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ASSESSMENT OF 3,4–*TRANS* AND 3,4–*CIS* RELATIVE CONFIGURATIONS IN THE A–SERIES OF (4,8)–LINKED PROANTHOCYANIDINS

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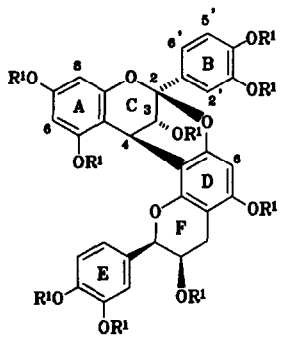
Abstract —— Proanthocyanidins of the A–type exhibit identical ^{1}H NMR coupling constants ($J_{3,4}$ = 3.5 Hz) irrespective of the relative configurations of their C-rings. The selective ^{1}H NOE association of 3–H (C-ring) to either 6–H(D) or 8–H(A) permits unequivocal differentiation of (4,8)-linked analogues with respectively 3,4-*trans* or 3,4-*cis* configurations of these heterocyclic rings.

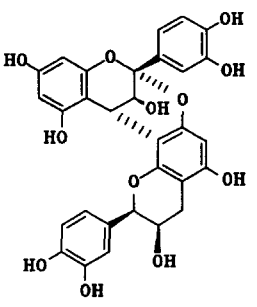
Since the first isolation[1] and structural elucidation[2,3] of proanthocyanidin A–2 1 [(–)-epicatechin-(4β → 8, 2β → O → 7)-(–)-epicatechin], a variety of analogues possessing the doubly-linked unit of either (2β,4β)- 1 or (2α,4α)-configuration 3 has been reported[4–7]. These compounds invariably display $^3J_{HH}$ = 3–4 Hz[2] for 3– and 4–H (C-ring), a phenomenon which by reference to X-ray data for procyanidin A–2 1 and ^{13}C NMR comparisons, has consequently been accepted to indicate 3,4-*trans* relative configuration for all known compounds in this class of naturally occurring condensed tannins. Consideration, however, of the structure of a putative A-type proanthocyanidin with 3,4-*cis* configuration 4 in conjunction with the conformational rigidity of the bicyclic ring system indicates very similar dihedral angles between 3– and 4–H(C) in both 3,4-*trans* 5 and 3,4-*cis* 6 homologues which should thus lead to almost identical coupling constants for these protons. We now disclose evidence demonstrating the inability to differentiate between these configurations in A-type proanthocyanidins on the basis of ^{1}H NMR coupling constants. In addition a method based on selective ^{1}H NOE association of 3–H(C) permitting such differentiation is described.

As part of our study of the base-catalyzed pyran rearrangements of proanthocyanidins[8], (–)-robinetinidol-(4β,8)-(+)-catechin mono-*O*-methyl ether 7 was treated with 0.1M Na_2CO_3 – 0.1M $NaHCO_3$ buffer solution (pH 10.0) for 3 h at 50^{0}C under nitrogen containing traces of oxygen. Column chromatography of the mixture using Sephadex LH–20/ethanol afforded amongst others[a], (–)-robinetinidol-(4β → 8, 2β → O → 7)-(+)-catechin mono-*O*-methyl ether 4 in 18% yield. Its ^{1}H NMR spectrum[9] at 300 MHz in $(CD_3)_2CO$ exhibited the characteristic AB-system [δ4.07, 4.15, both d, J3.5 Hz; 3– and 4–H(C) respectively] associated with A-type proanthocyanidins[2]. The (2β,4β)-orientation and hence the absolute configuration depicted in formulation 4 was confirmed by a high-amplitude positive Cotton effect at 240 nm in the CD spectrum[10].

[a]Details of the remaining compounds will be published elsewhere.



1 R^1=H
2 R^1=Ac



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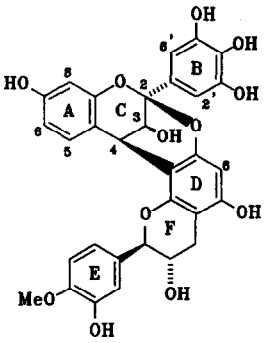
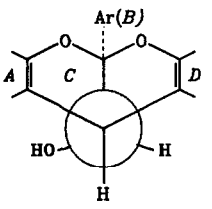
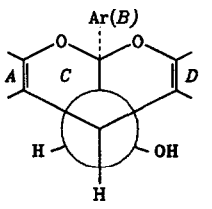


