1.93 (3-C), 2.09 (4-C), each s	1.84 (3-C), 2.13 (4-C), each s	1.84 (3-C), 2.03 (4-C), each s

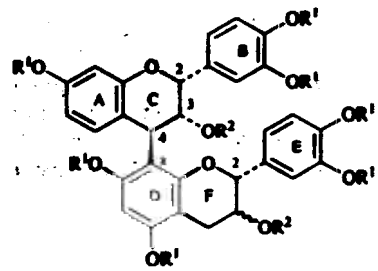
[a] In $(CD_3)_2CO$ + 5% D_2O. [b] Chemical shift values for derivatives in $CDCl_3$ in parentheses. [c] Positions of the groups on the ring are given in parentheses.

Table 2 ^{13}C NMR peaks (δ_C, 300 MHz) of flavan-3,4-diols at 296 K in $(CD_3)_2CO$ + 5% D_2O

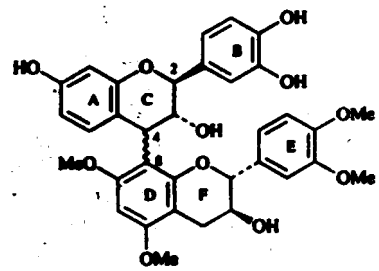
Carbon	3	4	6	8
5-C(A)	133.2	129.6	129.3	132.3
6-C(A)	109.3	109.1	109.3	109.2
8-C(A)	103.1	102.7	102.6	102.8
2-C(B)	115.2	115.2	115.7	115.6
5-C(B)	115.4	115.3	115.5	115.5
6-C(B)	119.2	119.2	120.6	120.2
2-C(C)	75.4	79.2	82.0	77.4
3-C(C)	72.2	70.0	74.2	71.2
4-C(C)	68.3	67.7	72.1	66.5

At ambient temperatures the ^{1}H NMR spectra (Table 3) of the derivatives **17** and **19** of the second pair of profisetinidin biflavanoids **16** and **18** exhibited broadened resonances reminiscent of the effects of dynamic rotational isomerism about the interflavanyl bond. At elevated temperatures (343 K) the protons of the heterocyclic rings displayed an AMX-[$J_{2,3(C)}$ = 2.5, 2.6, $J_{3,4(C)}$ = 3.5, 4.2 Hz for **17** and **19**, respectively] and an ABMX-system [$J_{2,3(F)}$ = 7.5 and 1.0 Hz for **17** and **19** respectively] suggesting the possibility of either a 2,3-*cis*-3,4-*trans* or a 2,3-*cis*-3,4-*cis* relative configuration of the C-ring in both products and with either 2,3-*trans* or 2,3-*cis* stereochemistry of the F-ring in **17** and **19**, respectively. Long range COSY experiments using the 2-H (for ABX-systems of rings B and E) and 4-H (for ABX-system of ring A) resonances as reference signals, permitted definition of the constitution of the 'upper' fisetinidol and 'lower' catechin and epicatechin units in derivatives **17** and **19** respectively. In addition to the aforementioned ABX-systems, the aromatic region of each spectrum displayed a one-proton singlet (δ 6.23, 6.24 for **17** and **19**, respectively). The chemical shifts of these singlets are reminiscent of the A-ring proton of a C-8 substituted catechin or epicatechin unit respectively.[23] This was confirmed by the strong NOE interaction of the 'residual' proton with both 5-OMe (6.3, 5.9% for **17** and **19**, respectively) and 7-OMe (8.6, 9.1% for **17** and **19**, respectively) of the 'lower' flavan-3-ol units. The high-amplitude positive Cotton effects in the 220–245 nm region of the CD spectra ($[\theta]_{241.9}$ +51 690, $[\theta]_{243.6}$ +44 590 for **17** and **19**, respectively), strongly indicated a 4β substituted ABC moiety in each instance.[24]

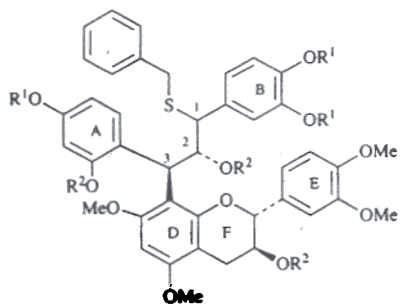
Since the ^{1}H NMR coupling constants did not permit unequivocal differentiation between 2,3-*cis*-3,4-*trans*- and 2,3-*cis*-3,4-*cis*-configurations of the 'upper' flavan-3-ol units, in both **17** and **19**, we embarked on the synthesis of compounds **16** and **18** from precursors of known absolute stereochemistry to obtain sufficient proof of the absolute configuration of both the upper and lower units in these compounds. Initial attempts were aimed at the selective C-2 (C-ring) epimerization of the *ent*-fisetinidol-(4,8)-tetra-*O*-methylcatechins **20** and **21**, available by acid-catalysed condensation of *ent*-fisetinidol-4β-ol



16 = , $R^1 = R^2 = H$
17 = , R^1 = Me, R^2 = Ac
18 = , $R^1 = R^2 = H$
19 = , R^1 = Me, R^2 = Ac



20 =
21 =



22 $R^1 = R^2 = H$
23 R^1 = Me, R^2 = Ac

(enantiomer of **8**) and 3′,4′,5,7-tetra-*O*-methylcatechin. Whereas efforts at converting the 2,3-*trans*-3,4-*cis* diastereomer **21** into its C-2(C) epimer by heating at alkaline pH (*ca.* 12)[25] under pressure invariably failed, the 3,4-*trans* isomer **20** could be epimerized at C-2, albeit in low yield (*ca.* 0.5%) and after prolonged reaction times. These poor results may presumably be attributed to stereoselective recyclization of an intermediate

Table 3 ^{1}H NMR peaks (δ_H, 300 MHz) of dimeric profisetinidin derivatives **17**, **19**, **30** and **32**, and of the propan-2-ol derivative **23** in $CDCl_3$[a]

