General and Convenient Approach to Flavan-3-ols: Stereoselective Synthesis of (−)-Gallocatechin

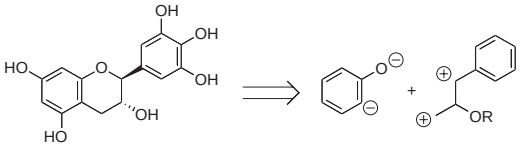
Takashi Higuchi, Ken Ohmori, and Keisuke Suzuki*
Department of Chemistry, Tokyo Institute of Technology, SORST-JST Agency, O-okayama, Meguro-ku, Tokyo 152-8551

(Received June 9, 2006; CL-060668; E-mail: ksuzuki@chem.titech.ac.jp)

General synthetic route to flavan-3-ols was developed. Union of two fragments was accomplished by an efficient three-step protocol, enabling the stereoselective synthesis of (−)-gallocatechin.

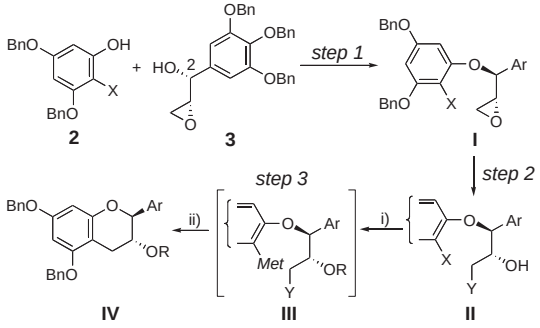
Considerable attention has recently been centered at the potential bioactivities of flavan-3-ols (catechins). However, detailed studies at molecular levels are hampered by their scarce availability of pure samples, because the natural sources are generally comprised of hardly separable mixture of closely related compounds. At this juncture, development of reliable synthetic methods is of keen necessity.[1,2]

We have developed a concise synthetic route to this class of compounds based on the assembly of two fragments for constructing the central pyran ring (Scheme 1). This communication features the generality and the efficiency of the route by the stereoselective synthesis of a highly oxygenated congener, (−)-gallocatechin (**1**).[3]

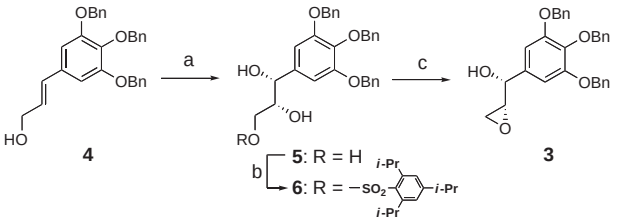


Scheme 1. Retrosynthetic analysis.

Scheme 2 shows three critical steps. Step 1 involves union of two building blocks, **2** and **3**, through the C–O bond formation in an inversion of the C(2) center. The anxiety was loss of the stereochemical integrity, since the electron-rich aromatic ring in **3** could strongly facilitate the S_N1 ionization. Step 2 is the opening of the oxirane ring to the corresponding halohydrin **II**, since consideration of the Baldwin's rule[4] suggested the inadequacy of epoxide **I** as a substrate for the pyran ring closure (6-*endo-tet*).



Scheme 2. Synthetic plan.



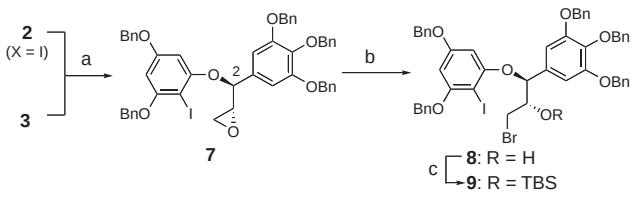
Scheme 3. Conditions: (a) $(DHQD)_2PHAL$ (1 mol %), $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (0.5 mol %), *t*-BuOH, H_2O, $MeSO_2NH_2$, 0 °C, 92%, 99% ee; (b) 2,4,6-triisopropylbenzene-1-sulfonyl chloride, pyridine, rt, 89%; (c) K_2CO_3, MeOH, 1,4-dioxane, 0 °C, 90%; $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether.

