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REGIO- AND STEREOSELECTIVE OXYGENATION OF FLAVAN-3-OL-, 4-ARYLFLAVAN-3-OL-, AND BIFLAVANOID-DERIVATIVES WITH POTASSIUM PERSULPHATE

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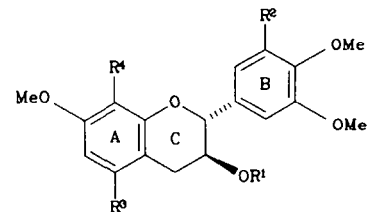
Abstract —— The phenolic methyl ethers of flavan-3-ols, 4-arylflavan-3-ols, and (-)-fisetinidol-(4,8)-(+)-catechin biflavanoids are susceptible to regio- and stereoselective hydroxylation at C-4 in moderate to high yields with potassium persulphate/cupric sulphate in aqueous acetonitrile. The resultant 4-functionalized analogues are of both synthetic and degradative significance in condensed tannin chemistry.

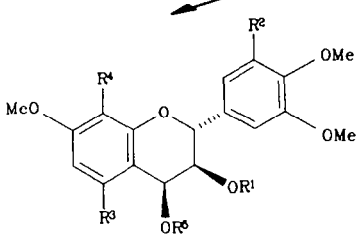
Flavan-3,4-diols play a key role as incipient electrophiles in the semi-synthetic sequence towards condensed tannins[1]. The utility of such an approach is, however, limited by the scant natural occurrence of these monomeric precursors. Oxidative functionalization of the prochiral benzylic methylene group in the more readily available flavan-3-ols thus offers considerable potential in synthetic condensed tannin chemistry. Amongst the plethora of reagents capable of effecting benzylic functionalization, only a few[2-6] have, however, been successfully applied to the C-4 methylene group of flavan-3-ols. Recent reports of the benzylic oxygenation of a variety of substrates with potassium persulphate ($K_2S_2O_8$)[7-11] hence prompted us to assess the potential of this reagent for introducing functionality at C-4 in a series of flavan-3-ol methyl ethers representing the constituent units in several classes of condensed tannin derivatives.

Separate treatment of the 3-*O*-acetyl and 3-*O*-pivaloyl esters 1 and 2 of (+)-catechin tetramethyl ether 3 with a double molar excess of $K_2S_2O_8$ and 0.2 molar equivalents of $CuSO_4$ in aqueous acetonitrile under nitrogen (80^0C, 3 and 2.5 h respectively) and subsequent acetylation afforded the 4β-acetoxy derivatives 7 and 8 in 46 and 48% yields (isolated) respectively. Under similar conditions (+)-catechin tetramethyl ether 3 (55 min) gave a mixture comprising tetramethyl-(+)-catechin-4β-ol 9 (48%), its 4α-ol analogue 13 (4%), tetramethyl-(+)-dihydroquercetin 17 (3%), and 3,4-dimethoxybenzaldehyde (7%). These results demonstrate the marginal effect of the 3-*O*-acyl groups in 1 and 2 on the course of oxygenation hence eliminating the necessity of protection at this site. Thus, application of the same conditions to tetramethyl-(+)-mesquitol 4

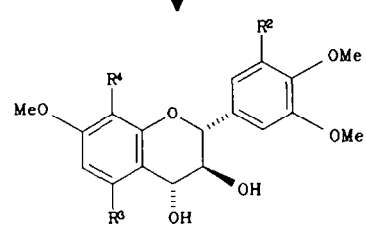


(1) R^1 = Ac, R^2 = R^4 = H, R^3 = OMe
(2) R^1 = COBu^t, R^2 = R^4 = H, R^3 = OMe
(3) R^1 = R^2 = R^4 = H, R^3 = OMe
(4) R^1 = R^2 = R^3 = H, R^4 = OMe
(5) R^1 = R^2 = R^3 = R^4 = H
(6) R^1 = R^3 = R^4 = H, R^2 = OMe

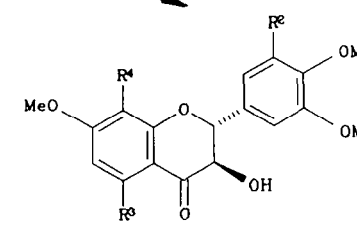
(i)



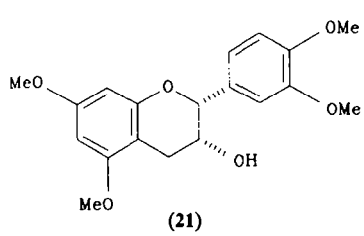
(7) R^1 = R^5 = Ac, R^2 = R^4 = H, R^3 = OMe (46%)
(8) R^1 = COBu^t, R^2 = R^4 = H, R^3 = OMe, R^5 = Ac (48%)
(9) R^1 = R^2 = R^4 = R^5 = H, R^3 = OMe (48%)
(10) R^1 = R^2 = R^3 = R^5 = H, R^4 = OMe (17%)
(11) R^1 = R^2 = R^3 = R^4 = R^5 = H (45%)
(12) R^1 = R^3 = R^4 = R^5 = H, R^2 = OMe (63%)



