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# Synthetic studies of proanthocyanidins. Part 3: Stereoselective 3,4-*cis* catechin and catechin condensation by TMSOTf-catalyzed intramolecular coupling method☆

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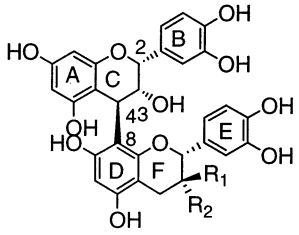
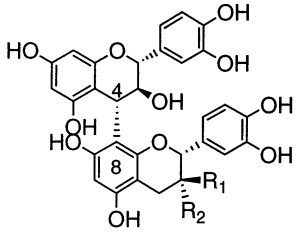
**Abstract**—TMSOTf-catalyzed intramolecular condensation for catechin and epicatechin units are described. A potential electrophile and a nucleophile were connected with diester linkers and TMSOTf-catalyzed condensation was examined. In comparison with intermolecular catechin and catechin condensation, the intramolecular condensation required high reaction temperature and reversed 3,4-*cis* product was obtained. The condensed product was transformed into the natural 3,4-*cis* (+)-catechin-(4β→8)-(+)-catechin dimer. 

Proanthocyanidins are known as condensed tannins and/or oligomeric flavonoids.[2,3] Many biological activities, powerful free-radical-scavenging activity[4] and an anti-tumor-promoting effect,[5] have been reported for flavonoids, and their investigation is now increasingly important. In the previous paper,[1] we described Lewis acid-catalyzed condensation of benzylated catechin as a potential nucleophile, with various 4-*O*-alkylated catechin derivatives as an electrophile. During the examination, we have been able to achieve high levels of 3,4-*trans* stereoselectivity in excellent isolation yields under the TMSOTf-catalyzed intermolecular condensation (Fig. 1).

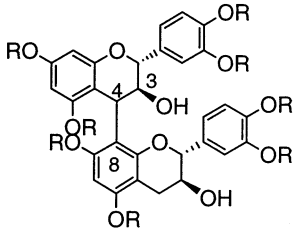
Natural B-type procyanidins, procyanidin B1 (**1**), B2 (**2**), B3 (**3**)[6–9] and B4 (**4**), are consisted from the combination of (+)-catechin and (−)-epicatechin units dominantly with 3,4-*trans* manner. The TMSOTf-catalyzed intermolecular condensation is well suited for the construction of 3,4-*trans* stereochemistry. However, the




**1**: $R_1$=OH, $R_2$=H, procyanidin B1 [(-)-epicatechin-(+)-catechin]
**2**: $R_1$=H, $R_2$=OH: procyanidin B2 [(-)-epicatechin-(-)-epicatechin]




**3**: $R_1$=OH, $R_2$=H: procyanidin B3 [(+)-catechin-(+)-catechin]
**4**: $R_1$=H, $R_2$=OH: procyanidin B4 [(+)-catechin-(-)-epicatechin]




**5**: R=Bn, octa-*O*-benzyl-3,4-*trans* (+)-catechin-(4α→8)-(+)-catechin dimer
**6**: R=Bn, octa-*O*-benzyl-3,4-*cis* (+)-catechin-(4β→8)-(+)-catechin dimer
**7**: R=H, 3,4-*cis* (+)-catechin-(4β→8)-(+)-catechin dimer

**Figure 1.**

*Keywords*: polyphenol; condensed tannin; oligomeric flavonoid; catechin dimer; procyanidin B3.

☆ See Ref. 1.

