Phytochemistry, Vol. 29, No. 9, pp. 2979–2989, 1990.
Printed in Great Britain.

0031–9422/90 $3.00+0.00

STRUCTURE AND SYNTHESIS OF PHLOBATANNINS RELATED TO (−)-FISETINIDOL-(−)-EPICATECHIN PROFISETINIDINS*

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(*Received* 30 *November* 1989)

Key Word Index—*Colophospermum mopane*; *Guibourtia coleosperma*; *Baikiaea plurijuga*; Leguminosae; Caesalpiniodeae; heartwood; (−)-fisetinidol-(−)-epicatechins; profisetinidins; phlobatannins; pyran rearrangement; C-2 epimerization.

Abstract—Several members of the class of natural 'phlobaphene' condensed tannins, representing the products of C-ring isomerization of (−)-fisetinidol-(4α,8) and (4β,8)-(−)-epicatechin profisetinidins have been characterized. These comprise four functionalized tetrahydropyrano[2,3-*h*]chromenes, two [2,3-*g*]-analogues and four[2,3-*f*]-regio-isomers. A novel protocol of effecting differentiation between the regio-isomers based on homonuclear NOE difference spectroscopy (^{1}H NMR) is proposed. The structures of some of the natural products were confirmed by synthesis via base-catalysed rearrangement of their presumed precursors. Under these mild alkaline conditions, the biflavanoids are susceptible to epimerization at C-2 (F-ring) hence leading to conversion of a (−)-epicatechin to a (−)-catechin DEF moiety. The natural occurrence of pyran rearranged analogues related to both these units presumably reflects similar mechanisms for the *in vivo* and *in vitro* processes.

INTRODUCTION

In contrast to the ubiquitous (−)-fisetinidol-(+)-catechin† profisetinidins [2, 3] the involvement of (−)-epicatechin [(2*R*,3*R*)-2,3-*cis*-flavan-3,3′,4′,5,7-pentaol] in this class of condensed tannins has only recently been demonstrated [4]. Such natural occurrence in three closely related species of the Caesalpiniodeae where (−)-fisetinidol-(+)-catechins coexist with their pyran rearranged analogues [5–7], indicates possible participation of the (−)-fisetinidol-(−)-epicatechins in C-ring isomerization. Application of the concise approach to the synthesis of the functionalized tetrahydropyrano-chromenes would then not only confirm the structures of the natural products but would also provide information regarding the behaviour of the (−)-epicatechin moiety under basic conditions. Such evidence could usefully serve as model for our study [8] of the economically important group of procyanidin condensed tannins where (−)-epicatechin figures prominently both as 'upper' and as 'terminal' units [9–11]. We thus now disclose detailed results of relevance to the natural occurrence and biomimetic synthesis of those tetrahydropyrano[2,3-*f*]-, [2,3-*g*]-, and [2,3-*h*]-chromenes related to (−)-fisetinidol-(−)-epicatechin profisetinidins.

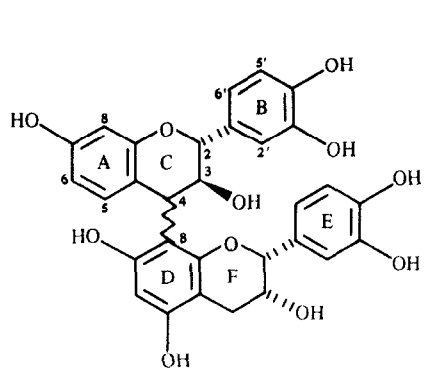
RESULTS AND DISCUSSION

The (−)-fisetinidol-(4α,8) and (4β,8)-(−)-epicatechins **1** and **2** are accompanied in the heartwoods of *Colophospermum mopane* (mopane) [12], *Guibourtia coleosperma* (false mopane) [12], and *Baikiaea plurijuga* (Rhodesian teak) [12] by a novel series of related pyran rearranged analogues. These comprise of the 8,9-*trans*-9,10-*cis*- and 8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano [2,3-*h*]chromenes **3** and **5**, the *trans*-*cis* C-2 (F-ring) epimer **7**, the 8,9-*cis*-9,10-*trans* analogue **11**, the 6,7-*trans*-7,8-*cis*- and 6,7-*cis*-7,8-*trans*-3,4,6,7-tetrahydro-2*H*, 8*H*-pyrano[2,3-*g*]chromenes **13** and **15**, the 6,7-*trans*-7,8-*cis*- and 6,7-*trans*-7,8-*trans*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano [2,3,-*f*]-chromenes **17** and **19**, and the 6,7-*cis*-7,8-*trans* C-2 (F) epimers **21** and **23**. In addition to these the natural occurrence of the synthetic 6,7-*trans*-7,8-*cis*-tetrahydropyrano[2,3-*g*]chromene and the *all*-*trans*-[2,3-*f*] analogue with (+)-catechin DEF units is demonstrated (cf. ref. [7], part 4). Owing to the complexity of the phenolic mixtures in the heartwoods of the above species, these metabolites were identified as heptamethyl ether diacetates, e.g. **4**, the additional chromatographic stages offered by such an approach being a prerequisite for compound purity.

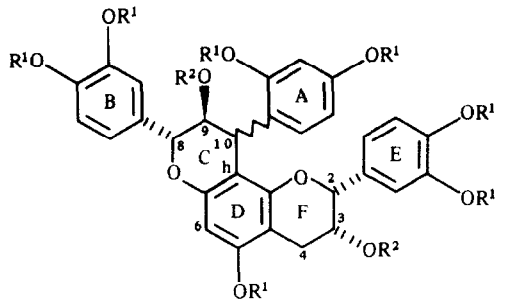
Analysis of the 1H NMR data (Tables 1–3) at 300 MHz of the series of heptamethyl ether diacetates reveals NOE associations of 2-OMe(A) with 3-H(A) and of 4-OMe(A) with both 3- and 5-H(A) and the absence of the effects of dynamic rotational isomerism at ambient temperatures. These features are reminiscent of the pyran rearranged nature, with concomitant 'release' of the resorcinol A-ring from heterocycle C, of this class of oligoflavanoids [5–7]. Differentiation of the tetrahydropyrano[2,3-*f*]- and [2,3-*h*]chromenes and the regio-isomeric [2,3-*g*]-analogues is effected by NOE experiments which indicate selective association of the D-ring singlet and the methoxy group of this ring for the [2,3-*f*]- and [2,3-*h*]-isomers only [13]. The latter groups are accordingly distinguished by the

* Part 12 in the series 'Oligomeric Flavanoids' [1].

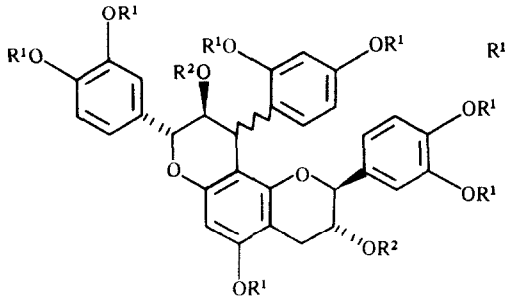
†(−)-Fisetinidol is (2*R*,3*S*)-2,3-*trans*-flavan-3,3′,4′,7-tetraol and (+)-catechin its 5-oxy analogue.



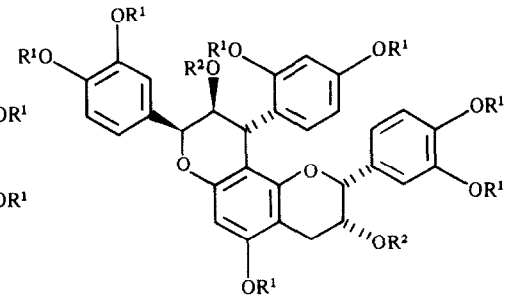
1 ~ = ⟋⟍
2 ~ = ◀



3 ~ = ◀, R^1 = R^2 = H
4 ~ = ◀, R^1 = Me, R^2 = Ac
5 ~ = ⟋⟍, R^1 = R^2 = H
6 ~ = ⟋⟍, R^1 = Me, R^2 = Ac



7 ~ = ◀, R^1 = R^2 = H
8 ~ = ◀, R^1 = Me, R^2 = Ac
9 ~ = ⟋⟍, R^1 = R^2 = H
10 ~ = ⟋⟍, R^1 = Me, R^2 = Ac

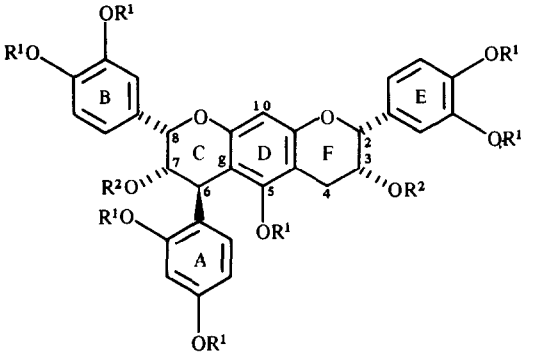


11 R^1 = R^2 = H
12 R^1 = Me, R^2 = Ac

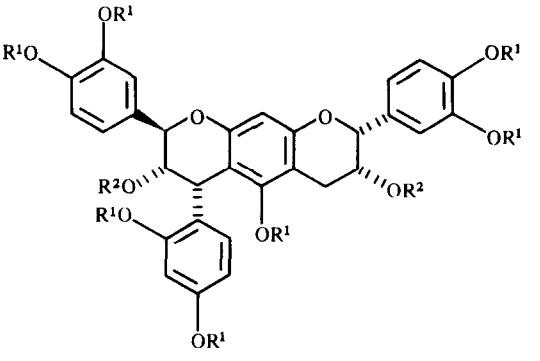
selective NOE association of the D-ring methoxy and the C-ring proton adjacent to the resorcinol moiety for the [2,3-*f*]-analogues only, e.g. 9-OMe(D)→8-H(C) (1.7%) for **18**. Confirmation of the tetrahydropyrano[2,3-*h*]chromene arrangement for those analogues having 2α- and 10β-aryl groups, e.g. **4**, or vice versa, e.g. the synthetic **10** (*vide infra*), are available via NOE association [5–7] of 10-H(C) with 2- and 6-H(E). The potentially useful association between 5-OMe(D) and 4-CH_2(F) for tetrahydropyrano-[2,3-*g*]- and [2,3-*h*]chromenes, e.g. 1.05% for **4**, are, however, inconsistent [13]. Despite our reluctance to utilize the aforementioned NOE phenomena previously [6, 7, 13], their consistency in the considerable collection of 'dimeric' analogues at our disposal [6, 7, 13–15] indicates that they may confidently be used as probe for differentiation of the tetrahydropyrano[2,3-*f*]-, [2,3-*g*]- and [2,3-*h*]chromenes.

