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Hemisynthesis of all the *O*-monomethylated analogues of quercetin including the major metabolites, through selective protection of phenolic functions

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Abstract—A new methodology for the hemisynthesis of all the five *O*-monomethylated analogues of quercetin (3′-*O*-methylquercetin (isorhamnetin), 4′-*O*-methylquercetin (tamarixetin), 3-*O*-methylquercetin, 5-*O*-methylquercetin (azaleatin) and 7-*O*-methylquercetin (rhamnetin)) through sequential protection of the different phenolic functions of quercetin is reported. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Flavonoids, such as flavones and flavonols, are secondary plant metabolites[1,2] particularly found in the upper parts of plants. As a consequence, they are present in a great variety of food and especially in fruit and vegetables. Quercetin is the main flavonoid occurring in food and is present at an average level of 10 mg/kg. Higher concentrations can even be found in some common vegetables like onions (300 mg/kg). Nowadays, according to dietary habits, the average daily intake[3] of flavonoid has been assessed from 6 mg in Finland to 70 mg in Japan, and more precisely, quercetin amount represents 60–75% of this average intake. Moreover, quercetin is a very efficient antioxidant[4] and appears to be active in many diseases related to ageing like cancer,[5] cardiovascular[6] and neurodegenerative[7] diseases, as widely described in the literature (see Refs. 8,9 for recent reviews). Furthermore, the quercetin skeleton is the main part of the drug Flavopiridol, which is now under clinical trials.[10,11] However in blood, quercetin is mainly found in conjugated forms. The few existing comparative studies made by using plasma samples show that the activities of the metabolites are rather different from those of quercetin.[12] Nevertheless, most of the in vitro studies are performed on quercetin itself and not on their metabolites as these latter are not readily available from commercial sources. Non-degradative metabolism of polyphenols involves three main modifications on the phenolic hydroxyl groups: methylation, sulfation and glucuronidation.[2] Plasma analysis of pig fed with quercetin-rich diets show there is no quercetin left but only methylated metabolites, such as the 3′-*O*-methylquercetin (isorhamnetin) and the 4′-*O*-methylquercetin (tamarixetin) along with the 3′-dehydroxylated quercetin (kaempferol), most of them being conjugated as glucuronide or sulfate.[13] The same metabolism was observed in rat[14] and in vivo cell culture[15] with some variations in the relative abundance of the methylation position. However, quercetin metabolism in human is still controversial as the different relative abundance depends of the diet habits and of the quercetin content.[16–19] These methylated metabolites are presumably the active molecules as the glucuronide or sulfate groups are readily deconjugated in tissues.[20] Therefore, we decided to develop a new general strategy leading to quercetin metabolites in order to better identify them and to provide enough materials for in vivo studies of metabolites. We report here on the synthesis of the two known methyl metabolites of quercetin, and on the synthesis of the three others *O*-methylquercetin isomers. These compounds will allow structure activity studies,[21] will help in the identification of unknown metabolites, and their easily obtained labeled form will give access to isotopic dilution dosage by LC-MS or LC-MS/MS.

2. Results and discussion

2.1. Regiochemistry of quercetin alkylation

Two pathways have already been developed for the synthesis of these quercetin analogues.

Keywords: quercetin; alkylation; metabolites.

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The first one is based on total synthesis using either: (i) condensation between an *ortho*-hydroxylated acetophenone and an activated benzoic acid according to the Allan–Robinson condensation or according to its variant, the Baker–Venkataraman rearrangement;[1] or (ii) an oxidative cyclisation of chalcones according to the Algar–Flynn–Oyamada reaction.[22] For example, the coupling strategy between an *ortho*-hydroxylated acetophenone and an activated benzoic acid has recently been reported for the synthesis of 3-*O*-methylquercetin,[23] 4′-*O*-β-D-glucoside quercetin[24] and modified flavonols.[25] Recently, a new method combining both strategies has been introduced by Brouillard et al.[26]

The second route is based on hemisynthesis starting from quercetin and relies on direct alkylation of the parent compound, which depends on the relative reactivity of the different positions. Rao et al.[27] have shown that this methylation occurs gradually following a specific sequential positions order: 4′>7>3>3′>5. Previous studies have revealed that the direct quercetin alkylation using a limited amount of alkyl halide gave mixtures composed of 'native' quercetin and highly *O*-alkylated products. Therefore, in the early sixties, Jurd[28,29] used quercetin pentaacetate as starting material. Acetyl groups, which are attached to the flavone skeleton, are successively replaced by alkyl groups with the preferential positions order 7>4′>3>5>3′. Therefore, this reaction presents an inversion of reactivity compared to the direct alkylation one and the reaction selectivity is slightly better. Farkas et al.[30] have developed a close method starting from quercetin pentabenzoate. However, in our hands, this method gave compounds of poor chemical purity.

Therefore, we first decided to reinvestigate the direct methylation of quercetin using up-to-date analytical techniques in order to get an insight into the reactivity of each position. In this aim, we performed direct methylation of quercetin using DMF as solvent in order to work at room temperature. The reaction mixture was then analyzed by (LC-ESI-MS/MS).[31] The reaction mixture was so separated by liquid chromatography on a reverse phase and the different products identified by mass spectrometry on the basis of their collision activated dissociation spectra: ions produced by electrospray ionization in positive mode were fragmented in a collision activated dissociation cell and the resulting fragmentation pattern allowed determination of the methylation position. Fig. 1 shows the UV traces at 280 nm obtained for different reagent amounts, from 1 to 3 equiv. of methyl iodide and 1.25 times more equivalent of sodium carbonate. This wavelength was used as it corresponds to a plate in quercetin and methylquercetin spectra exhibiting small sensitivity to the substitution pattern. Therefore, for the following discussion and quantification (Table 1), a similar molar extinction coefficient was assumed for all the compounds. Fig. 1 and Table 1 show that even using 1 equiv. of methyl iodide, the reaction is not selective and leads to a mixture of mono, di and a trace of tri *O*-methylated compounds.

