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REGIO- AND STEREOSELECTIVE OXIDATION OF FLAVAN-3-OL-, 4-ARYLFLAVAN-3-OL-, AND BIFLAVANOID DERIVATIVES WITH 2,3-DICHLORO-5,6-DICYANO-1,4-BENZOQUINONE (DDQ)

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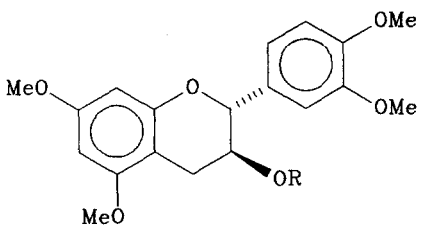
Abstract ——— The phenolic methyl ethers of flavan-3-ols, 4β-arylflavan-3-ols, and (-)-fisetinidol-(4β,8)-(+)-catechin biflavanoids are susceptible to regio- and stereoselective methoxylation at C-4 in moderate yields with DDQ in $CHCl_3$-MeOH solution. The observed asymmetric induction with exclusive formation of 2,4-*trans* products is compatible with the intermediacy of a diastereogenic donor-acceptor interaction, DDQ acting as the acceptor and oxidant. The 4-funtionalized analogues are of both synthetic and degradative significance in condensed tannin chemistry.

Flavan-3,4-diols figure prominently as incipient electrophiles in the biomimetic synthesis of proanthocyanidins[1]. The applicability of such an approach is, however, dependent on the availability of these monomeric precursors from natural sources. Owing to the inaccessibility of C-5 oxygenated flavan-3,4-diols, the synthesis of procyanidin oligomers has been approached by alternative methods[2-5]. Oxidative functionalization of the prochiral benzylic methylene group of (+)-catechin and (-)-epicatechin, *viz.* the constituent flavan-3-ol units of the procyanidins, thus offers considerable potential in the synthesis of this economically important class of condensed tannins. It has previously been pursued by Brown *et al.*[6,7] with lead tetraacetate and by us *via* potassium persulphate[8] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] as oxidants. Detailed results of relevance to the utilization of the latter reagent are now disclosed.

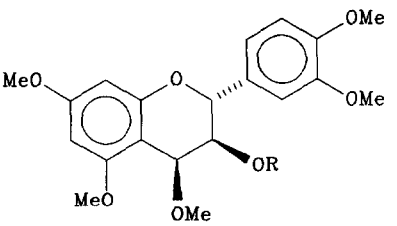
Separate treatment of (+)-catechin tetramethyl ether 1 and its 3-*O*-acetate 2 with a double molar excess of DDQ in chloroform[10]/methanol at ambient temperatures (*ca.* 25^{0}C, 3 and 5 h respectively) afforded the 4β-methoxy derivatives 3 and 4 in 48 and 52% isolated yields respectively (Scheme 1). Under similar conditions (-)-epicatechin tetramethyl ether 5 (3 h), its 3-*O*-acetate 6 (5 h), and 3-*O*-benzyl ether 7 (2 h), were oxidatively transformed to their respective 4β-methoxy analogues 8 (50%), 9 (40%), and 10 (53%).

The relative configurations of the C-4 functionalized compounds were assessed by ^{1}H NMR analysis which indicated $J_{2,3}$ *ca.* 10.0, $J_{3,4}$ *ca.* 3.0 Hz for 2,3-*trans*-3,4-*cis*- (3 and 4) and $J_{2,3}$ *ca.* 1.0, $J_{3,4}$ *ca.* 3.0 Hz for 2,3-*cis*-3,4-*trans*-4-methoxyflavan-3-ols 8, 9, and 10. These flavan-3,4-diol equivalents, *e.g.* 3, could in principle then serve as electrophiles *via* C-4 carbocations in a biomimetic synthesis of procyanidin-type con-

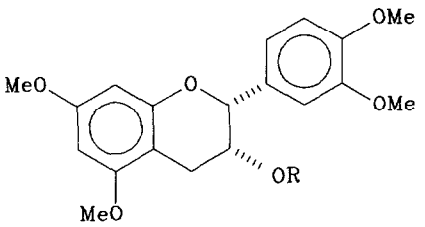


(1) R = H
(2) R = Ac

(i)

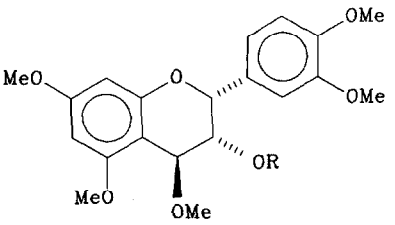


(3) R = H (48%)
(4) R = Ac (52%)

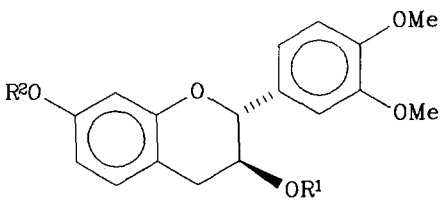


(5) R = H
(6) R = Ac
(7) R = Bz

(i)

