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Effects of Functional Groups and Sugar Composition of Quercetin Derivatives on Their Radical Scavenging Properties

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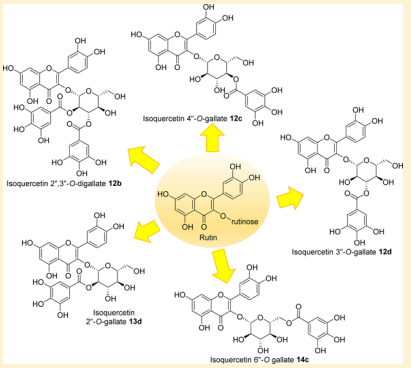
Supporting Information

ABSTRACT: Quercetin derivatives are widespread in the plant kingdom and exhibit various biological actions. The aim of this study was to investigate the structure−activity relationships of quercetin derivatives, with a focus on the influence of functional groups and sugar composition on their antioxidant capacity. A series of quercetin derivatives were therefore prepared and assessed for their DPPH radical scavenging properties. Isoquercetin *O*-gallates were more potent radical scavengers than quercetin. The systematic analysis highlights the importance of the distribution of hydroxy substituents in isoquercetin *O*-gallates to their potency.



Flavonoids constitute a large family of polyphenols that are ubiquitous in higher plants. The basic phenylchromane (C_6−C_3−C_6) skeleton comprises two parts that differ in their biosynthetic origins, the polyketide (C_6) and phenylpropanoid (C_6−C_3) moieties, which are produced from the acetate−malonate and the shikimic acid pathways, respectively.[1] Flavonoids assume prominent functions in plant physiology, biochemistry, and chemical ecology, including UV protection, pigmentation, defense, and interspecies interaction.[2,3] Flavonoids have also been shown to exhibit significant and varied biological effects on human health, and there has been an increased interest in the study of these nutritionally valuable phytochemicals.[4]

Found naturally in many common foods, quercetin is one of the more abundant flavonols. Quercetin has attracted a great deal of attention due to a number of reported pharmacological activities, including antimicrobial,[5] anti-inflammatory,[6] antiobesity,[7] and neuroprotective effects,[8] as well as contributing to a decreased risk of cancer and cardiovascular disease.[9,10] As a known radical scavenger, the role of quercetin as an antioxidant is an active area of research.[11] These properties of quercetin are attributable to the presence of five hydroxy groups. While modified quercetins (*O*-methylated, 3-*O*-glycosidic, and galloylated derivatives) have been isolated from plants,[12−16] only a few systematic structure−activity relationship studies of these compounds have been conducted. This study focuses on verifying the importance of both the degree of hydroxylation and the sugar composition of quercetin derivatives with respect to their radical scavenging potency toward DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals.

RESULTS AND DISCUSSION

Quercetin (**1**) has five hydroxy groups; its B-ring comprises a catechol group, and the 5-OH group of the A-ring forms an intramolecular hydrogen bond with the C-4 carbonyl group. In order to establish which quercetin derivative is most beneficial in promoting antioxidant effects, each hydroxy group of the quercetin skeleton was selectively protected. Because direct monomethylation of quercetin is difficult to achieve, benzyl protection was initially employed (Scheme 1). Reactivity of the quercetin hydroxy groups obeys the following sequence: 4′ ≥ 7 > 3 > 3′ > 5.[17] Careful control of the number of benzyl bromide equivalents provided two protected products: 3,4′,7-tri-*O*-benzyl- (**1a**, 70%) and 3,3′,4′,7-tetra-*O*-benzylquercetin (**1d**, 65%). Further methylation with methyl iodide produced **1b** (62%) and **1e** (100%), which upon debenzylation using catalytic hydrogenation afforded isorhamnetin (**1c**, 92%) and azaleatin (**1f**, 84%), respectively (Scheme 1). For preparation of tamarixetin (**2b**), hesperidin (**2**) was selected as a starting material (Scheme 2). The Algar−Flynn−Oyamada oxidation[18] afforded an intermediate flavanol rutinoside, which was immediately converted to quercetin 7-*O*-rutinose (**2a**, 20% in three steps) by refluxing with $Na_2S_2O_5$. Poor solubility of **2a** in EtOH required the acetylation of hydroxy groups using Ac_2O/pyridine. Subsequent acidic hydrolysis yielded tamarixetin (**2b**) in 25% yield over two steps (Scheme 2). Likewise, rutin (**3**) was utilized for the synthesis of 3-*O*-methylquercetin (**3c**).[19]

