

Oligomeric Flavanoids. Part 24^a. Controlled Biomimetic Synthesis of Profisetinidin Triflavanoid Related Phlobatannins

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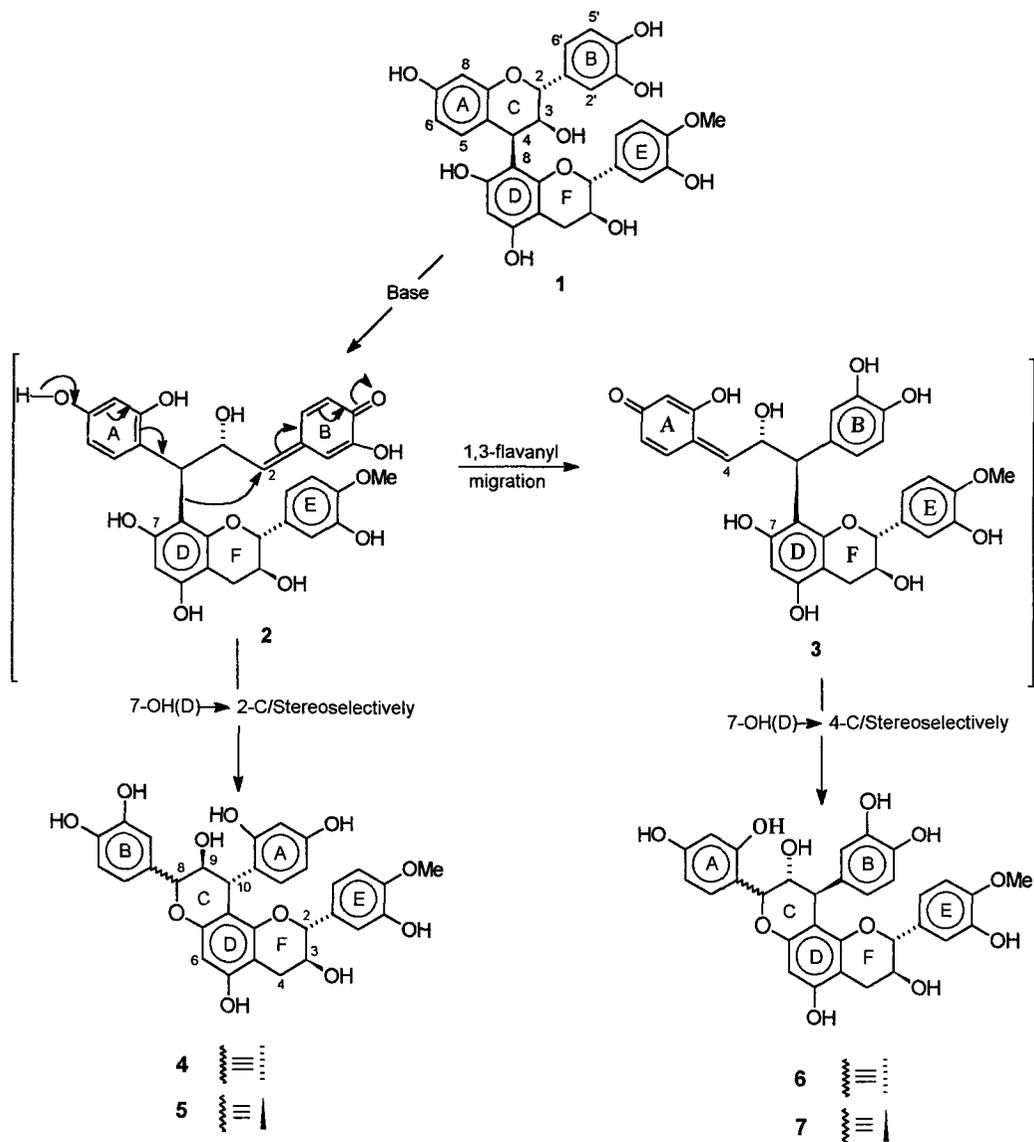
Abstract. The complex structures of the economically important group of profisetinidin triflavanoid related phlobatannins are synthetically accessible in a controlled biomimetic fashion *via* the repetitive formation of the interflavanyl bond and pyran ring rearrangement of the chain extender unit under mild alkaline conditions. Copyright © 1996 Elsevier Science Ltd

