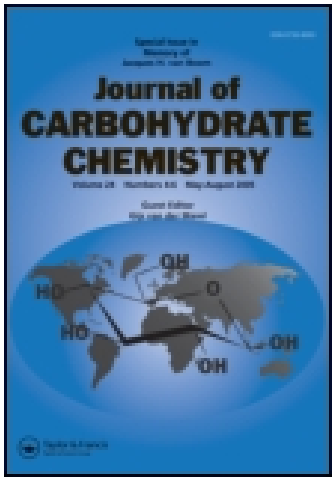




Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

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Published online: 03 Feb 2015.

To cite this article: Zhiling Cao, Yingying Qu, Jiexing Zhou, Weiwei Liu & Guowei Yao (2015) Stereoselective Synthesis of Quercetin 3-O-Glycosides of 2-Amino-2-Deoxy-d-Glucose Under Phase Transfer Catalytic Conditions, Journal of Carbohydrate Chemistry, 34:1, 28-40, DOI: 10.1080/07328303.2014.996290

To link to this article: http://dx.doi.org/10.1080/07328303.2014.996290

*Journal of Carbohydrate Chemistry, 34:28–40, 2015*

*ISSN: 0732-8303 print / 1532-2327 online*
*DOI: 10.1080/07328303.2014.996290*



# Stereoselective Synthesis of Quercetin 3-O-Glycosides of 2-Amino-2-Deoxy-D-Glucose Under Phase Transfer Catalytic Conditions

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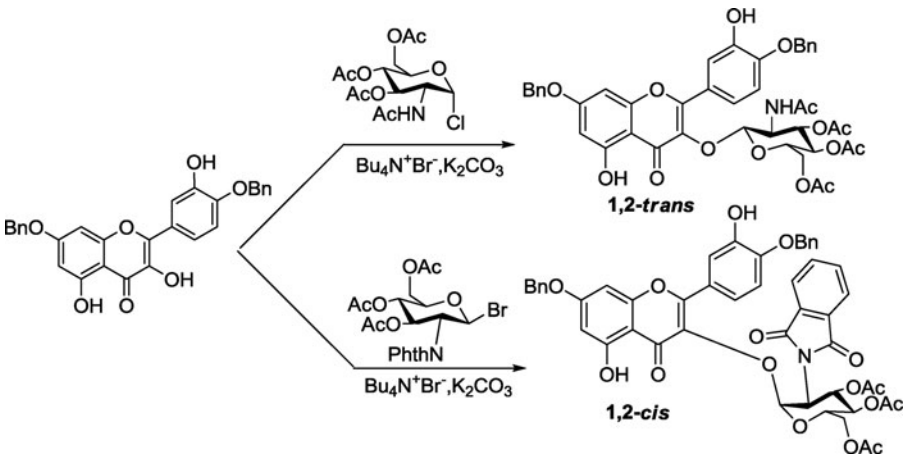
GRAPHICAL ABSTRACT




Received October 8, 2013; accepted December 4, 2014.
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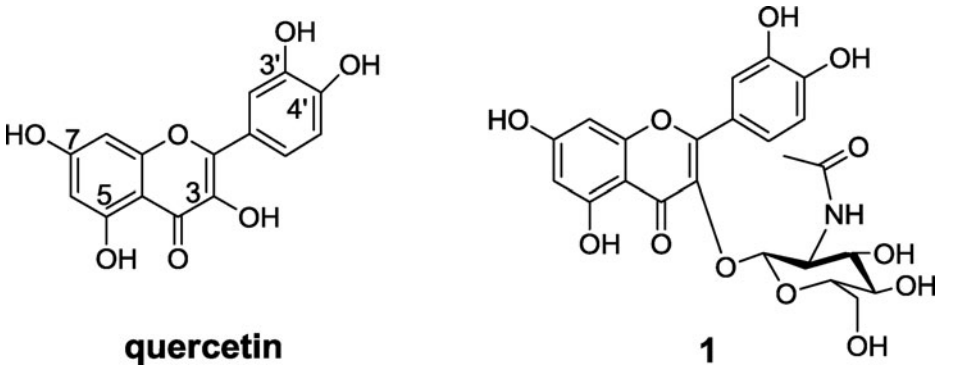



**Figure 1:** Structures of quercetin and its 1,2-*trans* glycoside of 2-amino-2-deoxy-D-glucose **1**.

This article describes the stereoselective synthesis of quercetin 3-*O*-glycosides of 2-amino-2-deoxy-D-glucose. Efficient 1,2-*trans*-glycosylation of protected quercetin with *N*-acetyl-protected 2-amino-2-deoxy-D-glucose chloride was achieved under phase transfer catalytic conditions in a 0.15 M aqueous $K_2CO_3$/chloroform system using tetrabutylammonium bromide as the catalyst. On the contrary, glycosylation with the *N*-phthalimido-protected bromide donor under the same conditions was found to give predominantly 1,2-*cis*-glycoside product.