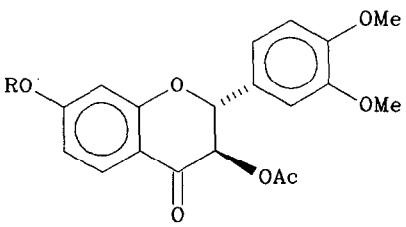


(8) R = H (50%)
(9) R = Ac (40%)
(10) R = Bz (53%)

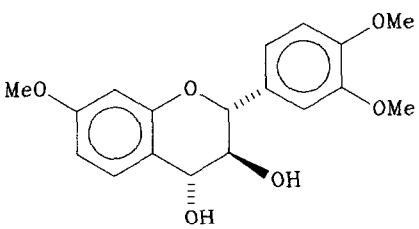


(11) R^1 = Ac, R^2 = Me
(12) R^1 = R^2 = H

(i)

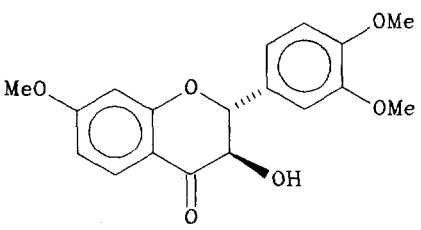


(13) R = Me (*ca* 20%)
(14) R = Ac (*ca* 20%)



(15)

(i)



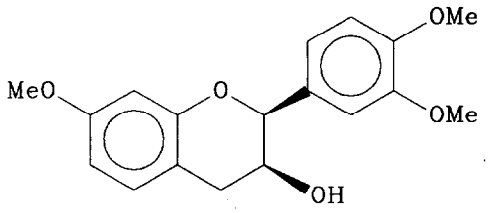
(16) (69%)

Scheme 1 Reagents/conditions: (i) DDQ, $CHCl_3$/MeOH, *ca* 25°C

densed tannin derivatives (*vide infra*).

The yields of the oxygenation products of the (+)-catechin and (-)-epicatechin derivatives are thus comparable for DDQ and $K_2S_2O_8$[8] but are substantially increased with these reagents in comparison to those for $Pb(OAc)_4$[5-7]. Utilization of DDQ and $K_2S_2O_8$ as oxidant offers the additional advantage of reduced reaction times compared to those for $Pb(OAc)_4$ hence minimizing side reactions[a], *e.g.* excessive anthocyanidin formation and also condensations to form procyanidin oligomers. Such improved yields and reduced reaction times achieved with DDQ relative to those of acetoxylation with $Pb(OAc)_4$ are dependent on the double molar excess of DDQ for rapid hydride ion abstraction (*vide infra*), and on the complete reduction of the excess of DDQ with sodium borohydride immediately after the specified reaction times.

Application of the optimized conditions to 3-*O*-acetyl-trimethyl-(-)-fisetinidol 11 (5 days) and 3',4'-di-*O*-methyl-(-)-fisetinidol 12 (3 h) afforded the corresponding dihydroflavonols 13 and 14 in *ca.* 20% yields following acetylation of the crude reaction mixtures. Similar low yields and extended times were also observed for trimethyl-(+)-epifisetinidol 17 and tetramethyl-(+)-mesquitol[11] 18 hence limiting the utility of DDQ as oxidant for the benzylic functionalization of 5-deoxy flavan-3-ols. (+)-Mollisacacidin tri-*O*-methyl ether 15 was, however, oxidized in 2 hours with 1 molar equivalent of DDQ to tri-*O*-methyl-(+)-fustin 16 in 69% yield. Such an approach usefully complements existing methodology[12] for the selective oxidative conversion of flavan-3,4-diol to dihydroflavonol with conservation of the integrity of absolute configuration at C-2 and C-3 (*cf.* Experimental).



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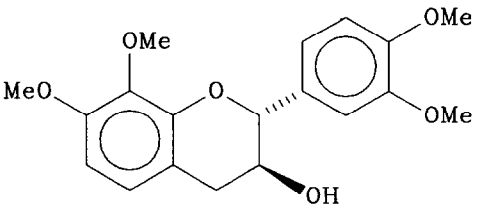
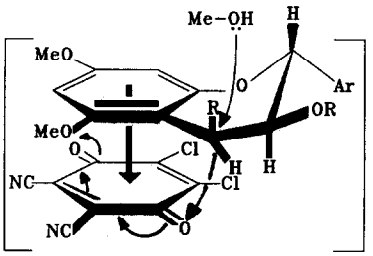


(18)

The functionalizations involving the (+)-catechin and (-)-epicatechin derivatives are characterized by a high degree of regio- and stereoselectivity. Both these features are presumably explicable in terms of the ability of DDQ to form charge-transfer complexes with aromatic substrates[13,14]. Owing to the higher electron density of the phloroglucinol-type A-ring compared to that of the pyrocatechol-type B-ring in *e.g.* 1, such a charge-transfer complex will preferentially involve the former ring hence explaining the selective oxygenation at C-4 *vs.* possible competing functionalization at C-2 *via* B-ring/DDQ complexes. Repulsive steric interactions between the axial H-2 and the bulky oxidant would facilitate association of DDQ from the α-face hence permitting the selective removal of the pro-*R* diastereotopic benzylic hydrogen as hydride ion within a

[a] These side reactions as were evidenced by strong coloration and the formation of highly polar compounds respectively, contributed significantly to the observed 'loss' of material.



