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Review

# Heterogeneity of the interflavanyl bond in proanthocyanidins from natural sources lacking C-4 (C-ring) deoxy flavonoid nucleophiles

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**Abstract**

The proanthocyanidin pool in the floral kingdom usually involves the presence of carbon–carbon bonds linking predominantly flavan-3-ol constituent moieties. Such an ensemble of flavan-3-ol units originates via electrophilic aromatic substitution of flavan-4-yl carbocations (or their equivalents) derived from flavan-4-ols and/or flavan-3,4-diols and the nucleophilic centers of the m-oxygenated A-rings of flavan-3-ol nucleophiles. In the absence of these potent flavan-3-ol nucleophiles with their aptitude for the formation of carbon–carbon bonds, alternative centers emerge as participants in interflavanyl bond formation. Such a phenomenon is demonstrated for the distribution of various profisetinidin-, prorobinetinidin-, proguibourtinidin-, promelacacinidin- and proteracacinidin-type pro- and leuco-anthocyanidins in several southern hemisphere heartwood species.


*Keywords:* *Acacia caffra*; *Acacia fasciculifera*; *Acacia galpinii*; *Acacia mearnsii* (black wattle); *Acacia melanoxylon*; *Burkea africana*; *Colophospermum mopane*; *Guibourtia coleosperma*; *Nelia meyeri*; *Peltophorum africanum*; *Prosopis glandulosa*; *Robinia pseudacacia*; Leguminosae; Aizoaceae; Proanthocyanidins; Leucoanthocyanidins; Proteracacinidins; Promelacacinidins

**Contents**



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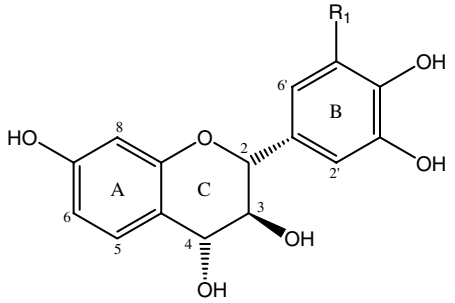
## 1. Introduction

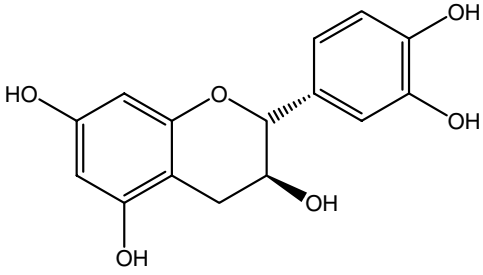
The predominance of carbon–carbon interflavanoid bonding between C-4 (C-ring) of electrophilic flavan-4-ol and/or flavan 3,4-diol units and C-6/C-8 of nucleophilic flavan-3-ol moieties in naturally occurring proanthocyanidins is well documented (Porter, 1988, 1994; Hemingway, 1989; Ferreira and Bekker, 1996; Ferreira and Li, 2000; Ferreira and Slade, 2002). However, in the 'absence' of potent flavan-3-ol nucleophiles, incipient flavan-4-yl carbocations in the biosynthetic pathway leading to the proanthocyanidins are often quenched by non-flavan-3-ol nucleophiles not only via carbon–carbon but also via carbon–oxygen linkages. This culminates in a remarkable variety of nucleophilic centers participating in interflavanyl bond formation, hence leading to the genesis of a vast array of proanthocyanidin prototypes. Their taxonomic distribution, structure elucidation and, where applicable, synthesis are discussed here.

## 2. Dioxane-linked leucofisetinidins and profisetinidins/prorobinetinidins with flavan-3,4-diol terminal units

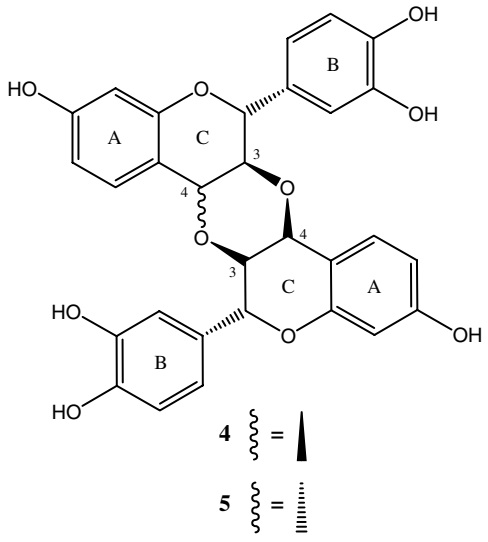
Besides the A-type proanthocyanidins with their unusual second ether linkage between an A-ring hydroxyl group of the bottom unit to C-2 of the T-unit (Ferreira and Slade, 2002), the ether-linked proanthocyanidins were until recently of rare natural occurrence. The heartwood of *Acacia mearnsii* De Wild (black wattle) is chemically unique in that it contains a preponderance of the flavan-3,4-diol, fisetinidol-4α-ol **1** [(+)-mollisacacidin or (+)-leucofisetinidin], but also the 'absence' of free (+)-catechin **3** which serves as a powerful nucleophile in initiating bi- and tri-flavanoid formation (Botha et al., 1981a). Considering this apparently atypical environment of potential proanthocyanidin precursors, it is not surprising that evidence of self-condensation of the flavan-3,4-diol was previously obtained via the isolation of two dioxane-linked leucofisetinidins **4** and **5** (Drewes and Ilsley, 1969; Young et al., 1983), as well as four dimeric profisetinidins **6**–**9** (Drewes et al., 1967; Viviers et al., 1982) and a trimeric analog **10** (Viviers et al., 1982) with flavan-3,4-diol terminal units.




**1** $R_1 = H$
**2** $R_1 = OH$



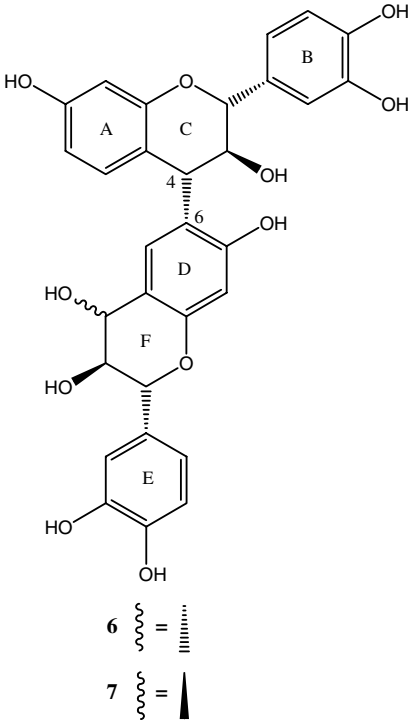

**3**

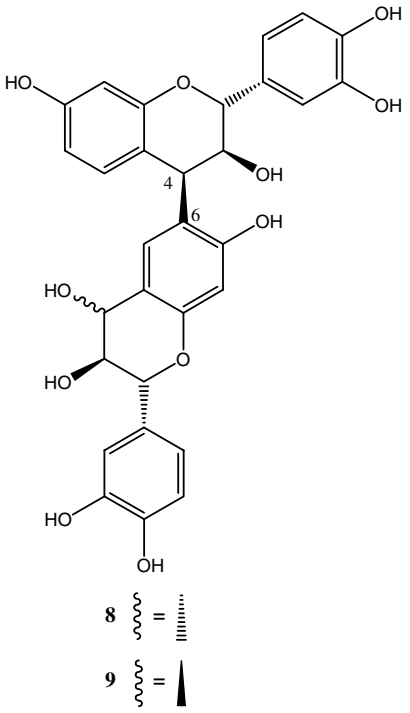


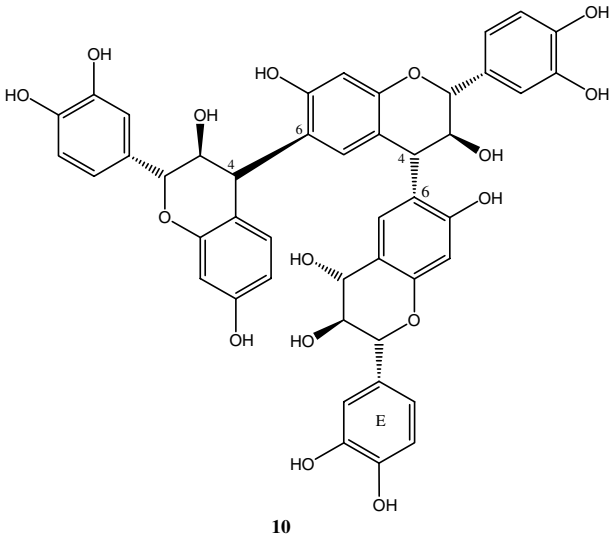

The dioxane-linked leucofisetinidins comprised the fisetinidol-(3 → 4β:4β → 3)-fisetinidol-4β-ol **4** and its C-4 (C) epimer **5**. Compound **4** possesses a C2 axis of symmetry and thus displayed a $^{1}$H NMR spectrum very similar to that of the parent flavan-3,4-diol, fisetinidol-4β-ol. The structures and absolute configurations of bis-leucofisetinidins **4** and **5**, as well as their presumed biogenetic relationship with the flavan 3,4-diol fisetinidol-4α-ol **1** were confirmed by self-condensation of the phenolic tri-*O*-methyl ether of **1** under acidic conditions (Young et al., 1983).

The heartwood of *A. meansii* was also the source of the first proanthocyanidins with a flavan-3,4-diol terminal unit. These compounds comprised the fisetinidol-(4α → 6)-fisetinidol-4α- and 4β-ols **6** and **7**, the fisetinidol-(4β → 6)-fisetinidol-4α- and 4β-ols **8** and **9** (Drewes et al., 1967; Viviers et al., 1982), and the trimeric fisetinidol-(4β → 6)-fisetinidol-(4α → 6)-fisetinidol-4α-ol **10** (Viviers et al., 1982). The C-4 (F) epimeric analogs **8** and **9** were also isolated from *Acacia fasciculifera* (Benth.) (Van Heerden et al., 1981).

In the heartwood of *Robinia pseudacacia* L., the flavan-3,4-diol, robinetinidol-4α-ol (leucorobinetinidin) **2**, as incipient electrophile for prorobinetinidin biosynthesis, co-exists with a variety of monomeric flavanoids (Roux and Paulus, 1962) as potential nucleophiles. These monomers, predominated by analogs with resorcinol A- and pyrogallol-type B-rings, however invariably exhibit C-4 oxygenation which reduces the nucleophilicity of their A-rings compared to that of the corresponding functionality in the C-4 deoxy compound, e.g. catechin **3**. *R. pseudacaccia* therefore represents a unique metabolic pool where oligomer formation occurs via the action of the very potent electrophile **2** (Viviers et al., 1982) on flavanyl moieties apparently lacking the nucleophilicity that is associated with natural sources in which proanthocyanidin formation is paramount. Amongst a variety of unique dimeric prorobinetinidins, robinetinidol-(4β → 6)-robinetinidol-4α- and 4β-ols **11** and **12**, and robinetinidol-(4α → 2′)-robinetinidol-4α- and 4β-ols **13** and **14** presumably originated via self-condensation of leucorobinetinidin **2** (Coetzee et al., 1995). Related compounds from the same source will be dealt with in Section 5.

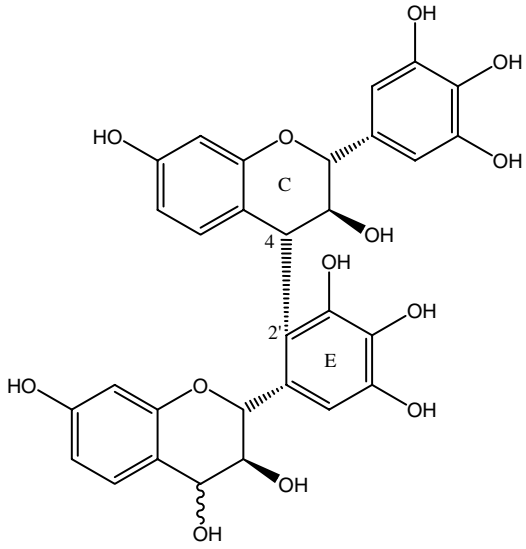




**10**

A plethora of promelacacinidins and proteracacinidins with flavan-3,4-diol terminal units will be discussed in Section 6.

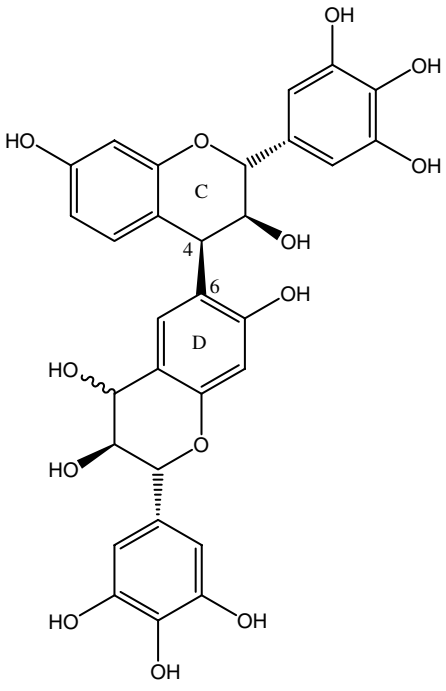


**13** = ⦚

**14** = ▲

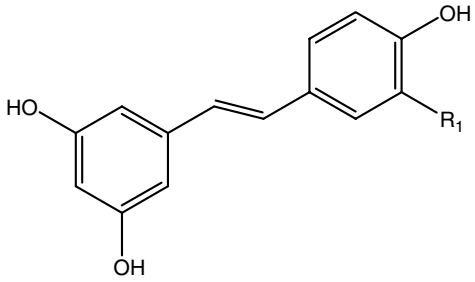
## 3. Proguibourtinidins with stilbene terminal units

In addition to a large number of conventional proguibourtinidins, profisetinidins and related analogs (Steynberg et al., 1990; Bonnet et al., 1996), the heartwood of the large false mopane, *Guibourtia coleosperma* (Benth.) J. Léonard, also contains the first proguibourtinidins with stilbenoid constituent units (Steynberg et al., 1983, 1987). These bi- and tri-flavanoids are uniquely based on nucleophilic *E*-3,3′,4,5′-tetrahydroxy- and 3′,4,5′-trihydroxy-stilbenes **15** and **16** and potentially electrophilic leucoguibourtinidins **17**–**20**, and comprised the guibourtinidol-(4α → 2)-tetrahydroxystilbene **21**, epiguibourtinidol-(4β → 2)-tetrahydroxystilbene **22**, and the trimeric analogs **23**–**25**.



