Oligomeric Flavanoids. Part 16.[a] Novel Prorobinetinidins and the First A-Type Proanthocyanidin with a 5-Deoxy A- and a 3,4-*cis* C-Ring from the Maiden Investigation of Commercial Wattle Bark Extract

Annemarie Cronjé, Jan P. Steynberg,* E. Vincent Brandt, Desmond A. Young and Daneel Ferreira*

Department of Chemistry, University of the Orange Free State, PO Box 339, Bloemfontein, 9300 South Africa

Structural examination of the phenolic metabolites of commercially used wattle bark extract reveals the presence of a range of novel flavanoids comprising (−)-epirobinetinidol **1**, the first C-methyl proanthocyanidin, (−)-fisetinidol-(4α,8)-6-methyl-(+)-catechin **3**, the first prorobinetinidins with 3,4-*cis* C-ring configurations **7** and **9**, and the unique A-type prorobinetinidin **11** representing the first entry amongst this class of oligoflavanoids exhibiting a 5-deoxy A- and a 3,4-*cis* C-ring. They are accompanied by a range of functionalized prorobinetinidin-type tetrahydropyrano[2,3-*f*]chromenes **20**, **23**, **25** and **28** and the trimeric 'isomerization-intermediate' **32**, all exhibiting the characteristic structural features that are essential for the use of 'Mimosa' extract in cold-setting adhesives and leather-tanning applications. In addition, evidence demonstrating that the dynamic A–E conformational equilibrium of flavan-3-ol moieties in condensed tannins may be influenced by external factors is presented.

Previous investigations of the economically important black wattle ('Mimosa') bark extract have revealed the presence of a variety of monomeric flavonoids based upon the 3',4',7-tri- and 3',4',5',7-tetra-oxygenated aromatic substitution patterns.[1,2] These included flavan-3,4-diols, flavan-3-ols, dihydroflavonols, flavonols, flavanones, chalcones,[3] and a complex mixture of proanthocyanidin oligomers[4–7] in which the prorobinetinidins (3,3',4',5',7-penta-oxygenated chain-extender units) predominate the profisetinidins (3,3',4',7-tetra-oxygenation) in the ratio ~3:1. Similar studies on the commercial commodity, *i.e.* the spray-dried aqueous bark extract, which is utilized extensively in tanning and cold-setting adhesives applications,[3] have, however, not yet been performed. We now disclose results of relevance to the phenolic metabolites which have been encountered in an initial investigation of the industrial product.

Results and Discussion

The methanol extract of the spray-dried aqueous extract of the bark of *Acacia mearnsii* afforded a series of known flavan-3-ol analogues, *i.e.* (+)-catechin, (+)-gallocatechin, (−)-robinetinidol and (−)-epicatechin, the latter compound being obtained from this source for the first time. These compounds are accompanied by the novel (−)-epirobinetinidol **1** which was identified as the tetramethyl ether acetate **2**. The 2,3-*cis* relative configuration of compound **2** was evident from the ^{1}H NMR coupling constants (Table 1) of its heterocyclic protons ($J_{2,3}$ ~1.0 Hz) while the (2*R*,3*R*) absolute configuration was confirmed by comparison of the CD data with those of the same derivative of (−)-epicatechin.[8] (+)-Epirobinetinidol, the enantiomer of compound **1**, was previously synthesized by Weinges.[9]

Although C-alkylation is an established natural phenomenon affecting mainly monomeric flavonoids,[10–12] participation of oligomers in this process has hitherto been restricted to a few biflavonoids.[13] This rare group of phenolic metabolites is now extended by identification of (−)-fisetinidol-(4α,8)-6-methyl-(+)-catechin **3**, the first proanthocyanidin in this class. The ^{1}H NMR spectrum of the methyl ether diacetate **4** (Table 1) exhibited the characteristic spin systems of an all-*trans* profisetinidinbiflavanoid, *i.e.* three aromatic ABX-systems and a heterocyclic AMX-[$J_{2,3(C)} = J_{3,4(C)} = 10.0$ Hz] and ABMX-system [$J_{2,3(F)} = 8.5$ Hz]. Absence of a residual D-ring singlet and the presence of a benzylic methyl resonance (δ 2.21) strongly indicated that methylation had occurred at the vacant D-ring carbon of a conventional (−)-fisetinidol-(+)-catechin analogue, *e.g.* compound **5**. The (4,8)-interflavanyl linkage and hence the C-6 location of the methyl group was evident from the nuclear Overhauser effect (NOE) association of both 7-OMe(D-ring, δ 3.76) and 5-OMe(D, δ 3.71) with 6-Me (δ 2.21, 3.0 and 2.4% respectively) and of 7-OMe(D) with both 4-H(C, δ 4.72) and 5-H(A). Confirmation of the 4α-DEF moiety and thus the 4*S* absolute configuration was obtained *via* the high-amplitude negative Cotton effect[14] at 234 nm in the CD spectrum of compound **4**.

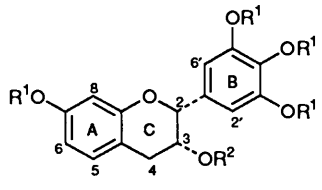
The 6-methylprofisetinidin **3** is accompanied by the known (−)-fisetinidol-(4α,8)-(+)-catechin **5** which was identified by comparison of the physical data of its heptamethyl ether diacetate **6** with those of an authentic sample.[15]

The known prorobinetinidin biflavanoids based on both (+)-catechin and (+)-gallocatechin as chain-terminating units from black wattle bark invariably display 3,4-*trans* configurations of their heterocyclic C-rings.[5,15] In the spray-dried extract these prorobinetinidins (see Experimental section) are accompanied by the (−)-robinetinidol-(4β,8)-(+)-catechin **7** and (−)-robinetinidol-(4β,8)-(+)-gallocatechin **9**, the first naturally occurring prorobinetinidins with 3,4-*cis* C-ring configurations. The novel metabolite **7** was again identified by comparison of the physical data of its octamethyl ether diacetate **8** with those of the synthetic counterpart.[15] Two two-proton singlets in the aromatic region of the ^{1}H NMR spectrum (Table 1) of the nonamethyl ether diacetate **10**, exhibiting the effects of dynamic rotational isomerism in $CDCl_3$ at 298 K (rotamer population ~78:22), were reminiscent of the pyrogallol-type B- (δ 6.54) and E-rings (δ 6.30). The chemical shifts of these signals were confirmed by a spin-decoupling experiment using the 2-H(C) and 2-H(F) resonances as reference signals. Coupling constants of the protons of the C-ring ($J_{2,3}$ 9.5; $J_{3,4}$ 6.5 Hz) confirmed the relative 2,3-*trans*-3,4-*cis* configuration. When considered in conjunction with the high-amplitude positive Cotton effect at 228 nm in the CD spectrum of compound **10**, indicative of a 4β-flavanyl substituent,[14] these coupling constants also reflect the

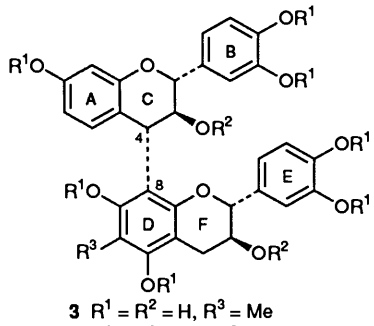
[a] Part 15, ref. 31.

Table 1 ^{1}H NMR peaks (δ_H) of the (−)-epirobinetinidol, profisetinidin, and prorobinetinidin permethyl ether acetates **2**, **4**, **8** and **10** in $CDCl_3$ (23 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

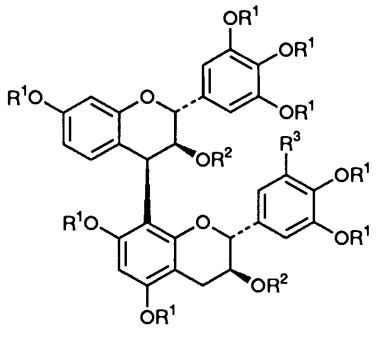
Ring	Proton	2	4	8	10
A	5	6.81 (d, 8.5)	6.66 (d, 8.0)	6.66 (d, 8.5)	6.65 (d, 8.5)
	6	6.60 (dd, 2.5, 8.5)	6.43 (dd, 2.5, 8.0)	6.23 (dd, 2.5, 8.5)	6.21 (dd, 2.5, 8.5)
	8	6.79 (d, 2.5)	6.38 (d, 2.5)	5.79 (d, 2.5)	5.78 (d, 2.5)
B	2/6	6.74 (s)		6.53 (s)	6.54 (s)
	2		6.58 (d, 2.0)		
	5		6.70 (d, 8.0)		
	6		6.74 (dd, 2.0, 8.0)		
C	2	4.70 (br s, ~ 1.0)	4.84 (d, 10.0)	5.25 (d, 9.5)	5.28 (d, 9.5)
	3	5.42 (m)	6.14 (t, 10.0)	5.54 (dd, 6.5, 9.5)	5.52 (dd, 6.5, 9.5)
	4	2.87 (m)	4.72 (d, 10.0)	4.91 (d, 6.5)	4.89 (d, 6.5)
D	6-H/6-Me		6-Me, 2.21 (s)	6.16 (s)	6.16 (s)
E	2/6				6.30 (s)
	2		6.52 (d, 2.0)	6.63 (d, 2.0)	
	5		6.65 (d, 8.0)	6.72 (d, 8.0)	
	6		6.46 (dd, 2.0, 8.0)	6.62 (dd, 2.0, 8.0)	
F	2		4.81 (d, 8.5)	4.12 (d, 8.5)	4.07 (d, 8.5)
	3		4.92 (m)	5.13 (m)	5.06 (m)
	4^{ax}		2.72 (dd, 9.0, 16.0)	2.57 (dd, 8.0, 17.0)	2.55 (dd, 8.0, 17.0)
	4^{eq}		3.13 (dd, 6.0, 16.0)	3.09 (dd, 6.5, 17.0)	3.10 (dd, 6.5, 17.0)
	OMe	3.28 [7-(A)], 3.45 [3-, 5-(B)], 3.85 [4-(B)], each s	3.55 [3-(B)], 3.70 [3-(E)], 3.71 [5-(D)], 3.72 [7-(A)], 3.76 [7-(D)], 3.81 [4-(B)], 3.83 [4-(E)], each s	3.48 [7-(A)], 3.71 [3-(E)], 3.79 [3-, 5-(B)], 3.80 [7-(D), 4-(B)], 3.83 [4-(E)], 3.84 [5-(D)],	3.49 [7-(A)], 3.69 [3-, 5-(E)], 3.78 [3-, 5-(B)], 3.80 (×2), 3.84 [5-, 7-(D)], each s
	OAc	1.43 (s)	1.55, 1.87, each s	1.73, 1.80, each s	1.75, 1.84, each s