(19) **R = H**

(20) **R = 2,4-dihydroxyphenyl**

(21) **R = 2,4,6-trihydroxyphenyl**

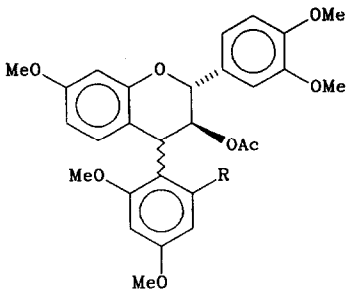
(22) **R = (2*R*,3*S*)-2,3-*trans*-3',4',5,7-tetramethoxy-3-*O*-acetylflavan-8-yl**

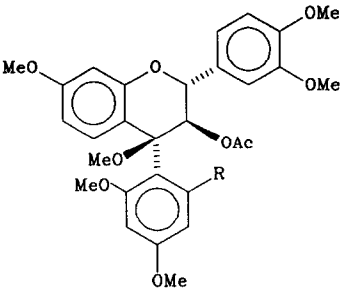
tightly bound complex 19. The incipient carbocationic species is then attacked simultaneously by the nucleophile (MeOH) from the opposite side, *i.e.* in an S_N2 fashion with the exclusive formation of 2,4-*trans* products. An intense green coloration which appeared when the reagents were first mixed and which disappeared as the reaction progressed was indicative of a charge-transfer interaction[14]. Additional evidence for the formation of the charge-transfer complex was derived from the observation that (+)-catechin tetramethyl ether 1 was functionalized in chloroform/methanol in 50% yield, *vs.* the 20% yield in methanol only, chloroform being capable of assisting the initial formation of the complex[10] 19.

The alignment of reactants in the intermediate complex may presumably be depicted as in formulation 19. Such a conformation permits the simultaneous abstraction of hydride ion at C-4 and the minimization of repulsive steric interactions by eclipsing H-6 and H-8 of the flavan-3-ol A-ring and the bulky chloro and cyano substituents (or *vice versa*) of DDQ.

The conjecture that steric interactions between the axial H-2 and the bulky oxidant inhibits its association from the β-face of the substrate, was demonstrated by subjecting the 4α- and 4β-arylflavan-3-ol derivatives 23, 24 and 25, 26 separately to reaction with DDQ under similar conditions. Thus, only the 4β-analogues 25 and 26 were stereoselectively oxygenated at C-4 to give the 4β-methoxy-4α-arylflavan-3-ol derivatives 27 (35%) and 28 (20%) presumably *via* the intermediate complexes 20 and 21. In the case of the 4β-(2,4,6-trimethoxyphenyl)-analogue 26, the 4β-methoxy derivative 28 was accompanied by the flav-3-en-3-ol derivative 29 in 15% yield. Substitution of H-4(C) in 25 and 26 by a methoxy group in 27 and 28 was evident from ^{1}H NMR data which indicated an AB-system (J10.5 Hz) for the heterocyclic protons (δ 5.50, 6.06; δ 5.56, 6.09: H-2 and -3 for 27 and 28 respectively) and a three-proton singlet (δ 3.19, 3.13 for 27 and 28 respectively) for the C-4 methoxy protons. A pronounced n.O.e. association (5.8 and 6.1% for 27 and 28 respectively) between these protons and H-2(C) strongly indicated a 4β-methoxy group and hence 4*S* absolute configuration for 27 and 4*R* for 28. The structure of the flav-3-en-3-*O*-acetyl derivative 29 was verified by ^{1}H NMR analysis which indicated the presence of a single deshielded and secondary coupled heterocyclic proton at δ 6.06 [H-2(C)].

The formation of the flavan-3-en-3-ol derivative 29 constitutes an important feature of the oxygenation reactions. Its generation may represent the first step towards the formation of an anthocyanidin derivative of type 30 hence explaining the considerable degree of reddening observed in all these oxidations. In the (+)-catechin derivatives the axial H-3(C) would facilitate rapid and concerted loss of a proton either in the

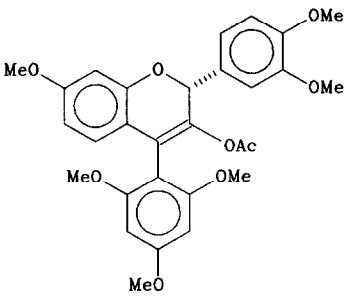




(23) , R = H
(24) , R = OMe
(25) , R = H
(26) , R = OMe

(27) R = H
(28) R = OMe

charge-transfer complex 19 or in the 4β-methoxy derivative 4 following protonation of the introduced functionality under the slightly acidic conditions ($DDQH_2$). In the 4α-arylflavan-3-ols where abstraction of the benzylic H-4(C) is apparently inhibited on steric grounds, functionalization presumably occurs at C-2, such analogues of the relevant derivatives then being unable to survive the prevailing reaction conditions.



