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RECENT SYNTHESES OF PROANTHOCYANIDINS

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Abstract – Recently proanthocyanidins have been paid much attention due to their significant biological activities and health benefitical effects. The author reviewed recent progress of the syntheses of proanthocyanidins including our work within this decade.

INTRODUCTION

Proanthocyanidins are known as condensed or non-hydrolysable tannins whose structures are basically consisted of flavan-3-ols.[1] These compounds are widely distributed in the vegetables, fruits and plant-originated beverage such as tea and wines.[2] Proanthocyanidins have been reported to exhibit strong free-radical scavenging and antioxidative activities.[3] Many significant biological activities such as antitumor,[4,5] antiviral,[6] anti-inflammatory,[7] and the inhibition of DNA polymerase were reported.[8] Thus proanthocyanidins are increasingly recognized as possessing health beneficial effects for humans. There are various type of proanthocyaidins in the nature. The large structural diversity of these compounds exhibits various types of the configurational differences such as C-3- and C-4 stereocenter and the regioisomers and stereochemistries of the inter-flavan bonds. Because their identification as well as purification is extremely difficult even using modern methods of isolation technique such as HPLC and UPLC, further investigation of the biological activities, i. e. mechanism of action of bioactivities remains unknown. In these days, in order to obtain pure proanthocyanidins, synthetic studies have been devoted.[9-11] As a result, some of total syntheses of procyanidins have been accomplished and their biological activities and their structure-activity relationship studies have been begun to be reported. However, the syntheses of high degree of oligomerised proanthocyanidins are still difficult although the degree of polimerization was reported to be enhanced biological activities.[12,13] Here the author wish to introduce the recent synthetic approaches toward procyanidins and prodelphinidins (Figure 1, 2).

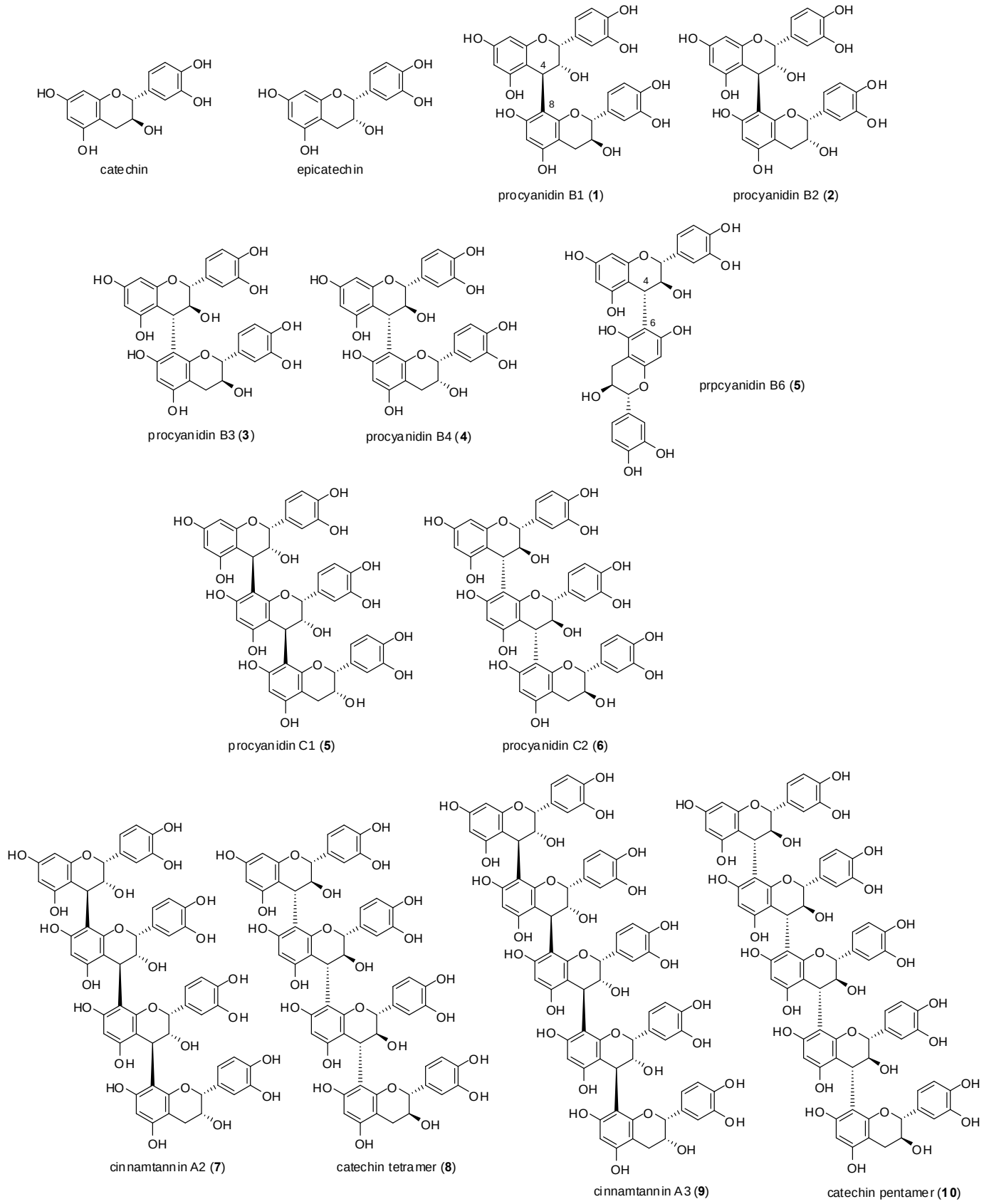


Figure 1. The structures of procyanidins

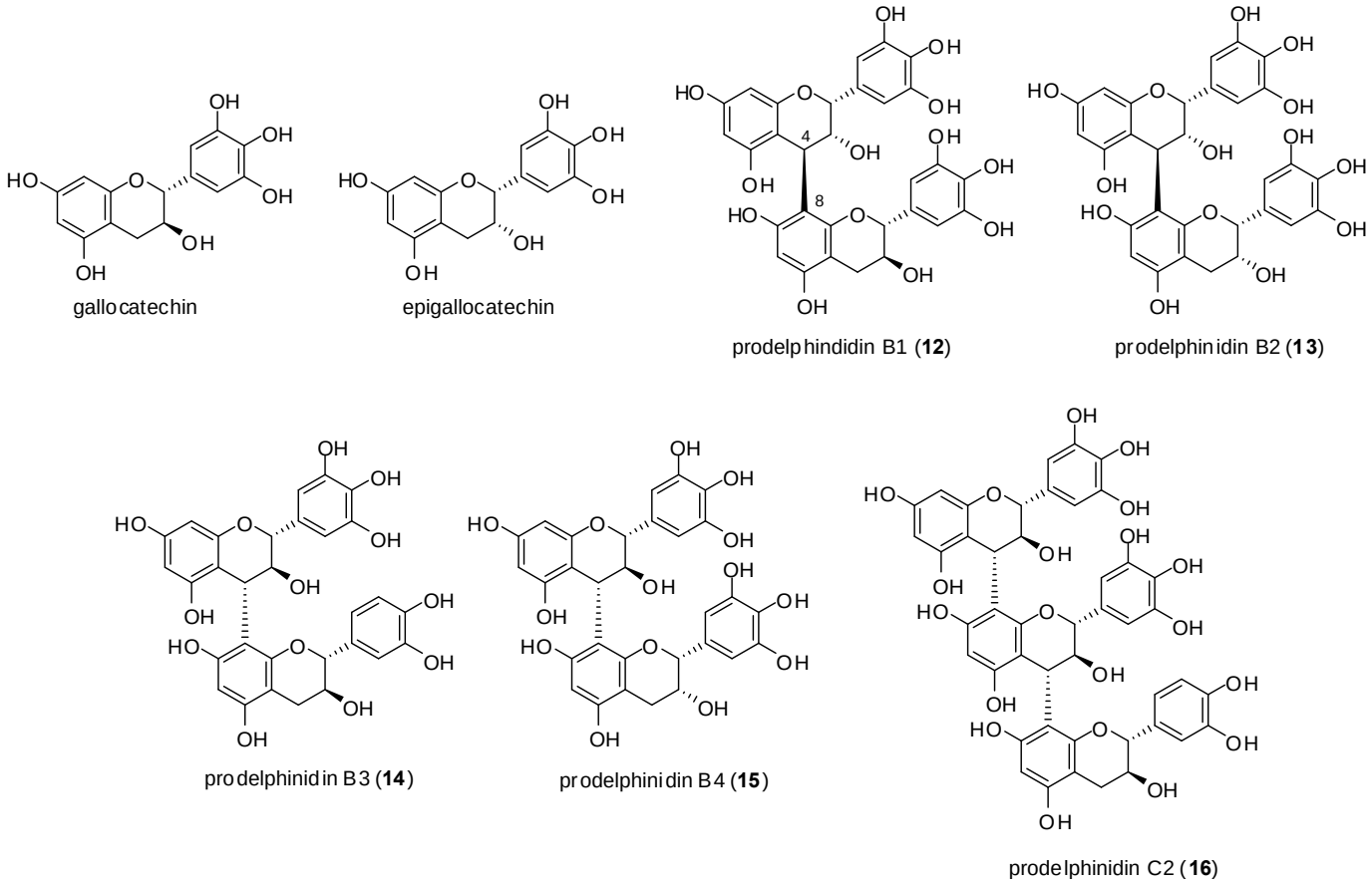
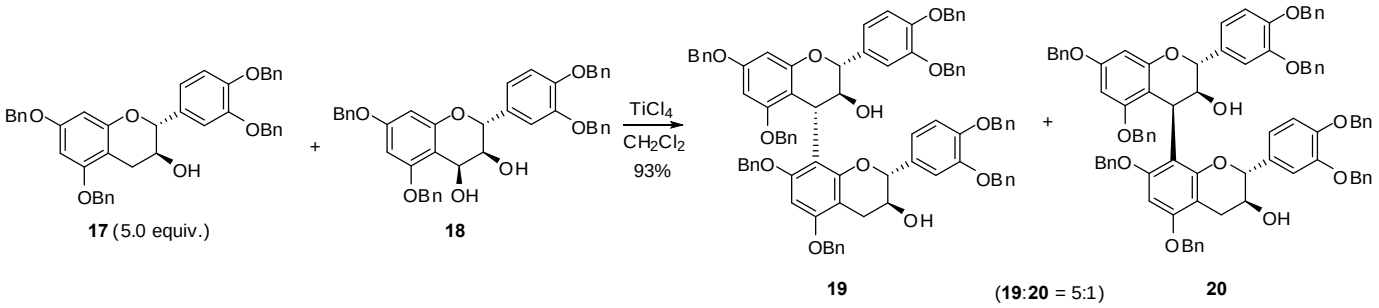


