Stereoselective C-4 Functionalisation of Flavan-3-ols. The Significance of Conformational Mobility of the Flavan Heterocycle in Stereoselectivity at the Benzylic Carbon

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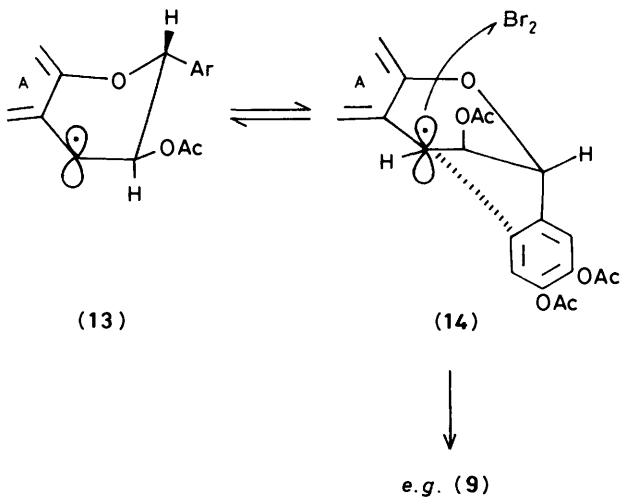
The peracetates of (+)-catechin [(2*R*,3*S*)-2,3-*trans*-3',4',5,7-tetrahydroxyflavan-3-ol] and a variety of related flavan-3-ols are very susceptible to formation of their 4β-bromo derivatives when treated with NBS in the presence of benzoyl peroxide. The observed stereospecific C-4-brominations, and the stereoselectivity displayed during substitution reactions of the functionalised flavan-3-ols, are explicable in terms of conformational mobility of the flavan heterocyclic ring.

Although C-4-oxygenated flavanoids, *e.g.* flavan-3,4-diols and flavan-4-ols, and C-4-halogenated flavans have been extensively utilised as electrophilic substrates in syntheses of condensed tannins and C-4-aryl- or aryloxy-flavans,[1-21] functionalisation of the prochiral C-4-benzylic methylene group in flavan-3-ols and flavans has received little attention.[22-25] In view of the promising results regarding bromination[22,24] and oxygenation[25] as well as the constant need for C-4-functionalised analogues in our continuing programme towards the synthesis of condensed tannins, we embarked on a strategy of introducing functionality *via* halogenation at the benzylic 4-carbon of a series of readily available flavan-3-ols. The resulting 4-bromo derivatives could, in principle, then serve as electrophiles in a synthetic route towards condensed tannins.

Results and Discussion

The method of bromination of the peracetates† of the flavan-3-ols (+)-catechin [(**1**), (2*R*,3*S*)-2,3-*trans*-3',4',5,7-tetrahydroxyflavan-3-ol], (−)-epicatechin [(**7**), (2*R*,3*R*)-2,3-*cis*-3',4',5,7-tetrahydroxyflavan-3-ol], (−)-robinetinidol[26] [(**3**), (2*R*,3*S*)-2,3-*trans*-3',4',5',7-tetrahydroxyflavan-3-ol], and (−)-fisetinidol[27] [(**5**), (2*R*,3*S*)-2,3-*trans*-3',4',7-trihydroxyflavan-3-ol] with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide was selected for the halogenation studies. Thus, penta-*O*-acetyl-(+)-catechin (**2**), when treated with NBS–benzoyl peroxide under nitrogen at the reflux temperature of CCl_4, gave 4β-bromopenta-*O*-acetyl-(+)-catechin (**9**) ($J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz) in 50% yield.‡ Similar treatment of penta-*O*-acetyl-(−)-epicatechin (**8**), penta-*O*-acetyl-(−)-robinetinidol (**4**), and tetra-*O*-acetyl-(−)-fisetinidol (**6**) led to the exclusive formation of the corresponding 4β-bromo derivatives (**12**) (62%; $J_{2,3}$ 1.0, $J_{3,4}$ 2.5 Hz), (**10**) (54%; $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz), and (**11**) (30%; $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz) respectively. The (−)-fisetinidol analogue is accompanied by tetra-*O*-acetyl-(+)-fustin (9%) [(2*R*,3*R*)-2,3-*trans*-3,3',4',7-tetra-acetoxyflavanone; $J_{2,3}$ 12.5 Hz)] which presumably originated *via* hydrolysis/dehydration of an intermediate 4,4-dibromo derivative during chromatography on silica.

