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STEREOSPECIFIC FUNCTIONALIZATION OF THE HETEROCYCLIC RING SYSTEMS OF FLAVAN-3-OL AND [4,8]-BIFLAVAN-3-OL DERIVATIVES WITH 2,3-DICHLORO-5,6-DICYANO-1,4-BENZOQUINONE (DDQ)

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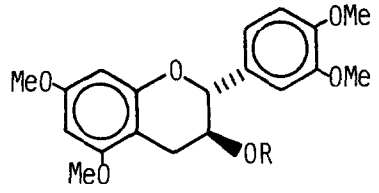
Summary: Efficient stereospecific 4-methoxylation of both 2,3-*trans*- and 2,3-*cis*-flavan-3-ol methyl ethers with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$-MeOH solution is of both synthetic and degradative significance in oligomeric flavanoid chemistry.

Oxidative 4-functionalization of the methyl ethers of 2,3-*trans*- and 2,3-*cis*-flavan-3-ols (catechins and epicatechins respectively) or of corresponding units in bi- and triflavanoids offers considerable potential in the synthesis of condensed tannin derivatives (*cf.* refs.[1,2]), while selective oxygenation at 4-C (C-ring) of biflavanoids confers lability on the interflavanoid bond, thus permitting recognition of both stereochemistry and aromatic bonding positions of constituent flavanyl units by degradative bromination.[3]

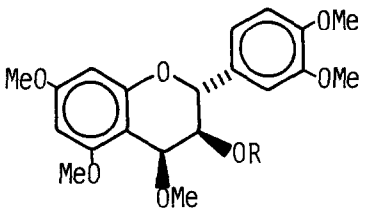
Hitherto, acyloxylation of the 4-benzylic function of (-)-epicatechin tetramethyl ether (5) with lead tetra-acetate in benzene solution (33% yield of 4-acetoxy derivative) over 24-28 h as developed by Betts, Brown and Shaw[4] represented the only reaction of this type. In our hands their conditions led directly to the 2,3-*cis*-3,4-*trans*-flavan-3,4-diol (leucocyanidin) analogue (20% yield; 33% on consumption of starting material), the product being used for synthesis of [4,8]- and [4,6]-2,3-*cis*-3,4-*trans*:2,3-*cis*-bi-(-)-epicatechin (procyanidins B_2 and B_5) derivatives.[1]

Such relatively lengthy reaction times and modest yields were overcome to a significant degree by adapting the usual reaction conditions for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to problems (see later) encountered with oxidative benzylic functionalization of flavan-3-ol derivatives when using this reagent. Under optimized conditions (+)-catechin tetramethyl ether (1) and its acetate (2) in chloroform are oxidized with a double molar excess of DDQ at 25°C over 5 h, using methanol as trapping agent for the incipient 4-carbenium ion, to provide their 2,3-*trans*-3,4-*cis* 4-methyl ether

derivatives (3) [$J_{2,3}$ 10.2, $J_{3,4}$ 3.5 Hz, δ 3.56 4-OMe ($CDCl_3$)] and (4) [$J_{2,3}$ 11.0, $J_{3,4}$ 2.2 Hz, δ 3.58 4-OMe (C_6D_6)] respectively in *ca.* 50% yields. Similarly (-)-epicatechin tetramethyl ether (5), its 3-*O*-acetate (6) and 3-*O*-benzylate (7) give their 2,3-*cis*-3,4-*trans* 4-methyl ether derivatives (8), (9) and (10) ($J_{2,3}$ 1.0-1.25, $J_{3,4}$ 2.75-3.0 Hz, δ 3.42-3.61 4-OMe in $CDCl_3$) respectively at further reduced (~ 3 h) reaction times. The improved yields

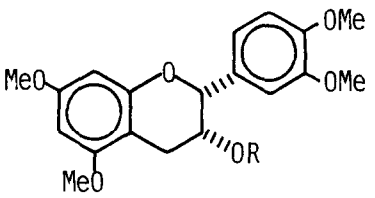


DDQ (2 mol)
$CHCl_3$/MeOH
5 h, ~25°C

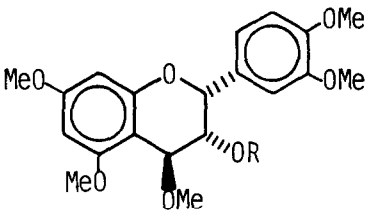


(1) R = H
(2) R = Ac

(3) R = H (48%)
(4) R = Ac (52%)