**Keywords** Quercetin; Glycosides; 2-Amino-2-deoxy-D-glucose; Stereoselective synthesis; Phase transfer catalysis



## INTRODUCTION

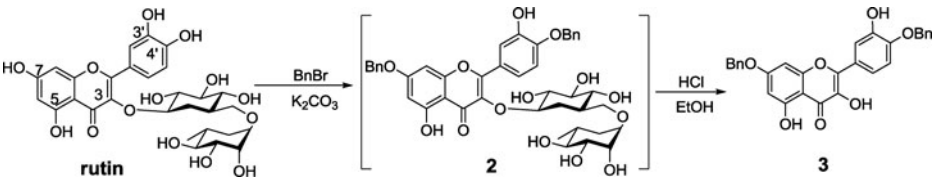
Glycosides, glycoconjugates, and polysaccharides are the most abundant nature products, in which sugar residues are attached to one another or to aglycones via *O*-glycosidic bonds.[1] Typical flavonoids, including quercetin and its glycosides, are polyphenolic compounds and widely distributed in plants.[2] Quercetin glycosides are not only dietary flavonoids but also promising compounds for disease prevention and therapy.[3–5] A variety of sugars (e.g., glucose, galactose, and arabinose) are present in quercetin glycosides, which can enhance quercetin solubility and absorption.[6] The demand for efficient methodologies to synthesize quercetin glycosides is now increasing.[7,8] However, regioselective synthesis of quercetin glycosides remains a difficult task.[9–13] Furthermore, amino sugar glycosides are rarely found in natural and unnatural flavonoid products. In a few reports, a 3-amino-ribopyranose flavonoid was isolated from a culture of *Streptomyces* sp., which has exhibited antibacterial activity against *Bacillus subtilis*.[14] Recently, Joong-Hoon Ahn and coworkers reported a novel quercetin glycoside, 3-*O*-$\beta$-glycoside of 2-amino-2-deoxy-D-glucose (**1**) (Fig. 1), which was isolated from the culture broth of an engineered *Escherichia coli*.[15] Compound **1** has the unique

flavonoid structure and potentially intriguing biological functions because 2-amino-2-deoxy-D-glucose is distributed in many living organisms and plays an important role in their life cycle.[16,17]

The isolation of **1** and its derivatives from nature has been limited by their low biosynthetic yields and diversity of the anomeric linkages. The chemical synthesis of 1,2-*cis* glycosides of 2-amino-2-deoxy-D-glucose is also challenging, and no successful general method for 1,2-*cis* glycosylation has emerged yet.[18–21] In this article, we report the efficient preparation of compound **1** from rutin. In the process, our efforts were focused on the stereoselective synthesis of quercetin 1,2-*cis*-glycosides of 2-amino-2-deoxy-D-glucose.

## RESULTS AND DISCUSSION

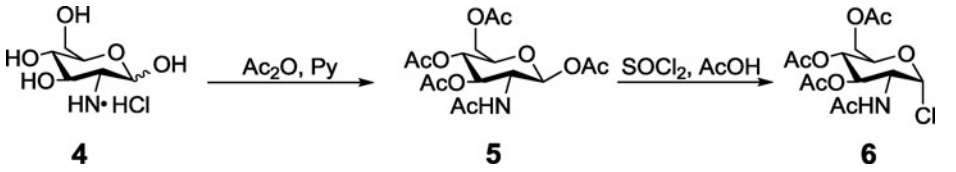
Quercetin aminosugar glycoside **1** was retrosynthetically disconnected into two distinct fragments—suitably protected quercetin and 2-amino-2-deoxy-D-glucosyl donor, respectively. For quercetin glycoside synthesis, *O*-benzyl-protected quercetins have always been used, and regioselective benzylation or glycosylation of quercetin is feasible due to the difference in reactivity among its phenolic OH groups. It has been proved that quercetin phenolic OH groups have the preferential glycosylation reactivity order of 7-OH > 3-OH > 4′-OH > 3′-OH > 5-OH.[22] Therefore, we first developed an efficient method for the synthesis of 7,4′-di-*O*-benzylquercetin (**3**), which should be good enough to be selectively glycosylated at 3-OH. Previously, Jurd and coworkers reported the preparation of **3** from quercetin via controlled benzylation of quercetin pentacetate.[23] Although Jurd's procedure has been cited and adapted by many researchers, the method is tedious and low yielding.[11] In our synthesis of **3**, rutin, quercetin-3-*O*-rudinoside, was used as the starting material (Sch. 1). Benzylation of rutin was well controlled by slow addition of two equivalents of benzyl bromide in DMF. Without the need for separation of benzylated rutin intermediate **2**, subsequent hydrolysis with concentrated hydrochloric acid gave **3** in a 58% yield.




