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CONDENSATION OF CATECHIN AND EPICATECHIN INCORPORATING A TBS-PROTECTING GROUP

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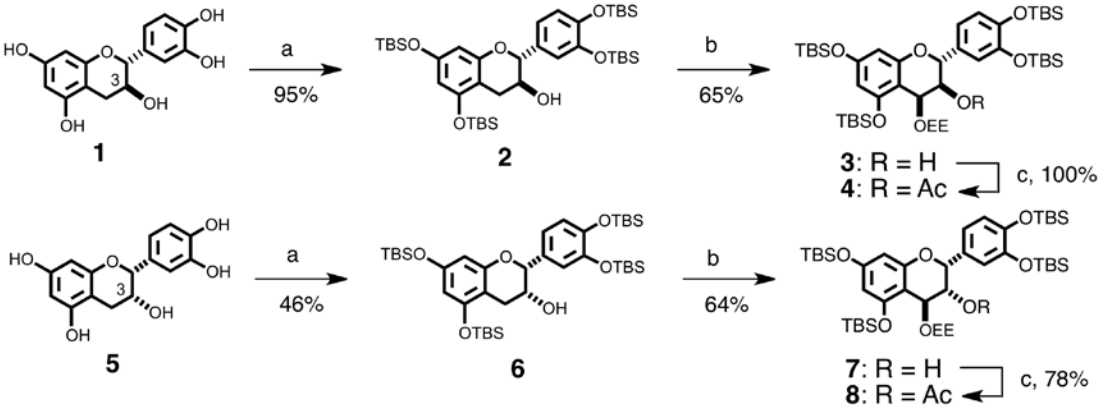
Abstract – Stereoselective synthesis of catechin and epicatechin dimers incorporating a *tert*-butyldimethylsilyl (TBS)-protecting group under intermolecular condensation is achieved using $SnCl_4$ as the Lewis acid. Four TBS-protected dimers were successfully converted to the deca-acetates of procyanidin B1, B2, B3, and B4 easily *via* the TBS-deprotection process. This procedure offers an advantage for dimmer synthesis in large-scale over existing benzyl-protecting methods.

Proanthocyanidins are condensed or noncondensed hydrolysable tannins.[1,2] Condensed tannins may be found in the foods such as fruits, beans, cocoa, and tea.[3-6] Many biological properties of these compounds have been reported, including anti-inflammatory,[7] hypotensive,[8] and antibacterial properties,[9] cancer-cell growth inhibition,[10] antimutagenic properties,[11] and the inhibition of HIV-1 replication *in vitro*,[12] suppression of ulcer formation,[13] neuroprotective properties,[14] and reduction of risk of heart disease.[15] Tannin extracts from plants are a source of various types of polyphenols. Because the identification and purification of these compounds is extremely difficult, further studies focusing on the procyanidins are required. Recently, considerable efforts have been devoted to synthesize procyanidin oligomers in pure state.[16-22] The results of these initial studies have addressed some of the complex, challenges of synthesis posed by the procyanidins, relating to the difficulty of controlling the interflavan regio- and stereoselectivity, as well as the sensitivity of the unprotected compounds to acid, alkali, and oxidizing environments. A benzyl group is the group most commonly used to protect the phenolic functionalities of procyanidins. However, the large-scale synthesis of benzyl (+)-catechin and (-)-epicatechin is very

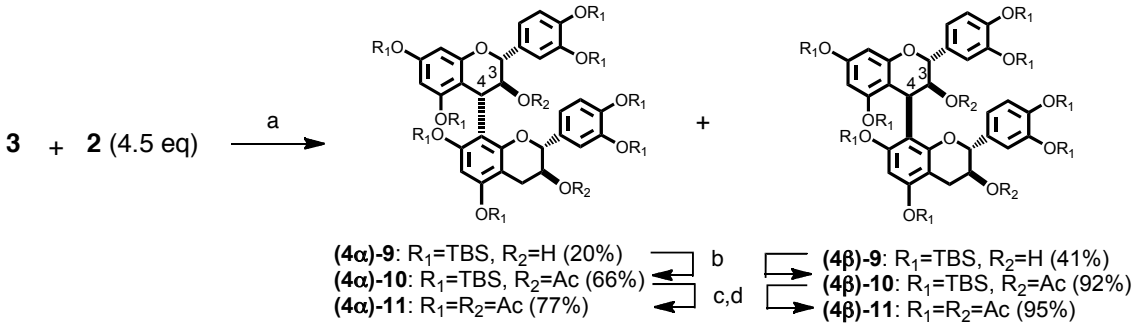
limited because of the by-products formation at benzyl-protection.[21a,23] We successfully synthesized procyanidin dimmers[24] using a silyl-protecting group (*tert*-butyldimethylsilyl: TBS) instead of the benzyl-protecting group.

