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An efficient synthesis of procyanidins. Rare earth metal Lewis acid catalyzed equimolar condensation of catechin and epicatechin

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Abstract—Stereoselective synthesis of catechin and epicatechin dimers under intermolecular condensation is achieved by an equimolar amount of coupling catalyzed by $Yb(OTf)_3$. The coupled products were successfully converted to procyanidin B1, B2, B3, and B4.

Proanthocyanidins are known as condensed or noncondensed hydrolyzable 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.[3] However, efficient syntheses are very limited because the formation of the intermolecular C-4–C-8 bond has some problems. The typical synthetic methods are as follows. The first example is nucleophilic addition of C-8 lithiated nucleophile onto a C-4 protected ketocatechin as a substrate.[4] This reaction generally proceeds with the regioselective and oligomerization control demands of the coupling reaction, however, it does not satisfy the stereochemical requirement of the newly formed C-4 asymmetric center. The next is the nucleophilic substitution method, which needs to use nucleophilic partner in large excess

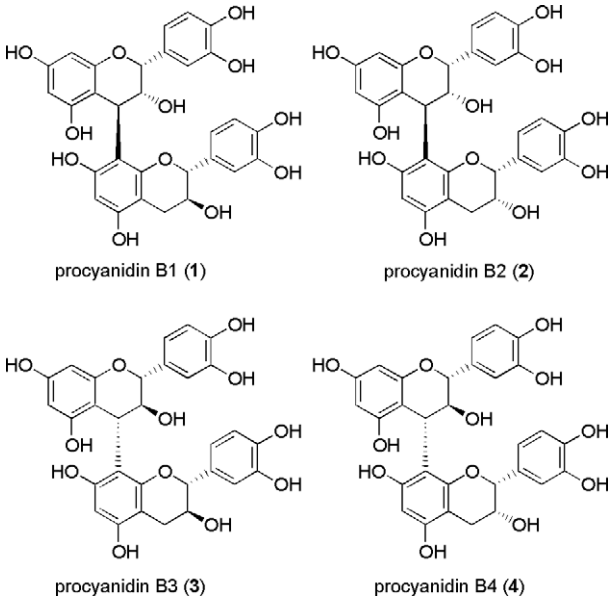

Figure 1. The structures of procyanidin B1 (**1**)–B4 (**4**).

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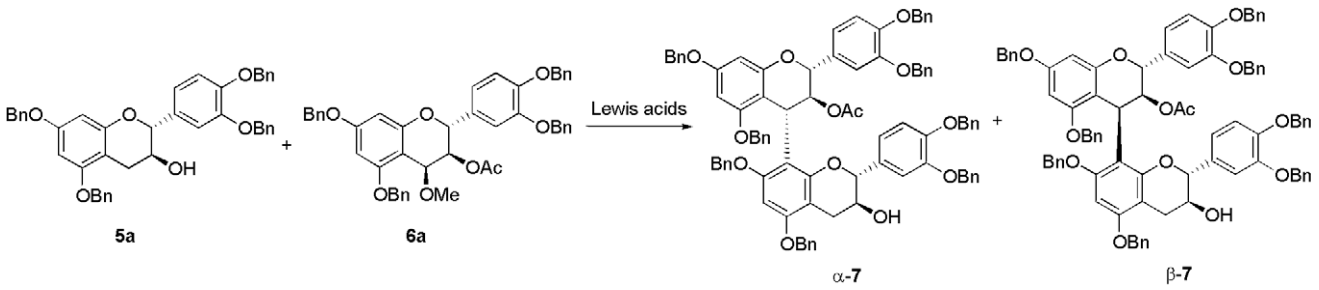


Scheme 1. Lewis acids mediated coupling reaction between **5a** and **6a**.

Table 1. Equimolar coupling reaction of **5a** and **6a** by Lewis acids[a]

Lewis acids[b]	Time	Yield (%)	Selectivity (α:β)[c]
$TiCl_4$	0.5	36	75:25
$BF_3{\cdot}Et_2O$	3	ND	—
$B(C_6H_5)_3$	2	38	89:11
$AgBF_4$	7.5	50	98:2
$Cu(OTf)_3$	0.5	43	91:9
$In(OTf)_3$	0.5	45	91:9
$Sc(OTf)_3$	0.5	50	67:33
$La(OTf)_3$	72	34	98:2
$Yb(OTf)_3$	2	64	98:2
10 mol % of $Yb(OTf)_3$	12	42	91:9

