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CONDENSED TANNINS: COMPETING NUCLEOPHILIC CENTRES IN BIOMIMETIC CONDENSATION REACTIONS

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Key Word Index—(4, 6)-(−)-fisetinidol-8-(4-hydroxybenzyl)-(+)-catechins; 4-(3-ethyl-2, 4, 6-trihydroxyphenyl)-3, 3', 4', 7-tetrahydroxyflavans; (4, 3:4, 5)-bi-[(−)-fisetinidol]-ethyl phloroglucinols; condensed tannins; nucleophilicity; steric hindrance.

Abstract—The relative contributions of nucleophilicity and steric hindrance in determining the course of the reaction during the formation of 'angular' triflavanoids are examined by biomimetic-type condensations involving model compounds.

INTRODUCTION

Our synthetic approach to condensed tannin chemistry [1–7] has shown, much in line with the earlier predictions by Creasy and Swain [8], that flavan-3,4-diols as potential 4-carbenium ions and nucleophilic flavan-3-ols jointly initiate a condensation sequence which leads by further elaboration via 'angular' triflavanoids [9] to the higher oligomeric tannins. Thus, under very mild acidic conditions a group of four (4, 6:4, 8)-linked natural triflavanoids were readily synthesized by successive condensation of two units of (+)-mollisacacidin with (+)-catechin as common nucleophile [10].

Considering that individual condensations of the flavan-3,4-diol, (+)-mollisacacidin (**1**), occur with almost equal ease with the 8-position of (+)-catechin (**6**) (but only to a limited extent at the 6-position) and with the 6-position of (−)-fisetinidol (**5**) [6, 7] the apparently regioselective course of its reaction with the biflavanoid comprising these units (e.g. **1** + **2** → **3** + **4**) (Scheme 1) [9] may at first be regarded as surprising. Apart from the relative stability of the reactants, the nucleophilicity and steric hindrance contributed by the flavan-3-ol or biflavanoid are obviously dominant factors regulating the course of the biomimetic-type reaction. These aspects were accordingly examined by setting up a series of competitive reactions under the same conditions.

RESULTS AND DISCUSSION

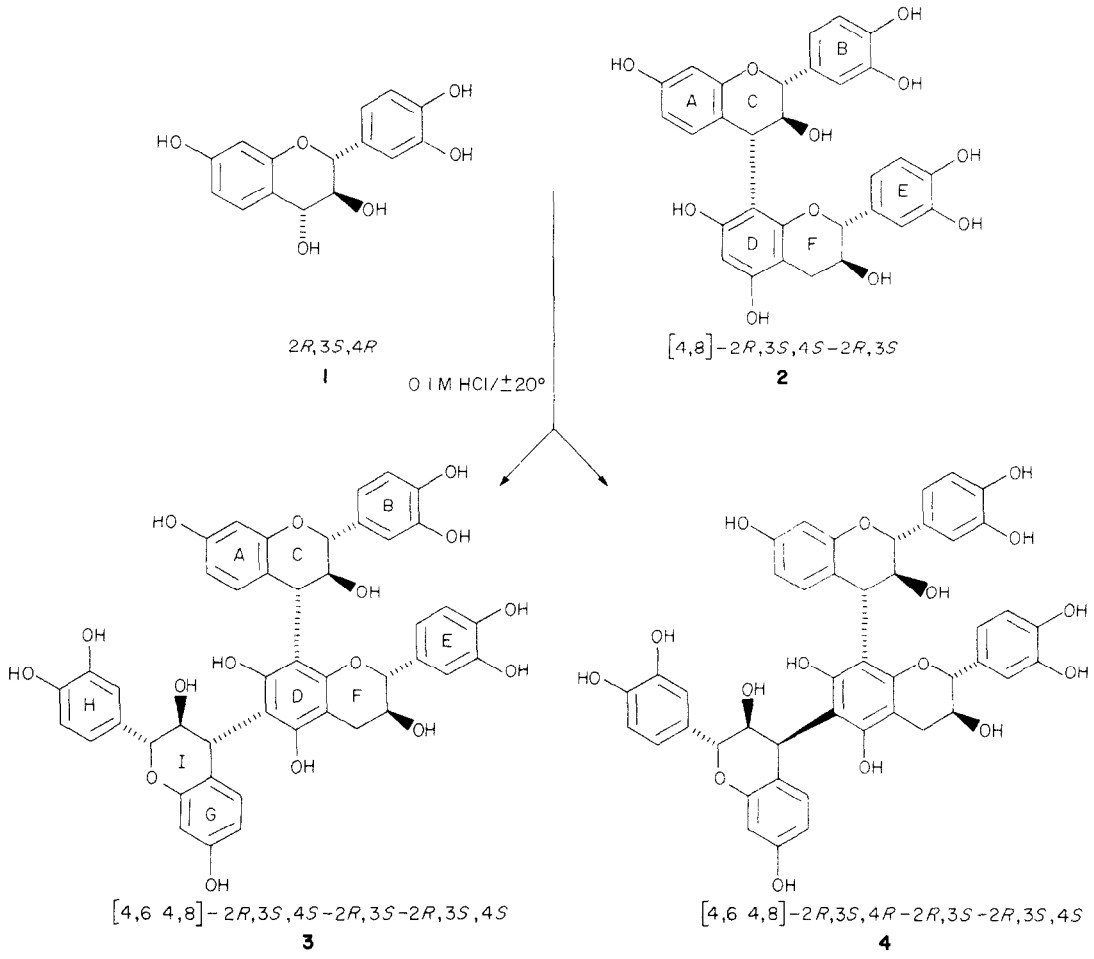
A mixture of **1** (0.002 mol) and excess (0.004 mol) of each of **5** and **6** when treated with 0.1 M hydrochloric acid at ambient temperatures for 2 hr, gave a 50.3% yield of a mixture of (4, 8)-3, 4-*trans*-(4, 8)-3, 4-*cis*- and (4, 6)-3, 4-*trans*-(−)-fisetinidol-(+)-catechins (Scheme 2) (cf. refs [6, 7]), calculated on flavan-3, 4-diol consumed. Unchanged **5** (80.4%)* and **6** (31.6%) were recovered. The inference derived from this result is that given competing conditions, condensation of the flavan-3, 4-diol with **6** at C-8 and also to a limited extent at C-6 occurs to the exclusion of significant substitution of the flavanyl unit at C-6 on **5**.

