Synthesis of Arecatannin A1 from Dimeric Epicatechin Electrophile

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Synthesis of arrecatannin A1 (1) was accomplished from dimeric epicatechin electrophile, which was prepared by $Zn(OTf)_2$ mediated self-condensation, and monomeric catechin nucleophile. The condensation was successfully worked using $Yb(OTf)_3$ as a Lewis acid in good yield.

Keywords: phenols, Lewis acid, oligomerization, natural products, stereoselective synthesis.

In this decade, proanthocyanidins have been paid much attention due to their significant biological activities and health benefitical effects. [1,2] Proanthocyaidins have broad biological activities, however, in most of cases, evaluation of biological activities was investigated using the mixture of various components such as "grape seeds extract". Thus the numbers of report of systematic structural activity relationship study (SAR) of proanthocyanidins are still limited. To solve this problem, efforts toward the synthesis of proanthocyanidins have been devoted to obtain pure sample because natural proanthocyanidins are difficult to isolate as pure materials [3-6]. The typical synthetic strategy of proanthocyanidins is condensation between catechin and/or epicatechin nucleophile and electrophile in the presence of Lewis acids. In most of cases, excess amount of nucleophilic partner is required to prevent polymerization. To avoid using excess amount of nucleophile, we have developed equimolar condensation [4l]. However, preparing both of nucleophilic and electrophilic partners is still necessary. In order to simplify to construct epicatechin dimers, we have recently developed using "self condensation" strategy [7]. To demonstrate the usefulness of this reaction, we wish to report an efficient synthesis of epicatechin-epicatechin-catechin {arecatannin A1 (1)}, which was isolated from azuki beans, apple and *Areca catechu* (Figure 1) [4j, 8, 9].
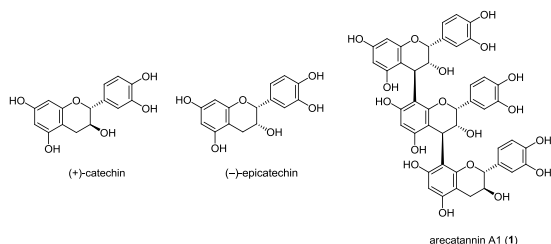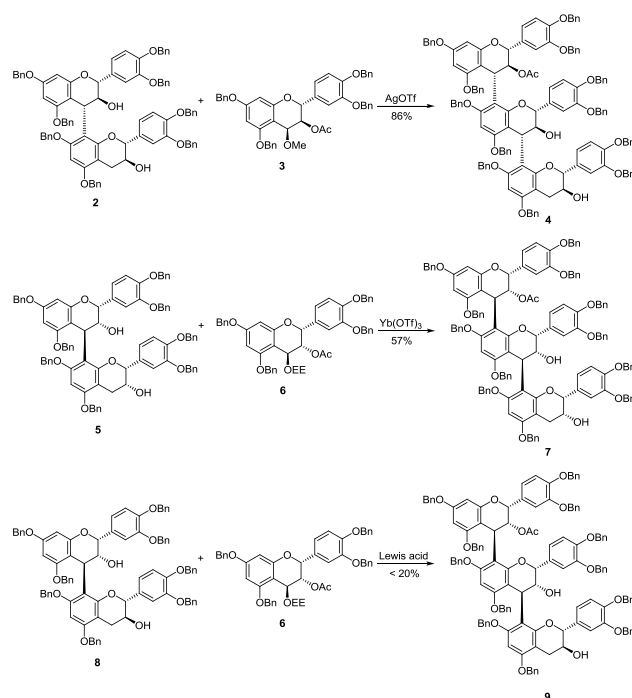

Figure 1. The structures of arecatannin A1 (1).

Scheme 1. Previous study to synthesize procyanidin trimer derivatives.

In our previous study, we reported the condensation between dimeric catechin or epicatechin nucleophile and monomeric catechin or epicatechin nucleophile to synthesize procyanidin C1 and C2. In case of the condensation of dimeric catechin nucleophile **2** and monomeric catechin electrophile **3** in the presence of AgOTf, condensed product **4** was obtained in high yield [5c]. In case of epicatechin, nucleophile **5** and electrophile **6** gave condensed

product **7** in moderate yield [5b]. However, in the case of the condensation between epicatechin-catechin nucleophile **8** and monomeric epicatechin electrophile **6**, the yield of condensed product **9** was less than 20% yield when we used various type of Lewis acids (Scheme 1).

