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# Oligomeric flavanoids. Part 34: Doubly-linked proteracacinidin analogues from *Acacia caffra* and *Acacia galpinii*☆

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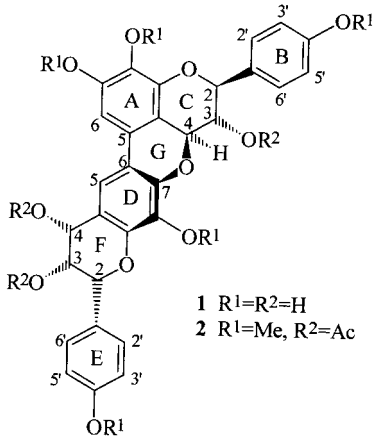
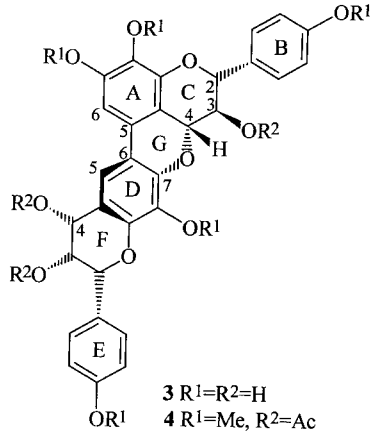
**Abstract**—The rare series of doubly-linked proteracacinidin-type oligoflavanoids is extended by identification of four new analogues, oritin-(4α→7, 5→6)-epioritin-4α-ol **3**, oritin-(4β→7, 5→6)-epioritin-4α-ol **5**, epioritin-(4β→7, 5→6)-epioritin-4α-ol **7** and epioritin-(4β→7, 5→6)-oritin-4α-ol **9**. The same sources also afforded epioritin-(4β→5, 3→4)-oritin-4α-ol **11** possessing a rare (4β→5)- as well as a unique (3→4)- ether linkage. Their structures and absolute configurations were established via spectroscopic methods. 

## 1. Introduction

The predominance of carbon–carbon interflavanoid bonding between C-4 (C-ring) and C-6/C-8 (D-ring) of flavanoid monomeric units in proanthocyanidins is well established.[1–4] Doubly-ether-linked dioxane-type dimers were first found in *A. mearnsii*[5,6] while (4-O-4) and (4-O-3) single ether-linked leucoanthocyanidins were recently reported from several *Acacia* species.[7–10] A guibourtinidol-(3′→4′)-*ent*-epimopane was obtained from the heartwood of *Colophospermum mopane*,[11] while two biscatechins with (3′-O-8) and (4′-O-8) couplings, respectively, were synthesized.[12] The doubly-linked A-type biflavanoids also possess an ether linkage between C-2 (C-ring) and C-5/C-7 (D-ring)[3,4,13–15] in addition to the common C($sp^3$)–C($sp^2$) bond. We have recently reported the identification of a proteracacinidin analogue **1** with a unique (4β→7) ether linkage as well as a rare (5→6) C($sp^2$)–C($sp^2$) bond between the A- and D-rings from the heartwood of *A. caffra*.[16] Here we describe the structure and attempted synthesis of four new (4→7, 5→6) doubly-linked pro-/leucoteracacinidins **3**, **5**, **7** and **9** from *A. galpinii* as well as the structure elucidation of the first (4β→5, 3→4) doubly-linked proteracacinidin-type dimer **11** from the heartwood of *Acacia caffra*.




☆ Part 34 in the series 'Oligomeric Flavanoids'. Part 33 (Bennie, Malan, Coetzee & Ferreira, *Phytochemistry*, 2000).

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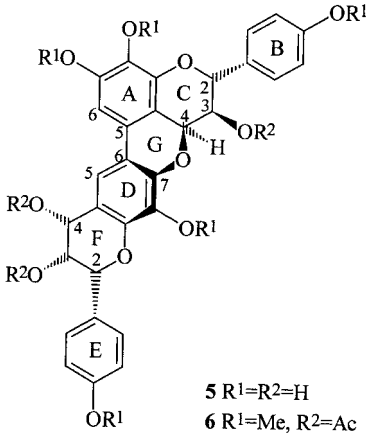
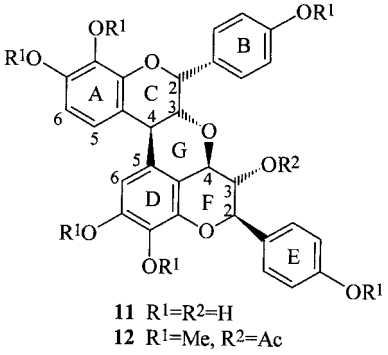
**Table 1.** $^1$H NMR (300 MHz, 296 K) data of derivatives **4**, **6**, **8**, **10** and **12** in $CDCl_3$. Splitting patterns and *J*-values are given in parentheses