(13) R^2 = R^4 = H, R^3 = OMe (4%)
(14) R^2 = R^3 = H, R^4 = OMe (10%)
(15) R^2 = R^3 = R^4 = H (5%)
(16) R^2 = OMe, R^3 = R^4 = H (4%)



(17) R^2 = R^4 = H, R^3 = OMe (3%)
(18) R^2 = R^3 = H, R^4 = OMe (18%)
(19) R^2 = R^3 = R^4 = H (19%)
(20) R^2 = OMe, R^3 = R^4 = H (16%)



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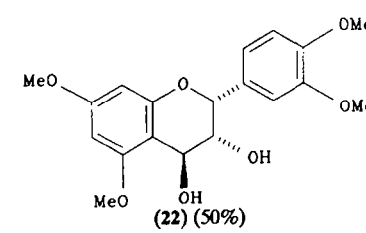
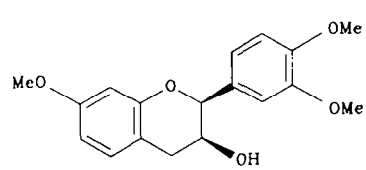
(i)

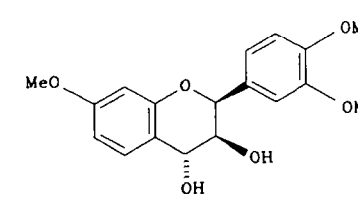


(22) (50%)



(23)

(i)



(24) (73%)

Scheme 1 Reagents/conditions: (i) $K_2S_2O_8$, $CuSO_4$, 80°C

(9 h), trimethyl-(-)-fisetinidol 5 (1.5 h), and tetramethyl-(-)-robinetinidol 6 (1.33 h) afforded the corresponding 4β-ols 10, 11, and 12, 4α-ols 14, 15, and 16, and dihydroflavonols 18, 19, and 20 in the yields* as indicated in Scheme 1. The phenolic methyl ethers of the 2,3-*cis*-flavan-3-ols, *i.e.* tetramethyl-(-)-epicatechin 21 (50 min) and trimethyl-(+)-epifisetinidol 23 (1.33 h) were susceptible to stereospecific C-4 hydroxylation yielding tetramethyl-(-)-epicatechin-4β-ol 22 and trimethyl-(+)-epifisetinidol-4α-ol 24 respectively. Relative configurations were assessed by ^{1}H NMR analysis which indicated $J_{2,3}$ *ca.* 10.0, $J_{3,4}$ *ca.* 4.0 Hz for 2,3-*trans*-3,4-*cis*-, $J_{2,3}$ *ca.* 10.0, $J_{3,4}$ *ca.* 8.0 Hz for all-*trans*-, and $J_{2,3}$ *ca.* 1.0, $J_{3,4}$ *ca.* 3.5 Hz for 2,3-*cis*-3,4-*trans*-diols, and $J_{2,3}$ *ca.* 12.0 Hz for the 2,3-*trans*-dihydroflavonols. The flavan-3,4-diols and, following reduction[1], also the dihydroflavonols could, in principle, then serve as electrophiles *via* incipient C-4 carbocations in a biomimetic synthesis[1] of condensed tannin derivatives. Hydroxylation of the (+)-epifisetinidol derivative 23 represents the first synthetic access to the 2,3-*cis*-flavan-3,4-diol[12] 24 and hence also to the rare group of naturally occurring profisetinidins with a (2*S*,3*S*)-2,3-*cis*-(+)-epifisetinidol 'upper' terminal unit[13].

Whereas the yields of the oxygenation products of (+)-catechin and (-)-epicatechin derivatives (*ca.* 55 and 50% respectively) are comparable to those observed for DDQ[5], the overall yields of products derived from the (-)-fisetinidol-(69%), (-)-robinetinidol-(83%), (+)-mesquitol-(45%), and (+)-epifisetinidol-(70%) derivatives are substantially improved with the former reagent. These yields are indeed superior to those in previous reports concerning the C-4 functionalization of flavan-3-ols[3-6]. Utilization of $K_2S_2O_8$ as oxidant offers the additional advantage of reduced reaction times compared to those for $Pb(OAc)_4$[3] and DDQ[5] hence minimizing side reactions, *e.g.* excessive anthocyanidin formation and also condensations to form oligomers under the slightly acidic conditions. These side reactions as were evidenced by strong coloration and the formation of highly polar compounds respectively, contribute significantly to the observed 'loss' of material.