DDQ (2 mol)
$CHCl_3$/MeOH
~3 h, ~25°C



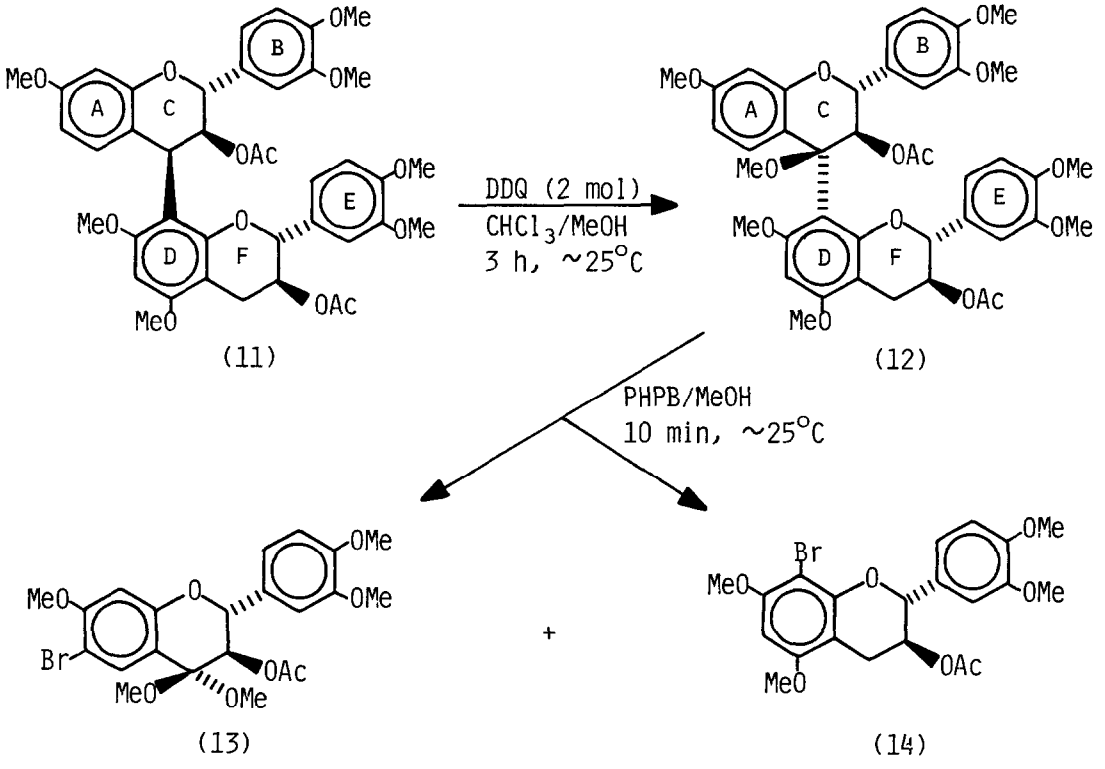
(5) R = H
(6) R = Ac
(7) R = Bz

(8) R = H (50%)
(9) R = Ac (40%)
(10) R = Bz (53%)

and high reaction rates achieved relative to those of acyloxylation with lead tetra-acetate are dependent on two conditions: (i) the double molar excess of DDQ is essential for rapid hydride ion abstraction, thus minimizing side reactions associated with extended reaction times, i.e. excessive anthocyanidin formation and also condensations to form [4,8]-procyanidin oligomers; and (ii) the excess DDQ must accordingly be neutralized by complete reduction with $NaBH_4$ immediately after specified reaction times. The above products have been applied by us for synthesising 'linear' [4,8]-linked procyanidin oligomers up to 'trimeric' levels.

No less important an objective, but aimed primarily at degradation, was the application of these optimized conditions to biflavanoid analogues of known interflavanoid bond strength. Thus, [4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-(-)-fisetinidol-(+)-catechin heptamethyl ether diacetate (11)[5] is selectively functionalized (37% yield) at the more susceptible benzylic position to give the 4-methoxy (C-ring) derivative of the 2,3-*trans*-3,4-*trans*:2,3-*trans* diastereoisomer (12) [$J_{2,3}$ 10.25 Hz, δ 3.08 4-OMe (C)]. The stereochemistry of

the product is based on a combination of intense negative Cotton effects {c.d. spectrum: $[\theta] \times 10^{-4}$ -9.0 (λ 233 nm) and -5.45 (221 nm)} at low wave-lengths[6] and the significantly low shift difference ($\Delta\delta_{2\text{-H},3\text{-H}}$ 0.28) of heterocyclic F-ring protons [contrasting with that of the 3,4-*cis* starting material (0.61)[7]].



Both observations are in line with effects induced by [4,8]-(2*R*,3*S*)-3,4-*trans*-flavanyl substituents on the (+)-catechin moiety.[6,7] Conformational inversion at 4-C (C-ring) presumably results from concerted hydride ion abstraction by the oxidant and solvolysis. However, the identical reaction when applied to the [4,8]-2,3-*trans*-3,4-*trans*:2,3-*trans* diastereoisomer of (11) proceeds with great difficulty affording amongst others a low yield of the flav-3-en-3-ol corresponding to the 'upper' unit. This indicates that hydride ion abstraction by DDQ is stereochemically-dependent, the quasi-*equatorial* 4-H(C) as in (11) being presumably accessible.*

The above conversion, (11) ⟶ (12), represents to our knowledge the first functionalization of the heterocyclic ring of a biflavanoid of this type.

*Related stereospecific reactions of the derivatives of (+)-catechin (1), (2) and (-)-epicatechin (5) - (7) support the conjecture that steric interaction between *axial*-2-H(C) and the bulky oxidant may inhibit abstraction of the quasi-*axial*-4-H(C).

Selective methoxylation of [4,8]-3,4-*cis* units (at the 4-C bonding position) could assist in their differentiation in higher oligomers, while concomitant weakening of strong interflavanoid bonds as existent in (11) permits application of degradative bromination methods previously developed by us,[3] using pyridinium hydrobromide perbromide (PHPB) [e.g. (12) ⟶ (13) + (14)]. Aromatic bonding positions (and the stereochemistry) of constituent profisetinidin units in condensed tannins may thus be assessed by thin layer chromatography using reference compounds, bromine serving as marker for the point of attachment[3] [*cf.* (14)]. However, 5 mg of methoxylated intermediate (12) was sufficient to provide (13) [$J_{2,3}$ 8.0 Hz, δ 6.52 (s, 8-H), 7.64 (s, 5-H), 3.27, 3.17 (2 x 4-OMe)] and (14) [δ 6.20, 6-H(A)][8] in yields which permit characterization also *via* sharply defined ^{1}H n.m.r. spectra.

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