In order to effect a closer analogy to triflavanoid formation, the same reaction was set up after blocking the 8-position of **6** with a *p*-hydroxybenzyl function. Competitive electrophilic substitution is thus confined to the C-6 nucleophilic centres on **5** and 8-(*p*-hydroxybenzyl)-(+)-catechin (**7**). As before, no evidence was obtained of condensation with **5** (recovery 67.3%* **5** and 29.8% **7**), while the novel biflavanoids (4, 6)-3, 4-*trans*- and (4, 6)-3, 4-*cis*-(−)-fisetinidol-8-(*p*-hydroxybenzyl)-(+)-catechins [(**8**) and (**9**) respectively] result in 25.3 and 18.1% yields respectively (cf. Scheme 2).

In an attempt at another analogy covering steric factors possibly introduced in biflavanoids by the mutual interaction of two bulky flavanyl units in close proximity undergoing 'intermittent' rotation about the interflavanoid bond, the condensation of the flavan-3, 4-diol (**1**) with a synthetic mixture of 2, 3-*trans*-3, 4-*trans*- and 2, 3-*trans*-3, 4-*cis*-4-(3-ethyl-2, 4, 6 - trihydroxyphenyl) - 3, 3', 4', 7 - tetrahydroxyflavans (**11** and **12**, respectively), was examined (Scheme 3). Reaction occurs regiospecifically at the 5-position of the 4-(3-ethyl-2, 4, 6-trihydroxyphenyl) unit as indicated by the formation of a mixture comprising the all-*trans*-(**13a**), 2, 3-*trans*-3, 4-*trans*: 2', 3'-*trans*-3', 4'-*cis*- (**14a**) and 2, 3-*trans*-3, 4-*cis*: 2', 3'-*trans*-3', 4'-*cis*-(4, 3:4, 5)-bi-[(−)-fisetinidol]-ethyl phloroglucinols† (**15a**) in yields of *ca* 1.0, 3.0, 0.02%; a reaction comparable in some respects to the triflavanoid synthesis (**1** + **2** → **3** + **4**).

*Strict control aimed at quantitative recovery was not exercised during these preparative separations.

†These compounds were isolated as nonamethyl ether diacetates (**13b**, **14b** and **15b**) and also in minor proportions as decamethyl ether acetates (**13c**, **14c**) after methylation with diazomethane and acetylation. Their structures and stereochemistry were confirmed by ^{1}H NMR spectroscopy at 170° (**13b** and **14b** giving simple spectra due to molecular symmetry) and by mass spectrometry.



Scheme 1.

The preceding experimental work leaves little doubt as to the dominance of the C-6 position of the (+)-catechin unit of the biflavanoid (**2**) as a reactive nucleophilic centre in triflavanoid synthesis [cf. bromination study on (+)-catechin [4, 5], thus overriding steric factors contributed by di-*ortho*-hydroxylation (at C-5 and C-7) relative to the coupling position. Yields are nevertheless reduced by a factor of ten indicating a considerable degree of overall steric hindrance. The evidence also serves to confirm that angular triflavanoids of types **3** and **4** and their remaining diastereoisomers are likely key intermediates in the further elaboration of condensed tannins to higher oligomeric forms, in a particular molecular environment governed mainly by resorcinol-type flavanoids where (+)-catechin and (+)-gallocatechin and their 3-epimers apparently initiate tannin condensation [11]. Finally, the present synthetic approach also supports the proposed sequential order and mode of condensations which lead to triflavanoids, i.e. nucleophilic phloroglucinol-type catechins + carbocations generated from flavan-3,4-diols → (4, 8)-linked biflavanoids → (4, 6 : 4, 8)-linked triflavanoids. Structurally and stereochemically related compounds in these categories are associated in natural tannin extracts, for example black wattle bark (*Acacia mearnsii*) extract [10, 11] and extracts of the woods of mopane (*Colophospermum mopane*) [9, 12], wattle (*A. mearnsii*) [9, 10], karee (*Rhus lancea*) [13] and quebracho (*Schinopsis* spp.) trees.

EXPERIMENTAL

Mps were determined with a hot-stage apparatus and are uncorr. ^{1}H NMR spectra were recorded at 80 MHz in $CDCl_3$ or DMSO-d_6 with TMS as int. standard. Coupling constants were determined after suitable scale expansion. MS were obtained with a EI instrument, and CD data in MeOH. C and H analyses were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, West Germany. TLC was carried out on DC-Plastikfolin Kieselgel 60 F_{254} (0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40 : 1) after development. Prep. TLC plates [20 × 20 cm, Kieselgel PF_{254} (1 mm)] were air-dried and used without prior activation. Methylations were performed with excess CH_2N_2, while acetylations were in Ac_2O–pyridine. Evapns were done under red. pres. at 50° in a rotary evaporator.