Proton	17 (343 K)	19 (343 K)	30 (343 K)	32 (343 K)	23 (297 K)
5-H(A)/6-H(A)	6.72 (dd, 1.0, 8.5)	6.76 (dd, 1.0, 8.5)		6.73 (dd, 1.0, 8.5)	6.96 (d, 9.0)
6-H(A)/5-H(A)	6.37 (dd, 2.5, 8.5)	6.35 (dd, 2.5, 8.5)		6.44 (dd, 2.5, 8.5)	6.08 (dd, 2.5, 9.0)
8-H(A)/3-H(A)	6.29 (d, 2.5)	6.26 (br d, *ca.* 2.5)		6.63 (d, 2.5)	6.46 (d, 2.5)
2-H(B)	6.94 (d, 2.0)	7.00 (d, 2.0)		7.02 (d, 2.5)	6.83 (d, 2.0)
5-H(B)	6.79 (d, 8.5)	6.80 (d, 8.5)		6.86 (d, 8.5)	6.70 (d, 8.0)
6-H(B)	6.87 (dd, 2.0, 8.5)	6.92 (dd, 2.0, 8.5)		6.96 (dd, 2.5, 8.5)	6.46 (dd, 2.0, 8.0)
2-H(C)/1-H	5.43 (d, 2.5)	5.58 (d, 2.6)		5.59 (d, 3.0)	5.39 (d, 11.5)
3-H(C)/2-H	5.54 (dd, 2.5, 3.5)	5.65 (dd, 2.6, 4.2)		5.72 (dd, 3.0, 5.0)	6.26 (dd, 2.0, 11.5)
4-H(C)/3-H	4.60 (d, 3.5)	4.68 (d, 4.2)		4.54 (dd, 1.0, 5.0)	3.68 (d, 2.0)
6-H(D)	6.23 (s)	6.24 (s)		—	6.06 (s)
8-H(D)	—	—		6.42 (s)	—
2-H(E)	6.77 (d, 2.0)	6.87 (d, 2.0)		7.05 (d, 2.5)	7.25 (d, 2.0)
5-H(E)	6.78 (d, 8.5)	6.77 (d, 8.5)		6.89 (d, 8.5)	6.77 (d, 8.5)
6-H(E)	6.74 (dd, 2.0, 8.5)	6.70 (dd, 2.0, 8.5)		6.98 (dd, 2.5, 8.5)	6.82 (dd, 2.0, 8.5)
2-H(F)	4.57 (d, 7.5)	4.66 (br s, *ca.* 1.0)		5.15 (d, 2.0)	4.35 (d, 9.5)
3-H(F)	5.27 (m)	5.37 (m)		5.50 (m)	4.99 (m)
4-Hα(F)	3.08 (dd, 5.8, 16.7)	2.93 (dd, 2.1, 17.7)		2.98 (dd, 3.0, 18.0)	3.14 (dd, 6.0, 16.0)
4-Hβ(F)	2.70 (dd, 7.5, 16.7)	3.01 (dd, 5.0, 17.7))		3.14 (dd, 5.0, 18.0)	2.34 (dd, 10.0, 16.0)
$PhCH_2$	—	—			3.34, 3.20 (both d, 13.0)
Ph	—	—		—	6.89–7.04
OMe	3.70 (7-A), 3.74 (5-D), 3.76, 3.82, 3.86 (7-D), 3.86, 3.87, each s	3.65, 3.74, 3.75, 3.83, 3.85, 3.86, 3.87 (7-D), each s		3.40 (×2), 3.88, 3.86, 3.81, 3.62, 3.43 (br), each s	3.92 (4-E), 3.90 (7-D), 3.86 (4-B), 3.74 (3-B), 3.73 (5-D), 3.70 (4-A), 3.44 (3-E), each s
OAc	1.87, 1.81, each s	1.94, 1.81, each s	2.00, 1.87, each s	.95, 1.86, each s	2.34 (2-A), 1.76 (3-F), 1.66 (2), each s

[a] Splitting patterns and *J* values (Hz) are given in parentheses.

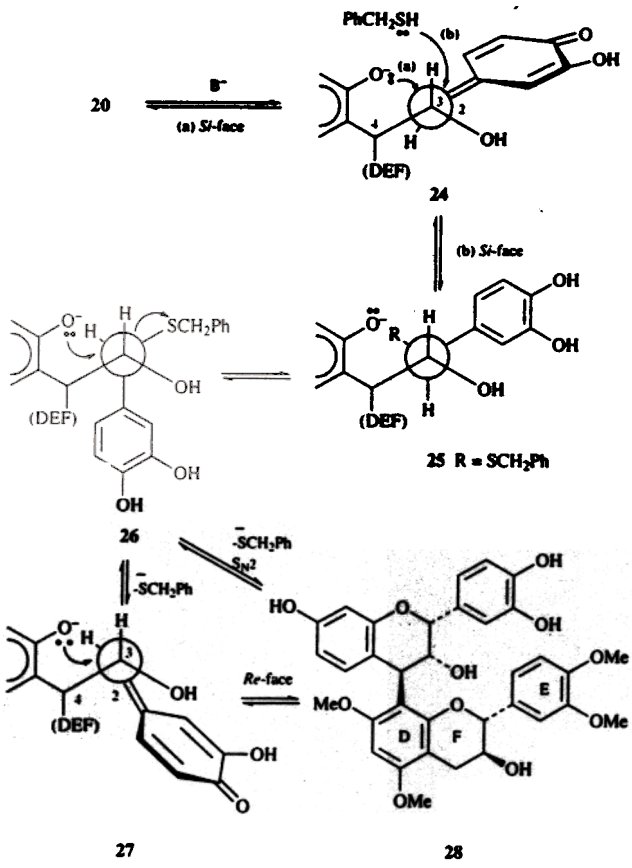
quinomethane of type **24**. The addition of an external nucleophile to scavenge the quinomethane may then possibly enhance product formation *via* an addition–substitution mechanism. Thus, treatment of profisetinidin **20** with base in the presence of phenylmethanethiol followed by the appropriate derivatizations, afforded the epifisetinidol-(4β,8)-catechin derivative **17** (*ca.* 5% yield) and the 2-acetoxy-1,3,3-triaryl-1-benzylthiopropane derivative **23** (^{1}H NMR data—Table 3). The ^{1}H NMR and CD spectra of the synthetic derivative **17** were identical to those of the same derivative of the natural product **16**, hence confirming the 2*R*,3*R*,4*S* absolute configuration of the upper epifisetinidol chain extender unit as well as the 2*R*,3*S* absolute configuration of the catechin DEF unit.

Formation of both the epimerized profisetinidin and the thioether **22** is explicable by the dual trapping of an intermediate quinomethane **24**, either intramolecularly by the A-ring phenoxide or intermolecularly by the sulfur nucleophile (Scheme 1). The former process regenerates the starting material **20** by rapid and highly stereoselective ring closure, while the latter affords the benzyl thioether **25**, both processes involving the π antibonding orbital at the *si*-face of C-2. Conformer **26** then permits the formation of the natural product analogue **28** with inversed C-2(C) configuration, either *via* S_N2 displacement of thiolate anion or by generation of the intermediate quinomethane **27** and subsequent cyclization involving the *re*-face at C-2.

