# Synthesis of Condensed Tannins. Part 14.† Biflavanoid Profisetinidins as Synthons. The Acid-Induced 'Phlobaphene' Reaction

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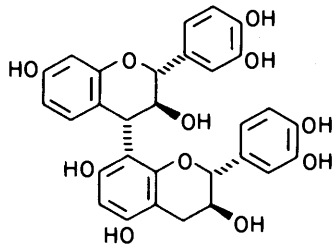
Free-phenolic [4,6]- and [4,8]-2,3-*trans*-(—)-fisetinidol-(+)-catechin diastereoisomers of both 3,4-*trans* and 3,4-*cis* configuration, which serve as synthons for higher oligomers, are available in improved yields from direct condensation, and also *via* novel 6-iodo-(+)-catechin as an intermediate substrate. Acid-induced transformations of the predominant [4,8]-all-*trans* isomer, illustrative of the well-known 'phlobaphene reaction' of condensed tannins, is shown to include ring-isomerization and fission of the inter-flavanoid bond, followed in the latter instance by the alternatives of anthocyanidin formation, positional rearrangement and self-condensation.

Synthetic proof of the structure of 'angular' profisetinidin tetraflavanoids[1] calls for the availability of a range of free-phenolic biflavanoid profisetinidins, each serving as a common substrate in two successive electrophilic aromatic substitutions. Revised reaction conditions (*cf.* ref. 2) and choice of suitable chromatographic procedures now provide for significant improvement in the overall yield and proportions in which these [4,6]- and [4,8]-linked synthons are formed. Investigation into the possible role of 6 and 8 monosubstituted (+)-catechins as intermediates in regiospecific syntheses has led to the first preparation and use of 6-iodo-(+)-catechin. The predominant product of biflavanoid synthesis, [4,8]-all-*trans*-(−)-fisetinidol-(+)-catechin, was selected as a model compound for studying the reactions which could occur during the acid-induced generation of insoluble 'phlobaphenes' or 'tanners reds' from condensed tannins in commercial vegetable-leather manufacture.[3]

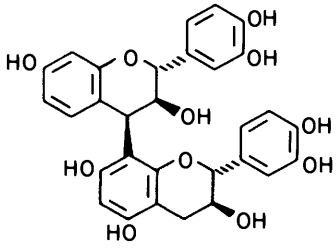
*Preparative Availability of Free Phenolic* [4,6]-*and* [4,8]-(—)-*Fisetinidol*-(+)-*catechins.*—A typical preparative generation of the biflavanoid mixture from the acid-induced condensation of molar equivalents of (+)-mollisacacidin and (+)-catechin under optimized conditions (progressive addition of the flavan-3,4-diol to an acidic aqueous solution of the flavan-3-ol) resulted in the recovery of 12.5% unchanged (+)-catechin; the generation of 53% of the theoretical yield of biflavanoids; and also formation of a low proportion (*ca.* 2.4%) of triflavanoids. Neglecting manipulative losses, these figures indicate a considerable degree of side-reaction on the part of the acid-sensitive flavan-3,4-diol which is consumed completely. Separation of the [4,8]-3,4-*cis*-isomer (**2**) in pure form (16% yield) is readily accomplished on Sephadex LH-20 columns,[4] whereas the remaining mixture of [4,8]-3,4-*trans*, [4,6]-3,4-*trans*, and [4,6]-3,4-*cis* isomers [(**1**), (**3**) and (**4**) respectively] was resolved by subsequent thin layer chromatography on Kieselgel in 26.3, 5.2 and 5.6% yields respectively.

Thus, under optimized conditions [4,8]- [(**1**) and (**2**)] relative to [4,6]-coupling [(**3**) and (**4**)] occurs in the proportion of 4:1, and 3,4-*trans*-[(**1**) and (**3**)] relative to 3,4-*cis*-isomers [(**2**) and (**4**)] are formed in the ratio of 3:2. Isolation of the free-phenolic [4,6]-3,4-*cis*-isomer (**4**) (*cf.* ref. 2) in relatively low but significant yield has led to an improved (*ca.* 11%) combined yields of [4,6]-isomers.

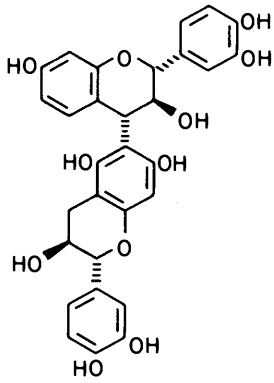
Since direct synthesis as above offers only a partial solution to the desired availability (*cf.* ref. 1) of free-phenolic [4,6]-isomers,



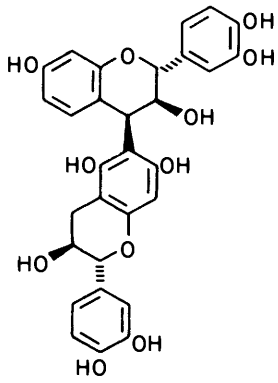
(**1**)



(**2**)



(**3**)

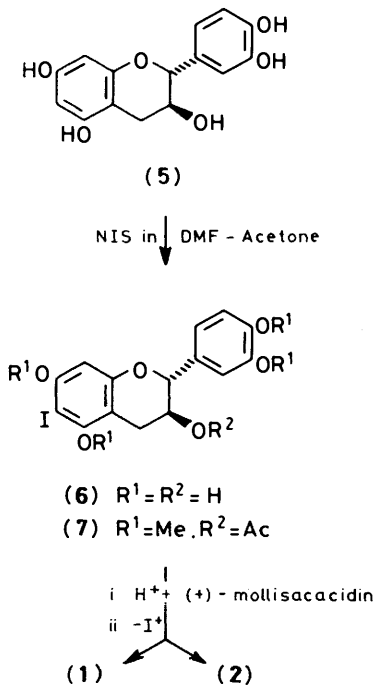


(**4**)

attempts were made at regioselective synthesis by blocking the 8-position on (+)-catechin with a 2,4-dihydroxybenzylic function and removing it preferentially after introduction of the flavanyl moiety at C-6. However, attempted selective hydrolysis of [4,6]-(−)-fisetinidol-8-(2,4-dihydroxybenzyl)-(+)-cate-

