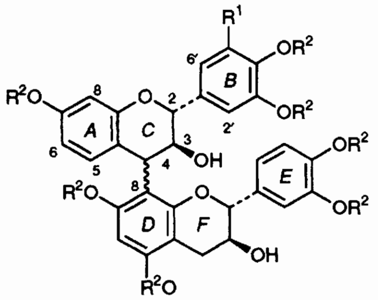
Cleavage of the Interflavanyl Bond in 5-Deoxy (*A* Ring) Proanthocyanidins

Petrus J. Steynberg, Jan P. Steynberg,* Barend C. B. Bezuidenhoudt and Daneel Ferreira*

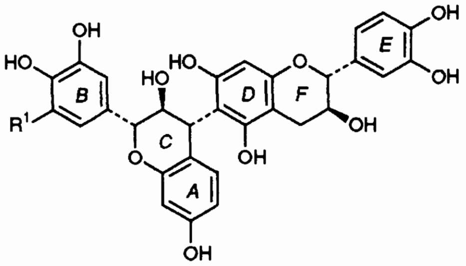
Department of Chemistry, University of the Orange Free State, PO Box 339, Bloemfontein, 9300 South Africa

The fisetinidol-(4,8) and (4,6)-catechin profisetinidin biflavanoids **1, 4** and **5** respectively, are subject to facile cleavage of the interflavanyl linkage with sodium cyanoborohydride in trifluoroacetic acid at 0 °C.

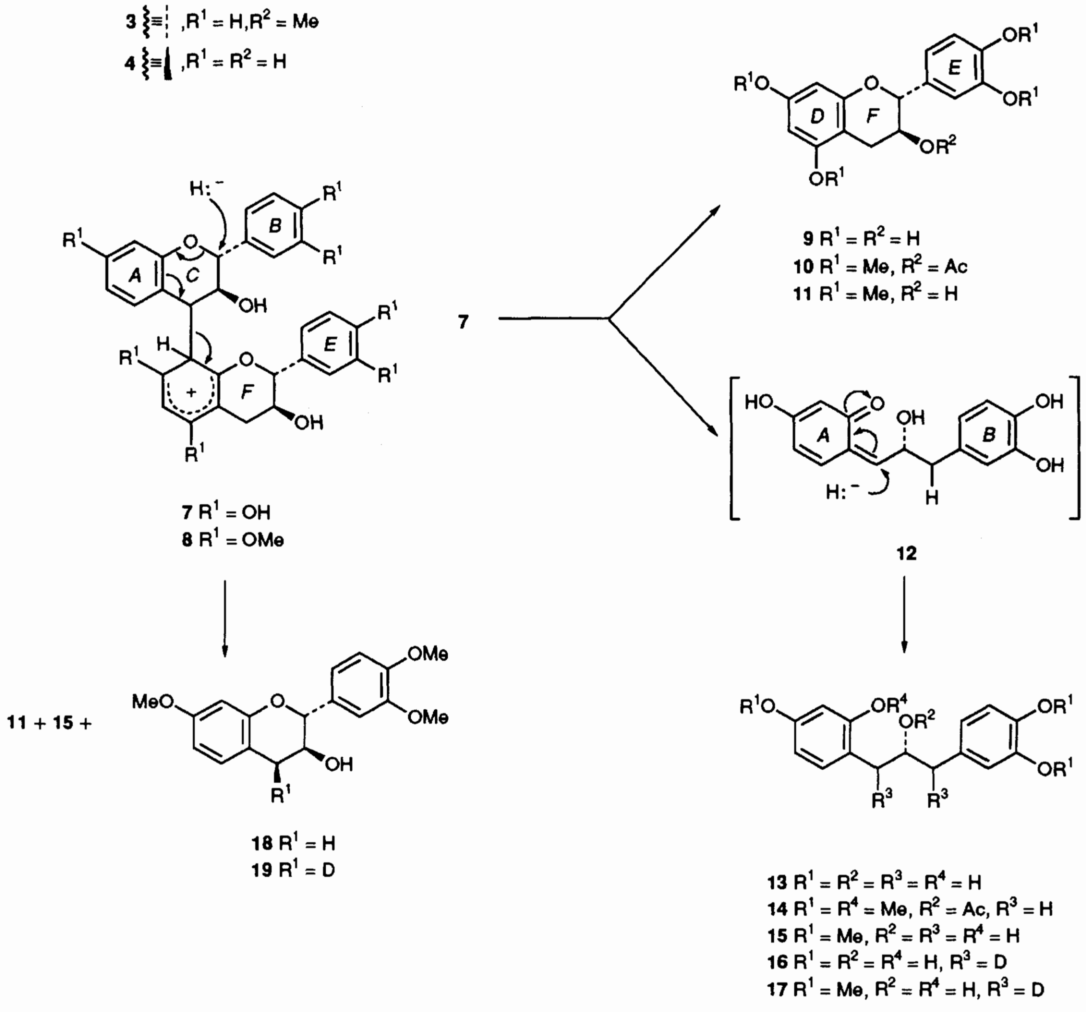
The interflavanyl bond in proanthocyanidins exhibiting oxygenation at C-5 of the *A* ring of their chain extender units is susceptible to facile cleavage with sulfur nucleophiles under acid catalysis.[1,2] In the 5-deoxy analogues, *e.g.* the fisetinidol-(4,8)- and (4,6)-catechin profisetinidins **1**, **4** and **5**, and the analogous prorobinetinidins **2** and **6** from the commercially important bark of *Acacia mearnsii* (black wattle),[3] the same bond is remarkably stable under a variety of conditions.[4,5] This C(sp^3)–C(sp^2) bond has hitherto resisted all efforts at cleavage in a controllable manner hence inhibiting both the



