

Condensed Tannins. Circular Dichroism Method of Assessing the Absolute Configuration at C-4 of 4-Arylflavan-3-ols, and Stereochemistry of their Formation from Flavan-3,4-diols

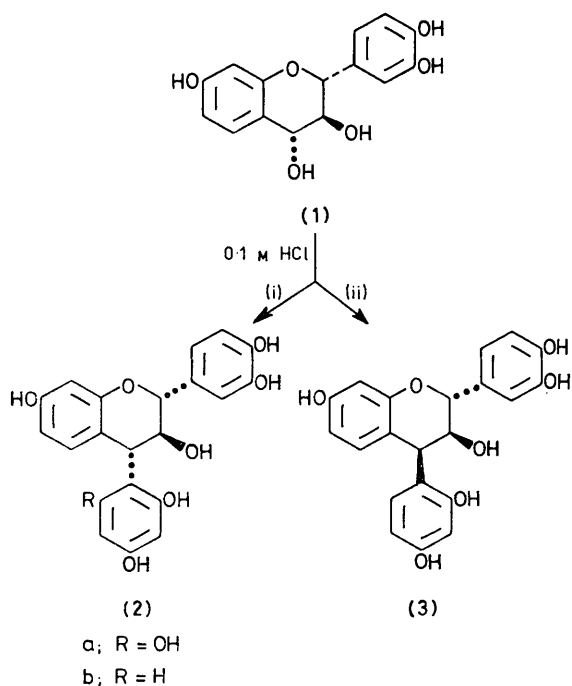
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Summary Stereoselective condensation at C-4 of flavan-3,4-diols of known absolute configuration with phloroglucinol and resorcinol proceeds at ambient temperatures with either partial or complete retention of configuration for 2,3-*trans*-isomers and with inversion for 2,3-*cis*-isomers, phenomena that are considered to be of prime significance in condensed tannin formation; multiple Cotton effects contributed by aryl chromophores at C-4 dominate the c.d. spectra of the resultant 4-aryl-2,3-*trans*- and 2,3-*cis*-flavan-3-ols, enabling unambiguous determination of their absolute configurations at this chiral centre.

OPTIMIZED conditions for generating carbonium ions at C-4 from the flavan-3,4-diol (+)-mollisacacidin, of known¹ (2*R*,3*S*,4*R*) configuration (**1**), were established as involving ambient temperatures ($\pm 20^\circ\text{C}$), low acid concentrations (0.1 M HCl), and short reaction times (20 min). Condensation with phloroglucinol present in 7 molar excess gave the 2,3-*trans*-3,4-*trans*-4-arylflavan-3-ol (**2a**) ($J_{2,3}$ 10.0; $J_{3,4}$ 9.8 \dagger) of 2*R*,3*S*,4*S* configuration as sole product (53%) without anthocyanidin formation, the reaction proceeding with retention of configuration. Similar reaction with resorcinol in place of phloroglucinol gave both 3,4-*trans*- (**2b**; $J_{2,3}$ 10.0, $J_{3,4}$ 9.0; \dagger 2*R*,3*S*,4*R*) and 3,4-*cis*-analogues

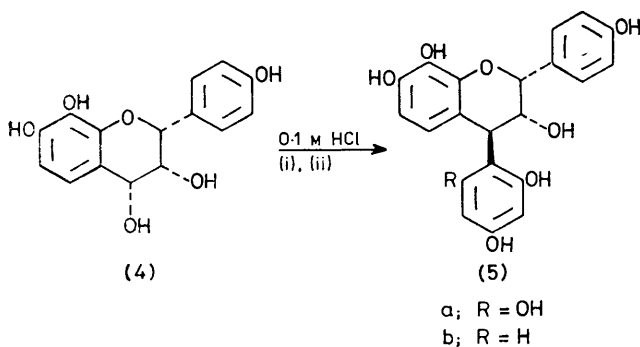
\dagger Coupling constants (in Hz) are those of methyl ether 3-*O*-acetates.



