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(4→6)-Coupled proteracacinidins and promelacacinidins from *Acacia galpinii* and *Acacia caffra*☆

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Abstract

The series of naturally occurring proanthocyanidins with 7,8-dihydroxylated A-rings is extended by identification of the proteracacinidins epioritin-(4β→6)-oritin-4α-ol, epioritin-(4β→6)-*ent*-oritin-4α-ol, *ent*-oritin-(4β→6)-epioritin-4α-ol, *ent*-oritin-(4β→6)-oritin-4α-ol, *ent*-oritin-(4α→6)-epioritin-4α-ol, *ent*-oritin-(4α→6)-oritin-4α-ol, *ent*-oritin-(4α→6)-epioritin-4β-ol, the 'mixed' proteracacinidins/-melacacinidins epioritin-(4β→6)-epimesquitol-4α-ol, epioritin-(4β→6)-epimesquitol-4β-ol and epimesquitol-(4β→6)-epioritin-4α-ol, and the promelacacinidin epimesquitol-(4β→6)-epimesquitol-4β-ol. © 2002 Published by Elsevier Science Ltd.

Keywords: *Acacia galpinii*; *Acacia caffra*; Leguminosae; Biflavanoids; Proteracacinidins; Promelacacinidins; Proanthocyanidins

1. Introduction

The natural occurrence of proanthocyanidins possessing 7,8-dihydroxylated (pyrogallol-type) A-rings was previously disputed (Fourie et al., 1972; Malan and Roux, 1975; Roux and Ferreira, 1982) because of the adverse effect of the 8-hydroxyl group on the stability of a flavan-3,4-diol presumed related C-4 electron deficient center, the transient electrophilic intermediate in the biosynthetic pathway to the proanthocyanidins (Jacques et al., 1977; Botha et al., 1981; Hemingway and Foo, 1983; Hemingway and Laks, 1985). Ongoing studies have, however, demonstrated that the flavan-3,4-diols melacacidin and teracacidin with their 7,8-dihydroxy A-rings are indeed susceptible to facile condensation with phenolic nuclei under mild acidic conditions (Botha et al., 1981; Foo, 1985). Thus, the biosynthesis of promelacacinidins and proteracacinidins should not be inhibited on chemical considerations. Indeed, several naturally occurring promelacacinidins (Foo, 1986, 1989; Young et al., 1986; Bennie et al., 2000) and proteracacinidins (Malan et al., 1994; Malan, 1995; Malan and Sireeparsad, 1995; Coetzee et al., 1998a,b; Bennie et al., 2000, 2001a,b, 2002) have been identified. Here we report the structure elucidation of 22 compounds, including a series of (4→6)-coupled proteracacinidins **1**, **3**, **5**, **7**, **9**, **11** and **13**, the 'mixed' proteracacinidins/-melacacinidins **15**, **17** and **19**, and the promelacacinidin **23** from the heartwoods of *Acacia galpinii* and *A. caffra* and their corresponding permethylaryl ether triacetates. Synthetic approaches towards some of the analogs are also described.

2. Results and discussion

Previous screening of the methanol extracts of the heartwoods of *A. galpinii* and *A. caffra* demonstrated the complexity of the mixture of mono-, di- and trimeric pro-/leucoanthocyanidins (Bennie et al., 2001b, 2002, and references cited). Continued investigation of the same sources have now revealed the presence of several new (4→6) coupled proteracacinidins epioritin-(4β→6)-oritin-4α-ol **1**,[1] epioritin-(4β→6)-*ent*-oritin-4α-ol **3**,[2] *ent*-oritin-(4β→6)-epioritin 4α-ol **5**,[2] *ent*-oritin(4β→6)-oritin-4α-ol **7**,[2] *ent*-oritin-(4α→6)-epioritin-4α-ol **9**,[1,2]

☆ Part 36 in the series 'Oligomeric flavanoids'. Part 35 (Bennie et al., 2002).

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ent-oritin-(4α→6)-oritin-4α-ol **11**[1,2] and *ent*-oritin-(4α→6)-epioritin-4β-ol **13**,[1] the 'mixed' pro-teracacinidins/-melacacinidins epioritin-(4β→6)-epimesquitol-4α-ol **15**,[1] epioritin-(4β→6)-epimesquitol-4β-ol **17**[1] and epimesquitol-(4β→6)-epioritin-4α-ol, **19**,[1] and the pro-melacacinidin epimesquitol-(4β→6)-epimesquitol-4β-ol **23**.[1] Owing to their complexity, the free phenolic mixtures could not be sufficiently resolved and hence the proanthocyanidins were instead purified as their permethylaryl ether triacetates **2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20** and **24**. Derivatization did not only permit two additional chromatographic steps which ensured sample purity, but also provided key ^{1}H NMR reference signals which facilitated unequivocal structure elucidation.

The structures and relative configurations of these derivatives were determined by analysis of MS and ^{1}H and ^{13}C NMR spectroscopic data (Tables 1 and 2, respectively). ^{1}H NMR spectral data are given for solutions in $CDCl_3$ and for those compounds showing poor resolution in key spectral regions also in C_6D_6 or acetone-d_6. Absolute stereochemistry was assessed via circular dichroic (CD) data, and ^{13}C resonances were assigned by HMQC and HMBC experiments. Since the ^{13}C NMR spectral data of the epioritin-(4β→6)-epioritin-4α-ol hexa-*O*-methylether triacetate, i.e. the 3-C(F-ring) diastereoisomer of derivative **2** were not previously recorded (Malan and Sireeparsad, 1995), these are included for comparative purposes (see Experimental).

FAB-MS analyses of the permethylaryl ether triacetates indicated molecular formulae of $C_{42}H_{44}O_{14}$ (*m*/*z* 772) for **2**, **4**, **6**, **8**, **10**, **12** and **14**, $C_{43}H_{46}O_{15}$ (*m*/*z* 802) for **16** and **18** and **20,** and $C_{44}H_{48}O_{16}$ (*m*/*z* 832) for **24**. When taken in conjunction with the number and nature of the *O*-methyl and *O*-acetyl resonances in their ^{1}H NMR spectra (Table 1), these formulas suggested proteracacinidin structures with carbon–carbon bonds linking the upper oritin- and lower teracacidin-type flavanyl units in **2**, **4**, **6**, **8**, **10**, **12** and **14**, the oritin- and melacacidin-type units in **16** and **18**, the mesquitol- and teracacidin-type units in **20**, and the mesquitol- and melacacidin-type moieties in **24**.

The ^{1}H NMR spectral data of the proteracacinidin derivatives **2**, **4**, **6**, **8**, **10**, **12** and **14** reflected the presence of an AB- and two AA′BB′-spin systems as well as a one-proton singlet for aromatic protons. In the spectra of **16**, **18** and **20** one of the AA′BB′-spin systems was replaced by an ABX-spin pattern, while in **24** both the AA′BB′-systems were replaced by two ABX-spin patterns. Protons of the heterocyclic rings of all the derivatives resonated as two AMX-spin systems, with conspicuously deshielded 4-H(F) resonances reminiscent of the flavan-3,4-diol-type DEF lower unit (Bennie et al., 2001a,b, 2002). Differentiation of the spin systems and the connections between aromatic and heterocyclic protons were effected with COSY experiments which indicated $^4J_{HH}$ coupling between the respective 2- and 2′,6′-protons. Prominent $^4J_{HH}$ benzylic coupling between 5-H(A) and 4-H(C) identified the AB-spin system as belonging to the A-ring. $^4J_{HH}$ coupling from the remaining broad aromatic singlet to both 4-H(F) and 4-H(C), supported by similar NOE associations observed in a phase sensitive NOESY experiment confirmed the C-4(C) → C-6(D) interflavanyl bonds. This was additionally supported by the three bond correlations between 4-H(C) and 5-C of both the A- and D-rings in the HMBC experiments.

The relative configurations of all the derivatives were evident from ^{1}H NMR coupling constants of heterocyclic protons. Those derivatives with 2,3-*cis*-3,4-*trans* constituent units (C-rings of **2**, **4**, **16**, **18**, **20** and **24**, F-rings of **14**, **18** and **24**) exhibited $^3J_{2,3} = 1.5$, $^3J_{3,4} = 3.0$ Hz coupling constants; those with 2,3-*trans*-3,4-*cis* configured moieties (C-rings of **10**, **12** and **14**, F-ring of **4**) showed $^3J_{2,3} = 6.5$–10.0, $^3J_{3,4} = 3.5$–4.9 Hz; compounds with 2,3-*trans*-3,4-*trans* flavanyl units (C-rings of **6** and **8**, F-rings of **2**, **8** and **12**) had $^3J_{2,3} = 10.0$, $^3J_{3,4}$ 8–10 Hz; and analogs with 2,3-*cis*-3,4-*cis* configured units (F-rings of **6**, **10**, **16** and **20**) exhibited $^3J_{2,3} = 1.0$ and $^3J_{3,4} = 4.5$ Hz couplings (Bennie et al., 2001a, b, 2002). Both 2,3-*trans*-3,4-*trans* and 2,3-*cis*-3,4-*cis* relative configurations were confirmed by NOE associations between 2- and 4-H indicating their cofacial arrangement in the respective C- and F-rings. 2,3-*Cis*-3,4-*trans* and 2,3-*trans*-3,4-*cis* relative stereochemistry of C-rings was similarly confirmed by NOE associations of 5-H(D) and 2-H(C). These NOE observations are essential for the unequivocal differentiation of *cis–trans* and *cis–cis* heterocyclic ring relative configurations. The stability of the 7,8-dihydroxy-2,3-*cis*-3,4-*cis*-flavan-3,4-diols and on the abundance of dimers with 2,3-*cis*-3,4-*cis*-flavanyl constituent units all possessing 7,8-dihydroxy A-rings and axial C-3 hydroxyl groups have been discussed recently (Coetzee et al., 1999).

