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EFFICIENT STEREOSELECTIVE SYNTHESIS OF CATECHIN TRIMER DERIVATIVE USING SILVER LEWIS ACID-MEDIATED EQUIMOLAR CONDENSATION

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Abstract – A stereoselective synthesis of benzylated catechin trimer under intermolecular condensasion is achieved using equimolar amount of dimeric catechin nucleophile and monomeric catechin electrophile catalyzed by AgOTf or $AgBF_4$. The coupled product can be transformed into procyanidin C2 by a known procedure.

Proanthocyanidins are known as condensed or noncondensed hydrolysable tannins.[1] These condensed tannins can be found in the vegetables kingdom.[2] In particular, they exist in grape seeds and skins and red wines. Many biological activities, mainly a powerful free-radical scavenging activity, have been reported for flavonoids, and their investigation is increasingly important. Tannin extracts from plants give various types of polyphenols. Because their identification as well as purification is extremely difficult, further studies of proanthocyanidins remains. Recently, to obtain procyanidin oligomers in pure state, synthetic efforts were devoted. There are several reports about condensation studies for procyanidin trimers such as procyanidin C2 (**1**) using catechin and/or epicatechin nucleophile and electrophile under Lewis acids.[3] However, excess amount of nucleophile was needed for oligomerization control. Thus we have pursued equimolar condensation of nucleophile and electrophile to construct the skeleton of procyanidin oligomers using various types of Lewis acids. We have already reported a stereoselective synthesis of catechin and/or epicatechin dimers from equimolar amount of catechin nucleophile and electrophile using $Yb(OTf)_3$ as a Lewis acid.[4] In this communication, we would like to describe the stereoselective synthesis

of the protected catechin trimer using equimolar amount of dimeric catechin nucleophile **2** and monomeric catechin electrophile **3** (Figure 1).

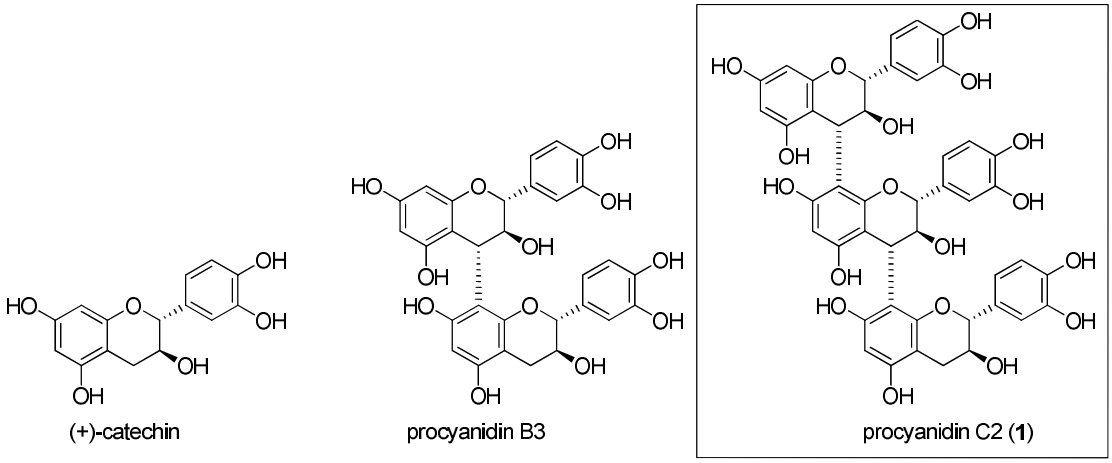
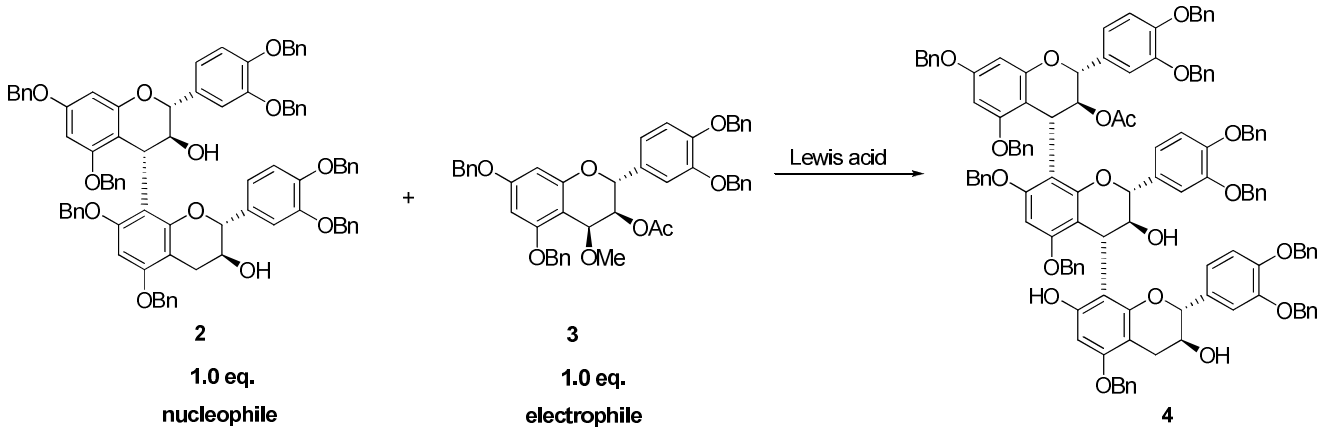


