

STRUCTURE AND FUNCTION IN THE BIOMIMETIC SYNTHESIS OF LINEAR, ANGULAR AND BRANCHED CONDENSED TANNINS

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Abstract—The course and rate of direct biomimetic condensations of flavan-3,4-diols, as potential electrophiles, with progressively complex nucleophilic flavanoids to form oligomeric tannins is generally regulated by the functionality and hence stability of the parent carbocation generated under mild acid conditions; by the stereochemistry of the electrophile; by the relative nucleophilicity of competing centres on the complex substrates; by steric effects contributed by both the functionality and the stereochemistry of the nucleophile; by contributory hyperconjugative effects in both electro- and nucleophiles; and by stoichiometric considerations. Analogies available from analysis of natural sources indicate that the same precepts are obeyed during tannin biogenesis.

Syntheses based on parent flavanoids of known absolute configuration, coupled with ultra high resolution ¹H n.m.r. spectroscopy for determining relative configurations and condensation sequence of flavanoid units in the resultant tannins, supported by circular dichroism, enable definition of their structures and absolute configurations.

Condensed tannins are probably the most ubiquitous of all plant phenolics, and their exceptional concentrations in the barks and heartwoods of a variety of tree species, e.g. *Acacia mearnsii* (black wattle), *Schinopsis* spp. (quebracho) and *Rhizophora* spp. (mangrove) have resulted in their commercial extraction with the initial objective of applying the extracts in leather manufacture. In most instances this has led to the exploitation of indigenous forests (quebracho, mangrove), but the wattle bark industry in South Africa and also elsewhere, is uniquely based on sustained afforestation.

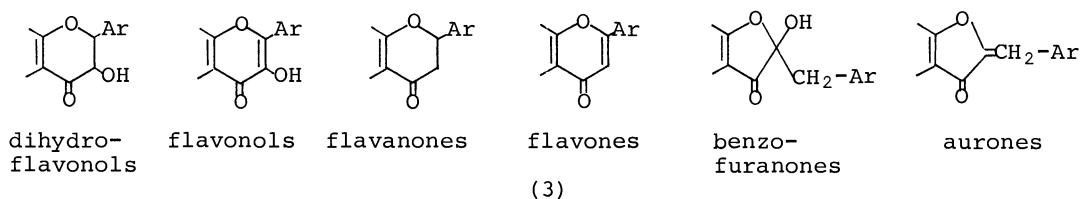
Due to a slow but progressive world-wide decline in the use of vegetable extracts as tanning materials, the range of industrial applications of wattle ('Mimosa') extract has been extended through sustained local development to flocculants for water treatment; to depressants in ore flotation; to a variety of cold and thermosetting adhesives for manufacturing composite wood products; and to adhesives designed for the packaging industry.¹ These established industrial uses are based on the 70% phenolic ('tannin') content of the natural extract, representing a molecular gradation over the mass range 300-3000 and with a number average mass approximating to 1250.² Knowledge of tannin structure and extract composition has contributed significantly to some of these developments.

The chemistry of those condensed tannins which are of commercial significance, and also of others of more academic interest, has until of late represented an unattractive and therefore much neglected area of research. Inhibiting factors have been the extreme complexity of tannin extract composition; the high chirality of the constituent oligomers; their relative sensitivity towards stereochemical inversion; and susceptibility to autoxidation. Our dissatisfaction with the obvious limitations of chemical and spectrometric analysis prompted an exploration into methods of direct synthesis.³⁻¹⁰ The approach was based on the premise that flavan-3,4-diols as potential electrophiles, and nucleophilic flavan-3-ols were involved in initiating condensation, while a combination of flavan-3,4-diols and the immediate condensation products presumably 'propagates' the condensation sequence. Generalized principles which have accrued from this study will constitute the subject of our review.

Selection and relative stabilities of electrophilic and nucleophilic flavanoids. In those flavanoid metabolic pools which possess the potential for condensed tannin formation, flavan-3,4-diols (1), when regarded as p-hydroxybenzyl alcohols, represent the only units capable of generating 4-carbenium



ions, while strongly nucleophilic centres are largely confined to ubiquitous flavan-3-ols (2) with *meta*-substitution of their A-rings. Others representative of the more commonly encountered groups of flavonoids (3) possess carbonyl function at the 4-position or its equivalent, thus effectively neutralizing the nucleophilicity of their aromatic A-rings. By the same token



the inductive effect of the 4-hydroxyl function of flavan-3,4-diols (1) or of the 4-carbenium ion resulting from its protonation, reduces their innate tendency for self-condensation.

Flavan-3,4-diols of the resorcinol-type, e.g. (+)- and (-)-leucofisetinidin (4, 5) and (+)-leucorobinetinidin (6), are relatively stable and therefore dominant in the heartwood perimeter of tree species (e.g. *A. mearnsii*,¹¹ *Schinopsis* spp.¹² and *Robinia pseudacacia*¹³) in which profisetinidin and pro-robinetinidin tannins predominate, but their concentrations generally decline towards the central heartwood.¹¹⁻¹³ By contrast, leucocyanidins and leuco-



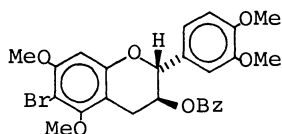
delphinidins (7,8) are generally absent from plant extracts containing their oligomeric equivalents, in spite of earlier indications to the contrary.



These observations are in line with the enhanced resonance stabilization of the 4-carbenium ions anticipated for these phloroglucinol-type species,¹⁴ and hence their high reactivity. Procyanidin and prodelphinidin oligomers therefore probably represent condensation products of highly reactive flavan-

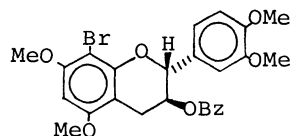
3,4-diols with stable but strongly nucleophilic substrates such as the omnipresent (+)-catechin (9) or (+)-gallocatechin (10).

