Procyanidin B3 synthesis: a study of leaving group and Lewis acid activator effects upon interflavan bond formation

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ABSTRACT

A range of electrophilic ethers were prepared via DDQ oxidation and alcoholic trapping (propanol, crotyl alcohol and propargyl alcohol) at the C4 position of (+)-catechin. The Lewis acid-mediated C4-substitution of each of these ethers was examined and it was found that the propargyl ether was the best overall electrophile. A range of Lewis acids were then examined as activators and it was found that $BF_3 \cdot OEt_2$ was the best in terms of both yield and stereochemical control at the C4 position. This newly developed set of conditions was then used to prepare the natural product nutraceutical procyanidin B3 with complete control of stereochemistry.

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The flavanoids are a large family of natural products isolated in high concentrations from many species of plants and trees.[1] They have been reported as beneficial components of the human diet (referred to as nutraceuticals) and are present in significant quantities in a range of foodstuffs including green tea, red wine, beer and chocolate.[2–4] They show antiviral, antibacterial and antitumor activity,[5] with their biological effects being attributed to the inhibition of essential cellular enzymes (e.g., 20S proteasome,[6] fatty acid synthase (FAS),[7] caspases-3, 7 and 2,[8] P-glycoprotein (P-gp),[9] vascular endothelial growth factor receptor (VEGFR) phosphorylation[10]) and to their general free-radical scavenging (antioxidant) behaviour.[11]

The condensed tannins (procyanidins) have a range of structures derived from flavanoid monomers linked typically via a C4→C8′ interflavanoid bond (e.g., procyanidin B2 (**1**) and procyanidin B3 (**2**), Fig. 1). The procyanidins are often isolated as complex stereochemical and oligomeric mixtures and it is difficult to obtain pure materials with which to conduct unambiguous biological evaluations. As a result of this problem, there has been much interest in the development of methods for their stereoselective construction[12,13] and we now report an efficient method for the preparation of the dimeric flavanoid procyanidin B3 (**2**).

Conceptually, the procyanidins can be disconnected to reveal two monoflavanoid-derived building blocks (Scheme 1). For example, **1** can be disconnected to reveal an electrophilic component (i.e., the epicatechin derived-cation **3**) and a nucleophilic component (i.e., epicatechin **5a**). Likewise, **2** can be disconnected to reveal the catechin-derived cation **4** and catechin **6a** as suitable building blocks.

As the starting materials (i.e., **5a** and **6a**) are readily available, the key synthetic challenge in preparing either **1** or **2** is associated with preparing the cationic intermediate (i.e., **3** or **4**) and then controlling the stereochemistry of the newly formed C4→C8′ interflavan bond. In the case of procyanidin B2 (**1**), controlling the stereochemistry of the interflavan bond proves to be quite straightforward as both the aromatic ring at C2 and the hydroxy at C3, in the proposed cationic intermediate **3**, direct nucleophilic attack to the β-face of the pyran ring. A range of C4 ethers (e.g., **5b**) have been used as precursors to the cation **3** and one example (R′ = H_2CH_2OH)[12] has recently been used in a large-scale synthesis of **1**. In contrast to this, the stereoselective synthesis of procyanidin B3 (**2**) is much more difficult due to the presence of the opposing directing effects of the C3 hydroxy (α-directing) and the C2 aromatic ring (β-directing) in the cation **4**. Neighbouring group participation has been studied as a way to overcome this problem by using C3 acetate derivatives of **6b**,[13] and whilst this is quite effective when an appropriate Lewis acid is employed, it does add two
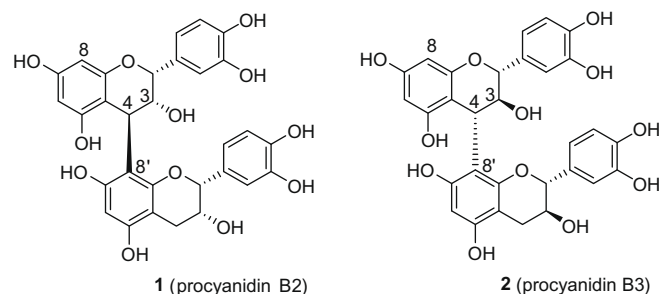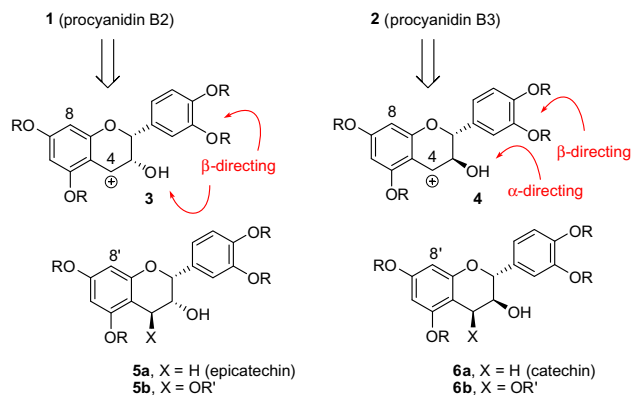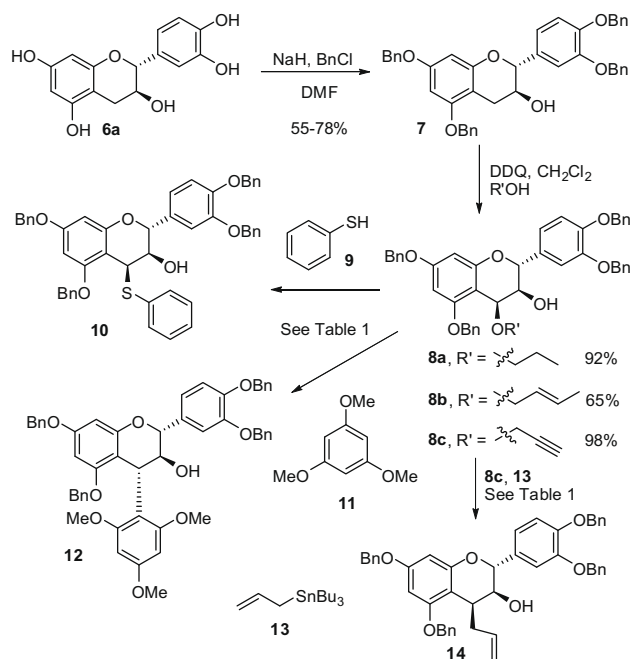