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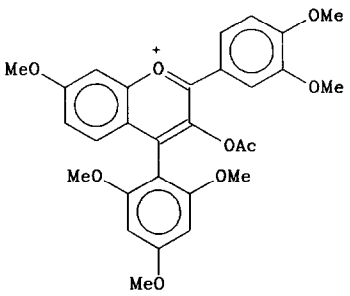
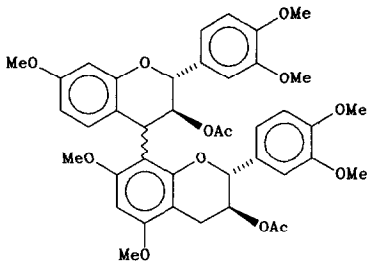


(30)

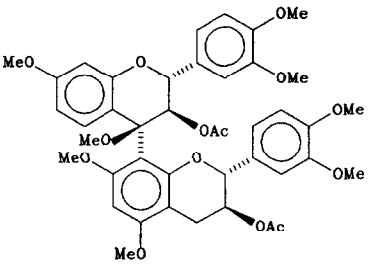
A similar selectivity for the exclusive removal of the 4α-hydrogen in the 2*R* series of profisetinidin biflavanoids was observed when the (-)-fisetinidol-(4α,8) and (4β,8)-(+)-catechin derivatives 31 and 32[1] were separately subjected to the optimized reaction conditions. Thus, only the (4β,8)-analogue 32 was susceptible to stereoselective oxygenation at C-4 of the (-)-fisetinidol ABC-moiety to give the 4β-methoxy derivative 33 in 37% yield [$J_{2,3}$(C) 10.5 Hz; δ 3.09, C4-OMe] again *via* a charge-transfer complex of type 22. The stereochemistry of the product 33 was based on a combination of an intense negative Cotton effect ([Θ], -9.0×10^4) in the low wavelength region (λ, 233 nm) of its CD spectrum, the significantly low shift difference ($\Delta\delta$H-2,H-3 0.28) of heterocyclic F-ring protons in contrast to that (0.61) of the starting material 32[15], and a strong n.O.e. association (4.2%) between 4-OMe(C) and the axial H-2(C). These observations are in accord with effects induced by a (4α,8)-(-)-fisetinidol substituent on the (+)-catechin moiety[15,16] thus confirming the 4β-orientation of the methoxy group and an *R* absolute configuration at this chiral centre. The identical reaction when applied to the (-)-fisetinidol-(4α,8)-(+)-catechin derivative 31 proceeded with great difficulty afford-

ing amongst others an insignificant yield of the flav-3-en-3-ol corresponding to the (-)-fisetinidol upper unit and a concomitant low recovery (30%) of the starting material. The conversion 32 ⟶ 33 nevertheless represents the first functionalization of the heterocyclic ring of a biflavanoid of this type.



(31) ⟨=≡

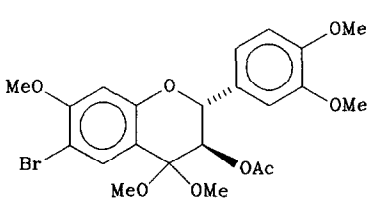
(32) ⟨=▲



(33)

Selective methoxylation of (-)-fisetinidol-(4β,8)-(+)-catechin derivatives at the C-4 bonding position could assist in their differentiation in higher oligomers. Concomitant weakening of strong interflavanyl bonds as existent in 32 permits application of degradative bromination methods using pyridinium hydrobromide perbromide (PHPB) *e.g.* 33 ⟶ 34 + 35. Aromatic bonding positions and the stereochemistry of constituent profisetinidin units in oligoflavanoids may hence be assessed by chromatography using reference compounds, bromine serving as marker for the point of attachment, *cf.* 35. Thus, 5 mg of the (-)-fisetinidol-(4α,8)-(+)-catechin-4β-methoxy derivative 33 was sufficient to provide the 6-bromo derivative 34 [$J_{2,3}$ 8.0 Hz, δ 6.52 (s, H-8), 7.64 (s, H-5), 3.27, 3.17 (2xs, 2x 4-OMe)] and the 8-bromo-(+)-catechin derivative 35 (δ 6.20, H-6)[17] in yields permitting characterization also *via* sharply defined ^{1}H NMR spectra.