We have recently demonstrated the natural occurrence of a comprehensive series of phlobaphene condensed tannins, representing the products of stereoselective C-ring isomerization of the 2,3-*trans*-3,4-*trans*- and 3,4-*cis* flavan-3-ol moieties of the four bis-fisetinidol-(4,6:4,8)-catechin profisetinidin triflavanoids^{1,2}. The complex structures of this economically important group^{3,4} of oligoflavanoids were elucidated by using ¹H NMR spectroscopic data and a biomimetic-type synthesis involving the base-catalyzed rearrangement of the pyran rings of the 'conventional' bis-fisetinidol-catechin triflavanoids^{1,2}. This approach, however, is hampered by the unrestrained course of reaction which led to the formation of sixteen compounds with rearranged heterocyclic rings when the bis-fisetinidol-(4 β ,6:4 β ,8)-catechin was subjected to base treatment (ref. 2, Part 21). Herein, we discuss a more concise synthetic access to 'trimeric' phlobatannins which should contribute significantly towards the structure elucidation of the naturally occurring analogues.

RESULTS AND DISCUSSION

The rampant course of reaction of bis-fisetinidol-catechin triflavanoids with 2,3-*trans*-3,4-*cis* constituent flavanyl units under alkaline conditions is attributable to the susceptibility of these units to 1,3-aryl migrations in an intermediate B-ring quinone methide. The mechanism of such migrations, leading to the formation of phlobatannins with 'interchanged' resorcinol A- and pyrocatechol B-rings and with inverted absolute configuration at the equivalent of C-3 (C-ring), has been fully elaborated for dimeric profisetinidins^{5,6} and appropriate 4-arylflavan-3-ol model compounds⁷, and is summarized in Scheme 1 for the fisetinidol-(4 β ,8)-catechin mono-*O*-methyl ether 1. Our initial approach towards the synthesis of the naturally occurring 'trimeric' phlobatannins that was based on the simultaneous rearrangement of the heterocycles of the ABC- and GHI-flavan-3-ol moieties of a triflavanoid, *e.g.* 8, was hence changed to a protocol involving the stepwise

^aPart 23. S.L. Bonnet, J.P. Steynberg, B.C.B. Bezuidenhout, C.M. Saunders and D. Ferreira, *Phytochemistry*, 1995, in the press.



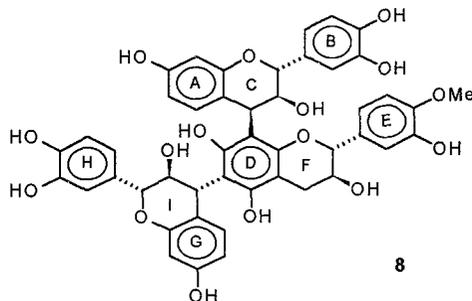
Scheme 1. Base-catalyzed pyran ring rearrangement of the fisetinidol-(4 β ,8)-catechin mono-O-methyl ether 1.

construction of the target molecule *via* the repetitive formation of the interflavanyl bond and rearrangement of the heterocycle of the chain extender unit. The utility of such a method is now demonstrated by the synthesis of a selection of the hexahydrodipyran[2,3-*f*:2',3'-*h*]chromene^a that would result from the base-catalyzed C-

^a Non-systematic name/numbering [*cf.* structure 14] to retain the heterocyclic oxygen of the catechin DEF-unit as position 1 for all compounds.

ring isomerization of the bis-fisetinidol-(4 α ,6:4 β ,8)-catechin mono-*O*-methyl ether **8**, a reaction which has indeed led to the formation of no less than eleven compounds with rearranged pyran rings (see ref. 2, Part 22).