† Part 13, J. A. Delcour, E. J. Serneels, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1985, 669.

chins* with toluene-α-thiol[5] proved unsuccessful owing to inconsistent results in spite of appreciably differing bond strengths.[6,7] A parallel approach using bromine as a blocking agent for the 8-position and its facile removal with sodium sulphite[8] proved unsatisfactory owing to exceptionally low and equivalent yields of 6 and 8 monobrominated isomers accompanied by outweighing 6,8-disubstitution, despite recovery of excess of unchanged (+)-catechin when offering a molar equivalent of bromine. Thus, although the problem of selective synthesis of [4,6]-isomers in acceptable yields remains, some progress towards regiospecific synthesis of [4,8]-isomers was possible through quantitative reaction of (+)-catechin (**5**) with 1 mol equiv. of *N*-iodosuccinimide (NIS) to give predominantly 6-iodo-(+)-catechin (**6**) as intermediate. The point of substitution was established by the chemical shift of the residual 8-proton (8-H, δ 6.24) (*cf.* ref. 10), and also by reaction of an excess of the crude product of iodination (**6**) with (+)-




mollisacacidin in an acid medium (0.1M-HCl, 25 °C) which led almost exclusively to a 1:1 ratio of [4,8]-3,4-*trans* (**1**) and [4,8]-3,4-*cis*-(−)-fisetinidol-(+)-catechins (**2**) in a 44% combined yield. The sequence of 8-substitution and de-iodination at C-6 (during work-up) is supported by formation of only trace amounts of [4,6]-isomers and recovery of some 50% unsubstituted (+)-catechin. Direct iodination of (+)-catechin with molecular iodine by contrast provides the 8-iodo isomer of (**6**) identified as the tetramethyl ether acetate (6-H, δ 6.03) but in a yield (*ca.* 2%) totally unsuitable for synthetic purposes. Rationalization of the differing course and apparent selectivity of these iodinations is at present unresolved, but comparison of the derivatives of 6- and 8-iodo-(+)-catechins enables their unambiguous identification.

The conformations of the heterocyclic C-rings of profisetinidins (**1**)—(**4**) are of significance as regards the overall conformation of tannin molecules. Judging by coupling constants ($J_{2,3}$ 9.0, 11.0, and $J_{3,4}$ 6.6, 7.5 Hz) in acetone and $D_2O$, the half-chair (or 'sofa') conformations of the heterocyclic C-rings ('upper unit') of the free-phenolic 3,4-*trans*-profisetinidins (**1**) and (**3**) are in line with those of their octamethyl ether acetates with all substituents assuming equatorial orientations. Exceptions are the free-phenolic 3,4-*cis*-isomers (**2**) and (**4**) (also the 8-benzyl derivative of the latter) with 'abnormal' coupling constants ($J_{2,3}$ 2.5—3.0 Hz, $J_{2,3}$ 3.0—3.5 Hz) which reflect boat C-ring conformations, with both 2-aryl and 4-flavanyl substituents again assuming equatorial orientations while serving as conformational anchors. The boat conformation of the free-phenolic 3,4-*cis*-biflavanoids could be stabilized by hydrogen bonding between the 7-(D-ring) and 3-axial (C-ring) hydroxy functions. The respective half-chair and boat conformations allowing for general planarity of large substituents are valid irrespective of whether 2,3-*trans*-fisetinidol substituents on (+)-catechin are attached at C-6 or C-8; an observation which indicates a high degree of planarity of free-phenolic tannin oligomers.