Notable in the above series of brominations is the exclusive formation of the 4β-bromo analogues (**9**)—(**12**) and also the increased rate§ of the (−)-robinetinidol peracetate (**4**) in comparison with those of the remaining flavan-3-ol derivatives (**2**), (**6**), and (**8**). The observed stereospecificity may presumably be rationalised in terms of initial abstraction of a diastereotopic methylene hydrogen by bromine radical and subsequent trapping of radical (**13**) from the β-face. Such a preference may be attributed to neighbouring group¶ participation of the π-system of ring B *via* non-preferred conformation[7,28] (**14**) (Scheme 1). Conformations of type (**14**) also furnish axially



Scheme 1. Ar = 3,4-diacetoxyphenyl

orientated 3-acetoxy functions capable of providing anchimeric assistance towards removal of a methylenic hydrogen. Such an intermediate would, however, facilitate the exclusive formation of 4α-bromo derivatives.

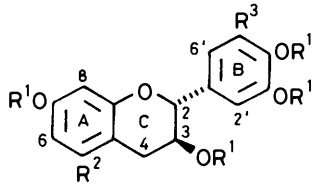
The significance of B-ring contributions *via* the non-preferred A-conformation (**14**) towards stabilisation of an electron-deficient C-4-benzylic centre is substantiated by the observation

† Owing to their highly activated *meta*-oxygenated A-rings, both the free phenols and their phenolic methyl ethers were susceptible to exclusive A-ring bromination.

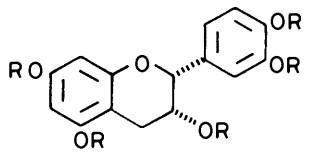
‡ Yields are based on the amount of starting material consumed.

§ Rates are relative and were compared by regular (15 min intervals) t.l.c. monitoring.

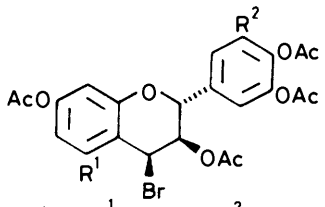
¶ The effect of neighbouring group participation and/or conformational restrictions in the substrate on the stereospecificity of bromination has been discussed in detail (P. S. Skell and P. D. Readio, *J. Am. Chem. Soc.*, 1964, **86**, 3334; E. S. Huyser and R. H. C. Feng, *J. Org. Chem.*, 1971, **36**, 731; K. R. Norris and R. J. Smyth-King, *J. Chem. Soc., Chem. Commun.*, 1981, 79).



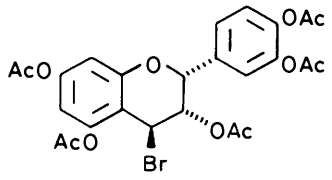
(1) $R^1 = R^3 = H$, $R^2 = OH$
(2) $R^1 = Ac$, $R^2 = OAc$, $R^3 = H$
(3) $R^1 = R^2 = H$, $R^3 = OH$
(4) $R^1 = Ac$, $R^2 = H$, $R^3 = OAc$
(5) $R^1 = R^2 = R^3 = H$
(6) $R^1 = Ac$, $R^2 = R^3 = H$



(7) R = H
(8) R = Ac



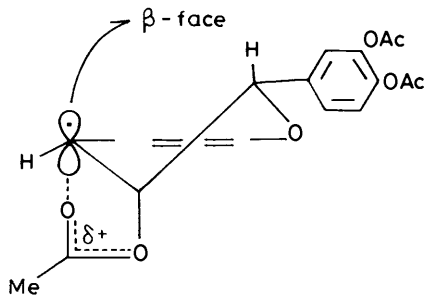
(9) $R^1 = OAc$, $R^2 = H$
(10) $R^1 = H$, $R^2 = OAc$
(11) $R^1 = R^2 = H$



(12)

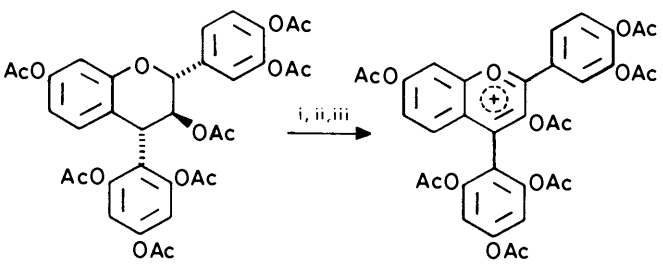
of the peracetate of (−)-robinetinidol, compound (**4**), reacting more rapidly * and with an increased yield when compared with the tetra-*O*-acetyl derivative (**6**) of (−)-fisetinidol. The more electron-rich trioxygenated B-ring of the (−)-robinetinidol derivative (**4**) should contribute more prominently towards stabilisation of the C-4 radical site than that of the dioxygenated B-ring of the (−)-fisetinidol analogue (**6**). Increased rate and yield of the (+)-catechin (**2**) and (−)-epicatechin (**8**) peracetates in comparison with those of the (−)-fisetinidol derivative (**6**), with their identical catechol B-rings, is attributable to enhanced stabilisation of the respective C-4 benzylic radicals by the *meta*-trioxygenated A-rings of the former flavan-3-ols (**2**) and (**8**) *vs.* the resorcinol-type A-ring of the (−)-fisetinidol peracetate (**6**).