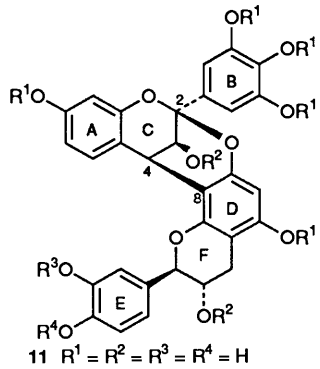
1 $R^1 = R^2 = H$
2 $R^1 = Me$, $R^2 = Ac$



3 $R^1 = R^2 = H$, $R^3 = Me$
4 $R^1 = R^3 = Me$, $R^2 = Ac$
5 $R^1 = R^2 = R^3 = H$
6 $R^1 = Me$, $R^2 = Ac$, $R^3 = H$



7 $R^1 = R^2 = R^3 = H$
8 $R^1 = Me$, $R^2 = Ac$, $R^3 = H$
9 $R^1 = R^2 = H$, $R^3 = OH$
10 $R^1 = Me$, $R^2 = Ac$, $R^3 = OMe$



11 $R^1 = R^2 = R^3 = R^4 = H$
12 $R^1 = R^2 = R^3 = H$, $R^4 = Me$
13 $R^1 = R^2 = H$, $R^3 = R^4 = Me$
14 $R^1 = R^3 = R^4 = Me$, $R^2 = Ac$

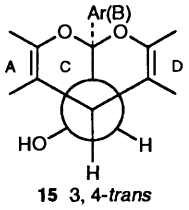
2*R*,3*S*,4*R* (C-ring) absolute configuration depicted in formulation **10**. The proposed (2*R*,3*S*)-configuration of the DEF-unit of the prorobinetinidin **9** which may be inferred from CD comparisons of the same derivatives of analogues **7** and **9** is, however, speculative[16] and requires assessment *via* synthesis. Confirmation of the (4,8)-interflavanyl linkage stems from the chemical shift of the residual D-ring singlet (δ 6.16) which indicated a C-8-substituted (+)-gallocatechin unit. Such an allocation was additionally confirmed by the mutual ^{1}H NOE association of 6-H with both 5- and 7-OMe (D-ring: δ 3.80, 3.84).[17]

Naturally occurring A-type proanthocyanidins possessing

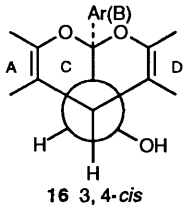
Table 2 ^{1}H NMR peaks (δ_H) of the A-type prorobinetinidin **12** and derivative **14**, and didehydro-(−)-robinetinidol-(4α,8)-(+)-catechin methyl ether acetates **43** and **45** at 300 MHz (23 °C). Splitting patterns and *J* values (Hz) are given in parentheses

Ring	Proton	**12** in $(CD_3)_2CO$–D_2O	**14** in $CDCl_3$	**43** in $CDCl_3$	**45** in $CDCl_3$
A	5	7.07 (d, 8.5)	7.13 (d, 8.5)	6.70 (d, 8.5)	6.91 (d, 8.5)
	6	6.38 (dd, 2.5, 8.5)	6.49 (dd, 2.5, 8.5)	6.41 (dd, 2.5, 8.5)	6.57 (dd, 2.5, 8.5)
	8	6.33 (d, 2.5)	6.54 (d, 2.5)	6.41 (d, 2.5)	6.27 (d, 2.5)
B	2/6	6.74 (s)	6.93 (s)		
	6			6.99 (s)	6.66 (s)
C	2			4.76 (d, 9.5)	5.16 (dd, 2.0, 3.0)
	3	4.07 (d, 3.5)	5.47 (d, 3.5)	4.68 (t, 9.5)	5.97 (t, 3.0)
	4	4.15 (d, 3.5)	4.44 (d, 3.5)	4.81 (d, 9.5)	3.30 (dd, 2.0, 3.0)
D	6	6.15 (s)	6.31 (s)	6.25 (s)	5.62 (s)
E	2	6.99 (d, 2.0)	6.76 (d, 2.0)	6.38 (d, 2.0)	6.66 (d, 2.0)
	5	6.96 (d, 8.0)	6.80 (d, 8.0)	6.43 (d, 8.5)	6.50 (d, 8.0)
	6	6.91 (dd, 2.0, 8.0)	6.84 (dd, 2.0, 8.0)	5.94 (dd, 2.0, 8.5)	6.00 (dd, 2.0, 8.0)
F	2	4.66 (d, 8.0)	5.11 (d, 7.0)	4.92 (d, 5.5)	4.26 (d, 10.0)
	3	3.93 (m)	5.25 (m)	5.11 (m)	4.95 (m)
	4^{ax}	2.54 (dd, 9.0, 16.0)	2.67 (dd, 7.0, 16.5)	2.62 (dd, 5.0, 16.5)	2.49 (dd, 10.0, 16.5)
	4^{eq}	2.95 (dd, 5.5, 16.0)	2.83 (dd, 5.0, 16.5)	2.71 (dd, 5.0, 16.5)	3.13 (dd, 6.5, 16.5)
	OMe	3.86 [4-(E)], s	3.70 [3-(E)], 3.72 [7-(A)], 3.77 [5-(D)], 3.86 [4-(B)], 3.88 [3-, 5-(B), 4-(E)], each s	3.65 [3-(E)], 3.71 [7-(A)], 3.75 [4-(E)], 3.82 3.83, 3.88, 3.90, 3.91 [5-(B)], each s	3.55, 3.62, 3.64, 3.71, 3.72, 3.76, 3.85, each s
	OAc		1.85, 1.93, each s	1.88 (s)	1.77, 1.96, each s

the characteristic doubly linked unit of either (2β,4β)- or (2α,4α)-configuration invariably exhibit C-5 (A-ring) hydroxylation and a 3,4-*trans* configuration of their C-rings.[18] In the bark of *Acacia mearnsii* the (−)-robinetinidol-(4β,8)-(+)-catechin **7** presumably served as precursor (*vide infra*) to (−)-robinetinidol-(2β→7;4β→8)-(+)catechin **11**, representing the first A-type analogue of the 5-deoxy (A-ring) oligoflavanoids and also the first entry amongst this class of proanthocyanidins with a 3,4-*cis* C-ring configuration. The ^{1}H NMR spectrum (Table 2) of the heptamethyl ether diacetate **14** displayed the characteristic AB-system [δ 5.47, 4.44, both d, *J* 3.5 Hz, 3- and 4-H(C), respectively][19] associated with the C-ring protons of A-type proanthocyanidins and also the conspicuous absence of the effects of dynamic rotational isomerism about the inter-flavanyl bond imposed by the additional carbon–oxygen linkage. The (2β,4β)-orientation and hence the absolute configuration depicted in formulation **11** was confirmed by a high-amplitude positive Cotton effect at 240 nm in the CD spectrum of derivative **13**, and by comparison of this spectrum with that of a synthetic sample (see below).

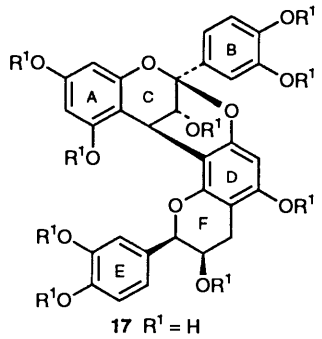


15 3,4-*trans*



16 3,4-*cis*

The known A-type proanthocyanidins display $^3J_{HH}$-values of 3–4 Hz for 3- and 4-H(C), a phenomenon which by reference to X-ray data[20] for procyanidin A-2 **17** and ^{13}C NMR comparisons,[21] has consequently been accepted to indicate a 3,4-*trans* relative configuration for all known analogues of this class of naturally occurring condensed tannins. Consideration, however, of the structure of an A-type proanthocyanidin with 3,4-*cis* configuration **13** in conjunction with the conformational rigidity of the bicyclic ring system indicates very similar dihedral angles between 3- and 4-H(C) in both 3,4-*trans* and 3,4-*cis* homologues (*cf.* Newman projections **15** and **16** which should therefore lead to almost identical coupling constants for these



17 R^1 = H
18 R^1 = Ac

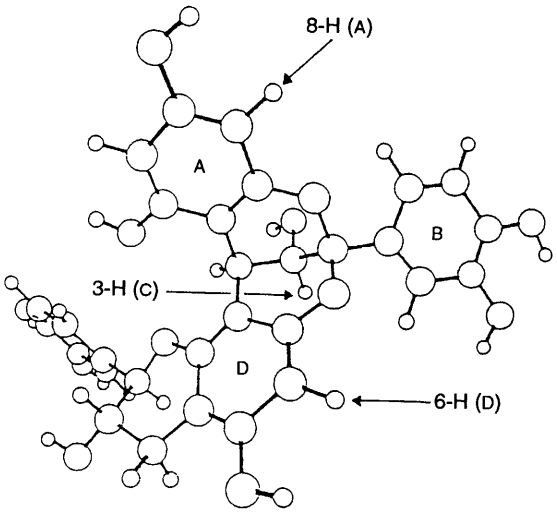
protons. Comparison of the ^{1}H NMR data of the 3,4-*cis* analogue **13** and those[21] of the peracetate **18** of procyanidin A-2 **17*** indeed revealed a conspicuous identity of their 3- and 4-H coupling constants ($J_{3,4}$ 3.5 Hz). This observation prompted assessment of the potential of the powerful ^{1}H NOE technique towards differentiation of A-type analogues exhibiting 3,4-*trans* or 3,4-*cis* configuration of their C-rings. Besides the stereochemically insignificant NOE association of 3-H(C) with 2- and 6-H(B) in both the prorobinetinidin-analogue **12** (*vide infra*) and peracetate **18** this proton showed a selective NOE effect to 6-H(D) (δ 6.47, s, 1.0%) in the procyanidin A-2 derivative **18** only. In the A-type 3,4-*cis* compound **12**, however, 3-H(C) exhibited selective association with both 5- and 8-H(A) (1.0 and 1.3% respectively), the corresponding effect between 3-H(C) and 8-H(A) being conspicuously absent in the procyanidin A-2 peracetate **18**. These highly selective NOE associations of 3-H(C) to 5- and 8-H(A) in compound **12** and of 3-H(C) to 6-H(D) in compound **18** are only permitted for an *axial* 3-proton in the former case and for an *equatorial* 3-proton in the latter instance, hence facilitating the unambiguous assignment of the 3,4-relative configuration in the A-type proanthocyanidins with (4,8)-interflavanyl linkages (see 3D-perspective **19**). Dreiding models furthermore indicate that the NOE associations should be independent of the absolute configurations, of

