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Spectroscopic Properties of Free Phenolic 4-Arylflavan-3-ols as Models for Natural Condensed Tannins

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A unique range of free phenolic 4-arylflavan-3-ols consisting of four sets (3′,4′,5,7-tetrahydroxyflavan-3-ol or its 5-deoxy analogue coupled to phloroglucinol or resorcinol), each composed of three diastereomers (2,3-*trans*-3,4-*trans*, 2,3-*trans*-3,4-*cis* and 2,3-*cis*-3,4-*trans*) were synthesized to assess their spectroscopic properties. ^{1}H and ^{13}C NMR and circular dichroism data are related to selected structural and stereochemical features with a view to modelling natural phenolic oligoflavanoids.

KEY WORDS 4-Arylflavan-3-ols ^{1}H NMR ^{13}C NMR Circular dichroism Condensed tannins

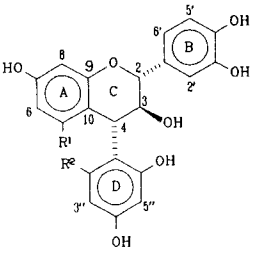
INTRODUCTION

The global abundance of condensed tannins in plants has been responsible for interest in their chemical utilization. The successful biological or industrial application of these polymeric proanthocyanidins, however, depends on an understanding of their composition, configuration and conformational behaviour, including rotation about the interflavanyl bonds and prefered conformers of the pyran rings. Owing to the ramification of such polymers, essential features of the dynamic behaviour of the heterocycles are reliant on projections from features of monomers and oligomers, which have hitherto mainly been restricted to derivatives of examples, but with limited structural variety.[1–5]

We have consequently synthesized a unique range of model 4-arylflavan-3-ols (**1–12**) for appraisal of selected structural and conformational[1] qualities by ^{1}H and ^{13}C NMR. The availability of these underivatized compounds offers the first opportunity of assessing their spectroscopic properties with a view to using the data for modelling of the natural phenolic oligoflavanoids. Four sets, each composed of three diastereomers (2,3-*trans*-3,4-*trans*, 2,3-*trans*-3,4-*cis* and 2,3-*cis*-3,4-*trans*), distinctive of natural products, represent all structural variations of procyanidins and profisetinidins most commonly encountered in nature.

RESULTS AND DISCUSSION

The well established procedure[6,7] of the stereoselective acid-catalysed condensation of (+)-mollisacacidin [(2*R*,3*S*,4*R*)-3′,4′,7-trihydroxyflavan-3,4-diol] as incipient electrophile with phloroglucinol at ambient temperatures (20–25 °C) gave (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-(**1**) and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-arylflavan-3-ols (**5**) in a *ca.* 3:1 ratio in good yield (94% overall). Contrary to our initial protocol,[7] however, the products were not derivatized but separated and purified as free phenols, using Sephadex LH-20 in EtOH as chromatographic substrate. Corresponding reaction with resorcinol as nucleophile afforded the analogous (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*- (**2**) and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-diastereomers (**6**) as sole products (51% overall yield). (+)-Leucocyanidin [(2*R*,3*S*,4*R*)-3′,4′,5,7-tetrahydroxyflavan-3,4-diol], obtained by *in situ* reduction of (+)-taxifolin



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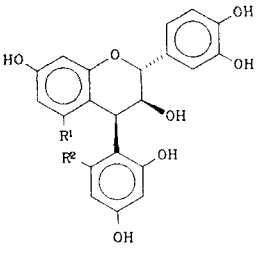
3 R^1=R^2=OH
4 R^1=OH, R^2=H



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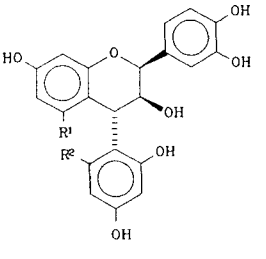

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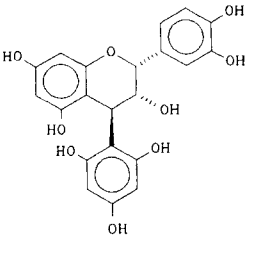

12

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[(2*R*,3*R*)-3′,4′,5,7-tetrahydroxydihydroflavonol] with sodium borohydride,[7] similarly gave the 2,3-*trans*-3,4-*trans*- (**3**) and 2,3-*trans*-3,4-*cis*-analogues (**7**) with phloroglucinol (9 and 3% yield, respectively), but only the 3,4-*trans*-analogue (**4**) (6% yield) with resorcinol. The low yields obtained for resorcinol are evidently the result of its lower nucleophilicity compared with that of phloroglucinol, hence resulting in the 4-arylflavan-3-ol (**4**) competing with resorcinol as nucleophile to give a high proportion of 'polymeric' material. As a consequence, the (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-isomer (**8**) was prepared by treatment of (−)-fisetinidol-(4α,2)-phloroglucinol (**1**) with mild base at 50 °C to induce a highly stereoselective pyran rearrangement,[8,9] involving the phloroglucinol D-ring functionality with simultaneous liberation of the resorcinol-type A-ring.

Separate application of the same approach[8,9] to (−)-fisetinidol-(4β,2)-phloroglucinol (**5**) and (−)-fisetinidol-(4β,4)-resorcinol (**6**), respectively, afforded (+)-*ent*-epicatechin-(4α,4)-resorcinol (**9**) and its 5-deoxy analogue (**10**) (5 and 3% yields, respectively). The higher nucleophilicity of phloroglucinol versus that of resorcinol favours liberation of the latter[8] (where applicable) during rearrangement and thus renders the method inappropriate for the preparation of (+)-epifisetinidol-(4α,2)-phloroglucinol (**11**). This compound was therefore obtained (2% yield) by C-2 epimerization[10] of the 2,3-*trans*-3,4-*trans*-diastereomer (**1**), acquired from the condensation outlined above. Its 5-oxy counterpart (**12**) was conveniently available (4% yield) *via* mild acid-catalysed degradation of purified tannin polymer[11] (from Loblolly pine) with phloroglucinol as nucleophilic trap. The 4-arylflavan-3-ol (**12**)[12] and several analogues[13] have also been encountered as natural products.