TBS protection of catechin **1** and epi-catechin **5** proceeded with TBS-Cl and imidazole in THF/CH_2Cl_2 to afford tetra-TBS products **2** and **6** in 95% and 46% yields, respectively. TBS-protection was carried out at hundred-gram scale within three hours to obtain TBS-ethers **2** and **6** after SiO_2 short column chromatography purification. Dichloro-dicyano-benzoquinone (DDQ) oxidation at the C_4 position of **2** and **6** with ethoxyethanol (EE) in CH_2Cl_2 afforded electrophiles **3** and **7** in 65% and 64% yields, respectively. The electrophiles obtained were acetylated to give acetates **4** and **8** in 100% and 78% yields, respectively (Scheme 1).



Reagents and Conditions: (a) TBSCl (4.4 eq.), imidazole (8.8 eq.), THF/CH_2Cl_2 = 3/1; (b) 2-ethoxyethanol (20 eq.), DDQ (2 eq.), CH_2Cl_2, rt, 18 h; (c) AcOH (2 eq.), DCC (2 eq.), DMAP (0.4 eq.), CH_2Cl_2, rt.

Scheme 1. Synthesis of silyl-catechin **2**, silyl-epicatechin **6** and their electrophiles



Reagents and Conditions: (a) TMSOTf (1 eq.), CH_2Cl_2 (0.005M), 0 °C, 5 min; (b) DCC (4 eq.), AcOH (4 eq.), DMAP (0.8 eq.), CH_2Cl_2 (0.01M); (c) TBAF (24 eq.), AcOH (24 eq.), THF; (d) Ac_2O (30 eq.), DMAP (1.6 eq.), Py.

Scheme 2. Coupling of **3** and **2**

Condensation between tetra-*O*-TBS catechin electrophile **3** and nucleophile **2** proceeded in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf: 1 eq.) at –78 ˚C to afford a mixture of the 3,4-*trans* compound (4α)-**9** and the 3,4-*cis* compound (4β)-**9** in 61% coupling yield with a 1 : 2 ratio.[25] Diastereoselectivity determination was performed after transformation into the deca-acetates (4α)-**11** and (4β)-**11**. Each dimer was acetylated with acetic acid (AcOH), and *N*, *N*'-dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) to give 3,3'-*O*-diacetyl-octa-*O*-TBS procyanidin-B3 (4α)-**10** and (4β)-**10** in 66% and 92% yields, respectively. Eight TBS protecting groups were submitted to deprotection with 4 eq. of tetra-butyl ammonium fluoride (TBAF) and AcOH in tetrahydrofuran (THF). Deprotection of the TBS-group at the phenolic position proceeded without any trouble. Full acetylation of eight hydroxy groups with Ac_2O and DMAP in pyridine afforded the deca-acetyl derivative (4α)-**11**[24a] in 77% yield and also (4β)-**11**[24a] in 95% yield (Scheme 2).

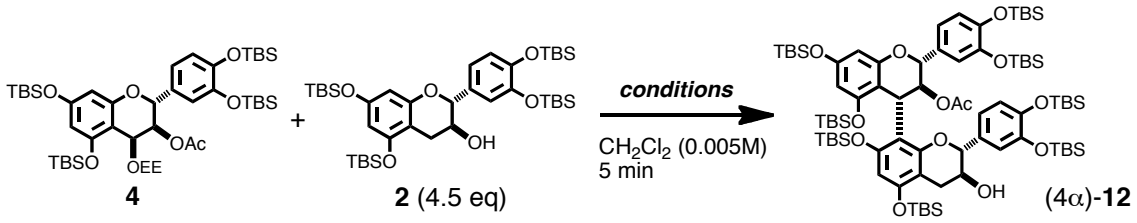


Table 1. Screening of Lewis acid activators for TBS-protected catechin **4** and **2**

