

## Oligomeric Flavanoids. Part 7.† Novel Base-catalysed Pyran Rearrangements of Procyanidins

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Procyanidin B-3 (1) is subject to readily occurring c-ring isomerizations in NaHCO<sub>3</sub>-Na<sub>2</sub>CO<sub>3</sub> buffer solution to form a novel 8,9-*cis*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (3) and a series of 2,3-*cis*-3,4-*trans*-4-aryl-2-flavanylbenzopyrans (6), (9), and (12) in which the C-2 pyrocatechol and C-4 (+)-catechin moieties are interchanged relative to their positions in the biflavanoid (1). These compounds presumably originate *via* 1,3-aryl migrations in intermediate quinone-methides with concomitant inversion of the absolute configuration at C-3. The lability of the interflavanyl bond at alkaline pH is reflected by the presence of considerable quantities of (+)-catechin as well as high-molecular-mass analogues of precursor (1).

Procyanidins that have been extracted or allowed to react at alkaline pH and elevated temperatures for prolonged times invariably exhibit increased acidity and lower reactivity towards aldehydes than those obtained by neutral-solvent extraction.<sup>1-3</sup> These observations were ascribed to the presence of catechinic acid-type rearrangement products<sup>1,4</sup> and have since led to extensive investigations of the base-catalysed reactions of the procyanidins.<sup>5,6</sup> Despite these efforts no evidence of the readily occurring c-ring isomerizations demonstrated for the profisetinidins under mild basic conditions<sup>7</sup> has yet been documented for oligomeric procyanidins. Such a lack of compelling data thus prompted us to apply the methodology recently developed<sup>8-10</sup> for the concise synthesis of (-)-fisetinidol-(+)-catechin-related tetrahydropyranochromenes, termed phlobatannins,<sup>11</sup> to procyanidin B-3, representing the economically important class of procyanidin condensed tannins.

### Results and Discussion

Treatment of (4 $\alpha$ ,8)-bis-(+)-catechin (1)<sup>12</sup> (procyanidin B-3) with 0.025M-NaHCO<sub>3</sub>-0.025M-Na<sub>2</sub>CO<sub>3</sub> buffer<sup>7</sup> (pH 10) for 1.5 h at 45 °C under nitrogen, *i.e.* conditions similar to those applied by Freudenberg<sup>13</sup> for epimerization at C-2 of (+)-catechin, gave complete conversion into a mixture consisting of oligomeric procyanidins (*ca.* 30%) and four mobile fractions (*ca.* 70%) following chromatography on Sephadex LH-20-ethanol (Scheme 1). The latter fractions afforded (+)-catechin (*ca.* 9.0%) and four compounds with modified c-rings. These comprised the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene (3) as the minor product, and the 2,3-*cis*-3,4-*trans*-4-aryl-2-flavanylbenzopyrans (6), (9), and (12). Owing to the complexity of the phenolic mixture these c-ring-isomerized analogues were identified as their octamethyl ether diacetates (4), (7), (10), and (13), the <sup>1</sup>H n.m.r. spectra of which are conspicuously free of the effects of dynamic rotational isomerism<sup>14</sup> at ambient temperatures. <sup>1</sup>H N.m.r. coupling constants in CDCl<sub>3</sub> at 300 MHz (Table) of the heterocyclic proton resonances [ $J_{8,9}$  *ca.* 2.0,  $J_{9,10}$  1.5 Hz for (4);  $J_{2,3}$  1.0-2.1,  $J_{3,4}$  *ca.* 2.0 Hz for (7), (10), and (13)] are in accord with *cis-trans* configurations of their c-rings.<sup>8-10</sup> Significant n.o.e. associations of 8-H(c) with 2- and 6-H(b) (2.3, 3.2% respectively) in the tetrahydropyranochromene (4) and of 2-H(c) with 2- and 6-H(b) in the 4-aryl-2-flavanylbenzopyrans [1.4, 2.5% for (7); 1.1, 2.4% for (10); 1.3, 2.7% for (13)] not only confirm these configurations but also indicate preferred sofa conformations for the heterocyclic c-

rings with near-axial ( $\beta$ ; see below) pyrocatechol substituents at C-10 for (4) and at C-4 for (7), (10), and (13).