(33) PHPB/MeOH ⟶



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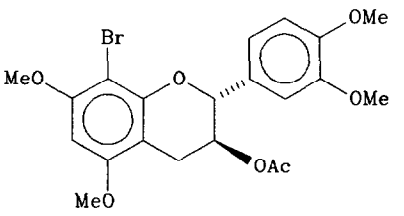
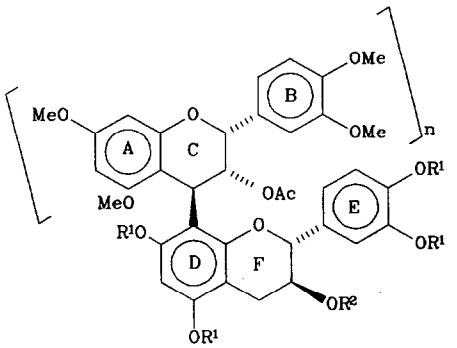
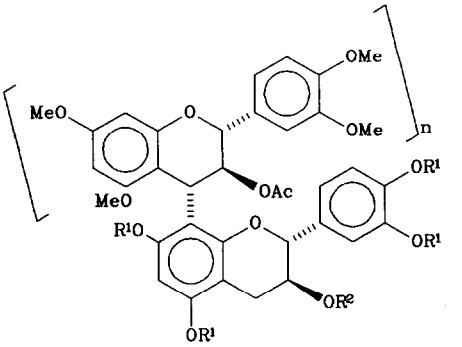


(35)

The absence of a flavan-3,4-diol- or dihydroflavonol analogue of (-)-epicatechin in natural sources, has seriously hampered the semi-synthetic approach[1] towards the structural elucidation of procyanidins with (2*R*,3*R*)-2,3-*cis* constituent units. The substantial increase in the yields of the flavan-3,4-diol equivalents 3 and 8 observed for DDQ in comparison to those for $Pb(OAc)_4$[6,7] hence prompted their utilization as incipient electrophiles in a biomimetic synthesis of procyanidin condensed tannin derivatives. Acid-catalyzed condensation of the 4β-methoxy-(-)-epicatechin derivative 8 and (+)-catechin (1:1 molar ratio) and subsequent methylation and acetylation afforded the (-)-epicatechin-(+)-catechin octamethyl ether diacetate

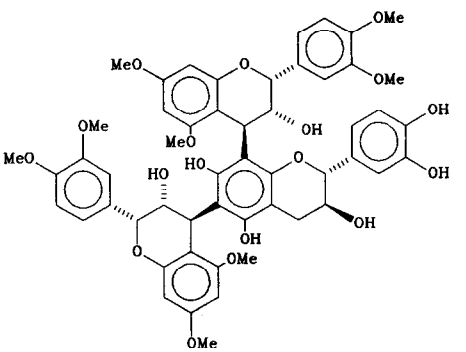
37[18] and the (-)-epicatechin-(4β,8)-(-)-epicatechin-(4β,8)-(+)-catechin dodecamethyl ether triacetate 39[19]. A similar sequence of the 4β-methoxy-(+)-catechin derivative 3 and (+)-catechin gave the (4α,8)-*bis*-(+)-catechin octamethyl ether diacetate 41[20] and the dodecamethyl ether triacetate 43[20] of the linear triflavanoid analogue.





(36)	n = 1, $R^1 = R^2 = H$	(40)	n = 1, $R^1 = R^2 = H$
(37)	n = 1, R^1 = Me, R^2 = Ac	(41)	n = 1, R^1 = Me, R^2 = Ac
(38)	n = 2, $R^1 = R^2 = H$	(42)	n = 2, $R^1 = R^2 = H$
(39)	n = 2, R^1 = Me, R^2 = Ac	(43)	n = 2, R^1 = Me, R^2 = Ac

A notable feature of both these condensation reactions is the exclusive formation of the linear analogues 38 and 42 at the trimeric level. Consideration of both electronic and steric effects at the vacant positions of the A- and D-rings in the putative biflavanoid precursors 36 and 40, indicates that C-6 (D-ring) may compete favourably with C-8 (A-ring) as nucleophilic site hence leading to the formation of an 'angular' trimeric pro-



(44)

cyanidin of type 44, the phenolic form of which was recently synthesized *via* an alternative route[21]. Despite the propensity of C-8(A) in phenolic procyanidin biflavanoids of types 36 and 40 to act as nucleophile in both the *in vivo* and *in vitro* formation of triflavanoid analogues, such a conspicuous preference for this carbon atom in the ensuing electrophylic substitution reactions of biflavanoids 36 and 40 is presumably the result of

abstrusive conformational facets. Studies aimed at verifying the correlation of conformation and chemical reactivity in this regard is presently actively pursued and will be the subject of future communications.

The results presented here not only demonstrate the potential of DDQ to effect regioselective oxidative hydroxylation of the constituent flavan-3-ol units of condensed tannins but also complements the rare occurrence of asymmetric control of oxidation by DDQ *via* a donor-acceptor interaction (*cf.* ref. 14).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WP-80 FT or AM-300 spectrometer in $CDCl_3$ and Me_4Si as internal standard. Mass spectra were obtained with a Kratos MS80 instrument and CD data in MeOH on a Jasco J-20 spectropolarimeter. TLC was performed on precoated Merck plastic sheets (DC-Alufolien Kieselgel 60 F_{254}, 0.25 mm) and the compounds were located by H_2SO_4-HCHO (40:1, v/v) spray reagent. Preparative plates (PLC), 20x20 cm, Silica Gel F_{254} (1.0 mm) were air-dried and used without prior activation. The chloroform used as solvent was thoroughly washed with water to remove ethanol. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallised (CH_2Cl_2) and not stored for longer than one month. All reactions were carried out under N_2.

