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Synthesis of Kaempferol 3-*O*-(3″,6″-Di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside, Efficient Glycosylation of Flavonol 3-OH with Glycosyl *o*-Alkynylbenzoates as Donors

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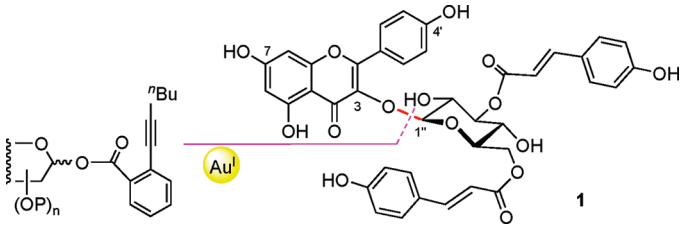

Kaempferol 3-*O*-(3″,6″-di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside (**1**), an optimal metabolite of Scots pine seedlings for protection of deep-lying tissue against damaging UV-B, represents a typical acylated flavonol 3-*O*-glycoside. This compound was synthesized for the first time via two approaches. The first approach, starting with kaempferol, featured formation of the flavonol 3-*O*-glycosidic linkage with a glycosyl bromide under conventional PTC conditions. In the second approach, 5,7,4′-tri-*O*-benzyl-kaempferol was readily prepared from 2′,4′,6′-trihydroxyacetophenone and *p*-hydroxybenzoic acid, which was coupled with a glucopyranosyl *o*-hexynylbenzoate under the catalysis of a gold(I) complex to provide the desired 3-*O*-glycoside in excellent yield. A variety of the glycosyl *o*-hexanylbenzoates equipped with the 2-*O*-benzoyl group were also proven to be highly efficient donors for construction of the flavonol 3-*O*-glycosidic linkages.

Introduction

More than 1500 flavonol *O*-glycosides have so far been isolated, mostly from higher plants.[1] The majority of these compounds (~80%) have a sugar linkage at the 3-OH, and over 20% possess one or more acyl groups attached through the sugar residues, which further enhances the structural diversity of flavonol *O*-glycosides.[1] These ubiquitous metabolites play a variety of important roles in the growth and development of plants, e.g., as interspecies signaling molecules.[1,2] They also demonstrate a wide spectrum of activities beneficial to humans, such as antimicrobial, anticancer, and radical-scavenging activities.[1,2] Kaempferol 3-*O*-(3″,6″-di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside (**1**), or 3″,6″-di-*O*-(*p*-coumaroyl)astragalin, is a representative acylated flavonol 3-*O*-glycoside,[3] which has been isolated from the needles of *Picea obovata* Ledeb.[4a] and the leaves of *Stenochlaena palustris*.[4b] In the seedlings of Scots pine (*Pinus sylvestris L.*), this compound was found to provide optimal protection for deep-lying tissue against damaging UV-B radiation.[4c]

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(2) Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley & Sons: Chichester, UK, 1999; Vol. 1.

(3) For some natural congeners of compound **1**, see: (a) Slimestad, R.; Andersen, Ø. M.; Francis, G. W.; Marston, F. A.; Hostettmann, K. *Phytochemistry* **1995**, *40*, 1537. (b) Imperato, F.; Minutiello, P. *Phytochemistry* **1997**, *45*, 199. (c) Park, S.-H.; Oh, S. R.; Jung, K. Y.; Lee, I. S.; Ahn, K. S.; Kim, J. H.; Kim, Y. S.; Lee, J. J.; Lee, H.-K. *Chem. Pharm. Bull.* **1999**, *47*, 1484. (d) Ercil, D.; Kaloga, M.; Radtke, O. A.; Sakar, M. K.; Kiderlen, A. F.; Kolodziej, H. *Turk. J. Chem.* **2005**, *29*, 437. (e) Hussein, A. A.; Barberena, I.; Correa, M.; Coley, P. D.; Solis, P. N.; Gupta, M. P. *J. Nat. Prod.* **2005**, *68*, 231.

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The wide occurrence and importance of the flavonol glycosides have attracted attention on the synthetic studies toward this group of natural products.[5,6] In that, the formation of the flavonol 3-*O*-glycosidic linkages resort mostly to the glycosylation protocol with glycosyl bromides as donors under phase-transfer catalysis (PTC) conditions or under the action of silver salts. Here we report two approaches to the synthesis of kaempferol 3-*O*-glycoside **1**, with the second one highlighted by an efficient alternative to the synthesis of flavonol 3-*O*-glycosidic linkages with the newly developed glycosyl *o*-alkynylbenzoates as donors and gold(I) as a catalyst.[7]

Results and Discussion

First Generation Synthesis. In line with the previous synthesis of kaempferol 3-*O*-glycosides,[5] coupling of 7,4′-di-*O*-benzyl-kaempferol **2** with glucopyranosyl α-bromide **3** would serve as the key step for the synthesis of target molecule **1** (Figure 1).

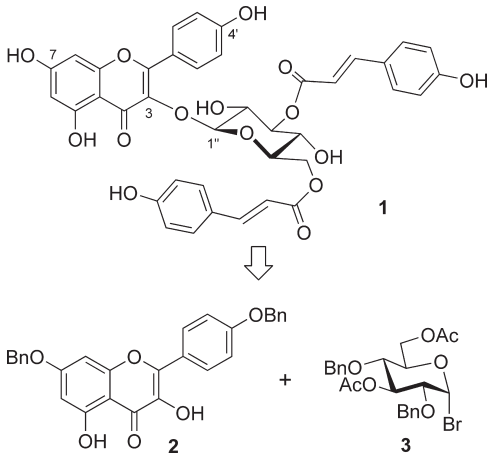
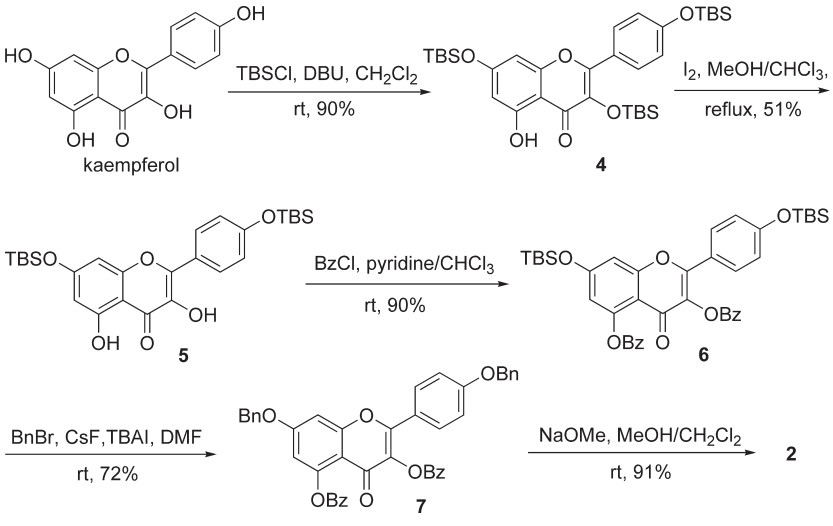


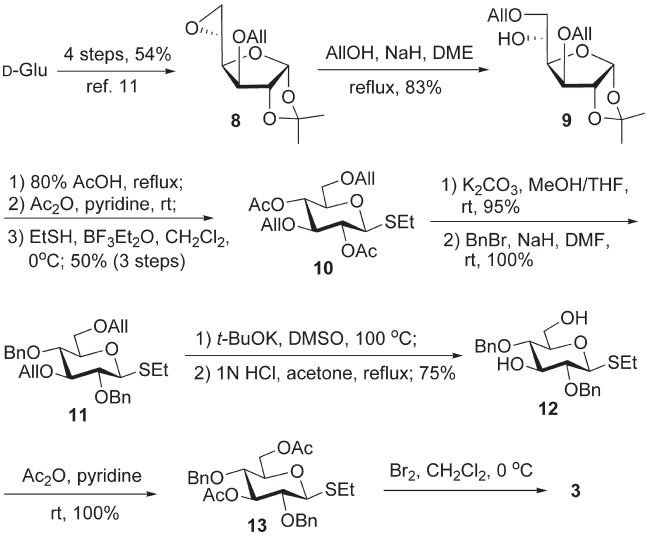
FIGURE 1. 3-*O*-(3″,6″-Di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside (**1**) and its retro-synthetic perspective.