N.o.e. associations of three different methoxy groups with a two-proton singlet ( $\delta$  6.03) in the octamethyl ether diacetate (4) of the tetrahydropyrano[2,3-*h*]chromene (3) indicate the 'liberation' of a phloroglucinol moiety from the A/C- ring system in procyanidin B-3 (1). The remaining one-proton singlet ( $\delta$  6.25) in the high-field aromatic region exhibits an n.o.e. effect with a single methoxy resonance ( $\delta$  3.78), hence establishing involvement of 7-OH(D) of (1) in the heterocyclic c-ring (pyran) of the rearranged analogue (3). A spin-decoupling experiment indicates a benzylic connection between 10-H(c) ( $\delta$  4.28) and the 2- and 6-protons of a pyrocatechol ring. Besides the n.o.e. effect of 8-H(c) ( $\delta$  5.58) with 2- and 6-H of the same pyrocatechol moiety, indicative of these structural types with a 3,4-disubstituted aryl group at C-10,<sup>8-10</sup> the former proton does not exhibit additional long-rang coupling, thus reflecting the presence of an *ortho*-disubstituted phenyl residue at C-8. Since the chemical shifts of 8- and 10-H(c) are in accord with those of analogous derivatives of the profisetinidins,<sup>8,10</sup> these features establish a tetrahydropyrano[2,3-*h*]chromene-type structure for (3) with phloroglucinol and pyrocatechol moieties at C-8 and -10 respectively. The [2,3-*h*]-arrangement is unequivocally confirmed by the n.o.e. association of 10-H(c) with 2- and 6-H(E) (*cf.* ref. 11).

In each of the octamethyl ether diacetates (7), (10), and (13) of the 4-aryl-2-flavanylbenzopyrans (6), (9), and (12), n.o.e. associations of a one-proton *m*-doublet [ $\delta$  5.92, 6.21, and 6.21 for (7), (10) and (13) respectively] in the high-field aromatic region with a single methoxy group, and of the remaining *m*-doublet [ $\delta$  6.02, 6.11, and 6.11 for (7), (10), and (13) respectively] with two methoxy groups, is indicative of an 'intact' phloroglucinol A/C-ring system. The n.o.e. effect of the high-field one-proton singlet [ $\delta$  6.26, 6.28 for (10) and (13)] to a single methoxy group in both (10) and (13), and of the singlet ( $\delta$  6.04) to two methoxy groups in (7), similarly reflects substitution of 5,7-dimethoxyflavan-3-ol moieties at C-6(D) for (10) and (13), and at C-8(D) for (7). These are defined as (+)-catechin [for (7) and (10)] and (+)-epicatechin [for (13)] units from coupling constants of F-ring protons [ $J_{2,3}$  5.5, 8.0, and *ca.* 1.0 Hz for (10), (7), and (13) respectively]. The observed benzylic coupling of 4-H(c) with 2- and 6-H(b) establishes the linkage of the pyrocatechol unit to C-4 in the 4-aryl-2-

† Part 6, ref. 16.

**Table.**  $^1\text{H}$  N.m.r. peaks of the tetrahydropyrans[2,3-*h*]chromene octamethyl ether diacetate (4) and the 4-aryl-2-flavanilbenzopyran octamethyl ether diacetates (7), (10), and (13) in  $\text{CDCl}_3$  (23 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

