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Reagent-controlled stereoselective synthesis of (±)-gallo- and (±)-epigallo-catechin gallates

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ABSTRACT

Synthesis of (±)-gallocatechin and (±)-epigallocatechin gallates by electrophilic cycloarylation is reported. The precursors for cyclization were prepared by reagent-controlled stereo-selective opening of epoxide with phenol. Activation of the *S*-oxidized *S*,*O*-acetal enabled electrophilic cycloarylation to stereoselectively provide the acylated catechins.

Introduction

(−)-Epigallocatechin gallate (EGCG **1**, Scheme 1) is an antioxidative phytochemical and the most abundant catechin found in green tea leaves. EGCG **1** is associated with various biological activities[1] and, for example, targeting the 67-kDa laminin receptor (67LR) mediating anti-cancer and anti-allergic actions.[2] The highly oxygenated aromatic moieties make EGCG unstable under basic, acidic, and oxidative conditions. In addition, EGCG easily undergoes epimerization at the C2 position when heated, or under acidic or basic conditions to provide gallocatechin gallate (GCG **2**) composed of a *trans*-2,3-disubstituted benzopyran. Therefore green tea contains a considerable amount of GCG in comparison with EGCG. Chemical synthesis of ample amounts of pure, well-characterized EGCG and GCG could strongly assist the elucidation of the biological activity and the mechanism of actions of these important phytochemicals.

Most of the established methods for the synthesis of EGCG and GCG derivatives are based on independent synthesis of *cis*- and *trans*-flavan-3-ol derivatives, followed by acylation of the alcohol with gallic acid. The syntheses of the flavan-3-ols are largely divided into two approaches. One is based on cycloetherification by a C2–O1 bond formation, which mainly provided thermodynamically most stable *trans*-flavanols.[3] Preparation of the *cis*-flavanols needs the inversion of stereochemistry at the C3 position. The other approach is based on cycloarylation by C4–Ar bond formation, which allows the preparation of both *trans*- and *cis*-flavanols from the corresponding acyclic precursors.[4] Suzuki and co-workers reported on the synthesis of *trans*- and *cis*-flavanols by intramolecular nucleophilic substitution with phenyl metal species.[5] On the other hand, we have recently reported on a unique method for the synthesis of EGCG involving reductive etherification of the α-acyloxyketones under acidic conditions to directly provide 3-*O*-acylated *cis*-flavanols.[6] The acyl moiety acts as a stereo-directing group for the synthesis of the 3-*O*-acyl *cis*-flavanol and stabilized the cyclized products under acidic conditions. However this C2–O1 bond formation approach cannot be used for the synthesis of GCG and their derivatives. Herein we report on a reagent-controlled stereoselective synthesis of racemic EGCG and GCG based on C4–Ar bond formation.

Strategy for the synthesis of EGCG **1** and GCG **2** involves an intramolecular electrophilic cycloarylation of acetal **3** and a reagent-controlled *anti*- and *syn*-opening of epoxide **6** (Scheme 1). The key 1,3-oxathiolane 3-oxide intermediates, the *S*-oxidized *S*,*O*-acetals **3** and **4**, undergo electrophilic cycloarylation via oxonium cation **9**. The remaining alkyloxy substituent at the benzylic position can be subsequently reduced under acidic conditions. The bromide on the A ring moderates reactivity of the aromatic moiety and prevents self-condensation of the cyclized product.[7] The precursors **3** and **4** could be prepared by reagent-controlled *syn*- and *anti*-epoxide opening of epoxide **6** with bromophenol **5**, followed by acylation of the resulting alcohol with gallic acid **7**. The epoxide **6** is prepared from the corresponding olefin **8**. The *S*-oxidized *S*,*O*-acetals tolerate epoxidation conditions and could

