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STRUCTURE AND SYNTHESIS OF PHLOBATANNINS RELATED TO THE (4β,6:4α,8)-BIS-FISETINIDOL-CATECHIN PROFISETINIDIN TRIFLAVANOID*

SUSAN L. BONNET, JAN P. STEYNBERG, BAREND C. B. BEZUIDENHOUDT, CATHARINA M. SAUNDERS and DANEEL FERREIRA†

Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 South Africa

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Key Word Index—*Baikiaea plurijuga*; *Colophospermum* mopane; Leguminosae; Caesalpinioideae; heartwood profisetinidins; phlobatannins; triflavanoids; pyran rearrangement.

Abstract—Several members of the class of natural phlobatannins, representing the products of stereoselective pyran rearrangement of the 2,3-*trans*-3,4-*trans*- and 3,4-*cis*-flavan-3-ol units in the (4β,6:4α,8)-bis-fisetinidol-catechin triflavanoid have been characterized. These comprise a functionalized hexahydro-dipyrano-[2,3-*f*:2′,3′-*h*]-chromene, two fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromenes and a pair of fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromenes. The proposed structures of these novel compounds were confirmed by synthesis *via* base-catalysed conversion of the 4-*O*(*E*)-methyl ether of their presumed triflavanoid biogenetic precursor.

INTRODUCTION

The natural occurrence and biomimetic synthesis of a series of functionalized tetrahydropyranochromenes, termed phlobatannins, related to profisetinidin, proguibourtinidin and prorobinetinidin biflavanoids have recently been mentioned [1, 2]. The phenomenon of oligoflavanoids possessing rearranged pyran heterocycles has also been encountered at the triflavanoid level [2, 3] and was reported in detail for analogues based on the (4α,6:4α,8)-bis-fisetinidol-catechin profisetinidin **1** [3]. The phlobatannins exhibit structural features that are apparently essential for the utilization of condensed tannins in cold-setting adhesives and leather tanning application [2, 4]. Since the majority of the industrial uses of condensed tannins involve their dissolution and/or reactions at alkaline pH [5, 6], an understanding of the intricate chemistry involved in the pyran rearrangements of triflavanoids under mild basic conditions is a prerequisite for eventually establishing a structure–reactivity relationship for the phlobatannins. Continued investigation of the phenolics in the heartwoods of *Baikiaea plurijuga* [Rhodesian (Zimbabwean) teak] [7] and *Colophospermum mopane* (mopane) [7] have revealed extensive structural and stereochemical diversity at the 'trimeric' level of this unique class of condensed tannins. Herein, we disclose detailed results of relevance to those naturally occurring and synthetic phlobatannins related to the (4α,6:4α,8)- and (4β,6:4α,8)-bis-fisetinidol-catechin triflavanoids.

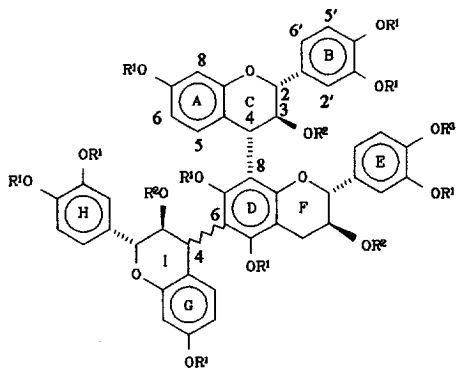
RESULTS AND DISCUSSION

It has been demonstrated that the functionalized tetrahydropyranochromenes in *B. plurijuga* are derived from the co-existing fisetinidol-catechin biflavanoids *via* the appropriate C-ring isomerizations [8]. When phlobatannins at the trimeric level were encountered it thus seemed reasonable to assume that these too were related structurally and stereochemically to the bis-fisetinidol-catechin triflavanoids with 2*R*,3*S*-absolute configuration of the constituent flavan-3-ol units. Since the chiroptical method in conjunction with ^{1}H NMR data [9] do not permit assignment of absolute configuration at this level, the base-catalysed transformation of the trimeric profisetinidin was performed and the structures of the natural products ascertained by comparison of the circular dichroic and other physical data with those of their synthetic counterparts. In order to avoid repetition, the following general protocol for structure elucidation was applied consistently and will not be repeated for the individual compounds. 1. The trimeric nature of each substance was evident from the presence of ten methoxy and three acetoxy signals in the ^{1}H NMR spectra, as well as the heterocyclic ABMX- and two AMX-systems with coupling constants reflecting the relative configurations of the different pyran rings. 2. Evidence for participation of one or both the heterocyclic rings in the pyran rearrangement was obtained *via* NOE experiments. As-

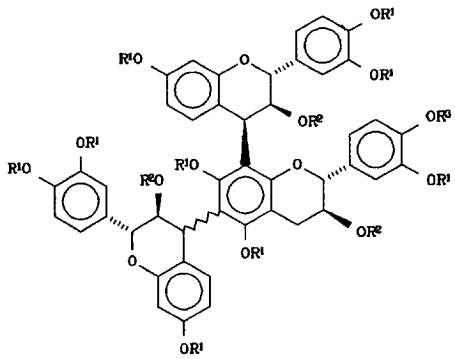
*Part 20 in the series 'Oligomeric Flavanoids'. For Part 19 see P. J. Steynberg, J. P. Steynberg, B. C. B. Bezuidenhoudt and D. Ferreira, *J. Chem. Soc., Perkin Trans.* 1, 1995, 3005.

†Author to whom correspondence should be addressed.

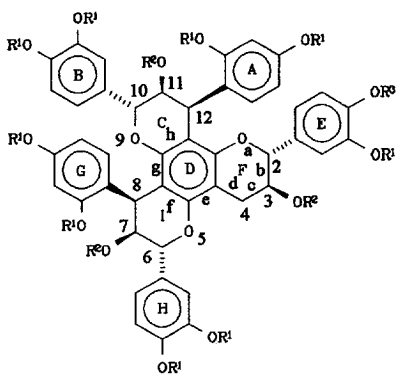
sociation of 2-OMe (A-ring)/(G) with 3-H(A)/(G) (cf. structure **15**) and of 4-OMe (A)/(G) with both 3- and 5-H(A)/(G) indicated the 'liberation' of two resorcinol moieties from the parent triflavanoid in the case of the hexahydrodipyranochromene, e.g. compound **15**, or NOE association of e.g. 2-OMe(A) with 3-H(A) and of 4-OMe(A) with both 3- and 5-H(A) and of only 7-OMe(G) with both 6- and 8-H(G) indicated the 're-



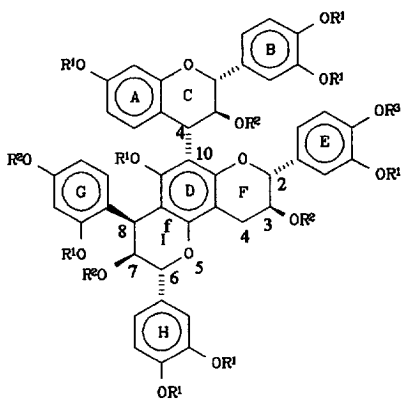
(1) ≡ ,R^1=R^2=R^3=H
(2) ≡ ,R^1=R^2=H,R^3=Me
(3) ≡ ,R^1=R^3=Me,R^2=Ac
(4) ≡ ,R^1=R^2=R^3=H
(5) ≡ ,R^1=R^2=H,R^3=Me
(6) ≡ ,R^1=R^3=Me,R^2=Ac



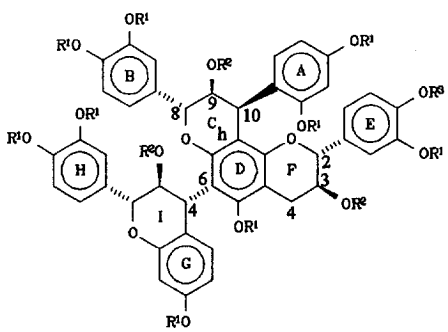
(7) ≡ ,R^1=R^2=R^3=H
(8) ≡ ,R^1=R^2=H,R^3=Me
(9) ≡ ,R^1=R^3=Me,R^2=Ac
(10) ≡ ,R^1=R^2=R^3=H
(11) ≡ ,R^1=R^2=H,R^3=Me
(12) ≡ ,R^1=R^3=Me,R^2=Ac



(13) R^1=R^2=R^3=H
(14) R^1=R^2=H,R^3=Me
(15) R^1=R^3=Me,R^2=Ac



(16) R^1=R^2=R^3=H
(17) R^1=R^2=H,R^3=Me
(18) R^1=R^3=Me,R^2=Ac



(19) R^1=R^2=R^3=H
(20) R^1=R^2=H,R^3=Me
(21) R^1=R^3=Me,R^2=Ac

Table 1. ^{1}H NMR peaks (ppm) of fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromenes **24**, **27** and **30** in $CDCl_3$ (296 K) at 300 MHz

Ring	H	**24**	**27**	**30**
A	5	6.66 (*d*, 8.5)	6.50 (*d*, 9.0)	6.82 (*d*, 8.5)
	6	6.45 (*dd*, 2.5, 8.5)	6.41 (*dd*, 2.5, 9.0)	6.49 (*dd*, 2.5, 8.5)
	8	6.38 (*d*, 2.5)	6.34 (*d*, 2.5)	6.40 (*d*, 2.5)
B	2	6.57 (*d*, 2.0)	6.57 } second order	6.49–6.54
	5	6.71 (second order)	6.70 } second order	6.68 (*d*, 8.0)
	6	6.71 (second order)	6.70 } second order	6.49–6.54
C	2	4.83 (*d*, 10.0)	4.71 (*d*, 10.0)	4.81 (*d*, 10.0)
	3	6.13 (*t*, 10.0)	6.19 (*t*, 10.0)	6.04 (*t*, 10.0)
	4	4.56 (*d*, 10.0)	4.54 (*d*, 10.0)	4.57 (*d*, 10.0)
E	2	6.54 (*d*, 2.0)	6.56 (*d*, 2.0)	6.49–6.54
	5	6.69 (*d*, 9.0)	6.67 (*d*, 8.0)	6.71 (*d*, 8.0)
	6	6.54 (*dd*, 2.0, 9.0)	6.49 (*dd*, 2.0, 8.0)	6.49–6.54
F	2	4.85 (*d*, 10.0)	4.87 (*d*, 9.0)	4.89 (*d*, 9.5)
	3	4.96 (*m*)	4.98 (*m*)	4.99 (*m*)
	4_{ax}	2.77 (*dd*, 10.0, 17.0)	2.67 (*dd*, 9.0, 17.0)	2.74 (*dd*, 9.5, 16.5)
	4_{eq}	3.28 (*dd*, 6.5, 17.0)	3.18 (*dd*, 6.0, 17.0)	3.32 (*dd*, 6.5, 16.5)
G	3	6.54 (*d*, 2.5)	6.39 (*d*, 2.5)	6.32 (*d*, 2.0)
	5	6.50 (*dd*, 2.5, 8.5)	6.34 (*dd*, 2.5, 8.5)	6.84 (*dd*, 2.0, 8.5)
	6	6.76 (*d*, 8.5)	6.74 (*d*, 8.5)	7.44 (*d*, 8.5)
H	2	6.88 } second order	6.82 (*d*, 2.0)	6.91 (*d*, 2.0)
	5	6.77 } second order	6.75 (*d*, 8.0)	6.71 (*d*, 8.0)
	6	6.77 } second order	6.88 (*dd*, 2.0, 8.0)	6.51 (*dd*, 2.0, 8.0)
I	6	5.07 (*d*, 1.5)	4.98 (*d*, 8.5)	5.41 (*br s*)
	7	5.37 (*dd*, 1.5, 2.5)	5.49 (*dd*, 8.0, 8.5)	5.31 (*dd*, 1.5, 2.5)
	8	4.68 (*d*, 2.5)	4.66 (*d*, 8.0)	4.40 (*d*, 2.5)
	OMe	3.43 (9-D), 3.55 (3-B), 3.71 (3-E), 3.74 (7-A), 3.83 (4-B), 3.84 (4-H), 3.85 (4-E), 3.88 (3-H), 3.91 (2-G), each *s*	3.50 (9-D), 3.54 (3-B), 3.72 (3-E, 7-A), 3.74 (4-G), 3.80, 3.83 (2-G, 4-E, 4-H), 3.84 (4-B, 3-H), each *s*	3.51 (2-G), 3.53, 3.54 (9-D), 3.71, 3.75 (4-A), 3.77 (4-G), 3.81 (4-H), 3.82 (4-E), 3.85 (4-B), 3.87 (3-H), each *s*
	OAc	1.58, 1.84, 1.86, each *s*	1.60, 1.78, 1.85, each *s*	1.51, 1.85, 1.94, each *s*

