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# Oligomeric Flavanoids, Part 29<sup>‡</sup>: Structure and Synthesis of Novel Ether-linked [4-O-4] Bis-teracacinidins

Johan Coetzee, Elfranco Malan\* and Daneel Ferreira\*

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

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Abstract: The rare series of proteracacinidin-type oligoflavanoids is extended by identification of two novel [4-O-4] ether-linked analogues 7 and 10 from the heartwood of *Acacia galpinii*. Their structures and absolute configuration were established *via* spectroscopic methods and by stereoselective synthesis from the appropriate leucoteracacinidin flavan-3,4-diol precursors. © 1998 Elsevier Science Ltd. All rights reserved.

Proanthocyanidins possessing ether-type interflavanyl linkages are extremely rare except for the A-type oligomers which contain the conventional C<sub>4</sub> (C-ring) $\rightarrow$ C<sub>6</sub>/C<sub>8</sub> (D-ring) bond as well as an additional ether linkage connecting C<sub>2</sub> (C-ring) and C<sub>5</sub>/C<sub>7</sub> (D-ring).<sup>1,2</sup> Analogues which possess exclusive ether bonds are hitherto restricted to the 1,4-dioxane-type profisetinidins from *Acacia mearnsii*,<sup>3,4</sup> the recently reported (4 $\rightarrow$ 7:5 $\rightarrow$ 6) doubly-linked proteracacinidin from *A. caffra*,<sup>5</sup> two (C<sub>4</sub>-O-C<sub>3</sub>)-proteracacinidins from *A. galpinii*<sup>6</sup> as well as two (C<sub>4</sub>-O-C<sub>4</sub>)-promelacacinidins from *A. melanoxylon*.<sup>7</sup> No attempt was made to synthesise the latter compounds or to establish their absolute stereochemistry. We now describe the structure and synthesis of two novel (C<sub>4</sub>-O-C<sub>4</sub>)-linked proteracacinidins from *A. galpinii*, representing only the third and fourth members of the class of proanthocyanidins exhibiting this mode of interflavanyl coupling.

## **RESULTS AND DISCUSSION**

In addition to the four leucoteracacinidins, oritin-4 $\alpha$ -ol, epioritin-4 $\alpha$ -ol 1, epioritin-4 $\beta$ -ol and ent-oritin-4 $\alpha$ ol 4, and the (C4-O-C3)-linked proteracacinidins, epioritin-(4 $\beta$ - $\rightarrow$ 3)-epioritin-4 $\alpha$ -ol and epioritin-(4 $\beta$ - $\rightarrow$ 3)oritin-4 $\alpha$ -ol described in Part 28,<sup>6</sup> the methanol extract of the heartwood of *A. galpinii* also contains two novel (C<sub>4</sub>-O-C<sub>4</sub>)-coupled proteracacinidins, *ent*-oritin-(4 $\alpha$ - $\rightarrow$ 4)-epioritin-4 $\alpha$ -ol 7 and epioritin-(4 $\beta$ - $\rightarrow$ 4)-epioritin-4 $\alpha$ ol 10. Owing to the complexity of the phenolic mixture the dimers 7 and 10 were identified as their hexamethyl ether diacetate derivatives 9 and 12, the additional chromatographic steps offered by derivatization being a prerequisite for sample purity.

<sup>&</sup>lt;sup>‡</sup>Part 28 is reference 6



The <sup>1</sup>H NMR data (Table) of derivatives 9 and 12 indicated the presence of two AB- and two AA'BB'spin systems for aromatic protons as well as two AMX-systems for protons of the heterocyclic rings hence indicating the dimeric nature of both compounds. Differentiation of the spin systems and the connectivities between aromatic and heterocyclic protons were effected with 2D COSY experiments. The presence of six *O*-methyl and two *O*-acetyl resonances as well as FAB-MS data, indicating a molecular ion at m/z 730 reminiscent of a molecular formula  $C_{40}H_{42}O_{13}$  for both compounds strongly suggested an ether-type interflavanyl linkage.