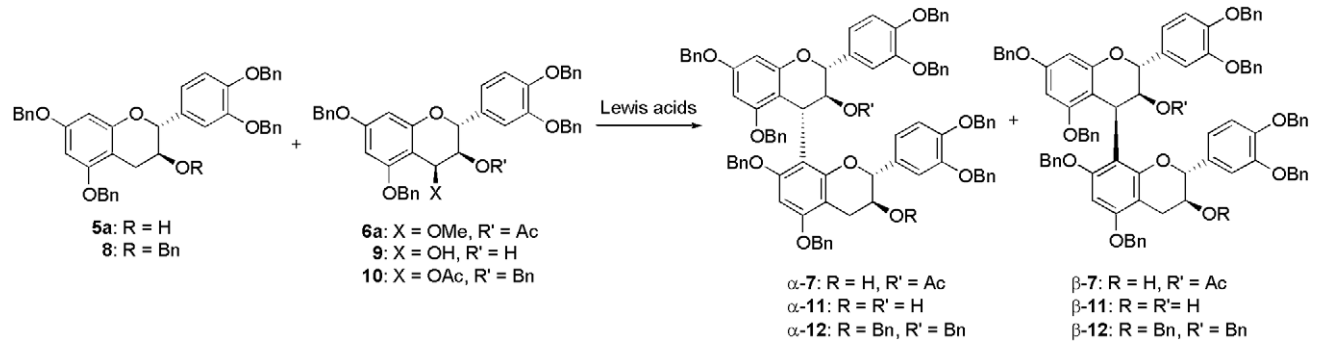
[a] The reaction was carried out at room temperature in CH_2Cl_2.
[b] 1 equiv of Lewis acid was used otherwise noted.
[c] The selectivity was determined by ^1H NMR analysis of C-3 position of diacetate derivative of α-**7** (5.80 and 5.83 ppm) and β-7 (5.53 and 5.58 ppm) according to the reported procedure.[3b]

(3.0–4.5 equiv) to prevent further oligomerization. Thus the efficient synthetic method to prepare procyanidin dimers has some restrictions, although recent advance was made in the regio and stereoselective reaction.[3] Until now, only a few attempts to prepare procyanidin dimers under stoichiometric conditions have been reported in the literature. The first example is an intramolecular coupling of monomeric units bound by a temporary diester link.[5] This method is suitable for synthesizing procyanidin B1 (**1**) and B3 (**3**), however, it suffers from low yield of condensation for synthesizing B2 (**2**) and B4 (**4**). The second is reported by Fouquet and co-workers.[6] They synthesized procyanidin dimers based on the intermolecular nucleophilic substitution of C-4 activated and C-8 halogenated monomer to prevent further oligomerization using $TiCl_4$ as a Lewis acid. This reaction needs large excess of $TiCl_4$. In the course of our research, we have developed a very simple and efficient intermolecular synthesis of procyanidin dimers. The key step is a coupling reaction between equimolar amounts of tetra-benzylated monomer **5a** (nucleophile) and a C-4 activated monomer **6a** (electrophile) using 1 equiv of rare earth metal Lewis acid such as $Yb(OTf)_3$ (Fig. 1).

Table 2. Examples of condensation of the catechin nucleophile and electrophile by Lewis acids