Oxygenation at the benzylic C-4 centre of the flavan-3-ols presumably occurs *via* a carbocationic intermediate with water as trapping agent (Scheme 2). These carbocations, represented by the (+)-catechin related 27, most likely originate[11,14,15] by the initial formation of an A-ring radical-cation 25 by $SO_4^{\cdot-}/Cu^{2+}$, subsequent loss of a diastereotopic proton resulting in the stabilized benzylic radical 26, and the oxidative conversion of the latter to 27. Owing to the conformational mobility[16,17] of the flavan heterocycle, the intermediate carbocation 27 may be additionally stabilized by electron donation from the π-system of the B-ring *via* the A-conformation 28. This conformation permits the preferential trapping of the carbocation from the β-face hence explaining the considerable degree of stereoselectivity for flavan-3-ol derivatives 3, 5, and 6 (Scheme 1). The apparent anomolous 4β-:4α-ol ratio (1.7:1) for the (+)-mesquitol derivative 4 is presumably explicable in terms of C-4 epimerization of the 4β-ol 10 as a result of the increased reaction time for 4 (9h *vs. ca.* 1h for 3, 5, and 6) at the relative high temperature.

Both the E- and A-conformers 29 and 30 of the benzylic carbocations, represented by the (-)-epicatechin

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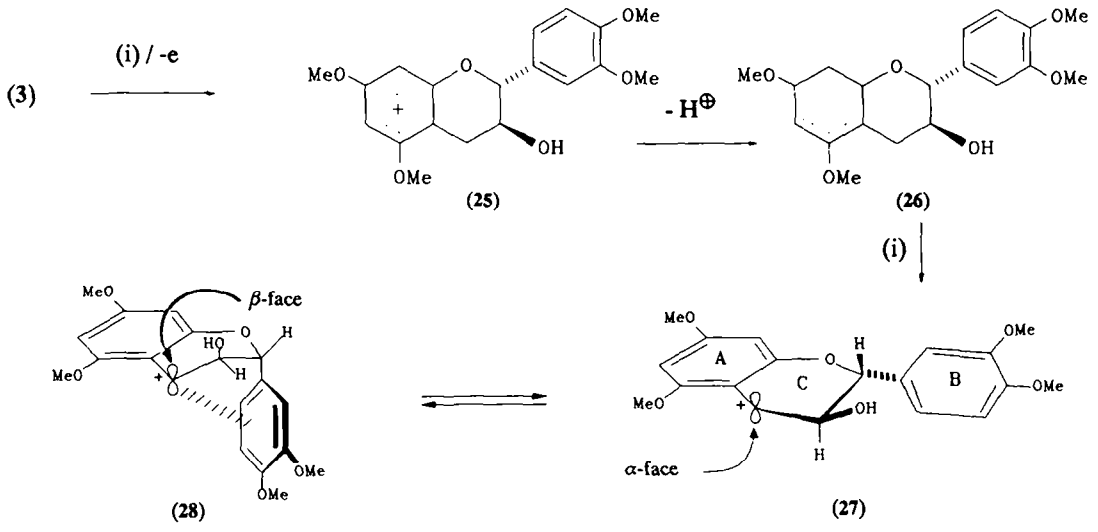
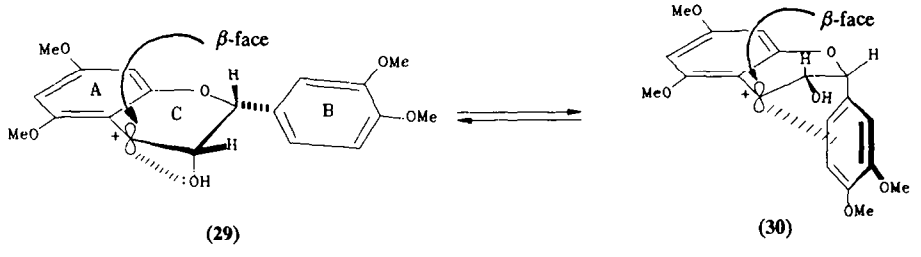
* Yields of the B-ring aldehydes are indicated in the Experimental section.