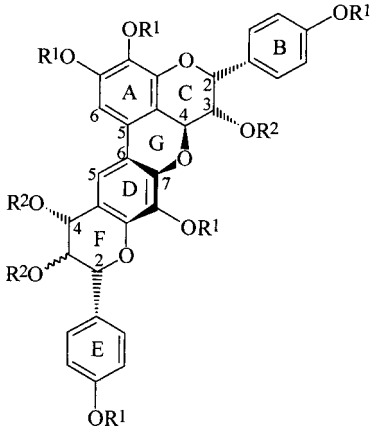
| Ring | H | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|
| A | 5 | – | – | – | – | 6.53 (d,8.5) |
| | 6 | 6.81 (s) | 6.80 (s) | 6.80 (s) | 6.79 (s) | 6.42 (d,8.5) |
| B | 2′,6′ | 7.44 (d,9.0) | 7.20 (d,9.0) | 7.23 (d,9.0) | 7.23 (d,9.0) | 7.22 (d,9.0) |
| | 3′,5′ | 6.94 (d,9.0) | 6.83 (d,9.0) | 6.84 (d,9.0) | 6.86 (d,9.0) | 6.88 (d,9.0) |
| C | 2 | 5.04 (d,10.5) | 5.63 (d,6.5) | 5.80 (d,3.0) | 5.79 (d,3.0) | 5.70 (d,2.5) |
| | 3 | 5.87 (dd,10.5,9.0) | 5.87 (dd,6.5,4.8) | 5.91 (dd,3.0,4.0) | 5.91 (dd,3.0,4.0) | 4.13 (dd,2.5,3.5) |
| | 4 | 5.22 (d,9.0) | 4.82 (d,4.8) | 4.89 (d,4.0) | 4.92 (d,4.0) | 3.75 (d,3.5) |
| D | 5 | 7.23 (br.s,1.0) | 7.22 (br.s,1.0) | 7.18 (s,1.0) | 7.17 (s,1.0) | – |
| | 6 | – | – | – | – | 6.57 (s,1.0) |
| E | 2′,6′ | 7.40 (d,9.0) | 7.40 (d,9.0) | 7.38 (d,9.0) | 7.31 (d,9.0) | 7.03 (d,9.0) |
| | 3′,5′ | 6.92 (d,9.0) | 6.92 (d,9.0) | 6.91 (d,.90) | 6.88 (d,9.0) | 6.75 (d,9.0) |
| F | 2 | 5.38 (br.s,1.5) | 5.38 (br.s,1.5) | 5.34 (br.s,1.5) | 5.25 (d,7.0) | 5.35 (d,4.5) |
| | 3 | 5.67 (dd,1.5,4.0) | 5.64 (dd,1.5,4.0) | 5.63 (dd,1.5,4.0) | 5.49 (dd,7.0,6.0) | 5.45 (dd,4.5,7.0) |
| | 4 | 6.36 (d,4.0) | 6.37 (d,4.0) | 6.34 (d,4.0) | 6.15 (d,6.0) | 4.15 (d,7.0) |
| OMe | | 3.83,3.86,3.87,3.88,3.96 (each s) | 3.79,3.83,3.91,3.94, 4.01 (each s) | 3.78,3.83,3.84,4.00, 4.02 (each s) | 3.78,3.80,3.83,4.00, 4.01 (each s) | 3.78,3.81,3.85,3.89, 3.91,3.93 (each s) |
| OAc | | 1.94,1.96,2.20 (each s) | 1.92,2.13,2.19 (each s) | 1.90,2.12,2.15 (each s) | 1.88,1.95,2.14 (each s) | 2.02 (s) |



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



**11** $R^1$=$R^2$=H
**12** $R^1$=Me, $R^2$=Ac



**7** ≡ , $R^1$=$R^2$=H
**8** ≡ , $R^1$=Me, $R^2$=Ac
**9** ≡ , $R^1$=$R^2$=H
**10** ≡ , $R^1$=Me, $R^2$=Ac

## 2. Results and discussion

The methanol extracts of the heartwoods of *A. galpinii* and *A. caffra* contain complex mixtures of mono-,[8,17] di-[8–10,16–19] and tri-meric[20] pro-/leucoanthocyanidins. These oligomers and the unique doubly-linked *ent*-oritin-(4β→7, 5→6)-epioritin-4α-ol **1**,[16] are accompanied by oritin-(4α→7, 5→6)-epioritin-4α-ol **3**, oritin-(4β→7, 5→6)-epioritin-4α-ol **5**, epioritin-(4β→7, 5→6)-epioritin-4α-ol **7** and epioritin-(4β→7, 5→6)-oritin-4α-ol **9**, in the MeOH extract of the heartwood of *A. galpinii*. Epioritin-(4β→5, 3→4)-oritin-4α-ol **11**, the first analogue with both a $C(sp^3)$–$C(sp^2)$ (4β→5) bond and a unique (3-O-4) ether linkage was identified in *A. caffra*. Despite extensive efforts to resolve the free phenolic mixture by partition and gel separation techniques, the oligomers could only be purified as their permethylaryl ether acetate derivatives **4**, **6**, **8**, **10** and **12**, respectively.

The structures and relative configuration of these derivatives were determined by analyses of $^1$H and $^{13}$C NMR data (Tables 1 and 2). Allocation of $^{13}$C resonances was facilitated by HMQC and HMBC experiments. The presence of a second interflavanyl linkage introduces a high degree of conformational stability which culminates in first order NMR spectra conspicuously free of the adverse effects of dynamic rotational isomerism about the interflavanyl bond.