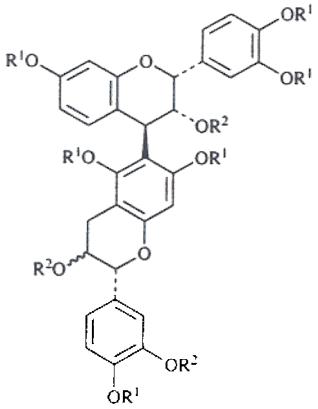
Conformational preferences appear to control the remarkable stereoselectivity of the pyran ring closure of quinomethanes of type **24**, and also reaction of the latter with thiol. In solution both the (4α,8)- and (4β,8)-profisetinidins **20** and **21** preferentially adopt compressed conformations about the interflavanyl bonds in which 4-H(C) and 7-OMe(D) are approximately eclipsed.[25,26] These conformations permit an offset face-to-face arrangement of the B- and E-rings hence leading to stabilizing π-stacking[27] of these rings. Such π–π interactions are especially prevalent in profisetinidin **21**, with its 3,4-*cis* (C-ring) configuration thus effectively preventing attack of the A-ring phenoxide ion at the *re*-face of C-2 in an intermediate quinomethane of type **24**. The increased distance between the B- and E-rings in the 3,4-*trans* profisetinidin **20**, partially alleviates the π–π interactions, thus permitting a low degree of attack at the *re*-face of C-2 in quinomethane **24**, and subsequent epimerization at this stereocentre with formation of the natural product derivative **28** in low yield. The formation of the benzyl thioether **26** presumably opens up the conformation hence allowing increased accessibility at the equivalent of the *re*-face of quinomethane **27** and permitting an S_N2 displacement of the thioether functionality.

Unequivocal structural proof for the novel compounds **16** and **18** followed from a small scale acid-catalysed condensation of epifisetinidol-4β-ol **3**, available *via* epimerization at C-2 of *ent*-fisetinidol-4β-ol,[22] and catechin and epicatechin respectively. The former reaction afforded the epifisetinidol-(4β,8)-catechin **16** and epifisetinidol-(4β,6)-catechin **29**, and the latter one the epifisetinidol-(4β,8)-epicatechin **18** and the (4β,6)-regioisomer **31**, both couplings occurring stereoselectively.[1] The ^{1}H NMR and CD data of the hepta-*O*-methyl ether acetate derivatives **17** and **19** were identical to those of the corresponding derivatives of the naturally occurring profisetinidins **16** and **18**. These compounds accordingly represent the first profisetinidins with (2*R*,3*R*)-2,3-*cis* fisetinidol (epifisetinidol) constituent units for which structural proof *via* synthesis is available. Analogue **18** complements the rate series of profisetinidins associated with epicatechin.[11] The same ^{1}H NMR and CD parameters that were used above to establish the structures of the hepta-*O*-methyl ether acetates **17** and **19**, were also applied to the structure elucidation of the same derivatives **30** and **32** of the (4β,6)-regioisomers **29** and **31**. Their ^{1}H NMR and CD data are collated in Table 3 and in the Experimental section, respectively.

The ^{1}H NMR spectra (Table 4) of the trimeric derivatives **34**, **36**, **38** and **40** were also characterized by severe line-broadening at ambient temperatures. At elevated temperatures (343 K) the spectra displayed ten methoxy and three acetoxy signals, five aromatic ABX patterns as well as an ABMX and two AMX spin systems in the heterocyclic region, reminiscent of the protons of the permethylaryl ether triacetates of bis-fisetinidol-catechin/epicatechin triflavanoids.[4] Owing to the small chemical shift differences of some key reference signals, *e.g.* H-4 of both the C- and I-rings in all four isomers, the spin systems of the constituent units could not be differentiated using a variety of NMR techniques, *e.g.* HMBC. Differentiation of these spin sys-



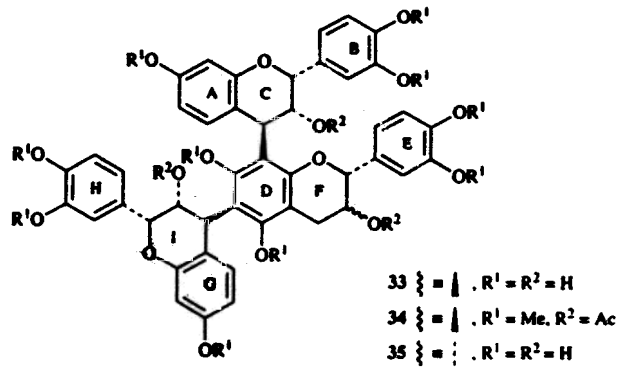
Scheme 1 Epimerization of *ent*-fisetinidol-(4β,8)-tetra-*O*-methylcatechin **20**, in the presence of phenylmethanethiol



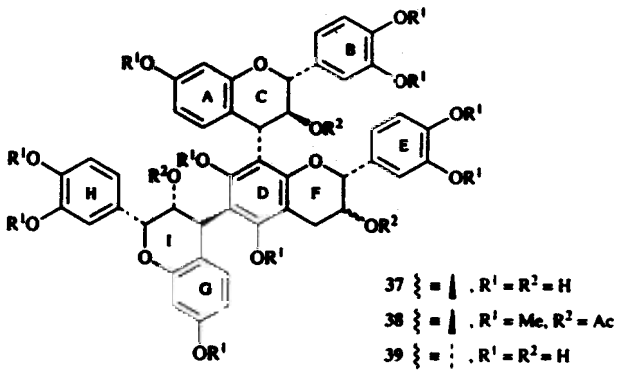
29 ≡ ▮ , $R^1 = R^2 = H$
30 ≡ ▮ , R^1 = Me, R^2 = Ac
31 ≡ ⋮ , $R^1 = R^2 = H$
32 ≡ ⋮ , R^1 = Me, R^2 = Ac

tems became possible for derivatives **38** and **40** (see Table 4) however, once the structures were confirmed by a concise synthesis (see below).

The coupling constants of the protons constituting the heterocyclic AMX systems tentatively indicated 2,3-*cis*-3,4-*trans*(C):2,3-*trans*(F):2,3-*cis*-3,4-*trans*(I) [$J_{2,3(C)}$ = 3.2, $J_{3,4(C)}$ = 5.1; $J_{2,3(F)}$ = 5.1; $J_{2,3(I)}$ = 3.2, $J_{3,4(I)}$ = 4.9 Hz] relative configuration for derivative **34** and 2,3-*cis*-3,4-*trans*(C):2,3-*cis*(F):2,3-*cis*-3,4-*trans*(I) [$J_{2,3(C)}$ = 3.2; $J_{3,4(C)}$ = 5.3; $J_{2,3(F)}$ = *ca.* 1.0; $J_{2,3(I)}$ = 3.5, $J_{3,4(I)}$ = 6.2 Hz] relative stereochemistry for derivative **36**. Compounds **38** and **40** are apparently based on the same flavan-3-ol DEF units [$J_{2,3(F)}$ = 6.5, *ca.* 1.0 Hz for **38** and **40** respectively] as was indicated for **34** and **36**. These derivatives, however, possess chain extender units with 2,3-*trans*-3,4-*trans*(C) and presumably 2,3-*cis*-3,4-*trans*(I) [$J_{2,3(C)}$ = 9.5, $J_{3,4(C)}$ = 9.5; $J_{2,3(I)}$ = *ca.* 3.0, $J_{3,4(I)}$ = *ca.* 5.0 Hz] relative configurations. When taken in conjunction with the structures of the dimeric analogues **12**, **14**, **16** and **18**, the triflavanoids presumably also comprise (2*R*,3*R*)-2,3-*cis*-epifisetinidol units (both



