Stereoselection of 3,4-*cis* and 3,4-*trans* Catechin and Catechin Condensation under Intramolecular Coupling Method[1]

Akiko Saito,*[a] Akira Tanaka,[b] Makoto Ubukata,[c] Noriyuki Nakajima*[d]

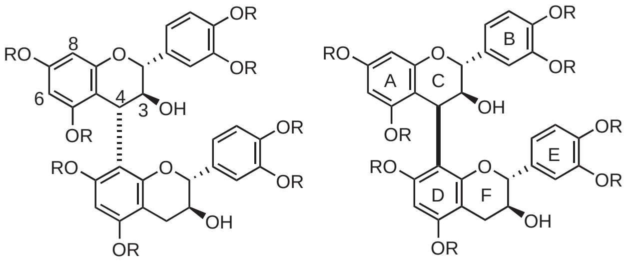
[a] Biotechnology Center, Toyama Prefecture, Kosugi, Toyama 939-0398, Japan
[b] Department of Bioresources Science, College of Technology, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan
[c] Graduate School of Agriculture, Hokkaido University, Kita-9, Nishi-9, Kita-ku, Sapporo 060-8589, Japan
[d] Biotechnology Center, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan
Fax +81(766)567500; E-mail: nori@pu-toyama.ac.jp

Received 23 April 2004

Abstract: A high level of stereoselection between 3,4-*cis* and 3,4-*trans* catechin–catechin condensation under intramolecular coupling method has been realized by changing the diester linker between the nucleophile and the electrophile. The azelaic acid linker gave exclusively 3,4-*trans* catechin–catechin dimer, whereas glutaric acid linker gave 3,4-*cis* catechin–catechin dimer as the sole product.

Key word: polyphenol, oligomeric flavonoid, catechin dimmer, B-type procyanidin, diester linker

Proanthocyanidins are known as condensed tannins and/or oligomeric flavonoids,[2,3] and has now great attention because of their various strong bioactivities.[4] A large amount of pure oligomeric proanthocyanidins has been required for the biological assay; however, efficient methods for the stereoselective synthesis of long oligomeric proanthocyanidin have not been reported yet. So we have embarked on research attempting to develop a simple and efficient method to synthesize pure proanthocyanidin oligomers. Using TMSOTf as the catalyst, the stereoselective condensation reaction proceeded smoothly to afford 3,4-*trans* dimers and trimers in excellent yields.[5–7] Disadvantages of this intermolecular condensation method are that the condensation reaction requires excess amount of nucleophile (4.5 equiv) to avoid higher oligomer formation. This makes it difficult to supply nucleophiles.



1: 3,4-*trans* (+)-catechin-(4α-8)-(+)-catechin
3: R = H

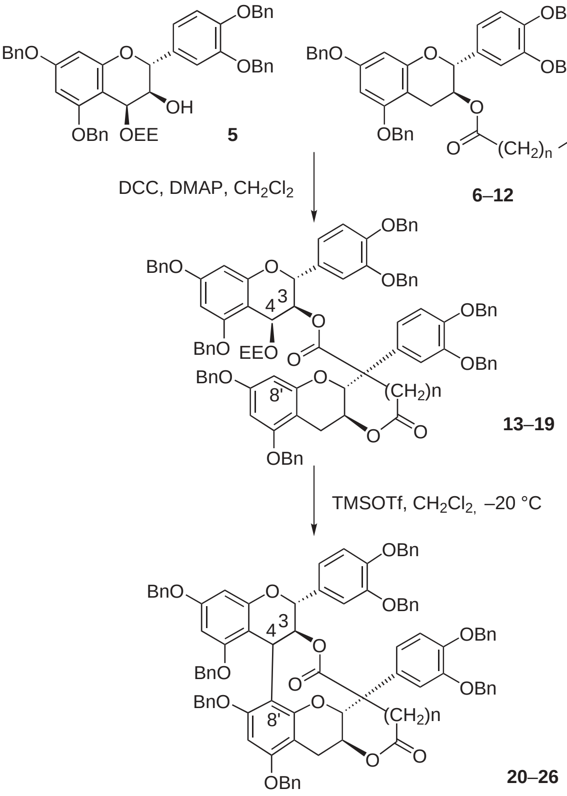
2: 3,4-*cis* (+)-catechin-(4ß-8)-(+)-catechin
4: R = H