Bonding positions on the nucleophile. Since the pre-eminence of (+)-catechin and (+)-gallocatechin as nucleophiles in initiating condensed tannin formation has been recognized, the alternative bonding positions on their A-rings require methods of differentiation. In what might now be regarded as a basic if not classic approach, both 6- and 8-bromo derivatives of (+)-catechin (11, 12) were synthesised,^{15,5} and after differentiation by X-ray crystallography,¹⁶ they were converted *via* lithio intermediates into analogues bearing 6- and 8-substituents which possess both electron withdrawing (COOH) and donating (OH, CH₂OMe) properties. Study of the absolute values of the chemical shifts of these compounds in CDCl₃ indicated that residual H-6 and H-8 resonances exhibit finite shifts without overlap, and also that differential values devolving mainly upon shifts of the *axial* H-2, provided criteria for differentiating between 6 and 8 substitution. Our subsequent work on



(11)

Bz = benzyl

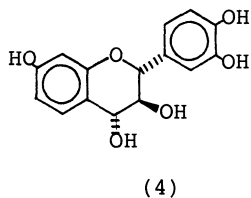


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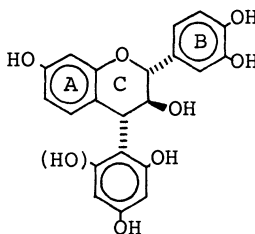
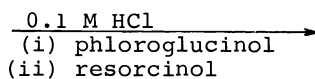
biflavanoids has shown these criteria to be reliable, provided that they are used in conjunction and also circumspectly.

Conditions for controlled electrophilic aromatic substitution and its stereochemical course. The generation of carbocations from typical flavan-3,4-diols and their participation in controlled biomimetic condensations require aqueous acidic conditions which are sufficiently mild to obviate both anthocyanidin formation and self-condensation, and to permit reaction under kinetic rather than thermodynamic control within reasonable time-lapse. The latter is obviously a variable factor in terms of its marked dependency on the nucleophilicity of the substrate. Acid conditions are also beneficial as regards ensuring maximum stability of catechol or pyrogallol B-ring function towards oxidation.

Condensation of a flavan-3,4-diol, e.g. (+)-2,3-*trans*-3,4-*trans*-leucopisetinidin (4) of known absolute configuration (2*R*:3*S*:4*R*) with phloroglucinol or resorcinol at low acidity (0.1 M HCl) and ambient temperatures (~20°C) proceeds rapidly (2-4 h) and stereoselectively,^{3,17} producing 3,4-*trans*- and 3,4-*cis*-4-arylflavan-3-ols (13, 14) in the proportions of *ca.* 1.5-2:1.

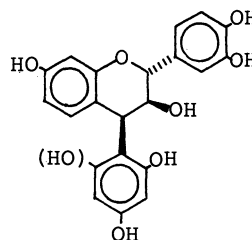


(4)



(13a) R = OH

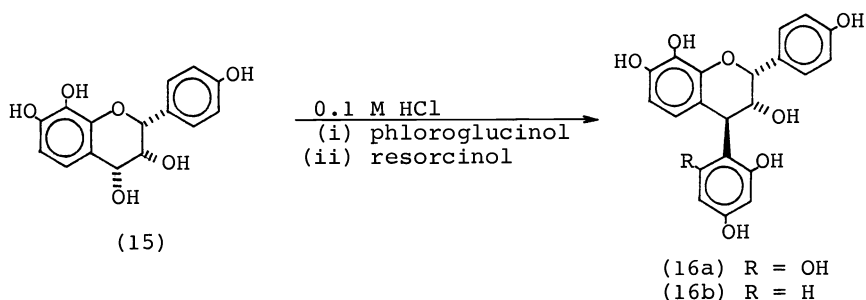
(13b) R = H



(14a) R = OH

(14b) R = H

By contrast both phloroglucinol and resorcinol are captured stereospecifically by the carbenium ion generated from (-)-2,3-*cis*-3,4-*cis*-teracacidin (15) to form 2,3-*cis*-3,4-*trans*-4-arylflavan-3-ol analogues (16) with inversion of configuration.



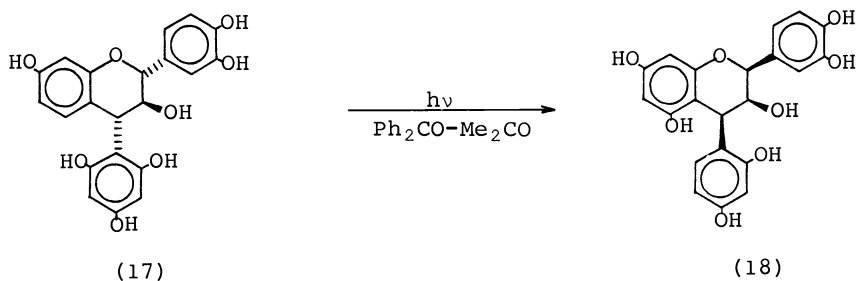
Assuming that both carbenium ion intermediates possess sofa conformations, nucleophilic attack on the 4-carbocation with 2,3-*cis* configuration [ex (15)] proceeds from the less hindered 'upper' side presumably with neighbouring group participation of the 3-*axial* hydroxyl, whereas reaction with a 2,3-*trans* carbocation intermediate [ex (4)] is directed as anticipated mainly from the less hindered 'lower' side. The degree of selectivity in the latter instance in which formation of the thermodynamically less stable 2,3-*trans*-3,4-*trans* isomer predominates, indicates that the reaction is primarily under kinetic control when applying mild reaction conditions.^{3,17}

The intermediacy of the 4-carbenium ion in the above reactions is supported by the observed difficulty in the course of acid induced condensations of (+)-peltogynol with the same nucleophilic phenols as judged by higher energy requirements and significantly lower yields; strain induced by the D-ring reinforcing the half-chair conformation of the heterocyclic C-ring, thus inhibiting the planarity required for stability of the 4-carbocation.¹⁸

Since flavan-3,4-diols and nucleophilic flavan-3-ols of the phloroglucinol- and resorcinol-type, as well as analogous bi- and triflavanoid condensation products (see below) accompany tannins, these mechanisms involving model phenols should accurately predict the configuration at C-4 of all constituent 2,3-*trans* and 2,3-*cis* flavanoid units in natural condensed tannins.