Ring	Proton	(4)	(7)	(10)	(13)
A	3/6	} 6.03(s)	6.02 (d, 2.5)	6.11 (d, 2.5)	6.11 (d, 2.5)
	5/8		5.92 (d, 2.5)	6.21 (d, 2.5)	6.21 (d, 2.5)
B	2	6.82 (d, 2.0)	} 6.58*	6.86 (d, 2.0)	6.86 (d, 2.0)
	5	6.72 (d, 9.0)		6.78 (d, 8.5)	6.78 (d, 8.5)
	6	6.67 (dd, 2.0, 8.0)		6.66 (dd, 2.0, 8.5)	6.65 (dd, 2.0, 8.5)
C	2/8	5.58 (br s, ca. 2.0)	5.63 (br d, 2.1)	5.54 (br s, ca. 1.0)	5.57 (br s, ca. 1.0)
	3/9	5.20 (dd, 1.5, 2.0)	5.32 (dd, 2.1, 2.1)	5.24 (dd, 1.0, 2.0)	5.24 (dd, 1.0, 2.0)
	4/10	4.28 (d, 1.5)	4.26 (d, 2.1)	4.27 (d, 2.0)	4.26 (d, 2.0)
D	6/8	6.25(s)	6.04(s)	6.26(s)	6.28(s)
E	2	6.64 (d, 2.0)	6.79 (d, 2.0)	6.82 (br d, ca. 2.0)	6.98 (d, 2.0)
	5	6.74 (d, 8.0)	6.70 (d, 8.5)	6.80 (d, 8.5)	6.84 (d, 8.5)
	6	6.65 (dd, 2.0, 8.0)	6.76 (dd, 2.0, 8.5)	6.85 (dd, 2.0, 8.5)	6.93 (dd, 2.0, 8.5)
F	2	4.83 (d, 6.0)	4.75 (d, 8.0)	5.08 (d, 5.5)	5.03(br s)
	3	5.33(m)	4.98(m)	5.30(m)	5.37(m)
	4	2.67 (dd, 6.0, 17.0)	2.60 (dd, 8.0, 17.0)	2.71 (dd, 6.0, 16.0)	} 2.98(m)
	4ax	2.83 (dd, 5.0, 17.0)	3.01 (dd, 6.0, 17.0)	2.79 (dd, 5.0, 16.0)	
4eq					
OMe		3.60 (2-A, 6-A), 3.75, 3.76, 3.77, 3.78 (5-A), 3.82, 3.83 (each s)	3.58, 3.59, 3.60, 3.66, 3.71, 3.76, 3.77 (5-A), 3.85 (7-A) (each s)	3.46 (5-D), 3.54 (7-D), 3.62 (5-A), 3.80 (7-A), 3.83 ( $\times 2$ ), 3.84, 3.85 (each s)	3.51 (5-D), 3.54 (7-D), 3.63 (5-A), 3.81 (7-A), 3.83, 3.85, 3.87, 3.88 (each s)
OAc		1.91, 1.97 (each s)	1.93, 1.94 (each s)	1.94, 1.97 (each s)	1.88, 1.94 (each s)

\* Second order.

flavanilbenzopyrans (7), (10), and (13). N.O.e. association of 7-OMe(D) with 2-H(C) in (7) and of 5- and 7-OMe(D) with 2-H(C) in (10) and (13), but absence of additional long-range (benzylic) coupling of the latter proton, similar localizes the (+)-catechin moiety at C-2. The chemical shifts of 2- and 4-H(C), and thus unambiguous proof of assignment of the positions of the pyrocatechol and (+)-catechin units, are confirmed by 2-D heteronuclear correlation of these protons with, respectively, C-2 and -4 ( $\delta$  68.7, 41.7 respectively). Owing to the lack of sufficient sample quantities the same approach could not be adopted to confirm the locations of these moieties in the benzopyrans (7) and (13). These features unequivocally establish the C-ring-isomerized nature of analogues (7), (10), and (13).

Additional structural information was sought *via* the mass spectral fragmentation data of compounds (4), (7), (10), and (13). The 'intact' nature of the catechin-type DEF-moieties in (7), (10), and (13) is confirmed by the *m/z* 327 fragment resulting from cleavage of the C-2(C)  $\rightarrow$  C-6/8(D) bond and subsequent loss of acetic acid. The high susceptibility of the C- and F-ring to both McLafferty- and R.D.A.-rearrangements and the close structural resemblance of ions resulting from these and other fragmentations, however, reduce the utility of mass spectrometry as a probe for differentiation of the ring-isomerized analogues and the octamethyl ether diacetate of procyanidin B-3 (1).\*

Under the mild basic conditions procyanidin B-3 (1) is presumably transformed to the B-ring quinone-methide (15)<sup>15</sup> which then serves as common precursor to the novel tetrahydropyrano[2,3-*h*]chromene (3) and the 4-aryl-2-flavanilbenzopyrans (6), (9), and (12). Migration of the (+)-catechin moiety, assisted by the strongly electron-releasing phloroglucinol unit at C-4, to the *re*-face at C-2 in (15)<sup>†</sup> and

subsequent pyran recyclization *via* 7-OH(D) and the *re*-face in quinone-methide (16) may feasibly rationalize genesis of the tetrahydropyrano[2,3-*h*]chromene (3). Such a sequence invariably leads to inversion of the absolute configuration at C-9,<sup>16</sup> the equivalent of C-3 in procyanidin B-3 (1) (see also below).