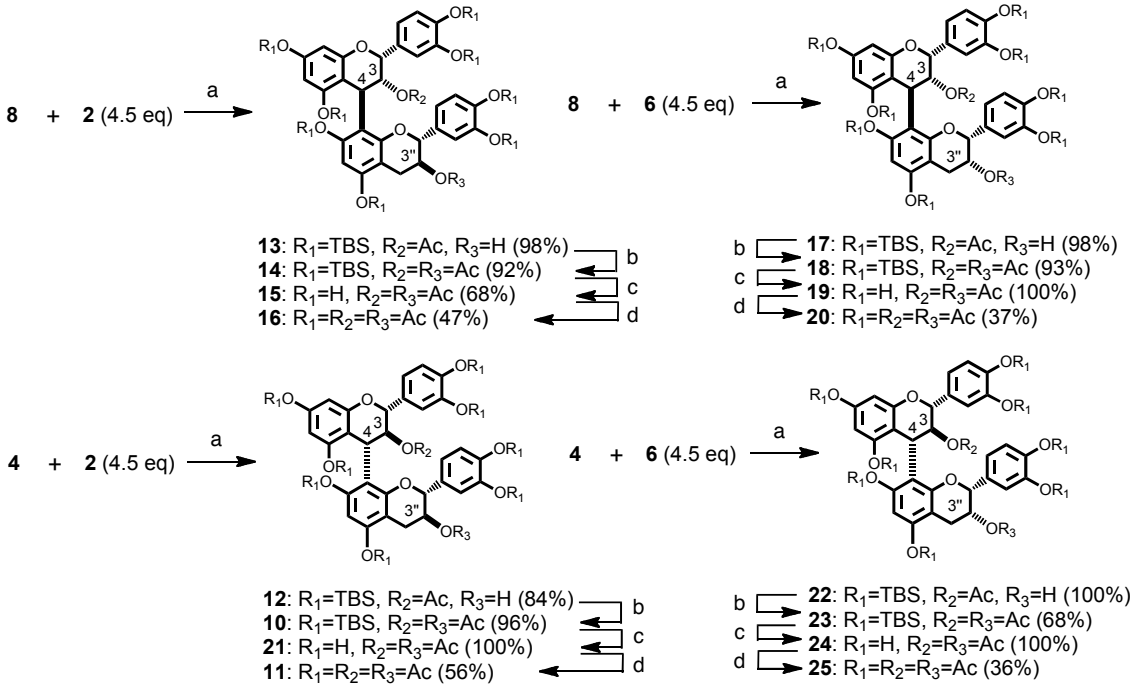
Entry	Lewis acid	Temperature, °C	Coupling yield, %
1	TMSOTf	0	21
2	TMSOTf	–22	29
3	TMSOTf	–41	62
4	TMSOTf	–63	63
5	TMSOTf	–78	67
6	BF_3OEt_2	0	58
7	BF_3OEt_2	–78	trace
8	$SnCl_4$	0	84
9	$SnCl_4$	–78	23

The intermolecular coupling of catechin and catechin units was examined with acetate **4** and **2** in the presence of a Lewis acid. In comparison with the benzyl-protected catechin and catechin coupling (97%, α:β = >48:1),[24a] the TMSOTf-mediated coupling reaction of a TBS-protecting catechin group was low isolation yield but only gave 3,4-*trans* procyanidin dimmer (4α-**12**). Coupling yields at –78 °C, –63 °C and –41 °C were 67, 63 and 62% yields, respectively; however, coupling yields have decreased to 29% and 21% yields as the reaction temperature increased up to –22 °C and 0 °C, respectively. When

BF_3•Et_2O was used as a Lewis acid, the desired compound was obtained in 58% yield at 0 °C and trace at –78 °C. The best yield was obtained using $SnCl_4$ at 0 °C (ice bath) to give 4α-**12** in 84% yield (Table 1, entry 8).[26]

This finding encouraged us to investigate alternative combinations of nucleophile and electrophile. We next examined intermolecular epicatechin-catechin, epicatechin-epicatechin, and catechin-epicatechin condensations using $SnCl_4$ as a Lewis acid at 0 °C. In all cases, the coupling reaction worked well to only give the corresponding 3,4-*trans* products, **13**, **17**, and **22** in 98, 98, and 100% yields, respectively (Scheme 3).

