# Selective Monomethylation of Quercetin

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**Abstract:** Quercetin was monomethylated under mild conditions in moderate yields through selective deprotection. The combined effects of the protecting group and the heating mode on the reactivity were investigated. The presence of borax and the use of microwave irradiation significantly improved the yield and selectivity of alkylation.

**Key words:** alkylations, regioselectivity, methylation, heterocycles, quercetin

Quercetins [2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one] (Figure 1) and its derivatives are widely distributed in the plant kingdom; for example, quercetin is found in the flowers of the pagoda tree, in onion, in tea, and in gingko nuts.

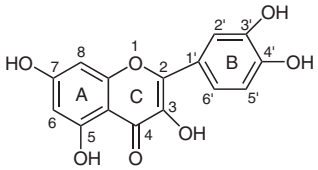


**Figure 1** Quercetin

Quercetin plays a key role in the preparation of many pharmacologically active compounds.[1–4] It is of particular interest that monomethylated derivatives of quercetin exhibit anticancer, anticarcinogenic, antibacterial, anti-inflammation, antiallergic, antiviral, antioxidant, antithrombogenic, and antiatherogenic properties. 3-*O*-Methylquercetin evidently possesses antiviral, anti-inflammation, and antioxidant properties, and regulates immune functions. 5-*O*-Methylquercetin (azaleatin) is used to relieve cough sputum and to treat cardiovascular disease. 7-*O*-Methylquercetin (rhamnetin) has anti-inflammatory and antitumor properties, and resists human immunodeficiency virus. 3′-*O*-Methylquercetin (isothamnetin) fights cardiovascular effects of ischemia, relieves heartstroke, regulates arrhythmia, and depresses cholesterol levels. 4′-*O*-Methylquercetin (tamarixetin) has antioxidation, anticancer, and heart-stimulation effects and eliminates free radicals. These five derivatives of flavones are rarely found as natural products. However, quercetin is the main flavonoid found in foods and in plants such as *Sophora japonic*a. Therefore, the partial synthesis of flavonoids from quercetin is would be an attractive option for the construction of monomethylated derivatives of quercetin. Although several monomethylquercetins have been prepared,[5–8] a number of challenges in their synthesis remain. These include achieving selectivity, purification from byproducts, achieving a high yield, and devising a convenient method that promotes rapid reactions, requires much less energy than existing methods, and uses less-toxic reagents and solvents under milder conditions. Moreover, flavone derivatives are widespread and attractive components of many natural and therapeutic products of biological significance. It is therefore a desirable goal to develop an efficient, novel, simple, and convenient method for the preparation of monomethylquercetins, preferably by means of a selective one-pot reaction that will save materials and time, while giving high yields.

Here, we report an efficient method for monomethylation of quercetin to give 5-*O*-methylquercetin, 3′-*O*-methylquercetin, 7-*O*-methylquercetin, or 4′-*O*-methylquercetin by using a boron complex as a protective group in a one-pot reaction with microwave assistance (Scheme 1).

We also report an intermolecular amidation of saturated C–H bonds of benzyl ethers catalyzed by copper(II) triflate and using 4-methyl-*N*-(phenyl-$\lambda^3$-iodanylidene)benzenesulfonamide (PhI=NTs) or tosyl azide as a nitrene source; we also report a debenzylation reaction catalyzed by a Lewis acid.

Inspired by our work on copper(II) triflate catalyzed amidation of ethers,[9] and as part of our continuing study on nitrene insertions into C–H bonds, we explored the amidation of dibenzyl ethers with bis(acetyloxy)(phenyl)-$\lambda^3$-iodane [$PhI(OAc)_2$] and tosylamide ($TsNH_2$) catalyzed by a metal complex in dichloromethane to form C–N bonds (for example, in benzylideneaniline) and benzyl alcohol.[10] Because this procedure is of no great practical use, we wondered if the catalytic amidation could be applied in debenzylation as a method for selective deprotection. We therefore examined the intermolecular amidation of saturated C–H bonds of pentabenzylquercetin in the presence of copper(II) triflate as a catalyst and PhI=NTs or $PhI(OAc)_2$ and $TsNH_2$ as a nitrene source. This reaction gave 3,3′,4′,5-tetrabenzylquercetin in ~40% yield. Subsequently, we demonstrated that intermolecular amidation