Figure 1. The structure of procyanidin C2 (**1**).

We chose octabenzylated catechin dimer **2** as a nucleophile and compound **3** as an electrophile prepared by us before.[4] Equimolar condensation of **2** with **3** was examined using transition metal Lewis acids and $Yb(OTf)_3$ in CH_2Cl_2 (Table 1). We paid attention to silver Lewis acid because condensation can be performed under neutral conditions. Ferreira and co-workers reported that using $AgBF_4$ as the thiophilic Lewis acid offered advantages to control the level of oligomeration in the procyanidin B1-B4 and C2 synthesis.[5] As shown in Table 1, $AgBF_4$ and AgOTf gave **4** in excellent yield. However, $Yb(OTf)_3$, which gave good results for dimer condensation, afforded low yield. Due to the bulkiness of $Yb(OTf)_3$, it seemed to be difficult for dimeric nucleophile **2**, which is more bulky than monomeric nucleophile, to attack C-4 position of electrophile **3** (Scheme 1, Table 1). In the case of $Cu(OTf)_2$, the yield was low although starting materials were consumed within 3h.



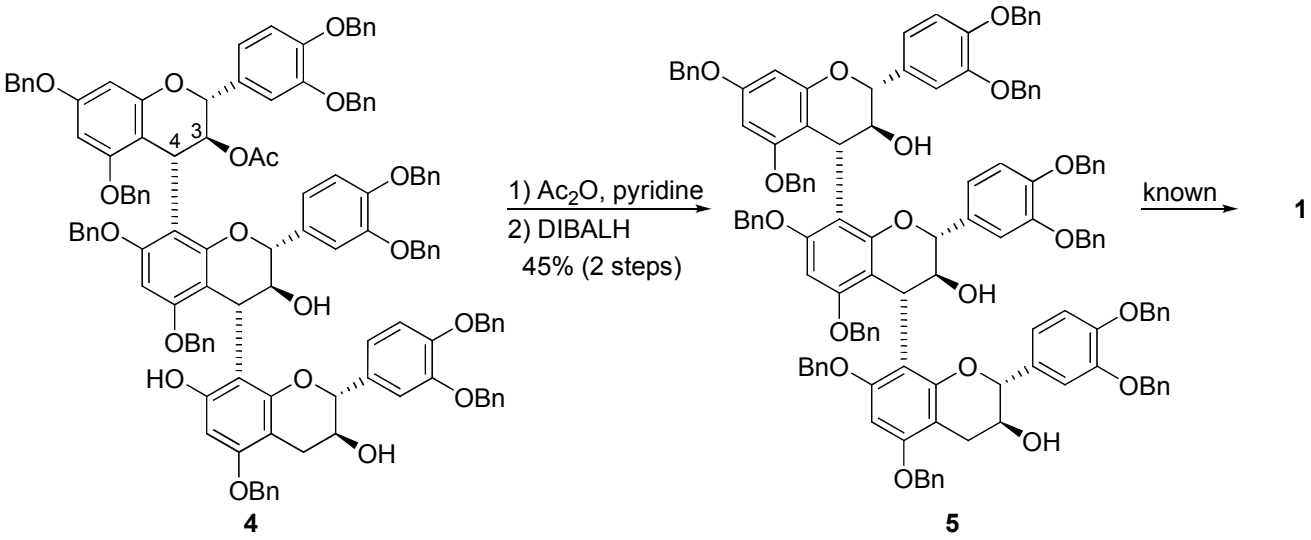
Scheme 1. Lewis acid catalyzed equimolar condensation between nucleophile **2** and electrophile **3**.

Table 1. Equimolar coupling reaction of **2** and **3** by Lewis acids[a]

Lewis acids[b]	Time (h)	Yield (%)
$Yb(OTf)_3$	12	13
$Cu(OTf)_2$	3	23
$AgBF_4$	3	85
AgOTf	3	86

[a]The reaction was carried out at room temperature in CH_2Cl_2.
[b]1.0 equivalent of Lewis acid was used.