Scheme 2 Reagents/conditions: (i) $K_2S_2O_8$, $CuSO_4$, 80°C



Scheme 3

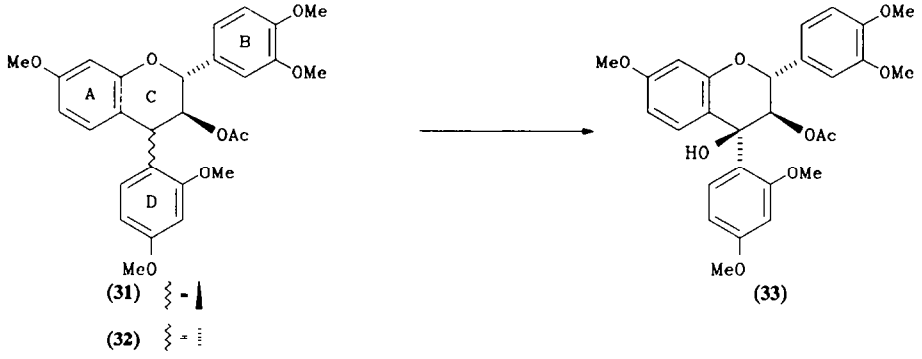
related 29, derived from the 2,3-*cis*-flavan-3-ol derivatives 21 and 23, are conducive to the observed stereospecific hydroxylation of these analogues (Scheme 3). In the E-conformation 29 the *axial* 3-hydroxy group contributes significantly towards stabilization of the electron-deficient C-4 benzylic centre, the oxirane-type structure resulting from such neighbouring group participation effectively blocking the α-face. The conspicuously higher yield of hydroxylation of the (+)-epifisetinidol derivative 23 (73%) compared to that for (-)-epicatechin tetramethyl ether 21 (50%) is attributable to the increased susceptibility of the 5-oxy flavan-3,4-diol 22 to oligomerization under the prevailing conditions.

The significant differences in the relative rates, assessed by regular (10 min intervals) t.l.c. monitoring, of the flavan-3-ols possessing phloroglucinol-, resorcinol-, and pyrogallol-type A-rings reflect the relative abil-

ities of these moieties to stabilize C-4 radicals (*e.g.* 26) and carbocations (*e.g.* 27). The additional and selective stabilization of these centres *via* A-conformations of type 28, compared to possible competing C-2 radical/carbocationic species, presumably explains the observed regioselectivity* of hydroxylation.

Notable from the results in Scheme 1 is the increased proportion of dihydroflavonol formation for the 5-deoxy flavan-3-ol derivatives 4, 5, and 6 in comparison to that of (+)-catechin tetramethyl ether 3. Such a preference for further oxidation of 4, 5 and 6 is to be sought in the orientation of H-4 in both the flavan-4α- and 4β-ols. In the 5-deoxy analogues, *e.g.* 11 and 15, these protons are virtually orthogonal to the plane of the A-ring hence facilitating their rapid abstraction. Steric repulsion between the bulky C-4 and C-5 oxygen functions in the (+)-catechin analogues 9 and 13 would force these protons coplanar with the π-system of the A-ring thus retarding the oxidative conversion of flavan-3,4-diol to dihydroflavonol.

No less important an objective, but aimed primarily at degradation[18], was the application of these optimized conditions to the 4-arylflavan-3-ol derivatives 31 and 32 as models for the profisetinidin biflavanoids (*vide infra*). Thus, both the 4β- and 4α-analogues 31 and 32 were selectively functionalized with $K_2S_2O_8/CuSO_4$ at 80^{0}C for 40 min to give the same 4β-hydroxy-4α-arylflavan-3-ol 33 in 40 and 68% yields respectively. Substitution of H-4(C) in 31 and 32 by a hydroxy group in 33 was evident from ^{1}H NMR data which indicated an AB-system (J10.5 Hz) for the heterocyclic protons (δ5.34, 6.19; H-2 and -3 respectively) and a broadened singlet (δ4.74) for the hydroxylic proton in compound 33. A pronounced n.O.e. association (5.3%) between the latter proton and H-2(C) strongly indicated a 4β-hydroxy group and hence 4*S* absolute

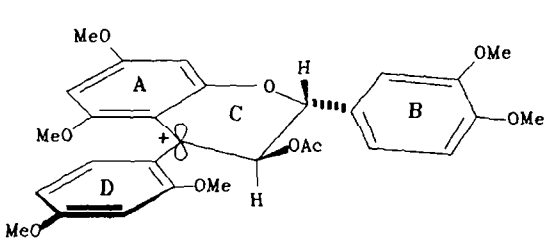


configuration for compound 33. This was confirmed by the high-amplitude negative Cotton effect at 235 nm in the CD spectrum reminiscent of the 4α-aryl group[19].