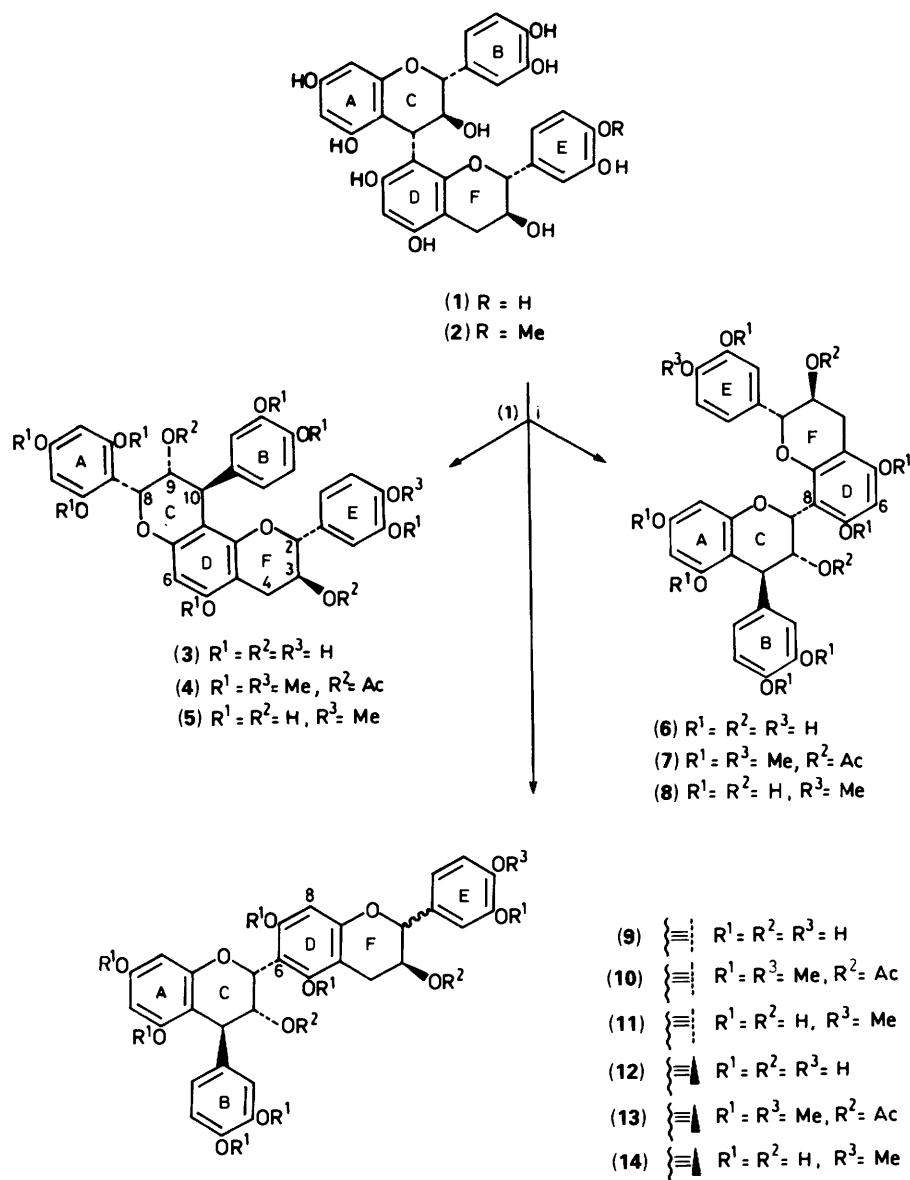
Owing to the superior migratory aptitude of the phloroglucinol A-ring compared with that of the (+)-catechin moiety, preferential migration of the former unit from C-4 to the *re*-face at C-2 in quinone-methide (15) would lead to intermediate (17). Recyclization involving 2-OH(A) and the *re*-face in quinone-methide (17) then generates the 4-aryl-2-flavanilbenzopyran (6), again with inversed absolute configuration at C-3. The same mechanism presumably also explains formation of a related product obtained by Hemingway and co-workers<sup>6</sup> during base-catalysed rearrangement of a dimeric procyanidin-phloroglucinol adduct, thus removing the necessity of successive addition and elimination of phloroglucinol in intermediate quinone-methides of type (15).

Alternatively, the (4,8)-linked quinone-methide (15) may be transformed to the (4,6)-coupled analogues (19) and (20) following formation of an E-ring quinone-methide (18), rotation about the C(3)-C(4) bond, and recyclization *via* 5-OH(D) thereby simultaneously achieving the observed positional and configurational isomerizations.<sup>7</sup> The 4-aryl-2-flavanilbenzopyrans (9) and (12) are subsequently formed by reconstruction of the pyran heterocycle *via* attack of 2-OH(A) and the *re*-face at C-4 in quinone-methides (21) and (22).