Thus we tried to prepare dimeric electrophile. However, as we have reported in the recent paper [7], 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 various alcohol. Thus we have developed using "self condensation" of monomeric electrophile **6** to prepare dimeric electrophile **10** using $Zn(OTf)_2$ as an activator. Compared to the reaction condition of the recent published paper by us [7], we have modified the reaction condition because the reaction time was too long. We found that using 0.7 eq. of $Zn(OTf)_2$ at 0°C to room temperature led the reaction time to be shortened form 24 h to 1.5 h (Scheme 2).
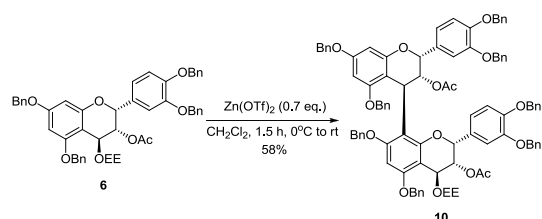
Scheme 2. Modified synthesis of dimeric epicatechin electrophile **10** using self-condensation.

As dimeric epicatechin electrophile **10** was in hand, we examined the condensation between dimeric epicatechin electrophile **5** and catechin nucleophile **6**. At first we tried $Zn(OTf)_2$ as a Lewis acid because we have found the condensation between dimeric epicatechin electrophile **5** and monomeric epicatechin nucleophile gave epicatechin trimer derivative in 67% yield as shown in the recent paper [7]. In the case of using monomeric catechin nucleophile, using 2.0 eq. of $Yb(OTf)_3$ as a Lewis acid gave epicatechin-epicatechin-catechin derivative **12** in good yield. On the other hand, AgOTf gave sluggish result. $Ni(OTf)_2$ and $Zn(OTf)_2$ gave moderate yield, respectively. We found that the stereostructure of nucleophile and choice of Lewis acid greatly affected the reactivity in the condensation (Table 1).

Table 1. Condensation between dimeric epicatechin electrophile **10** and catechin nucleophile **11**.
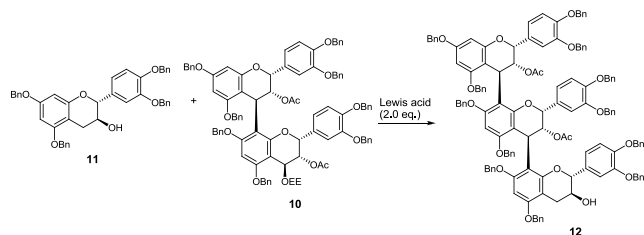

Lewis acid	Time (h)	Yield of **12** (%)
AgOTf	5	10
Ni(OTf)₂	6	59
Zn(OTf)₂	5	61
Yb(OTf)₃	**4**	**79**

The reaction was carried out at room temperature in CH₂Cl₂.

Because the condensed product **12** was obtained, the next attention was turned towards synthesis of arecatannin A1 (**1**). Removal of the two acetyl groups was achieved by treatment with *n*-Bu₄NOH to afford triol **13**. The ¹H and ¹³C-NMR spectral data of **13** were consistent with those of the reported values [5e]. Thus we

confirmed that newly formed 4' position in compound **12** was exclusively β by comparing with the reported NMR data [5e]. Finally, deprotection of the twelve benzyl groups using $Pd(OH)_2$ in the presence of hydrogen atmosphere in THF-MeOH-H₂O followed by lyophilization afforded arecatannin A1 (**1**) in good yield. We confirmed synthetic **1** was pure by HPLC analysis [10]. The physicochemical and spectral data of **1** were consistent with those of the reported values [5e]. The ¹H and ¹³C NMR spectral data of peracetate of **1** (**14**) were also in good agreement with those of the reported values (Scheme 3) [5e].
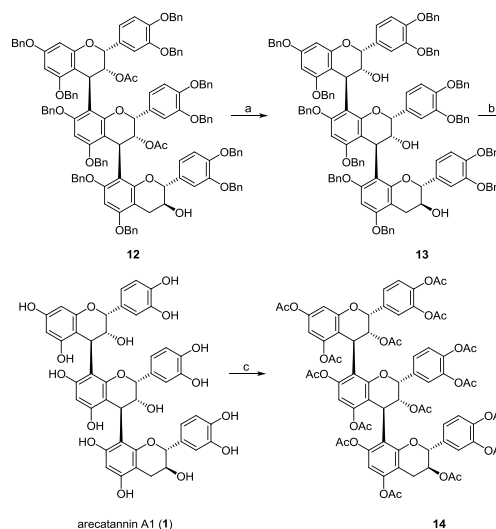
Scheme 3. Synthesis of arecatannin A1 (**1**) and its peracetate **14**. Reagents and conditions: (a) *n*-Bu₄NOH, THF, 7 d, 94%; (b) H₂, Pd(OH)₂-C, THF/MeOH/H₂O (20/20/1), 5.5 h, quant.; (c) Ac₂O, pyridine, DMAP, 24h, 38%.