The ^{1}H NMR spectra of the heptamethyl ether diacetates invariably display heterocyclic AMX and ABMX spin systems for the C- and F-rings respectively thus facilitating definition of the relative configurations of these rings {$J_{2,3}$ *ca* 1.0, 6.0–7.5 Hz for 2,3-*cis* and *trans* F-rings respectively; $J_{6,7}=J_{7,8}=J_{8,9}$ 10.5, *ca* 1.0, 5.5–6.5 Hz, and $J_{7,8}=J_{6,7}=J_{9,10}$ 6.0, *ca* 2.0, 4.5–5.5 Hz for *trans-cis*, *cis-trans*, and *trans-trans* C-rings of the [2,3-*f*]-, [2,3-*g*]- and [2,3-*h*]-analogues respectively}. Prominent NOE association of 6- and 8-H(C) with 6-H(A) in the appropriate regio-isomers not only confirm the *trans-cis*-[for **4**, **8**, **16**, and **18**] and *cis-trans*-[for **12**, **14**, **22**, and **24**] relative configurations but also indicate a preferred sofa conformation (C-ring) in which the resorcinol moiety occupies a near axial orientation [6, 7]. The conspicuously small *J*-values for the *all-trans* (C) isomers **6** and **20** presumably reflect significant contributions of A-forms towards the conformations of these heterocycles [16]. Studies aimed at verifying this assumption is presently being undertaken, details of which will be presented in an impending publication.

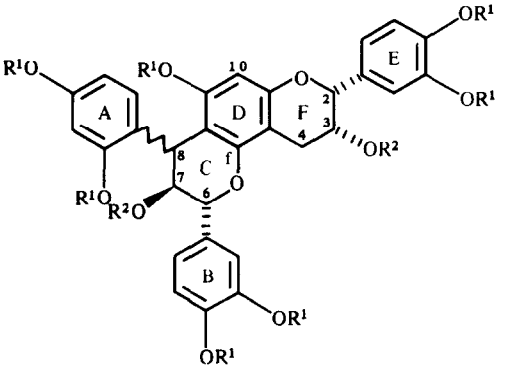
Having initially correlated the spin systems of the constituent ABC- and DEF-moieties by decoupling experiments using the benzylic protons of the C- and F-rings as reference signals, and established the aromatic oxygenation pattern by appropriate NOE studies, attention is focussed on the absolute configuration of these novel metabolities. The coexistence of the 2-C(F) epimeric 8,9-*trans*-9,10-*cis*-tetrahydropyrano[2,3-*h*]chromenes and their presumed (−)-fisetinidol-(4α,8)-(+)-catechin precursor in *B. plurijuga* (cf. ref. [7], Part 3) indicates that 2,3-*cis* and 2,3-*trans* configuration of the F-ring may be compatiable with (−)- or (+)-epicatechin (e.g. **4**) and (+)- or (−)-catechin (e.g. **8**) DEF-units [17] respectively. Such ambiguity prompted recourse to the synthetic protocol recently developed for this class of natural condensed tannins [6, 7].



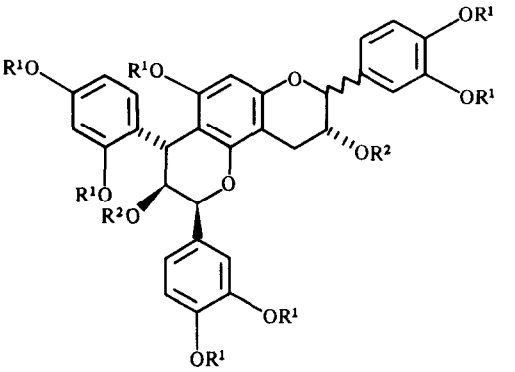
13 $R^1 = R^2 = H$
14 R^1 = Me, R^2 = Ac



15 $R^1 = R^2 = H$
16 R^1 = Me, R^2 = Ac



17 ∿∿ = ◄, $R^1 = R^2 = H$
18 ∿∿ = ◄, R^1 = Me, R^2 = Ac
19 ∿∿ = ıı, $R^1 = R^2 = H$
20 ∿∿ = ıı, R^1 = Me, R^2 = Ac



21 ∿∿ = ıı, $R^1 = R^2 = H$
22 ∿∿ = ıı, R^1 = Me, R^2 = Ac
23 ∿∿ = ◄, $R^1 = R^2 = H$
24 ∿∿ = ◄, R^1 = Me, R^2 = Ac

Owing to the anticipated and undesired susceptibility to regioisomerization and epimerization via an E-ring quinone methide under basic conditions [18], the (−)-fisetinidol-(−)-epicatechins **1** and **2** are to be utilized preferably as 4′-*O*(*E*)-methyl ethers. Selective methylation of (−)-epicatechin under conditions similar to those for the formation of (+)-catechin-4′*O*-methyl ether (ref. [7], Part 3), however, gave a mixture comprising the 3′-*O*-methyl ether as main product but in low yield, and a series of derivatives randomly methylated at the phenolic hydroxyl groups. These differences in behaviour of (+)-catechin and (−)-epicatechin may be attributed to an increase of the pK_a of 3′-OH in the latter relative to that 4′-OH in both flavan-3-ols [19]. Such a failure to selectively protect the 4′-OH of (−)-epicatechin also reflects negatively on the prospects of using the 4′-*O*(*E*)-methyl ethers of those procyanidin-type biflavanoids possessing a (−)-epicatechin DEF-moiety [10] in base-catalysed pyran rearrangements [8]. We are presently investigating the adaptation of experimental conditions aimed at the formation of the 4′-*O*-methyl ether.

Condensation of (−)-epicatechin and (+)-mollisacacidin[(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3′4,4′,7-pentaol] under acid catalysis [2] affords (−)-fisetinidol-(4α,8) and (4β,8)-(−)-epicatechins **1** and **2** in a *ca* 1:1 ratio. Because formation of (4,6)-analogues are insignificant, the aforementioned regioisomerization anticipated for **1** and **2** thus represents the sole possible access to the functionalized tetrahydropyrano[2,3-*f*]- and [2,3-*g*]-chromenes, e.g. **17** and **13**. Treatment of (−)-fisetinidol-(4α,8)-(−)-epicatechin **1** with 0.025 M $NaHCO_3$–0.025 M Na_2CO_3 buffer (pH 10) for 5 hr at 50° under nitrogen, i.e. conditions similar to those applied for the C-2 epimerization of (+)-catechin [20], gave conversion to a mixture comprising the C-2 (F) epimer of biflavanoid **1**, the 8,9-*trans*-9,10-*cis*-tetrahydropyrano-[2,3-*h*]chromene **3**, and its C-2 (F) epimer **7** (Scheme 1). During column chromatography on Sephadex LH-20/ethanol these compounds migrate in a narrow band hence complicating their identification in the phenolic form. Successive methylation/PLC and acetylation/PLC of the mixture facilitate isolation of the pure heptamethyl ether diacetates **4** and **8** with ^1H NMR and CD properties identical to those of the natural products thus unequivocally establishing the (2*R*,3*R*)-(−)-epicatechin and (2*S*,3*R*)-(−)-catechin DEF-moieties of **3** and **7** respectively. The 10β-aryl group in both **4** and **8** and thus 8*R*,9*S*,10*S* absolute configuration is confirmed by the high-amplitude positive Cotton effects (CEs) in the 220–240 nm region of their CD spectra. As the novel C-2 (F) epimer of **1**, i.e. (−)-fisetinidol-(−)-catechin has been synthesized via an alternative route, its detail and related pyran rearrangements will be presented elsewhere.