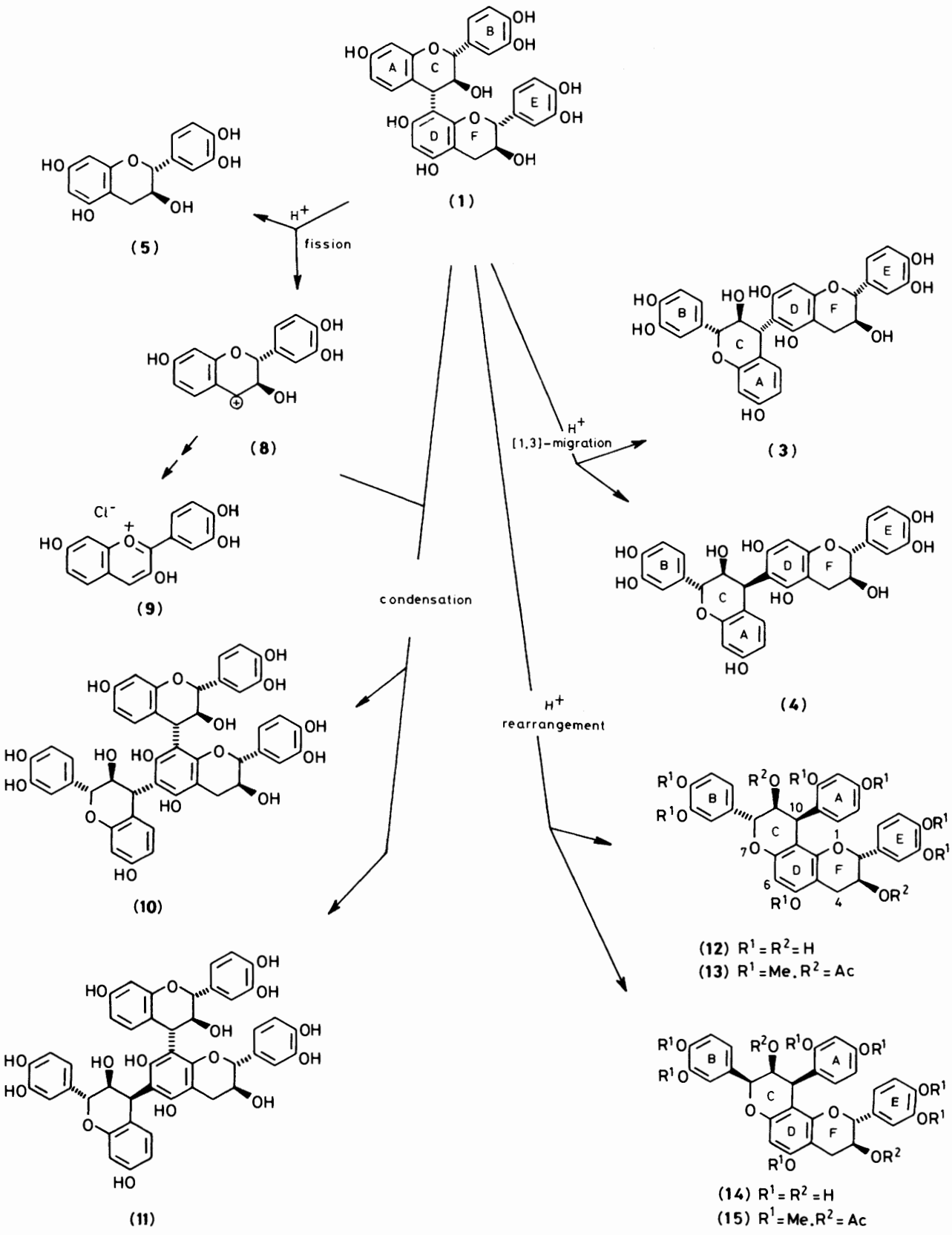
*Acid-Induced Transformations of* [4,8]-3,4-trans-(−)-*Fisetinidol*-(+)-*Catechin*: *The 'Phlobaphene' Reaction of Condensed Tannins*.—Interesting aspects of the mechanisms which are likely to be involved in 'phlobaphene' formation during commercial vegetable tanning (see introduction) are illustrated by the transformations which occasion the heating under reflux of a typical tannin unit of commercial extracts (*cf.* refs. 11, 12), the all-*trans*-(−)-fisetinidol-(+)-catechin (**1**), with weak to medium strength acids (acetic and monochloroacetic acids). Although heterocyclic ring opening mechanisms followed by self-condensation such as those examined by Freudenberg and Weinges[13] for (+)-catechin cannot be excluded (depending on the acidic strength of the medium), the following results offer the first concrete evidence of the nature of the presumed 'polymerization' which promotes both insolubility and reddening (see Scheme).

The liberation of (+)-catechin (**5**) and fisetinidin chloride (**9**) provides evidence of interflavanoid C–C bond fission. The putative intermediate carbenium ion (**8**) is converted spontaneously into the anthocyanidin (**9**) *via* the often-postulated rearrangement to the flav-3-en-3-ol and hence to oxidative removal of the hydride ion at C-2; or condenses, amongst others, at C-6 (D-ring) of the starting material (**1**) to give the known 'angular' triflavanoids (**10**) and (**11**) as initial step in the 'polymerization' sequence to higher oligomers, a process which may also involve the intermediate products of migration (**3**) and (**4**) and rearrangement (**12**) and (**14**).

The [4,6]-biflavanoids (**3**) and (**4**) of 3,4-*trans* and 3,4-*cis* configuration presumably originate through acid-catalysed 1,3-intraflavanyl migration. Recovery alone of the [4,8]-3,4-*trans*-biflavanoid (**1**) from the reaction products {*i.e.* absence of the [4,8]-3,4-*cis*-isomer (**2**)} indicates the absence of an equilibrium between positional isomers, and possibly reflects on the relative strength of the [4,6]-interflavanoid bond as postulated by McGraw and Hemingway.[6] The structures of compounds (**3**), (**4**), (**10**), and (**11**) were confirmed by direct comparison of the $^1H$ n.m.r. spectra of their methyl ether acetates at high temperatures (150—170 °C) with those of reference compounds (*cf.* refs. 14, 15).

The structures of the products of rearrangement (**12**), and (**14**) of the heterocyclic ring of the parent [4,8]-biflavanoid (**1**) are based mainly on $^1H$ n.m.r. spectra of their heptamethyl ether diacetates (**13**) and (**15**). A significant observation indicative of structural rigidity is the complete absence of dynamic rotational isomerism, thus contrasting with the well-known behaviour of similar derivatives of most singly [4,6]- and [4,8]-bonded biflavanoids. Only slight sharpening of aromatic proton resonances of the derivatives (**13**) and (**15**) occur with temperature elevation. For discussion purposes the rings of

* Obtained by condensation with (+)-mollisacacidin (*cf.* analogous preparation of 4-hydroxybenzyl analogue[9]).


(1)
(5)
H+
fission
(8)
(9)
Cl-
condensation
H+
[1,3]-migration
(3)
(4)
H+
rearrangement
(10)
(11)
(12) R1 = R2 = H
(13) R1 = Me, R2 = Ac
(14) R1 = R2 = H
(15) R1 = Me, R2 = Ac

**Scheme.**

compounds (**13**) and (**15**) are labelled according to the original allocations in parent biflavanoid (**1**). Considering that phloroglucinol D-ring functionality possesses higher nucleophilicity than that of its resorcinol counterpart (*cf.* analogous photochemical reaction of 4-arylflavan-3-ols),[16] protonation of the C-ring heteroatom, and ring opening to form a 2-carbenium ion, is followed by recyclization through attack by the 7-OH of the 'lower' (+)-catechin unit, with either retention or inversion of configuration as in (**12**) and (**14**) respectively.