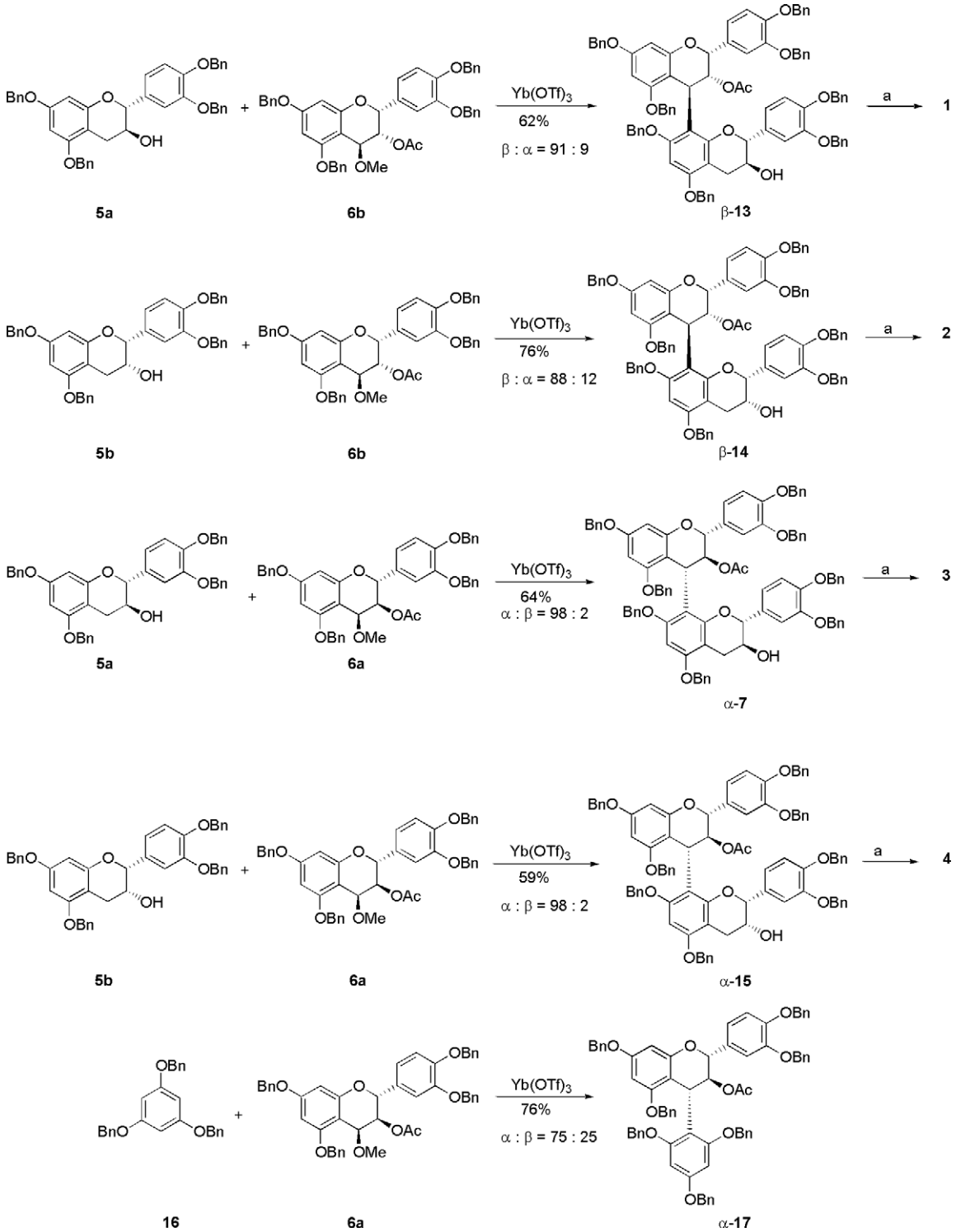
Entry	Nucleophile	Electrophile	Nucleophile/electrophile	Lewis acids	*T* (°C)	Product	Yield (%)	Selectivity (α:β)
1	**5a**	**9**	5	$TiCl_4$	0	**11**	92	60:40
2	**5a**	**6a**	4.5	$TiCl_4$	−20	**7**	83	96:4
3	**5a**	**6a**	4.5	TMSOTf	−78	**7**	Quant.	97:3
4	**5a**	**6a**	**1.0**	$Yb(OTf)_3$	rt	**7**	64	98:2[a]
5	**8**	**10**	3	$BF_3{\cdot}Et_2O$	−30	**12**	94	90:10
6	**8**	**10**	1.2	$BF_3{\cdot}Et_2O$	−30	**12**	59	90:10

[a] The selectivity was determined by ^1H NMR analysis of C-3 position of diacetate derivative of α-**7** (5.80 and 5.83 ppm) and β-**7** (5.53 and 5.58 ppm) according to the reported procedure.[3b]



Scheme 2. Examples of Lewis acids mediated coupling reaction between catechin nucleophile and catechin electrophile.

We chose tetra-benzylated catechin **5a**, a nucleophilic unit, prepared by the Kawamoto's procedure[7] and electrophile unit **6a** prepared by the Saito's method.[8] Equimolar condensation of **5a** and **6a** at room temperature was examined using various Lewis acids including rare earth metal at room temperature in CH_2Cl_2 (Scheme 1, Table 1). The first attempt at the coupling reaction was conducted with equimolar amounts of the protected catechin **5a** and the acetylated substrate **6a** to obtain α-**7**, which is the precursor of procyanidin B3 (**3**). Typical Lewis acids, such as $TiCl_4$ and $BF_3{\cdot}Et_2O$ gave sluggish results. These reactions required a large excess of the



Scheme 3. Equimolar coupling of epicatechin–catechin, epicatechin–epicatechin, catechin–catechin, and catechin–epicatechin using $Yb(OTf)_3$ as a Lewis acid toward the synthesis of procyanidin B1(**1**)–B4 (**4**). Reagents and conditions: (a) (i) K_2CO_3, MeOH; (ii) H_2, 20 wt % $Pd(OH)_2$, THF–MeOH–H_2O (47–67%).