* The magnitude of $J_{3,4}$ is not influenced by derivatization of procyanidin A-2.[21]

Table 3 ^{1}H NMR peaks (δ_H) of the tetrahydropyrano[2,3-*f*]chromene octamethyl ether diacetates **22**, **24**, **27** and **29** at 300 MHz (23 °C). Splitting patterns and *J* values (Hz) are given in parentheses

Ring	Proton	**22** in C_6D_6	**24** in $CDCl_3$	**27** in C_6D_6	**29** in $CDCl_3$
A	3	6.31 (d, 2.5)	6.19 (d, 2.5)	6.39 (d, 2.5)	6.15 (d, 2.5)
	5	6.41 (dd, 2.5, 8.5)	6.09 (dd, 2.5, 8.5)	6.31 (dd, 2.5, 8.0)	5.99 (dd, 2.5, 8.5)
	6	7.29 (d, 8.5)	6.37 (d, 8.5)	7.12–7.16[a]	6.24 (d, 8.5)
B	2/6	6.80 (s)	6.44 (s)	6.83 (s)	6.37 (s)
C	8	5.50 (d, 10.0)	5.11 (d, 6.0)	5.54 (br s, ~ 1.0)	5.19 (d, 5.0)
	9	6.14 (dd, 6.0, 10.0)	5.71 (dd, 5.0, 6.0)	6.10 (dd, 1.0, 2.0)	5.82 (dd, 4.0, 5.0)
	10	5.75 (d, 6.0)	4.43 (d, 5.0)	5.23 (d, 2.0)	4.38 (d, 4.0)
D	6	6.44 (s)	6.30 (s)	6.60 (s)	6.34 (s)
E	2/6				6.10 (s)
	2	6.83 (d, 2.0)	6.33 (d, 2.0)	6.58 (d, 2.0)	
	5	6.40 (d, 8.0)	6.58 (d, 8.0)	6.45 (d, 8.0)	
	6	6.76 (dd, 2.0, 8.0)	6.26 (dd, 2.0, 8.0)	6.53 (dd, 2.0, 8.0)	
F	2	4.93 (d, 6.5)	4.69 (d, 9.0)	4.78 (d, 7.5)	4.95 (d, 9.0)
	3	5.49 (m)	4.87 (m)	5.33 (m)	4.87 (m)
	4^{ax}	2.90 (dd, 6.5, 16.5)	2.59 (dd, 9.0, 16.0)	2.86 (dd, 8.0, 16.0)	2.60 (dd, 9.5, 16.0)
	4^{eq}	3.19 (dd, 5.5, 16.5)	3.10 (dd, 5.5, 16.0)	3.37 (dd, 5.0, 16.0)	3.18 (dd, 6.0, 16.0)
	OMe	3.14 [2-(A)], 3.27 [4-(A)], 3.31 [3-, 5-(B)], 3.32 [4-(E)], 3.34 [5-(D)], 3.49 [3-(E)], 3.80 [4-(B)], each s	3.53 [3-(E)], 3.55 [2-(A)], 3.67 [4-(A)], 3.73 [3-, 5-(B)], 3.74 [4-(B)], 3.80 [4-(E)], 3.81 [5-(D)], each s	3.27 [4-(A)], 3.29 [3-, 5-(B)], 3.31 [2-(A)], 3.33 [4-(E)], 3.37 [3-(E)], 3.39 [5-(D)], 3.79 [4-(B)], each s	3.54 [3-, 5-(E)], 3.60 [2-(A)], 3.63 [4-(A)], 3.70 [3-, 5-(B)], 3.71 [4-(E)],[b] 3.75 [4-(B)],[b] 3.84 [5-(D)], each s
	OAc	1.46, 1.49, each s	1.85, 1.90, each s	1.44, 1.60, each s	1.87, 1.96, each s

[a] Overlapped by C_6H_6 signal. [b] Peaks may be interchanged.



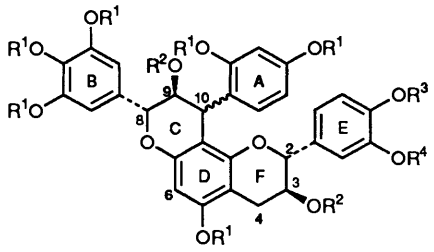
19

C-2 and -4, *i.e.* applicable also to analogues with the (2α,4α)-configuration.

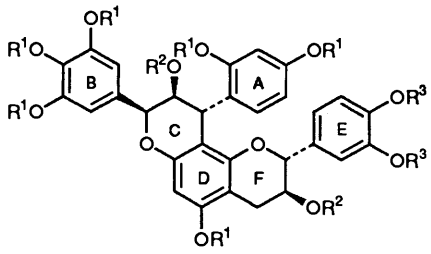
Our recent demonstration[22,23] of the natural occurrence of a series of C-ring isomerized oligoflavanoids, dubbed phlobatannins,[24] exhibiting the characteristic structural features that are essential for the utilization of condensed tannins in cold-setting adhesives and leather-tanning applications, provided the main impetus for our first examination of the phenolic metabolites in the spray-dried black wattle bark extract. The phenolic compounds in the preceding paragraphs are indeed accompanied by several 'dimeric' phlobatannins **20**, **23**, **25** and **28** which apparently originate from prorobinetinidins of types **7** and **9**, *i.e.* those based upon both (+)-catechin and (+)-gallocatechin as 'terminating' units, and the 'trimeric' analogue **32** derived similarly from a putative precursor of type **35**.

The structures of these functionalized 3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*f*]chromenes **20**, **23**, **25** and **28** were established by application of ^{1}H NMR NOE difference spectroscopy to their phenolic methyl ether acetates, *e.g.* compound **22**.[24] In each instance, NOE associations of 2-OMe (A-ring) with 3-H(A) and of 4-OMe(A) with both 3-H(A) and 5-H(A) indicate the 'liberation' of resorcinol-type moieties from pyran heterocycles, compared with involvement in the C-ring of the presumed prorobinetinidin biflavanoid precursor of type **7**. In addition, the ^{1}H NMR spectra (Table 3) of the derivatives are characterized by the conspicuous absence of the effects of dynamic rotational isomerism at ambient temperatures. The relative configurations were evident from comparison of the ^{1}H NMR coupling constants of heterocyclic protons of derivatives **22**, **24**, **27** and **29** with those of the closely related profisetinidin-type analogues, *i.e.* $^3J_{2,3(F)}$ 6.5–9.0 Hz for 2,3-*trans*; $^3J_{8,9(C)}$ 10.0, $^3J_{9,10(C)}$ 6.0 Hz for 8,9-*trans*-9,10-*cis*; $^3J_{8,9(C)}$ 5.0–6.0, $^3J_{9,10(C)}$ 4.0–5.0 Hz for 8,9-*trans*-9,10-*trans*; and $^3J_{8,9(C)}$ ~ 1.0, $^3J_{9,10(C)}$ ~ 2.0 Hz for 8,9-*cis*-9,10-*trans*-configurations. A notable feature in the spectra of all these compounds is the two-proton singlet in the aromatic region reminiscent of the presence of a pyrogallol-type B- and/or E-ring. A simple decoupling experiment using the heterocyclic 2-H resonances as reference signals not only facilitated differentiation of the two singlets for the pyrogallol-type B- and E-rings in compound **29** but also provided unambiguous evidence for the location of pyrogallol and pyrocatechol rings in analogues **22**, **24** and **27**.

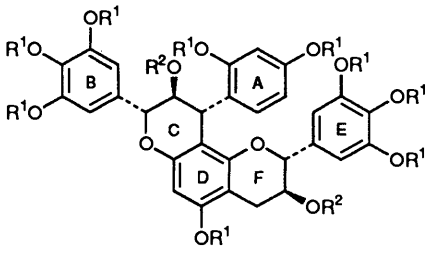
The absolute configuration at the stereocentres of the C-rings of the tetrahydropyrano[2,3-*f*]chromene derivatives **22**, **24**, **27** and **29** was established by using their chiroptical data combined with the aforementioned coupling constants. Whereas a positive Cotton effect at 240 nm in the CD spectrum of the 8,9-*trans*-9,10-*cis* compound **22** indicates a 10β aryl substituent, negative Cotton effects in the same region of 8,9-*trans*-9,10-*trans* (**24** and **29**), and 8,9-*cis*-9,10-*trans* (**27**) derivatives are reminiscent of 10α orientations of the resorcylic A-rings.[14] Confirmation of the absolute configuration of the C-rings, *i.e.* 8*R*,9*S*,10*S* for compound **22** and 8*S*,9*S*,10*R* for derivative **27** was obtained *via* synthesis (*vide infra*) which also enabled definition of the



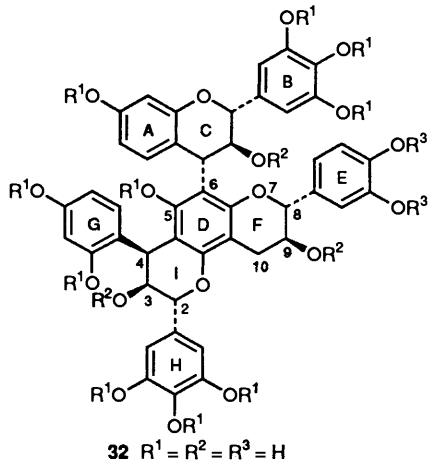
20 ≡ **A** $R^1 = R^2 = R^3 = R^4 = H$
21 ≡ **A** $R^1 = R^2 = R^4 = H$, $R^3 = Me$
22 ≡ **A** $R^1 = R^3 = R^4 = Me$, $R^2 = Ac$
23 ≡ **I** $R^1 = R^2 = R^3 = R^4 = H$
24 ≡ **I** $R^1 = R^3 = R^4 = Me$, $R^2 = Ac$



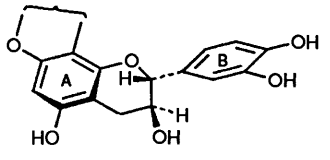
25 $R^1 = R^2 = R^3 = H$
26 $R^1 = R^2 = H$, $R^3 = Me$
27 $R^1 = R^3 = Me$, $R^2 = Ac$



