Oligomeric Flavanoids. Part 28.† Structure and Synthesis of Ether-linked (4-O-3)-Bis-teracacidins, a Novel Class of Naturally Occurring Proanthocyanidins

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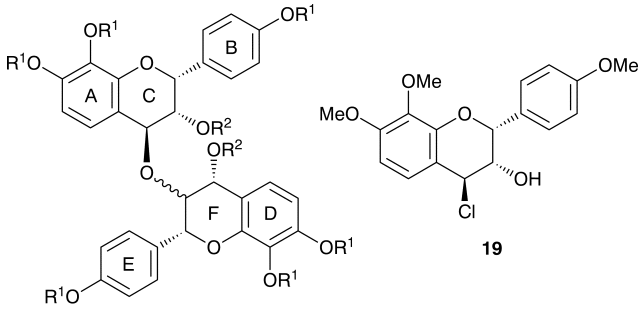
The range of natural dimeric proteracacinidins is extended by identification of the first (4-O-3)-linked bis-teracacidins, epioritin-(4$\beta \rightarrow$3)-epioritin-4α-ol **13** and epioritin-(4$\beta \rightarrow$3)-oritin-4α-ol **16** in the heartwood extract of *Acacia galpinii*.

The predominance of carbon–carbon interflavanyl bonding between C-4 (C-ring) and C-6/C-8 (D-ring) of flavanoid monomeric units in proanthocyanidins is well established.[1] Analogues displaying a single ether bond, presumably generated *via* a two-electron coupling process, are extremely rare and are restricted to two (4-O-4)-linked bis-melacacidins from the heartwood of *Acacia melanoxylon*.[10] Herein we report on the structure and synthesis of epioritin-(4$\beta \rightarrow$3)-epioritin-4α-ol **13** and epioritin-(4$\beta \rightarrow$3)-oritin-4α-ol **16**, representing the first examples of C-4 (C-ring) to C-3 (F-ring) ether-linked proanthocyanidin dimers.

The methanol extract of the heartwood of *Acacia galpinii* comprises a complex mixture of mono- and oligo-meric proteracacinidins. The leucoteracacinidins oritin-4α-ol, epioritin-4α-ol, epioritin-4β-ol and *ent*-oritin-4β-ol are accompanied by the two unique (4-O-3)-linked bis-teracacidins **13** and **16** which were identified as their permethylaryl ether diacetates **15** and **18**. Owing to their importance in the structure elucidation of the oligomers, the structures as well as the relative and absolute configuration of the leucoteracacindins[14] were accurately established *via* ^{1}H NMR and CD data.



13 ≡ , $R^1 = R^2 = H$
15 ≡ , R^1 = Me, R^2 = Ac
16 ≡ , $R^1 = R^2 = H$
18 ≡ , R^1 = Me, R^2 = Ac

Analysis of the ^{1}H NMR data of each of the proteracacinidin permethylaryl ether diacetates **15** and **18** indicated the presence of two AB and two AA′BB′ spin systems for aromatic protons, two AMX three spin systems for heterocyclic ring protons, six *O*-methyl and two *O*-acetyl resonances. The different spin systems as well as the connectivities between heterocyclic and aromatic ring protons were readily defined with a 2D COSY experiment. When taken in conjunction with the absence of benzylic F-ring methylene protons reminiscent of C-4 → C-6/C-8 linked bis-flavan-3-ols,[15] the ^{1}H NMR data collectively indicated dimeric structures [FAB-MS: molecular formula, $C_{40}H_{42}O_{13}$ (*m*/*z* 730)] with an interflavanyl ether bond connecting the heterocyclic rings for both derivatives **15** and **18**. A (4-O-3) mode of linkage was evident by comparison of the chemical shifts of the 3- and 4-H resonances of both the C- and F-rings with those of the same protons in the tri-*O*-methyl-3,4-di-*O*-acetyl derivatives of appropriate flavan-3,4-diols, *e.g.* epioritin-4β-ol, and by some key NOE associations using the heterocyclic ring protons as reference signals.

Coupling constants for the AMX spin systems of the C-ring protons ($J_{2,3} = 1.5$; $J_{3,4} = 3.0$ Hz for both **15** and **18**) indicated 2,3-*cis*-3,4-*trans* relative configuration[17,18] for these rings, whereas those for the second AMX system ($J_{2,3} = 1.0$; $J_{3,4} = 4.0$ Hz for **15**; $J_{2,3} = 8.5$; $J_{3,4} = 7.0$ for **18**) were reminiscent of 2,3-*cis*-3,4-*cis* and 2,3-*trans*-3,4-*trans* relative configurations for compounds **15** and **18**, respectively. The CD spectra of the proteracacinidin derivatives exhibited strong Cotton effects near 270 (negative for both **15** and **18**), 240 (negative for both **15** and **18**) and 220 nm (positive for **15**, negative for **18**). These could be correlated with 2*R*,3*R*,4*S* (C-ring): 2*R*,3*R*,4*R* (F-ring) and 2*R*,3*R*,4*S* (C): 2*R*,3*R*,4*R* (F) absolute configuration for the novel proteracacinidins **13** and **16**, respectively, once derivative **18** became available *via* synthesis from the appropriate flavan-3,4-diol precursors of known absolute configuration.

Owing to the susceptibility of the C-4β benzylic ether functionality in *e.g.* compound **16** to solvolysis in aqueous acidic medium,[10] the conditions usually employed to establish the C-4 → C-6/C-8 interflavanyl bond[15] would be less suitable for generating the crucial C–O–C linkage. The formation of the ether bond and hence the synthesis of the proteracacinidin biflavanoid derivative **18** near neutral pH was affected by transforming epioritin-4α-ol tri-*O*-methyl ether quantitatively into (2*R*,3*S*,4*S*)-4-chloro-3-hydroxy-7,8,4′-trimethoxyflavan **19** with thionyl chloride. Subsequent coupling of **19** with oritin-4α-ol tri-*O*-methyl ether in anhydrous THF followed by acetylation afforded the permethylaryl ether diacetate **18** (15.4% yield) of the epioritin-(4$\beta \rightarrow$3)-oritin-4α-ol **16** with ^{1}H NMR and CD data identical to those of the same derivative of the natural product from *A. galpinii*.

The co-occurrence of the novel ether-linked proanthocyanidins **13** and **16** and their carbon–carbon coupled analogues in *A. galpinii*[17] presumably reflects the poor nucleophilicity of the pyrogallol A-ring monomeric precursors, hence permitting alternative centres to participate in interflavanyl bond formation.

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†For Part 27, see P. J. Steynberg, R. J. J. Nel, H. van Rensburg, B. C. B. Bezuidenhoudt and D. Ferreira, *Tetrahedron*, 1998, in press.

Techniques used: ^{1}H NMR, FAB-MS, CD

References: 22

Table 1: ^{1}H NMR data of teracacidin-type flavan-3,4-diols

Table 2: ^{1}H NMR data of (4-O-3)-linked proteracacinidin derivatives **15** and **18**

Schemes: 1

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