Figure 2. The structures of prodelphinidins

SYNTHESIS OF DIMERIC PROCYANIDINS

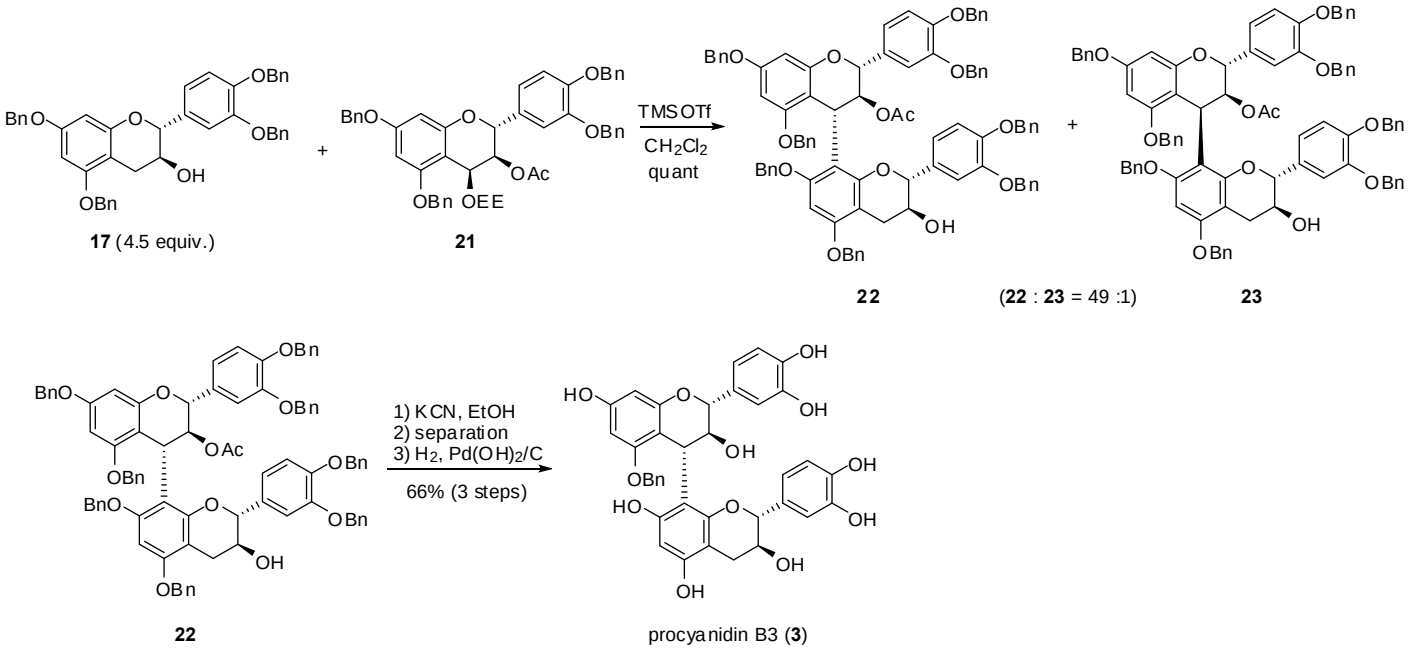
Synthesis of procyanidin B1 (1)-B4 (4)

Early synthetic studies of procyanidin dimer can be dated back to 1965 reported by Creasy and Swain.[14] They condensed 4-hydroxylated catechin with catechin using aqueous 0.4 M HCl to give corresponding dimer in good yield. However, the selectivity of regio- and stereochemistry of newly formed interflavan bond was not determined. They showed that 4-hydroxylated flavan was activated by acid and protonation at the C-4 hydroxy group generates cationic spieces. The synthesis of catechin dimers using non-protected catechins was ideal, however, the difficulty to purify the products because of the sensitivity by air and acids made synthesis problematic. Thus protected catechin derivatives were used to prepare dimeric products using Lewis acids. In 1991, Kawamoto and co-workers reported the condensation of per-*O*-benzylated catechin derivative **17** as a nucleophile using five times excess amount with electrophile **18** using $TiCl_4$ as a Lewis acid to give the corresponding dimer **19** in high yield with good selectivity (α:β = 5:1).[15] It is notable that attack at the C-8 position was occurred exclusively (Scheme 1).



Scheme 1. Condensation of Bn-protected catechin nucleophile and electrophile

Since this report had been appeared, further synthetic studies have been reported. Ubukata and Nakajima reported excellent regio- and stereoselective condensation using 4-ethoxyethoxy group as an electrophile and TMSOTf as a Lewis acid and they synthesized procyanidin B3 (**3**) (Scheme 2).[16]



Scheme 2. Highly stereoselective condensation of Bn-protected catechin nucleophile and electrophile and its application to the synthesis of procyanidin B3 (**3**)

The neighboring group participation of C-3 acetoxy group seemed to be effective to form 3,4-*anti* selective interflavan bond (Figure 3).[16,17]

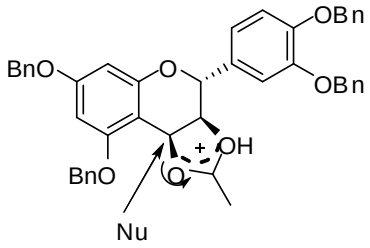
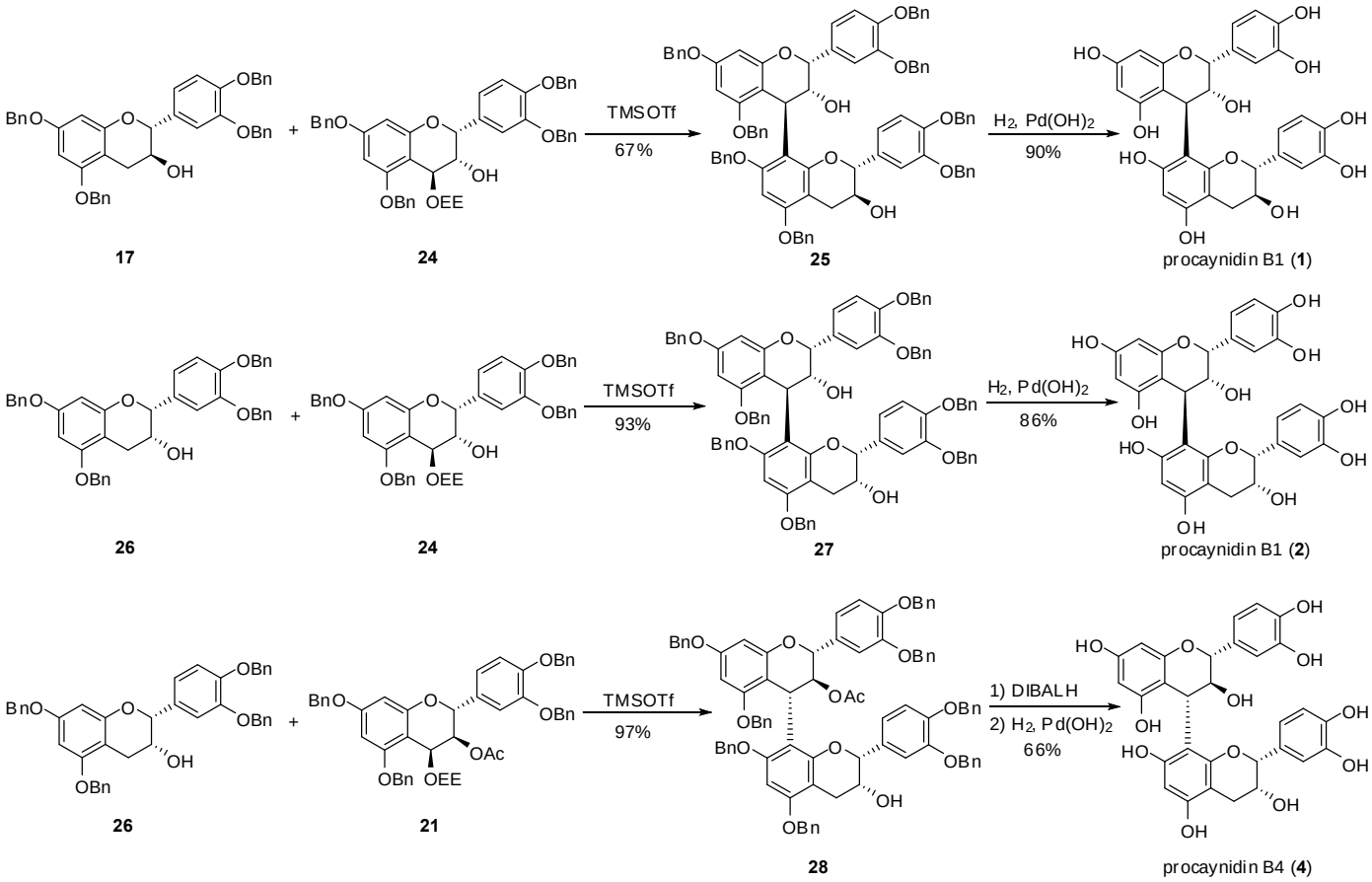


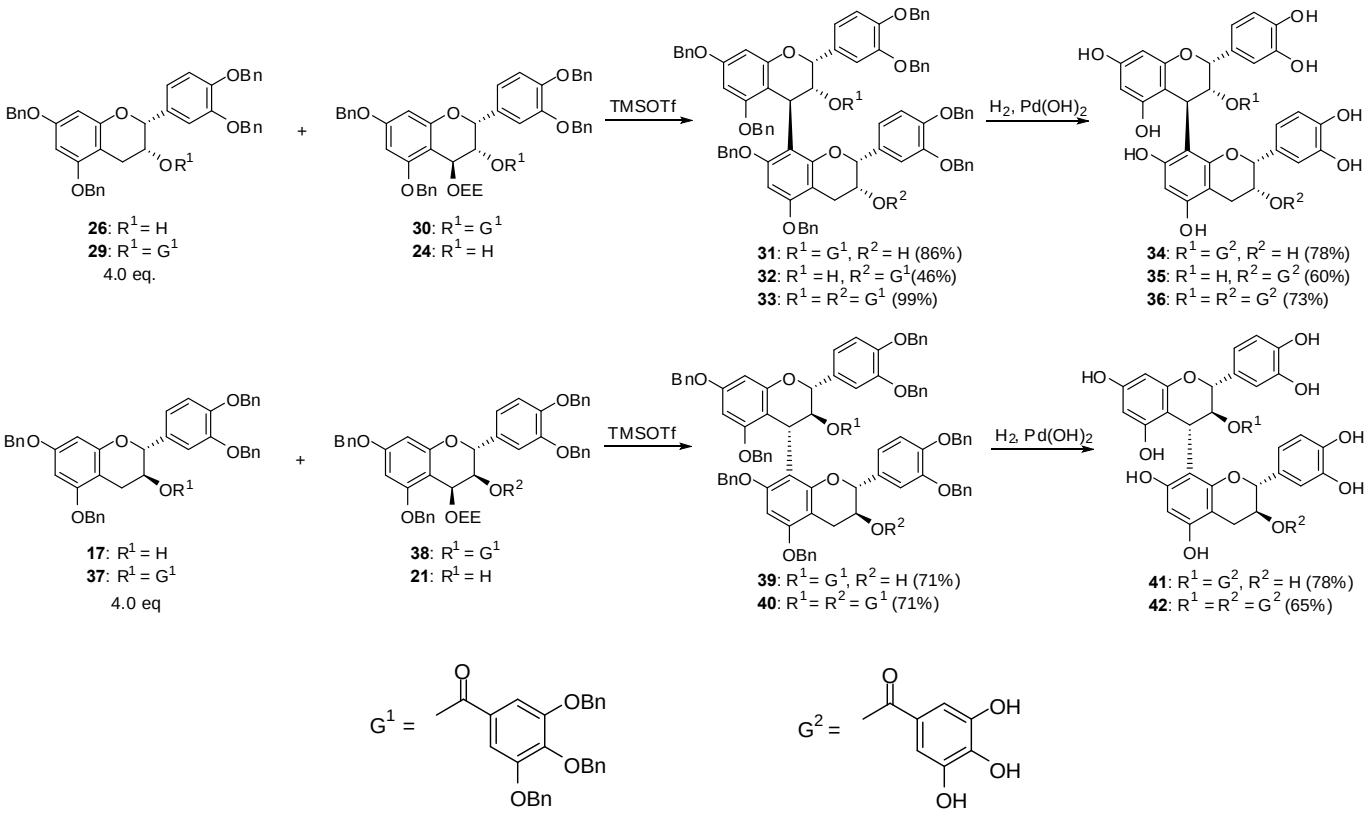
Figure 3. Neighboring group participation of 3-acetoxy electrophile in the condensation

