Pergamon

Tetrahedron, Vol. 53, No. 7, pp. 2591-2598, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01149-0

Oligomeric Flavanoids. Part 25[a]. Cleavage of the Acetal Functionality in A-type Proanthocyanidins

Petrus J. Steynberg, Annemarie Cronjé, Jan P. Steynberg, Barend C.B. Bezuidenhoudt, E. Vincent Brandt and Daneel Ferreira*

Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 South Africa

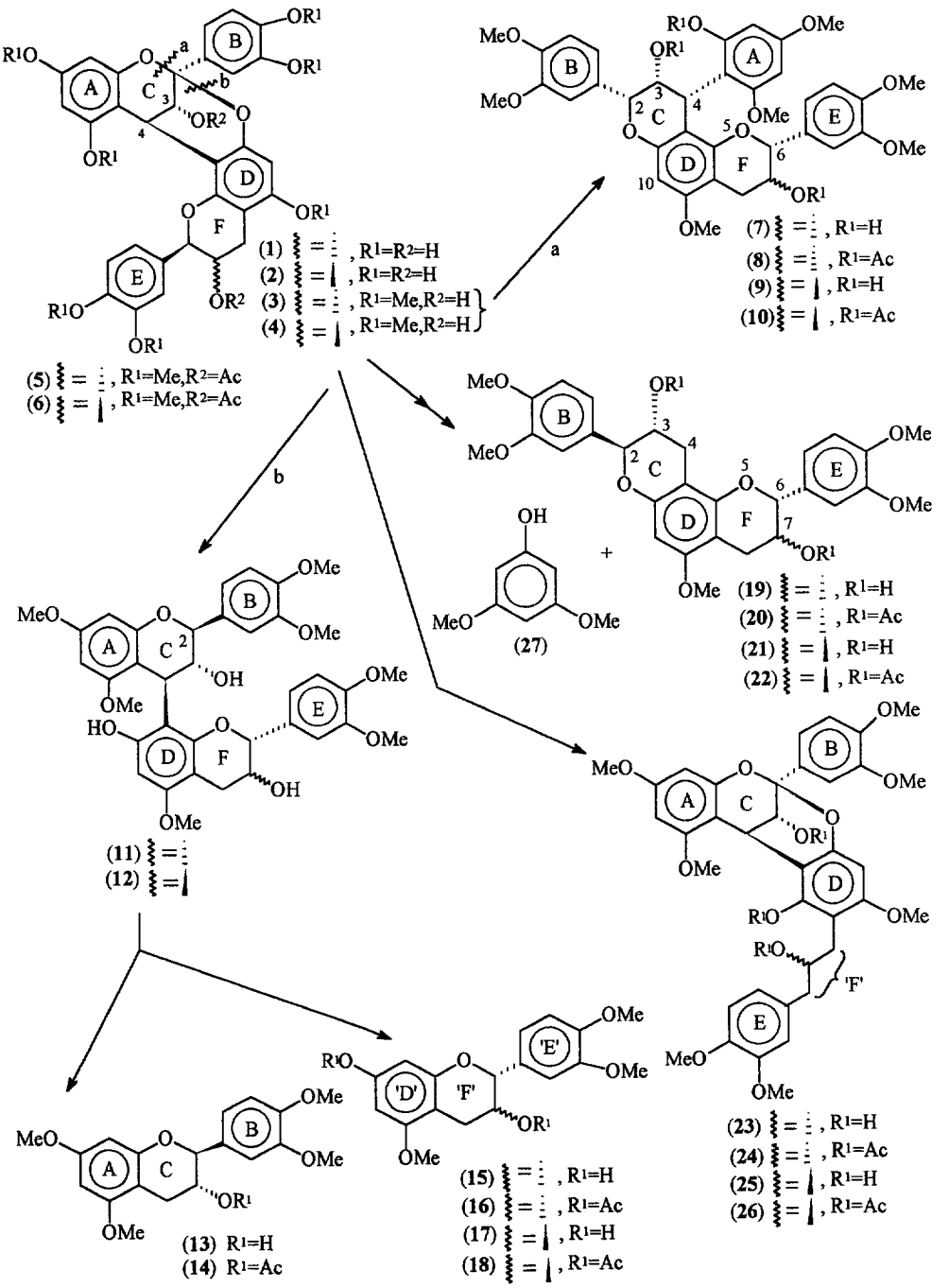
Abstract. The hepta-*O*-methyl ethers **3** and **4** of procyanidin A-1 **1** and A-2 **2** are subject to facile cleavage of the acetal functionality with sodium cyanoboranuide in trifluoroacetic acid at 0°C. This straight forward chemical method permits the unambiguous establishment of the absolute configuration of the DEF-flavanyl unit and the D-ring carbon and oxygen atoms that are involved in the double linkage of the A-class proanthocyanidins.