(i) Phloroglucinol; (ii) resorcinol.

(3; $J_{2,3}$ 8.0, $J_{3,4}$ 5.0; † 2*R*,3*S*,4*S*), the former predominating (38 and 22% yields). ‡ The mechanism and reaction conditions (presumed absence of inversion to thermodynamically more stable 3,4-*cis* product) permit high net retention of configuration.

From both mechanistic and stereochemical viewpoints it is of interest that the carbonium ion formed under identical conditions from 2,3-*cis*-3,4-*cis*-(-)-teracacidin² (4, 2*R*,3*R*,4*R*) is captured stereoselectively by both phloroglucinol and resorcinol to form 2,3-*cis*-3,4-*trans*-4-arylflavan-3-ol analogues§ (5a, 5b; $J_{2,3} < 1$, $J_{3,4} 3.8$, 1.9; † 2*R*,3*R*,4*R* and 2*R*,3*R*,4*S*) with inversion of configuration.



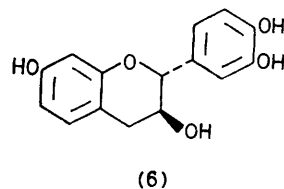
(i) Phloroglucinol; (ii) resorcinol.

A plausible explanation for these stereoselective reactions at C-4 for 2,3-*trans*- and 2,3-*cis*-flavan-3,4-diols centres on

‡ *Added in proof*: Stereochemically analogous condensations of phloroglucinol and resorcinol in 0.05 M HCl occur with the pro-cyanidin (2*R*, 3*S*, 4*R*)-3',4',5,7-tetrahydroxyflavan-3,4-diol, product of reduction of (2*R*, 3*R*)-3,3',4',5,7-pentahydroxyflavan 3-one [(+)-taxifolin] with NaBH₄.

§ Distinguished from 2,3-*cis*-3,4-*cis*-isomers also by extensive secondary couplings of 2-H and 4-H with aromatic protons, characteristic of 2,3-*cis*-flavan-3,4-*trans*-diols (cf. J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Austral. J. Chem.*, 1964, **17**, 632), and by evidence of strong interaction between the 2-*axial*-proton and 4-*quasi-axial*-phenyl groups.

the premise that the heterocyclic rings of carbocations resulting from both (1) and (4) possess a sofa conformation. The course of subsequent nucleophilic attack appears to be subject to varying degrees of 'steric approach control' depending on the *equatorial* and *axial* orientation respectively of the 3-hydroxy-group, and on the relative bulk of the nucleophile. Since flavan-3,4-diols invariably accompany condensed tannins, we suggest that the above mechanism (cf. ref. 3) also predicts the configuration at C-4 of those 2,3-*trans*- and 2,3-*cis*-flavan-3-ol units which constitute condensed tannins.



Comparison of the c.d. curves of the methyl ether 3-*O*-acetates of the 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-4-arylflavan-3-ols [(2a), (2b), and (3); m.p. 135–136 °C for

