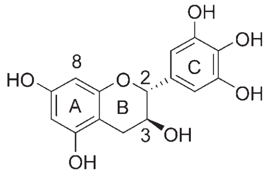
Diversity-Oriented Synthesis

DOI: 10.1002/anie.200701276

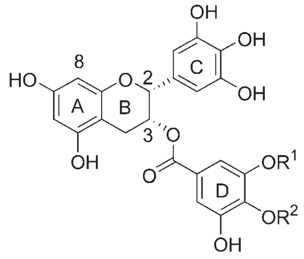
Solid-Phase Synthesis of Epigallocatechin Gallate Derivatives**

*Hiroshi Tanaka, Haruko Miyoshi, Yu-Cheng Chuang, Yoshio Ando, and Takashi Takahashi**

Catechin (**1**) and epigallocatechin gallate (EGCG, **2**) are biologically active polyphenols found in tea leaves.[1] The methylated EGCG derivatives **3** and **4** were reported recently to be effective drug candidates, as the hydrophilicity of the methyl groups improves the bioavailability of the compounds. Furthermore, Tachibana and co-workers reported that the blocking of the 67-kDa laminin receptor (67LR) is fundamental to both the antiallergic effect of the methylated EGCGs **3** and **4**[2,3] and the anticancer action of the parent compound **2**. However, knowledge about the available structural diversity of methylated epicatechins from natural sources is limited. Several chemical approaches to the synthesis of epicatechin derivatives have been reported in which the epicatechin skeleton is constructed by an indirect method based on the epimerization of the hydroxy group at C3 of the catechin skeleton, which has a 2,3-*trans* configuration.[4] We recently reported a direct and efficient method for the construction of the epicatechin skeleton through the reductive cyclization of a α-acyloxy ketone.[5] However, these established approaches are based mainly on target-oriented solution-phase synthetic strategies, and the development of an effective method based on a diversity-oriented synthetic strategy for the rapid assembly of epicatechin derivatives remains a worthwhile goal. Herein, we describe the efficient solid-phase synthesis of epigallocatechin gallate (**2**) and the combinatorial synthesis of protected methylated epicatechin derivatives.

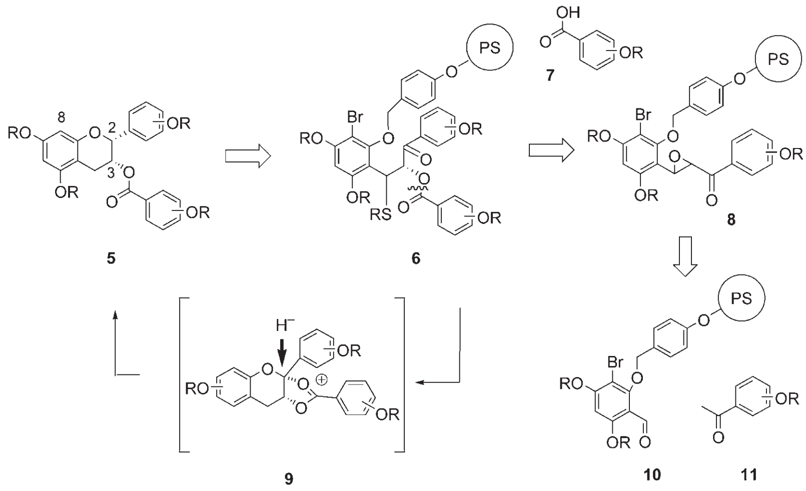


catechin (**1**)



2 : $R^1 = R^2 = H$; epigallocatechin gallate
3 : $R^1 = Me$, $R^2 = H$
4 : $R^1 = H$, $R^2 = Me$

Our strategy for the solid-phase synthesis of epicatechin derivatives **5** begins with the solid-supported aldehyde **10** linked through an acid-labile Wang linker at the phenol group (Scheme 1). We planned to couple this aldehyde with the ketone **11** and carboxylic acid **7**, to construct the epicatechin skeleton by cleavage of the Wang linker and subsequent reductive etherification of the α-acyloxy ketone, and finally to cleave the protecting groups in the solution phase. Reductive etherification of the α-acyloxy ketone was expected to provide the *cis*-substituted benzopyran ring system through neighboring-group participation.[5,6] We anticipated that the bromine substituent at the 8-position would prevent a Friedel–Crafts alkylation at this position with the cleaved Wang linker.[7] The solid-supported α-acyloxy ketone **6** could be prepared from the epoxide **8** by the regioselective opening of the epoxide with a thiol followed by esterification of the resulting alcohol.[8] The resulting sulfide group at the benzyl position would be removed under the conditions used for the reductive etherification. The epoxide **8** can be prepared by the aldol condensation of the solid-supported aldehyde **10** with the ketone **11**, followed by epoxidation. We believed that this three-component coupling strategy would be effective for the



Scheme 1. Strategy for the solid-phase synthesis of epicatechin derivatives **5**.