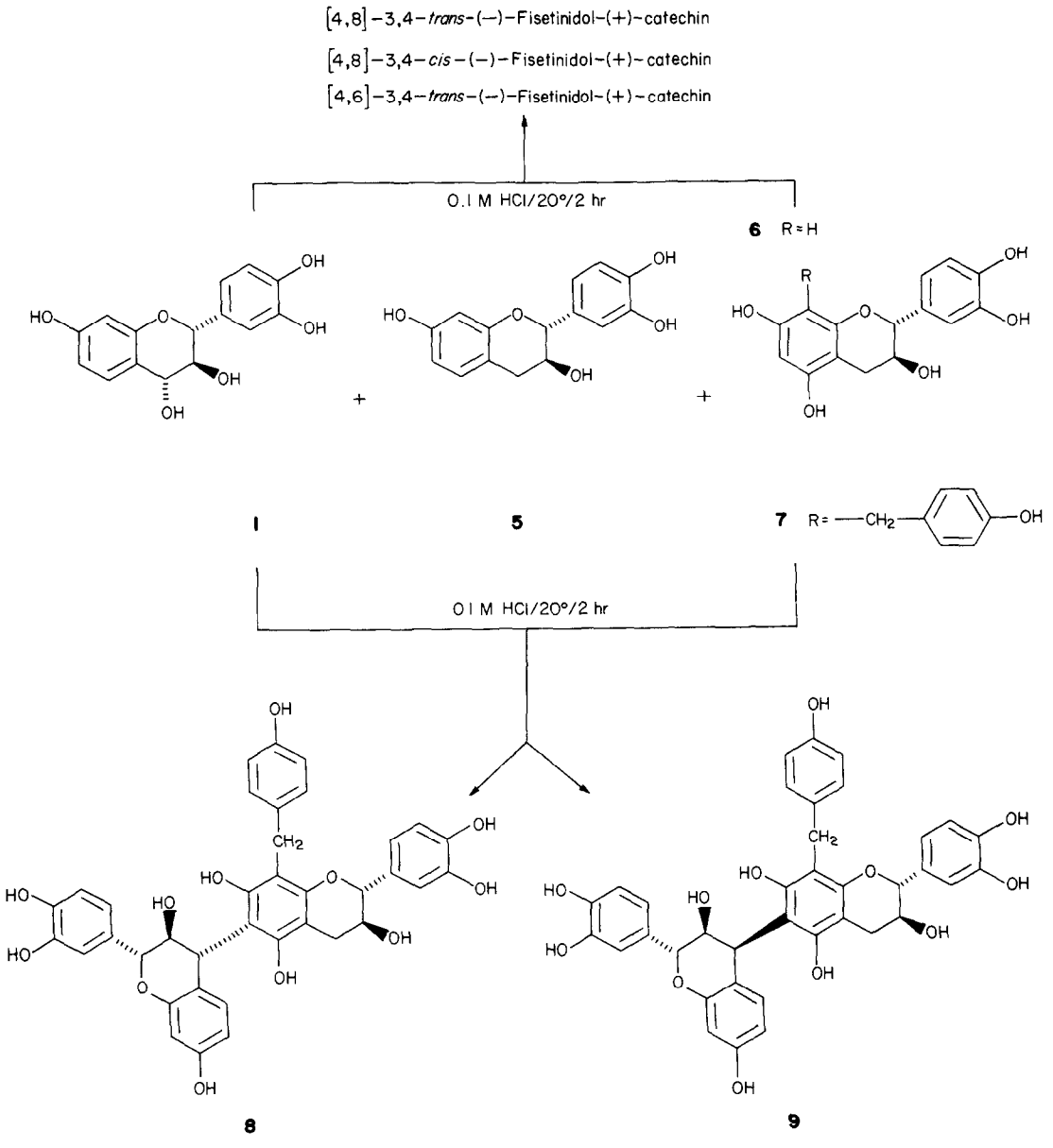
General condensation and work-up procedures. The (+)-3′, 4′, 7-trihydroxyflavan-3, 4-diol [(+)-mollisacacidin (**1**)], and each of the flavan-3-ols (**5**, **6** or **7**) and 4-arylflavan-3-ols (**11**, **12**) were dissolved in 0.1 M HCl (50 ml) and stirred at room temp. for *ca* 24 hr. The soln was extracted with EtOAc (4 × 150 ml) and the combined

extracts dried (Na_2SO_4) after treatment with a minimum of bicarbonate soln. Evaporation of the solvent to low vol. (10 ml) followed by prep. TLC afforded the condensed product.

Condensations with competing nucleophilic centres. (i) *Condensation of (+)-leucofisetinidin with a mixture of phloroglucinol- and resorcinol-type flavan-3-ols.* A soln of **1** (580 mg, 0.002 mol), **6** (1.16 g, 0.004 mol) and **5** (1.096 g, 0.004 mol) in 0.1 M HCl (250 ml) was stirred for 2 hr at room temp. The reaction soln was extracted with EtOAc (4 × 100 ml), and the extract vol. reduced to 10 ml after drying. Prep. TLC on 40 plates (C_6H_6–Me_2CO–MeOH, 6:3:1) gave four bands at R_F 0.45, 0.39, 0.27 and 0.21. The R_F 0.45 fraction consisted exclusively of **5** (881 mg, 80.4% recovery) and that at R_F 0.39 similarly contained **6** (367 mg, 31.6% recovery).

The R_F 0.27 (285 mg) and 0.21 (280 mg) fractions were both methylated; the former yielded two products at R_F 0.31 and 0.24 on prep. TLC separation in C_6H_6–Me_2CO (8:2). After acetylation these compounds were shown to consist of the heptamethyl ether diacetates of the all-*trans*-(4,6)-(8 mg) and 2,3-*trans*,3,4-*cis*:2′,3′-*trans*-(4,8)-(−)-fisetinidol-(+)-catechins (73 mg) [6, 7]. The R_F 0.21 fraction after acetylation and purification by prep. TLC. [20 plates, C_6H_6–Me_2CO (9:1)] gave the all-*trans*-(4,8)-(−)-fisetinidol-(+)-catechin (106 mg, R_F 0.26) [4]. The 2*R*, 3*S*, 4*S*:2*R*, 3*S* and 2*R*, 3*S*, 4*R*:2*R*, 3*S* configurations of the all-*trans*- and 3,4-*cis*-biflavanoids respectively, are confirmed by CD [6, 7].