The three mono *O*-methylquercetin isomers were identified as 3, 7 and 4′ isomers obtained respectively in a 20, 55, 25 relative yield; whereas the two *O*-dimethylquercetin

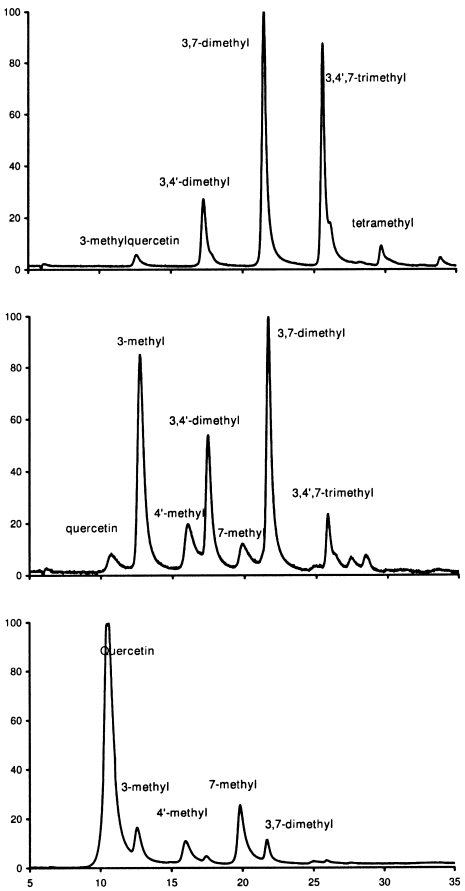


Figure 1. LC-UV (reverse phase C18 column, 280 nm) trace of the reaction mixture from the alkylation of quercetin using different amounts of methyl iodide and sodium carbonate. Bottom: 1 equiv; middle: 2 equiv; top: 3 equiv.

isomers were assigned to be 3,7 and 3,4′-*O*-dimethylquercetin (67,33 relative yield respectively). No *C*-alkylated products can be detected in those conditions. Inspection of the results with 1 equiv. leads to ascertain a reactivity order 7>3≈4′, which is in agreement with Jurd data but not with Rao's results. The relative reactivity appeared preserved in the synthesis of *O*-dimethylquercetins, which leads preferentially to the formation of 3,7-*O*-dimethylquercetin.

Therefore, this brute force route only allows synthesis of three of the five monomethylquercetin and involves tedious

Table 1. Direct methylation of quercetin **1** in DMF at room temperature

	1 equiv.[a]	2 equiv.[a]	3 equiv.[a]
Quercetin[b]	70	4	0
Monomethyl[b,c]	25 (20, 55, 25)	45 (72, 8, 20)	2 (100,0,0)
Dimethyl[b,d]	4 (67, 33)	46 (63,37)	57 (77,23)
Trimethyl[b,e]	0	5	35
Tetramethyl[b,f]	0	0	5

[a] 1 equiv. is defined as the stoichiometric amount of MeI in presence of 1.25 equiv. of K_2CO_3.
[b] Yield determined by LC-UV at 280 nm assuming a similar molar extinction coefficient for all the compounds.
[c] Total yield of methylquercetin, (3-*O*-methylquercetin, 7,4′, composition%).
[d] Total yield of dimethylquercetin (3,7-*O*-dimethylquercetin, 3,4′, composition%).
[e] Yield of 3,7,4′-*O*-trimethylquercetin.
[f] Yield of 3,7,3′,4′-*O*-tetramethylquercetin.

Table 2. Benzylation of quercetin **1** with various quantities of BnBr

Conditions[a]	0.5 equiv.[a]	1 equiv.[a]	2 equiv.[a]	3 equiv.[a]	3.5 equiv.[a]	6 equiv.[a]
Monobenzyl[b]	70	32	0	0	0	0
Dibenzyl[b]	25	49	48	0	0	0
Tribenzyl[b]	5	19	44	52	24	0
Tetrabenzyl[b]	0	0	8	36	72	0
Pentabenzyl[b]	0	0	0	12	4	100

[a] 1 equiv. is defined as the stoichiometric amount of BnBr in presence of 1.25 equiv. of K_2CO_3.
[b] Relative proportion determined by infusion ESI-MS assuming the same ionization yield for all the compounds.

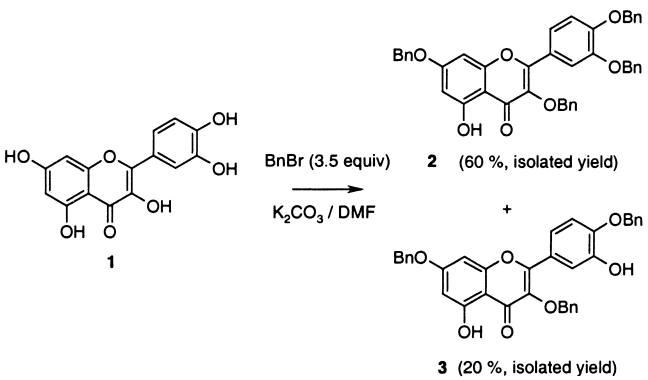
separations if pure compounds are required. So we chose to develop a synthesis strategy based on successive and selective protections of the different quercetin phenolic functions for synthesizing the five monomethylated isomers with the methyl group in position 3′ (isorhamnetin), 4′ (tamarixetin), 3 (3-*O*-methylquercetin), 5 (azaleatin) and 7 (rhamnetin).

2.2. Optimization of quercetin benzylation

We decided first to optimize the partial benzylation of quercetin **1** using different amounts of benzyl bromide and K_2CO_3 (Table 2).

The inspection of Table 2 shows that quercetin benzylation occurs in several steps. The use of 1 equiv. of benzyl bromide provides a mixture of mono-, di- and tribenzylated isomers of quercetin, respectively in 32:49:19 proportions. The relative proportions of mono- and dibenzylated analogues decrease when 2 or 3 equiv. of benzyl bromide are used, whereas proportions of tri- and tetrabenzylated analogues increase. Quercetin benzylation with 3.5 equiv. of benzyl bromide and K_2CO_3 leads mainly to the formation of two products: a tetrabenzylated isomer **2** (60% isolated yield) and a tribenzylated one **3** (20% isolated yield) (Scheme 1 and Table 2). Pentabenzylquercetin is also detected as traces (3% isolated yield). The melting points reported in the literature for the tetrabenzylated isomer **2** varies from 128[32] to 145 °C,[33] which pushed us to ascertain the structure of the obtained compound.