Table 1. ^{1}H NMR peaks (ppm) of compounds **4**, **6**, **8**, **10** and **12** ($CDCl_3$, 297 K, at 300 MHz)

Ring	H	**4**	**6**	**8**	**10**	**12**
A	3	6.28 *d* (2.5)	6.29 *d* (2.5)	6.40 *d* (2.5)	6.03 *d* (2.5)	6.50 *d* (2.5)
	5	6.34 *dd* (2.5, 8.5)	6.00 *dd* (2.5, 8.5)	6.46 *dd* (2.5, 8.5),	6.12 *dd*, (2.5, 8.5)	6.38 *dd* (2.5, 8.5)
	6	6.82 *d* (8.5)	6.34 *d* (8.5)	6.88 *d* (8.5)	6.56 *d* (8.5)	6.79 *d* (8.5)
B	2	6.86 *d* (2.0)	6.30 *d* (2.0)	6.86 *d* (2.0)	6.84 *d* (2.0)	6.91 *d* (2.0)
	5	6.78 *d* (8.5)	6.58 *d* (8.5)	6.78 *d* (8.0)	6.73 *d* (8.0)	6.76–6.79*
	6	6.90 *dd* (2.0, 8.5)	6.20 *dd* (2.0, 8.5)	6.91 *dd* (2.0, 8.0)	6.90 *dd* (2.0, 8.0)	
C	8	4.99 *d* (10.5)	5.18 *d* (5.5)	5.00 *d* (10.5)	4.96 *d* (8.0)	4.91 *br s* (*ca* 1.0)
	9	5.51 *dd* (6.0, 10.5)	5.75 *dd* (4.5, 5.5)	5.47 *dd* (6.0, 10.5)	5.56 *dd* (7.0, 8.0)	5.49 *dd* (1.0, 2.0)
	10	5.25 *d* (6.0)	4.48 *d* (4.5)	5.06 *d* (6.0)	4.59 *d* (7.0)	4.49 *d* (2.0)
D	6	6.17 *s*	6.33 *s*	6.15 *s*	6.23 *s*	6.30 *s*
E	2	6.84 *d* (2.0)	6.64 *d* (2.0)	6.43 *d* (2.0)	6.61 *d* (2.0)	6.36 *d* (2.0)
	5	6.71 *d* (8.5)	6.62 *d* (8.5)	6.53 *d* (8.5)	6.73 *d* (8.0)	6.63 *d* (8.5)
	6	6.76 *dd* (2.0, 8.5)	6.78 *dd* (2.0, 8.5)	6.21 *dd* (2.0, 8.5)	6.59 *dd* (2.0, 8.0)	6.41 *dd* (2.0, 8.5)
F	2	4.65 *br s* (*ca* 1.0)	4.86 *br s* (*ca* 1.0)	4.85 *d* (7.5)	4.29 *d* 7.0	4.95 *br s* (*ca* 1.0)
	3	5.42 *m*	5.23 *m*	5.00 *m*	5.23 *m*	5.29 *m*
	4_{ax}	2.85 *br s*	2.89–2.92 *m*	2.85 *dd* (5.5, 16.0)	2.94 *dd* (6.0, 16.5)	2.94 *br s*
	4_{eq}			2.61 dd (7.5, 16.0)	2.56 dd (7.0, 16.5)	
	OMe	3.61 (2-A), 3.71 (4-A), 3.75 (5-D), 3.82 (3-B, 4-E), 3.83 (4-B), 3.85 (3-E) (each *s*)	3.47 (3-B), 3.64 (2-A), 3.67 (4-A), 3.72 (3-E), 3.78 (4-E), 3.79 (4-B), 3.84 (5-D) (each *s*)	3.53 (2-A), 3.65, 3.75 (5-D), 3.80 (4-A, 4-E), 3.83, 3.84 (each *s*)	3.44 (2-A), 3.65 (4-A) 3.77 (5-D), 3.81 (3-B, (3-E), 3.82 (4-B), 3.85 (4-E) (each *s*)	3.47 (3-E), 3.77 (2-A), 3.79 (4-A), 3.81 (4-E), 3.82 (4-B), 3.83 (5-D), 3.85 (3-B) (each *s*)
	OAc	1.69, 1.85 (each *s*)	1.72, 1.93 (each *s*)	1.66, 1.92 (each *s*)	1.75, 1.85 (each *s*)	1.75, 1.91 (each *s*)

*Second order.

J values (Hz) are given in parentheses.

Table 2. ^{1}H NMR peaks (ppm) of compounds **14** and **16** in ($CDCl_3$, 296 K, at 3000 MHz)

Ring	H	14	16
A	3	6.51 *d* (2.5)	6.48 *d* (2.5)
	5	6.34 *dd* (2.5, 8.5)	6.43 *dd* (2.5, 8.5)
	6	6.66 *d* (8.5)	6.88 *d* (8.5)
B	2		6.84 *d* (2.5)
	5	6.76–6.85*	6.78 *d* (8.5)
	6		6.89 *dd* (2.0, 8.5)
C	6	4.51 *d* (2.0)	5.19 *d* (6.0)
	7	5.44 *dd* (1.0, 2.0)	5.40 *dd* (6.0, 10.5)
	8	4.96 *br s* (*ca* 1.0)	5.00 *d* (10.5)
D	10	6.25 *s*	6.47 *s*
E	2	7.07 *d* (2.0)	7.00 *d* (2.0)
	5	6.87 *d* (8.0)	6.85 *d* (8.5)
	6	6.97 *dd* (2.0, 8.0)	6.95 *dd* (2.0, 8.5)
F	2	5.11 *br s* (*ca* 1.0)	5.05 *br s* (*ca* 1.0)
	3	5.48 *m*	5.38 *m*
	4_{ax}	3.06–3.16 *m*	2.98 *br s*
	4_{eq}		
	OMe	3.60 (5-D), 3.79 and 3.83 (3- and 4-B), 3.84 (4-E), 3.88 (3-E), 3.89 and 3.91 (2- and 4-A) (each *s*)	3.19 (5-D), 3.79 (4-A), 3.81 (2-A), 3.84 (3-B), 3.85 (4-B), 3.87 (4-E), 3.88 (3-E) (each *s*)
	OAc	1.89, 1.97 (each *s*)	1.71, 1.91 (each *s*)

*Second order.
J values (Hz) are given in parentheses.

Similar treatment of the (−)-fisetinidol-(4β,8)-(−)-epicatechin (**2**) (3.5 hr) afforded seven C-ring isomerized compounds (Scheme 2), two of which correspond to natural products by comparison of the ^{1}H NMR and CD data of their heptamethyl ether diacetates **12** and **24**. A high-amplitude negative CE at 234 nm in the CD spectrum of the 2,3-*cis*-8,9-*cis*-9,10-*trans*-tetrahydropyrano-[2,3-*h*]chromene **12** is compatible with a 10α-aryl group and hence 2*R*,3*R*:8*S*,9*S*,10*R* absolute configuration. The tetrahydropyrano[2,3-*f*]chromene **24**, reputed for inconsistent chiroptical behaviour [7], however, exhibited a positive CE at 236 nm which apparently reflects an 8β-aryl group. ^{1}H NMR coupling constants and assumption of a mechanism [7] (cf. Scheme 2) prescribing retention of configuration at C-3 (C) of biflavanoid **2**, are preferred as evidence in favour of an 8α-aryl group and hence 6*S*,7*S*,8*R* absolute configuration. The above features collectively also confirm the (−)-catechin DEF-moiety with 2*S*,3*R* configuration. Combination of ^{1}H NMR data (Table 1), a high-amplitude negative CE at 238 nm in its CD spectrum, and the pronounced NOE association of 10-H (C) with 2- and 6-H (E), also facilitates characterization of the (−)-catechin based 8,9-*trans*-9,10-*trans*-tetrahydropyrano[2,3,-*h*]chromene **10**, its phenol **9** being hitherto unknown in Nature.

The ^{1}H NMR spectra (Table 4) of the derivatives of the remaining pyran rearranged analogues are characterized by the conspicuous deshielding of 6-H (A), reminiscent of phlobatannins in which the resorcinol A- and pyrocatechol B-rings are interchanged relative to their positions in the more common analogues, e.g. **3** [6, 7]. These were identified as the 8,9-*trans*-9,10-*trans*- and 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromenes **28** and **30**, the latter's C-2 (F) epimer **32**, and the 6, 7-*cis*-7,8-*trans* [2,3-*f*]-regio-isomer **34** based on a (−)-catechin DEF-moiety, by application of the ^{1}H NMR criteria outlined above to their heptamethyl ether diacetates, e.g. **29**.

Under the mild basic conditions **1** and **2** are presumably converted to quinone methides **25*** and **26*** respectively involving both the B- and E-rings. Stereospecific pyran recyclization of **25** (Scheme 1) involving 7-OH (D) and C-2 and stereoselective regeneration of the F-ring via 2-OH (D) and C-2′ at the faces indicated may feasibly explain the formation of the C-2 (F) epimeric pair of 8,9-*trans*-9,10-*cis*-tetrahydropyrano[2,3-*h*]-chromenes **3** and **7** (cf ref. 7, Part 3). For the 3,4-*cis* quinone methide **26** (Scheme 2) both these recyclizations proceed stereoselectively (cf. refs [6, 7]) hence leading to the 8,9-*trans*-9,10-*trans*- and 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3,-*h*]chromene C-2 (F) epimers **9** and **11**. The 6,7-*cis*-7,8-*trans*-[2,3-*f*]-analogue **23** with its (−)-catechin DEF-moiety, is similarly formed but for involvement of 5-OH (D) and the *si*-face at C-2′ in **26**. Formation of the ring interchanged analogues, e.g. **28** is explicable in terms of initial migration of the lower 'unit' to the *re*-race at C-2 in quinone-methide **26** [6, 7]. Pyran recyclization of **27** via

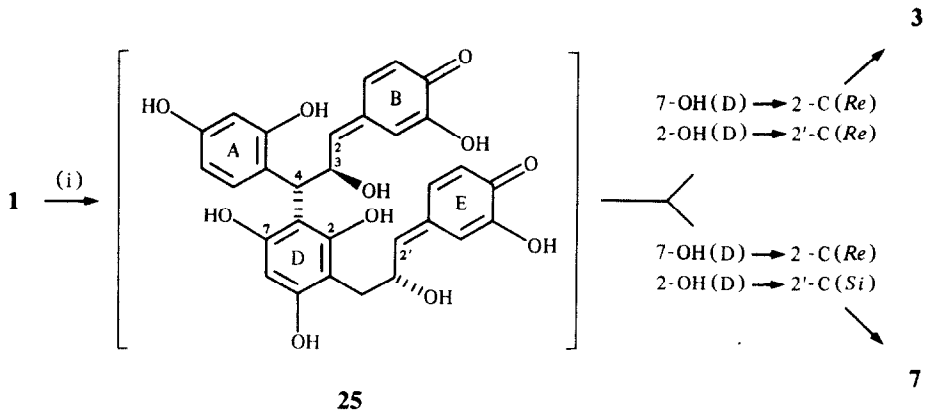
*Quinone methides **25** and **26** are postulated and have not been isolated.

