ORGANIC LETTERS

2009
Vol. 11, No. 11
2233−2236

Concise Synthesis of Chafurosides A and B

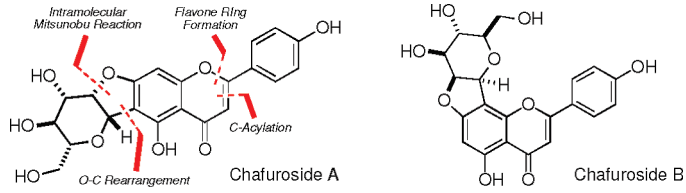
Takumi Furuta,† Miho Nakayama, Hirotaka Suzuki, Hiroko Tajimi, Makoto Inai, Haruo Nukaya, Toshiyuki Wakimoto,* and Toshiyuki Kan*

School of Pharmaceutical Sciences, University of Shizuoka and Global COE Program, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

wakimoto@u-shizuoka-ken.ac.jp; kant@u-shizuoka-ken.ac.jp

Received March 2, 2009

ABSTRACT



The regioselective synthesis of chafurosides A (1) and B (2) from the same methyl ketone 5 was accomplished using a novel protecting group strategy. Both flavone rings were constructed from β-diketone intermediate 4, which was readily obtained by condensation of an acyl donor and ketone 5. Construction of the dihydrofuran ring was achieved via an intramolecular Mitsunobu reaction.

Oolong tea extract exhibits a suppressive effect for type I and IV reactions related to atopic dermatitis.[1] A novel flavone *C*-glycoside, chafuroside A (**1**),[2] which displays potent inhibitory activity against DNFB (2,4-dinitrofluorobenzene) induced contact hypersensitivity in mice, at a concentration of 1.0−10 μg/kg, has been isolated as the active ingredient. Flavonoids typically exhibit moderate anti-inflammatory activity, but **1** shows significantly potent anti-inflammatory activity compared to other flavonoids, including isovitexin, vitexin, and apigenin.[3] Although oolong tea has a particularly high content of **1**, the compound provided by the natural source is not enough for further study of its biological functions.

Due to the remarkable bioactivity of **1** and the regioisomeric skeleton of newly isolated chafuroside B (**2**)[4] composed of a dihydrofuran ring between the 2′ and 7-OH and a *C*-glycoside bond at the C8 position, efficient total syntheses of **1** and **2** are highly desired. Because **1** and **2** possess similar skeleta, an efficient synthetic method for construction of the flavone ring should be a key step for the synthesis of these minor nutritional ingredients. Since we could not achieve efficient formation of the flavone ring in the previous study in 2004,[5] we have continuously made efforts to develop an efficient synthetic method for obtaining the flavone ring[6] and we succeeded in applying a new protocol in the second generation of total synthesis of **1** and

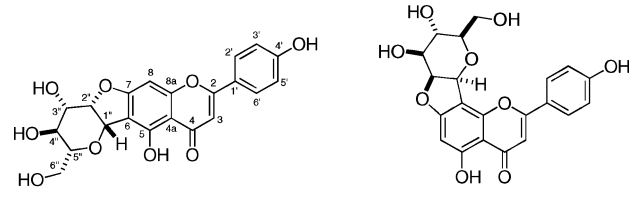


Figure 1. Structures of **1** and **2**.[7]

† Present Address: Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan.

(1) Uehara, M.; Sugiura, H.; Sakurai, K. *Arch. Dermatol.* **2001**, *137*, 42.

(2) Ishikura, Y.; Tsuji, K.; Nukaya, H. *Jpn. Kokai Tokkyo Koho* **2002**, 194828.