Figure 1. Structures of procyanidin B2 and procyanidin B3.

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Scheme 1. Retrosynthetic analysis of procyanidins B2 and B3.

Scheme 2.

Table 1
BF$_3$·OEt$_2$-mediated substitution at C4 of **8a**, **b**, **c**[a]

Entry	Electrophile	Nucleophile[b]	Product	Yield (%)	α:β[c]
1	**8a**	**9**	**10**	67	β only
2	**8a**	**11**	**12**	68	14:1
3	**8b**	**9**	**10**	78	β only
4	**8b**	**11**	**12**	75	17:1
5	**8c**	**9**	**10**	97	β only
6	**8c**	**11**	**12**	85	13:1
7	**8c**	**13**	**14**	72	β only

[a] Conditions: CH$_2$Cl$_2$, −78 °C, BF$_3$·OEt$_2$ (1.5 equiv).
[b] 3 equiv of nucleophile used.
[c] Stereochemistry determined by examination of ^{1}H NMR vicinal coupling constants (J) and NOE studies.

Table 2
Screening of Lewis acid activators for C4 substitution of **8c**[a]

Entry	Nucleophile[b]	Lewis acid	Product	Yield (%)	α:β[c]
1	**9**	TMSOTf	**10**	88	β only
2	**11**		**12**	70	5:1
3	**7**		**15**	54	6:1[d]
4	**9**	Cp$_2$HfCl$_2$	**10**	90	β only
5	**11**	·AgClO$_4$	**12**	75	2:1
6	**7**		**15**	72	8:1[d]
7	**9**	SnCl$_4$	**10**	95	β only
8	**11**		**12**	85	2:1
9	**7**		**15**	Trace	—
10	**7**	BF$_3$·OEt$_2$	**15**	78	9:1[d]

[a] Conditions: CH$_2$Cl$_2$, −78 °C, Lewis acid (1.5 equiv).
[b] 3 equiv of nucleophile used.
[c] Stereochemistry determined by examination of ^{1}H NMR vicinal coupling constants (J) and NOE studies.
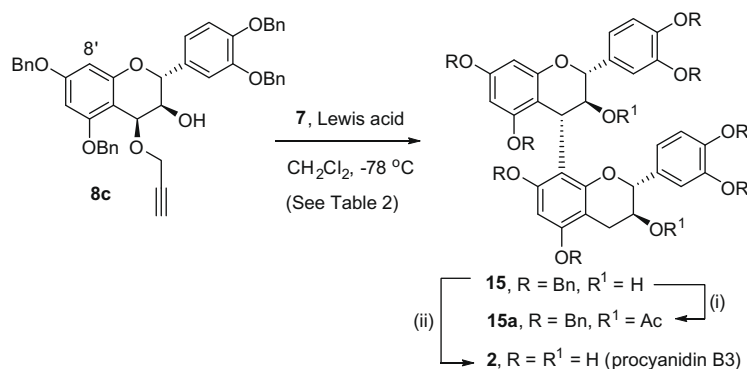[d] Selectivity was determined by ^{1}H NMR analysis of the diacetate derivative **15a** of α-**15** and β-**15**.

in related systems,[15] so we exposed **8c** to the allyl stannane **13** in the presence of BF$_3$·OEt$_2$. Pleasingly this gave the desired allylated material **14** as a single β-isomer[16] in 72% isolated yield, which represents a dramatic improvement to that previously reported.