28 $R^1 = R^2 = H$
29 $R^1 = Me$, $R^2 = Ac$



32 $R^1 = R^2 = R^3 = H$
33 $R^1 = R^2 = H$, $R^3 = Me$
34 $R^1 = R^3 = Me$, $R^2 = Ac$



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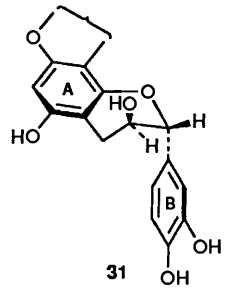
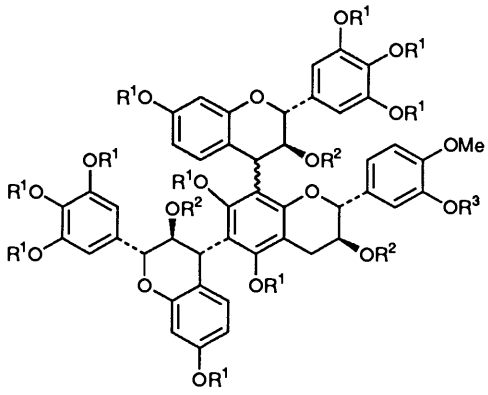


31

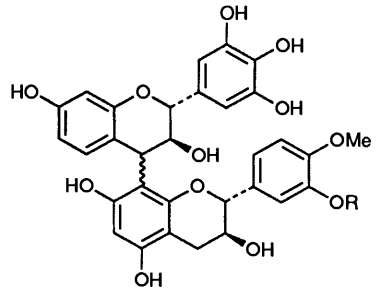
absolute stereochemistry of the F-rings of these compounds as 2*R*,3*S*. Allocation of this latter configuration to the stereocentres of the corresponding rings in analogues **24** and **29** also is, however, tentative and requires confirmation by synthesis (see below, however).

The conspicuously small ^3J values for the C-ring protons in the tetrahydropyrano[2,3-*f*]chromenes with 8,9-*trans*-9,10-*trans* configuration (**24** and **29**) (see Table 3) are, as before,[22] attributable to significant contributions of A-forms[25,26] (see below) towards the conformation of these heterocyclic rings.

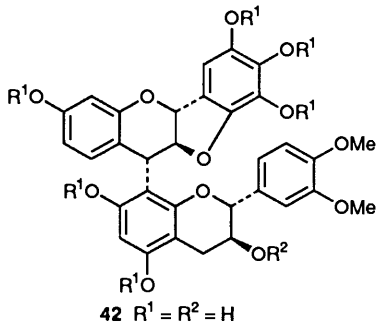
Comparison of the coupling constants of 2-H(F) of the variety of tetrahydropyrano[2,3-*f*]chromenes with 2,3-*trans* configuration of their DEF moieties in our collection (see ref. 27 for entry to parts 3–5, 7, 8 and 11 in the series 'Oligomeric Flavanoids') indicates a remarkable dependence of the magnitude of these ^3J values on the relative orientations of the aryl groups at C-2(F) and C-10(C). When these substituents occupy the same face of the molecule (2,10-*cis* relationship as in analogue **24**), $^3J_{2,3(F)}$ consistently falls within the 8.0–9.0 Hz limit, while for a 2,10-*trans* relationship of the aryl groups (as in compound **22**) the coupling constant lies between 6.0 and 7.5 Hz. Owing to the assumption that the magnitude of the $^3J_{2,3}$ coupling constant of 2-H of flavan-3-ols is determined by the ratio of A- and E-conformers, **31** and **30** respectively, of the C-ring,[25] *i.e.* small J values (6.0–7.5 Hz) reflecting significant contributions of A-forms, the aforementioned variation of $^3J_{2,3(F)}$ may be attributed to similar phenomena operating in the 2,3-*trans* flavan-3-ol units of the [2,3-*f*]phlobatannins. It furthermore indicates for the first time that external factors may exert a profound effect on the dynamic A–E conformational equilibrium which mutates the 2-H, 3-H dihedral angle and hence the observed coupling constant. Whereas 2,10-*cis*-related aryl groups would inhibit the conformational itinerary of the E-ring, hence discriminating against the participation of A-forms and resulting in larger coupling constants of 2-H (8.0–9.0 Hz), 2,10-*trans* aryl substituents would have no suppressing effect on the aforementioned conformational equilibrium, hence freely 'allowing' the A-forms with concomitant decrease in ^3J-values. These fundamental issues may now additionally be employed to establish the absolute configuration at the stereocentres of the F-ring in tetrahydropyrano[2,3-*f*]chromenes, a problem which has recently been compounded by the demonstration of the first condensed tannins with (−)-catechin chain-terminating units.[16,22] Since the orientation of the C-10 aryl group is



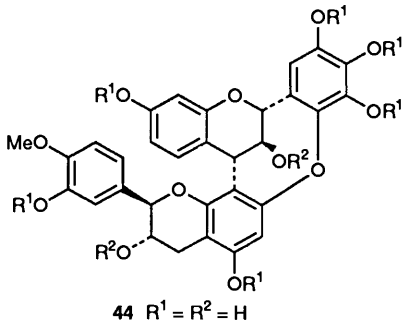
35 $R^1 = R^2 = R^3 = H$
36 $R^1 = R^3 = Me$, $R^2 = Ac$
37 $R^1 = R^2 = H$, $R^3 = Me$



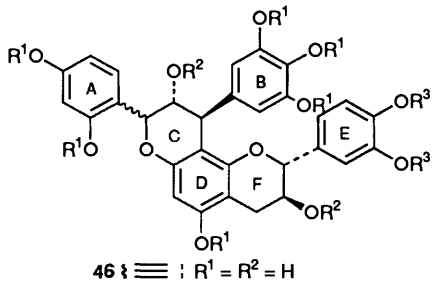
38 ≡ ; R = H
39 ≡ ▲ R = H
40 ≡ ; R = Me
41 ≡ ▲ R = Me



42 $R^1 = R^2 = H$
43 $R^1 = Me$, $R^2 = Ac$



44 $R^1 = R^2 = H$
45 $R^1 = Me$, $R^2 = Ac$



46 ≡ ; $R^1 = R^2 = H$
47 ≡ ; $R^1 = Me$, $R^2 = Ac$
48 ≡ ▼ $R^1 = R^2 = H$
49 ≡ ▲ $R^1 = Me$, $R^2 = Ac$

assessable *via* CD data, this dependence of the value of $^3J_{2,3(F)}$ on the relative positions of the aryl substituents at these crucial stereocentres now also affords access to the absolute configuration at C-2 and C-3 of the F-ring. Despite the lack of synthetic evidence for the structures of compounds **23** and **29** we thus strongly favour the 2*R*,3*S* absolute configuration for both analogues.

Comparison of the ^{1}H NMR spectral features of the (−)-robinetinidol-(4α,6)-tetrahydropyrano[2,3-*f*]chromene derivative **34** with those of the (−)-fisetinidol-related analogue from *Colophospermum mopane*[27] greatly simplified the structural elucidation of compound **34**. Since the spectroscopic approach has been fully described[27] only the key features characterising the constitution of the methyl ether triacetate **34** are indicated. The 'trimeric' nature of the compound is evident from the presence of two AMX- and a single ABMX spin system in the heterocyclic region. The magnitude of the coupling constants of the AMX systems is reminiscent of, respectively, an 'intact' all-*trans* flavanyl unit ($J_{2,3} = J_{3,4} = 10.0$ Hz) and a moiety comprised of a rearranged pyran ring with *trans–cis* configuration ($J_{2,3}$ 10.0, $J_{3,4}$ 6.0 Hz). These allocations were confirmed by an NOE experiment which indicated association of 2-OMe(G) with 3-H(G) and of 4-OMe(G) with both 3-H(G) and 5-H(G) and hence a 'liberated' resorcinol unit. In contrast the association of 7-OMe(A) with 6-H(A) and of only 7-OMe(A) with 8-H(A) in conjunction with the presence of a two-proton aromatic singlet (δ 6.43) defined the (−)-robinetinidol ABC moiety. The 6-flavanyltetrahydropyrano[2,3-*f*]chromene arrangement was confirmed by the NOE association of 5-OMe(D) with 4-H(C), 4-H(I) and 5-H(A). The presence of a 8,9-*trans* DEF-unit, hence defining this as either a (+)- or (−)-catechin moiety, was evident from the $^3J_{8,9(F)}$-value of 9.5 Hz for the heterocyclic AMBX system. Owing to the fact that CD data do not permit stereochemical assignment at this level, final proof of structure **34** was sought *via* synthesis. The trimeric compound **32** is accompanied by a series of conventional prorobinetindin-type triflavanoids based on both (+)-catechin, *e.g.* **35**, and (+)-gallocatechin as chain-terminating units (see Experimental section).

To prevent the characteristic side-reactions associated with

Table 4 ^{1}H NMR peaks (δ_H) of the tetrahydropyrano[2,3-*f*]-chromene octamethyl ether diacetates **47** and **49** in $CDCl_3$ (23 °C) at 300 MHz. Splitting patterns and *J* values (Hz) are given in parentheses