lease' of a single resorcinol unit with one fisetinidol unit remaining intact, e.g. compound **21** [3, 8]. 3. Spin-decoupling experiments using the benzylic protons of the C-, F- and I-rings as reference signals were used in combination with COSY experiments to identify the aromatic ring-systems and to differentiate the molecules where ring interchange had occurred [8]. Assignment of the benzylic reference protons were based on typical coupling constants and comparison with authentic analogues where HETCOR experiments were employed to allocate the resonances of the heterocycles [8] unequivocally. 4. NOE experiments were used to differentiate between [2,3-*f*]-, [3,2-*g*]- and [2,3-*h*]-chromene arrangements in the 6- and 10-fisetinidol-tetrahydropyrano-chromenes*. Association of 5-OMe(D) with 4-H(I), 5-H(G) and 4-H($F)_{ax.}$ and $_{eq.}$ indicated a 6-fisetinidol-tetrahydropyrano[2,3-*h*]chromene, e.g. compound **21**, association of 5-OMe(D) with 6-H(I) and 4-H($F)_{ax.}$ and $_{eq.}$ reflected a 10-fisetinidol-tetrahydropyrano-[3,2-*g*]chromene, e.g. compound **33** while association of 9-OMe(D) with both 8-H(I) and 4-H(C) was reminiscent of a 10-fisetinidol-tetrahydropyrano-[2,3-*f*]chromene, e.g. compound **18**.

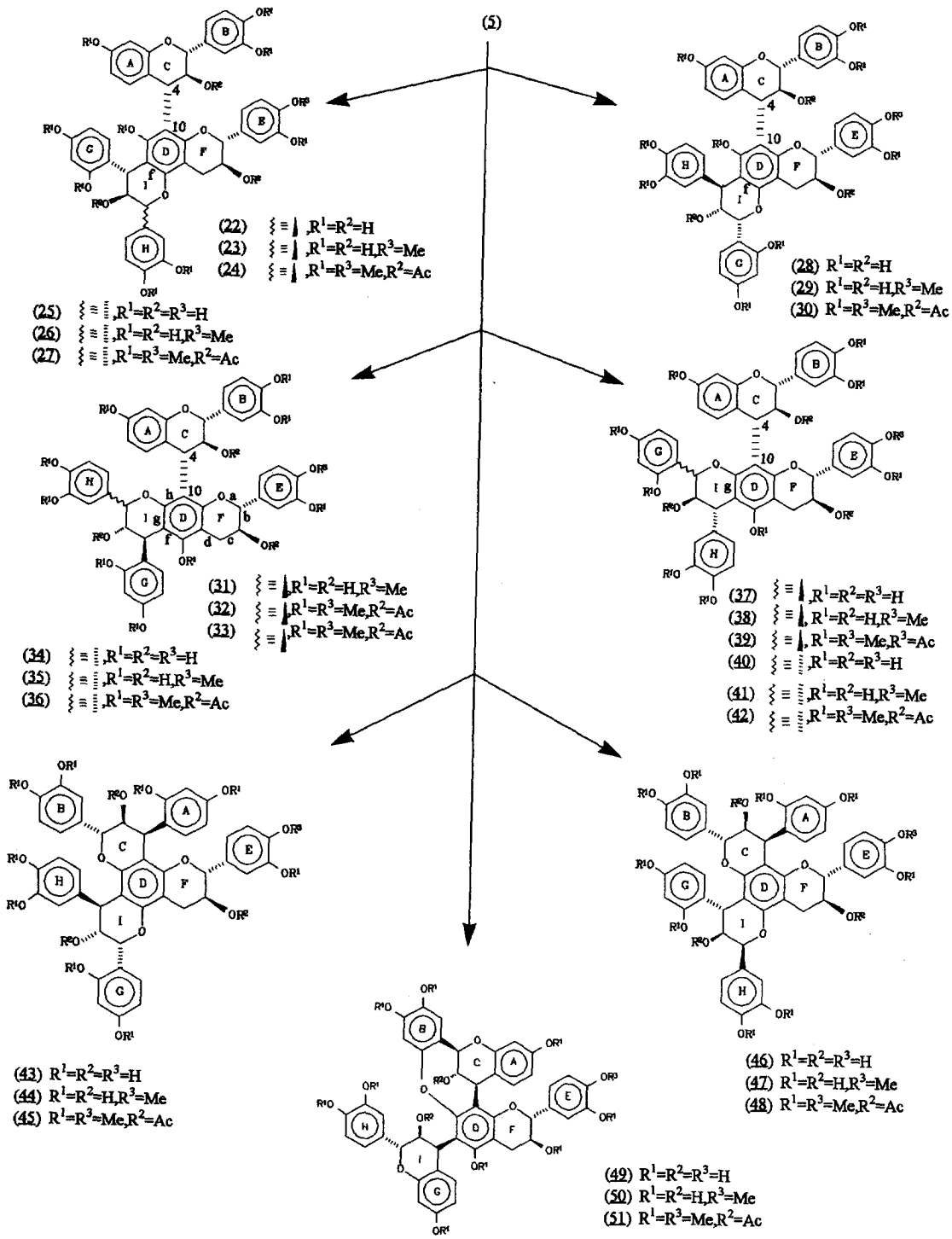
The functionalized tetrahydropyrano[2,3-*f*]-, [3,2-*g*]- and [2,3-*h*]chromenes of diverse structure and stereochemistry which are derived from the fisetinidol-(4,6)- and (4,8)-catechin profisetinidins [8], are accompanied in the heartwood of *B. plurijuga* by a series of 'trimeric' compounds related to the bis-fisetinidol-catechin triflavanoids **1**, **4**, **7** and **10**. The naturally occurring hexahydro-dipyrano-[2,3-*f*:2′,3′-*h*]chromene, **13** and the fisetinidol-(4α,10)-tetrahydropyrano-[2,3-*f*]chromene, **16**, together with the fisetinidol-(4α,6)-tetrahydropyrano[2,3-*h*]chromene, **19**, were previously synthesized as mono-*O*-methyl ethers **14**, **17** and **20** from the bis-fisetinidol-(4α,6:4α,8)-catechin mono-*O*-methyl ether, **2**, and identified as their decamethyl ether triacetates, **15**, **18** and **21** [3]. Compound **19** has now been obtained from *B. plurijuga* and was again characterized by comparison of the physical data (see Table 1 for ^{1}H NMR data) of derivative **21** with those of the same derivative of the synthetic sample.

Owing to the susceptibility of constituent units in oligoflavanoids to epimerization at C-2 at alkaline pH [10], the triflavanoids had to be selectively protected at 4-OH(E). This was affected by using fisetinidol-(4α,8)- and (4β,8)-catechin 4-*O*(E)-methyl ethers [8] as nucleophiles in the acid-catalysed condensations [11] with mollisacacidin [(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol]. Subsequent gel chromatography of the resultant mixtures afforded, respectively, the bis-fisetinidol-(4α,8:4α,6 and 4β,6)-catechin mono-*O*-methyl ethers, **2** and **5** and the bis-fisetinidol-(4β,8:4α,6 and 4β,6)-catechin mono-*O*-methyl ethers,

*Non-systematic name/numbering (cf. structure **13**) to retain the heterocyclic oxygen of the catechin DEF-unit as position 1 for all compounds.

8 and **11**, all of which are incapable of epimerization at 2-C(F) under basic conditions. These four triflavanoids were characterized by comparison of ^{1}H NMR and CD data of their methyl ether triacetates, **3**, **6**, **9** and **12** with those of the permethyl ether triacetates of reference compounds [11].

Treatment of triflavanoid **5** with 0.025 M-$NaHCO_3$–0.025 M-Na_2CO_3 buffer (pH 10) for 5.5 hr at 50° under nitrogen (Scheme 1), i.e. conditions similar to those applied by Freudenberg and Purrmann [10] for epimerization at C-2 of catechin, gave complete conversion into a mixture comprising nine ring-isomerized analogues and a didehydro-bis-fisetinidol-(4α,8:4β,6)-catechin, **50**. The compounds with rearranged pyran



Scheme 1. Base-catalysed conversion of the (4α,8:4β,6)-bis-fisetinidol-catechin mono-*O*-methyl ether **5**.

rings are the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromenes **23**, **26** and **29**, the fisetinidol-(4α,10)-tetrahydropyrano-[3,2-*g*]chromenes **32**, **35**, **38** and **41**, and the hexahydrodipyrano[2,3-*f*:2′,3′-*h*]-chromenes **44** and **47**. Owing to difficulties in purifying these as 'free' phenols and to facilitate comparison with their natural counterparts (see below), identification was performed on the decamethyl ether triacetates, e.g. compound **24**.

The ^{1}H NMR spectra (Table 1) of the decamethyl ether triacetates **24**, **27** and **30** of the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromenes **23**, **26** and **29** were free of the effects of dynamic rotational isomerism. Confirmation for the [2,3-*f*]-chromene arrangement in all three compounds was obtained by the observed NOE association of 9-OMe(D) to both 4-H(C) and 8-H(I) in derivatives **24**, **27** and **30**. The coupling constants of the heterocyclic ABMX system ($J_{2,3}$ 10.0, 9.0 and 9.5 Hz for **24**, **27** and **30** respectively) were reminiscent of the 2,3-*trans* flavan-3-ol DEF moiety, while the two AMX spin systems in the same region of the spectra corresponded to, respectively, a tetrahydropyranochromene unit with a 6,7-*cis*-7,8-*trans* ($J_{6,7}$ 1.5, $J_{7,8}$ 2.5 Hz for both **24** and **30**) and a 6,7-*trans*-7,8-*trans* ($J_{6,7}$ 8.5, $J_{7,8}$ 8.0 Hz for **27**) I-ring configuration [8], and an intact 2,3-*trans*-3,4-*trans* flavanyl ABC unit ($J_{2,3} = J_{3,4}$ 10.0 Hz for **24**, **27** and **30**).