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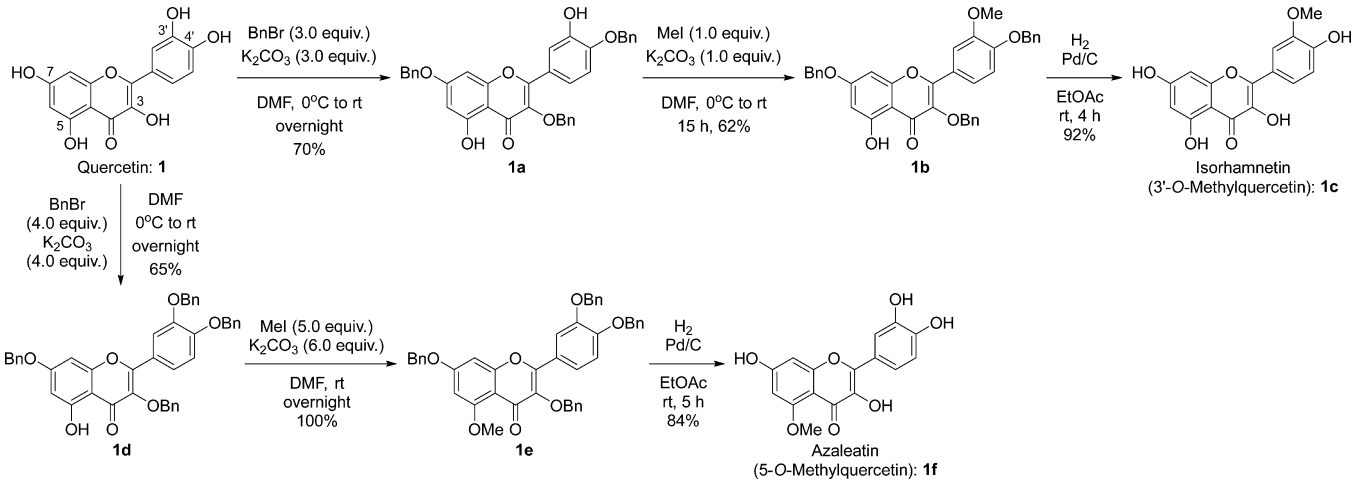
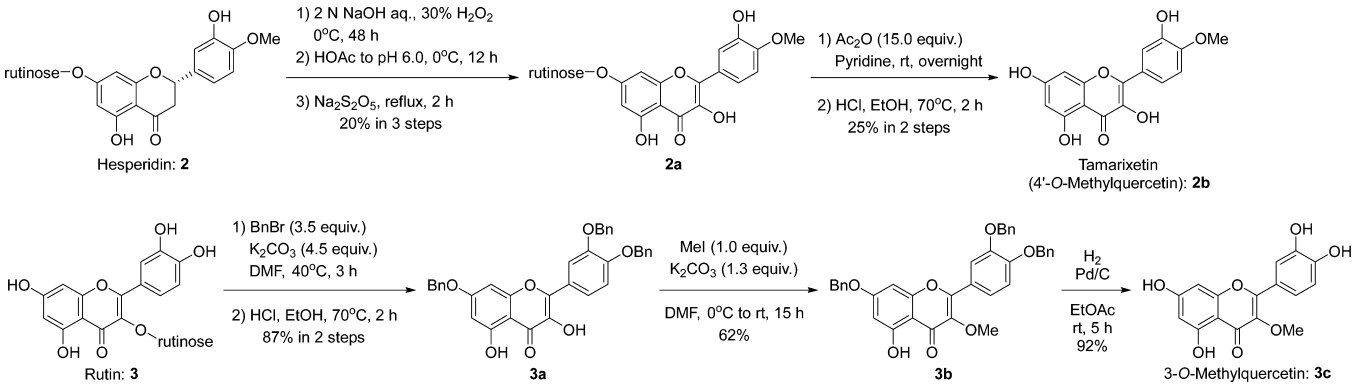
Scheme 1. Synthesis of Isorhamnetin 1c and Azaleatin 1f from Quercetin



Scheme 2. Synthesis of Tamarixetin 2b and 3-*O*-Methylquercetin 3c



Following benzylation and acid hydrolysis, 3′,4′,7-tri-*O*-benzylquercetin (**3a**, 87% over two steps) was methylated at the 3-OH group to yield **3b** (62%). Debenzylation afforded 3-*O*-methylquercetin (**3c**) in 92% yield.

With **3a** in hand, the synthesis of quercetin glycosides was targeted. The synthesis protocol is shown in Scheme 3. The first step involved the Koenigs–Knorr reaction of **3a** with tetra-*O*-acetylglucosyl or tetra-*O*-acetylgalactosyl bromides in Ag_2CO_3/pyridine[20] and afforded the *O*-acetylglycosides **4a** (78%) and **4b** (78%). Debenzylation to give **5a** (99%) and **5b** (75%) was followed by deacetylation, which smoothly afforded isoquercetin (**6a**, 67%) and hyperin (**6b**, 87%). Alternatively, benzylation of **5a** and **5b** using 2.0 equiv of benzyl bromide afforded the benzyl analogues **7a** (61%) and **7b** (59%). Methylation of the 3′-OH group of **7** afforded **8a** (48%) and **8b** (55%), and subsequent deprotection gave isorhamnetin glucoside (**9a**, 81%) and galactoside (**9b**, 92%). Monomethylation of the 5-OH group in **4** afforded **10a** (87%) and **10b** (83%), and exhaustive debenzylation and deacetylation afforded the azaleatin glucoside **11a** (78%) and galactoside **11b** (66%).