---

[*] Dr. H. Tanaka, H. Miyoshi, Y.-C. Chuang, Dr. Y. Ando, Prof. Dr. T. Takahashi
Department of Applied Chemistry, Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2884
E-mail: ttak@apc.titech.ac.jp

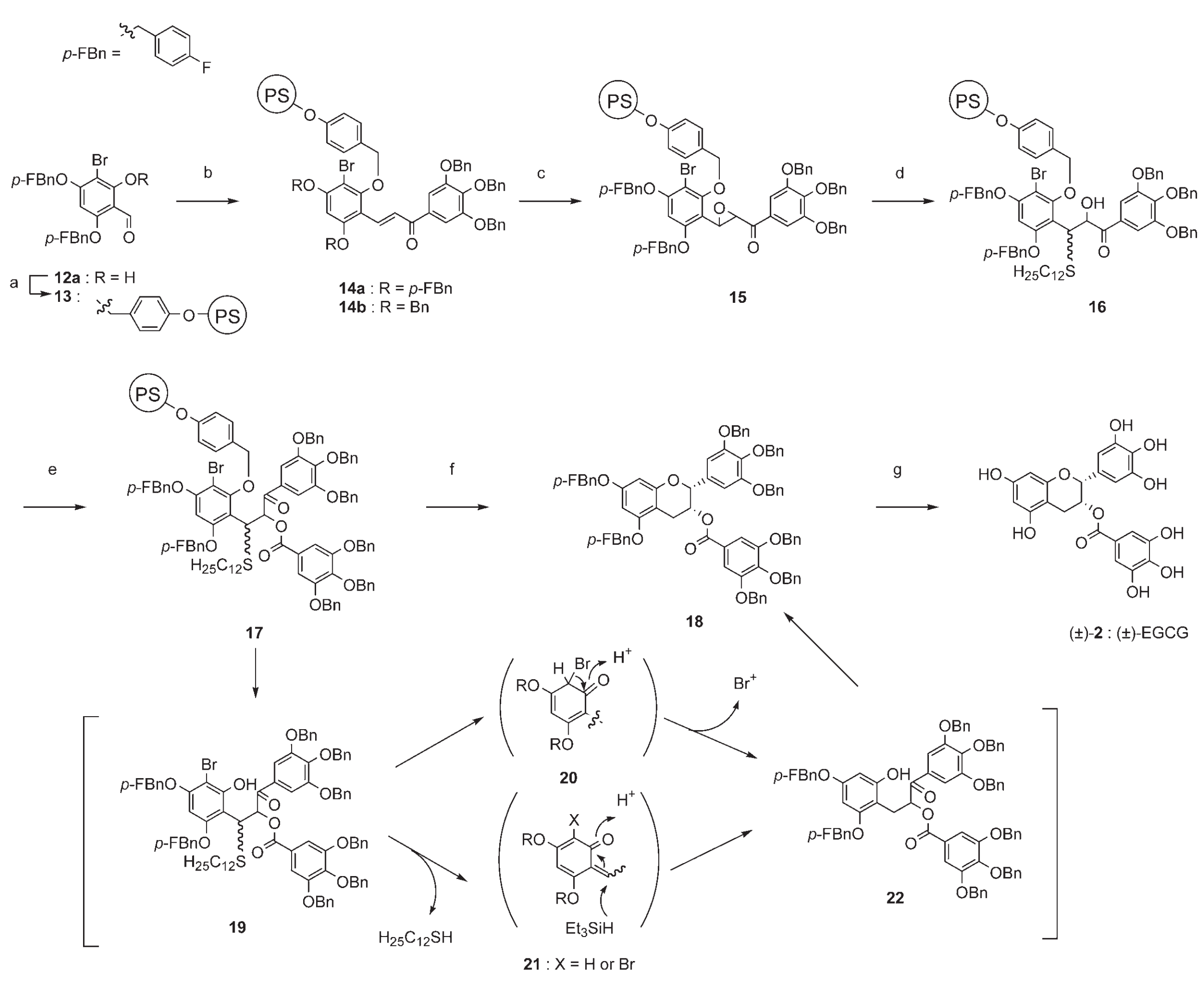
[**] This research was supported financially by the Naito Foundation. We thank Prof. Dr. Takao Ikariya and Prof. Dr. Shigeki Kuwata at the Tokyo Institute of Technology for determining the structure of the bromoarene.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