They also accomplished stereoselective condensation of catechin and/or epicatechin nucleophile and electrophile and total synthesis of procyanidins B1 (**1**), B2 (**2**), and B4 (**4**), respectively (Scheme 3).[18]



Scheme 3. Catechin and/or epicatechin nucleophile and electrophile and total synthesis of procyanidins B1 (**1**), B2 (**2**), and B4 (**4**)

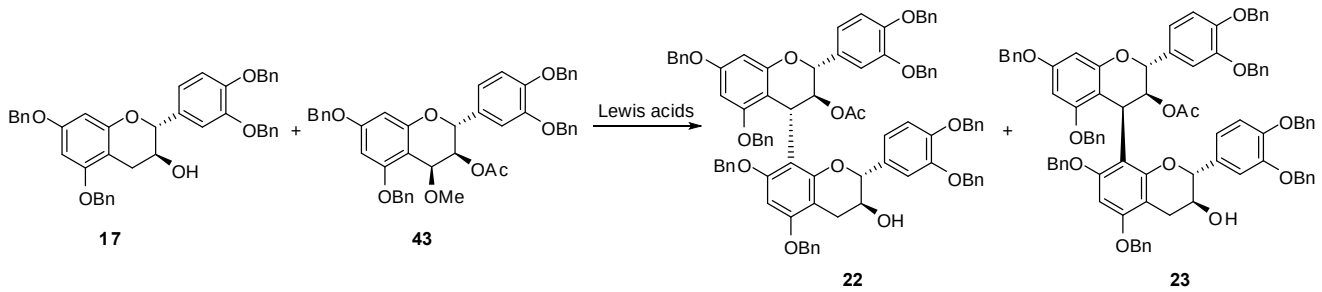
The same group also reported the synthesis of procyanidin B2 and B3 gallates using same strategy (Scheme 4).[8,19]



Scheme 4. Synthesis of procyanidin B2 and B3 gallates using TMSOTf as a Lewis acid

Using protected catechin delivatives blocks provided promising dimeric products with excellent regio- and stereoselectivity. However, this reaction requires a large excess amount of the nucleophile (4-5 equiv.) in order to suppress forming the higher oligomers. In view of purification after condensation, the remained nucleophile needs to be removed. To overcome this problem, Makabe and co-workers investigated Lewis acid mediated equimolar condensation.[20,21] They chose tetrabenzylated catechin **17**, as a nucleophilic unit, prepared by the Kawamoto's procedure [15] and electrophile unit **43** prepared by the Saito's method.[16] Equimolar condensation of **17** with **43** at room temperature was examined using various Lewis acids including rare earth metal at room temperature (Table 1).

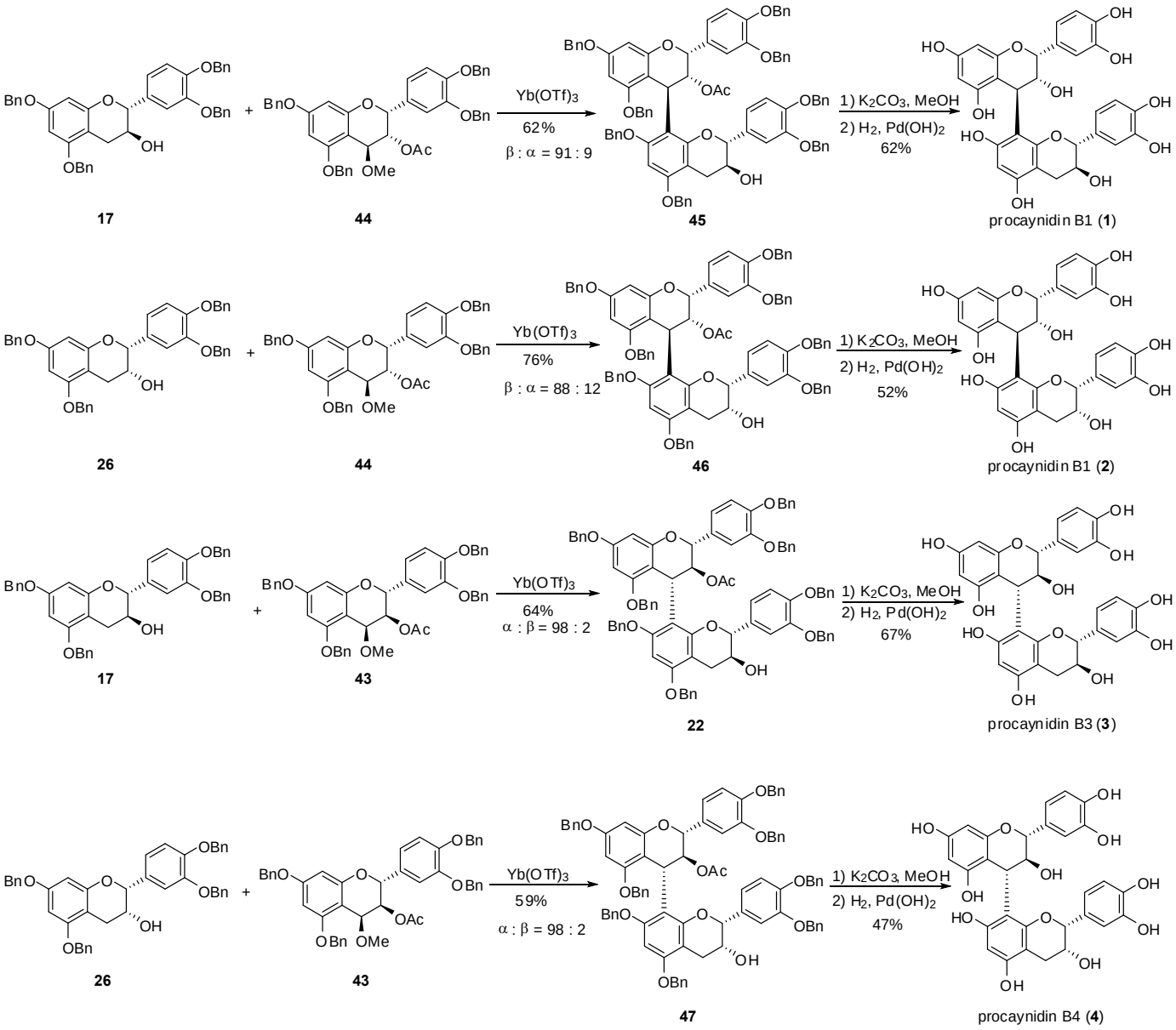
Table 1. Lewis acids mediated equimolar coupling reaction between catechin nucleophile **17** and its electrophile **43**



Lewis acids[a]	Time (h)	Yield (%)	Selectivity (**22** : **23**)[b]
$TiCl_4$	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
$Gd(OTf)_3$	72	NR	–
$Lu(OTf)_3$	72	NR	–
$Yb(OTf)_3$	2	64	98 : 2
10 mol% of $Yb(OTf)_3$	12	42	91 : 9

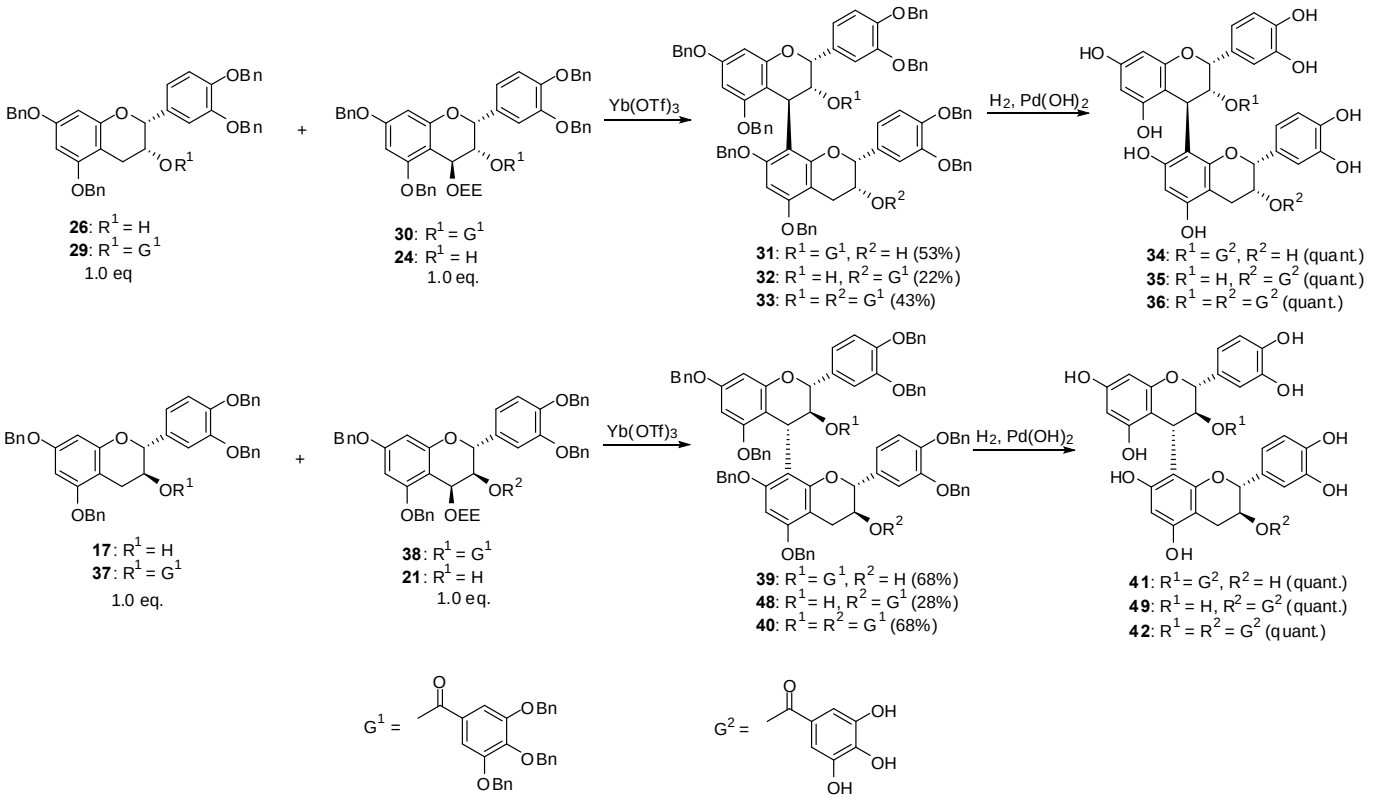
[a]1 equivalent of Lewis acid was used otherwise noted.
[b]The selectivity was determined by ^{1}H NMR analysis of C-3 position of diacetate derivative of **22** (5.80 and 5.83 ppm) and **23** (5.53 and 5.58 ppm) according to the reported procedure.[16]

Using $TiCl_4$ and $BF_3{\bullet}Et_2O$ gave sluggish results. The next attempt was examined using late transition metals as Lewis acids. Among them, $AgBF_4$ gave a good selectivity with moderate chemical yield. They 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 only 34%. Finally, replacing La to Yb furnished condensed product in 64% yield with excellent selectivity. Interestingly, $Gd(OTf)_3$ and $Lu(OTf)_3$ did not give any condensed product. Next, they expanded the condensation of the combination of catechin nucleophile **17** and epicatechin nucleophile **26** with catechin electrophile **43** and/or epicatechin electrophile **44** using $Yb(OTf)_3$ as a Lewis acid. In each case, the reaction worked well. In view of the stereoselectivty, however, the epicatechin electrophile **44** gave a little bit poor results compared to catechin electrophile **43**. Condensed compounds **45**, **46**, **22**, and **47** were subjected to the hydrolysis of the acetate with K_2CO_3 in MeOH followed by debenzylidation by $Pd(OH)_2$ to give procyanidin B1 (**1**)-B4 (**4**), respectively (Scheme 5).