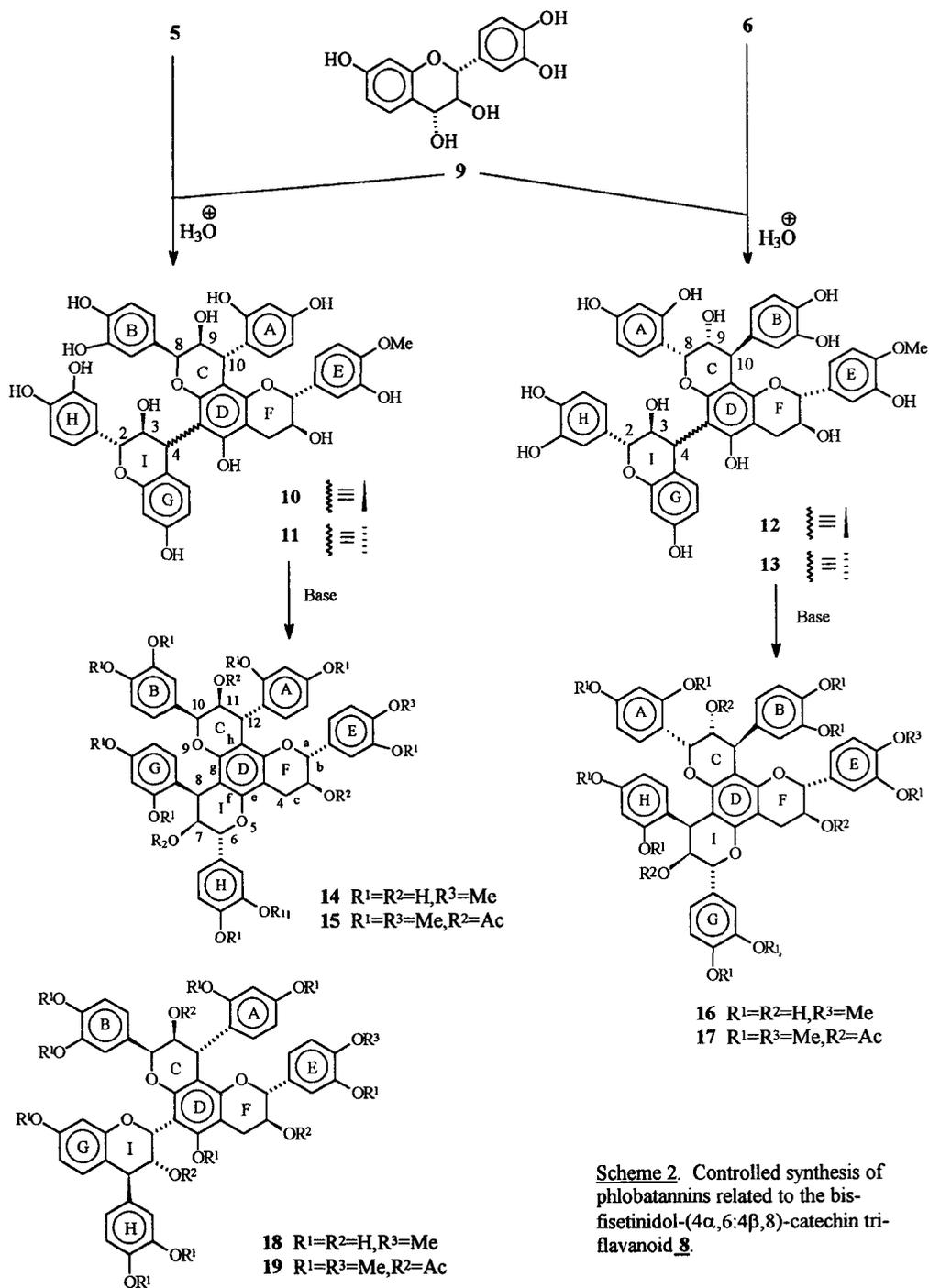
The fisetinidol-(4 β ,8)-catechin mono-*O*-methyl ether **1**, representing the ABC-DEF structural moiety in profisetinidin triflavanoid **8**, was available *via* the acid-catalyzed⁸ condensation of fisetinidol-4 α -ol [(+)-mollisacacidin] and 4'-*O*-methylcatechin⁹ and was utilized in this protected form to avoid unwanted reactions associated with the possible formation of an E-ring quinone methide^{9,10} under basic conditions. Treatment of biflavanoid **1** with 0.025M NaHCO₃-0.025M Na₂CO₃ buffer solution¹¹ (pH 10) for 3h at 50°C under nitrogen as before⁵ afforded a mixture comprising the four ring-isomerized products **4-7**. (Scheme 1). These compounds presumably originated *via* the putative quinone methides **2** and **3**. Refinement of the