Owing to the lability of the interflavanil bond in procyanidins at alkaline pH,<sup>17</sup> however, the (4,6)-linked quinone-methide intermediates (19) and (20), required as precursors to the 4-aryl-2-flavanilbenzopyrans (9) and (12) with their C-6(D)-substituted (+)-catechin and (+)-epicatechin moieties, may feasibly originate *via* an A-ring quinone-methide (23). Substitution at C-6 of the liberated (+)-catechin moiety would then lead to a (4 $\alpha$ ,6)-bis-(+)-catechin (24) capable of undergoing base-catalysed transformation to the 4-aryl-2-flavanilbenzopyrans (9) and (12) *via* the pathway indicated in

\* Mass spectral fragmentation data of (4), (7), (10), and (13) are available as a supplementary publication [SUP 56765 (19 pp.). See Instructions for Authors, section 4.4, January issue].

† Quinone-methide intermediates (15)–(22) are *postulated* and have not been isolated.



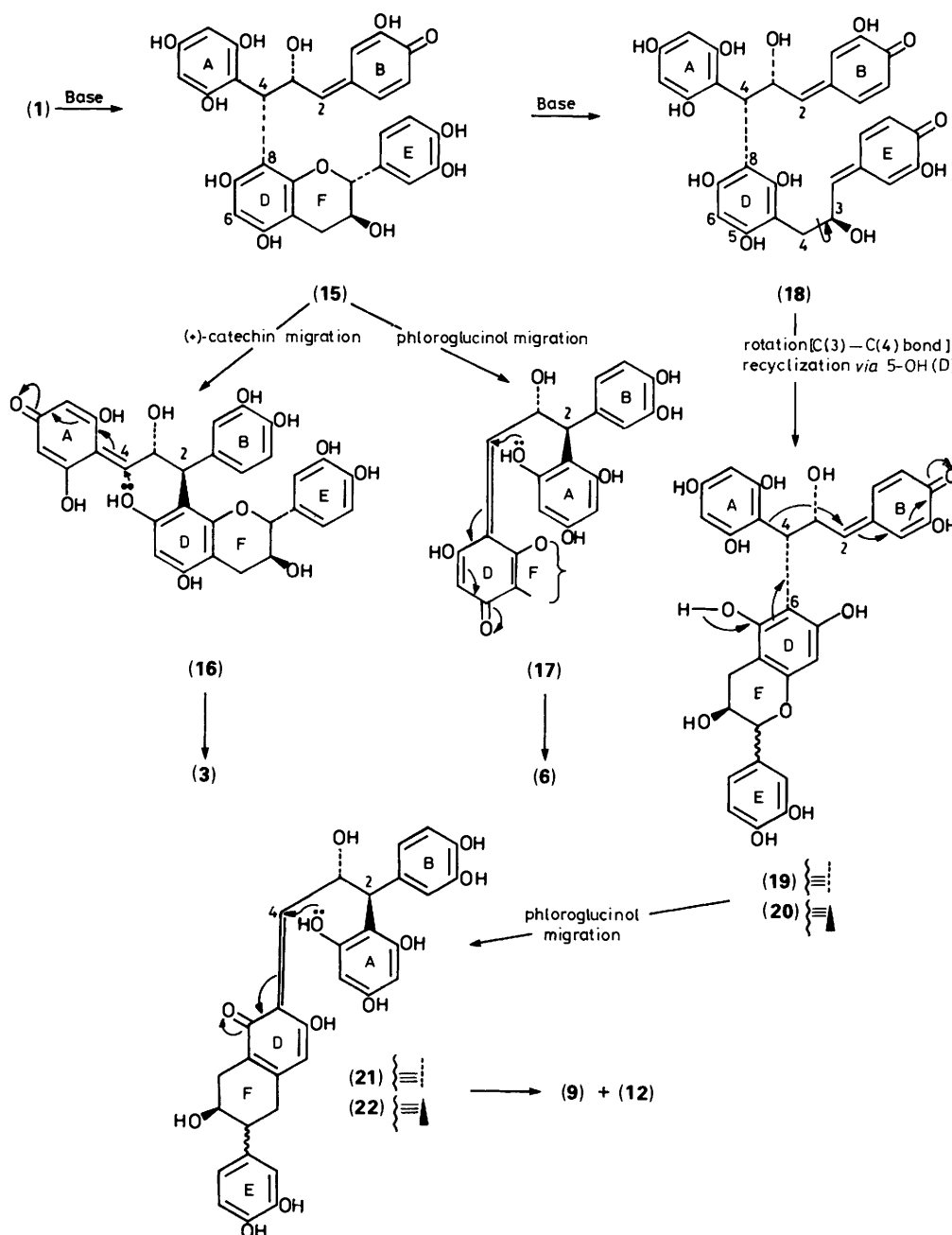
**Scheme 1.** Base-catalysed conversion of procyanidin B-3 (1). Reagents and conditions: i, 0.025M-NaHCO<sub>3</sub>-0.025M-Na<sub>2</sub>CO<sub>3</sub> buffer (pH 10), 1.5 h, 45 °C, N<sub>2</sub>.