It is well-known that the hydroxyl function on the 5 position resists to benzylation under these conditions. This group is indeed less acidic than the other quercetin phenolic functions, which may be accounted for by an acid-weakening effect of an intramolecular H-bond between the 5-hydroxyl group and the 4-keto group.[34,35] Secondly, the quercetin acidic 3-hydroxyl group can be readily benzylated. Assuming that the 5-hydroxyl group remains free, there are four possibilities left for the tribenzylation of Quercetin leading to the potential tribenzyl ethers **3** regioisomers: 3,3′,4′; 3,3′,7; 3,4′,7 and 3′,4′,7. The position of the benzyl group in **3** was unambiguously determined using one-dimensional (1D)-nuclear Overhauser effect (NOE) spectroscopy on the *O*-dimethylated analogue **3a** obtained in a near quantitative yield by permethylation in mild conditions (methyl iodide in DMF and K_2CO_3 as base). The irradiation of the methyl peaks results in an increase of H-6 and H-2′ resonance frequencies, while H-8 and H-5′ frequencies are not affected, indicating that the methyl groups are located on the 5 and 3′ positions. Consequently, the benzyl groups are located on the 3, 4′,7 positions. These results are in agreement with the recently reported NMR spectra of 3,7,4′-tri- and 3,7,3′,4′-*O*-tetrabenzylquercetin obtained using harder alkylation conditions (*t*-BuOK, DMF) and two successive additions of benzyl bromide.[36]



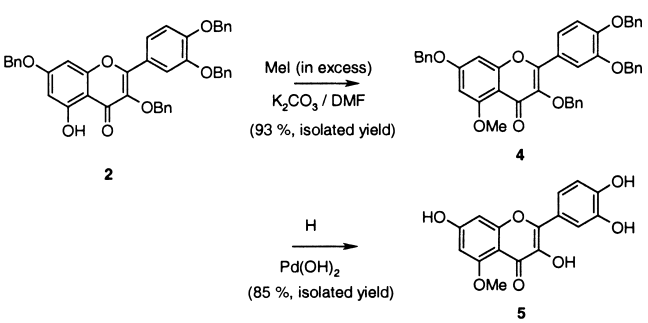
Scheme 1. Synthesis of 3,7,4′-*O*-tribenzylquercetin and 3,7,3′,4′-*O*-tetrabenzylquercetin.

2.3. Synthesis of 5-*O*-methylquercetin

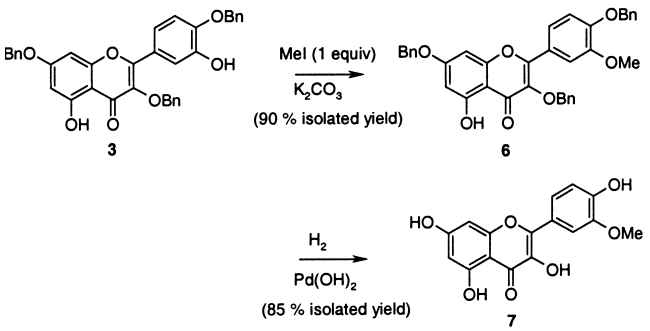
The synthesis of 5-*O*-methylquercetin (azaleatin) **5** is performed in two steps starting from **2**: methylation of the free phenolic function at 5 position with an excess of MeI and K_2CO_3 gives **4**; a final deprotection step, involving the cleavage of the benzyl groups by hydrogenolysis on palladium hydroxide in EtOH–THF at room temperature affords **5** (Scheme 2). As expected from the behavior of quercetin for which the most common crystalline form is the dihydrate, 5-*O*-methylquercetin (azaleatin) crystallizes also as the dihydrate as shown by the elemental analysis data. In all the series, in fact, the unprotected compounds crystallize as hydrates.

2.4. Synthesis of 3′-*O*-methylquercetin

The synthesis of 3′-*O*-methylquercetin (isorhamnetin) **7** was



Scheme 2. Synthesis of 5-*O*-methylquercetin (azaleatin).

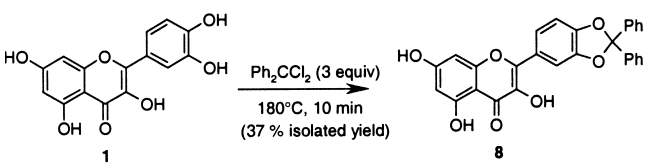


Scheme 3. Synthesis of 3′-*O*-methylquercetin (isorhamnetin).

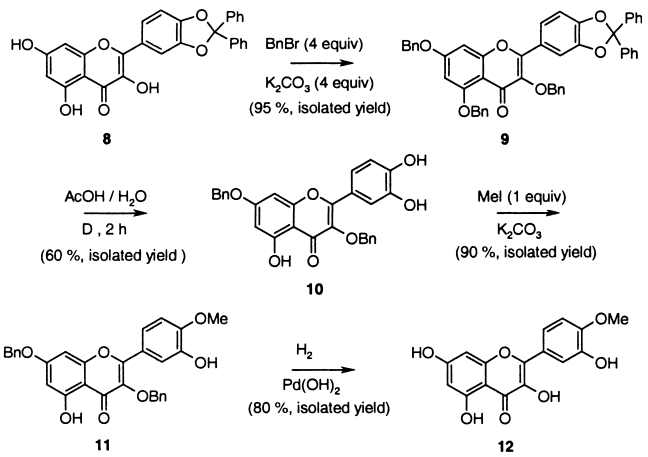
carried out under the same conditions starting from 3,7,4′-*O*-tribenzylquercetin **3**. The partial methylation of the 3′ position free phenolic function with one equivalent of MeI and K_2CO_3 (the 5 position is less reactive) which leads to **6** (90% yield) is followed by a final deprotection of the benzyl groups to reach isorhamnetin **7** in a 85% yield (Scheme 3).