The preparation of kaempferol derivative **2** commenced with commercially available kaempferol (Scheme 1). Thus, treatment of kaempferol with TBSCl and DBU in CH_2Cl_2 at rt led to 3,7,4′-tri-*O*-silyl ether **4** in an excellent 90% yield,[8] leaving only the 5-OH intact, which forms a hydrogen bond with the 4-carbonyl group. Selective removal of the 3-*O*-silyl group, which is vicinal to the 4-carbonyl group, was effected with I_2 in MeOH (reflux for 6 h), providing 3,5-diol **5** in moderate yield (51%).[9] Protection of the 3,5-OH with the benzoyl group gave **6** (90%). Direct conversion of the 7,4′-*O*-silyl group into benzyl protection was realized with BnBr in the presence of CsF and TBAI (tetrabutylammonium iodide) in DMF at rt,[10] leading to 4′,7-di-*O*-benzyl-3,5-di-*O*-benzoyl-kaempferol **7** in good yield (72%). Subsequent removal of the 3,5-*O*-benzoyl group (NaOMe, MeOH, rt) provided **2** (91%).[5a]

SCHEME 1. Preparation of 7,4′-Di-*O*-benzyl-Kaempferol (2)



SCHEME 2. Preparation of 3,6-Di-*O*-acetyl-2,4-di-*O*-benzyl-α-D-glucopyranosyl Bromide (3)

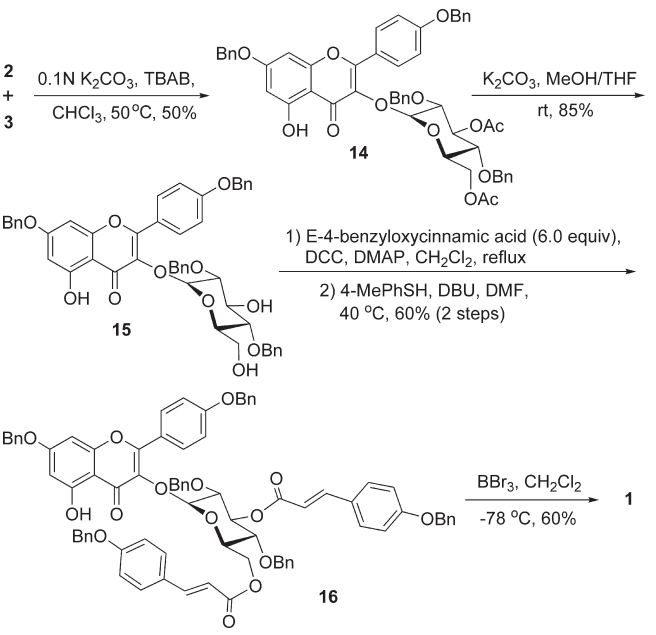


The required 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-α-D-glucopyranosyl bromide (**3**) was prepared as shown in Scheme 2. 5,6-Anhydro-3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose **8**, which was easily obtained from D-glucose (4 steps, 54% overall yield),[11] was chosen as a key precursor. Thus, treatment of epoxide **8** with AllOH in the presence of NaH in DME (1,2-dimethoxyethane) at reflux afforded 3,6-di-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose **9** in a good

83% yield. Alternatively, treatment of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose with AllBr under PTC conditions (NaOH, Bu_4NBr, CH_2Cl_2, H_2O) led to **9** in only moderate yield (< 50%).[11a] Compound **9** was then converted into ethyl 1-thio-β-D-glucopyranoside **10** via three convenient steps (50% overall yield), i.e., deacetonidation (80% HOAc), acetylation (Ac_2O, pyridine), and ethyl thioglycoside formation (EtSH, BF_3OEt_2, CH_2Cl_2). The 2,4-*O*-acetyl group in **10** was converted into benzyl protection (2 steps, 95% yield) to provide **11**. The 3,6-*O*-allyl group in thioglycoside **11** could not survive during conversion into the corresponding glycosyl bromide, thus were replaced with acetyl protection via deallylation (*t*-BuOK, DMSO, 100 °C; and then 1 N HCl, acetone, reflux; 75%) and acetylation, leading to **13**. Thioglycoside **13** was then transformed smoothly into the desired α-bromide **3** with Br_2 in CH_2Cl_2 at 0 °C. Bromide **3** was found unstable, thus was used directly without further purification.

Under the previously optimized PTC conditions (TBAB, 0.1 N K_2CO_3, $CHCl_3$, rt),[6] glycosylation of kaempferol 3,5-diol **2** with the crude glucopyranosyl α-bromide **3** led to the desired 3-*O*-β-glucoside **14** (H-1″: 5.53 ppm, J = 7.5 Hz) in 50% yield, with 40% of the starting **2** being recovered (Scheme 3). Although the yield was moderate, the stereo- and regioselectivity were perfect, with no α-glycoside or 5-*O*-glycoside being detected. Subsequent removal of the 3″,6″-*O*-acetyl group (K_2CO_3, MeOH, THF, rt) provided **15** (85%). Introduction of the *E*-4-benzyloxycinnamyl group onto the 3″,6″-OH on **15** was found to be problematic. Under mild conditions (2.0 equiv of *E*-4-benzyloxycinnamic acid, DCC, DMAP, CH_2Cl_2, rt), only monoacylated product was detected (presumably at the 6″-OH). Either increasing the equivalents of the acid or prolonging the reaction time did not result in satisfactory results. When **15** was treated with 6.0 equiv of the acid under reflux, a mixture of the 5,3″,6″-tri-*O*-acyl and 3″,6″-di-*O*-acyl products was obtained, which could not be separated by silica gel column chromatography due to their similar polarity and poor solubility. Thus, the mixture was subjected to selective removal of the phenolic 5-*O*-acyl group, and under the action of 4-MePhSH in the presence of DBU in DMF at 40 °C, the desired 3″,6″-di-*O*-acyl product **16** was obtained in 60% yield (based on **15**).[12] Finally, global debenzylation was effected with BBr_3 in CH_2Cl_2 at low temperature (−78 °C), furnishing the target molecule **1** in 60% yield. The ^1H and ^{13}C NMR data of the synthetic sample are identical with those reported for the natural product.[4,23]

SCHEME 3. Completion of the Synthesis of Target Molecule 1



Second Generation Synthesis. In the preceding synthetic approach, two steps are especially unsatisfactory: (1) Glycosylation of kaempferol **2** with glycosyl bromide **3** under PTC conditions gave the desired product **14** in 50% yield, in that the bromide **3** was unstable and thus had to be used immediately after preparation. For the preparation of bromide **3**, additional steps were required to replace the 3″,6″-*O*-allyl protection (**11**→**13**). (2) Introduction of the coumaroyl group onto the 3″,6″-OH of triol **15** led to a mixture of the inseparable 3″,6″-di-*O*-acyl and 5,3″,6″-tri-*O*-acyl derivatives, which required an additional step to remove selectively the phenolic 5-*O*-acyl group. To avoid this impediment, we decided to investigate the glycosylation of 5,7,4′-tri-*O*-benzylkaempferol (i.e., **22**) with a glycosyl *o*-alkynylbenzoate as donor toward the synthesis of target **1**. The glycosyl *o*-alkynylbenzoates are shelf stable and could be activated by a catalytic amount of gold(I) complexes for glycosidation. This mild protocol should be advantageous in the glycosylation of flavonols, considering many conventional glycosylation protocols involve acidic conditions or strongly electrophilic promoters, which might be detrimental to the flavonol substrates.

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(11) (a) Ding, X.; Kong, F. *J. Carbohydr. Chem.* **1999**, *18*, 775. (b) Hanaya, T.; Sugiyama, K.; Kawamoto, H.; Yamamoto, H. *Carbohydr. Res.* **2003**, *338*, 1641.

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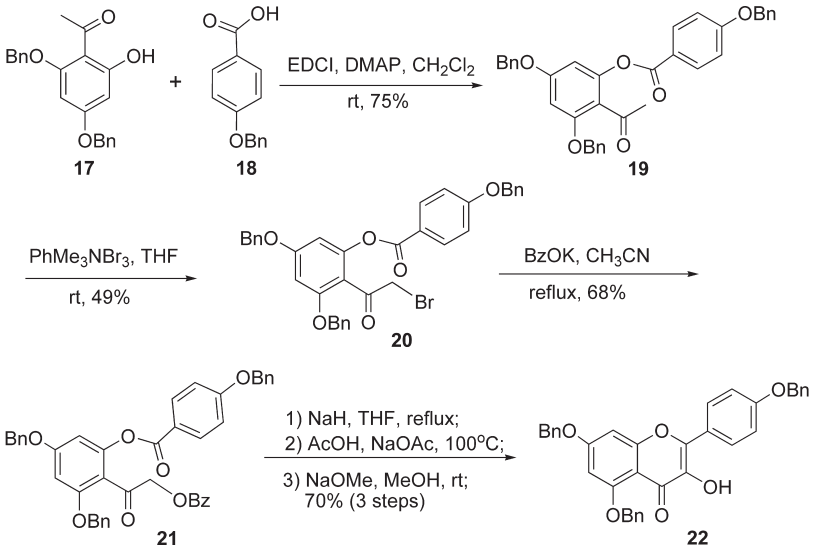
SCHEME 4. Synthesis of 5,7,4′-Tri-*O*-benzyl-Kaempferol (22)