synthesis of combinatorial libraries of epicatechin derivatives, the three aromatic rings of which could be varied. Furthermore, no specific functional groups are required on any of the three aromatic rings for attachment to the resin because the phenol group used for linking to the solid support becomes an element of the pyran ring.

The solid-phase synthesis of EGCG began with the treatment of a 2.0 M solution of the aldehyde **12a** with polystyrene–Wang bromide (1.6 mmolg^{-1}) to provide the solid-supported aldehyde **13** (Scheme 2).[9] The loading yield with respect to the resin was estimated to be 48% upon cleavage from the resin. The treatment of the solid-supported aldehyde **13** with the ketone **11a** (see Scheme 3) under basic conditions provided the solid-supported enone **14a**, which underwent epoxidation with *t*BuOOH under basic conditions to give the solid-supported epoxide **15**. In contrast, the epoxidation of the corresponding benzyl-protected derivative **14b** proved difficult under the same reaction conditions. The electron-withdrawing *para*-fluoro substituents on the benzyl ether groups on the A ring might facilitate the formation of the epoxide **15** not only by enhancing the reactivity of enone **14a** toward nucleophilic addition, but also by preventing the generated epoxide **15** from decomposing during the epoxidation and workup. The regioselective epoxide-ring opening[10] of **15** with 1-dodecanethiol[11] in the presence of Zn(OTf)$_2$ proceeded without cleavage of the Wang linker to afford the solid-supported α-hydroxyketone **16**, the acylation of which with 3,4,5-tribenzyloxybenzoic acid (**7a**) then gave the precursor **17** for reductive cyclization.

The exposure of **17** to 15% TFA in CH$_2$Cl$_2$ in the presence of a PS–benzaldehyde resin at −10 °C for 5 h followed by the addition of triethylsilane at the same temperature promoted the cleavage of the Wang linker, reduction of the sulfide and the bromide, and reductive etherification to provide the protected epigallocatechin **18**. PS–benzaldehyde scavenged the released thiol and facilitated the purification of **18**. The purity of the crude material was estimated by HPLC on the basis of UV absorption to be 32%. The *p*-fluorobenzyl