The double interflavanyl linkage in A-type proanthocyanidins introduces a high degree of conformational stability which culminates in high-quality and unequivocal NMR spectra, conspicuously free of the effects of dynamic rotational isomerism at the dimeric level. Compounds of this class are readily recognizable from the characteristic AB-doublet ($^3J_{3,4}$ = 3-4 Hz) of C-ring protons in the heterocyclic region of their ^{1}H NMR spectra[1], and may possess either (2α,4α)- or (2β,4β)-double interflavanyl bonds. Two fundamental structural problems, *i.e.* establishment of the mode of linkage of the D- to the C-ring, and assignment of the absolute configuration at the stereocentres of the F-ring, have however limited progress in this field. These and related problems have hitherto been approached *via* exotic spectroscopic methods[2-5] which prompted us to search for a more simple and general chemical method that is based upon the reductive cleavage of the acetal functionality. The potential to address the aforementioned problems by reduction of either of the C-O acetal bonds is now demonstrated for the known procyanidins A-1 **1** and A-2 **2**, available from the skins of mature peanuts (*Arachus hypogea L.*)[6], using sodium cyanoboranuide [Na(CN)BH_3] in trifluoroacetic acid (TFA)[7]. The readily accessable hepta-*O*-methyl ethers **3** and **4** were selected as model compounds with a view to using the *O*-substituents of the D-ring as probes for ^{1}H NMR studies.

RESULTS AND DISCUSSION

Separate treatment of the hepta-*O*-methylprocyanidins A-1 **3** and A-2 **4** with Na(CN)BH_3 (1:2.4 molar ratio) in TFA for 1.5h at 0°C under N_2 (Scheme), gave conversion to mixtures comprising the starting materials (**3**, 3.4% and **4**, 4.4% respectively), and as anticipated from cleavage 'a' the tetrahydropyrano[2,3-*f*]chromene derivatives (**9**, 5.2% and **7**, 7% respectively). The envisaged biflavanoids **11** and **12** from the 'b' pathway were,

[a] Part 24. Saunders, C.M.; Bonnet, S.L.; Steynberg, J.P.; Ferreira, D. *Tetrahedron*, 1996, 52, 6003



Scheme. Cleavage of the acetal functionality of procyanidin A-1 and A-2 hepta- *O*-methyl ethers **3** and **4** with $Na(CN)BH_3$ in THF

however, not obtained but instead, the respective monomeric units, *i.e.* tetra-*O*-methyl-*ent*-catechin (**13**, 4%) and tri-*O*-methylcatechin (**17**, 3.4%) from the A-1 derivative **3**, and tetra-*O*-methyl-*ent*-catechin (**13**, 3%) and tri-*O*-methylepicatechin (**15**, 1.3%) from the A-2 derivative **4** were isolated (*vide infra*). These compounds were accompanied by the tetrahydropyrano[2,3-*f*]chromene derivatives (**21**, 3.9% and **19**, 4.5% respectively), the doubly linked epicatechin-1,3-diarylpropan-2-ol derivatives (**25**, 2.6% and **23**, 2.5% respectively), and 3,5-dimethoxyphenol (**27**, 3.8 and 4% respectively). The formation of compounds **19**, **21**, **23**, **25**, and **27** became more prominent under more drastic conditions.

The structures of the aforementioned products were unequivocally elucidated by comparison of the physical data of their *O*-acetyl derivatives, *e.g.* **8**, with those of similar derivatives of suitable reference compounds from our collection of related substances[8-10]. ^{1}H NMR data are collated in Tables 1 and 2 while circular dichroic (CD) data are given in the Experimental.