Ring	Proton	47	49
A	3	6.32 (d, 2.5)	6.14 (d, 2.5)
	5	6.48 (dd, 2.5, 8.5)	6.34 (dd, 2.5, 8.5)
	6	7.47 (d, 8.5)	7.21 (d, 8.5)
B	2/6	6.44 (s)	6.10 (s)
C	8	5.35 (br s, ~ 1.0)	5.37 (d, 6.0)
	9	5.30 (dd, 1.0, 2.0)	5.95 (d, 5.0, 6.0)
	10	4.29 (d, 2.0)	4.14 (d, 5.0)
D	6	6.26 (s)	6.30 (s)
E	2	6.66 (d, 2.0)	6.59 (d, 2.0)
	5	6.73 (d, 8.5)	6.70 (d, 8.0)
	6	6.64 (dd, 2.0, 8.5)	6.55 (dd, 2.0, 8.0)
F	2	4.87 (d, 6.0)	4.58 (d, 7.0)
	3	5.35 (m)	5.32 (m)
	4^{ax}	2.67 (dd, 5.5, 17.0)	2.62 (dd, 6.0, 17.0)
	4^{eq}	2.83 (dd, 5.0, 17.0)	2.90 (dd, 5.5, 17.0)
	OMe	3.52 [2-(A)], 3.74 [3-, 5-(B)], 3.75 [3-(E)], 3.77 [4-(A)], 3.81 [5-(D)], 3.82 [4-(B), 4-(E)], each s	3.59 [3-, 5-(B)], 3.66 [2-(A)], 3.69 [4-(B)], 3.71 [4-(A)], 3.75 [3-(E)], 3.81 [5-(D), 4-(E)], each s
	OAc	1.89, 1.91, each s	1.87, 1.91, each s

an E-ring quinone methide,[22] the (−)-robinetinidol-(4,8)-(+)-catechins were used as the E-ring 4′-*O*-methyl[22] (**38** and **39**) or 3′,4′-di-*O*-methyl ethers (**40** and **41**). These were formed *via* acid-catalysed condensation[15] of (+)-leucorobinetinidin and either 4′-*O*-methyl-(+)-catechin[22] or 3′,4′-di-*O*-methyl-(+)-catechin[28] and identified by comparison of the physical data of their permethyl ether diacetates with those of authentic samples.[15] The bis-(−)-robinetinidol-(+)-catechin triflavanoid **37** and the (4α,6)-isomer were similarly formed by a further condensation using the (−)-robinetinidol-(4α,8)-(+)-catechin di-*O*-methyl ether **40** and was identified as the methyl ether triacetate **36**.[7] These syntheses are characterized by relatively low yields (see Experimental section) when compared with similar sequences involving the 5′-deoxy analogue, (+)-mollisacacidin[15,22] and may presumably be attributed to the increased susceptibility of the pyrogallol functionality of (+)-leucorobinetinidin towards oxidation. Partial proof for such a conjecture stems from the observation that the (−)-robinetinidol-(+)-catechin di-*O*-methyl ethers, *e.g.* compounds **40** and **41**, are accompanied by the didehydro-(−)-robinetinidol-(4α,8)-(+)-catechin dimethyl ether **42**. The (4α,8)-prorobinetinidin **40** apparently serves as precursor to the didehydro analogue **42** *via* oxidation of the pyrogallol-type B-ring in compound **40** to an *o*-quinone followed by an intramolecular 1,4-Michael addition involving 3-OH(C) and subsequent aromatization *via* loss of a proton. Coupling constants of the C-ring protons ($J_{2,3}$ = $J_{3,4}$ = 9.5 Hz) of derivative **43** (Table 2) confirms its all-*trans* configuration while the chemical shift of 3-H(C) (δ 4.68) indicates involvement of the 3-OH in an ether linkage and thus also the dihydrobenzofuran arrangement in compound **43**. Involvement of C-2(B) of biflavanoid **40** during formation of the dihydrobenzofuran system is evident from the selective NOE association (11.9%) of a single methoxy resonance (δ 3.91) with an aromatic one-proton singlet (δ 6.99). The (4,8)-interflavanyl linkage was similarly confirmed by the NOE effect of 6-H(D) (δ 6.25) with both 5- and 7-OMe of the same aromatic ring.

Under the standard mild basic reaction conditions,[22] the (−)-robinetinidol-(4α,8)-(+)-catechin mono-*O*-methyl ether **38** was converted in low yield into the 8,9-*trans*-9,10-*cis*-tetrahydropyrano[2,3-*f*]chromene **21** and the didehydro-(−)-robinetinidol-(4α,8)-(+)-catechin **44**. The methyl ether diacetate **22** of the synthetic tetrahydropyrano[2,3-*f*]chromene **21** was identical with the same derivative of the natural product by comparison of ^{1}H NMR (Table 3) and CD data hence not only establishing the constitution but also the absolute configuration at all the stereocentres of this compound. Structural elucidation of the didehydro compound **44** was effected by comparison of the physical data (see Table 2 for ^{1}H NMR data) of derivative **45** with those of the closely related (−)-fisetinidol analogue.[22] The considerable proportion of the didehydro product **44** relative to both that of the tetrahydropyranochromene **21** and the (−)-fisetinidol-related compound[22] presumably again reflects the reduced redox potential of the pyrogallol B-ring in precursor **38** compared with that of the pyrocatechol ring in the (−)-fisetinidol-derived compound.

Exposure of the (−)-robinetinidol-(4β,8)-(+)-catechin methyl ether **39** to the standard conditions aimed at formation of the mono-*O*-methyl ether of the tetrahydropyrano[2,3-*f*]-chromene **23** and of analogue **26**, however, gave a low percentage conversion into (−)-robinetinidol-(2β→7;4β→8)-(+)-catechin mono-*O*-methyl ether **12** as the sole product. Its methyl ether diacetate **14** was identical with the same derivative of the natural product **11** by comparison of ^{1}H NMR (Table 2) and CD data. Although the base-catalysed pyran rearrangements are usually performed under nitrogen no attempts have thus far been made rigorously to exclude oxygen. Since the transformation of B- to A-type proanthocyanidins, *e.g.* **39**→**12**, presumably involves an oxidative step at C-2(C) in precursors having 2-H(C) and the 4-flavanyl unit *cis* relative to each other,[29] the exclusive formation of the A-type prorobinetinidin **12** and the absence of similar products in related reactions of the profisetinidins with their pyrocatechol B-rings, emphasizes the crucial role of both oxygen and the pyrogallol-type B-ring in compound **39** for the observed oxidative conversion. In order to define the role of oxygen an aqueous alkaline solution of the (−)-robinetinidol-(4β,8)-(+)-catechin di-*O*-methyl ether **41** was repeatedly degassed with nitrogen and was then stirred under nitrogen for 3 h at 50 °C. This procedure afforded a mixture comprising the A-type prorobinetinidin **13**, albeit in much reduced yield, the 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*f*]chromene **26**, their methyl ether diacetates **14** and **27** again corresponding to the same derivatives of the natural products **11** and **25**, and, as could be anticipated, a pair of 8,9-*cis*-9,10-*trans*- and 8,9-*trans*-9,10-*trans*-tetrahydropyrano[2,3-*f*]chromenes **46** and **48** with interchanged resorcinol A- and pyrogallol B-rings[22] as well as inversed absolute configuration at C-9(C) compared to that at C-3(C) in its precursor **41**.[30] The genesis of the pyran-rearranged product **26** and of the ring-interchanged analogues **46** and **48** has been firmly established[22,30] and need not be repeated. Their structures were elucidated by comparison of ^{1}H NMR (Table 4) and CD data of their methyl ether diacetates **47** and **49** with those of the same derivatives of the fisetinidol-related analogues.[22] The 'free' conformational itinerary of the F-ring culminating in considerable contributions of A-forms is, as before, reflected by the characteristic small $^3J_{2,3(F)}$-values (6.0 and 7.0 Hz for **45** and **47**, respectively). This provides unambiguous proof for the *trans*-relationship of the E- and B-rings and hence the 10β orientation of the B-ring and (*S*) absolute configuration at the C-10 stereocentre. These observations provide conclusive evidence for the inversion of the absolute configuration at C-9 associated with 1,3-flavanyl migration and the concomitant interchange of A-and B-rings (*cf.* ref. 30). Our proposals regarding the mechanism of the oxidative transformation of B- to A-type proanthocyanidins have previously been published.[19,31] We are, however, currently focussing much attention on defining the nature of the oxidizing species as either oxygen or *via* this reagent effecting the oxidation of the pyrogallol B-ring to an *o*-quinone which may be sufficiently powerful effectively to remove 2-H, presumably as hydride ion.

Similar treatment of the (4α,8;4α,6)-bis-(−)-robinetinidol-(+)-catechin di-*O*-methyl ether **37** gave low-percentage conversion into the 'isomerization-intermediate', (−)-robinetinidol-(4α,6)-2,3-*trans*-3,4-*cis*-tetrahydropyrano[2,3-*f*]chromene **33**, the methyl ether diacetate **34** of which again was identical with the same derivative of the 'trimeric' product from *Acacia mearnsii*. Absence of the anticipated hexahydrodipyrano[2,3-*f*:2′,3′-*h*]chromene representing the product of rearrangement of both pyran heterocycles and of the alternative 'isomerization-intermediate', *i.e.* (−)-robinetinidol-(4α,6)-tetrahydropyrano-[2,3-*f*]chromene, as was observed for the bis-(−)-fisetinidol-(+)-catechin triflavanoid,[27] probably results from their presence in such low yields that would escape detection by means of the relatively crude experimental procedures which were employed.

The phenolic metabolites described here represent only a small part of the constituents of spray-dried wattle bark extract. Since these compounds differ so markedly from those obtained by the cold methanol extract of 'Mimosa', we cannot claim with any degree of certainty whether they are truly natural products or whether they represent artefacts of the relative harsh conditions of spray-drying. We are currently thus embarking on a programme of re-investigating the 'mild process' and to compare such results with those described here. This investigation, however, clearly demonstrates the presence in the commercial commodity of phenols exhibiting the structural features that are essential for their utilization in cold-setting adhesives and leather-tanning applications.[32] Our continued investigations of the spray-dried extract will, no doubt, lead to the identification of many more examples of the phlobatannins with their interesting application possibilities.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$, C_6D_6, and $(CD_3)_2CO$ with Me_4Si as internal standard. *J* Values are given in Hz. Mass spectra were obtained with a Kratos MS80 instrument, and CD data in methanol on a JASCO J-20 spectropolarimeter. TLC was performed on pre-coated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40:1 v/v) after development. Preparative plates (PLC), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Separations on Sephadex LH-20 and Fractogel TSK HW-40(S) were on various column sizes and at differing flow rates in different solvent systems (to be specified in each instance). Methylations were performed with an excess of diazomethane in methanol–diethyl ether over a period of 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at ambient temperature. Water-soluble phenolics were freeze-dried with a Virtis Freezemobile 12SL. Evaporations were done under reduced pressure at ~60 °C in a rotary evaporator. The commercially used spray-dried aqueous extract of the bark of *A. mearnsii* was kindly supplied by Dr. N. P. Slabbert of the Wattle Industry Centre at Pietermaritzburg.

Phenolic Metabolites from the Spray-dried Aqueous Extract of the Bark of A. mearnsii.—Separate portions (10 × 30 g) of the bark extract were repeatedly extracted with methanol (5 × 300 cm^3) at room temperature over a period of 24 h. Evaporation of the solvent afforded a red-brown powder (250 g), a portion (56 g) of which was subjected to column chromatography on Sephadex LH-20 (column size 5 × 105 cm; 28 g/column; 18.0 cm^3 fractions) in ethanol to give nine fractions: A [tubes 150–185 (680 mg)], B [230–285 (500 mg)], C [296–349 (531 mg)], D [350–405 (515 mg)], E [406–475 (622 mg)], F [510–645 (2.52 g)], G [646–879 (3.82 g)], H [880–1124 (3.23 g)] and I [1125–1420 (4.50 g)].