**Scheme 1:** Synthesis of 7,4′-di-*O*-benzylquercetin **3**.

In previous syntheses of quercetin *O*-glycosides, glycosyl bromides or chlorides have been generally employed as donors for glycosylations under Koenigs–Knorr conditions promoted by silver salts, inorganic base, or phase

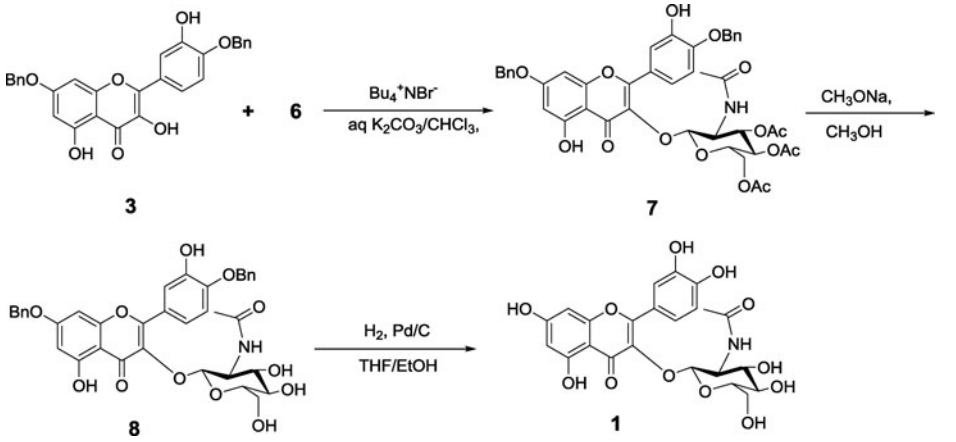
transfer catalysis (PTC).[24] For the glycosylation of **3**, we chose the easily accessible 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl chloride **6** as glycosyl donor, which was prepared in a high yield by treatment of 1,2-*trans*-glucosamine penta-acetate **5** with a mixture of thionyl chloride and acetic acid (Sch. 2).




**4** **5** **6**

**Scheme 2:** Synthesis of chloride donor **6**.

For the glycosylation of **3** with **6**, we initially investigated conditions using $Ag_2O$, AgOTf, or inorganic base as activators but without success. After multiple attempts, the glycosylation reaction was achieved under mild PTC conditions in a 15 mg/mL $K_2CO_3/CHCl_3$ system with tetrabutylammonium bromide as the catalyst to yield 1,2-*trans*-quercetin glycoside **7** (68% yield, Sch. 3). The resulting glycoside **7** was *O*-deacetylated using sodium methoxide in a mixture of methanol and THF. Further debenzylation of **8** with 10% Pd/C and $H_2$ in THF afforded quercetin glycoside **1** (45% total yield). Glycoside **1** was identified as the 1,2-*trans*-$\beta$-anomer based on the anomeric proton coupling constant $J_{1,2}$ (8.4 Hz) of its sugar residue observed in $^1$H NMR spectra. Furthermore, correlation in the HMBC spectrum between anomeric proton ($\delta$ 5.62) and C-3 carbon ($\delta$ 133.2) was also observed (Fig. 2) to clearly indicate that the glycosidic linkage was indeed at 3-OH.




**Scheme 3:** Synthesis of quercetin 1,2-*trans*-glycoside **1**.

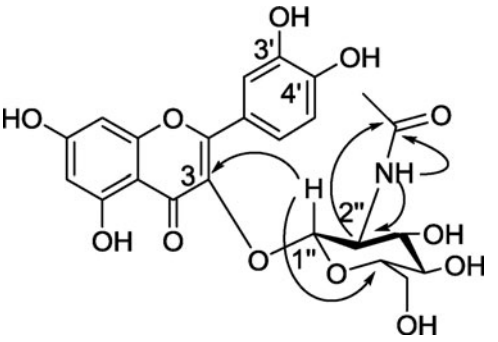
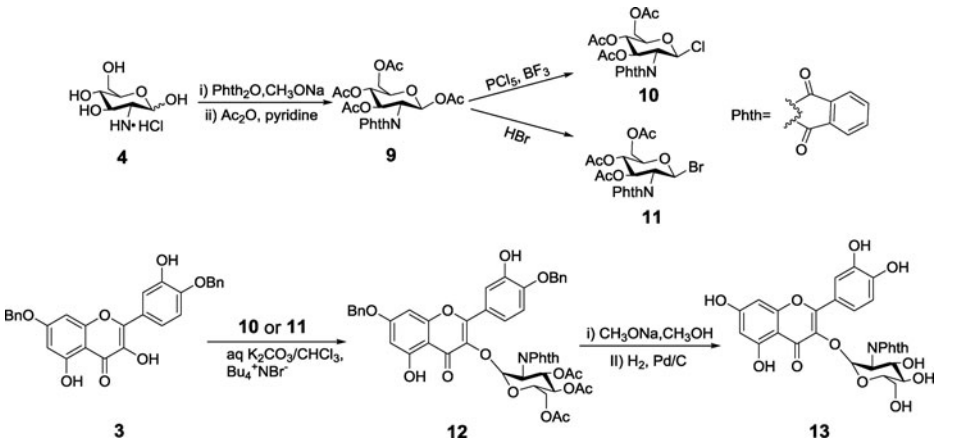