On the presumption that the newly-formed C-ring of (**12**) adopts the half-chair conformation, the dihedral angles (180°, 45°) match the observed coupling constants ($J_{2,3}$ 10.0, $J_{3,4}$ 6.00 Hz) of the heptamethyl ether diacetate derivative (**13**) and correspond to a 2,3-*trans*-3,4-*cis* configuration with the 4-aryl (resorcinol) group assuming a full axial orientation; strong non-bond interaction between the 2-methoxy (A-ring) group on the one hand and both the 3-equatorial-acetoxy (C-ring) and heterocyclic oxygen (F-ring) of the catechin unit on the other, being indicated from Dreiding models. The high-field methoxy resonance (δ 3.55) is accordingly allocated to the C-2 position of the resorcinol A-ring. Dreiding models show that the combined effects of the heterocyclic oxygen of the (+)-catechin moiety and 3-acetoxy function could exercise such shielding effects during 'free rotation' of the A-ring.

Where the alternative inversion of configuration on re-cyclization occurs at C-2 as in (**14**) the C-ring must undergo conformational inversion as the result of the 2-aryl group assuming an equatorial position. The small coupling constants ($J_{2,3}$ 1.25, $J_{3,4}$ 1.9 Hz in $C_6D_6$) and of the heptamethyl ether diacetate (**15**) are possibly indicative of an equilibrium between a half-chair and boat conformations with the 4-aryl (resorcinol) substituent again assuming an *axial* conformation typical of 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols.[16] The high-field methoxy group (δ 3.52) is assigned to the C-2 position of the A-ring as above. Differences in the chemical shifts between the 2,3-*trans*-(**13**) and 2,3-*cis*-(**15**) derivatives are the significant relative deshielding (Δδ 0.71) of 6-H(A) (δ 7.50), and strong relative shielding (Δδ −0.75) of 4-H(C) (δ 5.09) in the spectrum ($CDCl_3$) of the latter. These effects may be attributed to the axial orientation of the 3-acetoxy (C-ring) function [compared with its equatorial orientation for (**13**)] in the latter instance.

Mass spectra of the 2,3-*trans*-3,4-*cis* and 2,3-*cis*-3,4-*cis* isomers show similar fragmentations but with peaks of divergent intensity. The respective $M^+ - 60 : M^+$ ratios of 1.3:1 and 14:1 are in reasonable agreement with those of stereochemically related compounds (*cf.* ref. 16).

The c.d. spectra of these compounds differ as is to be expected in the long wavelength region (250—290 nm), but both give strong negative Cotton-effects at short wavelengths (230—210 nm), which is at variance with the expected[15,16] positive effects resulting from aryl (resorcinol) A-rings above the plane of the B- and C-rings in both these instances. However, the 'deviant' behaviour of 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ol derivatives was established by us as due to the axial orientation of the 4-aryl function,[16] the negative Cotton-effect of the corresponding product of rearrangement (**15**) thus being in line with previous observations. The c.d. spectrum of the 2,3-*trans*-3,4-*cis* isomer (**13**) may similarly be rationalized in terms of the aromatic quadrant rule (*cf.* ref. 16) owing to the axial orientation of the resorcinol A-ring.

Evidence of the progressive formation of higher oligomers, *e.g.* 'trimers' (**10**) and (**11**) from the 'dimer' (**1**) through intermolecular condensation following fission of the latter, and also of the 'liberation' of more strongly nucleophilic free-phenolic resorcinol units, *i.e.* A-ring of compounds (**12**) and (**14**), which should promote condensation, support the idea that progressive insolubility which accompanies 'phlobaphene' formation is attributable to the increased mass of tannin units.

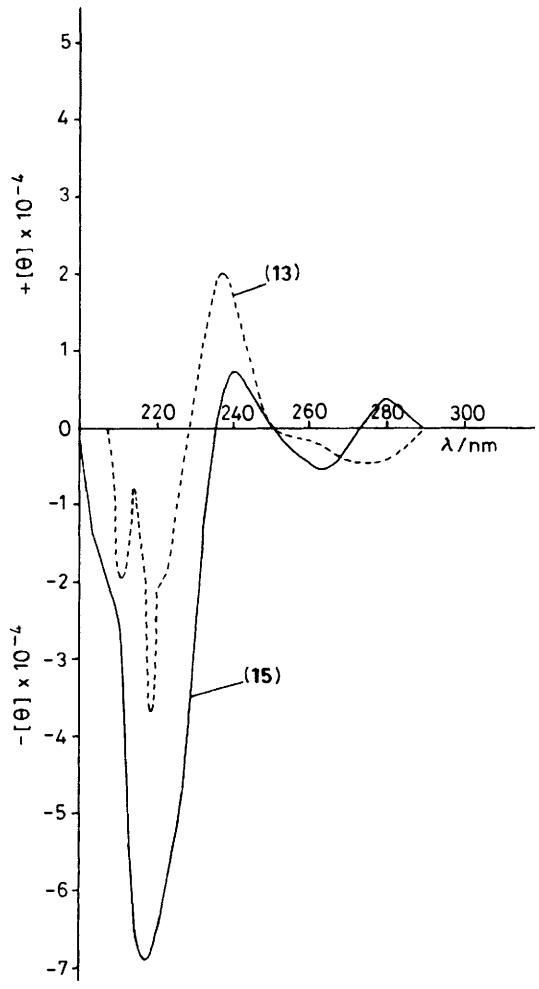



**Figure.** C.d. spectra of derivatives (**13**) and (**15**) of the products of rearrangement: tetrahydrobenzodipyrans

Development of 'tanners reds' in terms of tannery parlance must at least be partly due to anthocyanidin formation.

## Experimental

$^1H$ n.m.r. spectra were recorded on a Bruker WP-80 FT spectrometer in $CDCl_3$ and $C_6D_6$ with $Me_4Si$ as an internal standard. Determination of coupling constants required suitable scale expansion. Mass spectra were obtained with a Varian CH-5 instrument, and circular dichroism (c.d.) data in methanol on a Jasco J-20 spectropolarimeter. Analyses (C & H) were performed by the Analytische Laboratorien, Postfach 1249, D-5250 Engelskirchen, West Germany. Thin layer chromatography (t.l.c.) was done on DC-Plastikfolin, Kieselgel 60 $PF_{254}$ (0.25 mm) and the plates sprayed with $H_2SO_4$–HCHO (40:1) after development. Preparative plates (p.l.c.) [20 × 20 cm, Kieselgel $PF_{254}$ (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether over 48 h, while acetylations were in acetic anhydride–pyridine. Evaporations were done under reduced pressure at 50 °C on a rotary evaporator.

