Selective Synthesis of Epicatechin Dimers By Zinc(II) Triflate Mediated Self-Condensation

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Abstract: Epicatechin dimers were synthesized by zinc(II) triflate mediated self-condensation reactions of epicatechin monomer derivatives. One synthesized dimer was successfully converted into procyanidin C1.

Key words: phenols, Lewis acids, oligomerization, natural products, stereoselective synthesis

Proanthocyanidins are condensed or nonhydrolyzable tannins with structures that basically consist of oligomerized flavan-3-ols.[1] Most of these compounds contain C-4 to C-8′ internal flavan bonds. Proanthocyanidins are widely distributed in nature, and are found in plants, vegetables, fruits, crops, and barks of trees.[2] They possess strong free-radical-scavenging and antioxidative activities,[3] and many significant biological activities have been reported, including antitumor,[4,5] antiviral,[6] and antiinflammatory activities[7] and inhibition of DNA polymerase.[8] Because of these potential beneficial effects for human health, many scientists have paid a great deal of attention to proanthocyanidins. However, the identification and purification of these compounds, especially the higher oligomers, is extremely difficult even with modern isolation techniques, so extended investigations on their biological activities, such as their mechanisms of action, have not been possible. Synthesis studies have therefore been devoted to obtaining pure proanthocyanidins, such as procyanidin B2 (**1**) and C1 (**2**), for biological testing (Figure 1).[9–12]

Typical strategies for synthesizing catechin and/or epicatechin oligomers involve the use of catechin and/or epicatechin nucleophiles and electrophiles in the presence of Lewis acids. In most cases, an excess of the nucleophilic partner is required.[10m] To avoid the use of an excess of the nucleophile, we have developed a strategy involving equimolar condensation.[10i] However, this strategy nevertheless requires the preparation of both the nucleophilic and the electrophilic partners. To simplify the construction of catechin and/or epicatechin dimers, we have developed a self-condensation strategy for the formation of epicatechin and/or epigallocatechin dimers. To demonstrate the usefulness of this reaction, we performed an efficient synthesis of an epicatechin trimer, procyanidin C1 (**2**).

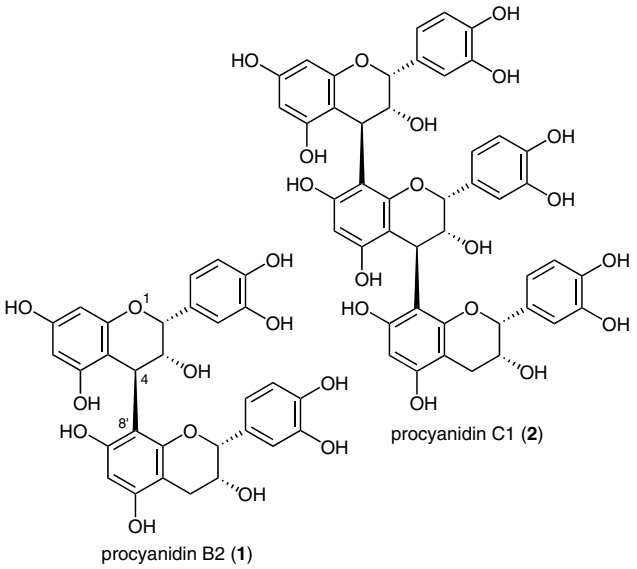

Figure 1 The structures of procyanidins B2 and C1

First, we examined the Lewis acid mediated self-condensation of epicatechin derivative **3**, previously prepared by Saito and co-workers,[11f] to form the epicatechin dimer **4**. The epicatechin derivative **3** gave the self-condensed product **4** in 58% yield when zinc(II) triflate was used as the Lewis acid (Table 1).[11b] Unidentified higher oligomers were also formed in this reaction. When the reaction was performed at 0 °C, the self-condensation product **4** was obtained in 55% yield, along with unreacted starting material (21%). The yield of the condensed product based on the recovery of starting material was 70%.