Application of the shielding phenomenon observed for 4-H(C) of the ABC chain extender unit of oligomeric proanthocyanidins relative to the chemical shifts of the same proton in the 3,4-di-O-acetyl derivative of the flavan-3,4-diol precursor,<sup>7-10</sup> indicated a C<sub>4</sub>-O-C<sub>4</sub> ether bond [4-H(C),  $\delta$  4.91, 4.73 for 9 and 12, respectively: 4-H(F),  $\delta$  5.13, 5.32 for 9 and 12, resp.: 4-H(C),  $\delta$  6.33, 5.43 for diacetates 3 and 6, resp., and  $\delta$  5.90 for the C-4 epimer of 3].<sup>6</sup> The chemical shifts of the 3-H resonances of both the C- and F-rings of derivatives 9 and 12 (*cf.* Table) are reminiscent of methine hydrogens of an O-acetyl substituted carbon, hence supporting the ether linkage involving C-4(C) of both flavanyl constituent units.

Prominent  ${}^{4}J_{HH}$  couplings, evident in the 2D COSY spectra of 9 and 12, between 2-H(C) ( $\delta$  5.65, 5.50 for 9 and 12, resp.) and 2',6'-H(B) ( $\delta$  7.37, 7.46 for 9 and 12, resp.), as well as between 2-H(F) ( $\delta$  5.29, 5.36 for 9 and 12, resp.) and 2',6'-H(E) ( $\delta$  7.43, 7.44 for 9 and 12, resp.) differentiated the AA'B'B' spin systems of the constituent flavanyl units. The A/C- and D/F-ring junctions were respectively connected *via* the observed benzylic coupling of 5-H(A) ( $\delta$  6.98, 7.10 for 9 and 12, resp.) with 4-H(C) ( $\delta$  4.91, 4.73 for 9 and 12, resp.) and of 5-H(D) ( $\delta$  6.84, 6.97 for 9 and 12, resp.) with 4-H(F) ( $\delta$  5.13, 5.32 for 9 and 12, resp.).

Table <sup>1</sup>H NMR peaks ( $\delta_{\rm H}$ ) of proteracacinidin derivatives 9 and 12 and the 4-chloroflavan-3-ol derivative 13 in CDCl<sub>3</sub> at 300 MHz (296K). Splitting patterns and J values (Hz) are given in parentheses.

Ring	Proton	9	12	13
A	5	6.98(d,8.5)	7.10(d,8.5)	7.10(d,9.0)
	6	6.59(d,8.5)	6.67(d,8.5)	6.66(d,9.0)
В	2',6'	7.37(d,9.0)	7.46(d,9.0)	7. <b>51(d,</b> 9.0)
	3',5'	6.89(d,9.0)	6.94(d,9.0)	7.01( <b>d</b> ,9.0)
с	2	5.65(d,10.5)	5.50(br s,1.5)	5.56(br s,1.0)
	3	5.34(dd,10.5,2.5)	5.27(dd,1.5,3.0)	4.26(dd,1.0,2.5)
	4	4.91(d,2.5)	4.73(d,3.0)	5.12(d,2.5)
D	5	6.84(d,9.0)	6.97(d,9.0)	-
	6	6.53(d,9.0)	6.58(d,9.0)	-
E	2',6'	7.43(d,9.0)	7.44(d,9.0)	-
	3',5'	6.94(d,9.0)	6.92(d,9.0)	•
F	2	5.29(br s,1.0)	5.36(br s,1.0)	-
	3	5.76(dd,1.0,4.0)	5.85(dd,1.0,4.0)	-
	4	5.13(d,4.0)	5.32(d,4.0)	•
ОМе		3.83,3.84,3.85,3.88	3.83,3.84,3.87,3.90	3.86,3.90,3.92,
		(x2),3.91 (each s)	, 3.93,3.95 (each s)	(each s)
OA¢		1.86,1.97 (each s)	1.85,1.98 (each s)	