FAB-MS analyses of the permethylaryl ether acetate

**Table 2.** $^{13}C$ NMR peaks ($\delta_C$) for compounds **4**, **6**, **8**, **10** and 1**2**

| Ring | Carbon | **4** | **6** | **8** | **10** | **12** |
|---|---|---|---|---|---|---|
| A | 5 | 118.1 | 118.3 | 118.1 | 118.1 | 123.2 |
| | 6 | 100.2 | 99.9 | 99.0 | 99.0 | 104.6 |
| B | 2′,6′ | 128.1 | 128.1 | 126.3 | 126.3 | 126.7 |
| | 3′,5′ | 114.1 | 114.1 | 114.2 | 114.1 | 114.5 |
| | 2 | 79.3 | 76.5 | 78.4 | 78.4 | 79.0 |
| C | 3 | 74.7 | 71.9 | 68.3 | 68.3 | 72.0 |
| | 4 | 71.2 | 71.3 | 66.8 | 66.8 | 35.0 |
| D | 5 | 115.5 | 115.9 | 115.8 | 118.0 | 132.3 |
| | 6 | 125.7 | 126.1 | 126.0 | 125.3 | 106.3 |
| E | 2′,6′ | 128.0 | 128.0 | 128.0 | 128.6 | 128.2 |
| | 3′,5′ | 114.2 | 114.2 | 114.8 | 114.8 | 113.9 |
| | 2 | 77.6 | 77.6 | 77.6 | 78.5 | 77.2 |
| F | 3 | 67.3 | 67.1 | 67.1 | 71.4 | 72.7 |
| | 4 | 67.8 | 67.5 | 67.5 | 69.3 | 66.8 |

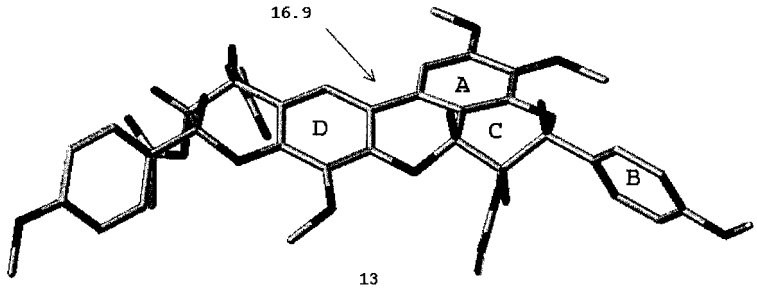
derivatives **4**, **6**, **8**, **10** and **12** indicate molecular formulas of $C_{41}H_{40}O_{14}$ (*m/z* 756) for **4**, **6**, **8** and **10**, and $C_{38}H_{38}O_{11}$ (*m/z* 670) for **12**. When taken in conjunction with the number of *O*-methyl and *O*-acetyl resonances in their $^1H$ NMR spectra (Table 1) these formulas strongly suggested doubly-linked structures containing both carbon–carbon and ether interflavanyl linkages. The $^1H$ NMR spectral data for compounds **4**, **6**, **8** and **10** indicated the presence of two AA′BB′-spin systems and two one-proton singlets for aromatic protons as well as two AMX-spin systems for protons in the heterocyclic region. In the $^1H$ NMR spectrum of derivative **12**, one of the one-proton singlets is replaced by an aromatic AB-spin system. Differentiation of the spin systems and the connectivities between aromatic and heterocyclic protons were effected with COSY experiments which indicated coupling ($^4J_{HH}$) between the respective 2- and 2′,6′-protons. Long range coupling ($^4J_{HH}$) observed between 4-H(F) and 5-H(D), together with n.O.e. associations of 5-H(D) with both 4-H(F) and 6-H(A) and of 6-H(A) with both 7-OMe(A) and 5-H(D) collectively differentiated between the two one-proton singlets [5-H(D) and 6-H(A)] and thereby defined the biphenyl linkage between C-5(A) and C-6(D) for derivatives **4**, **6**, **8** and **10**. Differentiation of the AB-system and one-proton singlet [6-H(D)] in derivative **12** was also possible via the observed $^4J_{HH}$ coupling between 5-H(A) and 4-H(C). n.O.e. Associations, observed in a phase sensitive NOESY experiment, of 5-H(A) with both 4-H(C) and 6-H(D) and of 6-H(D) with both 5-H(A) and 7-OMe(D) together with the conspicuous absence of association between the one-proton singlet [6-H(D)] and [4-H(F)] defined the C-4(C)⟶C-5(D) linkage.

In combination with the spin systems and conspicuously deshielded 4-H(F) heterocyclic resonances, the presence of only five *O*-methyl and three *O*-acetyl resonances in the $^1H$ NMR spectra of derivatives **4**, **6**, **8** and **10**, suggested structures comprising two derivatized 7,8,4′-trihydroxyflavan-3,4-diol units where, in addition to the biphenyl linkage, two of the oxygen functionalities were involved in the formation of the $C_4$–O–$C_7$ ether bond. The latter bond was confirmed by FAB-MS (*m/z* 756) and the observed coupling of 4-H(C) with 7-C(D), in an HMBC experiment. The $^1H$ NMR spectral data of derivative **12** showed one *O*-acetyl and six *O*-methyl signals indicative of the involvement of two of the heterocyclic oxygen functionalities in a $C_3$–O–$C_4$ ether linkage. FAB-MS (*m/z* 670) together with long range carbon–hydrogen coupling, of 4-H(C) with 5-C(D), 3-H(C) with 4-C(F) and of 4-H(C) with 3-C(C) observed in an HMBC experiment, confirmed the C-4(C)⟶C-5(D) and $C_3$–O–$C_4$ linkages in **12**.

