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

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Acetic acid-catalyzed cleavage of proanthocyanidins in the presence of phloroglucinol gives a series of 2*R* procyanidin- and prodelphinidin-phloroglucinol adducts together with a novel 2*S* all-*cis* derivative implicating cleavage of the pyran ring and subsequent inversion of stereochemistry at C-2_C. These flavan-4-phloroglucinol adducta 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 Scars and Casebier[1] 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 *oo the* condensed tannins from pecan nut pith indicated that these polymers were ma& 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 mtthylation and acetylation of the products, a series of proanthocyanidin derivatives including the known methyl ether 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]

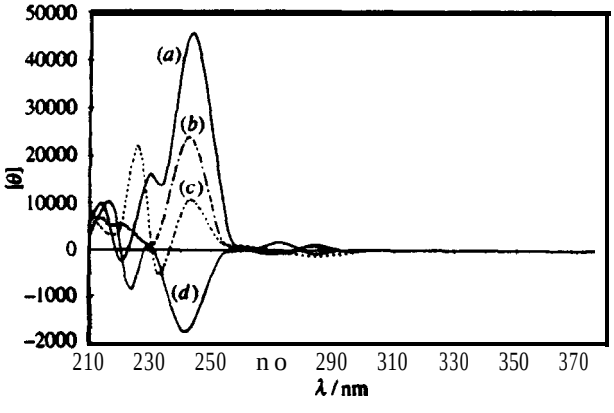
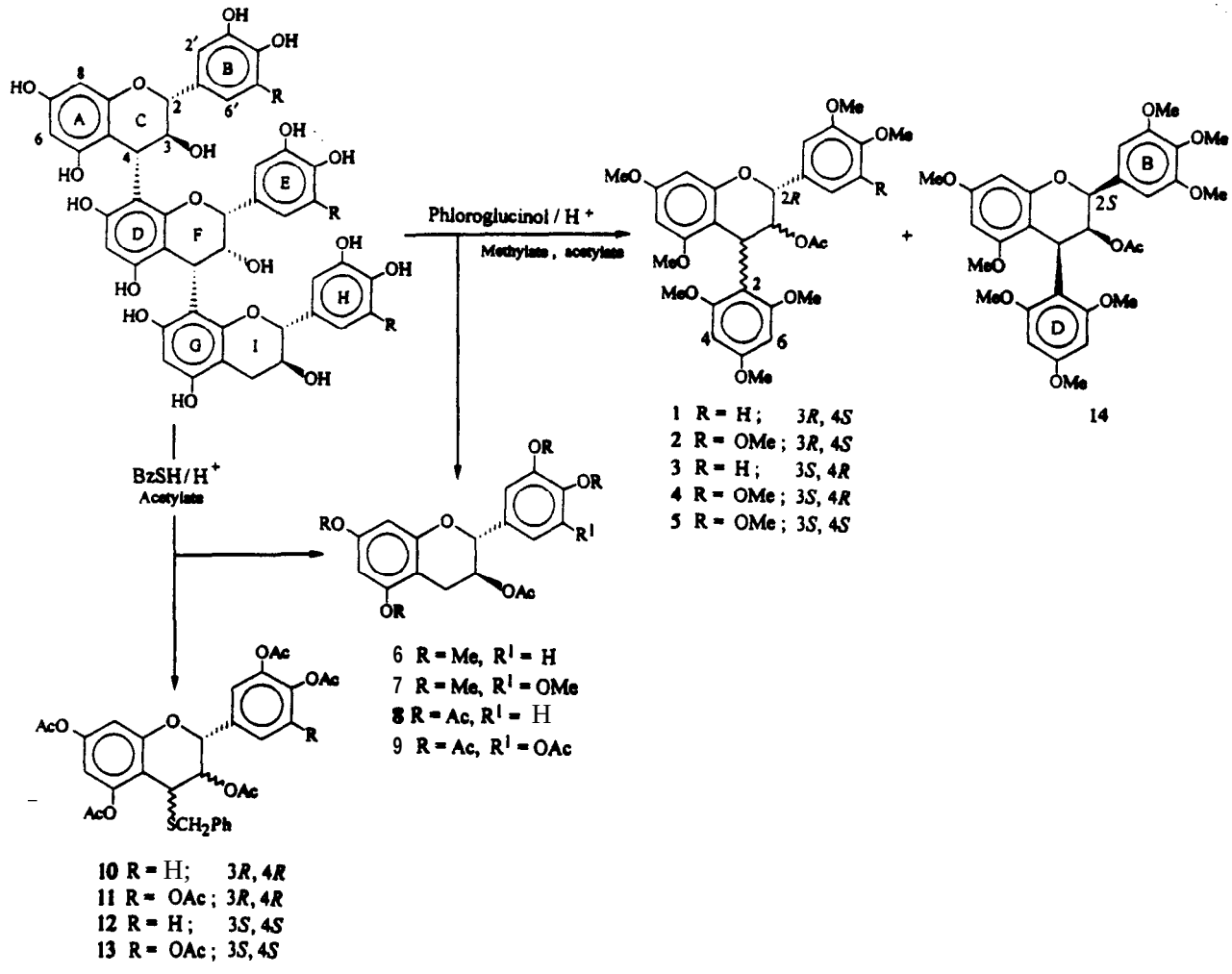