Table 3. ^{1}H NMR peaks (ppm) of compounds **18**, **20**, **22** and **24** ($CDCl_3$, 296 K, at 300 MHz)

Ring	H	18	20	22	24
A	3	6.47 *d* (2.5)	6.31 *d* (2.5)	6.51 *d* (2.5)	6.51 *d* (2.5)
	5	6.41 *dd* (2.5, 8.5)	6.04 *dd* (2.5, 8.5)	6.34 *dd* (2.5, 8.5)	6.35 *dd* (2.5, 8.5)
	6	6.82 *d* (8.5)	6.34 *d* (8.5)	6.63 *d* (8.5)	6.65 *d* (8.5)
B	2	6.80 *d* (2.0)	6.69 *d* (2.5)	6.81 *d* (2.0)	6.88 *d* (2.0)
	5	6.78 *dd* (2.0, 8.5)	6.66 *d* (8.5)	6.78 *d* (9.0)	6.76–6.79*
	6	6.88 *d* (8.5)	6.78 *dd* (2.5, 8.5)	6.83 *dd* (2.0, 9.0)	
C	6	4.97 *d* (10.5)	5.08 *d* (6.5)	4.97 *br s* (*ca* 1.0)	4.95 *br s* (*ca* 1.0)
	7	5.34 *dd* (6.0, 10.5)	5.64 *dd* (5.5, 6.5)	5.46 *dd* (1.0, 2.0)	5.40 *dd* (1.0, 2.0)
	8	5.07 *d* (6.0)	4.50 *d* (6.5)	4.52 *d* (2.0)	4.50 *d* (2.0)
D	10	6.16 *s*	6.19 *s*	6.23 *s*	6.17 *s*
E	2	7.03 *d* (2.0)	7.05 *d* (2.0)	7.06 *d* (2.0)	6.95 *d* (2.0)
	5	6.85 *d* (8.5)	6.86 *d* (8.0)	6.86 *d* (8.5)	6.86 *d* (8.5)
	6	6.97 *dd* (2.0, 8.5)	6.98 *dd* (2.0, 8.0)	6.99 *dd* (2.0, 8.5)	6.99 *dd* (2.0, 8.5)
F	2	5.03 *br s* (*ca* 1.0)	5.07 *br s* (*ca* 1.0)	5.07 *br s* (*ca* 1.0)	4.96 *d* (6.0)
	3	5.44 *m*	5.49 *m*	5.50 *m*	5.40 *m*
	4_{ax}	2.86–3.08 *m*	3.03–3.13 *m*	3.05–3.15 *m*	3.22 *dd* (6.0, 16.0)
	4_{eq}				2.76 *dd* (8.5, 16.0)
	OMe	3.57 (9-D), 3.79(2-A, 4-A), 3.81 (3-B), 3.85 (4-B), 3.87 (4-E), 3.90 (3-E) (each *s*)	3.44 (9-D), 3.67 (4-A), 3.76 (3-B), 3.80 (4-B), 3.81 (2-A), 3.88 (4-E), 3.90 (3-E) (each *s*)	3.60 (9-D), 3.78 (4-A), 3.80 (3-B), 3.83 (4-B), 3.88 (4-E), 3.90 (3-E, 2-A) (each *s*)	3.57(9-D), 3.79 (4-A), 3.81 (3-B), 3.82 (4-B), 3.86 (3-E), 3.88 (4-E), 3.89 (3-A) (each *s*)
	OAc	1.72, 1.96 (each *s*)	1.90, 1.94 (each *s*)	1.87, 1.98 (each *s*)	1.88, 1.91 (each *s*)

*Second order

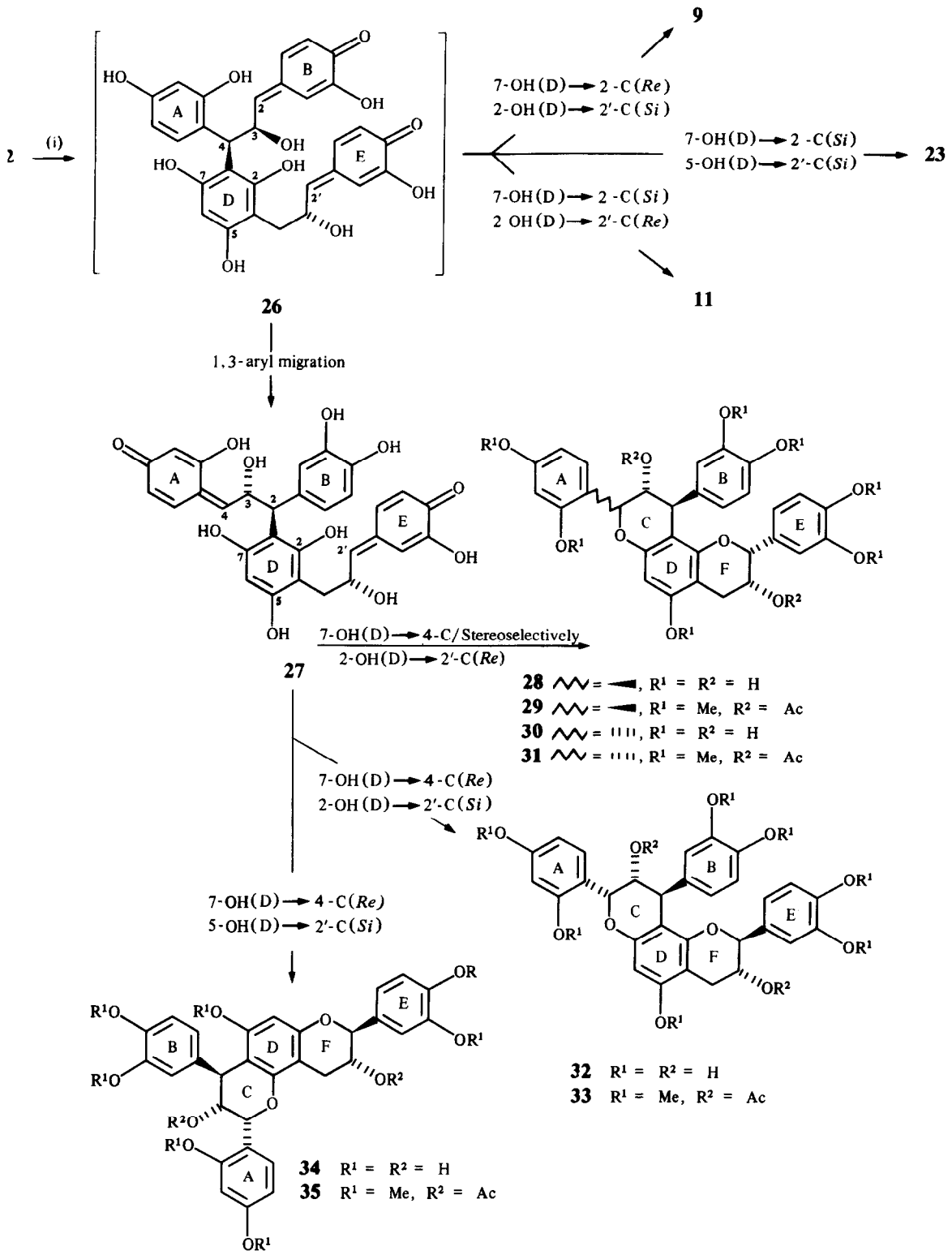
J values (Hz) in parentheses.



Scheme 1. Proposed route to the formation of the C-2(F) epimeric tetrahydropyrano [2, 3 -*h*]chromenes **3** and **7**. Reagents and conditions: (i) $NaHCO_3$–Na_2CO_3, 50°, 5 hr, N_2.

the pathways and stereochemistry indicated in Scheme 2 generates the tetrahydropyrano[2,3-*h*]-chromenes **28**, **30** and **32**, and the [2,3-*f*]-regio-isomer **34**, enantiomerically related to analogues having the resorcinol A- and pyrocatechol B-rings in the 'normal' positions, with respect to their C-rings, e.g. **5** and **28**. The inversion of the absolute configuration at C-3(C) of the parent biflavanoid **2** associated with such a ring interchange [6, 7, 22] is confirmed by positive CEs in the 225–240 nm region of the CD spectra of **31**, **33** and **35**. These indicate *β*-orientation of the pyrocatechol B-rings and hence 8*R*,9*R*,10*S* absolute configuration for **31** and **33**, and 6*R*,7*R*,8*S* for **35**. The 8,9-*trans*-9,10-*trans*-analogue (**29**), however, displayed a negative CE in the same CD region apparently reflecting a 10α-aryl group. Such a deviation in the sign of the low wavelength CE is analogous to observations [6, 7] for isomers with a DEF (+)-catechin moiety. We thus favour the 8*S*,9*R*,10*S* absolute configuration depicted in **29**.