Scheme 5. Synthesis of procyanidin B1-B4 (**1**-**4**) using equimolar condensation mediated by $Yb(OTf)_3$

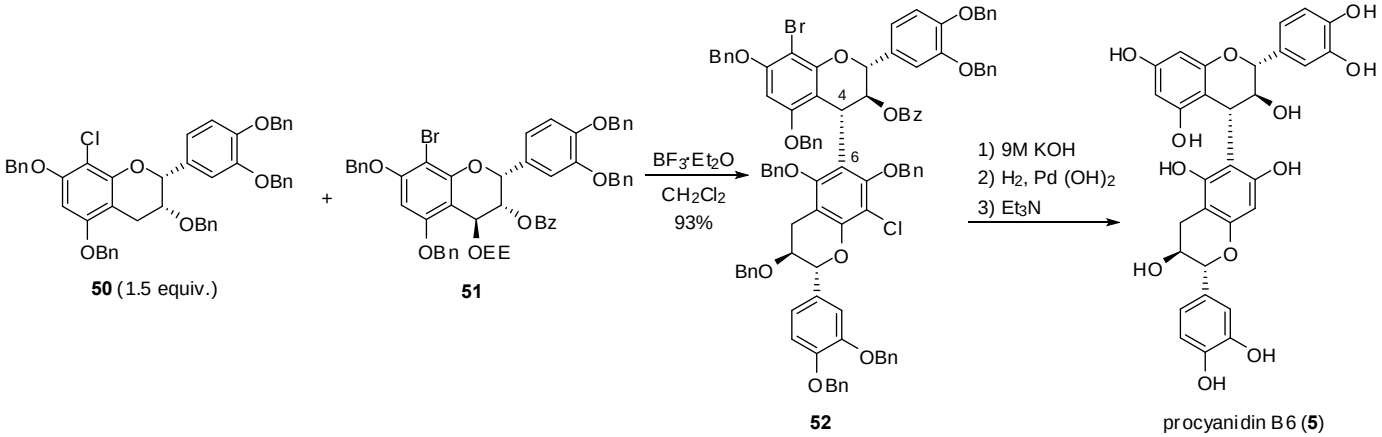
The author's group also reported procyanidin B2 and B3 gallates and their anticancer activity using equimolar condensation (Scheme 6).[22]



Scheme 6. Synthesis of procyanidin B2 and B3 gallates using equimolar condensation mediated by $Yb(OTf)_3$

Synthesis of procyanidin B6 (5)

Quite recently, Ohmori and Suzuki *et al.* accomplished first total synthesis of procyanidin B6 (**5**) which has a rare 4,6-inter-flavan bond. They succeeded regioselective linkage by the halogen-capping strategy followed by removal of the benzyl groups and halogen-caps by one-pot hydrogenolysis (Scheme 7).[23]

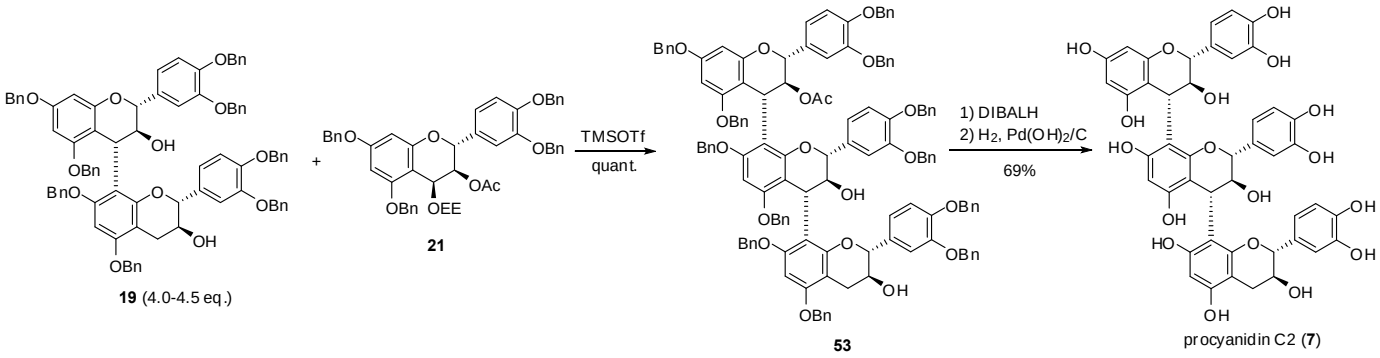


Scheme 7. Synthesis of procyanidin B6 (**5**)

SYNTHESIS OF TRIMERIC PROCYANIDINS

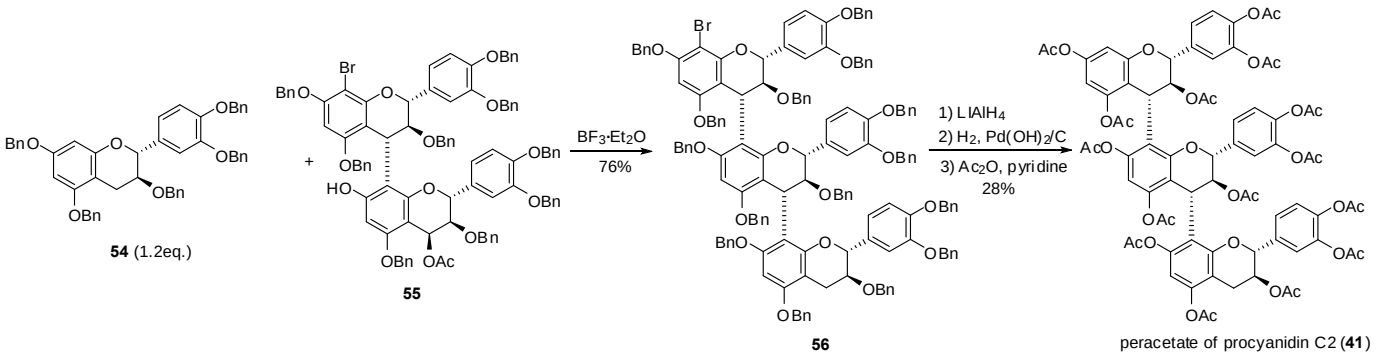
Synthesis of procyanidin C1 (6) and C2 (7)

Saito and Nakajima *et al.* reported TMSOTf mediated condensation of monomeric catechin electrophile **21** with nucleophilic dimer **19** for synthesis of procyanidin C2 (**7**). However, this reaction needed a large excess amount of nucleophilic dimer **19** (4.0-4.5 equiv.) to avoid further oligomer formation (Scheme 8).[24,25]



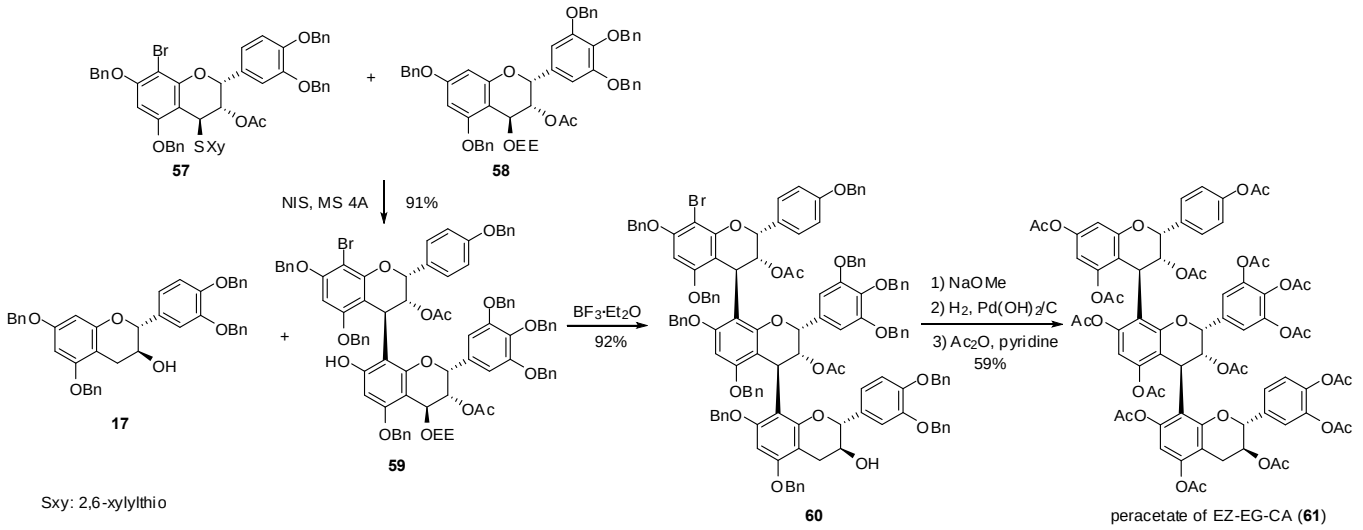
Scheme 8. Synthesis of procyanidin C2 (**7**) using excess amount of dimeric nucleophile

To overcome this problem, Ohmori and Suzuki *et al.* developed the orthogonal approach for synthesis of catechin trimer.[26] The acetoxy group served as an orthogonal leaving group that was activated hard Lewis acid ($BF_3 \cdot OEt_2$). Another important chemical feature of this reaction is the Br-capping of the C-8 position to suppress the self-condensation. Thus the amount of nucleophile could be reduced to 1.2 equivalent (Scheme 9).



