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Synthesis of Kaempferitrin

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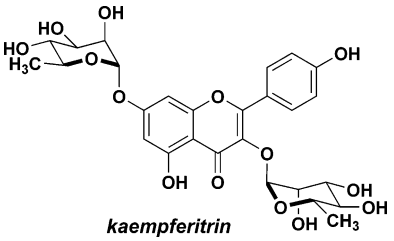
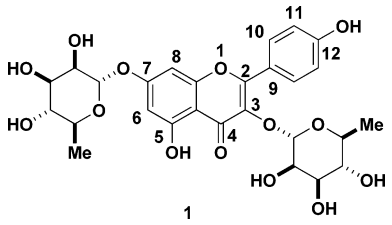


A short synthesis of Kaempferitrin (**1**), a 3,7-diglycosylflavone, is reported. Key features include the synthesis of a protected form of kaempferol in which all four hydroxy groups are differentiated and the first bis-glycosylation of a dihydroxyflavone. This synthesis will allow the preparation of derivatives for further explorations into the origins of this compound's biological activity.

Glycosylated flavanoids are ubiquitous in plants and exhibit a broad spectrum of biological activities[1] including antimicrobial[2] and antidiabetic[3] properties as well as inhibition of HIV reverse transcriptase[4] and DNA topoisomerase I.[5] Kaempferitrin (**1**), a 3,7-diglycosylflavone (Figure 1), is produced by several plant species and is reported to have a significant hypoglycemic effect in diabetic rats and has antioxidant properties comparable to those of quercetin.[6] A report in 2001[7] indicated that this compound, isolated from *L. corniculatus*,[8] exhibited antimicrobial activity comparable to several antibiotics against Gram positive and Gram negative bacteria. This report also notes that Kaempferitrin caused filamentation in *E. coli*, which can be indicative of DNA damage,[9] inhibition of DNA topoisomerase II (DNA gyrase),[10] or inhibition of bacterial cell division.[11] Our interest in natural products which inhibit bacterial cell division, including the tubulin-like protein FtsZ,[12] prompted us to develop a synthesis of **1** as a basis for studies to elucidate the origin of this compound's biological activity.



1

FIGURE 1. Structure of Kaempferitrin (kaempferol 3,7-di-*O*-rhamnoside, **1**).

The synthesis of mono-glycosyl flavones has witnessed considerable attention from the synthetic community.[13] On the other hand, preparation of bis-glycosylated flavones has largely remained unexplored. In fact, to the best of our knowledge, calabricoside A represents the only example of a bis-glycosylated flavone synthesized to date.[14] Here, we report the first synthesis of Kaempferitrin, a bis-glycosylated flavone, and its biological study. A feature of our synthetic approach is that *O*-glycosylation at any position of Kaempferol is potentially possible due to the orthogonality of the protecting groups that are employed.

Our retrosynthetic plan (Scheme 1) relies on the formation of protected Kaempferitrin **5** upon bis-*O*-glycosylation of a suitably protected 3,7-dihydroxyflavone **4**. We hoped to obtain this compound from the cyclization of benzoate ester **3**. Commercially available phloroglucinol **2** could then serve as the starting point. At the outset, we realized that the judicious choice of protecting groups for the phenolic hydroxyl groups at the 3-, 5-, 7-, and 12-positions would be vital for making this synthesis general.

Our synthetic approach to **1** commenced with the preparation of protected 3,7-dihydroxyflavone **11**, as illustrated in Scheme 2. The α-methoxy ketone functionality in **6** was introduced by using the Houben−Hoesch reaction of phloroglucinol.[15] Taking