chromatographic techniques using Sephadex LH-20⁵ in ethanol or ethanol/water permitted the complete resolution of this mixture to give besides the tetrahydropyrano[2,3-*h*]chromenes **4**, **5** and **6** (see ref. 5), also the all-*trans* analogue **7** ($J_{8,9}$ 9.5, $J_{9,10}$ 7.5 Hz) with 'interchanged' resorcinol A- and pyrocatechol B-rings and inversed C-9 absolute configuration in essentially pure form. The 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromenes **5** and **6** with 'normal' and 'abnormal' C-rings respectively, were then selected to develop the controlled synthetic approach further.

Thus, separate acid-catalyzed condensation of the tetrahydropyrano[2,3-*h*]chromenes **5** and **6** with fisetinidol-4 α -ol **9** afforded the anticipated fisetinidol-(4 α ,6)- and (4 β ,6)-tetrahydropyrano[2,3-*h*]chromenes **10**, **11** and **12**, **13** respectively (Scheme 2). It should be emphasized that the latter four compounds are often target molecules in their own right since they are common in the natural sources containing this class of condensed tannins (see refs. 1 and 2), their isolation being permitted in essentially free phenolic form by the vastly simplified reaction mixtures offered by this more controlled synthetic procedure.

¹H NMR details for compounds **10-13** are collated in the Table representing the first detailed analysis of phenolic 5-deoxy (A-ring) oligoflavanoids at the 'trimeric' level. Assignment of signals is based upon coupling over four bonds between relevant protons of the heterocyclic- and aromatic rings that was evident from a COSY experiment. The spectra of the fisetinidol-(4 β ,6)-tetrahydropyrano[2,3-*h*]chromenes **10** and **12** are conspicuously free of the effects of dynamic rotational isomerism about the (4,6)-interflavanyl bond. The relative configurations of the C- and I-heterocyclic rings were evident from coupling constants [$J_{8,9}$ 1.0, $J_{9,10}$ 2.5; $J_{2,3(0)}$ 2.5, $J_{3,4(0)}$ 3.5 Hz for **10** and $J_{8,9}$ 1.0, $J_{9,10}$ 2.0; $J_{2,3(0)}$ 2.0, $J_{3,4(0)}$ 2.5 Hz for **12**] which are in agreement with an 8,9-*cis*-9,10-*trans*-tetrahydropyranochromene⁵ and a 2,3-*trans*-3,4-*cis* free phenolic fisetinidol-catechin biflavanoid moiety¹² respectively. The unusual small coupling constants of the 2,3-*trans*-3,4-*cis* fisetinidol-type GHI-moiety are attributable to significant contributions of A-forms towards the conformational equilibrium of this heterocycle^{13,14}. Duplication of signals due to rotational restrictions about the (4 α ,6)-interflavanyl bonds in compounds **11** and **13** complicated proton assignments in their ¹H NMR spectra. Couplings over three and four bonds that were evident from COSY spectra nevertheless permitted allocation of the majority of resonances for both the rotamers of each of the compounds (see Table). The magnitude of the



coupling constants [$J_{2,3(0)}$ 10.0, 9.0; $J_{3,4(0)}$ 10.0, 9.0 Hz for **11** and **13** respectively] of the I-ring protons confirmed the 3,4-*trans* configuration for each of compounds **11** and **13**. A conspicuous feature of the spectrum of the (4 α ,6)-isomer **13** is the shielding of 6-H(A) (δ 5.92) in the main rotamer compared to the 'normal' chemical shift⁵ (δ 7.24) of this proton in the minor rotamer. Such shielding results from a hitherto undefined anisotropic effect operating in the more crowded conformer that is predominantly populated¹⁵ in the main rotamer.