The identical F-ring heterocyclic systems of derivatives **4** and **6** exhibited coupling constants reminiscent of 2,3-*cis*-3,4-*cis* ($^3J_{2,3}$=1.5 Hz; $^3J_{3,4}$=4.0 Hz) relative configuration.[8,9,16] Such all-*cis* configurations were confirmed by n.O.e. associations between 2- and 4-H which indicated that these protons are cofacial. The relative 2,3-*trans*-3,4-*trans* configuration of the C-ring of compound **4** was evident[21] from $^1H$ NMR coupling constants of heterocyclic protons ($^3J_{2,3}$=10.5 Hz; $^3J_{3,4}$=9.0 Hz). These values were less informative ($^3J_{2,3}$=6.5 Hz; $^3J_{3,4}$=4.8 Hz) for derivative **6**. Such small coupling constants ($^3J_{2,3}$=6.0 Hz; $^3J_{3,4}$=4.9 Hz) were previously documented[22] for 2,4-diaryl-6-(2-benzopyranyl)-chromanes with 2,3-*trans*-3,4-*cis* stereochemistry of the C-ring. The conspicuous absence of n.O.e. association between 2- and 4-H(C) in **6**, was interpreted as confirmation of the 2,4-*trans* relative configuration of the ABC moiety. The heterocyclic AMX-spin systems of derivatives **8** and **10** exhibited coupling constants reminiscent of 2,3-*cis*-3,4-*cis*[16] ($^3J_{2,3}$=1.5 Hz; $^3J_{3,4}$=4.0 Hz) and 2,3-*trans*-3,4-*trans*[23] ($^3J_{2,3}$=7.0 Hz; $^3J_{3,4}$=6.0 Hz) relative configurations for the F-rings of **8** and **10**, respectively. Although the coupling constants ($^3J_{2,3}$=3.0 Hz; $^3J_{3,4}$=4.0 Hz) of the identical C-rings of **8** and **10** were less characteristic, similar heterocyclic coupling constants were previously reported[24] for 2,3-*cis*-3,4-*trans* relative configurations. The absence of an n.O.e. association between 2- and 4-H(C) supported the 2,4-*trans* relative configuration in **8** and **10**. The heterocyclic C-ring of derivative **12** exhibited coupling constants ($^3J_{2,3}$=2.5 Hz; $^3J_{3,4}$=3.5 Hz) of the same magnitude which were also interpreted as 2,3-*cis*-3,4-*trans* relative configuration after no n.O.e. could be detected between 2- and 4-H(C). However, significant n.O.e. associations between 2′,6′-H(B) and 4-H(C) for derivatives **6**, **8**, **10** and **12** unambiguously confirmed these 2,3-*trans*-3,4-*cis* and 2,3-*cis*-3,4-*trans* relative configurations. The relative 2,3-*trans*-3,4-*trans* configuration for the F-ring of **12** was evident[16] from the coupling constants ($^3J_{2,3}$=4.5 Hz; $^3J_{3,4}$=7.0 Hz) and the n.O.e. association that was observed between 2- and 4-H(F).

The aforementioned n.O.e associations between 4-H(C) and 2′,6′-H(B) and deviations in coupling constants of heterocyclic protons have lately been ascribed to significant contributions of A-conformers towards the C-ring conformational equilibrium.[23,25] However, the relative small coupling constants for the protons of these rings may also be attributed to a distorted ring, probably a sofa instead of the half-chair. From Dreiding models it is evident that for the G-ring to form, the C-ring conformation must change from the well-known sofa to a distorted chair with the G-ring then in a twisted half-boat. Despite these conformational deviations, the 'central core' of the molecules exhibits a remarkable degree of planarity.

The UV spectra of derivatives **4**, **6**, **8** and **10** showed three major absorption bands in the 225–235, 275–285 and 315–325(inflexion) nm regions. Their CD spectra all exhibited high amplitude Cotton effects near 255 nm (positive for **6**, **8**

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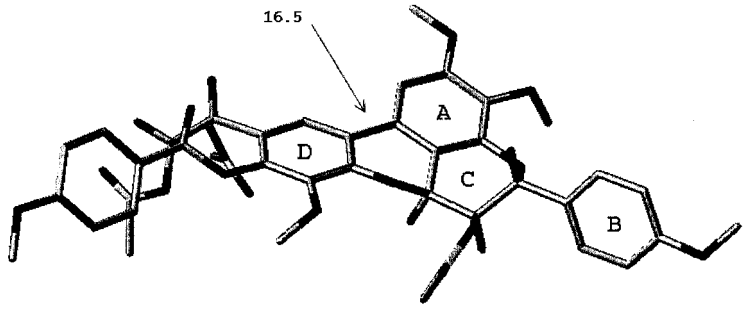


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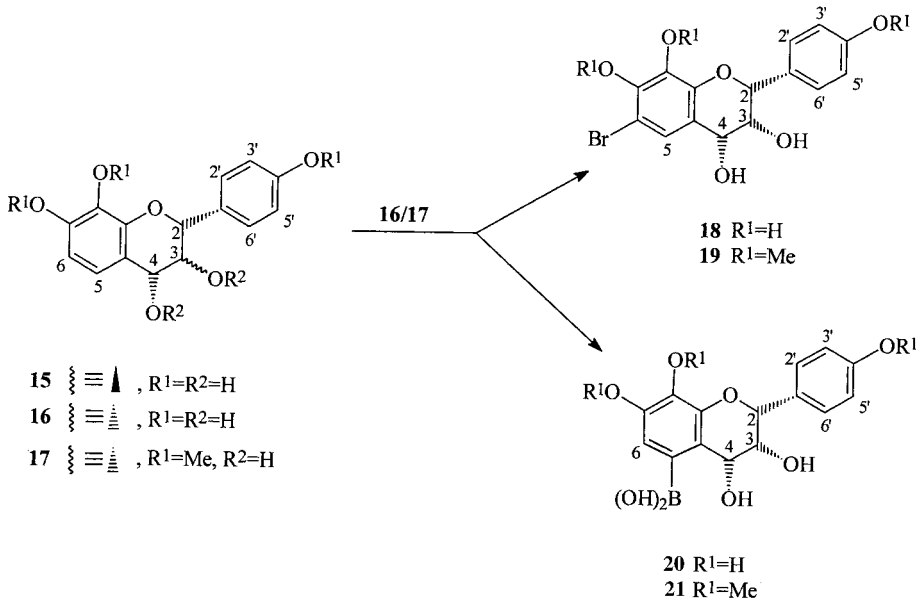
**Figure 1.** Lowest energy conformers **13** and **14** of derivatives **4** and **6**, respectively. Only heterocyclic hydrogens are displayed.