Scheme 9. Orthogonal approach for the synthesis of peracetate of procyanidin C2 (**41**)

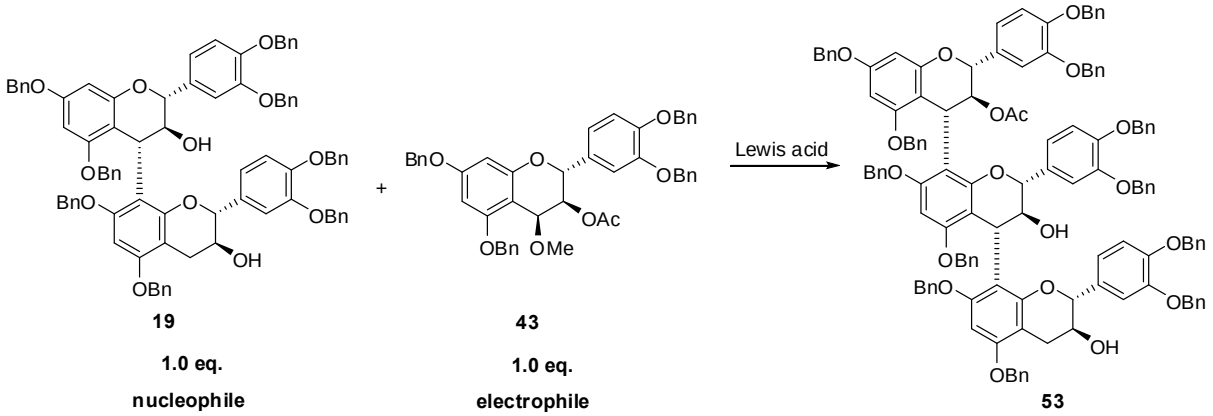
The same group also synthesized epiafzelechin-epigallogatechin-catechin (EZ-EG-CA) (**61**) using similar strategy (Scheme 10).[27]



Scheme 10. Synthesis of EZ-EG-CA (**61**) using orthogonal approach

Makabe and co-workers also reported the synthesis of catechin and epicatechin trimer (procyanidin C1 (**6**) and C2 (**7**)) using equimolar condensation.[28,29] Equimolar condensation of **19** with **43** was examined using transition metal Lewis acids and $Yb(OTf)_3$ in CH_2Cl_2. They paid attention to silver Lewis acid because condensation could be performed under neutral conditions. According to Ferreira and co-workers' report, using $AgBF_4$ as the thiophilic Lewis acid offered advantages to control the level of oligomeration in the procyanidin B1-B4 and C2 synthesis.[30] As shown in Table 1, $AgBF_4$ and AgOTf gave **53** in excellent yield, respectively. However, $Yb(OTf)_3$ afforded low yield. Due to the steric hindrance of $Yb(OTf)_3$, it seemed to be difficult for dimeric nucleophile **19** to attack C-4 position of electrophile **43** (Table 2).

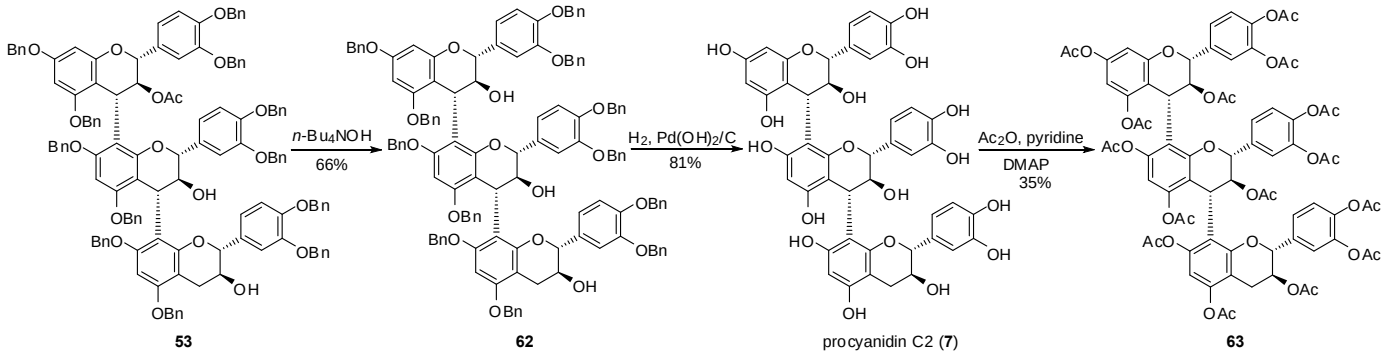
Table 2. Equimolar coupling reaction of **19** with **43** by Lewis acids[a]



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.

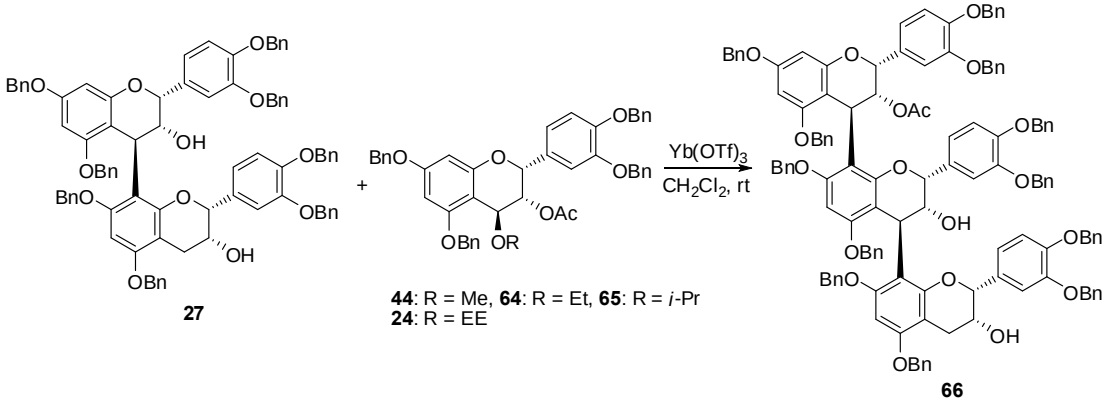
Condensed product **53** was successfully converted into procyanidin C2 (**7**) and its peracetate (**63**). The ^1H NMR spectral data of peracetate **63** was in good agreement with that of the reported value[31] (Scheme 11).



Scheme 11. Synthesis of procyanidin C2 (**7**) and its peracetate **63**

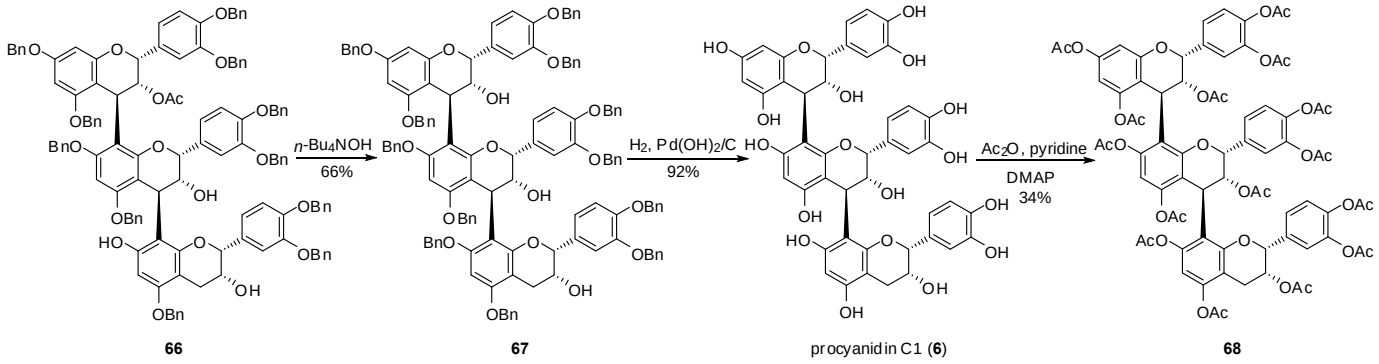
As to the synthesis of procyanidin C1 (**6**), equimolar condensation of **27** with **44** was examined using transition metal Lewis acids and $Yb(OTf)_3$ in CH_2Cl_2. Condensation using $AgBF_4$ and AgOTf resulted condensed product **66** in low yield. Next we examined equimolar condensation of **27** with various 4-alkoxy-epicatechin derivatives **44**, **64**, **65**, and **24** using $Yb(OTf)_3$. As shown in Table 3, 4-(2”-ethoxyethoxy) derivative **24** afforded condensed product **66** in 57% yield. Other 4-alkoxy derivatives gave **66** in low yield and both of the nucleophile and electrophile remained. We found that 4-(2”-ethoxyethoxy) group was suitable for $Yb(OTf)_3$ mediated activation at C-4 position of electrophile.

Table 3. Equimolar condensation of 4-alkoxy-epicatechin derivatives **44**, **64**, **65** and **24** with dimeric epicatechin nuceophile **27** by $Yb(OTf)_3$



Entry	electrophile	Time (h)	Yield (%)
1	**44**	3	36
2	**64**	3	18
3	**65**	3	15
4	**24**	1	57

The condensed product **66** was transformed into triol **67** using *n*-Bu_4NOH. Finally deprotection of the benzyl group of **67** subsequent lyophilization afforded procyanidin C1 (**6**) in good yield.[29] The ^1H NMR spectral datum of peracetate **68** was in good agreement with that of the reported value (Scheme 12).[31]

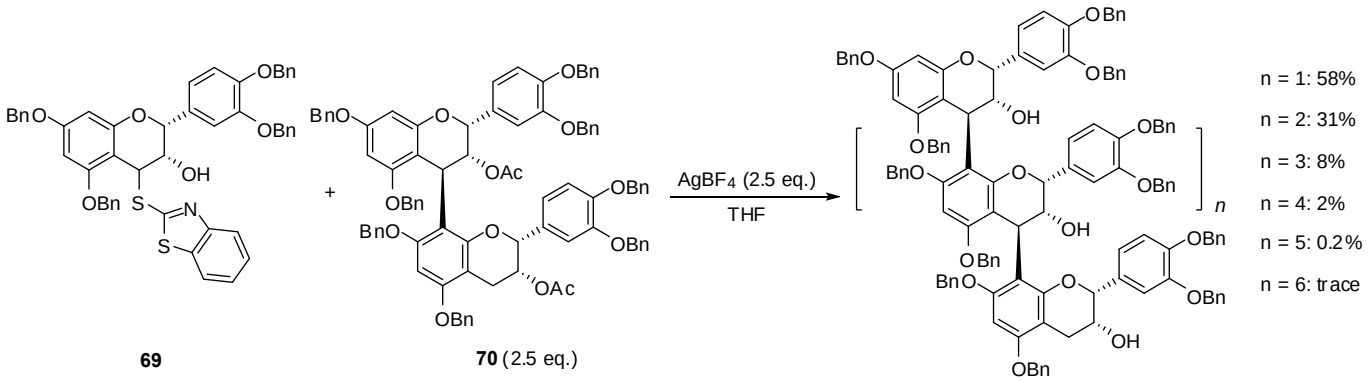


Scheme 12. Synthesis of procyanidin C1 (**6**) and its peracetate **68**

SYNTHESIS OF HIGHER OLIGOMERS

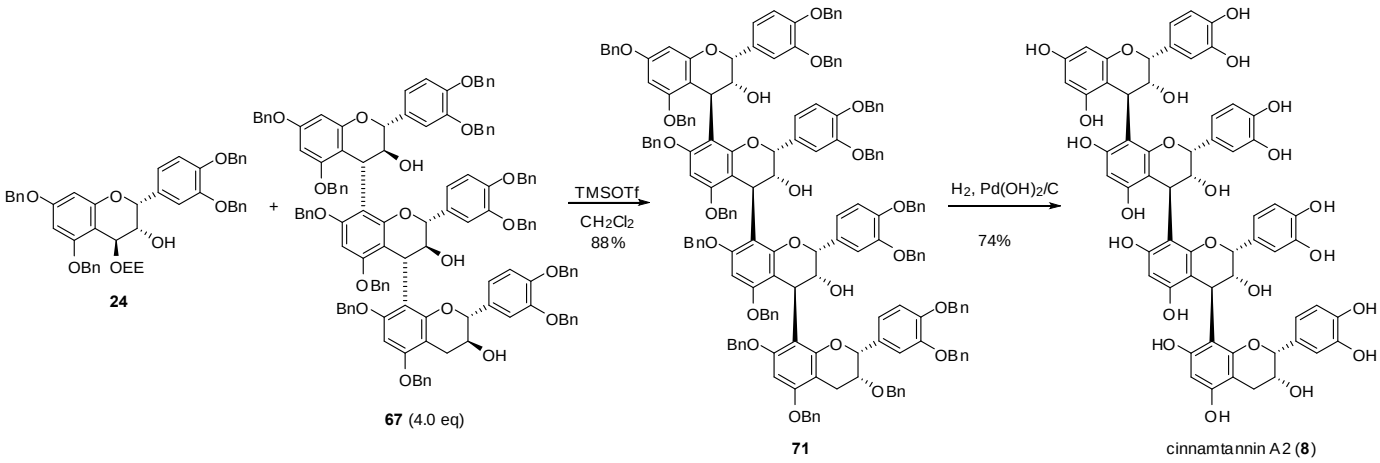
First challenge of the synthesis procyanidin oligomer was reported by Kozikowski and co-workers.[32] Thio ether **69** and epicatechin dimer derivative **70** were treated with excess amount of $AgBF_4$ gave multiple

oligomerized products. Each compound was separated by HPLC and isolated products were evaluated antitumor activity (Scheme 13).