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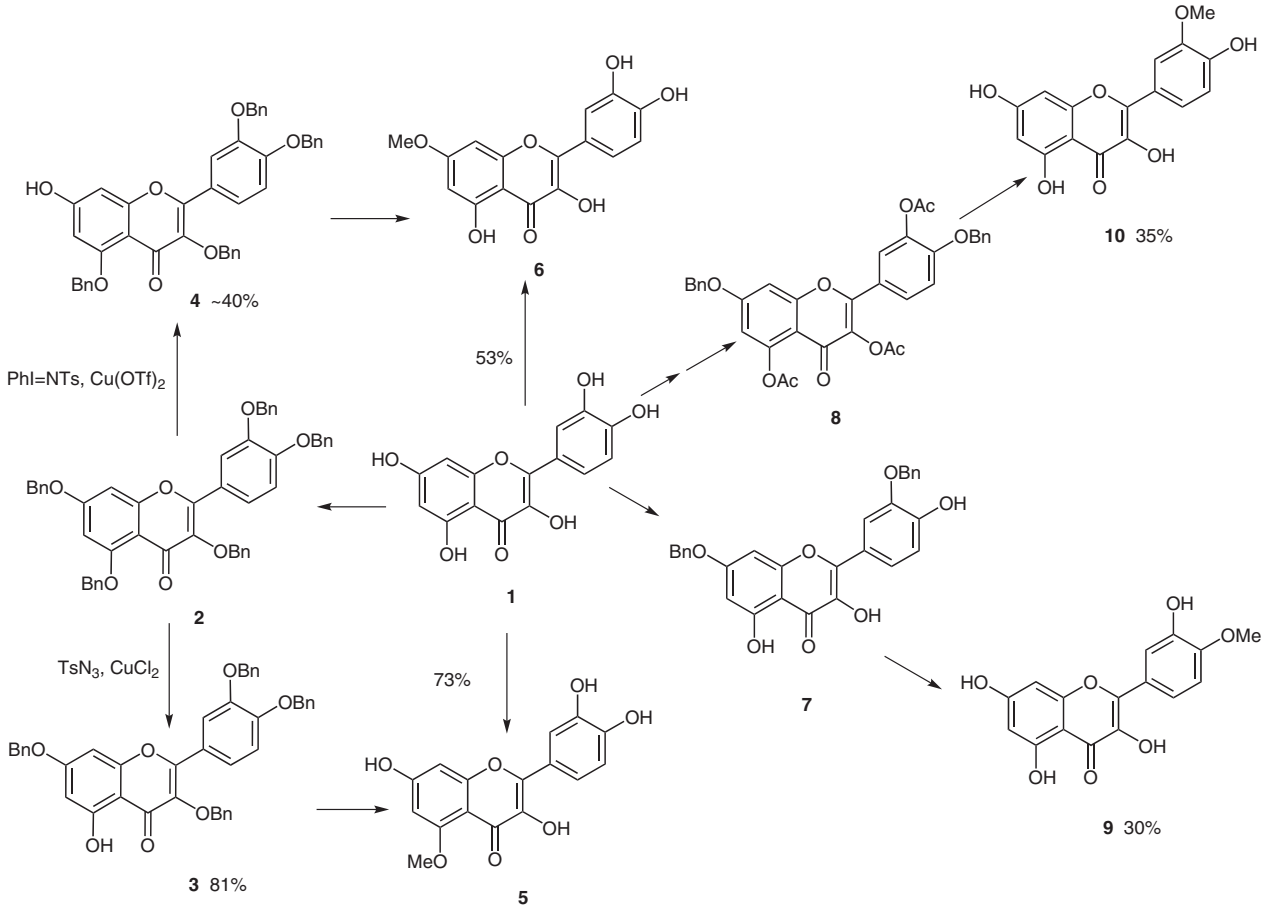
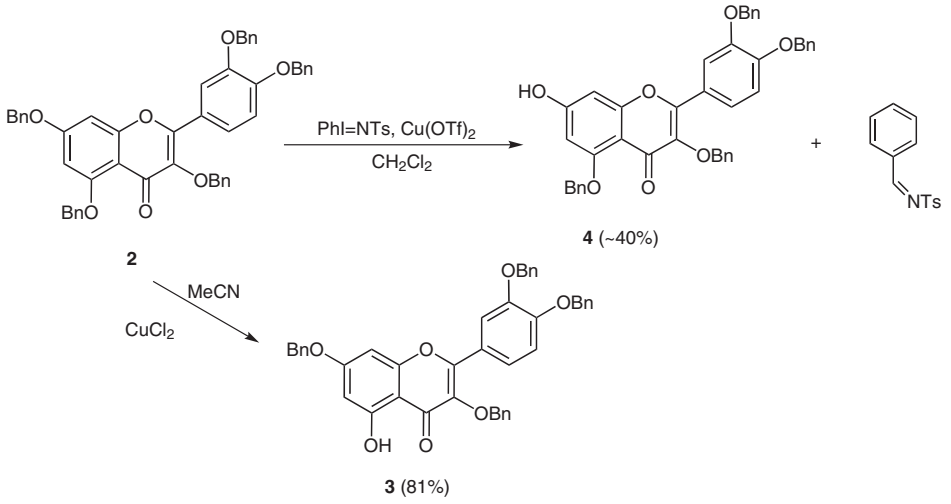



**Scheme 1** Synthesis pathways of monomethylation products of quercetin

by using tosyl azide as the nitrogen source in the presence of copper(II) chloride under microwave irradiation for ten minutes is an effective method for the selective preparation of 3,3′,4′,7-tetrabenzylquercetin in 81% yield (Scheme 2). When this reaction was carried out in the absence of $TsN_3$ as a nitrogen source under identical conditions, the same product was obtained in an identical yield. Strangely, the debenzylation reaction hardly proceeded when chloramine-T (*N*-chloro-4-methylbenzenesulfonamide, sodium salt) was used as the nitrogen source in the presence of copper(II) chloride under identical conditions.

Under appropriate conditions, 3,3′,4′,7- tetrabenzylquercetin underwent methylation and hydrogenolysis to give 5-*O*-methylquercetin (Scheme 3). We therefore achieved a selective deprotection of pentabenzylquercetin through nitrene insertion into the benzyl ether by using PhI=NTs in presence of copper(II) chloride as a Lewis acid.