**Figure 2:** Observed correlations in the HMBC spectrum of **1**.

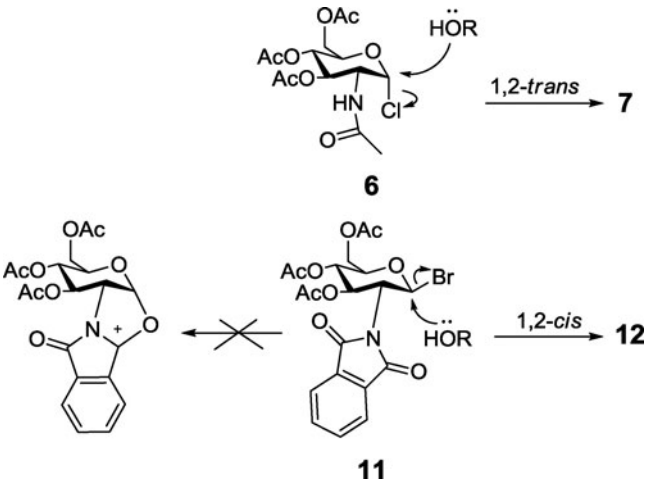
In recent decades, a number of new glycosylation methods have been developed for carbohydrate synthesis. For example, glycosyl trichloroacetimidate and peracetate donors have been used successfully in the glycosylation of phenols.[25,26] This prompted us to investigate other donors for synthesis of **1.** We first tried glycosylation of the 3-OH in **3** with trichloroacetimidate and penta-acetate donors of 2-amino-2-deoxy-D-glucose in the presence of Lewis acid. However, our attempts under various conditions failed. We then tried the traditional Koenigs–Knorr BTC method using glycosyl halide donors **10** and **11** bearing a phthaloyl (Phth) protecting group at *N*-2-position, which were prepared by reacting 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-$\beta$-D-glucopyranose **9** with $PCl_5$-$BF_3$ and HBr, respectively (Sch. 4). It was observed that glycosyl bromide **11** exhibited higher reactivity than glycosyl chloride




**Scheme 4:** Synthesis of glycosylate in higher yield 1,2-*cis*-glycoside **13.**

**10** in the glycosylation of quercetin **3**. More interestingly, both reactions afforded 1,2-*cis*-glycoside **12** unexpectedly, which after deprotection was converted to **13**. The 1,2-*cis*-configuration of **12** and **13** was determined based on the anomeric proton coupling constants $J_{1,2}$ (3.7 Hz and 3.6 Hz, respectively) of its sugar residues observed in their $^1$H NMR spectra.

Phthalimido and acetyl groups are classical neighboring participation groups; thus, normally glycosylation reactions of 2-deoxy-2-acetamido/phthalimidoglycosyl halides have the tendency to form 1,2-*trans*-2-amino glycosides.[27,28] The abnormal phenomenon that occurred in our synthesis of 1,2-*cis* glycoside **12** may be due to the assumed $S_N2$ mechanism, shown in Scheme 5. In the BTC system, there is no powerful promoter for the departure of the bromide anion from glycosyl donors to form a reactive bicyclic acyloxonium ion intermediate. Moreover, the enolic hydroxyl group at the C-3 position of quercetin appeared to be more nucleophilic in the basic BTC system, and its efficient attack at the anomeric position of the glycosyl donor was primarily from the opposite direction of the halogen atom. Accordingly, reversed-phase HPLC was used for monitoring the glycosylation reaction of **11**, and the 1,2-*trans*-glycoside product was not detected.




**Scheme 5:** Proposed mechanism for the glycosylation of quercetin.

## CONCLUSION

In summary, we described the efficient stereoselective synthesis of quercetin 3-*O*-glycosides of 2-amino-2-deoxy-D-glucose. 1,2-*Trans*-glycosylation of protected quercetin was achieved with *N*-acetyl-protected chloride of 2-acetamino-2-deoxy-D-glucose under PTC conditions in 0.15 M aqueous $K_2CO_3$/chloroform with tetrabutylammonium bromide as the catalyst. On the contrary, the *N*-phthalimido-protected bromide donor was found to give predominantly 1,2-*cis* glycoside product. In carbohydrate chemistry, stereoselective synthesis

of 1,2-*cis*-glycosides is more challenging than that of 1,2-*trans*-glycosides.[29] The glycosylation approach based on *N*-phthalimido-protected glycosyl halide donors and BTC offers an exciting strategy for the synthesis of 1,2-*cis*-2-amino glycosides of quercetin. Extension of this method to the preparation of other flavonol glycosides of 2-acetamino-2-deoxy-D-glucose appeared worthy of further exploration.



## EXPERIMENTAL

### General

All reagents were purchased from TCI Shanghai Co. unless otherwise specified. Melting points were measured on an XT-4 melting point apparatus and are uncorrected. NMR spectra were obtained using Bruker AQS AVANCE 300-MHz and 400-MHz spectrometers with tetramethylsilane as the internal standard. Mass spectra were performed with an Agilent Technologies MSD SL Trap mass spectrometer with ESI source coupled with an 1100 Series HPLC system. Silica gel GF254 plates (Yantai Chemical Industrials) were used for thin-layer chromatography (TLC) observed under ultraviolet light ($\lambda$ 254 nm).