Scheme 13. Multiple formation of epicatechin oligomers

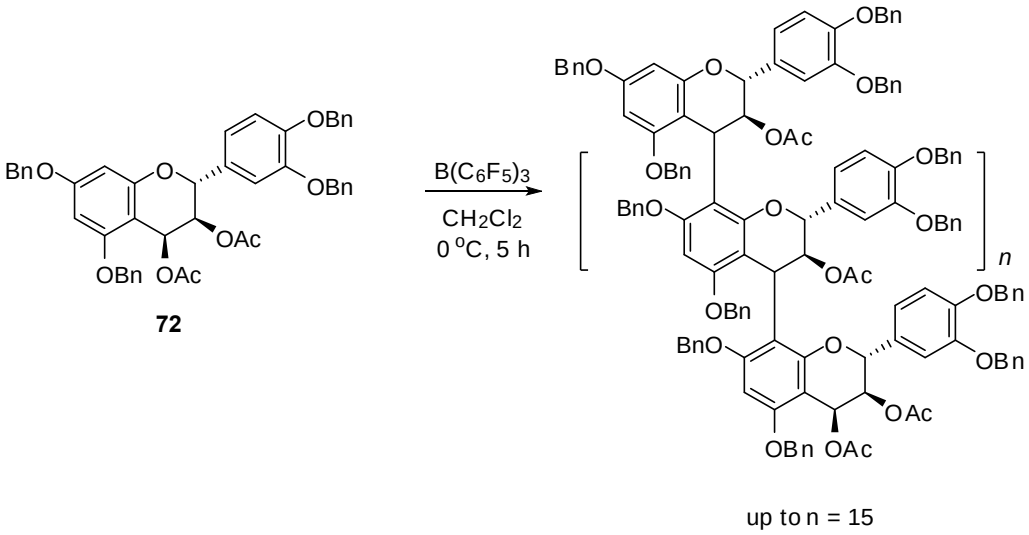
Saito and Nakajima *et al.* reported TMSOTf mediated condensation of monomeric epicatechin electrophile **24** with nucleophilic trimer **67** to afford **71**. This reaction also needed a large excess amount of nucleophilic trimer **67** (4.0 equiv.) to avoid further oligomer formation. The condensed product **71** was successfully converted to cinnamtannin A2 (**8**) (Scheme 14).[33]



Scheme 14. Synthesis of cinnamtannin A2 (**8**)

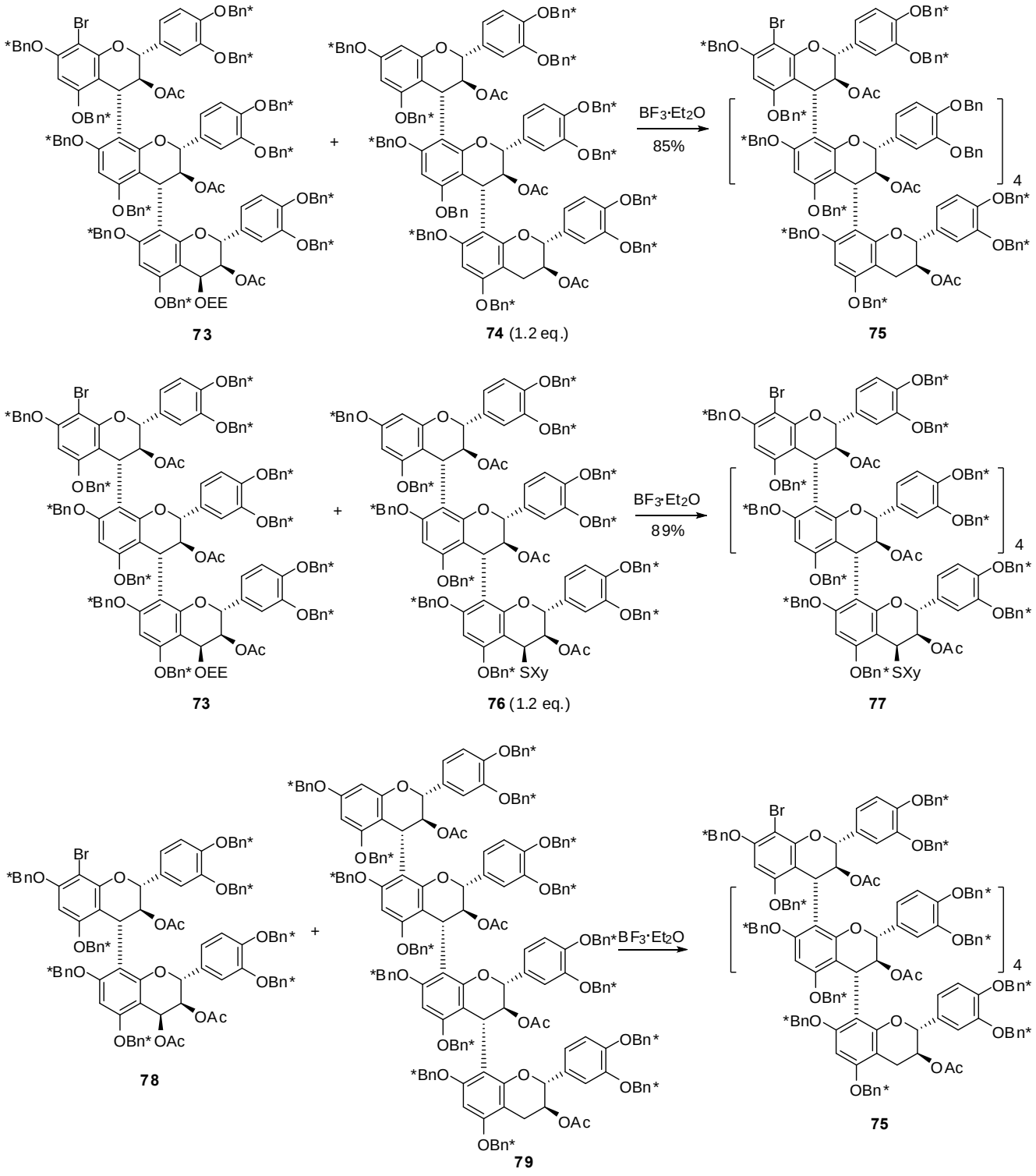
Several studies demonstrated non-oligomeric selective self-polymerization. Kondo and co-workers performed non-selective oligomerization of 3,4-diacetoxy-flavan **72** mediated by $B(C_6F_5)_3$. They obtained

the mixture of higher oligomers up to pentadecamer. The stereochemistry of newly formed interflavan bonds was not determined (Scheme 15).[34]



Scheme 15. Oligomerization of 3,4-diacetoxy-flavan mediated by $B(C_6F_5)_3$

Recently, an elegant selective synthesis of higher oligomers up to the tetracosamer was accomplished using orthogonal strategy by Ohmori and Suzuki *et al*.[35] The important matter for the orthogonal activation was the choice of leaving groups at C-4 position. They selected 4-ethoxyethoxy group for hard activation and the 2,6-xylylthio (SXy) group for soft activation. The bromo-capped electrophiles could be subjected to equimolar condensation with large nucleophiles (up to dodecamer). First, they prepared catechin hexamers **75** and **77** in a stereoselective manner. To confirm a stereochemistry of newly formed inter-flavan bond, they synthesized hexamer **75** independently by {2 + 4} coupling using structurally defined dimer **78** and tetramer **79** (Scheme 16).