The transformation of both 4-arylflavan-3-ol derivatives 31 and 32 to the 4β-hydroxy-4α-arylflavan-3-ol 33 at comparable relative rates, suggests that oxygenation occurred *via* a common C-4 carbocationic intermedi-

* C-2 Hydroxylated analogues of the flavan-3-ol derivatives would presumably not survive the prevailing conditions.

ate 34, generated by steps similar to those in Scheme 2. Significant contributions towards stabilization of carbocation 34 *via* an A-conformation 35 would presumably again allow the selective trapping by water at the



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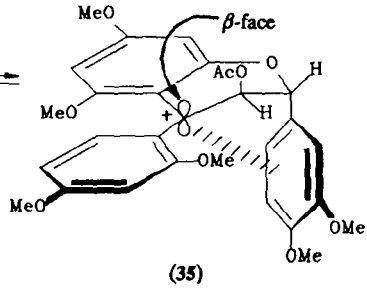

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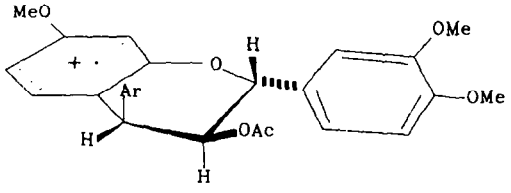
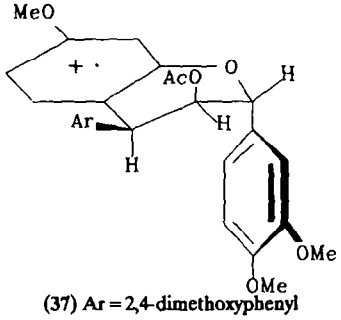
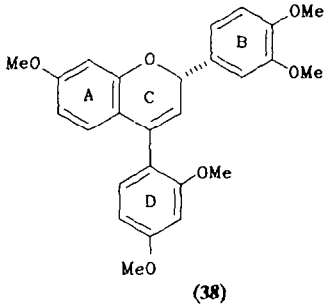


(36) Ar = 2,4-dimethoxyphenyl



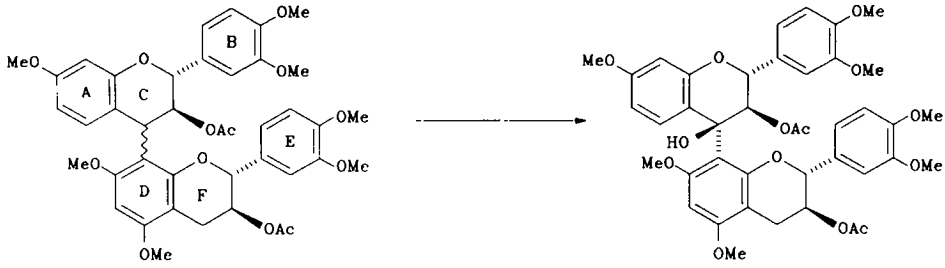
(37) Ar = 2,4-dimethoxyphenyl



(38)

less hindered β-face. The considerably reduced yield of hydroxylation of the 4β-arylflavan-3-ol derivative 31 (40%) in comparison to that of the 4α-analogue 32 (68%) is presumably explicable in terms of the different orientations of H-4 and the C-3 acetoxy group in these compounds. The *trans-diequatorial* arrangement of H-4 and 3-OAc in the E-conformer 36 of the 4β-arylflavan-3-ol 31, and hence *trans-diaxial* in the A-conformation 37, should facilitate competition between the solvolytic step and concerted loss of H-4 and 3-OAc to give a 4-arylflav-3-ene 38 incapable of surviving the prevailing reaction conditions.

Application of similar conditions to the (-)-fisetinidol-(4α,8)- and (4β,8)-(+)-catechin profisetinidin derivatives 39 (2 h) and 40 (2.5 h) led to formation of the common 4β-hydroxy-(-)-fisetinidol-(4α,8)-(+)-catechin



(39) ⦚ - ▌

(40) ⦚ = ⁞

(41)

derivative 41 in 12 and 6.5% yields respectively. Hydroxylation at C-4 (C-ring) of the biflavanoids 39 and 40 was again evident by the AB-system (δ5.21, 5.90; J10.5Hz) in the ^{1}H NMR spectrum of compound 41 in CD_3CN at 80^{0}C. The 4*R* absolute stereochemistry of the product was based on a combination of a negative Cotton effect at 246 nm in its CD spectrum and the significantly low shift difference (Δδ 0.21) of the 2- and 3-protons of the F-ring in contrast with that of the (4β,8)-biflavanoids 40 (0.61)[20]. Both observations are in accord with effects induced by (4α,8)-linked flavanyl constituents with (2*R*,3*S*)-configuration on the (+)-catechin DEF-moiety[19,20].

Stabilized carbocations of types 34 and 35 may again be invoked to rationalize genesis of the single 4β-hydroxy-(-)-fisetinidol-(4α,8)-(+)-catechin 41 from the biflavanoid derivatives 39 and 40. The low yields of formation of compound 41 presumably results from its susceptibility to further oxidation with $K_2S_2O_8$ at the C-4 benzylic centre of ring F and subsequent oligomerization of the flavan-3,4-diol equivalent. Such an assumption was confirmed by the formation of a considerable proportion of highly polar condensed tannin analogues on TLC.

