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Efficient synthesis of kaempferol 3,7-*O*-bisglycosides via successive glycosylation with glycosyl *ortho*-alkynylbenzoates and trifluoroacetimidates

Weizhun Yang [a,b], Jiansong Sun [b,*], Zhongyi Yang [b], Wei Han [a,*], Wei-Dong Zhang [c], Biao Yu [b,*]

[a] School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China
[b] State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[c] Department of Phytochemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, China

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ABSTRACT

Selective glycosylation of the 3-OH of 5,4′-di-*O*-acetyl-kaempferol was achieved with glycosyl *ortho*-alkynylbenzoates as donors under the catalysis of $Ph_3PAuNTf_2$, and subsequent glycosylation of the remaining 7-OH with glycosyl trifluoroacetimidates under the catalysis of $BF_3{\cdot}OEt_2$, after global deprotection, afforded the kaempferol 3,7-*O*-bisglycosides conveniently.

As a major type of the flavonol *O*-glycosides, over 450 of the kaempferol glycosides have been identified from plant kingdom; many of them have their saccharide residues attached at the 3,7-OH.[1] Kaempferol 3,7-*O*-bisglycosides have shown a broad spectrum of bioactivities, including antioxidant,[2] antifungal,[3] glucosidase inhibition,[4] antitumor,[5] and hypoglycemic activities.[6] However, there are only two reports on the synthesis of kaempferol 3,7-*O*-bisglycosides,[7–9] both employing the glycosylation method with glycosyl bromides as donors and silver salt or potassium carbonate as promoter. For the synthesis of kaempferol 3,7-*O*-bisglycosides flanked with different saccharide residues, tedious protecting groups manipulation was required to differentiate these two hydroxyl groups prior to each glycosylation.[8] Herein, we report a concise approach to synthesize kaempferol 3,7-*O*-bisglycosides, taking advantage of a selective glycosylation of the 3-OH of 5,4′-di-*O*-acetyl-kaempferol with glycosyl *ortho*-alkynylbenzoates as donors under the catalysis of $Ph_3PAuNTf_2$.

We have recently found that glycosyl *ortho*-alkynylbenzoates could be effectively applied to glycosylate the 3-OH of 5,7,4′-tri-*O*-benzyl-kaempferol.[10,11] However, attempts at glycosylation of the 7-OH of kaempferol or quercetin derivatives under similar conditions were not successful. It is known that the 7-OH in flavonol derivatives is deactivated due to its *para* position to the electron-withdrawing 4-carbonyl group.[12] These results prompted us to examine the feasibility of a selective glycosylation of the kaempferol 3-OH in the presence of the free 7-OH with glycosyl *ortho*-alkynylbenzoates as donors.

The required 5,4′-di-*O*-acetyl-kaempferol (**2**) was synthesized as shown in Scheme 1. Thus, treatment of the commercially available kaempferol with BnBr (2.1 equiv) and K_2CO_3 (2.5 equiv) led to 3,7-di-*O*-benzyl-kaempferol (**1**)[11] in 40% yield. Although the yield is moderate, this transformation can be easily scaled up to provide **1** in grams quantity. The free 4′,5-OHs in **1** were then blocked with acetyl groups, and the two benzyl groups were removed via hydrogenolysis (H_2, Pd/C) to furnish the kaempferol derivative **2** in high yield (80% for two steps).

Perbenzoyl glucopyranosyl *o*-hexynylbenzoate **3a** (1.5 equiv to **2**) was applied first to couple with 5,4′-di-*O*-acetyl-kaempferol (**2**) under standard conditions (0.2 equiv $Ph_3PAuNTf_2$, CH_2Cl_2, 4 Å MS, rt).[13] The desired kaempferol 3-*O*-glucoside **4** was isolated in 20% yield, with the remaining **2** being fully recovered. To enhance the coupling yield to a practically useful level, the donor quantity was increased to 6.0 equiv; to our delight, a good 78% yield of the 3-*O*-glucoside **4** was obtained, without detection of the 7-*O*-glucosides (Scheme 2, entry 1). Such a tactic has been used successfully in our synthesis of cassiaside C_2.[14] Glucopyranosyl *o*-cyclopropylethynylbenzoates **3b** and **3c** also coupled with **2** smoothly to afford the kaempferol 3-*O*-glucosides **5** and **6** in 70% and 66% yields, respectively (entries 2 and 3). Glucosyl donors **3b** and **3c** which bear electron-donating protecting groups on the 3,4,6-positions are much more reactive than **3a**, however, only trace amounts of the 3,7-*O*-bisglycosides were detected on

* Corresponding authors. Fax: +86 21 4166128.
E-mail addresses: jssun@sioc.ac.cn (J. Sun), byu@mail.sioc.ac.cn (B. Yu).