Conversely, we hoped that halohydrin **II** would be a good substrate for Step 3, that is, the C–C bond formation to construct the pyran ring (6-*exo-tet*). Two critical processes are relevant, (1) the halogen–metal exchange (X → Met) to generate aryl anion species **III**, (2) displacement to form the pyran ring. The first stage requires the chemoselectivity in that the other halogen Y needs to remain intact.[5,6]

Scheme 3 shows the preparation of epoxide **3**.[7] Asymmetric dihydroxylation of allyl alcohol **4** by using $(DHQD)_2PHAL$[8] as the chiral ligand gave the corresponding triol **5** (92% yield, 99% ee).[9] Selective sulfonylation of the *prim*-hydroxy group in **5**[10] followed by treatment with K_2CO_3 gave epoxide **3** in high yield.

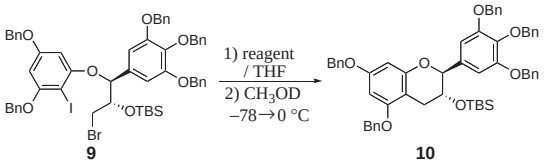
Union of epoxyalcohol **3** with phenol **2** (X = I) posed a stereochemical challenge by the potentially facile loss of stereospecificity (vide supra). Delightedly, however, the Mitsunobu reaction[11] gave us a clean solution to this issue. When epoxyalcohol **3** was allowed to react with Bu_3P and TMAD,[12] ether **7** was obtained in 93% yield as a single diastereomer. Complete inversion of the benzylic stereocenter was proven at a later stage.[13] Oxirane **7** was then regioselectively cleaved by Li_2NiBr_4,[14] giving **8** in 98% yield, and the resulting alcohol was masked with TBS group to afford bromide **9** in 93% yield (Scheme 4).

Faced with the pivotal transformation, i.e., construction of the flavan skeleton from **9**, we examined various reaction condi-



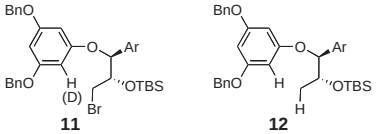
Scheme 4. Conditions: (a) TMAD, *n*-Bu_3P, toluene, 0 °C, 93%. (b) Li_2NiBr_4, THF, 0 °C, 98%; (c) TBSOTf, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 0 °C, 93%; TMAD = *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide, TBS = *t*-butyldimethylsilyl.

Table 1. Cyclizaiton via halogen–metal exchange



9 **10**

Run	Reagent (equiv.)	Additive (equiv.)	Yield/% **10**	**11** (D%)	Recovery of **9**
1	*n*-BuLi (1.0)[a]	—	77	5 (0)	6
2	*t*-BuLi (2.0)[a]	—	53[c]	—	—
3	*i*-PrMgCl (1.2)[b]	—	—	28 (100)	72
4	*n*-Bu_3MgLi (1.2)	—	84	12 (0)	—
5	Ph_3MgLi (1.2)	—	76	14 (86)	—
6	Ph_3MgLi (2.5)	HMPA (10)	96	—	—



11 **12**

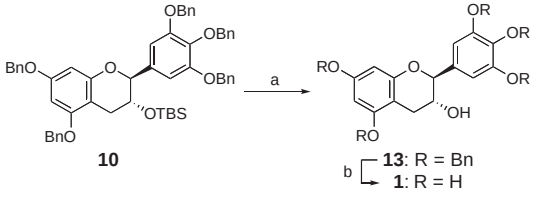
[a]At −78 °C. [b]At −40 °C. [c]13% yield of byproduct **12** was obtained; HMPA = hexamethylphosphoramide.

tions by using alkylmetals for the chemoselective halogen–lithium exchange (Table 1). All the reactions were quenched by adding CH_3OD in order to assess the amount of "living" anionic species.

When *n*-BuLi was employed for the halogen–metal exchange, the cyclized product **10** was obtained in 77% yield along with a small amount of non-cyclized product **11** (Run 1). *t*-BuLi (2.0 equiv.) led to a poorer yield. Among various by-products, compound **12** was obtained, showing that the double lithiation occurred to some extent (Run 2).

Having only limited success with organolithium reagents, we turned our attention to organomagnesium reagents, which gave eventually an excellent result after thorough screening of the reaction conditions. The initial attempt with *i*-PrMgCl[15] only effected slow halogen–metal exchange at −40 °C, and gave no cyclized product (Run 3). Notably, however, the non-cyclized product **11** was completely deuterated, showing that the aryl anion species was still present before the quenching. Further attempts allowed us to find that the use of the Mg ate complexes[16] improved the yield of **10** (Runs 4 and 5). Although the yields of **10** were similar, an important difference in these results was the extent of deuterium incorporation in **11**. Namely, **11** was highly deuterated in the case of Ph_3MgLi (Run 5), while no deuterium atom was incorporated in the case of *n*-Bu_3MgLi (Run 4). Thus, we chose to use Ph_3MgLi as the metalation agent.

