

Acid-catalyzed rearrangements of flavan-4-phloroglucinol derivatives to novel 6-hydroxyphenyl-6a,11b-dihydro-6H-[1]benzofuro[2,3-c]-chromenes and hydroxyphenyl-3,2'-spirobi[dihydro[1]benzofurans]

PERKIN

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Acetic acid-catalyzed cleavage of proanthocyanidins in the presence of phloroglucinol gives a series of 2R procyanidin- and prodelphinidin-phloroglucinol adducts together with a novel 2S all-cis derivative implicating cleavage of the pyran ring and subsequent inversion of stereochemistry at C-2_C. These flavan-4-phloroglucinol adducts also suffer dehydration to products with novel fused dihydrobenzopyran-dihydrobenzofuran rings. In addition, cleavage of the flavan C-10_A-C-4_C bond followed by dehydration results in unique 3,2'-spirobi[dihydro[1]benzofurans].

The thesis that the interflavanyl bond of polymeric procyanidins and prodelphinidins can be cleaved and chain extender units recovered (without inversion of stereochemistry at C-2_C), as first advanced by Sears and Casebier¹ and refined by Brown and Shaw,² has led to routine use of acid-catalyzed cleavage in the presence of thiols or phloroglucinol as capture nucleophiles in the characterization of the 5,7-dihydroxypolyflavanoids (Scheme 1).³ Because of the power of these reactions in defining the constituent units in polymeric procyanidins and prodelphinidins, acid-catalyzed cleavage reactions have been exploited as a 'quantitative' analytical approach to a definition of the structure of condensed tannin polymers.^{4,5} However, we have consistently failed to obtain quantitative yields of flavan-4-thiol or phloroglucinol adducts from acetic acid-catalyzed cleavage of condensed tannins.^{6,7} This problem prompted further study of the products of acetic acid-catalyzed cleavage of these tannins with particular emphasis on defining the rearrangements that might occur when reactions at 100 °C are extended to 24 h or more. Rearrangement products with the novel title heterocyclic ring structures were obtained.

Results and discussion

Phloroglucinol adducts

Pecan (*Caraya illinoensis*) nut pith constitutes an exceptionally rich source of condensed tannins with potential for use in leather manufacture, adhesives and other speciality chemicals based on renewable resources.⁶ Previous work on the condensed tannins from pecan nut pith indicated that these polymers were made up of 3,3',4',5,5',7-hexahydroxyflavans (R = OH, prodelphinidins) and 3,3',4',5,7-pentahydroxyflavans (R = H, procyanidins) in relative proportions of about 6 : 1 (Scheme 1).⁶ The chain extender units were made up of approximately equal proportions of 2,3-*trans* (i.e. C-ring) and 2,3-*cis* (i.e. F-ring) flavan-3-ols. Both catechin (H-ring, R = H) and gallocatechin (H-ring, R = OH) but no 2,3-*cis* (i.e. I-ring) flavan-3-ols were isolated as terminal unit cleavage products.

In the present work, pecan nut pith tannins were reacted with phloroglucinol and acetic acid at 100 °C for 24 or 48 h. After methylation and acetylation of the products, a series of proanthocyanidin derivatives including the known methyl ether

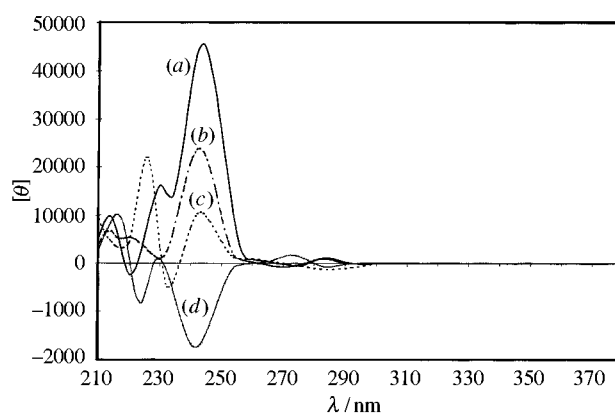
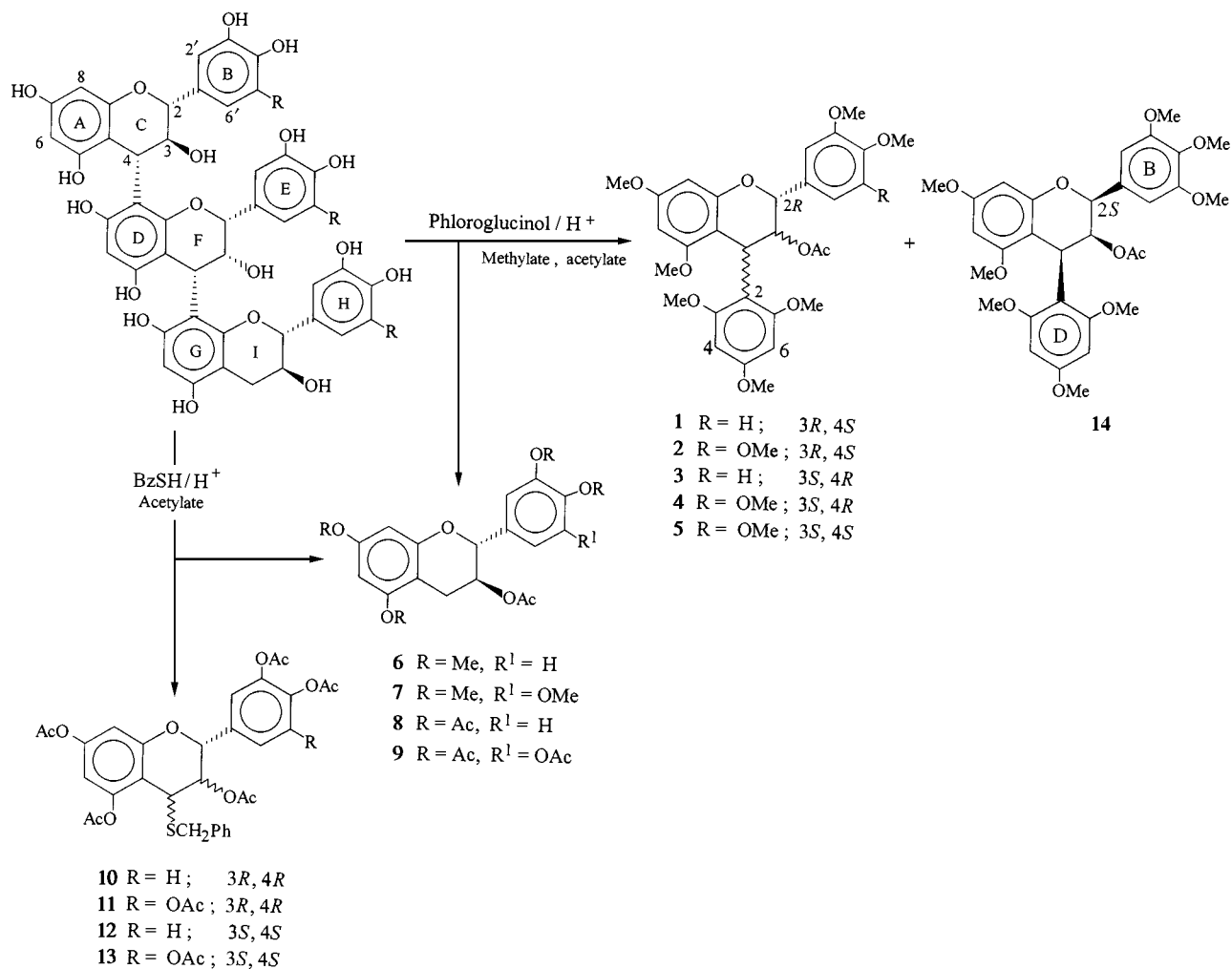


Fig. 1 CD spectra of (a) **2**, (b) **1**, (c) **14** and (d) **4**

acetate derivatives epicatechin-(4β → 2)-phloroglucinol † **1**, epigallocatechin-(4β → 2)-phloroglucinol **2**, catechin-(4α → 2)-phloroglucinol **3**, gallocatechin-(4α → 2)-phloroglucinol **4** and gallocatechin-(4β → 2)-phloroglucinol **5** were isolated. The methyl ether acetate derivatives catechin **6** and gallocatechin **7** were also isolated but no 2,3-*cis* flavan-3-ols representing the terminal units were recovered from cleavage of the polymer as was noted in a study of the acetate derivatives of products of thiolytic cleavage, where the peracetate derivatives **8** and **9** were obtained.⁷