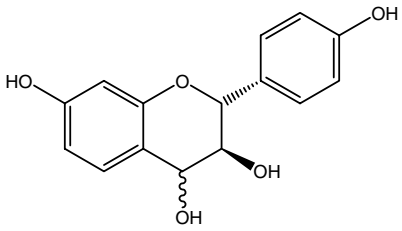
**11** = ⦚

**12** = ▲



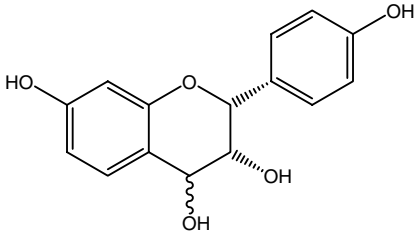
**15** $R_1 = OH$

**16** $R_1 = H$



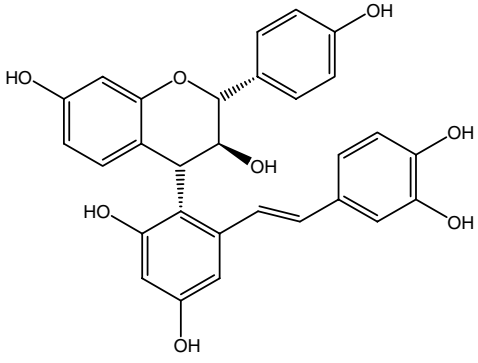
**17** = ≡

**18** = ▲

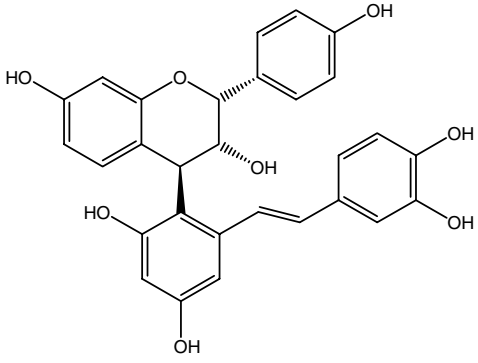


**19** = ≡

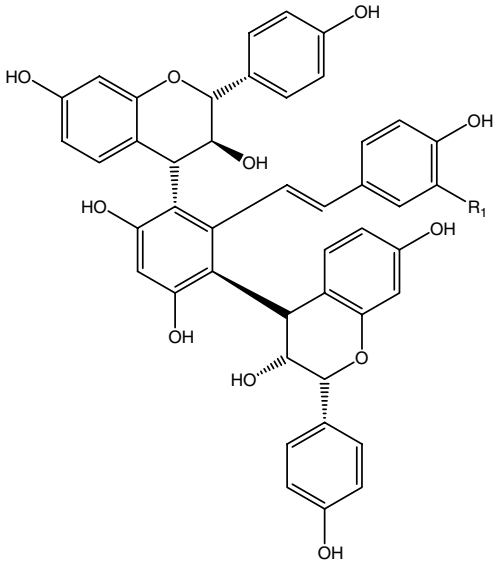
**20** = ▲



**21**

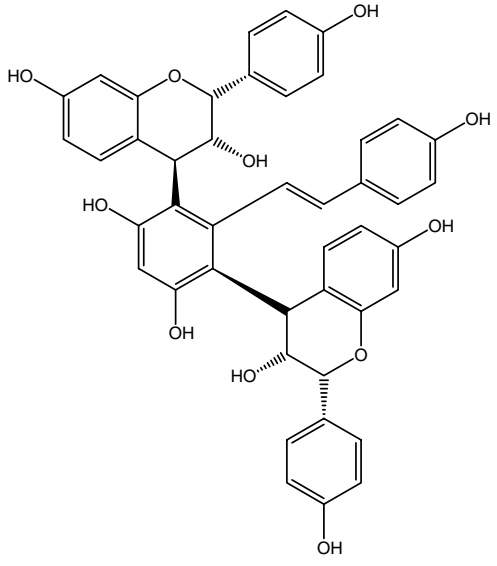


**22**



**23** $R_1$ = H

**24** $R_1$ = OH



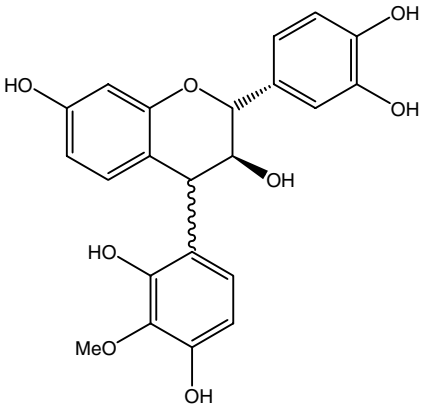
**25**

Structural analysis of the phenolic permethylaryl ether acetate derivatives of all five guibourtinidol-stilbenoids **21**–**25** were complicated by extensive dynamic rotational isomerism about the flavanyl-stilbenoid bonds and the exceptional energy requirements for the coalescence of $^1$H NMR resonances. In addition, all the compounds proved unstable; *E*/*Z* isomerism of their stilbenoid moieties occurring readily, even in indirect light.

Concise definition of structure and absolute configuration of the di- and tri-meric analogs was facilitated

via synthesis using the appropriate guibourtinidol-4-ols **17**–**20** and the *E*-stilbene **15** (Steynberg et al., 1987). Synthesis of the bis-guibourtinidol-stilbene trimer **24** comprising constituent guibourtinidol moieties of 'mixed' configuration was challenging but was surmounted by condensation of epiguibourtinidol-4β-ol **20** with the guibourtinidol-stilbenoid **21**, and also independent condensation of a mixture of guibourtinidol-4-ols **17** and **18** with the epiguibourtinidol-stilbenoid **22**, both affording a single product identical to the naturally occurring trimeric proguibourtinidin **24** (Steynberg et al., 1987).

Condensation of the guibourtinidol-4-ols with the *E*-stilbene **15** occurred at a faster rate than the analogous condensation of fisetinidol-4α-ol **1** with (+)-catechin **3** (Steynberg et al., 1987). Such an effect is attributed to enhanced nucleophilicity of the resorcinol-type ring of the stilbene due to conjugation with the 4-OH function of the second aromatic ring via the vinylic group.

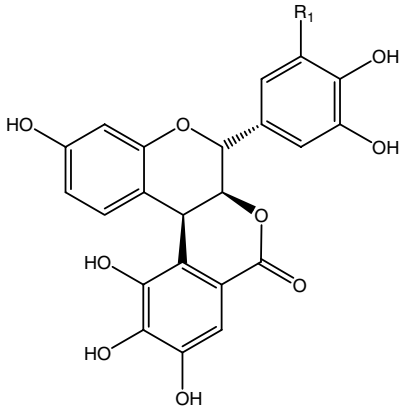



**27** ≋ = ⋮

**28** ≋ = ▲

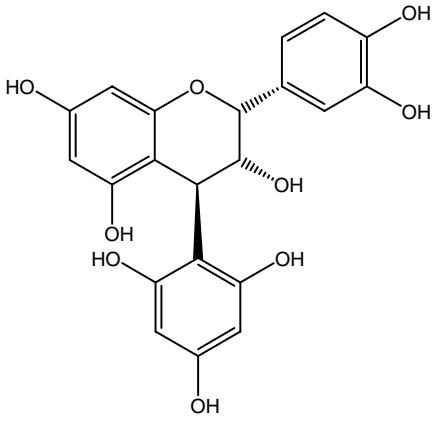
## 4. 4-Arylflavan-3-ols and related δ-lactones

Although synthetic 4-arylflavan-3-ols have been extensively used as model compounds for proanthocyanidins, their natural occurrence is limited to the succulent *Nelia meyeri* Schwant. (Kolodziej, 1983) and the heartwoods of *Burkea africana* Hook and *Peltophorum africanum* Sonder (Bam et al., 1990). These compounds comprise epicatechin-(4β → 2)-phloroglucinol **26** from *N. meyeri*, the pyrogallol-type profisetinidins **27** and **28** and the related δ-lactone **29** from *P. africanum*. In the heartwood of *B. africana* the δ-lactone **29** is accompanied by its prorobinetinidin analog **30**, and the 3-*O*-galloyl ester **31** of (−)-robinetinidol. The biogenetic relationship between the 4-arylflavan-3-ols **27** and **28**, the δ-lactones **29** and **30**, and the galloyl ester **31** were discussed.

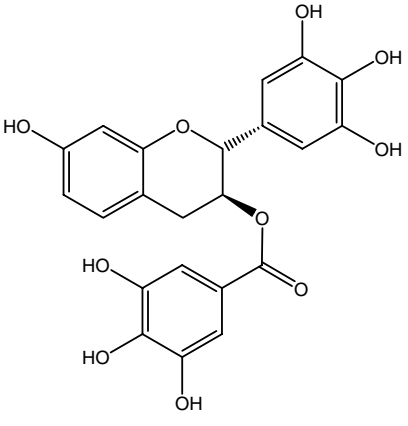



**29** $R_1 = H$

**30** R = OH



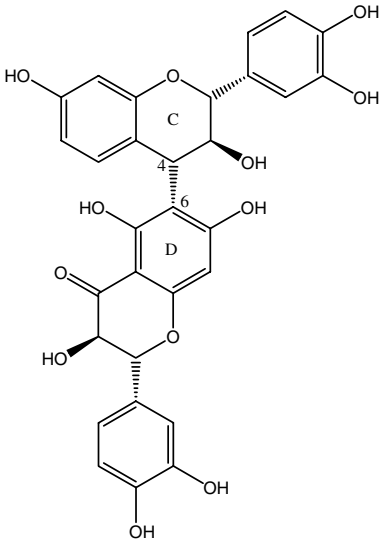

**26**



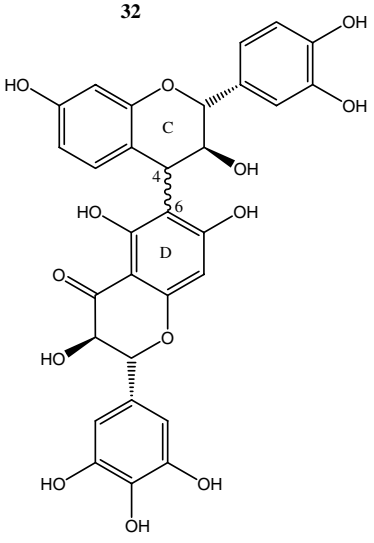

**31**

## 5. Profisetinidins and prorobinetinidins with dihydroflavonol, flavonol or flavone constituent units

The heartwood of *Burkea africana* afforded several dimeric profisetinidins with dihydroflavonol and flavonol terminal units (Malan et al., 1988). These compounds comprised the fisetinidol-(4α → 6)-dihydroquercetin **32**, fisetinidol-(4α-and 4β → 6)-dihydromyricetins **33** and **34**, and the C → E-ring coupled fisetinidol-(4α → 2′)-myricetin **35**. The fisetinidol-(4α → 8)-dihydromyricetin **36** was not isolated, but was presumably transformed into the benzoxonin-5-one analog **37** via facile ring expansion by methylene insertion during diazomethane methylation. The absolute configuration of analogs **32**–**35** were rigorously assessed via synthesis and circular dichroic (CD) data.