**Scheme 2** Debenzylation of pentabenzylquercetin under various reaction conditions



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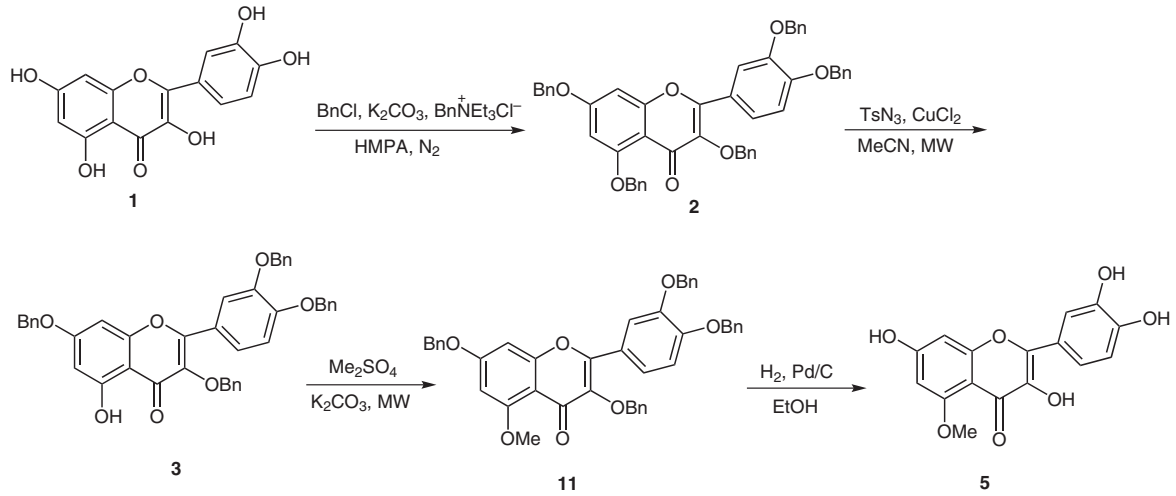
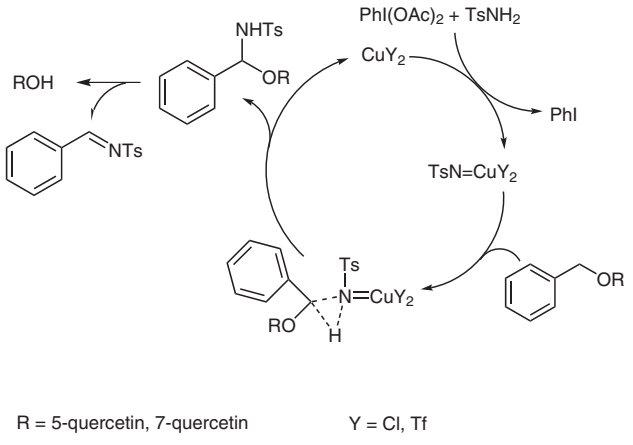



**Scheme 3** Synthesis of 5-*O*-methylquercetin

The intermolecular C–N bond-formation reaction mediated by 20% copper(II) salt provides a convenient access to deprotection products. When pentabenzylquercetin was used as the substrate together with $PhI(OAc)_2$ and $TsNH_2$ in a 1:3:1.5 molecular ratio, a tetrabenzylquercetin was obtained. The reaction may proceed by intermolecular transfer of a nitrogen atom from the copper imido complexes to the benzyl position of pentabenzylquercetin. The C–H insertion intermediate is converted into a tetrabenzyl(α-tosylaminobenzyl)quercetin, which undergoes elimination of PhCH=NTs to give a tetrabenzylquercetin (Scheme 4).




**Scheme 4** Mechanism for the amidation of pentabenzylquercetin

The structure of the debenzylated products were confirmed by $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy. The positions of the benzyl groups in the mondebenzylated products **3** and **4** were determined by means of nuclear Overhauser effect spectroscopy. NOE difference spectroscopy of 3,3',4',7-tetra-*O*-benzylquercetin (**3**) gave the following NOE correlations (Figure 2): from the proton in the 5′-position (δ = 6.96) to the methylene proton in the 4′-position (δ = 5.25); from the proton in the 2'-position (δ = 7.71) to the methylene proton in the 3′-position (δ = 4.99); from the proton in the 6-position (δ = 6.44) and the proton in the 8-position (δ = 6.46) to the methylene proton in the 7-position (δ = 5.13); and from the methylene proton in the 7-position (δ = 5.13) to the protons in the 6-position (δ = 6.44) and the 8-position (δ = 6.46). NOE difference spectroscopy of 3,5,3′,4′-tetra-*O*-benzylquercetin (**4**) gave the following NOE correlations: from the proton in the 5-position (δ = 6.98) to the methylene proton in the 4′-position (δ =5.25); and from the proton in the 2′-position (δ = 7.89) to the methylene proton in the 3′-position (δ = 4.98). NOE difference spectroscopy showed no NOE correlation from the proton in the 8-position proton (δ = 5.58) to the methylene protons in any position.

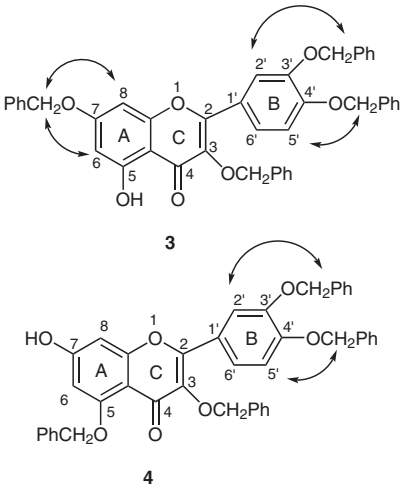



**Figure 2** Nuclear Overhauser effect spectroscopy of variously deprotected derivatives

Jain and coworkers found that *o*-dihydroxy groups can be protected by chelation with a boron complex prepared by treatment with borax.[11–15] We investigated the effects of this complexation on the selective alkylation of quercetin and its derivatives, and we found that borax-type protection of adjacent hydroxy groups could be effective in inducing selective alkylation (Figure 3).