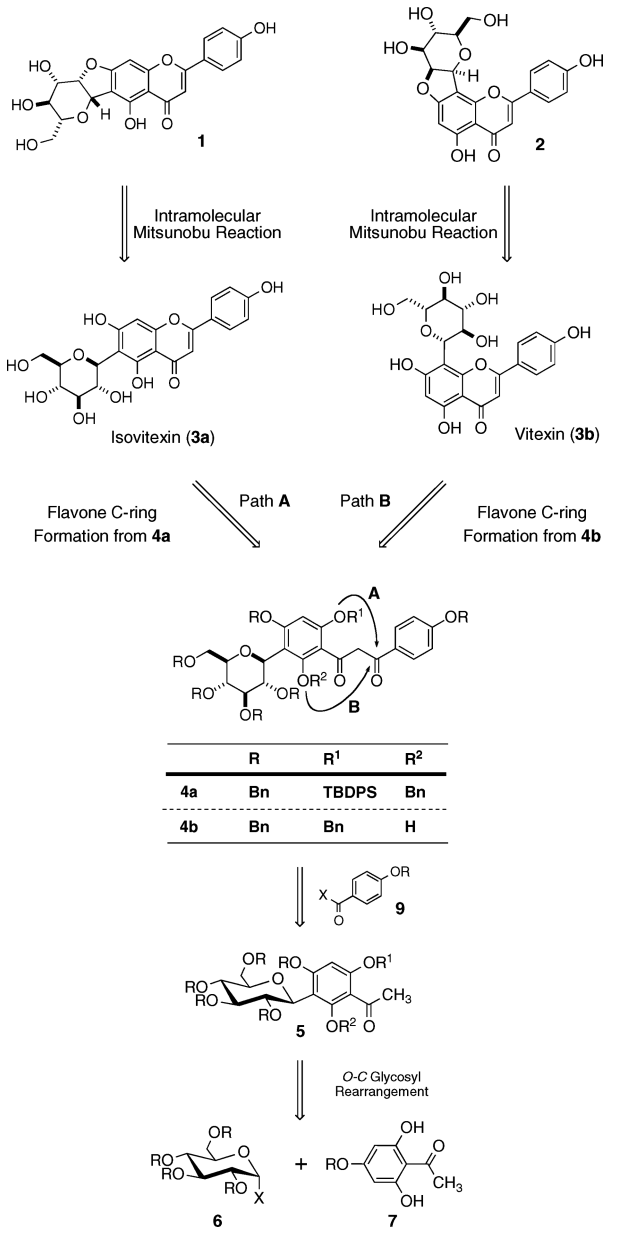
(3) (a) Whiting, D. A. *Nat. Prod. Rep.* **2001**, *18*, 583. (b) Marinova, K.; Kleinschmidt, K.; Weissenböck, G.; Klein, M. *Plant Physiol.* **2007**, *144*, 432.

(4) Detailed data of isolation and structure elucidation of chafuroside B are described in Supporting Information sections II and III.

10.1021/ol900689m CCC: $40.75
Published on Web 04/27/2009

2. Herein we report the details of these synthetic investigations.

Scheme 1. Retrosynthetic Analysis of **1** and **2**



Scheme 1 illustrates our synthetic plan. According to our previous synthetic investigation of **1**,[5a] the dihydrofuran ring of **1** and **2** could be constructed by Mitsunobu conditions[8] at a late stage in the synthesis. Thus, the crucial step in the syntheses of **1** and **2** would be regioselective construction of isovitexin (**3a**) and vitexin (**3b**). Because the conversion of the flavone ring from a β-diketone intermediate has been reported,[9,10] **3a** and **3b** could be derived from appropriately protected **4a** and **4b**, respectively.[11] To construct β-diketone **4**, an alkylation reaction between acyl donor equivalent **9** and methyl ketone **5** would be suitable because *C*-glycoside **5** is readily available from *O*-glycosidation and a subsequent *O*−*C* rearrangement between glucosyl imidate **6** and an acetophenone derivative **7**.[12]

As shown in Scheme 2, the synthesis of chafuroside A (**1**) began from tetra-*O*-benzyl-D-glucosyl imidate (**6**)[12a] and acetophenone derivative **7**, which was synthesized according to Cairns' method.[13] Upon treatment of **6** and **7** with TMSOTf, *O*-glycosidation and successive *O*−*C* rearrangement (Fries rearrangement)[14] proceeded smoothly to give an aryl *C*-glucoside **5**. In this reaction, *O*-glucoside **8** was detected by terminating the reaction after a short time.[12] Because of the different reactivity for each phenolic hydroxyl group of **5**, various protecting groups were incorporated in a stepwise manner.[15] The less hindered **8a**-OH of **5** was selectively protected by treatment with TBDPSCl and imidazole to give mono-TBDPS ether. The reactivity of the remaining free phenol was low due to hydrogen bonding with the neighboring carbonyl group as well as steric hindrance from both substituents at the *ortho* positions. After several attempts to protect the phenol,[15] we found that the Mitsunobu conditions were suitable for alkylation of the remaining phenol. Thus, treatment of the phenol with benzyl alcohol

(5) (a) Furuta, T.; Kimura, T.; Kondo, S.; Mihara, H.; Wakimoto, T.; Nukaya, H.; Tsuji, K.; Tanaka, K. *Tetrahedron* **2004**, *60*, 9375. (b) Nakatsuka, T.; Tomimori, Y.; Fukuda, Y.; Nukaya, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3201. (c) Kan, T.; Furuta, T. *Jpn. Kokai Tokkyo Koho* **2008**, 13.

(6) 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.

(7) Numbering for **1** and **2** was according to flavone style.

(8) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

(9) Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 2192.

(10) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767. (c) von Kostanecki, S.; Rózycki, A. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 102.