Owing to their importance to the protocol developed here, the structures of the tetrahydropyrano[2,3-*f*]-chromene derivatives **8** and **10**, and of the flavan-3-ol derivatives **14**, **16** and **18** should be emphasized. Whereas the high amplitude negative Cotton effect ($[\theta]_{239.5}$ -75000; $[\theta]_{242.4}$ -110000 for **8** and **10** respectively) in the CD spectra of the tetrahydropyrano[2,3-*f*]chromene derivatives **8** and **10** are reminiscent of the 4α orientation of their A-rings[8], the 2,3-*cis*-3,4-*cis* relative configurations were evident from the ^{1}H NMR coupling constants of C-ring protons[9] ($^3J_{2,3}$ = *ca* 1.0; $^3J_{3,4}$ = 6.5 Hz for both **8** and **10**). The 2,4-*cis* relationship of A- and B-rings in these compounds was unequivocally established by the observed NOE associations[11] between 2-H(C) and 3-H(C) (7.3 and 7.0% respectively), and of 2-H(C) with 4-H(C) (5.4% for both **8** and **10**). In compound **10** the 2,4-*cis* orientation of A- and B-rings was additionally supported by the NOE effects between 2-OAc(A) and both 2-H(B) (0.9%) and 6-H(B) (0.7%). Although similar NOE's were absent in compound **8**, this derivative displayed an NOE-interaction between 2-OAc(A) and both 2- and 6-H(E) (1.1 and 1.0% respectively), thus confirming the 4,6-*cis* orientation of the A- and E-rings. Coupling constants of the F-ring protons ($^3J_{6,7}$ = *ca* 1.0 and 9.0 Hz for 8 and **10** respectively) were indicative of a 6,7-*cis* and 6,7-*trans* configuration for compounds **8** and **10** respectively. Collectively these data confirmed the absolute configuration at the stereocentres as indicated in the tetrahydropyrano[2,3-*f*]chromene derivatives **8** and **10**, and especially the *R* configuration at C-3. The 5-*O*-methyl-7-*O*-acetyl substitution pattern of the A-ring of the epicatechin and catechin derivatives **16** and **18** was established by the observed NOE associations of 6-H(A) (δ 6.21 for both **16** and **18**) with both 5-OMe (δ 3.78, 3.76 for **16** and **18** respectively) and 7-OAc (δ 1.90, 1.95 for **16** and 18 respectively). Comparison of CD data of the flavan-3-ol derivatives **14**, **16** and **18** with those of the 3′,4′,5,7-tetra-*O*-methyl-3-*O*-acetyl derivatives of *ent*-catechin, epicatechin and catechin respectively, confirmed the 2*S*,3*R* absolute configuration of compound **13**, 2*R*, 3*R* of **15** and 2*R*,3*S* of **17**. These three flavan-3-ols originated from the reductive cleavage of the interflavanyl bond in the intermediate B-type procyanidin derivatives **11** and **12** (see also below).

Table 1. ^{1}H NMR peaks (δ_H) of the tetrahydropyranochromene derivatives **8**, **10**, **20** and **22** and the doubly linked epicatechin derivatives **24** and **26** at 300 MHz (23°C) in $CDCl_3$. Splitting patterns and J-values(Hz) are given in parentheses.

Proton	8	10	20	22 (C_6D_6)	24	26
3/6-H(A) 5/8-H(A)	6.37(d,2.5) 6.27(d,2.5)	6.15(d,2.5) 6.08(d,2.5)	-	-	6.31,6.10(each d,2.5)	6.28,5.94(each d,2.5)
2-H(B) 5-H(B) 6-H(B)	7.01(d,2.0) 6.82(d,8.5) 6.98(dd,2.0,8.5)	7.00(d,2.0) 6.80(d,8.5) 6.96(dd,2.0,8.5)	7.04-6.79	7.12(d,2.0) 6.63(d,8.5) 7.16(dd,2.0,8.5)	7.23-6.59	7.30-6.52
2-H(C) 3-H(C) 4-H(C)	5.02(br.s) 5.77(dd,1.0,6.5) 5.07(d,6.5)	5.01(br.s) 5.60(dd,1.0,6.5) 5.01(d,6.5)	4.98(d,7.0) 5.33(m) 3.10-2.71 (2xdd,1xm)	5.40(d,6.5) 5.77(m) 3.39(dd,6.0, 10.5 3.15(dd,6.0,10.5)	- 5.48(d,3.0) 4.30(broadened)	- 5.57(d,3.0) 4.89(d,3.0)
6/10-H(D)	6.26(s)	6.25(s)	6.21(s)	6.48(s)	6.48(s)	6.18(s)
2-H(E) 5-H(E) 6-H(E)	6.47(d,2.0) 6.54(d,8.5) 6.03(dd,2.0, 8.5)	6.55(d,2.5) 6.58(d,8.5) 6.31(dd,2.5, 8.5)	7.04-6.79	7.03(d,2.2) 6.64(d,8.5) 7.05(dd,2.2, 8.5)	7.23-6.59	7.30-6.52
6-H(F)/CH_2 7-H(F)	4.80(br.s) 5.23(m)	4.51(d,9.0) 5.02(m)	5.00(br.s) 5.48(br.s)	5.24(d,6.5) 5.77(m)	5.20(m)	5.34(m)
8α-H(F) 8β-H(F)	2.90(d,3.5)	3.17(dd,6.0,16.0) 2.50(dd,9.5,16.0)	3.10-2.71 (2xdd,1xm)	3.34(dd,6.0,10.5) 3.10(dd,6.0,10.5)	3.00-2.42 (2xCH_2)	2.78-2.15 (2xCH_2)
OMe	3.89(3-B),3.85 (4-B),3.82(4-E), 3.78(9-D),3.76 (4-A),3.72(3-E), 3.62(6-A), each s	3.88(3-B),3.84 (4-B),3.82(4-E), 3.77(9-D),3.73 (4-A,3-E),3.46 (6-A), each s	3.89-3.78(x5), each s	3.52(3-E),3.50 (3-B),3.45(4-B, 4-E),3.40(10-D), each s	3.91-3.70(x7) each s	3.91,3.89,3.81, 3.75,3.69,3.41, 3.19,each s
OAc	1.62,1.70,1.82 (2-A),each s	1.64,1.71,1.79 (2-A),each s	1.93,1.92,each s	1.67,1.58,each s	2.39(D, br.s), 1.82(br.s) 1.73(s)	2.09(D),1.71, 1.55,each s