Scheme 2. Such an assumption is substantiated by the observation that the O-4(E) methyl ether (2) of procyanidin B-3, being incapable of undergoing regioisomerization,<sup>8-10</sup> is transformed under basic conditions to a mixture matching closely that from the unprotected phenol (1) (see Experimental section). We are currently investigating the selective protection of procyanidin B-3 (1) at 5- and 7-OH(A) prior to its treatment with base. Such an approach should not only inhibit cleavage of the interflavanil bond and thus formation of the condensed analogues *via* condensation of procyanidin B-3 with the A-ring quinone-methide (23), but would also facilitate differentiation of the mechanisms proposed for the genesis of the C-ring-rearranged products (3), (6), (9), and (12).

The inversion of configuration at the equivalent of C-3 in procyanidin B-3 associated with the observed ring interchange is substantiated by c.d. data for the tetrahydropyrano[2,3-*h*]chromene (4) and the 4-aryl-2-flavanilbenzopyrans (10) and (13) which show positive high-amplitude Cotton effects in the 220–240 nm region. These are consistent with 4- and 10β-aryl substituents<sup>18</sup> which, when taken in conjunction with coupling

constants of C-ring protons, facilitates definition of the absolute configuration as 2*R*,3*S*:8*R*,9*R*,10*S* for (4), 2*R*,3*S*(F):2*R*,3*R*,4*S* for (10), and 2*S*,3*S*(F):2*R*,3*R*,4*S* for (13). The 4-aryl-2-flavanilbenzopyran (7), however, exhibits a strong negative Cotton effect in the same region of the c.d. spectrum. At present we cannot explain this reversal of the sign of the low-wavelength Cotton effect. Such peculiar chiroptic properties should become clear once our continuing investigations of the base-catalysed conversions of procyanidins B-1, B-2, and B-7 are completed. We favour the 2*R*,3*S*:2*R*,3*R*,4*S* absolute configuration as depicted in structure (7).

Notable in the base-catalysed conversion of the 2,3-*trans*-3,4-*trans*-procyanidin (1) is the exclusive formation of products arising from 1,3-aryl migrations of predominantly the phloroglucinol moiety and to a lesser extent of the (+)-catechin unit in intermediate quinone-methides. This contrasts with the profisetinidins where similar migrations function less prominently and are restricted to migration of the (+)-catechin moiety in analogues with 2,3-*trans*-3,4-*cis*-(-)-fisetinidol 'upper' units.<sup>8,10</sup> These differences are attributable to



**Scheme 2.** Proposed route to the formation of tetrahydropyrano[2,3-*h*]chromene (3) and the 4-aryl-2-flavanylbenzopyrans (6), (9), and (11)

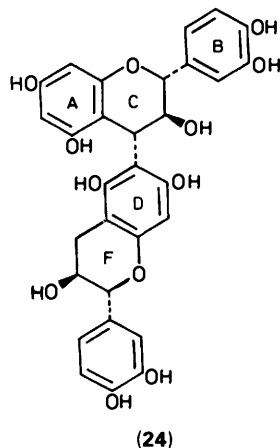
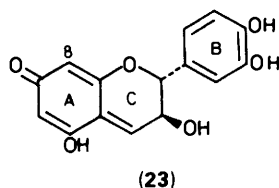
the enhanced migratory aptitude of 'released' phloroglucinol A-rings compared with those of either (+)-catechin or resorcinol A-rings in the profisetidin-type quinone-methides.

Under these mild conditions we could find no evidence of rearrangements of procyanidin B-3 to catechinic acid-type products reputed for either decreasing its reactivity towards aldehydes or enhancing acidity. Our results thus indicate that, with proper selection of conditions, extraction of conifer barks at alkaline pH may be performed without the adverse effects which have hitherto hampered the successful application of such an approach.