After acetylation of C-3" hydroxy group, the eight-TBS protecting groups of **14**, **18**, **10** and **23** were removed with TBAF in the presence of AcOH in THF to give **15**, **19**, **21**, and **24** in 68, 100, 100%, and 100% yields, respectively. All the spectral data [NMR, IR, MS] of the corresponding deca-acetyl-procyanidins **16**,[24c] **20**,[24e] **11**,[24a] and **25**[24c] were identical to those of authenticated samples.



Reagents and Conditions: (a) $SnCl_4$ (1 eq.), CH_2Cl_2 (0.005 M), 0 °C, 5 min; (b) DCC (4 eq.), AcOH (4 eq.), DMAP (0.8 eq.), CH_2Cl_2 (0.01M); (c) TBAF (24 eq.), AcOH (24 eq.), THF; (d) Ac_2O (30 eq.), DMAP (1.6 eq.), Py.

Scheme 3. Synthesis of procyanidin dimers

In conclusion, we prepared TBS-protected catechin derivatives as a procyanidin unit. TBS-protected catechin derivatives showed high efficiency in condensation with $SnCl_4$ at 0 °C (ice bath). This procedure offers a real advantage for dimmer synthesis over existing methods in this area. The longer procyanidin oligomers synthesis using TBS-protected catechin and epicatechin units are in progress.

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REFERENCES AND NOTES

1. J. B. Harborne, The Flavonoids: Advances in research from 1986; Chapman and Hall: London, 1993.
2. J. B. Harborne and H. Baxter, The Handbook of Natural Flavonoids; John Wiley & Sons: NY, 1999.
3. D. Ferreira and X.-C. Li, *Nat. Prod. Rep.,* 2000, **17**, 193.
4. R. Corder, W. Mullen, M. Q. Khan, S. C. Marks, E. G. Wood, M. J. Carrier, and A. Crozier, *Nature,* 2006, **444**, 566.
5. C. L. Keen, *J. Am. Coll. Nutr.,* 2001, **20**, 4365.
6. C. S. Yang, P. Maliakal, and X. Meng, *Annual Review of Pharmacology and Toxicology,* 2002, **42**, 25.
7. C. Hartisch, H. von Kolodziej, and F. Bruchhausen, *Planta Med.*, 1977, **63**, 106.
8. K. Kameda, T. Takau, H. Okuda, Y. Kimura, T. Okuda, T. Hatano, I. Agata, and S. Arichi, *J. Nat. Prod.,* 1987, **50**, 680.
9. A. Scalbert, *Phytochemistry,* 1991, **30**, 3875.
10. a) F. V. So, N. Guthrie, A. F. Chambers, and K. K. Carroll, *Cancer Lett.,* 1997, **112**, 127; b) H. Kolodziej, C. Haberland, H. Woerdenbag, and A. W. T. Konigs, *Phytotherapy Res.,* 1995, **9**, 410; c) D. Ramljak, L. J. Jr. Romanczyk, L. J. Metheny-Barlow, N. Thompson, V. Knezevic, M. Galaperin, A. Ramesh, and R. B. Dickson, *Mol. Cancer Ther.,* 2005, **4**, 537.
11. a) L. Liviero, P. P. Puglisis, P. Morazzoni, and E. Bombardelli, *Fitoterapia,* 1994, **65**, 203; b) A. Constable, N. Varga, J. Richoz, and R. H. Stadler, *Mutagenesis,* 1996, **11**, 189; c) O. Inanami, Y. Watanabe, B. Syuto, M. Nakano, and M. Kuwabara, *Free Radical Res.,* 1998, **29**, 359.
12. A. A. Shahat, S. I. Ismail, F. M. Hammouda, S. A. Azzam, G. Lemiere, T. De Bruyne, S. De Swaet, L. Piteters, and A. Vlietinck, *Phytomedicine,* 1998, **5**, 133.
13. M. Saito, H. Hosoyama, T. Ariga, S. Kataoka, and M. Yamaji, *J. Agric. Food. Chem.,* 1998, **46**, 1460.
14. O. Inanami, Y. Watanabe, B. Syuto, M. Nakano, and M. Kuwabara, *Free Radical Res.,* 1998, **29**, 359.
15. a) M. Aviram and B. Fuhrman, *Artherosclerosis,* 1998, **137**, S45; b) J. Yamakoshi, S. Kataoka, T. Koga, and T. Ariga, *Artherosclerosis,* 1999, **142**, 139.

