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Enantioselective Synthesis of Epigallocatechin-3-gallate (EGCG), the Active Polyphenol Component from Green Tea

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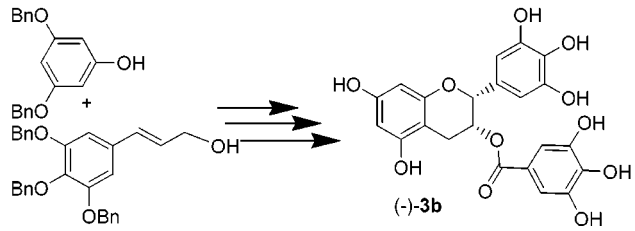
ABSTRACT



Enantioselective synthesis of epigallocatechin-3-gallate (EGCG, 3b), the active polyphenol component from green tea, has been achieved by using a stereospecific cyclization of the Sharpless asymmetric dihydroxylation product 7c as the key step.

Second to water, tea is probably the most widely consumed beverage worldwide. Regular consumption of tea has been associated with reduced risk of several forms of cancer and other health benefits according to some epidemiological studies.[1] Tea leaves contain many constituents,[2] and the biological effects of tea are often attributed to the polyphenols among the tea constituents.[3] In freshly harvested tea leaves, the following flavanols, known collectively as the catechins, are present: (+)-catechin (**1a**), (+)-gallocatechin (**1b**), (−)-epicatechin (**2a**), (−)-epigallocatechin (**2b**), (−)-epicatechin-3-gallate (**3a**), and (−)-epigallocatechin-3-gallate (**3b**, EGCG). In particular, (−)-epigallocatechin-3-gallate (**3b**, EGCG), the main ingredient of green tea extract, has been shown to inhibit growth in a number of tumor cell lines such as human leukemia cell lines, mouse NFS60 cell line,[4] MCF-7 breast carcinoma, HT-29 colon carcinoma, A-427 lung carcinoma, UACC-375 melanoma,[5] the prostate cancer cell lines LNCaP, PC-3 and DU145,[6] leukemia blast cells from AML patients,[7] and human epidermoid carcinoma cell line A431.[8] In 1996, the Division of Cancer Prevention and Control, National Cancer Institute of the United States, published a clinical development plan with respect to tea.[9] At the present time, EGCG (**3b**) can be obtained by isolation from green tea extract, and the yield depends on the processing and the source of the tea. As far as we are aware, no synthesis of

(1) For selected recent reviews, see: (a) Bushman, J. L. *Nutr. Cancer* **1998**, *31*, 151. (b) Weisburger, J. H. *Proc. Soc. Exp. Biol. Med.* **1999**, *220*, *271*. (c) Hollman, P. C.; Feskens, E. J.; Katan, M. B. *Proc. Soc. Exp. Biol. Med.* **1999**, *220*, 198. (d) Stensvold, I.; Tverdal, A.; Solvoll, K.; Per Foss O. *Prev. Med.* **1992**, *21*, 546.

(2) Haslam, E. *Plant Polyphenols. Vegetable Tannins Revisited.* Cambridge University Press: Cambridge, 1989.

(3) The effect of the nonpolyphenolic fraction of green tea leaves has recently been studied: Higashi-Okai, K.; Otani, S.; Okai, Y. *Cancer Lett.* **1998**, *129*, 223.

(4) Otsuka, T.; Ogo, T.; Eto, T.; Asano, Y.; Suganuma, M.; Niho, Y. *Life Sci.* **1998**, *63*, 1397.

(5) Valcic, S.; Timmermann, B. N.; Alberts, D. S.; Watcher, G. A.; Krutzsch, M.; Wymer, J.; Guillen, J. M. *Anticancer Drugs* **1996**, *7*, 461.

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(7) Asano, T.; Okamura, S.; Ogo, T.; Eto, T.; Otsukat, T.; Niho, Y. *Life Sci.* **1997**, *60*, 135.

(8) Liang, Y. C.; Lin-Shiau, S. Y.; Chen, C. F.; Lin, J. K. *J. Cell. Biochem.* **1997**, *67*, 55.

(9) Kelloff, G. J.; Crowell, J. A.; Hawk, E. T.; Steele, V. E.; Lubet, R. A.; Boone, C. W.; Covey, J. M.; Doody, L. A.; Omenn, G. S.; Greenwald, P.; Hong, W. K.; Parkinson, D. R.; Bagheri, D.; Baxter, G. T.; Blunden, M.; Doeltx, M. K.; Eisenhauer, K. M.; Johnson, K.; Knapp, G. G.; Longfellow, D. G.; Malone, W. F.; Nayfield, S. G.; Seifried, H. E.; Swall, L. M.; Sigman, C. C. *J. Cell. Biochem. Suppl.* **1996**, *26*, 54.

