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Synthesis of procyanidins by stepwise- and self-condensation using 3,4-*cis*-4-acetoxy-3-*O*-acetyl-4-dehydro-5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin and (−)-epicatechin as a key building monomer

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Abstract

3,4-*cis*-4-Acetoxy-3-*O*-acetyl-4-dehydro-5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (**1a**) or (−)-epicatechin (**1b**) reacted high regio- and stereo-selectively with 1.5 equiv of the 5,7,3′,4′-tetra-*O*-benzyloxyflavan-3-ol (**4a** or **4b**) in the presence of 1 equiv of TMSOTf to give the corresponding procyanidins. On the other hand, the self-condensation of **1a** in the presence of a catalytic amount of $B(C_6F_5)_3$ afforded wide-range procyanidins from dimer to 15-mer like a biomass.

Keywords: Procyanidin; Stepwise- and self-condensation; 4-Acetoxy-3-acetylcatechin; 4-Acetoxy-3-acetylepicatechin

Procyanidins (condensed tannins) are widely distributed in food such as fruits, beans, cocoa, and tea and show multiple biological activities such as antioxidant, anti-inflammatory, anti-atherosclerotic, and anti-allergy effects.[1–3] Thus, diets containing procyanidins are important for maintaining and improving health. However, naturally occurring procyanidins are composed of complex mixtures from dimer to about 15-mer with various linkages and stereochemical differences.[2–4] Furthermore, procyanidins are highly sensitive to air,[1] thus, isolation of each component is difficult. To investigate the biological activities and medicinal utilities of procyanidins, a synthetic supply of the desired procyanidin oligmers is required. For this purpose, development of controlled regio- and stereo-selective oligomerization is essential.

There are two strategies on the synthetic approach of procyanidin oligomers. One is stepwise-condensation, which is able to synthesize defined oligomers with an unambiguous stereo- and regiochemistry.[5] The other is self-condensation, which produces at once biomass-mimetic materials having various oligomers.[6] We designed a highly reactive and relatively stable monomer of 3,4-*cis*-4-acetoxy-3-*O*-acetyl-(+)-catechin and (−)-epicatechin as a donor. Here, we report the synthesis of various 4,8-linked procyanidins by using two kinds of Lewis acids, TMSOTf and $B(C_6F_5)_3$ as catalysts.

After Kawamoto's report,[5a,6] many condensation conditions for procyanidin oligomers using catechin derivatives and Lewis acids have been studied.[5,6] However, there were several synthetic problems, such as the reactive efficiency and the oligomerization control. From the previous reports,[5–7] the reactivity and the stereoselectivity might depend on the leaving group of the C4-position and the protecting group of C3–OH (Fig. 1). Recently, Suzuki et al. reported that the C4-acetoxy derivatives might be excellent candidates as building blocks for procyanidin synthesis.[7,8] Furthermore, the protecting group of C3–OH influences the stereoselectivity as well as the reactivity

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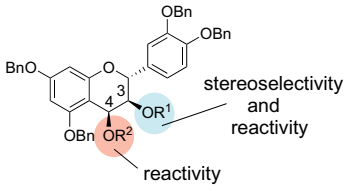


1a: R^1 = Ac, R^2 = Ac
2: R^1 = TBS, R^2 = Ac

Fig. 1.