16. a) H. Kawamoto, F. Nakatsubo, and K. Murakami, *J. Wood. Chem. Technol.,* 1990, **10**, 59; b) H. Kawamoto, F. Nakatsubo, and K. Murakami, *Mokuzai Gakkaishi,* 1991, **37**, 488; c) S. Yoneda, H. Kawamoto, and F. Nakatsubo, *J. Chem. Soc., Perkin Trans. 1,* 1997, 1025.
17. a) W. Tückmantel, A. P. Kozikowski, and L. J. Romanczyk Jr., *J. Am. Chem. Soc.,* 1999, **121**, 12073; b) A. P. Kozikowski, W. Tückmantel, and Y. Hu, *J. Org. Chem.*, 2001, **66**, 1287; c) W. Tückmantel, G. Böttcher, and L. J. Romanczyk Jr., *J. Org. Chem.*, 2003, **68**, 1641.
18. a) K. Ohomori, N. Ushimaru, and K. Suzuki, *Tetrahedron Lett.,* 2002, **43**, 7753; b) K. Ohomori, N. Ushimaru, and K. Suzuki, *PNAS,* 2004, **101**, 12002.
19. 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, Y. Morimura, K. Hamauzu, T. Kamo, M. Hirota, and H. Makabe, *Heterocycles,* 2009, **79**, 549.
20. I. Tarascou, K. Barathieu, Y. Andé, I. Pianet, E. J. Dufourc, and E. Fouquet, *Eur. J. Org. Chem.*, 2006, 5367.
21. a) S. Nakayama, K. Oyama. T. Kondo, and K. Yoshida, *Heterocycles,* 2007, **73**, 451; b) K. Oyama, M. Kuwano, M. Ito, K. Yoshida, and T. Kondo, *Tetrahedron Lett.,* 2008, **49**, 3176.
22. R. D. Alharthy and C. J. Hayes, *Tetrahedron Lett.*, 2010, **51**, 1193.
23. P. K. Sharma, A. Kolchinski, H. A. Shea, J. J. Nair, Y. Gou, L. J. Romanczyk Jr., and H. H. Schmitz, *Org. Process Res. Dev.,* 2007, **11**, 422.
24. a) A. Saito, N. Nakajima, A. Tanaka, and M. Ubukata, *Tetrahedron,* 2002, **58**, 7829; b) A. Saito, N. Nakajima, A. Tanaka, and M. Ubukata, *Biosci. Biotechnol. Biochem.,* 2002, **66**, 1764; c) A. Saito, N. Nakajima, A. Tanaka, and M. Ubukata, *Heterocycles,* 2003, **61**, 287; d) A. Saito, N. Nakajima, A. Tanaka, and M. Ubukata, *Tetrahedron Lett.,* 2003, **44**, 5449; e) A. Saito, N. Nakajima, N. Matsuura, A. Tanaka, and M. Ubukata, *Heterocycles,* 2004, **62**, 479; f) A. Saito, A. Tanaka, M. Ubukata, and N. Nakajima, *Synlett,* 2004, 2040.
25. The ratio of (4α)-**9** and (4β)-**9** was determined by the isolation yields of each compound from silica gel preparative TLC separation (Merck 1.0 mm, hexane/EtOAc= 10/1, 3 times development).
26. General Procedure for the coupling reaction using $SnCl_4$ (Table 1, entry 8): To a solution of nucleophile **2** (600 mg, 0.80 mmol) and electrophile **4** (157 mg, 0.18 mmol) in CH_2Cl_2 (36 mL) under an argon atmosphere was added $SnCl_4$ (46.5 mg, 0.18 mmol). After the resulting mixture had been stirred for 30 min, the reaction was quenched with water. The mixture was extracted with EtOAc, and the combined organic layer were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified with silica gel chromatography (hexane/EtOAc = 25/1) to give only 4α-**12** (231 mg, 0.15 mmol, 84%) as an oil.