The stereospecificity of C-4 bromination of the peracetate of (−)-epicatechin, compound (**8**), is paralleled by previous observations [18] of substitution, in the case of it being an oxygenated electrophilic centre, which invariably afforded 4β-products. Here the 3-axial acetoxy function (*E*-conformation) is ideally orientated for providing anchimeric assistance in removal of the 4β-hydrogen *via* the acyloxonium-type species (**15**).



(15)

Having established the experimental conditions for the selective bromination of the C-4 benzylic position in the flavan-3-ol acetates, the same procedures were extended to the peracetates of a 4-arylflavan-3-ol [compound (**16**)], (−)-fisetinidol-(4α,8)-(+)-catechin, and (4α,6)-bi-(−)-fisetinidol.† Under these conditions the starting materials disappeared rapidly while the colour of the reaction mixture invariably turned to a deep red. These observations are explicable in terms of initial bromination of the highly activated double benzylic C-4-centre. Owing to the expected lability of the bromine atom an intermediate 4-bromo derivative would be susceptible to HBr elimination to give a flav-3-ene which may be oxidised to an anthocyanidin of type (**17**).



(16) (17)

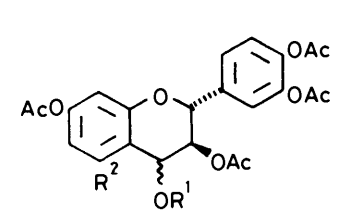
Reagents/conditions: i, NBS, peroxide; ii, −HBr; iii, oxidation

Availability of the 4β-bromoflavan-3-ol peracetates (**9**)—(**12**) offered us the opportunity of subjecting these as electrophiles to substitution reactions with simple oxygen nucleophiles and eventually also with phenolic units in a synthetic sequence which would complement existing methodology towards the synthesis of condensed tannins (see refs. 8—15). Thus, treatment of 4β-bromopenta-*O*-acetyl-(+)-catechin (**9**) with water in 2,2,2-trifluoroethanol (TFE) in the presence of silver nitrate at room temperature, followed by acetylation, led to stereospecific formation of the 4β-acetoxy derivative (**18**) (14%; $J_{2,3}$ 11.0, $J_{3,4}$ 4.0 Hz). Similar treatment of compound (**9**) with ethanolic silver nitrate at 50 °C afforded a mixture of the 4α-[(**19**); $J_{2,3} = J_{3,4} = 5.0$ Hz]‡ and 4β-[(**20**); $J_{2,3}$ 10.5, $J_{3,4}$ 4.0 Hz] ethoxy

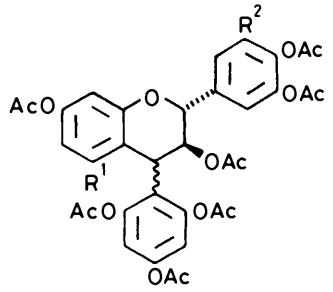
* Similar increased rate was also observed for coupling with nucleophilic phenolic substrates under acidic conditions when the flavan-3,4-diol (+)-leucorobinetinidin was compared with competing (+)-mollisacacidin (see ref. 11).

† See ref. 8 for their structural formulae.

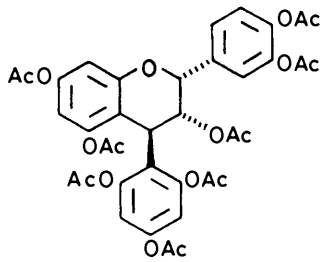
‡ These small coupling constants presumably reflect significant contributions of A-forms towards the total C-ring conformation.