The protons of the 2,3-*trans*-3,4-*cis* C-rings of **10**, **12** and **14** exhibited "abnormal" coupling constants ($^3J_{2,3} = 6.5$, $^3J_{3,4} = 4.9$ Hz). Previously we documented similar coupling constants ($^3J_{2,3} = 6.0$, $^3J_{3,4} = 4.9$ Hz) for a 2,4-diaryl-6-(2-benzopyranyl)-chromane with 2,3-*trans*-3,4-*cis* stereochemistry (Malan et al., 1990a). Since the 2,3-*trans*-3,4-*cis* relative configuration of the C-rings of all three derivatives was unequivocally established by the observed NOE association between 5-H(D) and 2-H(C), the small $^3J_{2,3}$ value presumably reflected substantial contributions of A-conformers towards the A-/E-conformational itinerary of the C-ring (Porter et al., 1986). Such a dynamic conformational equilibrium would reduce the average dihedral angle of 2- and 3-H(C) and hence the observed ^{1}H NMR coupling constant.

The chemical shifts of the C-2 (C-ring) resonances in the ^{13}C NMR spectra of all the derivatives (Table 2) fully supported these relative configurations. Those

Table 1
(a) ^{1}H NMR peaks (δ_H) of compounds **2**, **4**, **6** and **8** at 300 MHz

Ring	Proton	**2**—$CDCl_3$	**4**—$CDCl_3$	**6**—$CDCl_3$	**6**—$(CD_3)_2CO$	**8**—$CDCl_3$	**8**—$(CD_3)_2CO$
A	5	6.68 (*d*, 9.0)	6.66 (*d*, 9.0)	6.48 (*br.s*)	6.44 (*d*, 9.0)	6.40 (*d*, 9.0)	6.39 (*d*, 9.0)
	6	6.56 (*d*, 9.0)	6.59 (*d*, 9.0)	6.48 (*br.s*)	6.58 (*d*, 9.0)	6.48 (*d*, 9.0)	6.58 (*d*, 9.0)
B	2′, 6′	7.31 (*d*, 9.0)	7.30 (*d*, 9.0)	7.41 (*d*, 9.0)	7.47 (*d*, 9.0)	7.38 (*d*, 9.0)	7.47 (*d*, 9.0)
	3′, 5′	6.88 (*d*, 9.0)	6.88 (*d*, 9.0)	6.91 (*d*, 9.0)	6.96 (*d*, 9.0)	6.91 (*d*, 9.0)	6.96 (*d*, 9.0)
C	2	5.14 (*br.s*, 1.5)	5.15 (*br.s*, 1.5)	4.97 (*d*, 10.0)	5.01 (*d*, 10.0)	4.99 (*br.d*, 10.0)	5.04 (*d*, 10.0)
	3	5.39 (*dd*, 1.5, 3.0)	5.37 (*dd*, 1.5, 3.0)	5.71 (*t*, 10.0, 10.0)	5.76 (*dd*, 10.0, 10.0)	5.72 (*br.t*, 10.0, 10.0)	5.76 (*dd*, 10.0, 10.0)
	4	4.43 (*d*, 3.0)	4.44 (*d*, 3.0)	4.45 (broadened)	4.45 (broadened)	4.45 (broadened)	4.52 (broadened)
D	5	6.20 (*s*)	6.40 (*s*)	6.72 (*br.s*)	6.91 (*br.s*)	6.68 (*br.s*)	6.84 (*br.s*)
E	2′, 6′	7.36 (*d*, 9.0)	7.37 (*d*, 9.0)	7.43 (*d*, 9.0)	7.53 (*d*, 9.0)	7.43 (*d*, 9.0)	7.48 (*d*, 9.0)
	3′, 5′	6.92 (*d*, 9.0)	6.93 (*d*, 9.0)	6.92 (*d*, 9.0)	6.98 (*d*, 9.0)	6.92 (*d*, 9.0)	6.98 (*d*, 9.0)
F	2	5.08 (*d*, 10.0)	5.25 (*d*, 10.0)	5.33 (*br.s*, 1.0)	5.63 (*br.s*, 1.0)	5.04 (*d*, 10.0)	5.22 (*d*, 10.0)
	3	5.46 (*dd*, 10.0, 8.0)	5.34, (*dd*, 10.0, 3.5)	5.62 (*dd*, 1.0, 4.5)	5.59 (*dd*, 1.0, 4.5)	5.50 (*dd*, 8.0, 10.0)	5.46 (*dd*, 8.0, 10.0)
	4	6.16 (*d*, 8.0)	5.99 (*d*, 3.5)	6.23 (*d*, 4.5)	6.32 (*d*, 4.5)	6.25 (*d*, 8.0)	6.24 (*d*, 8.0)
OMe		4.00, 3.98, 3.90, 3.88, 3.84, 3.82 (each *s*)	4.02, 3.99, 3.93, 3.89, 3.84, 3.81 (each *s*)	3.67, 3.83, 3.84, 3.85, 3.89 (×2) (each *s*)	3.63, 3.76, 3.79, 3.83, (×2), 3.85 (each *s*)	See $(CD_3)_2CO$ spectrum	3.68, 3.74, 3.78 (×2), 3.83, 3.84 (each *s*)
OAc		1.91, 1.82, 1.81 (each *s*)	2.12, 1.91, 1.83 (each *s*)	1.68, 1.95, 2.14 (each *s*)	1.63, 1.92, 2.05 (each *s*)	1.68, 1.84, 2.10 (each *s*)	1.65, 1.78, 2.02 (each *s*)

(b) ^{1}H NMR peaks (δ_H) of compounds **10**, **12**, and **14** at 300 MHz

Ring	Proton	**10**—$CDCl_3$	**12**—$CDCl_3$	**12**—C_6D_6	**14**—$CDCl_3$	**14**—C_6D_6
A	5	6.67 (*d*, 8.5)	6.56 (*d*, 8.5)	6.82 (*d*, 8.5)	6.57 (*d*, 9.0)	6.84 (*d*, 9.0)
	6	6.53 (*d*, 8.5)	6.47 (*d*, 8.5)	6.46 (*d*, 8.5)	6.51 (*d*, 9.0)	6.44 (*d*, 9.0)
B	2′, 6′	7.33 (*d*, 9.0)	7.33 (*d*, 9.0)	7.37 (*d*, 9.0)	7.31 (*d*, 9.0)	7.52 (*d*, 9.0)
	3′, 5′	6.90 (*d*, 9.0)	6.90 (*d*, 9.0)	6.78 (*d*, 9.0)	6.90 (*d*, 9.0)	6.81 (*d*, 9.0)
C	2	5.34 (*d*, 6.5)	5.39 (*d*, 6.5)	5.76 (*d*, 6.5)	5.41 (*br.s*, 6.5)	5.78 (*br.s*, 6.5)
	3	5.43 (*dd*, 6.5, 4.9)	5.43 (*dd*, 6.5, 4.9)	6.00 (*dd*, 6.5, 4.9)	5.41 (*dd*, 6.5, 4.9)	6.05 (*dd*, 6.5, 4.9)
	4	4.67 (*d*, 4.9)	4.64 (*d*, 4.9)	5.17 (*d*, 4.9)	4.66 (*d*, 4.9)	5.23 (*d*, 4.9)
D	5	6.55 (*br.s*)	6.57 (*br.s*)	7.13 (*br.s*)	6.86 (*br.s*)	7.67 (*br.s*)
E	2′, 6′	7.42 (*d*, 9.0)	7.38 (*d*, 9.0)	7.47 (*d*, 9.0)	7.41 (*d*, 9.0)	7.55 (*d*, 9.0)
	3′, 5′	6.93 (*d*, 9.0)	6.93 (*d*, 9.0)	6.83 (*d*, 9.0)	6.94 (*d*, 9.0)	6.91 (*d*, 9.0)
F	2	5.33 (*br.s*, 1.0)	5.07 (*d*, 10.0)	4.80 (*d*, 10.0)	5.28 (*br.s*, 1.5)	5.55 (*br.s*, 1.5)
	3	5.59 (*dd*, 1.0, 4.5)	5.49 (*dd*, 10.0, 8.0)	5.96 (*dd*, 10.0, 8.0)	5.22 (*dd*, 1.5, 3.0)	5.74 (*dd*, 1 .5, 3.0)
	4	6.25 (*d*, 4.5)	6.21 (*d*, 8.0)	6.60 (*d*, 8.0)	5.76 (*d*, 3.0)	6.19 (*d*, 3.0)
OMe		3.82, 3.84, 3.87, 3.91, 3.93, 3.96 (each *s*)	3.74, 3.82, 3.84, 3.85, 3.87, 3.97 (each *s*)	3.32, 3.33, 3.56, 3.75, 3.76, 4.10 (each *s*)	3.98, 3.93, 3.91, 3.85, 3.82, 3.78 (each *s*)	4.17, 3.87, 3.73, 3.49, 3.36, 3.33 (each *s*)
OAc		1.87, 1.94, 1.96 (each *s*)	1.83, 1.89, 1.92 (each *s*)	1.55, 1.80, 1.87 (each *s*)	2.11, 1.92, 1.92 (each *s*)	1.82, 1.62, 1.39 (each *s*)