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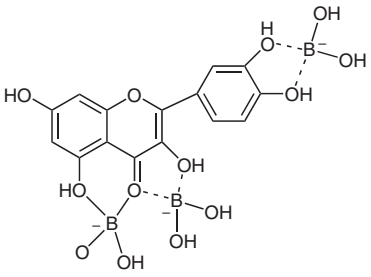


**Figure 3** The boron complex of quercetin

When the methylation of quercetin was carried in the presence of borax as a complexant by using sodium bicarbonate as the base and dimethyl sulfate as the methylating agent at 60 °C, 7-*O*-methylquercetin was obtained in 53% yield (Scheme 5). We also examined the effect of the solvent on the methylation of quercetin. *N*,*N*-Dimethylformamide was found to be the most effective solvent for this reaction (Table 1).

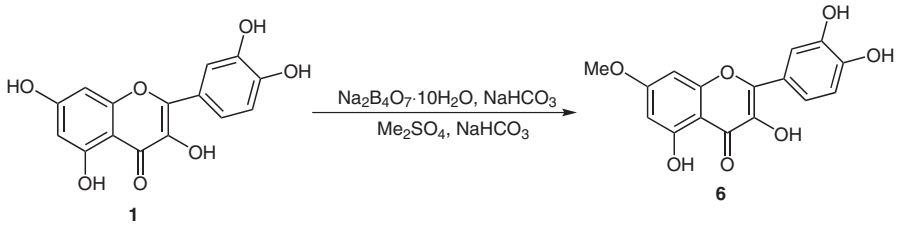
Thus, 4′-*O*-Methylquercetin (**9**) was synthesized three steps and 30% overall yield, starting from quercetin, by selective benzylation, partial methylation in the presence of borax, and final deprotection of the benzyl groups (Scheme 6).

Once we had developed the protection system using borax, we examined the selective benzylation of quercetin derivatives by using microwave irradiation and conventional heating (Scheme 7). Only the 7- and 4′-positions of quercetin pentaacetate underwent rapid benzylation with the benzyl chloride/sodium bicarbonate/benzyl(triethyl)ammonium chloride system under microwave irradiation at 545 W for 10 min. This reaction gave 7,4′-dibenzylquercetin triacetate (**8**) in 55% yield, as a result of the lower degree of steric hindrance at the 7- and 4′-positions. When quercetin pentaacetate was treated with a the same reagents under identical condition for 40 minutes, the stable tetrabenzyl derivative **3**, in which the hydroxy group at the 5-position forms a hydrogen bond with the carbonyl group, was obtained in 55% yield (Table 2).

**Table 1** Optimization of the Solvent

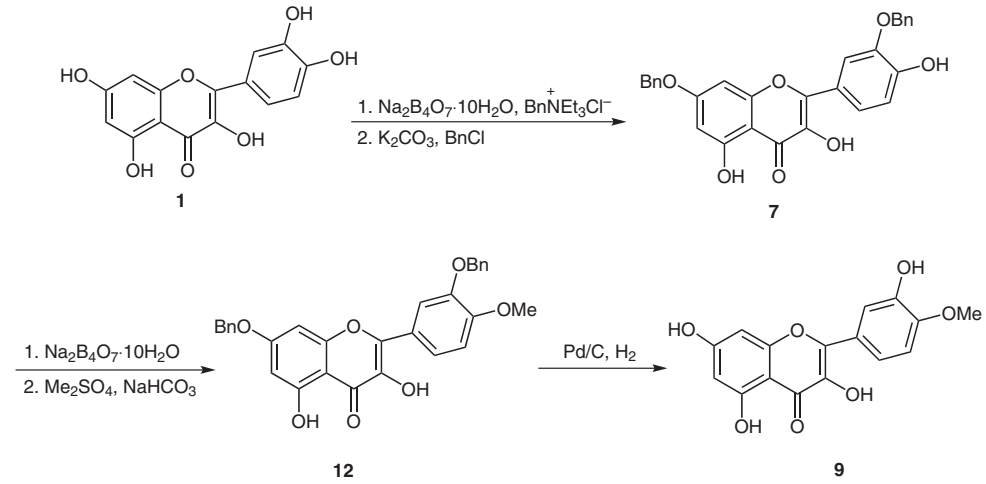
| Entry[a] | Solvent | Temp | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | MeCN | r.t. | 24 | – | – |
| 2 | MeOAc | r.t. | 24 | mixture[c] | – |
| 3 | DMF | 60 °C | 24 | mixture[d] | – |
| 4 | DMF | r.t. | 24 | **7** | 52 |
| 5 | DMF–$H_2O$ (2:1) | r.t. | 24 | mixture[e] | – |
| 6 | DMA–$H_2O$ (2:1) | r.t. | 24 | mixture[f] | – |
| 7 | HMPA | r.t. | 35 | **7**[g] | 53 |

[a] All reactions were carried out a quercetin/borax/BnCl/$K_2CO_3$/$BnN(Et_3)Cl$ molar ratio of 1:3:4:3:0.1.
[b] Yield of isolated product.
[c] Mixture of di-, tri-, tetra-, and pentabenzylquercetins (3:3:2:2).
[d] Mixture of di-, tri-, tetra-, and pentabenzylquercetins (1:3:3:3).
[e] Mixture of di-, tri-, tetra-, and pentabenzylquercetins (5:2:2:1).
[f] Mixture of di-, tri-, tetra-, and pentabenzylquercetins (2:3:3:3).
[g] Mixture of di-, tri-, tetra-, and pentabenzylquercetins (8:1:1:0).