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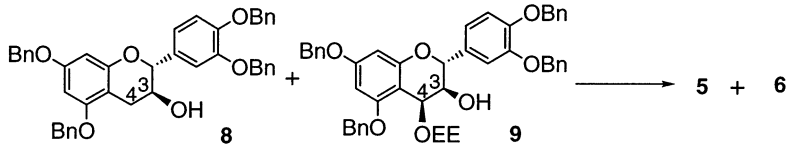
reaction required 4.5-fold excess nucleophile to avoid higher oligomer formation. In this paper, we challenge to find the coupling conditions, which used just equimolar amount of nucleophile and electrophile in good yield. After several attempts, we were pleased to find the intramolecular [4,8]-catechin–catechin coupling proceeded in good yield with reversed 3,4-*cis* stereoselectivity. The 3,4-*cis* catechin units are rare in nature and there is a few report accessible through 3,4-*cis* dimer construction.[10] The most straightforward method for 3,4-*cis* formation is $TiCl_4$-catalyzed intermolecular condensation between tetra-*O*-benzylated 3-hydroxycatechin (**8**) and (2*R*,3*S*,4*S*)-5,7,3′,4′-tetrabenzyloxy-4-ethoxyethoxyflavan (**9**) to provide 2:1 ratio of **5** and **6** in 84% yield (Scheme 1).[1]

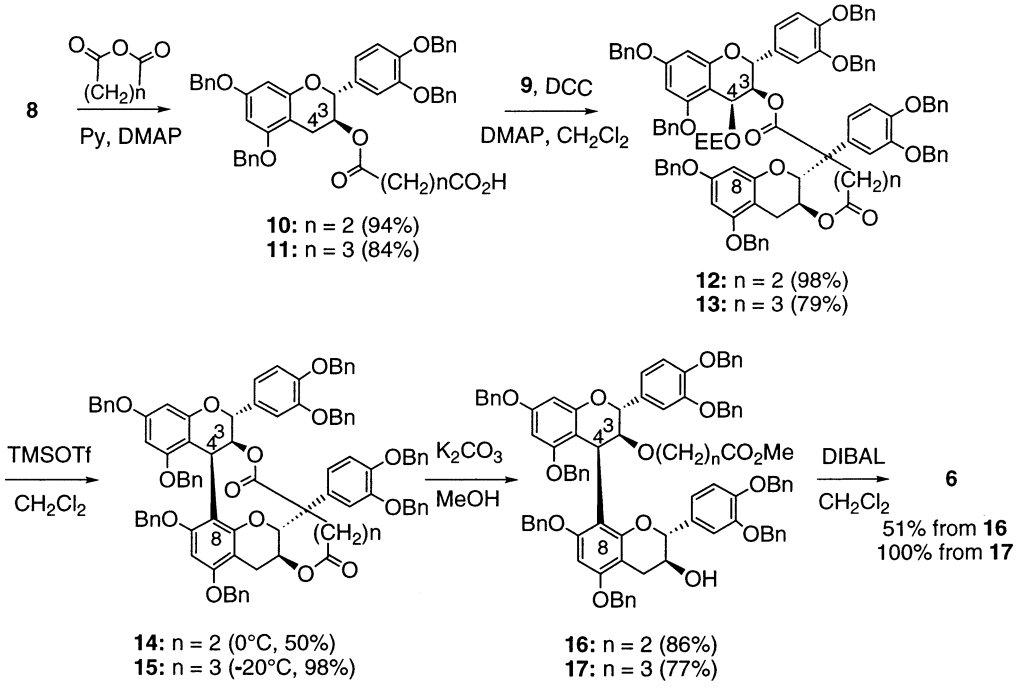
We designed to connect two units, a potential electrophile and a nucleophile, with diester linker and reinvestigated the TMSOTf-catalyzed condensation at various temperatures. Tetra-*O*-benzylated catechin (**8**) was esterified with succinyl and glutaryl anhydride and the resulting carboxylic mono-esters (**10** and **11**) were coupled with an electrophile unit (**9**) by the DCC method to give diesters (**12** and **13**) in 94 and 84% yield, respectively. Intramolecular TMSOTf-catalyzed coupling of succinyl diester (**12**) was first performed at −78°C to give [4,8]-condensed product (**14**) in 20% yield with unconsumed **12**. An improved isolation yield was successfully obtained by increasing the reaction temperature, and **14** was obtained in 35% yield at −20°C and in 50% yield at 0°C. Best results were obtained by using glutaryl diester **13** under the same conditions, 98% yield of cyclization product (**15**) was generated at −20°C as the sole product.[11] All peaks except for the benzyl group were easily assigned by the usual NMR measurement.[12] The conformations of **14** and **15** were analyzed using the combination of NOE data and molecular mechanics calculation.[13,14] It was found that cyclized product has rigid conformation, rotational isomerism about the interflavanyl linkages was not observed in NMR (Scheme 2).