In order to study structure–activity relationships, the quercetin derivatives were assessed for their antioxidant capacity using a DPPH radical scavenging assay in MeOH/H_2O solution. Relative to Trolox, an antioxidant derived from water-soluble vitamin E, quercetin (**1**) and its derivatives **1f**, **3c**, **6a**, **11a**, **6b**, and **11b** exhibited a relatively high activity (less than 70% remaining DPPH, Figure 1) at a concentration of 5.0 μM. Compounds with an underivatized catechol B-ring, therefore, showed the highest activity. This is in line with the ability of quercetin to be transformed into a *p*-quinonoid intermediate via the loss of two electrons and two protons.[21,22] Comparing quercetin with 3-*O*-methylquercetin (**3c**), 3-*O*-methylation decreased the potency. A similar decrease in potency was observed following methylation at 5-OH (**1f**). By using quantitative kinetic analysis, Goupy and co-workers proposed an oxidative degradation pathway of flavonols during radical capture in protic solvents.[22] The HRESITOFMS analysis of the reaction mixture of quercetin with DPPH detected the MeOH adduct peak at m/z 355.0442 $[M + Na]^+$, implying that the B-ring catechol moiety was regenerated from the intermediate by the addition of MeOH at the C-2. This is in agreement with the degradation theory advanced by Goupy and co-workers.[22] Next, the Cu^{2+} ion additive effects in the DPPH assay system were assessed. Pretreatment of quercetin derivatives with 2.0 equiv of $CuSO_4{\cdot}5H_2O$ enhanced their radical scavenging activity. However, no improvement was observed for Trolox. The coordination of Cu^{2+} ions relative to the catechol moiety, either between 3-OH and the carbonyl group or between 5-OH and the carbonyl group, altered the electronic characteristics of the quercetin derivatives, facilitating electron and proton transfer.[23,24]

Flavonol galloylglycosides are quite rare derivatives that can be isolated from plants. Generally, a galloyl group is found in the sugar moiety of the framework and is known to influence the biological activities of these compounds.[25,26] However, due to their structural complexity, their synthesis is challenging.

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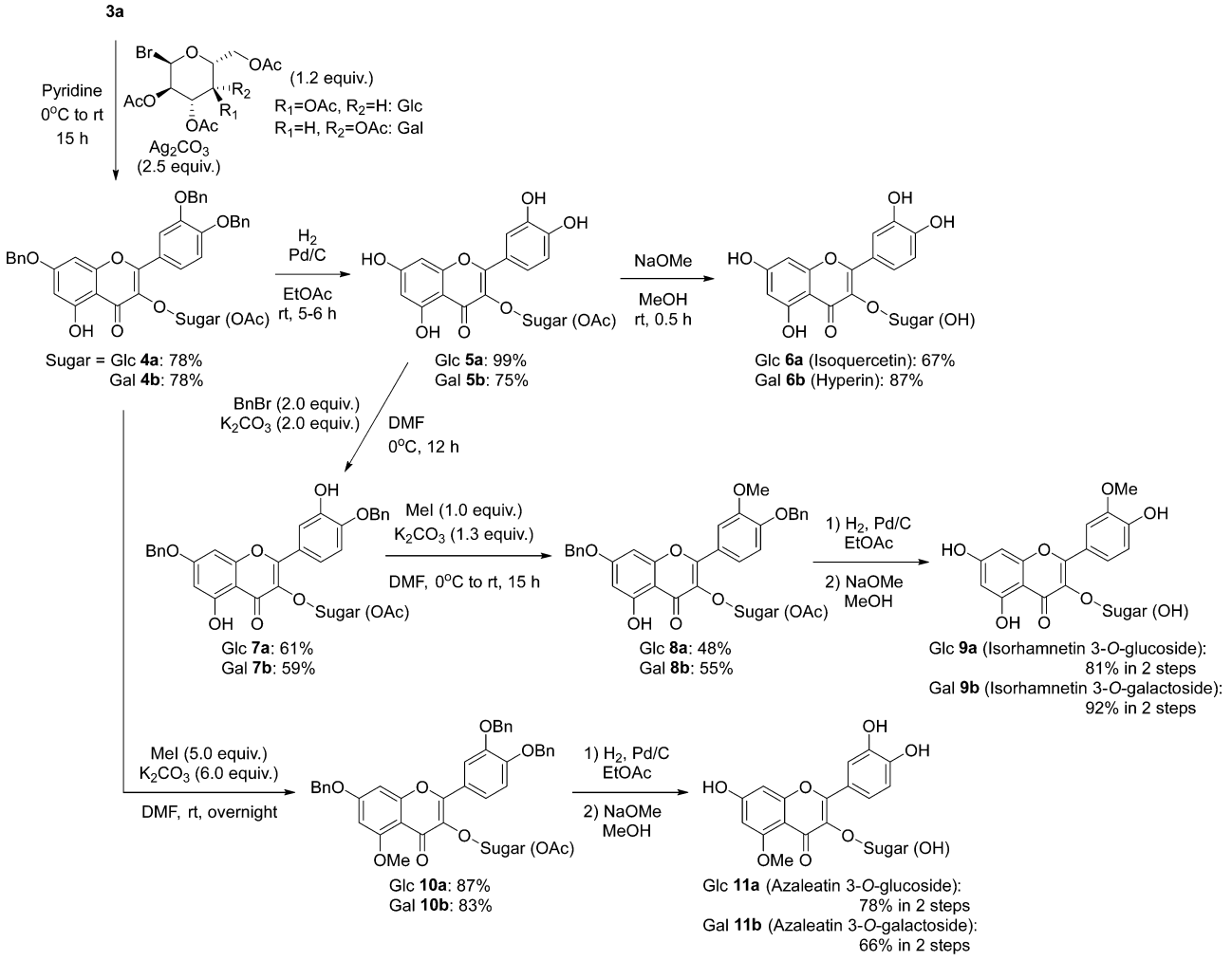
Scheme 3. Synthesis of Quercetin 3-*O*-Glycoside Analogues