The coupling constants of the two heterocyclic ring systems  $[J_{2,3(C)} = 10.5, 1.5; J_{3,4(C)} = 2.5, 3.0 \text{ Hz for 9}$ and 12 resp.:  $J_{2,3(F)} = 1.0; J_{3,4} = 4.0 \text{ Hz for both 9 and 12}$  indicated 2,3-*trans*-3,4-*cis*(C): 2,3-*cis*-3,4-*cis*(F) and 2,3-*cis*-3,4-*trans*(C): 2,3-*cis*-3,4-*cis*(F) relative configurations for the proteracacinidin derivatives 9 and 12, resp.<sup>5,10,11</sup> In both compounds a strong NOE association was observed between 2- and 4-H(F) which confirmed the 2,4-*cis* relative configurations of the DEF constituent units. By the same token the conspicuous absence of NOE association between 2- and 4-H(C) in both derivatives was interpreted as confirmation of the 2,4-*trans* relative configuration of the ABC moieties.

A phase sensitive NOESY experiment of derivative 9 showed associations of 5-H(D) with 5-H(A), 2-H(C) and 4-H(C), of 5-H(A) with 3-H(F), 4-H(F) and 5-H(D) and of 4-H(C) with 4-H(F). The same experiment using derivative 12 indicated association of both 5-H(A) and 4-H(C) with 3-H(F), 4-H(F) and

5-H(D), as well as of 5-H(D) with 2- and 3-H(C). Collectively these NOE effects are only reconcilable with  $C_4$ -O- $C_4$  interflavanyl linkages for both derivatives 9 and 12 of the novel proteracacinidin dimers 7 and 10.

The CD spectra of the proteracacinidin derivatives 9 and 12 exhibited strong Cotton effects near 275 (positive and negative for 9 and 12, resp.), 240 (- for both 9 and 12), 225 (+ and - for 9 and 12, resp.) and 220 nm (- and + for 9 and 12 resp.). The aromatic quadrant rule<sup>12</sup> is a powerful probe for establishing the absolute configuration at C-4 of 'conventional'  $C_4 \rightarrow C_6/C_8$  coupled dimeric proanthocyanidins<sup>8,13,14</sup> but it cannot be used to the same effect for ether linked analogues. The CD data were only useful in a comparative capacity when derivatives 9 and 12 were also available via synthesis using flavan-3,4-diol precursors with established absolute configurations at C-2 and -3.

It was anticipated that the C-4 benzylic ether bonds in the proteracacinidins 7 and 10 would be highly susceptible to solvolysis in aqueous acidic medium. These conditions,<sup>8</sup> which have been applied universally for the formation of  $C(sp^3) \rightarrow C(sp^2)$  interflavanyl linkages, would thus be less applicable to the formation of the ether linkage in compounds 7 and 10. We thus opted to activate the eletrophilic attributes of one of the flavan-3,4-diols *via* formation of the 4-chloroflavan-3-ol derivative 13 in order to permit the formation of the crucial ether bond at near a neutral pH value.



Scheme: Synthesis of the C<sub>4</sub>-O-C<sub>4</sub> proteracacinidin derivatives 9 and 12: *Reagents and conditions*: i, SOCl<sub>2</sub>/THF; ii, flavan-3,4-diol derivative 5, then  $K_2CO_3$ ; iii, flavan-3,4-diol derivative 2, then  $K_2CO_3$ ; iv, Ac<sub>2</sub>O/pyridine.