(*continued on next page*)

Table 1 (*continued*)
(c) ^{1}H NMR peaks (δ_c) for compounds **16**, **18**, **20**, **22** and **24** at 300 MHz (296 K)

Ring	Carbon	**16**—$CDCl_3$	**16**—$(CD_3)_2CO$	**18**—$CDCl_3$	**18**—$(CD_3)_2CO$	**20**—$CDCl_3$	**22**—$CDCl_3$	**24**—$CDCl_3$
A	5	6.74 (*d*, 8.5)	6.74 (*d*, 8.5)	6.69 (*d*, 8.5)	6.70 (*d*, 8.5)	6.75 (*d*, 8.5)	6.71 (*d*, 8.5)	6.70 (*d*, 8.5)
	6	6.59 (*d*, 8.5)	6.69 (*d*, 8.5)	6.58 (*d*, 8.5)	6.65 (*d*, 8.5)	6.59 (*d*, 8.5)	6.59 (*d*, 8.5)	6.58 (*d*, 8.5)
B	2′, 6′	7.30 (*d*, 8.5)	7.31 (*d*, 8.5)	7.31 (*d*, 8.5)	7.32 (*d*, 8.5)			
	3′, 5′	6.88 (*d*, 8.5)	6.91 (*d*, 8.5)	6.88 (*d*, 8.5)	6.92 (*d*, 8.5)			
	2′					7.00 (*d*, 2.0)	7.03 (*d*, 8.5)	7.03 (*d*, 2.0)
	5′					6.83 (*d*, 8.5)	6.83 (*dd*, 2.0)	6.83 (*d*, 8.5)
	6′					6.88 (*dd*, 2.0, 8.5)	6.87 (*dd*, 2.0, 8.5)	6.88 (*dd*, 2.0, 8.5)
C	2	5.15 (*br.s*, 1.5)	5.15 (*br.s*, 1.5)	5.18 (*br.s*, 1.5)	5.19 (*br.s*, 1.5)	5.14 (*br.s*, 1.5)	5.17 (*br.s*, 1.5)	5.18 (*br.s*, 1.5)
	3	5.43 (*dd*, 1.5, 3.0)	5.45 (*dd*, 1.5, 3.0)	5.36 (*dd*, 1.5, 3.0)	5.32 (*dd*, 1.5, 3.0)	5.46 (*dd*, 1.5, 3.0)	5.41(*dd*, 1.5, 3.0)	5.41(*dd*, 1.5, 3.0)
	4	4.43 (*d*, 3.0)	4.45 (*d*, 3.0)	4.46 (*d*, 3.0)	4.49 (*d*, 3.0)	4.44 (*d*, 3.0)	4.46 (*d*, 3.0)	4.46 (*d*, 3.0)
D	5	6.29 (*br.s*)	6.31 (*br.s*)	6.63 (*br.s*)	6.72 (*br.s*)	6.27 (*br.s*)	6.62 (*br.s*)	6.64 (*s*)
E	2′, 6′					7.40 (*d*, 8.5)	7.40 (*d*, 8.5)	
	3′, 5′					6.93 (*d*, 8.5)	6.94 (*d*, 8.5)	
	2′	7.03 (*d*, 2.0)	7.22 (*d*, 2.0)	7.03 (*d*, 2.0)	7.17 (*d*, 2.0)			7.03 (*d*, 2.0)
	5′	6.88 (*d*, 8.5)	6.99 (*d*, 8.5)	6.90 (*d*, 8.5)	7.00 (*d*, 8.5)			6.90 (*d*, 8.5)
	6′	7.04 (*dd*, 2.0, 8.5)	7.14 (*dd*, 2.0, 8.5)	7.04 (*dd*, 2.0, 8.5)	7.11 (*dd*, 2.0, 8.5)			7.03 (*dd*, 2.0, 8.5)
F	2	5.33 (*d*, 1.0)	5.61 (*br.s*, 1.0)	5.29 (*d*, 1.5)	5.39 (*br.s*, 1.5)	5.33 (*br.s*, 1.0)	5.30 (*d*, 1.5)	5.30 (*br.s*, 1.5)
	3	5.64 (*dd*, 1.0, 4.5)	5.60 (*dd*, 1.0, 4.5)	5.26 (*dd*, 1.5, 3.0)	5.28 (*d*, 1.5, 3.0)	5.59 (*dd*, 1.0, 4.5)	5.22 (*dd*, 1.5, 3.0)	5.26 (*dd*, 1.5, 3.0)
	4	6.19 (*d*, 4.5)	6.28 (*d*, 4.5)	5.66 (*d*, 3.0)	5.63 (*d*, 3.0)	6.20 (*d*, 4.5)	5.66 (*d*, 3.0)	5.67 (*d*, 3.0)
OMe		3.99 (×2), 3.98, 3.91 (×2), 3.89, 3.81 (each *s*)	4.01, 3.97, 3.86, 3.85, 3.83 (×2), 3.79 (each *s*)	4.02, 4.01, 3.99, 3.93 (×2), 3.92, 3.81 (each *s*)	4.02, 3.98, 3.86, 3.85, 3.84, 3.83, 3.79 (each *s*)	4.01, 3.99, 3.98, 3.89, 3.88, 3.87, 3.84 (each *s*)	4.03, 4.01, 4.00, 3.92, 3.88 (×2), 3.84 (each *s*)	4.03, 4.01 (×2), 3.93, 3.92, 3.91, 3.88 (×2) (each *s*)
OAc		1.95, 1.92, 1.88 (each *s*)	1.91, 1.86, 1.80 (each *s*)	2.12, 1.91, 1.90 (each *s*)	2.10, 1.88, 1.87 (each *s*)	1.95, 1.92, 1.87 (each *s*)	2.10, 1.91, 1.89 (each *s*)	2.11, 1.91, 1.90 (each *s*)

Splitting patterns and *J*-values (Hz) are given in parentheses.

Table 2
^{13}C NMR peaks (δ_c) for compounds **2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22** and **24**

Ring	Carbon	**2**— $CDCl_3$	**4**— $CDCl_3$	**6**— $(CD_3)_2CO$	**8**— $(CD_3)_2CO$	**10**— $CDCl_3$	**12**— C_6D_6	**14**— $CDCl_3$	**16**— $(CD_3)_2CO$	**18**— $(CD_3)_2CO$	**20**— $CDCl_3$	**22**— $CDCl_3$	**24**— $CDCl_3$
A	5	125.26	125.24	123.30	123.39	124.47	124.32	123.99	125.35	125.59	125.42	125.14	125.10
	6	105.73	106.03	106.17	106.19	105.17	106.03	105.39	106.15	106.65	105.59	105.81	105.85
B	2′, 6′	128.03	128.01	128.24	129.28	127.95	129.42	127.54	128.07	128.65			
	3′, 5′	113.99	113.99	113.86	113.86	114.28	114.49	114.37	113.86	114.34			
	2′										110.36	110.39	110.45
	5′										111.23	111.19	111.23
	6′										119.18	119.17	119.17
C	2	73.59	73.66	80.62	80.51	76.18	76.66	76.55	73.49	73.97	73.73	73.74	73.75
	3	72.19	72.35	72.45	72.27	71.68	71.90	71.65	71.98	72.70	72.17	72.37	72.34
	4	41.45	40.94	45.30	[a]	36.00	36.55	34.54	41.50	41.24	41.74	41.05	41.04
D	5	124.28	127.03	122.88	123.66	123.55	124.84	127.96	123.52	128.16	123.40	127.84	127.89
	6	129.49	129.04	126.87	127.57	126.25	127.91	126.37	128.67	129.62	128.87	128.95	129.01
E	2′, 6′	128.33	129.14	129.33	129.30	127.95	128.82	128.10			127.94	128.09	
	3′, 5′	114.23	114.28	114.02	114.04	114.25	114.29	114.24			114.25	114.24	
	2′								110.88	111.60			110.23
	5′								111.97	112.44			111.44
	6′								119.36	120.07			119.34
F	2	79.43	75.11	77.26	79.13	77.51	79.55	74.54	77.46	75.19	77.62	74.64	74.60
	3	71.46	70.36	67.30	71.67	67.09	71.47	69.19	67.17	69.16	67.01	68.99	68.90
	4	70.76	66.84	66.98	70.67	67.09	71.37	66.53	66.92	66.63	67.13	66.46	66.43

[a] Chemical shift not defined.

compounds with a 2,4-*trans* configuration (**2**, **4**, **10**, **12**, **14**, **16**, **18**, **20** and**24**) displayed shielded 2-C(C) signals (ca. 4–7 ppm) compared to the chemical shifts of these carbons in derivatives with a 2,4-*cis* configuration (**6** and **8**) due to the γ-*gauche* effect (Fletcher et al., 1977).