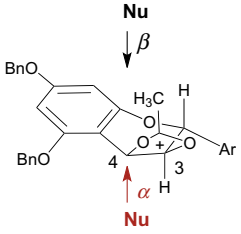


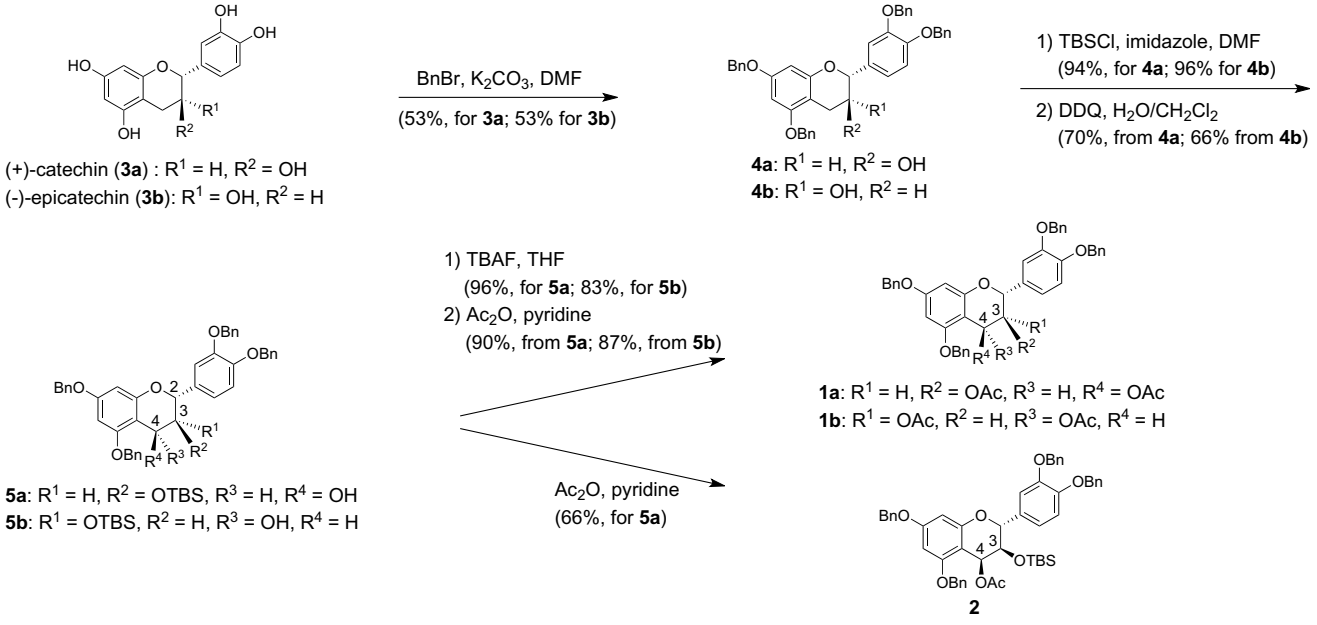
Fig. 2.

due to the steric factor and the neighboring participation-effect like the case of glycosylation (Fig. 2).[5–7] Considering these experimental observations we designed two monomers, 3-*O*-acetyl- and 3-*O*-TBS-, 4-acetoxy-perbenzylcatechin, **1a** and **2**.

5,7,3′,4′-Tetra-*O*-benzylcatechin (**4a**) was prepared from (+)-catechin (**3a**) (53%) according to Kawamoto's procedure.[6a,9] **4a** was then protected with TBSCl-imidazole (94%), and oxidized with DDQ in a suspension of CH_2Cl_2 and H_2O to give the 4-hydroxy **5a** in 70% yield (Scheme 1). The configuration of **5a** was determined to be 3,4-*cis* by NMR analysis.[10] **5a** was acetylated with Ac_2O in pyridine to give the 4-acetoxy-3-*O*-TBS derivative **2** in 66% yield. The TBS-group of **5a** was deprotected with TBAF (96%), then, the obtained product was acetylated with Ac_2O in pyridine to give the 3,4-*cis*-4-acetoxy-3-*O*-acetyl-4-dehydro-5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (**1a**)[11] in 90% yield (Scheme 1).

Condensation between **2** and **4a** was performed in the presence of $BF_3{\cdot}Et_2O$ to give only a trace amount of the partially desilylated dimers.[12] The low reactivity may be due to a large steric-hindrance of TBS at 3-OH of **2**. Instead of 3-*O*-TBS compound **2**, 3,4-*O*-diacetoxy **1a** was reacted with **4a** in the presence of $BF_3{\cdot}Et_2O$. Compound **1a** and **4a** smoothly condensed at 0 °C within 5 min to give oligomers, dimer **6** (57%), trimer **7** (20%), and tetramer **8** (3%) (Table 1, entry 1).[13] Concerning the configuration of 4,8-linkage of the oligomers, all of them were determined to be *trans* to 3*C*-OAc by $J_{3,4} = 9$–10 Hz.[13] Various Lewis acids were examined as promoters for the condensation reaction of **1a** and **4a** in CH_2Cl_2 (Table 1). Surprisingly, with only 1 equiv of TMSOTf at −78 °C for 5 min, the dimer was yielded up to 82% with high stereoselectivity (α/β 97/3)[14] (Table 1, entry 2).[15] The stereoselectivity and reactivity might arise from the neighboring participation-effect at 3-*O*-acetylate.[5f] After deacetylation of **6** (97%), careful hydrogenolysis by $H_2/Pd(OH)_2$ was carried out to give procyanidin B3 (**9**) in 91% yield (Scheme 2).[16]

For structural determination of procyanidins isolated from seed coats of red adzuki bean, *Vigna angularis*,[3] we synthesized a trimer by using **1b** and **4a** in the presence of TMSOTf. The 4-acetoxyepicatechin derivative **1b** was synthesized from (−)-epicatechin (**3b**) according to the same procedure as **1a** (Scheme 1).[10] The condensation between **1b** and **4a** in the presence of TMSOTf in CH_2Cl_2 for 5 min at −78 °C gave dimer **10** in 70% yield with a small



Scheme 1.