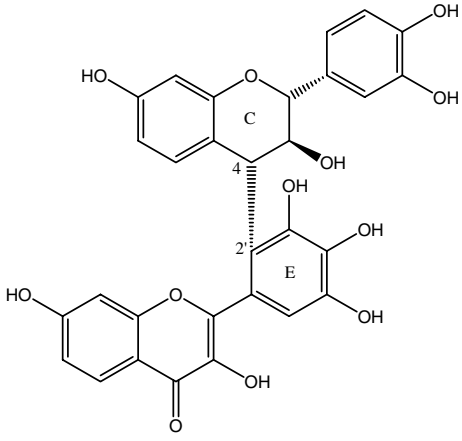



**32**



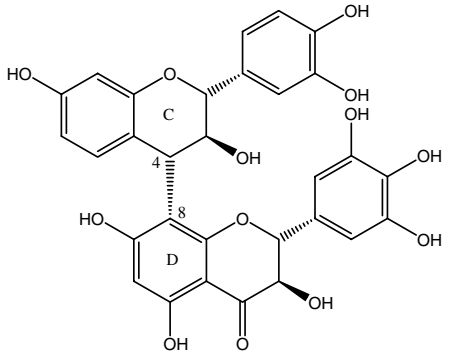

**33** ≡

**34** ≡

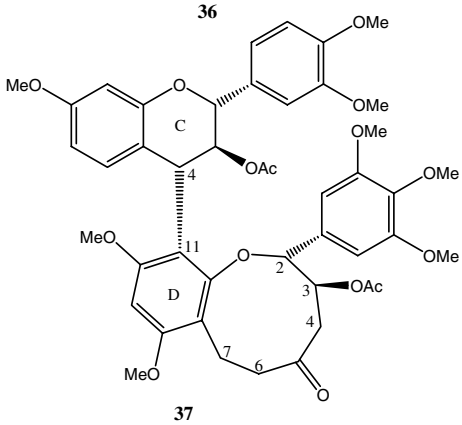



**35**

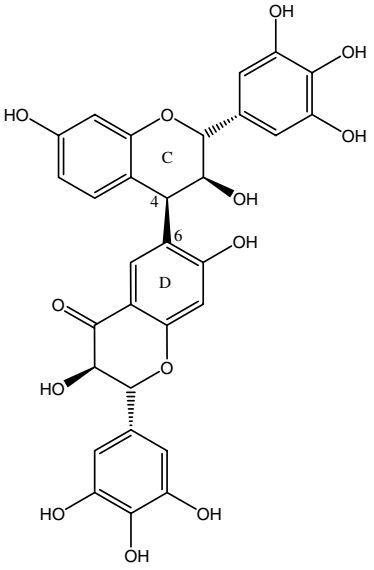
In the heartwood of *Robinia pseudacacia*, the prorobinetinidins **11**–**14** are accompanied by several analogs with dihydroflavonol, flavonol and flavone constituent units (Coetzee et al., 1995). The dihydroflavonol, (+)-dihydrorobinetin, appeared as terminal DEF-units in prorobinetinidins **38**, **39** and **40**, the flavonol, robinetin, in dimer **41** and 7,3′,4′,5′-tetrahydroxyflavone in coumpound **42**. Acid-catalyzed condensation of (+)-leucorobinetinidin **2** and the dihydroflavonol, (+)-dihydrorobinetin afforded low yields of the (4 → 2′)-coupled prorobinetinidin **39** and its F-ring oxidized analog **41**. Comparison of the CD data of compound **39** with those of the remaining metabolites with dihydrorobinetin constituent units **38** and **40**, permitted unequivocal definition of their absolute configuration.




**36**




**37**



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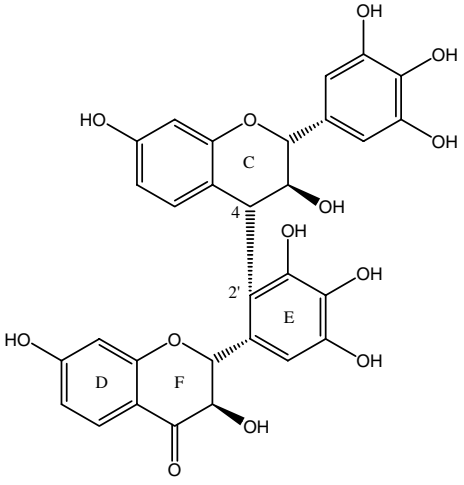
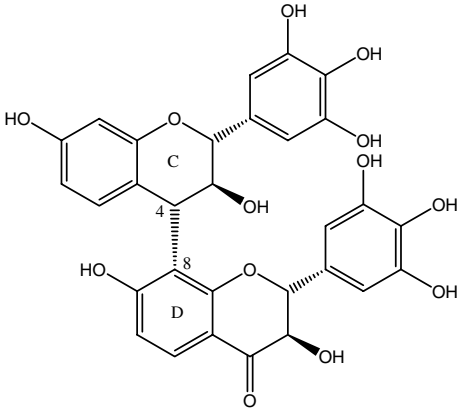


**39**

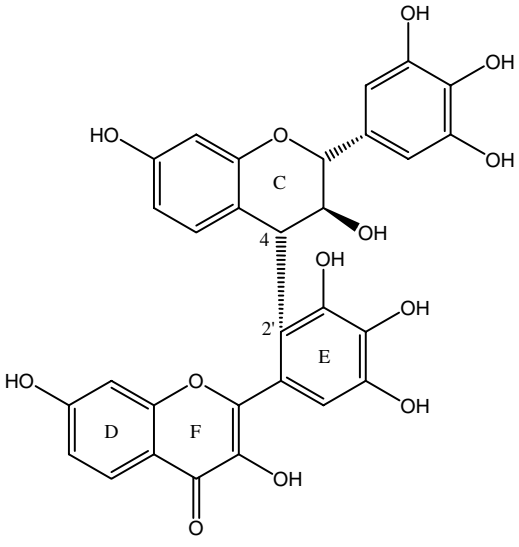


**40**

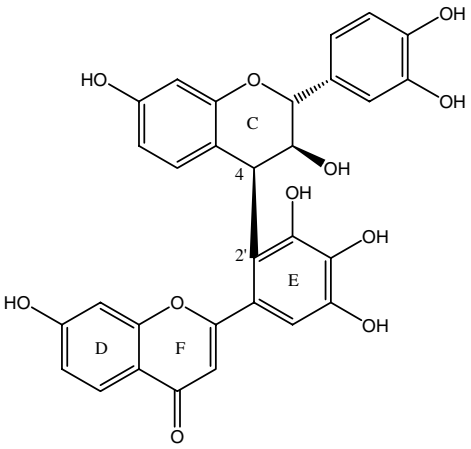
The chain terminating DEF-units in the eight dimeric prorobinetinidins **11**–**14** and **38**–**41** exhibit a remarkable diversity regarding the oxidation level of the heterocycle. This suggests that the biflavanoids in *R. pseudacacia* may biogenetically be interrelated via oxidation/reduction of the terminal DEF-units.

## 6. The promelacacinidin and proteracacinidin case

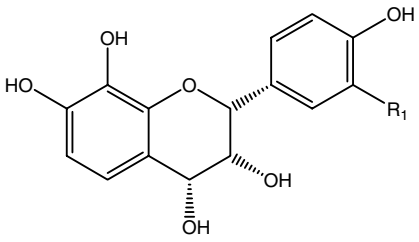
The natural occurrence of proanthocyanidins possessing 7,8-dihydroxylated (pyrogallol-type) A-rings was previously disputed (Roux and Ferreira, 1982) because of the adverse effect of the 8-hydroxyl group on the stability of a presumed flavan-3,4-diol related C-4 electron deficient center. Consequently it was suggested that on electronic grounds polymers that coexist with the flavan-3,4- diols, epimesquitol-4α-ol (melacacidin) **43** and epioritin-4α-ol (teracacidin) **44**, are probably resulting from phenol oxidative coupling. Ongoing studies have, however, demonstrated that epimesquitol-4α-ol **43** and epioritin-4α-ol **44** with their 7,8-dihydroxylated A-rings are indeed susceptible to facile condensation with phenolic nuclei under mild acidic conditions (Botha et al., 1981b; Foo, 1985). Thus, the biosynthesis of promelacacinidins and proteracacinidins should not be inhibited on chemical considerations. Here we review the multitude of naturally occurring analogs with bonding sites other than the ordinary C-4(C) → C-6/8(D) linkage between two flavan-3-ol constituent units.



**41**



**42**



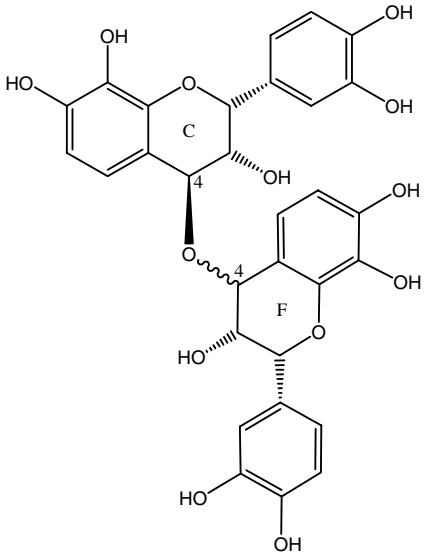
**43** $R_1 = OH$

**44** $R_1 = H$

### 6.1. Promelacacinidins/proteracacinidins with carbon–oxygen interflavanyl linkages

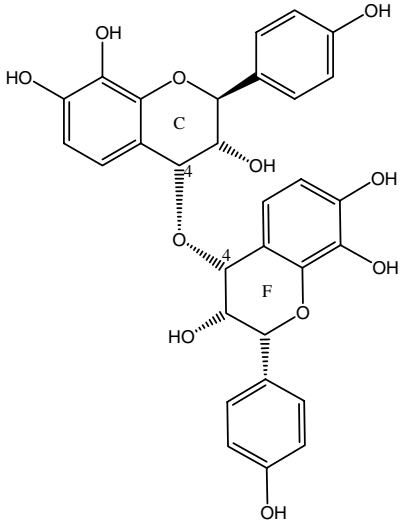
The heartwood of *Prosopis glandulosa* Torrey (mesquite) contains a single promelacacinidin with a catechin terminal unit and several biphenyl and *m*-terphenyl analogs possessing a mesquitol moiety linked via a C($sp^2$)–C($sp^2$) bond to a second mesquitol or catechin unit, or two mesquitol moieties linked to a catechin unit (Young et al., 1986, 1987; Brandt et al., 1987). However, the vast majority of naturally occurring promelacacinidins and proteracacinidins comprise mesquitol- or oritin-type units, respectively, linked to at least one of the flavan-3,4-diols, melacacinidin or teracacinidin, respectively.

The first (4-*O*-4)-linked leucomelacacinidins, epimesquitol-(4β → 4)-epimesquitol-4α-ol **45** and epimesquitol-(4β → 4)-epimesquitol-4β-ol **46** were identified in the heartwood of *Acacia melanoxylon* R. Br. (Foo, 1989). This was followed by characterization of *ent*-oritin-(4α → 4)-epioritin-4α-ol **47** and epioritin-(4β → 4)-epioritin-4α- and 4β-ols **48** and **49** from the heartwood of *Acacia galpinii* Burtt Davy (Coetzee et al., 1998a) and epimesquitol-(4β → 4)-epioritin-4β-ol **50** from the heartwood of *Acacia caffra* (Thunb.) Willd (Bennie et al., 2000). In the heartwood of *A. galpinii* the (4-*O*-4)-linked leucoteracacinidins **48** and **49** are accompanied by first (4-*O*-3)-ether linked analogs, epioritin-(4β → 3)-epioritin- and -oritin-4α-ols **51** and **52** (Coetzee et al., 1998b), while in *A. caffra* epioritin-(4β → 3)-epioritin-4β-ol **53** was additionally found (Bennie et al., 2000). The structures of these compounds were established via the usual physical methods and the absolute configuration eventually corroborated by synthesis and/or chemical degradation studies.