We also applied this reaction to the epigallocatechin derivative **5**,[13] and we found that this was useful for the synthesis of the epigallocatechin dimer **6** (Scheme 1). We confirmed the structure of **6** by two-dimensional NMR spectroscopy; the small coupling constants in the heterocyclic ring ($J_{2,3}$ and $J_{3,4} < 2.5$ Hz) confirmed the relative 2,3-*cis*-3,4-*trans* stereochemistry. When we used catechin and gallocatechin derivatives, no selective formation of dimeric products was observed. We found that the stereochemistry at the C-3 position greatly affected the self-condensation reaction.

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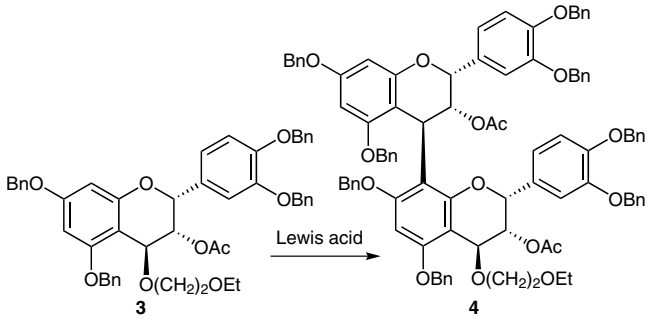
Table 1 Self-Condensation of Epicatechin Derivative **3**

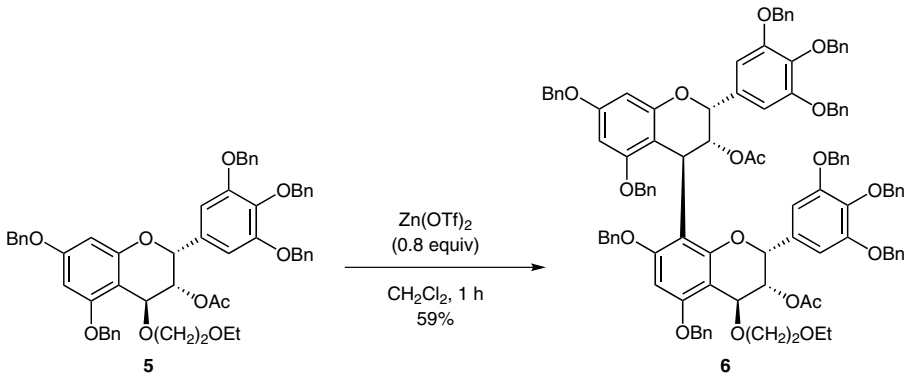


Lewis acid (equiv)	Time (h)	Yield (%) of **4**
$Yb(OTf)_3$ (0.5)	24	38
$Yb(OTf)_3$ (0.8)	24	52
$Yb(OTf)_3$ (1.0)	21	38
$Zn(OTf)_2$ (0.5)	24	48
$Zn(OTf)_2$ (0.8)	24	58

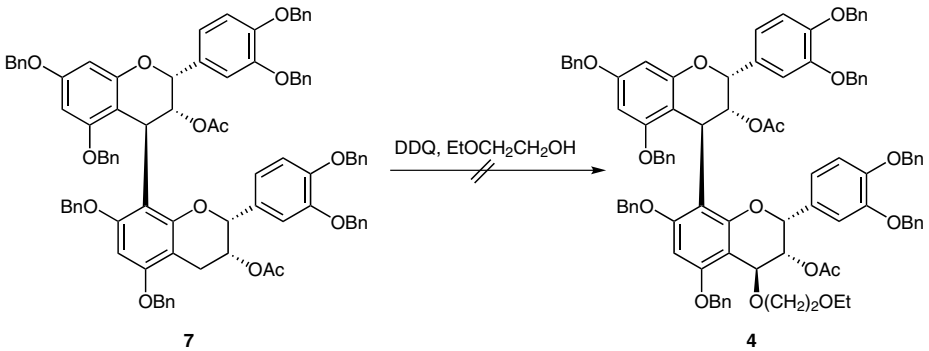
Because the condensed product **4** has an alkoxy group at the C-4′ position, it is possible to activate this position with a Lewis acid. Product **4** might, therefore, act as an electrophile for the synthesis of epicatechin oligomers. Attempts at the direct introduction of an alkoxy group at the C-4′ position of dimer **7** by treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of 2-ethoxyethanol did not proceed satisfactorily (Scheme 2). Therefore, compound **4**, prepared by zinc(II) triflate-mediated self-condensation, is useful for preparing dimeric epicatechin and/or epigallocatechin electrophiles.