Methylation of fraction A (680 mg) followed by PLC [benzene–acetone (9:1, v/v, ×2)] gave two bands, A_1 (R_f 0.47, 85 mg) and A_2 (R_f 0.42, 73 mg). Acetylation of fraction A_1 and separation by PLC [hexane–acetone–ethyl acetate (7:1:2, v/v, ×2)] gave (+)-catechin tetra-*O*-methyl ether acetate (R_f 0.47, 36 mg) and the same derivative of (−)-epicatechin (R_f 0.41, 6 mg). Fraction A_2 was similarly acetylated and the mixture was resolved by PLC in hexane–acetone–ethyl acetate (7:1:2, v/v) to give (−)-robinetinidol tetra-*O*-methyl ether acetate (R_f 0.41, 45 mg) and (2R,3R)-2,3-cis-(−)-*epirobinetinidol tetra-O-methyl ether acetate* **2** as a *white amorphous solid* (R_f 0.34, 8 mg) (Found: M^+, 388.1522. $C_{21}H_{24}O_7$ requires *M*, 388.1522); δ_H (Table 1); CD $[\theta]_{244}$ 0, $[\theta]_{228}$ 1.5 × 10^3, and $[\theta]_{200}$ 2.4 × 10^2.

Fraction B (500 mg) was methylated and the mixture was resolved by PLC to give two bands, B_1 (R_f 0.49, 70 mg) and B_2 (R_f 0.28, 56 mg), the former of which comprised penta-*O*-methyl-(+)-gallocatechin. Acetylation of band B_2 followed by PLC in hexane–acetone–ethyl acetate (60:25:15, v/v) afforded (−)-fisetinidol-(4β,8)-(+)-catechin hepta-*O*-methyl ether diacetate.[15]

Methylation of fraction C (531 mg) and PLC separation [benzene–acetone (8:2, v/v)] afforded a main band (R_f 0.39, 177 mg), which was acetylated, and purified by PLC [hexane–acetone–ethyl acetate (60:25:15, v/v)] to give (−)-robinetinidol-(4β,8)-(+)-catechin octa-*O*-methyl ether diacetate[15] **8** (R_f 0.25, 113 mg).

Fraction D (515 mg) was methylated and the mixture was resolved by PLC [benzene–acetone (8:2, v/v)] to give a main band at R_f 0.26 (136 mg). Acetylation followed by PLC in hexane–acetone–ethyl acetate (60:25:15, v/v, ×2) afforded two fractions, D_1 (R_f 0.47, 23 mg) and D_2 (R_f 0.42, 76 mg). The D_1 band gave (−)-*fisetinidol-(4α,8)-6-methyl-(+)-catechin hepta-O-methyl ether diacetate* **4** as an *amorphous solid* (Found: M^+, 758.2921. $C_{42}H_{46}O_{13}$ requires *M*, 758.2939); δ_H (Table 1), CD $[\theta]_{292}$ 0, $[\theta]_{277}$ −4.0 × 10^3, $[\theta]_{255}$ −4.5 × 10^2, $[\theta]_{234}$ −1.8 × 10^4, and $[\theta]_{200}$ −4.2 × 10^3. Band D_2 comprised (−)-fisetinidol-(4α,8)-(+)-catechin hepta-*O*-methyl ether diacetate **6**.[15]

Methylation of fraction E (622 mg) followed by PLC in dichloromethane–acetone (8:2, v/v) afforded two bands, E_1 (R_f 0.52, 46 mg) and E_2 (R_f 0.44, 93 mg). Band E_1 was acetylated and purified by PLC [hexane–acetone–ethyl acetate (60:25:15, v/v, ×2)] to give (2R,3S;8R,9S,10S)-2,3-trans-8,9-trans-9,10-cis-3,9-*diacetoxy*-10-(2,4-*dimethoxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-5-*methoxy*-8-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3-f]*chromene* **22** as an *amorphous solid* (R_f 0.46, 5 mg) (Found: M^+, 774.2891. $C_{42}H_{46}O_{14}$ requires *M*, 774.2888); δ_H (Table 3); CD $[\theta]_{276}$ 0, $[\theta]_{264}$ − 5.6 × 10^3, $[\theta]_{250}$ 0, $[\theta]_{240}$ 1.9 × 10^4, and $[\theta]_{210}$ 0. Acetylation of band E_2 and PLC in hexane–acetone–ethyl acetate (60:25:15, v/v, ×2) gave a main band at R_f 0.48 (40 mg), which was further purified by PLC [benzene–acetone (9:1, v/v, ×2)] to give the (−)-*robinetinidol*-(4β,8)-(+)-*gallocatechin nona-O-methyl ether diacetate* **10** as an *amorphous solid* (R_f 0.43, 21 mg) (Found: M^+, 804.2996. $C_{43}H_{48}O_{15}$ requires *M*, 804.2993); δ_H (Table 1); CD $[\theta]_{252}$ 0, $[\theta]_{228}$ 1.9 × 10^4, and $[\theta]_{200}$ 5.1 × 10^3.

A portion (522 mg) of fraction F was methylated, and separated by PLC [dichloromethane–acetone (8:2, v/v)] to give a main band at R_f 0.36 (189 mg). Acetylation, followed by PLC in benzene–acetone (9:1, v/v, ×2) afforded the (−)-fisetinidol-(4α,8)-(+)-catechin hepta-*O*-methyl ether diacetate **6**.[15]

Fraction G (3.82 g) was further resolved by column chromatography (3 × 50 cm column, 15 cm^3/tube, first 500 cm^3 of eluent discarded) on Fractogel TSK HW-40(S) in ethanol to give three fractions, G_1 [tubes 99–170 (104 mg)], G_2 [171–251 (337 mg)] and G_3 [296–344 (328 mg)].

Methylation of fraction G_1 (104 mg) followed by PLC in benzene–acetone (8:2, v/v) gave a main band at R_f 0.29 (19 mg), which was acetylated, and resolved by PLC [hexane–acetone–ethyl acetate (60:25:15, v/v)] into two bands, at R_f 0.32 (2 mg) and 0.26 (9 mg). The former band consisted of (−)-*robinetinidol*-(2β→7;4β→8)-(+)-*catechin hepta*-O-*methyl ether diacetate* **14** as an *amorphous solid* (Found: M^+, 758.2574. $C_{41}H_{42}O_{14}$ requires *M*, 758.2575); δ_H (Table 2); CD $[\theta]_{270}$ 0, $[\theta]_{262}$ 6.4 × 10^3, $[\theta]_{248}$ 3.1 × 10^3, $[\theta]_{240}$ 4.5 × 10^3, $[\theta]_{235}$ 3.5 × 10^3, and $[\theta]_{222}$ 0.

The R_f 0.26 band consisted of (2*R*,3*S*;8*R*,9*S*,10*R*)-2,3-*trans*-8,9-*trans*-9,10-*trans*-3,9-diacetoxy-10-(2,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-5-methoxy-8-(3,4,5-trimethoxyphenyl)-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*f*]chromene **24** as an amorphous solid (Found: M^+ − HOAc, 714.2677. $C_{42}H_{46}O_{14}$ − HOAc requires *m/z*, 714.2676); δ_H (Table 3); CD $[\theta]_{294}$ 0, $[\theta]_{247}$ 1.7 × 10^4, $[\theta]_{239}$ 0, $[\theta]_{234}$ − 7.2 × 10^3, and $[\theta]_{210}$ 0.

Fraction G_2 (337 mg) was methylated, and separated by PLC [benzene–acetone (8:2, v/v)] to give a main band at R_f 0.33 (38 mg). This was acetylated and the mixture was resolved by PLC in hexane–acetone–ethyl acetate (60:25:15, v/v, × 2) into two bands, $G_{2.1}$ (R_f 0.45, 11 mg) and $G_{2.2}$ (R_f 0.43, 23 mg). The $G_{2.1}$ fraction was further purified by PLC in 1,2-dichloroethane–acetone (19:1, v/v, × 2) to give two compounds, at R_f 0.36 (4 mg) and 0.23 (4 mg). The former compound was identified as (2R,3S;8S,9S,10R)-2,3-trans-8,9-cis-9,10-trans-3,9-*diacetoxy*-10-(2,4-*dimethoxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-8-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3-f]*chromene* **27** as an *amorphous solid* (Found: M^+, 774.2882. $C_{42}H_{46}O_{14}$ requires *M*, 774.2888); δ_H (Table 3); CD $[\theta]_{324}$ 0, $[\theta]_{278}$ −4.0 × 10^2, and $[\theta]_{200}$ −5.9 × 10^2. The R_f 0.23 band gave (2R,3S;8R,9S,10R)-2,3-trans-8,9-trans-9,10-trans-3,9-*diacetoxy*-10-(2,4-*dimethoxyphenyl*)-5-*methoxy*-2,8-*bis*-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3-f]-*chromene* **29** as an *amorphous solid* (Found: M^+, 804.2950. $C_{43}H_{48}O_{15}$ requires *M*, 804.2993); δ_H (Table 3); CD $[\theta]_{292}$ 0, $[\theta]_{246}$ 9.5 × 10^3, $[\theta]_{239}$ 0, $[\theta]_{214}$ −3.7 × 10^4, and $[\theta]_{200}$ 0. Fraction $G_{2.2}$ was subjected to further PLC separation in 1,2-dichloroethane–acetone (9:1, v/v, × 2) to give (−)-robinetinidol-(4α,8)-(+)-gallocatechin nona-*O*-methyl ether diacetate (R_f 0.46, 2 mg).[6]

Methylation of fraction G_3 (328 mg) and separation by PLC in benzene–acetone (8:2, v/v) afforded two main bands, $G_{3.1}$ (R_f 0.47, 25 mg) and $G_{3.2}$ (R_f 0.25, 53 mg). Band $G_{3.1}$ was acetylated, and separated by PLC [1,2-dichloroethane–acetone (9:1, v/v, × 2)], to give two fractions, $G_{3.1.1}$ (R_f 0.58, 5 mg) and $G_{3.1.2}$ (R_f 0.54, 3 mg). Fraction $G_{3.1.1}$ consisted of a mixture of *O*-methyl ethers involving the alcoholic hydroxy functions and was not further investigated. Fraction $G_{3.1.2}$ still comprised a mixture of at least two pyran-rearranged compounds as well as a (−)-robinetinidol-(+)-gallocatechin nona-*O*-methyl ether diacetate and was discarded. Band 3.2 also comprised a complex mixture and was not further investigated.