In the absence of synthetic evidence the 2*R*,3*R* configuration of the tetrahydropyrano[2,3-*g*]chromenes **14** and **16** are tentative with the 6*R*,7*S*,8*S* and 6*S*,7*S*,8*R* absolute



Scheme 2. Proposed route to the formation of tetrahydropyranochromenes **9**, **11**, **23** and the ring-interchanged analogues, **28**, **30**, **32** and **34**. Reagents and conditions: (i) $NaHCO_3$–Na_2CO_3, 50°, 3 hr, N_2.

Table 4. ^{1}H NMR peaks (ppm) of compounds **29**, **31**, **33** and **35** ($CDCl_3$, 296 K at 300 MHz)

Ring	H	**29**	**31**	**35**	**33**
A	3	6.14 *d* (2.5)	6.32 *d* (2.5)	6.30 *d* (2.5)	6.31 *d* (2.5)
	5	6.36 *dd* (2.5, 8.5)	6.48 *dd* (2.5, 8.5)	6.47 *dd* (2.5, 8.5)	6.47 *dd* (2.5, 8.5)
	6	7.22 *d* (8.5)	7.47 *d* (8.5)	7.42 *d* (8.5)	7.47 *d* (8.5)
B	2	6.52 *d* (2.0)	6.92 *d* (2.0)	6.87 *d* (2.0)	6.89 *d* (2.0)
	5	6.37 *d* (8.0)	6.76 *d* (2.0, 8.0)	6.77 *d* (8.0)	6.79 *d* (8.0)
	6	6.41 *dd* (2.0, 8.0)	6.71 *dd* (8.0)	6.61 *dd* (2.0, 8.0)	6.65 *dd* (2.0, 8.0)
C	6/8	5.39 *d* (6.0)	5.32 *br* (*ca* 1.0)	5.26 *br s* (*ca* 1.0)	5.36 *br s* (*ca* 1.0)
	7/9	5.91 *dd* (5.5, 6.0)	5.36 *dd* (1.0, 2.0)	5.32 *dd* (1.0, 2.0)	5.25 *dd* (1.0, 2.0)
	8/10	4.26 *d* (5.5)	4.43 *d* (2.0)	4.29 *d* (1.0, 2.0)	4.25 *d* (2.0)
D	6/10	6.32 *s*	6.31 *s*	6.18 *s*	6.28 *s*
E	2	6.55 *d* (2.0)	6.58 *d* (2.0)	6.94 *d* (2.0)	6.43 *d* (2.0)
	5	6.67 *d* (8.0)	6.72 *d* (8.5)	6.84 *d* (8.0)	6.61 *d* (8.5)
	6	6.48 *dd* (2.0, 8.0)	6.59 *dd* (2.0, 8.5)	6.97 *dd* (2.0, 8.0)	6.42 *dd* (2.0, 8.5)
F	2	4.53 *br s* (*ca* 1.0)	4.78 *br s* (*ca* 1.0)	5.00 *d* (8.0)	4.78 *d* (8.5)
	3	5.54 *m*	5.71 *m*	5.38–5.45 *m*	4.88–4.96 *m*
	4_{ax}	2.90–2.93 *m*	2.94–2.97 *m*	3.16 *dd* (6.0, 16.0)	3.11 *dd* (6.0, 16.0)
	4_{eq}			2.82 *dd* (8.0, 16.0)	2.64 *dd* (8.5, 16.0)
	OMe	3.58 (3-B), 3.66 (4-B), 3.67 (2-A, 3-E), 3.71 (4-A), 3.81 (4-E), 3.82 (5-D) (each *s*)	3.51 (2-A), 3.66 (3-E), 3.77 (4-A), 3.79 (3-B), 3.82 (4-E), 3.83 (4-B), 3.84 (5-D) (each *s*)	3.20 (2-A), 3.33 (9-D), 3.47 (4-A), 3.56 (4-B, 4-E), 3.60 (3-B), 3.62 (3-E) (each *s*)	3.64 (2-A), 3.71 (3-E), 3.91 (4-A), 3.96 (4-E), 3.98 (3-B, 5-D), 4.01 (4-B) (each *s*)
	OAc	1.89, 1.91 (each *s*)	1.89, 1.92 (each *s*)	1.88, 1.94 (each *s*)	1.87, 1.89 (each *s*)

* Chemical shifts of methoxy resonances are given for solutions in chloroform-*d*–benzene-d_6 (4:1) to obtain sufficient shift differences for NOE experiments.

J values (Hz) are given in parentheses.

configurations of **14** and **16** being confirmed by ^{1}H NMR coupling constants in conjunction with the sign of the low wavelength CEs in their CD spectra [positive for **16**, negative for **14**]. CD data of the 6,7-*trans*-7,8-*cis*-tetrahydropyrano[2,3-*f*]-chromene (**18**) and the *cis-trans* analogue (**22**) similarly confirm the respective 8β- and 8α-aryl groups and hence the absolute configurations as depicted. The 8,9-*trans*-9,10-*trans*-tetrahydropyrano-[2,3-*h*]chromene (**6**) and the 6,7-*trans*-7,8-*trans*-[2,3-*f*]-analogue (**20**) based on a 2,3-*cis* DEF unit, both showed positive CEs in the low-wavelength region which apparently reflect 10β- and 8β-aryl groups respectively. Proposed absolute configurations of these metabolites are, however, opposite to these and are based on ^{1}H NMR coupling constants and assumption of a mechanism for their formation from a 3,4-*cis* biflavanoid prescribing retention of the absolute configuration at 9- and 7-C (cf. refs [6, 7]).

The peculiar incapability of Sephadex LH-20/ethanol to resolve the mixtures of the base-catalysed conversions of **1** and **2** with subsequent recourse to TLC on silica, preclude comprehensive assessment of the range of phlobatannins formed under these conditions. Notably, however, is the predominance of tetrahydropyrano[2,3-*h*]chromenes which presumably indicates preference for pyran rearrangement via 7-OH (D) and C-2 to regio-isomerization via 5-OH (D) and C-2′ in quinone-methides of type **26**. Because the sequential occurrence of C-ring- and regio-isomerization should lead to significant formation of [2,3-*g*]-analogues, their apparent absence suggests that the latter process precedes pyran rearrangement *en route* the tetrahydropyrano[2,3-*f*]- and [2,3-*g*]-chromenes. Such an assumption, however, holds true only for biflavanoids with identical B- and E-rings hence implying comparable rates of formation of quinonemethides involving these rings.

The significance of these features for the base-catalysed conversions of procyanidins with (−)-epicatechin and (+)-catechin constituent units, e.g. **B-1**, and also of prorobinetinidins and proguibourtinidins (3,7,3′,4′,5′-pentahydroxy- and 3,7,4′-trihydroxy-flavan upper units respectively), where differences in the acidities of the 4′-OH functions will effect the rates of quinone-methide formation at the B- and E-rings, is evident. Demonstration of the coexistence of the (−)-fisetinidol-(−)-epicatechins and related tetrahydropyranochromenes furthermore indicates a taxonomic distribution of the latter class of compounds similar to that of 'conventional' biflavanoids.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ and C_6D_6 with TMS as int. standard. CD data in MeOH. TLC was performed on pre-coated Merck plastic sheets (silica gel $60F_{254}$, 0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40:1) after development. Prep. plates, 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Compounds were recovered from the adsorbent with Me_2CO. CC was on Sephadex

LH-20 and Fractogel TSK HW-40(S) in EtOH. Methylations were performed with an excess of CH_2N_2 in MeOH–Et_2O at −15° for 48 hr, while acetylations were in Ac_2O–pyridine at ambient temps. Evaps were done under red. pres. at *ca* 60° in a rotary evaporator.

Phlobatannins from Guibourtia coleosperma. The extraction (moist EtOAc) and fractionation (Craig countercurrent and CC Sephadex LH-20/EtOH) procedures of the heartwood leading to fractions 2A–2H were fully described in Part 3[7]. A portion (4 g) of fraction 2E (10.89 g) was methylated and the mixture resolved by PLC in C_6H_6–Me_2CO (4:1, × 2) to give six bands, $2E_1$ (R_f 0.62, 186 mg), $2E_2$ (R_f 0.58, 253 mg), $2E_3$ (R_f 0.54, 222 mg), $2E_4$ (R_f 0.48, 268 mg) $2E_5$ (R_f 0.45, 251 mg), and $2E_6$ (R_f 0.36, 678 mg). Only those fractions which exhibited the characteristic purple-red colouration with H_2SO_4–HCHO (40:1) spray reagent on TLC [7] were further investigated.

Band $2E_4$ was acetylated and the mixture resolved by PLC in C_6H_6–Me_2CO–MeOH (95:4:1, × 3) to give a main band at R_f 0.32 (105 mg). Subsequent purification by PLC in hexane–Me_2CO–EtOAc (13:4:3) afforded (2*R*,3*R*:8*R*,9*S*,10*S*)-3,9-diacetoxy-5-methoxy-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 (**4**) as an amorphous solid (67 mg, R_f 0.29) (Found: $[M]^+$, 744.2743. $C_{41}H_{44}O_{13}$ requires $[M]^+$, 744.2782); ^{1}H NMR data (Table 1); CD $[\theta]_{287}$ 0, $[\theta]_{278}$ 6.4×10^4, $[\theta]_{260}$ -3.4×10^4, $[\theta]_{237}$ 12.2×10^4, and $[\theta]_{233}$ 0. Fraction $2E_6$ consisted of the (−)-fisetinidol-(4α,8) and (4β,8)-(−)epicatechins (**1** and **2**)[4].