*Acid-catalysed Condensation of Equimolar Proportions of* (+)-*Mollisacacidin and* (+)-*Catechin.*—(+)-Catechin (2 g, 6.9

mmol) in ethanol (20 ml) was treated with 0.1M-HCl (150 ml) and (+)-mollisacacidin (2 g, 6.9 mmol) was added in small portions to ensure a continued large excess of the substrate while the mixture was stirred at 60 °C. After consumption of all the (+)-mollisacacidin (*ca.* 6 h) the mixture was extracted with ethyl acetate, the dried solvent removed under reduced pressure (60 °C) and the residual brown amorphous powder subjected to column chromatography (2.5 × 55 cm) on Sephadex LH-20 in ethanol. The eluate was collected in 10 ml aliquots.

Fractions 5—41 consisted of unchanged (+)-catechin (500 mg), identified by comparison of its $^1$H n.m.r. spectrum with that of an authentic sample.

(2R,3S)-2,3-trans-8-[(2R,3S,4R)-2,3-trans-3,4-cis-3,3′,4′,7-*Tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentrahydroxyflavan* (2). The free-phenolic [4,8]-3,4-*cis*-biflavanoid was isolated as a light brown amorphous powder (653 mg) from fractions 52—112, and crystallized as *buff cubes* from water, m.p. 200—203 °C (Found: C, 62.4; H, 5.2. $C_{30}H_{26}O_{11}\cdot H_2O$ requires C, 62.1; H, 4.9%); δ [80 MHz; $(CD_3)_2CO$; 95 °C] 6.88—6.44 (m, 7 × ArH), 6.38 [d, *J* 2.5 Hz, 8-H(A)], 6.30 [dd, *J* 8.0 and 2.5 Hz, 6-H(A)], 6.16 [s, 6-H(D)], 5.30 [dd, *J* 3.25 and 0.5 Hz, 2-H(C)], 4.70 [dd, *J* 3.5 and 1.0 Hz, 4-H(C)], 4.54 [d, *J* 7.5 Hz, 2-H(F)], 4.39 [dd, *J* 3.50 and 3.25 Hz, 3-H(C)], 4.04 [6 line m, *J* 8.0, 7.0, and 5.5 Hz, 3-H(F)], 3.06 [dd, *J* 15.75 and 5.5 Hz, 4-$H_{eq}$(F)], and 2.62 [dd, *J* 15.75 and 8.0 Hz, 4-$H_{ax}$(F)]; δ[80 MHz, $(CD_3)_2CO$, 30 °C] a degree of line-broadening is evident, but the chemical shifts of heterocyclic protons are almost identical with the above, while the coupling constants [$J_{2,3}$ 2.5; $J_{3,4}$ 2.75 Hz (C-ring); $J_{2,3}$ 7.0 Hz (F-ring)] are similar but slightly reduced at the reduced temperature; δ (80 MHz; $D_2O$; 100 °C) 7.09—6.66 (m, 7 × Ar H), 6.59 [d, *J* 2.5 Hz, 8-H(A)], 6.50 [dd, *J* 8.0 and 2.5 Hz, 6H-(A)], 6.34 [s, 6-H(D)], 5.40 [d, *J* 3.75 Hz, 2-H(C)], 4.78 [dd, *J* 4.0 and 0.6 Hz, 4-H(C)], 4.50 [d, *J* 7.5 Hz, 2-H(F)], 4.50 [t, Σ*J* 7.8 Hz, 3-H(C)], 4.25 [six line m, *J* 8.0 and 5.5 Hz, 3-H(F)], 3.22 [dd, *J* 16.25 and 5.75 Hz, 4-$H_{eq}$(F)], and 2.69 [dd, *J* 16.25 and 8.0 Hz, 4-$H_{eq}$(F)].

Methylation and acetylation of the [4,8]-3,4-*cis*-biflavanoid gave the heptamethyl ether diacetate,[2] δ (80 MHz; $CDCl_3$; 100 °C) 5.56 [dd, *J* 8.5 and 6.5 Hz, 3-H(C)], 5.27 [d, *J* 8.5 Hz, 2-H(C)], and 4.95 [d, *J* 6.5 Hz, 4-H(C)].

Fractions 146—300 (1.817 g) consisted of two components which were separated by p.l.c. [benzene–acetone–methanol (6:3:1 v/v)] at $R_F$ 0.29 and 0.40.

(2R,3S)-2,3-trans-8-[(2R,3S,4S)-2,3-trans-3,4-trans-3,3′,4′,7-*Tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentahydroxyflavan* (**1**). The [4,8]-all-*trans*-biflavanoid ($R_F$ 0.29) was obtained as an *amorphous brown powder* (1.05 g) which failed to crystallize from water (Found: C, 62.2; H, 5.0. $C_{30}H_{26}O_{11}\cdot H_2O$ requires C, 62.1; H, 4.9%); δ (80 MHz; $D_2O$; 120 °C) 6.88—6.53 (m, 7 × Ar H), 6.50 [s, 6-H(D)], 6.27 [dd, *J* 8.5 and 2.5 Hz, 6-H(A)], 6.16 [d, *J* 2.5 Hz, 8-H(A)], 4.50 [d, *J* 7.5 Hz, 2-H(F)], 4.45 [d, *J* 9.0 Hz, 2-H(C)], 4.43 [d, *J* 6.6 Hz, 4-H(C)], 3.81 [6 line m, 3-H(F)], 2.88 [dd, *J* 16.0 and 5.5 Hz, 2-$H_{eq}$(F)], and 2.46 [dd, *J* 16.0 and 8.25 Hz, 4-$H_{ax}$(F)].