Synthesis of the proteracacinidin derivatives 9 and 12 (Scheme) hence involved the initial conversion of epioritin-4 $\alpha$ -ol tri-*O*-methylether 2 into the 4 $\beta$ -chloroflavan-3-ol derivative 13 in quantitive yield using thionyl chloride in dry THF. Addition of a solution of a two molar excess of *ent*-oritin-4 $\alpha$ -ol tri-*O*-methylether 5 in dry THF as the potential flavanyl-*O*-nucleophile followed by the immediate addition of anhydrous potassium carbonate then afforded a mixture comprising the epioritin-4 $\alpha$ -ol and unchanged *ent*-oritin-4 $\alpha$ -ol derivatives 3 and 6, and the *ent*-oritin-(4 $\alpha$ -4)-epioritin-4 $\alpha$ -ol hexa-*O*-methylether diacetate 9 (14.9% yield) following separation by PLC and acetylation. A similar procedure using epioritin-4 $\alpha$ -ol tri-*O*-methylether 2 as the nucleophile, gave epioritin-(4 $\beta$ -4)-epioritin-4 $\alpha$ -ol hexa-*O*-methylether diacetate 12 (23.7% yield). The <sup>1</sup>H NMR, CD and MS data of derivatives 9 and 12 were identical to those of the same derivatives of the novel (C<sub>4</sub>-O-C<sub>4</sub>) coupled proteracacinidins 7 and 10 from *A. galpinii*. Unequivocal definition of

 $2S_{3R},4R(C):2R_{3R},4R(F)$  absolute configuration for 7 and  $2R_{3R},4S(C):2R_{3R},4R(F)$  for 10 then followed from the known absolute stereochemistry of flavan-3,4-diol precursors 1 and 4 which had been meticulously established in Part 28.<sup>6</sup>

The stereoselective coupling of the  $4\beta$ -chloroflavan-3-ol derivative 13 and epioritin-4 $\alpha$ -ol tri-Omethylether 2 to give the (C<sub>4</sub>-O-C<sub>4</sub>)-bis-epioritin derivative 11 with retention of the C-4 configuration of the electrophilic precursor 13, may be explained in terms of a neighbouring group mechanism involving intramolecular displacement of the *quasi*-axial C-4 chloro nucleofuge by the axial C-3 hydroxyl group.<sup>15</sup> The transient protonated epoxide 14 then permits preferential attack of the nucleophilic C-4 hydroxyl group of the epioritin-4 $\alpha$ -ol derivative 2 from the less hindered  $\beta$ -face resulting in a highly stereoselective coupling step.

The retention of configuration at C-4 of the 4 $\beta$ -chloroflavan-3-ol electrophile 13 during formation of the epioritin-(4 $\beta$ ->4)-epioritin-4 $\alpha$ -ol derivative 11 is in agreement with the stereochemical course of the coupling of 13 and oritin-4 $\alpha$ -ol tri-O-methylether *via* participation of C<sub>3</sub>-OH (Part 28).<sup>6</sup> We anticipated that coupling of 13 and the *ent*-oritin-4 $\alpha$ -ol derivative 5 would also proceed *via* the neighbouring group mechanism. The rather unexpected formation of the 4 $\alpha$ -ether bond (F-ring) in 8, *i.e.* with inversion of configuration at C-4 of the 4 $\beta$ -chloroflavan-3-ol 13, presumably reflects reaction conditions incapable of triggering the neighbouring group mechanism hence resulting in an S<sub>N</sub>2-type mechanism which requires the approaching hydroxyl nucleophile to force out the nucleofugal chloride. The requisite alignment for such a concerted process may be facilitated by mutual hydrogen bonding of the C-3 hydroxyl groups of both 5 and 13 which is effectively permitted by the *axial* C-4 hydroxyl group of flavan-3,4-diol 5 compared to the equatorial orientation of the same functionality in nucleophile 2. In addition, unfavourable 1,3-diaxial interaction between H-2 *ax* of a putative oxirane of type 14 and the approaching nucleophile 5 would not favour a neighbouring group



mechanism. The stereochemical course of the coupling steps in the formation of the dimeric proteracacinidins 8 and 11 (Scheme) must, incidentally, closely resemble the biosynthetic process leading to 7 and 10 where the same flavan-3,4-diols 4 and 1 with their respective *axial* and *equatorial* C-4 hydroxyl groups presumably serve as the nucleophilic flavanyl units. The formation of the all-*cis*-flavan-3,4-diol derivative 2 in the

coupling reaction of the 4 $\beta$ -chloro-flavan-3-ol 13 and the *ent*-oritin-4 $\alpha$ -ol derivative 5 is explicable in terms of solvolysis of the former compound during workup and chromatography. Inversion of configuration is effected by intermolecular hydrogen bonding between the *axial* C-3 hydroxyl group and water hence permitting S<sub>N</sub>2 displacement of chloride.