In conclusion, arecatannin A1 (**1**) was synthesized from dimeric epicatechin electrophile **10**, which was prepared by $Zn(OTf)_2$ mediated self-condensation,[7] and monomeric catechin nucleophile **11**. The condensation between **10** and **11** was successfully worked using $Yb(OTf)_3$ as a Lewis acid.

Experimental

General Procedure: Air- and moisture-sensitive reactions were carried out in ovendried (>120 °C) glassware sealed under positive pressure of dry argon from a manifold or balloon. Sensitive reagents and solvents were transferred using a syringe-septa technique. THF was distilled from sodium-benzophenone ketyl under argon, and CH₂Cl₂ was distilled from CaH₂ under argon. Other commercially available reagents were used without further purification. Column chromatography was performed on silicagel 60 (230-400 mesh). NMR spectra are reported as chemical shifts in parts-per-million based on tetramethylsilane (0 ppm) or one of the signals of the solvents (¹³C NMR: 77.0 ppm for CHCl₃ in CDCl₃, 49.0 ppm for CD₃OD). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, and the combinations derived from those listed. Coupling constants (*J*) are shown in Hertz (Hz).

[4,8:4",8"]-2,3-*cis*-3,4-*trans*: 2",3"-*cis*-3",4"-*trans*: 2'''',3''''-*trans*-3,3"-*O*-Diacetyl-dodeca-*O*-benzyl-(−)-epicatechi-n-(−)-epicatechin-(+)-catechin (12): To a solution of **10** (21 mg, 0.014 mmol) and **11** (9 mg, 0.014 mmol) in CH₂Cl₂ (5.0 mL) was added Yb(OTf)₃ (18 mg, 0.029 mmol) at room temperature. After being stirred for 4 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 MgSO₄, and concentrated. The

residue was purified with preparative TLC (hexane : EtOAc : CH_2Cl_2 = 5 : 1 : 2) to afforded **12** (23 mg, 79%) as a pale yellow oil. $[\alpha]^{19}_D$: +100 (*c* 1.35, $CHCl_3$).

IR (film): 3478, 3031, 2869, 1740, 1599, 1512, 1454, 1427, 1373, 1264, 1219, 1121, 1028, 737, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 0.75:0.25 mixture of rotational isomer, major isomer): 7.46-6.70 (69H, m), 6.38 (1H, d, *J* = 8.0 Hz), 6.33 (1H, s), 5.97 (1H, d, *J* = 2.0 Hz), 5.84 (1H, s), 5.64 (1H, d, *J* = 2.0 Hz), 5.52 (1H, s), 5.18 (1H, s), 5.12-4.23 (27H, m), 4.39 (1H, d, *J* = 12.0 Hz), 3.57 (1H, m), 3.04 (1H, dd, *J* = 16.0, 5.5 Hz), 2.54 (1H, dd, *J* = 16.0, 9.0 Hz), 1.74 (3H, s), 1.59 (1H, d, *J* = 3.5 Hz), 1.23 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$, 0.75:0.25 mixture of rotational isomer, major isomer): 169.2, 168.5, 158.3, 158.0, 156.7, 155.8, 155.7, 155.6, 155.4, 155.3, 154.6, 152.5, 149.2, 148.8, 148.7, 148.6, 148.5, 148.1, 138.0, 137.5-137.0, 132.5, 131.3, 131.1, 128.5-126.0, 120.6, 119.8, 119.6, 113.7, 113.5, 112.3, 110.9, 109.9, 106.4, 104.6, 102.5, 93.8, 93.3, 91.9, 90.2, 81.0, 76.2, 75.8, 74.7, 72.8, 72.3, 71.4-71.0, 70.8, 70.4, 69.8, 69.7, 69.6, 69.5, 69.1, 67.8, 34.3, 33.0, 27.8, 20.8, 20.3.