When the intramolecular condensation of epicatechin–catechin and catechin–epicatechin combination (**18** and **20**) were performed under the same conditions at 0°C, 3,4-*trans* products (**19** and **21**) were isolated in 47 and 43% yield, respectively.[15] Any amounts of 3,4-*cis* products were not detected in the reaction mixture. Unfortunately, (−)-epicatechin and (−)-epicatechin condensation provided no any amount of dimer product (Scheme 3).

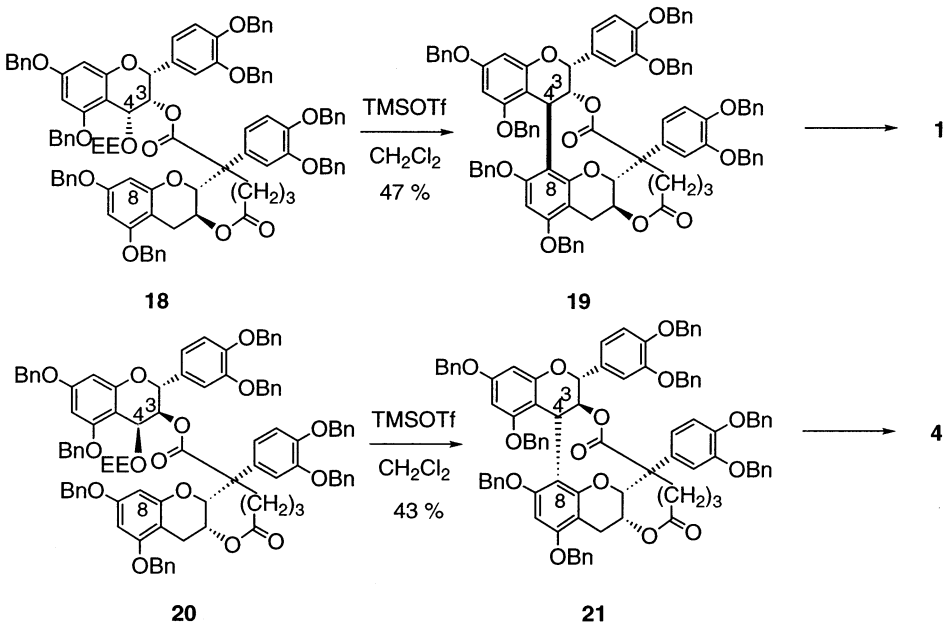
Succinyl linker was removed by DIBAL treatment at −30°C, desired 3,3′-diol (**6**) was obtained in 55% yield from **14**. A better result was obtained in two-step sequences via methyl ester. By the $K_2CO_3$/MeOH treat-




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

ment of **15**, less hindered F ring ester was first cleaved and the following DIBAL treatment furnished **6** in 77% yield. All the spectral data [NMR, IR, mass] collected for **6** were identical with those of authentic samples reported before.[1b] Compound **6** was finally converted into 3,4-*cis*-(+)-catechin-(4β→8)-(+)-catechin dimer (**7**)[16] by $Pd(OH)_2$–catalyzed hydrogenolysis in 67% yield.

## Conclusion

The TMSOTf-catalyzed intramolecular one-to-one coupling method was developed. (+)-Catechin and (+)-catechin condensation produced 3,4-*cis* condensed product. This method will be expected to develop a good oligomerization method.