The co-occurrence of the ether-linked proteracacinidins 7 and 10 in the heart-wood of *A. galpinii* in addition to some carbon-carbon bonded analogues, is a further manifestation of the much reduced nucleophilicity of the pyrogallol A-ring which permits other centres to participate in the formation of interflavanyl bonds.

#### **EXPERIMENTAL**

<sup>1</sup>H NMR Spectra were recorded on a Bruker AM-300 spectrometer for solutions as indicated, with Me<sub>4</sub>Si as internal standard. FAB Mass spectra were recorded on a VG 70-70E instrument with a VG 11-250J data system and an iontech saddlefield FAB gun. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF<sub>254</sub>, 0.25 mm) and the plates were sprayed with H<sub>2</sub>SO<sub>4</sub>-HCHO (40:1, v/v) after development. Preparative plates (PLC) [20x20 cm, Kieselgel PF<sub>254</sub> (1.0 mm)] were air dried and used without prior activation. Methylations were performed with an excess of diazomethane in MeOH-diethyl ether over a period of 48h at -15 °C, while acetylations were conducted in acetic anhydride-pyridine at ambient temperature. Evaporations were done under reduced pressure at ambient temperature in a rotary evaporator.

The extraction of the heartwood of A. galpinii and fractionation using a Craig contercurrent distribution to give the three fractions A (59.3 g), B (70.8 g) and C (27.3 g), and the separation of a portion (25 g) of fraction B using Sephadex LH-20 in EtOH, affording fractions A-Z were described in Part  $28^6$  and need not be repeated.

Ent-oritin-(4 $\alpha$ ->4)-epioritin-4 $\alpha$ -ol hexa-O-methylether diacetate 9. A portion (80 mg) of fraction K was methylated and the mixture separated by PLC in hexane-C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO-MeOH (40:40:13:7, v/v) to give four bands at R<sub>F</sub> 0.53 (28 mg), 0.70 (12 mg), 0.76 (6 mg) and 0.86 (3 mg). The quantities and complexity of the R<sub>F</sub> 0.70, 0.76 and 0.86 did not merit further investigation. Acetylation of the R<sub>F</sub> 0.53 band followed by PLC in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (97:3, v/v, x4) afforded a band at R<sub>F</sub> 0.44 (12 mg). Further purification by PLC in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (97:3, v/v, x4) afforded a band at R<sub>F</sub> 0.44 (12 mg). Further purification by PLC in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO-MeOH (47:46:5:2, v/v) gave the title compound 9 (R<sub>F</sub> 0.46, 5 mg) as white amorphous solid. (Found: M<sup>+</sup>, 730.2705. C<sub>40</sub>H<sub>42</sub>O<sub>13</sub> requires M, 730.2704);  $\delta_{\rm H}$  (Table); CD [ $\theta$ ]<sub>280.5</sub> 1830, [ $\theta$ ]<sub>245</sub> -2838, [ $\theta$ ]<sub>235.8</sub> 3429, [ $\theta$ ]<sub>225.4</sub> 17970, [ $\theta$ ]<sub>218.2</sub> -8651 and [ $\theta$ ]<sub>211.7</sub> 8434.

Epioritin-(4 $\beta$ →4)-epioritin-4 $\alpha$ -ol hexa-O-methylether diacetate 12. A portion (100 mg) of fraction M was methylated and subjected to the same procedure of separation and purification as for compound 9. The first separation gave band M-3 (R<sub>F</sub> 0.31, 21 mg) which was acetylated and purified as above to give the title compound 12 (R<sub>F</sub> 0.42, 9 mg) as a white amorphous solid. (Found: M+, 730.2706. C<sub>40</sub>H<sub>42</sub>O<sub>13</sub> requires M,

730.2704);  $\delta H$  (Table); CD [ $\theta$ ]<sub>274.2</sub> -3976, [ $\theta$ ]<sub>241</sub> -14370, [ $\theta$ ]<sub>228.6</sub> -4458, [ $\theta$ ]<sub>221.9</sub> 13560, [ $\theta$ ]<sub>213.1</sub> 6262 and [ $\theta$ ]<sub>206</sub> 20300.