Fig. 1 CD spectra of (*a*) 2, (*b*) 1, (*c*) 14 and (*d*) 4

^{1}H NMR (Tab& 1), ^{13}C 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 nlativt 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-4α-benzyl sulfide 10, gallocatechin-4α-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.[7]



Scheme 1

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

Surprisingly, two **epigallocatechin phloroglucinol adducts,** 2 and **14.** each with simii 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 **4*S*** (a g-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 **2*S*,3*S*,4*S* (all-*cis*)** absolute **stereochemistry for** the novel ***ent*-epigallocatechin-(4β ⟶ 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 phloroghrcinol 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 group of the **B-** and D-rings as were seen in 14. Therefore, 2 is assigned **2*R* 2,3-*cis*-3,4-*trans* stereochemistry.**

Isolation of a **2*S* 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, **Kolodziej**[13] 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 a-substitution of the 2R **2,3-*cis* carbocation** is rarely observed." 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 quioomethane 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]

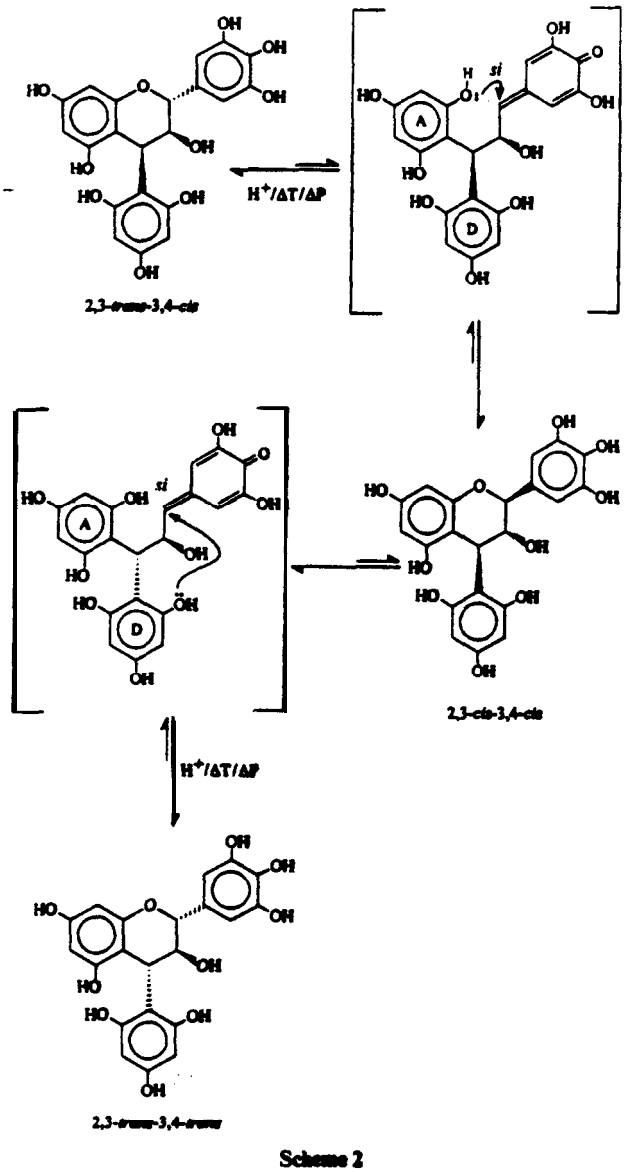
The similarity of the heterocyclic ring coupling constants for the **2,3-*cis*-3,4-*trans*** and **2,3-*cis*-3,4-*cis*** isomers of these compounds **serves** as a warning that **one** cannot predict the relative stereochemistry at **C-4$_C$** in **2,3-*cis*** isomers only on the basis of the heterocyclic ring coupling constants The presence of 14 in reaction products otherwise dominated by **flavan-4-phloroglucinol adducts** of **2*R*** 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 literature**[16] 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, for selected compounds were **verified** by NOE experiments using **MeO-5$_A$** and **MeO-7$_A$,** the former showing a correlation to H-6, and the latter showing a correlation to both **H-6$_A$** and H-8,. A C-H **HETCOR** experiment then **showed** a correlation between the consistently higher field ***meta*-coupled** H-6, doubkt 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] Discrepanci**a arising from analysis of the **^{13}C** NMR spectra of polymers and the relative yields of the