Table 2. ^{1}H NMR peaks (δ_H) of the flavan-3-ol derivatives **14**, **16** and **18** at 300 MHz (23°C) in $CDCl_3$. Splitting patterns and J-values (Hz) are given in parentheses

Proton	14	16	18
6-H(A) 8-H(A)	6.07(d,25) 6.15(d,2.5)	6.21(d,2.0) 6.39(d,2.0)	6.21(d,2.0) 6.35(d,2.0)
2-H(B) 5-H(B) 6-H(B)	6.86(d,2.0) 6.80(d,8.0) 6.90(dd,2.0,8.0)	7.00(d,2.0) 6.84(d,8.5) 6.93(dd,2.0,8.5)	6.85(d,2.0) 6.80(d,8.0) 6.88(dd,2.0,8.0)
2-H(C) 3-H(C) 4α-H(C) 4β-H(C)	5.0(d,7.0) 5.33(m) 2.89(dd,5.5,16.5) 2.65(dd,6.5,16.5)	5.0(br.s) 5.42(m) 2.94(d,3.0)	5.02(d,7.0) 5.33(m) 2.90(dd,5.5,17.0) 2.67(dd,6.5,17.0)
OMe	3.85(4-B),3.84(3-B),3.76(5-A), 3.75(7-A), each s	3.88(4-B),3.87(3-B),3.78(5-A), each s	3.85(4-B),3.83(3-B),3.76(5-A), each s
OAc	1.94(3-C)(s)	1.90(3-C),2.28(7-A),each s	1.95(3-C),2.27(7-A),each s

The ^{1}H NMR spectra (Table 1) of the tetrahydropyrano[2,3-*f*]chromene derivatives **20** and **22** each exhibited two ABM spin systems and a singlet in the aromatic region, two heterocyclic ABXY systems, five *O*-methyl and two *O*-acetyl resonances. Both compounds thus lack the oxygenated phenyl substituent at C-4 when compared to the 'normal' tetrahydropyrano[2,3-*f*]chromene derivatives **8** and **10**. Owing to the overlapping of some key *O*-methyl resonances, the two very similar aromatic ABM systems could not be differentiated in derivative **20**[12]. In the ^{1}H NMR spectra (Table 1) of the doubly linked epicatechin-1,3-diarylpropan-2-ol derivatives **24** and **26** partial rotational barriers were observed at 23^{0}C, but at 80^{0}C nine aromatic and seven heterocyclic protons as well as seven *O*-methyl and three *O*-acetyl resonances were evident. The characteristic signals of the intact doubly linked epicatechin moiety (AB-doublet, $^3J_{3,4}$ = 3.5 Hz for both **24** and **26**) in conjunction with the one-proton multiplet and two sets of benzylic methylene protons confirmed the proposed structures. Since compounds **20**, **22**, **24** and **26** do not contribute significantly towards the methodology developed here, their structure elucidation need not be discussed further.

Both the carbon-oxygen bonds of the acetal functionality in the procyanidin A-1 and A-2 derivatives **3** and **4** are thus susceptible to reductive cleavage under acidic conditions. This process is presumably triggered by the random protonation of the acetal oxygens and concomitant delivery of the equivalent of a hydride ion at the antibonding (σ^*) orbitals of the carbon-oxygen bonds in a predominant S_N2 manner. Such a transfer of hydride ion apparently occurs from a complex between the reducing agent and the axial C-3 (C-ring) oxygen lone pair, the proximity of the boron-hydrogen bonds to the backside of the acetal carbon atom being a prerequisite for reduction of either one of the acetal bonds. Reduction thus leads to 'inversion' of configuration at C-2(C) of both B-type procyanidin intermediates **11** and **12**, and of the tetrahydropyrano[2,3-*f*]chromene derivatives **7** and **9**.