### Experimental

$^1\text{H}$  N.m.r. spectra were recorded on a Bruker AM-300

spectrometer, for  $\text{CDCl}_3$  solutions with  $\text{Me}_4\text{Si}$  as internal standard. Mass spectra were obtained with a Kratos MS80 instrument, and c.d. data in methanol on a Jasco J-20 spectropolarimeter. T.l.c. was performed on precoated Merck plastic sheets (DC-Plastikfolien Kieselgel 60 PF<sub>254</sub>, 0.25 mm) and compounds were located by  $\text{H}_2\text{SO}_4\text{-HCHO}$  (40:1 v/v) spray reagent. Preparative plates (p.l.c.), 20 × 20 cm, Kieselgel PF<sub>254</sub> (1.0 mm) were air-dried and used without prior activation. Separation on Sephadex LH-20 columns were in ethanol at a flow rate of 1.0  $\text{cm}^3 \text{min}^{-1}$ . Methylations were performed with an excess of diazomethane in methanol-diethyl ether for 48 h at  $-15^\circ\text{C}$ , while acetylations were carried out in acetic anhydride-pyridine at ambient temperatures. Evaporations were done under reduced pressures at ca. 60  $^\circ\text{C}$  in a rotary evaporator.



**Base-catalysed Conversion of (4 $\alpha$ ,8)-Bis-(+)-catechin (1).**—Procyanidin B-3 (1) (300 mg), available *via* standard literature procedures,<sup>19</sup> was dissolved in a 0.025M-NaHCO<sub>3</sub>-0.025M-Na<sub>2</sub>CO<sub>3</sub> buffer (200 cm<sup>3</sup>) and the mixture was stirred for 1.5 h at 45 °C under nitrogen. The mixture was chilled with crushed ice, acidified (0.1M-HCl), and extracted with ethyl acetate (4 × 250 cm<sup>3</sup>). Drying (Na<sub>2</sub>SO<sub>4</sub>) of the extract followed by evaporation of the solvent afforded a brown, amorphous solid (250 mg). This was subjected to column chromatography (3 × 90 cm column, Sephadex LH-20/ethanol; 16 ml/tube; first 300 cm<sup>3</sup> of eluant discarded) to give the following fractions: 1 (tubes 9—13, 29 mg), 2 (24—28, 27 mg), 3 (29—33, 30 mg), 4 (42—65, 30 mg), and 5 (66—150, 93 mg).

Fraction 1 consisted of (+)-catechin and fraction 5 consisted of high-molecular-mass analogues of procyanidin B-3. Owing to its complexity this mixture was not further investigated.

Fraction 2 (27 mg) was methylated and the mixture was purified by p.l.c. [benzene-acetone, 8:2 v/v (×2)] to give a prominent band at *R*<sub>F</sub> 0.52 (6 mg). Acetylation afforded (2R,3R,4S)-2,3-cis-3,4-trans-3-acetoxy-2-[(2R,3S)-2,3-trans-3-acetoxy-3',4',5,7-tetramethoxyflavan-8-yl]-4-(3,4-dimethoxyphenyl)-5,7-dimethoxybenzopyran (7) as a white amorphous solid (7 mg) (Found: *M*<sup>+</sup>, 774.2873. C<sub>42</sub>H<sub>46</sub>O<sub>14</sub> requires *M*, 774.2888); <sup>1</sup>H n.m.r. data (Table); c.d. [θ]<sub>290</sub> 0, [θ]<sub>280</sub> -0.41 × 10<sup>4</sup>, [θ]<sub>270</sub> 0, [θ]<sub>250</sub> -0.23 × 10<sup>4</sup>, [θ]<sub>240</sub> -1.38 × 10<sup>4</sup>, [θ]<sub>235</sub> -5.30 × 10<sup>4</sup>, [θ]<sub>230</sub> -6.9 × 10<sup>4</sup>, and [θ]<sub>220</sub> 0.

Methylation of fraction 3 (30 mg) followed by p.l.c. (benzene-acetone-methanol, 80:19:1 v/v) gave two bands, at *R*<sub>F</sub> 0.42 (1 mg) and 0.30 (7 mg). Acetylation of the former band afforded (2R,3S:8R,9R,10S)-3,9-diacetoxy-2,10-bis-(3,4-dimethoxyphenyl)-5-methoxy-8-(2,4,6-trimethoxyphenyl)-2,3-trans-8,9-cis-9,10-trans-3,4,9,10-tetrahydro-2H,8H-pyrano[2,3-*h*]chromene (4) as a white solid (1.2 mg) (Found: *M*<sup>+</sup>, 774.2869. C<sub>42</sub>H<sub>46</sub>O<sub>14</sub> requires *M*, 774.2888); <sup>1</sup>H n.m.r. data (Table); c.d. [θ]<sub>330</sub> 1.9 × 10<sup>4</sup>, [θ]<sub>300</sub> 1.9 × 10<sup>4</sup>, [θ]<sub>288</sub> 0, [θ]<sub>278</sub> -10.4 × 10<sup>4</sup>, [θ]<sub>260</sub> 0, [θ]<sub>250</sub> 5.8 × 10<sup>4</sup>, [θ]<sub>245</sub> 25.2 × 10<sup>4</sup>, [θ]<sub>242</sub> 41.4 × 10<sup>4</sup>, and [θ]<sub>235</sub> 0. The *R*<sub>F</sub> 0.30 band consisted of the octamethyl ether diacetate of procyanidin B-3 (1).<sup>16</sup>