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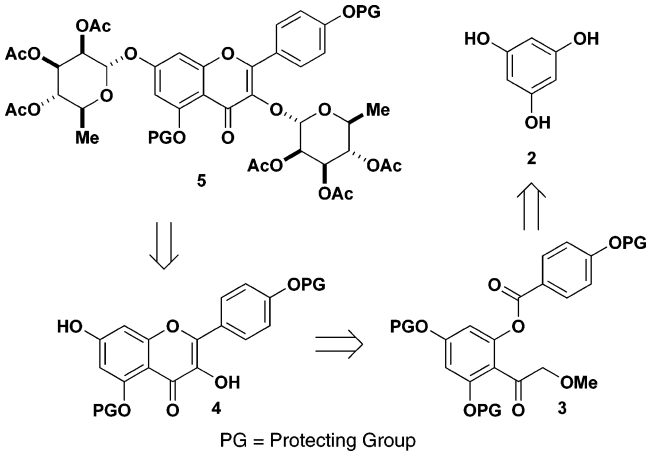
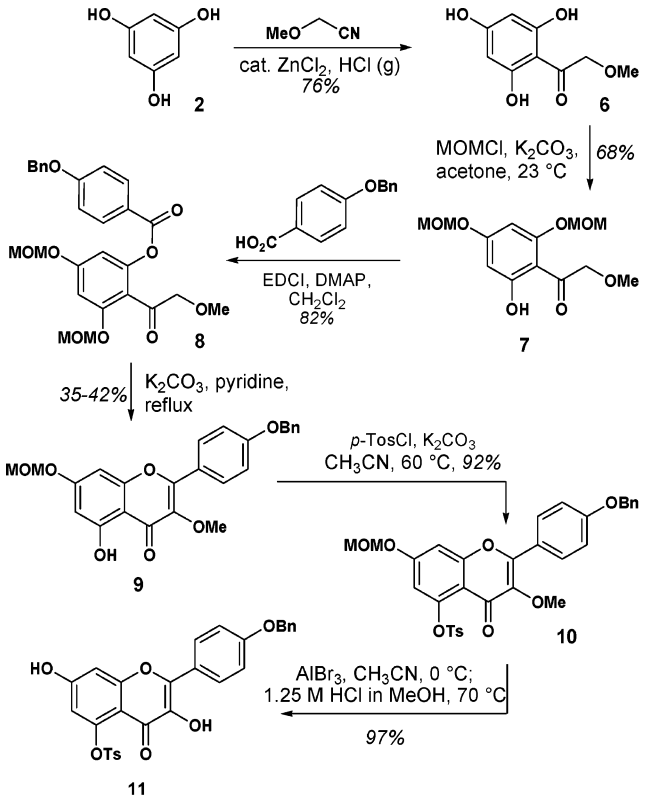
SCHEME 1. Synthetic Plan



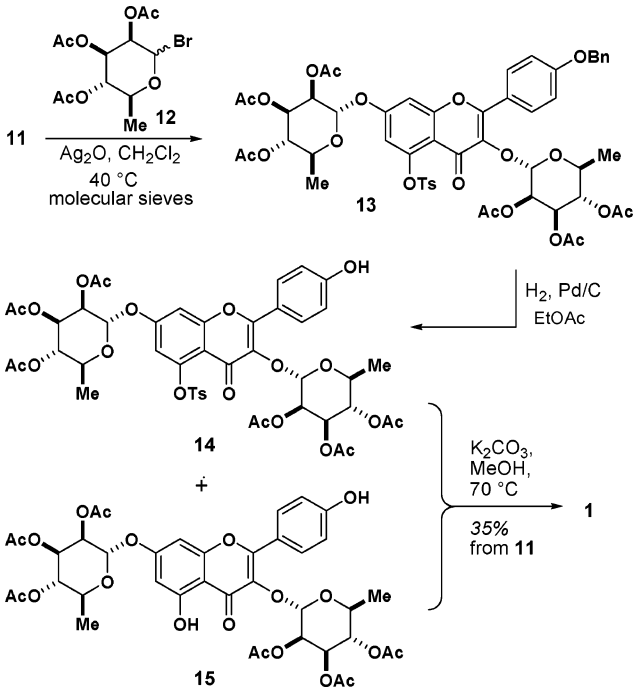
SCHEME 2. Synthesis of Protected 3,7-Dihydroxyflavone (11)



EDCI = *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

advantage of hydrogen bonding between the carbonyl and an ortho phenolic −OH group, **6** was selectively protected as the bis-MOM ether **7** in 68% yield. Benzoylation of the free phenolic −OH group of **7** afforded **8** in 82% yield. Next, the key cyclization of benzoate ester **8** to 5-hydroxyflavone **9** was attempted. Satisfyingly, heating of **8** in the presence of K_2CO_3 in pyridine resulted in the desired transformation in moderate yield (35−42%).[5a,13j,16] Notably, the MOM group ortho to the carbonyl was cleaved under the basic conditions. Interestingly,