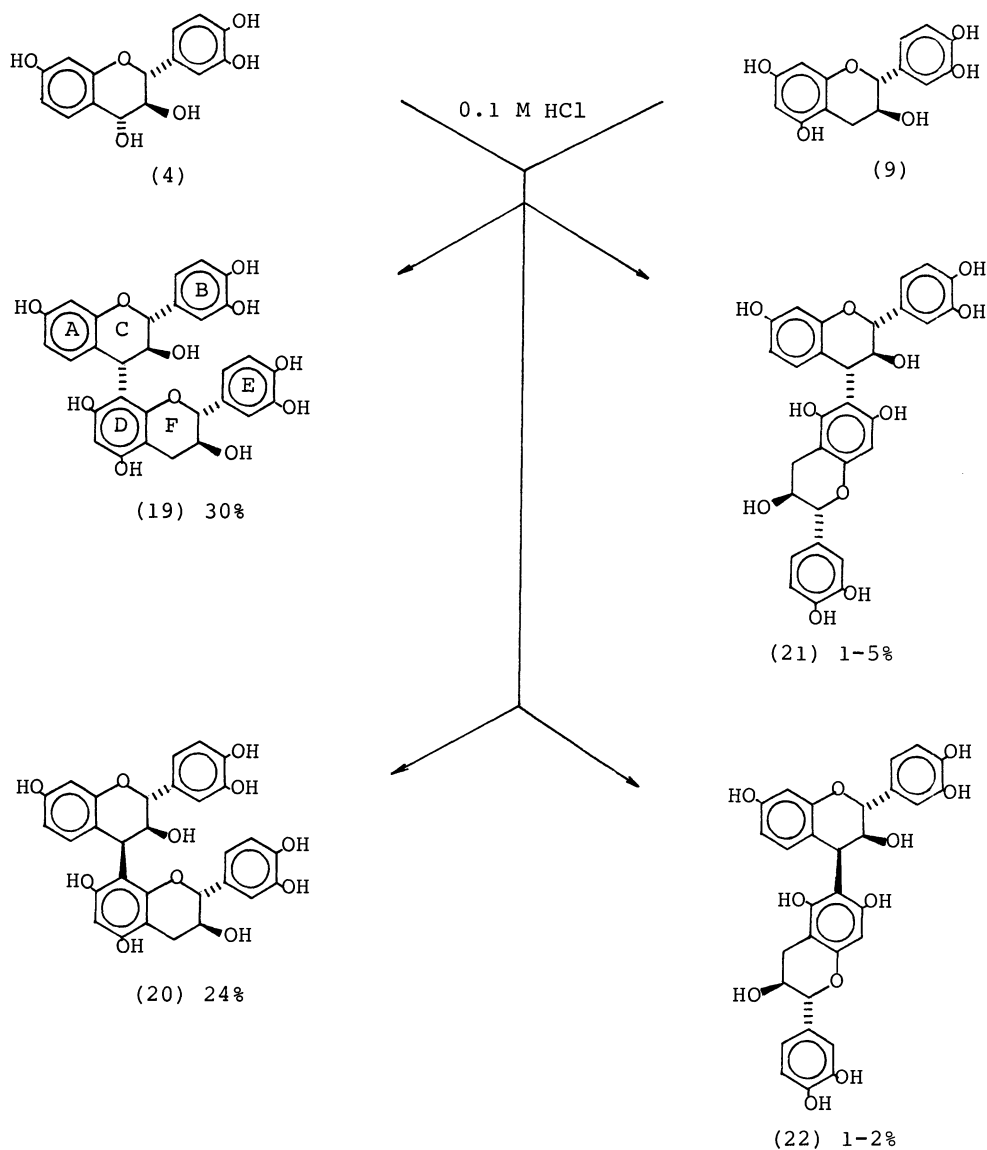
Stereochemistry at C-4 of 4-arylflavan-3-ols and the aromatic quadrant rule.

¹H n.m.r. coupling constants of the heterocyclic ring systems in the methyl ether acetates of the classes of 2,3-*trans*-3,4-*trans*-, 2,3-*trans*-3,4-*cis*- and 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols cited above, indicate that their heterocyclic ring systems exhibit half-chair conformations. In these instances their c.d. spectra exhibit intense Cotton effects at low wave-lengths through interaction of the A- and D-ring phenolic chromophores at the C-4 chiral centre,^{3,17} negative effects correlating with the D-ring below, and positive effects with the D-ring above the general plane of the benzopyran system. These observations are in agreement with the aromatic quadrant rule.⁴ The remaining class of 2,3-*cis*-3,4-*cis* isomers, available by photochemical isomerisation only in those instances where D-ring nucleophilicity exceeds that of the A-ring [e.g. (17) → (18)], do not fall in line with the rule. However, their heterocyclic protons do not exhibit coupling constants consistent with the half-chair conformation.



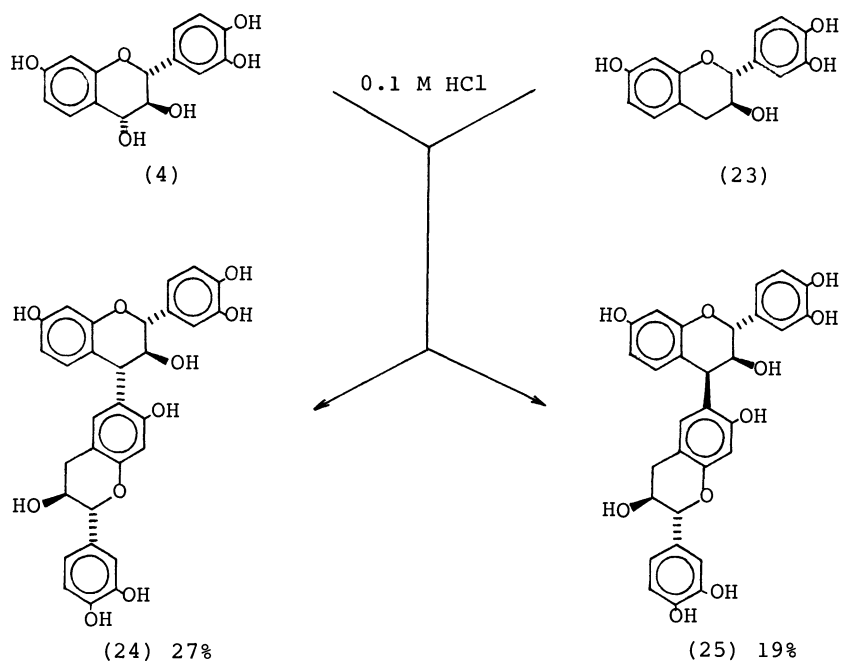
Biomimetic condensations for generating biflavonoids: Stoichiometric, stereo- and regiochemical considerations. Application of the conditions of the above carbenium ion mediated condensations upon substituting (+)-catechin for the nucleophilic phenols, permits syntheses of a range of natural biflavonoids.^{6,19} From these the following generalizations are possible.