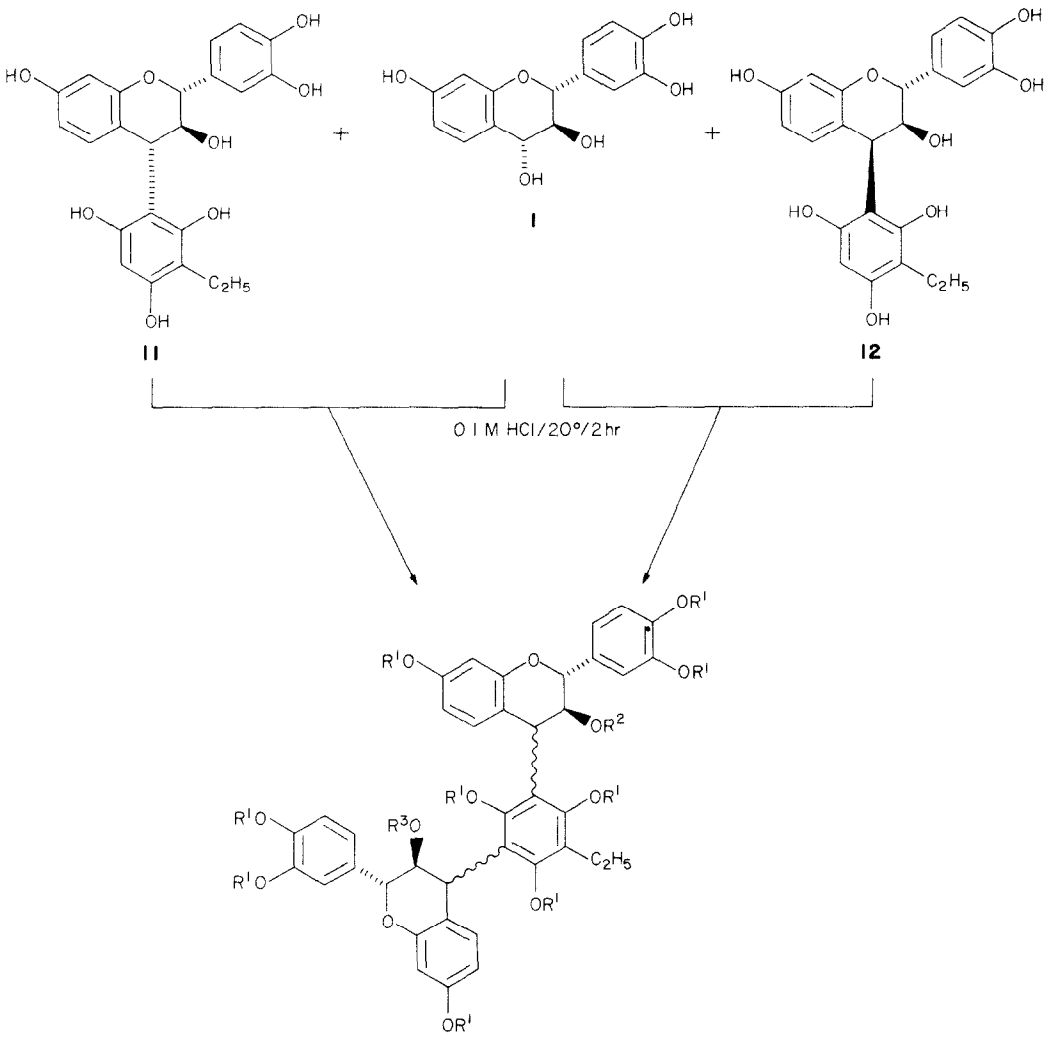
(ii) *Condensation of (+)-leucofisetinidin with resorcinol- and 8-substituted phloroglucinol-type flavan-3-ols.* (2R, 3S)-8-(4-*hydroxybenzyl*)-(+)-*catechin.* A soln of



Scheme 2.

p-hydroxybenzyl alcohol (620 mg, 0.005 mol) prepared by $NaBH_4$ reduction of *p*-hydroxybenzaldehyde, and crystallized from H_2O, mp 124–125° and **6** (5.8 g, 0.020 mol) in 0.1 M HCl (200 ml) was stirred for 15 min at room temp. The 8-substituted product had a mobility very similar to that of **6** on TLC but was observed at slightly lower R_F after three successive developments in C_6H_6–Me_2CO–MeOH (7:2:1). Excess H_2O was added and the soln extracted with EtOAc (4 × 200 ml). Removal of the solvent and re-soln in H_2O permitted selective crystallization of the (+)-catechin. The mother liquor was taken to dryness under vacuum, while adding EtOH to form an azeotrope. Prep. TLC sepn in C_6H_6–Me_2CO–MeOH as above, employing not more than 20 mg/plate gave a single product, R_F 0.32, after two developments, brown-black with HCHO–H_2SO_4 spray. The product gave a yellow colour with bis-diazotized benzidine spray on PC, compared with the brick red of (+)-catechin.