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

[4,8:4",8"]-2,3-*cis*-3,4-*trans*: 2",3"-*cis*-3",4"-*trans*: 2'''',3''''-*trans*-Dodeca-*O*-benzyl-(−)-epicatechin-(−)-epicatechi-n-(+)-catechin (13): To a solution of **12** (40 mg, 0.020 mmol) in THF (4.0 mL) was added *n*-Bu$_4$NOH (1.0 mL, 40% in water). After being stirred for 164 h, the reaction mixture was diluted 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 **13** (36 mg, 94%) as a pale yellow oil.

$[\alpha]^{19}_D$: +130 (*c* 0.500, $CHCl_3$). {lit. $[\alpha]^{25}_D$: +92.0 (*c* 1.12, $CHCl_3$) [5e]

IR (film): 3567, 3031, 2906, 1740, 1598, 1508, 1454, 1420, 1376, 1264, 1216, 1119, 1026, 735, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 0.55:0.45 mixture of rotational isomer, major isomer): 7.51-6.73 (69H, m), 6.40 (1H, d, *J* = 8.5 Hz), 6.34 (1H, s), 6.26 (1H, d, *J* = 2.0 Hz), 6.19 (1H, s), 6.06 (1H, d, *J* = 2.0 Hz), 5.91 (1H, s), 5.72 (1H, d, *J* = 8.5 Hz), 5.51 (1H, s), 5.21-4.38 (24H, m), 4.39 (1H, d, *J* = 12.0 Hz), 3.99 (1H, d, *J* = 6.5 Hz), 3.56 (1H, brs), 3.43 (1H, m), 3.03 (1H, dd, *J* = 16.0, 5.0 Hz), 2.61 (1H, dd, *J* = 16.0, 9.0 Hz), 1.68 (1H, d, *J* = 6.0 Hz), 1.55 (1H, brs), 1.27 (1H, d, *J* = 6.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$, 0.55:0.45 mixture of rotational isomer, major isomer): 158.3, 158.1, 158.0, 157.4, 156.7, 156.4, 156.0, 155.9, 155.7, 155.6, 155.5, 155.4, 155.2, 154.8, 153.2, 152.9, 152.6, 149.2, 149.0, 148.8, 148.7, 148.6, 148.2, 148.1, 147.9, 138.2, 137.6-136.9, 132.9, 132.6, 132.5, 132.3, 131.3, 131.0, 128.5-127.0, 126.8, 126.6, 126.4, 126.1, 119.9-119.3, 118.8, 115.0, 114.6, 114.5, 114.1, 113.6, 113.2, 113.0, 111.1, 110.8, 110.6, 110.2, 106.2, 105.6, 104.6, 102.3, 101.9, 94.3, 94.0, 93.8, 93.4, 92.4, 92.1, 92.0, 90.2, 81.3, 76.2, 75.8, 75.6, 72.6, 72.5, 71.3-71.0, 70.3, 69.9, 69.8, 69.7, 69.6, 69.3, 68.3, 68.2, 36.5, 36.1, 35.5, 27.8, 27.5.

HRMS-FAB: *m/z* [M+Na]$^+$: calcd for $C_{129}H_{110}O_{18}Na$; 1969.7590, found: 1969.7607.

Arecatannin A1 (1): A solution of **13** (31 mg, 16 μmol) in THF/MeOH/H$_2$O (20/20/1) (4.1 mL) was hydrogenated over 20% Pd(OH)$_2$/C (22 mg) for 5.5h at room temperature. The mixture was filtered and the filtration residue was washed with MeOH (10 mL). The combined filtrates were evaporated, and the residue was taken up in distilled water (5.0 mL). The solution was filtered and lyophilized to give **1** (14 mg, quant.) as a fluffy amorphous solid.

$[\alpha]^{19}_D$: +51.1 (*c* 0.180, EtOH), +91.1 (*c* 0.295, MeOH), {lit. $[\alpha]^{25}_D$: +56.9 (*c* 0.30, EtOH) [5e]

IR (KBr): 3366, 1610, 1520, 1445, 1420, 1283, 1216, 1107cm^{-1}.