Methylation and acetylation of the [4,8]-3,4-*trans*-biflavanoid gave the heptamethyl ether diacetate,[2] δ (80 MHz; $CDCl_3$; 100 °C) 6.03 [t, Σ*J* 19.5 Hz, 3-H(C)], 4.84 [dd, *J* 9.5 and 1.0 Hz, 4-H(C)], and 4.80 [d, *J* 10.0 Hz, 2-H(C)].

(2R,3S)-2,3-trans-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3,3′,4′,7-*Tetrahydroxyflavan*-4-*yl*]-8-[(2R,3S,4R)-2,3-trans-3,4-cis-3,3′,-4′,7-*tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentahydroxyflavan*. The free-phenolic [4,6:4,8]-3,4-*trans*- 3,4-*cis*-triflavanoid ($R_F$ 0.40) was isolated as an amorphous colourless solid (96 mg); δ [80 MHz; $(CD_3)_2SO$; 150 °C] 5.22 [d, *J* 2.8 Hz, 2-H(C)], 4.66 [d, *J* 3.0 Hz, 4-H(C)], 4.22 [t, Σ*J* 5.8 Hz, 3-H(C)], 3.91 [6 line m, *J* 7.5 and 5.5 Hz, 3-H(F)], 2.78 [dd, *J* 16.0 and 5.5 Hz, 4-$H_{eq}$(F)], and 2.47 [dd, *J* 16.0 and 8.0 Hz, 4-$H_{ax}$(F)].

Methylation and acetylation gave the decamethyl ether triacetate with $^1$H n.m.r. spectrum [$(CD_3)_2SO$; 170 °C] identical with that recorded in the literature.[15] The fractions 310—415 (540 mg) consisted of two components which were readily separable by p.l.c. in benzene–acetone–methanol (6:3:1 by vol) at $R_F$ 0.24 and 0.40.

(2R,3S)-2,3-trans-6-[(2R,3S,4R)-2,3-trans-3,4-cis-3,3′,4′,7-*Tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentahydroxyflavan* (**4**). The [4,6]-3,4-*cis*-biflavanoid ($R_F$ 0.24) was isolated as a pale brown amorphous powder (225 mg) (Found: C, 62.8; H, 5.2. $C_{30}H_{26}O_{11}\cdot H_2O$ requires C, 62.1; H, 4.9%); δ[80 MHz; $(CD_3)_2CO$; 90 °C] 6.91—6.43 (m, 7 × Ar H), 6.43 [d, *J* 2.5 Hz, 8-H(A)], 6.27 [dd, *J* 8.0 and 2.5 Hz, 6-H(A)], 6.01 [s, 8-H(D)], 5.43 [dd, *J* 3.0 and 0.5 Hz, 2-H(C)], 4.72 [d, *J* 3.0 Hz, 4-H(C)], 4.53 [d, *J* 7.0 Hz, 2-H(F)], 4.41 [t, Σ*J* 6.0 Hz, 3-H(C)], 4.04 [overlapping ddd, *J* 8.0, 7.0, and 5.0 Hz, 3-H(F)], 2.91 [dd, *J* 16.0 and 5.0 Hz, 4-$H_{eq}$(F)], and 2.50 [dd, *J* 16.0 and 8.0 Hz, 4-$H_{ax}$(F)].

Methylation and acetylation of the [4,6]-3,4-*cis*-biflavanoid gave the heptamethyl ether diacetate,[12] δ (80 MHz; $CDCl_3$; 100 °C) 5.50 [dd, Σ*J* 15.0 Hz, 3-H(C)], 5.21 [d, *J* 8.5 Hz, 2-H(C)], and 4.98 [d, *J* 6.5 Hz, 4-H(C)].

(2R,3S)-2,3-trans-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3,3′,4′,7-*Tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentahydroxyflavan* (**3**). The [4,6]-3,4-*trans*-biflavanoid ($R_F$ 0.40) was isolated as a *brown amorphous powder* (206 mg) (Found: C, 62.7; H, 5.1. $C_{30}H_{26}O_{11}\cdot H_2O$ requires C, 62.1; H, 4.9%); δ [80 MHz, $(CD_3)_2CO$, 95 °C] 7.09—6.64 (m, 7 × Ar H), 6.36 [d, *J* 2.5 Hz, 8-H(A)], 6.36 [dd, *J* 8.0 and 2.5 Hz, 6-H(A)], 6.06 [s, 8-H(D)], 4.67 [d, *J* 11.0 Hz, 2-H(C)], 4.66 [d, *J* 7.5 Hz, 2-H(F)], 4.59 [d, *J* 7.5 Hz, 4-H(C)], 4.36 [dd, *J* 11.0 and 7.5 Hz, 3-H(C)], 4.03 [6-line m, *J* 7.5 and 5.5 Hz, 3-H(F)], 2.97 [dd, *J* 15.5 and 5.5 Hz, 4-$H_{eq}$(F)], and 2.53 [dd, *J* 15.5 and 7.75 Hz, 4-$H_{ax}$(F)].

Methylation and acetylation of the [4,6]-3,4-*trans*-biflavanoid gave the heptamethyl ether diacetate,[2] δ (80 MHz; $CDCl_3$; 100 °C) 6.03 [t, Σ*J* 19.5 Hz, 3-H(C)], 4.88 [d, *J* 9.75 Hz, 2-H(C)], and 4.78 [br d, *J* 9.75 Hz, 4-H(C)].