33 ≡ ▮ , $R^1 = R^2 = H$
34 ≡ ▮ , R^1 = Me, R^2 = Ac
35 ≡ ⋮ , $R^1 = R^2 = H$
36 ≡ ⋮ , R^1 = Me, R^2 = Ac



37 ≡ ▮ , $R^1 = R^2 = H$
38 ≡ ▮ , R^1 = Me, R^2 = Ac
39 ≡ ⋮ , $R^1 = R^2 = H$
40 ≡ ⋮ , R^1 = Me, R^2 = Ac

ABC and GHI moieties of **33** and **35**, GHI moieties of **37** and **39**) and (2*R*,3*S*)-2,3-*trans*-fisetinidol units (ABC moieties of **37** and **39**). Since the circular dichroism method does not permit reliable stereochemical assignment at this molecular level we took recourse to the semi-synthetic approach[1,4] in order to establish configuration at the eight stereocentres, and especially the stereochemistry at C-4 of both the C- and the I-rings.

Thus, acid-catalysed condensation of epifisetinidol-4β-ol **3** with either catechin or epicatechin in a 1:6 molar ratio, stereoselectively afforded, in addition to the dimeric profisetinidins **16** or **18**, the angular trimeric profisetinidins **33** or **35**. The appropriate derivatizations gave the permethylaryl ether triacetates **34** and **36**, with ^{1}H NMR and CD data identical to those of the same derivatives of the natural products **33** and **35**. Although all naturally occurring (2*R*)-proanthocyanidins with 2,3-*cis* relative configuration have been assigned a 3,4-*trans* 4β-linkage, evidence for such an assignment is entirely based upon the upfield shift of the C-2 (C-ring) carbon resonances (γ *gauche* effect)[28] and chiroptical data.[29] Evidence for the 4β-orientation of both the C- and I-rings in derivatives **34** and **36** was obtained from the high intensity positive Cotton effects [+104 700 (245.8 nm), +108 700 (245.7 nm) for **34** and **36**, respectively] in the CD spectra of these compounds. The dimeric profisetinidins **16** and **17** accompanying the trimers **33** and **35** were identical to those synthesized by acid-catalysed condensation of epifisetinidol-4β-ol **3** with catechin and epicatechin, respectively, thus proving the 4β linkage between the C- and D-rings.

A similar approach was used in assigning the structures of the trimeric profisetinidins **37** and **39**. Since CD data were inconclusive due to the presence of both 4α and 4β interflavanyl bonds, the trimer **37** was synthesized by acid-catalysed reaction of fisetinidol-(4α,8)-catechin **12** and epifisetinidol-4β-ol **3**. The appropriate derivatizations afforded the decamethyl ether triacetate **38** with ^{1}H NMR and CD data identical to those of the same derivative of the natural product. Trimer **39** was synthesized by condensation of epifisetinidol-(4β,6)-epicatechin **31**, available from the reaction between epifisetinidol-4β-ol **3**

Table 4 ^{1}H NMR peaks (δ_H, 300 MHz) of trimeric profisetinidin derivatives 34, 36, 38 and 40

Proton	34*	36*	38	40
5-H(A)	7.06 (dd, 1.0, 8.2)	7.08 (d, 8.5)	7.19 (dd, 1.0, 8.0)	7.15 (dd, 1.0, 8.5)
6-H(A)	6.58 (dd, 2.5, 8.2)	6.60 (dd, 2.5, 8.5)	6.74–6.64	6.69 (dd, 2.5, 8.5)
8-H(A)	6.94 (d, 2.5)	6.94 (d, 2.5)		6.81 (d, 2.5)
2-H(B)	7.32 (d, 2.0)	7.32 (d, 2.0)	7.12 (d, 2.0)	7.04 (d, 2.0)
5-H(B)	6.78 (d, 8.2)	6.79 (d, 8.5)	6.75 (d, 8.0)	6.69 (d, 8.0)
6-H(B)	7.24 (dd, 2.0, 8.2)	7.25 (dd, 2.0, 8.5)	7.01 (dd, 2.0, 8.0)	6.94 (dd, 2.0, 8.0)
2-H(C)	6.13 (d, 3.2)	6.10 (d, 3.2)	4.97 (d, 9.5)	5.05 (d, 9.5)
3-H(C)	6.26 (dd, 3.2, 5.1)	6.28 (dd, 3.2, 5.3)	6.68 (t, 9.5)	6.75 (t, 9.5)
4-H(C)	5.01 (dd, 1.0, 5.1)	5.01 (d, 5.3)	5.07 (dd, 1.0, 9.5)	5.09 (dd, 1.0, 9.5)
2-H(E)	7.03 (d, 2.2)	7.11 (d, 2.0)	6.87 (br s)	6.85 (d, 2.0)
5-H(E)	6.74 (d, 8.0)	6.76 (d, 8.0)	6.74–6.64	6.81 (d, 8.2)
6-H(E)	6.97 (dd, 2.2, 8.0)	6.84 (dd, 2.0, 8.0)		6.74 (dd, 2.0, 8.2)
2-H(F)	4.97 (d, 5.1)	4.66 (br s)	5.49 (d, 6.5)	5.33 (br s)
3-H(F)	5.53 (m)	5.46 (m)	5.42 (m)	5.50 (m)
4-Hα(F)	2.99 (d, 5.1)	3.08 (d, 4.6)	3.07 (dd, 5.0, 16.0)	3.34 (d, 3.5)
4-Hβ(F)			2.95 (dd, 6.5, 16.0)	
5-H(G)	7.09 (dd, 1.0, 8.5)	7.05 (d, 8.5)	7.11 (dd, 1.0, 8.5)	7.14 (dd, 1.0, 8.5)
6-H(G)	6.65 (dd, 2.5, 8.5)	6.59 (dd, 2.5, 8.5)	6.63 (dd, 2.5, 8.5)	6.62 (dd, 2.5, 8.5)
8-H(G)	6.76 (d, 2.5)	6.66 (d, 2.5)	6.98 (d, 2.5)	6.99 (d, 2.5)
2-H(H)	7.18 (d, 2.0)	7.23 (d, 2.0)	7.32 (d, 2.1)	7.32 (d, 2.0)
5-H(H)	6.75 (d, 8.2)	6.74 (d, 8.5)	6.78 (d, 8.0)	6.79 (d, 8.2)
6-H(H)	7.13 (dd, 2.0, 8.2)	7.14 (dd, 2.0, 8.5)	7.23 (dd, 2.1, 8.0)	7.25 (dd, 2.0, 8.2)
2-H(I)	5.79 (d, 3.2)	5.94 (d, 3.5)	6.15 (d, 3.0)	6.16 (d, 2.8)
3-H(I)	6.30 (dd, 3.2, 4.9)	6.39 (dd, 3.5, 6.2)	6.25 (dd, 3.0, 4.5)	6.26 (dd, 2.8, 5.0)
4-H(I)	4.97 (d, 4.9)	5.03 (d, 6.2)	5.05 (dd, 1.0, 4.5)	5.06 (dd, 1.0, 5.0)
OMe	3.73, 3.64, 3.62, 3.56, 3.55, 3.54, 3.50, 3.49, 3.28 (br), each s	3.84, 3.65, 3.62, 3.57 (×2), 3.55, 3.51, 3.47 (br), 3.44, 3.39 (br), each s	3.76 (br), 3.69, 3.67, 3.65, 3.56, 3.55, 3.55, 3.51, 3.48, 3.22 (br), each s	3.74, 3.72 (br), 3.65, 3.57, 3.56 (×2), 3.55, 3.52 (×2), 3.35 (br), each s
OAc	1.75, 1.73 (×2), each s	1.79, 1.77, 1.72, each s	1.78, 1.72, 1.61, each s	1.71, 1.59, 1.56, each s