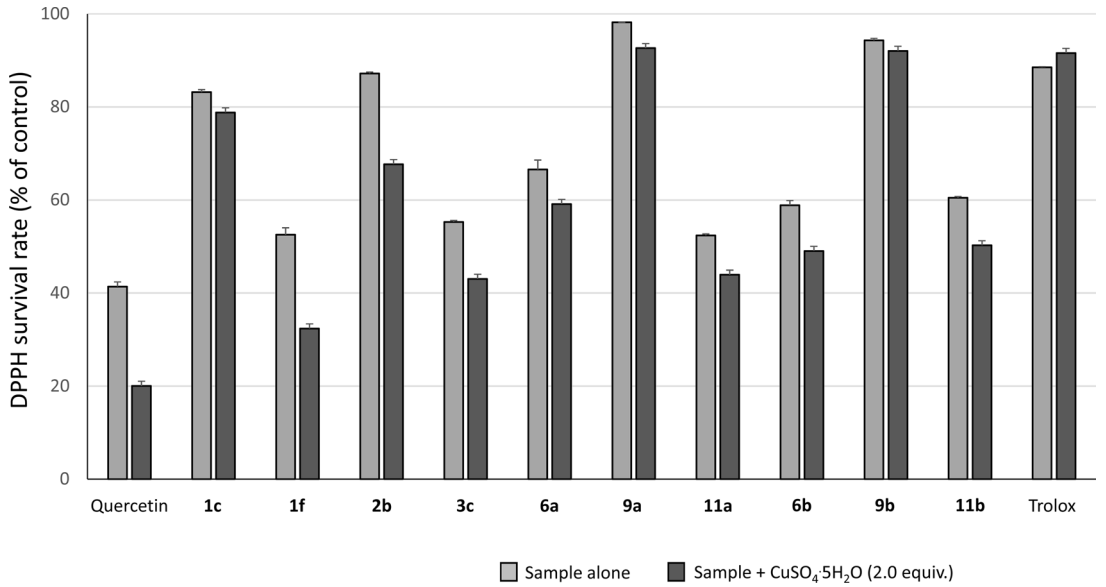


Figure 1. DPPH scavenging activity of quercetin derivatives at a final concentration of 5.0 μM (means ± SEMs, n = 3).

Compound **12a**, formed via deacetylation of **4a** (83%), was thought to possess potential as a starting material for the preparation of flavonol galloylglycosides (Scheme 4). Through the use of the primary hydroxy group at C-6″ of glucose,[27] the introduction of a galloyl group appeared feasible. Esterification of **12a** with tri-*O*-benzylated gallic acid using 1-ethyl-3-(3-