SCHEME 3. Completion of the Synthesis of Kaempferitrin (1)



when the above cyclization was performed with the TBDPS-protected (instead of MOM-protected) benzoate ester, the only product isolated was 5,7-dihydroxyflavone (not shown) underlining the importance of the MOM group protection. Tosylation of the resulting phenol **9** gave fully protected Kaempferol **10** in 92% yield. In principle, protecting groups on **10** could be selectively removed thereby providing each site for glycosylation. Transformation of protected Kaempferol **10** into the key intermediate **11** was achieved in high yield in one pot with use of $AlBr_3$ followed by treatment with HCl (1.25 M in MeOH).[17]

With 3,7-dihydroxyflavone **11** in hand, the bis-glycosylation reaction was investigated (Scheme 3). An initial attempt to effect the bis-glycosylation with tri-*O*-acetylrhamnose trichloroacetimidate[18] as the donor and TMSOTf as an activator proved to be unsuccessful. Monitoring the reaction by LC/MS suggested that the reaction proceeded initially but decomposition occurred with time probably due to the sensitive nature of the flavone to acidic conditions. Gratifyingly, switching the donor to tri-*O*-acetylrhamnose bromide **12**[19] and the activator to Ag_2O gave the desired bis-glycosylated flavone **13** in high conversion (>95% by LC/MS and exclusively α-isomer was formed) with trace amounts of mono-glycosylated product. Increasing the amount of **12** relative to Ag_2O did not result in complete conversion. At this point it is important to mention that it was necessary to protect the C5 −OH group of **9** (conversion of **9** to **10**, Scheme 2) as our model study on glycosylation of chrysin, a 5,7-dihydroxyflavone, showed no selectivity and both −OH groups were glycosylated with **12**/Ag_2O.

The final task in completing the synthesis of Kaempferitrin involved the removal of all protecting groups (Scheme 3). We

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decided to first debenzylate **13**. Surprisingly, subjection of **13** to standard hydrogenation conditions, i.e., H_2 (1 atm, balloon), 10% Pd/C in EtOH−EtOAc (1:1) or pure EtOAc, afforded a mixture of compounds that were identified as the expected debenzylated flavone **14** and the unexpected flavone **15** resulting from debenzylation as well as detosylation of **13**, in almost 1:1 ratio (LC/MS). Although this result was unforeseen it did not have any implications on our final step.

Without purification, the mixture of **14** and **15** was treated with K_2CO_3 in MeOH at 70 °C for 1 h providing Kaempferitrin in 35% yield from **11**. Purification of Kaempferitrin was performed by using reverse-phase HPLC. The ^{1}H NMR and ^{13}C NMR spectra of synthetic **1** were consistent with published values[20] and with the spectrum of an authentic sample,[21] as were the retention time and mass spectrum as observed by LC/MS.

We have examined the antibacterial activity of **1** and found that growth of *E. coli* is not significantly affected by concentrations of up to 80 μM. Although this conflicts directly with one previous report,[7] it is consistent with a more recent study.[22] Further studies to elucidate the origin of antimicrobial activities of extracts from *L. corniculatus* are underway.

In conclusion, we report the first synthesis of Kaempferitrin, which was completed in 9 steps from commercially available phloroglucinol. The judicious choice of protecting groups employed offers the potential to effect *O*-glycosylation at any position of Kaempferol after selectively removing the protecting group of that position. We have also accomplished the first bis-glycosylation of a dihydroxyflavone.

Experimental Section

4′-Benzyloxy-5-hydroxy-3-methoxy-7-(methoxymethyloxy)flavone (9). A mixture of **8** (261 mg, 5.26 mmol, 1.0 equiv) and anhydrous K_2CO_3 (581 mg, 4.20 mmol, 8.0 equiv) in dry pyridine (2 mL) was refluxed for 1 h. After cooling, the solvent was removed in vacuo and the resulting residue was directly subjected to flash column chromatography (0 to 20% EtOAc/hexanes) to yield **9** as yellow viscous oil that solidified upon standing. Yield: 96 mg, 42%. This reaction provided lower yields when performed on a larger scale. R_f 0.86 in 50% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.11−8.07 (m, 2H), 7.48−7.36 (m, 5H), 7.11−7.08 (m, 2H), 6.63 (d, J = 2.1 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 5.24 (s, 2H), 5.16 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.8, 162.8, 161.8, 160.8, 156.5, 156.0, 138.9, 136.2, 130.2, 128.7, 128.2, 127.5, 122.9, 114.9, 106.6, 99.6, 94.2, 94.0, 70.1, 60.1, 56.4. HRMS (ESI) m/z calcd for $C_{25}H_{22}O_7$ $(M + H)^+$ 435.1444, found 435.1436.