(2R,3S)-2,3-trans-6,8-*bis*-[(2R,3S,4R)-2,3-trans-3,4-trans-3,3′,-4′,7-*Tetrahydroxyflavan*-4-*yl*]-3,3′,4′,5,7-*pentahydroxyflavan*. Fractions 423—460 (175 mg) consisted mainly of the [4,6:4,8]-all-*trans*-triflavanoid. Methylation (100 mg) and acetylation followed by p.l.c. [hexane–acetone–ethyl acetate (12:5:3 v/v)] gave the decamethyl ether triacetate as the major product $R_F$ 0.34 (58 mg). The $^1$H n.m.r. spectrum [$(CD_3)_2SO$; 170 °C] proved identical with that recorded in the literature.[15]

[4,8]-(−)-*Fisetinidol*-(+)-*Catechins* (1), (2): *Enhanced Regioselectivity* via *a* 6-*Iodo*-(+)-*Catechin Intermediate*.—*Iodination of* (+)-*catechin with* $I_2$. (+)-Catechin (290 mg, 1 mmol) dissolved in ethanol (20 ml) was treated with iodine (254 mg, 1 mmol) in ethanol (30 ml) added dropwise over 30 min at 40 °C. After a further 5 min, the excess $I_2$ was destroyed with $Na_2S_2O_3$ solution. The reaction products were methylated with diazomethane, and the methyl ethers extracted with dichloromethane. After removal of the solvent in a stream of nitrogen the solids (385 mg) were separated by p.l.c. eluting with hexane–acetone–ethyl acetate (60:25:15 v/v) to give fractions at $R_F$ 0.72 (1.2 mg), 0.70 (4 mg) and 0.65 (5 mg).

3-O-*Acetyl*-8-*iodo*-3′,4′5,7-*tetra*-O-*methyl*-(+)-*catechin*. The $R_F$ 0.65 (5 mg) fraction was acetylated to give a *colourless solid* (5 mg), δ($CDCl_3$) 6.94—6.81 (m, 3 × Ar H), 6.14 [s, 6-H(A)], 5.44 [m, 3-H(C)], 5.21 [d, $J_{2,3}$ 5.0 Hz, 2-H(C)], 3.90, 3.85, 3.84, 3.81 (s, 4 × OMe), 2.74 [d, $CH_2$(C)], and 2.03 [s, 3-OAc(C)]; *m/z* 514 ($M^+$, 10.5%), 554 ($M^+$ − 60, 91), 293 (23), 292 (6.2), 222 (9.3), 180 (100), 165 (28), and 151 (32).

The $R_F$ 0.70 fraction consisted of (+)-catechin.

*Iodination of* (+)-*Catechin with* N-*Iodosuccinimide* (NIS).—(+)-Catechin (580 mg, 2 mmol) dissolved in dimethylformamide

(DMF) was treated at 4 °C with NIS (450 mg, 2 mmol) dissolved in dry acetone (20 ml) by dropwise addition over 30 min. The reaction effected the quantitative conversion of (+)-catechin. The product was extracted with ethyl acetate and the solution was washed successively with 0.1M-HCl and -$NaHCO_3$ solutions and finally dried ($Na_2SO_4$). The product obtained after evaporation was methylated and separated by p.l.c. eluting with hexane–acetone–ethyl acetate (60:25:15 v/v). The following fractions were obtained: $R_F$ 0.76 (10 mg), 0.65 (16 mg), 0.54 (250 mg), 0.49 (25 mg), and 0.27 (8 mg).

3-O-*Acetyl*-6-*iodo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (**7**). The $R_F$ 0.54 (260 mg) fraction was acetylated to give a *colourless solid* (265 mg) (Found: C, 43.6; H, 3.3. $C_{15}H_{13}IO_6$ requires C, 43.3; H, 3.2%); δ($CDCl_3$) 6.57 [s, 3 × Ar H(B)], 6.37 [s, 8-H(A)], 5.34 [m, 3-H(C)], 5.06 [d, *J* 6.1 Hz, 2-H(C)], 3.90, 3.88, 3.87, 3.78 (s, 4 × OMe), 3.03 [dd, *J* 16.2 and 5.0 Hz, 4-$H_{eq}$(C)], 2.80 [dd, *J* 16.2 and 6.0 Hz, 4-$H_{ax}$(C)], and 2.00 [s, 3-OAc(C)].

The $R_F$ 0.76 (10 mg) fraction consisted of an iodinated pentamethyl ether of catechin; and fraction $R_F$ 0.49 (25 mg) consisted of equivalent amounts of the 6- and 8-iodotetra-O-methyl-(+)-catechin.

*Coupling of* (+)-*Mollisacacidin with* 6-*Iodo*-(+)-*catechin*.—The conditions set out above were repeated, but after completing the addition of NIS, (+)-mollisacacidin (290 mg, 1 mmol) and 0.1 M-HCl (0.7 ml) were added and the mixture allowed to stand overnight. The condensed products were taken to dryness in a current of nitrogen and the solids were separated on a 3.3 × 44 cm Sephadex LH-20 column in 15 ml aliquots with ethanol as the eluant at a flow-speed of 0.5 ml $min^{-1}$. Distribution of the products was as follows: tubes 32—40 [251 mg, (+)-catechin], 41—45 (24 mg), 52—81 {130 mg, [4,8]-3,4-*cis*-biflavanoid (**2**)}, 82—114 {124 mg, [4,8)-3,4-*trans*-biflavanoid (**1**)}, 115—184 {9 mg, [4,8]-3,4-*trans*- + [4,6]-3,4-*cis*- (**4**) biflavanoids} and 185—210 {5 mg, [4,6]-3,4-*trans*-biflavanoid (**3**) + 'trimers'}.

*Acid-Induced Conversions of a* [4,8]-*Biflavanoid: Study of the Phlobaphene Reaction*

[4,8]-3,4-*trans*-(−)-Fisetinidol-(+)-catechin (**1**) (2 × 500 mg) was dissolved in ethanol (2 × 50 ml). Acetic acid (5 ml) and monochloroacetic acid (2 g) was added to each and the mixture was refluxed for 24 h under nitrogen. Separation on Sephadex LH-20 columns 2 × (46 × 3.5 cm) in 15 ml aliquots with ethanol as the eluant gave the following fractions: tubes 31—35 (8 mg), 38—40 (53 mg), 53—69 (135 mg), 72—84 (247 mg), 85—97 (47 mg), 119—170 (85.5 mg), and 171—250 (97 mg).