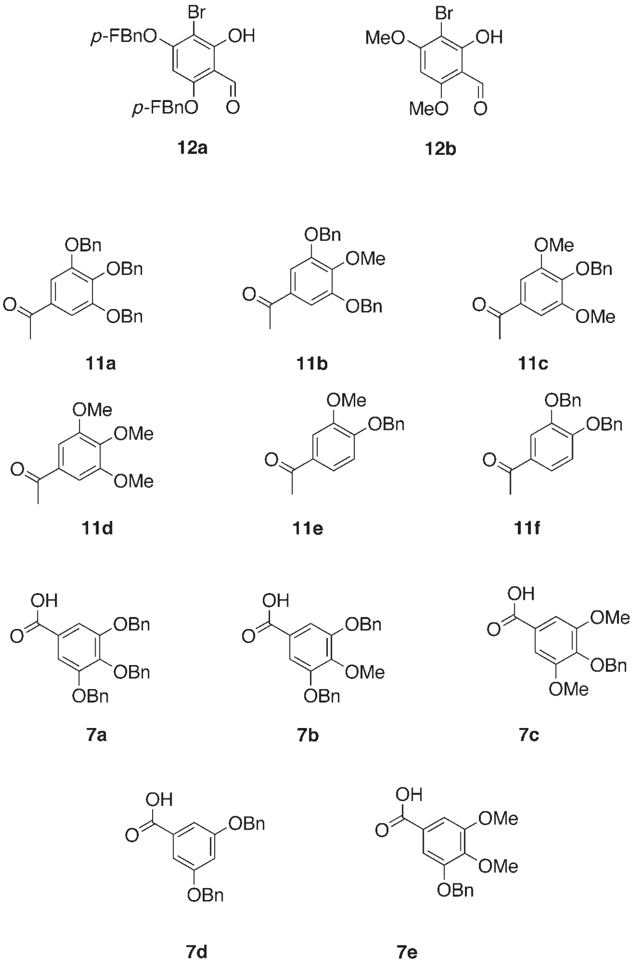


Scheme 2. Solid-phase synthesis of (±)-epigallocatechin gallate ((±)-**2**). Reagents and conditions: a) PS–Wang bromide (1.6 mmolg^{-1}), Cs$_2$CO$_3$ (0.2 M), NaI (0.06 M), DMF, RT, 24 h, 48% (based on the resin); b) **11a** (0.5 M), NaOMe (0.1 M), THF/MeOH (4:1), RT, 24 h; c) TBHP (1.5 M), KOH (0.2 M), CH$_2$Cl$_2$/MeOH/decane (100:12:38), RT, 72 h; d) C$_{12}$H$_{25}$SH (0.05 M), Zn(OTf)$_2$ (0.01 M), CH$_2$Cl$_2$/CH$_3$CN (1:1), RT, 3 h; e) **7a** (0.2 M), EDCI (0.2 M), DMAP (0.06 M), pyridine/DMF (1:1), 50 °C, 48 h; f) 15% TFA, CH$_2$Cl$_2$, PS–benzaldehyde resin (1.13 mmolg^{-1}, 4.0 equiv with respect to **13**), −10 °C, 5 h, then Et$_3$SiH, 19 h, 62% yield with 36% purity, 19% yield of the isolated product; g) Pd(OH)$_2$, HCO$_2$H, THF/MeOH (1:1), 82%. Bn = benzyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *p*-FBn = *p*-FC$_6$H$_4$CH$_2$, TBHP = *tert*-butylhydroperoxide, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

protecting groups improve the purity of the protected EGCG **18**, as benzyl protecting groups on the A ring were cleaved gradually under the conditions for the reductive cyclization. The crude material was purified by gel-permeation chromatography to provide the protected EGCG **18** in 19% yield from **13**. We propose the following mechanism for the reductive cleavage of the bromide and sulfide functional groups: Compound **19** undergoes debromination through a retro-Friedel–Crafts mechanism via the intermediate **20**; the bromonium ion thus generated is reduced by the hydrosilane. The thiol is released to give an intermediate species **21**, which undergoes reduction at the benzylic position with the hydrosilane. The resulting ketone **22** is thought to be the precursor for reductive etherification. Finally, the epicatechin derivative **18** was deprotected by conventional hydrogenolysis in the solution phase by using a palladium catalyst to provide (±)-epigallocatechin gallate ((±)-**2**) in 82% yield.

We next examined the combinatorial synthesis of a library of protected polymethylated epicatechin derivatives **5**.[12] The two aldehydes **12a** and **12b**, six ketones **11a–f**, and five carboxylic acids **7a–e** (Scheme 3) were used as building blocks for the synthesis of 60 epicatechin derivatives. Methyl ether, benzyl ether, and *p*-fluorobenzyl ether groups protect the phenol functionalities in the substrates. The benzyl ethers can be cleaved selectively without the decomposition of the epicatechin during the final stage of the synthesis. The library was synthesized on the basis of the split-and-pool strategy by using Irori MiniKans encoded with color tags with 70 mg of the polystyrene resin.[13] The purity of the library compounds was estimated by HPLC–MS analysis on the basis of UV absorption at 254 nm (see the Supporting Information). A total of 59 of 60 possible compounds were detected by LC–MS. The purity of 48 of the compounds was in the range 15–58%. Purification of the 59 crude products by recycling preparative HPLC based on gel-permeation chromatography led to the isolation of 51 pure protected EGCG derivatives in yields of 3.1 to 26 mg. The remaining eight compounds could not be isolated from the crude product mixture as result of their low purity or the presence of inseparable by-products.

In conclusion, we have developed a solid-phase synthesis of (±)-epigallocatechin gallate ((±)-**2**). A reductive etherification reaction proceeded simultaneously with the release of the final synthetic intermediate from the resin to provide a protected form of (±)-**2** in moderate overall yield. When we applied this method to the solid-phase combinatorial synthesis of 60 protected methylated epicatechin derivatives **5**, we detected 59 compounds by HPLC–MS and isolated 51 epicatechin derivatives.



