doi:10.1246/cl.2011.324

Published on the web February 23, 2011

Efficient Synthesis of a Bisglycosyl Kaempferol from *Fagonia taeckholmiana*

Qingchao Liu,*[1] Wenhong Li,[1] Tiantian Guo,[2] Dong Li,[1] Zhen Fan,[1] and Suihong Yan[1]
[1]*Department of Pharmaceutical Engineering, Northwest University, Xi'an 710069, Shaanxi, P. R. China*
[2]*Department of Medical Science, Xi'an Creation College, Yanan University, Xi'an 710100, Shaanxi, P. R. China*

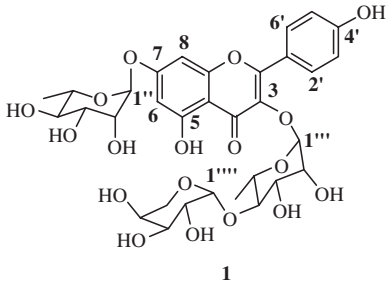
(Received November 29, 2010; CL-101008; E-mail: liuqc21@nwu.edu.cn)

The first total synthesis of kaempferol-3-*O*-β-L-arabinopyranosyl-(1→4)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**1**), a 3,7-triglycosylflavone, which was isolated from the aerial parts of *Fagonia taeckholmiana*, was accomplished in 13 steps and 9.2% overall yield from commercially available kaempferol. We efficiently employed phase-transfer-catalyzed (PTC) glycosylation for the construction of phenol glycosides. Applying this approach will allow the preparation of derivatives for further study of structure–activity relationships (SAR).

Glycosylated flavonoids are a specific class of natural products widely distributed in the plant kingdom, which consist of a flavonol skeleton bearing one or more sugar chains.[1–4] They exhibit a wide range of biological activities such as protection against UV light,[5] flower color development,[6] insect stimulants,[7] and more interestingly, present a variety of medicinal properties which might be beneficial to humans, including anticancer,[8,9] antimicrobial,[10] anti-inflammatory,[11] inhibitors against influenza virus sialidase,[12] radical scavenging,[1,2] hepatoprotectant,[13] antidiabetic,[14] neuroprotective,[15] and inhibition of HIV reverse transcriptase and DNA topoisomerase I.[16] In contrast to the widespread distribution and important biological activities of glycosylated flavonoids, access to this class of natural products via facile chemical synthesis presents a formidable task. The major bottleneck to the synthesis of flavonoid glycosides are the poor solubility of most flavonoids in common organic solvents and the lack of sophisticated protecting-group strategies. Despite the considerable attention to synthesis of monoglycosyl flavones has attracted in the last decade,[9,17–25] preparation of bisglycosyl flavones has been scarcely reported to date.[26–30]

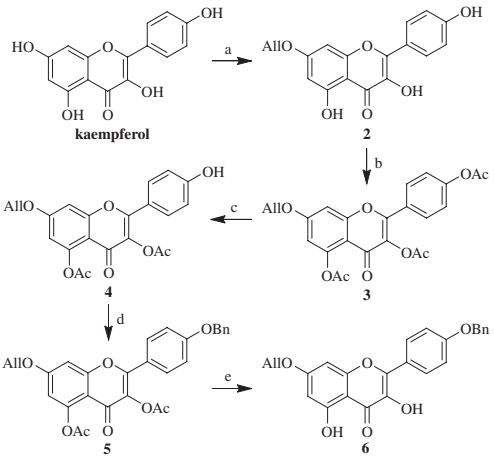
Recently, kaempferol-3-*O*-β-L-arabinopyranosyl-(1→4)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**1**), a 3,7-triglycosylflavone (Figure 1), was isolated from the aerial parts of *Fagonia taeckholmiana*. The cytotoxic activity of the alcohol and water extracts including bisglycosyl kaempferol **1** against MCF7 human breast tumor cells in culture exhibited an IC_{50} of 8.72 and 9.80 $\mu g\,mL^{-1}$, respectively.[31] Bisglycosyl kaempferol **1** may be one of the major active components of *Fagonia taeckholmiana*, yet the difficulties in obtaining compound **1** (12 mg from 2 kg of the dried powdered plant) have hindered further pharmacological studies, so chemical synthesis is needed and appears to be a rational way to gain access to adequate amounts for thorough pharmacological research and further SAR investigation. We report here the first total synthesis of this natural product.