(18) ≷ = ▲, R^1 = Ac, R^2 = OAc
(19) ≷ = ⋮, R^1 = Et, R^2 = OAc
(20) ≷ = ▲, R^1 = Et, R^2 = OAc
(21) ≷ = ▲, R^1 = Ac, R^2 = H



(22) ≷ = ⋮, R^1 = OAc, R^2 = H
(23) ≷ = ▲, R^1 = OAc, R^2 = H
(24) ≷ = ⋮, R^1 = H, R^2 = OAc
(25) ≷ = ▲, R^1 = H, R^2 = OAc



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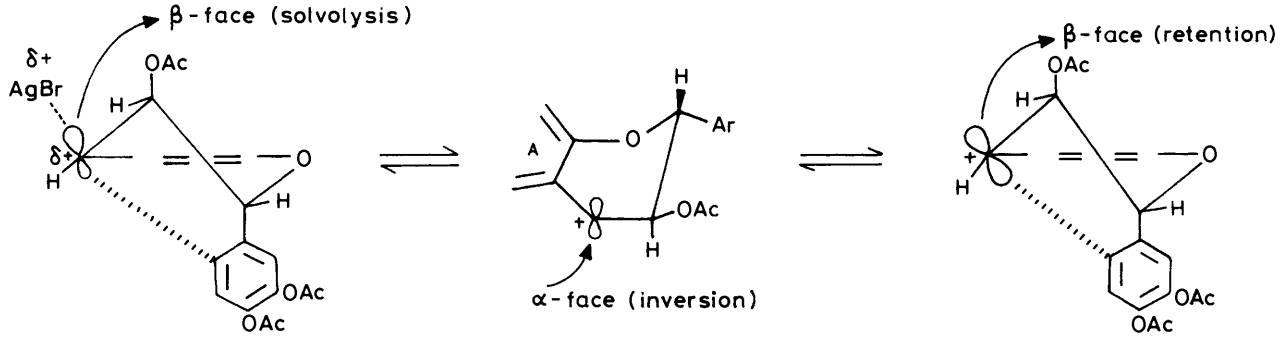

(27) (28) (29)

Scheme 2. Ar = 3,4-diacetoxyphenyl

derivatives in 10% overall yield. The stereochemical course of these reactions is in agreement with the results obtained by Brown *et al.*[16] during nucleophilic substitutions of 4β-bromoflavans by a variety of nucleophiles and will not be further discussed.

Under conditions similar to the above, but with phloroglucinol as the nucleophile, the 4β-bromo derivatives of (+)-catechin and (−)-robinetinidol peracetates, compounds (**9**) and (**10**), gave both the 4α- [(**22**) and (**24**) respectively; 12 and 25%; $J_{2,3}$ 10.5 and 10.0, $J_{3,4}$ 10.5 and 10.0 Hz] and 4β- [(**23**) and (**25**) respectively; 3 and 6%; $J_{2,3}$ 8.0 and 8.5, $J_{3,4}$ 6.0 and 5.0 Hz] aryl derivatives in relatively low yields. The 4β-bromo-(−)-epicatechin peracetate (**12**) afforded the 4β-arylated product (**26**) (12%; $J_{2,3}$ 1.25, $J_{3,4}$ 2.50 Hz) only. In all three cases the C-4-substituted products (**22**)—(**26**) were accompanied by the 4β-trifluoroethoxy derivatives, representative of the products of stereospecific solvolysis of the starting materials. These compounds were formed in low proportions and were identified by comparison of ^{1}H n.m.r. data with those of the (−)-robinetinidol derivative which was fully characterised (see Experimental section). Similar efforts at coupling of (+)-catechin (**1**) and (−)-fisetinidol (**5**) to 4β-bromotetra-*O*-acetyl-(−)-fisetinidol (**11**) in aq. TFE–silver nitrate led to formation of the 3,4-*cis*-diacetate (**21**) only.

The stereospecific substitution at C-4 of the 4β-bromo-(−)-epicatechin peracetate (**12**) is reminiscent of the bromination of penta-*O*-acetyl-(−)-epicatechin (**8**) except for replacement of the radical C-4-centre (**15**) by a formal carbocationic intermediate. Stereoselectivity with net inversion of configuration at C-4 in the case of the (+)-catechin and (−)-robinetinidol analogues (**9**) and (**10**) presumably reflects a predominant S_N1 mechanism for the replacement of bromine by phloroglucinol. Silver ion-mediated removal of the 4β-bromo substituent would lead to an intimate ion-pair which may be stabilised by B-ring participation as in (**27**). Owing to steric compression such an arrangement is susceptible to solvolysis from the β-face (see ref. 29), but not to attack from the same face by the more bulky phloroglucinol nucleophile. Dissociation of the C(4)–Br bond leads to the formal benzylic carbocation (**28**), again stabilised *via* electron donation from the B-ring (**29**) (Scheme 2). Unfavourable 1,3-diaxial interaction between 2-H and the incoming nucleophile in conformation (**28**), and thus preference for α-face attack, could then feasibly explain the predominant occurrence of inversion of the C-4 configuration.