A portion (3.0 g) of fraction H was further resolved by column chromatography (3 × 47 cm column, 15 cm^3/tube, first 500 cm^3 of eluent discarded) on Fractogel TSK HW-40(S) in ethanol into subfractions H_1 [tubes 120–175 (86 mg)], H_2 [180–320 (390 mg)] and H_3 [321–480 (386 mg)].

Fraction H_1 (86 mg) was methylated, and purified by PLC in benzene–acetone (8:2, v/v) to give bands $H_{1.1}$ (R_f 0.30, 7 mg) and $H_{1.2}$ (R_f 0.26, 28 mg). Acetylation of band $H_{1.1}$ and PLC separation in 1,2-dichloroethane–acetone (9:1, v/v) gave the tetrahydropyrano[2,3-*f*]chromene **29** (R_f 0.40, 1 mg). Acetylation of the $H_{1.2}$ band afforded (−)-robinetinidol-(4α,6)-(+)-catechin octa-*O*-methyl ether diacetate.[5]

The only identifiable product from fraction H_2 (390 mg) following methylation, acetylation, and the appropriate PLC separations was the (−)-robinetinidol-(4α,8)-(+)-gallocatechin nona-*O*-methyl ether diacetate[6] (3 mg).

Methylation of fraction H_3 (386 mg) and PLC separation in benzene–acetone (8:2, v/v, × 2) afforded four bands, $H_{3.1}$ (R_f 0.41, 34 mg), $H_{3.2}$ (R_f 0.35, 34 mg), $H_{3.3}$ (R_f 0.30, 29 mg) and $H_{3.4}$ (R_f 0.18, 32 mg). Acetylation of fraction $H_{3.1}$ and separation by PLC [benzene–1,2-dichloroethane–acetone (5:4:1, v/v, × 3) gave (−)-robinetinidol-(4α,6)-(+)-gallocatechin nona-*O*-methyl ether diacetate.[5] Fraction $H_{3.2}$ was acetylated, and purified by PLC in 1,2-dichloroethane–acetone (9:1, v/v, × 3) to give (2R,3S,4S,8R,9S)-2,3-trans-3,4-cis-8,9-trans-3,9-*diacetoxy*-6-[(2R,3S,4S)-2,3-trans-3,4-trans-3-*acetoxy*-3′,4′,5′,7-*tetramethoxyflavan*-4-*yl*]-4-(2,4-*dimethoxyphenyl*)-8-(3,4-*dimethoxyphenyl*)-5-*methoxy*-2-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-*pyrano* [2,3-f]*chromene* **34** (R_f 0.47, 5 mg) (Found: M^+, 1160.4252. $C_{63}H_{68}O_{21}$ requires M, 1160.4253); δ_H[300 MHz; $(CD_3)_2CO$; 23 °C] 6.79 [d, *J* 2.0, 5-H(A)], 6.55 [dd, *J* 2.5 and 8.5, 6-H(A)], 6.41 [d, *J* 2.5, 8-H(A)]; 6.43 [s, 2- and 6-H(B)]; 6.12 [t, *J* 10.0, 3-H(C)], 4.88 [d, *J* 10.0, 2-H(C)], 4.57 [d, *J* 10.0, 4-H(C)]; 6.81 [d, *J* 8.0, 5-H(E)], 6.63 [d, *J* 2.0, 2-H(E)], 6.53 [dd, *J* 2.0 and 8.0, 6-H(E)]; 4.86 [d, *J* 9.5, 8-H(F)], 4.80 [m, 9-H(F)], 3.19 [dd, *J* 6.5 and 17.0, 10-H^{eq}(F)], 2.66 [dd, *J* 9.0 and 17.0, 10-H^{ax}(F)]; 6.72 [d, *J* 8.5, 6-H(G)], 6.63 [d, *J* 2.0, 3-H(G)], 6.47 [dd, *J* 2.0 and 8.5, 5-H(G); 6.73 [s, 2- and 6-H(H)]; 5.36 [dd, *J* 6.0 and 10.0, 3-H(I)], 5.23 [d, *J* 6.0, 4-H(I)]; 5.06 [d, *J* 10.0, 2-H(I)]; 3.45 [s, 5-OMe(D)], 3.55 [s, 3- and 5-OMe(B)], 3.64 [s, 4-OMe (B or H)], 3.68 [s, 3-OMe(E)], 3.70 [s, 4-OMe (H or B)], 3.77 [s, 4-OMe(G)], 3.78 [s, 3- and 5-OMe(H)], 3.79 [s, 7-OMe(A)], 3.80 [s, 4-OMe(E)], 3.91 [s, 2-OMe(G)]; 1.45 (s, OAc), 1.78 (s, OAc) and 1.86 (s, OAc); CD $[\theta]_{298}$ 0, $[\theta]_{274}$ 5.8 × 10^3, $[\theta]_{250}$ 2.2 × 10^3, $[\theta]_{242}$ 4.2 × 10^3, and $[\theta]_{200}$ 6.9 × 10^2. Acetylation of fraction $H_{3.3}$ (29 mg) followed by PLC in 1,2-dichloroethane–acetone (9:1, v/v, × 2) afforded a mixture of 'trimeric' pyran-rearranged analogues which could not be sufficiently purified to allow their identification. Fraction $H_{3.4}$ afforded the permethyl ether triacetate of (4β,6;4α,8)-bis-(−)-robinetinidol-(+)-catechin[7] (R_f 0.39, 4 mg) after acetylation, and purification by PLC in 1,2-dichloroethane–acetone (9:1, v/v, × 2).

Methylation of a portion (503 mg) of fraction I and purification by PLC in benzene–acetone (8:2, v/v) gave a main band at R_f 0.18 (113 mg). This was acetylated and the resulting mixture was resolved by PLC in benzene–acetone (8:2, v/v, × 2) to give two bands, at R_f 0.61 (16 mg) and 0.54 (22 mg). Further purification of the R_f 0.61 band by PLC in 1,2-dichloroethane–acetone (9:1, v/v, × 2) gave the permethyl ether triacetate of (4α,6;4α,8)-bis-(−)-robinetinidol-(+)-gallocatechin[7] (R_f 0.43, 3 mg). Similar treatment of the R_f 0.54 band gave the permethyl ether triacetate of (4α,6;4α,8)-bis-(−)-robinetinidol-(+)-catechin[7] **36** (R_f 0.40, 3 mg).

Synthesis of the Prorobinetinidin-type Oligoflavanoids from Spray-dried Wattle Bark Extract

Synthesis and Base-catalysed Conversions of (−)-Robinetinidol-(+)-catechin Mono-O-methyl Ethers **38** *and* **39**.—(+)-Leucorobinetinidin (1.86 g) was added in portions over a period of 12 h at room temperature to a solution of 4′-*O*-methyl-(+)-catechin[22] (3.71 g) in 0.1 mol dm^{-3} HCl (800 cm^3) containing ethanol (20 cm^3). The mixture was stirred for 48 h at room temperature, and extracted with ethyl acetate (6 × 200 cm^3), and the combined extracts were dried over Na_2SO_4 and evaporated to dryness. The light brown solid (4.8 g) was subjected to column chromatography (3.5 × 80 cm column; flow rate 0.8 cm^3 min^{-1}; 26 cm^3/tube, first 1.5 dm^3 of eluent discarded) on Sephadex LH-20 in ethanol to give three

fractions, 1 [tubes 10–25 (1.7 g)], 2 [90–111 (440 mg)] and 3 [170–200 (675 mg)]. Fraction 1 afforded unchanged 4′-*O*-methyl-(+)-catechin while fractions 2 and 3 comprised the (−)-robinetinidol-(4β,8)- and -(4α,8)-(+)-catechin mono-*O*-methyl ethers **39** and **38**, respectively.

(−)-Robinetinidol-(4α,8)-(+)-catechin mono-*O*-methyl ether **38** (675 mg) was dissolved in a 0.025 mol dm^{-3} Na_2CO_2–0.025 mol dm^{-3} $NaHCO_3$ buffer solution (250 cm^3; pH 10.0) and the solution was stirred for 4.5 h at 50 °C under nitrogen.[24] The mixture was cooled to 0 °C, acidified with 0.1 mol dm^{-3} HCl, and extracted with ethyl acetate (6 × 200 cm^3). Drying (Na_2SO_4) of the combined organic phases and evaporation of the solvent gave a tan powder (410 mg), which was subjected to column chromatography (3 × 40 cm column; flow rate 0.3 cm^3 min^{-1}; 10 cm^3/tube, first 1 dm^3 of eluent discarded) on Sephadex LH-20 in ethanol to afford three fractions, 1 [tubes 18–30 (55 mg)], 2 [40–42 (18 mg)] and 3 [52–68 (180 mg)]. Fraction 1 was methylated and acetylated and the mixture was separated by PLC in 1,2-dichloroethane–acetone (8:2, v/v) to give the *didehydro-(−)-robinetinidol-(+)-catechin hepta-O-methyl ether diacetate* **45** as a *solid* (R_f 0.43, 3 mg) (Found: M^+, 758.2571. $C_{41}H_{42}O_{14}$ requires *M*, 758.2575); δ_H (Table 2). Methylation and subsequent acetylation of fraction 2 (18 mg) followed by PLC in hexane–acetone–ethyl acetate (60:25:15, v/v) gave a single compound (R_f 0.40, 2 mg) identical with the same derivative **22** of the naturally occurring tetrahydropyrano[2,3-*f*]chromene **20**. Fraction 3 (180 mg) was methylated, acetylated, and purified by PLC to give eventually only 9 mg of the permethyl ether diacetate of the starting biflavanoid **38**, hence demonstrating the poor yields which characterize the experimental manipulation of oligoflavanoids with pyrogallol B- and/or E-rings.