Biflavanoids **11** and **12** are prone to facile cleavage of their interflavanyl bonds *via* protonation of the electron-rich phloroglucinol D-ring[14] and attack of hydride ion at C-4(C)[15] to give the *ent*-catechin derivative **13** from the ABC-unit and respectively the epicatechin and catechin derivatives **15** and **17** from the DEF-moieties[13]. The doubly linked epicatechin-1,3-diarylpropan-2-ols **23** and **25** presumably results from the reductive cleavage of the benzyl ether functionality (F-ring) of hepta-*O*-methylprocyanidins A-1 **3** and A-2 **4**, in a process similar to the formation of 1,3-diarylpropanes when flavanones are treated with $Na(CN)BH_3$ in TFA[16]. The functionalized tetrahydropyrano[2,3-*f*]chromenes **7** and **9** may serve as the precursors to the tetrahydropyrano[2,3-*f*]chromene derivatives **19** and **21** *via* acid-catalyzed reductive rupturing of the labile C-10—phloroglucinol A-ring bond, thus also explaining the formation of 3,5-dimethoxyphenol **27**. The observed inversion of configuration at C-2(C) in compounds **19** and **21**, compared to that of the same stereocentres in the tetrahydropyrano[2,3-*f*]-chromenes **7** and **9**, may indicate that the transfer of hydride ion in the acetal cleavage partially followed an S_N1 pathway. It may also be effected *via* acid-catalyzed epimerization to afford the thermodynamically more stable 2,3-*trans* isomer. The latter process presumably occurs at a late stage when the diminished concentration of

$Na(CN)BH_3$ does not permit hydride transfer to the equivalent of an incipient C-2-carbocation which is a prerequisite for epimerization.

The 'liberation' of the chain terminating flavan-3-ol units **15** and **17** unambiguously defines the D-ring oxygen that is involved in the acetal functionality of the parent compounds **1** and **2**. It furthermore provides a powerful probe towards addressing the hitherto unsolved problem of establishing the absolute configuration at the stereocentres of this moiety in naturally occurring A-type proanthocyanidins. The flavan-3-ol unit **13**, albeit with inversed C-2 configuration should facilitate the assignment of the absolute configuration at C-3 of the parent compounds **1** and **2**, especially in view of the inability to differentiate between 3,4-*cis*- and 3,4-*trans*-configuration in these compounds on the basis of $^3J_{HH}$ values[2]. The mode of the C-C linkage between the constituent flavan-3-ol units in the A-type procyanidin, *e.g.* (4,6) or (4,8), is defined by the nature of the tetrahydropyranochromene, *i.e.* [2,3-*f*], [2,3-*g*] or [2,3-*h*], that is formed *via* reductive cleavage 'a'. The tetrahydropyranochromenes of type **8** represent a class of compounds with a well established method of structure elucidation[8,12,17]. This development should thus contribute substantially towards a straight forward chemically orientated structure definition of proanthocyanidins of the A-class.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard. J-values are given in Hz. Accurate mass estimations were obtained with a Varian CH-5 instrument with double focus. CD data were obtained in methanol on a JASCO J-710 spectropolarimeter. Preparative layer chromatography (PLC) was performed on plates (20x20 cm) with Merck Kieselgel PF_{254} (1.0 mm) which were air-dried and used without prior activation. Acetylations were done in acetic anhydride/pyridine at ambient temperature. Evaporations were done under reduced pressure at *ca* 50^0C in a rotary evaporator.

Reductive cleavage of procyanidin A-2 hepta-O-methyl ether **4**. — $Na(CN)BH_3$ (37 mg, $5.0x10^{-4}$ mole) was added in portions over 30 min to a solution of the title compound **4** (50 mg, $7.57x10^{-5}$ mole) in TFA (3 cm^3) at 0^0C under N_2. After 1h the reaction was quenched by the careful addition of water (20 cm^3) and the pH was adjusted to *ca* 6.9 (Merck special indicator, pH 4.0-7.0) with *aq*. $NaHCO_3$ (2%). The mixture was extracted with ethyl acetate (3x50 cm^3) and the combined extract was stirred for 15 min with 3 drops of a solution of tetrabutylammonium fluoride (TBAF) in THF. Drying over Na_2SO_4 followed by evaporation of the solvent afforded a mixture (45 mg) which was separated by PLC in benzene-acetone (8:2, v/v) to give five bands: 1 (R_F 0.8, 3 mg), 2 (R_F 0.54, 6 mg), 3 (R_F 0.34, 5 mg), 4 (R_F 0.29, 9 mg) and 5 (R_F 0.18, 5.5 mg). The ^1H NMR spectrum of band 1 was identical to that of an authentic specimen of 3,5-dimethoxyphenol **27**.