and **10**, negative for **4**) while **12** showed a positive Cotton effect at 240 nm. These Cotton effects in **4**, **6**, **8** and **10** result from the helicity imposed by the twisted biaryl chromophore ($\pi \rightarrow \pi^*$ transition) similar to observations in the aporphine class of benzyltetrahydroisoquinolines.[26] Thus, the positive Cotton effects near 255 nm for **2**,[16] **6**, **8** and **10** reflects *P*-helicity of the biaryl bond and hence an (*S*) absolute configuration at C-4(C). The negative Cotton effect in the same region for derivative **4** is accordingly indicative of *M*-helicity of the biaryl bond and therefore (*R*) absolute stereochemistry at C-4(C). The high amplitude positive Cotton effect at 240.4 nm in the CD spectrum of compound **12** indicated a C-4(C) stereocenter carrying a β substituent and hence (*S*) absolute configuration by application of the aromatic quadrant rule.[27] Lowest energy conformations **13** and **14** (Fig. 1) of derivatives **4** and **6**, respectively, were found with a Monte Carlo-style conformational search using the MM2 force field.[28] These indicated dihedral angles of ca. 17° between the planes of the aromatic A- and D-rings in both **4** and **6**. Collectively the Cotton effects and $^1$H NMR coupling constants of the C-ring protons suggested 2*R*,3*S*,4*S* absolute configurations for the ABC-moieties of **8**, **10** and **12**, 2*R*,3*R*,4*S* for **6**, and 2*R*,3*S*,4*R* for **4**. Both oritin-4α-ol **15** and epioritin-4α-ol **16** with their 2*R*,3*S*,4*R*- and 2*R*,3*R*,4*R*-absolute configurations, respectively, occur abundantly in the heartwood and are therefore the most likely biogenetic precursors of the lower DEF units of **10**, **12** and **4**, **6** and **8**, respectively. The absolute configurations of the F-rings depicted in formulations **4**, **6**, **8**, **10** and **12** are therefore tentative and based on the assumption that the DEF flavanyl units are biogenetically interrelated to monomers **15** and **16**.

Possible synthetic routes to the dimers **4**, **6**, **8** and **10** were investigated with a view to unambiguously establish the absolute configuration of their DEF-units. The interflavanyl linkages of these doubly-linked analogues are presumably established via a combined one-electron (5⟶6 bond) and two-electron (7-O⟶4 bond) process. Methods to form a C–O–C interflavanyl linkage between proteracacinidin units were already established[8–10] and we therefore decided to first exploit the Suzuki protocol[29–32] to form the C-5 (A-ring) to C-6 (D-ring) biphenyl linkage. The Suzuki reaction has been used extensively in the synthesis of natural products[33] and we first assessed the cross-coupling reaction of organoboron compound **20** with organic halide **18**. Bromination of epioritin-4α-ol **16** at −78°C in methyl acetate for 10 min. gave the 6-bromo derivative **18** in 85% yield. Attempts were also made to brominate the 5-position of **16**, after 'blocking'[22] the more nucleophilic 6-position, in order to form boronic acid **20** via metal–halogen exchange. The latter bromination attempts, as well as efforts to form the boronic acid from 6-bromoepioritin **18** or via direct metalation,[34] failed. In order to prevent acid-base reactions between the phenolic hydroxyl groups and BuLi during metal-halogen exchange, 6-bromo-tri-*O*-methylepioritin-4α-ol **19** was prepared from starting material **17**. However, all attempts to effect the formation of the boronic acid failed. The benzylic C-4 hydroxyl functionality as well as the C-8 hydroxyl group play an important role in the chemistry of the A-ring[35–37] and the inability to form the boronic acid derivative may presumably be ascribed to the combined 'buttressing effect' of the 7,8-dimethoxy function on H-6(A),[38] leaving insufficient space for the $B(OH)_2$-group (Scheme 1).

Attempts to effect the oxidative dimerization of epioritin-4α-ol **16** using $K_3Fe(CN)_6$,[38] or by employing a series of solid Lewis acids such as $FeCl_3/Al_2O_3$, $FeCl_3/SiO_2$ and $Fe^{3+}$ exchange montmorillonite as catalysts and aerial oxygen as oxidant[39] also failed. Reductive cleavage of the acetal functionality in A-type proanthocyanidins[15,40] and the ether bond in C–O–C coupled bi- and tri-flavanoids[20] is




**Scheme 1.** Organic halides **18**, **19** and boronic acids **20** and **21**.

now an established method used in structure elucidation of these classes of oligoflavanoids. However, attempts at cleavage of the (4→7) ether linkage in derivatives **4**, **6**, **8** and **10** using sodium cyanoborohydride [$Na(CN)BH_3$] in trifluoroacetic acid invariably failed. It appears that intramolecular ring closure occurs faster than the delivery of hydride ion to an intermediate benzylic C-4 carbocation, following protonation of the ethereal oxygen function. In addition, inspection of the minimum energy conformers, e.g. **13**, indicates a severely hindered $C_4$–O(C-ring) $\sigma^*$ antibonding orbital which would impede hydride ion delivery at this site from a Lewis acid/base complex involving the reducing agent and either $O_1$ -or $C_3$–OH(C-ring).