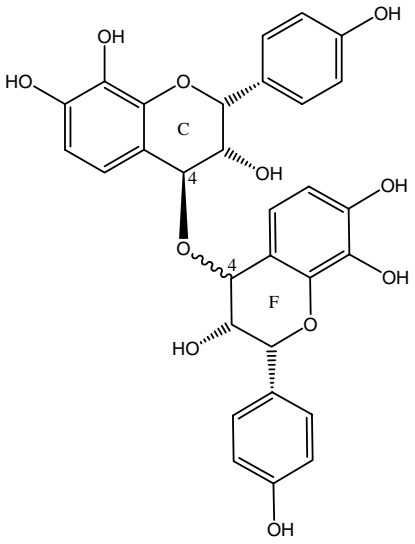


**45** =

**46** =

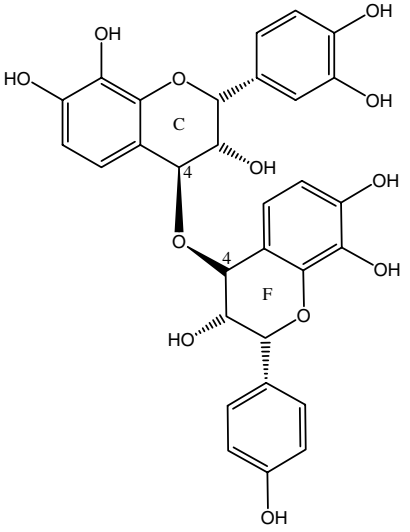


**47**

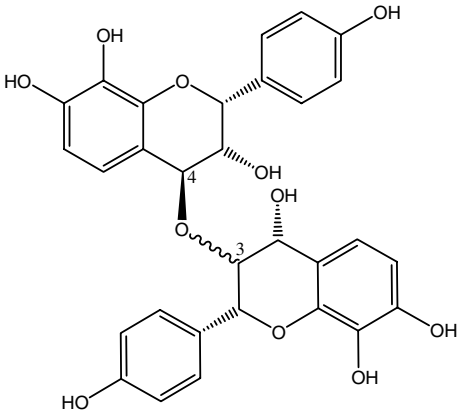


**48** = 

**49** = 

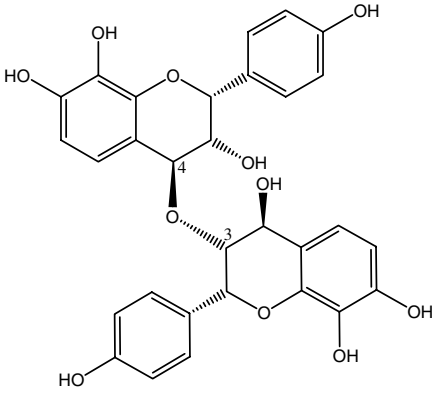


**50**



**51** = 

**52** = 

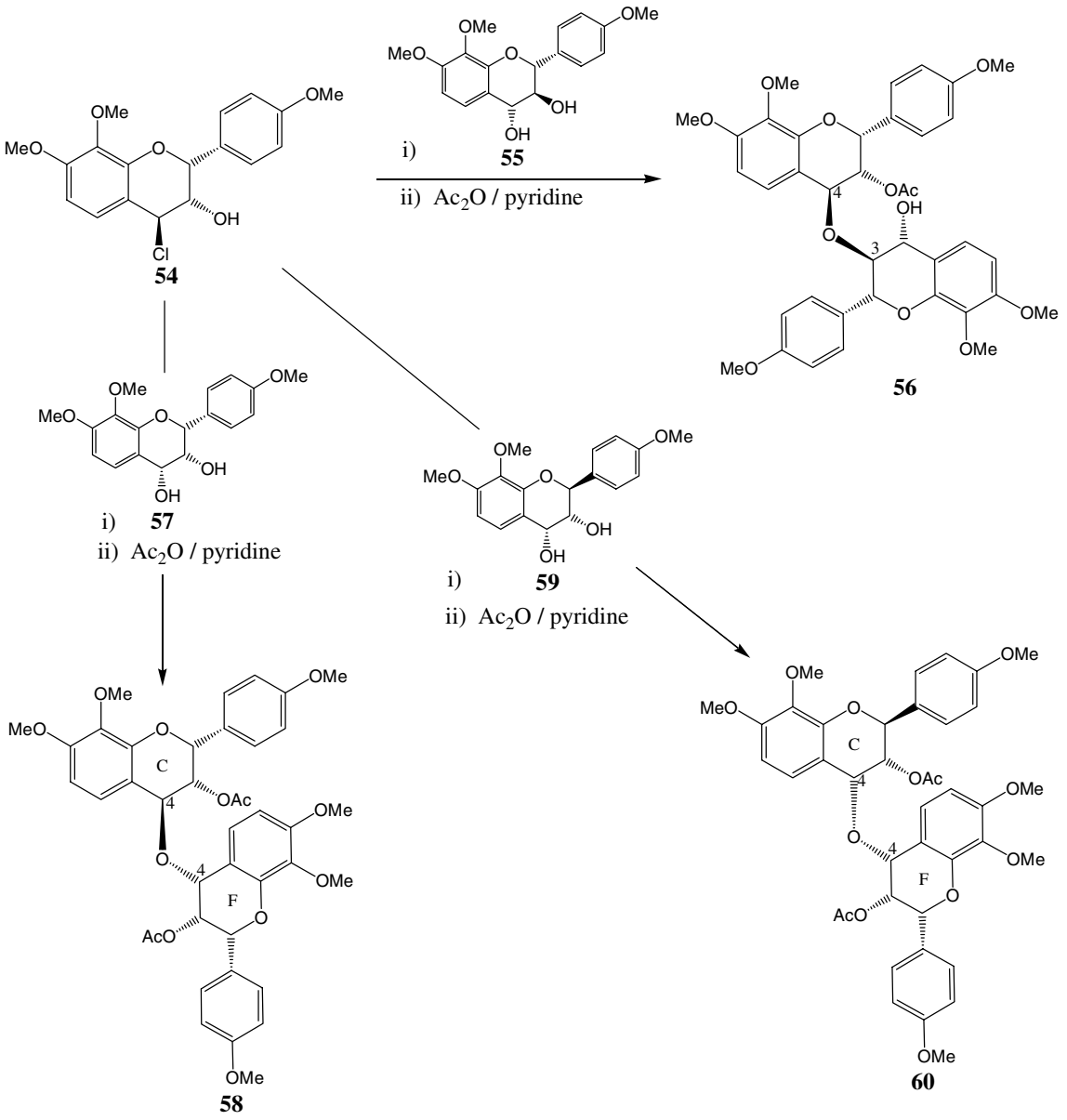


**53**

Owing to the susceptibility of the C-4β benzylic ether functionality in, e.g., compound **50** to solvolysis in aqueous acidic medium (Foo, 1989), the conditions usually employed to establish interflavanyl C–C linkages (Botha et al., 1981a,b) would be less suitable for generating the ethereal interflavanyl bond. The electrophilic attributes of one of the flavan-3,4-diols, e.g., **43**, were thus enhanced via formation of the 4β-chloroflavan-3-ol derivative **54** in Scheme 1 in order to permit the formation of the crucial bond at near a neutral pH value.

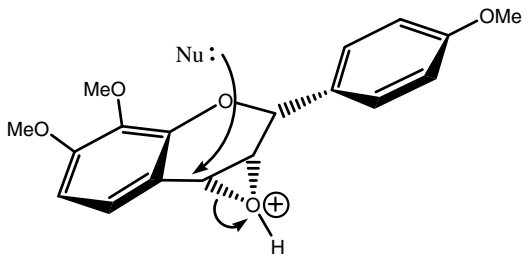
Synthesis of the proteracacinidin derivatives **56**, **58** and **60** (Scheme 1) thus involved the initial conversion of epioritin-4α-ol tri-*O*-methyl ether **57** into the 4β-chloroflavan-3-ol derivative **54** in quantitative yield using $SOCl_2$ in dry THF. Compound **54** reacted with oritin-4α-ol tri-*O*-methyl ether **55** to give the epioritin-(4β → 3)-oritin-4α-ol derivative **56** after acetylation (Coetzee et al., 1998b). The epioritin-(4β → 4)-epioritin-4α-ol and *ent*-oritin-(4α → 4)-epioritin-4α-ol derivatives **58** and **60** were similarly formed by treatment of the 4β-chloroflavan-3-ol **54** with the epioritin-4α-ol and *ent*-oritin-4α-ol derivatives **57** and **59**, respectively (Coetzee et al., 1998a,b).

The stereoselective coupling between 4β-chloroflavan-3-ol derivative **54** and the flavan-3,4-diol derivatives **55** and **57** to give the (4-*O*-3)- and (4-*O*-4)-proteracacinidin derivatives **56** and **58**, respectively, with retention of the C-4 configuration of the electrophilic precursor **54**, is explicable in terms of a neighboring group mechanism involving intramolecular displacement of the quasi-axial C(4)-chloro nucleofuge by the axial C(3)-hydroxy



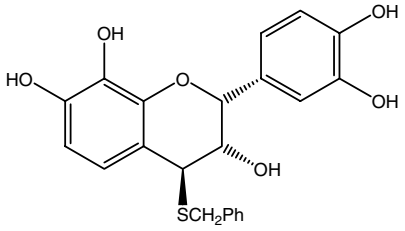

Scheme 1. Synthesis of ether-linked proteracacinidin derivatives **56**, **58** and **60**.

group. The transient protonated epoxide **61** then permits preferential attack of the nucleophillic C(4)-hydroxy group of the flavan-3,4-diol derivatives **55** and **57** from the less hindered β-face resulting in a highly stereoselective coupling step. Coupling of electrophile **54** and the *ent*-oritin-4α-ol derivative **59** led to the formation of a 4α-ether bond in the *ent*-oritin-(4α → 4)-epioritin-4α-ol derivative **60**, *i.e.* with inversion of configuration at C-4 of **54**. This presumably reflects reaction conditions incapable of triggering the neighboring group mechanism, hence resulting in an $S_N2$-type mechanism which requires the approaching hydroxy 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)-hydroxy group of **54** and **59** which is effectively permitted by the axial C(4)-hydroxy group of flavan-3,4-diol derivative **59** compared to the equatorial orientation of the same functionality in the nucleophiles **55** and **57**.




**61**

Alternatively, the epioritin-(4β → 3)-epioritin-4β-ol **53** was prepared by $AgBF_4$-catalyzed self-condensation of epioritin-4β-ol **44** (Bennie et al., 2000). The epimesquitol-(4β → 4)-epimesquitol-4β-ol **46** was formed when the 4β-benzylsulfanyl derivative **62** of epimesquitol-4α-ol **43** was activated by the thiophilic Lewis-acid $AgBF_4$ (Steynberg et al., 1998) and then treated with epioritin-4β-ol **63** (see Scheme 2 for structure).

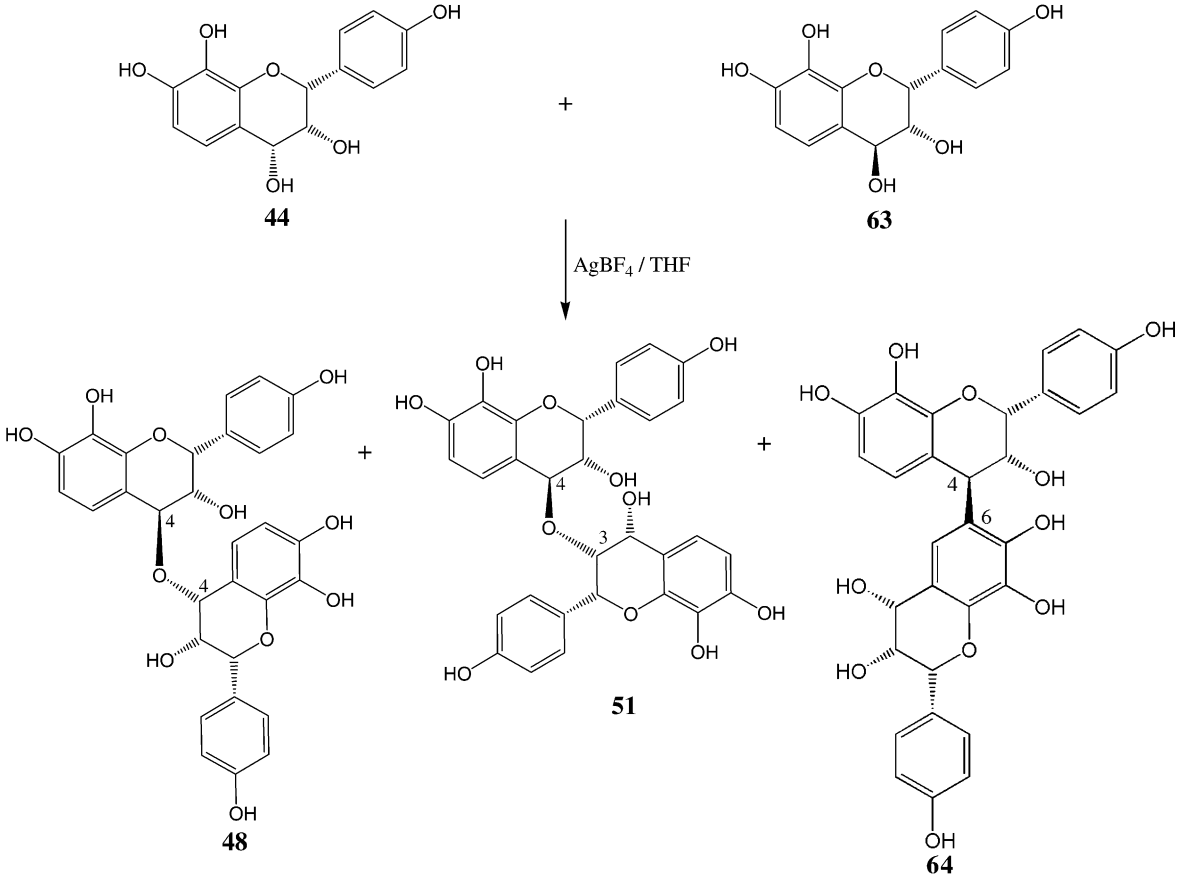



**62**

Pursuing our studies on the synthesis of free phenolic pro- and leuco-anthocyanidins, the $AgBF_4$ catalyzed process was applied to a mixture of epioritin-4α- and 4β-ols **44** and **63** (Scheme 2) with a view to form epioritin-(4β → 4)-epioritin-4α-ol **48** and epioritin-(4β → 3)-epioritin-4α-ol **51**, previously synthesized as permethylaryl ether diacetates (Coetzee et al., 1998b). Both the ether-linked compounds **48** (ca. 9% yield) and **51** (ca. 8%), and the C–C linked proteracacinidin, epioritin-(4β → 6)-epioritin-4α-ol **64** (ca. 7%) indeed formed. Formation of the ether-linked analogs **48** and **51** is explicable in terms of activation of the more reactive axial C-4 hydroxyl group of epioritin-4β-ol **63** (Clark-Lewis and Williams, 1967), epioritin-4α-ol **44** with its remarkable stable equatorial C-4 hydroxyl group (Clark-Lewis and Williams, 1967; Coetzee et al., 1999) then serving as the ambident nucleophile. Although the yields of the ether-linked analogs were consistently below 10%, the semisynthesis provided invaluable chiroptical data facilitating establishment of the absolute configuration of this class of naturally occurring leucoanthocyanidins.