^{1}H NMR spectra (Table 1) of compounds with a resorcinol-type A-ring (**1**, **2**, **5**, **6**, **10** and **11**) display the expected ABX spin system. Where this feature is accompanied by a 4-(2,4-dihydroxyphenyl) substituent (**2**, **6** and **10**), a second similar ABX system occurs which may be distinguished from that of the A-ring by spin decoupling and dipolar association of H-6(D) with H-3(C) and/or H-2(C) (see Table 3). In cases where the D-ring emanates from phloroglucinol (**1**, **5** and **11**), the second ABX system is replaced by a well shielded AA′ or AB system (δ5.86–6.00, $J \approx 2.5$ Hz), usually broadened by intermediate rotation on the NMR time-scale about the C-4(C)—C-1(D) bond. The nature of the AA′ spin system displayed by **5** was confirmed by its transformation into an AB system at −40 °C.

A well defined AB system (δ 5.88–6.41, $J = 2.0$–2.5 Hz) is produced by compounds with a phloroglucinol-type A-ring and is accompanied by either an ABX system (**4**, **8** and **9**) or a second broadened AA′/AB system (**3**, **7** and **12**), as mentioned above, depending on the hydroxylation pattern (2,4- or 2,4,6-) of the D-ring. All products display comparable deshielded ABC systems for the pyrocatechol B-rings (δ 6.57–6.95, $J = 8.0$–8.5 and 2.0–2.5 Hz) which are differentiated from the related spin systems of the A- (and D)-rings by spin decoupling (see below).

Heterocyclic protons typically resonate as two doublets [δ 4.36–5.30, $J = 10.0$–1.2 Hz, H-2(C) (the letter in parentheses denotes the corresponding ring) and δ 4.26–4.74, $J = 10.0$–2.0 Hz, H-4(C)] with mutual coupling to the doublet of doublets [δ 3.91–4.57, H-3(C)]. Unambiguous differentiation between the doublets [H-2(C) and H-4(C)] is accomplished by association *via* HETCOR experiments of these protons respectively with C-2(C) and C-4(C) in the ^{13}C NMR spectra (Table 2), which reveal distinctive deshielding of the oxygenated C-2(C) (δ 84.16–74.71) relative to C-4(C) (δ 43.95–31.39). This facilitates confirmation of the linkage of the pyrocatechol unit to C-2(C) by benzylic spin decoupling with H-2(C) as reference signal, hence ruling out possible confusion with B- and D-ring interchanged artifacts which might develop during pyran rearrangement[8] of 2,3-*trans*-3,4-*cis*-substrates. All structures (**1**–**12**) were confirmed by the mass spectra, which typically display retro-Diels–Alder fragmentation and loss of the 4-aryl moiety.

The relative configuration of products prepared by acid-catalysed condensation of a flavan-3,4-diol with an appropriate nucleophile is governed by attack from either the α- or β-face of the C-4 carbocation,[7] to yield the 2,3-*trans*-3,4-*trans* (**1**–**4**) or 2,3-*trans*-3,4-*cis* epimers (**5**–**7**) only. All-*trans* products (**1**–**4**) display 'normal' ^3J(HH) for the heterocyclic protons [$^3J(2,3) = 9.0$–9.5 and $^3J(3,4) = 8.0$–10.0 Hz], in contrast to smaller ^3J(HH) values observed for some permethyl ether acetates.[8] The second-order spectrum, resulting from coincidental equivalence of the heterocyclic protons observed for **1**, was simplified to a typical ABC system at −40 °C, while severe broadening of H-3(C) and H-4(C) displayed by **2**, reminiscent of slow rotation about the C-4(C)—C-1(D) bond at 300 MHz, virtually disappeared at 80 MHz. This phenomenon is explicable on the basis that the same rotation rate leads to more facile coalescence at 80 MHz due to smaller chemical shift differences. All-*trans* isomers are hence unambiguously distinguished from the *trans*–*cis* analogues (**6**–**8**) [$^3J(2,3) = 6.5$–10.0 and $^3J(3,4) = 4.5$–5.5 Hz], including **8**, obtained as the sole product from an anticipated stereoselective rearrangement of the all-*trans* isomer (**1**).[8,9] Atypical ^3J(HH) magnitudes displayed by the 2,3-*trans*-3,4-*cis* analogue (**5**) [$^3J(2,3) = 3.0$ and $^3J(3,4) = 3.0$ Hz] are in agreement with values currently observed by us for analogous free phenolic 5-deoxy (A-ring) proanthocyanidins and are presumably explicable in terms of dominating proportions of A as opposed to E conformers[1] in solution. These phenomena will be dealt with in a subsequent paper.

Allowing for notable contributions by A- as opposed to E-conformers for the pyran heterocycle,[1] NOE associations in *trans*–*cis*-epimers (Table 3) between both H-2(C) and H-6(D) (**6** and **8**) and between H-4(C) and H-2(B) and/or -6(B) (**5**–**8**) unambiguously establish the 2,4-*trans* arrangement of the B- and D-rings. Such NOE associations are conspicuously absent for all-*trans*-epimers (**1**–**4**) with a 2,4-*cis* arrangement of substituent rings.

Cis–*trans* compounds (**9** and **10**), also with a 2,4-*trans* arrangement of substituent rings, derived from pyran rearrangement of *trans*–*cis*-isomers, are differentiated from possible by-products (2,3-*cis*-3,4-*cis* and 2,3-*trans*-3,4-*trans*, both 2,4-*cis* isomers)[8] by NOE associations similar to those displayed by 2,3-*trans*-3,4-*cis*-isomers, which are not possible for 2,4-*cis* configurations. The

same observations apply to *cis–trans*-isomers (**11** and **12**) prepared by C-2 epimerization and the degradation of tannin polymer, respectively. These products (**9–12**), however, display conspicuously smaller 2,3-coupling constants [$^3J(2,3) = 1.0–2.5$ and $^3J(3,4) = 2.0–5.0$ Hz] than those of the *trans–cis* analogues (**5–8**). The relatively large ^3J(HH) observed for **11** [$^3J(2,3) = 2.5$ and $^3J(3,4) = 5.0$ Hz] are, similarly to **5**, probably reminiscent of unexpected E/A proportions.