Figure 1 Structure of procyanidin dimers

Therefore, we developed an intramolecular condensation method in which just equimolar amount of the nucleophile and the electrophile is used to improve that point. As results of intramolecular reaction using succinic acid (n = 2) and glutalic acid (n = 3) as a linker, only the case of catechin and catechin condensation gave 3,4-*cis* dimer **2** (Figure 1),[8,9] although 3,4-*trans* oligomers are major isomers in nature.[10,11] In this paper, we challenge to find the conditions to synthesize 3,4-*trans*-(+)-catechin dimer **1** under intramolecular condensation conditions by changing the diester linker.

Nucleophile-carboxylic acid units **6**–**12** (n = 2–8), were derived from (+)-catechin and succinic and glutaric anhydride or the corresponding dicarboxylic acid (adipic acid, pimelic acid, suberic acid, azelaic acid and sebacic acid). Following condensation with electrophile unit **5**[5] by the DCC method afforded diester compounds **13**–**19** (n = 2–8) in 98%, 76%, 69%, 41%, 19%, 40% and 51% yields, respectively (Scheme 1). TMSOTf-catalyzed intramolecular condensations were examined at –20 °C for 5 minutes. These results are summarized in Table 1 and Figure 2. The cyclic catechin dimers **20**–**26** (n = 2–8) were obtained in 35% (n = 2), 98% (n = 3), 23% (n = 4), 14% (n = 5), 49% (n = 6), 42% and 41% (n = 7 and 8) yields, respectively. It is thought that the linker length is very important for *cis*/*trans* selection and reaction yields. Only when the linker length matched with neighboring group participation effect, the sole product was obtained in good yield. Short linkers (n = 2–4) dominantly formed 3,4-*cis* products. As linker lengthened, the proportion of 3,4-*trans* products tended to increase and the selectivity came closer to the no linker (intermolecular) condensation.[5] Particular results are as follows; glutalic acid linker (n = 3) gave only 3,4-*cis*-catechin dimer **24**[8] in 98% yield and azelaic acid linker (n = 7) gave the 3,4-*trans*-catechin dimer **25**[12] in 42% yield as the sole product. In contrast, adoption of the other linkers gave the dimers in moderate yields as *cis*:*trans* mixtures, **23** (n = 4) with 7:1 (14%), **24** (n = 5) with 1:3 (49%), **25** (n = 6) with 1:8 (42%) and **26** (n = 8) with 1:2 ratios (41%), respectively, in which so many by-products were observed. As the temperature is lowered, *cis*:*trans* ratio changed from 1:2 up to 1:5 in the case of **26**. However, the yields of dimeric products were dramatically dropped to less than 5%.

SYNLETT 2004, No. 11, pp 2040–2042
Advanced online publication: 28.07.2004
DOI: 10.1055/s-2004-830848; Art ID: U12204ST



Scheme 1

Table 1 Condensation of Nucleophile Unit with Electrophile Unit

n	Carboxylic acid	Diester	Yield (%)	Cyclic diester	Yield (%)
2	**6**	**13**	98	**20**	35
3	**7**	**14**	76	**21**	98
4	**8**	**15**	69	**22**	23
5	**9**	**16**	41	**23**	14
6	**10**	**17**	19	**24**	49
7	**11**	**18**	40	**25**	42
8	**12**	**19**	51	**26**	41