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EGCG has been reported.[10] A totally synthetic approach will provide access to both the racemate and the individual enantiomers of EGCG as well as its analogues. Their biological studies might reveal more information about how EGCG acts as an anticancer agent. Our retrosynthetic

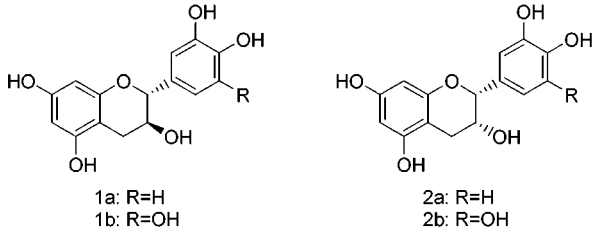
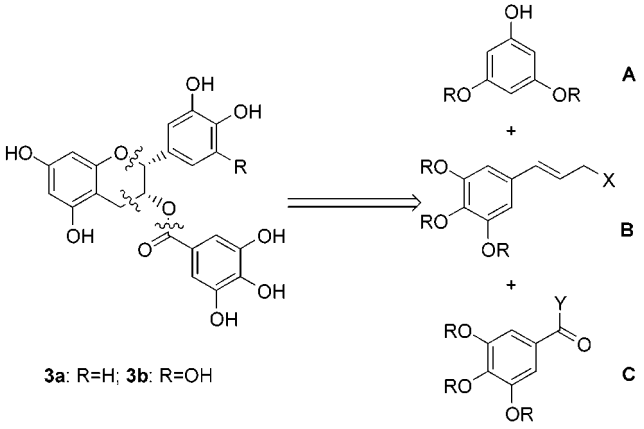


Figure 1.

approach to the total synthesis of (−)-epigallocatechin-3-gallate and its analogues is depicted in Scheme 1. By

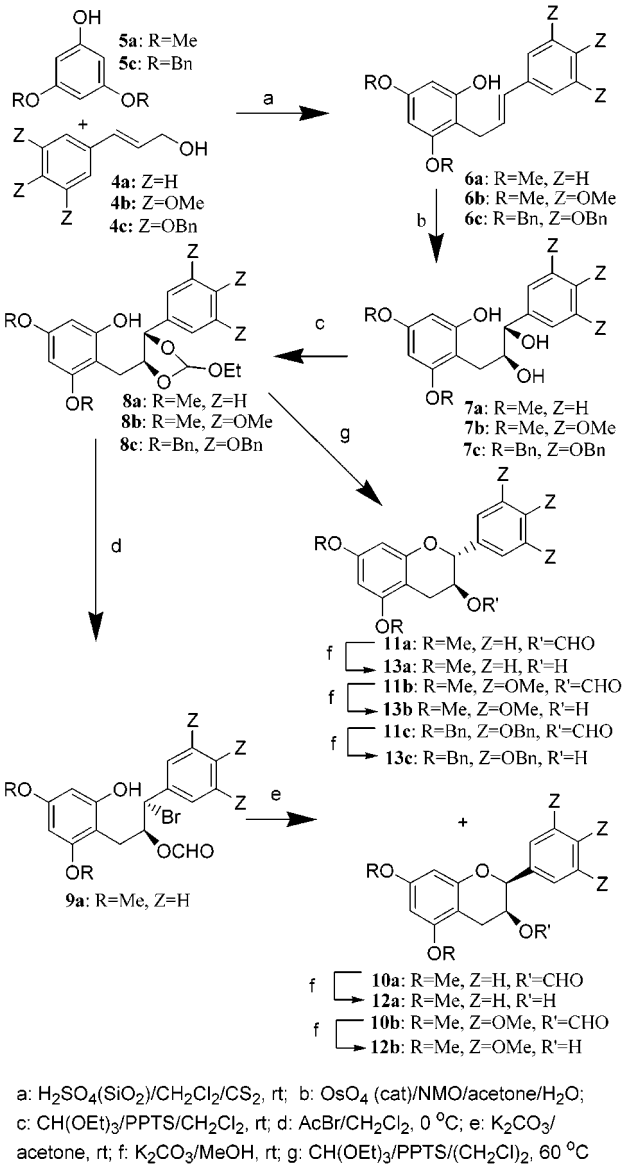
Scheme 1



assembling the structure using the three separate aromatic fragments A, B, and C, the scheme provides a potential route to combinatorial library construction. The challenge resides in the selective formation of the thermodynamically less stable *cis*-disubstituted benzopyran and in the maintenance of stereochemical integrity at the benzylic 2-position, which is activated by the electron-donating oxygen functions on the B phenyl ring.