Since the 4-aryl substituent in compounds **1–12** is attached directly to the C-4 stereocentre, its orientation (α or β) with respect to the plane of the C-ring and therefore the absolute configuration at C-4 is confirmed by circular dichroism (CD) data[7,10,14] *via* the aromatic quadrant rule.[15] The low-wavelength (220–240 nm) negative Cotton effect consistently exhibited by the all-*trans* isomers (**1–4**) is thus in agreement with an α-location of the D-ring, but its persistence contrasts with the unpredictable behaviour of the Cotton effects observed for the permethyl ether acetates.[8] The C-4 epimers (**5–8**) and also the *cis–trans* analogue (**12**) show similar but positive Cotton effects, reflecting a β-orientation of the D-ring. The remaining *cis–trans*-isomers (**9–11**) possess, by virtue of their method of synthesis, a quasi-enantiomeric relationship with **12** and display negative Cotton effects compatible with α-orientated D-rings. The sharply reduced amplitudes of the Cotton effects observed for **4**, **9** and **10** are attrib-

Table 1. ^{1}H NMR chemical shifts (δ in acetone-d_6 + 5% D_2O), coupling constants (Hz) and multiplicities

Ring	Proton	2,3-*trans*-3,4-*trans*-4-Arylflavan-3-ols (**1–4**)			
		1	**3**	**2**	**4**
C	H-2	4.57 (m)[a]	4.36 (d, 9.5)	4.61 (d, 9.0)	4.40 (d, 9.5)
	H-3	4.57 (m)[a]	4.50 (dd, 9.5, 8.0)	4.04 (br s)	3.91 (dd, 9.5, 8.0)
	H-4	4.57 (m)[a]	4.41 (d, 8.0)	4.37 (br s)	4.28 (d, 8.0)
A	H-5	6.54 (d, 8.5)	—	6.52 (d, 8.0)	—
	H-6	6.22 (dd, 8.5, 2.5)	5.85 (s)[c]	6.24–6.30 (m)[c]	5.94 (d, 2.5)[d]
	H-8	6.20 (d, 2.5)	5.85 (s)[c]	6.24–6.30 (m)[c]	5.98 (d, 2.5)[d]
B	H-2	6.95 (d, 2.0)	6.95 (d, 2.0)	6.95 (d, 2.0)	6.88 (d, 2.0)
	H-5	6.77 (d, 8.0)	6.76 (d, 8.0)	6.77 (d, 8.0)	6.76 (d, 8.0)
	H-6	6.80 (dd, 8.0, 2.0)	6.80 (dd, 8.0, 2.0)	6.81 (dd, 8.0, 2.0)	6.72 (dd, 8.0, 2.0)
D	H-3	6.00 (d, 3.0)[d]	6.00 (br d, 2.5)[d]	6.39 (d, 2.5)	6.34 (d, 2.5)
	H-5	5.86 (d, 3.0)[d]	5.89 (br d, 2.5)[d]	6.24–6.30 (m)[c]	6.19 (dd, 8.0, 2.5)
	H-6	—	—	6.24–6.30 (m)[c]	6.54 (d, 8.0)
		2,3-*trans*-3,4-*cis*-4-Arylflavan-3-ols (**5–8**)			
		5	**7**	**6**	**8**
C	H-2	5.30 (d, 3.0)	5.02 (d, 7.0)	4.88 (d, 6.5)	4.51 (d, 10.0)
	H-3	4.30 (dd, 3.0, 3.0)	4.19 (dd, 7.0, 5.0)	4.29 (dd, 6.5, 4.5)	4.20 (dd, 10.0, 5.5)
	H-4	4.61 (d, 3.0)	4.68 (d, 5.0)	4.26 (d, 4.5)	4.74 (d, 5.5)
A	H-5	6.42 (d, 8.5)	—	6.57 (d, 8.0)	—
	H-6	6.22 (dd, 8.5, 2.5)	5.87 (d, 2.5)[d]	6.32 (dd, 8.0, 2.5)	5.88 (d, 2.0)[d]
	H-8	6.40 (d, 2.5)	5.92 (d, 2.5)[d]	6.36 (d, 2.5)	5.89 (d, 2.0)[d]
B	H-2	6.77 (d, 2.0)	6.81 (d, 2.5)	6.79 (d, 2.0)	6.79 (d, 2.0)
	H-5	6.74 (d, 8.0)	6.73 (d, 8.5)	6.75 (d, 8.5)	6.72 (d, 8.5)
	H-6	6.60 (dd, 8.0, 2.0)	6.63 (dd, 8.5, 2.5)	6.61 (dd, 8.5, 2.0)	6.60 (dd, 8.5, 2.0)
D	H-3	5.89 (br d, 2.5)[c,e]	5.92 (s)[c]	6.36 (d, 2.5)	6.38 (d, 2.5)
	H-5	5.89 (br d, 2.5)[c,e]	5.92 (s)[c]	6.26 (dd, 8.5, 2.5)	6.25 (dd, 8.5, 2.5)
	H-6	—	—	6.61 (d, 8.5)	6.46 (d, 8.5)
		2,3-*cis*-3,4-*trans*-4-Arylflavan-3-ols (**9–12**)			
		11	**12**	**10**	**9**
C	H-2	5.29 (d, 2.5)	5.00 (br d, 1.5)	4.76 (br d, 1.2)	4.69 (br d, 1.2)
	H-3	4.32 (dd, 5.0, 2.5)	3.93 (dd, 2.0, 1.5)	4.04 (br dd, 2.5, 1.2)	4.03 (br dd, 2.0, 1.2)
	H-4	4.38 (d, 5.0)	4.50 (d, 2.0)	4.34 (br d, 2.5)	4.46 (br d, 2.0)
A	H-5	6.64 (d, 8.5)	—	6.72 (d, 8.5)	—
	H-6	6.26 (dd, 8.5, 2.5)	5.96 (d, 2.5)[d]	6.41 (m)[c]	5.97 (d, 2.5)[d]
	H-8	6.32 (d, 2.5)	5.99 (d, 2.5)[d]	6.41 (m)[c]	6.01 (d, 2.5)[d]
B	H-2	6.95 (d, 2.0)	6.96 (d, 2.0)	6.92 (d, 2.0)	6.90 (d, 2.0)
	H-5	6.72 (d, 8.0)	6.74 (d, 8.5)	6.73 (d, 8.0)	6.71 (d, 8.5)
	H-6	6.68 (dd, 8.0, 2.0)	6.65 (dd, 8.5, 2.0)	6.60 (dd, 8.0, 2.0)	6.57 (dd, 8.5, 2.0)
D	H-3	5.92 (br s)[c]	5.88 (br s)[c]	6.44 (d, 2.5)	6.41 (d, 2.5)
	H-5	5.92 (br s)[c]	5.88 (br s)[c]	6.23 (dd, 8.0, 2.5)	6.19 (dd, 8.5, 2.5)
	H-6	—	—	6.38 (d, 8.0)	6.45 (d, 8.5)