Intramolecular condensation combined with epicatechin series was also attempted using glutaric linker in the presence of TMSOTf at –20 °C and 0 °C (Figure 3). From the catechin electrophile, 3,4-*trans*-octa-O-benzylated (+)-catechin-(4 α→8)-(–)-epicatechin dimer (**27**) was obtained in 40% at –20 °C and in 84% yield at 0 °C. The epicatechin electrophile was less reactive than catechin electrophile and 3,4-*trans*-octa-O-benzylated (–)-epicatechin-(4 β→8)-(+)-catechin dimer (**28**) was obtained only in 41% at –20 °C and in 43% yield at 0 °C. Interestingly, (–)-epicatechin and (–)-epicatechin cyclization provided only a messy product. No detectable amount of dimer **29** was observed in the reaction mixture. After several attempts, desired dimer **29** was finally obtained by use of 1,2-phenylenediacetic acid linker at 0 °C in 8% yield. Used linkers were easily removed by DIBAL treatment at –78 °C to room temperature or 2 step sequences; K_2CO_3–MeOH and DIBAL treatment. The 3,3′-diols (**3** and **4**) were isolated in 44% (for **20**), 77% (for **21**), 100% (for **22** and **23**), 54% (for **24**), 67% (for **25**), and 71% yield (for **26**), respectively.

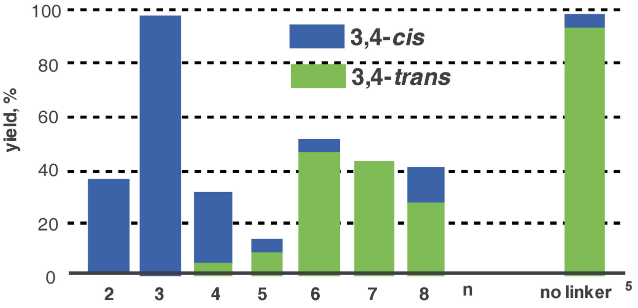


Figure 2 Stereoselectivity of intramolecular condensation

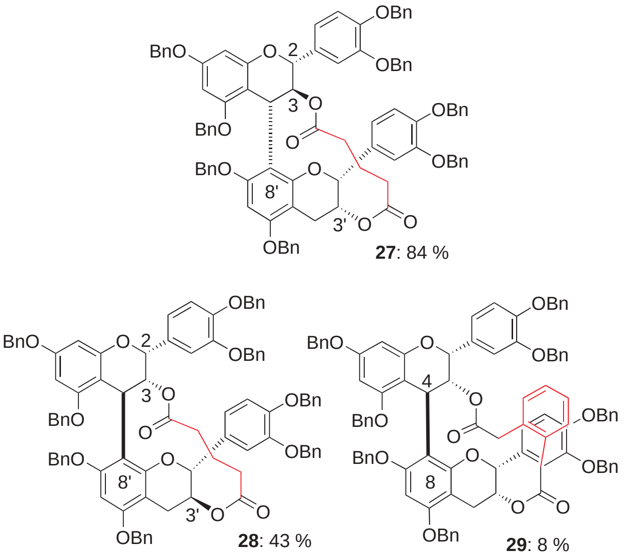


Figure 3 Results of intramolecular condensation

To our knowledge, this is the first example of simple stereoselection in proanthocyanidin synthesis, in which only the linker length was changed between an electrophile and a nucleophile. Further investigations are in progress to the synthesis of longer oligomer, and application to other combinations of catechin and epicatechin.

Acknowledgment

We gratefully acknowledge the Japan Society for the Promotion of Science (JSPS) for the Young Scientists Research Fellowship (to A. S.).

References

(1) This report is Part 7 in the series ‘Synthetic studies of proanthocyanidins’. For part 6 see ref.[7]

(2) Harborne, J. B. *The Flavonoids: Advances in research from 1986*; Chapman and Hall: London, **1993**.

(3) Harborne, F. R. S. J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley and Sons: New York, **1999**.

(4) There are many reports describing the biological activities of proanthocyanidins. A recent noteworthy report is: Kozikowski, A. P.; Tuckmantel, W.; Böttcher, G.; Romanczyk, L. J. Jr. *J. Org. Chem.* **2003**, *68*, 1641.

(5) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron* **2002**, *58*, 7829.

(6) Saito, A.; Nakajima, N.; Matsuura, N.; Tanaka, A.; Ubukata, M. *Heterocycles* **2004**, *62*, 479.

(7) Saito, A.; Tanaka, A.; Ubukata, M.; Nakajima, N. *Synlett* **2004**, 1069.

(8) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron Lett.* **2003**, *44*, 5449.