Despite the observed low yields of formation of the C-4 functionalized biflavanoid 41, the selective hydroxylation at the C-4 bonding position should lead to weakening of strong interflavanoid bonds as existent in 39 and 40 hence permitting application of degradative bromination methods using pyridinium hydrobromide perbromide[18]. The potential of $K_2S_2O_8$ in condensed tannin chemistry is, however, not to be sought in degradative applications but rather in its ability to effect regioselective oxidative hydroxylation of the constituent flavan-3-ol units of condensed tannins.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ and $(CD_3)_2CO$. Mass spectra were obtained with a Kratos MS80 instrument. 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), 20 x 20 cm, Silica Gel F_{254} (1.0 mm) were air-dried and used without prior activation. CD data were obtained in methanol on a Jasco J-20 spectropolarimeter. Column chromatography was carried out under flash conditions at a pressure of *ca.* 75 kPa giving a flow rate of 10 cm^3

min^{-1}. Methylations were performed with an excess of diazomethane in MeOH-diethyl ether over 48 h at -15°C, while acetylations were carried out in Ac_2O-pyridine at ambient temperatures. Evaporations were done under reduced pressure at *ca.* 60°C in a rotary evaporator. In most instances the structures of the products were confirmed by comparison of their physical data with those of authentic samples.

General Oxygenation and Work-up Procedures

$K_2S_2O_8$ (2 mole equivalents) and $CuSO_4 \cdot 5H_2O$ (0.2 mole equivalents) were dissolved in H_2O (12 cm^3) and the solution was degassed with N_2 over a period of 2 h. This solution was added to a degassed solution of the flavan-3-ol derivative (*ca.* 0.3 mmol) dissolved in acetonitrile (20 cm^3) and the resulting mixture was stirred at reflux temperature (80°C) under N_2.

The mixture was poured into ice-water (150 g) and the products were extracted with EtOAc (5 x 50 cm^3). The extract was washed with ice-water (3 x 25 cm^3), dried (Na_2SO_4) and the solvent evaporated. Column chromatography (Flash) of the residue, followed by acetylation of the various fractions and subsequent chromatography (PLC) afforded the products.

Oxygenation of Flavan-3-ol Derivatives

Tetra-O-*methyl*-3-O-*acetyl*-(+)-*catechin* 1. —— Oxygenation of the title compound (72 mg; 0.185 mmol) for 3 h at 70°C afforded, after acetylation and PLC in C_6H_6-Me_2CO (9:1), 4β-acetoxy-tetra-*O*-methyl-3-*O*-acetyl-(+)-catechin 7 as a solid (42 mg; R_f 0.53), and minute quantities of the 4α-acetoxy derivative and tetra-*O*-methyl-3-*O*-acetyl-(+)-dihydroquercetin.

Tetra-O-*methyl*-3-O-*pivaloyl*-(+)-*catechin* 2. —— Oxygenation of the title compound (55 mg; 0.128 mmol) for 2.5 h at 70°C followed by acetylation and PLC in C_6H_6-Me_2CO (98:2), afforded 4β-acetoxy-tetra-*O*-methyl-3-*O*-pivaloyl-(+)-catechin 8 as a solid (30 mg; R_f 0.46).

Tetra-O-*methyl*-(+)-*catechin* 3. —— Reaction of the title compound (88 mg; 0.254 mmol) followed by acetylation and subsequent column chromatography with C_6H_6-Me_2CO (90-70% C_6H_6, polarity gradient), afforded 4β-hydroxy-tetra-*O*-methyl-(+)-catechin (9; 44 mg), the 4α-isomer (13; 3.7 mg), tetra-*O*-methyl-(+)-dihydroquercetin (17; 2.5 mg), and 3,4-dimethoxybenzaldehyde (3 mg).

Tetra-O-*methyl*-(+)-*mesquitol* 4. —— Oxygenation of the title compound (200 mg; 0.578 mmol) for 9 h [a further portion of $K_2S_2O_8$ (100 mg) was added after 5 h] followed by column chromatography with C_6H_6-Me_2CO-EtOAc [C_6H_6-Me_2CO (8:2); C_6H_6-Me_2CO-EtOAc (8:2:2); polarity gradient], afforded 4β-hydroxy-tetra-*O*-methyl-(+)-mesquitol (10; 39 mg), the 4α-isomer (14; 26 mg), the dihydroflavonol (18; 38 mg), unchanged starting material (16 mg), and 3,4-dimethoxybenzaldehyde (14 mg).