### 7,4'-Di-O-Benzylquercetin (3)

To a solution of rutin (1.22 g, 2.0 mmol) in DMF (20 mL) was added $K_2CO_3$ (0.41 g, 3.0 mmol). The mixture was stirred at 60°C, and then a solution of BnBr (0.48 mL, 4.0 mmol) in DMF (10 mL) was added slowly. After further stirring for 2 h, the mixture was concentrated under vacuum. Ethanol (30 mL) and concentrated HCl (3 mL) were added in succession to the residue, and the suspension was refluxed for 1 h. After cooling to rt, the precipitates were filtered and recrystallized from ethanol to give **3** (0.53 g 57.6%) as a yellow solid.[11] m.p. 182–183°C (lit.[23] 181–182°C). $^1$H NMR (300 MHz, DMSO): $\delta$ 12.43 (d, $J = 9.0$ Hz, 1H, 5-OH), 9.61 (s, 1H, 3'-OH), 9.42 (s, 1H, 3-OH), 7.76 (d, $J = 2.2$ Hz, 1H, H-2'), 7.63 (dd, $J = 8.6$, 2.2 Hz, 1H, H-6'), 7.54–7.28 (m, 10H, 2 × Ph), 7.17 (d, $J = 8.8$ Hz, 1H, H-5'), 6.81 (d, $J = 2.1$ Hz, 1H, H-8), 6.44 (d, $J = 2.1$ Hz, 1H H-6), 5.23 (s, 2H, $CH_2$Ph), 5.21 (s, 2H, $CH_2$Ph); ESI-MS m/z: 505 $[M+Na]^+$. Anal. calcd. for $C_{29}H_{22}O_7$: C, 72.19; H, 4.60. Found: C, 72.25; H, 4.51.

### 2-Acetamido-1,3,4,6-tetra-O-Acetyl-2-Deoxy-$\beta$-D-Glucopyrano-Side (5)

To a mixture of acetic anhydride (6 mL) and pyridine (8 mL) in an ice bath was added 2-amino-2-deoxy-D-glucose hydrochloride **1** (1.5 g, 8.3 mmol). The mixture was allowed to gradually warm to ambient temperature and was

stirred overnight. The reaction mixture was then poured into ice water. The resulting precipitates were collected by filtration, washed with ice water, and dried to give compound **5** (3.07 g, 95%). m.p. 186–187°C.[30] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.78 (d, $J = 9.5$ Hz, 1H), 5.69 (d, $J = 8.8$ Hz, 1H), 5.21–5.05 (m, 2H), 4.36–4.19 (m, 2H), 4.11 (dd, $J = 12.5$, 2.2 Hz, 1H), 3.87–3.76 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H).



## 2-Acetamido-3,4,6-tri-O-Acetyl-2-Deoxy-α-D-Glucopyranosyl Chloride (6)

To a solution of **5** (2.0 g, 5.1 mmol) in $CH_2Cl_2$ (20 mL) in an ice bath was added thionyl chloride (6 mL) and acetic acid (1 mL). The mixture was stirred at ambient temperature for 20 h and then concentrated in vacua. The residue was recrystallized from ether to give **6** (1.66 g, 89%). m.p. 125–127°C.[31] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.18 (d, $J = 3.7$ Hz, 1H), 5.86 (d, $J = 8.7$ Hz, 1H), 5.35–5.28 (m, 1H), 5.21 (t, $J = 9.7$ Hz, 1H), 4.53 (ddd, $J = 10.6$, 8.8, 3.7 Hz, 1H), 4.31–4.22 (m, 2H), 4.17–4.08 (m, 1H), 2.10 (s, 3H), 2.05 (s, 6H), 1.98 (s, 3H).