2.5. Selective protection of quercetin catechol ring

For the synthesis of the 4′, 3 and 7 monomethylated quercetins (**12**, **17** and **20**), we decided to adopt an alternative strategy which relies upon a selective protection of the catechol ring, so as to make the selective methylation and benzylation easier. Quercetin *O*-dihydroxyl groups may be protected after chelation with borax.[37] However, Wender et al. reported that quercetin methylation under these conditions provided a complex mixture with at least three non-identified partially methylated Quercetin ethers.[38] A similar behavior was observed, in our laboratory, for catechin methylation in presence of borax.[39] So we decided to use the same strategy we developed for catechin based on the protection of the *O*-dihydroxyphenyl group with dichlorodiphenylmethane.[39,40] On the contrary to Jurd,[41] who reported that quercetin protection with dichlorodiphenylmethane cannot be achieved directly and requires a first protection step of the 7-hydroxyl group, but in agreement with the recent paper by Alluis and Dangles,[36] we observed that dichlorodiphenylmethane is an efficient protecting group for the quercetin B ring vicinal hydroxyl group. We first tested the conditions developed for the very sensitive compound catechin. However, the reaction of quercetin **1** with 1.1 equiv. of dichlorodiphenylmethane and 5 equiv. of base (K_2CO_3 or NEt_3) in acetonitrile at room temperature provides the desired compound **8** but with a very low yield (10%). Variations in dichlorodiphenylmethane or base amount do not change the reaction yield. On the other hand, the protected quercetin **8** is readily prepared by heating **1** at 180°C for 10 minutes with 3 equiv. of dichlorodiphenylmethane The desired product **8** is so obtained with a 37% yield after recrystallization (Scheme 4).



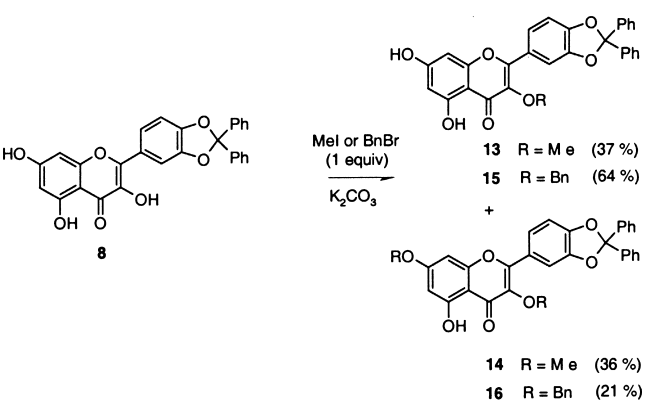
Scheme 4. Synthesis of B-ring protected quercetin.



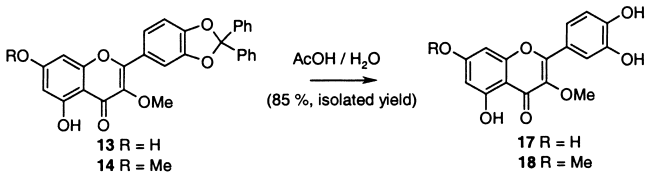
Scheme 5. Synthesis of 4′-*O*-methylquercetin (tamarixetin).

2.6. Synthesis of 4′-*O*-methylquercetin

Treatment of **8** with an excess of benzyl bromide (4 equiv.) and K_2CO_3 (4 equiv.) in DMF leads to the formation of **9**, whose all phenolic functions are protected. Synthesis of 4′-*O*-methylquercetin (tamarixetin) **12** is then performed in three steps (Scheme 5). Starting from **9**, we first focus on the catechol ring deprotection by cleaving the diphenylmethylene ketal. Two different methods are available for the cleavage of such diphenylmethylene ketal: either hydrogenolysis or hydrolysis. As may be expected, hydrogenolysis catalyzed by palladium hydroxide fails in the partial deprotection of **9**, as the ketal seems more resistant to hydrogenolysis than the benzyl group. Nonetheless, we were delighted that under acidic conditions the ketal can be cleaved selectively. The best results were obtained using a mixture of acetic acid/water (80:20) heated. TLC monitoring shows that the reaction is completed after 2 hours at reflux. This method allows deprotection in a 60% yield and no side products are detected by TLC or NMR analysis. This method appears to be easy, efficient and fast. TLC monitoring shows that the reaction is completed after 2 h at reflux. Hence, flavonol **10** is reached after the deprotection of the catechol ring and the selective debenzylation of the 5-hydroxy group. This phenomenon may account for by the assistance from the benzopyran skeleton carbonyl group. Three phenolic functions, the 3′, 4′ and 5 ones, are free at this stage of the synthesis. Treatment of **10** with 1 equiv. of



Scheme 6. Methylation and benzylation of B-ring protected quercetin (isolated yield).



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

MeI leads selectively to **11** presenting a methyl group in the 4′ position, in a 90% yield. The methyl group position is confirmed by a one-dimensional (1D)-nuclear Overhauser effect (NOE) spectroscopy. Irradiation of this methyl group (3.95 ppm) results in a strong enhancement of the doublet (J=8.6 Hz) at 6.88 ppm, corresponding to H-5′ resonance. The ultimate step of this synthesis consists of the hydrogenolysis of the protecting group catalyzed by palladium hydroxide, which provides the 4′-*O*-methylquercetin (tamarixetin) **12**. The overall yield from **8** to **12** is 41% (Scheme 5).

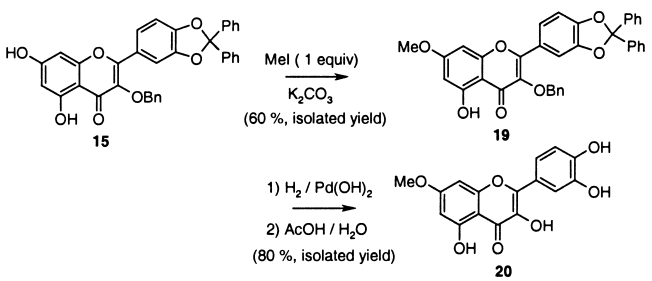
2.7. Synthesis of 3-*O*-methylquercetin

The synthesis of quercetin 3- and 7-*O*-monomethyl isomers (**17** and **20**) is based on the same synthetic strategy. This synthesis, which is depicted in Scheme 6, involves one single step, the selective alkylation of compound **8** on the 3 position. Treatment of **8** with 1 equiv. of MeI or BnBr in the presence of K_2CO_3 affords a mixture of two products: the 3-methyl (or benzyl) isomer (**13** or **15**) and the 3,7-dimethyl (or dibenzyl) isomer (**14** or **16**) (Scheme 6) which are readily separated by chromatography on silica gel.