Fraction 2F (5.19 g) was methylated and the mixture separated by PLC in C_6H_6–Me_2CO (4:1, × 2) to give nine bands, $2F_1$ (R_f 0.60, 130 mg), $2F_2$ (0.52, 300 mg), $2F_3$ (0.45, 286 mg), $2F_4$ (0.41, 704 mg), $2F_5$ (0.34, 886 mg), $2F_6$ (0.28, 490 mg), $2F_7$ (0.21, 474 mg), $2F_8$ (0.14, 510 mg), and $2F_9$ (0.10, 393 mg). The $2F_2$ band was further resolved by PLC in $CHCl_3$–hexane–MeOH (45:3:2, × 3) to give four fractions at R_f 0.69 (41 mg), 0.64 (55 mg), 0.59 (41 mg), and 0.56 (38 mg). The R_f 0.64 fraction consisted of the known [2] heptamethyl ether diacetate of (−)-fisetinidol-(4β,6)-(+)-catechin. Acetylation of the R_f 0.69 fraction afforded (2*R*,3*R*:8*R*,9*S*,10*R*)-3,9-diacetoxy-5-methoxy-2, 8-bis(3, 4-dimethoxyphenyl-10-(2, 4-dimethoxyphenyl)-2, 3-*cis* 8,9-*trans*-9,10-*trans*-3, 4, 9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*] chromene (**6**) as a solid (45 mg) (Found: [M–HOAc], 648.2589. $C_{39}H_{40}O_{11}$ requires M, 684.2571); ^{1}H NMR data (Table 1); CD $[\theta]_{305}$ 0, $[\theta]_{284}$ 9.6×10^4, $[\theta]_{260}$ 2.9×10^4, $[\theta]_{245}$ 21.4×10^4, and $[\theta]_{235}$ 2.42×10^4. The R_f 0.59 band was acetylated and the mixture resolved by PLC in hexane–EtOAc–Me_2CO–MeOH (60:22:15:3, × 4) to give (2*R*,3*R*:6*R*,7*S*,8*S*)-3,7-diacetoxy-9-methoxy-2, 6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethyoxyphenyl)-2,3-*cis*-6,7-*trans*-7, 8-*cis*-3,4,7,8-*tetrahydro*-2*H*, 6*H*-pyrano [2,3-*f*]chromene (**18**) as a solid (15 mg, R_f 0.36) Found: $[M]^+$, 744.2802, $C_{41}H_{44}O_{13}$ requires [M], 744.2782; ^{1}H NMR data (Table 3); CD $[\theta]_{298}$ 0, $[\theta]_{280}$ 2.0×10^4, $[\theta]_{258}$ 0.2×10^4, $[\theta]_{242}$ 2.9×10^4, and $[\theta]_{237}$ 0.4×10^4. Band $2F_4$ was dealt with in Part 3 [7].

Band $2F_5$ was resolved by PLC in hexane–Me_2CO–EtOAc (5:3:1, × 4) to five fractions, $2F_5A$ (R_f 0.60, 39 mg), $2F_5B$ (0.54, 79 mg), $2F_5C$ (0.50, 100 mg), $2F_5D$ (0.48, 160 mg), and $2F_5E$ (0.45, 185 mg). Fraction $2F_5B$ was subjected to an additional PLC separation in $(CH_2Cl)_2$–Me_2CO (17:3, × 3) to give three bands at R_f 0.47 (9 mg), 0.43 (25 mg), and 0.34 (13 mg). The R_f 0.43 band has been dealt with in Part 4 [7]. The R_f 0.34 band was acetylated to give (2*R*,3*R*:6*S*,7*S*,8*R*)-3, 7-diacetoxy-9-methoxy-2, 6-bis(3,4-dimethoxyphenyl)-8-(2, 4-dimethoxyphenyl)-2,3-*cis*-6,7-*cis*-7,8-trans-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano [2,3-*f*]chromene (**22**) as a solid (14 mg) (Found: $[M–HOAc]^+$, 684.2588. $C_{39}H_{40}O_{11}$ requires [M], 684.2571); ^{1}H NMR data (Table 3); CD $[\theta]_{280}$ 0, $[\theta]_{266}$ 5.4×10^4, $[\theta]_{244}$ 0, $[\theta]_{237}$ -4.4×10^4, and $[\theta]_{235}$ 0.

Phlobatannins from Baikiaea plurijuga. The procedures for the extraction (MeOH) and fractionation (Craig countercurrent distribution and CC on Sephadex LH-20/EtOH) of the heartwood leading to fractions 3A-3P were fully described in Part 3[7] and will not be repeated. Detail of the C-ring isomerized analogues of fraction 3H may similarly be found in Parts 3 and 4 [7].

Fraction 3G (3.08 g) was further resolved by CC on Fractogel TSK HW-40(S)/EtOH to sub-fractions $3G_1$-$3G_6$ by the procedure in Part 3 [7]. The phlobatannins in $3G_1$ and $3G_3$ were also reported in Part 3. Methylation of $3G_2$ (876 mg) and subsequent purification by PLC in C_6H_6–EtOAc–Me_2CO (7:2:1, × 2) afforded two bands at R_f 0.46 (126 mg) and 0.44 (218 mg). The R_f 0.46 band was further resolved by PLC in $CHCl_3$–EtOAc (17:3, × 2) to two fractions at R_f 0.42 (11 mg) and 0.36 (32 mg). Acetylation of the former afforded (2*S*,3*R*:8*R*,9*S*,10*S*)-3,9-diacetoxy-5-methoxy-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 (**8**) as a solid (13 mg) (Found: $[M]^+$, 744.2773. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1}H NMR data (Table 1); CD $[\theta]_{287}$ 0, $[\theta]_{277}$ 0.8×10^5, $[\theta]_{265}$ 0, $[\theta]_{251}$ 0, $[\theta]_{230}$ 6.9×10^5, $[\theta]_{225}$ 6.6×10^5, $[\theta]_{222}$ 6.8×10^5, $[\theta]_{218}$ 4.4×10^5, and $[\theta]_{202}$ 0. Acetylation of the R_f 0.36 fraction gave the known C-2 (F) epimer of the ring interchanged analogue **31** (cf. ref. [7], Part 4). Following acetylation the R_f 0.44 band afforded the tetrahydropyrano[2,3-*h*]-chromene heptamethyl ether diacetate (**4**) with physical data identical to those of the product from *G. coleosperma*.

A portion (2.32 g) of fraction 3K (2.53 g), exhibiting the characteristic purple-red colouration with the spray reagent on TLC was resolved by CC (MPLC) on Fractogel TSK HW-40(S) (3 × 55 cm column, 2.7 bar, flow rate 7.5 ml min^{-1}, 15 ml eluant-/tube, first 500 ml of eluant discarded) to eight sub-fractions, $3K_1$ (tubes 20–43, 119 mg), $3K_2$ (44–52, 52 mg), $3K_3$ (53–76, 152 mg), $3K_4$ (77–94, 16 mg), $3K_5$ (95–121, 206 mg), $3K_6$ (122–235, 809 mg), $3K_7$ (236–322, 308 mg), and $3K_8$ (323–483, 205 mg). Methylation of $3K_3$ followed by PLC in hexane–C_6H_6–Me_2CO–MeOH (8:8:3:1, × 3) afforded five bands at R_f 0.55 (28 mg), 0.51 (17 mg), 0.38 (16 mg), 0.28 (5 mg), and 0.20 (2 mg). Acetylation of the R_f 0.55 band and subsequent PLC in hexane–C_6H_6–Me_2CO–MeOH (10:6:3:1, × 2) gave the tetrahydro-pyrano[2,3-*h*]-chromene heptamethyl ether diacetate **6** with physical data identical to those of the product from *G. coleosperma*. The R_f 0.38 band was acetylated and purified by PLC in hexane–C_6H_6–Me_2CO–MeOH (10:6:3:1, × 3) to give (2*R*,3*S*:6*R*,7*S*,8*R*)-3, 7-diacetoxy-9-methoxy-2, 6-bis(3,4-dimethoxyphenyl)-8-(2, 4-dimethoxyphenyl)-2, 3-*trans*-6, 7-*trans*-7, 8-*trans*-3,4, 7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*] chromene with physical data identical to those of the synthetic product (cf. ref. 7, Part 4).