* The allocations of the protons of the ABC- and GHI-moieties may be interchanged

and epicatechin (see above), and fisetinidol-4α-ol **8** under mild acidic conditions. Its permethylaryl ether triacetate **40** proved to be identical to the natural product derivative by comparison of ^{1}H NMR and CD data. The absolute configuration at C-4 of the ABC moiety is then defined by the coupling constants ($^3J_{2,3} = {}^3J_{3,4} = 9.5$ Hz) reminiscent of 2,3-*trans*-3,4-*trans* stereochemistry.

Triflavanoids **33**, **35**, **37** and **39** accordingly represent the first trimeric profisetinidins with epifisetinidol chain extender units. Together with the dimeric analogues **16** and **18** they are hitherto the only profisetinidins with a 2,3-*cis* relative configuration whose structures have been rigorously established by synthesis.

We have thus demonstrated an extended stereochemical diversity among the economically important group of profisetinidin oligomers. The compounds with epifisetinidol constituent units, *e.g.* **16** and **18** represent the 5-deoxy (A-ring) analogues of the epicatechin-(4β,6/8)-catechin or -epicatechin oligomers which are ubiquitous in the class of procyanidin condensed tannins.

Experimental

^{1}H NMR Spectra were recorded on a Bruker AM-300 spectrometer for solutions as indicated, with Me_4Si as internal standard. FAB Mass spectra were recorded on a VG 70-70E instrument with a VG 11-250J data system and an iontech saddlefield FAB gun. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates were 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. Column chromatography was performed on Sephadex LH-20 or Cellulose (Avicell®, 20–100 μm particle size) in various columns, solvent systems and flow rates (to be specified in each instance). Methylations were performed with an excess of diazomethane in MeOH–diethyl ether over a period of 48 h at −15 °C, while acetylations were conducted in acetic anhydride–pyridine at ambient temperature. Evaporations were done under reduced pressure at ambient temperature in a rotary evaporator, and freeze drying of aqueous solutions on a Virtis 12SL freeze-mobile.

Isolation of phenolic compounds

A Craig enriched fraction (20 g) (top and bottom phases of tubes 7–13) from a 20 tube countercurrent assembly [water–butan-2-ol–hexane (5:4:1, v/v), 100 ml underphase] of the methanol extract of Guamúchil bark was separated on Sephadex LH-20 in ethanol (5 × 160 cm column, flow rate 1 ml min^{-1}, 16 min fractions, first 2.0 l of eluent discarded) to give the following fractions: GA (tubes 60–90, 139 mg), GB (105–130, 74 mg), GC (137–170, 72 mg), GD (171–200, 80 mg), GE (201–258, 182 mg), GF (259–300, 167 mg), GG (301–380, 570 mg), GH (381–420, 430 mg), GI (421–520, 3.17 g), GJ (521–620, 2.13 g), GK (621–760, 2.8 g), GL (761–800, 540 mg), GM (801–1000, 2.48 g) and GN (1001–1130, 1.01 g).

Fraction GA gave epifisetinidol-4β-ol **3**[18] as a white solid (139 mg); δ_H(Table 1); CD $[\theta]_{328.8}$ −53, $[\theta]_{286.2}$ −1700, $[\theta]_{267.3}$ 75, $[\theta]_{237.3}$ −1100, $[\theta]_{229.8}$ 190, $[\theta]_{221.7}$ −770, $[\theta]_{215.8}$ −32 and $[\theta]_{209.1}$ 1600.

Fraction GB (74 mg) was methylated and subsequently separated by PLC in benzene–acetone (7:3, v/v) to give two bands, R_F 0.31 (17 mg) and 0.27 (19 mg). Acetylation of the R_F 0.31 band followed by PLC in benzene–acetone (9:1, v/v) gave tri-*O*-methyl-3,4-di-*O*-acetylfisetinidol-4β-ol **7** (15 mg, R_F 0.51).[20] Similar treatment of the R_F 0.27 band afforded the same derivative **9** of fisetinidol-4α-ol **8** (R_F 0.49, 17 mg).[20]

Fraction GC (72 mg) was methylated and purified by PLC in benzene–acetone (7:3, v/v) to give a methyl ether (R_F 0.45, 25 mg) which was acetylated and eventually purified by PLC in benzene–acetone (9:1, v/v) to afford tetra-*O*-methyl-3-*O*-acetylrobinetinidol **11**[21] as a white solid, CD $[\theta]_{328}$ 15, $[\theta]_{298}$ −320, $[\theta]_{283.3}$ −9600, $[\theta]_{264.3}$ −101, $[\theta]_{256.7}$ 11, $[\theta]_{242.8}$ 5900, $[\theta]_{235}$ 1500, $[\theta]_{229}$ 3500, $[\theta]_{224.4}$ −170, $[\theta]_{221.5}$ −3100, $[\theta]_{216.5}$ 1500, $[\theta]_{212.3}$ −1600 and $[\theta]_{206.5}$ 3500.