Scrutiny of the literature has revealed that (2*R*,3*S*)-flavan-3,4-diols, irrespective of their C-4 configuration, afford predominantly 4α-substituted products when treated with nucleophilic species under acidic conditions at ambient temperatures.[8] At higher temperatures (*ca.* 40 °C) the same flavan-3,4-diols, however, exhibit marked preference for the formation of 4β-derivatives[12] (see also ref. 16 for similar observations with 4-bromoflavans). These phenomena have now been verified by acid-catalysed coupling of phloroglucinol to (+)-mollisacacidin [(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-3′,4′,7-trihydroxyflavan-3,4-diol]. While the 4α-derivative [type (**22**)] is the major product up to 50 °C, the 4β-analogue [type (**23**)] predominates at 80 °C. It would thus appear that at room temperatures the stereochemical course of coupling is dictated by the occurrence of unfavourable 1,3-diaxial interactions [β-face attack in conformation (**28**)], while at elevated temperatures B-ring-stabilised C-4-carbo-

cations of type (**29**) determine the stereochemistry of coupling *via* a predominant S_N1 mechanism. Although the observed stereospecificity may also be explained in terms of an S_N2 mechanism, we favour the S_N1 mode, since the elevated temperatures should be conducive for participation of conformations such as (**29**) with known higher energies than those of the more preferred *E*-conformations.

Experimental

^{1}H N.m.r. spectra were recorded on a Bruker WP-80 and an AM-300 spectrometer in $CDCl_3$ and $(CD_3)_2CO$ with Me_4Si as internal standard. Mass spectra were obtained with a Varian CH-5 instrument. T.l.c. was performed on precoated Merck plastic sheets (DC-Plastikfolien Kieselgel 60 F_{254}, 0.25 mm) and compounds were located by H_2SO_4–HCHO (40:1 v/v) spray reagent. Preparative plates (p.l.c.), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Acetylations were carried out in acetic anhydride–pyridine at ambient temperatures. Evaporations were done under reduced pressures at *ca.* 60 °C in a rotary evaporator. Owing to their instability, satisfactory microanalytical data (C and H analyses, accurate mass estimations) could not be obtained for the 4β-bromoflavan-3-ol acetates (**9**)—(**12**). Their purity could, however, be assessed by ^{1}H n.m.r. data at 80 MHz. Since the aromatic substitution patterns of the parent compounds are not altered, coupling constants for the benzenoid protons are indicated for a narrow selection of derivatives only. In most instances the majority of substitution products represent the full acetates of compounds which have previously been fully identified as phenolic methyl ether acetates. ^{1}H N.m.r. data based on established spin patterns for these peracetates are thus taken as sufficient structural evidence.

General Bromination and Work-up Procedures

A mixture of the peracetate of the flavan-3-ol (1 mol), NBS[30] (1 mol), and benzoyl peroxide (5% of the mass of NBS) was stirred in anhydrous, freshly distilled carbon tetrachloride (100 ml/1 g substrate) at reflux temperature under a nitrogen blanket. The reaction mixture was cooled and filtered. Evaporation of the solvent under reduced pressure followed by chromatography (p.l.c.) of the residue afforded the products.

4β-*Bromopenta*-O-*acetyl*-(+)-*catechin* (**9**).—Bromination of penta-*O*-acetyl-(+)-catechin (**2**) (500 mg, 1 mmol) for 5 h afforded, after p.l.c. in methylene dichloride–acetone (97.5:2.5), starting material (84 mg) and the 4β-bromoflavan-3-ol derivative (**9**) as an *oil* (300 mg; R_F 0.61); δ($CDCl_3$; 80 MHz; 304 K) 7.31—7.00 [m, 2′, 5′, and 6′-H(B)], 6.53 [d, *J* 2.5 Hz, 8-H(A)], 6.43 [d, *J* 2.5 Hz, 6-H(A)], 5.50 [d, $J_{3,4}$ 3.5 Hz, 4-H(C)], 5.31 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 4.78 [dd, 3-H(C)], 2.25—2.19 (m, 3′-, 4′-, 5′-, and 7-OAc), and 1.94 (s, 3-OAc).