Fraction $3K_5$ (206 mg) was methylated and the mixture resolved by PLC in $CHCl_3$–hexane–Me_2CO (45:3:2, × 2) to give four bands, $3K_5A$ (R_f 0.63, 47 mg), $3K_5B$ (0.47, 42 mg), $3K_5C$ (0.42, 36 mg), and $3K_5D$ (0.35, 35 mg). The $3K_5A$ band was further resolved by PLC in C_6H_6–$(CH_2Cl)_2$–Me_2CO (5:4:1, × 4) to two bands at R_f 0.45 (9 mg) and 0.35 (8 mg). Acetylation of the former afforded (2*R*,3*R*:8*S*,9*S*,10*R*)-3,9-diacetoxy-5-methoxy-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2, 3-*cis*-8, 9-*cis*-9, 10-*trans*-3, 4, 9, 10-tetrahydro-2*H*, 8*H*-pyrano [2, 3-*h*] chromene (**12**) as an amorphous solid (10 mg) (Found: $[M]^+$, 744.2771. $C_{41}H_{44}O_{13}$ requires $[M]^+$, 744.2782; ^{1}H NMR data (Table 1); CD $[\theta]_{288}$ 0, $[\theta]_{264}$ 4.2×10^4, $[\theta]_{248}$ 1.9×10^4, $[\theta]_{239}$ 0, $[\theta]_{234}$ -5.4×10^4, and $[\theta]_{232}$ 0. Acetylation of the R_f 0.35 band gave the tetrahydropyrano[2,3-*f*]chromene hep-

tamethyl ether diacetate (**18**) with physical properties identical to those of the derivative of the product from *G. coleosperma*. Acetylation of the $3K_5B$ band afforded the (+)-catechin analogue of the tetrahydropyrano[2,3-*g*]chromene **16** [7]. The $3K_5C$ band was further resolved by prep. TLC in hexane–C_6H_6–Me_2CO–MeOH (8:8:3:1, × 2) to two bands at R_f 0.37 (5 mg) and 0.32 (6 mg). Acetylation of the former gave (2*S*,3*R*:6*S*,7*S*,8*R*)-3,7-diacetoxy-9-methoxy-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-7,8-*trans*-3,4,7,8-tetrahydro-2H,6*H*-pyrano-[2,3-*f*]-chromene (**24**) as a solid (5.5 mg) (Found: $[M]^+$, 744.2751. $C_{41}H_{44}O_{13}$ requires [M], 744.2782; ^{1}H NMR data (Table 3); CD $[\theta]_{298}$ 0, $[\theta]_{284}$ 0.9 × 10^4, $[\theta]_{280}$ 0.8 × 10^4, $[\theta]_{264}$ 3.8 × 10^4, $[\theta]_{249}$ 2.7 × 10^4, $[\theta]_{240}$ 0.5 × 10^4, $[\theta]_{236}$ 3.1 × 10^4, and $[\theta]_{232}$ 0. Acetylation of the R_f 0.32 band followed by PLC in C_6H_6–$(CH_2Cl)_2$–MeCO (5:4:1, × 2) afforded (2*R*, 3*R*:6*R*, 7*S*, 8*R*)-3,7-diacetoxy-9-methoxy-2,6-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*cis*-6, 7-*trans*-7, 8-*trans*-3, 4, 7, 8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene **20** as a solid (4 mg, R_f 0.59) (Found: $[M]^+$, 744.2773. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1}H NMR data (Table 3); CD $[\theta]_{302}$ 0, $[\theta]_{291}$ 3.1 × 10^4, $[\theta]_{283}$ 0, $[\theta]_{272}$ −2.7 × 10^4, $[\theta]_{262}$ 0, $[\theta]_{246}$ 14.8 × 10^4, and $[\theta]_{236}$ 0.

Fraction $3K_6$ (809 mg) was methylated and the mixture resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO (45:3:2, × 2) to give seven bands, $3K_6A$ (R_f 0.58, 18 mg), $3K_6B$ (0.47, 32 mg), $3K_6C$ (0.39, 84 mg), $3K_6D$ (0.30, 155 mg), $3K_6E$ (0.25, 93 mg), $3K_6F$ (0.20, 38 mg), and $3K_6G$ (0.15, 29 mg). Acetylation of $3K_6A$ followed by successive PLC in hexane–C_6H_6–Me_2CO–MeOH (12:4:3:1: R_f 0.45) and C_6H_6–$(CH_2Cl)_2$–Me_2CO (5:4:1) afforded (2*R*, 3*R*:6*R*, 7*S*, 8*S*)-3, 7-diacetoxy-5-methoxy-2, 8-bis (3, 4-dimethoxyphenyl)-6-(2, 4-dimethoxyphenyl)-2, 3-*cis*-6, 7-*trans*-7, 8-*cis*-3, 4, 6, 7-tetrahydro-2*H*, 8*H*-pyrano[2, 3-*g*]chromene (**14**) as a solid (4 mg, R_f 0.65) (Found: $[M]^+$, 744.2771. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1}H NMR data (Table 2); CD $[\theta]_{292}$ 0, $[\theta]_{286}$ −9.4 × 10^3, $[\theta]_{278}$ 0, $[\theta]_{269}$ 7.8 × 10^3, $[\theta]_{255}$ 0, $[\theta]_{242}$ −10.9 × 10^3, $[\theta]_{236}$ −78.1 × 10^3, and $[\theta]_{230}$ 0. Acetylation of $3K_6C$ (84 mg) and PLC in hexane–C_6H_6–Me_2CO–MeOH (12:4:3:1, × 4) gave (2*R*, 3*R*:6*S*,7*S*,8*R*)-3, 7-diacetoxy-5-methoxy-2, 8-bis(3, 4-dimethoxyphenyl)-6-(2, 4-dimethoxyphenyl)-2, 3-*cis*-6, 7-*cis*-7, 8-*trans*-3, 4, 6, 7-tetrahydro-2*H*,8*H*-pyrano[2,3-*g*]chromene (**16**) as a solid (8 mg, R_f 0.32) (Found: $[M]^+$, 744.2799. $C_{41}H_{44}O_{13}$ requires, [M], 744.2782); ^{1}H NMR data (Table 2); CD $[\theta]_{298}$ 0, $[\theta]_{274}$ 4.3 × 10^4, $[\theta]_{252}$ 1.60 × 10^4, $[\theta]_{244}$ 2.2 × 10^4, $[\theta]_{242}$ 1.6 × 10^4, $[\theta]_{240}$ 1.9 × 10^4, and $[\theta]_{238}$ 0. Fraction $3K_6D$ comprised of the methyl ethers of the (+)-catechin analogue of **21** [6] and a novel hexahydro-dipyrano-[2,3-*f*:2′,3′-*h*]chromene with a (−)-epicatechin DEF moiety, detail of which will be presented elsewhere. Acetylation of $3K_6E$ (93 mg) and PLC separation in C_6H_6–$(CH_2Cl)_2$–Me_2CO (5:4:1, × 2) afforded three bands at R_f 0.75 (8 mg), 0.60 (7 mg), and 0.52 (16 mg). The R_f 0.75 band was further purified by PLC in hexane–C_6H_6–Me_2CO–MeOH (12:4:3:1, × 5) to give (2*R*,3*S*:6*S*,7*R*,8*R*)-3, 7-diacetoxy-5-methoxy-2, 6-bis(3, 4-dimethoxyphenyl)-8-(2, 4-dimethoxyphenyl)-2, 3-*trans*-6, 7-*trans*-7, 8-*cis*-3, 4, 6, 7-tetrahydro-2*H*,8*H*-pyrano[2,3-*g*] chromene (3 mg, R_f 0.43) with physical data identical to those of its synthetic counterpart (cf. ref. 7, Part 4). Further purification of the R_f 0.60 band by PLC in hexane–C_6H_6–Me_2CO–MeOH (12:4:3:1, × 5) afforded the tetrahydropyrano[2,3-*f*]chromene heptamethyl ether diacetate (**22**) (3 mg, R_f 0.28) identical to the corresponding derivative of the product from *G. coleosperma*. The R_f 0.52 band consisted of a hexahydro-dipyrano-[2, 3-*f*:2′, 3′-*h*]chromene with a (−)-epicatechin DEF moiety, detail of which will be published separately. Fractions $3K_6G$ and $3K_7$ similarly comprised of phlobatannins related to bis-(−)-fisetinidol-(−)-epicatechins.

Phlobatannin (**3**) *from* Colophospermum mopane. The enriched methanol extract [23] (6 × 20 g) was subjected to CC (MPLC) on Sephadex LH-20 (5 × 105 cm column, flow rate: 9 ml min^{-1}, 0.8 bar pressure) to give four frs, A (RR_t 0–0.5 hr, 7.5 g), B (RR_t 0.5–1.2 hr, 4.5 g), C (RR_t 1.2–4 hr, 7.5 g), and D (RR_t 4.0–8.6 hr, 13.9 g) starting with appearance of the first phenolic compounds (UV-monitor). A portion (7 g) of fraction C was re-subjected to CC on Sephadex LH-20 as above to afford four sub-fractions, 1 (RR_t 0–1.8 hr, 618 mg), 2 (RR_t 1.8–3.6 hr, 1.952 g), 3 (RR_t 3.6–4.6 hr, 771 mg), and 4 (RR_t 4.6–8.8 hr, 1.707 g). The metabolites in frs 1, 2, 4 and part of those in 3 were described in Part 8 [14]. Fraction 3 was further resolved by CC on Fractogel TSK HW-40(S) (3.5 × 45 cm column, flow rate 4 ml min^{-1}, 0.3–6.0 bar pressure) into two subfractions, 3.1 (to be dealt with separately) (RR_t 0.0–0.9 hr, 156 mg) and 3.2 (RR_t 1.0–1.9 hr, 181 mg). Fraction 3.2 was methylated and the mixture resolved by prep. TLC in C_6H_6–EtOAc–Me_2CO (7:2:1, × 2) to give four bands, 3.2.1 (to be dealt with separately) (R_f 0.50, 27.1 mg), 3.2.2 (R_f 0.39, 28.8 mg), 3.2.3 (to be dealt with separately) (R_f 0.33, 23.0 mg), and 3.2.4 (to be dealt with separately) (R_f 0.28, 13.3 mg). Acetylation of 3.2.2 and PLC sepn in C_6H_6–hexane–Me_2CO (6:3:1, × 6) gave four bands at R_f 0.38 (3.4 mg), 0.33 (2.3 mg), 0.27 (5.1 mg), and 0.22 (4.3 mg). The first three bands were described in Part 8 [14]. The R_f 0.22 band comprised of the tetrahydropyrano [2,3-*h*]*chromene* heptamethyl ether diacetate (**4**) with physical data identical to those cited above.