[a] H-2(C) [δ 4.58 (d, 9.5 Hz)], H-3(C) [δ 4.67 (dd, 9.5, 9.5 Hz)] and H-4(C) [δ 4.55 (d, 9.5 Hz)] at −40 °C.
[b] 80 MHz ^{1}H NMR yields H-3(C) and H-4(C) as well defined signals (dd, 9.0, 10.0 and d, 10.0 Hz, respectively).
[c] Chemical equivalent protons.
[d] Allocations may be interchanged.
[e] H-3(D) [δ 5.80 (d, 2.5 Hz)] and H-5(D) [δ 5.92 (d, 2.5 Hz)] determined at −40 °C.

Table 2. ^{13}C NMR chemical shifts (δ relative to TMS) for 4-arylflavan-3-ols (1–12)

Ring	Carbon	1	3	2	4	5	7	6	8	11	12	10	9
C	2	84.16	83.16	83.15	81.18	81.59	79.13	79.01	77.36	78.18	76.89	75.20	74.71
	3	70.22	72.19	74.17	77.36	72.79	72.42	72.19	73.23	71.95	72.41	71.59	70.66
	4	41.37	37.32	43.95	40.65	31.39	31.61	40.54	36.87	39.05	36.85	43.72	39.17
A	5	129.31	[a]	130.66	[a]	129.54	[a]	130.89	[a]	130.61	[a]	132.61	[a]
	6[b]	108.66	96.60	109.01	95.03	108.35	95.79	108.97	94.62	108.77	95.71	109.61	94.90
	7	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
	8[b]	102.92	95.57	102.91	96.64	102.80	95.04	102.73	96.28	103.17	96.20	103.31	96.21
	9	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
	10	118.47	105.62	117.21	103.94	113.73	101.53	114.43	103.06	116.13	100.42	113.66	101.07
B	1	132.23	131.19	131.14	130.12	132.79	131.79	131.64	131.23	132.03	132.25	132.03	131.94
	2	115.71	115.45	115.41	114.70	112.88	114.54	114.43	115.65	115.14	115.05	115.15	115.01
	3[c]	145.42	144.89	145.38	144.92	145.62	145.16	145.45	145.73	145.10	145.22	145.34	145.16
	4[c]	145.18	144.56	145.04	144.59	144.92	144.96	145.33	145.34	144.69	145.05	145.16	144.13
	5	115.27	115.31	115.17	114.70	115.93	115.44	115.61	115.45	115.28	115.36	115.49	115.35
	6	120.45	119.96	120.31	119.44	117.08	116.95	118.88	120.69	119.26	119.02	119.14	118.83
D	1	106.75	106.47	120.92	121.91	105.04	104.41	119.34	120.31	107.53	106.71	122.70	121.89
	2	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
	3[d]	95.09	94.69	103.49	103.07	96.25	96.27	104.20	104.74	95.98	96.20	103.15	103.05
	4	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
	5[d]	96.24	96.19	107.59	107.08	96.25	96.27	107.44	107.59	95.98	96.20	107.22	106.62
	6	[a]	[a]	130.66	127.74	[a]	[a]	133.26	132.03	[a]	[a]	132.07	130.73

[a] C—O— for A- and D-rings, δ 159–155.
[b] Chemical shifts for C-6 and C-8 in phloroglucinol-type rings may be interchanged.
[c] Chemical shifts for C-3 and C-4 may be interchanged.
[d] Chemical shifts for C-3 and C-5 in phloroglucinol-type rings may be interchanged.

uted to the proximity of the D-ring to the nodal planes of the quadrants,[15] resulting from conformational ramifications. Contrary to perceptions so far, honoured also by referees on occasion, we find that rigid application of the Cahn–Ingold–Prelog sequence rules[16] to the C-4(C) stereocentre of free phenolic 4-arylflavan-3-ols always yield a 4*R* configuration for an α-orientation of the D-ring and *vice versa*, irrespective of the resorcinol or phloroglucinol nature of either the A- or D-ring. This results from C-9(A)—O-1(C)—C-2(C) taking precedence

Table 3. ^1H NMR NOE effects (%) for 4-arylflavan-3-ols

2,3-*trans*-3,4-*trans*-4-Arylflavan-3-ols (**1**–**4**)

		1			3			2			4		
		C			C			C			C		
Ring	Proton	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4
A	H-5									3.2			
B	H-2				[a]			6.7			6.3	3.4	
	H-6				[a]			3.4			2.0	0.6	
D	H-6									0.5		2.7	5.5