Prominent NOE association between 6-H(I) and 6-H(G) in compound **24** not only confirms the *cis–trans* relative configuration for the I-ring, but also indicates a preferred half-chair conformation (I-ring) in which the resorcinol G-ring occupies a near-axial orientation. In the *cis–trans* analogue **30**, 6-H(I) exhibits a strong NOE association with both 2- and 6-H(H). The 6- and 8-protons of ring I in this compound was correlated *via* a COSY experiment with, respectively, the protons of the resorcinol G-ring and the pyrocatechol H-ring. When taken in conjunction with the conspicuous deshielding of 6-H(G) ($\Delta\delta = 0.67$ ppm), these features collectively indicated an interchange of the resorcinol G- and pyrocatechol H-rings with concomitant inversion of the absolute configuration at C-7 (I-ring) relative to the array prevailing in a 'normal' isomer, e.g. compound **24**. The mechanism explaining these phenomena has been described previously [8, 12] with the essence being dealt with in Scheme 2.

Owing to the inapplicability of the chiroptical method at the triflavanoid level, the absolute configurations depicted in structures **24**, **27** and **30** are based on the ^{1}H NMR data, the known absolute configuration of the starting triflavanoid **5** and the mechanism of their genesis from **5**. Thus, the absolute configuration of compound **24** follows as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*S*,7*S*,8*R*, that of **27** as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*R*,7*S*,8*R* and that of **30** as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*R*,7*R*,8*S*. Comparison of the ^{1}H NMR and CD data (see Experimental) of compounds **27** and **30** with those of the same derivatives of the natural products **25** and **28**, isolated from *C. mopane* and *B. plurijuga*, respectively, proved their identity and, hence, confirmed the structures of the natural products unambiguously.

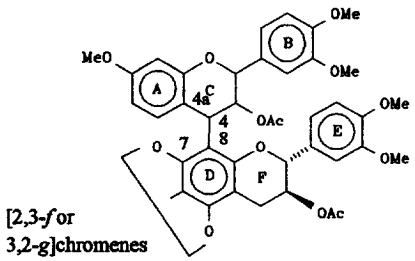
Amongst the decamethyl ether triacetates, **33**, **36**, **39** and **42** of the fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromenes **31**, **34**, **37** and **40**, the ^{1}H NMR spectra (Table 2) of derivatives **33**, **39** and **42** displayed the typical effects of dynamic rotational isomerism. For compounds exhibiting such effects in their ^{1}H NMR spectra, e.g. compound **33**, the numbering e.g. compounds **33a** and **33b** will be used to differentiate the rotamers and the numbering e.g. 3-H(A) and 3′-H(A) to distinguish between the respective protons of the rotamers. Since conformational studies have shown that the preferred conformations about the interflavanyl bond are encountered when 4-H(C) and the 4-aryl substituent approach an eclipsed conformation [13], the rotamers that are observed in the ^{1}H NMR spectra of several of the 6- and 10-fisetinidol-tetrahydropyranochromenes are differentiated in terms of the dihedral angle, θ (+ or −90°), which is defined as indicated [14–16] in structures **52** and **53** for the (4,8)- and (4,6)-analogues, respectively. NOE experiments permitted assignment of the tetrahydropyrano[3,2-*g*]chromene arrangement in compounds **33**, **36**, **39** and **42** *via* the association of 5/5′-OMe(D) with both 6/6′-H(I) and 4-H(F)$_{ax.}$ and $_{eq.}$ for the rotamers of **33**, of 5-OMe(D) with both 6-H(I) and 4-H(F)$_{ax.}$ and $_{eq.}$ for **36** and **42**, and of 3-H(C) with 8-H(I) and 5/5′-OMe(D) with 6/6′-H(I) for the rotamers of compound **39**. The observed NOE association of 3-H(C) with 8-H(I) established **39a** as the major rotamer with $\theta = +90°$ and, thus, **39b** with $\theta = -90°$ as the minor rotamer. For compound **33** the NOE effect of 3′-H(C) with 2′-H(E) claimed **33b** as the minor rotamer with $\theta = -90°$, thus for the major rotamer **33a**, $\theta = +90°$. A shortage of material prevented similar definition of the rotamers in compound **42**.

The coupling constants of the heterocyclic ABMX systems ($J_{2,3}$ 8.5 and 9.0 Hz for **33a** and **33b**, respectively, 9.0 Hz for **36**, 7.0 Hz for **39a** and **39b** and 7.5 and 9.0 Hz for **42a** and **42b**, respectively) confirmed the 2,3-*trans* flavan-3-ol DEF moieties. The two AMX systems in the same region of the ^{1}H NMR spectra corresponded to a tetrahydropyranochromene moiety with, respectively, 6,7-*trans*-7,8-*trans*-($J_{7,8}$ 9.0 and 7.5 Hz, $J_{6,7}$ 8.0 and 6.5 Hz for **33a** and **33b**, respectively, $J_{7,8}$ 6.0 and 8.5 Hz, $J_{6,7}$ 5.0 and 7.0 Hz for **42a** and **42b**, respectively) and 6,7-*trans*-7,8-*cis*-($J_{7,8}$ 1.5 Hz, $J_{6,7}$ 2.5 Hz for **36** and **39b**, $J_{7,8}$ 1.0 Hz, $J_{6,7}$ 2.5 Hz for **39a**) I-ring configuration, while the other was indicative of an intact fisetinidol ABC unit ($J_{2,3} = J_{3,4} = 10.0$ Hz for **35**, **36**, **39** and **42**]. The *cis–trans* relative configuration of the I-rings in compounds, **36** and **39** was again confirmed by the relevant NOE associations (*vide supra*), while the 'interchanged' resorcinol G- and pyrocatechol H-rings in compounds **39** and **42** were evident from the indicated COSY experiments and the conspicuously deshielded 6-H(G) ($\Delta\delta = 0.96$ ppm for **39b**, and 0.36, 0.88 ppm for **42a** and **42b**, respectively). Notable in the spectrum of compound **39**, is the

Table 2. ^{1}H NMR peaks (ppm) of fisetinidol-(4α, 10)-tetrahydropyrano[3,2-*g*]chromenes **33**, **36**, **39** and **42** in $CDCl_3$ (296 K) at 300 MHz

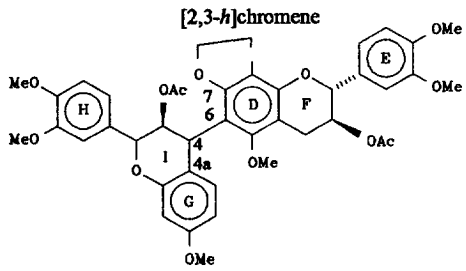
Ring	H	**33a**	**33b**	**36**	**39a**	**39b**	**42a**	**42b**
A	5	6.82 (*d*, 8.5)	6.69 (*d*, 8.5)	6.91 (*d*, 8.5)	6.78 (*d*, 8.5)	6.73 (*d*, 8.5)	6.87 (*d*, 8.5)	6.59 (*d*, 8.5)
	6	6.49 (*dd*, 2.5, 8.5)	6.46 (*dd*, 2.5, 8.5)	6.49 (*dd*, 2.5, 8.5)	6.46 (*dd*, 2.5, 8.5)	6.44 (*dd*, 2.5, 8.5)	6.53 (*dd*, 2.5, 8.5)	6.30 (*dd*, 2.5, 8.5)
	8	6.39 (*d*, 2.5)	6.36 (2.5)	6.41 (*d*, 2.5)	6.57 (*d*, 2.5)	6.36 (*d*, 2.5)	6.38 (*d*, 2.5)	5.92 (*d*, 2.5)
B	2	6.51 (*d*, 2.0)	6.53 (*d*, 2.0)	6.60 (second order)	6.62 (*d*, 2.0)	6.55 (*d*, 2.0)	—	6.92 (*d*, 2.0)
	5	6.66 (*d*, 8.5)	6.67 (*d*, 8.5)	6.71 (second order)	6.70 (*d*, 8.5)	6.67 (*d*, 8.5)	—	6.85 (*d*, 8.5)
	6	6.63 (*dd*, 2.0, 8.5)	6.46 (*dd*, 2.0, 8.5)	6.71 (second order)	6.79 (*dd*, 2.0, 8.5)	6.47 (*dd*, 2.0, 8.5)	—	6.96 (*dd*, 2.0, 8.5)
C	2	4.78 (*d*, 10.0)	4.80 (*d*, 10.0)	4.79 (*d*, 10.0)	4.90 (*d*, 10.0)	4.85 (*d*, 10.0)	4.79 (*d*, 10.0)	4.74 (*d*, 10.0)
	3	6.09 (*t*, 10.0)	6.14 (*t*, 10.0)	6.25 (*t*, 10.0)	6.24 (*t*, 10.0)	6.16 (*t*, 10.0)	6.05 (*t*, 10.0)	6.07 (*t*, 10.0)
	4	4.96 (*d*, 10.0)	4.96 (*d*, 10.0)	5.09 (*d*, 10.0)	5.05 (*d*, 10.0)	5.08 (*d*, 10.0)	4.96 (*d*, 10.0)	4.88 (*d*, 10.0)
E	2	6.96 (*d*, 2.0)	6.61 (*d*, 2.0)	6.58 (*d*, 2.0)	6.92 (*br s*)	6.67 (*d*, 2.0)	6.53 (*d*, 2.0)	—
	5	6.82 (*d*, 8.5)	6.72 (*d*, 8.0)	6.69 (*d*, 8.0)	6.89 (*d*, 8.5)*	6.80 (*d*, 8.5)*	6.67 (*d*, 8.0)	—
	6	6.92 (*dd*, 2.0, 8.5)	6.75 (*dd*, 2.0, 8.0)	6.55 (*dd*, 2.0, 8.0)	6.72 (*dd*, 2.0, 8.5)	6.81 (*dd*, 2.0, 8.5)	6.47 (*dd*, 2.0, 8.0)	—
F	2	4.97 (*d*, 8.5)	4.80 (*d*, 9.0)	4.86 (*d*, 9.0)	5.17 (*d*, 7.0)	5.23 (*d*, 7.0)	4.90 (*d*, 7.5)	5.23 (*d*, 9.0)
	3	5.04 (*m*)	4.86 (*m*)	4.92 (*m*)	4.99 (*m*)	5.24 (*m*)	4.98 (*m*)	5.22 (*m*)
	4_{ax}	2.78 (*dd*, 8.5, 16.0)	2.67 (*dd*, 9.0, 16.0)	2.69 (*dd*, 9.0, 16.0)	2.85 (*dd*, 7.0, 16.0)	2.73 (*dd*, 9.0, 16.0)	2.68 (*dd*, 8.5, 17.0)	—
	4_{eq}	3.03 (*dd*, 5.5, 16.0)	3.07 (*dd*, 6.0, 16.0)	3.18 (*dd*, 5.0, 16.0)	2.97 (*dd*, 5.0, 16.0)	3.09 (*dd*, 6.5, 16.0)	3.07 (*dd*, 6.0, 17.0)	—
G	3	6.35 (*d*, 2.5)	6.36 (*d*, 2.5)	6.53 (*d*, 2.5)	6.19 (*d*, 2.5)	6.33 (*d*, 2.5)	6.27 (*d*, 2.5)	6.20 (*d*, 2.5)
	5	6.35 (*dd*, 2.5, 8.5)	6.19 (*dd*, 2.5, 8.5)	6.29 (*dd*, 2.5, 8.5)	6.14 (*dd*, 2.5, 8.5)	6.49 (*dd*, 2.5, 8.5)	6.34 (*dd*, 2.5, 8.5)	6.38 (*dd*, 2.5, 8.5)
	6	6.81 (*d*, 8.5)	6.49 (*d*, 8.5)	6.52 (*d*, 8.5)	6.09 (*d*, 8.5)	7.49 (*d*, 8.5)	7.17 (*d*, 8.5)	7.36 (*d*, 8.5)
H	2	6.56 (*d*, 2.0)	6.79 (*d*, 2.0)	6.86 (second order)	6.85 (*d*, 2.0)	6.92 (*br s*)	—	—
	5	6.67 (*d*, 8.5)	6.73 (*d*, 8.5)	6.71 (second order)	6.78 (*d*, 8.5)*	6.80 (*d*, 8.5)*	—	—
	6	6.61 (*dd*, 2.0, 8.5)	6.90 (*dd*, 2.0, 8.5)	6.71 (second order)	6.73 (*dd*, 2.0, 8.5)	6.90 (*dd*, 2.0, 8.5)	—	—
I	6	4.52 (*d*, 8.0)	4.73 (*d*, 6.5)	4.77 (*d*, 2.5)	4.31 (*d*, 2.5)	4.45 (*d*, 2.5)	4.32 (*d*, 5.0)	4.16 (*d*, 7.00)
	7	5.14 (*dd*, 8.0, 9.0)	5.54 (*dd*, 6.5, 7.5)	5.47 (*dd*, 1.5, 2.5)	5.16 (*dd*, 1.0, 2.5)	5.40 (*dd*, 1.5, 2.5)	5.71 (*dd*, 5.0, 6.0)	5.44 (*dd*, 7.0, 8.5)
	8	4.85 (*d*, 9.0)	4.96 (*d*, 7.5)	5.08 (*d*, 1.5)	5.46 (*br s*)	5.46 (*br s*)	5.24 (*d*, 6.0)	4.51 (*d*, 8.5)
	OMe	3.17 (5-D), 3.49 (3-B), 3.69 (3-H), 3.73 (×2), 3.75 (7-A), 3.8 3.41 (4-H), 3.81 (4-B), 3.87 (4-E), 3.88 (3-E), each *s*	3.26 (5-D), 3.56 (3-E), 3.69 (4-G), 3.72 (3-B), 3.73, 3.77 (3-H, 2-G), 3.82 (4-H), 3.83 (4-E), 3.84 (4-B), each *s*	3.30 (5-D), 3.55 (3-B), 3.63 (3-H), 3.72 (3-E), 3.75 (7-A), 3.78 (4-G), 3.82 (4-H, 4-B), 3.85 (4-E), 3.92 (2-G), each *s*	3.28 (5-D), 3.4 (3-B), 3.42 (2-G), 3.70 (4-G), 3.79 (×2), 3.83, 3.85 (3-E, 3-H), 3.89 (4-E), each *s*	3.40 (5-D), 3.55 (2-G), 3.63 (3-E), 3.72 (3-B, 7-A), 3.83, 3.84 (4-B, 4-E), 3.86 (4-H), 3.93 (3-H), each *s*	3.14 (5′-D), 3.37 (5-D), 3.54 (×2), 3.56, 3.61, 3.63, 3.69, 3.71, 3.74 (×3), 3.77, 3.78, 3.80, 3.81, 3.82, 3.83, 3.85, 3.88, each *s*	
	OAc	1.63, 1.74, 1.92, each *s*	1.75, 1.82, 1.83, each *s*	1.66, 1.84, 1.91, each *s*	1.65, 1.70, 2.02, each *s*	1.74, 1.75, 1.86, each *s*	1.16, 1.64, 1.75, 1.86, 1.88, each *s*	