(2R,3S,4S)-2,3-cis-3,4-trans-4-chloro-3-hydroxy-7,8,4'-trimethoxyflavan 13. Epi-oritin-4 $\alpha$ -ol tri-Omethylether 2 (50 mg) was dissolved in dry THF (10 ml) and treated with 1.2 equivalents of SOCl<sub>2</sub> (0.013 ml) under an N<sub>2</sub>-atmosphere at room temperature for 10 min. The solvent was removed under vacuum to give the 4-chloroflavan-3-ol derivative 13 in quantative yield;  $\delta_{\rm H}$  (Table).

## Synthesis of the C<sub>4</sub>-O-C<sub>4</sub> proteracacinidin derivatives 9 and 12.

Ent-Oritin-( $4\alpha \rightarrow 4$ )-epioritin- $4\alpha$ -ol hexa-O-methylether 8. Ent-oritin- $4\alpha$ -ol tri-O-methylether 5 (100 mg) was dissolved in dry THF (10 ml) and added to the chlorinated product 13. Anhydrous K<sub>2</sub>CO<sub>3</sub> (250 mg) was added immediately. The mixture was stirred under nitrogen for 12h at 22<sup>o</sup>C and a further 2h at 40<sup>o</sup>C. The K<sub>2</sub>CO<sub>3</sub> was removed and the reaction volume was reduced under vacuum. PLC separation in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (4:1, v/v) gave three main bands at R<sub>F</sub> 0.33 (12 mg), 0.31 (53 mg) and 0.27 (9.6 mg). Bands R<sub>F</sub> 0.31 and 0.27 yielded *ent*-oritin- $4\alpha$ -ol tri-O-methylether 5 and epioritin- $4\alpha$ -ol tri-O-methylether 2 respectively.

*Ent*-oritin-(4 $\alpha$ ->4)-epioritin-4 $\alpha$ -ol hexa-O-methylether diacetate 9. Acetylation of the R<sub>F</sub> 0.33 band followed by purification by PLC in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (9:1, v/v) yielded the title compound (R<sub>F</sub> 0.46, 10 mg) as an amorphous solid;  $\delta_{\rm H}$  (CDCl<sub>3</sub>) (Table); M<sup>+</sup>, 730.2704, C<sub>40</sub>H<sub>42</sub>O<sub>13</sub> requires M<sup>+</sup>, 730.2704; CD data were in accordance with those of the same derivative of the natural product.

Epioritin-( $4\beta \rightarrow 4$ )-epioritin- $4\alpha$ -ol hexa-O-methylether 11. The procedure and the quantities used were the same as for compound 8 but for epioritin- $4\alpha$ -ol tri-O-methylether 2 was used as nucleophile. PLC separation of the reaction mixture in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (4:1, v/v) gave two bands at R<sub>F</sub> 0.43 (20 mg) and 0.27 (56 mg). The band at R<sub>F</sub> 0.27 was identified as epioritin- $4\alpha$ -ol tri-O-methylether 2.

Epioritin-(4 $\beta$ →4)-epioritin-4 $\alpha$ -ol hexa-O-methylether diacetate 6. Acetylation of the band at R<sub>F</sub> 0.43 and subsequent PLC separation in C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (9:1, v/v) yielded the title compound (18 mg, R<sub>F</sub> 0.51) as an *amorphous solid*.  $\delta_{\rm H}$  (CDCl<sub>3</sub>) (Table), M<sup>+</sup>, 730.2704, C<sub>40</sub>H<sub>42</sub>O<sub>13</sub> requires M<sup>+</sup>, 730.2704; CD data were in accordance with those of the same derivative of the natural product.

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