Coupling of cinnamyl alcohol (**4a**) and 3,5-dimethoxyphenol (**5a**) with H_2SO_4/SiO_2 as catalyst in CS_2/CH_2Cl_2 gave the product **6a** in 55% isolated yield (Scheme 2). Dihydroxylation of **6a** with NMO in the presence of a catalytic amount of OsO_4 to give the diol **7a** was accomplished readily. Conversion of **7a** to the *ortho* ester **8a** was achieved by reaction with triethyl orthoformate in the presence of PPTS in CH_2Cl_2. When **8a** was treated with acetyl bromide, compound **9a** was formed together with minor amounts of its regioisomer. Without purification, the crude **9a** was treated with potassium carbonate in acetone to afford the cyclized benzopyrans **10a** and **11a**. After removal of the formate ester group, compound **12a** was obtained together with its *trans* isomer **13a** in a ratio of 9:1. When the same sequence of reactions was repeated starting from 3,4,5-trimethoxycinnamyl alcohol (**4b**) and **5a**, the cyclization of **9b** followed by removal of the formate group gave instead a mixture of *cis*-**12b** and *trans*-**13b** in a ratio of 1:4, i.e., with the *trans* isomer predominating. This suggested that the activated benzylic position in the methoxy-substituted **9b** could not maintain its stereochemical integrity under these reaction

Scheme 2



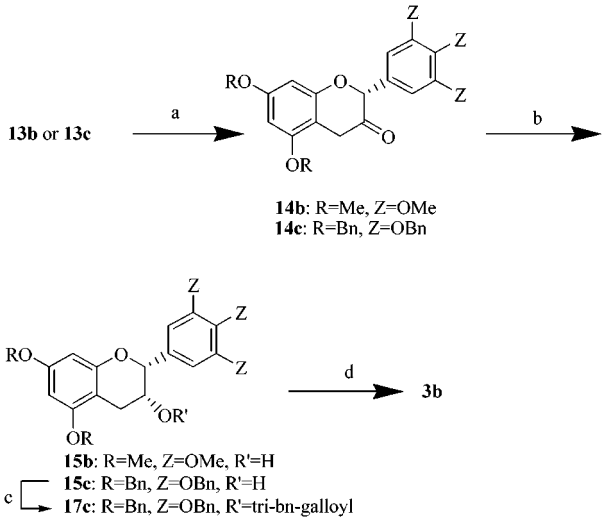
a: $H_2SO_4(SiO_2)/CH_2Cl_2/CS_2$, rt; b: OsO_4 (cat)/NMO/acetone/H_2O; c: $CH(OEt)_3$/PPTS/CH_2Cl_2, rt; d: AcBr/CH_2Cl_2, 0 °C; e: K_2CO_3/acetone, rt; f: K_2CO_3/MeOH, rt; g: $CH(OEt)_3$/PPTS/$(CH_2Cl)_2$, 60 °C

(10) For the syntheses of simpler catechins, see: (a) Keogh, E. J.; Philbin, E. M. *Chem. Ind.* **1961**, 2100. (b) Jain, A. C.; Prabhat, A.; Nayyar, N. K. *Indian J. Chem.* **1983**, *22B*, 1116. (c) van Rensburg, H.; van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron Lett.* **1997**, *38*, 3089. (d) van Rensburg, H.; van Heerden, P. S.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3415. (e) Jew, S.; Kim, H.; Bae, S.; Kim, J.; Park, H. *Tetrahedron Lett.* **2000**, *41*, 7925. (f) Nay, B.; Monti, J.-P.; Nuhrich, A.; Deffieux, G.; Merillon, J.-M.; Vercauteren, J. *Tetrahedron Lett.* **2000**, *41*, 9049.

conditions. We also found that the *ortho* ester **8b** could be cyclized directly to *trans*-**11b** in good yield with PPTS in 1,2-dichloroethane. Methanolic K_2CO_3 treatment of **11b** gave the pentamethylated gallocatechin **13b**.