(2R, 3S)-2, 3-Trans-3-*acetoxy*-8-(4-*methoxybenzyl*)-3', 4', 5, 7-*tetramethoxyflavan*. Methylation of the free phenol (150 mg) followed by prep. TLC in C_6H_6–Me_2CO (9:1) gave the 8-(*p*-hydroxybenzyl)-(+)-catechin pentamethyl ether as a white solid (95 mg). Acetylation gave the monoacetate from EtOH as fine colourless needles, mp 135° (Found: C, 68.3; H, 6.1. $C_{29}H_{32}O_8$ requires C, 68.5; H, 6.3%.) ^{1}H NMR δ ($CDCl_3$) 7.03 [*d*, J = 8 Hz, H −2 +6(D)], 6.63 −6.78 (*m*, H −2' +5' +6'), 6.58 [*d*, H −3 +5(D)], 6.03 (*s*, H −6), 5.17 (*m*, H −3), 4.92 (*d*, J = 7 Hz, H −2), 3.81 (*br d*, 8-CH_2), 3.75, 3.73, 3.70, 3.63 (×2) (*s*, 5 × OMe), 2.90 (*dd*, J = 5, 16 Hz, H-4*eq*), 2.59 (*dd*, J = 7, 16 Hz, H-4*ax*), 1.88 (*s*, 3-COMe); in C_6D_6 the 8-CH_2 resonance is displayed as an



13 2,3-*trans*-3,4-*trans*:2',3'-*trans*-2',3'-*trans*

14 2,3-*trans*-3,4-*trans*:2',3'-*trans*-3',4'-*cis*

15 2,3-*trans*-3,4-*cis*:2',3'-*trans*-3',4'-*cis*

a $R^1 = R^2 = R^3 = H$

b R^1 = Me, $R^2 = R^3$ = Ac

c $R^1 = R^2$ = Me, R^3 = Ac

Scheme 3.

AB-system (δ 4.08, 4.28, J = 13.75 Hz); *m/z* 508 $[M]^+$, (14.8), 448(100), 417(14.2), 328(31), 297(85), 286(7.2), 285(34.6), 222(7.0), 180(98), 179(53), 151(50), 107(7.9).

1, (435 mg, 0.0015 mol), **5** (617 mg, 0.0022 mol) and **7** (840 mg, 0.0022 mol) were mutually dissolved in 0.1 M HCl (200 ml) and the soln stirred for 2 hr at room temp. The soln was extracted, the extract vol. reduced to 10 ml and the products separated by prep. TLC (30 plates; C_6H_6–Me_2CO–MeOH, 6:3:1) into three fractions, R_F 0.46 (415 mg), 0.33 (250 mg) and 0.24 (496 mg).

Fraction R_F 0.46 comprised only **5** (415 mg, *ca* 0.0015 mol), representing a 67.3% recovery. The R_F 0.33 fraction consists of unchanged **7** (250 mg, 0.00063 mol), a 29.8% recovery. The R_F 0.24 fraction was methylated to give a single fraction R_F 0.35 (240 mg), following prep. TLC (40 plates; C_6H_6–Me_2CO, 4:1). The fraction appeared to be homogeneous (TLC) in a variety of solvent systems, but was shown to be a mixture of two compounds by ^{1}H NMR. The mixture was accordingly acetylated and resolution effected by the following prep. TLC method (40 plates). The chromatograms were developed ×3 in hexane–C_6H_6–Me_2CO (4:5:1) and placed overnight in a refrigerator (1°) Two subsequent developments in CH_2Cl_2–Me_2CO (19:1) gave two fractions, R_F 0.58 and 0.51.

(2R, 3S)-2, 3-Trans-3-*acetoxy*-6-[(2R, 3S, 4S)-2, 3-trans-3, 4-trans-3-*acetoxy*-3′, 4′, 7-*trimethoxyflavan*-4-*yl*]-8-(4-*methoxybenzyl*)-3′, 4′, 5, 7-*tetramethoxyflavan* (**8b**). The all-*trans* isomer, R_F 0.51, was obtained as a non-crystalline colourless solid (49 mg) (Found: C, 67.8; H, 6.0. $C_{49}H_{52}O_{14}$ requires C, 68.0; H, 6.1%.) ^{1}H NMR δ (DMSO, 80 MHz, 170°) 6.91 [*d*, J = 8 Hz, H − 5(D)], 6.89 [*d*, J = 8 Hz, H − 2 + 6(G)], 6.78–6.67 [*m*, H − 2′ + 6′(G)], 6.67 [*d*, J = 8 Hz, H − 5′ (B or E)], 6.58 [*d*, J = 8 Hz, H − 3 + 5(G)], 6.37 [*d*, J = 2 Hz, H − 8(D)], 6.33 [*dd*, J = 2, 8 Hz, H − 6(D)], 5.81 [*t*, ΣJ = 19 Hz, H − 3(F)], 5.0 [*m*, H − 3(C)], 4.86 [*d*, J = 9.5 Hz, H − 2(F)], 4.84 [*d*, J = 7 Hz, H − 2(C)], 4.67 [*dd*, J = 1, 9.5 Hz, H − 4(F)], 3.81 (*br s*, 8-CH_2), 3.71 (×2), 3.69, 3.64, 3.61, 3.59, 3.41 (*br*), 3.34 (*br*) (*s*, 8 × OMe), 3.03 [*dd*, J = 16, 5 Hz, H-4*eq*(C)], 2.75 [*dd*, J = 16, 7.5 Hz, H − 4*ax*(C)], 1.81 [*s*, 3-COMe(C)], 1.53 [*s*, 3-COMe(F)].

(2R, 3S)-2, 3-Trans-3-*acetoxy*-6[(2R, 3S, 4R)-2, 3-trans-3, 4-cis-3-acetoxy-3′, 4′, 7-*trimethoxyflavan*-4-*yl*]-8-(4-*methoxybenzyl*)-3′, 4′, 5, 7-*tetramethoxyflavan* (**9b**). The R_F 0.58 fraction gave the 3, 4-*cis* isomer only (35 mg) as fine colourless needles from EtOH, mp 178–180° (Found: C, 68.1; H, 6.2. $C_{49}H_{52}O_{14}$ requires C, 68.0; H, 6.1%.) ^{1}H NMR δ (DMSO, 80 MHz, 170°) 6.93 [*d*, J = 8 Hz, H − 2 + 6(G)], 6.58 [*d*, J = 8 Hz, H − 3 + 5(G)], 6.47 − 6.88 (*m*, 7 × arom. H), 6.39 [*d*, J = 2 Hz, H − 8(D)], 6.34 [*dd*, J = 8, 2 Hz, H − 6(D)], 5.37 [*dd*, J = 6.25, 8.75 Hz, H − 3(F)], 5.16 [*d*, J = 8.75 Hz, H − 2(F)], 5.06 [*m*, J = 6 Hz, H − 2(C)], 5.0 [*d*, J = 6 Hz, H − 2(C)], 4.73 [*d*, J = 6.25 Hz, H − 4(F)], 3.83 (*br s*, 8-CH_2), 3.69, 3.67 (×2), 3.66, 3.62, 3.53, 3.25 (*br*), 3.21 (*br*) (*s*, 8 × OMe), 2.98 [*dd*, J = 16, 5 Hz, H − 4*eq*(C)], 2.75 [*dd*, J = 16, 8 Hz, H − 4*ax*(C)], 1.86 [*s*, 3-COMe(C)], 1.47 [*s*, 3-COMe(F)].