Acetylation of band 2 and PLC in benzene-acetone (9:1, v/v) afforded 3′,4′,5,7-tetra-*O*-methyl-3-*O*-acetyl-*ent*-catechin **14** as a *white amorphous solid* (R_F 0.63, 5 mg) (Found: M^+, 388.1521. Calculated for $C_{21}H_{24}O_7$ M, 388.1522; δ_H (Table 2); CD $[\theta]_{306.4}$ 26, $[\theta]_{279.4}$ 4500, $[\theta]_{267.6}$ 1300, $[\theta]_{251.6}$ -7.0, $[\theta]_{243.9}$ -2400, $[\theta]_{239.2}$ 2.0, $[\theta]_{232}$ 5900, $[\theta]_{221.1}$ 790, $[\theta]_{215.8}$ 4400 and $[\theta]_{210.4}$ -5.2.

Acetylation of band 3 followed by PLC in benzene-acetone (9:1, v/v) gave two bands, 3.1 (R_F 0.55, 1.5 mg) and 3.2 (R_F 0.43, 2.2 mg). Band 3.1 afforded 3′,4′,5-tri-*O*-methyl-3,7-di-*O*-acetylepicatechin **16** as a *white*

amorphous solid (Found: M^+, 416.1463. $C_{22}H_{24}O_8$ requires M, 416.1471); δ_H (Table 2); CD $[\theta]_{310}$ -300, $[\theta]_{284}$ -340, $[\theta]_{270.6}$ -1900, $[\theta]_{255.6}$ -950, $[\theta]_{235.6}$ -1300, $[\theta]_{219.9}$ -46 and $[\theta]_{210}$ 3300. Band 3.2 comprised of the di-*O*-acetyl derivative **6** of the starting material **4**.

Band 4 was acetylated and the mixture was resolved by PLC in benzene-acetone (9:1, v/v) to give two fractions, 4.1 (R_F 0.3, 2 mg) and 4.2 (R_F 0.22, 5.4 mg). Fraction 4.1 afforded 3-*O*-acetyl-3′,4′,5,7-tetra-*O*-methylepicatechin-(2β,1:4β,2)-3-*O*-acetyl-4-[2*S*-acetoxy-3-(3,4-dimethoxyphenyl)propyl]-5-*O*-methylphloroglucinol **24** as a *white amorphous solid* (Found: M^+, 802.2839. $C_{43}H_{46}O_{15}$ requires M, 802.2837); δ_H (Table 1); CD $[\theta]_{300}$ -290, $[\theta]_{283.9}$ 1000, $[\theta]_{278.9}$ -53, $[\theta]_{269.9}$ -23000, $[\theta]_{259.5}$ -14000, $[\theta]_{245.1}$ -66000, $[\theta]_{232.5}$ -130, $[\theta]_{225.6}$ 33000, $[\theta]_{217.2}$ 60, $[\theta]_{213.8}$ -15000, $[\theta]_{210.5}$ -250, $[\theta]_{207.7}$ 9100, $[\theta]_{205.1}$ 7400 and $[\theta]_{200.1}$ 29000. Fraction 4.2 gave 2*R*,3*R*,4*R*,6*R*,7*R*-3,7-diacetoxy-9-methoxy-2,6-bis(3,4-dimethoxyphenyl)-4-(2-acetoxy-4,6-dimethoxyphenyl)-2,3-*cis*-3,4-*cis*-6,7-*cis*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromene **8** as a *white amorphous solid* (Found: M^+, 802.2831. $C_{43}H_{46}O_{15}$ requires M, 802.2837); δ_H (Table 1); CD $[\theta]_{300}$ -750, $[\theta]_{280.7}$ 8800, $[\theta]_{262.2}$ 370, $[\theta]_{255.1}$ -580, $[\theta]_{239.5}$ -75000, $[\theta]_{221.6}$ 120, $[\theta]_{216.4}$ 25000, $[\theta]_{209.3}$ 3100 and $[\theta]_{202.6}$ 20000.