Upon further experimentations, choice of an additive offered us the optimal conditions for obtaining the cyclized product **10** exclusively. Thus, upon addition of **9** into a mixture of 2.5 mole equiv. of Ph_3MgLi and 10 mole equiv. of HMPA in THF, the desired product **10** was obtained in 96% yield (Run 6).[17]



10

Scheme 5. Conditions: (a) *n*-Bu_4NF, THF, 0 °C, 87%; (b) H_2, $Pd(OH)_2$, THF, MeOH, H_2O (4:4:1), rt., 82%.

Scheme 5 shows the final stage of the synthesis. After removal of the silyl group in **10**, all the benzyl protecting groups in the resulting alcohol **13** were removed by hydrogenolysis over 20% $Pd(OH)_2$ in a mixed solvent (THF, MeOH, H_2O = 4:4:1) for 12 h to give (−)-gallocatechin (**1**) as an amorphous solid in 82% yield. All the physical data of the synthetic sample **1** (^1H and ^{13}C NMR, IR, $[\alpha]_D$) coincided with those of the natural product.[3]

In summary, a convergent, stereoselective synthesis of (−)-gallocatechin (**1**) was achieved, which opened a flexible synthetic approach to various flavan analogs.

This work was partially supported by a Grant-in-Aid for Scientific Research (No. 17685007) from MEXT, Japan, Kurata Memorial Hitachi Science and Technology Foundation, and 21st Century COE Program (Chemistry).

References and Notes

1 a) *The Handbook of Natural Flavonoids*, ed. by J. B. Harborne, H. Baxter, Wiley, Chichester, **1999**. b) D. Ferreira, D. Slade, *Nat. Prod. Rep.* **2002**, *19*, 517.
2 a) L. Li, T. H. Chan, *Org. Lett.* **2001**, *3*, 739. b) N. T. Zaveri, *Org. Lett.* **2001**, *3*, 843. c) 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.
3 R. Seto, H. Nakamura, F. Nanjo, Y. Hara, *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1434.
4 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.
5 Chemoselective halogen–metal exchange of aryl bromide in the presence of aliphatic bromide has appeared: C. K. Bradsher, D. C. Reames, *J. Org. Chem.* **1981**, *46*, 1384.
6 A similar approach was used in the simpler chroman synthesis: a) K. J. Hodgetts, *Tetrahedron Lett.* **2000**, *41*, 8655. b) K. J. Hodgetts, *Tetrahedron* **2005**, *61*, 6860.
7 Epoxyalcohol **3** was prepared by the Ren's protocol: X. Ren, X. Chen, K. Peng, X. Xie, Y. Xia, X. Pan, *Tetrahedron: Asymmetry* **2002**, *13*, 1799. See, also Supporting Information.
8 K. B. Sharpless, W. Amberg, Y. L. Bennni, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu, X. L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768.
9 Enantiomeric purity of **5** was assessed by HPLC analysis. See Supporting Information.
10 Tosyl chloride gave a mixture of mono-/di-sulfonylated products.
11 O. Mitsunobu, *Synthesis* **1981**, 1.
12 T. Tsunoda, J. Otsuka, Y. Yamamiya, S. Ito, *Chem. Lett.* **1994**, 539.
13 The relative stereochemistry of C(2) and C(3) stereogenic centers was assigned by NMR analysis after conversion to cyclized product **10** ($J_{2,3}$ = 8.4 Hz).
14 R. D. Dawe, T. F. Molinski, J. V. Turner, *Tetrahedron Lett.* **1984**, *25*, 2061.
15 F. F. Kneisel, Y. Monguchi, K. M. Knapp, H. Zipse, P. Knochel, *Tetrahedron Lett.* **2002**, *43*, 4875.
16 a) K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. b) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333.
17 The amount of Ph_3MgLi was important. For example, use in 1.2 equimolar amounts gave only 36% yield of **10** with recovery of **9** in 62% yield.

Published on the web (Advance View) July 29, 2006; doi:10.1246/cl.2006.1006