Table I ^1H NMR spectral data[a,b] for the methyl ether acetate derivatives of pmdelphinidin- and procyanidin-phloroglucinol adducts

Compound	A-Ring		B-Ring		C-Ring			D-Ring		
	H-6	U-8	H-2	H-5	H-6	H-2	H-3	H-4	H-4	H-6
1 Epicatechin-(4β ⟶ 2)-phloroglucinol	6.02 (2.5)	6.25 (2.5)	6.93 (2.2)	6.77 (8.5)	6.87	5.33	5.23	4.55 (2.2)	6.20, br s, 2H	
2 Epigallocatechin-(4β ⟶ 2)-phloroglucinol	6.04 (2.3)	6.27 (2.3)	6.62. s	—	(2.2, , 8.5) 6.62 s	(1.5) 5.34	(1.5, 2.2) 5.28	4.59 (1.4)	6.20. br s, 2H	
14 ent-Epigallocatechin-(4β ⟶ 2)-phloroglucinol	6.10 (2.5)	6.24 (2.5)	6.47, s	—	6.47, s	(≤1) (1.5)	(1, 1.5) (1.5, 2.0)	4.25 (2.0)	6.03, s, 2H	
3 Catechin-(4α ⟶ 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-(4α ⟶ 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. brr
5 Gallocatechin-(4β ⟶ 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; /values are given in Hz in parentheses.



Scheme 2

acid-catalyzed cleavage product8 led us to study additional rearrangement reaction8 that might be occurring under acetic acid-catalyzed condition&

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 tho 6% acetic acid dimension in additioo 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 oo silica gel. A series of compounds with dihydrobenzofuran rings were isolated. The 2*R*,3*R*,4*R* (2,3-*cis*-3,4-*cis*) and 2*R*,3*S*,4*S* (2,3-*trans*-3,4-*cis*) [1]benzofuro[2,3-c]chromenes IS and 16 as well as their analogs with an acetoxy in place of a methoxy at the C-4′$_D$ positiona 17 and 18 were isolated. A general structural search of *Chemical Abstracts* revealed oo compounds with this ring system in the literature.¶ Their formation suggested an S_N2 attack of the phloroglucinol hydroxy group oo C-3$_C$, thereby inverting tho stereochemistry of the oxygen at C-3$_C$ (Scheme 3).

The structure of 15 was evident from the ^1H NMR spectrum which showed seven mothoxy groups (δ_H 3.66–3.89), two *meta*-coupkd aromatic proton doubkts (δ_H 5.89-5.98) assigned to 6-H$_A$ and 8-H$_A$, a two proton siogkt at δ_H 6.17 assigned to H-5′$_D$ and H-7′$_D$, and a two proton singkt at δ_H 6.73 for the H-2. and H-6, 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 angk of the α,α orkntation of the fused dihydrobenzopymo and dihydrobenzofuran rings.

Additional evidence for the structure of 15 came from the isolation of the related derivative 17 carrying an acetoxy group (Tabk 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 bo 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 impossibk 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.