As **8c** was both the best overall electrophilic component (see Table 1) and the easiest to form (98% yield from **7**, Scheme 2), we next examined the nature of the Lewis acid activator. In addition to BF$_3$·OEt$_2$ used in Table 1, we chose to study the use of TMSOTf, Cp$_2$HfCl$_2$·AgClO$_4$ and SnCl$_4$ (Table 2)[17] and we also expanded the study to include tetra-O-benzyl catechin **7** as a nucleophile (Scheme 3 and Table 2, entries 3, 6, 9 and 10).

In general, all the Lewis acids gave similar results when thiophenol (**9**) was used as the nucleophile, with good yields and excellent β selectivity being observed in all cases (Table 2, entries 1, 4 and 7). Differences were observed between the Lewis acids when using 1,3,5-trimethoxybenzene (**11**) as a nucleophile. The expected product **12** was obtained in good yield in all cases but stereocontrol at C4 varied significantly (Table 2, entries 2, 5 and 8), and none of the Lewis acids were able to match the levels of stereocontrol afforded by BF$_3$·OEt$_2$ (Table 1). A similar reactivity pattern emerged when **8c** was treated with tetra-O-benzylcatechin (**7**) as a nucleophile. The poorest performing Lewis acid was SnCl$_4$, with only trace amounts of the desired dimer **15** being produced (Table 2, entry 9). Both TMSOTf and Cp$_2$HfCl$_2$·AgClO$_4$ gave the desired flavanoid dimer **15** (54% and 72%, respectively, Table 2, entries 3 and 6), with BF$_3$·OEt$_2$ once again giving the best overall result in terms of isolated yield and stereocontrol[18] (Table 2, entry 10). Deprotection of **15** [H$_2$, Pd(OH)$_2$] using Pearlman's catalyst under standard hydrogenolysis conditions[14] finally afforded procyanidin B3 **2** in excellent yield (80–98%).

In summary, our optimised conditions (BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −78 °C) using **8c** as the electrophile and **7** as nucleophile gave

extra steps to the synthesis of **2**. Our efforts in this area have instead focussed upon the effects of the leaving group (X = OR′, **6b**) and the Lewis acid activator on the stereochemical outcome of the interflavanoid bond formation, with the intention of developing conditions for the stereoselective formation of procyanidin B3 (**2**) without the need to protect and then deprotect the C3 hydroxy.

Our studies began by first preparing tetra-O-benzylcatechin **7** (Scheme 2),[14] which was then oxidised with DDQ and the intermediate cation was trapped with a range of alcohols (n-propanol, crotyl alcohol and propargyl alcohol) to afford the corresponding ethers **8a** (R′ = CH$_2$CH$_2$CH$_3$), **8b** (R′ = CH$_2$CH=CHCH$_3$) and **8c** (R′ = CH$_2$C≡CH) in good to excellent yields. In order to evaluate the effectiveness of the alkoxy-leaving group, each of the ethers **8a–c** was activated with BF$_3$·OEt$_2$ in the presence of two standard nucleophiles **9** and **11** to afford the corresponding C4 substituted products **10** and **12**. We were pleased to see that the desired products were produced in all cases and that there was an improvement in yield in moving down the series from propyl **8a** to crotyl **8b** to propargyl **8c** (Table 1) when either of the two nucleophiles was used. Allylation at the C4 position is known to be challenging

Scheme 3. Reagents: (i) Ac$_2$O, DMAP, Py 84–89%; (ii) H$_2$, Pd(OH)$_2$, Et$_3$N, THF/MeOH, 80–98%.

the desired (4α→8) dimer **15** as the major product in good yield without the need to protect either the C3-OH or the C8 nucleophilic position. This procedure offers a real advantage over existing methods in this area of research and we are currently examining its further use in the synthesis of other flavanoid-derived natural products.

Acknowledgements

Supplementary data

Supplementary data (experimental procedures for the preparation of **8c**, **10**, **12**, **14**, **15**, **15a** and **2**. ^{1}H and ^{13}C NMR spectra for procyanidin B3 **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.100.

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18. Due to the presence of overlapping signals in the ^{1}H NMR spectrum of **15**, determination of the ratio of α and β isomers was performed on the bis-acetate derivative **15a** (Scheme 3). The ratio was determined by comparing the magnitude of the integrals for the signals at 5.83 ppm (α-isomer) and 5.58 ppm (β-isomer).