¹H NMR (Table 1), ¹³C NMR (Table 2) and CD spectral data (Fig. 1) provided the evidence needed for definition of the structures of the phloroglucinol adducts obtained from the reaction of pecan tannins with phloroglucinol. The relative proportions of these products were consistent with the results obtained when pecan pith tannins were reacted in the presence of toluene-*α*-thiol.⁷ After acetylation, the major products of thiolysis were the peracetate derivatives catechin-4_α-benzyl sulfide **10**, gallocatechin-4_α-benzyl sulfide **11**, epicatechin-4β-benzyl

† Numbering of the phloroglucinol D-ring in compounds **1–5** and **14** retains the numbering of phloroglucinol and starts with a carbon carrying a hydroxy group so as to be consistent with the system for proanthocyanidins proposed by Hemingway *et al.*⁸



Scheme 1

sulfide **12** and epigallocatechin-4 β -benzyl sulfide **13** analogous to the phloroglucinol adducts described above (Scheme 1).⁷

Surprisingly, two epigallocatechin phloroglucinol adducts, **2** and **14**, each with similarly small heterocyclic ring coupling constants ($J_{2,3} < 1$ Hz; $J_{3,4} = 1.4$ and $J_{2,3} = 1.5$ Hz; $J_{3,4} = 2.0$ Hz), respectively, were isolated from the reaction product mixture. Proof of the absolute stereochemistry at C-4_C of **14** as being 4S (a β -configuration for the bond at C-4_C) came from the CD spectrum (Fig. 1).^{9,10} A NOESY experiment showed a correlation between the methoxy protons of the pyrogallol B-ring and the phloroglucinol D-ring, thus establishing the 2S,3S,4S (all-*cis*) absolute stereochemistry for the novel *ent*-epigallocatechin-(4 β \rightarrow 2)-phloroglucinol derivative **14**. As expected, the CD spectrum of **2** also showed a strong positive Cotton effect at about 244 nm indicating a β -configuration of the phloroglucinol unit (Fig. 1); the heterocyclic ring coupling constants were also consistent with 2,3-*cis* stereochemistry. A NOESY experiment on **2** did not show correlations between the methoxy groups of the B- and D-rings as were seen in **14**. Therefore, **2** is assigned 2R 2,3-*cis*-3,4-*trans* stereochemistry.

Isolation of a 2S all-*cis* product representing a chain extender unit in a polymer that otherwise gives products of 2R absolute stereochemistry is a remote possibility^{11,12} unless it is a rearrangement product. In studies of the thiolysis of 2,3-*cis*-3,4-*trans* oligomers terminated with the 2,3-*trans* catechin unit, Kolodziej¹³ isolated very small (1:35) proportions of all-*cis* flavan 4-thioether derivatives in addition to the predominant 2,3-*cis*-3,4-*trans* isomers. Because an α -substitution of the 2R 2,3-*cis* carbocation is rarely observed,¹⁴ the most likely source of an all-*cis* derivative would be through opening of the pyran ring followed by attack of either the A- or D-ring hydroxy on a

quinomethane intermediate to reform a pyran ring. The product **14** could be formed either from the 2,3-*trans*-3,4-*cis* phenolic form of **5** by attack of the A-ring hydroxy group from the *si*-face or from the 2,3-*trans*-3,4-*trans* phenolic form of **4** by attack of the D-ring hydroxy group, also from the *si*-face, on the respective quinomethanes (Scheme 2).¹⁵

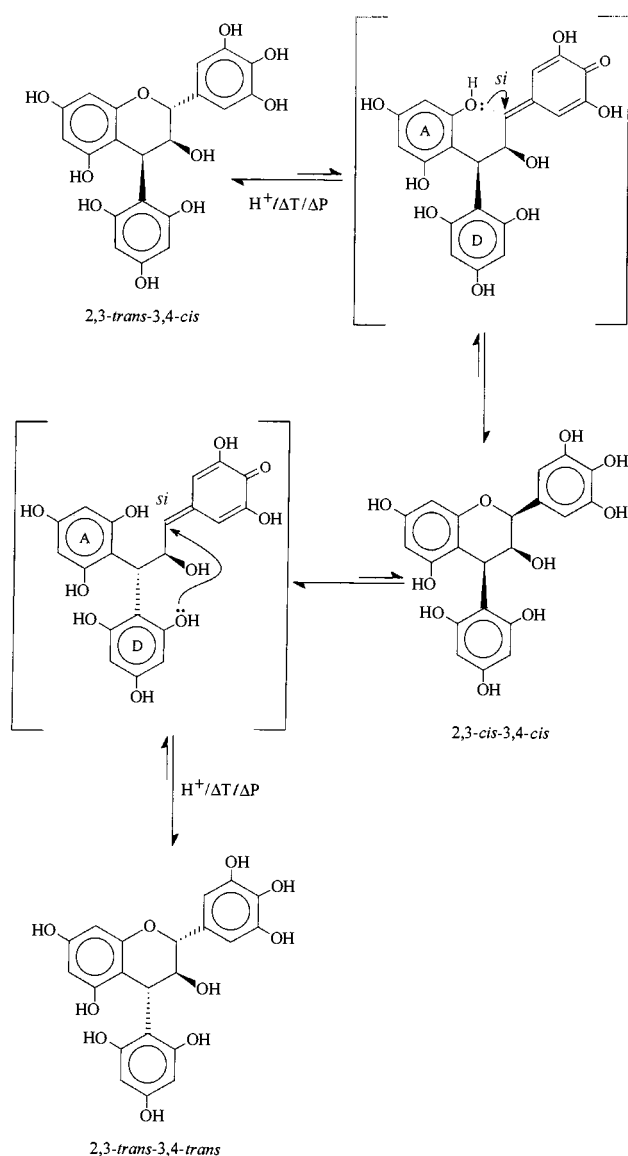
The similarity of the heterocyclic ring coupling constants for the 2,3-*cis*-3,4-*trans* and 2,3-*cis*-3,4-*cis* isomers of these compounds serves as a warning that one cannot predict the relative stereochemistry at C-4_C in 2,3-*cis* isomers only on the basis of the heterocyclic ring coupling constants. The presence of **14** in reaction products otherwise dominated by flavan-4-phloroglucinol adducts of 2R absolute stereochemistry forces one to the conclusion that there is inversion of stereochemistry at C-2_C under acetic acid-catalyzed cleavage reaction conditions when these reactions are pushed to increase product yields by long reaction times.

Note that the assignment of the chemical shifts for the C-6_A and C-8_A carbons (Table 2) are inverted with respect to those published in the earlier literature¹⁶ but are consistent with assignments for the methyl ether acetate derivatives of flavan-3-ols.¹⁷ The assignments of H-6_A and H-8_A for selected compounds were verified by NOE experiments using MeO-5_A and MeO-7_A, the former showing a correlation to H-6_A and the latter showing a correlation to both H-6_A and H-8_A. A C-H HETCOR experiment then showed a correlation between the consistently higher field *meta*-coupled H-6_A doublet with the higher field A-ring carbon resonance (Table 2), thus clarifying the carbon assignments in these and related compounds studied by Van Zyl *et al.*¹⁸ Discrepancies arising from analysis of the ¹³C NMR spectra of polymers and the relative yields of the

Table 1 ^1H NMR spectral data ^{a,b} for the methyl ether acetate derivatives of prodelphinidin- and procyanidin-phloroglucinol adducts

Compound	A-Ring		B-Ring			C-Ring			D-Ring	
	H-6	H-8	H-2	H-5	H-6	H-2	H-3	H-4	H-4	H-6
1 Epicatechin-(4 β \rightarrow 2)-phloroglucinol	6.02 (2.5)	6.25 (2.5)	6.93 (2.2)	6.77 (8.5)	6.87 (2.2, 8.5)	5.33 (1.5)	5.23 (1.5, 2.2)	4.55 (2.2)	6.20, br s, 2H	
2 Epigallocatechin-(4 β \rightarrow 2)-phloroglucinol	6.04 (2.3)	6.27 (2.3)	6.62, s	—	6.62, s	5.34 (<1)	5.28 (1, 1.5)	4.59 (1.4)	6.20, br s, 2H	
14 <i>ent</i> -Epigallocatechin-(4 β \rightarrow 2)-phloroglucinol	6.10 (2.5)	6.24 (2.5)	6.47, s	—	6.47, s	5.58 (1.5)	5.15 (1.5, 2.0)	4.25 (2.0)	6.03, s, 2H	
3 Catechin-(4 α \rightarrow 2)-phloroglucinol	5.98 (2.7)	6.15 (2.7)	6.98 (2.2)	6.83 (8.5)	7.02 (2.2, 8.5)	4.73 (10.5)	5.78 (8.5, 10.5)	4.73 (8.5)	6.00–6.11, br s + 2 d (2.5)	
4 Gallocatechin-(4 α \rightarrow 2)-phloroglucinol	5.99 (2.5)	6.16 (2.5)	6.69, s	—	6.69, s	4.73 (10.0)	5.78 (8.5, 10.0)	4.72 (8.5)	6.06, br s	6.06, br s
5 Gallocatechin-(4 β \rightarrow 2)-phloroglucinol	5.99 (2.5)	6.16 (2.5)	6.59, s	—	6.59, s	5.16 (10.5)	5.42 (6.2, 10.5)	5.04 (6.2)	6.10 (2.2)	6.16 (2.2)
6 Catechin	6.07 (2.5)	6.15 (2.5)	6.87 (2.0)	6.80 (9.0)	6.89 (2.0, 9.0)	5.00 (7.5)	5.33, m	2.64 (7.0, 16.5)	2.88 (5.5, 16.5)	
7 Gallocatechin	6.07 (2.5)	6.15 (2.5)	6.56, s	—	6.56, s	4.99 (7.0)	5.33, m	2.64 (7.0, 16.5)	2.88 (5.5, 16.5)	