4β-*Bromopenta*-O-*acetyl*-(−)-*robinetinidol* (**10**).—Bromination of penta-*O*-acetyl-(−)-robinetinidol (**4**) (337 mg, 0.6 mmol) for 3 h afforded, after p.l.c. [ethylene dichloride–acetone (95:5)], only the title compound as an *oil* (210 mg; R_F 0.65); δ[$(CD_3)_2CO$; 80 MHz; 304 K] 7.40—7.06 [m, 2′- and 6′-H(B) and 5-H(A)], 6.64 [dd, 6-H(A)], 6.56 [d, 8-H(A)], 5.69 [d, $J_{3,4}$ 3.5 Hz, 4-H(C)], 5.38 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 5.00 [dd, 3-H(C)], 2.27—2.18 (m, 3′-, 4′-, 5′-, and 7-OAc), and 1.92 (s, 3-OAc).

4β-*Bromotetra*-O-*acetyl*-(−)-*fisetinidol* (**11**).—Bromination of tetra-*O*-acetyl-(−)-fisetinidol (**6**) (200 mg, 0.4 mmol) for 4 h afforded, after p.l.c. [benzene–acetone (95:5)], unchanged starting material (42 mg), tetra-*O*-acetyl-(+)-fustin * (14 mg; R_F 0.58) and the title compound as an *oil* (57 mg; R_F 0.63); δ($CDCl_3$; 80 MHz; 304 K) 7.31—6.94 [m, 2′-, 5′-, and 6′-H(B) and 5-H(A)], 6.66—6.34 [m, 6- and 8-H(A)], 5.50 [d, $J_{3,4}$ 3.5 Hz, 4-H(C)], 5.31 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 4.84 [dd, 3-H(C)], 2.22—2.16 (m, 3′-, 4′-, and 7-OAc), and 1.94 (s, 3-OAc).

4β-*Bromopenta*-O-*acetyl*-(−)-*epicatechin* (**12**).—Bromination of penta-*O*-acetyl-(−)-epicatechin (**8**) (500 mg, 1 mmol) for 8 h afforded, after p.l.c. [ethylene dichloride–acetone (9:1)], unchanged starting material (140 mg) and the title compound as an *oil* (260 mg; R_F 0.54); δ[$(CD_3)_2CO$; 80 MHz; 304 K] 7.34—7.00 [m, 2′-, 5′-, and 6′-H(B)], 6.56 [s, 6- and 8-H(A)], 5.75 [d, $J_{2,3}$ 1.0 Hz, 2-H(C)], 5.30 [dd, 3-H(C)], 5.25 [d, $J_{3,4}$ 2.5 Hz, 4-H(C)], 2.34—2.18 (m, 3′-, 4′-, 5-, and 7-OAc), and 1.84 (s, 3-OAc).

General Substitution and Work-up Procedures

A solution of $AgNO_3$ (100 mg/1 ml water) was added to a stirred solution of the brominated flavan-3-ol and the nucleophilic reagent (1:2 mol equiv.) in TFE (10 ml/200 mg brominated flavan-3-ol) at room temperature and under a nitrogen blanket. Saturated aqueous NaCl (10 ml/100 mg $AgNO_3$) was added on completion and the reaction mixture was filtered. Water (200 ml/200 mg brominated flavan-3-ol) was added to the filtrate and the product was extracted with ethyl acetate. Drying and evaporation of the solvent afforded a residue, which was acetylated and chromatographed.

4β-*Acetoxypenta*-O-*acetyl*-(+)-*catechin* (**18**).[31]—A solution of silver nitrate (2 ml) was added to a solution of 4β-bromopenta-*O*-acetyl-(+)-catechin (**9**) (*ca.* 300 mg) in TFE (15 ml) and the mixture was stirred for 24 h at room temperature. Purification by p.l.c. in ethylene dichloride–acetone (9:1) afforded the title compound (**18**) as an oil (77 mg; R_F 0.56); δ($CDCl_3$; 80 MHz; 304 K) 7.25—6.94 [m, 2′-, 5′-, and 6′-H(B)], 6.47 [s, 6- and 8-H(A)], 6.19 [d, $J_{3,4}$ 4.0 Hz, 4-H(C)], 5.29—4.94 [m,† 2- and 3-H(C)], 2.22 (m, 4 × OAc), 2.06 (s, 4-OAc), and 1.81 (s, 3-OAc).

