Selective Synthesis of Epicatechin Dimers Using $Zn(OTf)_2$ Mediated Self-Condensation

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Abstract: Synthesis of epicatechin dimer using $Zn(OTf)_2$ mediated self condensation of epicatechin monomer derivative was accomplished. Synthesized dimer was successfully converted to procyanidin C1.

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

Proanthocyanidins which are condensed or non-hydrolysable tannins whose structures are basically oligomerized flavan-3-ols.[1] Most of compounds have C-4 to C-8' internal flavan bonds. These compounds are widely distributed in the nature such as plants, vegetables, fruits, crops and bark of the trees.[2] Proanthocyanidins possess strong free-radical scavenging and antioxidative activities.[3] Many significant biological activities were reported such as antitumor,[4,5] antiviral,[6] anti-inflammatory,[7] and the inhibition of DNA polymerase.[8] Threfore proanthocyanidins have been paid much attention to many scientists because these compounds possess health beneficial effects for humans. However, their identification as well as purification is extremely difficult especially highly origomerized compounds even using modern methods of isolation technique, further investigation of the biological activities such as mechanism of action remains unknown. In these days, in order to obtain pure proanthocyanidins such as procyanidin B2 (**1**) and C1 (**2**) for biological tests, synthetic studies have been devoted (Figure 1).[9-12]

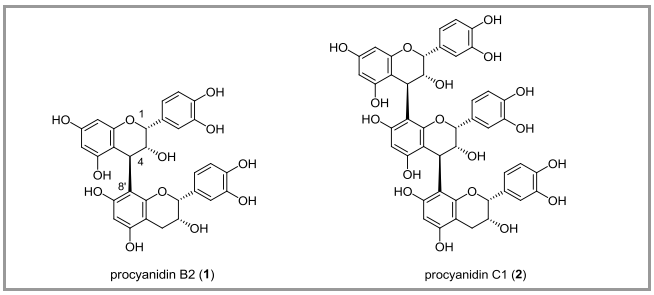


Figure 1 The structures of procyanidin B2 and C1.

The typical strategy to synthesize catechin and/or epicatechin oligomer is using catechin and/or epicatechin nucleophile and electrophile under Lewis acids. In the most of cases excess amount of nucleophilic partners were also required.[10m] To avoid using excess amount of necleophile, we have developed equimolar condensation.[10i] However, preparing both of nucleophilic and electrophilic partners is required in these strategy. In order to simplify to construct catechin and/or epicatechin dimers, we have developed using "self condensation" strategy to form epicatechin and/or epigallocatechin dimers. To demonstrate the usefulness of this reaction, an efficient synthesis of epicatechin trimer (procyanidin C1 (**2**)) was performed.

Self condensation of epicatechin and epigallocatechin derivatives.

We examined Lewis acid mediated self condensation using epicatechin derivative **3**, which was prepared by Saito and co-workers,[11f] to form epicatechin dimer **4**. As shown in Table 1, 4-(2"-ethoxyethoxy) derivative **3** afforded self condensed product **4** in 58% yield when $Zn(OTf)_2$ was used as Lewis acid.[11b] In this reaction, unidentified higher oiligomers were observed. When this reaction was performed at 0°C, self condensed product **4** was obtained in 55% yield along with unreacted starting material (21%). Based on the recovery of starting material, the yield of condensed product was 70%.

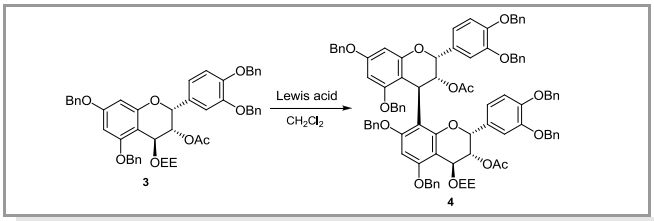
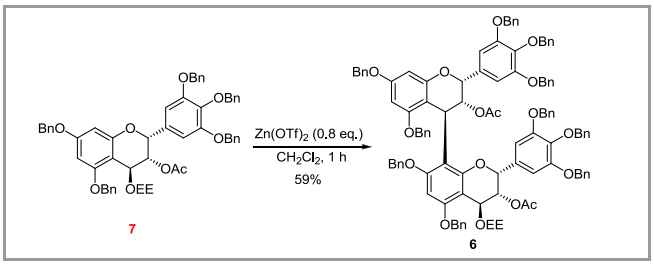


Table 1. Self condensation of epicatechin derivative **3**.