Our characterization of the first entry **11** to a new series of doubly-linked proteracacinidin-type oligoflavanoids together with identification of analogues **3**, **5**, **7** and **9** extends these rare classes of oligomers and further demonstrates the heterogeneity of the interflavanyl bonds among natural oligomeric pro-/leuco-anthocyanidins. The co-occurrence of these unique doubly-linked compounds with ether-linked and carbon–carbon coupled analogues in *A. galpinii*[8–10] and *A. caffra*[17–19] presumably reflects the poor nucleophilicity of the pyrogallol A-ring of monomeric precursors hence permitting alternative centres to participate in interflavanyl bond forming processes.

## 3. Experimental

$^1$H NMR spectra were recorded on a Bruker AVANCE DPX 300 spectrometer 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. Column chromatography 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–$Et_2O$ over a period of 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.

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[8] and 32[10] and need not to be repeated.

### 3.1. Standard procedure for the brominations with NBS

The starting material was dissolved in methyl acetate [$MeCO_2Me$] (5 ml) and added in one portion to a slurry of NBS (1.05 equiv.) in $MeCO_2Me$ (5 ml) under an $N_2$-atmosphere at −78°C. The mixture was stirred for 10 min. at −78°C before it was filtered and the solvent evaporated under reduced pressure.

### 3.2. Standard procedure for synthesis of boronic acid derivatives

The appropriate 6-bromo derivative was dissolved in dry THF (2 ml) under an $N_2$-atmosphere and cooled to −78°C before a hexane solution of *n*-BuLi (6–10 equiv.) was added dropwise over a period of 15 min. The mixture was treated with trimethylborate [$B(OMe)_3$] (3.5 equiv.) and allowed to warm to room temperature (22°C) over a 12 h period. The reaction mixture was cooled to 0°C, acidified (pH 6.5) with aq. HCl (10%) and extracted with EtOAc (5×10 ml). The combined organic layers were washed with brine and then dried ($Na_2SO_4$) before evaporation under reduced pressure.

### 3.3. Isolation of phenolic compounds

**3.3.1. Oritin-(4α→7, 5→6)-epioritin-4α-ol penta-*O*-methylether triacetate 4.** Methylation of a portion (100 mg) of fraction U, from *A. galpinii*, followed by PLC in benzene–$Me_2CO$ (4:1; ×2; v/v) gave five bands at $R_f$ 0.65 (20.0 mg), 0.42 (8.0 mg), 0.35 (18.0 mg), 0.26 (9.0 mg) and 0.11 (6.0 mg). Acetylation of the $R_f$ 0.42 band followed by PLC in benzene–$Me_2CO$ (9:1; v/v) afforded a main band at $R_f$ 0.39 (6.0 mg) which yielded the title compound **4** as a *white amorphous solid*. (Found: $M^+$, 756.2416. $C_{41}H_{40}O_{14}$ requires M, 756.2418); $\delta_H$ (Table 1); $^{13}C$ NMR ($CDCl_3$, 20°C): $\delta$ 20.9 [*C*$H_3$COO–], 21.1 [*C*$H_3$COO–], 21.5 [*C*$H_3$COO–], 55.7 (×2) [–O*C*$H_3$], 56.9 [–O*C*$H_3$], 61.4 [–O*C*$H_3$], 61.6 [–O*C*$H_3$], 67.3 [3-C(F)], 67.8 [4-C(F)], 71.2 [4-C(C)], 74.8 [3-C(C)], 77.6 [2-C(F)], 79.3 [2-C(C)], 100.2 [6-C(A)], 108.7 [10-C(A)], 113.7 [10-C(D)], 114.1 (×2) [3′,5′-C(B)], 114.2 (×2) [3′,5′-C(E)], 115.5 [5-C(D)], 118.1 [5-C(A)], 125.7 [6-C(D)], 128.0 (×2) [2′,6′-C(E)], 128.1 (×2) [2′,6′-C(B)], 128.8 [1′-C(B)], 129.5 [1′-C(E)], 136.5 [8-C(A)], 137.6 [8-C(D)], 146.5 [9-C(A)], 147.5 [9-C(D)], 148.6 [7-C(D)], 154.6 [7-C(A)], 160.0 [4′-C(B), 160.5 [4′-C(E)], 169.4 [$CH_3$*C*OO–], 170.7 [$CH_3$*C*OO–], 171.2 [$CH_3$*C*OO–]; CD $[\theta]_{240.5}$ 4288, $[\theta]_{246.7}$ 69, $[\theta]_{255.0}$ −33260, $[\theta]_{264.4}$ 32, $[\theta]_{269.7}$ 3711, $[\theta]_{284.7}$ −1526, $[\theta]_{307.5}$ 11140, $[\theta]_{343.4}$ 94; UV $\lambda_{max}$ (MeOH)/nm: 228, 281, 316(sh); IR ($\nu_{max}$/$cm^{-1}$, $CHCl_3$): 1749, 1614, 1515, 1467, 1374, 1248, 1032.