## 7,4′-Di-O-Benzylquercetin 3-O-(2″-Acetamido-3″,4″,6″-tri-O-Acetyl-2″-Deoxy)-β-D-Glucopyranoside (7)

To the solution of quercetin **3** (0.96 g, 2.0 mmol) in $CHCl_3$ (15 mL) was added tetrabutyl ammonium bromide (0.32 g, 1.0 mmol) and 0.15 M $K_2CO_3$ (15 mL). The mixture was vigorously stirred at 45°C for 1 h. Then glycosyl donor **6** (1.46 g, 4.0 mmol) was added. After further stirring for 5 h, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL), and the layers were separated. The organic phase was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc) to yield **7** (1.11 g 68.2%) as a yellow solid. m.p. 215–217°C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 12.29 (s, 1H, 5-OH), 7.75 (d, $J = 2.0$ Hz, 1H, H-2′), 7.67 (dd, $J = 8.7$, 2.0 Hz, 1H, H-6′), 7.49–7.29 (m, 10H, Ph), 7.03 (d, $J = 8.3$ Hz, 1H, H-5′), 6.93 (d, $J = 8.7$ Hz, 1H, NH), 6.47 (d, $J = 1.9$ Hz, 1H, H-6), 6.45 (s, 1H, 3′-OH), 6.41 (d, $J = 2.0$ Hz, 1H, H-8), 5.46 (d, $J = 8.7$ Hz, 1H, H-1″), 5.22–5.10 (m, 4H, $CH_2$Ph, H-4″, H-3″), 5.09 (s, 2H, $CH_2$Ph), 4.41 (dd, $J = 18.3$, 8.6 Hz, 1H, H-2″), 4.05 (d, $J = 3.5$ Hz, 2H, H-6″), 3.74–3.59 (m, 1H, H-5″), 2.06, 2.02, 2.01, 1.90 (s, 4 × 3H, $CH_3C=O$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 177.3, 170.8, 170.5, 170.3, 169.0, 164.4, 161.2, 156.7, 156.3, 148.3, 145.2, 135.5, 135.2, 134.5, 128.4, 128.4, 128.1, 128.0, 127.4, 127.1, 122.5, 121.9, 115.3, 111.5, 105.4, 100.1, 98.6, 92.8, 73.3, 72.0, 70.6, 70.1, 68.0, 61.6, 54.0, 23.0, 20.4, 20.22, 20.1. ESI-MS m/z: 834 $[M+Na]^+$. Anal. calcd. for $C_{43}H_{41}NO_{15}$: C, 63.62; H, 5.09; N, 1.73. Found: C, 63.69; H, 5.00; N, 1.59.

## 7,4′-Di-O-Benzylquercetin 3-O-(2″-Acetamido2″-Deoxy)-β-D-Glucopyranoside (8)

A mixture of glycoside **7** (0.85 g, 1.05 mmol) and MeONa (85.4 mg 1.58 mmol) in methanol (15 mL) was stirred at 30°C for 10 h, and the solvent was removed under vacuum. The residue was dissolved in ethanol (30 mL), and its pH was adjusted to 6.0 with acetic acid. The solution was refluxed for 0.5 h. After cooling, the precipitates were filtered, washed with water, and dried to give **8** (0.56 g 78.6%) as a yellow solid. m.p. 171–173°C. $^1$H NMR (300 MHz, DMSO): $\delta$ 12.66 (s, 1H, 5-OH), 9.42 (s, 1H, 3′-OH), 8.09 (d, $J$ = 9.3 Hz, 1H, NH), 7.83–7.67 (m, 2H, H-2′, H-6′), 7.59–7.26 (m, 10H, Ph), 7.11 (d, $J$ = 8.7 Hz, 1H, H-5′), 6.81 (d, $J$ = 1.8 Hz, 1H, H-6), 6.44 (d, $J$ = 2.0 Hz, 1H, H-8), 5.65 (d, $J$ = 8.5 Hz, 1H, H-1″), 5.27–5.13 (m, 4H, 2 × $CH_2$Ph), 4.36 (s, 1H, OH), 3.75 (dd, $J$ = 18.6, 9.3 Hz, 1H, H-2″), 3.56 (d, $J$ = 11.2 Hz, 1H, H-6″), 3.50–3.15 (m, 2H, H-3″, H-6″, overlapped with signal of $H_2O$), 3.14–3.01 (m, 2H, H-4″, H-5″), 1.85 (s, 3H, $CH_3C$ = O). $^{13}$C NMR (75 MHz, DMSO) $\delta$ 177.6, 169.7, 164.2, 161.2, 156.3, 155.6, 149.2, 146.4, 137.0, 136.2, 133.9, 128.6, 128.5, 128.2, 127.9, 127.8, 122.8, 121.5, 116.2, 113.2, 105.2, 99.0, 98.6, 93.0, 77.8, 74.1, 70.6, 70.0, 69.8, 60.9, 56.1, 23.3. ESI-MS m/z: 686 $[M+H]^+$. Anal. calcd. for $C_{37}H_{35}NO_{12}$: C, 64.81; H, 5.15; N, 2.04. Found: C, 64.74; H, 5.24; N, 2.08.