Penta-O-*acetyl*-4β-*ethoxy*-(+)-*catechin* (**20**) *and Penta*-O-*acetyl*-4α-*ethoxy*-(+)-*catechin* (**19**).[31]—A solution of silver nitrate (1 ml) was added to a solution of 4β-bromopenta-*O*-acetyl-(+)-catechin (**9**) (*ca.* 300 mg) in ethanol (20 ml) and the mixture was stirred for 7 h at 50 °C. P.l.c. [ethylene dichloride–acetone (9:1)] afforded the 4β-ethoxy-(+)-catechin derivative (**20**) (15 mg; R_F 0.56) as a white amorphous solid; δ($CDCl_3$; 80 MHz; 304 K) 7.28—6.97 [m, 2′-, 5′-, and 6′-H(B)], 6.47—6.41 [2 × d, 6- and 8-H(A)], 5.25 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 5.00 [dd, 3-H(C)], 4.56 [d, $J_{3,4}$ 3.0 Hz, 4-H(C)], 3.64 (q, OCH_2Me), 2.22 (m, 3′-, 4′-, 5-, and 7-OAc), 1.88 (s, 3-OAc), and 1.19 (t, OCH_2Me); and the 4α-ethoxy-(+)-catechin derivative (**19**) as a white solid (40 mg; R_F 0.52); δ($CDCl_3$; 80 MHz; 304 K) 7.19—6.86 [m, 2′-, 5′-, and 6′-H(B)], 6.53—6.44 [2 × d, 6- and 8-H(A)], 5.44 [dd, 3-H(C)], 5.13 [d, $J_{2,3}$ 5.0 Hz, 2-H(C)], 4.44 [d, $J_{3,4}$ 5.0 Hz, 4-H(C)], 3.28 (q, OCH_2 Me), 2.22 (m, 3′-, 4′-, 5- and 7-OAc), 1.94 (s, 3-OAc), and 0.84 (t, OCH_2Me).

4β-*Acetoxytetra*-O-*acetyl*-(−)-*fisetinidol* (**21**).—A solution of silver nitrate (1 ml) was added to a solution of 4β-bromotetra-*O*-acetyl-(−)-fisetinidol (**11**) (*ca.* 200 mg) in TFE (20 ml) and the mixture was stirred at room temperature for 24 h. P.l.c. [ethylene dichloride–acetone (9:1)] afforded the title compound (**21**)‡ as an oil (77 mg; R_F 0.56); δ($CDCl_3$; 80 MHz; 304 K)

* Identified by comparison of the physical data with those of the peracetate of an authentic sample (T. G. Fourie, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1977, 125).

* Second-order at 80 MHz.

‡ Identified by comparison of physical data with those of the penta-*O*-acetyl derivative of (+)-gleditsin (ref. 27).

7.47—7.13 [m, 2′-, 5′-, and 6′-H(B) and 5-H(A)], 6.81—6.59 [m, 6- and 8-H(A)], 6.16 [d, $J_{3,4}$ 3.5 Hz, 4-H(C)], 5.47—5.13 [m,* 2- and 3-H(C)], 2.25 (m, 3′-, 4′-, and 7-OAc), 2.13 (s, 4-OAc), and 1.88 (s, 3-OAc).

Penta-O-acetyl-(+)-catechin-(4β,2)-tri-O-acetylphloroglucinol (**23**)[32] *and Penta-O-acetyl-(+)-catechin-(4α,2)-tri-O-acetylphloroglucinol* (**22**).[33]—A solution of silver nitrate (1 ml) was added to a solution of 4β-bromopenta-*O*-acetyl-(+)-catechin (**9**) (*ca.* 200 mg) and phloroglucinol (100 mg) in TFE (15 ml) and the mixture was stirred for 4 days at room temperature. P.l.c. [benzene–acetone (9:1)] afforded the 4β-phloroglucinol-(+)-catechin derivative (**23**) as a white solid (12 mg; R_F 0.28); δ($CDCl_3$; 80 MHz; 304 K) 7.21—6.96 [m, 2′-, 5′-, and 6′-H(B)], 6.75 [s, 4- and 6-H(D)], 6.56 [d, 8-H(A)], 6.44 [d, 6-H(A)], 5.25 [m, 2- and 3-H(C)], 4.53 [m, 4-H(C)], 2.22 (m, 5 × OAc), and 1.75, 1.78, and 1.80 (each s, 3 × OAc); and the 4α-phloroglucinol-(+)-catechin derivative (**22**) as a white solid (45 mg; R_F 0.21); δ($CDCl_3$; 80 MHz; 304 K) 7.25—6.97 [m, 2′-, 5′-, and 6′-H(B)], 6.75 [s, 4- and 6-H(D)], 6.53 [d, 8-H(A)], 6.34 [d, 6-H(A)], 5.53 [dd, 3-H(C)], 4.75 [d, $J_{2,3}$ 10.5 Hz, 2-H(C)], 4.47 [d, $J_{3,4}$ 10.5 Hz, 4-H(C)], 2.19 (m, 6 × OAc), and 1.91 (each s, 2 × OAc).