The reactions, for example, of (+)-2,3-*trans*-3,4-*trans*-leucofisetinidin (4) with (+)-catechin (9) and also (-)-fisetinidol (23) in the presence of excess of the nucleophiles proceed more slowly (48 h, 7 days) at ambient temperatures than previously indicated; the reactions having been monitored previously by t.l.c. (silica), and the products separated on the same substrate. These procedures appear to accelerate the reaction to completion.

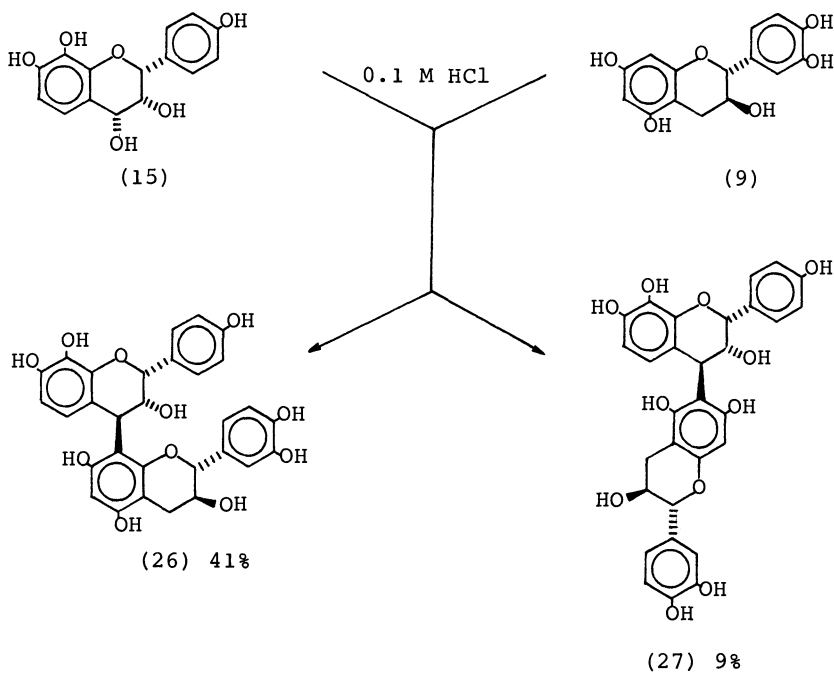


Thus, condensation of (+)-leucofisetinidin (4) with an excess of (+)-catechin (9) as bifunctional nucleophile gives four products (19-22); the structures and stereochemistry of their methyl ether diacetates indicating both regio- and stereoselective condensations.^{6,19} The 8-position on the (+)-catechin unit is sterically less hindered than the 6-position under conditions of attack by a bulky electrophile, while 3,4-*trans* attachment of the flavan-3-ol to the carbenium ion exhibits a degree of preference over 3,4-*cis* attachment at C-4. The series of four 4,6- and 4,8-linked biflavonoids (19-22) permit definition of the chemical shift parameters of their heterocyclic protons.

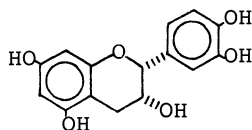
Other noteworthy phenomena⁶ in biflavanoid formation are examples of the regiospecificity of the condensation of (+)-leucofisetinidin (4) with the resorcinol-type flavan-3-ol substrate, (-)-fisetinidol (23), which again proceeds stereoselectively as above. The exclusive 4,6-linkages in the products (24, 25) also demonstrate the dominance of steric effects in resorcinol-type



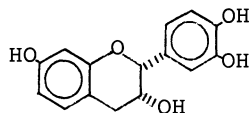
substrates; a phenomenon of particular significance in higher oligomers. Stereospecificity in biflavanoid formation when employing a 2,3-*cis*-3,4-*cis*-flavan-3,4-diol (15) is of note, in that the reaction follows the same course as with phenols, and is markedly regioselective [*cf.* (26) and (27)].⁶



The versatility of the method is obvious⁶ from analogous combinations of the same flavan-3,4-diols with 2,3-*cis*-flavan-3-ols [(-)-epicatechin (28) and (+)-epifisetinidol (29)], and from condensation of (-)-leucofisetinidin (5)



(28)

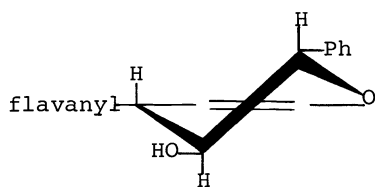
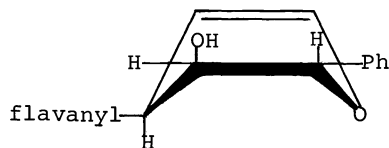


(29)

with (+)-catechin (9), the fore-mentioned affording a group of four biflavanoids identical to those which populate the heartwoods of Anacardiaceae (e.g. *Schinopsis* spp.), and bearing a diastereoisomeric relationship to profisetinidins (19-22) generated from (+)-leucofisetinidin and (+)-catechin.

Condensations leading to biflavanoids may be controlled stoichiometrically by employing, for example, molar equivalents of either (+)- or (-)-leucofisetinidins and (+)-catechin. Under ambient conditions the reaction terminates after consumption of the reactants but without formation of triflavanoids (*cf.* below), while good yields of [4,8]-all-*trans* and 2,3-*trans*-3,4-*cis*:2',3'-*trans* isomers, separable by gel filtration (Sephadex LH 20) (*cf.* ref.²⁰) are obtained; compounds which represent useful synthons for access to angular triflavanoids of known absolute configuration.