(9) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Heterocycles* **2003**, *61*, 287.

(10) Kolodziej, H. *Phytochemistry* **1985**, *24*, 2460.

(11) Schleep, S.; Friedrich, H.; Kolodziej, H. *J. Chem. Soc., Chem. Commun.* **1986**, 392.

(12) Data for **23**: To a solution of (2*R*,3*S*,4*S*)-5,7,3′,4′-tetrabenzyloxy-4-ethoxyethyloxy-flavan-3-yl (2*R*,3*S*)-5,7,3′,4′-tetrabenzyloxy-flavan-3-yl azelate (44 mg, 0.028 mmol) in CH_2Cl_2 (20 mL) was added dropwise TMSOTf (0.056 mL, 0.028 mmol, 0.5 M solution in CH_2Cl_2) at –20 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with sat. $NaHCO_3$. The aq solution was extracted with $CHCl_3$ and the combined organic phase were washed with H_2O and brine, and dried (Na_2SO_4). Filtration, concentration and preparative silica gel TLC purification (hexane–EtOAc, 2:1) afforded 17 mg (0.012 mmol, 42%) of cyclic compound **23** as a single product. $[\alpha]_D^{25}$ –93.1 (*c* 0.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.18 (35 H, m), 7.06–6.93 (5 H, m), 6.84–6.76 (3 H, m), 6.56 (1 H, d, *J* = 2.2 Hz), 6.37 (1 H, d, *J* = 8.3 Hz), 6.10 (1 H, d, *J* = 2.1 Hz), 6.01 (1 H, dd, *J* = 9.6, 10.0 Hz), 6.00 (1 H, d, *J* = 2.1 Hz), 5.89 (1 H, s), 5.87 (1 H, dd, *J* = 2.2, 8.3 Hz), 5.36 (1 H, br s), 5.25–5.22 (1 H, m), 5.08–4.81 (8 H, m), 5.05 (1 H, d, *J* = 9.6 Hz), 4.86 (1 H, d, *J* = 11.9 Hz), 4.77 (1 H, d, *J* = 11.9 Hz), 4.75 (1 H, d, *J* = 11.4 Hz), 4.73 (1 H, d, *J* = 12.0 Hz), 4.68 (1 H, d, *J* = 10.0 Hz), 4.64 (1 H, d, *J* = 11.4 Hz), 4.61 (1 H, d, *J* = 11.7 Hz), 4.56 (1 H, d, *J* = 12.0 Hz), 4.46 (1 H, d, *J* = 11.7 Hz), 2.99–2.93 (1 H, m), 2.32–2.22 (1 H, m), 2.03 (1 H, dd, *J* = 2.4, 16.6 Hz), 1.97–1.90 (1 H, m), 1.84–1.74 (2 H, m), 1.25–0.80 (10 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 171.4, 158.4, 157.5, 157.4, 155.7, 151.7, 148.9, 148.6, 148.51, 148.48, 138.0, 137.5, 137.31, 137.25, 137.21, 137.17, 136.9, 132.1, 130.8, 128.5-126.9 (C × 27), 121.0, 118.9, 117.1, 114.8, 114.6, 114.4, 112.0, 109.8, 108.2, 100.9, 94.8, 94.5, 90.4, 80.7, 71.6, 71.4, 71.11, 71.05, 70.2, 70.1, 70.0, 69.9, 69.0, 35.4, 34.4, 32.9, 29.7, 26.3, 24.9, 24.0, 23.0, 19.0. IR (neat): 3065 (w), 3032 (w), 2930 (m), 2862 (w), 2361 (w), 1732 (s), 1606 (s), 1512 (s), 1454 (s), 1379 (m), 1263 (m), 1213 (m), 1124 (s), 1026 (m), 910 (w), 851 (w), 812 (w), 737 (s), 696 (s) cm^{-1}. FAB-MS: *m/z* = 1450.6 (81), 1451.6 (100) $[M + H]^+$, 1452.6 (79), 1453.6 (43). FAB-HRMS: *m/z* calcd for $C_{95}H_{87}O_{14}$ $[M + H]^+$: 1451.6096. Found: 1451.6136.