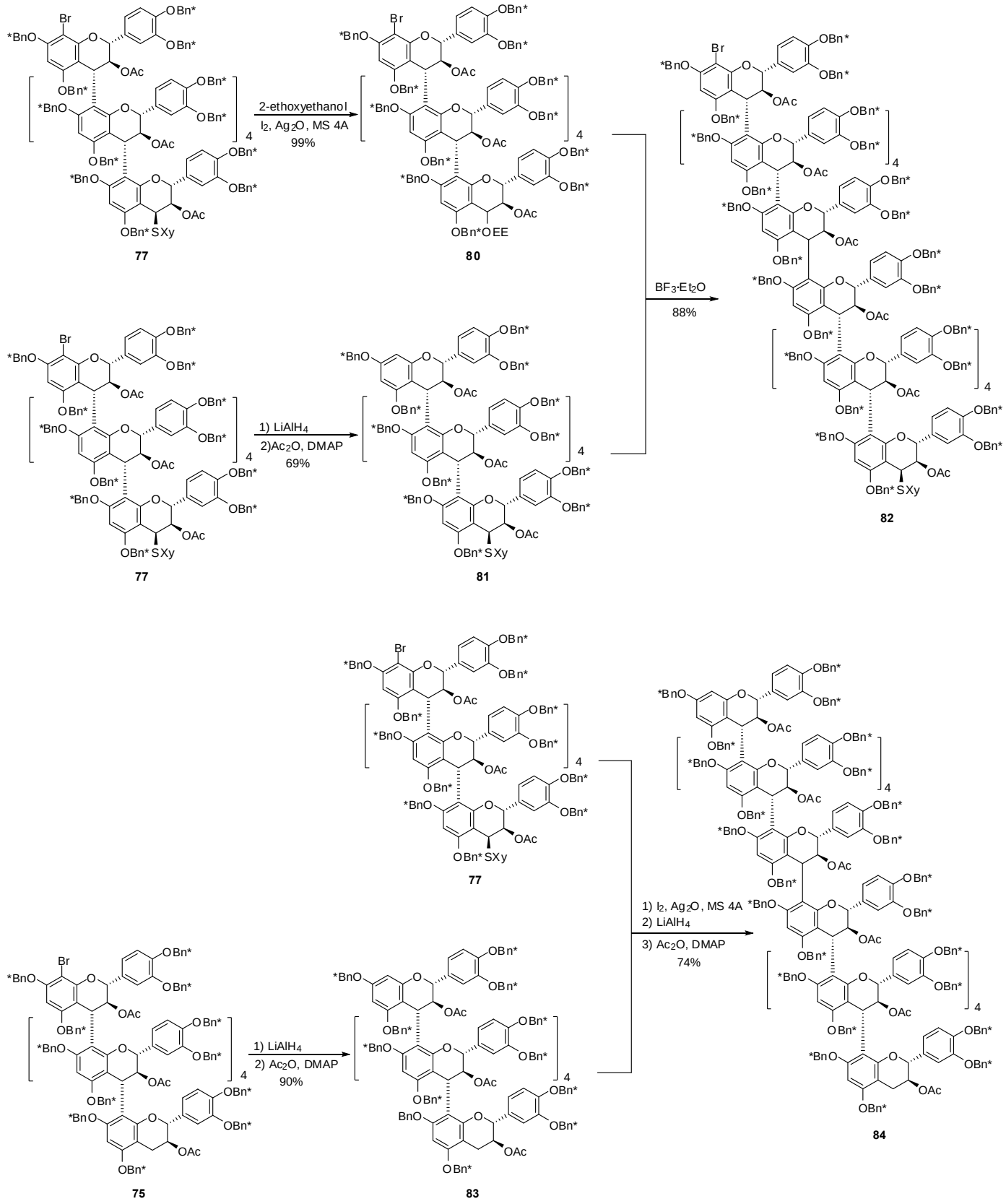
73 **74** (1.2 eq.) **75**

73 **76** (1.2 eq.) **77**

78 **79** **75**

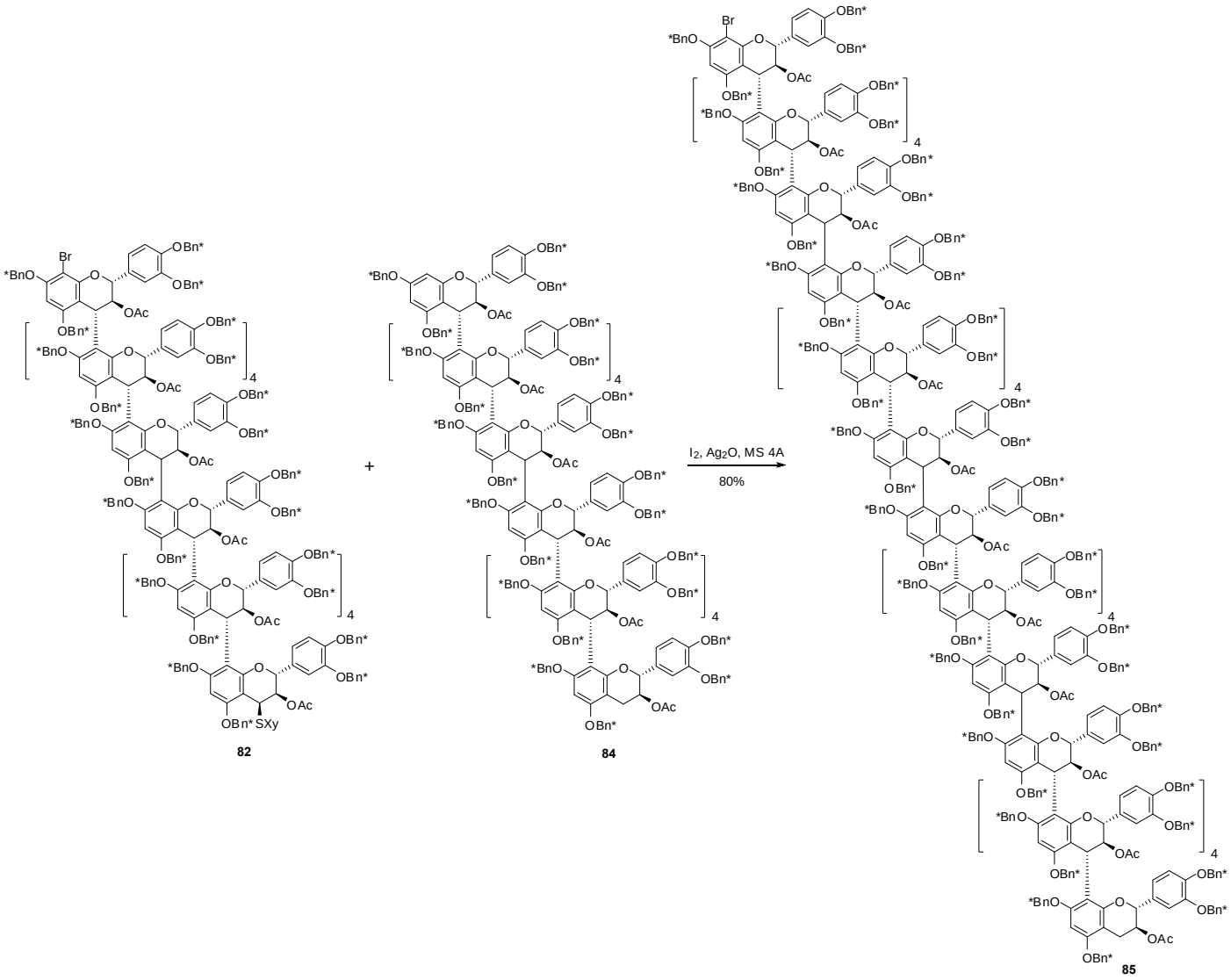
Scheme 16. Synthesis of catechin hexamers by the {3 + 3} coupling using orthogonal strategy

Next, they prepared two dodecamers **82** and **84** using {6 + 6} coupling. The stereochemistry of newly formed interflavan bonds was not determined (Scheme 17).



Scheme 17. Synthesis of catechin dodecamers by the {6 + 6} coupling using orthogonal strategy

Finally, the condensation between dodecamers **82** and **84** using I_2 and Ag_2O gave desired tetracosamer **85** cleanly in 80% yield (Scheme 18).

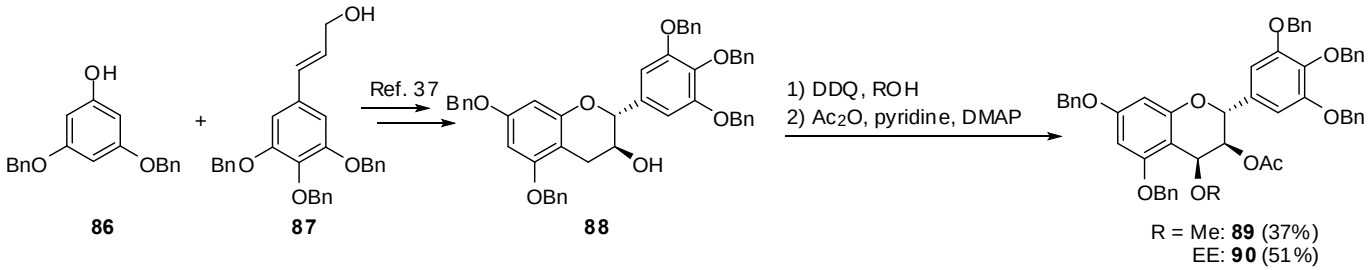


Scheme 18. Synthesis of protected catechin tetracosamer **85** using {12 + 12} coupling

SYNTHESIS OF PRODELPHINIDINS

As describes above, many examples of the syntheses of procyanidins were reported in this decade including our syntheses, however, synthetic studies on prodelphinidins are quite limited due to the difficulty in obtaining (–)-gallocatechin or (+)-epigallocatechin as synthetic starting materials.[36] Until now only an example of total synthesis of prodelphinidin B3 (**14**) and C2 (**16**) has been reported by Makabe and co-workers using equimolar coupling between nucleophilic and electrophilic partners in the presence of Lewis acid.[5] The gallocatechin-derived building block **88** was constructed as Chan and

co-workers reported with slight modification.[37] DDQ oxidation in the presence of methanol or ethoxyethanol gave electrophiles **89** and **90**, respectively (Scheme 19).

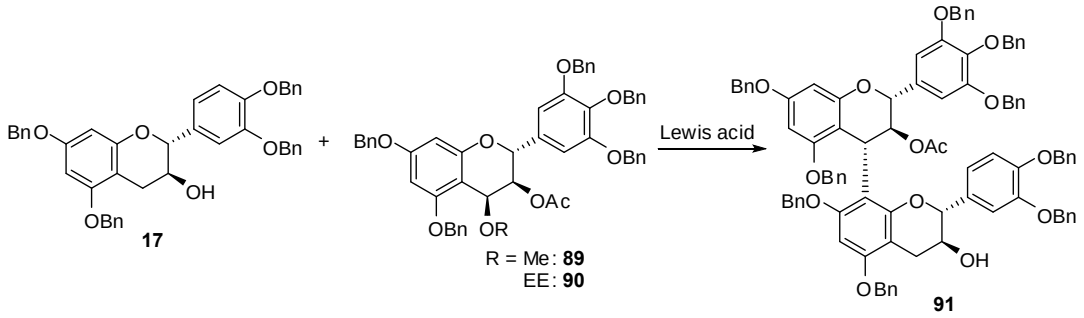


86 **87** **88**

Scheme 19. Synthesis of gallocatechin nucleophile and electrophile

They examined the condition of equimolar condensation of catechin nucleophile **17** with gallocatechin electrophile **89** or **90**. As shown in Table 4, 4-(2”-ethoxyethoxy) derivative **90** afforded condensed product in good yield when $Yb(OTf)_3$ was used as Lewis acid. On the other hand, using methoxy derivative **89** gave **91** in very low yield. The choice of leaving the group at the C-4 position was important in this condensation (Table 4).

Table 4. Equimolar condensation of gallocatechin electrophile **89** or **90** with catechin nucleophile **17**[a]

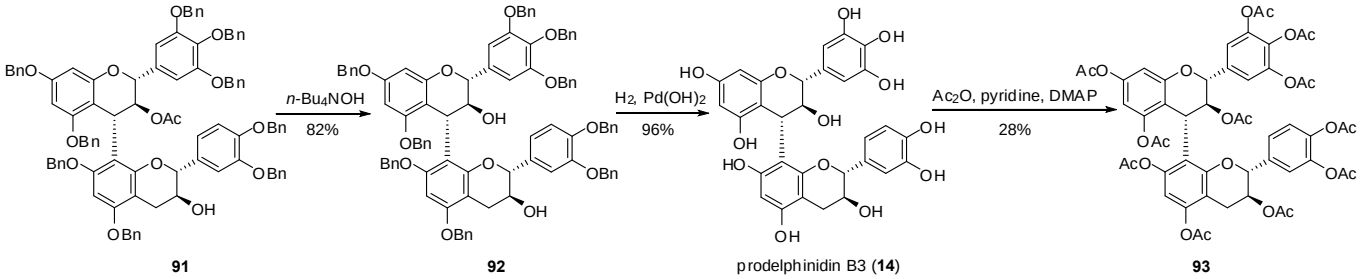


17 **91**

Electrophile	Lewis acid	Time (h)	Yield (%)
89	$AgBF_4$	7	48
89	$Yb(OTf)_3$	7	4
90	$AgBF_4$	7	45
90	$Yb(OTf)_3$	3	86

[a]The reaction was carried out in CH_2Cl_2 at room temperature.