**3.3.2. Epioritin-(4β→7, 5→6)-oritin-4α-ol penta-*O*-methylether triacetate 10.** Acetylation of the $R_f$ 0.26 band followed by PLC in benzene–$Me_2CO$ (9:1; v/v) gave a single band at $R_f$ 0.48 (5.0 mg) which yielded the title compound **10** as a *white amorphous solid*. (Found: $M^+$, 756.2418. $C_{41}H_{40}O_{14}$ requires M, 756.2418); $\delta_H$ (Table 1); $^{13}C$ NMR ($CDCl_3$, 20°C): $\delta$ 21.1 [*C*$H_3$COO–], 21.3 [*C*$H_3$COO–], 21.6 [*C*$H_3$COO–], 55.6 [–O*C*$H_3$], 55.7 [–O*C*$H_3$], 56.8 [–O*C*$H_3$], 61.6 (×2) [–O*C*$H_3$], 66.8 [4-C(C)], 68.3 [3-C(C)], 69.3 [4-C(F)], 71.7 [3-C(F)], 78.4 [2-C(C)], 78.5 [2-C(F)], 99.0 6-C(A)], 107.5 [10-C(A)], 114.1 (×2) [3′,5′-C(B)], 114.5 10-C(D)], 114.8 (×2) [3′,5′-C(E)], 118.0 [5-C(D)], 118.1 [5-C(A)], 125.3 [6-C(D)], 126.3 (×2) [2′,6′-C(B)], 128.4 (×2) [2′,6′-C(E)], 128.6 [1′-C(B)], 129.2 [1′-C(E)], 136.3 [8-C(A)], 137.5 [8-C(D)], 145.7 [9-C(A)], 148.2 [9-C(D)], 148.9 [7-C(D)], 154.7 [7-C(A)], 159.8 [4′-C(B)], 160.0 [4′-C(E)], 169.9 [$CH_3$*C*OO–], 171.2 [$CH_3$*C*OO–], 171.4 [$CH_3$*C*OO–]; CD $[\theta]_{233.6}$ 1628, $[\theta]_{241.7}$ 7, $[\theta]_{254.5}$ 61780, $[\theta]_{270.8}$ 37, $[\theta]_{284.5}$ −1848, $[\theta]_{290.6}$ −1028, $[\theta]_{321.4}$ −5469, $[\theta]_{343.6}$ 3; UV $\lambda_{max}$ (MeOH)/nm: 230, 282, 321(sh); IR ($\nu_{max}$/$cm^{-1}$, $CHCl_3$): 1749, 1617, 1515, 1470, 1374, 1233, 1029.

**3.3.3. Epioritin-(4β→7, 5→6)-epioritin-4α-ol penta-*O*-methylether triacetate 8.** Acetylation of the $R_f$ 0.11 band followed by PLC in benzene–$Me_2CO$ (9:1; v/v) gave a band at $R_f$ 0.42 (4.7 mg) which yielded the title compound **8** as a *brownish amorphous solid*. (Found: $M^+$, 756.2417. $C_{41}H_{40}O_{14}$ requires M, 756.2418; $\delta_H$ (Table 1); $^{13}C$ NMR ($CDCl_3$, 20°C): $\delta$ 20.9 [*C*$H_3$COO–], 21.4 [*C*$H_3$COO–], 21.5 [*C*$H_3$COO–], 55.6 [–O*C*$H_3$], 55.7 [–O*C*$H_3$], 56.8 [–O*C*$H_3$], 61.4 [–O*C*$H_3$], 61.7 [–O*C*$H_3$], 66.8 [4-C(C)], 67.1 [3-C(F)], 67.5 [4-C(F)], 68.3 [3-C(C)], 77.6 [2-C(F)], 78.4 [2-C(C)], 99.0 [6-C(A)], 107.5 [10-C(A)], 113.9 [10-C(D)], 114.2 (×2) [3′,5′-C(B)], 114.8 (×2) [3′,5′-C(E)], 115.8 [5-C(D)], 118.1 [5-C(A)], 126.0 [6-C(D)], 126.3 (×2) [2′,6′-C(B), 128.0 (×2) [2′,6′-C(E)], 128.6 [1′-C(B)], 128.8 [1′-C(E)], 136.6 [8-C(A)], 137.5 [8-C(D)], 145.7 [9-C(A)], 147.8 [9-C(D)], 148.8 [7-C(D)], 154.8 [7-C(A)], 159.9 [4′,C(B)], 160.1 [4′-C(E)], 169.9 [$CH_3$*C*OO–], 170.9 [$CH_3$*C*OO–], 171.4 [$CH_3$*C*OO–]; CD $[\theta]_{233.3}$ 1814, $[\theta]_{237.3}$ −742, $[\theta]_{255.3}$ 111800, $[\theta]_{267.0}$ 69, $[\theta]_{318.0}$ −13550, $[\theta]_{345.7}$ −174; UV $\lambda_{max}$ (MeOH)/nm: 228, 281, 319(sh); IR ($\nu_{max}$/$cm^{-1}$, $CHCl_3$): 1749, 1614, 1515, 1467, 1380, 1251, 1029.