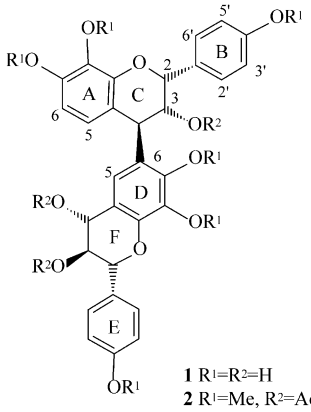
A conspicuous feature of the ^1H NMR spectral data (Tables 1, 2; $CDCl_3$) of derivatives with 2,3-*trans*-3,4-*cis* (**4**) or 2,3-*cis*-3,4-*trans* (**14**, **18** and **24**) F-ring configurations, i.e. having 2-H(F) and 4-OAc(F) in a *cis*-diaxial orientation, is the large shielding of their 4-H(F) resonances (δ 5.99, 5.76, 5.66 and 5.67 for **4**, **14**, **18** and **24**, respectively) relative to their chemical shifts in derivatives with 2,3-*cis*-3,4-*cis* (e.g. δ 6.25 for **10**) or 2,3-*trans*-3,4-*trans* configured F-rings (e.g. δ 6.21 for derivative **12**). In order to minimize *cis*-1,3-diaxal van der Waals strain between 2-H(F) and 4-OAc(F), the F-ring half-chair conformation is probably distorted, pushing the 4-H(F) bond close to an orthogonal orientation relative to the D-ring. Donation of electron density from this aromatic ring into the 4-H(F) σ*-antibonding orbital could then explain the observed shielding of this proton. A similar shielding of the 4-H resonances was also recorded for the permethylaryl ether acetate derivatives of dimeric epioritin-(4β→6)-epioritin-4β-ol [4-H(F)] and the monomeric flavan-3,4-diol epioritin-4β-ol [4-H(C)] when compared to the same derivatives of epioritin-(4β→6)-epioritin-4α-ol and epioritin-4α-ol (Malan and Sireeparsad, 1995).

A further notable but less readily explicable feature of the ^1H NMR spectra of derivatives **6** and **8**, i.e. those with 2,3-*trans*-3,4-*trans* configured C-rings, is the severe line-broadening of their 4-H(C) resonances, and to a lesser degree also of 3-H(C), 5-H(A), 5-H(D) and 7-OMe(D). Since similar effects were not observed for (4→6)-linked dimeric proanthocyanidins with 2,3-*trans*-3,4-*trans* C-rings and resorcinol-type D-rings (Steenkamp et al., 1988; Malan et al., 1990b), such broadening presumably results from the presence of the 8-OMe D-ring substituent in derivatives **6** and **8**. Inspection of Dreiding models indicated that free rotation about the interflavanyl bond in these derivatives will mainly be impeded by steric interaction between 7-OMe of the quasi-axial DEF moiety and the axial 3-H(C). The buttressing effect of 8-OMe(D) on 7-OMe(D) would intensify such interaction, hence retarding the rate of rotation to such an extent that broadening of the aforementioned resonances is observed. Small effects of steric hindrance to free rotation will obviously have the strongest influence on the line-shape of resonances closest to the atoms comprising the restricted rotor.

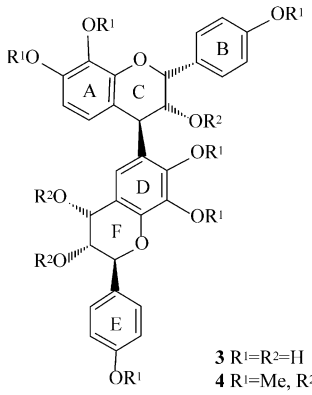
Also notable is the peculiar ''disappearance'' of the 4-C(C) resonances in the ^{13}C NMR spectra of **6** and **8**, i.e. those showing restricted rotation about the interflavanyl bond, and also in derivatives **10** and **12** which exhibit sharp ^1H NMR resonances at ambient temperatures. Such a phenomenon is presumably explicable in terms of the long relaxation time of this carbon on the NMR time scale. The chemical shifts of these carbon atoms were however evident in the HMQC experiment for **6** (at 45 °C), **10** and **12**, probably due to the shorter

relaxation time of H compared to C. Only in the case of **8** could the 4-C(C) resonance be not observed at all.

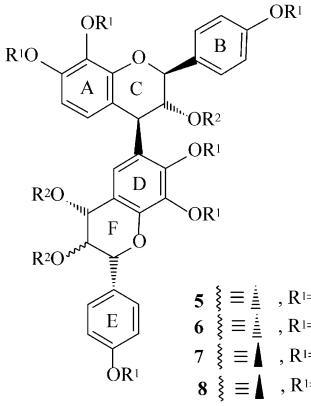
Derivatives **2**, **4**, **6**, **8**, **16**, **18**, **20** and **24** displayed high-amplitude positive Cotton effects {$[\theta]_{240.3}$ $+1.05\times10^4$ (**2**); $[\theta]_{243.4}$ $+1.35\times10^4$ (**4**); $[\theta]_{245.3}$ $+1.64\times10^4$ (**6**); $[\theta]_{246.5}$ $+1.09\times10^4$ (**8**); $[\theta]_{243.1}$ $+6.66\times10^3$ (**16**); $[\theta]_{239.2}$ $+9.04\times10^5$ (**18**); $[\theta]_{234.9}$ $+7.78\times10^3$ (**20**); $[\theta]_{237.9}$ $+2.53\times10^4$ (**24**)} near 240 nm in their CD spectra. These indicated a 4β-orientation of the DEF-flavanyl units at C-4(C) (Van der Westhuizen et al., 1981), and in conjunction with coupling constants of the protons of this ring, defined 2*R*,3*R*,4*R*(C) absolute configuration for **1**, **3**, **15**, **17**, **19** and **23**, and 2*S*,3*R*,4*R* absolute stereochemistry for **5** and **7**. Negative high-amplitude Cotton effects in the same wavelength region of the CD spectra of derivatives **10**, **12** and **14** {$[\theta]_{240.2}$ -2.88×10^5 (**10**); $[\theta]_{244.7}$ -2.8×10^4 (**12**); $[\theta]_{245.4}$ -1.36×10^4 (**14**)} similarly indicated 4α-(C) DEF-flavanyl moieties and hence 2*S*,3*R*,4*S* absolute configuration for the stereocenters of the C-rings of **9**, **11** and **13**. Oritin-4α-ol, oritin-4β-ol, epioritin-4β-ol and *ent*-oritin-4α-ol, as the most likely biogenetic precursors of the DEF flavanyl moieties of **1**, **3**, **5**, **7**, **9**, **11**, **13** and **19**, occur abundantly in both *A. galpinii* and *A. caffra* (Malan, 1995). Thus, these units possess 2*R*,3*S*,4*R* absolute configuration in **1**, **7** and **11** (oritin-4α-ol derived DEF units), 2*S*,3*R*,4*R* in **3**



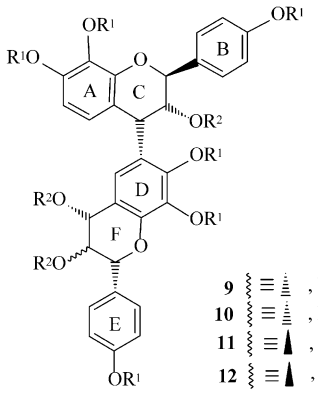
1 R1=R2=H
2 R1=Me, R2=Ac



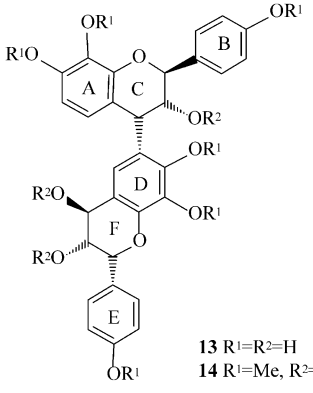
3 R1=R2=H
4 R1=Me, R2=Ac



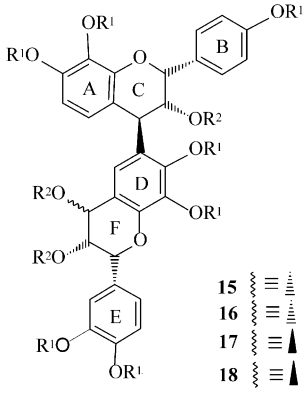
5 ≡ , R1=R2=H
6 ≡ , R1=Me, R2=Ac
7 ≡ , R1=R2=H
8 ≡ , R1=Me, R2=Ac



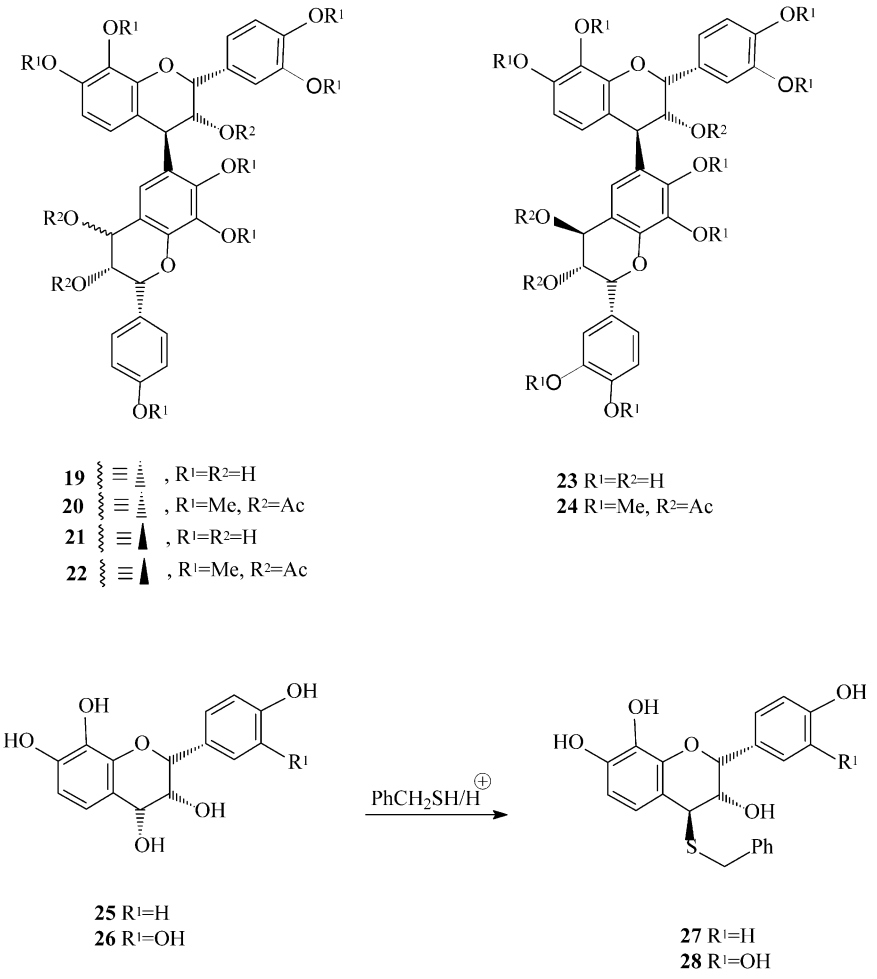
9 ≡ , R1=R2=H
10 ≡ , R1=Me, R2=Ac
11 ≡ , R1=R2=H
12 ≡ , R1=Me, R2=Ac



