Direct Synthesis of the First Natural Bi-isoflavonoid

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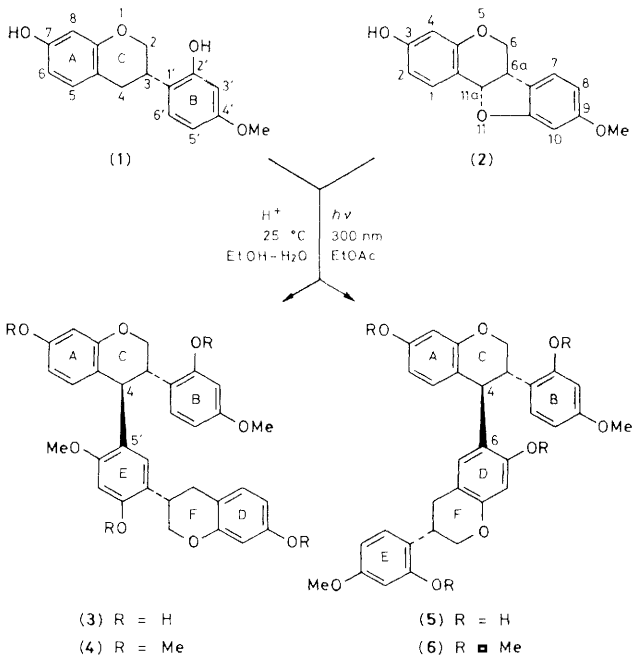
The structure and stereochemistry of the first bi-isoflavonoid (3*S*, 4*S*)-3,4-*trans*-2′,7-dihydroxy-4′-methoxy-4-[(3*S*)-2′,7-dihydroxy-4′-methoxyisoflavan-5′-yl]isoflavan (**3**) from *Dalbergia nitidula* are established by acid-induced condensation or photolysis of the appropriate pterocarpan and isoflavan precursors.

Re-examination of the metabolites from the purple heartwood of *Dalbergia nitidula* Welw. *ex* Bak. (*cf.* ref.[1]) has revealed the existence of bi-isoflavonoids, thus providing the first indication of oligomers amongst metabolites of this class. Isolation of one of these, an amorphous phenol, m.p. 144 °C, in low yield (0.05%) by t.l.c. (Kieselgel, benzene–acetone 7:3, R_F 0.41) from the methanol extract, led to its characterization as the dimeric (3*S*,4*S*)-3,4-*trans*-2′,7-dihydroxy-4′-methoxy-4-[(3*S*)-2′,7-dihydroxy-4′-methoxyisoflavan-5′-yl]isoflavan (**3**). The structure and stereochemistry were assigned on the basis of spectrometry (^{1}H n.m.r., m.s., c.d.) of the compound and its fully methylated ether (**4**), and by its biomimetic and photolytic synthesis from (3*S*)-2′,7-dihydroxy-4′-methoxyisoflavan (**1**) [(+)-vestitol][2] which was isolated from the same plant and the analogous (6a*S*,11a*S*)-3-hydroxy-9-methoxypterocarpan (**2**) [(+)-medicarpin].[3]

Under conditions similar to those used in the synthesis of condensed tannins[4] (2 M HCl, 25 °C, 12 h) their condensation in ethanol–water gives two products, the [4,5′]-bi-isoflavan (**3**), which is identical to its natural counterpart, and its [4,6] positional isomer (**5**) in 20 and 15% yields respectively. Their ^{1}H n.m.r. spectra in [$^2H_6$]acetone are similar, both showing 11 aromatic, 9 heterocyclic, and 2 methoxy-resonances, thus confirming their dimeric nature. No differentiation by mass spectrometry (M^+ 542) is possible, since fragmentation is dominated in both instances by the flavanyl ions of constituent units [*m/z* 272 (88%) and 270 (100%)], presuming hydrogen transfer. Both products (**3**) and (**5**) readily afford their fully methylated ether derivatives (**4**) and (**6**) (M^+ 598) on methylation with MeI–K_2CO_3 in dry acetone.