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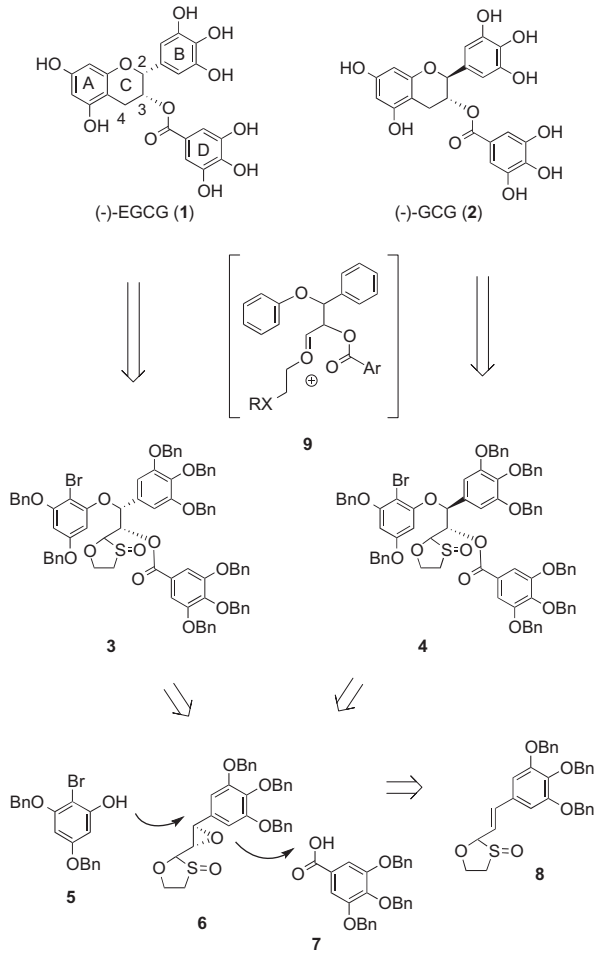
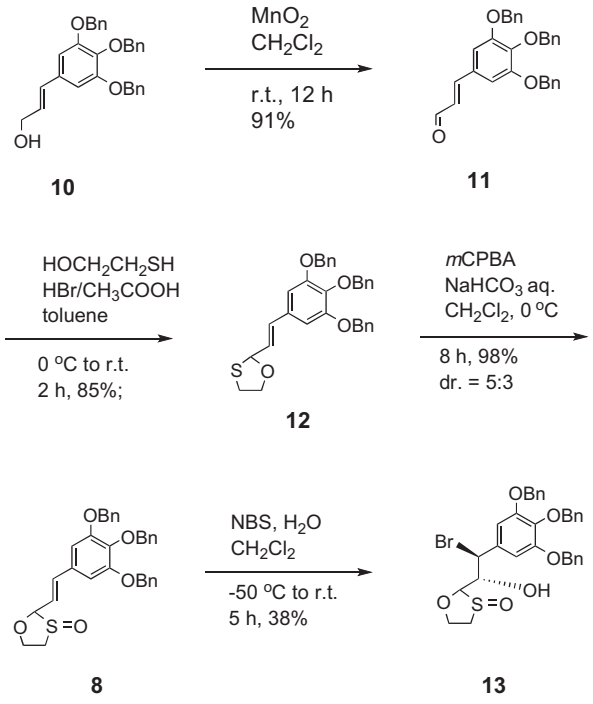


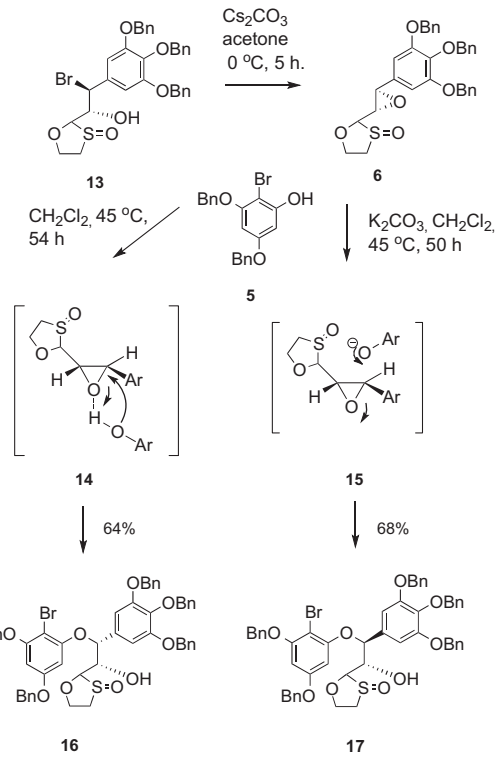
Scheme 1. Strategy for the synthesis of EGCG **1** and GCG **2**.