**1** **6**

**Scheme 5** Synthesis of 7-*O*-methylquercetin




**1** **7** **12** **9**

**Scheme 6** Synthesis of 4′-*O*-methylquercetin



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Benzylation of quercetin pentaacetate by conventional refluxing gave mixtures in low yields. Microwave irradiation evidently has the advantages of producing good yields, high selectivities, and shorter reaction times compared with conventional heating.

**Table 2** Comparison of Reactivity for Microwave and Conventional Heating

| Entry[a] | Time (min) | Conventional | Microwave[b] | Product yield[c] |
|---|---|---|---|---|
| 1 | 3 | – | ~100:0 | ~30% |
| 2 | 10 | trace | ~99:0 | 55% |
| 3 | 15 | trace | ~98:0 | 50% |
| 4 | 18 | trace | ~50:50 | – |
| 5 | 25 | trace | ~90:10 | 55% |
| 6 | 40 | ~20% | ~100:0 | 55% |

[a] All reactions were carried out with a quercetin pentaacetate/BnCl/$NaHCO_3$/$BnN(Et_3)Cl$ molar ratio of 1:7:12:0.1.
[b] Ratio of **8** and **3**.
[c] Yield of isolated product.

Finally, we synthesized of 3′-*O*-methylquercetin (**10**) from quercetin in four steps and 35% overall yield (Scheme 7). Benzylation of quercetin pentaacetate at 4′,7-position with the benzyl chloride/sodium bicarbonate/benzyl(triethyl)ammonium chloride system under microwave irradiation (545 W, 160 °C) for 10 minutes gave compound **8**. This underwent methylation at the 3′-position with an excess of dimethyl sulfate and sodium bicarbonate in the presence of borax to give the dibenzyl monomethyl ether **14**. Hydrogenolysis of the benzyl groups on palladium-on-carbon in ethanol at room temperature gave the desired 3'-*O*-methylquercetin.

In summary, we have demonstrated an efficient procedure for the synthesis of monomethylated quercetins by using amidation in the presence of a Lewis acid to achieve selective debenzylation; the resulting products are then methylated to give the desired derivatives. The use of borax and heating by microwave irradiation have the advantages of greater selectivity and shorter reaction times than earlier procedures.

The reactions were carried out in an MCL-II microwave reactor. Silica gel $F_{254}$ plates were used for TLC, and spots were examined under UV light at 254 nm and developed with $I_2$ vapor. Flash chromatography was performed on silica gel H. NMR spectra were recorded on Bruker AC-E 200 MHz, Varian Mercury 400 MHz, and Bruker Avance 600 MHz spectrometers. Mass spectra were recorded on a Bruker Daltonics Data Analysis 3.2 mass spectrometer.

**Pentabenzylquercetin (2)**

A mixture of quercetin (**1**; 2.00 g, 6.617 mmol), BnCl (8.38 g, 0.0662 mol), HMPA (11.86 g, 0.0662 mol), $K_2CO_3$ (5.49 g, 0.0397 mol), and $BnN(Et_3)Cl$ (0.20 g) was stirred at r.t. under $N_2$ for 35 h. $H_2O$ (30 mL) was added, and the resulting mixture was filtered. The residue was washed with $H_2O$ (3 × 30 mL) to give a yellow solid that was crystallized (EtOAc) to give a white solid; yield: 4.73 g (95%); mp 156–158 °C (lit.[16] 156–159 °C).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.98 (s, 2 H), 5.11 (s, 2 H), 5.12 (s, 2 H), 5.26 (s, 2 H), 5.30 (s, 2 H), 6.48 (d, *J* = 2.4 Hz, 1 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.24–7.64 (m, 25 H), 7.56 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.74 (d, *J* = 2.0 Hz, 1 H).