13 R1=R2=H
14 R1=Me, R2=Ac



15 ≡ , R1=R2=H
16 ≡ , R1=Me, R2=Ac
17 ≡ , R1=R2=H
18 ≡ , R1=Me, R2=Ac



Scheme 1. Formation of the 4β-benzylsulfanylepioritin **27** and the 4β-benzylsulfanylepimesquitol **28**.

(*ent*-oritin-4α-ol derived), 2*R*,3*R*,4*R* in **5**, **9**, **19** (epioritin-4α-ol derived) and **15** (epimesquitol-4α-ol derived), and 2*R*,3*R*,4*S* in **13** (epioritin-4β-ol derived), **17** and **21** (epimesquitol-4β-ol derived). The *ent*-oritin-4α-ol derived DEF unit in **4** was confirmed by comparing its CD data in the 280 nm region with those of *ent*-oritin-4α-ol tri-*O*-methyl ether diacetate (Coetzee et al., 1998a).

The structures of epioritin-(4β→6)-epioritin-4α-ol and epioritin-(4β→6)-epioritin-4β-ol were previously confirmed by semisynthesis via acid-catalyzed self condensation of epioritin-4α-ol (Malan and Sireeparsad, 1995). Unequivocal confirmation of the structures of the 'mixed' proanthocyanidin **16**, **18**, **20** and **24** was thus sought by using thiophilic Lewis acid catalysed coupling of an appropriate 4-benzylsulfanylflavan-3-ol to the relevant teracacidin- or melacacidin-type flavan-3,4-diol (Steynberg et al., 1998). 4β-Benzylsulfanylepioritin **27** and 4β-benzylsulfanylepimesquitol **28** were readily available via acid-catalyzed thiolysis (Hemingway et al., 1983) of epioritin-4α-ol **25** and epimesquitol-4α-ol **26**, respectively (Scheme 1). The structures of **27** and **28** were evident from comparison of their ^{1}H NMR and CD data (see Experimental) with those of related compounds and from the mechanism of their formation (Coetzee et al., 1999).

Treatment of a mixture comprising epimesquitol-4α-ol **26** (2 molar excess) and 4β-benzylsulfanylepioritin **27** with silver tetrafluoroborate in THF at 30 °C[3] followed by an aqueous work-up and the appropriate derivatization, afforded the epioritin-(4β→6)-epimesquitol-4α-ol and epioritin-(4β→6)-epimesquitol-4β-ol derivatives **16** (4.1%) and **18** (4.4%). Their ^{1}H NMR and CD data were identical to those of the similar derivatives of the natural products **15** and **17**. Formation of **17** is explicable in terms of solvolysis at C-4 of the all-*cis* F-ring of **15** during the aqueous work-up (Coetzee et al., 1999). A similar protocol using 4β-benzylsulfanylepimesquitol **28** and epioritin-4α-ol **25** gave the epimesquitol-(4β→6)-epioritin-4α-ol and epimesquitol-(4β→6)-epioritin-4β-ol derivatives **20** (4.3%) and **22** (4.6%). Derivative **20** was identical to the same derivative of the natural product **19** by comparison of their ^{1}H

[3] At 0 °C the formation of ether-linked derivatives (Coetzee et al., 1998a) predominated.

NMR and CD data. The inverted C-4 (F-ring) configuration of **22** was conspicuously evident from the now familiar shielding of the 4-H resonance (δ 5.66) (Table 2) compared to its chemical shift in **20** (δ 6.20) with 2,3-*cis*-3,4-*cis* F-ring configuration. Finally, condensation of 4β-benzylsulfanylepimesquitol **28** and epimesquitol-4α-ol **26** and subsequent derivatization afforded the epimesquitol-(β→6)-epimesquitol-4β-ol derivative **24** with spectral characteristics identical to those of the same derivative of the natural product **23**.

Our identification of eleven new (4→6)-linked proanthocyanidins of the teracacinidin- and/or melacanidin-type from the heartwoods of *A. galpinii* and *A. caffra* further demonstrates the remarkable diversity of the phenolic pool in *A. galpinii* and *A. caffra*. These natural sources possess high concentrations of 7,8-dihydroxylated flavan-3,4-diols as potential biosynthetic precursors, but lack C-4(C) deoxy flavanoids as potent nucleophiles to effectively trap the flavan-3,4-diol-derived electrophiles in the pathway leading to the proanthocyanidins.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 and a Bruker Avance DRX 500 spectrometer, respectively, for solns. as indicated, with Me_4Si as internal standard. FAB mass spectra were recorded on a VG-70E instrument with a VG 11–250J data system and an iontech saddlefield FAB gun. UV-Vis spectra of solutions (MeOH) were measured using a Cary 50 Conc spectrophotometer. TLC was performed on precoated 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) [20×22 cm, Kieselgel PF_{254} (1.0 mm)] were air dried and used without prior activation. CC was done on Sephadex LH-20 in various columns, solvent systems and flow rates (to be specified in each instance). Methylations were performed with an excess of CH_2N_2 in MeOH/Et_2O for 48 h at −15 °C while acetylations were conducted in Ac_2O–pyridine at ambient temperature. Evaporations were done under reduced pressure at ambient temp. in a rotary evaporator, and freeze drying of aqueous solutions on a Virtis 12 SL freezemobile.

3.1. Isolation of phenolic compounds

The extraction of the heartwoods of *A. caffra* and *A. galpinii* and column separations to give fractions A–UU and A–Z, respectively, were comprehensively described in Parts 28 (Coetzee et al., 1998a) and 32 (Bennie et al., 2000).

3.2. Epioritin-(4β → 6)-oritin-4α-ol hexa-O-methylether triacetate 2

Methylation of a portion (200 mg) of fraction X from *A. caffra* followed by PLC in benzene–Me_2CO–EtOAc (7:2:1; v/v) gave three bands at R_f 0.58 (32 mg), 0.44 (31 mg) and 0.30 (18 mg). Acetylation of the R_f 0.30 band followed by PLC purification in hexane–benzene–Me_2CO–MeOH (43:42:10:5; ×2; v/v) afforded two main bands at R_f 0.63 (4.1 mg) and 0.49 (1.5 mg). The former band yielded **2** as a white amorphous solid. (Found: M^+, 772.2734. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 20.81, 20.91, 21.28 [3×*C*H_3COO–], 41.45 [4-C(C)], 55.62 (×2), 55.65, 56.73, 61.28, 61.48 [6×–O*C*H_3], 70.76 [4-C(F)], 71.46 [3-C(F)], 73.59 [2-C(C)], 72.19 [3-C(C)], 79.43 [2-C(F)], 105.73 [6-C(A)], 113.99 (×2) [3,5-C(B)], 114.23 (×2) [3,5-C(E)], 115.27 [10-C(A)], 116.18 [10-C(D)], 124.28 [5-C(D)], 125.26 [5-C(A)], 128.03 (×2) [2,6-C(B)], 128.33 [1-C(E)], 128.33 (×2) [2,6-C(E)], 129.49 [6-C(D)], 130.91 [1-C(B)], 137.74 [8-C(A)], 141.05 [8-C(D)], 148.93 [9-C(D)], 149.33 [9-C(A)], 152.00 [7-C(D)], 152.60 [7-C(A)], 159.67 [4-C(B)], 160.44 [4-C(E)], 169.62, 170.05, 170.96 [3×CH_3*C*OO–]; CD $[\theta]_{221.4}$ 1388, $[\theta]_{225.6}$ 839, $[\theta]_{240.3}$ 10 520, $[\theta]_{247.3}$ 70, $[\theta]_{249.6}$ −1000, $[\theta]_{257.1}$ 90, $[\theta]_{285.2}$ −5754, and $[\theta]_{295.8}$ 4. ^{13}C NMR data of epioritin-(4β→6)-epioritin-4α-ol hexa-*O*-methylether triacetate, i.e. the 3-C(F-ring) diastereoisomer of **2**. ^{13}C NMR ($CDCl_3$, 27 °C): δ 20.76, 20.99, 21.27 [3×*C*H_3COO–], 41.71 [4-C(C)], 55.59, 55.64, 56.74, 61.33, 61.45, 61.52 [6×-O*C*H_3], 67.02 [3-C(F)], 67.15 [4-C(F)], 72.28 [3-C(C)], 73.73 [2-C(C)], 77.59 [2-C(F)], 105.64 [6-C(A)], 113.97 (×2) [3,5-C(B)], 114.24 (×2) [3,5-C(E)], 114.63 [10-C(D)], 115.18 [10-C(A)], 123.39 [5-C(D)], 125.39 [5-C(A)], 127.95 (×2) [2,6-C(E)], 128.02 (×2) [2,6-C(B)], 128.66 [6-C(D)], 128.91 [1-C(E)], 130.24 [1-C(B)], 137.66 [8-C(A)], 141.03 [8-C(D)], 148.29 [9-C(D)], 149.31 [9-C(A)], 151.67 [7-C(D)], 152.61 [7-C(A)], 159.65 [4-C(B)], 160.09 [4-C(E)], 170.06, 170.40, 170.76 [3×CH_3*C*OO–].