Lewis acid (eq.)	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

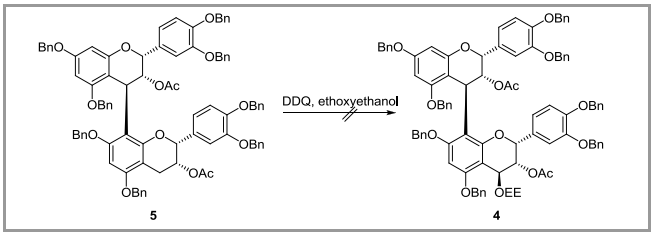
We also applied this reaction to epigallocatechin derivative **5**.[13] We found that this reaction was useful for the synthesis of epigallocatechin dimer **6** (Scheme 1). We confirmed the structure of **6** by 2D NMR and small coupling constants in the heterocyclic ring ($J_{2,3}$ and $J_{3,4}$ <2.5 Hz) confirmed the relative 2,3-*cis*-3,4-*trans*

stereochemistry. When we used catechin and gallocatechin derivatives, selective formation of dimeric products was not observed. We found that the stereochemistry at C-3 position greatly affected self condensations.



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

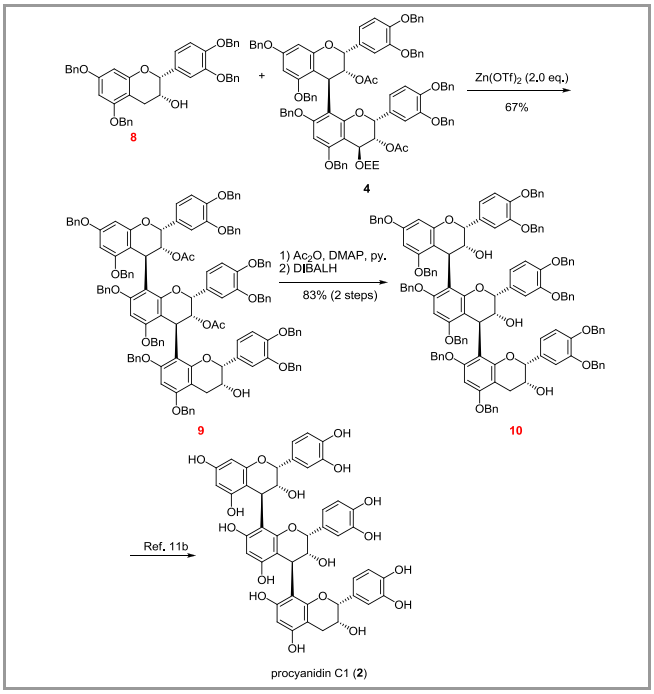
Because the condensed product **4** has an alkoxy group at C-4' position it is possible to activate at C-4' position by a Lewis acid. Thus this compound could be acted as an electrophile for the synthesis of epicatechin oligomer. Direct introduction of the alkoxy group at C-4' position of compound **5** was very difficult when compound **5** was treated with DDQ in the presence of ethoxyethanol (Scheme 2). Thus compound **4** which was prepared $Zn(OTf)_2$ mediated self condensation is useful method to prepare dimeric epicatchin and/or epigallocatechin electrophiles.



Scheme 2 Attempt to prepare dimeric epicatechin electrophile using DDQ and ethoxyethanol.

Synthesis of procyanidin C1 (epicatechin trimer) using self-condensed dimer 4.

Next we examined condensation of dimeric epicatchin electrophile **4** with epicatechin nucleophile **7** to prepare epicatechin trimer drivative. As shown in Scheme 3, using 2.0 equivalent of $Zn(OTf)_2$ as a Lewis acid gave epicatechin trimer derivative **8** in 67% yield. Removal of the two acetyl groups using *n*-Bu_4NOH took very long time. Thus we changed the method of deacetylation as follows. Acetylation of the hydroxy group of **8** with Ac_2O and DMAP in pyridine followed by reduction of the three acetyl groups with DIBALH afforded triol **9**. The spectral data of **9** were in good accordance with those of the reported values by us.[11b] Finally, deprotection of the twelve benzyl groups using $Pd(OH)_2$ in the presence of hydrogen atmosphere followed by lyophilization afforded procyanidin C1 (**2**) in good yield. We found synthetic **2** was pure by HPLC analysis.[14] The physical and spectral data of **2** were consistent with those of the reported values (Scheme 3).[11b]



Scheme 3 Synthesis of procynidin C1 (**2**) using self-condensed product **4**.

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In conclusion, we have accomplished synthesis of epicatechin dimer using $Zn(OTf)_2$ mediated self condensation of epicatechin monomer derivative. Synthesized dimer acted as an electrophile for the synthesis trimer. Synthesized epicatechin trimer derivative was successfully converted to procyanidin C1 (**2**).

