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Synthesis of Proanthocyanidins. Part 1. The First Oxidative Formation of the Interflavanyl Bond in Procyanidins

Matthew C. Achilonu, Susan L. Bonnet, and Jan H. van der Westhuizen*

Department of Chemistry, University of the Free State, Nelson Mandela Avenue, Bloemfontein, 9301, South Africa

vdwestjh.sci@ufs.ac.za

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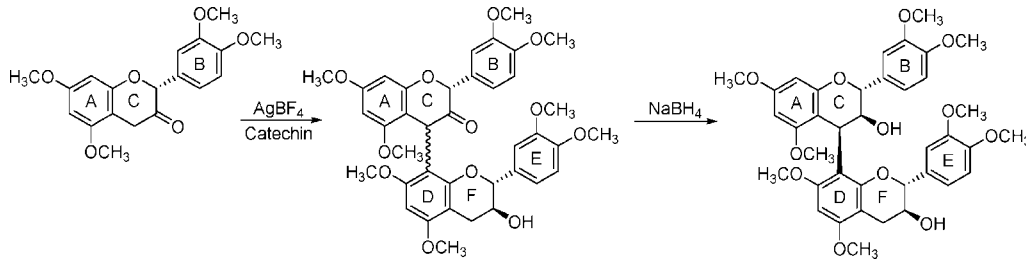
ABSTRACT



A novel and efficient method for the oxidative condensation of tetra-*O*-methyl-3-oxocatechin 4 with tetra-*O*-methylcatechin is described. Treatment of a solution of 3 (2 equiv) and 4 (1 equiv) with silver tetrafluoroborate readily affords the phenolic per-*O*-methyl ethers of 3-oxocatechin-(4–8)-catechin 18 and 19. Subsequent metal hydride reduction provides access to procyanidin B-3 analogues with the 3,4-*cis* diastereomers predominating.

Condensed tannins or proanthocyanidins are ubiquitous in plants and are important constituents of the human diet. A wide range of potentially significant biological activities including antioxidant,[1] antiatherosclerotic,[2] anti-inflammatory,[3] antitumor,[4] antiosteoporotic,[5] and antiviral[6] effects have been attributed to this class of compounds. The procyanidins consist of oligo- and polymers having (+)-catechin **1** or (−)-epicatechin **2** (Figure 1) as constituent units and linked via the 4- and 8- or 4- and 6-positions. Progress in the chemistry and biology of these compounds has been slow due to the difficulty of isolating and synthesizing pure free phenolic compounds.

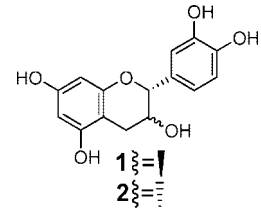


Figure 1. Structures of catechin **1** and epi-catechin **2**.

The introduction of phenolic and flavanyl moieties at C-4 of flavan-3,4-diols was affected by acid-catalyzed condensation of the appropriate nucleophilic and electrophilic flavanoid units.[7] These initial stereoselective syn-

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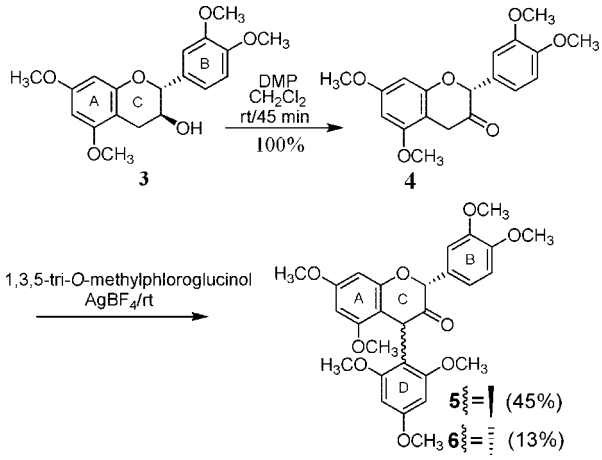
thetic methods played an important role in the structure elucidation of the economically important profisetinidins and prorobinetinidins from *Acacia mearnsii* (Black Wattle) and *Schinopsis spp* up to the tetrameric level.[7e,f,8,9] However, such methods were hampered by the laborious extraction procedures required to obtain optically active starting materials that occur in low concentrations in plant material.