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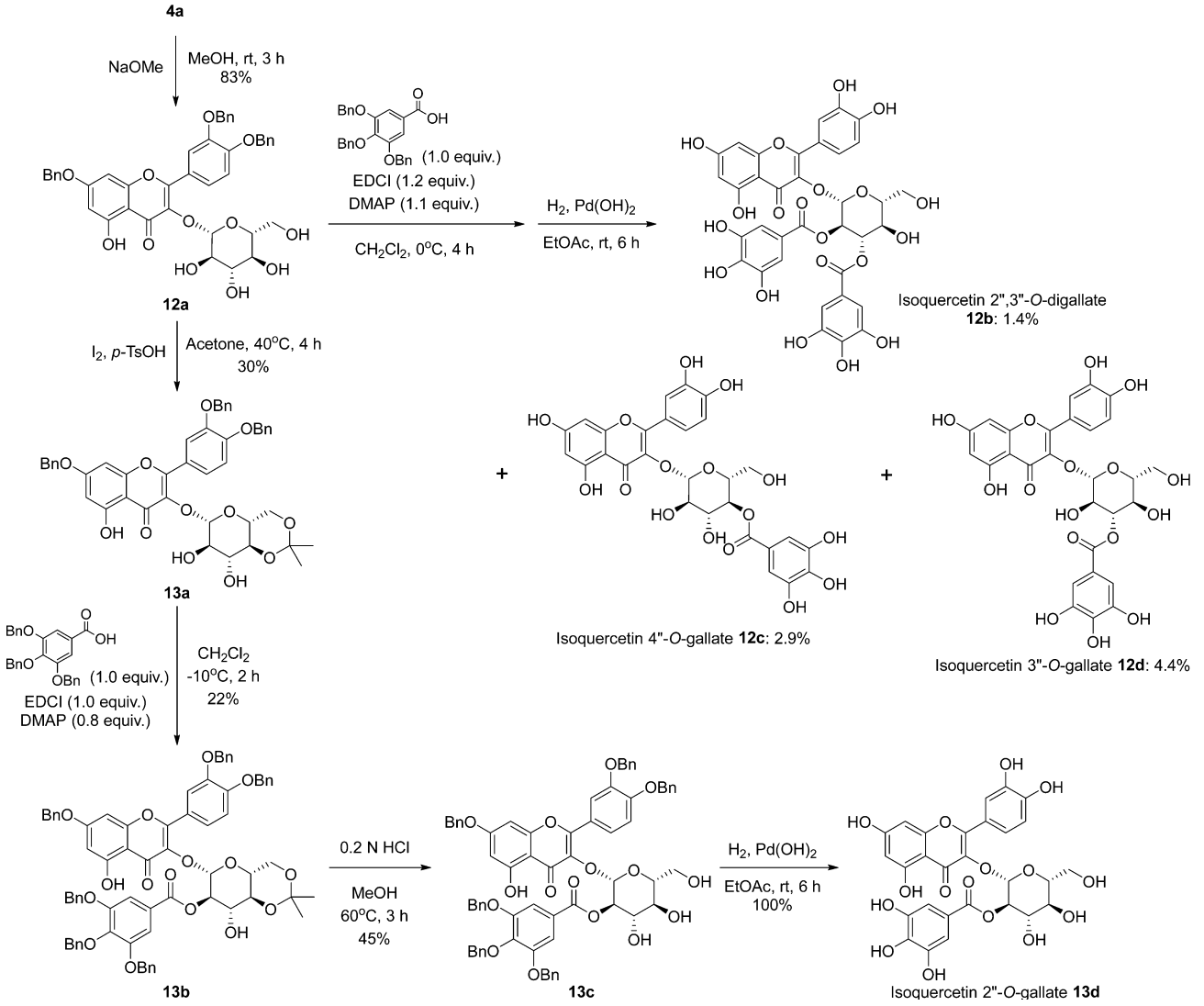
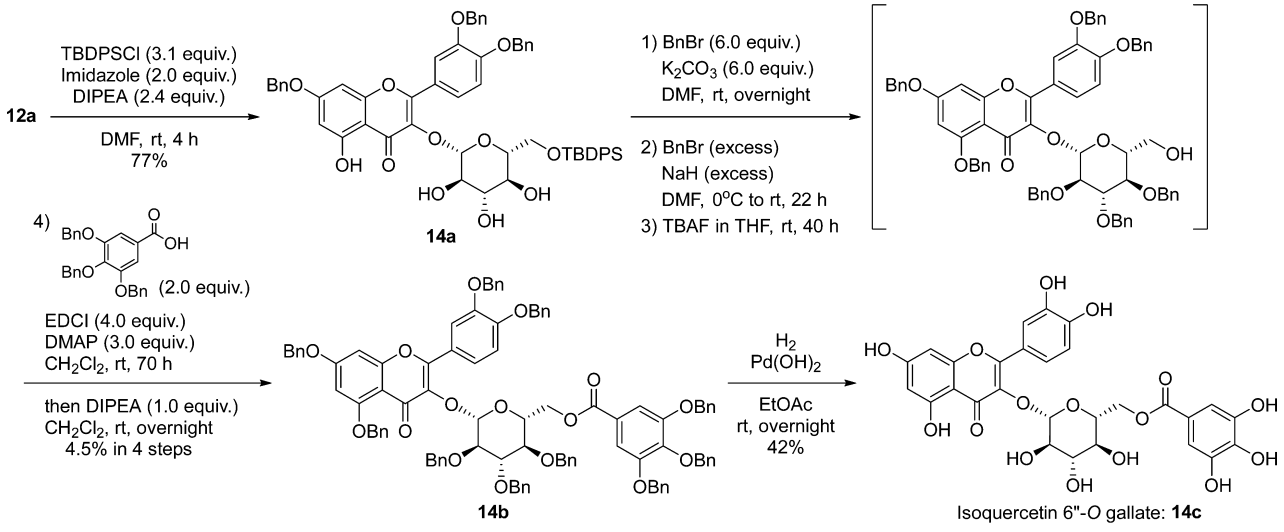
Scheme 4. Synthesis of Various Isoquercetin *O*-Gallates



Scheme 5. Synthesis of Isoquercetin 6″-*O*-Gallate, 14c



(dimethylamino)propyl)carbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) gave a small amount of a mixture of products, while large amounts of starting material remained unreacted. Following debenzylation and purification by Sephadex LH-20 CC and HPLC, three pure products (**12b**–**d**) were obtained. The molecular formula of one of these

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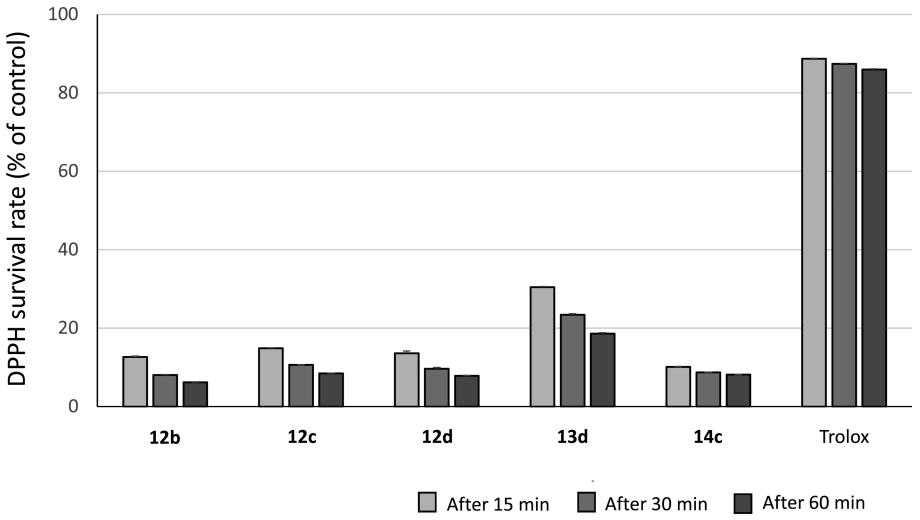