4′-Benzyloxy-3-methoxy-7-(methoxymethyloxy)-5-[((4-methylphenyl)sulfonyl)oxy]flavone (10). A mixture of flavone **9** (60 mg, 0.14 mmol, 1.0 equiv), *p*-TosCl (106 mg, 0.55 mmol, 4.0 equiv), and anhydrous K_2CO_3 (150 mg, 1.08 mmol, 7.83 equiv) in dry MeCN (5 mL) was heated at 60 °C for 3 h. The remaining K_2CO_3 was filtered off and the filtrate was evaporated until dryness. The crude product was purified by flash column chromatography (0 to 30% EtOAc/hexanes) to yield **8** as a white solid. Yield: 75 mg, 92%. R_f 0.29 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−8.00 (m, 4H), 7.47−7.32 (m, 7H), 7.09−7.06 (m, 3H), 6.92 (d, J = 2.1 Hz, 1H), 5.23 (s, 2H), 5.14 (s, 2H), 3.77 (s, 3H), 3.49 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1, 160.6, 160.1, 157.3, 153.6, 147.6, 145.2, 141.0, 136.4, 132.9, 129.9, 129.5, 129.0, 128.6, 128.1, 127.4, 123.0, 114.8, 110.0, 102.4, 94.6, 70.1, 59.8, 56.5, 21.7. HRMS (ESI) m/z calcd for $C_{32}H_{28}O_9S$ $(M + H)^+$ 589.1525, found 589.1533.

4′-Benzyloxy-3,7-dihydroxy-5-[((4-methylphenyl)sulfonyl)oxy]-flavone (11). To an ice-cold solution of **10** (85 mg, 0.144 mmol, 1.0 equiv) in 3 mL of dry CH_3CN was added $AlBr_3$ (43 mg, 0.16 mmol, 1.1 equiv) and the mixture was stirred at that temperature for 1 h. Then, 3 mL of 1.25 M HCl in MeOH was added to the mixture which was then refluxed for 1 h. The mixture was concentrated and the crude product was purified by flash column chromatography (0 to 10% MeOH/hexanes) to yield **11** as a yellow solid. Yield: 74.6 mg, 97%. R_f 0.52 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz, CD_3COCD_3) δ 8.07−8.04 (m, 2H), 7.79−7.77 (m, 2H), 7.40−7.21 (m, 7H), 7.07−7.04 (m, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 5.10 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 172.0, 163.3, 162.0, 159.6, 149.8, 147.6, 144.7, 139.4, 134.9, 131.5, 131.0, 130.8, 130.4, 129.8, 129.5, 125.6, 116.8, 110.7, 110.4, 103.9, 71.7, 22.6. HRMS (ESI) m/z calcd for $C_{29}H_{22}O_8S$ $(M + Na)^+$ 553.0927, found 553.0933.