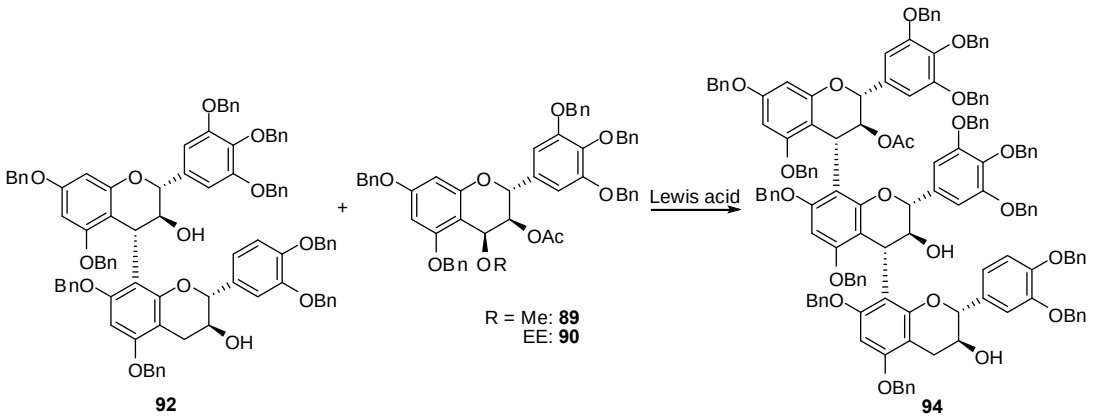
The condensed product **91** was transformed into diol **92** using *n*-Bu_4NOH, subsequent deprotection of the benzyl ethers of **92** afforded prodelphinidin B3 (**14**) in good yield. The ^1H NMR spectral data of peracetate **93** was in good agreement with that of the reported value (Scheme 20).[31]



Scheme 20. Synthesis of prodelphinidin B3 (**14**) and its peracetate **93**

Diol **92** was used as a nucleophile for the synthesis of prodelphinidin C2 (**16**). They examined equimolar condensation of **92** with electrophile **89** or **90**. The authors have found that silver Lewis acids were effective for the construction of catechin trimer derivatives.[28,29] Thus they used $AgBF_4$ and AgOTf as Lewis acid, respectively. As shown in Table 5, the 4-methoxy derivative **89** afforded condensed product **94** in good yield when AgOTf was used. The reaction using $AgBF_4$ as Lewis acid and 4-methoxy derivative **89** as an electrophile afforded **94** in poor yield. The combination of the C-4 leaving group and silver Lewis acid was very important (Table 5).

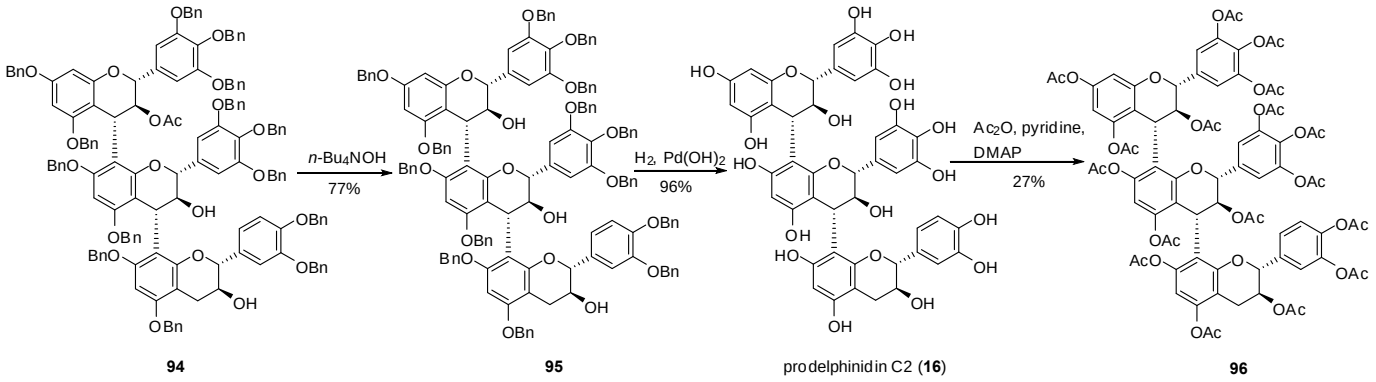
Table 5. Condensation of gallocatechin electrophile **89** or **90** with nucleophile **92**[a]



Electrophile	Lewis acid	Time (h)	Yield (%)
89	$AgBF_4$	3	14
89	AgOTf	5	73
90	$AgBF_4$	1	63
90	AgOTf	1	11

[a]The reaction was carried out in CH_2Cl_2 at room temperature.

The condensed product **94** was transformed into triol **95** using *n*-Bu_4NOH.[32] Finally deprotection of the benzyl ethers of **95** and subsequent lyophilization afforded prodelphinidin C2 (**16**) in good yield. The ^1H NMR spectral data of peracetate **96** was in good agreement with that of the reported value (Scheme 21).[31]



Scheme 21. Synthesis of prodelphinidin C2 (**16**) and its peracetate **96**

The authors examined the antitumor activities of synthesized prodelphinidins B3 (**14**) and C2 (**16**) against PC-3 prostate cancer cell lines together with procyanidin B3 (**3**), C1 (**6**) and C2 (**7**) which were prepared by same group (Figure 4).

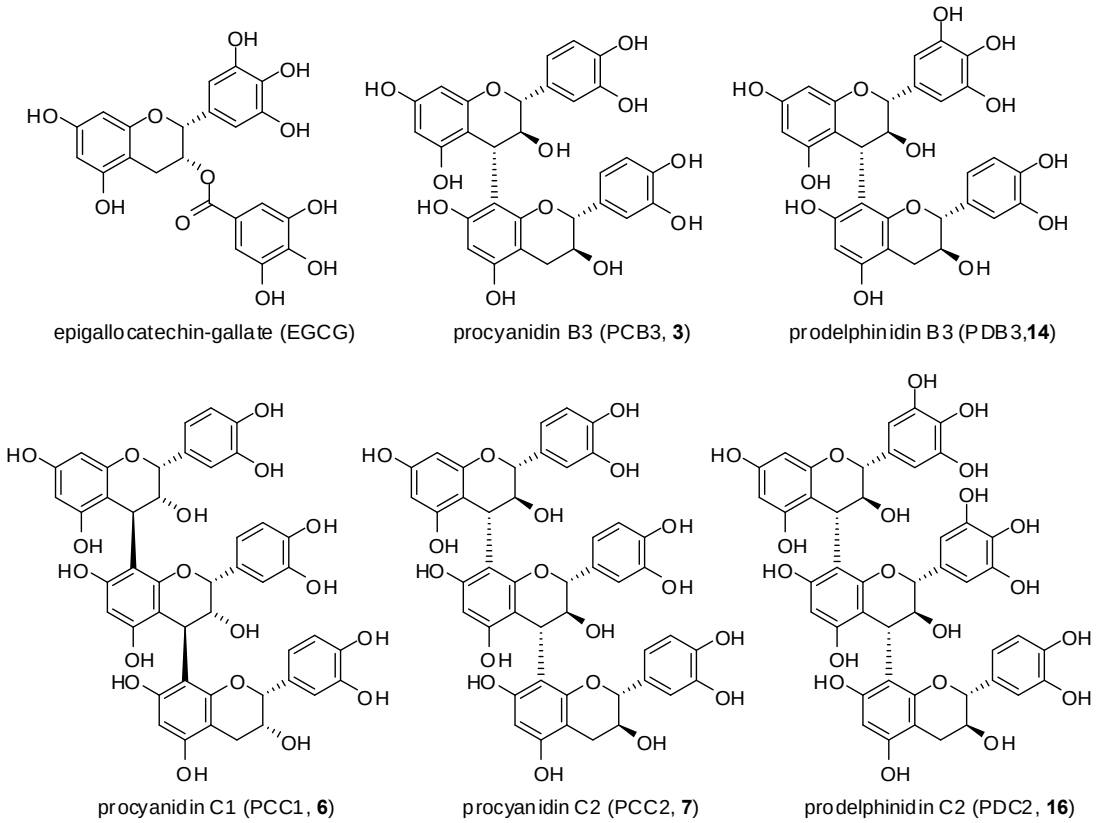
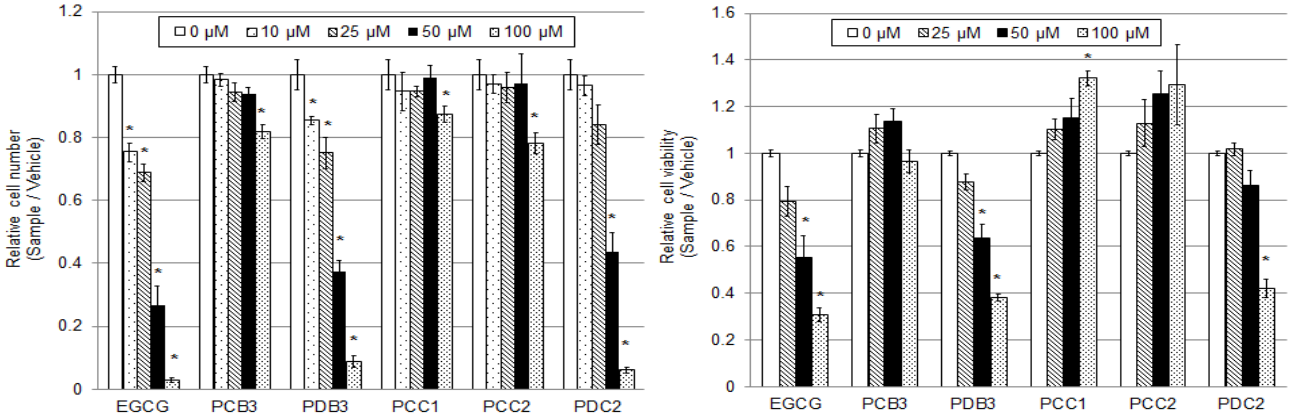


Figure 4. The structures of test compounds for PC-3 prostate anticancer activity

Results were obtained by two independent methods: cell count measurement and MTT assay. Epigallocatechin gallate (EGCG), which is well known as an antitumor agent, was used as a positive control. As shown in Figure 4, EGCG, prodelphinidin B3 (**14**) and C2 (**16**) exhibited significant cytotoxic

activity with IC_{50} values below 50 μM. Making a comparison of the potencies of **14** with procyanidin B3 (**3**), suggested that the cytotoxic effects were clearly associated with the presence of the pyrogallol moiety. The PDB3 (**14**) and PCB3 (**3**) have the same carbon skeleton. The only difference is that PDB3 (**14**) has an additional hydroxy group at the B ring. The authors showed that this hydroxy group greatly affected the cytotoxic effect. As for **16** and procyanidin C1 (**6**) or C2 (**7**), the data showed that the pyrogallol moiety was essential for their activity. This tendency was also observed in the MTT assay. These findings might be useful in searching for antitumor compounds among the proanthocyanidins (Figure 5).



(A) **(B)**

Figure 5. Effects of various concentrations of test compounds on cell proliferation using cell count (A) and MTT assay (B). After treatment of cells with EGCG, PCB3, PCC1, PCC2, PDB3, PDC2, or CPT for 48 h, the cell proliferation was determined by cell count (A) and MTT assay (B). The values were represented as the rate of inhibition of cell proliferation by the treated sample compared to the untreated control (vehicle). Values are means ± S.Ds. for three independent experiments. Asterisks indicated a significant difference between the control- and test-compound-treated cells, as analyzed by Student's test ($p < 0.001$).

CONCLUSION

Proanthocyanidins have been paid attention to the synthetic and biological researchers due to their unique structures and significant biological activities. Synthetic efforts toward proanthocyanins have performed mainly using condensation of C-4 to C-8 flavan bonds. Flavan-3-ols as nucleophiles and flavan-3,4-diols and its derivatives were subjected for the condensation in the presence of a Lewis acid. Recent progress of this reaction made a regio- and stereoselective synthesis of proanthocyanidin oligomers in good yield. However, there is still much room to develop synthetic methodologies especially for the highly polymerized proanthocyanidins. When synthetic methods of this complex molecule will be fully developed, proanthocyanidins will be candidate drugs for treating various diseases.

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