^a Recorded in CDCl_3 with SiMe_4 as internal standard. ^b δ_{H} ; J values are given in Hz in parentheses.



acid-catalyzed cleavage products led us to study additional rearrangement reactions that might be occurring under acetic acid-catalyzed conditions.

Formation of [1]benzofuro[2,3-c]chromenes ‡

Two dimensional cellulose thin layer chromatography (TLC)¹⁹ showed a complex mixture of products that had low R_f values in the 6% acetic acid dimension in addition to the flavan-4-phloroglucinol adducts described above. Column chromatography of the free phenols on LH-20 Sephadex§ failed to resolve these compounds. Therefore their methyl ether acetate derivatives were prepared and separated by preparative TLC on silica gel. A series of compounds with dihydrobenzofuran rings were isolated. The *2R,3R,4R* (2,3-*cis*-3,4-*cis*) and *2R,3S,4S* (2,3-*trans*-3,4-*cis*) [1]benzofuro[2,3-*c*]chromenes **15** and **16** as well as their analogs with an acetoxy in place of a methoxy at the C-4'_D positions **17** and **18** were isolated. A general structural search of *Chemical Abstracts* revealed no compounds with this ring system in the literature.¶ Their formation suggested an $\text{S}_{\text{N}}2$ attack of the phloroglucinol hydroxy group on C-3_C, thereby inverting the stereochemistry of the oxygen at C-3_C (Scheme 3).

The structure of **15** was evident from the ^1H NMR spectrum which showed seven methoxy groups (δ_{H} 3.66–3.89), two *meta*-coupled aromatic proton doublets (δ_{H} 5.89–5.98) assigned to 6- H_{A} and 8- H_{A} , a two proton singlet at δ_{H} 6.17 assigned to H-5'_D and H-7'_D, and a two proton singlet at δ_{H} 6.73 for the H-2_B and H-6_B protons (Table 3). The all-*cis* stereochemistry of this compound was evident from the heterocyclic ring couplings of $J_{2,3} = 2.0$ and $J_{3,4} = 10$ Hz, the latter being consistent with a 0° dihedral angle of the α, α orientation of the fused dihydrobenzopyran and dihydrobenzofuran rings.

Additional evidence for the structure of **15** came from the isolation of the related derivative **17** carrying an acetoxy group (Table 4). The proton spectrum of **17** showed the acetate CH_3 at δ_{H} 2.07 and only six methoxy groups in the region of δ_{H} 3.69–3.89. Through a series of NOE experiments using the A- and D-ring methoxy groups, two of these methoxy groups showed enhancement of two *ortho* aromatic protons, demonstrating that the acetoxy group must be at either the C-5_A or C-4'_D positions. Near symmetry along the C-4_C–C-3_C axis made the assignment of the location of the acetoxy group in **17** impossible without reference to a long-range proton–carbon correl-

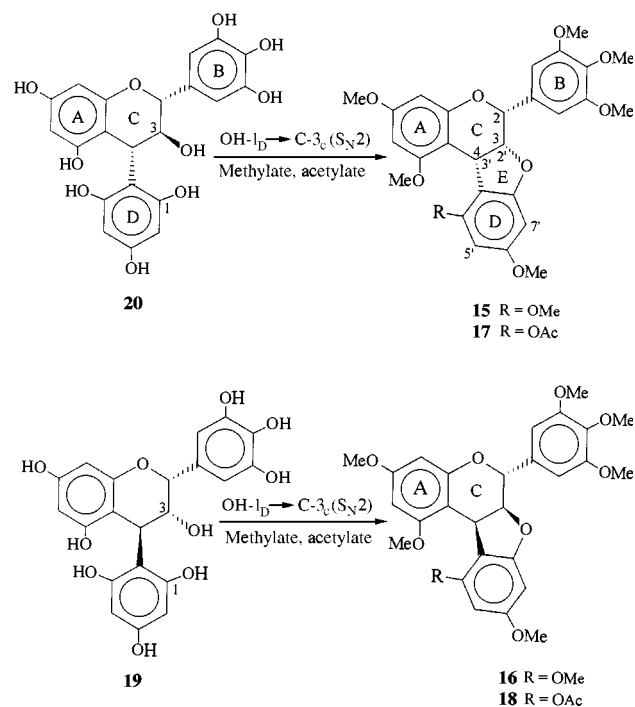
‡ Systematic IUPAC names (with the systematic numbering) for compounds **15**–**18**, **21**, **24** and **25** are given in the Experimental section. However, the numbering system used throughout the discussion and in the reporting of NMR data in the tables is the natural product numbering system shown in Scheme 1.

§ Mention of trade names does not constitute endorsement by the US Department of Agriculture.

¶ The authors thank Mr Mitchell Brown, Louisiana State University, Department of Chemistry for structural searches.

Table 2 ^{13}C NMR spectral data^a for the methyl ether acetate derivatives of prodelphinidin- and procyanidin-phloroglucinol adducts

Compound	A-Ring		B-Ring			C-Ring			D-Ring	
	C-6	C-8	C-2	C-5	C-6	C-2	C-3	C-4	C-4	C-6
1 Epicatechin-(4 β \rightarrow 2)-phloroglucinol	91.35	92.73	111.40	110.55	118.91	74.77	71.91	32.53	-91.5	-91.5
2 Epigallocatechin-(4 β \rightarrow 2)-phloroglucinol	91.51	92.89	103.95	—	103.95	75.00	71.70	32.55	-91.7	-91.7
14 <i>ent</i> -Epigallocatechin-(4 β \rightarrow 2)-phloroglucinol	91.64	93.16	105.34	—	105.34	73.54	68.23	42.28	91.29	91.29
3 Catechin-(4 α \rightarrow 2)-phloroglucinol	93.24	93.32	110.51	110.42	120.27	80.33	72.82	35.03	-92	-92
4 Gallocatechin-(4 α \rightarrow 2)-phloroglucinol	93.5	93.5	104.85	—	104.85	80.76	72.91	35.29	92	92
5 Gallocatechin-(4 β \rightarrow 2)-phloroglucinol	92.44	92.74	104.59	—	104.59	76.85	71.97	29.88	91.34	91.34

^a δ_{C} , recorded in CDCl_3 .**Scheme 3**

ation experiment (see discussion of **18** below). However, a COLOC experiment provided the data necessary, and when taken in conjunction with other NMR experiments, all proton and carbon assignments could be made. The heterocyclic proton couplings showed an all-*cis* stereochemistry with $J_{2,3} = 2.0$ and $J_{3,4} = 9.5$ Hz.

The ^1H NMR spectrum of the 2,3-*trans*-3,4-*cis* isomer **16** showed the same general structural features as **15**, but when recorded in CDCl_3 , the heterocyclic ring proton signals overlapped each other. Therefore, the data reported in Table 3 are from the spectrum recorded in $[\text{D}_6]\text{acetone}$. The comparatively small $J_{2,3}$ and $J_{3,4}$ couplings (8.0 and 7.5 Hz, respectively) are probably due to rocking of the C-ring to provide relief for the steric hindrance between MeO-5_{A} and MeO-4_{D} . While contributing only to a reduction in $J_{2,3}$ it is also possible that an *A/E* conformational flip of the C-ring could occur.²⁰

As for **15**, additional support for the assignment of the structure of **16** came from the isolation of a related derivative **18** that carried an acetoxy group (δ_{H} 2.07) and only six methoxy groups in the region of δ_{H} 3.72–3.84 (Table 4). In CDCl_3 four *meta*-coupled aromatic protons in the region of δ_{H} 6.09–6.30, a two proton singlet at δ_{H} 6.60 for H-2_B and H-6_B, and three C-ring protons with similar couplings (but nearly coincident chemical shifts for two protons) at δ_{H} 4.75–4.85 are consistent with this structure. In $[\text{D}_6]\text{acetone}$ (Table 4) the heterocyclic ring protons

were clearly resolved as δ_{H} 4.80, $J_{2,3}$ 8.5 Hz; δ_{H} 4.75, $J_{3,4}$ 7.5 Hz; and δ_{H} 5.00 for H-2_C, H-4_C and H-3_C, respectively. Like **15**, both the $J_{2,3}$ and $J_{3,4}$ coupling constants would be expected to be larger for the *E*-conformer than those observed.