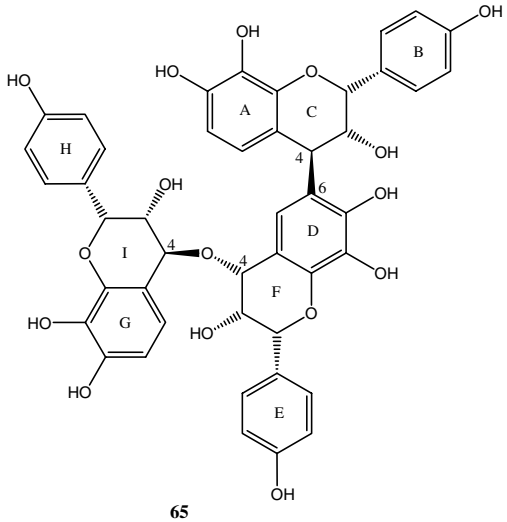
### *6.2. Trimeric proteracacinidins and a 'mixed' promelacacinidin/proteracacinidin containing both ether and carbon–carbon interflavanyl bonds*

The first trimeric proteracacinidins and a promelacacinidin possessing both C–C and C–O–C interflavanyl bonds, epioritin-(4β → 6)-epioritin-(4α → 4)-epioritin-4β-ol **65**, epioritin-(4β → 3)-epioritin-(4β → 6)-epioritin-4β-ol **66**, and epioritin-(4β → 3)-epioritin-(4β → 6)-

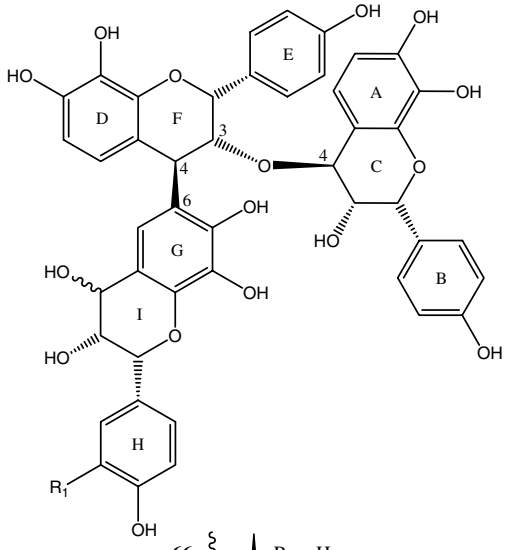



Scheme 2. Synthesis of ether-linked leucoteracacinidin **48** and **51** and the C–C linked analog **64**.

epimesquitol-4α-ol **67** were also identified in the heartwood of *A. caffra* (Bennie et al., 2001a).



**65**

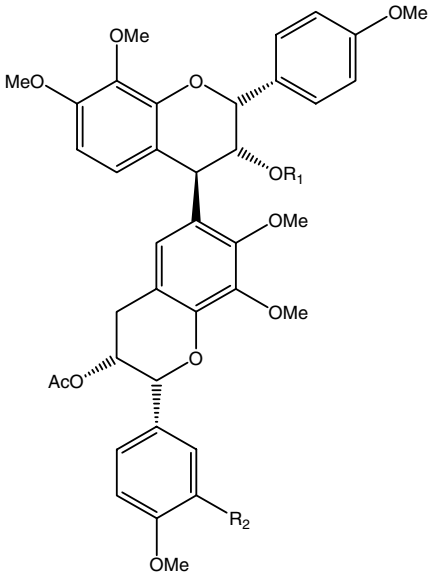


**66** = R$_1$ = H

**67** = R$_1$ = OH

The absence of a second aromatic chromophore in close proximity of the C-4 stereocentre in ether-linked leucoanthocyanidins precludes assessment of their C-4 absolute configurations by application of the chiroptical aromatic quadrant rule (DeAngelis and Wildman, 1969). The permethylaryl ether triacetates of analogs **65**–**67** exhibited negative and positive Cotton effects in the ca. 280 and 220–250 nm regions, respectively, in their CD spectra. The negative Cotton effects near 280 nm probably indicated the cumulative effects of the $^1L_b$ transitions of all the constituent units exhibiting 2*R* absolute configuration (Nel et al., 1999; Ferreira et al., 2004). Positive Cotton effects in the 220–250 nm region were then reminiscent of $^1L_a$ transitions as well as contributions resulting from the biphenylmethylidine chromophore at C-4(C) (DeAngelis and Wildman, 1969; Van der Westhuizen et al., 1981).

However, the ethereal interflavanyl bond in both the di- and tri-meric analogs are readily susceptible to reductive cleavage with $Na(CN)BH_3$ in TFA/DCM which permitted the unequivocal assignment of the absolute configuration of constituent flavanyl units. Such a protocol is demonstrated in Scheme 3 for cleavage of the permethylaryl ether diacetate **58** of epioritin-(4β → 4)-epioritin-4α-ol **48** (Bennie et al., 2001a; Steynberg et al., 1997). Treatment of **58** with $Na(CN)BH_3$ in TFA/DCM for 45 min at 0 °C afforded epioritin-tri-*O*-methylether acetate **70** (65%). Under these conditions the protonated C(4)-β-hydroxyl group of the C-ring is presumably preferentially cleaved due to the anchimeric effect of the axial C(3)-OH bond (Coetzee et al., 1998a). The resulting flavan-3,4-diol derivative **69** that accompanies the epioritin derivative **70** is eventually also reduced to afford the latter compound as sole product of the reductive cleavage process.

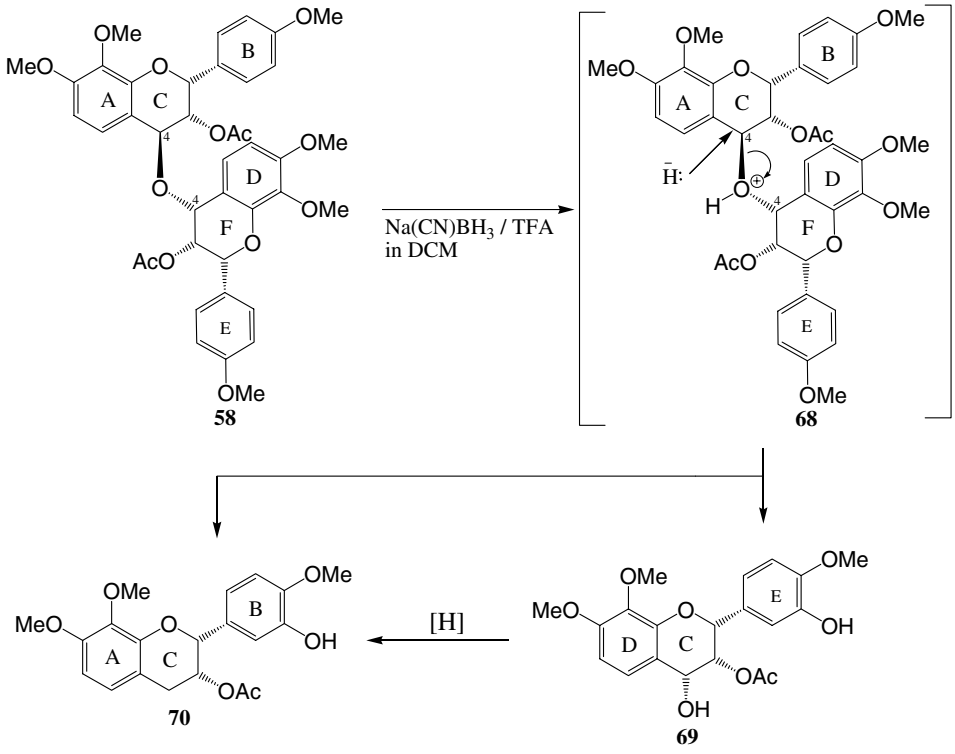


**71** R$_1$ = Ac, R$_2$ = H

**72** R$_1$ = R$_2$ = H

**73** R$_1$ = H, R$_2$ = OMe

A similar protocol was also used to reductively cleave the benzylic interflavanyl ether linkages of the permethylaryl ether triacetate derivatives of trimeric




Scheme 3. Reductive cleavage of the C–O–C bond in leucoteracacinidin derivative **58**.

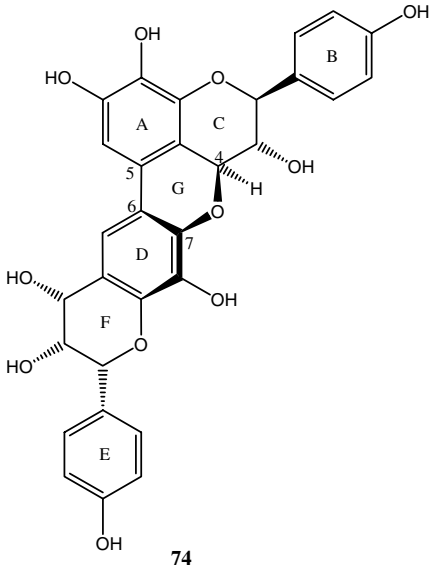
analogs **65**–**67**. Treatment of the derivative of compound **65** with $Na(CN)BH_3$ (7 molar excess) and TFA (10 molar excess) in $CH_2Cl_2$ for 2 h at 0 °C under $N_2$, afforded a mixture comprising the starting material (26%), the epioritin-(4β → 6)-epioritin derivative **71** (33%) and epioritin-tri-*O*-methylether acetate **70** (40%). Separate treatment of the derivatives of compounds **66** and **67** under similar conditions gave the corresponding bis-epioritin and epioritin-(4β → 6)-epimesquitol derivatives **72** (41%) and **73** (36%), respectively, as well as epioritin-tri-*O*-methylether acetate **70** (30 and 60%, resp.). Cleavage products **72** and **73** had a 'free' hydroxyl group at C-3 of the upper epioritin moiety, hence 'labeling' the location of the C–O–C ether linkage in the parent derivatives of triflavanoids **66** and **67**.

The structures and relative configuration of the dimeric derivatives **71**–**73** were readily evident from the $^1H$ NMR spectroscopic data. The CD data of all three derivatives were virtually identical to those of their synthetic counterparts (Bennie et al., 2002a). Thus, the high-amplitude negative Cotton effect at ca. 280 nm is indicative of the $^1L_b$ transition of flavan-3-ol constituent units with 2*R* absolute configuration. The high-amplitude positive Cotton effect at ca. 240 nm reflects the 4β-flavanyl substituent (DeAngelis and Wildman, 1969; Van der Westhuizen et al., 1981). When taken in conjunction with the CD data of the epioritin derivative **70**, the absolute configuration of the dimeric ether-linked leucoteracacinidins as well as the three unique trimers **65**–**67** was thus unequivocally established.

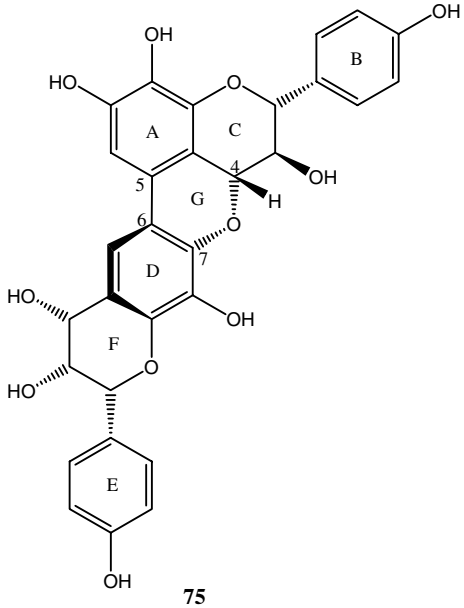
### 6.3. Doubly linked proteracacinidins

Naturally occurring proanthocyanidins possessing both C–C and C–O–C bonds that link two contiguous flavanyl units are restricted to mainly the A-type proanthocyanidins. These compounds possess an ether linkage between C-2(C) and C-5/C-7(D) in addition to the common $C(sp^3)$–$C(sp^2)$ bond (Porter, 1988, 1994; Ferreira and Bekker, 1996; Ferreira and Li, 2000; Ferreira and Slade, 2002). However, continued investigation of the heartwood components from *A. caffra* and *A. galpinii* revealed the presence of a unique series of doubly linked proteracacinidin analogs (Malan et al., 1994; Bennie et al., 2001b). These compounds comprised *ent*-oritin-(4α → 7;5 → 6)-epioritin-4α-ol **74**, oritin-(4α → 7;5 → 6)-epioritin-4α-ol **75**, oritin-(4β → 7;5 → 6)-epioritin-4α-ol **76**, epioritin-(4β → 7;5 → 6)-epioritin-4α-ol **77**, epioritin-(4β → 7;5 → 6)-oritin-4α-ol **78**, and epioritin-(4β → 5;3 → 4)-oritin-4β-ol **79**. The UV spectra of the permethylaryl ether acetate derivatives of compounds **74**–**78** 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 (negative for **75** and positive for **74**, **76**–**78**) while **79** showed a high-amplitude

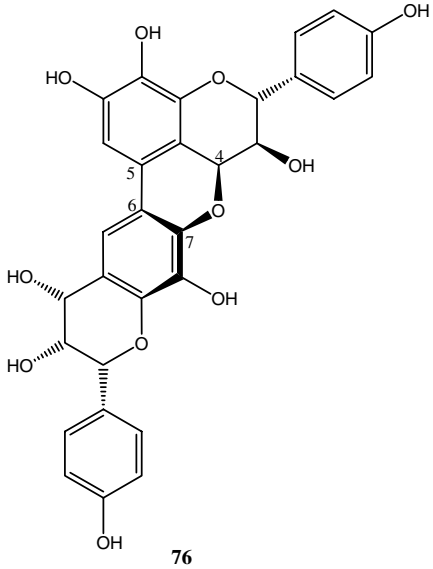
positive Cotton effect at 240 nm. The 255 nm Cotton effects in analogs **74**–**78** result from the helicity imposed by the twisted biaryl chromophore ($\pi \rightarrow \pi^*$ transition). Thus, the negative Cotton effect near 255 nm for **75** reflects *M*-helicity of the biaryl bond and hence *R* absolute configuration at C-4(C). The positive Cotton effects in the same region for the derivatives **74** and **76**–**78** are accordingly indicative of *P*-helicity of the biaryl bond and hence *S* absolute configuration at C-4(C). The high-amplitude positive Cotton effect at 240 nm in the CD spectrum of the derivative of compound **79** indicated a β-flavanyl substituent at C-4(C) and hence *S* absolute configuration by application of the aromatic quadrant rule (DeAngelis and Wildman, 1969; Van der Westhuizen et al., 1981). The combined $C(sp^2)$–$C(sp^2)$ and C–O–C interflavanyl bonds, most likely generated