Next, we examined the condensation of the dimeric epicatechin electrophile **4** with the epicatechin nucleophile **8** with the aim of preparing the epicatechin trimer derivative **9** (Scheme 3). The use of 2.0 equivalents of zinc(II) triflate as a Lewis acid gave the epicatechin trimer **9** in 67% yield. The removal of the two acetyl groups by treatment with tetrabutylammonium hydroxide, however, took a long time. We therefore adopted an alternative method for deacetylation. Acetylation of the hydroxy group of trimer **9** with acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine in pyridine, followed by reduction of the three acetyl groups of the resulting triacetate with diisobutylaluminum hydride (DIBAL-H) gave triol trimer **10**. The spectral data for trimer **10** agreed well with the values that we previously reported.[11b] Finally, deprotection of the twelve benzyl groups by treatment with palladium(II) hydroxide in a hydrogen atmosphere followed by lyophilization gave a good yield of procyanidin C1 (**2**). HPLC analysis confirmed the purity of the synthetic **2**.[14] The physical and spectral data for **2** were consistent with the reported values for procyanidin C1.[11b]

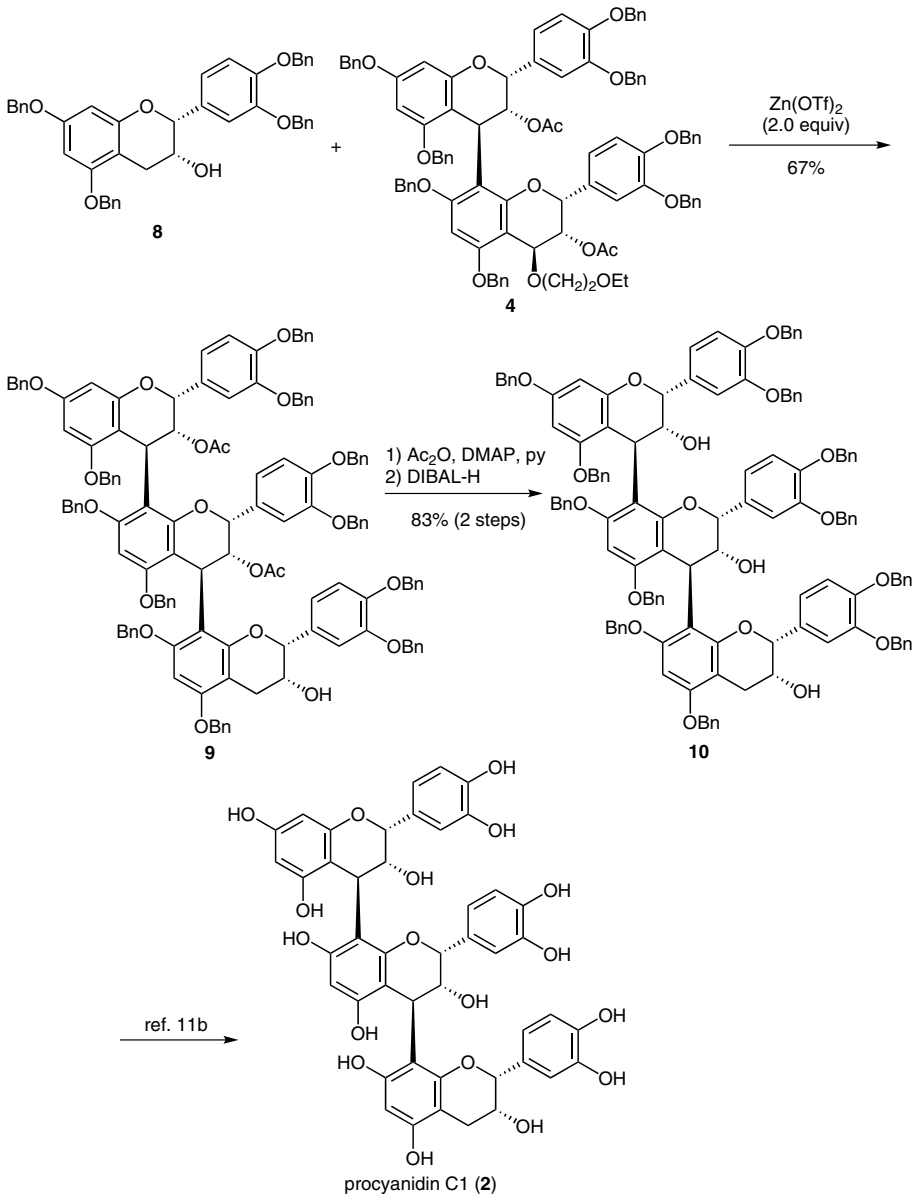
In conclusion, we synthesized an epicatechin dimer by zinc(II) triflate mediated self-condensation of an epicate-