2,3-*trans*-3,4-*cis*-4-Arylflavan-3-ols (**5**–**8**)

		5			7			6			8		
		C			C			C			C		
Ring	Proton	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4
A	H-5			6.3						4.9			
B	H-2	5.4	3.5	1.8	7.9		1.8	3.1	3.7	1.2	10.4	3.1	
	H-6	4.2	2.3	1.6	5.7		4.5	2.4	2.6	0.9	2.7	0.6	
D	H-6							1.9	1.6	3.6	6.9		8.2

2,3-*cis*-3,4-*trans*-4-Arylflavan-3-ols (**9**–**12**)

		11			12			10			9		
		C			C			C			C		
Ring	Proton	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4	H-2	H-3	H-4
A	H-5			10.1						5.5			
B	H-2	7.2		1.0	5.9		0.8	6.3			5.6		
	H-6	3.4		3.6	3.3			5.6			5.2		
D	H-6							2.9		0.6	4.3		4.6

[a] H-2(B) and H-6(B) overlap; NOE with H-2(C) not quantifiable.

over C-2(D)—OH and would also hold true for *O*-methyl ether derivatives, but not for acetylated derivatives.

^{13}C allocations are based on extensive HETCOR correlations with well defined proton spectra and previously established analogies.[17–20] Hence, resonances of the heterocyclic carbons of all products display a distinctive succession with C-3(C) (δ 70.66–77.36) constantly shielded by $\Delta\delta$ 13.94–3.61, relative to C-2(C) (δ 84.16–74.71) and C-4(C) expectedly occurring at higher field (δ 31.39–43.95), irrespective of the hydroxylation pattern of the A- and D-rings or stereochemistry involved. Of particular interest for stereochemical assignments, however, is the apparent dependence of the chemical shift of C-2(C) on the relative configuration of the pyran moiety. Thus, C-2(C) for compounds with a 2,3-*trans*-3,4-*trans* configuration resonate at lower field by $\Delta\delta$ 2.57–4.82 than 2,3-*trans*-3,4-*cis*-isomers, which in turn are less shielded by $\Delta\delta$ 2.65–3.41 than 2,3-*cis*-3,4-*trans*-isomers. The phenomena are consistent with the shielding of C-2(C) by a γ-*gauche* effect,[20–22] resulting from the presence of a quasi-axial (for *trans–cis*) as opposed to a quasi-equatorial (for all-*trans*) aryl group at C-4(C). Increased shielding of C-2(C) in the *cis–trans*- in comparison with the *trans–cis*-isomers is attributed to additive β-shielding by the quasi-axial 3(C)-OH in the former as opposed to its quasi-equatorial orientation in the latter. These observations are in line with previous reports of diagnostic chemical shift differences of C-2(C) for 2,3-*trans*- and 2,3-*cis*-procyanidins.[17] Progressive shielding of C-2(C) between sets of diastereomers with differing hydroxylation patterns [catechin-(4,4)-resorcinol > fisetinidol-(4,4)-resorcinol > catechin-(4,2)-phloroglucinol > fisetinidol-(4,2)-phloroglucinol] (Fig. 1) is inconsistent with expected inductive effects[21,22] and more probably associated with conformational behaviour of the pyran ring.[1]

The chemical shift of C-4(C), on the contrary, is conspicuously dominated by the π-inductive effect,[21,22] with phloroglucinol-type A- and/or D-rings contributing to greater shielding than resorcinol types which possess reduced electron-donating properties (Fig. 2). Specific sets of diastereomers, however, display consistent shielding of *trans–cis*- relative to all-*trans*-isomers but unexpected deshielding of *cis–trans*-isomers. While shielding may be attributed to an α-effect[21,22] (4-aryl quasi-axial for *trans–cis*- and quasi-equatorial for all-*trans*-isomers), the deshielding is not fully understood but constant for *cis–trans* analogues.

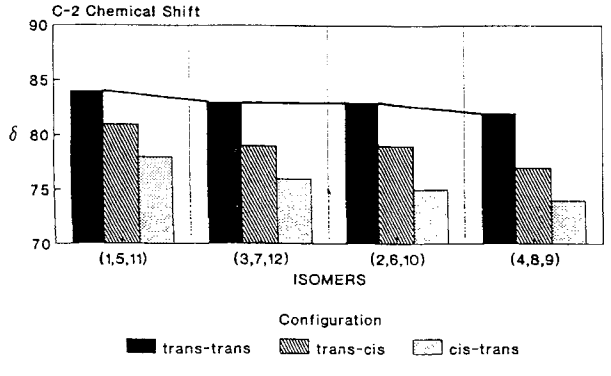

Figure 1. ^{13}C chemical shifts of C-2 for isomers **1–12**.

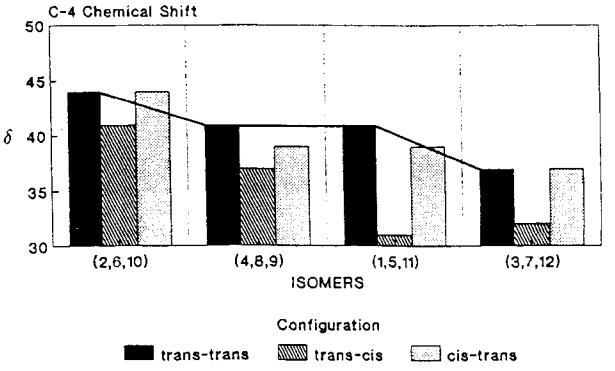

Figure 2. ^{13}C chemical shifts of C-4 for isomers **1–12**.

^{13}C NMR data for model 4-arylflavan-3-ols thus exhibit distinctive features which are autonomously dependent on specific structural, configurational and possibly conformational qualities of the molecule and are available for extrapolation to higher levels of condensation, albeit with the necessary caution.