The previous preparation of flavonol derivatives (such as **22**) mostly employed Baker−Venkataraman rearrangement[13] and subsequent oxidation of the resulting flavone. The oxidation step required such oxidants as dimethyldioxirane (DMDO) and hypervalent iodine derivatives[5,14−16] that has discouraged scale-up synthesis. Brouillard et al. developed an alternative approach, in that the flavonol 3-OH was introduced by a sequence of bromination of an acetophenone derivative followed by substitution of the bromide with a benzoate group.[17a] The feasibility of this approach to the synthesis of 5,7,4′-tri-*O*-benzyl-kaempferol (**22**) was examined (Scheme 4). Thus, condensation of hydroxyacetophenone **17**[18] and 4-benzyloxybenzoic acid **18**[19] was effected under EDCI in CH_2Cl_2, providing ester **19** (75%). Bromination of methyl ketone **19** with phenyltrimethylammonium tribromide (PTT) in THF afforded bromide **20** in a moderate yield of 49%; the corresponding dibromomethyl ketone was found to be the major byproduct. Substitution of the bromide in **20** with benzoate took place in refluxing acetonitrile, leading to **21** in 68% yield. The Baker−Venkataraman rearrangement on **21** proceeded smoothly under the action of sodium hydride in THF under reflux. However, the reported conditions (H_2SO_4/HOAc, 60 °C)[17] for the subsequent cyclization/dehydration led to a complex mixture, due to partial cleavage of the phenolic benzyl groups under the strong acidic conditions. After trying a variety of conditions,[17] we finally found that sodium acetate in acetic acid at 100 °C could effect this transformation smoothly.[20] Subsequent saponification of the 3-*O*-benzoate furnished **22** in a high yield of 70% (for 3 steps).

Glycosyl *o*-hexynylbenzoates **23a−g** were readily prepared via condensation of the corresponding lactols with *o*-hexynylbenzoic acid (DCC, DMAP, CH_2Cl_2, >90%).[7] These compounds are shelf stable. Under the standard glycosylation conditions (0.2 equiv of $Ph_3PAuNTf_2$, 4 Å MS, CH_2Cl_2, rt),[7] glycosylation of 5,7,4′ -tri-*O*-benzyl-kaempferol (**22**) with glycosyl *o*-hexynylbenzoates **23a−g** was examined (Table 1). The glycosylation reaction with 2,4-di-*O*-acetyl-3,6-di-*O*-allyl-D-glucopyranosyl *o*-hexynylbenzoate **23a**[23] led to poor yield (14% when 3 equiv of **23a** was used) of the coupled *β*-*O*-glycoside **24a** (entry 1). Similarly, glycosylation with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl *o*-hexynylbenzoate **23c**[7] did not provide the *β*-*O*-glycoside at all (entry 3). These results were in accordance with our previous findings that glucopyranosyl *o*-hexynylbenzoates bearing a 2-*O*-acetyl group easily underwent ortho-ester formation and decomposition under the glycosylation conditions. Evidently, the corresponding 2-*O*-benzoyl counterparts **23b** and **23d**[7] behaved as excellent donors, providing the expected *β*-*O*-glycosides **24b** and **24d** in 90% and 82% yield, respectively (entries 2 and 4). It was noted that an excess amount of donors (3.0 equiv) and prolonged reaction time (12 h) were required to achieve the good yields of kaempferol 3-*O*-*β*-glycosides, testifying that 5,7,4′-tri-*O*-benzyl-kaempferol (**22**) is a poorly nucleophilic acceptor. In comparison, when 2-*O*-benzoyl-3,-4,6-tri-*O*-benzyl-D-glucopyranosyl *o*-hexynylbenzoate **23e**,[7] which was equipped with a superarmed protecting pattern,[21] was used as donor, the glycosylation with kaempferol derivative **22** proceeded more smoothly: 1.5 equiv of **23e** and 1 h reaction time ensured completion of the reaction to afford the desired *O*-*β*-glycoside **24e** in 95% yield (entry 5).

α-L-Rhamnosyl residue is also frequently found at the 3-OH of natural flavonol glycosides. However, the conventional

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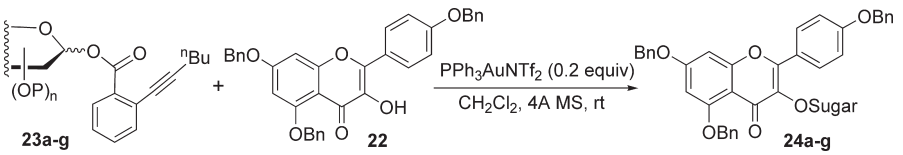
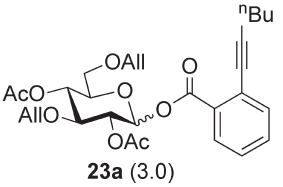
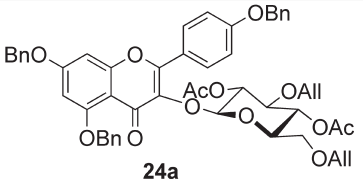
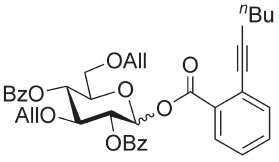
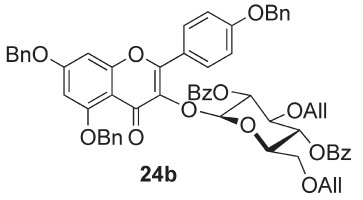
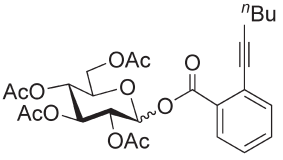
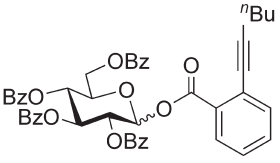
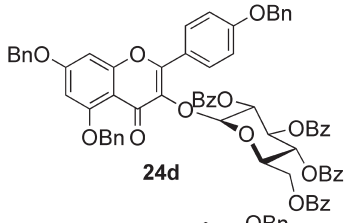
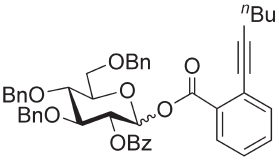
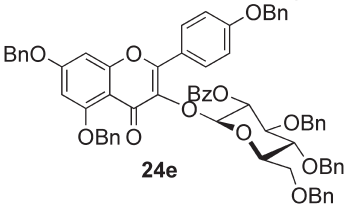
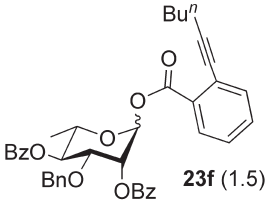
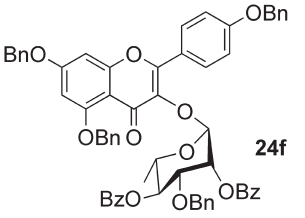
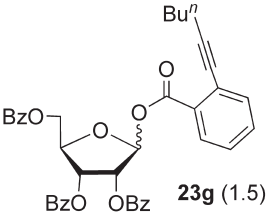
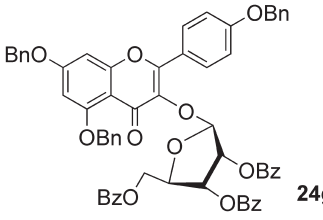
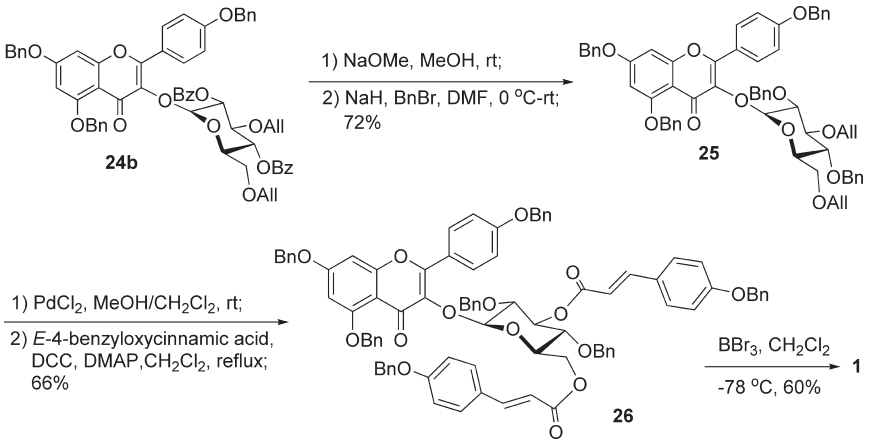
TABLE 1. Glycosylation of Kaempferol 3-OH 22 with Glycosyl *o*-Hexynylbenzoates 23a−g As Donors and $Ph_3PAuNTf_2$ As a Catalyst



Entry	Donor (equiv)	Product	Yield[a]
1	 **23a** (3.0)	 **24a**	14%[b]
2	 **23b** (3.0)	 **24b**	90%[b]
3	 **23c** (3.0)	No 3-*O*-glycoside	0
4	 **23d** (3.0)	 **24d**	82%[b]
5	 **23e** (1.5)	 **24e**	95%[c]
6	 **23f** (1.5)	 **24f**	91%[c]
7	 **23g** (1.5)	 **24g**	93%[c]

[a]Isolated yield. [b]12 h was required. [c]1 h was required.