nucleophile at low temperature in order to limit the reaction of the activated monomer with itself or with the dimeric product leading in both cases to oligomeric side products.[7,8] The next attempt at the coupling reaction was conducted with late transition metals as Lewis acids. Among Ag, Cu, and In, especially $AgBF_4$ gave a good selectivity with moderate chemical yield. We further paid attention to rare metal Lewis acids such as Sc and La. While Sc gave poor stereoselectivity, La afforded high selectivity although the chemical yield was 34%. This result encouraged us to replace La by Yb. The reaction furnished good selectivity with 64% yield.[9] The catalytic amount of $Yb(OTf)_3$ (10 mol %) also afforded a coupled product in 42% yield at 91:9 ratio of the desired product. This result indicates that this reaction could be carried out using catalytic amount of $Yb(OTf)_3$. Further optimization of the catalytic reaction system is now underway.

As shown in Table 2, the reported condensation reaction between catechin nucleophile **5a** or **8** and catechin electrophile **6a**, **9**, and **10** required large amount excess of catechin nucleophile **5a** or **8** to obtain desired dimer in high yield. As shown in entry 1, the first report of condensation by Kawamoto et al. used 5 equiv of nucleophile **5a**. They obtained coupled product in high yield, however, the stereoselectivity of α-**11** and β-**11** was only 60:40 ratio.[7] Saito et al. used nucleophile **5a** and electrophile **6a** and the combination of which was same as ours. This condensation afforded a coupled product in high yield with good stereoselectivity, however, it required 4.5 equiv of nucleophile.[3b,8] Suzuki and co-workers reported the condensation reaction using **8** and **10** to obtain **12**.[10] Although the amount of nucleophile was smaller than Kawamoto and Saito, they still used 3 equiv of nucleophile with 90:10 selectivity of the desired product. When they used 1.2 equiv of nucleophile **8**, the yield was 59% with same selectivity. Our result of equimolar condensation between **5a** and **6a** was shown in entry 4. Although the yield was lower than other groups, the stereoselectivity was superior to others. Using large excess amount of nucleophile is a big problem because composition of the desired coupled product is only a small part in the reaction system and it is necessary to get rid of large amount of starting material by chromatography. Optimized equimolar condensation is extremely important for an efficient synthesis of catechin dimers (Scheme 2, Table 2).

Next, we examined the condensation of the combination of catechin nucleophile **5a** and epicatechin nucleophile **5b** with catechin electrophile **6a** and/or epicatechin electrophile **6b** using $Yb(OTf)_3$ as a Lewis acid. In each case, the reaction worked well. As to the stereoselectivity, however, the epicatechin electrophile **5b** gave a little bit poor result compared to catechin nucleophile **5a**. In case of tri-benzylated phloroglucinol, the stereoselectivity of **16** showed 75:25 ratio.[11] Some stereochemical requirement of the nucleophile seems to be necessary to get high selectivity (Scheme 3).

Finally, condensed compounds α-**7**, β-**13**, β-**14**, and α-**15** were subjected to the hydrolysis of the acetate with K_2CO_3 in MeOH followed by debenzylidation by $Pd(OH)_2$ in THF–MeOH–H_2O catalyzed hydrogenolysis to give procyanidin B1 (**1**)–B4 (**4**). All the spectral data for **1**–**4** were similar to those of the reported value.[3a,d,5a]

Acknowledgement

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Supplementary data

Physical data of procyanidin B1 (**1**), B2 (**2**), B3 (**3**), B4 (**4**), ^1H NMR spectra for **1**–**4**, ^{13}C NMR spectra for **3**, **4**, and their data in the literature can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.047.

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9. *General procedure for the equimolar coupling reaction using Yb(OTf)$_3$ (Table 1)*: To a solution of nucleophile **5a** (190 mg, 0.263 mmol) and electrophile **6a** (171 mg, 0.263 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere was added $Yb(OTf)_3$ (163 mg, 0.263 mmol). After the resulting mixture had been stirred for 2 h, the reaction was quenched with water. The mixture was extracted with diethyl ether, and the combined organic layer were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified with silica gel chromatography (hexane–EtOAc–CH_2Cl_2 = 4:1:2) to give diastereomeric mixture α-**7** and β-**7** (226 mg, 64%) as a colorless oil. ^1H NMR analysis of diacetate derivative showed more than 98:2 ratio of α-**7** and β-**7**.[3b,7] The selectivity was determined by ^1H NMR analysis of C-3 position of diacetate derivative of α-**7** (5.80 and 5.83 ppm) and β-**7** (5.53 and 5.58 ppm) according to the reported procedure.[3b]
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