EXPERIMENTAL

Spectra and separation of compounds

Unless indicated otherwise, ^{13}C and ^{1}H NMR spectra were recorded on a Bruker AM300 spectrometer (75 and 300 MHz PFT, respectively) at 23 °C. Solutions were in $(CD_3)_2CO$–D_2O (95:5) at *ca.* 10 mg ml^{-1} for ^{1}H and 60 mg ml^{-1} for ^{13}C with chemical shifts (δ_H and δ_C) referenced to tetramethylsilane. Standard pulse sequences were used for ^{1}H–^{13}C correlation experiments (HETCOR)[22] with parameters adjusted for $^{1}J(C,H) = 160$ Hz. 1D NOE difference experiments were used for the ^{1}H spectra (NOE). Mass spectra (MS) were obtained with a Kratos MS80 instrument *via* electron impact ionization and circular dichroism (CD) data, in MeOH at indicated concentrations (*c*) and 21 °C, on a Jasco J-710 spectropolarimeter. Sephadex LH-20 was used as stationary phase for separations by column chromatography (CC) on columns of various sizes, at differing flow-rates and in different solvent systems (to be specified). Separations were monitored by thin-layer chromatography (TLC) performed on pre-coated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm), sprayed with H_2SO_4–CH_2O (40:1, v/v) after development. Solutions were evaporated under reduced pressure at *ca.* 60 °C in a rotary evaporator or freeze-dried with a Virtis Freezemobile 12SL.

Syntheses

Acid-catalysed condensation of phloroglucinol with (2*R*,3*S*,4*R*)-3′,4′,7-trihydroxyflavan-3,4-diol [(+)-mollisacacidin][6,7]. (+)-Mollisacacidin (1.55 g, 0.0053 M) was added in portions to a solution of phloroglucinol (4.20 g, 0.0259 M) in 0.1 M HCl (350 ml) over a period of 20 min and stirred at 20–25 °C for 27 h. The mixture was diluted with H_2O (350 ml), extracted with EtOAc (5 × 200 ml), dried (Na_2SO_4) and the solvent evaporated to yield a brown solid (5.4 g). Application of CC (135 × 5 cm i.d. column, EtOH as eluent, flow-rate 1.3 ml min^{-1}) gave

two compounds, **1** and **5** [retention time (t_R) 108.5 and 85.0 h, respectively].

(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (1). Brown amorphous solid (1.47 g, 69.8%). Found, [M$^+$] *m/z* 398.1002; $C_{21}H_{18}O_8$ requires 398.1002. ^{1}H NMR, see Table 1. ^{1}H NMR [$(CD_3)_2CO$, −40 °C], δ_H 6.92 [1H, d, J = 2.0 Hz, H-2(B)], 6.78 [1H, dd, J = 8.0, 2.0 Hz, H-6(B)], 6.75 [1H, d, J = 8.0 Hz, H-5(B)], 6.55 [1H, d, J = 8.5 Hz, H-5(A)], 6.22 [1H, dd, J = 8.5, 2.5 Hz, H-6(A)], 6.18 [1H, d, J = 2.5 Hz, H-8(A)], 6.00 [1H, d, J = 3.0 Hz, H-3(D)], 5.86 [1H, d, J = 3.0 Hz, H-5(D)], 4.58 [1H, d, J = 9.5 Hz, H-2(C)], 4.67 [1H, ddd, J = 9.5, 9.5, 5.0 Hz, H-3(C)], 4.55 [1H, d, J = 9.5 Hz, H-4(C)], 4.14 [1H, d, J = 5.0 Hz, 3(C)-OH]. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 398 [M]$^+$ (0.1), 380 [M − H_2O]$^+$ (1.7), 258 (6.9), 229 (8.7), 152 (2.5), 126 (32), 123 (12), 110 (100). CD (*c* 0.2261 mM), $[\theta]_{298}$ 0, $[\theta]_{283}$ −4491, $[\theta]_{280}$ 0, $[\theta]_{272}$ 8556, $[\theta]_{250}$ 0, $[\theta]_{237}$ −22980, $[\theta]_{219}$ 0.

(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (5). Brown amorphous solid (505 mg, 24.5%). Found, [M$^+$] *m/z* 398.1003; $C_{21}H_{18}O_8$ requires 398.1002. ^{1}H NMR, see Table 1. ^{1}H NMR [$(CD_3)_2CO$–D_2O (95:5), −40 °C], δ_H 6.73 [1H, d, J = 8.5 Hz, H-5(B)], 6.71 [1H, d, J = 2.0 Hz, H-2(B)], 6.53 [1H, dd, J = 8.0, 2.0 Hz, H-6(B)], 6.37 [1H, d, J = 2.5 Hz, H-8(A)], 6.27 [1H, d, J = 8.5 Hz, H-5(A)], 6.21 [1H, dd, J = 8.5, 2.5 Hz, H-6(A)], 5.93 [1H, d, J = 2.5 Hz, H-5(D)], 5.80 [1H, d, J = 2.5 Hz, H-3(D)], 5.28 [1H, d, J = 3.0 Hz, H-2(C)], 4.54 [1H, dd, J = 3.0, 3.0 Hz, H-3(C)], 4.33 [1H, d, J = 3.0 Hz, H-4(C)]; ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 398 [M]$^+$ (0.5), 380 [M − H_2O]$^+$ (2.2), 258 (6.8), 229 (24), 152 (14), 126 (81), 123 (57), 110 (100). CD (*c* 0.2764 mM), $[\theta]_{310}$ 0, $[\theta]_{290}$ −7242, $[\theta]_{282}$ −1056, $[\theta]_{272}$ −5981, $[\theta]_{248}$ O, $[\theta]_{237}$ 12950, $[\theta]_{221}$ 0.