The methyl group position in **13** is confirmed once more by a 1D difference nuclear Overhauser experiment, whereas irradiation of the methyl group does not affect the H-6 and H-8 resonance frequencies. The 3-*O*-methylquercetin **17** and 3,7-*O*-dimethylquercetin are directly obtained after an acidic hydrolysis, with a mixture of acetic acid/water (80:20) (Scheme 7) in a 85% yield.

2.8. Synthesis of 7-*O*-methylquercetin

Finally, the synthesis of 7-*O*-methylquercetin **20** (rhamnetin) requires the methylation of the 7-hydroxyl position using 1 equiv. of MeI and K_2CO_3 (60% yield) to give **19** followed by the hydrogenolysis of the benzyl protecting group in 3 position using palladium hydroxide in a EtOH/THF (1:1) mixture at room temperature. The deprotection of the catechol ring with a mixture of acetic acid/water 80:20 (80% yield, Scheme 8) affords the target compound 7-*O*-methylquercetin **20** (rhamnetin).



Scheme 8. Synthesis of 7-*O*-methylquercetin (rhamnetin).

3. Conclusion

In conclusion, we have developed a general methodology for the hemisynthesis of the five *O*-monomethylquercetin isomers. Our strategy relies, on one hand on the difference in reactivity of the different sites and, on the other hand, on the selective protection of the catechol group with dichlorodiphenylmethane. Using the same strategy, we succeeded in synthesizing several *O*-dimethylquercetin, such as 3′,4′-*O*-dimethylquercetin and 3,7-*O*-dimethylquercetin which will be reported elsewhere. The reported protocol could be applied to the synthesis of other quercetin metabolites, which include non-labile groups such as a sulfate or a glucuronide groups.

4. Experimental

4.1. General

All commercially available products were purchased from Aldrich (Saint-Quentin Fallavier, France) and used as received. Deuterated solvents (99.9% or better) were purchased from Euriso-Top (Saint-Aubin, France). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon before use. Dimethylformamide (DMF) was distilled at atmospheric pressure before use. For flash chromatography, Merck silica-gel 60 (230–400 mesh ASTM) was used. The melting points were measured on an Electrothermal (Dubuque, Iowa USA) 9100 apparatus and were not corrected. NMR were recorded on a Bruker (Wissembourg, France) AM 300 spectrometer (300 and 75 MHz, for ^1H and ^{13}C, respectively) using $CDCl_3$, [D_6]acetone, [D_4]MeOH, [D_6]DMSO as solvents and TMS as internal standard; chemical shifts and J values are given in δ and Hz, respectively. MS experiments: Electron Ionization were carried out on a JEOL Mass Station 700 spectrometer at the Ecole Normale Supérieure (Paris, France), ESI on a Micromass (Manchester, United-Kingdom) Quattro II spectrometer fitted with a Hewlett–Packard (Palo Alto, USA) series 1100 HPLC using a C18 reverse stationary phase column (250×2.1 mm) from Beckman (Coulter Fullerton, California, USA). Microanalyses were performed by the CNRS 'Service Central d'Analyse' (Vernaison, France).

4.2. Quercetin benzylation. Synthesis of compounds 2 and 3

To a solution of quercetin **1** (5.00 g, 14.79 mmol) in DMF (100 mL), potassium carbonate (3.5 equiv., 7.14 g, 51.77 mmol) and benzyl bromide (3.5 equiv., 6.19 mL, 51.77 mmol) were added under argon. After vigorous stirring at 0°C for 2 h, the reaction mixture was allowed to warm to room temperature over 2 h and the stirring was maintained for 12 h. The resulting mixture was diluted with water (400 mL), extracted with EtOAc (500 mL), then the organic layer was washed with water (400 mL) and dried over $MgSO_4$. The residue obtained after removal of the solvent was purified by flash column chromatography using dichloromethane as eluent to afford three products: the tribenzylether **3** (1.69 g, 20% yield), the tetrabenzylether **2**

(5.88 g, 60% yield) and traces of pentabenzylether (0.33 g, 3% yield).

4.2.1. 3,7-Bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-5-hydroxychromen-4-one 2. Mp 140–142°C [lit.[32] 128°C, lit.[33] 140–142°C]. ^{1}H NMR ($CDCl_3$): 4.96 (s, 2H, OCH_2Ph), 5.01 (s, 2H, OCH_2Ph), 5.12 (s, 2H, OCH_2Ph), 5.25 (s, 2H, OCH_2Ph), 6.44 (d, *J*=2.1 Hz, 1H, aromatic H), 6.46 (d, *J*=2.1 Hz, 1H, aromatic H), 6.96 (d, *J*=8.7 Hz, 1H, aromatic H), 7.21–7.45 (m, 20H, aromatic H), 7.54 (dd, *J*=8.7, 2.1 Hz, 1H, aromatic H), 7.72 (d, *J*=2.1 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 70.4 (OCH_2Ph), 70.8 (OCH_2Ph), 71.0 (OCH_2Ph), 74.3 (OCH_2Ph), 93.0, 98.5, 106.1, 113.6, 115.2, 122.6, 123.4, 127.2, 127.4, 127.5, 127.9, 128.0, 128.3, 128.4, 128.5 128.6, 128.8, 128.9, 135.8, 136.0, 136.7, 136.9, 137.5, 148.2, 151.1, 156.2, 156.7, 162.1, 164.4, 178.8 (C═O).