General Oxygenation and Work-up Procedures.

Unless otherwise stated, a solution of DDQ (2 mole equivalents) in dry MeOH (100 mg in 1 ml) was slowly added to a stirred solution of the flavanoid substrate in $CHCl_3$ (100 mg in 20 ml) at room temperature. The reaction was terminated by the addition of MeOH (equivalent to the volume $CHCl_3$ used). Excess $NaBH_4$ (2 mole equivalents to 1 mole DDQ) was added to the cooled reaction mixture and stirred for 30 minutes. Ice-cold water (200 ml for 100 mg substrate) was added and the products were extracted with ether (3x50 ml). The yellow extract was continuously washed with water until the organic layer was almost colourless. Drying (Na_2SO_4) and evaporation of the solvent, afforded the crude product which was subjected to PLC.

Oxygenation of Flavan-3-ol Derivatives.

Tetra-O-methyl-(+)-catechin 1. Oxygenation of the title compound (100 mg) for 3 h afforded, after PLC in hexane-EtOAc-Me_2CO (60:25:15, x2), 4β-methoxy-tetra-*O*-methyl-(+)-catechin 3 as a solid (49 mg; R_f 0.48) the physical data of which were in agreement with those of an authentic sample[1].

Tetra-O-methyl-3-O-acetyl-(+)-catechin 2. Oxygenation of the title compound (320 mg) for 5 h afforded, following PLC in C_6H_6-hexane-Me_2CO (4.5:4.5:1, x2), 4β-methoxy-tetra-*O*-methyl-3-*O*-acetyl-(+)-catechin 4 as a solid (151 mg; R_f 0.49) the physical data of which were identical to those of an authentic sample[1].

Tetra-O-methyl-(-)-epicatechin 5. Reaction of the title compound (200 mg) with DDQ for 3 h, followed

by PLC in hexane-EtOAc-Me_2CO (6:3:1, x2) afforded 4β-methoxy-tetra-*O*-methyl-(-)-epicatechin 8 as a white solid (93 mg; R_f 0.63) (Found: M^+, 376.1519. $C_{20}H_{24}O_7$ requires M, 376.1522); δ ($CDCl_3$, 80 MHz, 303K), 7.18-6.97 [m, H-2,6(B)], 6.88 [d, H-5(B)], 6.13 [2xd, H-6,8(A)], 5.13 [br. d, $J_{2,3}$ 1 Hz, H-2(C)], 4.41 [d, $J_{3,4}$ 3.0 Hz, H-4(C)], 4.00 [m, H-3(C)], 3.84 [4xOMe], 3.53 [s, 4-OMe].

Tetra-O-methyl-3-O-acetyl-(-)-epicatechin 6. Oxygenation of the title compound (56 mg) for 5 h afforded, after PLC in hexane-EtOAc-Me_2CO (7:2:1, x2), 4β-methoxy-tetra-*O*-methyl-3-*O*-acetyl-(-)-epicatechin 9 as a white amorphous solid (24 mg; R_f 0.45), the physical data of which were identical to those of the 3-*O*-acetyl derivative of compound 8 (*vide supra*).

Tetra-O-methyl-3-O-benzyl-(-)-epicatechin 7. Oxygenation of the title compound (100 mg) for 2 h afforded, after PLC in C_6H_6-hexane-Me_2CO (5:4:1, x2), 4β-methoxy-tetra-*O*-methyl-3-*O*-benzyl-(-)-epicatechin 10 as a white solid (54 mg; R_f 0.41), the physical data of which were identical to those of the benzylated derivative of compound 8.

Tri-O-methyl-3-O-acetyl-(-)-fisetinidol 11. Reaction of the title compound (250 mg) with DDQ for 5 days, followed by evaporation of the solvent *via* a N_2-stream[a], and PLC [C_6H_6-hexane-Me_2CO (6:3:1, x3)] of the residue, afforded tri-*O*-methyl-3-*O*-acetyl-(+)-fustin 13[22] (8 mg; R_f 0.42), tri-*O*-methyl-(+)-fustin 16[22] (36 mg; R_f 0.36), and unreacted starting material (17 mg).

3',4'-Di-O-methyl-(-)-fisetinidol 12. Oxygenation of the title compound[b] (100 mg) for 3 h, followed by evaporation of the solvent *via* a N_2-stream[b], and PLC [CH_2Cl_2-Me_2CO (95:5, x3)] of the residue, gave one prominent band at R_f 0.53. Acetylation of this fraction and subsequent PLC in CH_2Cl_2-Me_2CO (95:5, x2) afforded 3,7-di-*O*-acetyl-3',4'-di-*O*-methyl-(+)-fustin 14 as white amorphous solid (22 mg; R_f 0.48) (Found: M^+, 400.1154. $C_{21}H_{20}O_8$ requires M 400.1158); δ [$CDCl_3$, 80 MHz, 303K], 7.91 [d, H-5(A)], 6.91 [m, 5xarom. protons], 5.81 [d, $J_{2,3}$ 12.5 Hz, H-3(C)], 5.34 [d, H-2(C)], 3.86 [2xOMe], 2.31 [s, 7-OAc], 2.00 [s, 3-OAc].