1 ⌇≡⋮ ,$R^1 = R^2 = H$
2 ⌇≡⋮ ,$R^1 = OH = R^2 = H$
3 ⌇≡⋮ ,$R^1 = H, R^2 = Me$
4 ⌇≡▌ ,$R^1 = R^2 = H$



5 $R^1 = H$
6 $R^1 = OH$



9 $R^1 = R^2 = H$
10 $R^1 = Me, R^2 = Ac$
11 $R^1 = Me, R^2 = H$

7 $R^1 = OH$
8 $R^1 = OMe$

12

11 + 15 +

18 $R^1 = H$
19 $R^1 = D$

13 $R^1 = R^2 = R^3 = R^4 = H$
14 $R^1 = R^4 = Me, R^2 = Ac, R^3 = H$
15 $R^1 = Me, R^2 = R^3 = R^4 = H$
16 $R^1 = R^2 = R^4 = H, R^3 = D$
17 $R^1 = Me, R^2 = R^4 = H, R^3 = D$

Scheme 1 Proposed route to the cleavage of the interflavanyl bond and of the heterocyclic *C* ring in profisetinidin **1**

structural elucidation of the polyflavanoid tannins in black wattle bark and of those from important other commercial sources, *e.g. Schinopsis spp.* (quebracho), as well as definition of the absolute configuration of the chain terminating flavan-3-ol moiety in the 5-deoxy oligoflavanoids. We now report on the efficiency of sodium cyanoborohydride to effect the first cleavage of the interflavanyl bond in profisetinidins under conditions sufficiently mild to allow the isolation and identification of the constituent flavanyl units.

Treatment of the fisetinidol-(4α,8)-catechin **1**,[5] representing a typical tannin unit of commercial wattle extract, with sodium cyanoborohydride[6] (24 molar excess) in trifluoroacetic acid (TFA) for 6 h at 0 °C under nitrogen, gave conversion to a mixture comprising the starting material **1** (24%), catechin **9** (15%) and the (2*S*)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)-propan-2-ol **13** (16%) (54% recovery of material). The structures of compounds **9** and **13** were elucidated by comparison of the physical data [^{1}H NMR and CD (circular dichroism) of their methyl ether acetates **10** and **14** with those of authentic samples (*cf.* ref. 7 for compound **13**). Similar treatment of the fisetinidol-(4β,8)- and (4α,6)-catechin profisetinidins[5] **4** and **5** with their respective more and less labile interflavanyl bonds compared to the C(4)–C(8) bond in compound **1** under acidic conditions,[8] also afforded a mixture consisting of starting material (**4**, **5**; 16, 12% respectively), catechin (**9**; 17, 4% respectively), and the 2*S*-1,3-diarylpropan-2-ol (**13**, 18, 4% respectively) (50 and 20% recovery of material). Although the yields of catechin **9** and the 1,3-diarylpropan-2-ol **13** could be increased to 24 and 25%, respectively, and that of starting material **1** decreased to 11% by employing more mild conditions (9 molar excess of sodium cyanoborohydride, 3 h), the recovery of material could not be improved beyond *ca.* 50%.