^{1}H NMR (500 MHz, CD$_3$OD): 7.10-6.70 (9H, m), 6.10-5.83 (4H, m), 5.25 (1H, brs), 5.05 (1H, brs), 4.89-4.62 (3H, m), 4.15-3.96 (3H, m), 2.69-2.61 (2H, m).

^{13}C NMR (125 MHz, CD$_3$OD): 158.6-153.8, 146.2, 146.0, 145.9, 145.6, 145.4, 132.7, 119.5-118.8, 116.2, 116.1, 115.2, 114.6, 110.8, 107.2, 105.0, 100.9, 97.4, 96.6, 96.3, 82.1, 77.2, 77.0, 76.9, 73.5, 72.3, 68.4, 37.4.

HRMS-ESI: *m/z* [M+H]$^+$: calcd for $C_{45}H_{39}O_{18}$; 867.2136, found: 867.2131.

Peracetate of arecatannin A1 (14): To a solution of pyridine (0.25 mL), acetic anhydride (0.25 mL), and DMAP (1.0 mg) was added **1** (11 mg, 13 μmol) in pyridine (0.1 mL). After the reaction mixture had been stirred for 24h, saturated aqueous NaHCO$_3$ (5 mL) was added, and the product was extracted with EtOAc (2 x 10 mL). The organic layers were washed with H$_2$O (5.0 mL), 0.5N H$_3$PO$_4$, saturated aqueous NaHCO$_3$ (5 mL), water (5.0 mL) and brine, dried over MgSO$_4$, filtered, and concentrated. The crude product was purified with preparative TLC (hexane:AcOEt = 1:5) to afford peracetate **14** (7.2 mg, 38%) as colorless amorphous solid. $[\alpha]_D^{19.0}$ = +100.4 (*c* 0.360, acetone), {lit. $[\alpha]^{25}_D$: +113.3 (*c* 0.30, acetone) [5e]

IR (film): 2936, 1770, 1598, 1507, 1428, 1371, 1203, 1109, 1038, 901 cm^{-1},

^{1}H NMR(500 MHz, CDCl$_3$, 0.4:0.4:0.2 mixture of rotational isomers) δ: 7.36-6.63 (13H), 6.29 (0.2H, dd, *J* = 8.5, 2.0 Hz), 6.26 (0.2H, d, *J* = 2.0Hz), 5.96 (0.2H, d, *J* = 2.5 Hz), 5.91 (0.2H, d, *J* = 2.5 Hz), 5.83 (0.2H, d, *J* = 2.5 Hz), 5.69 (0.2H, s), 5.62 (0.2H, s), 5.41 (0.4H, s), 5.37 (0.4H, s), 5.34 (0.8H, brs), 5.27 (0.2H, d, *J* = 3.0Hz), 5.16-5.02 (2.4H), 4.92 (0.2H, s), 4.86 (0.2H, s), 4.74 (0.4H, s), 4.63-4.59 (1H, m), 4.48 (0.2H, d, *J* = 2.0 Hz), 4.44 (0.2H, d, *J* = 2.0 Hz), 4.36 (0.2H, d, *J* = 2.0 Hz), 3.13 (0.4H, dd, *J* = 16.0, 5.5 Hz), 3.06 (0.2H, dd, *J* = 16.0, 5.5 Hz), 2.79-2.50 (1.4H, m), 2.36-1.25 (45H, m).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 171.0, 170.0, 169.0-167.1, 154.9, 151.7, 151.6, 149.9, 149.8, 148.4, 148.1, 147.4, 142.2-141.8, 136.7, 135.7, 135.3, 124.6-121.3, 117.6, 117.5, 71.0, 70.5, 68.3, 35.5, 35.1, 34.4, 29.8, 25.6, 21.2-19.7.

References

[1]   Ferreira D, Li XC. (**2000**) Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles. *Natural Product Report, 17*, 193-212.
[2]   Ferreira D, Slade D. (**2002**) Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles. *Natural Product Report*, *19*, 517-541.
[3]   Recent review of synthesis of proanthocyanidins: (a) Oyama K, Yoshida K, Kondo T. (**2011**) Recent progress in the synthesis of flavonoids: From monomers to supra-complex. *Current Organic Chemistry*, *15*, 2567-2607. (b) Ohmori K, Suzuki K. (**2012**) Synthetic strategies and tactics for oligomeric proanthocyanidins. *Current Organic Chemistry*, *16*, 566-577. (c) Makabe H. (**2013**) Recent syntheses of proanthocyanidins. *Heterocycles*, *87*, 2225-2248.