An alternative approach to the *cis* isomer was therefore sought.[11] Dess−Martin oxidation of **13b** gave the ketone **14b**, which on reduction with L-selectride in THF gave selectively cis-**15b**. We have therefore a route to either diastereoisomer at hand. The removal of the methyl protection proved to be inconvenient. The whole sequence according to Scheme 2 was therefore repeated starting with the coupling of 3,4,5-tris(benzyloxy)cinnamyl alcohol (**4c**) and 3,5-bis(benzyloxy)-phenol (**5c**). In this manner, the pentabenzylated epigallocatechin **15c** was obtained uneventfully. Esterification of **15c** with 3,4,5-tri-*O*-benzylgalloyl chloride (**16**) and DMAP in CH_2Cl_2 gave the ester **17**. Catalytic hydrogenation of **17** with 20% $Pd(OH)_2$ afforded racemic epigallocatechin-3-gallate (**3b**). Preliminary investigations showed that Sharpless asym-

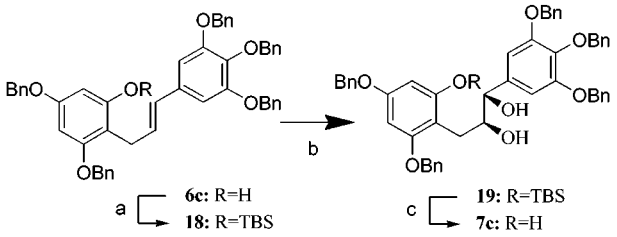
Scheme 3



a: Dess-Martin periodinane/CH_2Cl_2, rt; b: L-Selectride/THF, - 78 °C-rt; c: 3,4,5-tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; d: H_2/$Pd(OH)_2$/MeOH/THF, rt

metric dihydroxylation[12] could not be performed on **6a** directly or on its acetate. However, protection of the free phenolic hydroxyl group as the *tert*-butyldimethylsilyl ether permitted the dihydroxylation to proceed with AD-mix. Compound **6c** was therefore converted to the TBS derivative **18**. Asymmetric dihydroxylations of **18** with either AD-mix-α or -*β* were carried out to give the two enantiomers of **19**. Desilylation of **19** with fluoride gave optically active **7c**. The same sequence of reactions as discussed above was

Scheme 4



a: TBSCl/imidazole/DMF, rt; b: AD-mix-α/CH3SO2NH2/H2O/t-BuOH/ CH2Cl2, 0 oC; c: TBAF/THF,rt

then applied to the enantiomer of **7c** derived from AD-mix-α to give (−)-epigallocatechin-3-gallate ((−)-**3b**), identical in all respects with natural EGCG. The enantiomeric (+)-**3b** obtained with AD-mix-*β* showed the same spectroscopic properties but opposite optical rotation.[13] NMR study of the Mosher ester derivatives of **15c** suggested that the two enantiomers were essentially enantiomerically pure. The overall yield of (−)-**3b**, based on the starting cinnamyl alcohol **4c**, is 19%.

We have therefore accomplished the diastereo- and enantioselective synthesis of EGCG. The approach should be amenable to the synthesis of analogues with diverse substitution patterns in the aromatic rings.

Acknowledgment. We thank Quebepharma Recherche Inc. for financial support of this research.

Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The sequence Dess−Martin oxidation/L-Selectride reduction has previously been applied to the stereochemical inversion at C-3 of 5,7,3′,4′-tetra-*O*-benzylcatechin: Tuckmantel, W.; Kozikowski, A. P.; Romanczyk, L. J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(13) Spectroscopic and optical data of (−)-EGCG: ^{1}H NMR (acetone/D_2O (2:1), 400 MHz) δ 6.96 (s, 2 H), 6.60 (s, 2 H), 5.97 (d, J = 2.4 Hz, 1 H), 5.36 (d, J = 1.2 Hz, 1 H), 4.96 (s, 1 H), 2.94 (dd, J = 17.2, 4.4 Hz, 1 H), 3.10 (dd, J = 17.2, 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 156.6, 156.0, 145.5, 145.2, 138.5, 132.4, 129.9, 120.5, 109.4, 106.1, 98.1, 95.8, 95.0, 77.4, 69.5, 25.9; $[\alpha]_D$ = −148 (c = 1.0, THF). The synthetic compound had completely identical NMR spectra as the commercially available sample (Sigma, $[\alpha]_D$ = −147.6 (c = 1.0, THF)). By using the same synthetic procedures described in the supplementary information, (+)-EGCG ($[\alpha]_D$ = +148.2 (c = 1.0, THF)) and the racemic form of EGCG were also obtained and had identical ^{1}H NMR spectra as the (−)-isomer.