Fraction GD (80 mg) was subjected to the same derivatizations and purifications as above to eventually give tri-*O*-

methyl-3,4-di-*O*-acetylepifisetinidol-4α-ol **5**[20] (R_F 0.31, 20 mg); δ_H(Table 1); CD $[\theta]_{320}$ −250, $[\theta]_{295.2}$ −430, $[\theta]_{282.2}$ −6700, $[\theta]_{252.2}$ −570, $[\theta]_{240.3}$ −14 000, $[\theta]_{228.5}$ 2500, $[\theta]_{222.4}$ −290, $[\theta]_{215.2}$ 1400 and $[\theta]_{208.5}$ 6400.

Methylation of fraction GG (570 mg) and PLC in benzene–acetone (8:2, v/v) gave a main band at R_F 0.26 (105 mg) which was further resolved by PLC in benzene–acetone (17:3, v/v, ×4) into two bands at R_F 0.42 (45 mg) and 0.35 (42.5 mg). The R_F 0.42 band was acetylated and purified by PLC in benzene–acetone (19:1, v/v, ×3) to give *epifisetinidol-(4β,8)-catechin hepta-O-methyl ether diacetate* **17** as a white amorphous solid (R_F 0.24, 28 mg) (Found: M^+, 744.2780. $C_{41}H_{44}O_{13}$ requires *M*, 744.2781); δ_H(Table 3); CD $[\theta]_{291.5}$ −1200, $[\theta]_{285.4}$ 390, $[\theta]_{275.1}$ −5400, $[\theta]_{241.9}$ 52 000, $[\theta]_{214.7}$ −1300 and $[\theta]_{208.6}$ 8700. Acetylation of the R_F 0.35 band followed by PLC purification in benzene–acetone (9:1, v/v) gave *epifisetinidol-(4β,8)-epicatechin hepta-O-methyl ether diacetate* **19** as a white amorphous solid (R_F 0.27, 35 mg) (Found: M^+, 744.2779. $C_{41}H_{44}O_{13}$ requires *M*, 744.2781); δ_H(Table 3); CD $[\theta]_{291}$ −2100, $[\theta]_{275.2}$ −6400, $[\theta]_{243.6}$ 45 000, $[\theta]_{230}$ −1700, $[\theta]_{219}$ 50 000 and $[\theta]_{201}$ −4700.

Fraction GH (430 mg) was methylated and the mixture was resolved by PLC in benzene–acetone (8:2, v/v) to give a main band at R_F 0.34 (126 mg). Acetylation of this fraction followed by PLC in benzene–acetone (9:1, v/v) afforded two main bands at R_F 0.28 (28 mg) and 0.24 (23 mg). The former band afforded fisetinidol-(4α,8)-catechin hepta-*O*-methyl ether diacetate **13**[1] and the latter one, fisetinidol-(4α,8)-epicatechin hepta-*O*-methyl ether diacetate **15**.[1]

A portion (200 mg) of fraction GI was methylated and the mixture was separated by PLC in benzene–acetone (7:3, v/v) to give two main bands at R_F 0.35 (51 mg) and 0.11 (23 mg). Acetylation of the former band followed by PLC in benzene–acetone (17:3, v/v) afforded *bis(epifisetinidol)-(4β,6:4β,8)-catechin deca-O-methyl ether triacetate* **34** as a white amorphous solid (R_F 0.42, 34 mg) (Found: M^+ 1099.3960. $C_{61}H_{63}O_{19}$ requires *M*, 1099.3963; δ_H(Table 4); CD $[\theta]_{300}$ −420, $[\theta]_{290}$ −7400, $[\theta]_{281.1}$ 420, $[\theta]_{259.1}$ 7800, $[\theta]_{245.8}$ 100 000, $[\theta]_{236.4}$ −2900, $[\theta]_{230.4}$ 11 000, $[\theta]_{225.4}$ 4100, $[\theta]_{220.4}$ 8800, $[\theta]_{214.8}$ 2.6 and $[\theta]_{208.7}$ 15 000. The R_F 0.11 band was acetylated and purified by PLC in benzene–acetone (7:3, v/v) to give *bis(epifisetinidol)-(4β,6:4β,8)-epicatechin deca-O-methyl ether triacetate* **36** as a white amorphous solid (R_F 0.26, 17 mg) (Found: M^+, 1099.3959. $C_{61}H_{63}O_{19}$ requires *M*, 1099.3963); δ_H(Table 4); CD $[\theta]_{300}$ −610, $[\theta]_{290}$ −7100, $[\theta]_{280.2}$ 130, $[\theta]_{274.2}$ 5800, $[\theta]_{259.2}$ 8500, $[\theta]_{245.7}$ 110 000, $[\theta]_{233.7}$ −2100, $[\theta]_{220}$ 7500, $[\theta]_{222.5}$ −5100 and $[\theta]_{209.5}$ 16 000.

A portion (200 mg) of fraction GJ was methylated and the mixture was resolved by PLC in benzene–acetone (7:3, v/v) to give a main band at R_F 0.29 (80 mg). This was acetylated and purified by PLC in benzene–acetone (17:3, v/v, ×2) to give *epifisetinidol-(4β,6)-epicatechin-(8,4α)-fisetinidol deca-O-methyl ether triacetate* **40** as a white amorphous solid (R_F 0.33, 20 mg) (Found: M^+, 1099.3962. $C_{61}H_{63}O_{19}$ requires *M*, 1099.3963); δ_H(Table 4); CD $[\theta]_{300}$ −440, $[\theta]_{287.5}$ −6900, $[\theta]_{281.6}$ −230, $[\theta]_{272.6}$ 7600, $[\theta]_{257.6}$ 3300, $[\theta]_{243.9}$ 4100, $[\theta]_{228.9}$ −37, $[\theta]_{222.9}$ 180, $[\theta]_{212.9}$ 6300 and $[\theta]_{206.9}$ −5900.

Methylation of a portion (200 mg) of fraction GK followed by PLC in benzene–acetone–methanol (6:3:1, v/v) afforded a main band at R_F 0.26 (80 mg). Acetylation and subsequent purification by PLC in benzene–acetone (17:3, v/v, ×2) gave *epifisetinidol-(4β,6)-catechin-(8,4α)-fisetinidol deca-O-methyl ether triacetate* **38** as a white amorphous solid (R_F 0.38, 35 mg) (Found: M^+, 1099.3961. $C_{61}H_{63}O_{19}$ requires *M*, 1099.3963); δ_H(Table 4); CD $[\theta]_{300}$ −98, $[\theta]_{288}$ −8700, $[\theta]_{281.6}$ −210, $[\theta]_{272.2}$ 9200, $[\theta]_{259.2}$ 5300, $[\theta]_{244.4}$ 49 000, $[\theta]_{235.4}$ 3300, $[\theta]_{231.5}$ 6600, $[\theta]_{227.9}$ −250, $[\theta]_{224.9}$ −5000, $[\theta]_{215.9}$ 3600 and $[\theta]_{207.9}$ −8700.

