The First Natural Procyanidin with a 3,4-*cis* Configuration

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Structural examination of the phenolic metabolites of *Potentilla erecta* (L) Raeuschel revealed the presence of the first natural procyanidin with a 3,4-*cis* configuration, which is associated with the 'conventional' biflavanoids B_3 and B_6, indicating that similar stereochemical control mechanisms operate in the formation of procyanidins as previously established for the formation of profisetinidins.

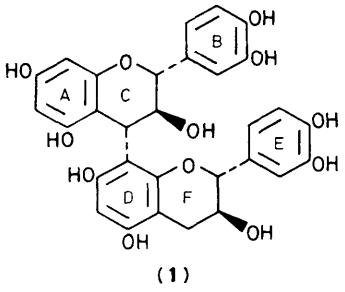
Biomimetic-type condensations of (+)-leucocyanidin with (+)-catechin have recently revealed evidence for the first 2,3-*trans*-3,4-*cis*:2,3-*trans*-[4,8]-bi-(+)-catechin in significant yield, suggesting the possibility of incorporation of constituent flavanyl units with 3,4-*cis* stereochemistry in natural procyanidins.[1] Similar evidence for the 3,4-*cis* procyanidin configuration, albeit its formation occurring in a much lower proportion, was provided by the reaction between (+)-leucocyanidin and (−)-epicatechin.[2] Natural condensed tannins of 3,4-*cis* stereochemistry have previously only been observed in profisetinidins and prorobinetinidins.[3] The present communication provides the first evidence for the existence of a natural procyanidin biflavanoid with 3,4-*cis* stereochemistry.

Re-examination of the ethyl acetate soluble portion of commercial rhizomes of tormentil, following earlier work on the same material by Ahn,[4] has resulted in the isolation of the expected [4,8]-all-*trans*-bi-(+)-catechin [procyanidin B_3, (**1**)], but afforded in addition two previously overlooked biflavanoids. These compounds were identified as the [4,6]-all-*trans* structural isomer [procyanidin B_6, (**2**)] and the [4,8]-3,4-*cis* analogue (**3**), respectively, the latter representing the first natural procyanidin of 2,3-*trans*-3,4-*cis* configuration ($J_{2,3}$ 9.6 Hz and $J_{3,4}$ 6.5 Hz). All phenolic metabolites were characterized as their fully acetylated derivatives by ^{1}H n.m.r. spectroscopy and circular dichroism and their structures confirmed by comparison of their spectral data with those of synthetic reference samples.[1,5]

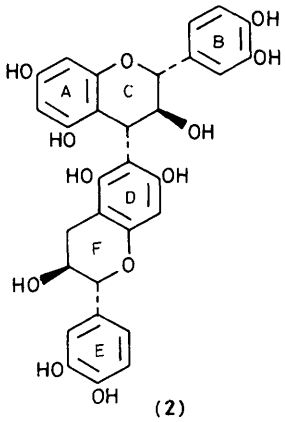
The natural occurrence of this same procyanidin with 3,4-*cis* stereochemistry and its association with the 'conventional' procyanidins B_3 and B_6 was also demonstrated by their isolation from *Potentilla erecta*. These phenols were distinguished from each other as before by a combination of coupling constants ($J_{3,4}$) and the chemical shifts of the 2-protons of their 'lower' flavanyl units [δ 4.94, 5.04, and 4.38 for (**1**), (**2**), and (**3**), respectively] and by the high intensity Cotton effects in the c.d. spectra [(**1**) and (**2**) negative, (**3**) positive].[1,5]

An excellent correlation between the proportions of the products obtained in the synthetic and biogenetic processes is found, the yields of the metabolites being in approximately the same ratio as their synthetic generation (8 : 1 : 1).[1]

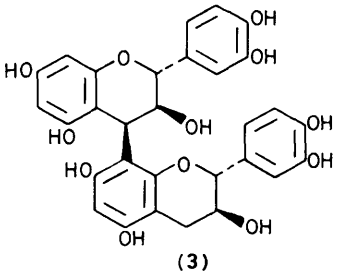
The regioselectivity observed in the synthesis of [4,6]- and



(1)



(2)



(3)

[4,8]-2,3-*trans*-procyanidins in favour of the sterically less hindered 8-position on (+)-catechin[1,2] is reflected in the relative natural abundance of the different procyanidin isomers,[6] which is analogous to the regioselectivity encountered in the formation of profisetinidins and to the natural distribution of the isomers.[3,7]

The stereochemistry of procyanidins at C-4 is invariably *trans* to the C-3 hydroxy group. The natural co-occurrence of the 3,4-*cis* procyanidin (**3**) and procyanidins B_3 and B_6, and the analogy evident from *in vitro* synthesis,[1] contrasts with such stereospecificity and is, therefore, indicative of stereochemical control mechanisms similar to those in profisetinidins.[3] The stereochemical course of the coupling is considered to be controlled primarily by the 2,3-stereochemistry of the 4-carbenium ion derived from flavan-3,4-diols.[3] Attack of the flavanyl carbenium ion with 2,3-*trans* stereochemistry yields predominantly products with the 3,4-*trans* configuration, but also the 3,4-*cis* isomer, while the 2,3-*cis* intermediate gives 3,4-*trans* products stereospecifically, on the assumption that both carbenium ions possess chair conformations. The discovery that procyanidins with a 3,4-*cis* configuration exist in nature allows expansion of the concept that the steric influences in procyanidins and profisetinidins are similar. Stereo- and regio-selectivity may accordingly be rationalized on the basis of an S_N1 mechanism combined with the 'stability–selectivity relationship'.[8,9]

It may be noted that our approach[1,9] to procyanidins using tetramethoxyflavan-3,4-diols as electrophiles for the condensation with nucleophilic flavan-3-ols supports the generation of 4-carbenium ions as reactive intermediates rather than quinone methides.[10,11] The question of the possible role of quinone methides in the biogenesis of condensed tannins under the acidic conditions in plants is therefore still open to doubt.

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