generate the intermediate oxonium ion under sufficiently mild acidic condition that do not leave to cleavage the benzyl phenyl ether.[8] Noteworthy, this strategy to EGCG **1** or GCG **2** involves only four diverse steps from epoxide **6**: regio- and stereo-selective opening of epoxide **6** with phenol **5**, esterification of the resulting alcohol with appropriately protected gallic acid, cycloarylation, and deprotection.

Preparation of bromohydrin **13** is shown in Scheme 2. Oxidation of the allyl alcohol **10**[3d] with MnO_2 provided aldehyde **11** in 91%. The aldehyde **11** was converted to the cyclic *S*,*O*-acetal **12** in 85% yield by treatment with 2-mercaptoethanol in the presence of HBr.[9] The oxidation of the *S*,*O*-acetal **12** with *m*CPBA at 0 °C provided the oxidized *S*,*O*-acetal **8** in 98% as a mixture of two diastereomers (5:3). Treatment of the stereoisomeric **8** with NBS in the presence of H_2O resulted in the disappearance of the substrates and the yield of bromohydrin **13** in 38% yield as a single diastereomer with a significant amount of enone **11**. Relative stereochemistry of the bromohydrin **13** was not determined. Dynamic kinetic or kinetic resolution of the oxidized *S*,*O*-acetal via epoxidation might be involved during the reaction.

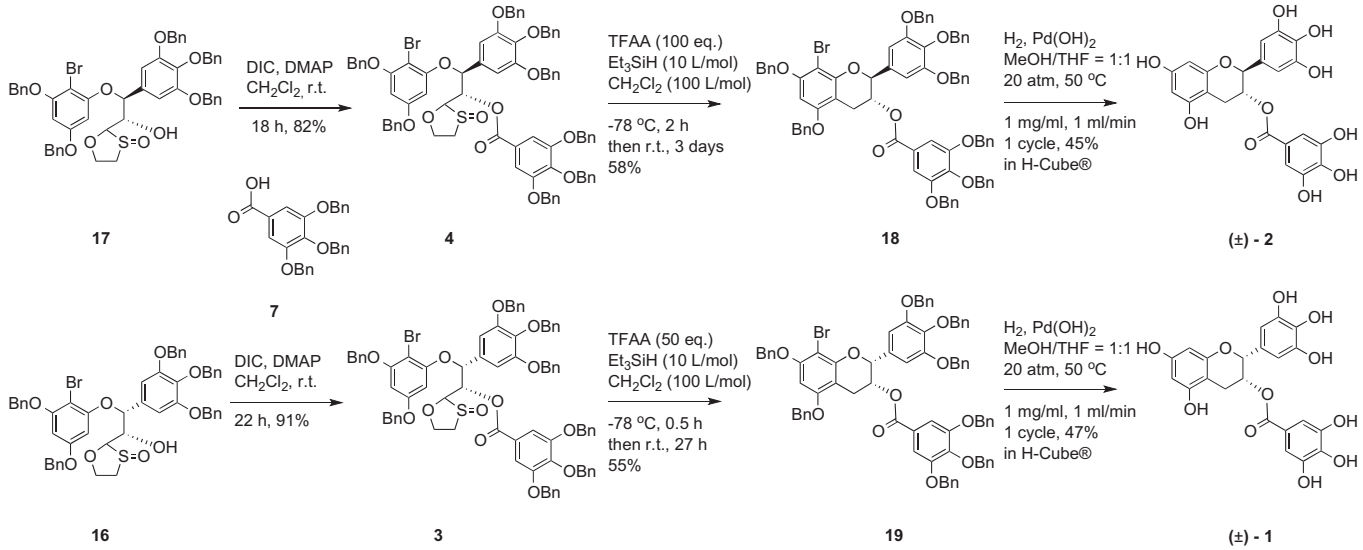


Scheme 2. Preparation of bromohydrine **13**.