C-2 Epimerization of *ent*-fisetinidol-4β-ol[22]

A solution of *ent*-fisetinidol-4β-ol (enantiomer of compound **8**) (10 g) in water (800 ml) was heated for 2 h in a pressure reaction vessel at a steam pressure of 200 kPa. The vessel was rapidly cooled in a waterbath and the reaction mixture was freeze-dried and separated on Sephadex LH-20 in ethanol–water (1:4, v/v) (5 × 140 cm column, flow rate 1 ml min^{-1}, 16 min fractions, first 1 l of eluent discarded) to give the following fractions: A (tubes 141–164, 1.1 g), B (165–178, 1.23 g), C (178–189, 500 mg), D (190–210, 1.04 g), E (211–245, 2.31 g), F (246–290, 1.80 g) and G (291–326, 1.02 g). Fraction B, comprising a mixture of *ent*-fisetinidol-4α-ol (enantiomer of **6**), epifisetinidol-4β-ol **3** and epifisetinidol-4α-ol **4** (10:25:12 by ^1H NMR analysis), was further resolved by flash column chromatography on cellulose in water to give the following fractions: B-1 (tubes 8–17, 523 mg), B-2 (19–21, 209 mg) and B-3 (24–26, 251 mg). Fractions A (see above) and B-2 afforded epifisetinidol-4β-ol 3;‡ δ_H(Table 1); δ_C(Table 2); CD $[\theta]_{336.9}$ −3.8, $[\theta]_{298.7}$ −54, $[\theta]_{286}$ −1300, $[\theta]_{278.7}$ −2.3, $[\theta]_{266.7}$ 32, $[\theta]_{254.7}$ −30, $[\theta]_{247.6}$ −9.3, $[\theta]_{237.4}$ −660, $[\theta]_{230.4}$ 58, $[\theta]_{222.9}$ 230, $[\theta]_{216.5}$ −130, $[\theta]_{212.5}$ 38, $[\theta]_{208.5}$ −280 and $[\theta]_{205.7}$ −1.8. Fraction F gave the starting material *ent*-fisetinidol-4β-ol; δ_H(Table 1); δ_C(Table 2); CD $[\theta]_{330}$ 56, $[\theta]_{229.6}$ 160, $[\theta]_{290.6}$ 1100, $[\theta]_{277.6}$ −200, $[\theta]_{254.6}$ 170, $[\theta]_{241.5}$ 8600, $[\theta]_{233.3}$ −250, $[\theta]_{228.1}$ 930 and $[\theta]_{203.9}$ −100. Fractions B-1 and C afforded *ent*-fisetinidol-4α-ol (enantiomer of **6**); δ_H(Table 1); δ_C(Table 2); CD $[\theta]_{330}$ 10, $[\theta]_{301.2}$ −30, $[\theta]_{290.7}$ 1500, $[\theta]_{283.4}$ −140, $[\theta]_{279.4}$ −180, $[\theta]_{269.3}$ −1800, $[\theta]_{251.6}$ −270, $[\theta]_{242.2}$ −1400, $[\theta]_{236.9}$ −35, $[\theta]_{234.9}$ 170, $[\theta]_{230.9}$ 11, $[\theta]_{220.2}$ 512, $[\theta]_{213.7}$ −170, $[\theta]_{208.1}$ 390 and $[\theta]_{202.6}$ −370. Fraction B-3 gave epifisetinidol-4α-ol **4**; δ_H(Table 1); δ_C(Table 2); CD $[\theta]_{330}$ −120, $[\theta]_{310}$ 220, $[\theta]_{296}$ 260, $[\theta]_{292.9}$ −4.1, $[\theta]_{285.9}$ −1600, $[\theta]_{278.9}$ −1900, $[\theta]_{253.3}$ −170, $[\theta]_{240.1}$ −6000, $[\theta]_{233}$ −18, $[\theta]_{231.1}$ 380, $[\theta]_{226.3}$ −340, $[\theta]_{213.7}$ 1100 and $[\theta]_{204.7}$ −370.

Synthesis of *ent*-fisetinidol-(4β,8)- and -(4α,8)-catechin tetra-*O*-methyl ether 20 and 21

Tetra-*O*-methylcatechin (14 g) and *ent*-fisetinidol-4β-ol (enantiomer of **8**, 5.8 g) were dissolved in 75% aq. methanol (700 ml), the pH was adjusted to 3 with 1 M HCl and the mixture was stirred at 60 °C for 48 h. Water (500 ml) was added, the mixture was neutralized with 2% aqueous $NaHCO_3$ and the methanol was evaporated. The aqueous solution was freeze-dried and the mixture was resolved on Sephadex LH-20 in ethanol–hexane (3:1, v/v) (4 × 130 cm column, flow rate 1 ml min^{-1}, 16 min fractions for tubes 1–120 and then 32 min fractions, first 1 l of eluent discarded) to give three fractions: A (tubes 1–80, 8.3 g), B (170–259, 5.1 g) and C (260–350, 5.8 g). Fraction A consisted of tetra-*O*-methylcatechin. Fractions B and C gave the title compounds **20** and **21** respectively by comparison of the physical data of the permethylaryl ether diacetates with those of authentic specimens.[1]

Base-catalysed C-2 epimerization of *ent*-fisetinidol(4β,8)-catechin tetra-*O*-methyl ether 20

The profisetinidin **20** (1 g) was dissolved in 'argon degassed' water (80 ml) and the pH was adjusted to *ca.* 12 with 1 M NaOH under an argon atmosphere. This mixture was heated at 90 °C for 25 h in a 'capped' reaction vial, cooled and the pH was adjusted to *ca.* 3 with 1 M HCl. Extraction with ethyl acetate (3 × 200 ml), drying (Na_2SO_4) and evaporation of the solvent followed by chromatography on Sephadex LH-20 in ethanol–hexane (7:3, v/v) (3 × 100 cm column, 1 ml min^{-1} flow rate, 16 min fractions) afforded two fractions: A (tubes 1–32, 17 mg) and B (tubes 33–80, 900 mg). Fraction B gave the starting material. Methylation of fraction A followed by PLC in benzene–acetone (7:3, v/v) gave a main band at R_F 0.3 (2 mg). This was acetylated and purified by PLC in benzene–acetone (9:1, v/v) to give epifisetinidol-(4β,8)-catechin hepta-*O*-methyl ether diacetate **17** with ^1H NMR and CD data identical to those of the same derivative of the natural product **16**.

‡ ^1H, ^{13}C and CD data for flavan-3,4-diol 3 and the remaining flavan-3,4-diols are presented for the first time.