SCHEME 5. Completion of the Synthesis of 1 from 24b



PTC conditions could not be applied to make this linkage with L-rhamnosyl bromides (because the α-bromide always prevails, which would lead to *β*-*O*-rhamnoside predominantly if glycosylation did take place).[22] Alternatively, Hecht and Maloney employed silver oxide to promote the glycosylation of **22** with 3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-rhamnopyranosyl bromide to provide the corresponding kaempferol 3-*O*-α-L-rhamnoside in 60% yield.[5e] Gratifyingly, under the present conditions, 2,4-di-*O*-benzoyl-3-*O*-benzyl-L-rhamnopyranosyl *o*-hexynylbenzoate **23f** coupled with **22** fluently, providing the desired *O*-α-L-rhamnoside **24f** in 91% yield within 1 h (entry 6). Similarly, 2,3,4-tri-*O*-benzoyl-D-ribofuranosyl *o*-hexynylbenzoate **23g** reacted with **22** to provide *O*-*β*-D-furanoside **24g** in 93% yield within 1 h (entry 7).

To continue the synthesis of target molecule **1**, the high yielding 5,7,4′-tri-*O*-benzyl-3-*O*-(3″,6″-di-*O*-allyl-2″,4″-di-*O*-benzoyl-*β*-D-glucopyranosyl)-kaempferol (**24b**) was used as an advanced precursor (Scheme 5). Removal of the 2″,4″-di-*O*-benzoyl group (NaOMe, MeOH, rt) followed by benzylation (BnBr, NaH, DMF, 0 °C−rt) provided compound **25** (72%). Subsequent cleavage of the 3″,6″-di-*O*-allyl group on **25** ($PdCl_2$, MeOH, CH_2Cl_2, rt) followed by acylation of the resulting 3″,6″-OH with *E*-4-benzyloxycinnamic acid (DCC, DMAP, CH_2Cl_2, reflux) afforded **26** in 66% yield. Finally, removal of the seven *O*-benzyl groups on **26** was achieved with BBr_3 in CH_2Cl_2 at −78 °C, furnishing the target molecule **1** in a satisfactory 60% yield.

Conclusion

3-*O*-(3″,6″-Di-*O*-*E*-*p*-coumaroyl)-*β*-D-glucopyranoside (**1**), a typical acylated flavonol 3-*O*-glycoside, has been synthesized for the first time via two approaches. The first approach, starting with kaempferol and glucose, employed a total of 24 steps (in 2.4% overall yield), in that the flavonol 3-*O*-glycosidic linkage was built (in 50% yield) by a conventional method with glycosyl bromide **3** as donor under PTC conditions. In the second approach, 5,7,4′-tri-*O*-benzyl-kaempferol (**22**) was readily prepared from 2′,4′,6′-trihydroxyacetophenone and *p*-hydroxybenzoic acid (6 steps, 17% overall yield), which was coupled with 3,6-di-*O*-allyl-2,4-di-*O*-benzoyl-*β*-D-glucopyranosyl *o*-hexynylbenzoate **23b** to provide the desired 3-*O*-glycoside **24b** in a high yield of 90%. Thus, the latter approach achieved a total of 21 steps with 6% overall yield from cheap starting materials. The glycosylation of flavonol 3-OH (i.e., **22**) with a variety of the glycosyl *o*-hexynylbenzoates has been examined; the results have demonstrated that glycosyl *o*-hexynylbenzoates bearing the 2-*O*-benzoyl group are excellent donors under the catalysis of $Ph_3PAuNTf_2$ complex for the glycosylation of flavonol 3-OH. Thus, a new and highly efficient alternative has been established for the synthesis of the widely occurring flavonol 3-*O*-glycosides.

Experimental Section[23]

3,7,4′-Tri-*O*-*tert*-butyldimethylsilyl-Kaempferol (4). To a suspension of kaempferol (423 mg, 1.5 mmol) and TBSCl (1.4 g, 9 mmol) in dry CH_2Cl_2 was added DBU (1.5 mL). The reaction mixture was stirred at room temperature for 15 min, then was diluted with CH_2Cl_2 and washed with water. After drying over Na_2SO_4, the solvent was evaporated to give a yellow oil, which was further purified by flash column chromatography on silica gel (EtOAc−petroleum ether, l:150) to provide **4** (988 mg, 90%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.68 (s, 1 H), 7.86 (d, J = 9.0 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 6.36 (s, 1 H), 6.27 (d, J = 1.8 Hz, 1 H), 1.00 (s, 9 H), 0.98 (s, 9 H), 0.84 (s, 9 H), 0.26 (s, 6 H), 0.23 (s, 6 H), 0.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 161.7, 157.6, 156.4, 153.1, 135.6, 130.5, 124.2, 120.0, 106.1, 103.0, 98.3, 25.7 (2 C), 25.5, 18.6, 18.3, 18.2, −4.0, −4.4 (2 C); HRMS (MALDI) calcd for $C_{33}H_{53}O_6Si_3$ $[M + H]^+$ 629.3150, found 629.3145.

7, 4′-Di-*O*-*tert*-butyldimethylsilyl-Kaempferol (5). To a solution of **4** (441 mg, 0.7 mmol) in MeOH/$CHCl_3$ (5 mL:5 mL) was added I_2 (2 mg, 0.007 mmol) at room temperature. The reaction mixture was refluxed for 6 h, and was then quenched with aq $Na_2S_2O_3$ at room temperature. The resulting mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were concentrated in vacuo. The residue was subjected to silica gel column chromatography (EtOAc−petroleum ether, l:100) to provide **5** (184 mg, 51% yield) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1 H), 8.05 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.65 (s, 1 H), 6.36 (d, J = 2.4 Hz, 1 H), 6.22 (d, J = 1.8 Hz, 1 H), 0.92 (s, 18 H), 0.20 (s, 6 H), 0.17 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 162.4, 160.7, 157.7, 156.5, 145.8, 135.7, 129.4, 123.7, 120.2, 104.4, 103.1, 98.7, 25.6, 25.5,

(22) Demetzos, C.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M. *Carbohydr. Res.* **1990**, *207*, 131.

(23) Experimental details and characterization data for compounds **23a**, **23f**,**g**, **24a**, and **24d**−**g**, and data comparison between the natural and synthetic target molecule **1** are provided in the Supporting Information.

18.3, 18.2, 1.0, −4.4. HRMS (MALDI) calcd for $C_{27}H_{39}O_6Si_2$ $[M + H]^+$ 515.2285, found 515.2280.

3,5-Di-*O*-benzoyl-7,4′-di-*O*-*tert*-butyldimethylsilyl-Kaempferol (6). To a solution of **5** (158 mg, 0.3 mmol) in pyridine/$CHCl_3$ (2.4 mL, v/v 1:3) at 0 °C was added BzCl (0.3 mL). After being stirred for 10 h, the reaction mixture was diluted with EtOAc and washed with water. After drying over Na_2SO_4, the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 1:25) to give **6** (211 mg, 95%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 7.5 Hz, 2 H), 8.14 (d, J = 7.2 Hz, 2 H), 7.81 (d, J = 8.7 Hz, 2 H), 7.60 (m, 2 H), 7.49 (m, 4 H), 6.90 (m, 3 H), 6.70 (d, J = 2.1 Hz, 1 H), 1.02 (s, 9 H), 0.97 (s, 9 H), 0.32 (s, 6 H), 0.20 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.1, 163.7, 160.2, 158.3, 157.8, 154.9, 150.8, 133.6, 133.3, 133.0, 130.6, 130.5, 129.8, 129.5, 128.6, 128.4 (2 C), 122.7, 120.2, 113.3, 112.0, 106.0, 25.5 (2 C), 18.2 (2 C), −4.4 (2 C); HRMS (MALDI) calcd for $C_{41}H_{47}O_8Si_2$ $[M + H]^+$ 723.2809, found 723.2804.