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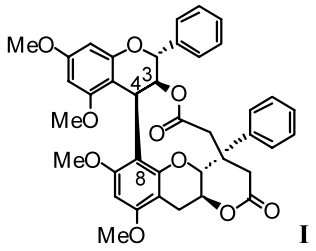
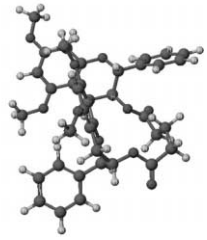
11. A typical procedure for Intramolecular TMSOTf-catalyzed coupling: To a solution of (2*R*,3*S*)-5,7,3′,4′-tetrabenzyloxy-flavan-3-yl (2*R*,3*S*,4*S*)-5,7,3′,4′-tetrabenzyloxy-4-ethoxyethyloxy-flavan-3-yl glutarate (206 mg, 0.139 mmol) in $CH_2Cl_2$ (80 mL) was added dropwise TMSOTf (0.28 mL, 0.14 mmol, 0.5 M solution in $CH_2Cl_2$) at −20°C. After stirring for 10 min, the pale yellow reaction mixture was quenched with sat. $NaHCO_3$. The aq. solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($Na_2SO_4$). Filtration, concentration and silica gel column purification (hexane/EtOAc, 6/1 to 2/1) afforded a 190 mg (0.136 mmol, 98%) of a mixture of **15** as a amorphous solid.
12. Data for **15**: $[\alpha]_D^{24}=+87.6$ (*c* 1.14, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) 7.52–6.90 (43H, m), 6.86–6.84 (1H, m), 6.26 (1H, s, D6), 6.21 (1H, d, $J=8.5$ Hz), 6.02 (1H, d, $J=2.2$ Hz, A6), 5.88 (1H, d, $J=2.2$ Hz, A8), 5.50 (1H, dd, $J=7.1$, 10.4 Hz, C3), 5.40 (1H, d, $J=7.1$ Hz, C4), 5.39 (1H, d, $J=1.7$ Hz, F2), 5.32 (1H, dd, $J=1.7$, 4.2 Hz, F3), 5.31 (1H, d, $J=10.4$ Hz, C2), 5.12 (2H, s), 5.09 (2H, s), 5.01 (1H, d, $J=12.0$ Hz), 4.98 (1H, d, $J=11.7$ Hz), 4.97 (1H, d, $J=11.7$ Hz), 4.94 (1H, d, $J=12.0$ Hz), 4.82–4.73 (4H, m), 4.66 (1H, d, $J=12.0$ Hz), 4.31 (1H, d, $J=12.0$ Hz), 2.84 (1H, d, $J=17.8$ Hz, F4), 2.36 (1H, dd, $J=4.2$, 17.8 Hz, F4), 2.39–2.20 (3H, m), 2.07–1.96 (1H, m), 1.93–1.75 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) 172.8, 171.0, 158.3, 157.4, 156.6, 155.9, 155.8, 152.6, 148.9, 148.8, 148.4,

148.3, 128.5–127.1 (48×C, Bn), 126.0 (×2), 121.2, 118.1, 114.7, 114.3, 114.1, 112.7, 109.3, 105.7, 100.7, 94.2, 93.6, 92.4, 77.2, 76.2, 75.6, 72.0, 71.5, 71.4, 71.3, 71.2, 70.6, 69.8, 69.0, 68.3, 34.9, 32.6, 30.7, 20.0, 18.3; FAB-MS ($m/z$) 1396 ($[M+H]^+$, 1.2); FAB-HRMS calcd for $C_{91}H_{79}O_{14}$ $[M+H]^+$, 1395.5470; found: 1395.5492.

13. CONFLEX calculations was carried out for 3′,4′-tetradeoxy-5,7-tetrametoxy-3,4-*cis* model (I) by CAChe 4.1 (Oxford Molecular Ltd.) on a Macintosh G3.
14. (a) Goto, H.; Osawa, E. CONFLEX 3, JCPE, P40; (b) Goto, H.; Osawa, E. CONFLEX: Generation of ring corner flapping algorithm, QECP, #592; JCPE, P21.




**I**



15. Stereochemistry of **17** and **19** were determined after conversion into **1** and **4**.
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