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

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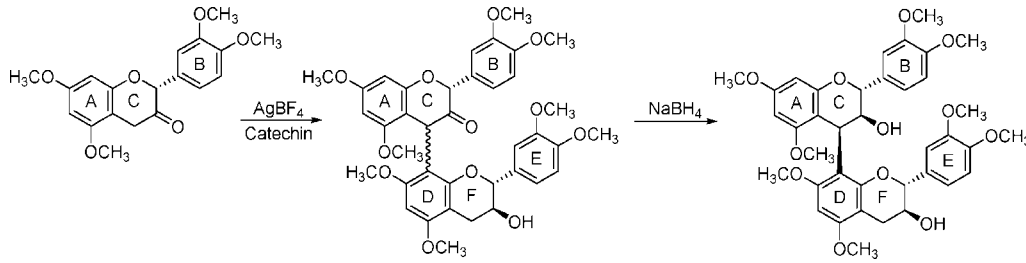
ABSTRACT



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.

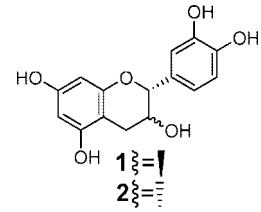


Figure 1. Structures of catechin **1** and epi-catechin **2**.

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-

(1) Korkina, L. G.; Afanas'ev, I. B. *ADV Pharmacol.* **1997**, *38*, 151–163.

(2) (a) Hertog, M. G.; Kromhout, D.; Aravanis, C.; Blackburn, H.; Buzina, R.; Fidanza, F.; Giampaoli, S.; Jansen, A.; Menotti, A.; Nedeljkovic, S. *Arch. Intern. Med.* **1995**, *155*, 381386; (b) Knekt, P.; Jarvinen, R.; Reunanen, A.; Matela, J. *BMJ* **1996**, *312*, 478–481.

(3) (a) Laughton, M. J.; Evans, P. J.; Morony, M.A.; Hoult, J. R.; Halliwell, B. *Biochem. Pharmacol.* **1991**, *42*, 1673–1681. (b) Yoshimoto, T.; Furukawa, M.; Yamamoto, S.; Horie, T.; Watanabi-Kohno, S. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 612–618.

(4) Stefani, E. D.; Boffetta, P.; Deneo-Pellegrini, H. *Nutr. Cancer* **1999**, *34*, 100–110.

(5) Hegarty, V. M.; May, H. M.; Khaw, K. T. *Am. J. Clin. Nutr.* **2000**, *71*, 1003–1007.

(6) Wang, H. K.; Xia, Y.; Yang, Z. Y.; Natschke, S. L.; Lee, K. H. *Adv. Exp. Med. Biol.* **1998**, *439*, 191–225.

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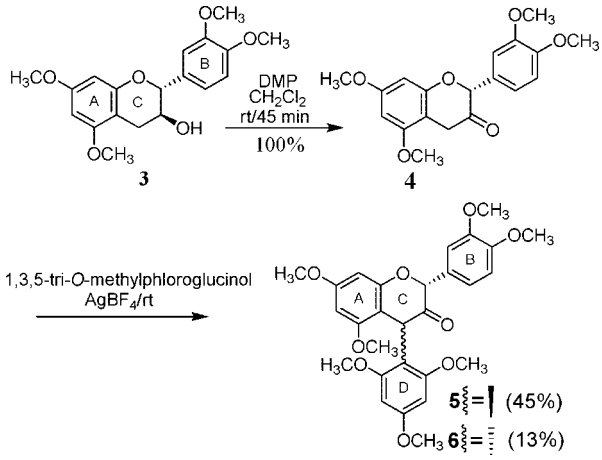
thetic methods played an important role in the structure elucidation of the economically important profisetinidins and prorobinetinidins from *Acacia mearnsii* (Black Wattle) and *Schinopsis spp* up to the tetrameric level.[7e,f,8,9] However, such methods were hampered by the laborious extraction procedures 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).