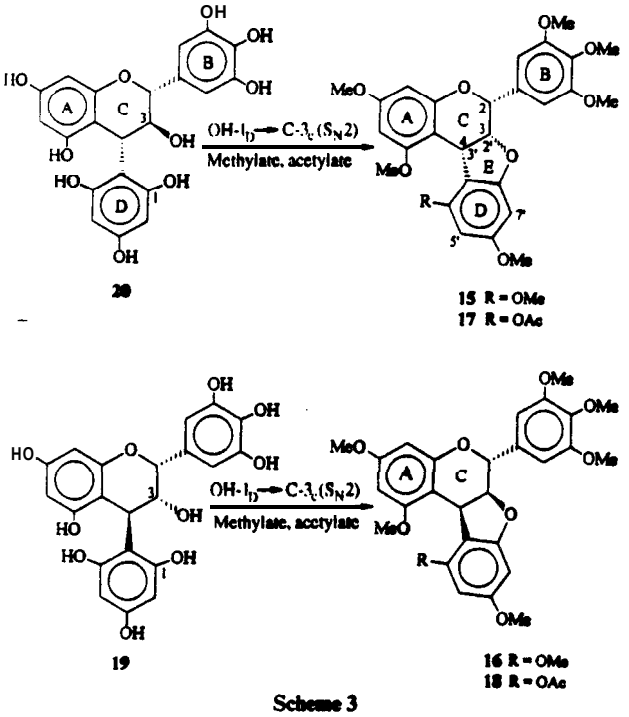
§ Mention of trade names does not constitute endorsemen t by the US Department of Agriculture.

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

Table 2 ^{13}CNMR spectral data' for the methyl ether acetate derivativa of prodelphinidin- and procyanidin-phloroglucinol adducts

Compound	A-Ring		B-Ring			C-Ring			D-Ring	
	C-6	c-a	c-2	C-5	C-6	c-2	c-3	C-4	C-4	C-6
1 Epicatechin-(4β ⟶ 2)-phloroglucinol	91.35	92.73	III.40	I IO.55	I18.91	74.71	71.91	32.53	-91.5	-91.5
2 Epigallocatechin-(4β ⟶ 2)-phloroglucinol	91.51	92.89	103.95	—	103.95	75.00	71.70	32.55	-91.7	-91.7
14 *ent*-Epigallocatechin-(4β ⟶ 2)-phloroglucinol	91.64	93.16	105.34	—	105.34	73.54	68.23	42.28	91.29	91.29
3 Catechin-(4α ⟶ 2)-phloroglucinol	93.24	93.32	I IO.51	I10.42	120.27	80.33	72.82	35.03	~92	-92
4 Gallocatechin-(4α ⟶ 2)-phloroglucinol	93.5	93.5	104.85	—	104.85	80.76	72.91	35.29	92	92
5 Gallocatechin-(4β ⟶ 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 ^{1}H 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 date reported in Table 3 are from the spectrum recorded in [$^2H_6$]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. 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 [$^2H_6$]acetone (Table 4) the heterocychc 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, 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 [$^2H_6$]benzene, rather than $CDCl_3$ or [$^2H_6$]acetone, as the solvent to overcome problems with overlapping signals. No cross peeks between H-2$_C$ at δ_H 5.07 and C-9,. 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_{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, 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, and H-8,. Therefore, the acetoxy group is at C-4′$_D$ as suggested by differences in the acetoxy and methoxy substituent effects on the aromatic carboa signals.

The relative stereochemistry of these products suggests that they might be formed by S_N2 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 methylatioa because of the proximity of the OH-5$_A$ and the OH-4′$_D$ and the resulting hydrogen bond.

Although the formation of these compounds through an S_N2 mechanism is consistent with the above products, additional work on the synthesis of catechin-(4α ⟶ 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 S_N2 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 ['H&enzene (Table 3).

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

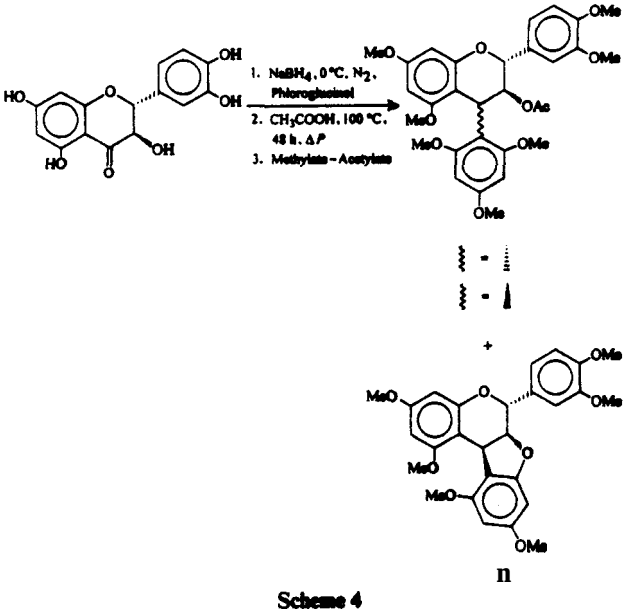
	A-Ring		B-Ring			C-Ring			D-Ring	
Compound	6	a	2	5	6	2	3	4	5	7
IS ^{1}H NMR in $CDCl_3$[b]	5.88 (2.0)	5.98 (2.0)	6.72, s	—	6.72. s	4.69 (2.5)	5.33 (2.5, 10.0)	5.11 (10.0)	6.17, s	6.17. s
16 ^{1}H NMR in [$^2H_6$]acetone[b]	6.09 (2.5)	6.19 (2.5)	6.74. s	—	6.74, s	4.79 (8.0)	5.03 (8.0, 7.5)	4.85 (7.5)	6.04 (2.5)	6.05 (2.5)
21 ^{1}H NMR in [$^2H_6$]benzene[b]	6.29 (2.3)	6.31 (2.3)	6.97 (2.0)	6.58 (8.7)	6.91 (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 [$^2H_6$]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 date for methyl ether acetate derivatives of 6-hydroxyphenyl-6a,11b-dihydro-6*H*-[1]benzofuro[2,3-*c*]chromenes[a]