To establish the location of the acetoxy group in **18**, a series of COLOC experiments ranging in J_{CH} from 2–10 Hz was made. These experiments were performed using $[\text{D}_6]\text{benzene}$, rather than CDCl_3 or $[\text{D}_6]\text{acetone}$, as the solvent to overcome problems with overlapping signals. No cross peaks between H-2_C at δ_{H} 5.07 and C-9_A at δ_{C} 156.66 were observed in any of these experiments. However, strong cross peaks between H-3_C at δ_{H} 4.62 with the signal at δ_{C} 162.03 established the resonance for C-8'_D. Correlation of a *meta*-coupled doublet at δ_{H} 6.48 with C-8'_D requires assignment of that proton signal to H-7'_D. When optimized for $J_{\text{CH}} = 2$ Hz, correlations between H-4_C at δ_{H} 4.68 and C-8'_D at δ_{C} 162.03, C-4'_D at δ_{C} 149.53, C-5_A at δ_{C} 160.7, and C-9_A at δ_{C} 156.66 were apparent. These long range C–H correlations, together with information obtained from the HETCOR experiment, allowed complete assignment of both the proton and carbon spectra. A NOESY experiment showed cross peaks between the high field methoxy group at δ_{H} 3.20 with both H-7'_D and H-5'_D at δ_{H} 6.19. The two methoxy groups on the A-ring were then correlated with H-6_A and H-8_A. Therefore, the acetoxy group is at C-4'_D as suggested by differences in the acetoxy and methoxy substituent effects on the aromatic carbon signals.

The relative stereochemistry of these products suggests that they might be formed by $\text{S}_{\text{N}}2$ attack of the phloroglucinol hydroxy group on the protonated aliphatic OH-3_{C} , thus inverting the stereochemistry at C-3_C (Scheme 3). Therefore, the 2,3-*cis*-3,4-*cis* prodelphinidin derivatives **15** and **17** would be obtained from the free phenolic form of 2,3-*trans*-3,4-*trans* isomer **20** and the 2,3-*trans*-3,4-*cis* derivatives **16** and **18** from the free phenolic form of the 2,3-*cis*-3,4-*trans* phloroglucinol adduct **19**. The two products carrying an aromatic acetate function **17** and **18** no doubt result from difficulty in achieving complete methylation because of the proximity of the OH-5_{A} and the $\text{OH-4}'_{\text{D}}$ and the resulting hydrogen bond.

Although the formation of these compounds through an $\text{S}_{\text{N}}2$ mechanism is consistent with the above products, additional work on the synthesis of catechin-(4 α \rightarrow 2)-phloroglucinol **3** through reduction of dihydroquercetin in the presence of sodium borohydride, followed by addition of acetic acid and heating for 48 h at 100 °C, gave the 2,3-*trans*-3,4-*cis* analog of **17**, the [1]benzofuro[2,3-*c*]chromene **21** without the inversion of stereochemistry at C-3_C required of an $\text{S}_{\text{N}}2$ mechanism (Scheme 4). This product was later found also as a product of the reaction of tannin with phloroglucinol under acetic acid-catalyzed cleavage conditions. The NMR spectrum of **21** in CDCl_3 showed severe overlap of the heterocyclic ring and methoxy signals, so additional experiments were performed in $[\text{D}_6]\text{benzene}$ (Table 3).

Table 3 NMR spectral data for methyl ether derivatives of 6-hydroxyphenyl-6a,11b-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromenes^a

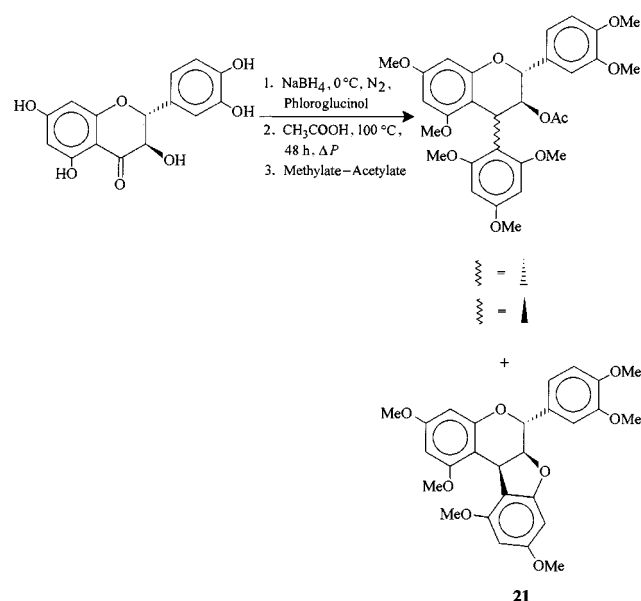
Compound	A-Ring		B-Ring			C-Ring			D-Ring	
	6	8	2	5	6	2	3	4	5	7
15 ¹ H NMR in CDCl ₃ ^b	5.88 (2.0)	5.98 (2.0)	6.72, s	—	6.72, s	4.69 (2.5)	5.33 (2.5, 10.0)	5.11 (10.0)	6.17, s	6.17, s
16 ¹ H NMR in [² H ₆]acetone ^b	6.09 (2.5)	6.19 (2.5)	6.74, s	—	6.74, s	4.79 (8.0)	5.03 (8.0, 7.5)	4.85 (7.5)	6.04 (2.5)	6.05 (2.5)
21 ¹ H NMR in [² H ₆]benzene ^b	6.29 (2.3)	6.31 (2.3)	6.97 (2.0)	6.58 (8.7)	6.97 (2.0, 8.7)	5.18 (8.1)	4.79 (8.1, 7.6)	5.11 (7.6)	6.10 (2.1)	6.29 (2.1)
21 ¹³ C NMR in [² H ₆]benzene ^c	94.30	93.19	112.64	112.48	121.24	76.26	82.45	37.80	93.32	90.16

^a Using the numbering scheme given in Scheme 1. ^b δ_{H} ; *J* values are given in Hz in parentheses. ^c δ_{C} .

Table 4 NMR spectral data for methyl ether acetate derivatives of 6-hydroxyphenyl-6a,11b-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromenes^a

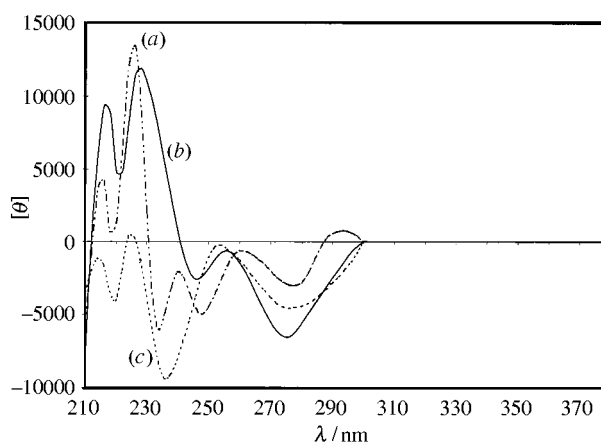
Compound	A-Ring		B-Ring		C-Ring			D-Ring	
	6	8	2	6	2	3	4	5	7
17 ¹ H NMR in CDCl ₃ ^b	5.99 (2.5)	6.23 (2.5)	6.71, s	6.71, s	4.69 (2.0)	5.33 (2.0, 9.5)	5.00 (9.5)	6.19 (2.5)	6.20 (2.5)
17 ¹³ C NMR in CDCl ₃ ^c	93.92	94.12	104.03	104.03	86.48	82.10	36.13	100.5	95.51
18 ¹ H NMR in [² H ₆]acetone ^b	6.08 (2.5)	6.28 (2.5)	6.74, s	6.74, s	4.80 (8.5)	5.00 (8.5, 7.5)	4.75 (7.5)	6.14 (2.2)	6.37 (2.2)
18 ¹³ C NMR in [² H ₆]acetone ^c	92.47	93.34	104.43	104.43	81.07	74.84	37.30	101.15	95.83
18 ¹ H NMR in [² H ₆]benzene ^b	6.19 (2.3)	6.30 (2.3)	6.62, s	6.62, s	5.07 (8.8)	4.62 (7.2, 8.8)	4.88 (7.2)	6.33 (2.1)	6.48 (2.1)
18 ¹³ C NMR in [² H ₆]benzene ^c	93.04	93.90	106.02	106.02	75.56	81.67	38.07	102.13	95.99

^a Using the numbering scheme given in Scheme 1. ^b δ_{H} ; *J* values are given in Hz in parentheses. ^c δ_{C} .