Conformation of the free phenolic forms of biflavanoids. Conformational analysis of the individual units in biflavanoids was previously confined to deductions from heterocyclic ¹H n.m.r. coupling constants of their derivatives, whereas similar knowledge of the free phenolic forms is of obvious importance, but was hitherto overlooked. The coupling constants of heterocyclic protons of some of the above-mentioned [4,8]-biflavanoids indicate that for units with 3,4-*cis* configuration [e.g. (20)] the C-ring of the substituent (-)-fisetinidol moiety exhibits a twisted boat conformation ($J_{2,3} = J_{3,4} = 3.0$ Hz) at variance with the half-chair arrangement in derivatives, while the F-ring of the (+)-catechin moiety retains the half-chair conformation ($J_{2,3} 7.5$, $J_{3,4ax} 8.0$, $J_{3,4eq} 5.5$ Hz). Corresponding coupling constants of free phenolic all-*trans*-biflavanoids [e.g. (19)] are generally less readily determined due to their poor chemical shift distributions, but indicate unambiguously the half-chair conformations of both their C- ($J_{2,3} 11.2$, $J_{3,4} 7.0$ Hz) and F-rings (J_s as above). From the illustration it is obvious

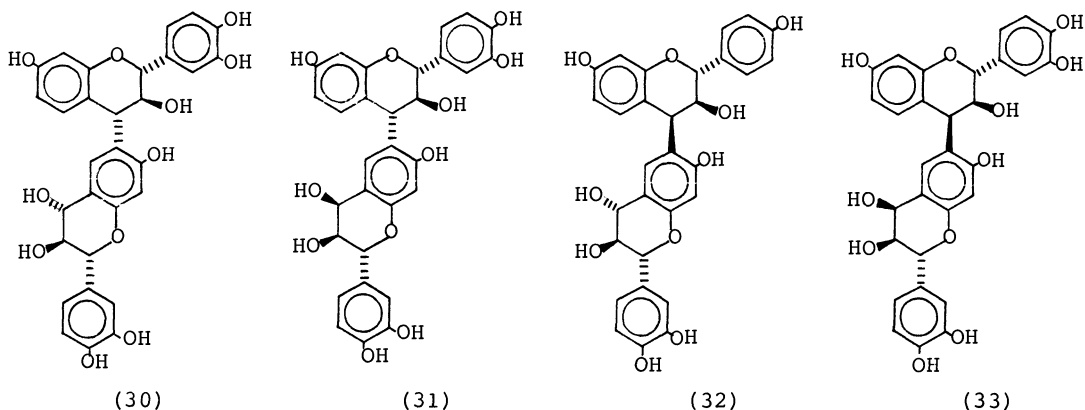
2,3-*trans*-3,4-*trans*2,3-*trans*-3,4-*cis*

C-ring conformations

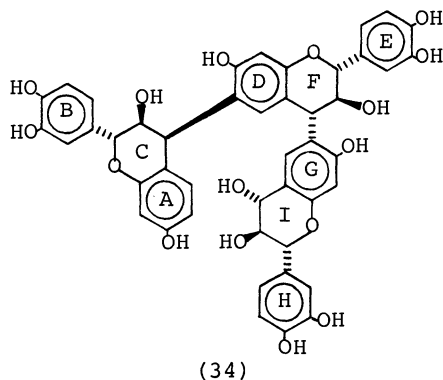
that in the free phenolic form the biflavanoid unit as a whole tends to maintain its planarity irrespective of the 3,4-*trans* or 3,4-*cis*-configuration of the 2,3-*trans* C-ring. This conclusion, if confirmed at higher oligomeric levels, has important implications regarding the general planarity of condensed tannins.

[4,6]-Biflavanoids and a linear [4,6:4,6]-triflavanoid with terminal 3,4-diol function as structural variants arising from self-condensation. The presence of a substantial fraction of [4,6]-biflavanoids with 'terminal' 3,4-diol function (30-33) accompanying an excess of (+)-leucofisetinidin [(4), (+)-mollisacacidin] in the heartwood of *A. mearnsii*^{8,21} is of interest considering that acid-catalysed self-condensation of the parent flavan-3,4-diol does not proceed significantly at ambient temperatures, and that when submitted to mild heat the reaction runs out of control to form high-mass oligomers. As

suggested before, this may indicate that *in vitro* self-condensation is inhibited by the inductive effect of the 4-hydroxyl, or of the protonated 4-hydroxyl, or of the 4-carbocation, but also that after initiating dimerization the inhibiting effect is lost in the 'upper' unit (*cf.* 30-33) and 'propagation' of the condensation proceeds rapidly under the conditions applied for its initiation.



The natural coexistence of the biflavanoids, and also of a 'linear' triflavanoid analogue (34), presumably indicates that self-condensation of the parent flavan-3,4-diol is enzyme-mediated, since under optimum *in vitro* conditions exceptionally low yields of the triflavanoid and two of the biflavanoids (32, 33) are obtained by acid-induced condensation. The 'upper' units of