	A-Ring		B-Ring		C-Ring			D-Ring	
Compound	6	a	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 [$^2H_6$]acetone[b]	6.08 (2.5)	6.28 (2.5)	6.74. s	6.14, 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 [$^2H_6$]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 [$^2H_6$]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 [$^2H_6$]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.



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Scheme 4

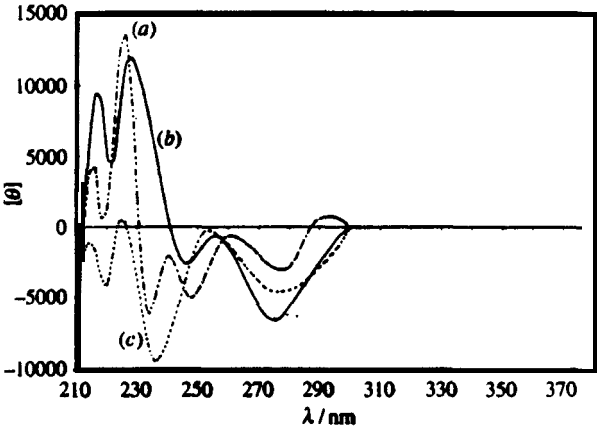


Fig. 2 CD spectra of (a) **21**, (*b*) **17** and (c) **18**

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-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.

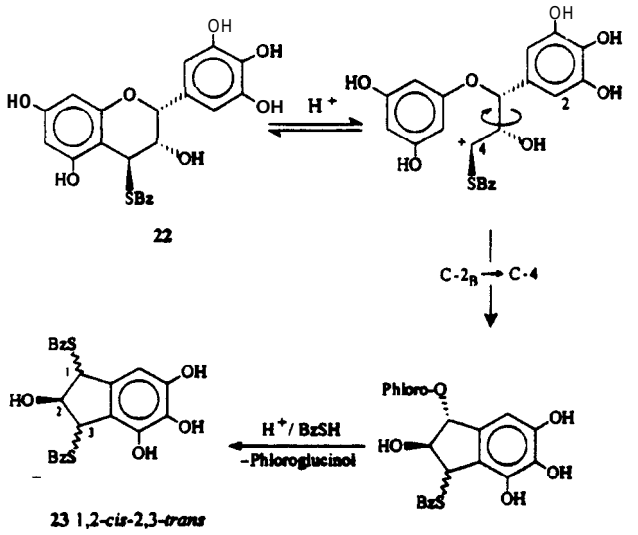
Whereas these correlations permitted a pairing of proton and carbon resonances, they did not permit assignment to the A- and D-rings. A COLOC experiment optimized for J_{CH} = 5 Hz showed correlations between the H-3_C and D-ring carbons similar to those described for 18. NOE difference experiments made by irradiating each of the well separated methoxy signals then permitted the assignment of H-6, 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 2R 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-a-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 diastereomcrs Cleavage of the **C-10$_A$–C-4$_C$** bond in **epigallocatechin-(4β)-benzyl** sulfide 22 (Scheme 5) is similar to