Band 5 was acetylated and purified by PLC in benzene-acetone (9:1, v/v) to give 2*S*,3*R*,6*R*,7*R*-3,7-diacetoxy-9-methoxy-2,6-bis(3,4-dimethoxyphenyl)-2,3-*trans*-6,7-*cis*-3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]-chromene **20** (R_F 0.4, 5 mg) as a *white amorphous solid* (Found: M^+, 608.2252. $C_{33}H_{36}O_{11}$ requires M, 608.2258); δ_H (Table 1); CD $[\theta]_{310}$ -650, $[\theta]_{256.6}$ -38, $[\theta]_{234.6}$ -11000, $[\theta]_{226.5}$ -9500, $[\theta]_{212.4}$ -33000, $[\theta]_{207}$ -1200 and $[\theta]_{200}$ 44000.

*Reductive cleavage of procyanidin A-1 hepta-*O*-methylether* **3**. — The title compound (50 mg) was reduced with $Na(CN)BH_3$ (37 mg) and the resulting mixture worked-up as was described above for the procyanidin A-2 derivative **4**. This mixture (47 mg) was resolved by PLC in benzene-acetone (8:2, v/v) to give five bands: 1 (R_F 0.8, 3 mg), 2 (R_F 0.54, 7 mg), 3 (R_F 0.33, 10 mg), 4 (R_F 0.29, 20 mg) and 5 (R_F 0.18, 33.5 mg). Band 1 again comprised 3,5-dimethoxyphenol **27**.

Acetylation of fraction 2 followed by PLC in benzene-acetone (9:1, v/v) afforded 3′,4′,5,7-tetra-*O*-methyl-3-*O*-acetyl-*ent*-catechin **14** (R_F 0.63, 5 mg) with ^1H NMR (Table 2) and CD data identical to those of the same compound described above.

Fraction 3 was acetylated and the mixture resolved by PLC in benzene-acetone (9:1, v/v) to give two bands, 3.1 (R_F 0.55, 2.5 mg) and 3.2 (R_F 0.43, 2.2 mg). Band 3.1 gave 3,7-di-*O*-acetyl-3′,4′,5-tri-*O*-methylcatechin **18** as a *white amorphous solid* (Found. M^+, 416.1461. $C_{22}H_{24}O_8$ requires M, 416.1471); δ_H (Table 2); CD $[\theta]_{310}$ -33, $[\theta]_{290.4}$ -240, $[\theta]_{281.8}$ 790, $[\theta]_{268}$ -1600, $[\theta]_{256}$ -780, $[\theta]_{242.9}$ -1800, $[\theta]_{236.7}$ 17, $[\theta]_{231.6}$ 2200, $[\theta]_{225.4}$ -140, $[\theta]_{220.4}$ 1500, $[\theta]_{214.4}$ 70, $[\theta]_{212.4}$ 130 and $[\theta]_{205.4}$ -1800. Band 3.2 afforded the di-*O*-acetyl derivative **5** of the starting material **3**.

Acetylation of fraction 4 followed by PLC in benzene-acetone (9:1, v/v) gave two bands, 4.1 (R_F 0.32, 2 mg) and 4.2 (R_F 0.21, 7 mg). Fraction 4.1 afforded the 2*R*-epimer **26** of compound **24** as a *white amorphous solid* (Found: M^+, 802.2823. $C_{43}H_{46}O_{15}$ requires M, 802.2837); δ_H (Table 1); CD $[\theta]_{300}$ -410, $[\theta]_{271.1}$ -14000, $[\theta]_{260.5}$ -9900, $[\theta]_{235.5}$ -81000, $[\theta]_{228.5}$ -76000, $[\theta]_{218.6}$ -470, $[\theta]_{213.9}$ 33000 and $[\theta]_{206.4}$ -940. Fraction 4.2 gave the 7*S*-epimer **10** of the tetrahydropyrano[2,3-*f*]chromene dervative **8** as a *white amorphous solid* (Found: M^+, 802.2828. $C_{43}H_{46}O_{15}$ requires M, 802.2837); δ_H (Table 1); CD $[\theta]_{295.8}$ -180, $[\theta]_{279.8}$ 13000, $[\theta]_{261.5}$ 420, $[\theta]_{254.5}$ -1200, $[\theta]_{242.4}$ -110000, $[\theta]_{235.8}$ 170, $[\theta]_{233.5}$ 12000, $[\theta]_{229.4}$ 9.5, $[\theta]_{226.5}$ -5000, $[\theta]_{223.7}$ -81, $[\theta]_{217.3}$ 18000, $[\theta]_{213.5}$ 190, $[\theta]_{210.2}$ -190 and $[\theta]_{207.6}$ -1800.