(iii) *Condensation of* (+)-*leucofisetinidin with* (2R, 3S)-2, 3-trans-4-(3-*ethyl*-2, 4, 6-*trihydroxyphenyl*)-3, 3′, 4′, 7-*tetrahydroxyflavans* (**11, 12**). A soln of **1** (967 mg, 0.0033 mol) and ethyl phloroglucinol (2.05 g, 0.0133 mol); ^{1}H NMR δ [$(CD_3)_2CO$, 41°] 5.49–7.80 (*br s*, 3 × OH), 5.87 (*s*, H − 3 + 5), 2.55 (*q*, J = 7 Hz, CH_2), 1.03 (*t*, J = 7 Hz, Me) was stirred for 45 min. Ethyl phloroglucinol was prepared by refluxing phloracetophenone (5 g) with borane–dimethylamine complex (5.5 g, Aldrich) in dry THF (250 ml) for 24 hr acidifying with 6 N H_2SO_4 (100 ml) and stirring for 30 min. extraction with EtOAc (3 × 100 ml) and washing the extract with H_2O (4 × 100 ml) in 0.1 M HCl. The resultant soln was extracted with EtOAc and the extractives subjected to prep. TLC (40 plates; C_6H_6–Me_2CO–MeOH, 6:3:1) to give a single fraction (R_F 0.52, 838 mg, 58% yield, purple with HCHO–H_2SO_4 spray). Methylation of the R_F 0.52 product (200 mg) followed by prep. TLC (C_6H_6–Me_2CO, 9:1) gave two products, R_F 0.46 and 0.40.

(2R, 3S, 4S)-2, 3-Trans-3, 4-trans-3-*acetoxy*-4-(3-*ethyl*-2, 4, 6-*trimethoxyphenyl*)-3′, 4′, 7-*trimethoxyflavan* (**11b**). The R_F 0.40 fraction gave the hexamethyl ether as a white solid (98 mg), which when acetylated yielded the all-*trans* monoacetate as a non-crystalline colourless solid (96 mg) (Found: C, 67.2; H, 6.5. $C_{31}H_{36}O_9$ requires C, 67.4; H, 6.6%.) ^{1}H NMR δ ($CDCl_3$, 110°) 6.95 [*d*, J = 2 Hz, H − 2(B)], 6.94 [*dd*, J = 2, 8 Hz, H − 6(B)], 6.74 [*d*, J = 8 Hz, H − 5(B)], 6.55 [*d*, J = 8 Hz, H − 5(A)], 6.39 [*d*, J = 2 Hz, H − 8(A)], 6.26 [*dd*, J = 2, 8 Hz, H − 6(A)], 6.16 [*s*, H − 5(D)], 5.91 (*t*, ΣJ_s = 19 Hz, H − 3), 4.83 (*d*, $J_{2,3}$ = 9.5 Hz, H − 2), 4.68 (*br d*, $J_{3,4}$ = 9.5 Hz, H − 4), 3.81, 3.78, 3.72, 3.66, 3.59 (*br*), 3.53 (*s*, 6 × OMe), 2.59 (*q*, J = 7 Hz, CH_2), 1.54 (*s*, 3-COMe), 1.13 (*t*, J = 7 Hz, Me); MS *m/z* 552 $[M]^+$, (13.4), 492 $[M-60]^+$, (100); CD (*c* 0.0512) $[\theta]_{290}$ 0, $[\theta]_{283}$ − 920, $[\theta]_{279}$ 0, $[\theta]_{270}$ 2700, $[\theta]_{254}$ 0, $[\theta]_{235}$ − 43000, $[\theta]_{218}$ − 13000, $[\theta]_{214}$ 25300, $[\theta]_{207}$ 3800, $[\theta]_{200}$ − 16200.

(2R, 3S, 4R)-2, 3-Trans-3, 4-cis-3-*acetoxy*-4-(3-*ethyl*-2, 4, 6-*trimethoxyphenyl*)-3′, 4′, 7-*trimethoxyflavan* (**12b**). The R_F 0.46 fraction gave the hexamethyl ether as a non-crystalline colourless solid (34 mg), which on acetylation yielded the *trans–cis* monoacetate as a non-crystalline colourless solid (34 mg) (Found: C, 67.1; H, 6.4. $C_{31}H_{36}O_9$ requires C, 67.4; H, 6.6%.) ^{1}H NMR δ (DMSO, 170°) 6.45 [*d*, J = 2 Hz, H − 8(A)], 6.26 [*dd*, J = 2, 8 Hz, H − 6(A)], 6.18 [*s*, H − 5(D)], 5.43 [*dd*, ΣJ_s = 14.5 Hz, H − 3], 5.26 [*d*, $J_{2,3}$ = 8.2 Hz, H − 2], 4.77 [*d*, $J_{3,4}$ = 6.4 Hz, H − 4], 3.69 (×2), 3.67, 3.50, 3.28 (*br*), 2.85 (*br*) (*s*, 6 × OMe), 2.60 (*q*, J = 7 Hz, CH_2), 1.57 (*s*, 3-COMe), 1.13 (*t*, J = 7 Hz, Me); ^{1}H NMR δ ($CDCl_3$, 120°) 6.19 [*s*, H − 5(D)]; MS *m/z* 522 $[M]^+$ (70), 492 $[M-60]^+$ (84); CD (*c* 0.0600) $[\theta]_{340}$ 0, $[\theta]_{278}$ − 920, $[\theta]_{250}$ − 690, $[\theta]_{237}$ − 6200, $[\theta]_{225}$ − 8300, $[\theta]_{222}$ − 10500, $[\theta]_{217}$ − 3700, $[\theta]_{213}$ − 1600, $[\theta]_{200}$ 0. (**1**) (1 g) was accordingly condensed with the 3:1 mixture of the free phenolic all-*trans*- and 2, 3-*trans*-3, 4-*cis*-4-(3-ethylphloroglucinol)-(−)-fisetinidols (**11, 12**; 1.89 g, R_F 0.52) in 0.1 M HCl (100 ml) for 4 hr at room temp. with stirring. Extraction by the usual procedure followed by prep. TLC (C_6H_6–Me_2CO–MeOH, 6:3:1) yielded two products, R_F 0.45 (252 mg) and 0.38 (800 mg).