Table. ¹H NMR peaks (p.p.m.) of the tetrahydropyrano[2,3-*h*]chromene **7** and of the fisetinidol-(4,6)-tetrahydropyrano[2,3-*h*]chromenes **10** - **13** in (CD₃)₂CO at 300 MHz (23°C). Splitting patterns and J-values are given in parentheses.

Ring	H	7	10	11*	12	13*
A	3	6.35(d,2.5)	6.42(d,2.5)	6.40,6.42(d,2.5)	6.21(d,2.0)	6.19,6.25(d,2.0)
	5	6.33(dd,2.5,8.0)	6.31(dd,2.5,8.0)	6.32,6.26(dd,2.5,8.5)	6.20(dd,2.0,8.0)	6.08,6.26-6.31 (dd,2.0,8.5)
	6	7.12(d,8.0)	6.63(d,8.0)	6.54,6.62(d,8.5)	6.65(d,8.0)	5.92,7.24(d,8.5)
B	2	6.49(d,2.0)	6.38(d,2.0)	6.69,6.93(d,2.0)	6.58(d,2.0)	6.58,6.68(d,2.0)
	5	6.48(d,8.0)	6.76(d,8.5)	6.79,6.73(d,8.5)	6.63(d,8.0)	6.58,6.70(d,8.0)
	6	6.32(dd,2.0,8.0)	6.19(dd,2.0,8.5)	6.54,6.67(dd,2.0,8.5)	6.42(dd,2.0,8.0)	6.42,6.49(dd,2.0,8.0)
C	8	4.92(d,9.5)	4.69(br.s,ca. 1.0)	4.48,4.89(br.s,ca. 1.0)	4.92(br.s,ca. 1.0)	5.12,5.20(br.s,ca. 1.0)
	9	3.95(dd,7.5,9.5)	3.98(dd,1.0,2.5)	4.02,4.08(dd,1.0,2.5)	4.22(dd,1.0,2.0)	4.16,4.06(dd,1.0,2.5)
	10	3.84(d,7.5)	4.52(d,2.5)	4.56,4.63(d,2.5)	4.26(d,2.0)	4.22,4.33(d,2.5)
D	6	6.08(s)	-	-	-	-
E	2	6.74(d,2.0)	6.62(d,2.0)	-	6.82(d,2.0)	7.00,-(d,2.5)
	5	6.80(d,8.0)	6.63(d,8.5)	6.62,-(d,8.5)	6.78(d,8.0)	6.85,-(d,6.0)
	6	6.52(dd,2.0,8.0)	6.26(dd,2.0,8.5)	6.28,-(dd,2.0,8.5)	6.67(dd,2.0,8.00)	6.82,-(dd,2.5,6.0)
F	2	4.08(d,8.0)	4.63(d,7.5)	4.67,4.63(d,7.0)	4.43(d,8.0)	4.45,4.52(d,8.0)
	3	3.95(m)	3.75(m)	3.75,3.75(m)	3.95(m)	3.98,3.98(m)
	4 _{eq}	2.93(dd,6.0,16.0)	2.72(dd,5.0,16.0)	2.85,2.78(dd,5.0,16.0)	2.85(dd,5.5,16.5)	3.02,2.81(dd,5.5,16.0)
	4 _{ax}	2.48(dd,8.5,16.0)	2.56(dd,8.0,16.0)	2.62,2.56(dd,8.0,16.0)	2.54(dd,8.0,16.5)	2.68,2.55(dd,8.0,16.0)
G	5		6.56(d,8.0)	6.67,6.92(d,8.5)	6.58(d,8.0)	6.74,6.68(d,8.5)
	6		6.25(dd,2.5,8.0)	6.24,6.33(dd,2.5,8.5)	6.26(dd,2.5,8.0)	6.26-6.31,6.34(dd,2.0,8.5)
	8		6.43(d,2.0)	6.13,6.28(d,2.5)	6.42(d,2.5)	-6.32(d,2.0)
H	2		6.84(d,2.5)	7.02,-(d,2.0)	6.75(d,2.0)	-
	5		6.72(d,8.0)	6.82,-(d,8.0)	6.41(d,8.5)	-
	6		6.66(dd,2.5,8.0)	6.88,-(dd,2.0,8.0)	6.52(dd,2.0,8.5)	-
I	2		5.39(d,2.5)	4.68,4.59-4.66(d,10.0)	5.31(d,2.0)	4.63,4.61(d,9.0)
	3		4.64(dd,2.5,3.5)	4.89,-(t,10.0)	4.46(dd,2.0,2.5)	4.54,4.58(t,9.0)
	4		4.90(d,3.5)	4.73,4.95(d,10.0)	5.01(d,2.5)	4.75,4.68(d,9.0)
	OMe	3.80(s)	3.74(s)	3.75,3.74(s)	3.77(s)	3.77,3.75(s)