12a **12b**

11a **11b** **11c**

11d **11e** **11f**

7a **7b** **7c**

7d **7e**

Scheme 3. Building blocks for the library synthesis.

Received: March 23, 2007
Revised: May 24, 2007

Keywords: catechins · combinatorial chemistry · etherification · natural products · solid-phase synthesis

---

[1] a) T. Yamamoto, L. R. Juneja, D.-c. Chu, M. Kim, *Chemistry and Applications of Green Tea*, CRC, Boca Raton, **1997**; b) E. C. Stuart, M. J. Scandlyn, R. J. Rosengren, *Life Sci.* **2006**, *79*, 2329–2336.

[2] Y. Fujimura, K. Yamada, H. Tachibana, *Biochem. Biophys. Res. Commun.* **2005**, *336*, 674–681.

[3] H. Tachibana, K. Koga, Y. Fujimura, K. Yamada, *Nat. Struct. Mol. Biol.* **2004**, *11*, 380–381.

[4] a) H. van Rensburg, P. S. Heerden, D. Ferreira, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3415–3421; b) B. Nay, V. Arnaudinaud, J. F. Peyrat, A. Nuhrich, G. Deffieux, J. M. Merillon, J. Vercauteren, *Eur. J. Org. Chem.* **2000**, 1279–1283; c) N. T. Zaveri, *Org. Lett.* **2001**, *3*, 843–846; d) L. Li, T. H. Chan, *Org. Lett.* **2001**, *3*, 739–741; e) S.-S. Jew, D.-y. Lim, S.-y. Bae, H.-a. Kim, J.-h. Kim, J. Lee, H.-g. Park, *Tetrahedron: Asymmetry* **2002**, *13*, 715–720; f) J. C. Anderson, C. Headley, P. D. Stapleton, P. W. Taylor, *Tetrahedron* **2005**, *61*, 7703–7712; g) S. B. Wan, Q. P. Dou, T. H. Chan, *Tetrahedron* **2006**, *62*, 5897–5904; h) T. Furuta, Y. Hirooka, A. Abe, Y. Sugata, M. Ueda, K. Murakami, T. Suzuki, K. Tanaka, T. Kan, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3095–3098.

[5] M. Kitade, Y. Ohno, H. Tanaka, T. Takahashi, *Synlett* **2006**, 2827–2829.

[6] The same type of reductive etherification was applied to the solution-phase stereoselective synthesis of *trans-* and *cis*-2,4-substituted benzopyran derivatives. The stereoselectivity of benzopyran formation was controlled by the bulkiness of the reducing reagents: K. Li, K. Vanka, W. H. Thompson, J. A. Tunge, *Org. Lett.* **2006**, *8*, 4711–4714.

[7] K. Ohmori, K. Ushimaru, K. Suzuki, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12002 – 12007.

[8] We first attempted to synthesize the solid-supported α-hydroxyketone by rhodium-catalyzed reduction of the solid-supported enone derivative with triethylsilane to provide the silyl enol ether, followed by oxidation of the vinyl ether with dimethyldioxirane. However, this approach did not work well, as the reactions should be carried out in polar solvents, such as acetone, at low temperature (−78 °C), and these conditions are not suitable for synthesis on a solid support.

[9] F. Micheli, F. Degiorgis, A. Feriani, A. Paio, A. Pozzan, P. Zarantonello, P. Seneci, *J. Comb. Chem.* **2001**, *3*, 224 – 228.

[10] S. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 2147 – 2155.

[11] Odorless 1-dodecanethiol is easy to use: M. Node, K. Kumar, K. Nishide, S. Ohsugi, T. Miyamoto, *Tetrahedron Lett.* **2001**, *42*, 9207 – 9210.

[12] The library of protected epicatechins was suitable for stock. The deprotected derivatives were not sufficiently stable to be stored for long periods.

[13] In our first attempt at the library synthesis we used 30 mg of the resin fully packed in MicroKans. The synthesis failed because the packing of the resin in MicroKans reduced the reactivity of the substrates on the resin, especially toward epoxidation. The mobility of the resin in the reaction mixture is an important factor in solid-phase synthesis. MiniKans, on the other hand, are amenable to the use of 100 mg of a resin.