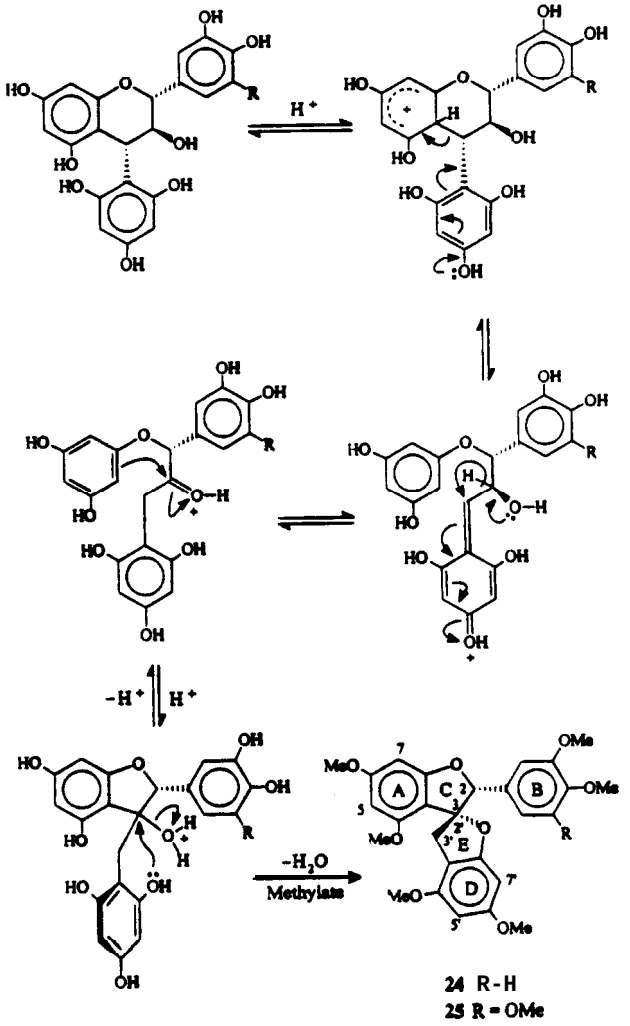
Scheme 5 (Bz = benzyl)

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, **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.** Fast 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 **pro-an**[t] **cyanidins** are subjected to **prolonged** heating in the **pr**[e] **ce** of **acetic** acid (Scheme 6). Roth prodelpbinidins and **pr** **nidins** suffer this rearrangement. A ***Chemical Abstracts*** sear. of this general ring structure found no entries indicating that **tnese** 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 R-ring) on the **protonated carbonyl** intermediate to form the dibydrofuran 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 stabk 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$_C$** bond' we favor the mechanism shown in Scheme 6.

Assignment of the structure of 24 followed from the ^{1}H and ^{13}C 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$_B$** doubk 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, relative to the Bring 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 hydroxypheny' 3,2'-spirobi[dihydro[1]benzofurans][a]

	A-Ring		B-Ring			C-Ring		D-Ring		E-Ring
Compound	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 I. [b] δ_H; /values arc given in Hz in parentheses. [c] δ_C.

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

HETCOR and COLOC experiments established the assign ments of the A- and D-ring resonances A COLOC experiment optimized for J_{CH} = 5 Hz gave cross peaks between both H-2_C at δ_H 4.55 and H-7, at δ_H 6.20 with the C-8, signal at δ_C 159.4. In the COLOC experiment, the H-7, proton is also correlated with carbon resonances at 6c92.93 and 88.85. whereas the HETCOR experiment shows connectivity between H-7, and the carbon at δ_C 88.85. This permits the assignment of H-5_A as the proton at δ_H 6.99. 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 upfitld shifts of the C-7, 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 ^{1}H and ^{13}C NMR spectra of the second product of this basic structure, but with a pyrogallol B-ring **25**, showed two methyknt protons at δ_H 2.89 and 2.96 for the H-$3'_B$ protons, seven methoxy groups over the range of δ_H 3.65 to 3.85, a sing. let at δ_H 4.50 assigned to H-2_C, four *meta*-coupled aromatic protons of the A- and D-ring between δ_H 6.05 and 6.19, and a two-proton singkt at δ_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 lint shape, it was not possible to make an assignment for each ring from the ^{1}H NMR spectrum.