We envisioned that bisglycosyl kaempferol **1** could be constructed from the suitably protected 7,4′-dihydroxyflavone **6**, a disaccharide donor **12**, and easily prepared rhamnopyranosyl donor **14**. As shown in Scheme 1, our synthetic approach to **6** commenced with the commercially available kaempferol, which



1

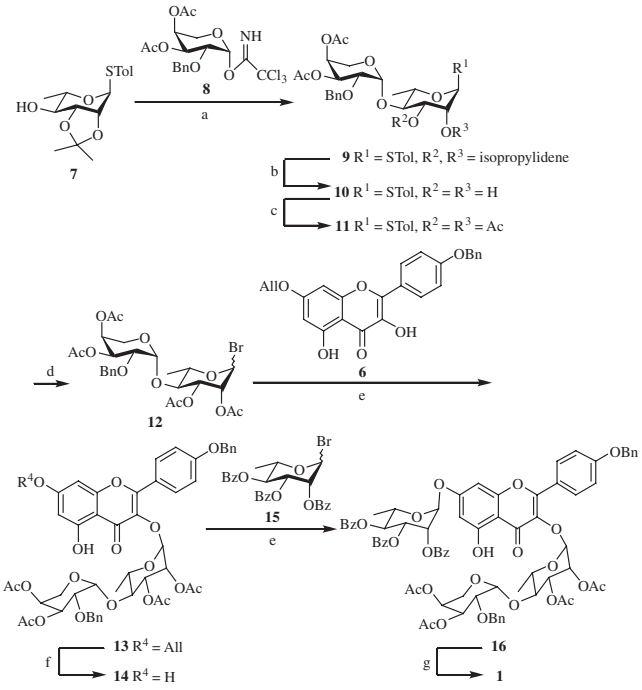
Figure 1. Chemical structure of bisglycosyl kaempferol **1**.



Scheme 1. Synthesis of acceptor **5**. Reagents and conditions: (a) allyl bromide (AllBr), TBAB, K_2CO_3, DMF–H_2O (v:v, 1:1), 50 °C, 69%; (b) Ac_2O, pyridine, 89%; (c) PhSH, imidazole, NMP, −20 °C, 85%; (d) BnBr, K_2CO_3, KI, DMF, 71%; (f) 10% aq NaOH, MeOH, reflux, 100%.

was treated with allyl bromide under PTC (phase-transfer-catalyzed) conditions, namely, in the presence of tetrabutylammonium bromide (TBAB) and K_2CO_3 in 1:1 DMF–H_2O at 50 °C, affording 7-*O*-allylkaempferol (**2**) in 69% yield.[25] Observing the NOE correlation between H-6 or H-8 and the allyl OCH_2 protons in compound **2** confirmed the position of the allylation. Acetylation of **2** with acetic anhydride in pyridine then provided 7-*O*-allylkaempferol triacetate (**3**) in 89% yield. With the 7-OH being blocked with an allyl group, compound **3**, upon treatment with PhSH and imidazole in *N*-methylpyrrolidone (NMP) at low temperature (−20 °C), gave the free 4′-OH product **4** in high selectivity (85%).[19] Finally benzylation of the 4′-OH followed by removal of the remaining 3- and 5-*O*-acetyl groups provided 4′-*O*-benzyl-7-*O*-allylkaempferol (**6**) conveniently.

Disaccharide bromide **12** was prepared through conventional glycosylation and protecting group manipulation. As



Scheme 2. Synthesis of target compound **1**. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, −78 °C, 79%; (b) 80% AcOH, reflux, 87%; (c) Ac_2O, pyridine, 90%; (d) Br_2, CH_2Cl_2, 0 °C, 85%; (e) K_2CO_3, TBAB, $CHCl_3$–H_2O, 50 °C, 79% for **13**; 80% for **16**; (f) $PdCl_2$, MeOH, 87%; (g) H_2, 10% Pd–C, EtOH–EtOAc, 40 °C; NaOMe, MeOH–CH_2Cl_2, rt, 86% for two steps.

depicted in Scheme 2, coupling of *p*-tolyl 2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (**7**)[32] with 2-*O*-benzyl-3,4-di-*O*-acetyl-β-L-alabinopyranosyl trichloroacetimidate (**8**)[33] under the promotion of TMSOTf stereoselectively provided disaccharide **9** in 79% yield. The isopropylidene of **9** was readily cleaved using 80% HOAc at 80 °C, and the free hydroxy groups were then acetylated with acetic anhydride in pyridine affording **11**. Finally, bromination of the anomeric position using elemental bromine at 0 °C gave disaccharide bromide **12** in 85% yield.

With efficient synthetic access to 4′-*O*-benzyl-7-*O*-allyl-kaempferol (**6**) and disaccharide bromide **12**, we next turned our attention to the synthesis of natural product **1** via PTC glycosylation, which was used for flavonoid glycosides by Li et al. and Du et al.[17,18,26] Treatment of diol **6** with disaccharide bromide **12** under PTC conditions regioselectively provided the desired 3-*O*-β-glycoside **13** in 79% isolation yield. After deprotection of the allyl group with $PdCl_2$, similar PTC conditions described above were employed for the coupling of diol **14** with easily prepared rhamnopyranosyl bromide **15**, affording the corresponding 7,4′-diglycoside **16** in a satisfactory 80% yield. Finally, removal of the benzyl group (H_2, 10% Pd–C) and all acyl groups (NaOMe) cleanly furnished the target kaempferol glycoside **1** in 86% yield,[34] whose analytical data are identical in all respects to those reported in the literature.[31]

In conclusion, we succeeded in the first total synthesis of bisglycosyl kaempferol **1** from commercially available kaempferol in 13 steps and 9.2% overall yield. The PTC glycosylation strategy proved to be very efficient for the construction of phenol glycosides. Further study on preparation and bioactivity evaluation of analogs and derivatives is in progress and will be reported in due course.