3,5-Di-*O*-benzoyl-7,4′-di-*O*-benzyl-Kaempferol (7). To a suspension of **6** (96 mg, 0.1 mmol) and CsF (102 mg, 0.6 mmol) in DMF (1.5 mL) was added BnBr (0.1 mL). After 10 min of stirring at rt, TBAI (96 mg, 0.3 mmol) was added. The resulting mixture was stirred for another 6 h, and was then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (EtOAc−petroleum ether, l:3) to provide **7** (65 mg, 72%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.8 Hz, 2 H), 8.13 (d, J = 7.5 Hz, 2 H), 7.84 (d J = 8.7 Hz, 2 H), 7.58 (m, 2 H), 7.45−7.34 (m, 14 H), 6.99 (m, 3 H), 6.83 (d, J = 1.8 Hz, 1 H), 5.14 (s, 2 H), 5.04 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 165.1, 163.6, 162.5, 160.8, 158.0, 154.6, 150.8, 136.1, 135.3, 133.6, 133.3, 133.0, 130.6, 130.5, 129.8, 129.4, 128.7, 128.6, 128.4, 128.3, 128.1, 127.5, 127,4, 122.2, 114.9, 111.5, 109.2, 99.9, 70.7, 70.0; HRMS (MALDI) calcd for $C_{43}H_{31}O_8$ $[M + H]^+$ 675.2019, found 675.2014.

7,4′-Di-*O*-benzyl-Kaempferol (2). To a solution of **7** (2.8 g, 4.2 mmol) in MeOH/CH_2Cl_2 (144 mL, v/v 1:5) at room temperature was added NaOMe (677 mg, 12.5 mmol). After being stirred for 5 h, the mixture was adjusted to neutral with Dowex 50W-X 8 (H^+) resin. The resin was filtered off. The filtrate was evaporated to give a residue, which was recrystallized with CH_2Cl_2 to afford **2** (1.8 g, 91%) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (s, 1 H), 9.64 (s, 1 H), 8.13 (d, J = 9.3 Hz, 2 H), 7.45−7.30 (m, 10 H), 7.16 (d, J = 9.0 Hz, 2 H), 6.79 (d, J = 1.8 Hz, 1 H), 6.38 (d, J = 2.1 Hz, 1 H), 5.17 (s, 2 H), 5.15 (s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 163.9, 160.4, 159.6, 156.0, 146.5, 136.6, 136.4, 136.1, 129.3, 128.5, 128.4, 128.1, 127.9, 127.8 (2 C), 123.3, 114.8, 104.2, 98.0, 92.8, 69.9, 69.3; HRMS (MALDI) calcd for $C_{29}H_{23}O_6$ $[M + H]^+$ 467.1495, found 467.1489.

3,6-Di-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose (9). To a suspension of sodium hydride (698 mg, 17.4 mmol) and allyl alcohol (9.1 mL, 133.3 mmol) in dry DME (14.0 mL) was added a solution of **8** (2.1 g, 8.7 mmol) in DME (14.0 mL) at 0 °C. The mixture was stirred at 50 °C for 6 h, and was then diluted with saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (100 mL) three times. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 1:5) to give **9** (2.2 g, 83%) as a colorless oil: $[\alpha]^{24}_D$ −34.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.85 (m, 3 H), 5.35−5.18 (m, 4 H), 4.58 (d, J = 3.9 Hz, 1 H), 4.22−4.04 (m, 7 H), 3.73 (m, 1 H), 3.60 (m, 1 H), 1.49 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 133.8, 117.7, 117.2, 111.6, 105.0, 82.2, 81.7, 79.6, 72.2, 71.8, 71.2, 67.8, 26.6, 26.1; HRMS (ESI) calcd for $C_{15}H_{24}O_6$ [M] 300.1573, found 300.1576.

Ethyl 2,4-Di-*O*-acetyl-3,6-di-*O*-allyl-1-thio-β-D-glucopyranoside (10). A solution of **9** (2.6 g, 7.2 mmol) in 80% HOAc/H_2O (54 mL) was refluxed for 3 h. After cooling, the solvent was removed under vacuum. The residue was dissolved in dry pyridine (15 mL), and then Ac_2O (5 mL) was added. The reaction mixture was stirred overnight, and was then concentrated. The resulting crude product was dissolved in dry CH_2Cl_2 (67 mL) and then treated with EtSH (10 mL) at 0 °C. BF_3OEt_2 (1 mL) was added dropwise to the reaction mixture, and stirring was continued for 2 h at 0 °C and then for 20 h at rt. Saturated aq $NaHCO_3$ was added and the mixture was stirred for 2 h. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 1:6) to yield **10** (1.4 g, 50% for 3 steps) as a white solid: $[\alpha]^{29}_D$ −23.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 2 H), 5.26 (m, 4 H), 5.00 (m, 2 H), 4.39 (d, J = 10.2 Hz, 1 H), 4.07 (d, J = 5.7 Hz, 2 H), 3.96 (d, J = 5.4 Hz, 2 H), 3.60 (m, 4H), 2.76 (m, 2 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 1.26 (t, J = 7.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 169.1, 134.2, 134.1, 117.0, 116.6, 83.3, 81.0, 72.9, 72.2, 71.1, 70.6, 69.5, 23.8, 20.8 (2 C), 14.6; HRMS (MALDI) calcd for $C_{18}H_{28}O_7SNa$ $[M + Na]^+$ 411.1453, found 411.1448.

Ethyl 3,6-Di-*O*-allyl-2,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside (11). A mixture of **10** (42 mg, 0.1 mmol) and K_2CO_3 (15 mg, 0.1 mmol) in MeOH/THF (1.5 mL, v/v 1:2) was stirred for 20 h at rt. The mixture was neutralized with Dowex 50W-X 8 (H^+) resin, and the resin was then filtered off. The filtrate was evaporated to give ethyl 3,6-di-*O*-allyl-1-thio-β-D-glucopyranoside (31 mg, 95%) as a white solid. To a solution of the above solid (31 mg, 0.1 mmol) in dry DMF (1 mL) was add NaH (16 mg, 0.4 mmol). After 10 min of stirring at 0 °C, BnBr (0.05 mL) was added. The reaction mixture was stirred at room temperature for 2 h, and was then cooled to 0 °C and quenched by slow addition of an icy saturated aq NH_4Cl solution. The resulting mixture was extracted twice with EtOAc (100 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 1:18) to provide **11** (50 mg, 100%) as a white solid: $[\alpha]^{29}_D$ −5.0 (c 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.27 (m, 10 H), 6.04 (m, 2 H), 5.33 (dd, J = 6.3, 1.8 Hz, 1 H), 5.28 (m, 1 H), 5.19 (s, 1 H), 5.16 (s, 1 H), 4.90 (m, 2 H), 4.75 (d, J = 9.9 Hz, 1 H), 4.65 (d, J = 10.8 Hz, 1 H), 4.43 (m, 3 H), 4.09−3.97 (m, 2 H), 3.73 (dd, J = 10.8, 2.1 Hz, 1 H), 3.64 (dd, J = 11.1, 4.8 Hz, 1 H), 3.56 (m, 2 H), 3.42 (m, 2 H), 2.84 (m, 2 H), 1.34 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 135.0, 134.7, 128.4 (2 C), 128.3, 128.0, 127.8 (2 C), 116.9, 116.7, 86.2, 84.9, 81.6, 78.9, 77.8, 75.5, 75.0, 74.4, 72.3, 69.0, 24.9, 15.0; HRMS (MALDI) calcd for $C_{28}H_{36}O_5SNa$ $[M + Na]^+$ 507.2181, found 507.2176.

Ethyl 2,4-Di-*O*-benzyl-1-thio-β-D-glucopyranoside (12). To a solution of **11** (400 mg, 0.8 mmol) in DMSO (6.2 mL) at room temperature under argon was added *t*-BuOK (194 mg, 1.7 mmol). The reaction mixture was heated to 100 °C for 20 min and then diluted with water. The resulting mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were concentrated in vacuum. The crude enol ether was dissolved in acetone (60 mL) and treated with 1 N HCl (10 mL). After 2 h of stirring at 60 °C, the reaction was quenched with concentrated NH_4OH. The resulting mixture was extracted three times with EtOAc (100 mL), then the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, l:3) to provide **12** (250 mg, 75%) as a white solid: $[\alpha]^{29}_D$ −3.3 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.28 (m, 10 H), 4.97 (d, J = 10.8 Hz, 1 H), 4.86 (d, J = 10.8 Hz, 1 H), 4.70 (d, J = 4.8 Hz, 1 H), 4.66 (d, J = 4.8 Hz, 1 H), 4.48 (d, J = 9.9 Hz, 1 H), 3.90 (dd, J = 12.0, 2.4 Hz, 1 H), 3.79 (m, 2 H), 3.50 (t, J = 9.3 Hz, 1 H), 3.37 (m, 1 H), 3.28 (t, J = 9.3 Hz, 1 H), 2.79 (m, 2 H), 1.34 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.9, 128.5(2 C), 128.2, 128.0, 127.9, 84.8, 81.4, 78.9, 78.3, 77.4,

75.2, 74.7, 62.1, 25.2, 15.1; HRMS (MALDI) calcd for $C_{22}H_{28}O_5SNa$ [M + Na]$^+$ 427.1555, found 427.1550.