*The second chemical shift is that of the minor rotamer

The final step of the controlled synthetic protocol involves the ring-isomerization of the fisetinidol-(4,6)-tetrahydropyrano[2,3-*h*]chromenes in Scheme 2 and is demonstrated using compounds **11** and **13**. Treatment of substrate **11** with the buffer solution at pH 10 (*vide supra*) afforded the functionalized hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene **14** and the 4-arylbenzopyranyl-(2 α ,6)-tetrahydropyrano[2,3-*h*]chromene **18**. Under the same conditions the substrate **13** was susceptible to highly stereoselective pyran rearrangement to give the hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene **16** as the predominant product. These compounds were identified as decamethyl ether triacetates **15**, **17** and **19** in order to facilitate comparison with authentic samples that were available from previous work (ref. 2, Part 22). Compound **14** is indeed identical

to the same derivative of a naturally occurring hexahydrodipyran[2,3-*f*:2',3'-*h*]chromene that was obtained from the heartwood extract of *Baikiaea plurijuga* (ref. 2, Part 22). The mechanism of the reaction leading to the formation of compound **18** was discussed in the same reference and need not be repeated.

Thus, in contrast to the unrestrained course of the base-catalyzed pyran ring rearrangement reactions of profisetinidin triflavanoids possessing 2,3-*trans*-3,4-*cis* flavanyl constituent units resulting in exceptionally complex reaction mixtures, the stepwise construction of the dipyranochromene framework *via* the repetitive formation of the interflavanyl bond and rearrangement of the heterocycle of the chain extender unit, now permits a more direct synthetic access to the phlobatannins at the trimeric level. This approach should contribute significantly towards simplification of the methods of structure elucidation of this economically important but complex group of naturally occurring condensed tannins.

EXPERIMENTAL

¹H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in CDCl₃ with Me₄Si as internal standard. FAB mass spectra were recorded on a VG 70-70E instrument with VG 11-250J data system and iontech saddlefield FAB gun. CD data was obtained in methanol on a JASCO J-710 spectropolarimeter. TLC was performed on pre-coated Merck plastic sheets (silica gel 60 PF₂₅₄, 0.25 mm) and the plates were sprayed with H₂SO₄-HCHO (40:1 v/v) after development. Preparative plates (PLC), 20x20 cm, Kieselgel PF₂₅₄ (1.0 mm) were air-dried and used without prior activation. Compounds were recovered from the absorbent with acetone. Separations on Sephadex LH-20 were on various column sizes and at differing flow rates in ethanol or ethanol/water mixtures. Methylations were performed with an excess of diazomethane in methanol-diethyl ether over a period of 48h at -15°C, while acetylations were in acetic anhydride-pyridine at ambient temperature. Phenolic material in aqueous solution was freeze-dried using a Virtis Freezemobile 12 SL. Evaporations were done under reduced pressure at ~50°C in a rotary evaporator.