4.2.2. 3,7-Bisbenzyloxy-2-(4-benzyloxy-3-hydroxyphenyl)-5-hydroxychromen-4-one 3. Mp 150–152°C [lit.[29] 144–145°C, lit.[33] 148–150°C]. ^{1}H NMR ($CDCl_3$): 5.03 (s, 2H, OCH_2Ph), 5.12 (s, 2H, OCH_2Ph), 5.18 (s, 2H, OCH_2Ph), 6.41 (d, *J*=2.1 Hz, 1H, aromatic H), 6.50 (d, *J*=2.1 Hz, 1H, aromatic H), 6.94 (d, *J*=8.7 Hz, 1H, aromatic H), 7.21–7.47 (m, 15H, aromatic H), 7.70 (dd, *J*=8.7, 2.1 Hz, 1H, aromatic H), 7.72 (d, *J*=2.1 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 70.4 (OCH_2Ph), 71.0 (OCH_2Ph), 74.2 (OCH_2Ph), 93.0, 98.7, 106.2, 111.6, 115.0, 121.9, 123.8, 127.5, 127.9, 128.2, 128.3, 128.6, 128.7, 128.8, 135.7, 135.8, 136.5, 137.6, 145.6, 148.0, 156.3, 156.7, 161.9, 164.4, 178.8 (C═O).

4.3. Methylation of 3 for NOE investigation

4.3.1. 3,7-Bisbenzyloxy-2-(4-benzyloxy-3-methoxyphenyl)-5-methoxychromen-4-one 3a. Methyl iodide (0.05 mL, 0.8 mmol) and potassium carbonate (140 mg, 1.02 mmol) were added to a solution of the tribenzylether **3** (200 mg, 0.34 mmol) in DMF (5 mL) under argon and stirring was maintained overnight. The resulting mixture was diluted with water (15 mL), extracted with EtOAc (20 mL), then the organic layer was washed with water (15 mL) and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was purified by recrystallization from EtOAc to afford **3a** (205 mg, 98% yield). Mp 112–116°C [lit.[33] 116–118°C]. ^{1}H NMR ($CDCl_3$): 3.54 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.98 (s, 2H, OCH_2Ph), 4.99 (s, 2H, OCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 6.17 (d, *J*=2.1 Hz, 1H, aromatic H), 6.43 (d, *J*=2.1 Hz, 1H, aromatic H), 6.83 (d, *J*=8.7 Hz, 1H, aromatic H), 7.17–7.40 (m, 15H, aromatic H), 7.43 (dd, *J*=8.6, 2.0 Hz, 1H, aromatic H), 7.63 (d, *J*=2.0 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 55.7 (OCH_3), 56.2 (OCH_3), 70.4 (OCH_2Ph), 70.6 (OCH_2Ph), 74.0 (OCH_2Ph), 93.2, 99.2, 109.3, 112.2, 112.8, 121.2, 123.7, 127.2, 127.8, 128.0, 128.2, 128.3, 128.5, 128.6, 128.9, 135.7, 136.5, 137.1, 139.8, 148.9, 152.9, 158.5, 160.7, 162.4, 162.8, 173.9 (C═O).

4.4. Synthesis of 5-*O*-methylquercetin

4.4.1. 3,7-Bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-5-methoxychromen-4-one 4. A solution of **2** (1.50 g, 2.28 mmol), potassium carbonate (2 equiv., 0.63 g, 4.55 mmol) and methyl iodide (2 equiv., 0.28 mL, 4.55 mmol) in DMF (50 mL) were stirred at room temperature for 12 h under argon. The resulting mixture was diluted in water (150 mL), extracted with EtOAc (200 mL) and the organic layer washed with water (150 mL). The organic layer was dried over $MgSO_4$ and the residue obtained after evaporation of the solvent was purified by recrystallization from EtOAc to afford **5** (1.42 g, 93% yield). Mp 156–158°C [lit.[32] 160°C]. ^{1}H NMR ($CDCl_3$): 3.90 (s, 3H, OCH_3), 4.95 (s, 2H, OCH_2Ph), 5.08 (s, 2H, OCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 5.22 (s, 2H, OCH_2Ph), 6.37 (d, *J*=2.0 Hz, 1H, aromatic H), 6.51 (d, *J*=2.0 Hz, 1H, aromatic H), 6.96 (d, *J*=8.6 Hz, 1H, aromatic H), 7.18–7.47 (m, 20H, aromatic H), 7.56 (d, *J*=8.6, 2.0 Hz, 1H, aromatic H), 7.78 (d, *J*=2.0 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 56.4 (OCH_3), 70.5 (OCH_2Ph), 70.8 (OCH_2Ph), 71.0 (OCH_2Ph), 74.0 (OCH_2Ph), 93.2, 96.3, 109.5, 113.7, 115.1, 122.0, 123.9, 127.2, 127.4, 127.8, 127.9, 128.0, 128.1, 128.3, 128.5, 128.6, 128.8, 129.0, 135.7, 136.8, 137.0, 137.1, 139.8, 148.2, 150.5, 153.0, 158.7, 161.0, 162.9, 174.0 (C═O).

4.4.2. 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-5-methoxychromen-4-one 5. A suspension of **4** (0.30 g, 0.6 mmol) in a mixture of EtOH (20 mL) and THF (20 mL) was treated at room temperature with 10% palladium hydroxide (10 mg) under a flow of hydrogen for 10 h. The reaction mixture was then filtered on Celite® and eluted with EtOH (20 mL). After concentration of the filtrate under vacuum, the resulting compound **5** was recrystallized in MeOH to afford a yellow solid (0.12 g, 85% yield). Mp 259–261°C. [lit.[42] 250–260°C]. ^{1}H NMR ([D_6]DMSO): 3.74 (s, 3H, OCH_3), 6.33 (d, *J*=2.1 Hz, 1H, aromatic H), 6.48 (d, *J*=2.1 Hz, 1H, aromatic H), 6.87 (d, *J*=8.4 Hz, 1H, aromatic H), 7.47 (dd, *J*=8.4, 2.1 Hz, 1H, aromatic H), 7.58 (d, *J*=2.1 Hz, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 56.0 (OCH_3), 94.6, 95.9, 105.0, 114.5, 115.6, 119.1, 120.3, 137.0, 141.9, 145.0, 146.9, 157.9, 160.5, 162.7, 170.9 (C═O). MS *m/z* 316 ($M^{+\cdot}$) 315,301,284, 270, 229, 205, 166, 141, 137, 110. HRMS (EI, 70 eV) ($C_{16}H_{12}O_7$) calcd: 316.0583; found 316.0586. $C_{16}H_{12}O_7$, $2H_2O$ (352.29): calcd C 54.55, H 4.58; found C 54.12, H 4.94.