(11) While preparing this manuscript, a similar strategy for ring formation of prenylflavones has been reported. In their method, a prenyl group and protecting group such as TBS and Pivaloyl groups were regioselectively introduced on the flavone A ring: Minassi, A.; Giana, A.; Ech-Chahad, A.; Appendino, G. *Org. Lett.* **2008**, *10*, 2267.

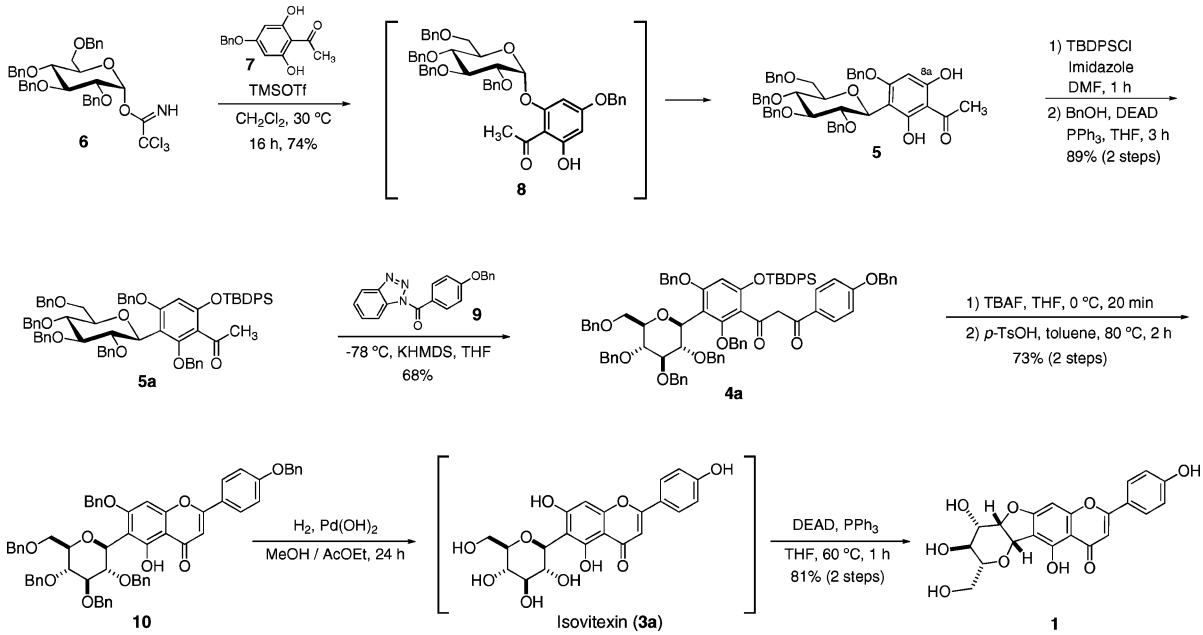
(12) For the synthesis of flavone glycosides, see: (a) Mahling, J.-A.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 461. (b) Mahling, J.-A.; Schmidt, R. R. *Synthesis* **1993**, 325. (c) Ohmori, K.; Hatakeyama, K.; Ohrui, H.; Suzuki, K. *Tetrahedron* **2004**, *60*, 1365. (d) Oyama, K.; Kawaguchi, S.; Yoshida, K.; Kondo, T. *Tetrahedron. Lett.* **2007**, *48*, 6005. (e) Seijas, J. A.; Vàzquez-Tato, M. P.; Carballido-Reboredo, R. *J. Org. Chem.* **2005**, *70*, 2855. (g) Li, M.; Han, X.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6842. (h) Urgaonkar, S.; Shaw, J. T. *J. Org. Chem.* **2007**, *72*, 4582. (i) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149. (j) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 1097. (k) Du, Y.; Wei, G.; Linhardt, R. J. *Tetrahedron Lett.* **2003**, *44*, 6887. (l) Zhu, C.; Peng, W.; Li, Y.; Han, X.; Yu, B. *Carbohydr. Res.* **2006**, *341*, 1047. (n) Sato, S.; Akiya, T.; Suzuki, T.; Onodera, J. *Carbohydr. Res.* **2004**, *339*, 2611. (m) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240. (o) Chen, Z.; Hu, Y.; Wu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3949.

(13) Cairns, H. *Tetrahedron* **1972**, *28*, 359. Phloroglucinol was acetylated with a boron trifluoride-acetic acid complex to afford *C*-diacetylphloroglucinol. Subsequent benzylation with BnBr and K_2CO_3 resulted in monobenzylation. Then hydrolysis of an acetyl group with 1 M NaOH gave desired acetophenone derivative **7**. For experimental details, see Supporting Information section IV.

(14) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935.