*Signals may be interchanged.



(52)

θ = 7-C(D), 8-C(D), 4-C(C), 4a-C(C)



(53)

θ = 7-C(D), 6-C(D), 4-C(I), 4a-C(I)

shielding of 6-H(G) ($\Delta\delta = -1.40$ ppm) relative to the chemical shift of 6′-H(G) ($\delta = 7.49$ ppm), a phenomenon that is explicable in terms of the anisotropic effect exerted on the G-ring by the A-ring in the conformation prescribed for rotamer **39a**.

Using the same criteria as described above, the absolute configuration of compounds **33**, **36**, **39** and **42** may be defined as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*R*,7*S*,8*R* **33**, 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*R*,7*S*,8*S* **36**, 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*S*,7*R*,8*R* **39** and 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):6*S*,7*R*,8*S* **42**. The decamethyl ether triacetates, **33** and **36**, of the fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromenes **31** and **34** were identical to the same derivatives of the natural products from *B. plurijuga* by comparison of their ^{1}H NMR and CD data.

Analysis of the ^{1}H NMR data (Table 3) of the dipyrano[2,3-*f*:2′,3′-*h*]chromene decamethyl ether triacetates **45** and **48** revealed the familiar absence [3] of the effects of dynamic rotational isomerism at ambient temperatures, while the relevant NOE experiments on the methoxyl protons of 'liberated' resorcinol rings reflected unequivocally participation of both the C- and

Table 3. ^{1}H NMR peaks (ppm) of hexahydrodipyranochromenes **45** and **48** and the didehydrotriflavanoid **51** in $CDCl_3$ (296 K) at 300 MHz

Ring	H	**45**	**48**	**51**
A	3/5	6.30 (*d*, 2.5)	6.32 (*d*, 2.5)	6.71 (*d*, 8.5)
	5/6	6.34 (*dd*, 2.5, 8.5)	6.41 (*dd*, 2.5, 8.5)	6.53 (*dd*, 2.5, 8.5)
	6/8	6.74 (*d*, 8.5)	6.91 (*d*, 8.5)	6.15 (*d*, 2.5)
B	2	6.58 (*d*, 2.0)	6.31 (*d*, 2.0)	—
	5/3	6.71 (*d*, 8.5)	6.48 (*d*, 8.0)	6.81 (*s*)
	6	6.65 (*dd*, 2.0, 8.5)	6.10 (*dd*, 2.0, 8.0)	6.22 (*s*)
C	10/2	4.73 (*d*, 10.0)	4.93 (*d*, 10.0)	5.24 (*t*, 4.3)
	11/3	5.44 (*dd*, 6.0, 10.0)	4.99 (*dd*, 6.0, 10.0)	6.13 (*dd*, 3.0, 6.0)
	12/4	5.12 (*d*, 6.0)	5.09 (*d*, 6.0)	3.48 (*dd*, 2.0, 3.0)
E	2	6.78 (*d*, 2.0)	6.81 second order	6.08 (*d*, 2.0)
	5	6.77 second order	6.76 second order	6.53 (*d*, 8.5)
	6	6.77 second order	6.76 second order	5.94 (*dd*, 2.0, 8.5)
F	2	4.59 (*d*, 8.5)	4.64 (*d*, 8.5)	4.15 (*d*, 10.0)
	3	5.28 (*m*)	5.22 (*m*)	5.02 (*m*)
	4_{ax}	2.70 (*dd*, 8.5, 16.5)	2.72 (*dd*, 8.5, 16.5)	2.41 (*dd*, 10.0, 17.5)
	4_{eq}	3.22 (*dd*, 5.5, 16.5)	3.22 (*dd*, 6.5, 16.5)	3.15 (*dd*, 6.5, 17.5)
G	3/5	6.31 (*d*, 2.5)	6.44 (*d*, 2.5)	6.46 (*d*, 2.5)
	5/6	6.48 (*dd*, 2.5, 8.5)	6.47 (*dd*, 2.5, 8.0)	6.38 (*dd*, 2.5, 8.5)
	6/8	7.46 (*d*, 8.5)	6.75 (*d*, 8.0)	6.90 (*d*, 8.5)
H	2	6.82, second order	6.87 (*d*, 2.0)	7.10 (*d*, 2.0)
	5		6.77 (*d*, 8.5)	6.79 (*d*, 8.0)
	6		6.82 (*dd*, 2.0, 8.5)	6.98 (*dd*, 2.0, 8.0)
I	6/2	5.32 (*br s*)	5.01 (*br s*)	5.33 (*d*, 10.0)
	7/3	5.35 (*dd*, 1.0, 2.0)	5.39 (*dd*, 1.0, 2.0)	5.69 (*dd*, 7.0, 10.0)
	8/4	4.32 (*d*, 2.0)	4.50 (*d*, 2.0)	5.04 (*d*, 7.0)
	OMe	3.48 (2-A), 3.52 (2-G), 3.73 (3-B), 3.76 (4-A), 3.77 (4-G), 3.81 (4-B), 3.83 (4-H), 3.86 (3-E, 4-E), 3.88 (3-H), each *s*	3.47 (2-B), 3.52 (2-A), 3.66 (2-G), 3.78 (4-A), 3.79 (4-B), 3.83 (3-H, 4-H, 4-G), 3.86 (4-E), 3.87 (3-E), each *s*	3.66 (7-A), 3.67 (3-E), 3.68 (7-G), 3.72 (5-B), 3.78 (4-E, 5-D), 3.84 (4-B), 3.85 (4-H), 3.87 (3-H), each *s*
	OAc	1.69, 1.88, 1.90, each *s*	1.65, 1.90, 1.95, each *s*	1.83, 1.98, 2.10, each *s*

I-rings of the triflavanoid precursor (**5**) in the pyran rearrangements. The coupling constants of the heterocyclic proton spin systems confirmed the 2,3-*trans* flavan-3-ol DEF units ($J_{2,3}$ 8.5 Hz for both **45** and **48**), the 10,11-*trans*-11,12-*cis* C-ring ($J_{10,11}$ 10.0 Hz, $J_{11,12}$ 6.0 Hz for both **45** and **48**) and the 6,7-*cis*-7,8-*trans* I-ring ($J_{6,7}$ 1.5, $J_{7,8}$ 2.0 Hz for **48**; $J_{6,7}$ 1.0, $J_{7,8}$ 2.0 Hz for **45**).