The generation of electrophilicity at the C-4 benzylic position of commercially available (+)-catechin **1** and (−)-epicatechin **2** by introducing a C-4 oxygen leaving group greatly enhanced the synthetic access to procyanidin dimers and oligomers.[10] Selective bromination at C-4 of compounds **1** and **2** is only possible with peracetates where the reactivity of the aromatic rings toward competing bromination is supressed by electron-withdrawing acetate groups.[11] To control the degree of polymerization, protection at C-8 of the electrophilic species prior to condensation was required.[10c,e]

Herein, we report a novel and facile method for the introduction of a phenolic unit at unfunctionalized C-4 of per-*O*-methylcatechin and hence to synthesize procyanidin B-3 type dimer derivatives. Treatment of tetra-*O*-methyl-3-oxo-catechin **4**, available almost quantitatively from tetra-*O*-methylcatechin **3** via Dess-Martin periodinane (DMP) oxidation,[10b] with 1,3,5-tri-*O*-methylphloroglucinol in the presence of $AgBF_4$ in THF afforded the C-4 phloroglucinol adducts **5** (45%) and **6** (13%) (Scheme 1).[12]

Scheme 1. Condensation Reaction between **4** and 1,3,5-Tri-*O*-methylphloroglucinol



Their respective (2*R*,4*S*)- and (2*R*,4*R*)- configurations were assessed via NMR NOESY spectral data (Figure 2).

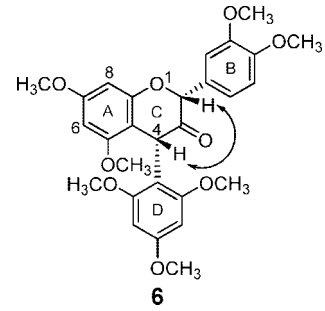


Figure 2. Observed NOE correlations between C-2 and C-4 of **6**.

The requirement of an excess of $AgBF_4$ and the observation of a silver mirror (reduction of Ag^I to Ag^0) indicate a two-electron oxidative mechanism (Scheme 2).

No self-condensation or further condensation products were evident, probably due to the deactivation of the nucleophilic properties of the A-ring of **4** via the enolic tautomer of the C-ring.

Subsequent reduction of **5** and **6** with $NaBH_4$ in aqueous NaOH/MeOH afforded the 4-arylflavan-3-ol derivatives **14** (98%) and **16** (95%), respectively (Scheme 3).

^{1}H NMR coupling constants[13] and CD data[14] permitted assignment of (2*R*,3*S*,4*S*) and (2*R*,3*S*,4*R*) absolute configuration for **14** and **16**, respectively.[7c]

The $AgBF_4$-catalyzed condensation reaction between **4** and **3** afforded the anticipated dimers **18** (38%) and **19** (6%) (Scheme 4) with [2*R*,4*S* (C-ring):2*R*,3*S* (F-ring)] and [2*R*,4*R* (C-ring):2*R*,3*S* (F-ring)] configurations, respectively, based on NMR coupling constants and NOESY data (Figure 3). The relatively low yields are explicable in terms of poor recovery for silica chromatography substrates, possible