Base-catalyzed Conversion of Fisetinidol-(4β,8)-catechin mono-O-methyl ether 1 – The protected biflavanoid **1** was subjected in two portions (1.57 g, 1.32 g) to a NaHCO₃-Na₂CO₃ buffer solution (pH 10) according to the procedure described in Part 4². Separation by column chromatography on Sephadex LH-20 in ethanol (81x3.5 cm and 69x4.5 cm columns, 0.57 ml/min and 0.61 ml/min flow rates, 18 and 20 ml eluants/tube, first 1.2 l of eluant discarded in each instance) afforded three main fractions: 1 [tubes 60-70 (284 mg), tubes 123-144 (403 mg)], 2 [tubes 71-79 (214 mg), tubes 145-169 (121 mg)] and 3 [tubes 95-125 (433 mg), tubes 170-214 (439 mg)]. Fraction 1 comprised of the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **6**⁵, fraction 3 of a mixture of the 8,9-*trans*-9,10-*trans*- and 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromenes **4** and **5** and fraction 2 of (2*R*,3*S*:8*S*,9*R*,10*S*)-3,9-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-8-(2,4-dihydroxyphenyl)-10-(3,4-dihydroxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene **7** as a *light brown amorphous solid* (Found: M⁺, 576.1635. C₃₁H₂₈O₁₁ requires M, 576.1632); δ_H (Table); CD [θ]₂₉₃ -1.05x10¹, [θ]_{267.6} -2.5x10³, [θ]_{242.8} -3.0x10⁴ and [θ]_{236.2} 1.9x10¹. Fraction 3 was subsequently resolved by column chromatography on Sephadex LH-20 in ethanol:water (1:1 v/v) (4.5x70 cm column, flow rate 0.63 ml/min, 20 ml eluant/tube, first 1.5 l of eluant discarded) into two fractions: 1 [tubes 190-233 (381 mg)] and 2 [tubes 242-300 (256 mg)]. Fraction 1 gave the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **5**⁵ and fraction 2 the 8,9-*trans*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **4**⁵.

Synthesis of Trimeric Phlobatannins 10-13 – The 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **5** (350 mg) and fisetinidol-4α-ol **9** (174 mg) was dissolved in 0.1M HCl (100 ml) and the mixture was left at room temperature for 12h. The mixture was extracted with EtOAc (5x100 ml), the combined extract washed with 1% NaHCO₃ solution (100 ml) and water (2x100 ml), dried (Na₂SO₄) and evaporated to dryness to give a light brown solid (462 mg). This was subjected to column chromatography on Sephadex LH-20 in ethanol (4.5x51 cm column, flow rate 0.47 ml/min, 15 ml eluant/tube, first 1.5 l of eluant discarded)

to give a fraction [tubes 175-270 (244 mg)] which was resolved on Sephadex LH-20 in ethanol-water (1:1 v/v) (3x76 cm column, flow rate 0.53 ml/min, 17 ml eluant/tube, first 1.5 l of eluant discarded) into two fractions: 1 [tubes 99-117 (184 mg)] and 2 [tubes 128-148 (25 mg)]. Fraction 1 comprised the fisetinidol-(4 α ,6)-8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **11** as a *light amorphous solid* (Found: M⁺, 848.2319. C₄₆H₄₀O₁₆ requires M, 848.2316); δ_H (Table); CD [θ]₂₈₈ -1.1x10⁴, [θ]₂₈₂ 9.2x10¹, [θ]₂₇₄ 1.2x10⁴, [θ]_{257.5} 2.8x10³, [θ]₂₄₉ 5.8x10³, [θ]_{245.5} -8.8x10², [θ]_{240.5} -2.2x10⁴ and [θ]_{234.5} 2.6x10². Fraction 2 afforded the fisetinidol-(4 β ,6)-8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **10** as a *light brown amorphous solid* (Found: M⁺, 848.2314. C₄₆H₄₀O₁₆ requires M, 848.2316); δ_H (Table); CD [θ]_{291.5} -5.9x10³, [θ]_{282.5} -1.7x10², [θ]₂₇₃ 6.9x10³, [θ]_{258.5} 2.2x10³ and [θ]₂₄₇ 1.1x10⁴.