Complete assignment of all proton and carbon resonances was possible through a combination of HETCOR, COLOC and NOE experiments. The closely spaced H-2_C and H-4_C protons were readily assigned from the correlation between the C-4_C carbon signal at δ_{C} 37.80 with the higher field doublet δ_{H} 5.11 and between the C-2_C carbon signal at δ_{C} 76.26 with the lower field doublet at δ_{H} 5.17. The A- and D-ring aromatic protons could be paired by line shape and a subsequent HETCOR experiment then permitted assignment of the carbon resonances.

Whereas these correlations permitted a pairing of proton and carbon resonances, they did not permit assignment to the A- and D-rings. A COLOC experiment optimized for $J_{\text{CH}} = 5$ Hz showed correlations between the H-3_C and D-ring carbons similar to those described for **18**. NOE difference experiments made

**Fig. 2** CD spectra of (a) **21**, (b) **17** and (c) **18**

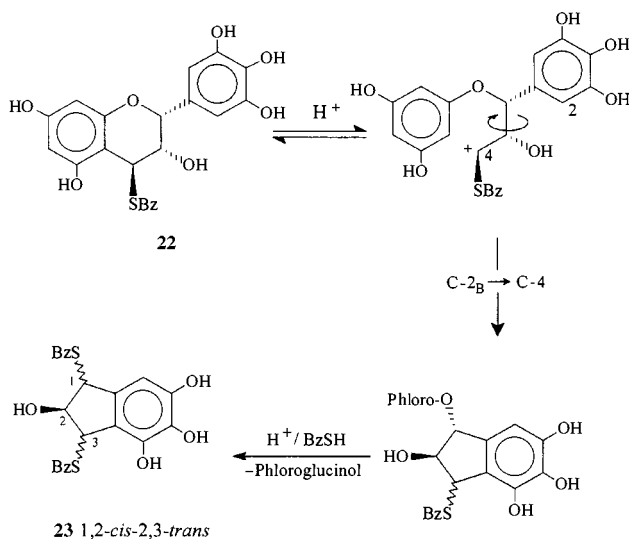
by irradiating each of the well separated methoxy signals then permitted the assignment of H-6_A at δ_{H} 6.29 and H-8_A at δ_{H} 6.31—H-5'_D and H-7'_D were assigned to signals at δ_{H} 6.10 and 6.29, respectively. As was seen in the other examples of dihydrobenzofurans,²¹ the chemical shift of the carbon *ortho* to a dihydrofuran ring is shifted upfield (C-7'_D at δ_{C} 90.16) from those *ortho* or *para* to a dihydropyran ring.

Whereas the sign of the Cotton effect for the peak at approximately 245 nm is a reliable indicator of the absolute stereochemistry at C-4_C in the flavan-4-phloroglucinol adducts, the orientation of the fused dihydrobenzopyran-dihydrobenzofuran ring cannot be established reliably from the CD spectra (Fig. 2). A similar problem exists when attempting to define the absolute stereochemistry of the A-type procyanidin dimers.¹⁴ Because of this problem, we must assume 2*R* stereochemistry for these derivatives parallel to the 2*R* absolute stereochemistry of the major flavan-4-phloroglucinol adducts found in the reaction products. An S_N2 reaction is not required in ring closure to form the dihydrofuran E-ring, therefore one cannot predict the relative stereochemistry of the precursors to

these products. This result is also significant to the formation of **24** and **25** described below.

Formation of hydroxyphenyl-3,2'-spirobi[dihydro[1]benzofuran] derivatives

In an earlier communication,⁷ we described a unique rearrangement involving cleavage of the C-10_A-C-4_C bond when pecan pith tannins were reacted with toluene- α -thiol and acetic acid at 105 °C for 24 to 72 h. The products included a mixture of 1,3-dithiobenzyl-2,4,5,6-tetrahydroxyindane diastereomers. Cleavage of the C-10_A-C-4_C bond in epigallocatechin-(4 β)-benzyl sulfide **22** (Scheme 5) is similar to



Scheme 5 (Bz = benzyl)

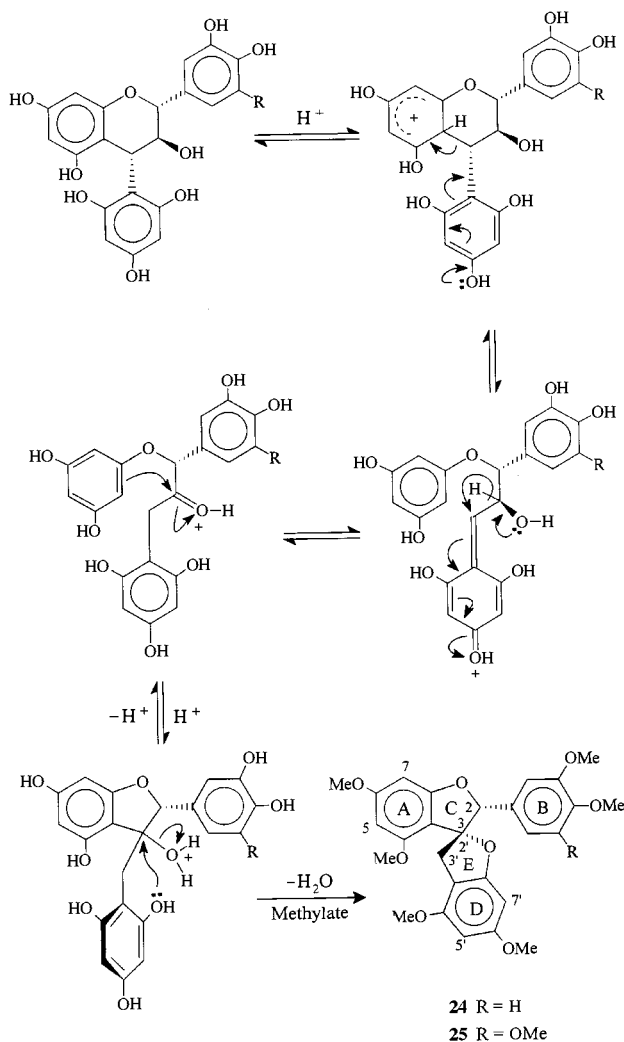
cleaving the interflavanoid bond (C-4_C-C-8_D) of a procyanidin under mild acidic conditions. Nucleophilic attack of C-2_B or C-6_B on the C-4_C carbocation results in ring closure to give two diastereomers. Cleavage of the ether linkage liberates phloroglucinol and allows phenylmethanethiol to attack at that position resulting in the formation of four potential diastereomers of 1,3-dithiobenzyl-2,4,5,6-tetrahydroxyindane. Three of the four possible diastereomers were found with the *cis-trans* isomer **23** being the major product.

A primary objective of this work was to establish whether or not rearrangements involving similar cleavage of the C-10_A-C-4_C bond could be demonstrated in reactions of pecan tannins with phloroglucinol as a capture nucleophile. Past experience has shown that phloroglucinol adducts usually serve as good models for reactions of the 5,7-dihydroxyprocyanidins and prodelphinidins. The isolation of the two products, also with novel ring structures **24** and **25** [(2*R*,3*R*)-2-(3,4-dimethoxyphenyl)-4,4',6,6'-tetramethoxy-3,2'-spirobi[2,3-dihydro[1]benzofuran] **24** and (2*R*,3*R*)-2-(3,4,5-trimethoxyphenyl)-4,4',6,6'-tetramethoxy-3,2'-spirobi[2,3-dihydro[1]benzofuran] **25**], confirms the lability of the C-10_A-C-4_C bond when the proanthocyanidins are subjected to prolonged heating in the presence of acetic acid (Scheme 6). Both prodelphinidins and procyanidins suffer this rearrangement. A *Chemical Abstracts* search of this general ring structure found no entries indicating that these compounds are unique both in specific structure and in terms of the basic ring system.