Tri-O--methyl-(+)-mollisacacidin 15. Oxidation of the title compound (200 mg; 0.6024 mmol) with DDQ (140 mg; 0.617 mmol) in $CHCl_3$ (30 ml) for 6 h, followed by evaporation of the solvent *via* a N_2-stream[b], and PLC [C_6H_6-hexane-Me_2CO (7:2:1, x2)] of the residue, afforded tri-*O*-methyl-(+)-fustin 16 (136 mg; R_f 0.48) the ^1H NMR[22] and CD data[23] of which were identical to those of an authentic sample.

Tri-O-methyl-(+)-epifisetinidol 17 and *tetra-O-methyl-(+)-mesquitol* 18. All attempts to oxygenate title compound 17 were unsuccessful. The reactions invariably resulted in intractable mixtures which did not merit further investigation. For oxygenation of the (+)-mesquitol derivative 18, see ref. 11.

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a Standard work-up procedure not applicable.

b Prepared by selective methylation of (-)-fisetinidol (MeI, K_2CO_3, Me_2CO).

Tri-O-methyl-3-O-acetyl-4β-(2,4-dimethoxyphenyl)-(-)-fisetinidol 25. Oxygenation of the title compound (72 mg) for 9 h afforded, after PLC in CH_2Cl_2-hexane-Me_2CO (8:1:1) 4β-methoxy-4α-(2,4-dimethoxyphenyl)-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol 27 as a white solid (37 mg; R_f 0.50) (Found: C, 67.07; H, 6.33. $C_{29}H_{32}O_9$ requires C, 65.40; H, 6.15%)[a]; δ [$CDCl_3$, 80 MHz, 303K], 7.46 [d, H-5(A)], 7.16 [dd, H-6(B)], 7.06 [d, H-2(B)], 6.19 [d, H-5(B)], 6.81 [d, H-5(D)], 6.68-6.38 [m, H-6,8(A) and H-2,6(D)], 6.06 [d, $J_{2,3}$ 10.5 Hz, H-3(C)], 5.50 [d, H-2(C)], 3.80 [4xOMe], 3.53 [s, 3-OMe(D)], 3.19 [s, 4-OMe(C)], 1.55 [s, 3-OAc].

Tri-O-methyl-3-O-acetyl-4α-(2,4-dimethoxyphenyl)-(-)-fisetinidol 23. All attempts to effect oxygenation of the title compound failed. The reaction mixtures were characterised by the development of a non-mobile red component associated with a substantial amount of unreacted starting material (even after 2 weeks of reaction time).

Tri-O-methyl-3-O-acetyl-4β-(2,4,6-trimethoxyphenyl)-(-)-fisetinidol 26. Oxygenation of the title compound (94 mg) for 3 h afforded, after PLC in C_6H_6-hexane-Me_2CO (8:1:1, x2) 4β-methoxy-4α-(2,4,6-trimethoxyphenyl)-3-*O*-acetyl-(-)-fisetinidol 28 as a white solid (20 mg; R_f 0.43) (Found: M^+, 554.2147. $C_{30}H_{34}O_{10}$ requires M, 554.2152); δ [$CDCl_3$, 80 MHz, 303K], 7.13 [dd, H-6(B)], 7.06 [d, H-2(B)], 6.97 [d, H-5(B)], 6.88 [d, H-5(A)], 6.56 [d, H-8(A)], 6.41 [dd, H-6(A)], 6.09 [d, $J_{2,3}$ 10.5 Hz, H-3(C)], 6.13 [s, H-3,5(D)], 5.56 [d, H-2(C)], 3.80 [6xOMe], 3.13 [s, 4-OMe(C)], 1.66 [s, 3-OAc]. A second product was identified as 3',4',7-trimethoxy-3-acetoxy-4-(2,4,6-trimethoxyphenyl)flav-3-ene 29 (14 mg; R_f 0.56) the physical data of which were in accordance with those of an authentic sample[24].

Tri-O-methyl-3-O-acetyl-4α-(2,4,6-trimethoxyphenyl)-(-)-fisetinidol 24. All attempts to effect oxygenation of the title compound failed. The reaction mixtures were characterised by development of a non-mobile red component associated with unreacted starting material (even after weeks of reaction time).