Penta-O-acetyl-(−)-robinetinidol-(4β,2)-tri-O-acetylphloroglucinol (**25**) *and Penta-O-acetyl-(−)-robinetinidol-(4α,2)-tri-O-acetylphloroglucinol* (**24**).—A solution of silver nitrate (1 ml) was added to a solution of 4β-bromopenta-*O*-acetyl-(−)-robinetinidol (**10**) (*ca.* 200 mg) and phloroglucinol (100 mg) in TFE (20 ml) and the mixture was stirred at room temperature for 5 days. P.l.c. [benzene–acetone (9:1)] afforded the 4β-*trifluoroethoxypenta-O-acetyl-(−)-robinetinidol* as an *oil* (13 mg; R_F 0.46) (Found: M^+, 598.1296. $C_{27}H_{25}F_3O_{12}$ requires M^+, 598.1298); δ($CDCl_3$; 80 MHz; 304 K) 7.34—7.06 [m, 2′- and 6′-H(B) and 5-H(A)], 6.85—6.66 [m, 6- and 8-H(A)], 5.38 [d, $J_{2,3}$ 10.0 Hz, 2-H (C)], 5.19 [dd, 3-H(C)], 4.69 [d, $J_{3,4}$ 3.5 Hz, 4-H(C)], 4.00 (m, CH_2CF_3), 2.25 (s, 3′-, 4′-, 5′-, and 7-OAc), and 2.00 (s, 3-OAc); the 4β-phloroglucinol-(−)-robinetinidol derivative (**25**) as a *white solid* (16 mg; R_F 0.31) (Found: C, 59.3; H, 4.6. $C_{37}H_{34}O_{17}$ requires C, 59.2; H, 4.6%); δ($CDCl_3$; 80 MHz; 304 K) 7.12 [s, 2′-, and 6′-H(B)], 6.91 [d, 5-H(A)], 6.88 [s, 4-, and 6-H(D)], 6.68 [d, 8-H(A)], 6.56 [dd, 6-H(A)], 5.46 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 5.32 [dd, 3-H(C)], 4.53 [d, $J_{3,4}$ 5.0 Hz, 4-H(C)], 2.19 (m, 6 × OAc), and 1.88 and 1.75 (each s, 2 × OAc); and the 4α-phloroglucinol-(−)-robinetinidol derivative (**24**) as a *white solid* (60 mg; R_F 0.26) (Found: C, 59.4; H, 4.5%); δ($CDCl_3$; 80 MHz; 304 K) 7.22 [s, 2′- and 6′-H(B)], 6.88 [s, 4- and 6-H(D)], 6.81 [d, 5-H(A)], 6.69 [d, 8-H(A)], 6.53 [dd, 6-H(A)], 5.69 [dd, 3-H(C)], 4.94 [d, $J_{2,3}$ 10.0 Hz, 2-H(C)], 4.56 [d, $J_{3,4}$ 10.0 Hz, 4-H(C)], 2.28 (m, 6 × OAc), and 1.78 and 1.72 (each s, 2 × OAc).

Penta-O-acetyl-(−)-epicatechin-(4β,2)-tri-O-acetylphloroglucinol (**26**).[34]—A solution of silver nitrate (1 ml) was added to a solution of 4β-bromopenta-*O*-acetyl-(−)-epicatechin (**12**) (*ca.* 250 mg) and phloroglucinol (100 mg) in TFE (20 ml) and the mixture was stirred for 4 days at room temperature. P.l.c. [benzene–acetone (9:1)] afforded the 4β-phloroglucinol-(−)-epicatechin derivative (**26**) as a white solid (85 mg; R_F 0.24); δ($CDCl_3$; 80 MHz; 304 K) 7.03—6.91 [m, 2′-, 5′-, and 6′-H(B)], 6.75—6.38 [4 × d, 4- and 6-H(D) and 6- and 8-H(A)], 5.28 [d, $J_{2,3}$ *ca.* 1.25 Hz, 2-H(C)], 4.97 [dd, 3-H(C)], 4.31 [d, $J_{3,4}$ 2.50 Hz, 4-H(C)], 2.22 (m, 5 × OAc), 1.94 (s, 1 × OAc), and 1.80 and 1.83 (each s, 2 × OAc).

* Second-order at 80 MHz.

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