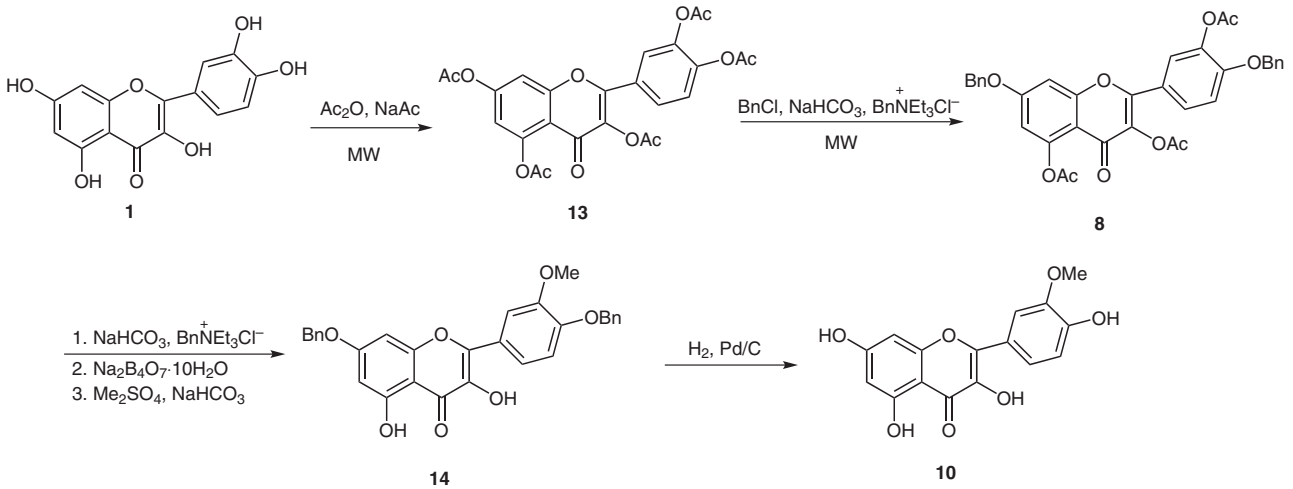
$^{13}$C NMR (100 MHz, $CDC1_3$): δ = 70.4, 70.8, 70.9, 71.0, 74.1, 93.7, 98.1, 110.0, 113.7, 115.2, 122.1, 123.9, 126.6, 127.2, 127.3, 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 128.7, 128.8, 135.7, 136.4, 136.8, 137.0, 139.8, 148.2, 150.5, 153.1, 158.6, 159.7, 162.7, 173.6.

**3,3′,4′,7-Tetra-*O*-benzylquercetin (3)**

$CuCl_2$ (89 mg, 0.664 mmol) and $TsN_3$ (0.20 g, 1.01 mmol) were added to a soln of pentabenzylquercetin (**2**; 0.50 g, 0.664 mmol) in MeCN (5 mL). The mixture was irradiated with microwaves (545 W) at 160 °C for 10 min. On completion of the reaction (TLC), the crude product was purified by flash column chromatography [silica gel, PE–EtOAc (4:1, 3:1, 2:1)] to give a light-yellow solid; yield: 0.36 g (81%). mp 139–142 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 2 H), 5.04 (s, 2 H), 5.13 (s, 2 H), 5.25 (s, 2 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H), 7.22–7.47 (m, 20 H), 7.55 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.71 (d, *J* = 2.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDC1_3$): δ = 70.4, 70.9, 71.2, 74.3, 93.0, 98.5, 113.8, 115.4, 122.6, 123.5, 125.6, 127.2, 127.3, 127.4, 127.9, 128.0,




**Scheme 7** Synthesis of 3′-*O*-methylquercetin



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128.2, 128.3, 128.5, 128.6, 128.8, 129.8, 135.8, 136.5, 136.7, 136.9, 137.5, 148.3, 151.1, 156.3, 156.7, 162.1, 164.5, 178.8.

MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{43}H_{34}NaO_7$: 685.2; found: 685.3.

**3,3′,4′,7-Tetra-*O*-benzyl-5-*O*-methylquercetin (11)**

$Me_2SO_4$ (2 mL) was added to a mixture of 3,3′,4′,7-tetra-*O*-benzylquercetin (**3**; 0.50 g, 0.664 mmol) and $K_2CO_3$ (0.021 g, 0.152 mmol), and the mixture was irradiated with microwaves (545 W) at 160 °C for 5 min. On completion of the reaction (TLC), the mixture was extracted with $CH_2C1_2$ (3 × 10 mL). The extracts were purified by flash column chromatography [silica gel, PE–EtOAc (1:1, 2:1, 3:1)] to give a white solid; yield: 0.025 g (99%); mp 157–159 °C (lit.[17] 160 °C). Starting material **3** (0.025 g) was also recovered.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 4.96 (s, 2 H), 5.07 (s, 2 H), 5.13 (s, 2 H), 5.23 (s, 2 H), 6.42 (d, *J* = 2.4 Hz, 1 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H), 7.22–7.47 (m, 20 H), 7.56 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.76 (d, *J* = 2.0 Hz, 1 H).

**5-*O*-Methylquercetin (5; Azaleatin)**

A mixture of 3,3′,4′,7-tetra-*O*-benzyl-5-*O*-methylquercetin (**11**; 0.41 g, 0.606 mmol), 10% Pd/C (0.041 g), and anhyd EtOH (20 mL) was stirred under $H_2$ at ordinary pressure at r.t. for 6 h. The mixture was then filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel, PE–EtOAC (1:3, 1:4, 1:6)] to give an off-white solid; yield: 0.18 g (95%); mp 260–263 °C (lit.[8] 259–261 °C).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.83 (s, 3 H), 6.35 (d, *J* = 2.0 Hz, 1 H), 6.45 (d, *J* = 1.6 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 7.48 (dd, *J* = 1.6, 8.8 Hz, 1 H), 7.62 (d, *J* = 1.6 Hz, 1 H), 8.63 (s, 1 H), 9.25 (s, 1 H), 9.46 (s, 1 H), 10.71 (s, 1 H).

**3,5,3′,4′-Tetra-*O*-benzylquercetin (4)**

$CuTf_2$ (0.019 g, 0.053 mmol), $TsNH_2$ (0.068 g, 0.398 mmol), $PhI(OAc)_2$ (0.385 g, 1.20 mmol), and $Al_2O_3$ (0.163 g, 1.59 mmol) were added to a soln of 3,3′,4′,5,7-pentabenzylquercetin (**2**; 0.20 g, 0.266 mmol) in $CH_2Cl_2$ (10 mL) under $N_2$. The mixture was stirred at r.t. under $N_2$. On completion of the reaction (TLC), the crude product was purified by flash column chromatography [silica gel, PE–EtOAc (4:1, 3:1)] to give a light-yellow solid; yield: 50 mg (40%).