4′-Benzyloxy-3,7-*O*-(2″,3″,4″-triacetyloxy-α-L-rhamnopyranosyl)-5-[((4-methylphenyl)sulfonyl)oxy]flavone (13). A mixture of 3,7-dihydroxyflavone **11** (47.5 mg, 0.089 mmol, 1.0 equiv), rhamnose bromide **12** (67 mg, 0.188 mmol, 2.1 equiv), and Ag_2O (46 mg, 0.196 mmol, 2.2 equiv) was heated at 40 °C in the presence of 4 Å molecular sieves in dry CH_2Cl_2 (2 mL) under argon atmosphere for 36 h. The LC-MS analysis of the crude reaction mixture showed the complete consumption of **11** and the formation of **13** in >95% and a trace amount of mono-glycosylated product. The reaction mixture was filtered off through celite and was used in the next step without further purification. However, for analytical purposes, compound **13** was purified by reverse phase HPLC. R_f 0.7 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.45−7.35 (m, 7H), 7.14−7.11 (m, 3H), 7.07 (d, J = 2.5 Hz, 1H), 5.70 (dd, J = 1.5 Hz, 1H), 5.55 (d, J = 1.0 Hz, 1H), 5.49 (d, J = 1.5 Hz, 1H), 5.46−5.44 (m, 2H), 5.31 (dd, J = 3.5, 6.5 Hz, 1H), 5.19−5.15 (m, 3H), 4.95 (t, J = 10 Hz, 1H), 3.94−3.88 (m, 1H), 3.41−3.35 (m, 1H), 2.46 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.25 (d, J = 6 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H); ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 7.38−7.29 (m, 6H), 7.18 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 2.0 Hz, 1H), 5.73 (br s, 1H), 5.59 (dd, J = 1.5 Hz, 1H), 5.49−5.48 (m, 1H), 5.40 (dd, J = 3.5, 6.5 Hz, 1H), 5.29 (d, J = 1.0 Hz, 1H), 5.22 (dd, J = 3.5, 7.0 Hz, 1H), 5.17 (s, 2H), 5.14 (t, J = 10 Hz, 2H), 3.96−3.91 (m, 1H), 3.17−3.14 (m, 1H), 2.42 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H), 1.21 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H), one proton is obscured due to the solvent peak; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.94, 169.92, 169.9, 169.8, 169.5, 160.9, 158.4, 157.3, 155.2, 147.9, 145.6, 136.6, 132.4, 130.5, 129.7, 129.1, 128.7, 128.2, 127.4, 122.4, 115.0, 113.7, 110.1, 103.1, 98.0, 95.7, 70.6, 70.4, 70.2, 69.2, 69.0, 68.9, 68.5, 68.2, 68.0, 29.7, 21.8, 20.9, 20.8, 20.75, 20.74, 20.7, 17.4, 17.1. HRMS (ESI) m/z calcd for $C_{53}H_{54}O_{22}S$ $(M + Na)^+$ 1097.2725, found 1097.2734.

Kaempferitrin (1). A mixture of crude compound **13** (obtained above) and 10% palladium on carbon (75 mg) were stirred in EtOAc (5 mL) under an atmosphere of hydrogen at room temperature for 14 h. The solution was filtered through a plug of celite eluting with EtOAc. The LC-MS analysis of filtrate showed the formation of two compounds which were identified as **14** and **15**. The filtrate was concentrated and without further purification was treated with anhydrous K_2CO_3 (50 mg) in 2 mL of dry MeOH at 70 °C for

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(21) Provided by M. G. Pizzolatti, Departamento de Química, Universidade Federal de Santa Catarina, Campus Trindade 88010-970 Florianópolis, SC, Brazil. Fax: (55) 048 3319711. E-mail: mgpizzo@qmc.ufsc.br.

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90 min. The reaction mixture was cooled to room temperature and then acidified to pH ca. 1−2 with Dowex-50 ion-exchange resin. The mixture was concentrated and purified by reverse phase HPLC to give **1** as a yellow solid. Yield: 18 mg, 35% from **11**. Reverse phase purification was carried out on an Xterra C18 column (19 × 50 mm^2, 5 μm). The flow rate was 30 mL/min with mobile phase A as water and B as acetonitrile. Both mobile phases had 0.01% formic acid added. The gradient ranged from 5% to 95% B over 10 min and was followed by a 3 min wash at the end with 95% B. ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (br s, 1H), 7.80 (d, J = 8 Hz, 2H), 6.94 (d, J = 7.5 Hz, 2H), 6.72 (s, 1H), 6.46 (s, 1H), 5.55 (s, 1H), 5.39 (s, 1H), 4.21 (d, J = Hz, 1H), 4.00 (br s, 1H), 3.83−3.81 (m, 1H), 3.71−3.70 (m, 1H), 3.60−3.57 (m, 1H), 3.48 (t, J = 9 Hz, 1H), 3.34−3.32 (m, 2H), 1.26 (d, J = 5.5 Hz, 3H), 0.93 (d, J = 4.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.9, 163.6, 163.1, 161.8, 159.9, 158.2, 136.5, 132.0, 122.5, 116.6, 107.6, 103.6, 100.6, 99.9, 95.7, 73.6, 73.2, 72.2, 72.14, 72.12, 72.0, 71.7, 71.3, 18.1, 17.7. HRMS (ESI) m/z calcd for $C_{27}H_{30}O_{14}$ $(M + Na)^+$ 601.1533, found 601.1523.

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Supporting Information Available: General methods, experimental procedures for compounds **6**−**8**, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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