Ethyl 3,6-Di-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside (13). To a solution of compound **12** (202 mg, 0.5 mmol) in pyridine (3.8 mL) at room temperature was added acetic anhydride (0.5 mL). After being stirred for 3 h, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, l:3) to provide **13** (244 mg, 100%) as a white solid: $[\alpha]^{29}_D$ +6.8 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.37−7.23 (m, 10 H), 5.33 (t, *J* = 8.7 Hz, 1 H), 4.88 (d, *J* = 11.1 Hz, 1 H), 4.58 (m, 4 H), 4.35 (dd, *J* = 12.0, 1.2 Hz, 1 H), 4.22 (dd, *J* = 12.3, 4.8 Hz, 1 H), 3.58 (m, 2 H), 3.42 (t, *J* = 9.3 Hz, 1 H), 2.80 (m, 2 H), 2.06 (s, 3 H), 1.88 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.6, 169.8, 137.5, 137.1, 128.5, 128.3, 128.1, 128.0 (2 C), 127.8, 85.2, 79.4, 77.0, 76.0, 74.8, 74.4, 63.1, 25.4, 20.9, 20.8, 15.0; HRMS (MALDI) calcd for $C_{26}H_{32}O_7SNa$ [M + Na]$^+$ 511.1766, found 511.1761.

7,4′-Di-*O*-benzyl-3-*O*-(3″,6″-di-*O*-acetyl-2″,4″-di-*O*-benzyl-*β*-D-glucopyranosyl)-Kaempferol (14). To a solution of compound **13** (58 mg, 1.2 mmol) in dry CH_2Cl_2 (1.5 mL) was added liquid bromine (0.05 mL) with stirring for 25 min at 0 °C, The solvent was evaporated in vacuo, then the resulting residue was coevaporated with toluene twice (2 × 10 mL) to give glucosyl bromide **3**, which was used in the glycosylation reaction without further purification. To the above glucosyl bromide in $CHCl_3$ (1.7 mL) was added compound **2** (30 mg, 0.07 mmol), aqueous K_2CO_3 (0.1 N, 1.7 mL), and TBAB (23 mg, 0.07 mmol). The mixture was stirred vigorously at 50 °C for 8 h, then the organic phase was collected, dried over Na_2SO_4, and concentrated. The residue was subject to column chromatography on silica gel (petroleum ether−acetone, 5:1) to provide **14** (31 mg, 54%) as a yellow solid: $[\alpha]^{25}_D$ −12.3 (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 12.61 (s, 1 H), 8.02 (d, *J* = 8.7 Hz, 2 H), 7.47−7.21 (m, 20 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 6.51 (d, *J* = 2.1 Hz, 1 H), 6.44 (d, *J* = 2.1 Hz, 1 H), 5.53 (d, *J* = 7.8 Hz, 1 H), 5.36 (t, *J* = 9.3 Hz, 1 H), 5.12 (s, 4 H), 5.03 (d, *J* = 11.7 Hz, 1 H), 4.76 (d, *J* = 11.7 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.49 (d, *J* = 11.1 Hz, 1 H), 4.17 (d, *J* = 11.4 Hz, 1 H), 4.01 (dd, *J* = 11.7, 3.6 Hz, 1 H), 3.60 (m, 3 H), 1.93 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 177.7, 170.2, 169.6, 164.4, 161.9, 160.6, 157.2, 156.6, 138.1, 137.2, 136.2, 135.6, 134.0, 130.7, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.4 (2 C), 123.1, 114.3, 106.0, 101.6, 98.6, 93.0, 78.9, 75.6, 75.2, 74.2, 73.4, 72.4, 70.3, 70.0, 62.1, 21.0, 20.5; HRMS (MALDI) calcd for $C_{53}H_{48}O_{13}Na$ [M + Na]$^+$ 915.2993, found 915.2987.

7,4′-Di-*O*-benzyl-3-*O*-(2″,4″-di-*O*-benzyl-*β*-D-glucopyranosyl)-Kaempferol (15). A solution of **14** (30 mg, 0.03 mmol) and K_2CO_3 (5 mg, 0.04 mmol) in MeOH/THF (1.5 mL, v/v 1:2) was stirred for 10 h at rt. The mixture was neutralized with Dowex 50W-X 8 (H^+) resin, and the resin was then filtered off. The filtrate was evaporated. The residue was subjected to silica gel column chromatography (acetone−petroleum ether, l:3) to give **15** (23 mg, 85%) as a yellow solid: $[\alpha]^{28}_D$ +11.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 12.59 (s, 1 H), 8.07 (d, *J* = 9.0 Hz, 2 H), 7.49−7.31 (m, 20 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 6.54 (d, *J* = 1.8 Hz, 1 H), 6.47 (d, *J* = 1.8 Hz, 1 H), 5.29 (m, 2 H), 5.14 (s, 4 H), 4.91 (d, *J* = 11.4 Hz, 1 H), 4.82 (d, *J* = 11.1 Hz, 1 H), 4.66 (d, *J* = 8.1 Hz, 1 H), 3.85 (t, *J* = 8.7 Hz, 1 H), 3.59 (dd, *J* = 12.3, 2.7 Hz, 1 H), 3.51 (m, 3 H), 3.26 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 177.8, 164.5, 162.0, 160.8, 157.6, 156.7, 138.1 (2 C), 136.1, 135.6, 134.5, 130.6, 128.7 (2 C), 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.4 (2 C), 123.2, 114.4, 106.1, 102.5, 98.7, 93.1, 81.2, 76.4, 76.1, 74.6, 74.5, 74.2, 70.4, 70.1, 61.5; HRMS (MALDI) calcd for $C_{49}H_{44}O_{11}Na$ [M + Na]$^+$ 831.2781, found 831.2776.

7,4′-Di-*O*-benzyl-3-*O*-[3″,6″-di-*O*-(4‴-*O*-benzyl-*E*-coumaroyl)-2″,4″-di-*O*-benzyl-*β*-D-glucopyranosyl]-Kaempferol (16). To a suspension of **15** (23 mg, 0.03 mmol), *E*-4-benzyloxycinnamic acid (43 mg, 0.2 mmol), and DCC (29 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) was added DMAP (3 mg). After 5 h of reflux, the suspension was filtered. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography to give a mixture of products. To a solution of the above product and 4-MeC_6H_4SH (30 mg, 0.244 mmol) in dry DMF (1 mL) was added DBU (0.01 mL). After being stirred for 7 h at 40 °C, the mixture was diluted with water, and was then extracted with EtOAc. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (acetone−petroleum ether, l:4) to provide **16** (22 mg, 60%, two steps) as a yellow solid: $[\alpha]^{25}_D$ −56.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 12.65 (s, 1 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 16.2 Hz, 1 H), 7.53−7.17 (m, 35 H), 7.04−6.90 (m, 6 H), 6.45 (s, 1 H), 6.39 (s, 1 H), 6.26 (d, *J* = 15.6 Hz, 1 H), 6.19 (d, *J* = 15.9 Hz, 1 H), 5.67 (d, *J* = 7.5 Hz, 1 H), 5.55 (t, *J* = 8.7 Hz, 1 H), 5.13 (s, 2 H), 5.09 (s, 2 H), 5.00 (m, 5 H), 4.81 (d, *J* = 11.7 Hz, 1 H), 4.59 (d, *J* = 10.8 Hz, 1 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 4.33 (m, 2 H), 3.72 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 177.8, 166.4, 165.9, 164.3, 162.0, 160.6, 160.5, 157.4, 156.7, 144.9, 144.5, 138.1, 137.2, 136.3 (3 C), 135.7, 134.0, 130.8, 129.8 (2 C), 128.7, 128.6 (3 C), 128.5, 128.4, 128.3, 128.1 (2 C), 127.9, 127.4 (2 C), 127.3, 127.1, 123.1, 115.3, 115.2, 115.1, 115.0, 114.3, 106.0, 101.6, 98.6, 93.0, 78.7, 75.7, 75.3, 74.2, 73.2, 72.8, 70.3, 70.1, 69.9, 69.8, 62.1; HRMS (ESI) calcd for $C_{81}H_{68}O_{15}Na$ [M + Na]$^+$ 1303.4456, found 1303.4450.