The formation of **24** and **25** is considered to result from cleavage of the C-10_A-C-4_C bond with the formation of a quinomethane. Donation of electrons from the C-3_C hydroxy group and a 1,2 hydride shift is followed by attack of the A-ring (probably directed to the side opposite the B-ring) on the protonated carbonyl intermediate to form the dihydrofuran C-ring (Scheme 6). As described in the formation of **15-18** and **21**, attack of the phloroglucinol D-ring hydroxy group on the C-ring carbon bearing a hydroxy group (with retention of con-

figuration of the oxygen as in the formation of **21**) results in formation of the dihydrofuran E-ring favoring this stereochemistry. Considering the similarity of the C-10_A-C-4_C and C-4_C-C-2_D bonds of the phloroglucinol adducts **1-6**, it seems logical that this reaction should readily occur in acid-catalyzed cleavage of these compounds. An alternate mechanism involving aryl-assisted solvolysis of the protonated alcohol at C-3 to form a dihydrobenzofuran, with a styrenyl unit at C-3 that could allow a second ring closure to form either stereochemistry of the E-ring, was proposed by one of the referees of this paper. Such an intermediate would be expected to be stable owing to conjugation and would have to be isolated to support that proposed mechanism. Because of previous evidence for the lability of the C-10_A-C-4_C bond⁷ we favor the mechanism shown in Scheme 6.

Assignment of the structure of **24** followed from the ¹H and ¹³C NMR spectra in which the two methylene protons at δ_{H} 2.85 and 2.93 for the H-3'_E protons, six methoxy protons over the range of δ_{H} 3.64-3.84, a one proton singlet for H-2_C at δ_{H} 4.54, two pairs of *meta*-coupled aromatic proton resonances over the range of δ_{H} 6.04-6.19 and a catechol ring evident from an ABX system (Table 5). Irradiation of the H-2_C singlet at δ_{H} 4.54 gave strong enhancement of *meta*-coupled H-2_B at δ_{H} 6.53 and the H-6_B double doublet at δ_{H} 6.58, thus establishing the location of H-2_C and the catechol ring. Irradiation of either of the two methylene protons at δ_{H} 2.85 and 2.93 resulted in the enhancement of H-2_C, although the correlation with the signal at δ_{H} 2.85 was stronger, thus establishing the stereochemistry at C-3_C relative to the B-ring as being *cis* to the oxygen and *trans* to the methylene. Similarly, a NOESY experiment with a mixing time



Scheme 6

Table 5 NMR spectral data for hydroxyphenyl-3,2'-spirobi[dihydro[1]benzofurans]^a

Compound	A-Ring		B-Ring			C-Ring		D-Ring		E-Ring
	5	7	2	5	6	2	3	5	7	3
24 ¹ H NMR in CDCl ₃ ^b	6.09 (2.0)	6.20 (2.0)	6.55 (2.0)	6.77 (8.2)	6.60 (2.0, 8.2)	4.55, s		6.04 (2.0)	6.10 (2.0)	2.85, 2.93 (17.0, 17.0)
24 ¹³ C NMR in CDCl ₃ ^c	92.93	88.85	111.28	120.32	111.28	53.70	124.85	92.09	88.84	34.05
25 ¹ H NMR in CDCl ₃ ^b	6.10 (1.9)	6.20 (1.9)	6.25, s	—	6.25, s	4.52, s		6.07 (1.9)	6.12 (1.9)	2.89, 2.97 (16.9, 16.9)
25 ¹³ C NMR in CDCl ₃ ^c	92.87	88.82	105.11		105.11	54.29	124.16	92.07	88.82	33.96

^a Using the numbering scheme given in Scheme 1. ^b δ_{H} ; J values are given in Hz in parentheses. ^c δ_{C} .

of 1 s showed cross peaks between the H-2_C and both methylene protons of the E-ring as well as H-2_B and H-6_B.

HETCOR and COLOC experiments established the assignments of the A- and D-ring resonances. A COLOC experiment optimized for $J_{\text{CH}} = 5$ Hz gave cross peaks between both H-2_C at $\delta_{\text{H}} 4.55$ and H-7_A at $\delta_{\text{H}} 6.20$ with the C-8_A signal at $\delta_{\text{C}} 159.4$. In the COLOC experiment, the H-7_A proton is also correlated with carbon resonances at $\delta_{\text{C}} 92.93$ and 88.85 , whereas the HETCOR experiment shows connectivity between H-7_A and the carbon at $\delta_{\text{C}} 88.85$. This permits the assignment of H-5_A as the proton at $\delta_{\text{H}} 6.09$. COLOC and HETCOR experiments established the assignments of the protons and connected carbons of the A- and D-rings as described for **25** below. The strong upfield shifts of the C-7_A and C-7_D carbon resonances are consistent with the assignments for aromatic ring protons that are *ortho* to the dihydrofuran bridge carbon observed in compounds **15–18** and **21** and also in other compounds with both dihydrobenzopyran and dihydrobenzofuran rings.²¹

The ¹H and ¹³C NMR spectra of the second product of this basic structure, but with a pyrogallol B-ring **25**, showed two methylene protons at $\delta_{\text{H}} 2.89$ and 2.96 for the H-3'_E protons, seven methoxy groups over the range of $\delta_{\text{H}} 3.65$ to 3.85 , a singlet at $\delta_{\text{H}} 4.50$ assigned to H-2_C, four *meta*-coupled aromatic protons of the A- and D-ring between $\delta_{\text{H}} 6.05$ and 6.19 , and a two-proton singlet at $\delta_{\text{H}} 6.23$ for H-2_B and H-6_B (Table 4). As was encountered in **24**, symmetry presented a challenge in assigning the resonances for the A- and D-rings of **25**. Although the *meta*-coupled aromatic protons for the A- and D-rings could be paired by line shape, it was not possible to make an assignment for each ring from the ¹H NMR spectrum.

A COLOC experiment optimized for a J_{CH} of 5 Hz showed a cross peak between H-2_C at $\delta_{\text{H}} 4.51$ and H-7_A at $\delta_{\text{H}} 6.20$ with the C-8_A resonance at $\delta_{\text{C}} 159.35$ as well as C-9_A at $\delta_{\text{C}} 109.16$, thus establishing the A-ring resonances. Correlations between H-7_A and C-8_A and H-5_A with C-9_A established the assignments for the two aromatic protons of the A-ring as $\delta_{\text{H}} 6.20$ and 6.10 . The H-5'_D and H-7'_D protons could then be assigned to the doublets at $\delta_{\text{H}} 6.33$ and 6.48 . A HETCOR experiment then permitted assignments of the relevant protonated carbon resonances and COLOC experiments optimized for J_{CH} of 5 and 10 Hz coupling, permitted assignments of the methoxy signals. Correlation of the MeO-4_B with C-4_B was only seen in the experiment optimized for 10 Hz coupling. A NOE difference experiment on **25**, irradiating the two H-3'_E protons, showed strong enhancement of the H-2_C proton and to H-2_B and H-6_B as well as H-7'_D. The strong enhancement of H-2_C, in particular, requires a 2,3-*cis* orientation of the B-ring with the oxygen connected to C-3.

Whereas the relative stereochemistry was readily established through NOE experiments, interpretation of the CD spectra of **24** and **25** is not straightforward (Fig. 3). There is a strong negative Cotton effect at about 240 nm and a positive signal at about 230 nm in **24** but the introduction of a pyrogallol moiety instead of a pyrocatechol ring in **25** results in a large shift to lower wavelength for the strong peaks in **25** and shows a strong positive Cotton effect at about 230 nm and a negative signal at 220 nm. Because both compounds were derived from flavans with *2R* absolute stereochemistry and both compounds showed

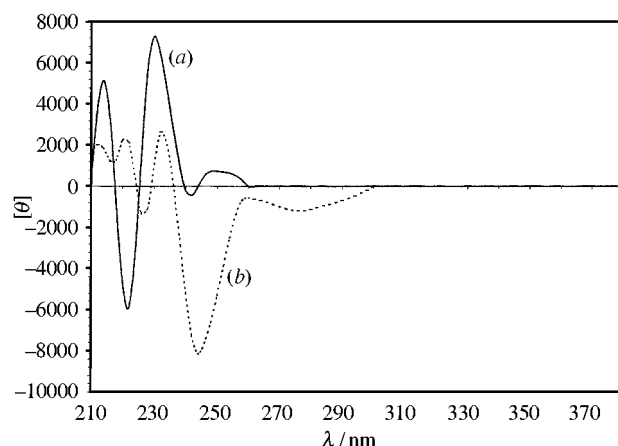


Fig. 3 CD spectra of (a) **25** and (b) **24**

significant NOE between the H-2_C and H-3'_E protons, the CD spectra do not seem to afford a consistent pattern that will allow assignment of the absolute stereochemistry of these compounds. For now, we must assume that these products have *2R* stereochemistry as drawn on the basis of the known absolute stereochemistry of the starting compounds.