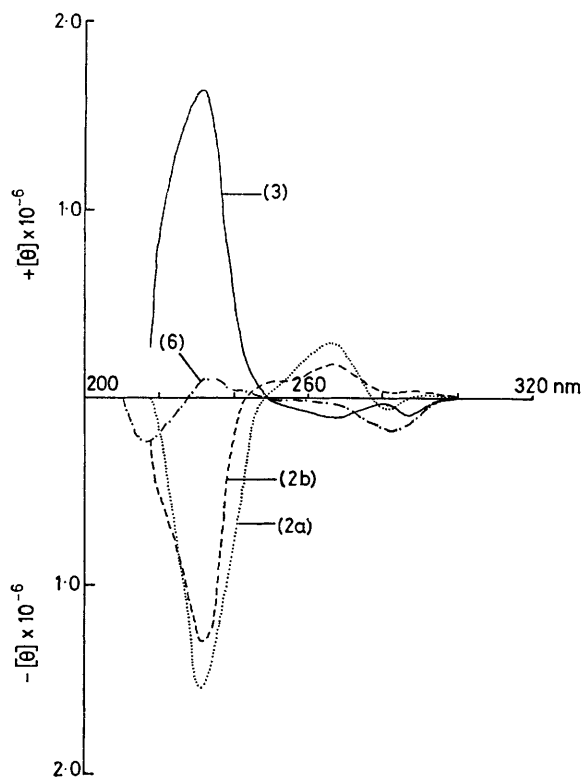


FIGURE 1. C.d. spectra of the methyl ether acetates of 2,3-*trans*-(-)-fisetinidol (6) and of 4-aryl-2,3-*trans*-flavan-3-ols (2a), (2b), and (3).

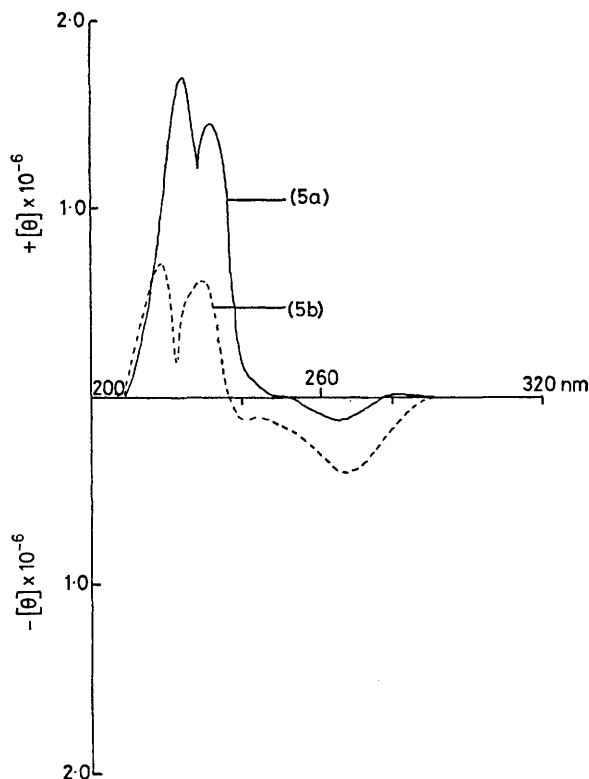


FIGURE 2. C.d. spectra of the methyl ether acetates of 4-aryl-2,3-*cis*-flavan-3-ols (**5a**) and (**5b**).

(**2b**), and the remainder non crystalline], along with that of (–)-fisetinidol (**6**) (Figure 1) indicates that Cotton effects due to chirality at C-2 and C-3 are completely dominated by the multiple effects of the two phenyl chromophores at C-4, introduced with 4-arylation. Also, the reversal of the sign of the high amplitude (220–240 nm) Cotton effects occurs with inversion at C-4, a strong positive effect correlating with 4*R*, and strongly negative with 4*S*, as defined for the 4-phloroglucinol substituent. This correlation also apparently applies to the corresponding derivatives of the 2,3-*cis*-4-arylflavan-3-ols [(**5a**), (**5b**); m.p.s 193–194, 156–157 °C] where the 4*R* configuration, as just defined, corresponds to a multiple high-amplitude positive Cotton effect in the aromatic region (Figure 2). The method thus provides an unambiguous and direct criterion for assessing the absolute configuration at the point of junction of 2,3-*trans*-2',3'-*trans*-biflavonoids (*cf.* ref. 4). Haslam *et al.*⁵ have recently demonstrated the value of ¹³C-n.m.r. spectrometry, as an indirect method based on small chemical shift differences, in achieving the same ends.

This work was supported by grants from the South African Council of Scientific and Industrial Research, Pretoria, the Wattle Bark Industry of South Africa Marketing Committee, and the Sentrale Navorsingsfonds of this University.

(Received, 19th December 1977; Com. 1282.)

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