3-*O*-(3″,6″-Di-*O*-*E*-*p*-coumaroyl)-*β*-D-glucopyranoside (1). To a solution of **16** (14 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (0.03 mL) at −78 °C. After being stirred for 4 h at this temperature, the mixture was quenched with MeOH (1 mL) and concentrated in vacuo. The residue was purified by preparative TLC (MeOH−$CHCl_3$, l:7) to afford **1** (5 mg, 60%) as a yellow solid: $[\alpha]^{27}_D$ −35.8 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3CN) *δ* 12.25 (s, 1 H), 8.04 (d, *J* = 8.7 Hz, 2 H), 7.73 (d, *J* = 16.2 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 2 H), 7.46 (d, *J* = 16.2 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 6.87 (m, 6 H), 6.43 (s, 1 H), 6.43 (d, *J* = 15.9 Hz, 1 H), 6.22 (s, 1 H), 6.14 (d, *J* = 16.5 Hz, 1 H), 5.31 (d, *J* = 7.8 Hz, 1 H), 5.12 (t, *J* = 9.0 Hz, 1 H), 4.27 (d, *J* = 11.7 Hz, 1 H), 4.21 (dd, *J* = 13.2, 3.9 Hz, 1 H), 3.68 (m, 1 H), 3.58 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD) *δ* 179.6, 169.3, 169.0, 166.2, 163.2, 161.8, 161.5 (2 C), 159.6, 158.7, 147.1, 146.9, 135.5, 132.5, 131.5, 127.6, 127.4, 123.0, 117.1 (2 C), 116.4, 115.7, 115.0, 105.9, 104.1, 100.3, 95.2, 79.0, 76.0, 74.4, 70.5, 64.4; LRMS (ESI) calcd for $C_{39}H_{31}O_{15}$ [M − H]$^+$ 739.2, found 739.1.

2′-(4″-(Benzyloxy)benzoyloxy)-4′,6′-dibenzyloxyacetophenone (19). To a suspension of **17** (348 mg, 1.0 mmol), **18** (342 mg, 1.5 mmol), and EDCI (576 mg, 3.0 mmol) in CH_2Cl_2 (8 mL) was added DMAP (122 mg). After being stirred for 4 h at rt, the mixture was diluted with EtOAc, and then washed with $NaHCO_3$ (aq) and brine successively. The organic phase was dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, l:8) to give **19** (419 mg, 75%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.14 (d, *J* = 8.7 Hz, 2 H), 7.47−7.34 (m, 15 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.56 (d, *J* = 2.1 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 5.16 (s, 2 H), 5.09 (s, 2 H), 5.05 (s, 2 H), 2.50 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 199.3, 164.6, 163.0, 161.1, 158.0, 149.7, 136.1, 135.9, 135.8, 132.4, 128.6, 128.2 (2 C), 127.6, 127.4 (2 C), 121.6, 118.0, 114.7, 101.3, 98.3, 70.8, 70.3, 70.1, 32.0; HRMS (MALDI) calcd for $C_{36}H_{30}O_6Na$ [M + Na]$^+$ 581.1940, found 581.1935.

2′-(4″-(Benzyloxy)benzoyloxy)-4′,6′-dibenzyloxy-2-bromoacetophenone (20). To a solution of **19** (56 mg, 0.1 mmol) in dry THF (1 mL) was added PTT (38 mg, 0.1 mmol) in portions. The reaction mixture was stirred at room temperature for 2 h, and was then poured into water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was concentrated. The residue was

purified by silica gel column chromatography (toluene−petroleum ether, 4:1) to give **20** (31 mg, 49%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.7 Hz, 2 H), 7.44 (m, 15 H), 7.04 (d, J = 8.7 Hz, 2 H), 6.54 (s, 2 H), 5.13 (s, 2 H), 5.08 (s, 2 H), 5.03 (s, 2 H), 4.35 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 164.5, 163.1, 162.0, 158.3, 151.1, 136.1, 135.7, 135.3, 132.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 127.6, 127.5, 127.4, 121.4, 114.7, 114.1, 102.0, 98.2, 71.2, 70.5, 70.1, 36.7; HRMS (MALDI) calcd for $C_{36}H_{29}O_6BrNa$ $[M + Na]^+$ 659.1045, found 659.1040.

2-Benzoyloxy-2′-(4″-(benzyloxy)benzoyloxy)-4′,6′-dibenzyloxyacetophenone (21). A mixture of **20** (31 mg 0.05 mmol) and BzOK (12 mg, 0.07 mmol) was stirred in CH_3CN (1 mL) at refluxing temperature for 36 h. The mixture was diluted with EtOAc, and was then washed with water and brine. After concentration in vacuo, the residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 1:5) to give **21** (22 mg, 68%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 2 H), 8.03 (d, J = 8.1 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1H), 7.46−7.36 (m, 17 H), 7.03 (d, J = 9.0 Hz, 2 H), 6.57 (s, 1 H), 6.55 (s, 1 H), 5.25 (s, 2 H), 5.12 (s, 2 H), 5.11 (s, 2 H), 5.05 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 165.7, 164.6, 163.0, 162.0, 158.8, 151.2, 136.1, 135.7, 135.4, 133.0, 132.6, 129.8, 129.6, 128.7 (2 C), 128.6, 128.4, 128.3, 128.2 (2 C), 127.6, 127.5, 127.4, 121.6, 114.6, 114.1, 102.2, 98.2, 71.1, 70.4, 70.0, 69.6; HRMS (MALDI) calcd for $C_{43}H_{34}O_8Na$ $[M + Na]^+$ 701.2151, found 701.2146.

5,7,4′-Tri-*O*-benzyl-Kaempferol (22). To a suspension of sodium hydride (230 mg, 5.76 mmol) in dry THF (20 mL) was added **21** (976 mg, 1.44 mmol) in THF (10 mL). The mixture was refluxed for 90 min with stirring. The cooled mixture was poured into a mixture of ice containing concentrated HCl (2 mL), and was then extracted with CH_2Cl_2 (3 × 100 mL). After the solvent was removed, the resulting residue was dissolved in AcOH (11 mL), then AcONa (181 mg) was added. After being stirred at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The mixture was washed with water and aq $NaHCO_3$ successively. The organic phase was concentrated to give a residue, which was dissolved in $MeOH/CH_2Cl_2$ (8 mL, v/v 1:1). After being stirred for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were filtered, then the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (acetone−petroleum ether−CH_2Cl_2, 1:20:8) to provide **22**[5e] (562 mg, 70%) as a yellow solid.

3,6-Di-*O*-allyl-2,4-di-*O*-benzoyl-D-glucopyranosyl *o*-Hexynylbenzoate (23b) (A Typical Procedure for the Synthesis of Glycosyl *o*-Hexynylbenzoates 23a−g). A solution of 3,6-di-*O*-allyl-2,4-di-*O*-benzoyl-D-glucopyranose [prepared from compound **9** via three steps in 58% yield, i.e., removal of the isopropylidene (80% HOAc, reflux), benzoylation (BzCl, pyridine, rt), and removal of the anomeric benzoate ($BnNH_2$, THF, rt)] (105 mg, 0.22 mmol), *o*-hexynylbenzoic acid (55 mg, 0.27 mmol), DMAP (27 mg, 0.22 mmol), and DCC (68 mg, 0.33 mmol) in dry CH_2Cl_2 was stirred for 3 h at rt. The resulting mixture was diluted with CH_2Cl_2 and was then filtered through a pad of Celite. The filtrate was washed with saturated aq $NaHCO_3$ solution and then concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether−EtOAc 7:1) to provide **23b** (134 mg, 92%) as a colorless oil. A small portion of the α and β anomers was separated for characterization. **23b-α**: $[\alpha]^{28}_D$ +65.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2 H), 7.98 (m, 3 H), 7.63 (m, 6 H), 7.41 (m, 3 H), 6.79 (d, J = 3.9 Hz, 1 H), 5.84 (m, 1 H), 5.69 (m, 3 H), 5.20 (m, 4 H), 4.40 (m, 2 H), 4.19 (m, 2 H), 3.97 (d, J = 6.0 Hz, 2 H), 3.68 (m, 2 H), 2.42 (t, J = 6.6 Hz, 2 H), 1.60 (m, 2 H), 1.48 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (2 C), 164.0, 134.9, 134.3, 134.1, 133.3, 133.2, 132.1, 130.6, 130.4, 129.7, 129.6, 129.3, 128.5, 128.4, 127.2, 125.1, 117.5, 117.0, 96.8, 90.5, 79.4, 76.9, 73.3, 72.6, 72.1, 71.9, 70.7, 68.8, 30.6, 22.0, 19.6, 13.6. **23b-β**: $[\alpha]^{28}_D$ 20.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.2 Hz, 2 H), 8.03 (d, J = 7.2 Hz, 2 H), 7.97 (d, J = 7.8 Hz, 1 H), 7.64 (m, 5 H), 7.43 (m, 3 H), 7.30 (m, 1 H), 6.17 (d, J = 8.1 Hz, 1 H), 5.84 (m, 1 H), 5.71 (m, 3 H), 5.19 (m, 4 H), 4.10 (m, 4 H), 3.96 (d, J = 6.0 Hz, 2 H), 3.72 (dd, J = 11.1, 3.3 Hz, 1 H), 3.64 (dd, J = 10.8, 5.1 Hz, 1 H), 2.50 (t, J = 6.9 Hz, 2 H), 1.67 (m, 2 H), 1.57 (m, 2 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 164.9, 163.5, 134.5, 134.2, 134.1, 133.4, 133.3, 132.3, 130.9, 129.7 (2 C), 129.5, 129.3 (2 C), 128.5, 128.4, 127.2, 125.7, 117.6, 117.4, 97.1, 92.4, 79.4, 79.0, 74.7, 73.2, 72.6, 72.1, 70.7, 68.8, 30.6, 22.0, 19.5, 13.6; HRMS (ESI) calcd for $C_{39}H_{40}O_9Na$ $[M + Na]^+$ 675.2570, found 675.2565.