Conclusions

Although acid-catalyzed cleavage of procyanidins and prodelphinidins has been proposed as a quantitative method for determination of condensed tannin polymer structure,^{5,6} we have not been successful in obtaining quantitative yields of thiol or phloroglucinol adducts from natural plant extracts. This work demonstrates that, if the reaction of procyanidins or prodelphinidins with phloroglucinol and acetic acid is forced by heating at 100 °C for 24 h or more, secondary rearrangements involving inversion of the stereochemistry of the pyran ring at C-2 in flavan-4-phloroglucinol adducts, and dehydration to [1]benzofuro[2,3-*c*]chromenes occur. In addition, rearrangements resulting from cleavage of the C-10_A-C-4_C bond, with the formation of either 1,3-dithiobenzyl-2,4,5,6-tetrahydroindanes in reactions with phenylmethane thiol or (*2R,3R*)-2-(3,4-dihydroxy or 3,4,5-trihydroxyphenyl)-3,2'-spirobi[2,3-dihydro[1]benzofurans] in reactions with phloroglucinol, are significant side reactions. Certainly, the use of acetic acid-catalyzed cleavage in the presence of capture nucleophiles for quantitative analysis of the structure of procyanidin and prodelphinidin polymers must be questioned particularly if prolonged heating at 100 °C is needed to obtain higher yields of flavan-4-adducts.

There is no reason to suggest that these same rearrangements are not occurring intermolecularly during industrial processing of tannin extracts where comparatively high temperatures and low pH environments are encountered. The condensed tannins such as those extractable from pecan nut pith offer a renewable resource base for manufacture of a broad spectrum of specialty chemicals. Compounds with these novel ring systems could be produced from renewable resources that currently represent

a solid waste management problem if high value uses could be found for them.

Experimental

The pith (lightweight tissue between the hard shell and the fruit) from pecan nut processing waste was provided by PX Inc., Memphis, TN. Extraction with acetone–water (1:1, v/v) afforded the crude tannin extract that was used in the reactions. A purified tannin fraction was obtained by chromatography on LH-20 Sephadex, removing any carbohydrate present by first eluting with methanol–water (1:1, v/v) leaving the tannin absorbed on the column and then with acetone–water (1:1, v/v) to remove the tannin from the column.

The purified tannin (2 g) and phloroglucinol (2 g) were dissolved in EtOH (75 ml) and glacial acetic acid (5 ml) was added. The mixture was flushed with N₂ before it was heated at 100 °C for 24 h in a 'capped' reaction vial. This procedure was repeated, once at 100 °C for 24 h and (in the case of 2 reactions) at 100 °C for 48 h. The reaction mixtures were freeze-dried and combined to yield the crude product (14.4 g). After EtOAc extraction from water, the combined organic layer was dried with Na₂SO₄ and concentrated to ca. 50 ml after which water (300 ml) was added and the mixture was freeze-dried. Column chromatography (CC) of 6.5 g of the product on Sephadex LH-20 (2.5 × 100 cm, EtOH, 16 min fractions at a flow rate of 1 ml min⁻¹) afforded the following fractions:

First 300 ml	Discarded	
Tubes 18–32	Fraction A	2.59 g
Tubes 33–49	Fraction B	143 mg
Tubes 50–66	Fraction C	206 mg
Tubes 67–81	Fraction D	267 mg
Tubes 82–95	Fraction E	343 mg
Tubes 96–124	Fraction F	584 mg
Tubes 125–143	Fraction G	229 mg
Tubes 144–195	Fraction H	327 mg
Tubes 196–210	Fraction I	58 mg
Column residue		2.199 g

Each of these fractions was methylated with diazomethane; fractions isolated by PLC on silica gel were acetylated with acetic anhydride–pyridine and compounds were isolated by PLC as described below. PLC solvents included H–EA–A = hexane–ethyl acetate–acetone, and B–A = benzene acetone in the proportions described below.

NMR spectra were recorded at 300.13 MHz for proton and 75.47 MHz for carbon spectra using Bruker AC300 and AM300 spectrometers. CD data were recorded in methanol. High resolution FAB MS was performed by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, NE.

(2*R*,3*R*)-2-(3,4-Dimethoxyphenyl)-4,4',6,6'-tetramethoxy-3,2'-spirobi[2,3-dihydro[1]benzofuran] 24

Methylation of the D fraction (267 mg) followed by PLC (H–EA–A, 7:2:1 v/v) gave four main bands, D-1 (*R*_f 0.49, 5 mg), D-2 (*R*_f 0.34, 25 mg), D-3 (*R*_f 0.27, 20 mg) and D-4 (*R*_f 0.14, 70 mg). Acetylation and PLC purification (B–A; 95:5 v/v) of the D-2 band gave two bands, D-2.1 (*R*_f 0.53, 4.5 mg) and D-2.2 (*R*_f 0.47, 5 mg). The former yielded the novel title compound as an amorphous solid [HRMS (FAB) Found: M⁺, 480.1738 (100%). C₂₇H₂₈O₈ requires *M*, 480.1739]; ¹H NMR (Table 5); ¹³C NMR (Table 5); CD [*θ*]_{208.9} 1.69 × 10³, [*θ*]_{212.9} 2.06 × 10³, [*θ*]_{216.9} 1.09 × 10³, [*θ*]_{220.9} 2.47 × 10³, [*θ*]_{226.7} -1.53 × 10³, [*θ*]_{232.4} 2.71 × 10³, [*θ*]_{244.4} -8.1 × 10³, [*θ*]_{259.2} -5.58 × 10² and [*θ*]₂₈₀ -1.13 × 10³.

(6*R*,6*a*,11*b*,11*s*)-6-(3,4-Dimethoxyphenyl)-1,3,9,11-tetramethoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 21

The D-2.2 band afforded the novel title compound as an

amorphous solid [HRMS (FAB) found: M⁺, 480.1770 (85%). C₂₇H₂₈O₈ requires *M*⁺, 480.1784]; ¹H NMR (Table 3); ¹³C NMR (Table 3).

(2*R*,3*R*)-2-(3,4,5-Trimethoxyphenyl)-4,4',6,6'-tetramethoxy-3,2'-spirobi[2,3-dihydro[1]benzofuran] 25

Methylation of the E fraction (343 mg) followed by PLC (B–A; 92:8) gave six bands, E-1 (*R*_f 0.64, 1.7 mg), E-2 (*R*_f 0.58, 15 mg), E-3 (*R*_f 0.5, 99 mg), E-4 (*R*_f 0.39, 15 mg), E-5 (*R*_f 0.29, 49 mg) and E-6 (*R*_f 0.22, 22 mg). Acetylation of the E-2 band gave the novel title compound as an amorphous solid [HRMS (FAB) found: M⁺, 510.1872 (100%). C₂₈H₃₀O₉ requires *M*⁺, 510.1889]; ¹H NMR (Table 5); ¹³C NMR (Table 5); CD [*θ*]_{205.9} -1.22 × 10⁴, [*θ*]_{213.7} 5.12 × 10³, [*θ*]_{222.2} -5.9 × 10³, [*θ*]_{229.7} 7.32 × 10³, [*θ*]_{241.7} -4.77 × 10² and [*θ*]_{247.7} 7.26 × 10².

(6*R*,6*a*,11*b*,11*s*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9,11-tetramethoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 16

The E-3 fraction was further resolved with PLC (H–EA–A; 7:2:1) to give two bands E-3.1 (*R*_f 0.41, 27 mg) and E-3.2 (*R*_f 0.32, 43 mg). Acetylation and PLC purification of the E-3.1 band (B–A; 95:5) gave the title compound (*R*_f 0.44, 25 mg) that was an analog of **18** as an amorphous solid; ¹H NMR (Table 3).

(6*R*,6*a*,11*b*,11*s*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9-trimethoxy-11-acetoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 18

Acetylation and PLC purification (B–A; 95:5) of the E-3.2 band gave the title compound as an amorphous solid (*R*_f 0.32, 40 mg) [HRMS (FAB) found: M⁺, 538.1825 (100%). C₂₉H₃₀O₁₀ requires *M*⁺, 538.1839]; ¹H NMR (Table 4); ¹³C NMR (Table 4); CD [*θ*]_{204.8} -1.04 × 10⁴, [*θ*]_{214.4} -1.08 × 10³, [*θ*]_{219.7} -4.13 × 10³, [*θ*]_{224.7} 5.98 × 10², [*θ*]_{236.7} -9.40 × 10³, [*θ*]_{253.7} -2.29 × 10² and [*θ*]_{276.7} -4.57 × 10³.