$^1$H NMR (400 MHz, $CDCl_3$): 4.98 (s, 2 H), 5.10 (s, 2 H), 5.15 (s, 2 H), 5.25 (s, 2 H), 6.50 (d, *J* = 2.4 Hz, 1 H), 6.58 (d, *J* = 2.4 Hz, 1 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 7.21–7.54 (m, 20 H), 7.78 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.89 (d, *J* = 2.0 Hz, 1 H).

HRMS (ESI): *m/z* [M + H] calcd for $C_{43}H_{35}O_7$: 663.2383; found: 663.2387.

**Quercetin Pentaacetate (13)**

A mixture of quercetin (**1**; 2.00 g, 6.62 mmol), NaOAc (1.60 g, 24.3 mmol), and $Ac_2O$ (20 mL, 0.21 mol) was subjected to microwave irradiation (545 W) at 160 °C for 10 min. On completion of the reaction (TLC), the mixture was poured into ice-water (250 mL) and filtered. The crude product was crystallized (95% EtOH) to give a white solid; yield: 3.15 g (93%); mp 190–193 °C (lit.[18] 192–194 °C).

**4′,7-Di-*O*-benzylquercetin 3,3′,5-Triacetate (8)**

A mixture of quercetin pentaacetate (**13**; 0.20 g, 0.390 mmol), BnCl (0.35 g, 2.73 mmol), $NaHCO_3$ (0.40 g, 4.76 mmol), and $BnN(Et_3)Cl$ (0.020 g) was irradiated with microwaves (545 W) at 160 °C for 10 min. On completion of the reaction (TLC), the mixture was washed with PE (3 × 10 mL) and the residue was purified by flash column chromatography [silica gel, PE–EtOAc–$CHCl_3$ (8:4:1, 7:4:1,6:4:1)] to give a light-yellow solid; yield: 0.13 g (55%); mp 152–154 °C (lit.[18] 154–156 °C).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.33 (s, 3 H), 2.43 (s, 3 H), 5.14 (s, 2 H), 5.17 (s, 2 H), 6.70 (d, *J* = 2.0 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 8.8 Hz, 1 H), 7.32–7.43 (m, 10 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 2.0, 8.8 Hz, 1 H).

**4′,7-Di-*O*-benzyl-3′-*O*-methylquercetin (14)**

A mixture of triacetate **8** (0.30 g, 0.493 mmol), $NaHCO_3$ (0.17 g, 1.97 mmol), $BnN(Et_3)Cl$ (0.030 g), anhyd MeOH (0.096 g, 3.00 mmol), and acetone (7 mL) was stirred at 50 °C for 5 h. $Na_2B_4O_7{\cdot}10\,H_2O$ (0.061 g, 0.170 mmol), $H_2O$ (8 mL), $Me_2SO_4$ (0.25 g, 1.98 mmol), $NaHCO_3$ (0.084 g, 1.00 mmol), and acetone (12 mL) added, and the mixture was stirred at 50–55 °C for 6.5 h. The mixture then was concentrated in vacuo to give a residue that was acidified to pH 3–4 with 10% HCl. The mixture was extracted with $CH_2Cl_2$ (3 × 30 mL), and the extracts were concentrated in vacuo. The residue was purified by chromatography [silica gel, PE–EtOAc–$CHCl_3$ (7:1.5:0.5, 7:2:0, 6:2:0, 5:2:0)] to give a yellow solid; yield: 0.18 g (75%); mp 170–174 °C (lit.[6] 172–174 °C).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.87(s, 3 H), 5.14 (s, 2 H), 5.21 (s, 2 H), 5.77 (s, 1 H), 6.43 (d, *J* = 2.4 Hz, 1 H), 6.51 (d, *J* = 2.0 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 7.34–7.45 (m, 10 H), 7.69 (dd, *J* = 2.0, 10.8 Hz, 1 H), 7.80 (d, *J* = 2.0 Hz, 1 H), 12.64 (s, 1 H).

**3′-O-Methylquercetin (10; Isothamnetin)**

A mixture of 3′-*O*-methyl-4′,7-di-*O*-benzylquercetin (**14**; 0.10 g, 0.201 mmol), 10% Pd/C (0.010 g), and anhyd EtOH (10 mL) was stirred under $H_2$ at ordinary pressure at r.t. for 5 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue that was purified by column chromatograph [silica gel, PE–EtOAc (4:1, 3:1, 2:1)] to afford a white solid; yield: 0.057 g (90%), mp 302–304 °C (lit.[5] 305–306 °C).

$^1$H NMR (600 MHz, acetone-$d_6$): δ = 3.95 (s, 3 H), 6.28 (d, *J* = 6.2 Hz, 1 H), 6.57 (d, *J* = 6.1 Hz, 1 H), 7.02 (d, *J* = 25.3 Hz, 1 H), 7.84 (dd, *J* = 6.1, 25.3 Hz, 1 H), 7.90 (d, *J* = 6.0 Hz, 1 H), 8.15 (s, 1 H), 8.38 (s, 1 H), 9.70 (s, 1 H), 12.20 (s, 1 H).