**3.3.4. Oritin-(4β→7, 5→6)-epioritin-4α-ol penta-*O*-methylether triacetate 6.** A portion (100 mg) of fraction T, from *A. galpinii*, was methylated and the mixture separated by PLC in benzene–$Me_2CO$ (4:1; v/v) to give three bands at $R_f$ 0.50 (5.0 mg), 0.43 (7.0 mg) and 0.28 (6.0 mg). Acetylation of the $R_f$ 0.28 band followed by PLC in benzene–$Me_2CO$ (9:1; v/v) afforded one main band at $R_f$ 0.44 (4.2 mg) which yielded the title compound **6** as a *white amorphous solid*. (Found: $M^+$, 756.2417. $C_{41}H_{40}O_{14}$ requires M, 756.2418); $\delta_H$ (Table 1); $^{13}C$ NMR ($CDCl_3$, 20°C): $\delta$ 20.9 [*C*$H_3$COO–], 21.4 [*C*$H_3$COO–], 21.5 [*C*$H_3$COO–], 55.6 [–O*C*$H_3$], 55.7 [–O*C*$H_3$], 57.0 [–O*C*$H_3$], 61.5 [–O*C*$H_3$], 61.7 [–O*C*$H_3$], 67.1 [3-C(F)], 67.5 [4-C(F)], 71.3 [4-C(C)], 71.9 [3-C(C)], 76.5 [2-C(C)], 77.6 [2-C(F)], 99.9 [6-C(A)], 108.5 [10-C(A)], 113.9 [10-C(D)], 114.1 (×2) [3′,5′-C(B)], 114.2 (×2) 3′,5′-C(E)], 115.9 [5-C(D)], 118.3 [5-C(A)], 126.1 [6-C(D)], 128.0 (×2) [2′,6′-C(E)], 128.1 (×2) [2′,6′-C(B)], 128.6 [1′-C(B)], 128.8 [1′-C(E)], 136.7 [8-C(A)], 137.5 [8-C(D)], 146.4 [9-C(A)], 147.8 [9-C(D)], 148.8 [7-C(D)], 154.8 [7-C(A)], 159.9 [4′-C(B)], 160.1 [4′-C(E)], 170.4 [$CH_3$*C*OO–], 170.6 [$CH_3$*C*OO–], 171.3 [$CH_3$*C*OO–]; CD $[\theta]_{237.8}$ −1779, $[\theta]_{240.3}$ 118, $[\theta]_{255.6}$ 59070, $[\theta]_{268.0}$ 91, $[\theta]_{321.1}$ −8867, $[\theta]_{345.8}$ 9; UV $\lambda_{max}$ (MeOH)/nm: 230, 282, 316(sh); IR ($\nu_{max}$/$cm^{-1}$, $CHCl_3$): 1749, 1614, 1515, 1470, 1374, 1233, 1029.

**3.3.5. Epioritin-(4β→5, 3→4)-oritin-4α-ol hexa-*O*-methylether acetate 12.** Methylation of a portion (200 mg) of fraction W, from *A. caffra*, followed by PLC in benzene–$Me_2CO$–EtOAc (7:2:1; v/v) gave five bands at $R_f$ 0.65 (12.6 mg), 0.57 (12.0 mg), 0.47 (13.0 mg), 0.39 (26.0 mg) and 0.19 (6.4 mg). Acetylation of the $R_f$ 0.65 band followed by PLC in benzene–$Me_2CO$ (9:1; ×2, v/v) gave four bands at $R_f$ 0.84 (1.0 mg), 0.76 (4.1 mg), 0.71 (1.1 mg) and 0.57 (1.5 mg). Further PLC purification of the $R_f$ 0.76 band in benzene–$Me_2CO$ (19:1; ×2, v/v) gave a band at $R_f$ 0.43 (2.8 mg) which yielded the title compound **12** as a *white amorphous solid*. (Found: $M^+$, 670.2413. $C_{38}H_{38}O_{11}$ requires M, 670.2414); $\delta_H$ (Table 1); $^{13}C$ NMR ($CDCl_3$, 20°C): $\delta$ 21.4 [*C*$H_3$COO–], 35.0 [4–C(C)], 55.5 [–O*C*$H_3$], 55.7 [–O*C*$H_3$], 56.4 [–O*C*$H_3$], 56.7 [–O*C*$H_3$], 61.3 [–O*C*$H_3$], 61.6 [–O*C*$H_3$], 66.8 [4-C(F)], 72.0 [3-C(C)], 72.7 [3-C(F)], 77.2 [2-C(F)], 79.0 [2-C(C)], 104.5 [6-C(A)], 106.3 [6-C(D)], 111.1 [10-C(D)], 113.9 (×2) [3′,5′-C(E)], 114.5 (×2) [3′,5′-C(B)], 114.6 [10-C(A)], 123.2 [5-C(A)], 126.7 (×2) [2′,6′-C(B)], 128.2 (×2) [2′,6′-C(E)], 129.0 [1′-C(E)], 131.6 [1′-C(B)], 132.3 [5-C(D)], 136.4 [8-C(D)], 136.7 [8-C(A)], 147.3 [9-C(D)], 148.2 [9-C(A)], 152.9 [7-C(A)], 153.4 [7-C(D)], 159.5 [4′-C(B)], 159.7 [4′-C(E)], 170.5 [$CH_3$*C*OO–]; CD $[\theta]_{231.9}$ −2096, $[\theta]_{234.3}$ 63, $[\theta]_{240.4}$ 18470, $[\theta]_{245.4}$ 14, $[\theta]_{248.4}$

−5575, $[\theta]_{254.5}$ 32, $[\theta]_{273.3}$ 6143, $[\theta]_{288.3}$ 6; IR ($\nu_{max}$/cm$^{-1}$, $CHCl_3$): 1743, 1614, 1500, 1461, 1248, 1101, 1029.

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