Similar reaction of the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **6** (633 mg) and fisetinidol-4 α -ol **9** (320 mg) in 0.1M HCl (200 ml) for 12h at ambient temperature and work up afforded a light brown solid (847 mg) which was resolved by column chromatography on Sephadex LH-20 in ethanol (4.5x74 cm column, flow rate 0.71 ml/min, 22 ml of eluant/tube, first 2 l eluant discarded) to give two fractions: 1 [tubes 126-154 (150 mg)] and 2 [tubes 174-209 (250 mg)]. Fraction 1 afforded the fisetinidol-(4 β ,6)-8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **12** as a *light brown amorphous solid* (Found: M⁺, 848.2318. C₄₆H₄₀O₁₆ requires M, 848.2316); δ_H (Table); CD [θ]₂₇₇ -1.7x10⁴, [θ]₂₅₉ -5.8x10³, [θ]_{247.5} -1.7x10⁴ and [θ]₂₄₁ 2.8x10². Fraction 2 comprised of the fisetinidol-(4 α ,6)-8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene **13** as a *light brown amorphous solid* (Found: M⁺, 848.2319. C₄₆H₄₀O₁₆ requires M, 848.2316); δ_H (Table); CD [θ]₂₉₉ 4.1x10¹, [θ]_{286.5} -9.2x10³, [θ]_{271.5} 7.7x10², [θ]_{243.5} -4.0x10⁴ and [θ]₂₃₇ -1.2x10³.

Base-catalyzed Conversion of Triflavanoids 11 and 13 – The fisetinidol-(4 α ,6)-tetrahydropyrano[2,3-*h*]chromene **11** (168 mg) was stirred in 0.025M NaHCO₃-0.025M Na₂CO₃ buffer solution (100 ml) under N₂ for 5h at 50°C. Chilling to 0°C followed by acidification with 1M HCl, extraction with ethyl acetate (5x100 ml), drying (Na₂SO₄) of the extract, and evaporation to dryness afforded a light brown residue (158 mg). This was methylated and the mixture was resolved by PLC in benzene-acetone-methanol (90:6:4, x2) to give three bands at R_F 0.47 (29.3 mg), 0.48 (28 mg) and 0.44 (10 mg). Acetylation of the R_F 0.47 fraction followed by PLC in benzene-acetone-methanol (85:10:5) afforded a single band at R_F 0.35 (20 mg) which comprised of the hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene derivative **15** (ref. 2, Part 22). The R_F 0.48 band was similarly acetylated and purified by PLC in benzene-acetone-methanol (85:10:5) to give a band at R_F 0.37 (4.3 mg) comprising the 4-arylbenzopyranyl-(2 α ,6)-tetrahydropyrano[2,3-*h*]chromene derivative **19** as a white amorphous solid (ref. 2, Part 22). The R_F 0.44 band still consisted of a mixture which was not further investigated.

Similar treatment of the fisetinidol-(4 α ,6)-tetrahydropyrano[2,3-*h*]chromene **13** (201 mg) with base and work up gave a light brown residue (160 mg) which was subjected to column chromatography on Sephadex LH-20 in ethanol-water (1:1) (4.5x74 cm column, flow rate 0.39 ml/min, 13 ml eluant/tube, first 1.7 l of eluant discarded) to give three fractions: 1 (tubes 1-20 (16 mg)), 2 [tubes 105-144 (85 mg)] and 3 [tubes 145-188 (10 mg)]. Fraction 1 and 3 still consisted of mixtures and were not further investigated. Fraction 2 was methylated and subsequently purified by PLC in benzene-acetone-methanol (7:2:1) to give a band at R_F 0.58 (49 mg). This was acetylated and purified by PLC in benzene-acetone-methanol (80:10:5) to give the hexahydrodipyrano[2,3-*f*:2',3'-*h*]chromene derivative **17** (R_F 0.68, 22 mg) as a white amorphous solid (ref. 2, Part 22).

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