NOE association of 10-H(C) with 6-H(A) confirmed the *trans–cis* relative configuration of the C-ring for both compounds **45** and **48**. The *cis–trans* stereochemistry of the I-ring was similarly supported by the NOE association of 6-H(I) with 6-H(G) for derivative **48** and of 6-H(I) with 2- and 6-H(H) for **45**. The latter observation, in conjunction with the fact that 6-H(I) was correlated with the recorcinol G-ring protons by spin-decoupling experiments and the conspicuously deshielded 6-H(G) resonance (δ 7.46) in derivative **45** relative to its shifts in compound **48** (δ 6.75), as above, indicated an interchange of the resorcinol G- and pyrocatechol H-rings and inversed I-ring absolute configuration for compound **45**. The absolute configurations were thus defined as 2*R*,3*S*:6*R*,7*R*,8*S*:10*R*,11*S*,12*S* for **45** and 2*R*,3*S*:6*S*,7*S*,8*R*:10*R*,11*S*,12*S* for **48**. Comparison of relevant physical data of the decamethyl ether triacetate **48** with those of the same derivative of the natural product **46** from *B. plurijuga* established their identity. It should be emphasized that all the aforementioned derivatives gave clear high-amplitude Cotton effects in the 230–290 nm region of their CD spectra. Although not permitting stereochemical assignment at this molecular level, the CD features could nevertheless be employed comparatively to assess the absolute configuration of all the related natural products.

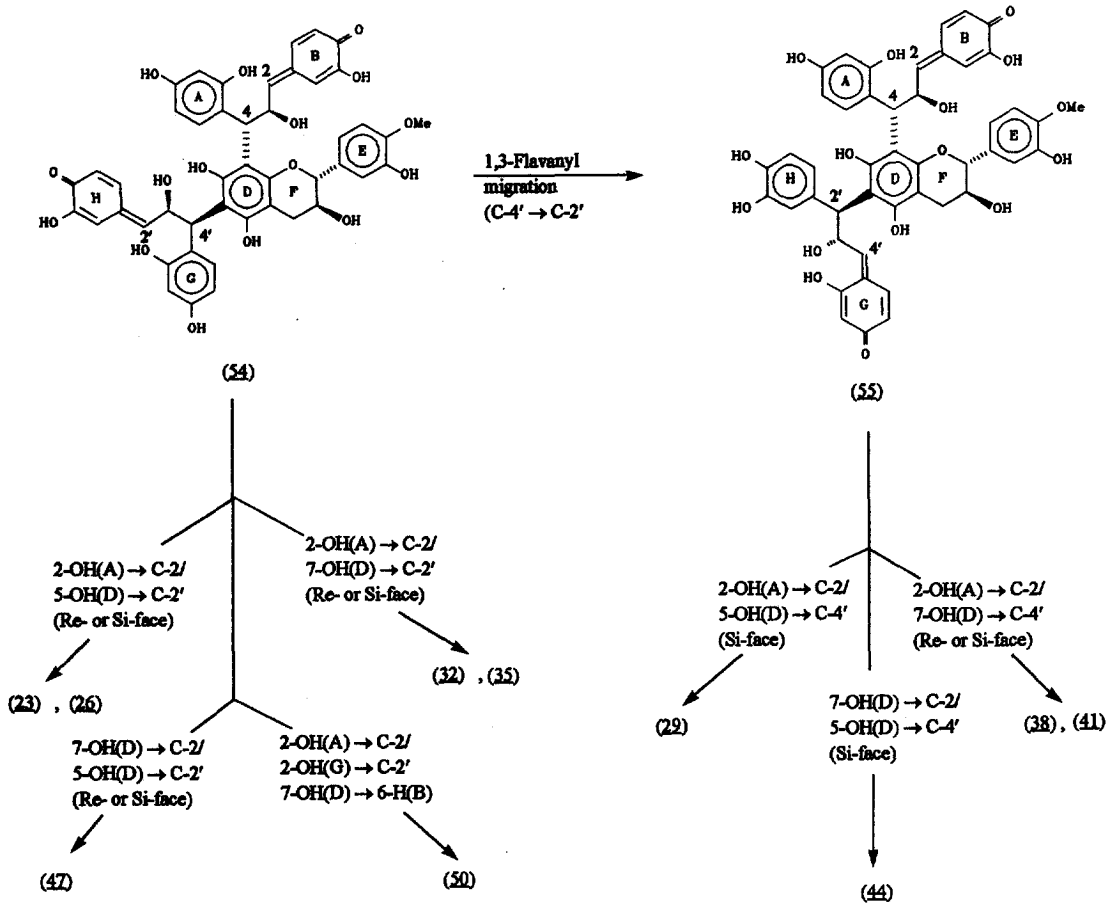
Since the fisetinidol-(4α,6 and 4α,10)-tetrahydropyranochromenes **23**, **26**, **29**, **32**, **35**, **38** and **41** may be regarded as 'isomerization-intermediates' that will probably proceed to dipyranochromenes *via* pyran rearrangement of the remaining flavanyl unit during the course of the reaction, a portion of the mixture was extracted after 2.5 hr and analysed by gel chromatography on Sephadex LH-20 in ethanol. The product composition, however, was very similar to that observed after 5.5 hr, which suggested that the reaction had reached equilibrium after 2.5 hr. The 6- and 10-fisetinidol-tetrahydropyranochromenes, therefore, represented relatively stable molecules on the potential energy surface of the isomerization reaction and should not be considered as short-lived intermediates. The preferred pyran rearrangement of the 2,3-*trans*-3,4-*cis* GHI fisetinidol unit relative to that of the all-*trans* ABC moiety that was observed in the base-catalysed ring isomerization of profisetinidin biflavanoids [8] was reflected in the distribution of the 6- and 10-fisetinidol-tetrahydropyranochromenes.

The ^{1}H NMR spectrum (Table 3) of derivative **51** is characterized by the presence of nine methoxy- and three acetoxy-proton signals, one-proton singlets (δ 6.23, 6.82) indicating substitution at C-6 of either the B- or H-ring of the parent triflavanoid **5**. The small coupling constants ($J_{2,3}$ 2.5, $J_{3,4}$ 3.5 Hz) of the protons of the heterocycle connected to the substituted B- or H-ring were compatible with dihedral angles approaching 90° as a result of conformation restrictions imposed on this ring by the eight-membered oxygen heterocycle. An AMX spin system in the heterocyclic range of the spectrum corresponded to an intact 2,3-*trans*-3,4-*cis* C-4 substituted fisetinidol unit, confirmed by the NOE association of its 7-OMe with both 6- and 8-H, which strongly indicated involvement of the fisetinidol ABC unit in the eight-membered ring. The abnormal shielding of 4-H(C) and 2- and 6-H(E) relative to the chemical shift of these protons in the same derivative of triflavanoid **5** is explicable in terms of anisotropy of proximal functionalities, e.g. 2- and 6-H(E) by the A-ring. Similar deshielding of 3-H(C) results from its close proximity to the oxygen of the 8-membered ring. Evidence for the A- and E-ring being locked together, and thus additional proof of the structure as fisetinidol-(4β,6)-didehydro-fisetinidol-(4α,8)-catechin **51**, was found in the NOE association of 4-OMe(E) with 6-H(A). The absolute configuration, derived by the same principles used before, followed as 2*R*,3*S*,4*S*(C):2*R*,3*S*(F):2*R*,3*S*,4*R*(I).

Additional structural information was sought *via* the mass spectral fragmentation data of the derivatives of the analogues with rearranged pyran rings utilizing the less severe FAB method. Besides confirmation of the molecular ion ($[M]^+$, *m/z* 1,000 for all compounds but *m/z* 1084 for **51**) the spectra were dominated by RDA-fragmentation leading to an *m/z* 878 ion, as well as by loss of acetic acid *via* McLafferty fragmentation affording the *m/z* 1,041 and 981 fragments. However, the considerable similarity of fragments largely reduces the utility of mass spectrometry as an additional probe for differentiation of the series of 'trimeric' phlobatannin derivatives.

Under basic conditions, the bis-fisetinidol-catechin **5** is presumably transformed into the quinone methide **54**, involving both the B- and H-rings (Scheme 2), which then serves as the common precursor to the series of phlobatannins in Scheme 1. The mechanisms explaining the formation of the individual compounds are similar to those that have previously been advanced in the biflavanoid series of compounds [1, 2, 3, 8, 12] and need not be repeated. Since the formation of the dipyranochromenes **44** and **47**, no doubt, requires intermediacy of a B/H-ring quinone methide, e.g. compound **54**, the absence of epimerization at C-2(C or I) in the tetrahydropyranochromenes is conspicuous. Such a phenomenon may presumably be attributed to either thermodynamic control or asymmetric induction, or both, during the recyclization step.

In contrast with the ionic mechanism proposed in Scheme 2, it has been suggested [17] that the base-catalysed epimerization of flavan-3-ols proceeds *via* a one-electron process. Such a radical mechanism was based on the observation that oxygen is a prerequisite for epimerization. These studies were, however, con-



Scheme 2. Proposed route to the formation of the pyran-rearranged analogues in Scheme 1. The quinone methides **54** and **55** are postulated and have not been isolated.

ducted at higher alkalinity than the conditions employed to induce the pyran ring rearrangements (pH 13.3 *vs* 10.0). Since the polyphenol is more highly ionized at the higher pH [18] a direct mechanistic comparison is not feasible. Since the mechanism of quinone methide formation will not influence the stereochemical course of the pyran rearrangements, the two-electron route to **54** and related intermediates will be retained in this and following papers.

Our recent demonstration of the diversity amongst the "dimeric' analogues of this class of condensed tannins [1] in conjunction with the results in this and other papers [2, 3] dealing with 'trimers', presumably indicate ubiquity similar to those of their 'conventional' bi- and tri-flavanoid precursors. The co-existence of these classes of oligomers in *B. plurijuga* and the ease of formation of the phlobatannins under mild basic conditions presumably reflects similar mechanisms for their *in vivo* and *in vitro* genesis.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ with TMS as int. standard. FAB-MS were recorded on a VG 70-70E instrument with VG 11-250J data system and iontech saddlefield FAB gun. CD data were obtained in MeOH. TLC was performed on precoated Merck plastic sheets (silica gel 60 F_{254}, 0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40:1) after development. Prep. TLC plates, Kieselgel PF_{254} (1.0 mm), were air-dried and used without prior activation. Compounds were recovered from the absorbent with Me_2CO. CC was on Sephadex LH-20 and Fractogel TSK HW-40(S) in EtOH and EtOH–H_2O mixts. Methylations were performed with excess CH_2N_2 in MeOH–Et_2O at −15° for 48 hr, while acetylations were in Ac_2O–pyridine at ambient temps. Evapns were done under red. pres. at *ca* 60° in a rotary evaporator. Phenolic material in aq. soln was freeze-dried.