## Quercetin 3-O-(2″-Acetamido-2″-Deoxy)-β-D-Glucopyranoside (1)

A mixture of compound **8** (0.34 g, 0.50 mmol) and 10% Pd/C (0.06 g) in ethanol (5 mL) and THF (5 mL) was stirred under a hydrogen atmosphere at ambient pressure and temperature for 5 h. After filtration, the solvent was evaporated and the residue was recrystallized from acetone to give **1** (0.21 g 85.6%) as a yellow solid. m.p. 210–212°C. $^1$H NMR (300 MHz, DMSO): $\delta$ 12.70 (s, 1H, 5-OH), 10.84 (s, 1H, OH), 9.73 (s, 1H, OH), 9.10 (s, 1H, OH), 8.04 (d, $J$ = 9.2 Hz, 1H, NH), 7.71–7.58 (m, 2H, H-2′, H-6′), 6.84 (d, $J$ = 8.3 Hz, 1H, H-5′), 6.40 (d, $J$ = 1.9 Hz, 1H, H-6), 6.19 (d, $J$ = 1.9 Hz, 1H, H-8), 5.62 (d, $J$ = 8.4 Hz, 1H, H-1″), 5.04 (s, 2H, OH), 4.27 (s, 1H, OH), 3.75 (dd, $J$ = 18.6, 9.2 Hz, 1H, H-2″), 3.54 (dd, $J$ = 11.3, 4.2 Hz, 1H, H-6″), 3.44–3.24 (m, 2H, H-6″, H-3″, overlapped with signal of $H_2O$), 3.15–3.01 (m, 2H, H-4″, H-5″), 1.86 (s, 3H, $CH_3C$ = O). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 177.5, 169.7, 164.1, 161.3, 156.3, 155.6, 148.5, 144.8, 133.2, 121.9, 121.1, 116.1, 115.5, 104.0, 98.9, 98.6, 93.5, 77.7, 74.2, 70.5, 60.9, 56.0, 23.3. ESI-MS m/z: 528 $[M+Na]^+$. Anal. calcd. for $C_{23}H_{23}NO_{12}$: C, 54.66; H, 4.59; N, 2.77. Found: C, 54.72; H, 4.47; N, 2.69.

## 2-Phthalimido-3,4,6-tri-*O*-Acetyl-2-Deoxy-$\beta$-D-Glucopyranosyl Chloride (10)

2-Phthalimido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-$\beta$-D-glucopyranoside **9** was prepared according to a reported method.[32,33] Phosphorus pentachloride (1.6 g, 7.7 mmol) and $BF_3{\cdot}Et_2O$ (80 $\mu$L) were added to a solution of **9** (2.5 g, 5.2 mmol) in $CH_2Cl_2$ (50 mL). The reaction mixture was stirred for 30 min at rt and was diluted with $CH_2Cl_2$ (20 mL). The mixture was washed with water, saturated $NaHCO_3$ solution, and saturated NaCl. After evaporation of solvent under reduced pressure, the residue was recrystallized from ether to produce **10** (2.16 g, 91.5%). m.p.: 150–153°C.[34] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.93–7.78 (m, 2H), 7.78–7.69 (m, 2H), 6.18 (d, $J$ = 9.3 Hz, 1H), 5.77 (dd, $J$ = 10.4, 9.3 Hz, 1H), 5.24 (t, $J$ = 9.4 Hz, 1H), 4.50 (dd, $J$ = 10.4, 9.6 Hz, 1H), 4.36–4.11 (m, 2H), 4.05–3.85 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.85 (s, 3H).

## 2-Phthalimido-3,4,6-tri-*O*-Acetyl-2-Deoxy-$\beta$-D-Glucopyranosyl Bromide (11)

To a solution of **9** (0.9 g, 1.88 mmol) in $CH_2Cl_2$ (20 mL) was added hydrogen bromide (30% in acetic acid, 2 mL). The mixture was stirred at rt for 2 h and then diluted with $CH_2Cl_2$ (10 mL). The reaction mixture was washed with water, saturated $NaHCO_3$ solution, and saturated NaCl in succession and then dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was recrystallized from ether to produce **11** (0.76 g, 81.5%). m.p.: 123–124°C.[35] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.91–7.84 (m, 2H), 7.79–7.72 (m, 2H), 6.40 (d, $J$ = 9.6 Hz, 1H), 5.76 (dd, $J$ = 10.3, 9.2 Hz, 1H), 5.25 (dd, $J$ = 10.0, 9.6 Hz, 1H), 4.66–4.58 (m, 1H), 4.32 (dd, $J$ = 12.6, 4.6 Hz, 1H), 4.19 (dd, $J$ = 12.6, 2.2 Hz, 1H), 3.96 (ddd, $J$ = 10.3, 4.6, 2.2 Hz, 1H), 2.13 (s, 3H), 2.03 (s, 3H), 1.86 (s, 3H).

## 7,4′-Di-*O*-Benzylquercetin 3-*O*-(2″-Phthalimido-3″,4″,6″-tri-*O*-Acetyl-2″-Deoxy)-$\alpha$-D-Glucopyranoside (12)

To a solution of quercetin **3** (0.96 g, 2.0 mmol) in $CHCl_3$ (15 mL) was added tetrabutyl ammonium bromide (0.32 g, 1.0 mmol) and 0.15 M $K_2CO_3$ (15 mL). The mixture was vigorously stirred at 45°C for 1 h. Then, glucosyl bromide **10** (1.99 g, 4.0 mmol) was added. After further stirring for 5 h, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL), and the layers were separated. The organic phase was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc) to give **12** (1.18 g, 65.6%) as a yellow solid. m.p. 228–229°C. [$\alpha$] + 6.2° ($c$ 0.60, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 12.0 (s, 1H, 5-OH), 7.99–7.82 (m, 2H, Ph), 7.74 (dd, $J$ = 5.5, 2.8 Hz, 2H, Ph), 7.57 (dd, $J$ = 8.4, 2.1 Hz, 1H, H-6′), 7.52 (d, $J$ = 2.1 Hz, 1H, H-2′), 7.50–7.31 (m, 10H, Ph), 7.16 (d, $J$ = 8.5 Hz, 1H, H-5′), 6.44 (d, $J$ = 2.2 Hz, 1H, H-6), 6.37 (s, 1H, 3′-OH), 6.32