Tri-O-*methyl*-(-)-*fisetinidol* 5. —— Reaction of the title compound (138 mg; 0.436 mmol) for 1.5 h, followed by column chromatography with C_6H_6-Me_2CO (90-75% C_6H_6; polarity gradient), gave tri-*O*-methyl-(+)-gleditsin (11; 65 mg), tri-*O*-methyl-(+)-mollisacacidin (15; 7 mg), tri-*O*-methyl-(+)-fustin (19; 27 mg), and 3,4-dimethoxybenzaldehyde (4.4 mg).

Tetra-O-*methyl*-(-)-*robinetinidol* 6. —— Oxygenation of the title compound (100 mg; 0.318 mmol) for 1.3 h, followed by column chromatography with C_6H_6-Me_2CO (90-70% C_6H_6; polarity gradient), afforded 4β-hydroxy-tetra-*O*-methyl-(-)-robinetinidol (12; 72.5 mg), the 4α-isomer (16; 4.3 mg), tetra-*O*-methyl-(+)-dihydrorobinetin (20; 19.6 mg), and 3,4,5-trimethoxybenzaldehyde (6.4 mg).

Tetra-O-*methyl*-(-)-*epicatechin* 21. —— Reaction of the title compound (158 mg; 0.456 mmol) for 50 min and subsequent separation by column chromatography with C_6H_6-Me_2CO (90-70% C_6H_6; polarity gradient). afforded 4β-hydroxy-tetra-*O*-methyl-(-)-epicatechin (22; 82 mg) and 3,4-dimethoxybenzaldehyde (2.3 mg).

Tri-O-*methyl*-(+)-*epifisetinidol* 23. —— Oxygenation of the title compound (67.6 mg; 0.214 mmol) for 1.3 h followed by PLC in C_6H_6-Me_2CO (88:12), afforded 4β-hydroxy-tri-*O*-methyl-(+)-epifisetinidol 24 as a solid (49.5 mg; Rf 0.32) which was characterised as the *methyl ether diacetate* (52 mg) (Found: M^+-60, 356.1264. $C_{20}O_6H_{20}$ requires M-60, 356.1260); δ ($CDCl_3$; 300 MHz, 296 K) 7.35 [d, $J_{5,6}$ 9.5 Hz, H-5(A)], 7.00 [d, $J_{2,6}$ 2.6 Hz, H-2(B)], 6.98 [dd, $J_{5,6}$ 9.0 and $J_{2,6}$ 2.6 Hz, H-6(B)], 6.86 [d, $J_{5,6}$ 9.0 Hz, H-5(B)], 6.57 [dd, $J_{5,6}$ 9.5 and $J_{6,8}$ 2.5 Hz, H-6(A)], 6.55 (d, $J_{6,8}$ 2.5 Hz, H-8(A)], 5.83 [d, $J_{3,4}$ 3.0 Hz, H-4(C)], 5.25 [d, $J_{2,3}$ 1.5 Hz, H-2(C)], 5.21 [dd, $J_{2,3}$ 1.5 and $J_{3,4}$ 3.0 Hz, H-3(C)], 3.90, 3.88 and 3.78 [3xs, 3xOMe], 2.12 (s, 4-OAc), 1.89 (s, 3-OAc).

Tri-O-*methyl*-3-O-*acetyl*-4β-(2,4-*dimethoxyphenyl*)-(-)-*fisetinidol* 31. —— Oxygenation of the title compound (102 mg) for 40 min, followed by column chromatography [C_6H_6-EtOAc (9:1) and C_6H_6-EtOAc-Me_2CO (80:12:8); polarity gradient], afforded 4β-hydroxy-4α-(2,4-dimethoxyphenyl)-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol 33 as a *white amorphous solid* (41.6 mg) (Found: M^+-60, 450.1684. $C_{28}H_{30}O_9$ requires M-60, 450.1679); δ [$(CD)_3CO$, 300 MHz, 296 K], 7.72 [br.d, $J_{5,6}$ 8.5 Hz, H-6(D)], 7.06 [d, $J_{2,6}$ 2.0 Hz, H-2(B)], 7.02 [dd, $J_{5,6}$ 8.8 and $J_{2,6}$ 2.0 Hz, H-6(B)], 6.92 [d, $J_{5,6}$ 8.8 Hz, H-5(B)], 6.66 [d, $J_{5,6}$ 8.5 Hz, H-5(A)], 6.53 [dd, $J_{5,6}$ 8.5 and $J_{3,5}$ 2.2 Hz, H-5(D)], 6.45 [d, $J_{3,5}$ 2.2 Hz, H-3(B)], 6.40 [d, $J_{6,8}$ 2.6 Hz, H-8(A)], 6.37 [dd, $J_{5,6}$ 8.5 and $J_{6,8}$ 2.6 Hz, H-6(A)], 6.19 [d, $J_{2,3}$ 10.5 Hz, H-3(C)], 5.34 [d, $J_{2,3}$ 10.5 Hz, H-2(C)], 4.74 [br.s, 4-OH(C)], 3.56, 3.74, 3.77, 3.79 and 3.81 [5xs, 5xOMe], 1.53 [s, 3-OAc], CD, $[\Theta]_{215}$ $-1.5x10^4$, $[\Theta]_{220}$ $-1.7x10^4$, $[\Theta]_{230}$ $-2.4x10^4$, $[\Theta]_{235}$ $-2.6x10^4$, $[\Theta]_{240}$ $-2.1x10^4$, $[\Theta]_{250}$ $-0.98x10^4$, $[\Theta]_{265}$ $-1.2x10^4$, $[\Theta]_{270}$ $-1.3x10^4$, $[\Theta]_{280}$ $-0.67x10^4$, $[\Theta]_{290}$ 0.