Phlobatannins from Baikiaea plurijuga. Extraction (MeOH) and fractionation (Craig countercurrent) procedures of the heartwood leading to frs 1–5 are described fully in Part 3 [8]. Fr. 2 was subjected in 2 portions of 11.85 g each to CC on Sephadex LH-20 in EtOH under medium pressure (MPLC, 1.0 bar pressure 8.5 ml min^{-1} flow rate, 4.5 × 120 cm column) to give the following frs (first 1.5 l of eluant was discarded;

17 ml eluant per tube): 2A (tubes 1–50, 110 mg), 2B (51–158, 364 mg), 2C (159–266, 5.91 g), 2D (267–370, 2.72 g), 2E (371–545, 2.62 g), 2F (546–640, 849 mg), 2G (641–727, 611 mg) and 2H (728–1208, 6.85 g). Fr. 2E (2.62 g) contained compounds that exhibited the diagnostic purple-red colouration of phlobatannins [8] with the spray reagent and was accordingly resolved on an MPLC column (2.7 bar, 4.5 ml min^{-1} flow rate, 3 × 55 cm column, 18 ml per tube) using Fractogel TSK HW-40(S) to afford the following frs (first 3.0 l of eluant discarded): $2E_1$ (tubes 1–82, 101 mg), $2E_2$ (83–180, 889 mg), $2E_3$ (181–221, 348 mg), $2E_4$ (222–318, 420 mg), $2E_5$ (319–400, 176 mg), $2E_6$ (401–480, 97 mg), $2E_7$ (481–614, 165 mg) and $2E_8$ (615–831, 117 mg). Owing to the appropriate colouration with the spray reagent on TLC frs $2E_2$ and $2E_4$ were further investigated. Thus, fr. $2E_2$ (889 mg) was methylated and the mixt. resolved by prep. TLC in hexane–Me_2CO–EtOAc (2:2:1, ×2) to give a main band at R_f 0.47 (274 mg) which was further separated by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (20:60:15:5, ×2) into 3 frs, $2E_{2.1}$ (R_f 0.61, 37 mg), $2E_{2.2}$ (R_f 0.58, 28 mg) and $2E_{2.3}$ (R_f 0.35, 9 mg). Acetylation of fr. $2E_{2.1}$, followed by purification by prep. TLC in toluene–1,2-dichloroethane–Me_2CO (30:55:15, ×3) afforded two main bands, $2E_{2.1.1}$ (R_f 0.48, 8 mg) and $2E_{2.1.2}$ (R_f 0.36, 5 mg). Band $2E_{2.1.1}$ gave (2*R*,3*S*:6*R*,7*S*,8*S*,10*R*,11*S*,12*R*)-3,7,11-triacetoxy-2,6,10-*tris*(3,4-dimethoxyphenyl)-8,12-bis(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-10,11-*trans*-11,12-*trans*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano-[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid, details of which will be presented in Part 22 (compound **14**) of this series. Band $2E_{2.1.2}$ afforded 2*R*,3*R*:6*R*,7*S*,8*R*:10*R*,11*S*,12*S*-3,7,11-triacetoxy-2,6,10-tris(3,4-dimethoxyphenyl)-8,12-bis-(2,4-dimethoxyphenyl)-2,3-*cis*-6,7-*trans*-7,8-*trans*-10,11-*trans*-11,12-*cis*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (see Part 23, compound **12**).

Fr. $2E_{2.2}$ (28 mg) was further purified by prep. TLC in hexane–toluene–Me_2CO–MeOH (20:60:15:5, ×4) to give 2 bands, $2E_{2.2.1}$ (R_f 0.31, 9 mg) and $2E_{2.2.2}$ (R_f 0.25, 7 mg). Acetylation of $2E_{2.2.1}$ afforded (2*R*,3*S*:6*R*,7*S*,8*S*:10*S*,11*S*,12*R*)-3,7,11-triacetoxy-2,6,10-*tris*(3,4-dimethoxyphenyl)-8,12-bis(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-10,11-*cis*-11,12-*trans*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano-[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid, 12 mg (see Part 22, compound **6**). Acetylation of band $2E_{2.2.2}$ followed by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×2) gave (2*R*,3*S*:6*S*,7*S*,8*R*:10*R*,11*S*,12*S*)-3,7,11-triacetoxy-2,6,10-*tris*(3,4-dimethoxyphenyl)-8,12-bis(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-10,11-*trans*-11,12-*cis*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene **48** as a white amorphous solid (2 mg) (Found: $[M]^+$, 1100.4046. $C_{61}H_{64}O_{19}$ requires $[M]^+$, 1100.4041). ^1H NMR data (Table 3). CD $[\theta]_{300}$ 2.4×10^2, $[\theta]_{284}$ 1.2×10^4, $[\theta]_{270}$ 1.0×10^2, $[\theta]_{265.5}$ -4.4×10^2, $[\theta]_{254}$ 5.3×10^2, $[\theta]_{252}$ 1.2×10^2, $[\theta]_{246}$ -2.2×10^3, $[\theta]_{243}$ 1.7×10^2.

The $2E_{2.3}$ band (9 mg) was further purified by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×4) to give a single band (R_f 0.24, 5.5 mg) which on acetylation afforded (2*R*,3*S*:6*R*,7*S*,8*R*)-3,7-diacetoxy-5-methoxy-10-[(2*R*,3*S*,4*S*-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*trans*-3,4,6,7-tetrahydro-2*H*,8*H*-pyrano[3,2-*g*]chromene **33** as a white amorphous solid (6 mg) (Found: $[M]^+$, 1100.4047. $C_{61}H_{64}O_{19}$ requires $[M]^+$, 1100.4041). ^1H NMR data (Table 2). CD $[\theta]_{300}$ 9.6×10^2, $[\theta]_{288}$ -1.7×10^4, $[\theta]_{282.5}$ -5.2×10^2, $[\theta]_{274}$ 1.4×10^4, $[\theta]_{254.5}$ 1.9×10^1, $[\theta]_{246.5}$ -3.0×10^4, $[\theta]_{239.5}$ 4.8×10^2.

The $2E_4$ band (420 mg) was further resolved by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×2) into two main bands, $2E_{4.1}$ (R_f 0.49, 70 mg) and $2E_{4.2}$ (R_f 0.46, 150 mg). Fr. $2E_{4.1}$ was purified by successive prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:14:5:1, ×2) (R_f 0.42, 10 mg) and hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×4) to give a single band at R_f 0.29 (5 mg).

Acetylation gave (2*R*,3*R*:6*R*,7*S*,8*S*:10*S*,11*S*,12*R*)-3,7,11-triacetoxy-2,6,10-*tris*(3,4-dimethoxyphenyl)-8,12-bis(2,4-dimethoxyphenyl)-2,3-*cis*-6,7-*trans*-7,8-*cis*-10,11-*cis*-11,12-*trans*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano-[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (5 mg) (see Part 23, compound **14**). Band $2E_{4.2}$ was further resolved by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:13:1, ×3) into two bands, $2E_{4.2.1}$ (R_f 0.63, 40 mg) and $2E_{4.2.2}$ (R_f 0.58, 42 mg). The $2E_{4.2.1}$ band was subjected to a further separation by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:14:5:1, ×2) which afforded a band at R_f 0.51 (19 mg). This was acetylated and purified by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×3) to give (2*R*,3*R*:8*R*,9*S*,10*S*)-3,9-diacetoxy-5-methoxy-6-[(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxy-flavan-4-yl]-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*cis*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene as a white amorphous solid (R_f 0.50, 5 mg) (see Part 23, compound **10**). Band $2E_{4.2.2}$ was further purified by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:14:5:1, ×3) to give a single fr. at R_f 0.22 (9 mg). Acetylation afforded (2*R*,3*S*:6*R*,7*S*,8*S*)-3,7-diacetoxy-5-methoxy-10-[(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxy-phenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-3,4,6,7-tetra-hydro-2*H*,8*H*-pyrano[3,2-*g*]chromene **36** as a white amorphous solid (10 mg) (Found: C, 66.5; H, 5.8. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%). ^1H NMR data (Table 2). CD $[\theta]_{300}$ -2.1×10^2, $[\theta]_{288.5}$ -2.4×10^4, $[\theta_{282.5}$ 1.1×10^{-3}, $[\theta]_{274}$ 2.4×10^4, $[\theta]_{255.5}$ -7.4×10^1, $[\theta]_{246.5}$ -2.5×10^4, $[\theta]_{238.5}$ 4.4×10^2.

The procedure for the separation of fr. 3 by CC on Sephadex LH-20–EtOH leading to subfrs 3A-3P was as

described in Part 3 [8], while that of the fractionation of subfr. 3K by MPLC on Fractogel TSK HW-40(S)–EtOH affording eight frs $3K_1$–$3K_8$, was documented in Part 12 [19]. The phlobatannins in frs $3K_3$, $3K_5$ and $3K_6$ were also described in Part 12 and comprised mainly of 'dimeric' analogues. Fr. $3K_4$ was subsequently acetylated and purified by successive prep. TLC in hexane–benzene–Me_2CO–MeOH (12:4:3:1, ×3) (R_f 0.30, 48 mg) and the same solvent (×5) to give (2*R*,3*R*:6*R*,7*S*,8*S*:10*R*,11*S*,12*S*) - 3,7,11 - triacetoxy - 2,6,10 - *tris*(3,4 - dimethoxyphenyl) - 8,12 - bis(2,4 - dimethoxyphenyl) - 2,3 - *cis* - 6,7 - *trans* - 7,8 - *cis* - 10,11 - *trans* - 11,12 - *cis* - 3,4,7,8,11,12 - hexahydro - 2*H*,6*H*,10*H* - dipyrano[2,3 - *f* : 2′,3′ - *h*]chromene as a white amorphous solid (R_f 0.29, 7 mg) (see Part 23, compound **6**).

Methylation of fr. $3K_7$ (308 mg) followed by prep. TLC in hexane–benzene–Me_2CO–MeOH (12:4:3:1, ×2) afforded two main bands, $3K_7A$ (R_f 0.45, 35 mg) and $3K_7B$ (R_f 0.38, 67 mg). Acetylation of the $3K_7A$ band and purification by prep. TLC in hexane–benzene–Me_2CO–MeOH (12:4:3:1 ×3) gave an additional portion of the aforementioned hexahydrodipyrano[2,3-*f* : 2′,3′-*h*]chromene (R_f 0.35, 14 mg). The $3K_7B$ band was acetylated and purified by successive prep. TLC in hexane–benzene–Me_2CO–MeOH (12:4:3:1, ×3) (R_f 0.27, 28 mg) and then benzene–1,2-dichloroethane–Me_2CO (5:4:1, ×4) (R_f 0.46, 14 mg) to give (2*S*,3*R*:6*S*,7*S*,8*R*:10*R*,11*S*,12*S*)-3,7,11-triacetoxy - 2,6,10 - *tris*(3,4 - dimethoxyphenyl) - 8,12 - bis(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans* - 10,11 - *trans* - 11,12 - *cis* - 3,4,7,8,11,12 - hexahydro - 2*H*,6*H*,10*H* - dipyrano[2,3 - *f* : 2′,3′ - *h*]chromene as a white amorphous solid (see Part 23, compound **18**).

Fr. 3L (1.17 g) was further resolved by CC on Fractogel TSK HW-40(S) in EtOH (3 × 55 cm column, flow rate 7.5 ml min^{-1}, 15 ml eluant per tube, first 1.5 l of eluant discarded) into frs $3L_1$ (tubes 27–35, 7 mg), $3L_2$ (39–45, 23 mg), $3L_3$ (46–72, 53 mg), $3L_4$ (73–103, 254 mg), $3L_5$ (104–128, 217 mg), $3L_6$ (129–171, 288 mg) and $3L_7$ (172–205, 74 mg). Frs $3L_5$ and $3L_6$ were again selected for further investigation based upon their colouration on TLC with HCHO–H_2SO_4.