The (−)-robinetinidol-(4β,8)-(+)-catechin mono-*O*-methyl ether **39** (440 mg) was treated with base (3 h) and worked up as above to give a tan solid (350 mg), which was purified by column chromatography (3.5 × 35 cm column; flow rate 0.3 cm^3 min^{-1}; 10 cm^3/tube, first 400 cm^3 of eluent discarded) on Sephadex LH-20 in ethanol to give only one fraction (tube 67–98, 71 mg) which proved worthy of further investigation. It consisted of the *(−)-robinetinidol-(2β→7;4β→8)-(+)catechin mono-O-methyl ether* **12** as a *tan amorphous solid* (Found: M^+, 758.2578. $C_{41}H_{42}O_{14}$ requires *M*, 758.2575); δ_H (Table 2); CD $[\theta]_{280}$ 0, $[\theta]_{266}$ 6.6 × 10^3, $[\theta]_{250}$ 3.3 × 10^3, $[\theta]_{242}$ 4.8 × 10^3, $[\theta]_{238}$ 2.8 × 10^3, $[\theta]_{236}$ 3.6 × 10^3 and $[\theta]_{220}$ 0. A portion (20 mg) of compound **12** was methylated, acetylated, and eventually purified by PLC in hexane–acetone–ethyl acetate (6:3:1, v/v) to give the heptamethyl ether diacetate **14** (R_f 0.41, 7 mg) of the A-type prorobinetinidin **11**, which was identical with the same derivative of the natural product by comparison of ^1H NMR and CD data.

Synthesis and Base-catalysed Conversions of (−)-Robinetinidol-(+)-catechin Di-O-methyl Ethers **40** *and* **41**

Selective Methylation of (+)-*Catechin* via *Benzyl Carbonates.*—(+)-Catechin (23 × 600 mg portions) was dissolved in a borate buffer solution (each 300 cm^3), prepared by dissolution of H_3BO_3 (6.0 g) in aq. NaOH (3.0 g/300 cm^3) and adjustment of the pH of the solution to 9 with 10 mol dm^{-3} HCl, and a 50% solution of benzyl chloroformate (1.7 g) in toluene was added during 0.5 h while the mixture was vigorously stirred at room temperature. After further stirring of the mixture for 1 h the pH was adjusted to 3–4 with 3 mol dm^{-3} HCl and the mixture was extracted with ethyl acetate (5 × 100 cm^3). The combined organic phases were dried (Na_2SO_4), the solvent was evaporated off, and the mixture was separated by flash chromatography (1.9 × 70 cm column, 4–6 bar* pressure) on silica in ethyl acetate–hexane (11:10, v/v) to give 5,7-bis-*O*-benzyloxycarbonyl-(+)-catechin (45% yield). This derivative (1–3 g portions) was methylated with diazomethane (*ca.* 4 h), the solvent was removed, and the resulting 5,7-bis-*O*-benzyloxycarbonyl-3′,4′-di-*O*-methyl-(+)-catechin (3 × 3.8 g portions) was dissolved in a mixture of acetone (6 cm^3) and methanol (130 cm^3), and was hydrogenated for 12 h under ambient conditions over 10% Pd/C. Filtration, and evaporation of the solvent, afforded 3′,4′-di-*O*-methyl-(+)-catechin (6.2 g), which was identical with an authentic sample.[28]

Synthesis of 'Protected' (−)-Robinetinidol-(+)-catechin Biflavanoids **40** *and* **41**.—(+)-Leucorobinetinidin (2.37 g) was added in portions over a period of 3 h to a solution of 3′,4′-di-*O*-methyl-(+)-catechin (7.4 g) in methanol (150 cm^3)–0.1 mol dm^{-3} HCl (500 cm^3), and the mixture was stirred at room temperature for 25 h under nitrogen. Extraction with ethyl acetate (6 × 300 cm^3), drying of the combined organic phases over Na_2SO_4, and evaporation of solvent afforded a light yellow powder (10.3 g) after freeze-drying. The mixture was resolved by column chromatography (4.0 × 150 cm column; flow rate 0.8 cm^3 min^{-1}; 13 cm^3/tube, first 1 dm^3 of eluent discarded) on Sephadex LH-20 in ethanol into six fractions, 1 [tubes 56–85 (3.8 g)], 2 [206–244 (692 mg)], 3 [245–328 (470 mg)], 4 [330–394 (900 mg)], 5 [425–486 (250 mg)] and 6 [713–778 (143 mg)]. Fraction 1 consisted of unchanged 3′,4′-di-*O*-methyl-(+)-catechin, fraction 2 of (−)-robinetinidol-(4β,8)-(+)-catechin di-*O*-methyl ether **41**, fraction 4 of the (4α,8)-analogue **40**, and fractions 5 and 6 of the (−)-robinetinidol-(4α,6)- and -(4β,6)-(+)-catechin di-*O*-methyl ethers. The (4,6)-isomers will be dealt with elsewhere. Comparison of the physical features of the permethyl ether diacetates of the (4,8)-isomers **40** and **41** with those of authentic specimens[15] confirmed their identity. Methylation of a portion (100 mg) of fraction 3 and PLC in benzene–acetone (8:2, v/v) gave a band at R_f 0.54 (9 mg), which was acetylated to give the *didehydro-(−)-robinetinidol-(+)-catechin octamethyl ether acetate* **43** (9.5 mg) as an *amorphous solid* (Found: M^+, 730.2623. $C_{40}H_{42}O_{13}$ requires *M*, 730.2626); δ_H (Table 2).

Water that was distilled twice was degassed by repeated evacuation under nitrogen and was finally refluxed for 6 h under nitrogen. A mixture of Na_2CO_3 (265 mg) and $NaHCO_3$ (210 mg) was dissolved in the degassed water (100 cm^3), the (−)-robinetinidol-(4β,8)-(+)-catechin derivative **41** was added and the mixture was treated and worked up as was described for the mono-*O*-methyl ether **39**. Separation of the mixture (370 mg) by column chromatography (3 × 80 cm column; flow rate 0.3 cm^3 min^{-1}; 10 cm^3/tube, first 500 cm^3 of eluent discarded) on Sephadex LH-20 in ethanol gave three fractions, 1 [tubes 119–132 (37 mg)], 2 [134–144 (13 mg)] and 3 [151–168 (64 mg)].

Fraction 1 was methylated, and purified by PLC in hexane–acetone–ethyl acetate (6:3:1, v/v) to give a main band at R_f 0.41 (11 mg), which was acetylated to give (2R,3S;8R,9R,10S)-2,3-trans-8,9-cis-9,10-trans-3,9-*diacetoxy*-8-(2,4-*dimethoxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-5-*methoxy*-10-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3-f]*chromene* **47** as an *amorphous solid* (11.3 mg) (Found: M^+, 774.2889. $C_{42}H_{46}O_{14}$ requires *M*, 774.2888); δ_H (Table 4); CD $[\theta]_{294}$ 0, $[\theta]_{263}$ −4.9 × 10^3, $[\theta]_{243}$ 0, $[\theta]_{240}$ 1.6 × 10^3, $[\theta]_{236}$ 0, $[\theta]_{219}$ −2.9 × 10^4, and $[\theta]_{200}$ −1.5 × 10^4. Methylation, acetylation, and PLC in hexane–acetone–ethyl acetate (6:3:1, v/v) of fraction 2 gave a single band at R_f 0.35 (4 mg) which consisted of (2R,3S;8S,9R,10S)-2,3-trans-8,9-trans-9,10-trans-3,9-*diacetoxy*-8-(2,4-*dimethoxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-5-*methoxy*-10-(3,4,5-*trimethoxyphenyl*)-3,4,9,10-*tetrahydro*-2H,8H-

* 1 bar = 10^5 Pa.

pyrano[2,3-f]*chromene* **49** as an *amorphous solid* (Found: M^+, 774.2877. $C_{42}H_{46}O_{14}$ requires *M*, 774.2888); δ_H (Table 4); CD $[\theta]_{248}$ 0, $[\theta]_{212}$ -2.7×10^4, and $[\delta\theta]_{200}$ -1.3×10^4. Fraction 3 was similarly methylated, acetylated, and resolved by PLC [hexane–acetone–ethyl acetate (6:3:1, v/v)] into two bands, at R_f 0.41 (29 mg) and 0.34 (13 mg). The R_f 0.41 band afforded the A-type prorobinetinidin derivative **14** and the R_f 0.34 band the tetrahydropyrano[2,3-*f*]chromene derivative **27**, both identical with the same derivatives of the natural products by comparison of ^{1}H NMR and CD data.

Synthesis and Base-catalysed Conversion of (4α,6;4α,8)-*Bis*-(−)-*robinetinidol*-(+)-*catechin Di*-O-*methyl Ether* **37**.—(+)-Leucorobinetinidin (675 mg) was added in portions over a period of 1 h to a solution of (−)-robinetinidol-(4α,8)-(+)-catechin di-*O*-methyl ether **40** (890 mg) in ethanol (15 cm^3)–0.1 mol dm^{-3} HCl (300 cm^3) at room temperature under nitrogen. After being stirred for 20 h the mixture was extracted with ethyl acetate (3 × 400 cm^3), the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated off. Column chromatography (3.5 × 100 cm column; flow rate 2 cm^3 min^{-1}; 15 cm^3/tube, first 1 dm^3 of eluent discarded) of the yellow freeze-dried extract (906 mg) on Sephadex LH-20 in ethanol afforded four fractions, 1 [tubes 102–112 (124 mg)], 2 [164–198 (216 mg)], 3 [552–659 (62 mg)] and 4 [705–809 (105 mg)]. Fraction 1 consisted of unchanged (+)-leucorobinetinidin, and fraction 2 of the starting biflavanoid **40**. Fractions 3 and 4 gave the (4β,6;4α,8)-bis-(−)-robinetinidol-(+)-catechin di-*O*-methyl ether and the (4α,6;4α,8)-analogue **37**, respectively, which were identified by comparison of ^{1}H NMR and CD data of their permethyl ether triacetates with those of the corresponding derivatives of authentic samples.[7]

The triflavanoid derivative **37** (90 mg) was dissolved in the Na_2CO_3–$NaHCO_3$ buffer system (50 cm^3) at pH 10 and the mixture was stirred for 2.5 h under nitrogen at 50 °C. The mixture was chilled to 0 °C, acidified with 0.1 mol dm^{-3} HCl to pH 3–4, and extracted with ethyl acetate (4 × 100 cm^3). The combined extracts were dried (Na_2SO_4), the solvent was evaporated off, and the mixture was freeze-dried to give a light yellow powder (66 mg). This was methylated, and separated by PLC in hexane–chloroform–methanol–acetone (50:40:5:5, v/v, × 3) to give a main band at R_f 0.32 (7 mg). Acetylation afforded the (−)-robinetinidol-(4α,6)-tetrahydropyrano[2,3-*f*]chromene permethyl ether triacetate **34** with ^{1}H NMR and CD data identical with those of the same derivative of the natural product from *A. mearnsii*.

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