Acid-catalysed condensation of resorcinol with (+)-mollisacacidin.[6,7] (+)-Mollisacacidin (1.50 g, 0.0052 M) was added in portions to a solution of resorcinol (2.84 g, 0.0258 M) in 0.1 M HCl (350 ml) during a period of 10 min and stirred at 20–25 °C for 43 h. Extraction according to the procedure above followed by CC (150 × 5 cm i.d. column, EtOH as eluent, flow-rate 2.1 ml min^{-1}) gave two compounds, **2** and **6** (t_R 46.6 and 40.6 h, respectively).

(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-(2,4-Dihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (2). Brown amorphous solid (705 mg, 35.5%). Found, [M$^+$] *m/z* 382.1053; $C_{21}H_{18}O_7$ requires 382.1053. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 382 [M]$^+$ (0.5), 231 (11), 213 (38), 152 (21), 123 (100), 122 (19), 110 (96). CD (*c* 0.2879 mM), $[\theta]_{305}$ 0, $[\theta]_{290}$ −2032, $[\theta]_{283}$ 0, $[\theta]_{276}$ 3787, $[\theta]_{248}$ O, $[\theta]_{237}$ −11390, $[\theta]_{219}$ 0.

(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4-Dihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (6). Brown amorphous solid (310 mg, 15.6%). Found, [M$^+$] *m/z* 382.1051; $C_{21}H_{18}O_7$ requires 382.1053. ^{1}H NMR, see Table 1. ^{1}H NMR NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 382 [M]$^+$ (0.3), 231 (6.5), 213 (35), 152 (6.4), 123 (42), 122 (4.2), 110 (100). CD (*c* 0.3403 mM), $[\theta]_{310}$ 0, $[\theta]_{294}$ −1499, $[\theta]_{287}$ 0, $[\theta]_{274}$ −4707, $[\theta]_{254}$ 0, $[\theta]_{238}$ 22400, $[\theta]_{221}$ 0.

Acid-catalysed condensation of phloroglucinol with (2*R*,3*S*,4*R*)-3′,4′,5,7-tetrahydroxyflavan-3,4-diol [(+)-leucocyanidin].[7] (2*R*,3*R*)-3′,4′,5,7-Tetrahydroxydihydroflavonol [(+)-taxifolin] (500 mg, 0.0036 M) in EtOH (200 ml) was treated with $NaBH_4$ (500 mg) for 1 h. A solution of phloroglucinol (3.50 g, 0.0270 M) in 0.1 M HCl (200 ml) was added and the mixture stirred at 20–25 °C for 30 min. Dilution with H_2O (1.0 l) followed by extraction with EtOAc (4 × 50 ml), drying (Na_2SO_4) and evaporation of the solvent produced an amorphous solid (3.70 g), which gave two compounds, **3** and **7** (t_R 66.0 and 56.8 h, respectively), on separation by CC (150 × 5 cm i.d. column, EtOH as eluent, flow-rate 2.0 ml min^{-1}).

(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (3). Brown amorphous solid (267 mg, 17.7%). Found, [M$^+$] *m/z* 414.0952; $C_{21}H_{18}O_9$ requires 414.0951. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel int., %) 414 [M]$^+$ (0), 152 (0.1), 137 (0.3), 126 (5.9), 123 (0.7), 110 (0.5). CD (*c* 0.3623 mM), $[\theta]_{308}$ 0, $[\theta]_{289}$ −839.4, $[\theta]_{283}$ 0, $[\theta]_{274}$ 2159, $[\theta]_{261}$ 0, $[\theta]_{241}$ −13980, $[\theta]_{224}$ 0.

(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (7). Brown amorphous solid (48 mg, 3.1%). Found, [M$^+$] *m/z* 414.0950; $C_{21}H_{18}O_9$ requires 414.0951. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 414 [M]$^+$ (0), 152 (2.9), 137 (3.4), 126 (7.3), 123 (10.1), 110 (3.3). CD (*c* 0.2174 mM), $[\theta]_{310}$ 0, $[\theta]_{296}$ 429.8, $[\theta]_{286}$ 778.5, $[\theta]_{272}$ 558.3, $[\theta]_{258}$ 809.2, $[\theta]_{235}$ 9086, $[\theta]_{211}$ 0.

Acid-catalysed condensation of resorcinol with (+)-leucocyanidin.[7] Reduction of (+)-taxifolin (2.00 g, 0.0070 M) with $NaBH_4$ (500 mg) for 1 h and coupling with resorcinol (6.20 g, 0.0560 M) for 3 h, followed by work-up as described for the (+)-taxifolin–phloroglucinol condensation, afforded a single product (**4**), which was purified by consecutive separations by CC [150 × 5 cm i.d. column, EtOH as eluent, flow-rate 3.3 ml min^{-1}, t_R 33.5 h, followed by a 90 × 3.5 cm i.d. column, EtOH–H_2O (60:40) as eluent, flow-rate 0.33 ml min^{-1}, t_R 76.8 h].

(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-(2,4-Dihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (4). Brown amorphous solid (80 mg, 6.5%). Found, [M$^+$] *m/z* 398.1003; $C_{21}H_{18}O_8$ requires 398.1002. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 380 [M − H_2O]$^+$ (0.7), 272 (1.6), 152 (1.6), 137 (1.1), 123 (9.9), 110 (100). CD (*c* 0.3158 mM), $[\theta]_{308}$ 0, $[\theta]_{286}$ −2682, $[\theta]_{281}$ 0, $[\theta]_{272}$ 8960, $[\theta]_{240}$ 0, $[\theta]_{235}$ −1228, $[\theta]_{213}$ 0.

Base-catalysed rearrangement of (−)-fisetinidol-(4α,2)-phloroglucinol (1).[8,9] 4-Arylflavan-3-ol (**1**) (48 mg, 0.001 09 M) was dissolved in 0.25 M Na_2CO_3–0.25 M $NaHCO_3$ buffer (pH 10, 200 ml) and stirred under N_2 at 50 °C for 8 h. The reaction mixture was cooled (0 °C), acidified with 0.1 M HCl, extracted with EtOAc (6 × 200 ml), dried (Na_2SO_4) and the solvent evaporated. The product (**8**) was purified (t_R 15.5 h) by CC (40 × 3 cm i.d. column, EtOH as eluent, flow-rate 1.1 ml min^{-1}).