A COLOC experiment optimized for a J_{CH} of 5 Hz showed a cross peak between H-2_C at δ_H 4.51 and H-7_A at δ_H 6.20 with the C-8_A resonance at δ_C 159.35 as well as C-9, at δ_C 109.16, thus establishing the A-ring resonances. Correlations between H-7_A and C-8, and H-5, with C-9, established the assignments for the two aromatic protons of the A-ring as δ_H 6.20 and 6.10. The H-$5'_D$ and H-$7'_D$ protons could then he assigned to the doublets at δ_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, was only seen in the experiment optimixed for 10 Hz coupling A NOE difference experiment on **25**, irradiating the two H-$3'_B$ protons, showed strong enhancement of the H-2, proton and to H-2. and H-6, 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). Them 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 2*R* absolute stereochemistry and both compounds showed

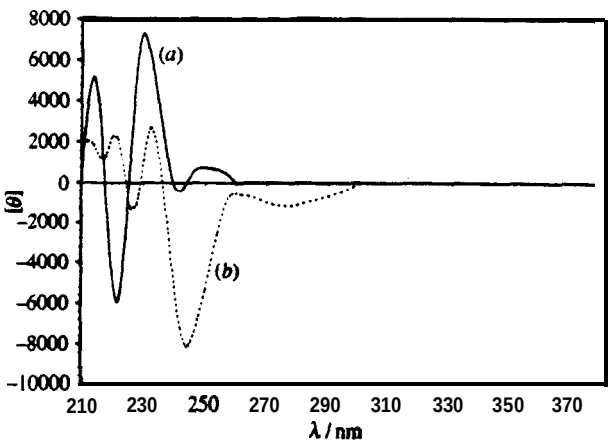


Fig. 3 CD spectra of (a) **25** and (b) 24

significant NOE between the H-2, and H-3', 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, rearrange. ments resulting from cleavage of the C-10_A–C-4_C bond, with the formation of either 1,3-dithiobenzyl-2,4,5,6-tetrahydroxyindanes in reactions with phenylmethane thiol or (2*R*,3*R*)-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 prodtlphinidin 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 inter-molecularly 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 speciality chemicala Compounds with these novel ring systems could be produced from renewable resources that currently represent

a solid w ste 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:I, 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 N_2 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 Na_2SO_4 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 mitt-') 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 67-8 1	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 methyiated 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 tbe Midwest Center for Man 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) foiiowai 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 ban4 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 titk compound as an *amorphous solid* [HRMS (FAB) Found: M^+, 480.1738 (IOU!!). $C_{27}H_{28}O_8$ requires *M*, 480.17391; ^1H NMR (Table 5); ^{13}C NMR (Table 5); CD $[\theta]_{288.9}$ 1.69 ×10^3, $[\theta]_{212.9}$ 2.06 ×10^3, $[\theta]_{216.9}$ 1.09 × 10^3, $[\theta]_{228.9}$ 2.47 × 10^3, $[\theta]_{236.7}$ -1.53 × IO', $[\theta]_{232.4}$ 2.71 × 10^3, $[\theta]_{244.4}$ -8.1 ×10^3, $[\theta]_{259.2}$ -5.58 ×10^2 and $[\theta]_{280}$ −1.13 × 10^3.

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

The D-2.2 band afforded the novel titk compound as an amorphous solid [HRMS (FAB) found: M^+, 480.1770 (85%). $C_{27}H_{28}O_8$ requires M^+, 480.17841; ^1H NMR (Table 3): ^{13}C 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%). $C_{28}H_{30}O_9$ requires M^+, 510.1889); ^1H NMR (Table 5); ^{13}C NMR (Table 5); CD $[\theta]_{295.9}$ − I.22 x 10^4, $[\theta]_{213.7}$ 5.12 × IO', $[\theta]_{222.2}$ -5.9 ×10^3, $[\theta]_{229.7}$ 7.32 ×10^3, $[\theta]_{241.7}$ -4.77 ×10^2 and $[\theta]_{247.7}$ 7.26 ×10^2.

(6*R*,6a*S*,11b*S*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9,11-tetramethoxy-6a,11b-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 (J?, 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*,6a*S*,11b*S*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9-trimethoxy-11-acetoxy-6a,11b-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 (loo"?). $C_{29}H_{30}O_{10}$ requires M^+, 538.1839); ^1H NMR (Table 4); ^{13}C NMR (Table 4); CD $[\theta]_{294.8}$ − 1.04 × 10^4, $[\theta]_{214.4}$ − 1.08 × 10^3, $[\theta]_{219.7}$ -4.13 ×10^3, $[\theta]_{224.7}$ 5.98 ×10^2, $[\theta]_{236.7}$ -9.40 × IO', $[\theta]_{253.7}$ -2.29 ×10^2 and $[\theta]_{276.7}$ -4.57 ×10^3.