3.3. Epioritin-(4β → 6)-epimesquitol-4β-ol hepta-O-methylether triacetate 18

The R_f 0.49 band (Section 3.2) afforded **18** as a white amorphous solid. (Found: M^+, 802.2836. $C_{43}H_{46}O_{15}$ requires M^+, 802.2837); δ_H (Table 1); ^{13}C NMR [$(CD_3)_2CO$), 27 °C]: δ 20.55, 20.72, 21.10 [3×*C*H_3COO-], 41.24 [4-C(C)], 55.47, 56.06, 56.19, 56.38, 60.75, 61.13, 61.63 [7×-O*C*H_3], 66.63 [4-C(F)], 69.16 [3-C(F)], 72.70 [3-C(C)], 73.97 [2-C(C)], 75.19 [2-C(F)], 106.65 [6-C(A)], 111.60 [2-C(E)], 112.44 [5-C(E)], 114.34 (×2) [3,5-C(B)], 114.73 [10-C(D)], 115.64 [10-C(A)], 120.07 [6-C(E)], 125.59 [5-C(A)], 128.16 [5-C(D)], 128.65 (×2) [2,6-C(B)], 130.16 [1-C(E)], 129.62 [6-C(D)], 130.97 [1-C(B)], 138.27 [8-C(A)], 141.75 [8-C(D)], 149.50 [9-C(D)], 149.85 [3-C(E)],

150.21 [9-C(A)], 150.45 [4-C(E)], 152.98 [7-C(A)], 153.34 [7-C(D)], 160.36 [4-C(B)], 169.36, 169.60, 169.93 [3×CH_3COO–]; CD $[\theta]_{230.3}$ 12, $[\theta]_{239.2}$ 9039, $[\theta]_{248.4}$ 21, $[\theta]_{250.3}$−194, $[\theta]_{261.0}$ 312, $[\theta]_{277.6}$ 477, and $[\theta]_{286.0}$−42.

3.4. Epioritin-(4β → 6)-ent-oritin-4α-ol hexa-O-methylether triacetate **4**

Acetylation and PLC purification in benzene–Me_2CO (9:1; v/v) of the R_f 0.44 band (Section 3.2) gave a single band at R_f 0.54 (3.3 mg) which yielded **4** as a white amorphous solid. (Found: M^+, 772.2731. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 20.85, 21.29, 21.59 [3×CH_3COO–], 40.94 [4-C(C)], 55.61, 55.67, 56.51, 61.22, 61.42 61.61 [6×-OCH_3], 66.84 [4-C(F)], 70.36 [3-C(F)], 72.35 [3-C(C)], 73.66 [2-C(C)], 75.11 [2-C(F)], 106.03 [6-C(A)], 113.99 (×2) [3,5-C(B)], 114.28 (×2) [3,5-C(E)], 114.55, 114.69 (×2) [10-C(A)]/[10-C(D)], 125.24 [5-C(A)], 127.03 [5-C(D)], 128.01 (×2) [2,6-C(B)], 129.04 [6-C(D)], 129.14 (×2) [2,6-C(E)], 129.16 [1-C(E)], 130.28 [1-C(B)], 137.50 [8-C(A)], 141.15 [8-C(D)], 148.78 [9-C(D)], 149.17 [9-C(A)], 152.66 [7-C(A)], 153.01 [7-C(D)], 159.66 [4-C(B)], 160.41 [4-C(E)], 169.74, 170.02, 170.50 [3×CH_3COO–]; CD $[\theta]_{220.5}$ 32, $[\theta]_{224.5}$ −1026, $[\theta]_{232.4}$ 13, $[\theta]_{243.4}$ 13 470, $[\theta]_{284.6}$ 247, and $[\theta]_{291.7}$ 1521. The remaining band from fraction X contained related pro-/leucoanthocyanidins that were reported elsewhere (Bennie et al., 2000, 2001a).

3.5. Ent-oritin-(4β → 6)-epioritin-4α-ol hexa-O-methylether triacetate **6**

Methylation of a portion (100 mg) of fraction V from *A. galpinii* followed by PLC in benzene–Me_2CO (4:1; v/v) gave four bands at R_f 0.63 (6.0 mg), 0.37 (40.0 mg), 0.27 (8.0 mg) and 0.21 (6.0 mg). Acetylation of the R_f 0.37 band followed by PLC purification in hexane–benzene–Me_2CO–MeOH (43:42:10:5; ×2; v/v) afforded **6** as a white amorphous solid. (Found: M^+, 772.2732. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR [$(CD_3)_2CO$), 27 °C]: δ 20.10 (×2), 20.33 [3×CH_3COO–], 45.30 [4-C(C)], 55.05 (×3), 56.02, 60.26, 60.47 [6×-OCH_3], 66.98 [4-C(F)], 67.30 [3-C(F)], 72.45 [3-C(C)], 77.26 [2-C(F)], 80.62 [2-C(C)], 106.17 [6-C(A)], 113.86 (×2) [3,5-C(B)], 114.02 (×2) [3,5-C(E)], 115.65 [10-C(D)], 120.15 [10-C(A)], 122.88 [5-C(D)], 123.30 [5-C(A)], 126.87 [6-C(D)], 128.24 (×2) [2,6-C(B)], 129.33 (×2) [2,6-C(E)], 129.75 [1-C(E)], 130.09 [1-C(B)], 137.94 [8-C(A)], 141.69 [8-C(D)], 148.57 [9-C(D)], 148.73 [9-C(A)], 152.53 [7-C(D)], 152.53 [7-C(A)], 160.17 [4-C(E)], 160.35 [4-C(B)], 168.37, 169.97, 170.52 [3×CH_3COO–]; CD $[\theta]_{225.2}$ 1765, $[\theta]_{234.0}$ −4253, $[\theta]_{238.9}$ 103, $[\theta]_{245.3}$ 16 390, $[\theta]_{253.9}$ 65.43, $[\theta]_{274.3}$ −12 320, and $[\theta]_{303.6}$−63. TLC showed no defined compounds in the remaining bands and they were therefore not further investigated.

3.6. Ent-oritin-(4β → 6)-oritin-4α-ol hexa-O-methylether triacetate **8**

Methylation of a portion (100 mg) of fraction T from *A. galpinii* followed by PLC in benzene–Me_2CO (4:1; v/v) gave four bands at R_f 0.50 (5.0 mg), 0.43 (7.0 mg), 0.28 (6.0 mg) and 0.24 (16.0 mg). Acetylation of the R_f 0.24 band followed by PLC purification in benzene–Me_2CO (9:1; v/v) afforded two main bands at R_f 0.70 (10.0 mg) and 0.64 (3.0 mg). Further purification of the R_f 0.70 band by PLC in hexane–Me_2CO–EtOAc (33:11:6; ×4; v/v) gave a single band at R_f 0.58 (8.0 mg) which yielded **8** as a white amorphous solid. (Found: M^+, 772.2731. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR [$(CD_3)_2CO$), 27 °C]: δ 19.97, 20.01, 20.43 [3×CH_3COO–], 55.04 (×2), 55.08, 56.01, 60.23, 60.48 [6×-OCH_3], 70.67 [4-C(F)], 71.67 [3-C(F)], 72.27 [3-C(C)], 79.13 [2-C(F)], 80.51 [2-C(C)], 106.19 [6-C(A)], 113.86 (×2) [3,5-C(B)], 114.04 (×2) [3,5-C(E)], 114.04 [10-C(D)], 119.79 [10-C(A)], 123.39 [5-C(A)], 123.66 [5-C(D)], 127.57 [6-C(D)], 128.79 [1-C(E)], 129.28 (×2) [2,6-C(B)], 129.30 (×2) [2,6-C(E)], 130.03 [1-C(B)], 137.89 [8-C(A)], 141.67 [8-C(D)], 148.67 [9-C(D)], 148.67 [9-C(A)], 152.58 [7-C(A)], 153.02 [7-C(D)], 160.33 [4-C(B)], 160.58 [4-C(E)], 168.49, 168.98, 170.94 [3×CH_3COO–]; CD $[\theta]_{230.2}$ 43, $[\theta]_{234.0}$ −3174, $[\theta]_{238.0}$ 42, $[\theta]_{246.5}$ 10 870, $[\theta]_{260.6}$ 10, $[\theta]_{274.9}$ −5263, and $[\theta]_{288.2}$ 1. The remaining bands were not further investigated.