Methylation of the R_F 0.45 fraction (252 mg) for 18 hr followed by prep. TLC [C_6H_6–Me_2CO, 9:1, (×2)] provided two products, R_F 0.40 (53 mg) and 0.46 (18 mg). Acetylation of these methyl ethers gave the 2, 3-*trans*-3, 4-*trans*- and 2, 3-*trans*-3, 4-*cis*-3-acetoxy-4-(3-ethyl-2, 4, 6-trimethoxyphenyl)-3′, 4′, 7-trimethoxyflavans (**11b, 12b**), respectively, representing derivatives of unchanged starting material.

Methylation of the R_F 0.38 fraction (800 mg) followed by prep. TLC (C_6H_6–Me_2CO, 9:1) gave four products at R_F 0.18 (76 mg), 0.25 (201 mg), 0.39 (43 mg) and 0.43 (56 mg).

(2R, 3S, 4S:2′R, 3′S, 4′S)-*All*-trans-3, 5-*bis*(3-*acetoxy*-3′, 4′, 7-*trimethoxyflavan*-4-*yl*)-2, 4, 6-*tri*-O-*methylethylphloroglucinol* (**13b**). Acetylation of the R_F 0.18 fraction followed by prep. TLC (CH_2Cl_2–Me_2CO, 19:1) gave the diacetate as a colourless solid (R_F 0.24, 31.2 mg) (Found: C, 67.3; H, 6.3. $C_{51}H_{56}O_{15}$ requires C, 67.4; H, 6.2%.) ^{1}H NMR δ (DMSO, 170°) 6.94–6.75 (*m*, 2 × H − 2′, H − 5′, H − 6′), 6.44 (*d*, J = 8 Hz, 2 × H − 5), 6.3 (*d*, J = 2 Hz, 2 × H − 8), 6.23 (*dd*, J = 8, 2 Hz, 2 × H − 6), 5.72 (*t*, ΣJ_s = 18.8 Hz, 2 × H − 3), 4.81 (*d*, $J_{2,3}$ = 9.4 Hz, 2 × H − 2), 4.63 (*d*, $J_{3,4}$ =

9.4 Hz, 2 × H − 4), 3.66 (*s*), 3.58 (*s*), 3.38 (*br s*), 3.25 (*br*) (*s*, 9 × OMe), 1.53 (*s*, 2 × COMe), 1.03 (*t*, Me); CD (*c* 0.0476) $[\theta]_{297}$ 0, $[\theta]_{285}$ − 3800, $[\theta]_{278}$ 0, $[\theta]_{266}$ 7600, $[\theta]_{251}$ 0, $[\theta]_{232}$ − 91000, $[\theta]_{218}$ − 36000, $[\theta]_{214}$ − 64000, $[\theta]_{200}$ 0.

(2R, 3S, 4S:2'R, 3'S, 4'R)-2, 3-Trans-3, 4-trans:2', 3'-trans-3', 4'-cis-3, 5-*bis*(3-*acetoxy*-3', 4', 7-*trimethoxyflavan*-4-*yl*)-2, 4, 6-*tri*-O-*methylethylphloroglucinol* (**14b**). Acetylation of the R_F 0.25 fraction (201 mg) followed by prep. TLC (CH_2Cl_2–Me_2CO, 19:1) gave two products (R_F 0.24 and 0.41), the latter as a non-crystalline colourless solid (137.3 mg) (Found: C, 67.2; H, 6.1. $C_{51}H_{56}O_{15}$ requires C, 67.4; H, 6.2%.) ^{1}H NMR δ (DMSO, 170°) 6.94–6.14 (*m*, 12 × arom. H), 5.92 [*t*, ΣJ_s = 18.7 Hz, H − 3(C)], 5.35 [*dd*, ΣJ_s = 14.6 Hz, H − 3(G)], 5.2 [*d*, $J_{2,3}$ = 8 Hz, H − 2(G)], 4.78 [*d*, *J* = 9.4 Hz, H − 2(C)], 4.72 [*br d*, *J* = 6.1 Hz, H − 4(G)], 4.63 [*d*, *J* = 9.4 Hz, H − 4(C)], 3.66(×2), 3.63, 3.61, 3.59, 3.58, 3.31, 3.28 (*br*), 2.97 (*br*) (*s*, 9 × OMe), 2.56 (*q*, *J* = 7 Hz, CH_2), 1.51, 1.49 (*s*, 2 × COMe), 1.10 (*t*, Me); CD (*c* 0.0544) $[\theta]_{286}$ 0, $[\theta]_{270}$ 10400, $[\theta]_{252}$ 5000, $[\theta]_{243}$ 13000, $[\theta]_{236}$ 4000, $[\theta]_{226}$ 27000, $[\theta]_{216}$ 0, $[\theta]_{212}$ 10000, $[\theta]_{207}$ 0, $[\theta]_{200}$ − 19200.