4.5. Synthesis of 3′-*O*-methylquercetin

4.5.1. 3,7-Bisbenzyloxy-2-(4-benzyloxy-3-methoxyphenyl)-5-hydroxychromen-4-one 6. Methyl iodide (0.13 mL, 2.08 mmol) and potassium carbonate (378 mg, 2.74 mmol) were added to a solution of the tribenzylether **3** (1.20 g, 2.08 mmol) in DMF (30 mL) under argon flow and stirring. After standing overnight, the resulting mixture was diluted with water (70 mL), extracted with EtOAc (100 mL), then the organic layer was washed with water (70 mL) and finally dried over $MgSO_4$. Solvent was removed under vacuum to leave a yellow solid **7**, which was purified by flash column chromatography using CH_2Cl_2/EtOAc (95:5) as eluent (1.11 g, 90% yield). Mp 142–144°C. ^{1}H NMR ($CDCl_3$): 3.71 (s, 3H, OCH_3), 5.06 (s, 2H, OCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 5.23 (s, 2H, OCH_2Ph), 6.43 (d, *J*=2.2 Hz, 1H, aromatic H), 6.50 (d, *J*=2.2 Hz, 1H, aromatic H), 6.93 (d, *J*=8.6 Hz, 1H, aromatic H), 7.26–7.49 (m, 15H, aromatic H), 7.55 (dd, *J*=8.6, 2.0 Hz, 1H, aromatic H), 7.72 (d, *J*=2.0 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 55.9 (OCH_3), 70.4 (OCH_2Ph), 70.7 (OCH_2Ph), 74.5

(OCH_2Ph), 93.1, 98.5, 106.2, 112.2, 112.8, 122.0, 123.3, 127.3, 127.5, 128.1, 128.3, 128.3, 128.7, 128.7, 135.8, 136.4, 136.5, 137.6, 149.0, 150.3, 156.4, 157.0, 162.1, 164.4, 178.8 (C═O).

4.5.2. 2-(4-Hydroxy-3-methoxyphenyl)-3,5,7-trihydroxychromen-4-one 7. A suspension of **6** (200 mg, 0.33 mmol) in a mixture of EtOH (30 mL) and THF (30 mL) was treated with palladium hydroxide (10%, 10 mg) under hydrogen flow for 6 h. The reaction mixture was then filtered on Celite® and eluted with EtOH (30 mL). The filtrate was concentrated under vacuum and the resulting product **7** was recrystallized from MeOH, to give a pale yellow solid (91 mg, 85% yield). Mp 301–303°C [lit.[28] 305–306°C]. ^{1}H NMR ([D_6]DMSO): 3.82 (s, 3H, OCH_3), 6.18 (s, 1H, aromatic H), 6.46 (s, 1H, aromatic H), 6.93 (d, J=8.4 Hz, 1H, aromatic H), 7.67 (d, J=8.4 Hz, 1H, aromatic H), 7.74 (s, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 55.7 (OCH_3), 93.6, 98.2, 102.9, 111.6, 115.5, 121.7, 122.0, 135.8, 146.5, 147.3, 148.7, 156.1, 160.6, 164.0, 175.8 (C═O).). MS m/z 316 ($M^{+\cdot}$) 315, 301, 287, 245, 217, 168, 151, 141, 125, 123. HRMS ($C_{16}H_{12}O_7$) calcd: 316.0583; found 316.0576. $C_{16}H_{12}O_7$, 2.25H_2O (356.80): calcd C 53.86, H 4.66; found C 53.96, H 4.87.

4.6. Synthesis of 4′-*O*-methylquercetin

4.6.1. Protection of quercetin catechol ring. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,5,7-trihydroxychromen-4-one 8. A mixture of quercetin **1** (2.00 g, 5.92 mmol) and dichlorodiphenylmethane (3 equiv., 3.39 mL, 17.76 mmol) was intimately mixed then heated at 180°C for 10 min. The crude resulting products mixture was then purified by flash column chromatography using CH_2Cl_2/EtOAc (85:15) as eluent and was recrystallized from $CHCl_3$ to afford **8** (1.00 g, 37% yield). Mp 222–224°C. ^{1}H NMR ([D_6]DMSO): 6.20 (d, J=1.9 Hz, 1H, aromatic H), 6.47 (d, J=1.9 Hz, 1H, aromatic H), 7.17 (d, J=8.3 Hz, 1H, aromatic H), 7.44–7.58 (m, 10H, aromatic H), 7.79 (dd, J=8.3, 1.6 Hz, 1H, aromatic H), 7.81 (d, J=1.6 Hz, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 93.6, 98.3, 103.1, 107.8, 108.8, 117.0, 123.0, 125.2, 125.7, 128.6, 129.5, 136.4, 139.4, 145.5, 146.6, 147.6, 156.2,160.7, 164.1, 178.0 (C═O).

4.6.2. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,5,7-tribenzyloxychromen-4-one 9. Compound **9** was prepared by benzylation of the parent phenolic compound **8** under classical conditions (BnBr 4 equiv., K_2CO_3 4 equiv., DMF at room temperature for 12 h). Compound **9** was then purified by recrystallization from EtOAc (3.00 g starting from 2.00 g of **8**, 95% yield). Mp 120–122°C. ^{1}H NMR ($CDCl_3$): 5.08 (s, 2H, OCH_2Ph), 5.09 (s, 2H, OCH_2Ph), 5.28 (s, 2H, OCH_2Ph), 6.47 (d, J=1.9 Hz, 1H, aromatic H), 6.56 (d, J=1.9 Hz, 1H, aromatic H), 6.90 (d, J=8.2 Hz, 1H, aromatic H), 7.12–7.25 (m, 2H, aromatic H), 7.37–7.65 (m, 15H, aromatic H). ^{13}C NMR ($CDCl_3$): 70.5 (OCH_2Ph), 70.8 (OCH_2Ph), 74.2 (OCH_2Ph), 93.9, 98.1, 108.2, 108.9, 110.0, 123.6, 124.7, 126.3, 126.7, 127.7, 128.0, 128.1, 128.5, 128.7, 128.8, 129.1, 129.4, 135.7, 136.8, 139.5, 139.9, 147.2, 148.7, 153.7, 158.7, 159.8, 162.8, 173.9 (C═O).