Scheme 1 Self-condensation of epigallocatechin derivative **5**



Scheme 2 Attempt to prepare a dimeric epicatechin electrophile by using DDQ and 2-ethoxyethanol



Scheme 3 Synthesis of procyanidin C1 (**2**) by using the self-condensed product **4**

chin monomer derivative. The synthesized dimer acted as an electrophile for the synthesis a trimer derivative that was successfully converted into procyanidin C1 (**2**).

CH_2Cl_2 was distilled from CaH_2; Silica gel and other materials were used as received. All reactions were carried out under argon. NMR spectra were recorded at r.t. on a Bruker Avance 500 MHz instrument with TMS as an internal standard. Mass spectra were recorded on JEOL JMS-SX102A and TMS-T100 LC mass spectrometers. IR spectra were recorded on a JASCO FT-IR 480 Plus spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

[4,8′]-2,3-*cis*-3,4-*trans*:2′,3′-*cis*-Octa-*O*-benzyl-3,3′-*O*-diacetyl-4′-(2-ethoxyethoxy)bi-(–)-epicatechin (4); Typical Procedure

A solution of epicatechin derivative **3** (81 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was treated with $Zn(OTf)_2$ (30 mg, 0.08 mmol) at r.t., and the mixture was stirred for 24 h, The reaction was then quenched with H_2O, and the mixture was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC (hexane–EtOAc–CH_2Cl_2, 5:1:2) to give a pale-yellow oil; yield: 44 mg (58%); $[\alpha]_D^{22}$ +28.2 (*c* 0.500, $CHCl_3$).

IR (film): 3088, 3062, 3032, 2928, 2870, 1742, 1604, 1513, 1498, 1429, 1373, 1266, 1222, 1122, 1028, 737, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (78:22 rotational isomers; major isomer) = 7.50–6.75 (m, 46 H), 6.55 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.25 (s, 1 H), 6.00 (d, *J* = 2.0 Hz, 1 H), 5.66 (s, 1 H), 5.62 (d, *J* = 2.5 Hz, 1 H), 5.40 (s, 1 H), 5.15–4.25 (m, 19 H), 3.95–3.85 (m, 1 H), 3.83–3.75 (m, 1 H), 3.56–3.45 (m, 2 H), 3.41 (q, *J* = 7.0 Hz, 2 H), 1.71 (s, 6 H), 1.12 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major isomer) = 169.9, 169.1, 158.4, 158.2, 157.6, 155.5, 154.7, 149.3, 149.0, 148.6, 148.5, 128.6–126.7, 119.9, 114.8, 114.1, 113.9, 112.9, 109.9, 104.3, 103.2, 93.9, 93.1, 91.3, 74.8, 74.4, 72.2, 71.6, 71.4, 71.3, 70.6, 70.3, 70.1, 69.9, 69.5, 69.4, 66.3, 33.1, 20.8, 15.2.

HRMS-FAB: *m/z* $[M + Na]^+$ calcd for $C_{94}H_{86}NaO_{16}$: 1493.5815; found: 1493.5819.

[4,8′]-2,3-*cis*-3,4-*trans*:2′,3′-*cis*-Dodeca-*O*-benzyl-3,3′-*O*-diacetyl-4′-(2-ethoxyethoxy)bi-(–)-epigallocatechin (6)

In the same manner as described above, derivative **5** (25 mg, 0.03 mmol) gave dimer **6** as a pale-yellow oil; yield: 14 mg (59%); $[\alpha]_D^{19}$ +26.7 (*c* 0.350, $CHCl_3$).