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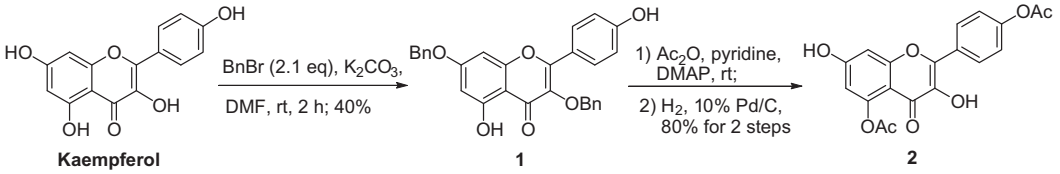
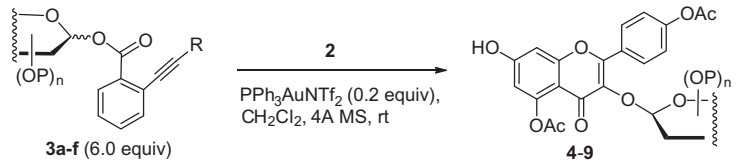
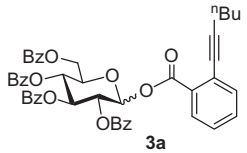
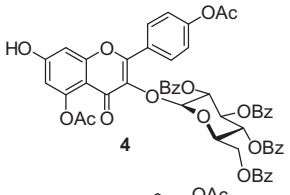
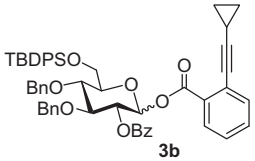
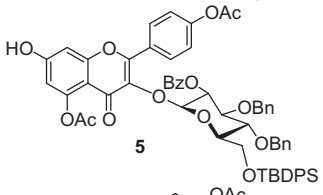
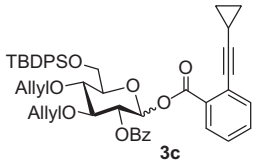
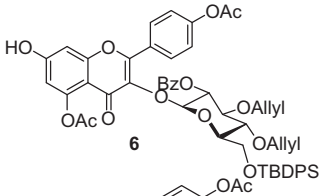
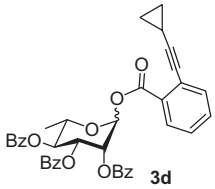
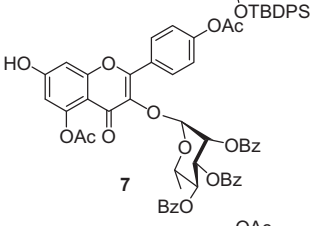
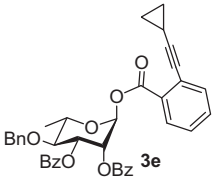
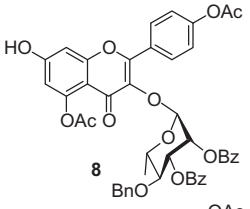
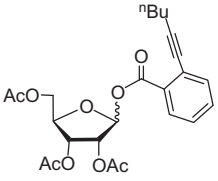
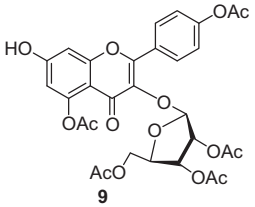


Scheme 1. Synthesis of 5,4′-di-*O*-acetyl-kaempferol **2**.



Entry	Donor	Product	Isolated Yield
1	 **3a**	 **4**	78%
2	 **3b**	 **5**	70%
3	 **3c**	 **6**	66%
4	 **3d**	 **7**	82%
5	 **3e**	 **8**	65%
6	 **3f**	 **9**	77%

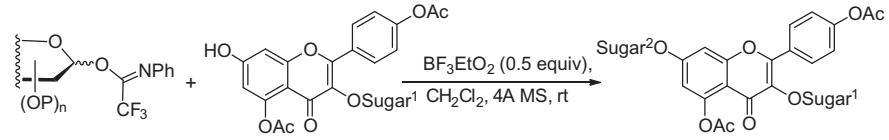
Scheme 2. Regioselective 3-*O*-glycosylation of 5,4′-di-*O*-acetyl-kaempferol **2** with glycosyl *ortho*-alkynylbenzoates.