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 I); ^{13}C NMR (Tabb 2); CD $[\theta]_{212.9}$ 6.81 × IO', $[\theta]_{219.8}$ 5.44 ×10^3, $[\theta]_{230}$ 9.92 ×10^2, $[\theta]_{243}$ 2.39 ×10^4 and $[\theta]_{283}$ 1.07 ×10^3.

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); ^{13}C NMR (Table 2).

Catechin-(4α ⟶ 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 I); ^{13}C NMR (Table 2), CD $[\theta]_{288.5}$ -1.77 × IO'. $[\theta]_{214.4}$ 1.09 × IO', $[\theta]_{221.1}$ -8.83, $[\theta]_{2.1}$ −4.14 × 10^2, $[\theta]_{230.7}$ -6.5 $[\theta]_{235.1}$ -2.54, $[\theta]_{243.9}$ -4.82 ×10^4, $[\theta]_{271.8}$ 3.68 and $[\theta]_{283.8}$ -2.G

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

Methyiation of the F fraction (675 mg) foiiowed by PLC (B–A; 95: 5) gave six bands, F-i (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-E&& 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%). $C_{31}H_{36}O_{11}$ requires MH^+, 585.2335; ^1H NMR (Table 1); ^{13}C NMR (Table 2); CD $[\theta]_{204.1}$ 2.45 ×10^4, $[\theta]_{219.1}$ 3.27 ×10^3, $[\theta]_{225.8}$ 2.22 ×10^4, $[\theta]_{232.4}$ -5.17 ×10^3, $[\theta]_{243.7}$ 1.06 × Wand $[\theta]_{279.7}$ − 1.03 ×10^3.

Epigallocatechin-(4β ⟶ 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; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); CD $[\theta]_{205.3}$ -1.06 ×10^4, $[\theta]_{213.6}$ 9.75 ×10^3, $[\theta]_{220.8}$ -2.49 × IO', $[\theta]_{229.9}$ 1.62 × IO', $[\theta]_{233.5}$ 1.35 ×10^4, $[\theta]_{243.7}$ 4.58 ×10^4 and $[\theta]_{282.2}$ 9.80 ×10^2.

(6*R*,6a*R*,11b*R*)-6-(3,4,5-Trimethoxyphenyl)-1,3,9,11-tetramethoxy-6a,11b-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-l (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-l band afforded the novel title compound as an amorphous solid; 'H NMR (Table 3).

(6*R*,6a*R*,11b*R*)-2-(3,4,5-Trimethoxyphenyl)-1,3,9-trimethoxy-11-acetoxy-6a,11b-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; ^{1}H NMR (Table 4); ^{13}C NMR (Table 4); CD $[\theta]_{209.2}$ -1.17 ×10^4, $[\theta]_{216.8}$ 9.84 × 10'. $[\theta]_{221.1}$ 4.03 ×10^3, $[\theta]_{227.3}$ 1.21 ×10^4, $[\theta]_{246.3}$ -2.59 ×10^3, $[\theta]_{256.3}$ -6.53 ×10^2 and $[\theta]_{278.3}$ -6.15 ×10^3.

Gallocatechin-(4α ⟶ 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; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); CD $[\theta]_{202.2}$ 3.42 × lo), $[\theta]_{206.7}$ 5.68 ×10^2, $[\theta]_{216.7}$ 1.03 ×10^4, $[\theta]_{223.3}$ -8.40 ×10^3, $[\theta]_{229.3}$ 1.14 ×10^3, $[\theta]_{242.3}$ -1.73 ×10^4 and $[\theta]_{272}$ 1.66 ×10^3.

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

Dihydroquercctin (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" 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 × 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 × 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 × 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 86112 TF-1 (96 mg), tubas 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; ^{1}H NMR (Table 3); ^{13}C NMR (Table 3). CD $[\theta]_{203.8}$ -3.8 ×10^3, $[\theta]_{208.8}$ -7.41 ×10^3, $[\theta]_{214.9}$ 4.78 ×10^3, $[\theta]_{218.9}$ 5.41 ×10^1, $[\theta]_{225.5}$ 1.37 ×10^4, $[\theta]_{233.7}$ -6.08 ×10^3, $[\theta]_{248.8}$ -2.08 ×10^3, $[\theta]_{248.1}$ -4.98 ×10^3, $[\theta]_{259.5}$ -6.87 ×10^3, $[\theta]_{279.8}$ -2.84 ×10^3 and $[\theta]_{288.8}$ 4.17 x 10^2. In addition, compound 3 and its 4β-isomer were also recovered from this synthesis

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