Scheme 3. *Anti*- and *syn*-epoxide opening of **6**.

Anti- and *syn*-opening of the epoxide **6** was examined (Scheme 3). The bromohydrin **13** was converted into epoxide **6** under basic conditions, which was used for the next reaction without further purification due to its instability. According to the reported method,[4] treatment of epoxide **6** with phenol **5**[10] under basic conditions at 45 °C for 5 days provided the *trans*-opening product **17** in 68% yield by a conventional S_N2 reaction via **15**. On the other hand, heating the mixture of epoxide **6** and phenol **5** at 45 °C without the presence of base provided the *cis*-opening product **16** in 64% yield based on **13**. The mechanism of the reaction might involve activation of epoxide **14** with the proton of incoming phenol **5**, followed by the attack of the phenol to the benzylic position at the same face of the epoxide.[11] The relative stereochemistry between the C2 and C3 stereogenic centers of each product was determined by analysis of the corresponding cyclized products.



Scheme 4. Synthesis of *rac*-EGCG ((±)-(**1**)) and *rac*-GCG ((±)-(**2**)).

Synthesis of *rac*-EGCG ((±)-(**1**)) and *rac*-GCG ((±)-(**2**)) is shown in Scheme 4. Acylation of the resulting alcohols **17** and **16** with the tri-*O*-benzylgallic acid **7** in the presence of *N,N′*-diisopropyl carbodiimide (DIC) provided esters **4** and **3** in 82% and 91% yields, respectively. We next examined the cyclization of **4** and **3**. Treatment of **4** with a large excess of trifluoroacetic anhydride (TFAA) in a solution of Et_3SiH and CH_2Cl_2 (1:10) at −78 °C for 2 h, followed by additional stirring at room temperature for 3 days successfully provided the protected GCG **18** as a single diastereomer. Based on the coupling constant between H2 and H3 ($J_{H2\text{-}H3}$ = 6.3 Hz), the relative stereochemistry between the C2 and C3 positions was assigned to be *trans*. Attempts to use trifluoroacetic acid instead of TFAA did not lead to the cyclized products, indicated that O-acylation of the sulfoxide could be an initial reaction leading to cyclization. Likewise, treating **3** with 50 equiv. of TFAA in a solution of Et_3SiH and CH_2Cl_2 (1:10) at −78 °C for 30 min, followed by additional stirring at room temperature for 27 h, provided the protected EGCG **19** as a single diastereomer. To our delight, these results indicated that epimerization at the C2 position did not occur during the required reaction conditions. The relative stereochemistry of the cyclized products depended only on that of the precursors. Deprotection of the protected GCG **18** and EGCG **19** was achieved by hydrogenolysis using a continuous flow hydrogen reactor H-Cube with a CatCart® (70 mm) containing 20% $Pd(OH)_2/C$ at 20 atm at 50 °C provided the racemic GCG **2** and EGCG **1** in 45% and 47% yields, respectively.[12]

In conclusion, we have described the synthesis of the racemic GCG **2** and EGCG **1** by reagent-controlled *anti*- and *syn*-epoxide opening and electrophilic cycloarylation. The epoxide **6** selectively undergoes *anti*- and *syn*-epoxide opening with phenol **5** with base and without base, respectively. The key *S*-oxidized *S,O*-acetals **3** and **4** (1,3-oxathiolane 3-oxides) can generate oxonium cation **9** by treatment with a mixture of Et_3SiH and TFAA and undergo electrophilic cycloarylation without cleavage and epimerization of the benzylic ethers. This method requires only four diverse steps from epoxide **6** to the acylated catechins **1** and **2** and would be effective for the synthesis of various acylated catechin derivatives composed of a 2,3-*cis*- or *trans*-substituted chroman skeleton.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.065.