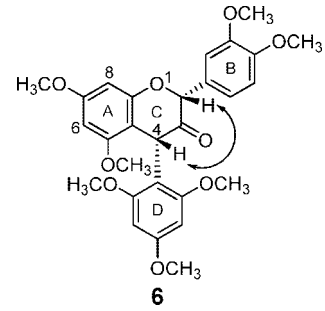


Figure 2. Observed NOE correlations between C-2 and C-4 of **6**.

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

(7) (a) Geissman, T. A.; Yoshimura, N. N. *Tetrahedron Lett.* **1966**, *7* (24), 2669–2773. (b) Barrett, M. W.; Klyne, W.; Scopes, P. M.; Fletcher, A. C.; Porter, L. J.; Haslam, E. *J. Chem. Soc., Perkin Trans. I* **1979**, 2376. (c) Botha, J. J.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Chem. Commun.* **1978**, 698–513. (d) Botha, J. J.; Young, D. A.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1213–1219. (e) Botha, J. J.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1235–1244. (f) Delcour, J. A.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1711–1717.

(8) Botha, J. J.; Viviers, P. M.; Young, D. A.; Du Preez, I. C.; Ferreira, D.; Roux, D. G.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 527–533.

(9) Young, D. A.; Kolodziej, H.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 25372544..

(10) (a) Steynberg, P. J.; Nel, R. J. J.; Van Rensburg, H.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1998**, 8153–8158. (b) Tückmantel, W.; Kozikowski, A. P.; Romanczyk, L. J. *J. Am. Chem. Soc.* **1999**, *121*, 12073–12081. (c) Kozikowski, A. P.; Tückmantel, W.; George, C. *J. Org. Chem.* **2000**, *65*, 5371–5381. (d) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Biosci. Biotechnol. Biochem.* **2002**, *66* (8), 1764–1767. (e) Ohmori, K.; Nakajima, N.; Suzuki, K. *PNAS* **2004**, *101* (33), 12002–12007. (f) Mohri, Y.; Sagehashi, M.; Yamada, T.; Hattori, Y.; Morimura, K.; Kamo, T.; Hirota, M.; Makabe, H. *Tetrahedron Lett.* **2007**, *48*, 5891–5894.

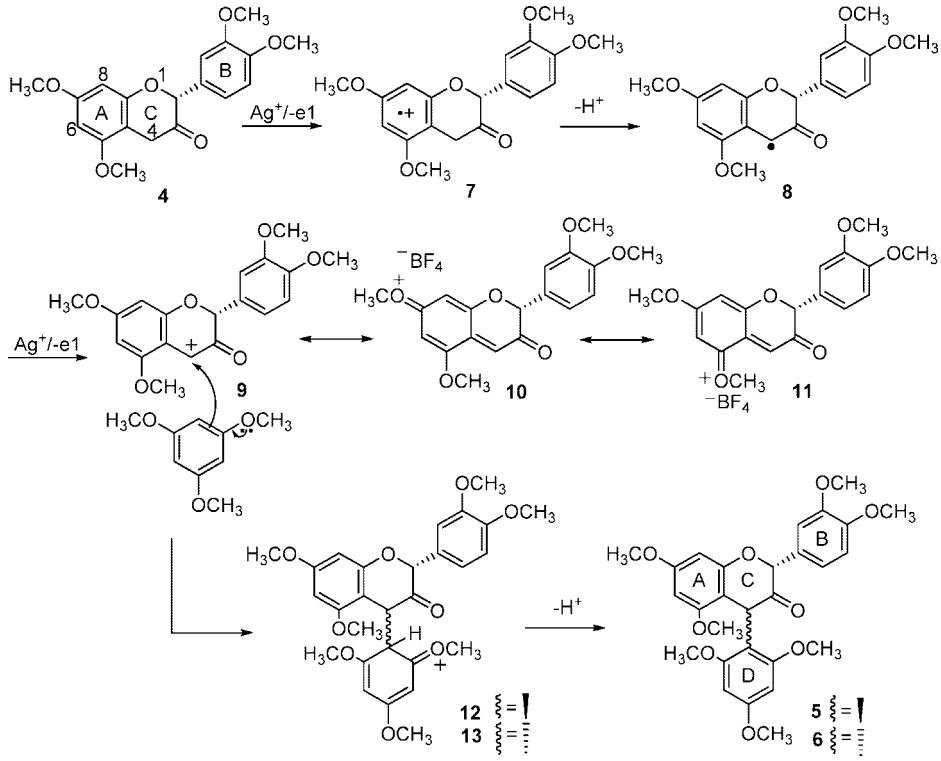
(11) Steenkamp, J. A.; Malan, J. C. S.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, *217*, 9–2183.