IR (film): 3089, 3062, 3032, 2926, 2869, 1743, 1594, 1498, 1454, 1432, 1372, 1226, 1120, 736, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (75:25 rotational isomers; major isomer) = 7.46–6.74 (m, 49 H), 6.85 (s, 2 H), 6.47 (s, 2 H), 6.03 (d, *J* = 2.0 Hz, 1 H), 5.64 (d, *J* = 2.0 Hz, 1 H), 5.44 (s, 1 H), 5.10–4.78 (m, 23 H), 4.69 (d, *J* = 10.5 Hz, 1 H), 4.58 (s, 1 H), 4.53 (d, *J* = 10.5 Hz, 1 H), 4.40 (d, *J* = 2.5 Hz, 1 H), 3.95–3.90 (m, 1 H), 3.82–3.77 (m, 1 H), 3.54–3.49 (m, 2 H), 3.44 (q, *J* = 7.2 Hz, 2 H), 1.68 (s, 3 H), 1.51 (s, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major isomer) = 169.9, 169.0, 158.3, 157.5, 156.6, 155.3, 153.0, 152.4, 138.3–136.8, 134.7, 132.5, 128.6–127.0, 109.7, 106.5, 106.1, 93.2, 91.2, 75.2, 74.9, 72.0, 71.4, 71.2, 70.4, 70.2, 70.0, 69.9, 69.7, 69.6, 69.4, 66.3, 32.9, 29.7, 20.8, 15.3. HRMS-FAB: *m/z* $[M + Na]^+$ calcd for $C_{108}H_{98}O_{18}Na$: 1705.6651; found: 1705.6658.

3,3′-*O*-Diacetyl-4′′-hydroxytris(5,7,3′,4′-tetra-*O*-benzyl)epicatechin (4β/8)$_2$-Trimer (9)

A solution of dimer **4** (25 mg, 0.017 mmol) and derivative **8** (11 mg, 0.017 mmol) in CH_2Cl_2 (3 mL) was treated with $Zn(OTf)_2$ (13 mg, 0.034 mmol) at r.t., and the mixture was stirred for 5.5 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC (hexane–EtOAc–CH_2Cl_2, 5:1:2) to give a pale-yellow oil; yield: 23 mg (67%); $[\alpha]_D^{20}$ +100 (*c* 0.800, $CHCl_3$).

IR (film): 3569, 3087, 3063, 3032, 2931, 2869, 1740, 1601, 1512, 1498, 1454, 1428, 1373, 1265, 1220, 1123, 1028, 910, 735, 697 cm^{-1}.

HRMS-FAB: *m/z* $[M + Na]^+$ calcd for $C_{133}H_{114}NaO_{20}$: 2053.7785; found: 2053.7793.

Tris(5,7,3′,4′-tetra-*O*-benzyl)epicatechin (4β/8)$_2$-Trimer (10)

Ac_2O (6.7 μL, 0.071 mmol) was added to a solution of diacetate **9** (72 mg, 0.035 mmol) and pyridine (5.7 μL, 0.071 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C, and the mixture was stirred for 7.5 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified with preparative TLC (hexane–EtOAc–CH_2Cl_2, 4:1:2) to give the corresponding triacetate as a pale-yellow oil. This was dissolved in CH_2Cl_2 (2.0 mL) and treated with a 1 M solution of DIBAL-H in hexane (0.35 mL, 0.35 mmol) at –78 °C. The mixture was stirred for 2 h and then the reaction was quenched with MeOH (5 mL). The mixture was filtered through Celite and the filtrate was concentrated. The residue was purified with preparative TLC (hexane–EtOAc–CH_2Cl_2, 6:1:2) to give trimer **10** as a pale-yellow oil; yield: 57 mg (83%, two steps). The physicochemical and spectral data for **10** were identical to those that we previously reported.[11b]

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(14) HPLC measurement conditions: column, Inertsil ODS-3, 250 × 4.6 mm GL-Sciences; eluent: MeOH–0.2% AcOH (5:95 to 25:75), flow rate: 0.8 mL/min; detection: UV, λ = 280 nm; retention time: 23.60 min.