TLC when coupling with **2**. Rhamnosyl *o*-cyclopropylethynylbenzoates **3d** and **3e**, were also proved to be good donors for the selective glycosylation of **2**, providing the 3-*O*-rhamnosides **7** and **8** in good yields (entries 4 and 5). Ribofuranosyl donor **3f** coupled with **2** under similar conditions to furnish the 3-*O*-furanoside **9** in a satisfactory 77% yield (entry 6). The resulting coupled glycosides **4**–**8** were

subjected to deprotection under conventional conditions to provide kaempferol 3-*O*-glucoside (from **4**–**6**) and 3-*O*-rhamnoside (from **7** and **8**), which showed identical analytical data to those reported for the natural products.[15,16] The glycosylation position in compound **9** was confirmed by acetylation of the remaining 7-OH in **9**, which led to the down-field shift of the H-6 and H-8 from 6.50 and 6.63 ppm to 6.78 and 7.20 ppm, respectively.

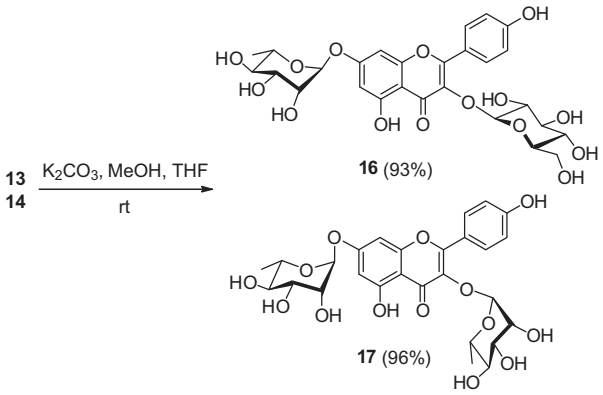
We have previously shown that the poorly nucleophilic flavonoid 7-OH could be effectively glycosylated with glycosyl trifluoroacetimidates[17] under the catalysis of $BF_3{\cdot}Et_2O$.[18] However, this protocol has not been applied to the glycosylation of the 7-OH of the flavonoid 3-*O*-glycosides, which bear the acidic labile 3-*O*-glycosidic linkage.[10] Thus, glycosylation of kaempferol 3-*O*-glucoside **4** with perbenzoyl glucopyranosyl trifluoroacetimidate **10a** was examined first under the action of 0.2 equiv of $BF_3{\cdot}Et_2O$ (CH_2Cl_2, 4 Å MS, rt); the reaction could not reach completion. Upon increasing the amount of $BF_3{\cdot}Et_2O$ to 0.5 equiv, the reaction proceeded smoothly to provide the coupled disaccharide **11** in a good 75% yield (Scheme 3, entry 1), and no cleavage of the 3-*O*-glycosidic linkage was detected. However, further increasing the catalyst amount to 1.0 equiv resulted in apparent decomposition of the resulting disaccharide. In the presence of 0.5 equiv of $BF_3{\cdot}Et_2O$, **10a** also coupled with kaempferol 3-*O*-rhamnoside **7** smoothly to give a satisfactory yield of **12** (entry 2). Under the similar conditions, rhamnosyl trifluoroacetimidate **10b** coupled with kaempferol 3-*O*-glucosides **4**, **7** and **5** effectively, leading to the desired 3,7-*O*-bisglycosides **13**, **14**, and **15** in 75–79% yields (entries 3, 4, and 5). The 7-*O*-glycosylation brought about the evident down-field shift of the kaempferol H-6 and H-8 from around 6.5 and 6.6 ppm to 6.8 and 7.1 ppm, respectively.[18]

After the successive glycosylation protocol has been successfully established,[19] the resulting 3,7-*O*-bisglycosides **13** and **14** were subjected to deprotection under basic conditions (K_2CO_3, MeOH, THF, rt), leading to the desired kaempferol 3,7-*O*-bisglycosides **16** and **17** in 86–96% yields (Scheme 4). The analytical data of these compounds were in good accordance with those reported for the natural products.[7,20] In addition, compounds **16** and **17** have been reported to posses interesting bioactivities.[7,21,22] Compound **17**, namely kaempferitrin, showed significant hypoglycemic effect, has been synthesized in nine steps and in 5.5% total yield.[7]