(d, $J$ = 2.2 Hz, 1H, H-8), 5.95 (d, $J$ = 3.7 Hz, 1H, H-1″), 5.25 (s, 2H, $CH_2Ph$), 5.08 (s, 2H, $CH_2Ph$), 4.96 (t, $J$ = 9.7 Hz, 1H, H-3″), 4.66 (dd, $J$ = 11.7, 3.7 Hz, 1H, H-2″), 4.12 (dd, $J$ = 14.3, 7.1 Hz, 1H, H-4″), 3.90 (dd, $J$ = 12.5, 3.9 Hz, 1H, H-6″), 3.60–3.51 (m, 2H, H-6″, H-5″), 1.98, 1.97, 1.92 (s, 4 × 3H, $CH_3C=O$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 176.9, 170.0, 169.3, 169.2, 164.1, 161.3, 156.8, 156.3, 148.1, 145.7, 135.3, 135.2, 133.7, 133.6, 130.4, 128.4, 128.2, 128.1, 127.8, 127.2, 126.9, 123.1, 122.6, 122.0, 114.8, 111.9, 105.4, 98.3, 97.4, 92.6, 70.7, 69.9, 69.2, 69.0, 66.6, 65.1, 60.8, 52.7, 20.3, 20.2, 20.1. ESI-MS m/z: 922 $[M+Na]^+$. Anal. calcd. for $C_{49}H_{41}NO_{16}$: C, 65.40; H, 4.59; N, 1.56. Found: C, 65.63; H, 4.62; N, 1.59.

## Quercetin 3-*O*-(2″-Phthalimido-2″-Deoxy)-α-D-Glucopyranoside (13)

A mixture of glycoside **12** (0.4 g, 0.45 mmol) and MeONa (36.4 mg, 0.67 mmol) in methanol (10 mL) was stirred at 30°C for 10 h. After evaporation of the solvent, the residue was dissolved in ethanol (30 mL), and its pH was adjusted to 6.0 with acetic acid. The solution was refluxed for 0.5 h. After cooling, the precipitates were filtered, washed with water, and dried. The resulting intermediate was dissolved in a mixture of ethanol (5 mL) and THF (5 mL) and was stirred with 10% Pd/C (0.08 g) under hydrogen at ambient pressure and temperature for 5 h. After filtration, the solvent was evaporated and the residue was recrystallized from acetone to give **13** (0.21 g, 80.2%) as a yellow solid. m.p. 227–230°C. [$\alpha$] + 11.0° ($c$ 0.35, $CH_3OH$). $^1H$ NMR (400 MHz, DMSO): $\delta$ 12.63 (s, 1H, 5-OH), 8.48 (s, 1H, 7-OH), 7.93 (s, 1H, 2′-H), 7.46–7.38 (m, 2H, Ph), 7.37–7.30 (m, 2H, Ph), 7.13 (d, $J$ = 8.3 Hz, 1H, H-6′), 6.84 (d, $J$ = 8.3 Hz, 1H, H-5′), 6.51 (d, $J$ = 3.6 Hz, 1H, H-1″), 6.28 (s, 1H, H-6), 6.07 (s, 1H, H-8), 4.02–3.89 (m, 1H, H-2″), 3.58–3.50 (m, 1H, H-3″), 3.44 (dd, $J$ = 14.0, 7.0 Hz, 1H, H-6″), 3.29–3.10 (m, 3H, H-6″, H-5″ H-4″). $^{13}C$ NMR (100 MHz, DMSO) $\delta$ 177.2, 174.0, 167.2, 160.9, 156.5, 155.1, 148.6, 145.8, 142.2, 131.1, 130.7, 130.2, 128.9, 127.3, 126.7, 120.4, 118.4, 116.7, 115.5, 102.6, 99.3, 94.9, 93.9, 74.6, 71.6, 68.9, 59.6, 56.0, 54.3. ESI-MS m/z: 616 $[M+Na]^+$. Anal. calcd. for $C_{29}H_{23}NO_{13}$: C, 58.69; H, 3.91; N, 2.36. Found: C, 58.96; H, 3.56; N, 2.59.

## FUNDING

The work described in this article was supported by the Natural Science Research Foundation of the Jiangsu Higher Education Institutions (13KJB150006, 12KJB350001), the Science and Technology Critical Project Foundation of Lianyungang (CN1304, CG1202), the PAPD Program (a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions), and the Open-ended Funds of Jiangsu Institute of Marine Resources (No. HK13004).

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