(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-(2,4-Dihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (8). Brown amorphous solid (140 mg, 32.1%). Found, [M$^+$ − H_2O] *m/z* 380.0894; $C_{21}H_{16}O_7$ requires 380.0896. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 380 [M − H_2O]$^+$ (0.1), 272 (0.9), 152 (1.6), 137 (1.8), 123 (9.9), 110 (100). CD (*c* 0.2632 mM), $[\theta]_{310}$ 0, $[\theta]_{284}$ 5757, $[\theta]_{279}$ 0, $[\theta]_{270}$ −8446, $[\theta]_{251}$ 0, $[\theta]_{239}$ 15050, $[\theta]_{222}$ 0.

Base-catalysed rearrangement of (−)-fisetinidol-(4β,2)-phloroglucinol (5).[8,9] Incubation (50 °C) of 4-arylflavan-4-ol (**5**) (2.00 g, 0.0050 M) in buffer (400 ml) as indicated for the 4α-analogue (**1**), gave **9** (t_R 91.6 h) following separation by CC (150 × 5 cm i.d. column, EtOH as eluent, flow-rate 0.9 ml min^{-1}). The product was further purified by CC [40 × 3 cm i.d. column, EtOH–H_2O (60:40) as eluent, flow-rate 0.5 ml min^{-1}].

(2*S*,3*S*,4*R*)-2,3-*cis*-3,4-*trans*-4-(2,4-Dihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (9). Brown amorphous solid (100 mg, 5.0%). Found, [M$^+$ − H_2O] *m/z* 380.0893; $C_{21}H_{16}O_7$ requires 380.0896). ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 380 [M − H_2O]$^+$ (1.3), 272 (1.6), 152 (3.0), 137 (1.3), 123 (14), 110 (100). CD (*c* 0.2623 mM), $[\theta]_{310}$ 0, $[\theta]_{288}$ 1189, $[\theta]_{272}$ 12050, $[\theta]_{249}$ 1619, $[\theta]_{238}$ 3693, $[\theta]_{224}$ 0.

Base-catalysed rearrangement of (−)-fisetinidol-(4β,4)-resorcinol (6).[8,9] Repetition of the above rearrangement of **5**, but with the 4-arylflavan-4-ol (**6**) (2.0 g, 0.0052 M) as substrate under Ar for 22 h, yielded **10** (t_R 167.0 h) after purification by CC (130 × 5 cm i.d. column, EtOH as eluent, flow-rate 0.4 ml min^{-1}).

(2*S*,3*S*,4*R*)-2,3-*cis*-3,4-*trans*-4-(2,4-Dihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (10). Brown amorphous solid (62 mg, 3.1%). Found, [M$^+$] *m/z* 382.1051; $C_{21}H_{18}O_7$ requires 382.1053. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 382 [M]$^+$ (0.2), 231 (3.0), 213 (11), 152 (6.2), 123 (28), 122 (4.2), 110 (26). CD (*c* 0.3926 mM), $[\theta]_{310}$ 0, $[\theta]_{290}$ −1698, $[\theta]_{286}$ 0, $[\theta]_{274}$ 6520, $[\theta]_{252}$ 0, $[\theta]_{240}$ −1113, $[\theta]_{227}$ 0.

C-2 epimerization of (−)-fisetinidol-(4α,2)-phloroglucinol (1).[10] The 4-arylflavan-3-ol (**1**) (3.20 g) in EtOAc (400 ml) was subjected to subdued sunlight for 48 h. Removal of the solvent followed by separation by CC (130 × 5 cm i.d. column, EtOH as eluent, flow-rate 4.2 ml min^{-1}) afforded **11** (t_R 31.9 h).

(2*S*,3*S*,4*R*)-2,3-*cis*-3,4-*trans*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,7-trihydroxyflavan-3-ol (11). Brown amorphous solid (95 mg, 2.04%). Found, $[M^+]$ *m/z* 398.1000; $C_{21}H_{18}O_8$ requires 398.1002. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 398 $[M]^+$ (0.5), 380 $[M - H_2O]^+$ (3.1), 258 (6.5), 229 (19), 152 (7.9), 126 (77), 123 (32), 110 (100). CD (*c* 0.2513 mM), $[\theta]_{310}$ 0, $[\theta]_{283}$ −4660, $[\theta]_{276}$ 0, $[\theta]_{271}$ 1936, $[\theta]_{261}$ 0, $[\theta]_{238}$ −36 540, $[\theta]_{225}$ 0.

Acid-catalysed degradation of tannin polymer. A mixture of purified Loblolly pine tannin polymer (3.5 g) and phloroglucinol (11.5 g) was treated as described in the literature[11] to yield the crude product (**12**) (580 mg), which was further purified by CC (90 × 1 cm i.d. column, EtOH as eluent, flow-rate 0.2 ml min^{-1}, t_R 71.7 h).

(2*R*,3*R*,4*S*)-2,3-*cis*-3,4-*trans*-4-(2,4,6-Trihydroxyphenyl)-3′,4′,5,7-tetrahydroxyflavan-3-ol (12). Brown amorphous solid (126 mg). Found, $[M^+]$ *m/z* 414.0953; $C_{21}H_{18}O_9$ requires 414.0951. ^{1}H NMR, see Table 1. ^{1}H NMR, NOE, see Table 3. ^{13}C NMR, see Table 2. MS, *m/z* (rel. int., %) 414 $[M]^+$ (0.1), 152 (0.1), 137 (0.5), 126 (0.3), 123 (0.8), 110 (0.4). CD (*c* 0.2179 mM), $[\theta]_{310}$ 0, $[\theta]_{288}$ 1642, $[\theta]_{273}$ 905, $[\theta]_{262}$ 2109, $[\theta]_{236}$ 15 100, $[\theta]_{219}$ 0.

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