In order to confirm the stereochemistry at C-4 position, compound **4** was transformed into known compound **5**.[3a] Hydrolysis of the acetate of **4** using NaOMe under reflux did not give **5**. Thus diol **4** was acetylated using Ac_2O in pyridine to give triacetate and subsequent DIBALH reduction afforded **5**.[6] The ^1H and ^{13}C NMR spectral data of **5** were identical with those of the reported values.[3a] This result indicated that electrophile **3** reacted with nucleophile **2** at C-4 position in a stereoselective manner to afford 3,4-*trans* trimer **4**. Triol **5** can be transformed into procyanidin C2 (**1**) by a known procedure (Scheme 2).[3a] The synthesis of various types of procyanidin oligomers using equimloar condensation of nucleophile and electrophile in the presence of Lewis acid are currently underway.



Scheme 2. Tranformation of known compound **5** from **4**.

REFERENCES AND NOTES

1. D. Ferreira and X. –C. Li, *Nat. Prod. Rep.*, 2000, **17**, 193.
2. D. Ferreira and X. –C. Li, *Nat. Prod. Rep.*, 2002, **19**, 517.
3. For recent synthetic studies on catechin and/or epicatechin trimer: A. Saito, A. Tanaka, M. Ubukata, and N. Nakajima, *Synlett*, 2004, 1069. (b) A. Saito, Y. Doi, A. Tanaka, N. Matsuura, M. Ubukata, and N. Nakajima, *Bioorg. Med. Chem.*, 2004, **12**, 4783. (c) K-i. Oyama, M. Kuwano, M. Ito, K. Yoshida, and T. Kondo, *Tetrahedron Lett.*, 2008, **49**, 3176. (d) A. Saito, Y. Mizushina, A. Tanaka, and N. Nakajima, *Tetrahedron*, 2009, **65**, 7422. (e) K. Ohmori, N. Ushimaru, and K. Suzuki, *Proc.*

Natl. Acad. Sci. U.S.A., 2004, **101**, 12002. (f) A. P. Kozikowski, W. Tückmantel, G. Boettcher, and L. J. Romanczyk, Jr., *J. Org. Chem.*, 2003, **68**, 1641.

4. (a) Y. Mohri, M. Sagehashi, T. Yamada, Y. Hattori, K. Morimura, T. Kamo, M. Hirota, and H. Makabe, *Tetrahedron Lett.*, 2007, **48**, 5891. (b) Y. Mohri, M. Sagehashi, T. Yamada, Y. Hattori, K. Morimura, Y. Hamauzu, T. Kamo, M. Hirota, and H. Makabe, *Heterocycles*, 2009, **79**, 549. (c) Y. Oizumi, Y. Mohri, M. Hirota, and H. Makabe, *J. Org. Chem.*, 2010, **75**, 4884.
5. P. J., Steynberg, R. J. J. Nel, H. van Rensberg, Bezuidenhoudt, B. C. B., and Ferreira, D, *Tetrahedron*, 1998, **54**, 8153.
6. The data for **5** (0.82:0.18 mixture of rotational isomers): $[\alpha]_D^{22}$ −143 (*c* 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ = 7.44-6.40 (57.4H, m), 6.17 (0.82H, d, *J* = 2.3 Hz), 6.17 (0.82H, d, *J* = 2.3 Hz), 6.09 (0.82H, d, *J* = 2.3 Hz), 6.08 (0.82H, s), 5.22-4.40 (21.32H, m), 4.25 (0.82H, d, *J* = 8.8 Hz), 4.05-3.95 (1.64H, m), 3.81-3.75 (0.82H, m), 3.60 (0.82H, d, *J* = 8.9 Hz), 3.10 (0.82H, dd, *J* = 16.0, 6.0 Hz), 2.96 (0.82H, d, *J* = 9.5 Hz), 2.37 (0.82H, dd, *J* = 16.5, 9.8 Hz), 1.33 (0.82H, d, *J* = 3.5 Hz), 1.14 (0.82H, d, *J* = 3.5 Hz); ^{13}C NMR (125MHz, $CDCl_3$, major isomer) δ = 157.9, 157.8, 156.7, 155.5, 155.4, 155.2, 155.1, 155.0, 153.8, 149.2, 149.2, 149.1, 148.8, 148.6, 137.7, 137.5, 137.5, 137.4, 137.3, 137.2, 137.2, 137.1, 137.1, 136.0, 132.4, 132.4, 131.7, 128.9-126.9, 121.1, 120.7, 120.6, 115.1, 114.9, 114.8, 114.6, 114.2, 113.8, 112.4, 109.4, 108.8, 102.4, 94.7, 93.8, 92.0, 91.8, 81.8, 81.0, 80.4, 73.1, 73.0, 71.9-69.8, 68.4, 37.6, 37.5, 28.5; ESIMS: *m/z* = 1969.8 $[M+Na]^+$