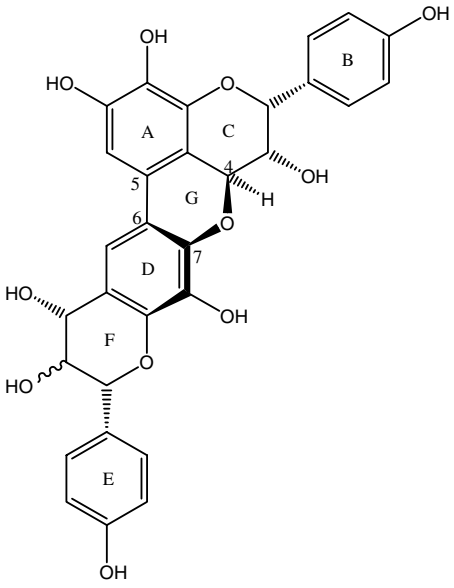

**74**




**75**

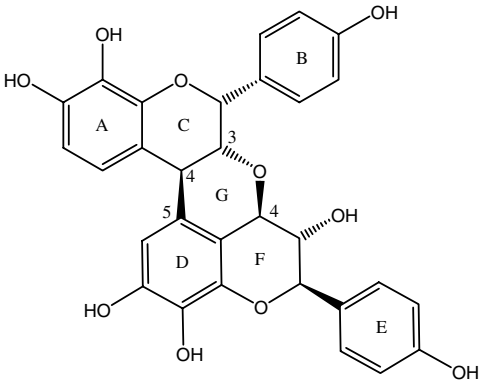



**76**




**77** ≋ = ≡

**78** ≋ = ▲

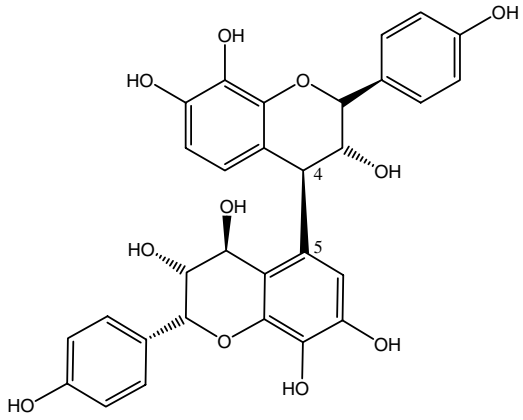



**79**

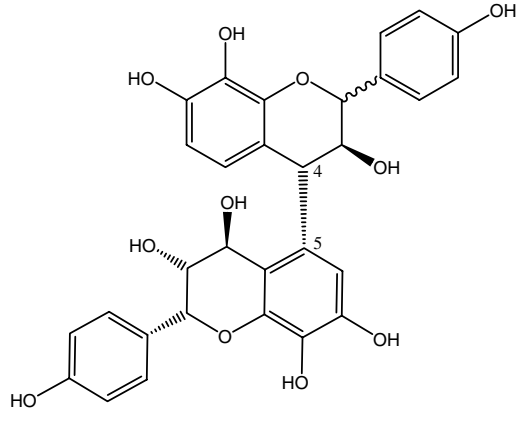
via one- and two-electron processes, respectively, are unique structural features in naturally occurring pro- and leuco-anthocyanidins.

### 6.4. Dimeric proteracacinidins possessing the rare C-4(C) → C-5(D) interflavanyl linkage

Proanthocyanidins with flavan-3-ol or flavan-3,4-diol terminating units possessing pyrogallol-type A-rings predominantly exhibit (4 → 6)-interflavanyl linkages (see Section 6.6). Continued investigation of the heartwood extracts of *A. caffra* and *A. galpinii* demonstrated the presence of five dimeric proteracacinidins exhibiting the rare (4 → 5)-linkage between constituent flavanyl units with pyrogallol-type A-rings (Malan, 1995; Bennie et al., 2002b). The compounds comprised *ent*-oritin-(4β → 5)-epioritin-4β-ol **80**, oritin-(4α → 5)-epioritin-4β-ol **81**, *ent*-epioritin-(4α → 5)-epioritin-4β-ol **82**, epioritin-(4β → 5)-epioritin-4α-ol **83**, and *ent*-oritin-(4β → 5)-epioritin-4α-ol **84**. The absolute configurations of all the analogs was again properly assessed using CD data in conjunction with appropriate $^{1}H$ and $^{13}C$ NMR spectroscopic data.

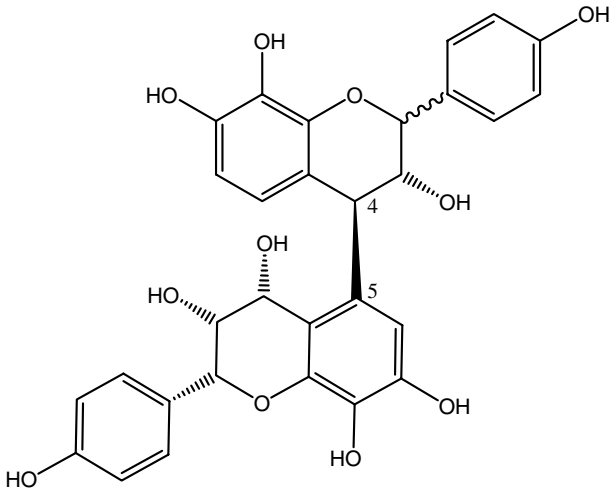



**80**




**81** ≡

**82** ≡




**83** ≡

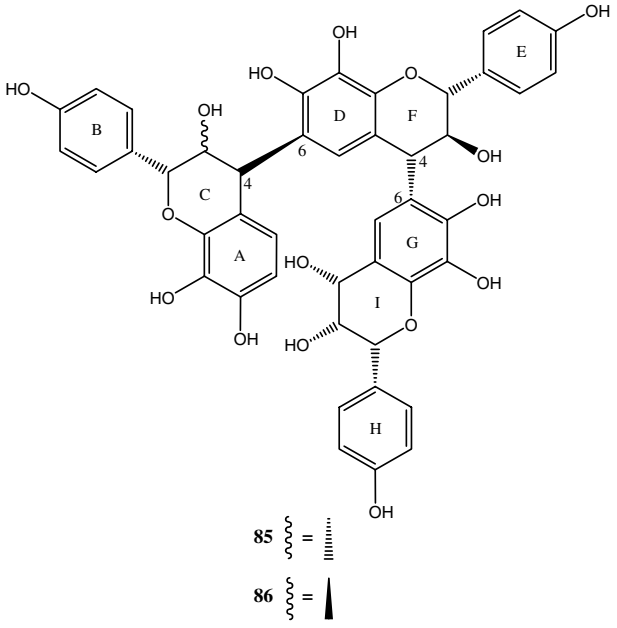
**84** ≡

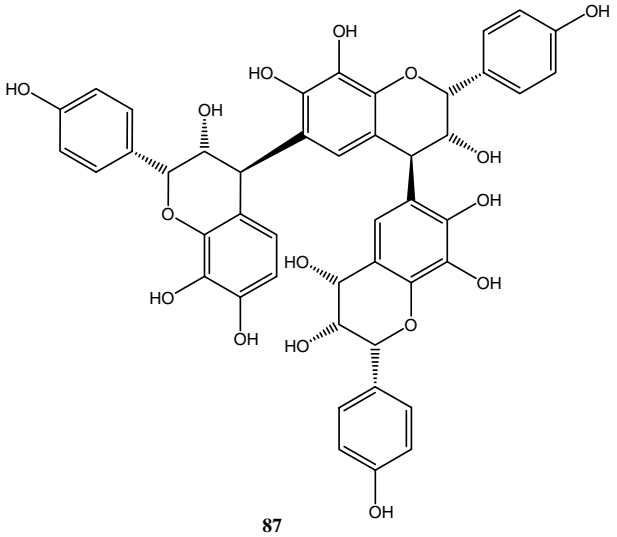
### 6.5. Trimeric proteracacinidins with exclusive C–C interflavanyl bonds

Besides the trimeric pro-/leuco-teracacinidins **65** and **66** and the 'mixed' pro-/leuco-teracacinidin/-melacacinidin **67** containing both ether and C–C interflavanyl bonds, the heartwood of *A. caffra* and *A galpinii* also afforded the first trimeric proteracacinidins with exclusive C–C interflavanyl linkages. These compounds are epioritin-(4β → 6)-oritin-(4α → 6)-epioritin-4α-ol **85**, oritin-(4β → 6)-oritin-(4α → 6)-epioritin-4α-ol **86** and epioritin-(4β → 6)-epioritin-(4β → 6)-epioritin-4α-ol **87** (Bennie et al., 2004).

The permethylaryl ether acetates of analogs **85**–**87** displayed negative and positive Cotton effects in the 280–290 and 230–250 nm regions of their CD spectra. The negative Cotton effects for the $^{1}L_{b}$ transitions of all three derivatives most likely indicated 2*R* absolute configuration at the C-2 stereocenters of all three heterocyclic rings (Korver and Wilkins, 1971; Nel et al., 1999). Positive Cotton effects near 240 nm in the CD spectra of dimeric C–C linked proanthocyanidins usually indicate 4β-orientation of the DEF-flavanyl units (Van der Westhuizen et al., 1981). It is, however, unclear how the sign of the Cotton effect is influenced by the presence of both 4α- and 4β-flavanyl units at the trimeric level. The indicated absolute configura-

tions for **85**–**87** are thus tentative and await confirmation via synthesis. We were thus far unsuccessful in efforts towards their synthesis.

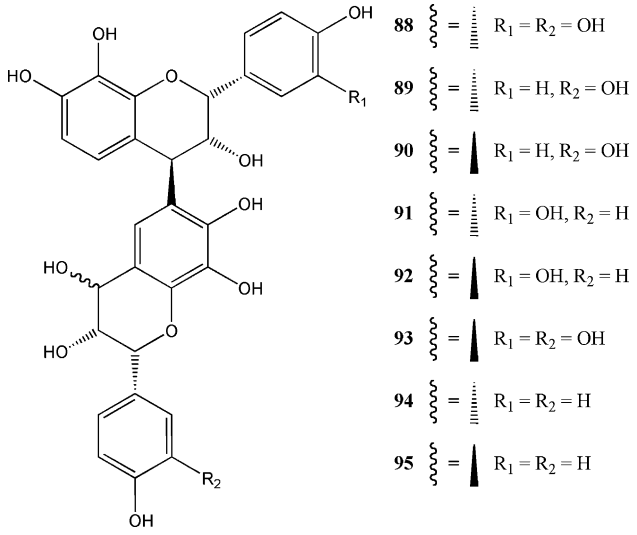


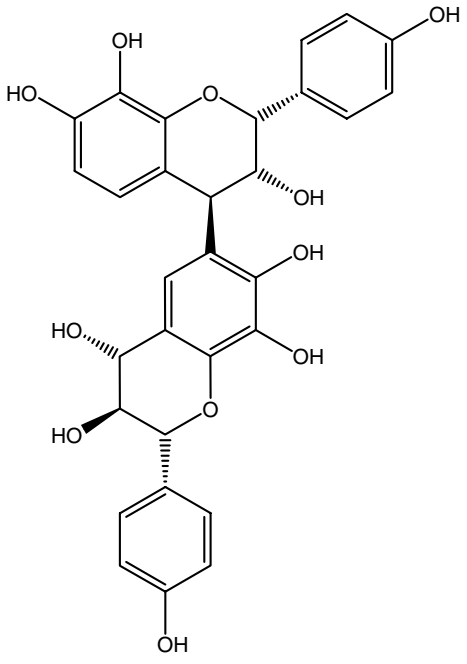



87

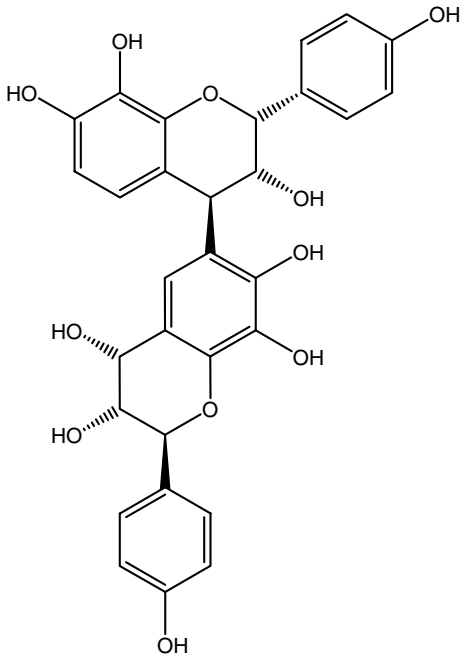
### 6.6. (4 → 6)-Coupled proteracacinidins and promelacacinidins

The multitude of proteracacinidins and promelacacinidins with flavan-3,4-diol constituent units discussed in Sections 6.1–6.4 were supplemented by a considerable number of analogs possessing the more 'conventional' (4 → 6)-interflavanyl linkage. This work was initiated by the demonstration of the facile acid catalyzed condensation of the flavan-3,4-diols with pyrogallol-type A-rings, melacacidin and teracacidin, with nucleophilic phenolic nuclei (Foo, 1985; Botha et al., 1981a,b). Foo (1986) subsequently identified the first example of the class, the promelacacinidin, epimesquitol-(4β → 6)-epimesquitol-4α-ol **88**. Since that time no less than 15 new analogs, **89**–**103**, comprising proteracacinidins, promelacacinidins and 'mixed' proteracacinidins/promelacacinidins were identified in the heartwoods of *A. caffra* and *A. galpinii* (Malan et al., 1997; Malan and Sireeparsad, 1995; Bennie et al., 2002a). Proteracacinidin **103** with its 7,8,4′-trihydroxyflavan extender unit is based on a flavan-4-ol that has not yet been identified.