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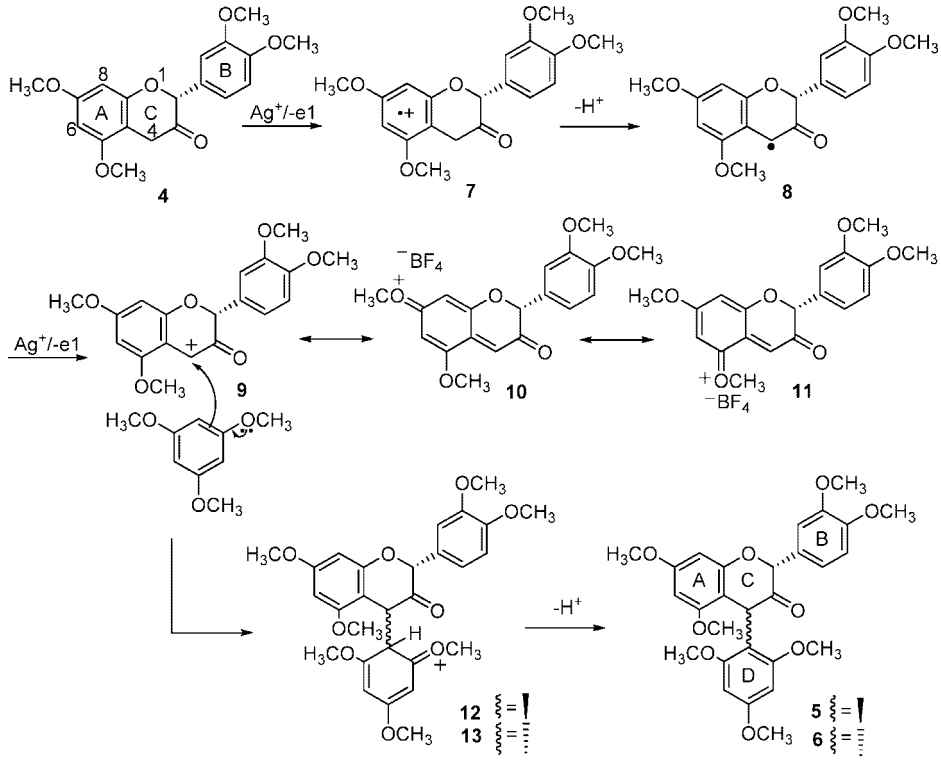
(12) Standard coupling method. A solution of tetra-*O*-methyl-catechin (0.435 mmol) in THF (3 mL) was added dropwise to a mixture of $AgBF_4$ (1.1 mmol) and tetra-*O*-methyl-3-oxocatechin (0.145 mmol) in THF (3 mL) and refluxed under nitrogen for 4 h. Filtration on SiO_2 and silica gel TLC yielded the desired products.

(13) ^{1}H NMR coupling constants of the C-ring resonances are used to distinguish between the four diastereoisomers of 4-arylflavan-3-ols. The characteristic coupling constants for 2,3-*trans*-3,4-*trans* isomers are $J_{2,3}$= 10 Hz and $J_{3,4}$ = 8.5−9.8 Hz, respectively. For 2,3-*trans*-3,4-*cis* isomers, it is 8−10 and 5.0−6.5; for the 2,3-*cis*-3,4-*cis*-isomers, it is 1.2 and 4.75−4.9; and for 2,3-*cis*-3,4-*trans*, it is <1 and 1.9−3.8.[16]

(14) Empirically established CD rules for 4-arylflavan-3-ols predicts a positive Cotton effect at 240 nm with β-configuration at C-4 and a negative Cotton effect at the same wavelength with α-configuration.[15,16]

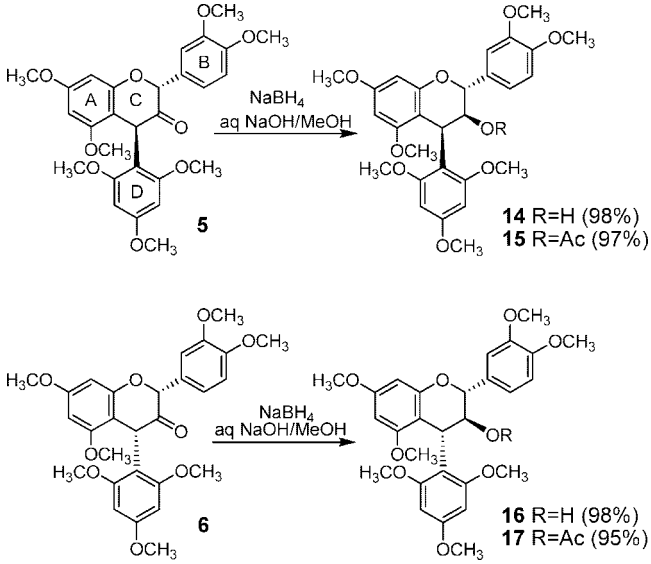
Scheme 2. Proposed Mechanism for the Oxidative Formation of the Interflavanyl Bond



oxidation of the enol form of the 3-keto flavan to the corresponding anthocyanidin, and the small scale of the reaction. We are currently investigating protocols to increase yields.