(15) To protect the remaining free phenol, allyl bromide was tentatively selected as the smaller protective group due to the expected steric hindrance of this phenol group. However, using a strong base such as NaH or LiHMDS removed the TBDPS group. On the other hand, conditions with a milder base such as K_2CO_3 did not result in a reaction. Subsequently, the desired compound was afforded in high yield using Mitsunobu conditions, which served as neutral protecting conditions using an allyl alcohol, PPh_3, and DEAD. This method was also applicable to benzyl alcohol.

Scheme 2. Synthesis of Chafuroside A (**1**)

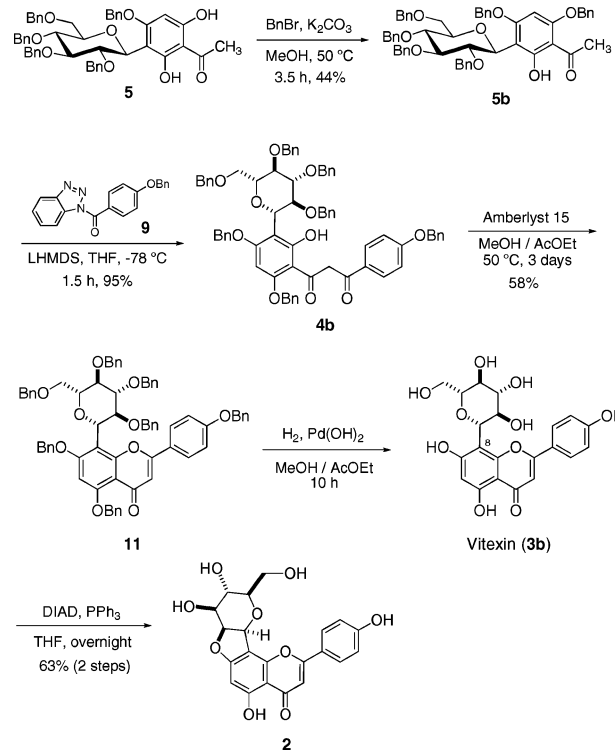


in the presence of PPh_3 and DEAD proceeded smoothly, and the protection reaction gave key intermediate **5a**. For the acyl donor unit, we selected a 1-acylbenzotriazole **9**[16] due to its stability under several conditions. Upon treatment of **5a** and **9** using KHMDS, the desired acylation reaction predominantly produced desired β-diketone **4a**. Treatment with TBAF removed the TBDPS group. Sequential cyclization and dehydration were performed by heating in toluene with *p*-TsOH to afford selectively protected isovitexin derivative **10**. Although a concomitant deprotection of benzyl group at 5-OH occurred during the cyclization reaction,[12h] the ring closure product with a hindered phenol such as the vitexin type was not detected in this step. Removal of the benzyl groups of **10** was carried out by hydrogenolysis conditions to provide the isovitexin **3a** in good yield. The critical dihydrobenzofuran ring was formed by the Mitsunobu reaction. Upon treatment of **3a** with DEAD and PPh_3, the desired ring was successfully formed, and **1** was afforded in 81% yield in two steps. Furthermore, intermolecular reactions and/or polymerized products were not observed even if free alcohol compound **3a** was employed (Scheme 2).

Next, we focused on the selective synthesis of chafuroside B (**2**) (Scheme 3). After selective protection of the reactive phenol of **5** as a benzyl group, **5b** was subjected to acylation with 1-acylbenzotriazole **9**. Upon treatment of **5b** and **9** with KHMDS, the acylation reaction afforded desired β-diketone **4b** in 95% yield, even with the free hydroxyl group in **5b**. The ring closing reaction of β-diketone **4b** was performed under acidic conditions with TsOH as well as Amberlyst 15 to give flavone **11**. In this reaction, the benzyl ether at C-5 was not affected by *p*-TsOH. Subsequently, removal of the benzyl groups followed by a Mitsunobu reaction of vitexin (**3b**) afforded **2** in 63% yield.

Thus, we accomplished the regioselective synthesis of **1** and **2** with 6- and 8-*C*-glycoside bonds, respectively.

Scheme 3. Synthesis of Chafuroside B (**2**)



(16) (a) Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W.-Q. *Tetrahedron* **1992**, *48*, 7817. (b) Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679.

The synthesis employs a β-diketone intermediate, which can be readily obtained by selective protection of **1** and **2**. Consequently, we developed a seven step sequence to **1** beginning from aryl-*C*-glycoside (**5**) in 32% overall yield. Moreover, newly identified **2** could be synthesized in 13% yield in five steps from **5**, and its stereochemistry was confirmed. Furthermore, considering the compatibility of this synthesis with a variety of functional groups, our synthetic strategy should be applicable to various flavone derivatives. Further synthetic investigation and biological evaluation of **1** and **2** are currently under investigation in our laboratory.

Acknowledgment. This work was financially supported by Takeda Science Foundation, Naito Foundation, Nagase Science and Technology Foundation, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supporting Information Available: General procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900689M