This work was financially supported by the Scientific Research Foundation of Northwest University (No. PR10035).

References and Notes

1 B. A. Bohm, *Introduction to Flavonoids: Chemistry and Biochemistry of Organic Natural Products*, Harwood Academic Publishers, Amsterdam, **1998**.
2 *The Handbook of Natural Flavonoids*, ed. by J. B. Harborne, H. Baxter, John Wiley & Sons, Chichester, **1999**, Vol. 1.
3 J. B. Harborne, C. A. Williams, *Nat. Prod. Rep.* **2001**, *18*, 310.
4 N. C. Veitch, R. J. Grayer, *Nat. Prod. Rep.* **2008**, *25*, 555.
5 M. Mori, K. Yoshida, Y. Ishigaki, T. Matsunaga, O. Nikaido, K. Kameda, T. Kondo, *Bioorg. Med. Chem.* **2005**, *13*, 2015.
6 Ø. M. Andersen, M. Jordheim, in *Flavonoids: Chemistry, Biochemistry and Applications*, ed. by Ø. M. Andersen, K. R. Markham, CRC Press, Boca Raton, **2006**, pp. 471–551.
7 P. Feeny, K. Sachdev, L. Rosenberry, M. Carter, *Phytochemistry* **1988**, *27*, 3439.
8 J. A. Smith, C. E. Poteet-Smith, Y. Xu, T. M. Errington, S. M. Hecht, D. A. Lannigan, *Cancer Res.* **2005**, *65*, 1027.
9 J. A. Smith, D. J. Maloney, S. M. Hecht, D. A. Lannigan, *Bioorg. Med. Chem.* **2007**, *15*, 5018.
10 M. M. Cowan, *Clin. Microbiol. Rev.* **1999**, *12*, 564.
11 K. Marinova, K. Kleinschmidt, G. Weissenböck, M. Klein, *Plant Physiol.* **2007**, *144*, 432.
12 T. Nagai, Y. Miyaichi, T. Tomimori, Y. Suzuki, H. Yamada, *Chem. Pharm. Bull.* **1990**, *38*, 1329.
13 A. S. Awaad, D. J. Maitland, G. A. Soliman, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4624.
14 A. P. Jorge, H. Horst, E. de Sousa, M. G. Pizzolatti, F. R. M. B. Silva, *Chem. Biol. Interact.* **2004**, *149*, 89.
15 S. H. Kim, C. N. Kumar, H. J. Kim, D. H. Kim, J. Cho, C. Jin, Y. S. Lee, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6009.
16 J. Ma, S. H. Jones, R. Marshall, X. Wu, S. M. Hecht, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 813.
17 M. Li, X. W. Han, B. Yu, *Tetrahedron Lett.* **2002**, *43*, 9467.
18 Y. Du, G. Wei, R. J. Linhardt, *J. Org. Chem.* **2004**, *69*, 2206.
19 W. Peng, Y. Li, C. Zhu, X. Han, B. Yu, *Carbohydr. Res.* **2005**, *340*, 1682.
20 J. A. Smith, D. J. Maloney, D. E. Clark, Y. M. Xu, S. M. Hecht, D. A. Lannigan, *Bioorg. Med. Chem.* **2006**, *14*, 6034.
21 S. T. Caldwell, H. M. Petersson, L. J. Farrugia, W. Mullen, A. Crozier, R. C. Hartley, *Tetrahedron* **2006**, *62*, 7257.
22 M. D. Shan, G. A. O'Doherty, *Org. Lett.* **2006**, *8*, 5149.
23 K. Oyama, S. Kawaguchi, K. Yoshida, T. Kondo, *Tetrahedron Lett.* **2007**, *48*, 6005.
24 W. Yang, J. Sun, W. Lu, Y. Li, L. Shan, W. Han, W.-D. Zhang, B. Yu, *J. Org. Chem.* **2010**, *75*, 6879.
25 L. Zhang, G. Wei, Y. Du, *Carbohydr. Res.* **2010**, *345*, 2714.
26 Y. Du, G. Wei, R. J. Linhardt, *Tetrahedron Lett.* **2003**, *44*, 6887.
27 C. Zhu, W. Peng, Y. Li, X. Han, B. Yu, *Carbohydr. Res.* **2006**, *341*, 1047.
28 S. Urgaonkar, J. T. Shaw, *J. Org. Chem.* **2007**, *72*, 4582.
29 Q. Gao, G. Lian, F. Lin, *Carbohydr. Res.* **2009**, *344*, 511.
30 J. Chen, W. Huang, G. Lian, F. Lin, *Carbohydr. Res.* **2009**, *344*, 2245.
31 L. F. Ibrahim, S. A. Kawashty, A. M. El-Hagrassy, M. I. Nassar, T. J. Mabry, *Carbohydr. Res.* **2008**, *343*, 155.
32 Z. Zhang, P. Wang, N. Ding, G. Song, Y. Li, *Carbohydr. Res.* **2007**, *342*, 1159.
33 For the synthesis of donor **8**, see ref. 34.
34 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