Self-condensation of the C-4-functionalized precursors in existing methods to synthesize procyanidin B-3 derivatives cannot be avoided, and a complex mixture of dimers, trimers, tetramers, and higher oligomers can be formed. Our 3-oxo-

Scheme 3. Reduction of **5** and **6** Using $NaBH_4$



Scheme 4. Condensation Reaction between **3** and **4**

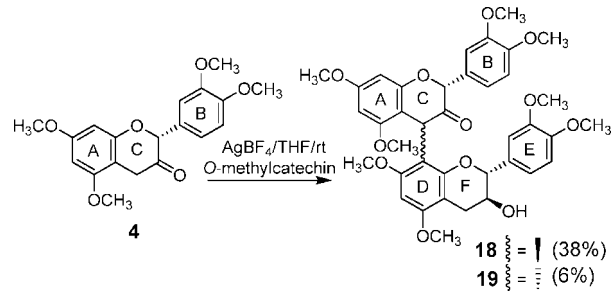
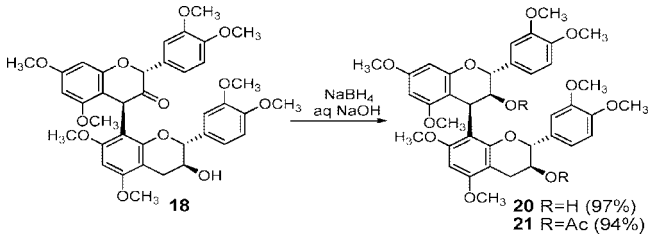


Figure 3. Observed NOESY interactions between H-4(C) and H-2(C) and H-2(F), respectively, for **19**.

catechin precursor does not undergo self-condensation and allows isolation of the dimer as the sole product. Oxidation of the 3″-hydroxyl group in the catechin moiety of the dimer **20** to a 3″-oxo group would allow introduction of a second catechin molecule and isolation of a trimer. We envisage a stepwise controlled synthesis of oligomers of catechin based on repeated cycles of oxidation and condensation.

Reduction of **18** afforded the 2,3-*trans*-3,4-*cis* octa-*O*-methyl ether of catechin-(4β→8)-catechin **20**, quantitatively (Scheme 5).[15,16]

Scheme 5. Reduction of **18** Using $NaBH_4$



Surprisingly and in contrast to the 3-hydroxy dimers **14** and **16** and **20**, respectively, the 3-oxo dimers **5** and **6** and **18** and **19**, respectively, did not demonstrate rotational isomerism in their NMR spectra.

Previously, formation of procyanidin B-3 derivatives from 4-functionalized flavan-3-ol precursors yielded predominantly the 3,4-*trans* isomer and only minute quantities of the 3,4-*cis* isomer. Stereochemistry is controlled by the 3-hydroxy substituent that directs attack from the anti position to give 3,4-*trans* configuration. In our reaction, the tetrahedral sp^3 3-hydroxy substituent has been replaced by a planar sp^2 carbonyl group, and stereochemistry is now controlled by the 2-aryl substituent. We observed the opposite distribution of diastereoisomers with a β:α ratio ranging from 3.5:1 (Scheme 2) to 6:1 (Scheme 4). Such a preference for β-face diastereoselectivity and hence the favoring of procyanidins with 3,4-*cis* interflavanyl bonds is, no doubt, caused by the α-orientated B-ring in intermediate **9** (Scheme 2).

We have thus developed a unique and facile synthesis of (+)-catechin dimer derivatives which circumvents the need for C-4 functionalization and avoids competing polymerization. This method, based upon oxidative C-4−C-8 interflavanyl bond formation will contribute significantly to ready synthetic access to proanthocyanidin analogues, especially procyanidins with 3,4-*cis* configured (+)-catechin chain extension units. Work is in progress to synthesize the free phenolic analogues of these dimers.

Supporting Information Available: Experimental details for the syntheses and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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