(2R, 3S, 4R:2'R, 3'S, 4'R)-3, 5-*bis*-(2, 3-*trans*-3, 4-*cis*-3-*acetoxy*-3', 4', 7-*trimethoxyflavan*-4-*yl*)-2, 4, 6-*tri*-O-*methylethylphloroglucinol* (**15b**). The acetate, R_F 0.24, obtained by acetylation of the R_F 0.25 methyl ether was isolated as a colourless solid (12 mg) (Found: C, 67.3; H, 6.2. $C_{51}H_{56}O_{15}$ requires C, 67.4; H, 6.2%.) ^{1}H NMR δ (DMSO, 170°) 7.09–6.26 (*m*, 12 × arom. H), 5.42 (*dd*, ΣJ_s = 14.7 Hz, H − 3), 5.24 (*d*, $J_{2,3}$ = 8.3 Hz, H − 2), 4.77 (*br d*, $J_{3,4}$ = 6.4 Hz, H − 4), 3.69(×2), 3.62(×2), 3.63(×2), 3.28(×2), 2.84 (*s*, 9 × OMe), 2.48 (*q*, *J* = 7 Hz, CH_2), 1.57 (*s*, 2 × COMe), 1.14 (*t*, Me); CD (*c* 0.0592) $[\theta]_{245}$ 0, $[\theta]_{231}$ 3100, $[\theta]_{223}$ 0, $[\theta]_{215}$ 21000, $[\theta]_{214}$ 3800, $[\theta]_{212}$ 18000, $[\theta]_{208}$ 0, $[\theta]_{200}$ − 17000.

(2R, 3S, 4S:2'R, 3'S, 4'S)-*All*-trans-3-(3-*acetoxy*-3', 4', 7-*trimethoxyflavan*-4-*yl*)-5-(3, 3', 4', 7-*tetramethoxyflavan*-4-*yl*)-2, 4, 6-*tri*-O-*methylethylphloroglucinol* (**13c**). Acetylation of the R_F 0.39 methyl ether (43 mg) followed by prep. TLC (C_6H_6–Me_2CO, 9:1) gave a single product, R_F 0.46, as a colourless solid (17.6 mg) (Found: C, 68.3; H, 6.4. $C_{50}H_{56}O_{14}$ requires C, 68.2; H, 6.4%.) ^{1}H NMR δ (DMSO, 170°) 7.00–6.09 (*m*, 12 × arom. H), 5.69 [*t*, ΣJ = 18.2 Hz, H − 3(G)], 4.83 [*d*, *J* = 9.2 Hz, H − 2(G)], 4.63 [*br d*, *J* = 9.2 Hz, H − 4(G)], 4.59 [*d*, *J* = 8.25 Hz, H − 2(C)], 4.46 [*br d*, *J* = 8.25 Hz, H − 4(C)], 4.08 [*t*, ΣJ = 18 Hz, H − 3(C)], 3.69(×2), 3.66(×2), 3.59, 3.58, 3.36 (*br*), 3.28 (*br* × 2) (*s*, 9 × OMe), 2.60 (*s*, 3-OMe), 1.50 (*s*, 3-COMe), 1.06 (*t*, *J* = 7 Hz, Me); CD (*c* 0.0588) $[\theta]_{295}$0, $[\theta]_{285}$ − 3000, $[\theta]_{279}$ 0, $[\theta]_{267}$ 7500, $[\theta]_{251}$ 0, $[\theta]_{231}$ − 88000, $[\theta]_{220}$ − 44000, $[\theta]_{216}$ − 67000, $[\theta]_{200}$ − 3000.

(2R, 3S, 4R:2'R, 3'S, 4'S)-3-(2, 3-Trans-3, 4-cis-3-*acetoxy*-3', 4', 7-*trimethoxyflavan*-4-*yl*)-5-(2', 3'-trans-3', 4'-trans-3, 3', 4', 7-*tetramethoxyflavan*-4-*yl*)-2, 4, 6-*tri*-O-*methylethylphloroglucinol* (**14c**). Acetylation of the R_F 0.43 methyl ether gave a single product (R_F 0.51) as a colourless solid (11.1 mg) (Found: C, 68.1; H, 6.3. $C_{50}H_{56}O_{14}$ requires C, 68.2; H, 6.4%.) ^{1}H NMR δ (DMSO, 170°) 6.96–6.03 (*m*, 12 × arom. H), 5.31 [*dd*, ΣJ_s = 14.5 Hz, H − 3(G)], 5.17 [*d*, $J_{2,3}$ = 8.5 Hz, H − 2(G)], 4.72 [*br d*, $J_{3,4}$ = 6 Hz, H − 4(G)], 4.55 [*d*, $J_{2,3}$ = 8.75 Hz, H − 2(C)], 4.43 [*br d*, $J_{3,4}$ = 8.75 Hz, H − 4(C)], 4.19 [*t*, ΣJ_s = 17.5 Hz, H − 4(C)], 3.63(×2), 3.59, 3.56(×2), 3.52, 3.23 (*br*), 3.19 (*br*), 2.95 (*br*) (*s*, 9 × OMe), 2.59 (*s*, 3-OMe), 2.52 (*q*, *J* = 7 Hz, CH_2), 1.45 (*s*, 3-COMe), 1.06 (*t*, *J* = 7 Hz, Me); CD (*c* 0.0468) $[\theta]_{290}$ 0, $[\theta]_{270}$ 9400, $[\theta]_{253}$ 5200, $[\theta]_{242}$ 13000, $[\theta]_{223}$ 19700, $[\theta]_{216}$ 0, $[\theta]_{212}$ 56400, $[\theta]_{200}$ 0.

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