5,7,4′-Tri-*O*-benzyl-3-*O*-(3″,6″-di-*O*-allyl-2″,4″-di-*O*-benzoyl-β-D-glucopyranosyl)-Kaempferol (24b) (A Typical Procedure for the Glycosylation of 22 with Glycosyl *o*-Hexynylbenzoates 23a−g). To a stirred mixture of glycosyl *o*-hexynylbenzoate **23b** (70 mg, 0.1 mmol), **22** (20 mg, 0.036 mmol), and 4 Å MS in CH_2Cl_2 (1.5 mL) was added $Ph_3PAuNTf_2$ (5 mg, 0.007 mmol). After being stirred at rt overnight, the mixture was filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by silica gel column chromatography (petroleum ether−EtOAc−CH_2Cl_2, 5:1:1) to provide **24b** (32 mg, 90%) as a yellowish oil: $[\alpha]^{25}_D$ −55 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.5 Hz, 2 H), 8.13 (d, J = 6.6 Hz, 2 H), 8.05 (d, J = 7.8 Hz, 2 H), 7.61−7.34 (m, 21 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.56 (s, 1 H), 6.44 (s, 1 H), 5.98 (d, J = 7.2 Hz, 1 H), 5.61 (m, 3 H), 5.35 (m, 3 H), 5.18 (s, 2 H), 5.07 (m, 6 H), 4.06 (m, 3 H), 3.74 (m, 1 H), 3.66 (m, 2 H), 3.50 (d, J = 11.1 Hz, 1 H), 3.39 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 165.9, 165.4, 163.0, 160.7, 160.0, 158.9, 154.6, 136.8, 136.2, 135.9, 134.7, 134.6, 133.5, 133.2, 130.9, 130.5, 130.0, 129.9, 128.9, 128.7, 128.6, 128.4, 128.0, 127.9, 127.0, 123.5, 117.7, 116.7, 114.7, 110.2, 99.0, 98.6, 94.2, 79.9, 74.7, 74.1, 73.5, 72.7, 71.5, 71.1, 70.7, 70.3, 69.4; HRMS (MALDI) calcd for $C_{62}H_{54}O_{13}Na$ $[M + Na]^+$ 1029.3462, found 1029.3457.

5,7,4′-Tri-*O*-benzyl-3-*O*-(3″,6″-di-*O*-allyl-2″,4″-di-*O*-benzyl-β-D-glucopyranosyl)-Kaempferol (25). To a solution of **24b** (23 mg, 0.023 mmol) in $MeOH/CH_2Cl_2$ (1.6 mL, v/v 1:3) at room temperature was added NaOMe (7 mg, 0.13 mmol). After being stirred overnight, the mixture was adjusted to neutral with Dowex 50W-X 8 (H^+) resin. The resin was then filtered off. The filtrate was concentrated and the residue was dissolved in dry DMF (1.5 mL). To the mixture was added NaH (4 mg, 0.08 mmol) and BnBr (0.01 mL) at 0 °C. After being stirred overnight at rt, the mixture was poured into ice water and extracted with EtOAc. The organic phase was washed with water and brine, and then dried and concentrated. The residue was purified by silica gel column chromatography (petroleum ether−EtOAc, 6:1) to give **25** (16 mg, 72%) as a yellow solid: $[\alpha]^{28}_D$ −6.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 2 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.49−7.26 (m, 23 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.58 (s, 1 H), 6.46 (s, 1 H), 6.03 (m, 1 H), 5.70 (m, 2 H), 5.31 (m, 3 H), 5.18−4.95 (m, 8 H), 4.85 (d, J = 10.5 Hz, 2 H), 4.64 (d, J = 10.8 Hz, 1 H), 4.48 (dd, J = 11.1, 4.8 Hz, 1 H), 4.32 (dd, J = 12.3, 5.1 Hz, 1 H), 3.70 (m, 6 H), 3.48 (d, J = 11.4 Hz, 1 H), 3.34 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 162.9, 160.5, 160.1, 159.0, 154.3, 139.2, 138.7, 136.8, 136.7, 136.5, 136.0, 135.5, 135.3, 130.8, 129.0, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.0, 124.0, 116.9, 116.1, 114.6, 110.3, 101.4, 98.4, 94.1, 84.3, 82.5, 77.8, 75.4, 75.2, 74.8, 74.2, 72.5, 71.1, 70.7, 70.3, 68.8; HRMS (MALDI) calcd for $C_{62}H_{58}O_{11}Na$ $[M + Na]^+$ 1001.3877, found 1001.3871.

5,7,4′-Tri-*O*-benzyl-3-*O*-[3″,6″-di-*O*-(4‴-*O*-benzyl-*E*-coumaroyl)-2″,4″-di-*O*-benzyl-β-D-glucopyranosyl]-Kaempferol (26). To a solution of **25** (16 mg, 0.016) in $MeOH/CH_2Cl_2$ (1.8 mL, v/v 1:2) was added $PdCl_2$ (3 mg, 0.017 mmol). After being stirred for 5 h, the

mixture was filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography (EtOAc−petroleum ether, 2:5) to provide the corresponding 3″,6″-diol, which was dissolved in dry CH_2Cl_2 (2 mL). To the mixture was added *E*-4-benzyloxycinnamic acid (25 mg, 0.1 mmol), DCC (10 mg, 0.05 mmol), and DMAP (2 mg). After 5 h of reflux, the suspension was filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether−acetone, 4:1) to provide **26** (15 mg, 66% for two steps) as a yellow solid: $[\alpha]^{28}_{D}$ −37.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.7 Hz, 2 H), 7.69 (m, 3 H), 7.51−7.19 (m, 38 H), 7.04 (m, 4 H), 6.88 (d, J = 7.8 Hz, 2 H), 6.51 (s, 1 H), 6.43 (m, 1 H), 6.27 (d, J = 15.6 Hz, 1 H), 6.17 (d, J = 15.9 Hz, 1 H), 5.90 (d, J = 7.2 Hz, 1 H), 5.52 (m, 1 H), 5.25 (s, 2 H), 5.13 (s, 2 H), 5.02 (m, 8 H), 4.58 (d, J = 10.5 Hz, 1 H), 4.50 (d, J = 10.5 Hz, 1 H), 4.31 (m, 2 H), 3.67 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 166.4, 166.0, 162.6, 160.6, 160.5, 160.1, 159.7, 158.7, 154.5, 144.8, 144.3, 138.4, 137.3, 136.4 (2 C), 136.3, 135.9, 135.6, 130.5, 129.8, 129.7, 128.7, 128.6 (2 C), 128.5, 128.3 (2 C), 128.1, 128.0, 127.8, 127.6 (2 C), 127.4 (2 C), 127.3, 127.2, 127.1, 126.5, 123.7, 115.4, 115.2, 115.0, 114.2, 109.9, 100.7, 98.0, 93.8, 78.4, 75.8, 75.2, 74.2, 72.6, 72.5, 70.7, 70.4, 70.0, 69.9, 69.8, 62.3; HRMS (MALDI) calcd for $C_{88}H_{74}O_{15}Na$ $[M + Na]^+$ 1393.4925, found 1393.4920.

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Supporting Information Available: Experimental details and characterization data for compounds **23a**, **23f**,**g**, **24a**, **24d**−**g**, and 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.