(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]

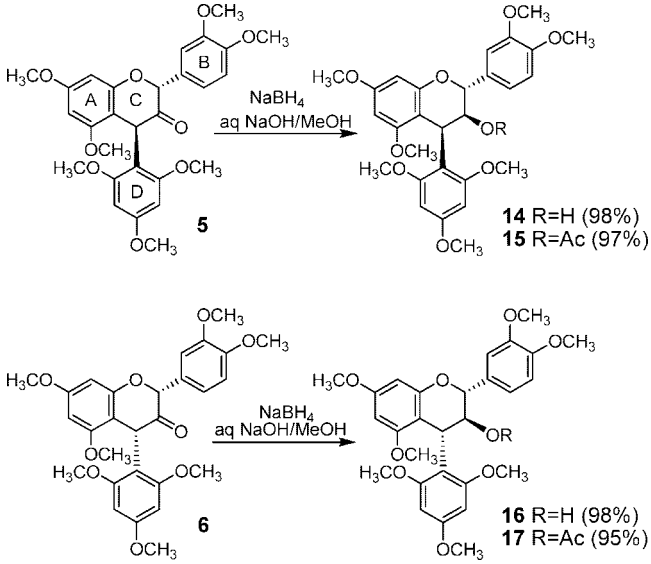
Scheme 2. Proposed Mechanism for the Oxidative Formation of the Interflavanyl Bond



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**

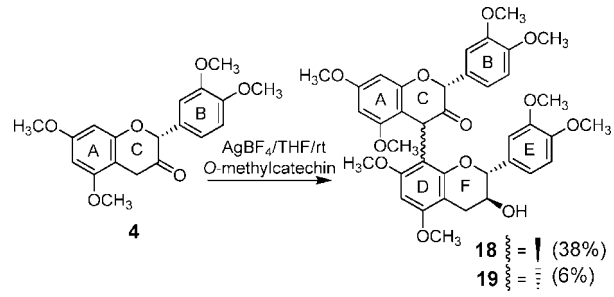
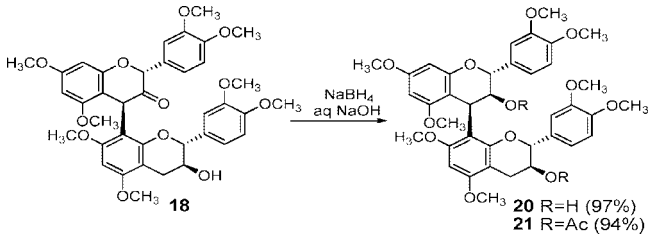


Figure 3. Observed NOESY interactions between H-4(C) and H-2(C) and H-2(F), respectively, for **19**.

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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(15) Van der Westhuizen, J. H.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. I* **1981**, *122*, 0–1226.
(16) Van der Westhuizen, J. H. 'n Nuwe Reeks Fotochemiese Reaksies in Flavonoïedsintese, Ph. D Thesis, 1979, 99.