However, the resolved low-field ^{1}H aromatic resonances of both methyl ether derivatives (**4**) and (**6**) in $CDCl_3$ are characterized by a *para*-coupled singlet and three *ortho*-coupled doublets of which two are either abnormally broadened or split by long-range coupling. Low-power decoupling of the multiplet, δ 2.71, attributed to 4-CH_2 (ring F) in the spectrum of compound (**4**) selectively sharpens the *ortho*-coupled doublet (δ 6.88, *J* 9.0 Hz), thus indicating association of the methylene function with the ABX-system of the D-ring, and by inference interflavanoid coupling with the nucleophilic 5′-position (E-ring) [or B-ring of the parent isoflavan (**1**) during condensation]. By contrast, similar decoupling of the multiplet, δ 2.74, attributable to 4-CH_2(F) of compound (**6**) results in selective sharpening of the *para*-coupled singlet [δ 6.59, *J* < 1 Hz, H-5(D)], indicating interflavanoid bonding with the alternative nucleophilic 6-position of the D-ring [or A-ring of the parent isoflavan (**1**)].

Such diagnostic differentiation is confirmed by decoupling the overlapping 3-protons (C- and F-rings) (m, δ 3.44—3.78) of the [4,5′]-bi-isoflavanoid derivative (**4**), which caused collapse of benzylic coupling associated with H-6′ (E) (*p*-coupled s, δ 6.69, *J* < 1 Hz) and H-6′ (B) (*o*-coupled d, δ 6.97, *J* 9.0 Hz). Irradiation of the 3-protons (C- and F-rings) (m, δ 3.38—3.73) of (**6**) has similar results in that the benzylic couplings exhibited by H-6′ (B) and H-6′ (E) collapse (both d, δ 6.91 and 6.94, *J* 8.8 Hz). The remaining aromatic low-field *ortho*-coupled doublet represented in both (**4**) and (**6**) (δ 6.63, 6.66; *J* 9.2, 9.0 Hz) exhibits perceptible but less pronounced sharpening when irradiating H-4(C) in each instance (2 × d, δ 4.69, 4.63; *J* 9.0, 9.0 Hz).



With the [4,5′]-linkage of the natural bi-isoflavanoid (**3**) beyond doubt, the 3,4-*trans* configuration ($J_{3,4}$ 9.0 Hz) of substituents on its C-ring, assuming a half-chair conformation, also defines its absolute configuration as (3*S*,4*S*:3*S*) when taken in conjunction with the synthesis. The c.d. spectra of the natural and synthetic compounds are identical, the high-amplitude positive Cotton effect at 240 nm confirming the (4*S*) configuration in terms of the aromatic quadrant rule.[5]

These results are consistent with condensation *via* electrophilic attack by an isoflavanyl-4-carbocation, generated from the pterocarpan (**2**) by protonation or by photolysis (*cf.* ref. 6) at suitable nucleophilic sites (C-5′ or C-6) provided by the bifunctional isoflavan (**1**), alternative nucleophilic sites being excluded on steric grounds when applying mild synthetic conditions.[4,7] The potential of the 6a,11a-*cis*-pterocarpan (**2**) as an electrophile is presumably enhanced by considerable steric strain within the fused heterocyclic ring systems,[8,9] and thus competition between intramolecular cyclization of the 2′-hydroxyisoflavanyl-4-carbocation and intermolecular nucleophilic attack is resolved in favour of the latter. The stereospecificity of the condensation and attendant inversion of configuration are the result of approach by the nucleophile from the sterically less hindered side of the 6a,11a-*cis*-pterocarpan (*cf.* refs. 8 and 9), and of steric repulsion between the 3-phenyl group of the generated isoflavanyl-4-carbenium ion and the intromittent nucleophile.

The bi-isoflavanoid (**3**) is accompanied in *D. nitidula* by at

least one other analogue, apparently of the same basic structure but with a fully oxidised heterocyclic F-ring.

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