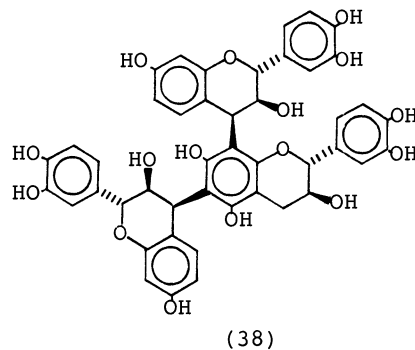
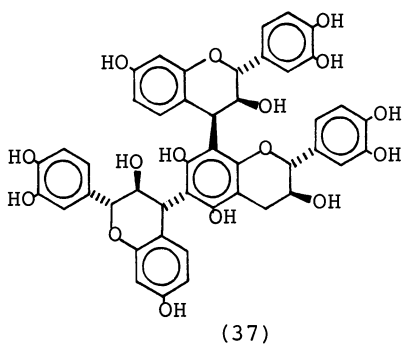
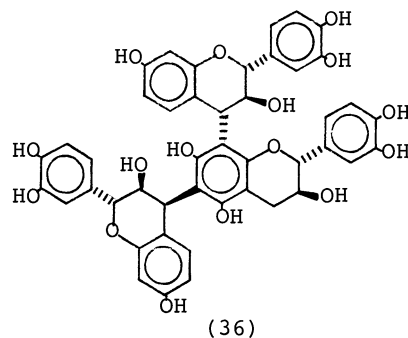
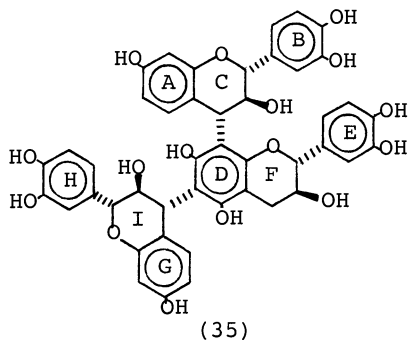


these synthetic products all possess 3,4-*cis* configurations; the same biflavanoids (32, 33) also predominating in the natural extract. The possible significance of this phenomenon will be discussed later (*cf.* synthetic tetraflavanoid).

The sequence of units in the [4,6:4,6]-2,3-*trans*-3,4-*cis*:2',3'-*trans*-3',4'-*trans*:2'',3''-*trans*-3'',4''-*trans*-bi-[-(-)-fisetinidol]-(+)-mollisacacidin (34) was determined by ultra high resolution ^1H n.m.r. spectroscopy using sequential spin-decoupling of protons at 4 and 5 positions; the allocation of all aromatic and heterocyclic protons being possible.⁸

Biomimetic synthesis of angular [4,6:4,8]-triflavanoids. In contrast to all previous assumptions of tannin oligomers based exclusively on [4,8]-linked 'linear' polyflavanoid structures, we have demonstrated the involvement of both 6- and 8-positions of (+)-catechin [and (+)-gallocatechin] in natural condensations by means of isolation and direct synthesis.^{7,22} Thus, condensations of (+)-2,3-*trans*-3,4-*trans*-leucofisetinidin (4) with synthetic [4,8]-all-*trans*-(-)-fisetinidol-(+)-catechin (19), and with the [4,8]-3,4-*cis* isomer (20) give four readily-definable [4,6:4,8]-diastereoisomers (35-38). The bonding position of the introduced unit is readily determined by high resolution (360 MHz) ^1H n.m.r. spectroscopy, the aromatic singlet due to H-5(D) in

the biflavanoids giving way to the high-field aromatic ABC-system (G-ring) of the new substituent, thus supplementing the equivalent system of the A-ring.^{7,9,22}



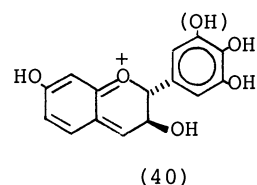
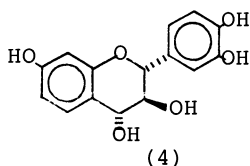
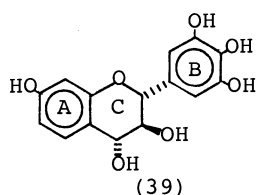
C.d. spectra of the derivatives of the triflavanoids (35-38) reflect the combined effects of 3,4-*trans* and 3,4-*cis* stereochemistry of the 6 and 8 flavanyl substituents on (+)-catechin by exhibiting doublets (35, 38) or couplets (36, 37) at low wave-lengths in agreement with the aromatic quadrant rule.⁴

Rotational isomerism about interflavanoid bonds, first demonstrated by us,²³ constitutes a problem in ¹H and ¹³C n.m.r. spectroscopy of the derivatives of some biflavanoid, and most tri- and tetraflavanoid derivatives in terms of spectral complexity. Thus at ambient temperatures the ¹H n.m.r. spectra of triflavanoid methyl ether triacetates exhibit both duplication of resonances and line-broadening, rendering analysis impossible.^{7,9,22} Exceptionally high temperatures (150°-200°C) are required for merging and sharpening of absorption, in order to overcome the effects of dynamic rotational isomerism.

As in the case of biflavanoids, direct syntheses of triflavanoids may be approached stoichiometrically from simple starting materials. For example, a 2:1 molar ratio of (-)-leucofisetinidin and (+)-catechin permits direct access to the mixture of triflavanoids present in the heartwoods of *Schinopsis lorentzii* and *S. balansae* (quebracho) with complete depletion of precursors and without the production of higher oligomers (*cf.* angular tetraflavanoids) under the conditions employed.²⁴

During the synthesis of an homologous series of triflavanoids with a higher degree of B-ring hydroxylation (pyrogallol *vs* catechol B-ring function) corresponding to those present in black wattle bark ('Mimosa') extract, the rate of condensation between (+)-leucorobinetinidin (39) and (+)-catechin, when reduced to first-order kinetics, was shown to be almost twice that involving (+)-leucofisetinidin (4).⁹ This B-ring dependent phenomenon may be attributed to the relative stabilities of the canonical forms (40) of the respective carbocations generated, coupled with hyperconjugative effects at C-2.⁹

This novel class of oligomers in which (+)-catechin contributes the role of bifunctional nucleophile is ubiquitous in nature, and they apparently constitute the basis for further elaboration to tannin units of higher mass

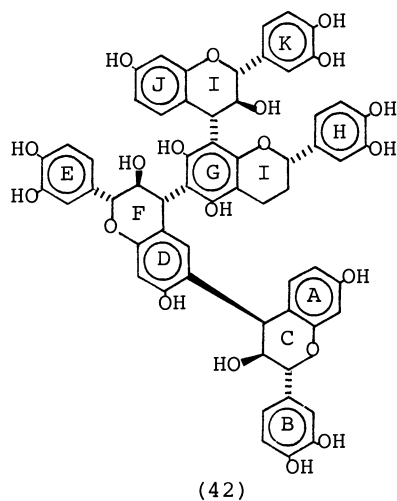
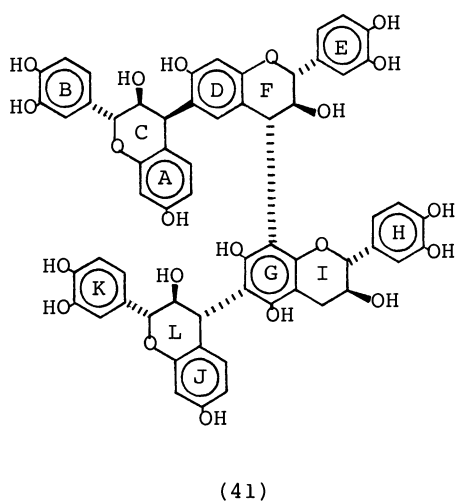


(*cf.* angular tetraflavanoids). They may, therefore, represent key intermediates in the biosynthesis of the more complex tannin molecules with advanced affinity characteristic for various substrates, e.g. collagen.