CH_2Cl_2 was distilled from CaH_2; Silicagel and other materials were used as received. All reactions were carried out under argon. NMR spectra were obtained at r.t. on a Bruker Avance 500 MHz instrument. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on, JEOL JMS-SX102A and TMS-T100 LC mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared 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'-ethoxyethoxy-bi-(−)-epicatechin (4).
To a solution of **3** (81 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added $Zn(OTf)_2$ (30 mg, 0.08 mmol) at room temperature. After being stirred for 24 h, the reaction was quenched with water. The mixture was extracted with EtOAc (10 mL x 2) and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc : CH_2Cl_2 = 5 : 1 : 2) to afforded **4** (44 mg, 58%) as a pale yellow oil. $[\alpha]_D^{22}$ +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, $CDCl_3$, 78:22 rotational isomers, major isomer) δ: 7.50-6.75 (46H, m), 6.55 (1H, dd, *J* = 8.0, 1.5 Hz), 6.25 (1H, s), 6.00 (1H, d, *J* = 2.0 Hz), 5.66 (1H, s), 5.62 (1H, d, *J* = 2.5 Hz), 5.40 (1H, s), 5.15-4.25 (19H, m), 3.95-3.85 (1H, m), 3.83-3.75 (1H, m), 3.56-3.45 (2H, m), 3.41 (2H, q, *J* = 7.0 Hz), 1.71 (6H, s), 1.12 (3H, t, *J* = 7.0 Hz); ^{13}C

NMR (125 MHz, $CDCl_3$, major isomer) δ: 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 ppm. HRMS-FAB: *m/z* $[M+Na]^+$: calcd for $C_{94}H_{86}O_{16}Na$; 1493.5815, found: 1493.5819.

[4,8']-2,3-*cis*-3,4-*trans*:2',3'-*cis*-Dodeca-*O*-benzyl-3,3'-*O*-diacetyl-4'-ethoxyethoxy-bi-(−)-epigallocatechin (6).
In the same manner as described above, **5** (25 mg, 0.03 mmol) afforded **6** (14 mg, 59%) as a pale yellow oil. $[\alpha]_D^{19}$ +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, $CDCl_3$, 75:25 rotational isomers, major isomer) δ: 7.46-6.74 (49H, m), 6.85 (2H, s), 6.47 (2H, s), 6.03 (1H, d, *J* = 2.0 Hz), 5.64 (1H, d, *J* = 2.0 Hz), 5.44 (1H, s), 5.10-4.78 (23H, m), 4.69 (1H, d, *J* = 10.5 Hz), 4.58 (1H, s), 4.53 (1H, d, *J* = 10.5 Hz), 4.40 (1H, d, *J* = 2.5 Hz), 3.95-3.90 (1H, m), 3.82-3.77 (1H, m), 3.54-3.49 (2H, m), 3.44 (2H, q, *J* = 7.2 Hz), 1.68 (3H, s), 1.51 (3H, s), 1.13 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer) δ: 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 ppm. 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"-hydroxy-tris(5,7,3',4'-tetra-*O*-benzyl)epicatechin (4β/8)$_2$-trimer (8).
To a solution of **4** (25 mg, 0.017 mmol) and **7** (11 mg, 0.017 mmol) in CH_2Cl_2 (3 mL) was added $Zn(OTf)_2$ (13 mg, 0.034 mmol) at room temperature. After being stirred for 5.5 h, the reaction was quenched with water. The mixture was extracted with EtOAc (10 mL x 2) and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc : CH_2Cl_2 = 5 : 1 : 2) to afforded **8** (23 mg, 67%) as a pale yellow oil. $[\alpha]_D^{20}$ +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 $C_{133}H_{114}O_{20}Na$; 2053.7785, found: 2053.7793.

Tris(5,7,3',4'-tetra-*O*-benzyl)epicatechin (4β/8)$_2$-trimer (9).
To a solution of **8** (72 mg, 0.035 mmol) and pyridine (5.7 μL, 0.071 mmol) in CH_2Cl_2 (2.5 mL) was added Ac_2O (6.7 μL, 0.071 mmol) at 0 °C. After being stirred for 7.5 h, the reaction was quenched with water. The mixture was extracted with EtOAc (10 mL x 2) and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc : CH_2Cl_2 = 4 : 1 : 2) to afforded triacetate as a pale yellow oil, which was dissolved in CH_2Cl_2 (2.0 mL). To this solution was added DIBALH (1.0 mol/L solution in hexane, 0.35 mL, 0.35 mmol) at -78 °C. After being stirred for 2 h, the reaction was quenched with MeOH. 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 afforded **9** (57 mg, 83% in 2 steps) as a pale yellow oil. The physicochemical and spectral data were identical with those of the reported values by us.[11b]

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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

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