Figure 2. DPPH scavenging activity of isoquercetin *O*-gallates at a final concentration of 5.0 μM (means ± SEMs, n = 3).

compounds was established using HRESITOFMS as $C_{35}H_{28}O_{20}$, indicating the presence of two galloyl groups. In the vicinity of an anomeric proton, two proton signals at δ_H 5.36 (H-2″) and 5.39 (H-3″) were correlated to ester carbonyl carbons in the HMBC spectrum. Therefore, the two galloyl groups were connected to the 2″- and 3″-OH positions of glucose, thus confirming the structure as isoquercetin 2″,3″-*O*-digallate,[14] **12b**. Using similar techniques, the structures of the other two compounds were defined as isoquercetin 4″-*O*-gallate (**12c**) and 3″-*O*-gallate[15] (**12d**) (Scheme 4). To prepare isoquercetin 6″-*O*-gallate (**14c**), we sought to protect both 3″-OH and 4″-OH using I_2, *p*-toluenesulfonic acid, and acetone in accordance with a previous report.[28] However, the reaction conditions gave mainly the 4″,6″-*O*-isopropylidene derivative **13a** in 30% yield. To exploit this unexpected formation of **13a**, isoquercetin 2″-*O*-gallate[16] (**13d**) was synthesized via the introduction of a galloyl group to give **13b** (22%). Deacetalization afforded **13c** (45%), and subsequent debenzylation gave **13d** (100%). Finally, isoquercetin 6″-*O*-gallate[13] (**14c**) was synthesized via a *tert*-butyldiphenylsilyl ether (TBDPS) protection strategy,[29] depicted in Scheme 5.

In order to gain insight into the influence of the galloyl unit on radical scavenging ability, antiradical activity of isoquercetin *O*-gallates was assessed. As indicated in Figure 2, the DPPH radical scavenging effects of galloyl derivatives **12b**, **12c**, **12d**, **13d**, and **14c** were dramatically improved (less than 35% of DPPH remaining in all cases) compared to that of Trolox. These compounds demonstrated higher potency than even isoquercetin **6a**. It is therefore apparent that the incorporation of a galloyl group into the isoquercetin structure leads to an increase in radical scavenging activity. Furthermore, galloyl derivatives seem to be excellent radical scavengers compared with quercetin **1**. To gain a better understanding of the mechanism of action, ^{13}C NMR spectroscopic analysis was used to determine which of the isoquercetin *O*-gallates is the most effective radical scavenger.[30,31] Since a glucose moiety appeared to be of minimal importance, methyl gallate and 3-*O*-methylquercetin (**3c**) were studied. After mixing equal proportions of methyl gallate and **3c** with 3.0 equiv of DPPH for 30 min, the reaction mixture was analyzed using ^{13}C NMR spectroscopic data. The individual and combined spectra are shown in Figure 3. The intensities of signals arising from methyl gallate decreased significantly, while only small changes

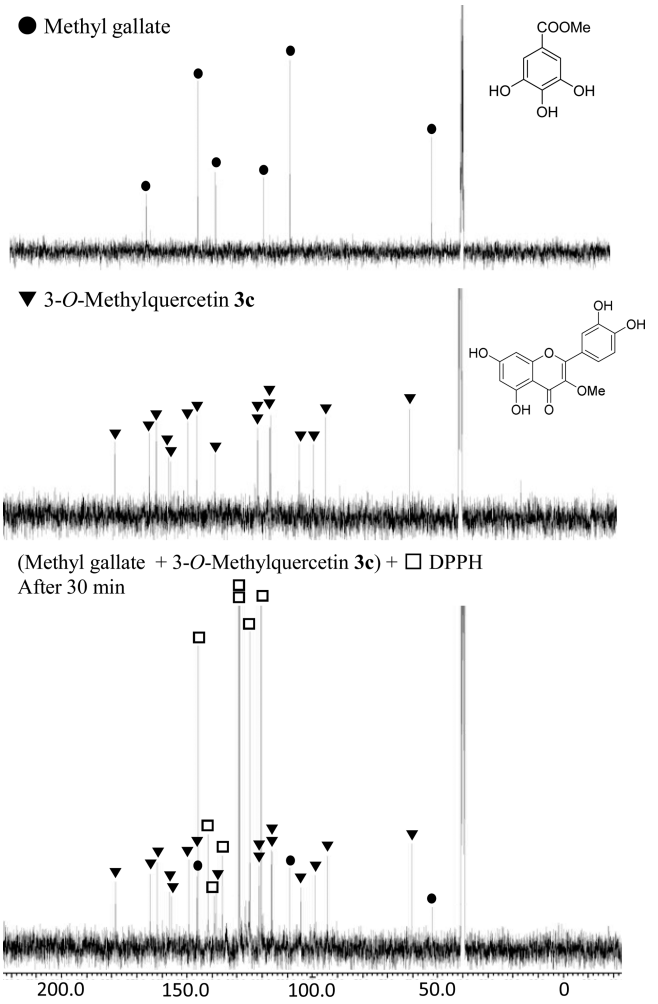

Figure 3. ^{13}C NMR analysis of a reaction mixture of DPPH, methyl gallate, and 3-*O*-methylquercetin (**3c**). DPPH (0.045 mmol) was added to the mixture of 0.015 mmol of methyl gallate and **3c** in DMSO-d_6.