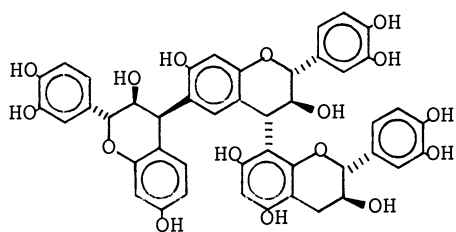
Angular tetraflavanoids. 'Propagation' of condensations *via* the carbenium mechanism using angular triflavanoids as substrates must involve one or more of the nucleophilic centres of the resorcinol-type A- or G-rings [*cf.* (35)] of the two flavanoid units substituent on (+)-catechin. From our model reactions in biflavanoid synthesis condensation at the 6-position of these (-)-fisetinidol units may be envisaged, neglecting steric effects introduced by molecular complexity.

The accuracy of this prediction is substantiated by the isolation of a number of tetraflavanoids from two sources in which triflavanoid analogues coexist. With the aid of mass and 500 MHz ^1H n.m.r. spectroscopy, facile analysis of those compounds which are amenable to spectral analysis is possible; two individually comprised of [4,6]-2,3-*trans*-3,4-*cis*:2',3'-*trans*-3',4'-*trans*-bi[(-)-fisetinidol] and 2,3-*trans*-3,4-*trans*-(-)-fisetinidol units which are 4,6 and 4,8 linked to (+)-catechin [e.g. (41) or (42), with ABC-DEF and JKL units linked to GHI]. Differentiation between these alternatives requires synthesis, since no contiguous benzylic proton system is available which permits differentiation between two all-*trans*-(-)-fisetinidol moieties directly linked to (+)-catechin.

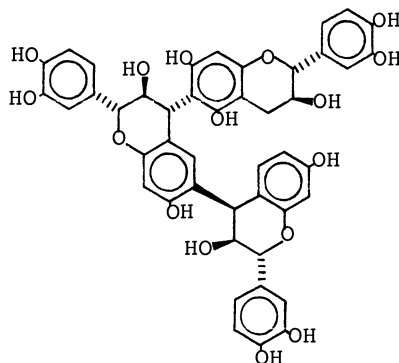
Our synthetic strategy must overcome the problem of introducing a suitable



leaving group in the 4-position of a [4,6]-2,3-*trans*-3,4-*cis*:2,3-*trans*-bi[(-)-fisetinidol] (25), considering that its 4-hydroxy (F-ring) derivative (32 or 33) which could serve as synthon for selective introduction of the biflavanoid moiety is not available in significant yields from self-condensation of the parent flavan-3,4-diol as previously outlined. However, both 4-halogenation of the acetate of the monoflavanoid, (-)-fisetinidol (23), followed by substitution at this position with oxygen function, have been achieved. Similar, but terminal functionalization of bi[(-)-fisetinidol] (25) is at present under investigation. In the meanwhile we have shown that natural biflavanoids with diol function [i.e. the pairs (30, 31) and (32, 33)] from the heartwood of *A. mearnsii* undergo facile condensation in both 6- and 8-positions to form a useful series of four triflavanoids, one of which [(43) or (44)] represents a partial synthesis of the tetraflavanoid.



(43)



(44)

Similar condensation with the biflavanoid all-*trans*-[4,8]-(-)-fisetinidol-(+)-catechin (19) in the place of (+)-catechin (9) is in progress, and steric factors do not appear to be inhibiting.