**7-*O*-Methylquercetin (Rhamnetin) (6)**

A mixture of quercetin (**1**; 0.050 g, 0.165 mmol), acetone (3 mL), $NaHCO_3$ (5.0 mg, 0.0595 mmol), $Na_2B_4O_7{\cdot}10\,H_2O$ (0.015 g, 0.0419 mmol), and $H_2O$ (6 mL) was stirred at 70 °C for 30 min. $Me_2SO_4$ (0.038 g, 0.297 mmol), $NaHCO_3$ (0.056 g, 0.667 mmol), and acetone (8 mL) were added, and the resulting mixture was stirred at 50 °C for 6 h. The mixture was then concentrated in vacuo, and the residue was acidified to pH 3–4 with 10% HCl and extracted with EtOAc (3 × 20 mL). The extracts were concentrated in vacuo to give a residue that was purified by column chromatograph [silica gel, PE–EtOAc (2:1, 1:1, 1:2)] to give a white solid; yield: 0.025 g (53%); mp 282–286 °C (lit.[19] 280–285 °C).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.87 (s, 3 H), 6.37 (d, *J* = 2.4 Hz, 1 H), 6.71 (d, *J* = 2.4 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 7.58 (dd, *J* = 2.4, 8.4 Hz, 1 H), 7.73 (d, *J* = 2.4 Hz, 1 H), 9.33 (s, 1 H), 9.52 (s, 1 H), 9.66 (s, 1 H), 12.46 (s, 1 H).

**3′,7-Di-*O*-benzylquercetin (7)**

A mixture of quercetin (**1**; 1.002 g, 3.315 mmol), $Na_2B_4O_7{\cdot}10\,H_2O$ (3.801 g (9.966 mmol), $BnN(Et_3)Cl$ (0.11 g), anhyd DMF (30 mL), BnCl (1.683 g, 13.29 mmol), and $K_2CO_3$ (1.376 g, 9.957 mmol) was stirred at r.t. for 24 h. The mixture was then poured into $H_2O$ (90 mL), and the mixture was extracted with EtOAc (4 × 30 mL). The extracts were washed with $H_2O$ (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography [silica gel, PE–EtOAc (6:1,4:1, 3:1, 2:1)] to give a light-yellow solid; yield: 0.827 g (52%); mp 201–204 °C



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$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 5.02 (s, 2 H), 5.24 (s, 2 H), 6.47 (d, *J* = 2.0 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 7.30–7.49 (m, 11 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 9.34 (s, 1 H), 9.82 (s, 1 H), 12.73 (s, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 70.2, 73.5, 93.3, 98.7, 105.5, 115.8, 116.0, 121.0, 121.2, 128.1, 128.3, 128.4, 128.5, 128.7, 128.8, 136.4, 136.7, 136.9, 145.2, 149.1, 156.5, 157.0, 161.3, 164.3, 178.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{22}NaO_7$: 505.1258; found: 505.1262.

**3′,7-Di-*O*-benzyl-4′-*O*-methylquercetin (12)**

A mixture of 3′,7-di-*O*-benzylquercetin (**7**; 0.20 g, 0.414 mmol), acetone (25 mL), $Na_2B_4O_7{\cdot}10\ H_2O$ (0.481 g, 1.26 mmol), and $H_2O$ (1 mL) was stirred and heated to 50 °C. $Me_2SO_4$ (0.225 g, 1.79 mmol) and $NaHCO_3$ (0.141 g, 1.67 mmol) were added, and the mixture was stirred at 50 °C for 4 h. The mixture was then cooled to r.t., and $H_2O$ (20 mL) was added. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatograph [silica gel, PE–EtOAc (6:1, 5:1, 4:1)] to give a light-gray solid; yield: 0.105 g, (72%); mp 157–161 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 5.08 (s, 2 H), 5.16 (s, 2 H), 5.66 (s, 1 H), 6.44 (d, *J* = 1.6 Hz, 1 H), 6.51 (d, *J* = 2.0 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 7.27–7.45 (m, 10 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.65 (dd, *J* = 2.0, 8.4 Hz, 1 H), 12.71 (s, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 55.9, 70.2, 73.5, 93.3, 98.7, 105.5, 111.8, 115.5, 120.9, 122.4, 128.1, 128.3, 128.4, 128.6, 128.8, 136.3, 136.8, 137.0, 146.5, 150.5, 156.5, 156.6, 161.2, 164.3, 178.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{30}H_{24}NaO_7$: 519.1414; found: 519.1410.

**4′-*O*-Methylquercetin (9; Tamarixetin)**

A mixture of 3′,7-di-*O*-benzyl-4′-*O*-methylquercetin (**12**; 0.071 g, 0.143 mmol), 10% Pd/C (0.007 g), and anhyd EtOH (8 mL) was stirred under $H_2$ at ordinary pressure at r.t. for 5.5 h. The mixture was then filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography [silica gel, PE–EtOAc (3:1, 2:1)] to give a yellow solid; yield: 0.036 g (81%), mp 246–248 °C (lit.[8] 252–254 °C).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.83 (s, 3 H), 6.18 (s, 1 H), 6.41 (s, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.66 (d, *J* = 2.4 Hz, 1 H), 9.33 (s, 1 H), 9.45 (s, 1 H), 9.80 (s, 1 H), 12.44 (s, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 55.8, 93.6, 98.4, 103.3, 112.0, 114.8, 120.0, 123.6, 136.4, 146.4, 146.6, 150.4, 156.4, 161.8, 164.2, 176.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{12}O_7Na$: 339.0475; found: 339.0471.

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