Fractions 31—35 proved to be the 3-*O*-monochloroacetyl derivative of 'liberated' (+)-catechin, and fractions 38—40 consisted of 'liberated' (+)-catechin (**5**). T.l.c. separation of the third fraction 53—69 in benzene–acetone–methanol (6:3:1 v/v) gave two fractions at $R_F$ 0.35 {16 mg, unchanged [4,8]-biflavanoid (**1**)} and $R_F$ 0.31 (39 mg). Methylation and acetylation of the latter followed by p.l.c. with 1,2-dichloroethane–acetone (9:1 v/v, × 3) gave two products with $R_F$ 0.47 (9 mg) and $R_F$ 0.41 (7.7 mg).

(2R,3S,8R,9S,10R)-2,3-trans-8,9-trans-9,10-cis-3,9-*diacetoxy*-2,8-*bis*(3,4-*dimethoxyphenyl*)-10-(2,4-*dimethoxyphenyl*-5-*methoxy*-3,4,9,10-*tetrahydro*-2H,8H-*benzo*[1,2-b;3,4-b′]*dipyran* (**13**). The benzodipyran, $R_F$ 0.47 (9 mg), was isolated as a *colourless solid* (Found: C, 64.7; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%); δ($CDCl_3$) 6.89—6.73 (m, 6 × Ar H), 6.79 [d, *J* 8.9 Hz, 6-H(A)], 6.39 [dd, *J* 8.9 and 2.5 Hz, 5-H(A)], 6.28 [d, *J* 2.5 Hz, 3-H(A)], 6.19 [s, 6-H(D)], 5.53 [dd, *J* 10.0 and 6.0 Hz, 3-H(C)], 5.24 [m, 3-H(F)], 5.09 [d, *J* 6.0 Hz, 4-H(C)], 4.98 [d, *J* 10.0 Hz, 2-H(C)], 4.62 [d, *J* 7.0 Hz, 2-H(F)], 3.86 (× 4), 3.8 (× 2), 3.55 (s, 7 × OMe), 2.9 [dd, 4-$H_{eq}$(F)], 2.6 [dd, 4-$H_{ax}$(F)], 1.88 [s, 3-OAc(F)], and 1.68 [s, 3-OAc(C)]; c.d. spectrum (Figure).

(2R,3S,8S,9S,10R)-2,3-trans-8,9-cis-9,10-cis-3,9-*Diacetoxy*-2,8-*bis*(3,4-*dimethoxyphenyl*)-10-(2,4-*dimethoxyphenyl*-5-*methoxy*-3,4,9,10-*tetrahydro*-2H,8H-*benzo*[1,2-b;3,4-b′]*dipyran* (**15**). The benzodipyran, $R_F$ 0.41 (7.7 mg), was isolated as a *colourless solid* (Found: C, 65.9; H, 6.1. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%); δ($CDCl_3$) 7.50 [d, *J* 8.0 Hz, 6-H(A)], 6.84—6.61 (6 × Ar H), 6.50 [dd, *J* 8.0 and 2.4 Hz, 5-H(A)], 6.31 [d, *J* 2.4 Hz, 3-H(A)], 6.30 [s, 6-H(D)], 5.26—5.47 [m, 2-H(C), 3-H(C), 3-H(F)], 4.85 [d, *J* 6.0 Hz, 2-H(F)], 4.34 [br d, *J ca.* 1.9 Hz, 4-H(C)], 3.9 (× 2), 3.8 (× 3), 3.52 (s, 6 × OMe), 2.73—2.88 [m, 4-$H_{eq}$(F) and 4-$H_{ax}$(F)] and 1.95, 1.91 (s, 2 × 3-OAc); δ($C_6D_6$) 8.05 [d, *J ca.* 8 Hz, 6-H(A) and 5-H (B and E)], 7.03—6.08 (m, 7 × Ar H), 6.00 [dd, *J* 1.25 and 1.9 Hz, 3-H(C)], 5.94 [s, *J ca.* 1 Hz, 2-H(C)], 5.56 [m, 3-H(F)], 5.00 [d, *J* 5.00 Hz, 2-H(F)], 4.94 [br d, *J ca.* 2 Hz, 4-H(C), 3.39 (× 3), 3.34, 3.30 (× 2), 3.00 (s, 7 × OMe), 3.14 [m, $CH_2$(F)], 1.59 and 1.53 [s, 3-OAc(C and F)]; c.d. spectrum (Figure).

Significant fragments in the mass spectra of the derivatives (**13**) and (**15**) of the 8,9-*trans*- and -*cis*-isomers (2,3-*trans* and 2,3-*cis* C-ring equivalents) and their respective relative abundances are: *m/z* 744 ($M^+$, 28, 7.1), 684 ($M^+$ − 60, 34, 98), 624 ($M^+$ − 120, 11.3, 27), 522 (1.5, 2.7), 491 (66, 4.9), 462 (19.9, 51), 431 (41, 6.7), 301 (15.6, 14.9), 300 (14.4, 8.1), 287 (100, 9.3), 269 (59, 14.1), 222 (8.5, 10.7), 180 (93, 100), and 151 (84, 92).

The remaining fractions gave the following products: 72—84 (247 mg), unchanged [4,8]-3,4-*trans*-biflavanoid (**1**); 85—97 (47 mg), p.l.c. separation in benzene–acetone–methanol (6:3:1 v/v) gave the [4,6]-3,4-*cis*- (**4**) (4 mg) and [4,8)-3,4-*trans*-biflavanoid (**1**) (10 mg) analogues; 119—170 (85.5 mg), p.l.c. separation in benzene–acetone–methanol (6:3:1 v/v) gave the [4,6]-3,4-*trans*-biflavanoid (**3**) (8 mg) isomer; and 171—250 (97 mg), methylation, p.l.c. separation [benzene–acetone (7:3 v/v)] and acetylation gave a mixture (4.3 mg) of the 'trimeric' [4,6:4,8]-all-*trans* (**10**) and [4,6:4,8]-3,4-*cis*:3,4-*trans* (**11**) isomers. The structures of these compounds were confirmed by direct comparison of their $^1H$ n.m.r. spectra by those of known compounds (*cf.* refs. 2, 15).

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