Acetylation of fraction 5 and subsequent PLC in benzene-acetone (9:1, v/v) afforded the 7*S*-epimer **22** of the tetrahydropyrano[2,3-*f*]chromene derivative **20** (R_F 0.4, 5 mg) as a *white amorphous solid* (Found: M^+, 608.2251. $C_{33}H_{36}O_{11}$ requires M, 608.2258); δ_H (Tabe 1); CD $[\theta]_{300}$ -210, $[\theta]_{293}$ -500, $[\theta]_{285}$ -2000, $[\theta]_{281.1}$ -2000, $[\theta]_{275}$ -2900, $[\theta]_{258}$ -1600, $[\theta]_{245}$ -11000, $[\theta]_{238}$ -3.9, $[\theta]_{231}$ 1700, $[\theta]_{227.4}$ 1700, $[\theta]_{213.9}$ 5700 and $[\theta]_{207.9}$ 3900.

ACKNOWLEDGEMENTS

Support by the 'Sentrale Navorsingsfonds' of this University, the Foundation for Research Development, Pretoria, and the Marketing Committee, Wattle Bark Industry of South Africa, Pietermaritzburg is gratefully acknowledged.

REFERENCES AND NOTES

1. Jacques, D; Haslam, E.; Bedford, G.R.; Greatbanks, D. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2663.
2. Cronjé, A.; Burger, J.F.W.; Brandt, E.V.; Kolodziej, H.; Ferreira, D. *Tetrahedron Lett.*, **1991**, *30*, 3789.
3. Kolodziej, H.; Sakar, M.J.; Burger, J.F.W.; Engelshowe, R.; Ferreira, D. *Phytochemistry*, **1991**, *30*, 2041.
4. Gonzales, A.G.; Irizar, A.C.; Ravela, A.G.; Fernandez, M.F. *Phytochemistry*, **1992**, *31*, 1432.
5. Balde, A.M.; De Bruyne, T.; Pieters, L.; Kolodziej, H.; Van den Berghe, D.; Claeys, M.; Vlietinck, A. *Phytochemistry*, **1995**, *38*, 719; **1995**, *40*, 933, and references cited therein.
6. Karchesy, J.J.; Hemingway, R.W. *J. Agric. Food Chem.*, **1986**, *34*, 966.
7. Lane, C.E. *Synthesis*, **1975**, 135, and references cited therein.
8. Steynberg, J.P.; Burger, J.F.W.; Young, D.A.; Brandt, E.V.; Steenkamp, J.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3323, 3331.
9. Steynberg, J.P.; Burger, J.F.W.; Young, D.A.; Brandt, E.V.; Ferreira, D. *Heterocycles*, **1989**, *28*, 923.
10. Steynberg, J.P.; Bezuidenhoudt, B.C.B.; Burger, J.F.W.; Young, D.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 203.
11. Inter-nuclear double resonance (INDOR) effects were avoided *via* multiple irradiation points for each on-resonance site - Kinns, M.; Sanders, J.K.M. *J. Magn. Res.*, **1984**, *56*, 518.
12. An NOE association between 10-H(D) and 2-H(C) in the ^{1}H NMR spectrum of derivative **22** in C_6D_6 permitted differentiation of both the aromatic and aliphatic spin systems and hence full assignment of the spectrum.
13. It should be emphasized that the stereochemistry of the flavan-3-ol derivative **13** from the reduction of the procyanidin A-1 derivative **3** is not compatible with the CD data of **3**. Such a discrepancy will be discussed in a forthcoming paper.
14. Beart, J.E.; Lilley, T.H.; Haslam, E. *J.Chem. Soc., Perkin Trans. 2*, **1985**, 1429.
15. Steynberg, P.J.; Steynberg, J.P.; Bezuidenhoudt, B.C.B.; Ferreira, D. *J. Chem. Soc., Chem. Commun.*, 1994, 31; *J. Chem. Soc., Perkin Trans. 1*, **1995**, 3005.
16. Lewin, G.; Bert, M.; Dlauguet, J.-C.; Schaeffer, C.; Guinamant, J.-L.; Volland, J.-P. *Tetrahedron Lett.*, **1989**, *30*, 7049.
17. Burger, J.F.W.; Kolodziej, H.; Hemingway, R.W.; Steynberg, J.P.; Ferreira, D. *Tetrahedron*, **1990**, *46*, 5733.

(*Received in UK* 24 *October* 1996; *revised* 11 *December* 1996; *accepted* 12 *December* 1996)