Entry	Donor	Acceptor	Product	Isolated Yield
1	**10a**	**4**	**11**	75%
2	**10a**	**7**	**12**	70%
3	**10b**	**4**	**13**	79%
4	**10b**	**7**	**14**	75%
5	**10b**	**5**	**15**	79%

Scheme 3. 7-*O*-Glycosylation of the kaempferol 3-*O*-glycosides **4**, **5**, and **7** with glycosyl trifluoroacetimidates.



Scheme 4. Synthesis of kaempferol 3,7-*O*-bisglycosides.

The present synthesis of **17** requires six steps and in 19% overall yield, starting from kaempferol, rhamnosyl *ortho*-alkynylbenzoate **3d** and rhamnosyl trifluoroacetimidate **10b**.

In summary, a facile approach to the synthesis of kaempferol 3,7-*O*-bisglycosides has been developed, taking advantage of the selective glycosylation of the 3-OH of 5,4′-di-*O*-acetyl-kaempferol with glycosyl *ortho*-alkynylbenzoates under the catalysis of $Ph_3PAuNTf_2$ and subsequent glycosylation of the remaining 7-OH with glycosyl trifluoroacetimidates under the promotion of $BF_3{\cdot}OEt_2$. A panel of the natural flavonol glycosides, including kaempferol 3-*O*-glucopyranoside, 3-*O*-rhamnopyranoside, 3,7-*O*-bisrhamnopyranoside (**17**), and 3-*O*-glucopyranosyl-7-*O*-rhamnopyranoside (**16**), have thus been conveniently synthesized.

Acknowledgment

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19. *General procedure for the regioselective glycosylation of the 3-OH of **2** with glycosyl ortho-alkynylbenzoates donors*: To a stirred mixture of glycosyl *o*-alkynylbenzoate (0.49 mmol), **2** (30 mg, 0.081 mmol), and 4 Å MS in CH_2Cl_2 (2.5 mL) was added $Ph_3PAuNTf_2$ (12 mg, 0.016 mmol). After being stirred at rt overnight, the mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography to give the corresponding glycoside. *General procedure for the glycosylation of kaempferol 3-O-monoglycosides with (N-phenyl)trifluoroacetimidate*: To a suspension of the kaempferol monoglycosides acceptor (0.05 mmol), glycosyl trifluoroacetimidate donor (0.15 mmol), and 4 Å molecular sieves in CH_2Cl_2 (2.5 mL) was added a solution of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (0.1 M, 0.25 mL). After stirring at room temperature overnight, the reaction was quenched with Et_3N. The mixture was then filtrated and concentrated, and the residue was purified by silica gel column chromatography to give the corresponding glycoside.
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22. *Analytic data for compound **16** and **17***: For compound **16**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.09 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.82 (s, 1 H), 6.44 (d, J = 1.8 Hz, 1 H), 5.55 (s, 1 H), 5.50 (d, J = 6.9 Hz, 1 H), 3.84 (s, 1 H), 3.65 (m, 9 H), 1.12 (d, J = 5.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.5, 161.6, 161.0, 156.8, 156.0 , 133.4, 131.0, 120.2, 115.3, 105.7, 100.8, 99.4, 98.4, 94.4, 79.2, 77.5, 76.5, 74.2, 71.6, 70.3, 70.0, 69.9, 69.8, 60.9, 17.9. For compound **17**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 6.72 (s, 1 H), 6.46 (s, 1 H), 5.56 (s, 1 H), 5.39 (s, 1 H), 4.22 (s, 1 H), 4.02 (s, 1 H), 3.84 (m, 1 H), 3.73 (m, 1 H), 3.60 (m, 1 H), 3.50 (t, J = 9.6 Hz, 1 H), 3.34 (m, 1 H) 1.27 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.4, 162.2, 161.6, 161.1, 158.3, 156.6, 135.0, 131.2, 120.7, 116.0, 106.3, 102.4, 100.0, 99.0, 95.0, 72.2, 71.7, 71.2, 70.9, 70.8, 70.6, 70.3, 18.4, 18.0.