[4]   Recent syntheses of proanthocyanidin dimers: (a) Ishihara S, Doi S, Harui K, Okamoto T, Okamoto S, Uenishi J, Kawasaki T, Nakajima N, Saito A. (**2014**) Development of a new synthetic strategy for procyanidin dimer condensation using peracetylated electrophiles *Heterocycles*, **88**, 1595-1602. (b) Fujii W, Toda K, Matsumoto K, Kawaguchi K, Kawahara S-i, Hattori Y, Fujii H, Makabe, H. (**2013**) Syntheses of prodelphinidin B1, B2 and B4 and their antitumor activities against human PC-3 prostate cancer cell lines. *Tetrahedron Letters, 54*, 7188-7192. (c) Suda M, Katoh M, Toda K, Matsumoto K, Kawaguchi K, Kawahara S-i, Hattori Y, Fujii H, Makabe, H. (**2013**) Syntheses of procyanidin B2 and B3 gallate derivatives using equimolar condensation mediated by Yb(OTf)₃ and their antitumor activities. *Bioorganic Medicinal Chemistry Letters*, **23**, 4935-4939. (d) Fujii W, Toda K, Kawaguchi K, Kawahara S.-I, Katoh M, Hattori Y, Fujii H, Makabe, H. (**2013**) Syntheses of prodelphinidin B3 and C2, and their antitumor activities through cell cycle arrest and caspase-3 activation. *Tetrahedron*, **69**, 3543-3550. (e) Nakajima N, Horikawa K, Takekawa N, Hamada M, Kishimoto T. (**2012**) Condensation of catechin and epicatechin incorporating a TBS-protecting group. *Heterocycles*, **84**, 349-354. (f) Katoh M, Oizumi Y, Mohri Y, Hirota M, Makabe, H. (**2012**) Synthesis of procyanidin B1, B2, and B4 and their anti-inflammatory activity. The effect of 4-alkoxy group of catechin and/or epicatechin electrophiles for condensation. *Letters in Organic Chemistry*, **9**, 233-238. (g) Alharthy RD, Hayes CJ. (**2010**) Procyanidin B3 synthesis: a study of leaving group and Lewis acid activator effects upon interflavan bond formation. *Tetrahedron Letters*, **51**, 1193-1195. (h) Oizumi Y, Mohri Y, Hirota M, Makabe H. Synthesis of procyanidin B3 and its anti-inflammatory activity. The effect of 4-alkoxy group of catechin electrophile in the Yb(OTf)₃-catalyzed condensation with catechin nucleophile. (**2010**) *Journal of the Organic Chemistry 75*, 4884-4886. (i) Mohri Y, Sagehashi M, Yamada T, Hattori, Y, Morimura K, Hamauzu Y, Kamo, T, Hirota M, Makabe H. (**2009**) An efficient synthesis of procyanidins using equimolar condensation of catechin and/or epicatechin catalyzed by ytterbium triflate. *Heterocycles*, **79**, 549-563. (j) Oyama K, Kuwano M, Ito M, Yoshida K, Kondo T. (**2008**) 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-(+)-catachin and (−)-epicatechin as a key building monomer. *Tetrahedron Letters, 49*, 3176-3180. (k) Viton F, Landreau C, Rustidge D, Robert F, Williamson G, Barron G. (**2008**) First total synthesis of ¹⁴C-labeled procyanidin B2-a milestone toward understanding cocoa polyphenol metabolism. *European Jounal of Organic Chemistry*, 6069-6078. (l) Mohri Y, Sagehashi M, Yamada T, Hattori Y, Morimura K, Kamo T, Hirota M, Makabe H. (**2007**) An efficient synthesis of procyanidins. Rare earth metal Lewis acid catalyzed equimolar condensation of catechin and epicatechin. *Tetrahedron Letters*, **48**, 5891-5894. (m) Tarascou I, Barathieu K, André Y, Pianet I, Dufourc EJ, Fouquet E. (**2006**) An improved synthesis of procyanidin dimers: regio-and stereocontrol of the interflavan bond. *European Jounal of Organic Chemistry*, 5367-5377. (n) Saito A, Nakajima N, Matsuura N, Tanaka A, Ubukata M. (**2004**) Synthetic studies of proanthocyanidins: Part 5. Highly stereoselective synthesis and inhibitory activity of Maillard reaction of 3,4-*trans* catechin and epicatechin dimers, procyanidin B1, B2, B3, B4 and their acetates. *Heterocycles*, **62**, 479-489; (o) Saito A, Nakajima N, Tanaka A, Ubukata M. (**2003**) Synthetic studies of proanthocyanidins. Part 4. The synthesis of procyanidin B1 and B4: TMSOTf-catalyzed cyclization of catechin and epicatechin condensation. *Heterocycles*, **61**, 287-298. (p) Saito A, Nakajima N, Matsuura N, Tanaka A, Ubukata M. (**2002**) Synthetic studies of procyanidins. Part 2: Stereoselective gram-scale synthesis of procyanidin-B3. *Tetrahedron*, **58**, 7829-7837.