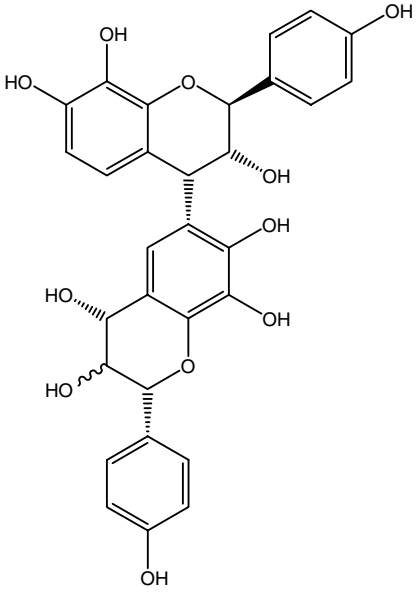


96

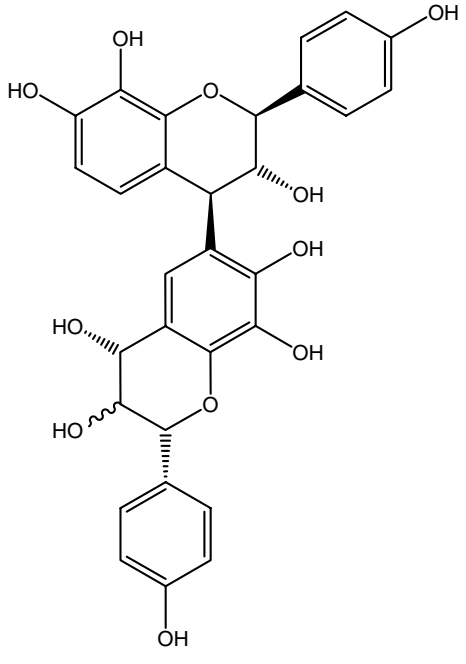


**97**



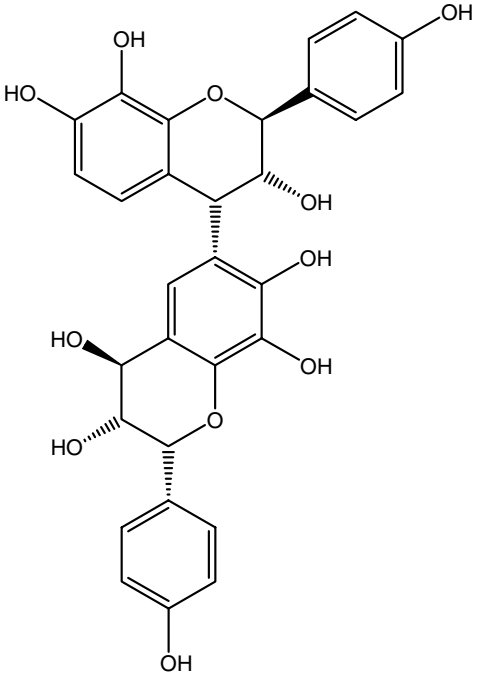
**100** ≈ ⋮

**101** ≈ ▲



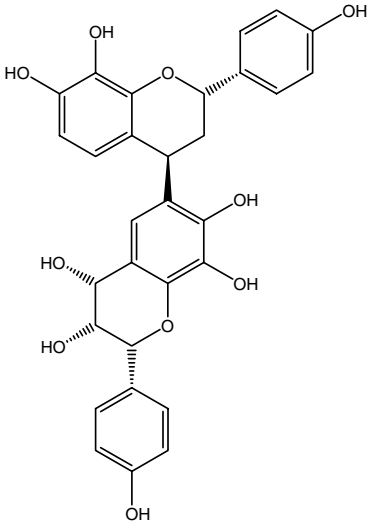
**98** ≈ ⋮

**99** ≈ ▲



**102**

For the majority of compounds **88**–**103** unequivocal assignment of structure and absolute configuration were done by $^{1}$H NMR spectroscopic and chiroptical data, appropriately supported by essential semisynthetic sequences.



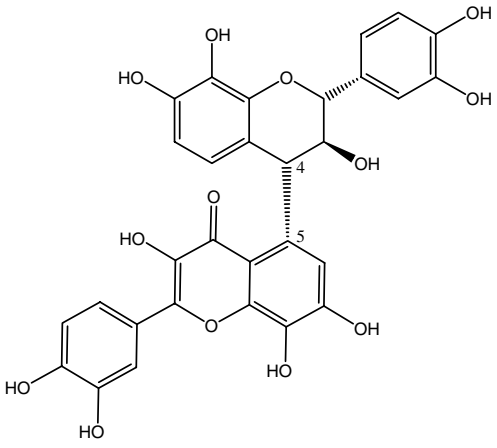

**103**

A conspicuous structural feature of the naturally occurring proteracacinidins and promelacacinidins is the abundance of analogs possessing 2,3-*cis*-3,4-*cis*-flavan-3,4-diol 'terminal' units, e.g., trimeric compounds **85**–**87**. This is presumably the consequence of the stability of such units towards the formation of electrophilic centers at C-4 (Coetzee et al., 1999).

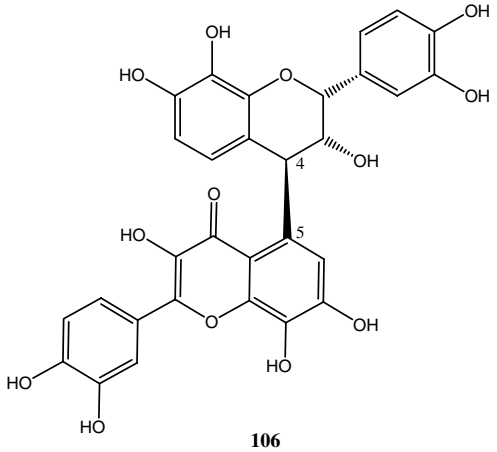
## 7. Miscellaneous

In addition to the considerable number of di- and tri-meric proteracacinidins and promelacacinidins described in the previous sections, the heartwood of *A. galpinii* also contained the first naturally occurring bis-flavan-3,4-diol, epioritin-4α-ol-(6 → 6)-epioritin-4β-ol **104**. Its biaryl interflavanyl bond is most likely formed via a one-electron phenol oxidative coupling process.

Two unique promelacacinidins, mesquitol-(4α → 5)-3′, 4′,7,8-tetrahydroxyflavonol **105** and epimesquitol-(4β → 5)-3′,4′,7,8- tetrahydroxyflavonol **106**, were obtained from the heartwood of *Acacia nigrescens* (Howell et al., 2002). These compounds not only extended the rare series of proanthocyanidins with pyrogallol-type A-rings exhibiting C-4(C):C-5(D) interflavanyl bonds (see Section 6.3), but also represented the first promelacacinidins with flavonol constituent units.

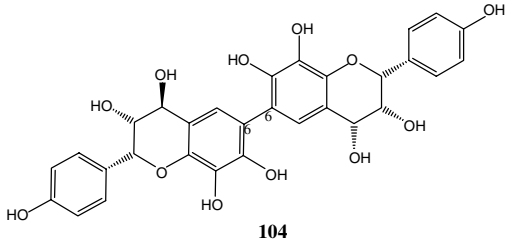



**105**

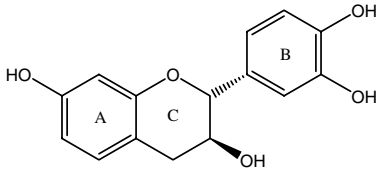



**106**

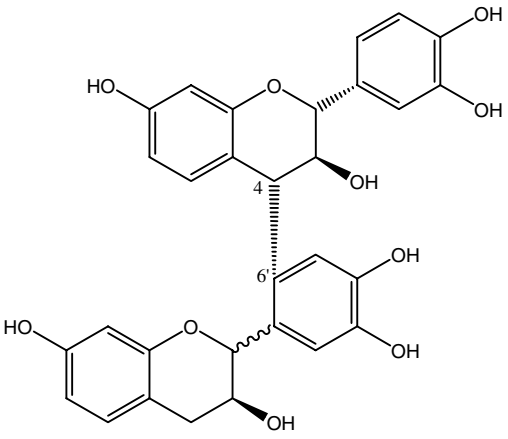
The heartwood of *Colophospermum mopane*, containing exceptionally high concentrations of the 5-deoxy flavan-3-ol, (−)-fisetinidol **107**, with its reduced A-ring nucleophilicity compared to that of (+)-catechin **3**, represents another fascinating source of 'unexpected' nucleophiles and bonding positions (Malan et al., 1990;




**104**

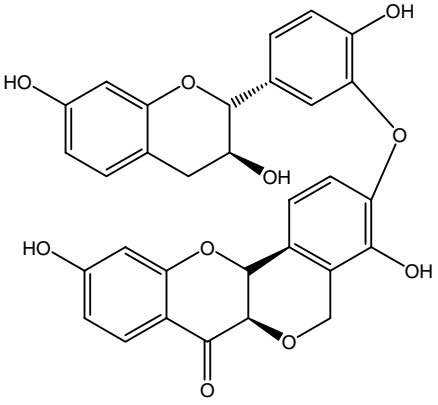



**107**

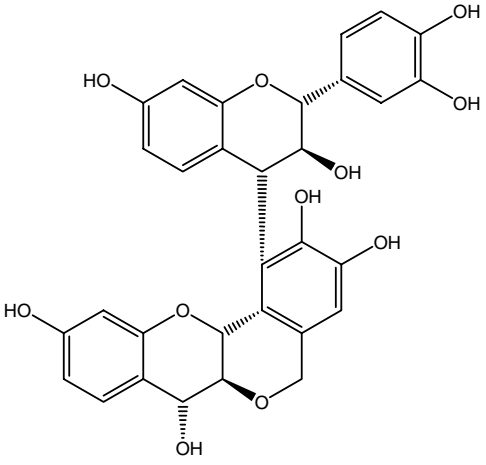



**108** ≈ ⫶

**109** ≈ ▲




**110**




**111**

Steenkamp et al., 1988). Among the ensuing compounds are the bis-(4α → 6′)-fisetinidol **108** and its C-2(F) epimer **109**, and the mopanidin/peltogynidin analogs **110** and **111**. Compound **111**, being both a profisetinidin and a leucopeltogynidin, complemented both the classes of B-ring linked proanthocyanidins and those with the equivalent of a terminal flavan-3,4-diol unit.

## 8. Conclusion

This review clearly demonstrates the remarkable diversity of nucleophilic centers participating in interflavanyl bond formation in natural sources lacking significant concentrations of powerful flavan-3-ol nucleophiles. Nowhere is it more prevalent than in the heartwoods of *A. caffra* and *A. galpinii* where, despite premature predictions (Roux and Ferreira, 1982) of their likely absence from natural sources, an extensive series of pro-/leuco-teracacinidns and pro-/leuco-melacacinidns have been identified. Our erroneous speculations highlighted the risks of venturing into predictions regarding the presence and especially the 'absence' of natural products based on limited data availability.

## Acknowledgements

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## References

Bam, M., Malan, J.C.S., Young, D.A., Brandt, E.V., Ferreira, D., 1990. Profisetinidin-type 4-arylflavan-3-ols and related δ-lactones. Phytochemistry 29, 283–287.

Bennie, L., Coetzee, J., Malan, E., Ferreira, D., 2001a. Structure and stereochemistry of triflavanoids containing both ether and carbon–carbon interflavanyl bonds. Phytochemistry 57, 1023–1034.

Bennie, L., Coetzee, J., Malan, E., Ferreira, D., 2002a. (4 → 6)-Coupled proteracacinidins and promelacacinidins from *Acacia galpinii* and *Acacia caffra*. Phytochemistry 60, 521–532.

Bennie, L., Coetzee, J., Malan, E., Ferreira, D., 2002b. Structure and stereochemistry of dimeric proteracacinidins possessing the rare C-4(C) → C-5(D) interflavanyl linkage. Phytochemistry 59, 673–678.

Bennie, L., Coetzee, J., Malan, E., Slade, D., Marais, J.P.J., Ferreira, D., 2004. Trimeric proteracacinidins and a (6 → 6)-bis-leucoteracacinidin from *Acacia galpinii* and *Acacia caffra*. Phytochemistry 65, 215–220.

Bennie, L., Coetzee, J., Malan, E., Woolfrey, J.R., Ferreira, D., 2001b. Oligomeric flavanoids. Part 34: Doubly-linked proteracacinidin analogues from *Acacia caffra* and *Acacia galpinii*. Tetrahedron 57, 661–667.

Bennie, L., Malan, E., Coetzee, J., Ferreira, D., 2000. Structure and synthesis of ether-linked proteracacinidin and promelacacinidin

proanthocyanidins from *Acacia caffra*. Phytochemistry 53, 785–793.

Bonnet, S.L., Steynberg, J.P., Bezuidenhoudt, B.C.B., Saunders, C.M., Ferreira, D., 1996. Oligomeric flavonoids. Part 23. Structure and synthesis of phlobatannins related to bis-fisetinidol-epicatechin profisetinidin biflavanoids. Phytochemistry 43, 253–263.

Botha, J.J., Viviers, P.M., Ferreira, D., Roux, D.G., 1981a. Synthesis of condensed tannins. Part 4. A direct biomimetic approach to [4,6]- and [4,8]-biflavanoids. Journal of the Chemical Society, Perkin Transactions 1, 1235–1245.