Tri-O-*methyl*-3-O-*acetyl*-4α-(2,4-*dimethoxyphenyl*)-(-)-*fisetinidol* 32. —— Oxygenation of the title compound (104 mg) for 40 min, followed by column chromatography [C_6H_6-EtOAc (9:1) and C_6H_6-EtOAc-Me_2CO (80:12:8); polarity gradient], afforded 4β-hydroxy-4α-(2,4-dimethoxyphenyl)-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol (33; 72.6 mg), the physical data of which were identical to those of the compound in the previous experiment.

Tri-O-*methyl*-3-O-*acetyl*-(-)-*fisetinidol*-(4β,8)-*tetra*-O-*methyl*-3-O-*acetyl*-(+)-*catechin* 39. —— Reaction of the title compound (83 mg) for 2 h, followed by column chromatography [C_6H_6-EtOAc (75:25) and C_6H_6-Me_2CO (65:35); polarity gradient] afforded 4β-hydroxy-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,8)-tetra-*O*-methyl-3-*O*-acetyl-(+)-catechin 41 as a *white amorphous solid* (10 mg) (Found: M^+-60, 688.2490. $C_{40}H_{44}O_{14}$ requires M-60, 688.2520). δ [CD_3CN, 300 MHz, 353 K], 6.86 [d, $J_{5,6}$ 8.5 Hz, H-5(B)], 6.85 [d, $J_{5,6}$ 8.2 Hz, H-5(E)], 6.80 [d, $J_{2,6}$ 2.0 Hz, H-2(B)], 6.79 [dd, $J_{5,6}$ 8.5 and $J_{2,6}$ 2.0 Hz, H-6(B)], 6.66 [d, $J_{2,6}$ 2.0 Hz, H-2(E)], 6.50 [dd, $J_{5,6}$ 8.2 and $J_{2,6}$ 2.0 Hz, H-6(E)], 6.95 [d, $J_{5,6}$ 8.5 Hz, H-5(A)], 6.50 [dd, $J_{5,6}$ 8.5 and $J_{6,8}$ 2.5 Hz, H-6(A)], 6.29 [d, $J_{6,8}$ 2.5 Hz, H-8(A)], 6.41 [s, H-6(D)], 6.45 [br.s, 4-OH], 5.90 [d, $J_{2,3}$ 10.2 Hz, H-3(C)], 5.21 [d, $J_{2,3}$ 10.2 Hz, H-2(C)], 4.95 [m, H-3(F)], 4.74 [d, $J_{2,3}$ 8.5 Hz, H-2(F)], 2.64 [dd, $J_{3,4}$ 8.6 and $J_{4,4}$ 16.8 Hz, H-4_{ax}(F)], 3.06 [dd, $J_{3,4}$ 6.5 and $J_{4,4}$ 16.8 Hz, H-$4_{eq.}$(F)], 3.89 (x2), 3.84, 3.81, 3.79, 3.77 and 3.68 [6xs, 7xOMe], CD $[\Theta]_{246}$ $-1.2x10^4$.

Tri-O-*methyl*-3-O-*acetyl*-(-)-*fisetinidol*-(4α,8)-*tetra*-O-*methyl*-3-O-*acetyl*-(+)-*catechin* 40. —— Oxygenation of the title compound (220 mg) for 2.5 h followed by column chromatography [C_6H_6-EtOAc (75:25) and C_6H_6-Me_2CO (65:35); polarity gradient] afforded 4β-hydroxy-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,8)-tetra-*O*-methyl-3-*O*-acetyl-(+)-catechin 41 as a white solid (14 mg), the physical data of which were identical to those of the compound in the previous experiment.

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