Similar conditions also effected cleavage of the interflavanyl bond in the fisetinidol-(4α,8)-catechin hepta-*O*-methyl ether **3** hence yielding tetra-*O*-methylcatechin (**11**, 21%), the 1,3-diarylpropan-2-ol (**15**, 12%), and tri-*O*-methylfisetinidol (**18**, 12%). Such a bond cleavage in the permethyl ether **3** adds an important dimension to these results in relation to the chemistry of 5-deoxy oligoflavanoids where derivatization is often a prerequisite for sample purity. The 'liberation' of the chain terminating flavan-3-ol unit **9** provides a powerful probe towards addressing the hitherto unsolved problem of defining the absolute configuration of this moiety in naturally occurring oligoflavanoids that are often synthetically inaccessable due to the unavailability of the flavan-3,4-diol and/or flavan-3-ol precursors.

Whereas the heterocyclic ring of the catechin moiety remains intact during the reductive process, cleavage of both the (4,6)- and (4,8)-interflavanyl bonds in the free phenols **1**, **4**, and **5** is apparently associated with the opening of the 'upper' chain extender unit. Protonation of the electron-rich phloroglucinol *D* ring[9] in the profisetinidin **1** (Scheme 1) and concomitant delivery of the equivalent of a hydride ion at C-2 (*C* ring) of intermediate **7**, effects the simultaneous rupture of the pyran *C* ring and of the C(4)–C(8) bond to give catechin **9** and the *o*-quinone methide **12** which is subsequently reduced to the 1,3-diarylpropan-2-ol **13**. Such interdependence of the cleavage of the O–C(2) and C(4)–C(8) bonds was demonstrated by the inability of the reagent to effect opening of the heterocycle of catechin **9**. The resistance to reductive cleavage of the benzyl ether functionality of catechin contrasts with the formation of flavans or 1,3-diarylpropanes during treatment of flavanones with Na(CN)BH$_3$/TFA.[10]

The mechanism of cleavage of the interflavanyl bond in profisetinidin biflavanoids was confirmed *via* utilization of sodium cyanoborodeuteride in TFA. Under these conditions the fisetinidol-(4α,8)-catechin **1** was converted to catechin **9** and the dideuterio-1,3-diarylpropan-2-ol **16**, while the permethylether **3** gave tetra-*O*-methyl catechin **11**, the dideuterio-1-3-diarylpropan-2-ol **17**, and the 4β-deuteriofisetinidol derivative **19** in yields comparable to those obtained with Na(CN)BH$_3$. Formation of the deuteriated 1,3-diarylpropan-2-ols **16** and **17** with retention of the absolute configuration at C(2)[11] confirms our conjecture regarding the genesis of the propan-2-ols *via* reduction of the *o*-quinone methide **12**. The protonated species **8** also serves as precursor to the 4β-deutero-tri-*O*-methylfisetinidol **19** *via* delivery of hydride ion from the β-face in an S$_N$2 mode.

The potential of this development towards the structural elucidation of the 5-deoxy proanthocyanidin condensed tannins from important commercial sources is clear. In addition the method should facilitate the ready definition of the absolute configuration of the chain terminating flavan-3-ol moiety in 5-deoxy oligoflavanoids, especially in view of the demonstration that these units may also comprise of *ent*-catechin,[12] and *ent*-epicatechin.[13]

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