3.7. Ent-oritin-(4α→6)-epioritin-4α-ol hexa-O-methylether triacetate **10**

Methylation of a portion (100 mg) of fraction R from *A. galpinii* followed by PLC (B:A; 4:1; ×2; v/v) gave four bands at R_f 0.60 (5.0 mg), 0.44 (4.0 mg), 0.38 (19.0 mg) and 0.31 (10.0 mg). Acetylation and PLC purification (B:A; 9:1; v/v) of the R_f 0.31 band gave a single band at R_f 0.50 (6.0 mg) which yielded **10** as a *white amorphous solid.* (Found: M^+, 772.2734. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 21.00 (×2), 21.32 [3×CH_3COO–], 36.00 [4-C(C)], 55.65 (×3), 56.64, 61.30, 61.34 [6×-OCH_3], 67.09 [4-C(F)], 67.09 [3-C(F)], 71.68 [3-C(C)], 76.18 [2-C(C)], 77.51 [2-C(F)], 105.17 [6-C(A)], 114.25 (×2) [3,5-C(E)], 114.28 (×2) [3,5-C(B)], 114.72 [10-C(D)], 116.65 [10-C(A)], 123.55 [5-C(D)], 124.47 [5-C(A)], 126.25 [6-C(D)], 127.95 (×2) [2,6-C(B)], 127.95 (×2) [2,6-C(E)], 128.95 [1-C(E)], 130.78 [1-C(B)], 137.38 [8-C(A)], 141.03 [8-C(D)], 147.99 [9-C(D)], 148.69 [9-C(A)], 152.66 [7-C(D)], 152.66 [7-C(A)], 159.84 [4-C(B)], 160.09 [4-C(E)], 170.45, 170.59, 170.96 [3×CH_3COO–]; CD $[\theta]_{222.3}$ −6070, $[\theta]_{228.6}$ 51 500, $[\theta]_{232.1}$ 2529, $[\theta]_{240.2}$−280820, $[\theta]_{252.1}$ −11 640, $[\theta]_{281.9}$ −137 000, and $[\theta]_{298.3}$−7977. The remaining bands contained related pro-/leucoteracacinidins that were reported previously (Coetzee, et al., 1998a,b).

3.8. *Ent-oritin-(4α → 6)-oritin-4α-ol hexa-O-methylether triacetate* **12**

Methylation of a portion (100 mg) of fraction M from *A. galpinii* followed by PLC in hexane-benzene–Me_2CO–MeOH (43:42:10:5; ×2; v/v) gave six bands at R_f 0.60 (3.0 mg), 0.36 (11.0 mg), 0.31 (21.0 mg), 0.20 (24.0 mg), 0.14 (7.0 mg) and 0.10 (6.0 mg). Acetylation of the R_f 0.20 band followed by PLC purification in hexane–benzene–Me_2CO–MeOH (47:46:5:2; ×4; v/v) afforded two main bands at R_f 0.65 (11.0 mg) and 0.60 (4.0 mg). The former band yielded **12** as a white amorphous solid. (Found: M^+, 772.2733. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR (C_6D_6, 27 °C): δ 20.25, 20.52, 20.94 [3×*C*H_3COO–], 36.55 [4-C(C)], 54.86, 54.89, 56.26, 60.79, 60.91, 61.03 [6×-O*C*H_3], 71.37 [4-C(F)], 71.47 [3-C(F)], 71.90 [3-C(C)], 76.66 [2-C(C)], 79.55 [2-C(F)], 106.03 [6-C(A)], 114.29 (×2) [3,5-C(E)], 114.49 (×2) [3,5-C(B)], 117.23 [10-C(D)], 117.46 [10-C(A)], 124.32 [5-C(A)], 124.84 [5-C(D)], 127.77 [1-C(B)], 127.91 [6-C(D)], 128.49 [1-C(E)], 128.82 (×2) [2,6-C(E)], 129.42 (×2) [2,6-C(B)], 138.74 [8-C(A)], 141.71 [8-C(D)], 148.74 [7-C(D)], 149.61 [9-C(A)], 153.47 [9-C(D)], 153.47 [7-C(A)], 160.16 [4-C(E)], 160.71 [4-C(B)], 168.92, 169.86, 170.85 [3×CH_3*C*OO-]; CD $[\theta]_{237.9}$ 207, $[\theta]_{244.7}$−28 090, $[\theta]_{258.1}$ −4188, $[\theta]_{274.2}$ −7557, and $[\theta]_{299.8}$−547. The remaining bands contained related pro-/leucoteracacinidins that were reported previously (Coetzee et al., 1998a,b).

3.9. *Ent-oritin-(4α → 6)-epioritin-4β-ol hexa-O-methylether triacetate* **14**

Methylation of a portion (200 mg) of fraction S of *A. caffra* followed by PLC in benzene–Me_2CO–EtOAc (7:2:1; v/v) gave four bands at R_f 0.43 (17 mg), 0.34 (13 mg), 0.31 (23 mg) and 0.21 (21 mg). Acetylation of the R_f 0.21 band followed by PLC in benzene–Me_2CO (9:1; v/v) afforded one main band at R_f 0.42 (5.1 mg). Further purification of this band by PLC in $CHCl_3$–Et_2O (98:2; ×3; v/v) yielded **14** at R_f 0.27 (3.2 mg) as a white amorphous solid. (Found: M^+, 772.2731. $C_{42}H_{44}O_{14}$ requires M^+, 772.2731); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 21.00, 21.34, 21.60 [3×*C*H_3COO-], 34.54 [4-C(C)], 55.66 (×2), 56.48, 61.33 (×2), 61.45 [6×-O*C*H_3], 66.53 [4-C(F)], 69.19 [3-C(F)], 71.65 [3-C(C)], 74.54 [2-C(F)], 76.55 [2-C(C)], 105.39 [6-C(A)], 113.62 [10-C(D)], 114.24 (×2) [3,5-C(E)], 114.37 (×2) [3,5-C(B)], 116.39 [10-C(A)], 123.99 [5-C(A)], 126.37 [6-C(D)], 127.54 (×2) [2,6-C(B)], 127.96 [5-C(D)], 128.10 (×2) [2,6-C(E)], 128.91 [1-C(E)], 130.91 [1-C(B)], 137.42 [8-C(A)], 141.38 [8-C(D)], 148.46 [9-C(A)], 148.75 [9-C(D)], 152.67 [7-C(D)], 153.62 [7-C(A)], 159.78 [4-C(B)], 160.05 [4-C(E)], 169.46 (×2), 170.70 [3×CH_3*C*OO–]; CD $[\theta]_{221.0}$ 11, $[\theta]_{226.7}$−897, $[\theta]_{231.4}$ 30, $[\theta]_{237.5}$ 5525, $[\theta]_{240.4}$ 282, $[\theta]_{245.4}$ −13 550, $[\theta]_{254.8}$ 14, $[\theta]_{275.5}$ 17, $[\theta]_{286.0}$ −4374, and $[\theta]_{294.2}$ 17. The remaining bands contained related pro-/leucoanthocyanidins that were reported elsewhere (Bennie et al., 2000, 2001b).

3.10. *Epioritin-(4β → 6)-epimesquitol-4α-ol hepta-O-methylether triacetate* **16**

Methylation of a portion (200 mg) of fraction HH from *A. caffra* followed by PLC in benzene–Me_2CO–EtOAc (7:2:1; ×2; v/v) gave five bands at R_f 0.68 (14 mg), 0.63 (21 mg), 0.51 (20 mg), 0.47 (21 mg) and 0.39 (19 mg). Acetylation of the R_f 0.39 band followed by PLC in benzene–Me_2CO (9:1; v/v) yielded **16** at R_f 0.33 (7.0 mg) as a white amorphous solid. (Found: M^+, 802.2837. $C_{43}H_{46}O_{15}$ requires M^+, 802.2837); δ_H (Table 1); ^{13}C NMR [$(CD_3)_2CO$), 27 °C]: δ 19.93, 20.07, 20.26 [3×*C*H_3COO–], 41.50 [4-C(C)], 54.99, 55.59, 55.67, 56.15, 60.37, 60.64, 61.07 [7×-O*C*H_3], 66.92 [4-C(F)], 67.17 [3-C(F)], 71.98 [3-C(C)], 73.49 [2-C(C)], 77.46 [2-C(F)], 106.15 [6-C(A)], 110.88 [2-C(E)], 111.97 [5-C(E)], 113.86 (×2) [3,5-C(B)], 115.29 [10-C(A)], 115.48 [10-C(D)], 119.36 [6-C(E)], 123.52 [5-C(D)], 125.35 [5-C(A)], 128.07 (×2) [2,6-C(B)], 128.67 [6-C(D)], 130.06 [1-C(E)], 130.49 [1-C(B)], 137.87 [8-C(A)], 141.09 [8-C(D)], 148.40 [9-C(D)], 149.37 [9-C(A)], 149.69 [3-C(E)], 149.92 [4-C(E)], 151.42 [7-C(D)], 152.98 [7-C(A)], 159.84 [4-C(B)], 169.15, 169.75, 170.04 [3×CH_3*C*OO–]; CD $[\theta]_{219.8}$ 34, $[\theta]_{225.4}$ −3334, $[\theta]_{230.1}$ 42, $[\theta]_{232.5}$ 1 033, $[\theta]_{236.1}$ 259, $[\theta]_{243.1}$ 6660, $[\theta]_{248.4}$ 102, $[\theta]_{251.4}$ −1384, $[\theta]_{258.1}$-765, and $[\theta]_{284.9}$ −9276.