Synthesis of (−)-*fisetinidol*-(−)-*epicatechins* **1** *and* **2**. (+) Mollisacacidin (4.22 g) was added in portions over 1 hr to a stirred solution of (−)-epicatechin (8.47 g) in 0.1 M HCl (200 ml). The mixture was stirred at room temp. for 48 hr and extracted with EtOAc (5 × 200 ml). Drying (Na_2SO_4) of the extract and removal of solvent gave a brown powder (12.26 g) which was subjected to CC (MPLC) on Sephadex LH-20 (4.0 × 120 cm column, flow rate–9.0 ml min^{-1}, 18.0 ml frs) to give fractions 1 (tubes 35–90, 3.3 g), 2 (120–174, 2.26 g), and 3 (195–200, 2.56 g). Fr. 1 consisted of (−)-epicatechin and frs 2 and 3 of (−)-fisetinidol-(4β,8) and (4α, 8)-(−)-epicatechins (**2** and **1**) by comparison of the ^{1}H NMR data of their heptamethyl ether diacetates with those of authentic samples [2].

Base-catalysed conversions of (−)*fisetinidol*-(−)-*epicatechins*. Compound **1** (798 mg) was dissolved in a 0.025 M $NaHCO_3$–0.025 M Na_2CO_3 buffer (pH 10, 100 ml) and the mixture was stirred at 50° for 5 hr, chilled with ice, acidified (0.1 M HCl), and extracted with EtOAc (6 × 100 ml). Drying (Na_2SO_4) of the extract and evapn of solvent afforded a light-brown powder (605 mg) which was methylated and sepd by prep. TLC in C_6H_6–Me_2CO (4:1) to give five bands at R_f 0.61 (7 mg), 0.51 (21 mg), 0.44 (21 mg), 0.38 (32 mg), and 0.29 (64 mg). The R_f 0.61 and 0.51 fractions consisted of 3-*O*-methyl derivatives of the heptamethyl ether of **1** and were not further investigated. The R_f 0.44 band was further purified by prep. TLC in C_6H_6–$(CH_2Cl)_2$–Me_2CO (5:4:1) to give a band at R_f 0.37 (2 mg). Acetylation afforded the tetrahydropyrano-[2,3-*h*]chromene heptamethyl ether diacetate **7** (2.5 mg) identical to the corresponding derivative of the natural product from *B. plurijuga*. Acetylation of the R_f 0.38 band followed by prep. TLC in hexane–Me_2CO–EtOAc (12:5:3, × 2) gave the tetrahydropyrano[2,3-*h*]chromene heptamethyl ether diacetate **4** (R_f 0.31, 16 mg) with physical data identical to those of the corresponding derivative of the natural product. The R_f 0.29 fraction was further purified by prep. TLC in $(CH_2Cl)_2$–Me_2CO (9:1, × 2) to give two bands at R_f 0.29 (2 mg) and 0.21 (42 mg). Acetylation of the former afforded an additional sample (2 mg) of **4**. The R_f 0.21 band was acetylated and the mixture resolved by prep. TLC in hexane–Me_2CO–EtOAc (12:5:3, × 2) to two bands at R_f 0.36 (9 mg) and

0.32 (22 mg). The latter band consisted of the heptamethyl ether diacetate of biflavanoid **1** and the former of the novel C-2(F) epimer, detail of which will be published elsewhere.

(−)-*Fisetinidol*-(4β,8)-(−)-*epicatechin* **2**. Biflavanoid **2** (850 mg) was treated with the buffer soln (100 ml) for 3.5 hr at 50° under N_2. Work-up as above afforded a light-brown powder (677 mg) which was methylated and a portion (478 mg) of the mixture subsequently resolved by prep. TLC in C_6H_6–Me_2CO (4:1) to three fractions at R_f 0.51 (90 mg), 0.39 (199 mg), and 0.29 (43 mg). The R_f 0.51 fraction was further purified by PLC in $CHCl_3$–hexane–Me_2CO (45:3:2, × 2) to a band at R_f 0.59 (13 mg). Acetylation and successive PLC in hexane–Me_2CO–EtOAc (12:5:3, R_f 0.27, 9 mg) and C_6H_6–Me_2CO (9:1) afforded the 8,9-*cis*-9,10-*trans*-tetrahydropyrano-[2,3-*h*]chromene heptamethyl ether diacetate **12**, R_f 0.38, 12 mg, identical to the corresponding derivative of the natural product.

The R_f 0.39 fraction (119 mg) was separated by PLC in $CHCl_3$–hexane–Me_2CO (45:3:2, × 2) into three bands at R_f 0.47 (4 mg), 0.42 (17 mg), and 0.35 (28 mg). Acetylation of the former gave (2S,3R:8R,9S,10R)-3,9-diacetoxy-5-methoxy-2,8-bis(3,4-dimethoxyphenyl)-10-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2H,8H-pyrano[2,3-*h*] chromene (**10**) as a solid (4.5 mg) (Found: $[M]^+$, 744.2773. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1}H NMR data (Table 1); CD $[\theta]_{298}$ 0, $[\theta]_{285}$ 3.1×10^3, $[\theta]_{255}$ 4.3×10^3, $[\theta_{250}$ 6.9×10^3, $[\theta]_{238}$ 12.8×10^3, and $[\theta]_{233}$ 0. The R_f 0.42 band comprised of a complex mixture of phenolic heptamethyl ethers partially methylated at their secondary OH-groups and was thus not further investigated. Acetylation of the R_f 0.35 band (28 mg) followed by prep. TLC in C_6H_6–Me_2CO (9:1) afforded four additional bands at R_f 0.46 (4 mg), 0.41 (5 mg), 0.35 (6 mg), and 0.31 (11mg). The latter band consisted of the heptamethyl ether diacetate of biflavanoid **2**. The R_f 0.46 band afforded (2S,3R:8R,9R,10S)-3,9-diacetoxy-5-methoxy-2,10-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*trans*-8,9-*cis*-9,10-*trans*-3,4, 9,10-tetrahydro-2*H*, 8*H*-pyrano[2,3-*h*]chromene (**33**) as a solid (Found: $[M]^+$, 744.2771. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1} NMR data (Table 4); CD $[\theta]_{289}$ 0, $[\theta]_{285}$ 0.7×10^3, $[\theta]_{277}$ 0, $[\theta]_{265}$ -0.8×10^3, $[\theta]_{244}$ -1.4×10^3, $[\theta]_{240}$ 0, $[\theta]_{238}$ 2.8×10^3 $[\theta]_{234}$ 7.0×10^3, and $[\theta]_{231}$ 0. The R_f 0.41 band (5 mg) afforded the 6,7-*cis*-7,8-*trans*-tetrahydropyrano[2,3-*f*]chromene heptamethyl ether diacetate **24** identical to the corresponding derivative of the natural product. The R_f 0.35 band (6 mg) comprised of (2*S*, 3*R*:6*R*, 7*R*, 8*S*)-3, 7-diacetoxy-9-methoxy-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*, 8*H*-pyrano[2, 3-*f*] chromene (**35**) as a solid (Found: $[M]^+$, 744.2791. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); ^{1}H NMR data (Table 4); CD $[\theta]_{280}$ 0, $[\theta]_{265}$ 1.4×10^3, $[\theta]_{250}$ 0.9×10^3, $[\theta]_{233}$ 25.8×10^3, $[\theta]_{225}$ 30.4×10^4, and $[\theta]_{220}$ 0.

The R_f 0.29 fraction (43 mg) was acetylated and sepd by prep.TLC in C_6H_6–Me_2CO (9:1) to two bands at R_f 0.52 (18 mg) and 0.42 (5 mg). The former fraction gave (2*R*,3*R*:8*R*,9*R*,10*S*)-3,9-diacetoxy-5-methoxy-2,10-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*cis*-8,9-*cis*-9,10-*trans*-3,4, 9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**31**) as a solid (Found: $[M]^+$, 744.2789. $C_{41}H_{44}O_{13}$ requires [M], 744.2782); 1H NMR data (Table 4); CD $[\theta]_{288}$ 0, $[\theta]_{275}$ -2.9×10^3, $[\theta]_{244}$ 0, $[\theta]_{240}$ 1.80×10^3, $[\theta]_{237}$ 0, $[\theta]_{236}$ -2.9×10^3, $[\theta]_{235}$ 0, $[\theta]_{234}$ 9.0×10^3, and $[\theta]_{230}$ 0. The R_f 0.42 band was further resolved by prep. TLC in $CHCl_3$–hexane–Me_2CO (45:3:2) to two fractions at R_f 0.72 (3 mg) and 0.65 (2 mg). The former fraction gave an additional sample of **31** and the latter (2*R*,3*R*:8*S*,9*R*,10*S*)-3,9-diacetoxy-methoxy-2,10-bis(3,4-dimethoxyphenyl)-8-(2,4-dimethoxyphenyl)-2,3-*cis*-8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**29**) as a solid (Found: $[M]^+$, 744.2791. $C_{41}H_{44}O_{13}$ requires [M], 744.2782): ^{1}H NMR data (Table 4); CD $[\theta]_{295}$0, $[\theta]_{265}$ 5.5×10^3, $[\theta]_{251}$ 0, $[\theta]_{234}$ -8.6×10^3, $[\theta]_{225}$ -15.9×10^3, end $[\theta]_{218}$0.

Acknowledgements—Support by the Sentrale Navorsingsfonds of this University, the Foundation for Research Development, C.S.I.R., Pretoria, the Marketing Committee, Wattle Bark Industry of South Africa, Pietermaritzburg, and the Citrus and Subtropical Fruit Research Institute, Nelspruit is acknowledged. Mass spectral data were supplied by Dr J. M. Steyn (Department of Pharmacology of this University).

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