Tri-O-methyl-3-O-acetyl-(-)-fisetinidol-(4β,8)-tetra-O-methyl-3-O-acetyl-(+)-catechin 32. Oxygenation of the title compound (97 mg) for 3 h afforded, after CC in C_6H_6-hexane-Me_2CO (7:2:1) 4β-methoxy-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,8)-tetra-*O*-methyl-3-*O*-acetyl-(+)-catechin 33 as a white amorphous solid (36 mg) (Found: C, 65.97; H, 6.27. $C_{42}H_{46}O_{14}$ requires C, 65.12; H, 5.98%)[b]; δ [$CDCl_3$, 300 MHz, 293K], 6.92 [d, H-5(A)], 6.65 [d, H-2(B)], 6.63 [d, H-5(B)], 5.58 [d, H-5(E)], 5.55 [d, H-2(E)], 6.45-6.42 [2xdd, H-6(B and E)], 6.35 [d, H-8(A)], 6.19 [dd, H-6(A)], 6.18 [s, H-6(D)], 6.11 [d, $J_{2,3}$ 10.5 Hz, H-3(C)], 5.45 [d, H-2(C)], 4.90-4.80 [m, H-3(F)], 4.58 [d, $J_{2,3}$ 10.0 Hz, H-2(F)], 3.90-4.75 [6xOMe], 3.55 [s, OMe], 3.09 [s, 4-OMe(C)], 1.80 [s, 3-OAc], 1.60 [s, 3-OAc]; CD, $[\Theta]_{200}$ 0, $[\Theta]_{221}$ -3.32×10^4, $[\Theta]_{227}$ -1.97×10^4, $[\Theta]_{233}$ -5.53×10^4, $[\Theta]_{248}$ 0, $[\Theta]_{265}$ 0.64×10^4, $[\Theta]_{274}$ 0.

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[a] This unsatisfactory analysis presumably results from facile elimination of MeOH during heating.

[b] Unsatisfactory analysis presumably resulting from elimination of MeOH during heating.

Tri-O-methyl-3-O-acetyl-(-)-fisetinidol-(4α,8)-tetra-O-methyl-3-O-acetyl-(+)-catechin 31. All attempts to oxygenate the title compound proved fruitless. The reactions were characterised by development of an intense red colour while TLC analysis revealed the formation of non-mobile components and the presence of a substantial amount of unreacted starting material even after prolonged reaction time.

Synthesis of Procyanidins

General Procedure

To a solution of the 4β-methoxy derivatives of (+)-catechin and (-)-epicatechin and (+)-catechin in EtOH (100 mg flavanoids to 10 ml) was added 0.5M HCl (20% of the reaction volume) at RT. The reaction was terminated by the addition of saturated $NaHCO_3$ solution and the products were extracted with ethyl acetate. Drying (Na_2SO_4) and evaporation of the solvent afforded the crude products which were subjected to PLC.

A. Acid-catalyzed condensation of 4β-methoxy-tetra-*O*-methyl-3-*O*-acetyl-(-)-epicatechin 9 and (+)-catechin. Reaction of the title compounds (180 and 140 mg respectively) for 8 h afforded, after methylation (diazomethane) and PLC in C_6H_6-Me_2CO (8:2, x2), two fractions at R_f 0.42 (77 mg) and 0.18 (41 mg):

Tetra-O-methyl-3-O-acetyl-(-)-epicatechin-(4β,8)-tetra-Omethyl-3-O-acetyl-(+)-catechin 37. Acetylation of the R_f 0.42 fraction and subsequent PLC in hexane-EtOAc-Me_2CO (55:30:15) gave the title compound (53 mg; R_f 0.30) the physical data of which were in agreement with those of an authentic sample[18].

Tetra-O-methyl-3-O-acetyl-(-)-epicatechin-(4β,8)-tetra-O-methyl-3-O-acetyl-(-)-epicatechin(4β,8)-tetra-O-methyl-3-O-acetyl-(+)-catechin 39. Acetylation of the R_f 0.18 fraction, followed by PLC in $C_2H_4Cl_2$-hexane-Me_2CO (5:4:1, x3) afforded the title compound (26 mg; R_f 0.28) of which the physical data were identical to those of an authentic sample[19].

B. Reaction of 4β-methoxy-tetra-*O*-methyl-(+)-catechin 3 and (+)-catechin. Condensation of the β-methoxy derivative of (+)-catechin (142 mg) with (+)-catechin (55 mg) for 24 h, followed by methylation of the crude products and subsequent PLC in C_6H_6-Me_2CO (7:3, x2), afforded two fractions at R_f 0.42 and 0.21:

Octa-O-methyl-di-3-O-acetyl-bis-(+)-catechin 41. Acetylation of the R_f 0.42 fraction afforded, after PLC in $C_2H_4Cl_2$-hexane-Me_2CO (6:3:1, x2), the title compound (18 mg; R_f 0.48) the physical data of which were identical to those of an authentic sample[20].

Methyl ether acetate of (+)-catechin-(4α,8)-(+)-catechin-(4α,8)-(+)-catechin 43. Acetylation of the R_f 0.21 fraction, followed by PLC in $C_2H_4Cl_2$-hexane-Me_2CO (6:3:1, x2) gave the title compound (9 mg) the physical data of which were identical to those of an authentic sample[20].

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