were observed in the intensities of signals arising from **3c**. This result suggests that methyl gallate traps DPPH radicals at a greater rate than does **3c**. Therefore, for isoquercetin *O*-gallates,

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the inclusion of a pyrogallol moiety in the galloyl unit was of greater importance in determining radical scavenging ability than the presence of a catechol moiety in the flavonol B-ring.

EXPERIMENTAL SECTION

General Experimental Procedures. All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. MS spectra were obtained using a JEOL JMS-700/GI spectrometer and the Waters UPLC-MS system (Aquity UPLC XevoQTof). The purities of compounds were assessed as >95% using analytical UPLC. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL ECX 400 spectrometer with tetramethylsilane as an internal standard. Silica gel column chromatography (CC) was performed on silica gel N-60 (40−50 μm). TLC spots on plates precoated with silica gel 60 F_{254} were detected with a UV lamp (254 nm). Fractionations for all CCs were based on TLC analyses.

Synthetic Methods. Detailed synthetic conditions and spectroscopic data of compounds are given in the Supporting Information. The physical data of isoquercetin *O*-gallates are shown here.

*Isoquercetin 2″,3″-O-digallate (**12b**):* yellow powder; IR (film) ν_{max} 3417, 1633, 1203, 1086 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.56 (1H, d, J = 1.8 Hz, H-2′), 7.50 (1H, dd, J = 8.7 and 2.3 Hz, H-6′), 7.00 (2H, s, galloyl), 6.97 (2H, s, galloyl), 6.81 (1H, d, J = 8.7 Hz, H-5′), 6.34 (1H, s, H-8), 6.17 (1H, s, H-6), 5.87 (1H, d, J = 7.3 Hz, H-1″), 5.39 (1H, t, J = 9.6 Hz, H-3″), 5.36 (1H, t, J = 7.8 Hz, H-2″), 3.83 (1H, dd, J = 12.4 and 1.8 Hz, H-6″α), 3.78 (1H, t, J = 9.2 Hz, H-4″), 3.68 (1H, dd, J = 12.4 and 5.5 Hz, H-6″β), 3.50−3.47 (1H, m, H-5″); ^{13}C NMR (100 MHz, methanol-d_4) δ 179.0, 167.8, 167.3, 165.7, 163.1, 158.3, 149.8, 146.3 (3C), 146.2 (2C), 146.0, 140.0, 139.9, 135.0, 123.3, 123.0, 121.1, 117.0, 116.1, 110.5 (2C), 110.4 (3C), 105.9, 100.4, 99.7, 94.5, 78.7, 77.0, 74.0, 69.6, 62.1; HRESITOFMS m/z 769.1238 [M + H]$^+$ (calcd for $C_{35}H_{29}O_{20}$, 769.1252), 791.1065 [M + Na]$^+$ (calcd for $C_{35}H_{28}O_{20}Na$, 791.1072).

*Isoquercetin 4″-O-gallate (**12c**):* yellow powder; IR (film) ν_{max} 3440, 1633, 1289, 1042 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.73 (1H, s, H-2′), 7.61 (1H, d, J = 7.3 Hz, H-6′), 7.07 (2H, s, galloyl), 6.84 (1H, d, J = 6.8 Hz, H-5′), 6.40 (1H, s, H-8), 6.21 (1H, s, H-6), 5.42 (1H, d, J = 7.3 Hz, H-1″), 5.01 (1H, t, J = 9.6 Hz, H-4″), 3.77 (1H, t, J = 9.2 Hz, H-3″), 3.63 (1H, t, J = 8.2 Hz, H-2″), 3.54−3.51 (2H, m, H-5″ and H-6″α), 3.44 (1H, dd, J = 12.4 and 5.5 Hz, H-6″β); ^{13}C NMR (100 MHz, methanol-d_4) δ 179.4, 167.7, 166.0, 163.1, 159.0, 158.5, 149.9, 146.5 (2C), 145.9, 140.0, 135.5, 123.2, 123.0, 121.1, 117.5, 116.0, 110.3 (2C), 105.7, 104.0, 99.9, 94.7, 76.6, 76.0, 75.9, 72.2, 62.2; HRESITOFMS m/z 617.1130 [M + H]$^+$ (calcd for $C_{28}H_{25}O_{16}$, 617.1143), 640.1027 [M + Na]$^+$ (calcd for $C_{28}H_{24}O_{16}Na$, 640.1040).