Fr. $3L_5$ (217 mg) was methylated and the mixt. resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO (90:3:7, ×2) to give two main bands, $3L_{5.1}$ (R_f 0.45, 40 mg) and $3L_{5.2}$ (R_f 0.29, 13 mg). The $3L_{5.1}$ band was further purified by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×3) and the resultant band (R_f 0.31, 11 mg) then acetylated and separated by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×3) to give (2*R*,3*S*:6*R*,7*S*,8*S*) - 3,7 - diacetoxy - 9 - methoxy - 10 - [(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan - 4 - yl] - 2,6 - bis(3,4 - dimethoxyphenyl) - 8-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*trans*-7,8-*cis*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene as a white amorphous solid (R_f 0.57, 8 mg) (see Part 11, [3]). The $3L_{5.2}$ fr. was similarly further purified by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×4) to give a band (R_f 0.35, 4 mg) which was acetylated and then subjected to prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×3) to give (2*R*,3*S*:8*R*,9*S*,10*S*) - 3,9 - diacetoxy - 5 - methoxy - 6 - [(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano-[2,3-*h*]chromene as a white amorphous solid (R_f 0.47, 3 mg) (see Part 11, [3]).

Fr. $3L_6$ (288 mg) was methylated and the mixt. then resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO (90:3:7, ×2) into two main bands, $3L_{6.1}$ (R_f 0.42, 38 mg) and $3L_{6.2}$ (R_f 0.38, 20 mg). Band $3L_{6.1}$ was resubjected to prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×3) to give bands $3L_{6.1.1}$ (R_f 0.42, 5 mg) and $3L_{6.1.2}$ (R_f 0.38, 6 mg). Acetylation of band $3L_{6.1.1}$, followed by purification by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×3), gave (2*R*,3*R*:6*R*,7*S*,8*S*) - 3,7 - diacetoxy - 9 - methoxy - 10 - [2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4 - dimethoxyphenyl) - 2,3 - *cis* - 6,7 - *trans* - 7,8 - *cis* - 3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene as a white amorphous solid (R_f 0.71, 4 mg) (see Part 23, compound **8**). Band $3L_{6.1.2}$ was similarly acetylated and resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×5) to give two bands at R_f 0.68 (2 mg) and R_f 0.62 (3 mg). The R_f 0.68 band comprised (2*R*,3*S*:6*R*,7*R*,8*S*) - 3,7 - diacetoxy - 9 - methoxy - 10 - [(2*R*,3*S*,4*S*) - 2,3 - *trans* - 3,4 - *trans* - 3 - acetoxy - 3′,4′,7-trimethoxyflavan-4-yl]-2,8-bis(3,4-dimethoxyphenyl)-6-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-3,4,7,8 - tetrahydro - 2*H*,6*H* - pyrano[2,3 - *f*]chromene (**30**) as a white amorphous solid. (Found: $[M]^+$, 1100.4045. $C_{61}H_{64}O_{19}$ requires $[M]^+$, 1100.4041). ^1H NMR data (Table 1). CD $[\theta]_{300}$ 5.0×10^2, $[\theta]_{290}$ 4.5×10^3, $[\theta]_{285}$ 3.0×10^3, $[\theta]_{274.5}$ 1.0×10^4, $[\theta]_{256}$ 1.3×10^3, $[\theta]_{248.5}$ 5.4×10^3, $[\theta]_{245}$ 2.0×10^2, $[\theta]_{242}$ -4.8×10^3, $[\theta]_{239.5}$ 4.6×10^1.

The R_f 0.62 band afforded (2*R*,3*S*:6*R*,7*R*,8*S*:10*S*,11*S*,12*R*) - 3,7,11 - triacetoxy - 2,8,10 - *tris*(3,4 - dimethoxyphenyl) - 6,12 - bis(2,4 - dimethoxyphenyl) - 2,3 - *trans* - 6,7 - *cis* - 7,8 - *trans* - 10,11 - *cis* - 11,12 - *trans* - 3,4,7,8,11,12 - hexahydro - 2*H*,6*H*,10*H* - dipyrano[2,3 - *f* : 2′,3′ - *h*] - chromene as a white amorphous solid (see Part 21, compound **14**). Sepn of band $3L_{6.2}$ (20 mg) by prep. TLC in hexane–toluene–Me_2CO–MeOH (4:12:3:1, ×2) afforded two main bands, $3L_{6.2.1}$ (R_f 0.32, 2 mg) and $3L_{6.22}$ (R_f 0.27, 2 mg). The $3L_{6.2.1}$ band was acetylated and further purified by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×4) to give (2*R*,3*S*:6*S*,7*S*,8*R*) - 3,7 - diacetoxy - 9 - methoxy - 10 - [(2*R*,3*S*,4*R*) - 2,3 - *trans* - 3,4 - *cis* - 3 - acetoxy - 3′,4′,7 - trimethoxyflavan-4-yl]-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4 - dimethoxyphenyl) - 2,3 - *trans* - 6,7 - *cis* - 7,8 - *trans* - 3,4,7,8 - tetrahydro - 2*H*,6*H* - pyrano[2,3 - *f*]chromene as a white amorphous solid (R_f 0.62, 1 mg) (see Part 21, compound **11**). Acetylation of the $3L_{6.2.2}$ band followed by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×5) gave (2*R*,3*S*:6*S*,7*S*,8*R*:10*R*,11*R*,12*S*) - 3,7,11 - triacetoxy - 2,6,12 - *tris*(3,4 - dimethoxyphenyl) -

8,10-bis(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-10,11-*cis*-11,12-*trans*-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (R_f 0.58, 2 mg) (see Part 21, compound **11**).

Phlobatannins from Colophospermum mopane. Drillings (3.5 kg) from the heartwood were repeatedly extracted with MeOH (6 × 2.5 l) at 20° over 10 days. The combined extract was evapd to *ca* 2 l, extracted with hexane (7 × 1 l) and the MeOH removed under vacuum to give a red-brown powder (485.3 g), which was subsequently extracted with Et_2O (3.5 l) in a Soxhlet apparatus for 48 hr. Portions (3 × 40 g) of the residual material (356 g) were subjected to Craig countercurrent distribution (Quickfit Steady State Model 20, 25 ml underphase, 103 tubes) in H_2O–2-BuOH–hexane (5:4:1) to give six frs based on 2D paper chromatograms and TLC [benzene–Me_2CO–MeOH (6:3:1)], A (tubes 1–23, 32 g), B (24–37, 7 g) C (38–49, 8 g), D (50–60, 8 g), E (61–83, 19.4 g) and F (84–103, 51 g) (31.4 g of the extract was insol. in the lower phase). Fr. B was further resolved by CC on Sephadex LH-20 in EtOH (5 × 63 cm column, 7 g per column, flow rate 1.6 ml min^{-1}, first 1.5 l of eluant discarded) to give five frs, B_1 (tubes 1–165, 505 mg), B_2 (166–275, 735 mg), B_3 (276–345, 552 mg), B_4 (346–645, 916 mg) and B_5 (646–1070, 2.43 g). Fr. C was resolved by CC on Sephadex LH-20 in EtOH (5 × 100 cm column, 8 g per column, flow rate 4 ml min^{-1}, first 2 l of eluant discarded) into five frs, C_1 (tubes 91–155, 892 mg), C_2 (156–324, 3.2 g), C_3 (325–435, 851 mg), C_4 (436–505, 323 mg) and C_5 (506–950, 1.12 g). Fr. D was further resolved by CC on Sephadex LH-20 in EtOH (5 × 95 cm column, 8 g per column, flow rate 0.7 ml min^{-1}, first 1.5 l of eluant discarded) to give 17 frs, D_1 (tubes 123–129, 29 mg), D_2 (161–173, 72 mg), D_3 (183–191, 38 mg), D_4 (201–207, 22 mg), D_5 (225–260, 302 mg), D_6 (261–270, 91 mg), D_7 (271–299, 272 mg), D_8 (300–315, 223 mg), D_9 (316–362, 561 mg), D_{10} (363–480, 1.53 g), D_{11} (481–562, 432 mg), D_{12} (563–670, 635 mg), D_{13} (671–771, 292 mg), D_{14} (771–891, 234 mg), D_{15} (892–933, 97 mg), D_{16} (934–1090, 1.49 g) and D_{17} (1091–1297, 661 mg). Fr. D_{10} (1.53 g) was further fractionated by MPLC on Fractogel TSK HW-40(S) in EtOH (3.5 × 45 cm column, 1.53 g per column, flow rate 2.6 ml min^{-1}, first 1.5 l of eluant discarded) to give eight subfrs, $D_{10.1}$ (tubes 1–20, 108 mg), $D_{10.2}$ (21–50, 127 mg), $D_{10.3}$ (51–90, 410 mg), $D_{10.4}$ (91–110, 167 mg), $D_{10.5}$ (111–140, 185 mg), $D_{10.6}$ (141–190, 193 mg), $D_{10.7}$ (191–255, 176 mg) and $D_{10.8}$ (256–284, 138 mg). Successive methylation–purification and acetylation–purification of fr. B_3 afforded the decamethyl ether triacetate **21** of the fisetinidol-(4α,6)-tetrahydropyrano[2,3-*h*]chromene **19** [3]. Fr. $D_{10.3}$ similarly afforded derivative **18** of the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]-chromene **16** [3].