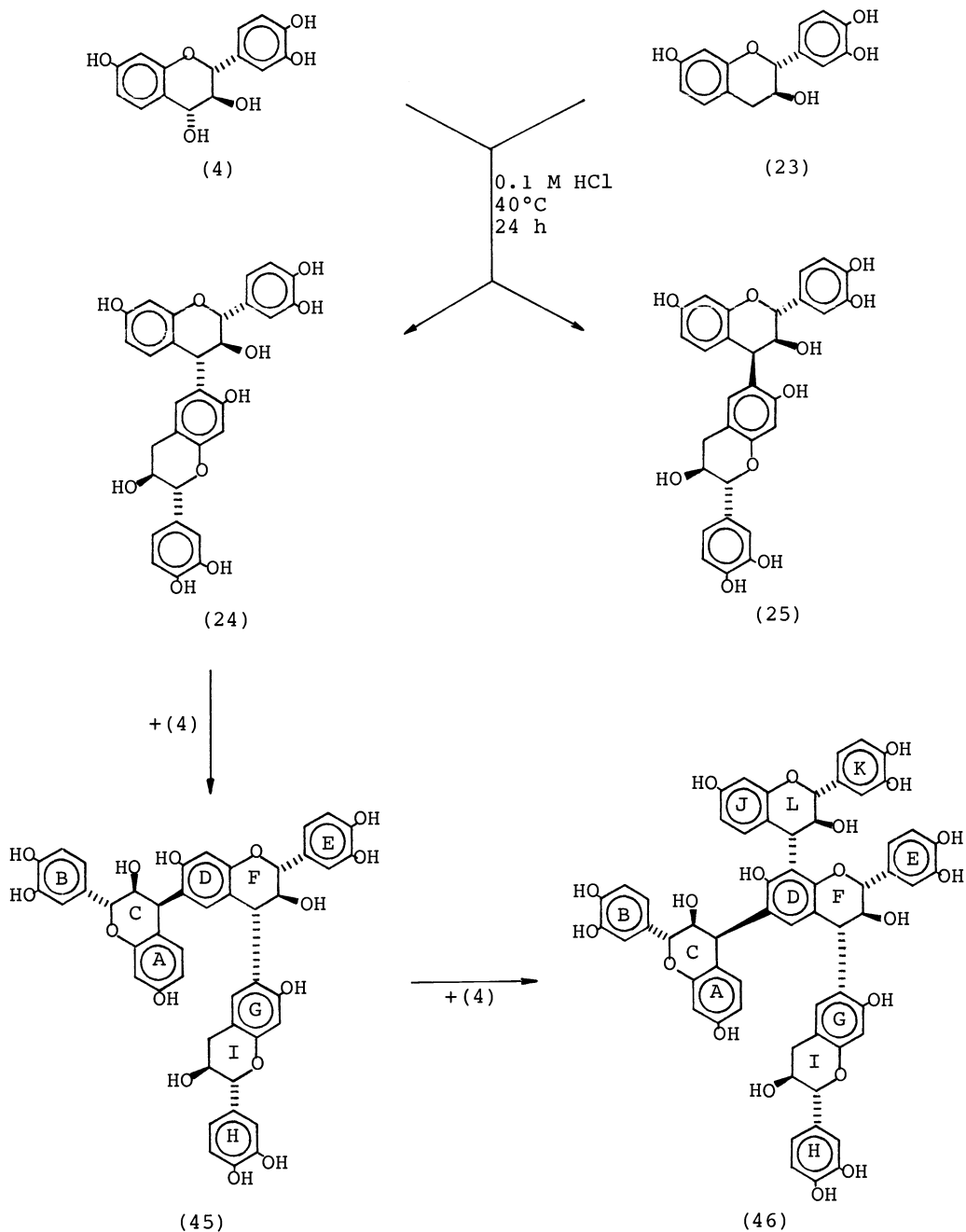
However, with other natural tetraflavanoids serious problems regarding the high energy requirements for 'fast' rotation about their interflavanoid bonds have been encountered during recording of the ^1H n.m.r. spectra of their derivatives; limitations being the boiling point of solvents and consideration of possible damage to equipment at temperatures above 200°C. Evidence has, nevertheless, been obtained of stereochemical variation in two diastereoisomers of the 'angular' tetraflavanoid (41/42), obtained from *A. mearnsii*.

A synthetic branched [4,6:4,8:4,6]-tetraflavanoid: Further elaboration of resorcinol-type flavanoid units attached to (+)-catechin. Cognizance of the fore-mentioned problem of high energy requirements of derivatives of higher oligomers, prompted a synthetic study of the condensation of (+)-leucofisetinidin (4) with an excess of (-)-fisetinidol (23) in order to predict the more advanced 'propagating' phases of tannin condensation involving exclusively resorcinol-type flavanoid environments. Reactions at both 25° and 40°C proceed with production of the same end-products (*cf.* Scheme) and with a minimum of side-reaction. In addition to the anticipated^{6,19} all-*trans*-biflavanoid (24) and its 3,4-*cis* isomer (25), a novel linear [4,6:4,6]-triflavanoid (45) and the first branched [4,6:4,8:4,6]-tetraflavanoid (46) were formed in the proportions of 3:14:10:4. The known biflavanoids were present in the reverse proportion to the 3:2 ratio anticipated from previous syntheses, while the [4,6:4,6]-triflavanoid (45) proved to be the 4"-deoxy analogue of the natural product (34) previously isolated from *A. mearnsii* heartwood. The oligomeric tetraflavanoid (46) is structurally related to the triflavanoid (45), and bonding at the C-8(D) position of the additional (JKL) 2,3-*trans*-3,4-*trans*-flavanyl substituent determined by sequential spin-decoupling at 500 MHz of 4- and 5-protons, including confirmation of the *para*-coupled relationship between H-5 and H-8 of the G-ring.

The generation of four main products in significant yields indicates a condensation sequence $(4) + (23) \longrightarrow (25) + (24) \xrightarrow{+(4)} (45) \xrightarrow{+(4)} (46)$.

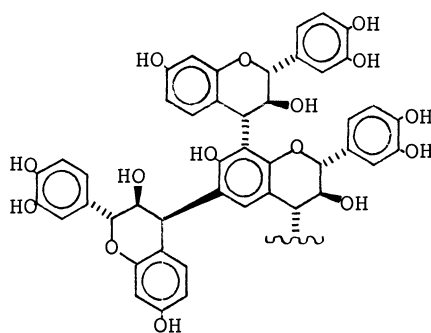
Steric constraints are presumably responsible for inhibition of continued linear condensation at C-6(A) in those oligomeric intermediates which embody 3,4-*cis* configurations in their 'upper' terminal units. However, steric effects inadequately cover selectivity of condensation with the all-*trans*-biflavanoid (24) and regiospecificity in condensation with the triflavanoid (45), since these steps occur despite competing nucleophilic centres on these and other potential substrates (25) and also despite the sustained excess of the parent nucleophile, (-)-fisetinidol (23). This apparent activation of the oligomers as nucleophiles has been explained¹⁰ by hyperconjugative effects²⁶ and their angular dependence.²⁷

Branched resorcinol-type tetraflavanoid substituents (47) located at both 6- and 8-positions of (+)-catechin accordingly appear to be a plausible if speculative representation of a heptaflavanoid condensed tannin (calculated M 1928) based on both electrophilic resorcinol- and nucleophilic phlorogluci-



nol-type precursors, their electrophilic homologues (as in Mimosa tannins) or enantiomers (as in quebracho tannins). Further speculative extrapolation is possible on the basis of our present work.

L'envoi. Successive *in vitro* condensations at ambient temperatures of flavanyl-4-carbenium ions with both nucleophilic flavan-3-ols and their progressively complex products constitute an almost exact analogy with the natural process leading to oligomeric mixtures which typify all condensed tannins. The condensations are subject to progressively complex constraints of structure and function, and logically follow paths of lowest energy requirements.



(47)

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