References and notes

1. (a) Yamamoto, T.; Juneja, L. R.; Chu, D.-C.; Kim, M. *Chemistry and Applications of Green Tea*; CRC: Boca Raton, 1997; (b) Stuart, E. C.; Scandlyn, M. J.; Rosengren, R. *J. Life Sci.* **2006**, *79*, 2329.
2. Tachibana, H.; Koga, K.; Fujimura, Y.; Yamada, K. *Nat. Struct. Mol. Biol.* **2004**, *11*, 380.
3. (a) Rensburg, H.; Heerden, P. S.; Ferreira, D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3415; (b) Nay, B.; Arnaudinaud, V.; Peyrat, J. F.; Nuhrich, A.; Deffieux, G.; Merillon, J. M.; Vercauteren, J. *Eur. J. Org. Chem.* **2000**, 1279; (c) Zaveri, N. T. *Org. Lett.* **2001**, *3*, 843; (d) Li, L.; Chan, T. H. *Org. Lett.* **2001**, *3*, 739; (e) Jew, S.-S.; Lim, D.-Y.; Bae, S.-Y.; Kim, H.-A.; Kim, J.-H.; Lee, J.; Park, H.-G. *Tetrahedron: Asymmetry* **2002**, *13*, 715; (f) Anderson, J. C.; Headley, C.; Stapleton, P. D.; Taylor, P. W. *Tetrahedron* **2005**, *61*, 7703; (g) Wan, S. B.; Dou, Q. P.; Chan, T. H. *Tetrahedron* **2006**, *62*, 5897; (h) Furuta, T.; Hirooka, Y.; Abe, A.; Sugata, Y.; Ueda, M.; Murakami, K.; Suzuki, T.; Tanaka, K.; Kan, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3095.
4. Liu, Y.; Li, Z.; Lin, G.; Xiang, Z.; Xiang, J.; Zhao, M.; Chen, J.; Yang, Z. Z. *J. Org. Chem.* **2008**, *73*, 4625.
5. (a) Ohmori, K.; Takeda, M.; Higuchi, T.; Shono, T.; Suzuki, K. *Chem. Lett.* **2009**, *38*, 934; (b) Higuchi, T.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2009**, *38*, 1006; (c) Ohmori, K.; Yano, T.; Suzuki Org, K. *Biomol. Chem.* **2010**, *8*, 2693.
6. (a) Tanaka, H.; Kitade, M.; Ohno, Y.; Tanaka, H.; Takahashi, T. *Synlett* **2006**, 2827; (b) Kitade, M.; Tanaka, H. T. Takahashi *Heterocycles* **2007**, *73*, 183; (c) Tanaka, H.; Miyoshi, H.; Chuang, Y.-C.; Ando, Y.; Takahashi Angew, T. *Chem. Int. Ed.* **2007**, *46*, 5934; (d) Tanaka, H.; Yamanouchi, M.; Miyoshi, H.; Hirotsu, K.; Tachibana, H.; Takahashi, T. *Chem. Asian J.* **2010**, *5*, 2231.
7. Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
8. Ohmori, K.; Ushimaru, K.; Suzuki, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12002.
9. Kamal, A.; Chouhan, G.; Ahmed, K. *Tetrahedron Lett.* **2002**, *43*, 6947.
10. Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.
11. Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426.
12. H-Cube® is made by ThalesNano; Richard, V. J.; Norbert, V.; Lajos, G.; Laszlo, U.; Daniel, S.; Ferenc, D. *J. Comb. Chem.* **2006**, *8*, 110.