A portion (67 mg) of fr. $D_{10.4}$ was methylated, purified by successive prep. TLC in benzene–Me_2CO–MeOH (17:2:1) (R_f 0.28, 12.1 mg) and benzene–EtOAc–Me_2CO (7:2:1, ×2) (R_f 0.11, 3.4 mg), acetylated and finally purified by prep. TLC in benzene–EtOAc–Me_2CO (90:7:3, ×2) to give (2*R*,3*S*:6*R*,7*S*,8*R*)-2,3-*trans*-6,7-*trans*-7,8-*trans*-3,7-diacetoxy-9-methoxy-10-[(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene **27** as a white amorphous solid (R_f 0.1, 2.4 mg) (Found: $[M]^+$, 1100.4048. $C_{61}H_{64}O_{19}$ requires $[M]^+$ 1100.4041). ^1H NMR data (Table 1). CD $[\theta]_{293.8}$ 1.1×10^3, $[\theta]_{284.9}$ -2.6×10^3, $[\theta]_{266}$ -6.6×10^1, $[\theta]_{230.7}$ -3.7×10^4, $[\theta]_{218.6}$ -5.7×10^4, $[\theta]_{211.7}$ 1.1×10^2. A portion (100 mg) of fr. $D_{10.5}$ was methylated and successively purified by prep. TLC in benzene–Me_2CO–MeOH (17:2:1) (R_f 0.54, 11.4 mg) and benzene–EtOAc–Me_2CO (7:2:1, ×2) to give a band at R_f 0.36 (5.2 mg). This was acetylated and separated by prep. TLC in benzene–EtOAc–Me_2CO (90:7:3, ×3) to give (2*R*,3*R*:6*R*,7*S*,8*S*)-2,3-*cis*-6,7-*trans*-7,8-*cis*-3,7-diacetoxy-9-methoxy-10-[(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3-acetoxy-3′,4′,7-trimethoxyflavan-4-yl]-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene as a white amorphous solid (R_f 0.20, 4.1 mg) (see Part 23, compound **8**). Fr. B_4 (915 mg) was methylated in four separate portions and separated by prep. TLC in benzene–Me_2CO–MeOH (85:12:3, ×2) to give a main band at R_f 0.28 (114 mg). This was further resolved by prep. TLC in the same solvent (×2) to give a band at R_f 0.16 (38.3 mg) which was acetylated and separated by successive prep. TLC in benzene–Me_2CO (9:1) (R_f 0.26, 3 mg) and benzene–Me_2CO (9:1, ×2) to give (2*R*,3*S*:6*S*,7*S*,8*R*:10*S*,11*S*,12*R*)-2,3-*trans*-6,7-*cis*-7,8-*trans*-10,11-*cis*-11,12-*trans*-3,7,11-triacetoxy-8,12-bis(2,4-dimethoxyphenyl)-2,6,10-*tris*(3,4-dimethoxyphenyl)-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (R_f 0.39, 2.5 mg) (see Part 21, compound **5**). Fr. C (2.05 g) was methylated in six separate portions and the combined mixt. separated by prep. TLC in hexane–Me_2CO–EtOAc (13:4:3, ×2) to give a main band at R_f 0.06 (768 mg). This was further resolved by prep. TLC in benzene–Me_2CO–MeOH (18:1:1, ×3) into two frs at R_f 0.53 (91.8 mg) and R_f 0.39 (69 mg). Acetylation of the R_f 0.53 band and purification by prep. TLC in 1,2-dichloroethane–Me_2CO (49:1, ×2) afforded 2*R*,3*S*:6*R*,7*S*,8*S*:10*R*,11*S*,12*R*)-2,3-*trans*-6,7-*trans*-7,8-*cis*-10,11-*trans*-11,12-*trans*-3,7,11-triacetoxy-8,12-bis(2,4-dimethoxyphenyl)-2,6,10-*tris*(3,4-dimethoxyphenyl)-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (R_f 0.15, 15.7 mg) (see Part 22, compound **14**). The R_f 0.39 band was further resolved by prep. TLC in benzene–Me_2CO–MeOH (18:1:1, ×2) to give a band at R_f 0.32 (32 mg) which was acetylated and purified by prep. TLC in 1,2-dichloroethane–Me_2CO (49:1, ×2) to afford (2*R*,3*S*:6*R*,7*S*,8*S*:10*S*,11*S*,12*R*)-2,3-*trans*-6,7-

trans-7,8-*cis*-10,11-*cis*-11,12-*trans*-3,7,11-triacetoxy-8,12-bis(2,4-dimethoxyphenyl)-2,6,10-*tris*(3,4-dimethoxyphenyl)-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[2,3-*f*:2′,3′-*h*]chromene as a white amorphous solid (R_f 0.11, 4 mg) (see Part 22, compound **6**).

Synthesis of triflavanoids (**2**), (**5**), (**8**) *and* (**11**). Synthesis of triflavanoids **2** and **5** was as described in Part 11 [3]. Fisetinidol-(4β,8)-catechin 4-*O*(E) methyl ether (4 g) [8] and mollisacacidin (2 g) were dissolved in 0.1 M HCl (450 ml) and the mixt. stirred at room temp. for 13 hr. The mixt. was then extracted with EtOAc (5 × 250 ml), the combined extracts dried (Na_2SO_4) and the solvent evapd. The light-brown residue (5.6 g) obtained was subjected to CC on Sephadex LH-20-EtOH (5 × 120 cm column, flow rate 0.8 ml min^{-1}, 24 ml eluant per tube, first 2.5 l of eluant discarded) to give five frs, 1 (tubes 106–182, 1.22 g), 2 (344–364, 210 mg), 3 (365–410, 1.32 g), 4 (411–470, 1.41 g) and 5 (471–554, 340 mg). Fr. 1 consisted of starting biflavanoid, fr. 2 of the (4β,6:4β,8) trimer **11**, frs 3 and 4 of a mixt. of trimer **11** and the (4α,6) isomer **8**, and fr. 5 of the (4α,6:4β,8) trimer **8**. Subsequent separation of combined frs 3 and 4 using Sephadex LH-20 in EtOH–H_2O (1:1) afforded an additional portion (780 mg) of the (4β,6:4β,8) trimer **11**.

Base-catalysed conversion of triflavanoid (**5**). The mono-*O*-methyl ether **5** (920 mg) was dissolved in a 0.025 M Na_2CO_3–0.025 M $NaHCO_3$ buffer soln (400 ml) (pH 10) and the mixt. stirred at 55° for 5.5 hr. Chilling to 0° followed by acidification with 1 M HCl, extraction with EtOAc (5 × 250 ml), drying (Na_2SO_4) of the extract and evapn to dryness, afforded a light-brown residue (900 mg). This was subjected to CC on Sephadex LH-20–EtOH (3 × 120 cm column, flow rate 0.8 ml min^{-1}, 24 ml of eluant per tube, first 2.1 l of eluant discarded) to give four frs, 1 (tubes 58–92, 34 mg), 2 (93–134, 476 mg), 3 (135–157, 170 mg) and 4 (158–195, 78 mg). Methylation of fr. 1 followed by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (60:28:10:1, ×2) afforded a band at R_f 0.42 (3.4 mg), which was acetylated to give the fisetinidol-(4β,6)-didehydro-fisetinidol-(3′,7:4α,8)-catechin hepta-*O*-methyl ether triacetate **51** as a white amorphous solid (4.2 mg) (Found: $[M]^+$, 1084.3733. $C_{60}H_{60}O_{19}$ requires $[M]^+$ 1084.3729). ^{1}H NMR data (Table 3). CD $[\theta]_{300}$ -2.2×10^4, $[\theta]_{291}$ -3.4×10^4, $[\theta]_{279}$ 1.1×10^2, $[\theta]_{272.5}$ 8.1×10^3, $[\theta]_{265.5}$ 5.7×10^3, $[\theta]_{236}$ 1.2×10^5. Methylation of fr. 2 followed by prep. TLC in hexane–Me_2CO–EtOAc (2:2:1) afforded four main bands, 2A (R_f 0.48, 100 mg), 2B (R_f 0.45, 42 mg), 2C (R_f 0.39, 42 mg) and 2D (R_f 0.36, 14 mg). The 2A band was further resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:13:5:2, ×2) into two main bands, $2A_1$ (R_f 0.54, 6 mg) and $2A_2$ (R_f 0.43, 47 mg). Acetylation of band $2A_1$ and PLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×3) afforded the hexahydrodipyrano-[2,3-*f*:2′,3′-*h*]chromene decamethyl ether triacetate **48** as a white amorphous solid (R_f 0.46, 2.5 mg) with ^{1}H NMR and CD data identical to those of the natural product. Acetylation of band $2A_2$ gave the fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromene decamethyl ether triacetate **36** as a white amorphous solid (56 mg) (Found: C, 66.7; H, 5.8. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%) with ^{1}H NMR and CD data identical to those of the natural product. Prep. TLC separation of the 2B band in $CHCl_3$–hexane–Me_2CO–MeOH (30:13:5:2, ×2) afforded a band at R_f 0.63 (13 mg), which on acetylation gave the fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromene derivative **33** as a white amorphous solid (15 mg) (Found: C, 66.6; H, 5.8. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%) with ^{1}H NMR and CD data identical to those of the natural product. The 2C band was resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (12:5:2:1, ×2) to give a main band at R_f 0.80 (4 mg). Acetylation followed by prep. TLC in $CHCl_3$–hexane–Me_2CO (5:4:1, ×2) gave the fisetinidol-(4α,10)-tetrahydropyrano[3,2-*g*]chromene decamethyl ether triacetate **42** as a white amorphous solid (R_f 0.56, 2 mg) (Found: $[M]^+$, 1100.4049. $C_{61}H_{64}O_{19}$ requires $[M]^+$ 1100.4041). ^{1}H NMR data (Table 2). CD $[\theta]_{290}$ -1.0×10^4, $[\theta]_{286}$ -5.1×10^2, $[\theta]_{276}$ 2.1×10^4, $[\theta]_{258.5}$ -1.7×10^2, $[\theta]_{248.5}$ -2.4×10^4, $[\theta]_{236.5}$ 8.4×10^2. Purification of fr. 2D by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (12:5:2:1, ×2) (R_f 0.85, 3 mg), followed by acetylation, afforded the fisetinidol-(4α,10)-tetrahydroprano[3,2-*g*]chromene derivative **39** as a white amorphous solid (3 mg) (Found: $[M]^+$, 1100.4045. $C_{61}H_{64}O_{19}$ requires $[M]^+$ 1100.4041). ^{1}H NMR data (Table 2). CD $[\theta]_{300}$ -7.9×10^2, $[\theta]_{289}$ -1.2×10^4, $[\theta]_{283.5}$ -1.6×10^1, $[\theta]_{274.5}$ 1.4×10^4, $[\theta]_{257.5}$ -4.1×10^2, $[\theta]_{246}$ -3.4×10^4.

Fr. 3 (170 mg) was methylated and the mixt. resolved by prep. TLC in hexane–Me_2CO–EtOAc (2:2:1) to give two bands, 3A (R_f 0.52, 29 mg) and 3B (R_f 0.41, 11 mg). The 3A band was further purified by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:14:5:1, ×2); the resulting band (R_f 0.49, 18 mg) was then acetylated to give the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromene decamethyl ether diacetate **30** as a white amorphous solid (22 mg) (Found: C, 66.7; H, 5.8. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%) with ^{1}H NMR and CD data identical to those of the natural product. Further purification of the 3B band by prep. TLC in $CHCl_3$–hexane–Me_2CO–MeOH (30:14:5:1, ×3) afforded a band at R_f 0.35 (9 mg), which was then acetylated to give the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromene decamethyl ether triacetate **27** as a white amorphous solid (12 mg) (Found: C, 66.6; H, 5.7. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%) with ^{1}H NMR and CD data identical to those of the natural product.

Prep. TLC separation of fr. 4 (78 mg) in hexane–Me_2CO–EtOAc (2:2:1) afforded a main brand at R_f 0.50 (29 mg), which was acetylated to give the fisetinidol-(4α,10)-tetrahydropyrano[2,3-*f*]chromene decamethyl ether triacetate **24** as a white amorphous solid (33 mg) (Found: C, 66.6; H, 5.7. $C_{61}H_{64}O_{19}$ requires C, 66.54; H, 5.86%). ^{1}H NMR data (Table 1).

CD $[\theta]_{300}$ 2.3×10^2, $[\theta]_{293.5}$ 3.1×10^1, $[\theta]_{285.5}$ -7.7×10^3, $[\theta]_{279.5}$ 1.6×10^2, $[\theta]_{270}$ 6.9×10^3, $[\theta]_{258}$ -1.6×10^2, $[\theta]_{246.5}$ -4.0×10^4, $[\theta]_{240}$ 5.7×10^2.

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