Methylation of fraction 4 (30 mg) and subsequent

purification by p.l.c. (benzene-acetone-methanol, 80:19:1 v/v) afforded two bands, at *R*<sub>F</sub> 0.45 (4 mg) and 0.36 (9 mg). The *R*<sub>F</sub> 0.45 band was acetylated to give the (2R,3R,4S)-2,3-cis-3,4-trans-3-acetoxy-2-[(2S,3S)-2,3-cis-3-acetoxy-3',4',5,7-tetramethoxyflavan-6-yl]-4-(3,4-dimethoxyphenyl)-5,7-dimethoxybenzopyran (13) as a white solid (4.5 mg) (Found: *M*<sup>+</sup>, 774.2871. C<sub>42</sub>H<sub>46</sub>O<sub>14</sub> requires *M*, 774.2888); <sup>1</sup>H n.m.r. data (Table); c.d. [θ]<sub>320</sub> 0.9 × 10<sup>4</sup>, [θ]<sub>305</sub> 0.8 × 10<sup>4</sup>, [θ]<sub>280</sub> 0, [θ]<sub>275</sub> -1.8 × 10<sup>4</sup>, [θ]<sub>260</sub> 0, [θ]<sub>250</sub> 0.8 × 10<sup>4</sup>, [θ]<sub>245</sub> 5.6 × 10<sup>4</sup>, [θ]<sub>240</sub> 15.6 × 10<sup>4</sup>, [θ]<sub>235</sub> 21.1 × 10<sup>4</sup>, and [θ]<sub>227</sub> 0.

Acetylation of the *R*<sub>F</sub> 0.36 band afforded the (2R,3R,4S)-2,3-cis-3,4-trans-3-acetoxy-2-[(2R,3S)-2,3-cis-3,4-trans-3-acetoxy-3',4',5,7-tetramethoxyflavan-6-yl]-4-(3,4-dimethoxyphenyl)-5,7-dimethoxybenzopyran (10) as a white solid (9.8 mg) (Found: *M*<sup>+</sup>, 774.2876. C<sub>42</sub>H<sub>46</sub>O<sub>14</sub> requires *M*, 774.2888); <sup>1</sup>H n.m.r. data (Table); δ<sub>C</sub> (*inter alia*) (CDCl<sub>3</sub>; 23 °C; 75.4 MHz) 120.3 (C-6, B-ring), 118.8 (C-2, B), 111.2 (C-6, E), 111.0 (C-5, E), 110.8 (C-5, B), 108.8 (C-2, E), 105.5 and 101.8 (C-10, A and C-10, D), 96.1 (C-8, D), 93.0 (C-8, A), 91.8 (C-6, A), 78.2 (C-2, F), 73.3 (C-3, C), 69.0 (C-3, F), 68.7 (C-2, c), 61.1 (5-OCH<sub>3</sub>, D), 56.0 (4 × OCH<sub>3</sub>), 55.9 (7-OCH<sub>3</sub>, D), 55.8 (5-OCH<sub>3</sub>, A), 55.3 (OCH<sub>3</sub>), 41.7 (C-4, c), 23.1 (C-4, F), 21.5 and 21.0 (2 × OCOCH<sub>3</sub>).

Similar treatment of procyanidin B-3 4-*O*(*E*)-monomethyl ether (2), available by replacement of (+)-catechin by (+)-catechin-4'-*O*-methyl ether<sup>9,10</sup> in the synthetic sequence<sup>16</sup> leading to compound (1), afforded a mixture comprising (+)-catechin 4'-*O*-methyl ether (*ca.* 10%), oligomeric procyanidins (*ca.* 35%), the tetrahydropyrano[2,3-*h*]chromene (5), and the 4-aryl-2-flavanylbenzopyrans (8) and (11). The 4-aryl-2-flavanylbenzopyran (14) with its (+)-epicatechin F-ring was absent in this reaction. These pyran rearranged analogues were identified as their octamethyl ether diacetates (4), (7), and (10) by comparison of their physical data with those from the 'unprotected' phenol (1).

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