*Isoquercetin 3″-O-gallate (**12d**):* yellow powder; IR (film) ν_{max} 3449, 1631, 1203, 1042 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.72 (1H, s, H-2′), 7.59 (1H, d, J = 7.4 Hz, H-6′), 7.15 (2H, s, galloyl), 6.86 (1H, d, J = 6.9 Hz, H-5′), 6.40 (1H, s, H-8), 6.21 (1H, s, H-6), 5.43 (1H, d, J = 7.8 Hz, H-1″), 5.19 (1H, t, J = 9.2 Hz, H-3″), 3.75 (2H, t, J = 5.0 Hz, H-2″ and H-6″α), 3.69−3.62 (2H, m, H-4″ and H-6″β), 3.39−3.35 (1H, m, H-5″); ^{13}C NMR (100 MHz, methanol-d_4) δ 179.4, 168.2, 166.0, 163.0, 158.9, 158.4, 149.9, 146.4 (2C), 145.9, 139.7, 135.5, 123.2, 123.0, 121.7, 117.5, 116.1, 110.4 (2C), 105.7, 104.0, 99.9, 94.7, 79.2, 78.3, 74.2, 69.5, 62.2; HRESITOFMS m/z 617.1135 [M + H]$^+$ (calcd for $C_{28}H_{25}O_{16}$, 617.1143), 639.0958 [M + Na]$^+$ (calcd for $C_{28}H_{24}O_{16}Na$, 639.0962).

*Isoquercetin 2″-O-gallate (**13d**):* yellow powder; IR (film) ν_{max} 3420, 1639, 1265, 1043 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.56 (1H, d, J = 1.8 Hz, H-2′), 7.53 (1H, dd, J = 8.7 and 1.8 Hz, H-6′), 7.12 (2H, s, galloyl), 6.82 (1H, d, J = 8.7 Hz, H-5′), 6.33 (1H, s, H-8), 6.16 (1H, d, J = 1.4 Hz, H-6), 5.74 (1H, d, J = 7.8 Hz, H-1″), 5.13 (1H, t, J = 9.6 Hz, H-2″), 3.80 (1H, dd, J = 12.4 and 1.8 Hz, H-6″α), 3.81 (1H, t, J = 9.2 Hz, H-3″), 3.62 (1H, dd, J = 11.9 and 5.0 Hz, H-6″β), 3.45 (1H, t, J = 9.2 Hz, H-4″), 3.35−3.32 (1H, m, H-5″); ^{13}C NMR (100 MHz, methanol-d_4) δ 179.1, 167.8, 165.7, 163.1, 158.3, 158.2, 149.7, 146.3 (2C), 145.9, 139.8, 135.0, 123.3, 123.1, 121.5, 117.0, 116.1, 110.6 (2C), 105.9, 100.7, 99.7, 94.5, 78.7, 76.4, 76.0, 71.5, 62.5; HRESITOFMS m/z 639.0952 [M + Na]$^+$ (calcd for $C_{28}H_{24}O_{16}Na$, 639.0962).

*Isoquercetin 6″-O-gallate (**14c**):* yellow powder; IR (film) ν_{max} 3449, 1728, 1287, 1073 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.55 (2H, m, H-2′ and H-6′), 6.93 (2H, s, galloyl), 6.71 (1H, d, J = 8.7 Hz, H-5′), 6.34 (1H, s, H-8), 6.17 (1H, s, H-6), 5.21 (1H, d, J = 7.8 Hz, H-1″), 4.34 (1H, dd, J = 11.9 and 4.6 Hz, H-6″α), 4.23 (1H, d, J = 11.4 Hz, H-6″β), 3.53−3.45 (4H, m, H-2″, H-3″, H-4″, and H-5″); ^{13}C NMR (100 MHz, methanol-d_4) δ 179.4, 168.2, 65.9, 162.9, 159.3, 158.4, 149.7, 146.3 (2C), 145.8, 139.7, 135.3, 123.5, 123.0, 121.2, 177.2, 115.9, 110.1 (2C), 105.5, 104.2, 99.9, 94.8, 78.0, 75.9, 75.7, 71.4, 64.3; HRESITOFMS m/z 639.0948 [M + Na]$^+$ (calcd for $C_{28}H_{24}O_{16}Na$, 639.0962).

DPPH Radical Scavenging Assay. A 10 μL amount of sample solutions (0.1 mM in MeOH) and 190 μL of DPPH solution (78 μM in distilled H_2O/MeOH = 5/3) were added to 96-well plates, resulting in final concentrations of 5 μM for the samples and 74 μM for DPPH. The solutions were vigorously mixed and allowed to stand. Visible absorption (λ = 545 nm) was measured after 15, 30, and 60 min using a microplate reader (E_{max} precision microplate reader, Molecular Devices Japan, Tokyo, Japan). Wells without the compounds were considered as negative controls. At least three replicates were performed for each compound and control.

Pretreatment of Samples with $CuSO_4$·5H_2O. A 50 μL amount of sample solutions (0.2 mM in MeOH) and 50 μL of $CuSO_4$·5H_2O solution (0.4 mM in MeOH) were mixed and incubated in Eppendorf tubes for 1.5 h at room temperature.

^{13}C NMR Analysis of a Mixture of Methyl Gallate and 3-*O*-Methylquercetin (3c) with DPPH. Methyl gallate (0.015 mmol), 3-*O*-methylquercetin (**3c**, 0.015 mmol), and DPPH (0.045 mmol) were dissolved in 0.8 mL of DMSO-d_6. After mixing for 30 min, the ^{13}C NMR spectrum of the mixture was recorded.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00274.

The synthetic protocols and physical data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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