[5]   Recent syntheses of proanthocyanidin trimers: (a) Yano T, Ohmori K, Takahashi H, Kusumi T, Suzuki K. (**2012**) Unified approach to catechin hetero-oligomers: first total synthesis of trimer-EZ-EG-CA isolated from *Ziziphus jujuba*. *Organic Biomolecular Chemistry*, **10**, 7685-7688. (b) Oizumi Y, Katoh M, Hattori Y, Toda K, Kawaguchi K, Fujii H, Makabe, H. (**2012**) Synthesis of procyanidin C2 and C1 using Lewis acid mediated equimolar condensation. *Heterocycles*, **83**, 739-742. (c) Oizumi Y, Mohri Y, Hattori Y, Makabe H. (**2011**) Efficient stereoselective synthesis of catechin trimer derivative using silver Lewis acid catalyzed equimolar condensation. *Heterocycles*, **83**, 739-742. (d) Ohmori K, Ushimaru N, Suzuki K. (2004) Oligomeric catechins: An enabling synthetic strategy by orthogonal activation and C(8) protection. *Proceedings of the National. Academy of Sciencesof the United States of America,101*, 12002-12007. (e) Saito A, Doi Y, Tanaka A, Matsuura N, Ubukata M, Nakajima N, (**2004**) Systematic synthesis of four epicatechin series procyanidin trimers and theis inhibitory activity on the Maillard reaction and antioxidant activity. *Bioorganic Medicinal Chemistry, 12*, 4783-4790. (f) Saito A, Tanaka A, Ubukata M, Nakajima N. (**2004**) Efficient stereoselective synthesis of proanthocyanidin trimers with TMSOTf-catalyzed intermolecular condensation. *Synlett*, 1069-1073.

[6]   Syntheses of procyanidin oligomers: (a) Ohmori K, Shono T, Hatakoshi Y, Yano T, Suzuki K. (**2011**) Integrated synthetic strategy for higher catechin oligomers. *Angewante Chemie International Edition in English*, **50**, 4862-4867. (b) Saito A, Mizushina Y, Tanaka A, Nakajima N. (**2009**) Versatile synthesis of epicatechin series procyanidin oligomers, and their antioxidant and DNA polymerse inhibitory activity. *Tetrahedron*, **65**, 7422-7428.

[7]   Suda M, Fujii W, Takanashi K, Hattori Y, Makabe H. (**2014**) Selective synthesis of epicatechin dimers using Zn(OTf)₂ mediated self-condensation. *Synthesis*, **46**, 3351-3355.

[8]   Shoji T, Mutsuga M, Nakamura T, Kanda T, Akiyama H, Goda Y. (**2003**) Isolation and structural elucidation of some procyanidins from apple by low-temperature nuclear magnetic resonance. *Journal of Agricultural and Food Chemistry*, **51**, 3806-3813.

[9]   Nonaka G, Nishioka, I. (**1981**) Structures of dimeric, trimeric, and tetrameric procyanidins from *Areca catechu L. Journal of the Chemical Society, Chemical Communications, 781-783.*

[10]   HPLC measurement condition: column; InertSustain C18, 250×4.6 mm GL-Sciences, eluent CH₃CN-0.2%AcOH (5:95~25:75), flow rate: 0.8 mL/min, detection: UV 280 nm, retention time: 26.18 min.