Epicatechin-(4β → 2)-phloroglucinol hepta-*O*-methyl ether 3-*O*-acetate 1

Acylation and PLC purification (B–A; 95:5) of the E-5 band gave two bands E-5.1 (*R*_f 0.35, 12 mg) and E-5.2 (*R*_f 0.3, 18 mg). The E-5.1 band afforded the previously described title compound as an amorphous solid; ¹H NMR (Table 1); ¹³C NMR (Table 2); CD [*θ*]_{212.8} 6.81 × 10³, [*θ*]_{219.8} 5.44 × 10³, [*θ*]₂₃₀ 9.92 × 10², [*θ*]₂₄₃ 2.39 × 10⁴ and [*θ*]₂₈₃ 1.07 × 10³.

Gallocatechin-(4β → 2)-phloroglucinol octa-*O*-methyl ether 3-*O*-acetate 5

The E-5.1 band afforded the previously described title compound as an amorphous solid; ¹H NMR (Table 1); ¹³C NMR (Table 2).

Catechin-(4*α* → 2)-phloroglucinol hepta-*O*-methyl ether 3-*O*-acetate 3

Acetylation of the E-6 band afforded the previously described title compound as an amorphous solid; ¹H NMR (Table 1); ¹³C NMR (Table 2), CD [*θ*]_{205.5} -1.77 × 10⁴, [*θ*]_{214.4} 1.09 × 10⁴, [*θ*]_{221.1} -8.83, [*θ*]_{225.1} -4.14 × 10², [*θ*]_{230.7} -6.5, [*θ*]_{235.1} -2.54, [*θ*]_{243.8} -4.82 × 10⁴, [*θ*]_{271.8} 3.68 and [*θ*]_{283.8} -2.34.

ent-Epigallocatechin-(4β → 2)-phloroglucinol octa-*O*-methyl ether 3-*O*-acetate 14

Methylation of the F fraction (675 mg) followed by PLC (B–A; 95:5) gave six bands, F-1 (*R*_f 0.56, 3 mg), F-2 (*R*_f 0.47, 27 mg), F-3 (*R*_f 0.39, 43 mg), F-4 (*R*_f 0.34, 36 mg), F-5 (*R*_f 0.25, 27 mg) and F-6 (*R*_f 0.17, 90 mg). Acetylation and PLC purification (H–EA–A; 7:2:1) of the F-5 band afforded the novel title compound as an amorphous solid [HRMS (FAB) found: [M + H]⁺, 585.2329 (100%). C₃₁H₃₆O₁₁ requires *MH*⁺, 585.2335]; ¹H NMR (Table 1); ¹³C NMR (Table 2); CD [*θ*]_{204.1} 2.45 × 10⁴, [*θ*]_{219.1} 3.27 × 10³, [*θ*]_{225.8} 2.22 × 10⁴, [*θ*]_{232.4} -5.17 × 10³, [*θ*]_{243.7} 1.06 × 10⁴ and [*θ*]_{279.7} -1.03 × 10³.

Epigallocatechin-(4 β \rightarrow 2)-phloroglucinol octa-*O*-methyl ether 3-*O*-acetate 2

Acetylation of the F-6 band afforded the previously described title compound as an amorphous solid; ^1H NMR (Table 1); ^{13}C NMR (Table 2); CD $[\theta]_{205.3} -1.06 \times 10^4$, $[\theta]_{213.6} 9.75 \times 10^3$, $[\theta]_{220.8} -2.49 \times 10^3$, $[\theta]_{229.9} 1.62 \times 10^4$, $[\theta]_{233.5} 1.35 \times 10^4$, $[\theta]_{243.7} 4.58 \times 10^4$ and $[\theta]_{282.2} 9.80 \times 10^2$.

(6*R*,6*aR*,11*bR*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9,11-tetra-methoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 15

Methylation of the G fraction (223 mg) followed by PLC (B-A; 9:1) gave four bands, G-1 (R_f 0.49, 7 mg), G-2 (R_f 0.44, 16 mg), G-3 (R_f 0.29, 25 mg) and G-4 (R_f 0.23, 27 mg). Acetylation of the G-1 band afforded the novel title compound as an amorphous solid; ^1H NMR (Table 3).

(6*R*,6*aR*,11*bR*)-2-(3,4,5-Trimethoxyphenyl)-1,3,9-trimethoxy-11-acetoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 17

Acetylation and PLC purification (B-A; 95:5) of the G-2 band gave three bands G-2.1 (R_f 0.41, 3 mg), G-2.2 (R_f 0.36, 3.2 mg) and G-2.3 (R_f 0.33, 3.5 mg). The G-2.3 band afforded the novel title compound as an amorphous solid; ^1H NMR (Table 4); ^{13}C NMR (Table 4); CD $[\theta]_{209.2} -1.17 \times 10^4$, $[\theta]_{216.8} 9.84 \times 10^3$, $[\theta]_{221.1} 4.03 \times 10^3$, $[\theta]_{227.3} 1.21 \times 10^4$, $[\theta]_{246.3} -2.59 \times 10^3$, $[\theta]_{256.3} -6.53 \times 10^2$ and $[\theta]_{278.3} -6.15 \times 10^3$.

Galocatechin-(4*a* \rightarrow 2)-phloroglucinol octa-*O*-methyl ether 3-*O*-acetate 4

Acetylation of the G-4 band gave the previously described title compound as an amorphous solid; ^1H NMR (Table 1); ^{13}C NMR (Table 2); CD $[\theta]_{202.2} 3.42 \times 10^3$, $[\theta]_{206.7} 5.68 \times 10^2$, $[\theta]_{216.7} 1.03 \times 10^4$, $[\theta]_{223.3} -8.40 \times 10^3$, $[\theta]_{229.3} 1.14 \times 10^3$, $[\theta]_{242.3} -1.73 \times 10^4$ and $[\theta]_{272} 1.66 \times 10^3$.

Synthesis of (6*R*,6*aS*,11*bS*)-6-(3,4-dimethoxyphenyl)-1,3,9,11-tetramethoxy-6*a*,11*b*-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromene 21

Dihydroquercetin (400 mg, 1.314×10^{-3} mol) and phloroglucinol (1.2 g, 9.516×10^{-3} mol) were dissolved in EtOH (80 ml) and stirred under N_2 at 0 °C. NaBH_4 (100 mg, 2.628×10^{-3} mol) was added and the reaction followed by TLC for the *in situ* formation of the resultant flavan-3,4-diol. The pH was then adjusted to ~4 with 5% aqueous acetic acid and the reaction mixture allowed to warm to room temp. overnight. After 12 h the pH was brought to ~3 with 0.1 M HCl and the mixture stirred for another 6 h. The mixture was extracted with EtOAc (5 \times 150 ml), the combined organic layer was concentrated to ca. 50 ml after which water (200 ml) was added and the mixture was freeze-dried. The residue was redissolved in EtOH (75 ml). Glacial acetic acid (5 ml) was added and the vial 'capped'. The mixture was then heated at 100 °C for 48 h, after which water (800 ml) was added and the resultant mixture extracted with EtOAc (5 \times 150 ml); the combined organic layer was dried with Na_2SO_4 and evaporated to dryness. The residue (1.7 g) was separated on a Sephadex LH-20 (EtOH) column (2 \times 50 cm, 1 ml min^{-1} flow rate, 16 min fractions, first 100 ml eluent discarded) and the fractions combined as follows: tubes 16–28 (recovered phloroglucinol), tubes 86–112 TF-1 (96 mg), tubes 121–158 TF-2 (77 mg).

Methylation of the TF-1 fraction (96 mg) followed by PLC (B-A, 9:1) gave five main bands, TF-1.1 (R_f 0.64, 5 mg), TF-1.2 (R_f 0.61, 20 mg), TF-1.3 (R_f 0.57, 22 mg), TF-1.4 (R_f 0.54, 10 mg) and TF-1.5 (R_f 0.36, 8.3 mg). The TF-1.2 fraction afforded the novel title compound as an amorphous solid; ^1H NMR (Table 3); ^{13}C NMR (Table 3), CD $[\theta]_{203.8} -3.8 \times 10^3$, $[\theta]_{208.8} -7.41 \times 10^3$, $[\theta]_{214.9} 4.78 \times 10^3$, $[\theta]_{218.9} 5.41 \times 10^4$, $[\theta]_{225.5} 1.37 \times 10^4$, $[\theta]_{233.7} -6.08 \times 10^3$, $[\theta]_{240.8} -2.08 \times 10^3$, $[\theta]_{248.1}$

-4.98×10^3 , $[\theta]_{259.5} -6.87 \times 10^2$, $[\theta]_{279.8} -2.84 \times 10^3$ and $[\theta]_{288.8} 4.17 \times 10^2$. In addition, compound 3 and its 4 β -isomer were also recovered from this synthesis.

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