Botha, J.J., Young, D.A., Ferreira, D., Roux, D.G., 1981b. Synthesis of condensed tannins. Part 1. Stereoselective and stereospecific syntheses of optically pure 4-arylflavan-3-ols, and assessment of their absolute stereochemistry at C-4 by means of circular dichroism. Journal of the Chemical Society, Perkin Transactions 1, 1213–1219.

Brandt, E.V., Young, D.A., Young, E., Ferreira, D., 1987. Absolute configuration of atropisomeric *m*-terphenyl-type flavan-3-ols. Journal of the Chemical Society, Perkin Transactions 2, 1365–1368.

Clark-Lewis, J.W., Williams, L.R., 1967. Flavan derivatives. XVII. Epimerization of the benzylic 4-hydroxyl group in flavan-3,4-diols and the formation of 4-alkyl ethers by solvolysis. Australian Journal of Chemistry 20, 2151–2167.

Coetzee, J., Malan, E., Ferreira, D., 1998a. Oligomeric flavanoids. Part 29. Structure and synthesis of novel ether-linked [4-*O*-4] bisteracacinidins. Tetrahedron 54, 9153–9160.

Coetzee, J., Malan, E., Ferreira, D., 1998b. Oligomeric Flavanoids. Part 28. Structure and synthesis of ether-linked (4-*O*-3)-bisteracacinidins, a novel class of naturally occurring proanthocyanidins. Journal of Chemical Research (S) 526–527 (M), 2287–2296.

Coetzee, J., Malan, E., Ferreira, D., 1999. The formation and stability of flavans with 2,3-*cis*-3,4-*cis* configuration. Tetrahedron 55, 9999–10004.

Coetzee, J., Steynberg, J.P., Steynberg, P.J., Brandt, E.V., Ferreira, D., 1995. Oligomeric flavanoids. Part 18. Dimeric prorobinetinidins from *Robinia pseudacacia*. Tetrahedron 51, 2339–2352.

DeAngelis, G.G., Wildman, W.C., 1969. Circular dichroism studies. I. A quadrant rule for the optically active aromatic chromophore in rigid polycyclic systems. Tetrahedron 25, 5099–5112.

Drewes, S.E., Ilsley, A.H., 1969. Dioxan-linked biflavanoid from the heartwood of *Acacia mearnsii*. Journal of the Chemical Society C, 897–900.

Drewes, S.E., Roux, D.G., Eggers, S.H., Feeney, J., 1967. Three diastereoisomeric 4,6-linked bileucofisetinidins from the heartwood of *Acacia mearnsii*. Journal of Chemical Society C, 1217–1227.

Ferreira, D., Bekker, R., 1996. Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles. Natural Product Reports 13, 411–433.

Ferreira, D., Li, X-C., 2000. Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles. Natural Product Reports 17, 193–212.

Ferreira, D., Marais, J.P.J., Slade, D., Walker, L.A., 2004. Circular dichroic properties of flavan-3,4-diols. Journal of Natural Products 67, 174–178.

Ferreira, D., Slade, D., 2002. Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles. Natural Product Reports 19, 517–541.

Foo, L.Y., 1985. Facile self-condensation of melacacidin: a demonstration of the reactivity of the pyrogallol A-ring. Journal of the Chemical Society, Chemical Communications, 1273–1274.

Foo, L.Y., 1986. A novel pyrogallol A-ring proanthocyanidin dimer from *Acacia melanoxylon*. Journal of the Chemical Society, Chemical Communications, 236–237.

Foo, L.Y., 1989. Isolation of [4-*O*-4]-linked biflavanoids from *Acacia melanoxylon*: first examples of a new class of single ether-linked proanthocyanidin dimers. Journal of the Chemical Society, Chemical Communications, 1505–1506.

Hemingway, R.W., 1989. Biflavonoids and proanthocyanidins. In: Rowe, J.W. (Ed.), Natural Products of Woody Plants: Chemicals Extraneous to the Lignocellulosic Cell Wall, vol. 1. Springer, New York, pp. 571–651.

Howell, H., Malan, E., Steenkamp, J.A., Brandt, E.V., Brand, J., 2002. Identification of two novel promelacacinidin dimers from *Acacia nigrescens*. Journal of Natural Products 65, 769–771.

Kolodziej, H., 1983. The first naturally occurring 4-arylflavan-3-ol. Tetrahedron Letters 24, 1825–1828.

Korver, O., Wilkins, C.K., 1971. Circular dichroism spectra of flavanols. Tetrahedron 27, 5459–5465.

Malan, E., 1995. A (4β → 5)-linked proteracacinidin dimer from the heartwood of *Acacia caffra*. Phytochemistry 40, 1519–1521.

Malan, E., Sireeparsad, A., 1995. The structure and synthesis of the first dimeric proteracacinidins from *Acacia galpinii*. Phytochemistry 38, 237–239.

Malan, E., Sireeparsad, A., Burger, J.F.W., Ferreira, D., 1994. A novel doubly-linked proteracacinidin analog from *Acacia caffra*. Tetrahedron Letters 35, 7415–7416.

Malan, E., Sireeparasad, A., Swinny, E., Ferreira, D., 1997. The structure and synthesis of a 7,8,4′-trihydroxyflavan-epioritin dimer from *Acacia caffra*. Phytochemistry 44, 529–531.

Malan, J.C.S., Young, D.A., Steenkamp, J.A., Ferreira, D., 1988. Oligomeric flavanoids. Part 2. The first profisetinidins with dihydroflavonol constituent units. Journal of the Chemical Society, Perkin Transactions 1, 2567–2572.

Malan, J.C.S., Young, D.A., Steynberg, J.P., Ferreira, D., 1990. Oligomeric flavanoids. Part 9. The first biflavanoids based on mopanol and peltogynol as inceptive electrophiles. Journal of the Chemical Society, Perkin Transactions 1, 219–225.

Nel, R.J.J., Van Rensburg, H., Van Heerden, P.S., Ferreira, D., 1999. Stereoselective synthesis of flavonoids. Part 8. Free phenolic flavan-3-ol diastereoisomers. Journal of Chemical Research (S) 606–607 (M), 2610–2625.

Porter, L.J., 1988. Flavans and proanthocyanidins. In: Harborne, J.B. (Ed.), The Flavonoids: Advances in Research Since 1980. Chapman & Hall, London, pp. 21–62.

Porter, L.J., 1994. Flavans and proanthocyanidins. In: Harborne, J.B. (Ed.), The Flavonoids: Advances in Research Since 1986. Chapman & Hall, London, pp. 23–55.

Roux, D.G., Ferreira, D., 1982. The direct biomimetic synthesis, structure and absolute configuration of angular and linear condensed tannins. Progress in the Chemistry of Organic Natural Products 41, 47–76.

Roux, D.G., Paulus, E., 1962. Interrelationships of flavonoid components from the heartwood of *Robinia pseudacacia*. Biochemical Journal 82, 324–330.

Steenkamp, J.A., Malan, J.C.S., Roux, D.G., Ferreira, D., 1988. Oligomeric flavanoids. Part 1. Novel dimeric profisetinidins from *Colophospermum mopane*. Journal of the Chemical Society, Perkin Transactions 1, 1325–1330.

Steynberg, J.P., Ferreira, D., Roux, D.G., 1983. The first condensed tannins based on a stilbene. Tetrahedron Letters 24, 4147–4150.

Steynberg, J.P., Ferreira, D., Roux, D.G., 1987. Synthesis of condensed tannins. Part 18. Stilbenes as potent nucleophiles in regio- and stereo-specific condensations: novel guibourtinidol-stilbenes from *Guibourtia coleosperma*. Journal of Chemical Society, Perkin Transactions 1, 1705–1712.

Steynberg, J.P., Steenkamp, J.A., Burger, J.F.W., Young, D.A., Ferreira, D., 1990. Oligomeric flavanoids. Part 11. Structure and synthesis of the first phlobatannins related to (4α,6:4α,8)-bis-(−)-fisetinidol-(+)-catechin profisetinidin biflavanoids. Journal of Chemical Society, Perkin Transactions 1, 235–240.

Steynberg, P.J., Cronje, A., Steynberg, J.P., Bezuidenhoudt, B.C.B., Brandt, E.V., Ferreira, D., 1997. Oligomeric flavanoids. Part 25. Cleavage of the acetal functionality in A-type proanthocyanidins. Tetrahedron 53, 2591–2598.

Steynberg, P.J., Nel, R.J.J., Van Rensburg, H., Bezuidenhoudt, B.C.B., Ferreira, D., 1998. Oligomeric flavanoids. Part 27. Interflavanyl bond formation in procyanidins under neutral conditions. Tetrahedron 54, 8153–8158.

Van der Westhuizen, J.H., Ferreira, D., Roux, D.G., 1981. Synthesis of condensed tannins. Part 2. Synthesis by photolytic rearrangement, stereochemistry, and circular dichroism of the first 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols. Journal of the Chemical Society, Perkin Transactions 1, 1220–1226.

Van Heerden, F.R., Brandt, E.V., Ferreira, D., Roux, D.G., 1981. Metabolites from the purple heartwood of the Mimosoideae. Part 4. *Acacia fasciculifera* F. Muell ex. Benth: Fasciculiferin, fasciculiferol, and the sythesis of 7-aryl- and 7-flavanyl-peltogynoids. Journal of the Chemical Society, Perkin Transactions 1, 2483–2490.

Viviers, P.M., Young, D.A., Botha, J.J., Ferreira, D., Roux, D.G., Hull, W.E., 1982. Synthesis of condensed tannins. Part 6. The sequence of units, coupling positions and absolute configuration of the first linear [4,6:4,6]-triflavanoid with terminal 3,4-diol function. Journal of the Chemical Society Perkin Transactions 1, 535–540.

Young, D.A., Ferreira, D., Roux, D.G., 1983. Synthesis of condensed tannins. Part 10. 'Dioxane-linked' profisetinidins. Journal of the Chemical Society, Perkin Transactions 1, 2031–2035.

Young, D.A., Young, E., Roux, D.G., Brandt, E.V., Ferreira, D., 1987. Synthesis of condensed tannins. Part 19. Phenol oxidative coupling of (+)-catechin and (+)-mesquitol. Conformation of bis-(+)-catechins. Journal of the Chemical Society, Perkin Transactions 1, 2345–2351.

Young, E., Brandt, E.V., Young, D.A., Ferreira, D., Roux, D.G., 1986. Synthesis of condensed tannins. Part 17. Oligomeric (2*R*,3*S*)-3,3′,4′,7,8-pentahydroxyflavans. Atropisomerism and conformation of biphenyl and *m*-terphenyl analogs from *Prosopis glandulosa* ('Mesquite'). Journal of the Chemical Society, Perkin Transactions 1, 1737–1749.

**Daneel Ferreira** graduated from the University of Pretoria, South Africa in 1964. He completed the B.Sc. (Hons.) and M.Sc. programmes of the Chemistry Department, University of the Orange Free State, Bloemfontein, South Africa through part time studies. In 1969, he was appointed as Technical Assistant in the Chemistry Department at UOFS, obtained the D.Sc. degree in Organic Chemistry in 1973 and progressed to the ranks of Professor of Organic Chemistry in 1985. He spent 1977 as a Visiting Lecturer at Imperial College, London where he worked under the supervision of the late Sir Derek Barton. His main area of research is in the study of the chemistry of flavonoids and proanthocyanidins where he focusses on structure elucidation (up to the tetraflavanoid level) via physical methods, especially NMR and CD, semisynthesis of oligomers, stereoselective syntheses of monomeric precursors, and the development of general methodologies to manipulate the molecular backbone of the C6.C3.C6 unit. He was invited to establish a Research Unit for Polyphenol- and Synthetic Chemistry at UOFS by the Foundation for Research Development, Pretoria and was duly appointed as Director in 1990. He held this position until 1998 before joining the Thad Cochran National Center for Natural Products Research, University of Mississippi in 1999 as Visiting Scholar, and was promoted to Principal Scientist in 2000. He was offered the Chair of the Department of Pharmacognosy, University of Mississippi, in 2004 where he continues with research of the chemistry of Natural Products.

**Jannie P.J. Marais** studied at the University of the Free State, Bloemfontein, South Africa where he obtained his Ph.D. in Organic Chemistry in 2002 under joint supervision of Prof. E.V. Brandt, Dr. H. van Rensburg and Dr. D. Ferreira. His research work focused on characterization of the free phenolic profile of South African red wine, and the stereoselective synthesis of constituent flavonoids, e.g., flavan-3,4-diols and flavanones. He joined the National Center for Natural Products Research at the University of Mississippi as a Postdoctoral Associate in July of 2002, where he currently works with Dr. Ferreira on the stereoselective synthesis of flavanoid precursors, the semisynthesis of proanthocyanidin oligomers, and characterization of the proanthocyanidin profiles of selected transgenic plants.

**Desmond Slade** graduated from the University of Stellenbosch, South Africa in 2000, where he obtained his Ph.D. (Chemistry) on the chemical characterization of the interdigital secretion of the black wildebeest under the supervision of Prof. Ben V. Burger. He started as a Postdoctoral Research Associate at the National Center for Natural Products Research, University of Mississippi, at the end of 2000, working on the synthesis of antimalarial 8-aminoquinolines and the synthesis of buprenorphine-3-β-D-glucuronide and norbuprenorphine-3-β-D-glucuronide and their deuterated analogs under the supervision of Dr. Daneel Ferreira. Since 2003, he is an Associate Research Scientist in the Center where he is also involved in cannabinoid research.