4

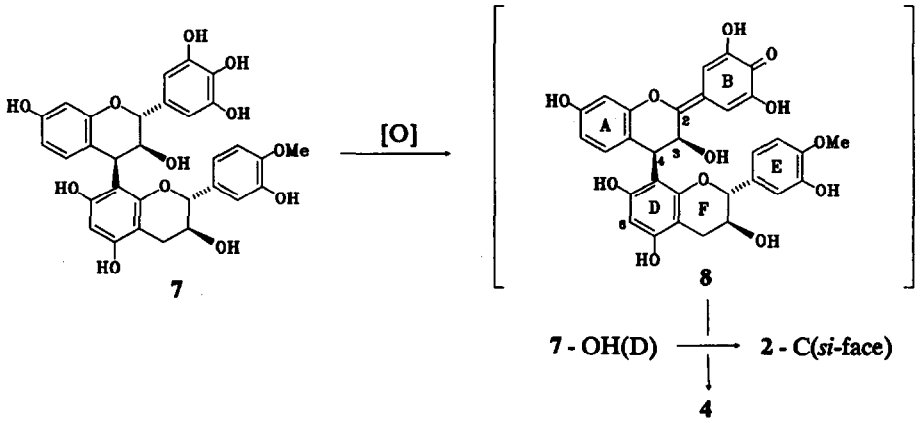


5 (3,4-*trans*)



6 (3,4-*cis*)

Newman projections along the C-4/C-3 axis of the A-type proanthocyanidins 1, and 4



Scheme: Proposed route to the formation of the A-type prorobinetinidin 4

This novel compound, represents both the first A-type analogue of the 5-deoxy (A–ring) oligoflavanoids and also the first entry amongst this class of proanthocyanidins with a 3,4-*cis* C-ring configuration. The mechanism for its formation *via* an intermediate quinone-methide 8 (Scheme) is similar to that established for the conversion of procyanidin B–2 to procyanidin A–4[11].

Comparison of the ^{1}H NMR data of the A-type prorobinetinidin 4 and those of the peracetate 2[12] of procyanidin A–2 1 revealed the conspicuous identity of their 3– and 4–H coupling constants ($J_{3,4}$ = 3.5 Hz for both 2 and 4). This observation prompted assessment of the potential of the powerful ^{1}H NOE technique towards differentiation of A-type analogues exhibiting 3,4-*trans* or 3,4-*cis* configuration of their C-rings. Besides the stereochemically insignificant[13] NOE association of 3–H(C) with 2– and 6–H(B) in both 2 and 4, this proton showed a selective NOE effect to 6–H(D) (δ6.47, s, 1.0%) in the procyanidin A–2 derivative 2 ONLY. In the A-type 3,4-*cis* prorobinetinidin 4, however, 3–H(C) exhibited selective association with both 5– and 8–H(A) (δ7.07, d, J8.5 Hz; δ6.33, d, J2.5 Hz; 1.0 and 1.3% resp.), the corresponding effect between 3–H(C) and 8–H(A) (δ6.79, d, J2.5 Hz) being conspicuously absent in the procyanidin A–2 peracetate 2. These highly selective NOE associations of 3–H(C) to 5– and 8–H(A) in 4 and of 3–H(C) to 6–H(D) in 2 are only permitted for an *axial* 3-proton in the former case and for an *equatorial* 3-proton in the latter instance hence facilitating the unambiguous assignment of the 3,4-relative configuration in the A-type proanthocyanidins. Dreiding models furthermore indicate that the NOE associations should be independent of the 2– and 4–C absolute configuration *i.e* applicable also to analogues of type 3 with (2α,4α)-configuration.

Acknowledgements

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9. ^{1}H NMR data in $(CD_3)_2CO$ for 4: δ7.07 [d, J8.5 Hz, 5–H(A)], 6.38 [dd, J2.5 and 8.5 Hz, 6–H(A)], 6.33 [d, J2.5 Hz, 8–H(A)], 6.75 [s, 2–/6-H(B)], 4.07 [d, J3.5 Hz, 3–H(C)], 4.15 [d, J3.5 Hz, 4-H(C)], 6.15 [s, 6-H(D)], 6.99 [d, J2.0 Hz, 2-H(E)], 6.96 [d, J8.0 Hz, 5-H(E)], 6.91 [dd, J2.0 and 8.0 Hz, 6-H(E)], 4.66 [d, J8.0 Hz, 2-H(F)], 3.93 [m, 3-H(F)], 2.54 [dd, J9.0 and 16.0 Hz, 4-$H_{ax.}$(F)], 2.95 [dd, J5.5 and 16.0 Hz, 4–$H_{eq.}$(F)], and 3.86 [s, 4-OMe(E)].

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12. The magnitude of $J_{3,4}$ is not influenced by derivatization of procyanidin A–2 (see ref. 2).

13. These effects, however, confirm the chemical shift of 3-H(C) (see ref. 11).

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