Base-catalysed *C*-2 epimerization of *ent*-fisetinidol-(4β,8)-catechin tetra-*O*-methyl ether 20 in the presence of toluene-α-thiol

Profisetinidin **20** (1 g) and toluene-α-thiol (790 mg) were dissolved in 'argon degassed' water (80 ml), the pH of the solution was adjusted to *ca.* 12 with 1 M NaOH under an argon atmosphere and the mixture was heated at 90 °C for 25 h in a 'capped' reaction vial. The mixture was cooled to room temperature and the resulting precipitate was filtered off and thoroughly washed with hexanes to remove the excess of toluene-α-thiol. Separation on Sephadex LH-20 in ethanol–hexane (7:3, v/v) (3 × 120 cm column, flow rate of 1 ml min^{-1}, 16 min fractions) afforded six fractions: A (tubes 26–36, 11 mg), B (46–56, 10.5 mg), C (58–68, 33 mg), D (72–82, 45 mg), E (86–94, 109 mg) and F (95–123, 560 mg). Fraction D was methylated and purified by PLC in benzene–acetone (7:3, v/v) to give a band at R_F 0.46 (40 mg) which was acetylated and finally purified by PLC in benzene–acetone (9:1, v/v) to give epifisetinidol-(4β,8)-catechin hepta-*O*-methyl ether diacetate **17** (R_F 0.30, 40 mg) with ^{1}H NMR and CD data identical to the same derivative of the natural profisetinidin **16**. Fraction C was similarly methylated and separated by PLC in benzene–acetone (4:1, v/v) to give a main band at R_F 0.23 (12 mg). This was acetylated and purified by PLC in benzene–acetone (9:1, v/v) to give (2R,3S)-2-*acetoxy*-1-*benzylthio*-3-(2,4-*dimethoxyphenyl*)-3-[(2R,3S)-3-*acetoxy*-3',4',5,7-*tetramethoxyflavan*-8-*yl*]-*propane* **23** as a white amorphous solid (R_F 0.30, 8 mg) (Found: M^+, 909.3150. $C_{50}H_{53}O_{14}S$ requires *M*, 909.3156); δ_H(Table 3).

Synthesis of di- and tri-meric profisetinidins

Catechin (3 g) and epifisetinidol-4β-ol (500 mg) were dissolved in 0.1 M HCl (200 ml) and the mixture was stirred for 12 h at room temperature under a nitrogen atmosphere. The mixture was extracted with ethyl acetate (4 × 200 ml), the combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The light-brown residue (3.3 g) was subjected to column chromatography on Sephadex LH-20 in ethanol (3 × 100 cm column, flow rate 1 ml min^{-1}, 16 min fractions, first 800 ml of eluent discarded) to give four fractions: A (tubes 112–154, 2.4 g), B (205–270, 545 mg), C (332–370, 184 mg) and D (388–420, 28 mg). Fraction A comprised of catechin, fraction B of epifisetinidol-(4β,8)-catechin **16**, fraction C of epifisetinidol-(4β,6)-catechin **29** and fraction D of bis(epifisetinidol)-(4β,6:4β,8)-catechin **33**. A portion (50 mg) of fraction C was subjected to consecutive methylation and acetylation. Purification by PLC in toluene–ethyl acetate–acetone (7:2:1, v/v, ×2) of the methyl ether acetate fraction afforded epifisetinidol-(4β,6)-catechin hepta-*O*-methyl ether diacetate **30** as a white amorphous solid (R_F 0.38, 40 mg) (Found: M^+, 744.2780. $C_{41}H_{44}O_{13}$ requires *M*, 744.2781); δ_H(Table 3); CD $[\theta]_{288}$ 6348, $[\theta]_{243.1}$ 85 080, $[\theta]_{234}$ 10 890, $[\theta]_{230.5}$ 12 890, $[\theta]_{215}$ −7279 and $[\theta]_{200}$ 5207.

Similar treatment of epicatechin (3 g) and epifisetinidol-4β-ol **3** (500 mg) afforded five fractions: A (tubes 50–90, 2.2 g), B (134–190, 620 mg), C (230–272, 106 mg), D (273–285, 95 mg) and E (286–305, 15 mg). Fraction A gave epicatechin, fraction B epifisetinidol-(4β,8)-epicatechin **18**, fraction C epifisetinidol-(4β,6)-epicatechin **31**, fraction E bis(epifisetinidol)-(4β,6:4β,8)-epicatechin **35** and fraction D a mixture of the (4β,6)-biflavanoid and triflavanoid **35**. A portion of fraction C (50 mg) was methylated and the resultant crude product acetylated and separated by PLC in toluene–ethyl acetate–acetone (7:2:1, v/v, ×2) to give bis(epifisetinidol)-(4β,6:4β,8)-catechin hepta-*O*-methyl ether diacetate **33** as a white amorphous solid (R_F 0.29, 36 mg) (Found: M^+, 744.2779. $C_{41}H_{44}O_{13}$ requires *M*, 744.2781); δ_H(Table 3); CD $[\theta]_{290.1}$ −3066, $[\theta]_{243.7}$ 67 580, $[\theta]_{234.3}$ −2435, $[\theta]_{225.5}$ 13 330, $[\theta]_{218.2}$ 1532 and $[\theta]_{211.6}$ 8871.

Fisetinidol-(4α,8)-catechin **12**[1] (100 mg) and epifisetindol-4β-ol **3** (52 mg) were dissolved in 0.1 M HCl (30 ml) and the mixture was stirred for 12 h at room temperature under nitrogen. The mixture was extracted with ethyl acetate (4 × 50 ml), the combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residual material (145 mg) was methylated and separated by PLC in benzene–acetone (8:2, v/v) to give two main bands at R_F 0.34 (41 mg) and 0.28 (92 mg). The former band gave biflavanoid **12**. Acetylation of the R_F 0.28 band and PLC in benzene–acetone (8:2, v/v) afforded the epifisetinidol-(4β,6)-catechin-(8,4α)-fisetinidol derivative **38** with ^{1}H NMR and CD data identical to those of the same derivative of the natural profisetinidin **37**.

When the epifisetinidol-(4β,6)-epicatechin biflavanoid **31** (100 mg) and fisetinidol-4α-ol (52 mg) were treated as above, the unchanged biflavanoid (42 mg) and epifisetinidol-(4β,6)-epicatechin-(8,4α)-fisetinidol **39** was obtained. The latter was methylated and purified by PLC in benzene–acetone (7:3, v/v) to give a band at R_F 0.28 (80 mg) which was acetylated and purified by PLC in benzene–acetone (8:2, v/v) to give the trimeric profisetinidin derivative **40** (R_F 0.35, 73 mg) with identical ^{1}H NMR and CD to the same derivative of the natural product **39**.

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