3.11. *Epimesquitol-(4β → 6)-epioritin-4α-ol hepta-O-methylether triacetate* **20**

Acetylation of the R_f 0.47 band (section 3.10) followed by PLC in benzene–Me_2CO (9:1; v/v) yielded **20** at R_f 0.35 (11.4 mg) as a white amorphous solid. (Found: M^+, 802.2835. $C_{43}H_{46}O_{15}$ requires M^+, 802.2837); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 20.77, 21.01, 21.36 [3×*C*H_3COO-], 41.74 [4-C(C)], 55.65, 56.25, 56.29, 56.72, 61.36, 61.40, 61.53 [7×-O*C*H_3], 67.01 [3-C(F)], 67.13 [4-C(F)], 72.17 [3-C(C)], 73.73 [2-C(C)], 77.62 [2-C(F)], 105.59 [6-C(A)], 110.36 [2-C(B)], 111.23 [5-C(B)], 114.25 (×2) [3,5-C(E)], 114.65 [10-C(D)], 115.17 [10-C(A)], 119.18 [6-C(B)], 123.40 [5-C(D)], 125.42 [5-C(A)], 127.94 (×2) [2,6-C(E)], 128.58 [1-C(E)], 128.87 [6-C(D)], 130.69 [1-C(B)], 137.58 [8-C(A)], 141.03 [8-C(D)], 148.31 [9-C(D)], 149.08 [3-C(B)], 149.13 [4-C(B)], 149.21 [9-C(A)], 151.68 [7-C(D)], 152.63 [7-C(A)], 160.10 [4-C(E)], 170.00, 170.40, 170.79 [3×CH_3*C*OO–]; CD $[\theta]_{213.4}$ 11, $[\theta]_{216.4}$ −1085, $[\theta]_{219.3}$ 40, $[\theta]_{228.2}$ 5228, $[\theta]_{233.8}$ 152, $[\theta]_{237.3}$ −3 68, $[\theta]_{240.3}$ 50, $[\theta]_{244.9}$ 7782, $[\theta]_{251.1}$ 51, and $[\theta]_{285.3}$ −12 560. The remaining bands contain related pro-/leucoanthocyanidins that were reported elsewhere (Bennie et al., 2001a).

3.12. Epimesquitol-(4β → 6)-epimesquitol-4β-ol octa-O-methylether triacetate **24**

Methylation of a portion (200 mg) of fraction FF from *A. caffra* followed by PLC in benzene–Me_2CO–EtOAc (7:2:1; v/v) gave two bands at R_f 0.42 (36 mg) and 0.33 (28 mg). Acetylation of the R_f 0.33 band and PLC purification in benzene–Me_2CO (B:A; 9:1; v/v) afforded two main bands at R_f 0.56 (2.6 mg) and 0.41 (3.2 mg). The latter band yielded **24** as a white amorphous solid. (Found: M^+, 832.2943. $C_{44}H_{48}O_{16}$ requires M^+, 832.2942); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 21.04, 21.53, 21.67 [3×*C*H_3COO–], 41.04 [4-C(C)], 56.31 (×4), 56.51, 61.28, 61.39, 61.61 [8×-O*C*H_3], 66.43 [4-C(F)], 68.90 [3-C(F)], 72.34 [3-C(C)], 73.75 [2-C(C)], 74.60 [2-C(F)], 105.85 [6-C(A)], 110.23 [2-C(E)], 110.45 [2-C(B)], 111.23 [5-C(B)], 111.44 [5-C(E)], 113.57 [10-C(D)], 114.97 [10-C(A)], 119.17 [6-C(B)], 119.34 [6-C(E)], 125.10 [5-C(A)], 127.89 [5-C(D)], 129.01 [6-C(D)], 129.24 [1-C(E)], 130.81 [1-C(B)], 137.52 [8-C(A)], 141.17 [8-C(D)], 148.97–149.53* (×6) [9-C(A), 3-C(B), 4-C(B), 9-C(D), 3-C(E), 4-C(E)], 152.65 [7-C(D)], 152.65 [7-C(A)], 169.41, 169.55, 169.99 [3×CH_3*C*OO–], *Signals overlap; CD $[\theta]_{216.9}-24$, $[\theta]_{224.4}$ 4142, $[\theta]_{229.9}$ 612, $[\theta]_{237.9}$ 25 270, $[\theta]_{251.0}-52$, $[\theta]_{258.6}$ 327, $[\theta]_{266.1}-93$, $[\theta]_{277.6}$ 1634, and $[\theta]_{282.1}$ 53.

3.13. Procedure for the synthesis of (2R,3S,4S)-2,3-cis-3,4-trans-3,3′,4′,7,8-pentahydroxy-4-benzylsulfanylflavan [4β-benzylsulfanylepimesquitol] **28**

Epimesquitol-4α-ol **26** (1.0 g) and an excess of toluene-α-thiol (2.2 ml) were dissolved in EtOH (15 ml) while the solution was purged with N_2 gas. The solution was transferred to an N_2-purged vial, HOAc (4 ml) was added and the vial was sealed. After 24 h at 100 °C in a steam bath, the solvent was removed under a stream of N_2. The residue was transferred into a container with H_2O (50 ml) and the excess toluene-α-thiol was removed by washing with hexane (2×50 ml). The aqueous layer was extracted with Et_2O (5×20 ml). The Et_2O was removed under a stream of N_2 and the oil was applied to a Sephadex LH-20 column (4 × 150 cm) with the use of a small amount of EtOH. The column was eluted with $CHCl_3$–EtOH (4:1), at a flow rate of 1 ml/min and 16 ml fractions were collected. The fractions were combined as follows: tubes 10–12 (42 mg), 13–25 (220 mg) and 26–44 (625 mg). The 625 mg fraction yielded **28** as a light yellow amorphous powder. (Found: M^+, 510.1713. $C_{28}H_{30}SO_7$ requires M^+, 510.1712); δ_H [$(CD_3)_2CO$, 20 °C]: δ 7.50–7.23 [*m*, 5×H(D)]; 7.34 [*d*, 9.0, 2,6-H(B)]; 6.83 [*d*, 9.0, 3,5-H(B)]; 6.53 [*d*, 8.5, 5-H(A)]; 6.43 [*d*, 8.5, 6-H(A)]; 5.33 [*br s*, 2-H(C)]; 4.07 [*dd*, 1.5, 4.0, 3-H(C)]; 4.04 (*d*, 14.0, CH_2); 3.95 [*d*, 4.0, 4-H(C)]; 3.92 (*d*, 14.0, CH_2); CD $[\theta]_{228.7}$ 96, $[\theta]_{230.7}$ −1533, $[\theta]_{232.6}$ 84, $[\theta]_{240.4}$ 14 940, $[\theta]_{248.1}$ 99, and $[\theta]_{282.7}$ −10 410.

3.14. Synthesis of epimesquitol-(4β → 6)-epioritin-4α-ol hepta-O-methylether triacetate **20**.

4β-Benzylsulfanylepimesquitol **28** (100 mg, 2.43×10^{-4} mole) and epioritin-4α-ol **25** (141 mg, 4.86×10^{-4} mol, 2 eq) in THF (10 ml) were stirred with $AgBF_4$ (118 mg, 6.07×10^{-4} mol, 2.5 eq) at 30 °C for 90 min. Methylation, acetylation and subsequent PLC separation in benzene–Me_2CO (9:1; v/v) of the reaction mixture yielded two main bands at R_f 0.59 (37 mg) and 0.36 (28 mg).

3.15. Epimesquitol-(4β → 6)-epioritin-4α-ol hepta-O-methylether triacetate **20**

Further purification of the R_f 0.59 band by PLC in $CHCl_3$–hexane–Me_2CO (90:6:4; ×2; v/v) yielded two bands at R_f 0.46 (5.7 mg) and 0.42 (5.3 mg). The former band yielded **20** (4.3%) as a white amorphous solid with NMR and CD data identical to those of the natural product derivative.

3.16. Epimesquitol-(4β → 6)-epioritin-4β-ol hepta-O-methylether triacetate **22**

The R_f 0.42 band afforded **22** (4.6%) as a white amorphous solid. (Found: M^+, 802. 2833. $C_{43}H_{46}O_{15}$ requires M^+, 802.2837); δ_H (Table 1); ^{13}C NMR ($CDCl_3$, 27 °C): δ 21.00, 21.35, 21.67 [3×*C*H_3COO–], 41.05 [4-C(C)], 55.66, 56.26, 56.33, 56.50, 61.35 (×2), 61.60 [7×-O*C*H_3], 66.46 [4-C(F)], 68.99 [3-C(F)], 72.37 [3-C(C)], 73.74 [2-C(C)], 74.64 [2-C(F)], 105.81 [6-C(A)], 110.39 [2-C(B)], 111.19 [5-C(B)], 113.55 [10-C(D)], 114.24 (×2) [3,5-C(E)], 114.93, [10-C(A)], 119.17 [6-C(B)], 125.14 [5-C(A)], 127.84 [5-C(D)], 128.09 (×2) [2,6-C(E)], 128.83 [1-C(E)], 128.95 [6-C(D)], 130.82 [1-C(B)], 137.54 [8-C(A)], 141.19 [8-C(D)], 149.07 [9-C(D)]/[3-C(B)], 149.12 [4-C(B)]/[9-C(A)], 152.64 [7-C(D)]/[7-C(A)], 160.06 [4-C(E)], 169.53 (×2), 169.97 [3×CH_3*C*OO–]; CD $[\theta]_{220.9}-36$, $[\theta]_{225.7}$ 3613, $[\theta]_{229.4}-15$, $[\theta]_{231.8}-1500$, $[\theta]_{235.8}-14$, $[\theta]_{245.7}$ 6026, $[\theta]_{279.1}-23$, $[\theta]_{285.1}$ −2387, $[\theta]_{292.0}-4$, $[\theta]_{294.6}$ 258, and $[\theta]_{299.6}-5$.

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