4.6.3. 3,7-Bisbenzyloxy-2-(3,4-dihydroxyphenyl)-5-hydroxychromen-4-one 10. Compound **9** was added (1.00 g, 1.36 mmol) to a mixture of acetic acid/water (80:20, 50 mL). The solution was refluxed for 2 h. Then EtOAc (50 mL) and water (50 mL) were added. The organic layer was washed with a $NaHCO_3$ saturated aqueous solution (40 mL) and dried over $MgSO_4$. After solvent evaporation, the residue was purified by recrystallization from CH_2Cl_2 to give **10** (390 mg, 60% yield). Mp 202–204°C. ^{1}H NMR ([D_6]DMSO): 5.01 (s, 2H, OCH_2Ph), 5.21 (s, 2H, OCH_2Ph), 6.43 (d, J=2.0 Hz, 1H, aromatic H), 6.75 (d, J=2.0 Hz, 1H, aromatic H), 6.87 (d, J=8.4 Hz, 1H, aromatic H), 7.28–7.46 (m, 11H, aromatic H), 7.55 (d, J=2.0 Hz, 1H, aromatic H), 9.36 (s, 1H, OH), 9.83 (s, 1H, OH), 12.7 (s, 1H, OH). ^{13}C NMR ([D_6]DMSO): 70.0 (OCH_2Ph), 73.3 (OCH_2Ph), 93.0, 98.4, 105.3, 115.5, 115.7, 120.8, 121.0, 136.1, 136.5, 136.6, 145.2, 148.8, 156.2, 156.8, 161.0, 164.1, 178.0 (C═O).

4.6.4. 3,7-Bisbenzyloxy-2-(3-hydroxy-4-methoxyphenyl)-5-hydroxychromen-4-one 11. Compound **11** was synthesized according to the procedure reported for **7**. Compound **11** was purified by flash column chromatography using EtOAc/petroleum ether (40:60) as eluent (185 mg starting from 200 mg of **10**, 90% yield). Mp 144–146°C. ^{1}H NMR ($CDCl_3$): 3.95 (s, 3H, OCH_3), 5.05 (s, 2H, OCH_2Ph), 5.12 (s, 2H, OCH_2Ph), 6.43 (d, J=2.0 Hz, 1H, aromatic H), 6.51 (d, J=2.0 Hz, 1H, aromatic H), 6.88 (d, J=8.6 Hz, 1H, aromatic H), 7.26–7.45 (m, 10H, aromatic H), 7.58–7.65 (m, 2H, aromatic H). ^{13}C NMR ($CDCl_3$): 56.0 (OCH_3), 70.4 (OCH_2Ph), 74.2 (OCH_2Ph), 93.0, 98.6, 106.2, 110.1, 122.0, 123.6, 127.5, 128.2, 128.3, 128.5, 128.7, 128.8, 135.8, 136.4, 137.5, 145.3, 148.7, 156.4, 156.7, 162.0, 164.4, 178.8 (C═O).

4.6.5. 2-(3-Hydroxy-4-methoxyphenyl)-3,5,7-trihydroxychromen-4-one 12. Compound **12** was synthesized using the same procedure as for **5**. The resulting residue was purified by recrystallization from MeOH to give **12**, a pale yellow solid, in 80% yield (94 mg starting from 185 mg of **11**). Mp 252–254°C [lit.[43] 253–256°C]. ^{1}H NMR ([D_6]DMSO): 3.81 (s, 3H, OCH_3), 6.17 (s, 1H, aromatic H), 6.41 (s, 1H, aromatic H), 7.03 (d, J=8.6 Hz, 1H, aromatic H), 7.60 (d, J=8.6 Hz, 1H, aromatic H), 7.63 (s, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 55.9 (OCH_3), 93.5, 98.3, 102.9, 111.6, 114.4, 119.8, 123.3, 136.0, 146.0, 146.2, 149.3, 156.2, 160.6, 164.2, 175.79 (C═O). MS m/z 316 ($M^{+\cdot}$) 315, 301, 287, 273, 245, 217, 153, 149, 123. HRMS ($C_{16}H_{12}O_7$) calcd: 316.0583; found 316.0576. $C_{16}H_{12}O_7$, H_2O (334.28): calcd C 57.49, H 4.22; found C 57.12, H 4.63.

4.7. Synthesis of 3-*O*-methylquercetin

Synthesis of compounds **13** and **14**. A solution of methyl iodide (0.134 mL, 2.15 mmol) in DMF (1 mL) and potassium carbonate (0.44 g, 3.22 mmol) were added under argon to a solution of **8** (1.00 g, 2.15 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with water (100 mL), extracted with EtOAc (150 mL), then the organic layer was washed with water (100 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash column chromatography using EtOAc/petroleum ether (30:70) as eluent. Two products were isolated: a monomethylated compound **13** (0.38 g, 37% yield) and a dimethylated compound **14** (0.38 g, 36% yield).

4.7.1. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-5,7-dihydroxy-3-methoxychromen-4-one 13. Mp 130–132°C. ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H, OCH_3), 6.43 (d, J=2.0 Hz, 1H, aromatic H), 6.51 (d, J=2.0 Hz, 1H, aromatic H), 6.97 (d, J=8.2 Hz, 1H, aromatic H), 7.35–7.48 (m, 6H, aromatic H), 7.53–7.62 (m, 4H, aromatic H), 7.72 (dd, J=8.2, 1.7 Hz, 1H, aromatic H), 7.76 (d, J=1.7 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 60.9 (OCH_3), 94.3, 99.6, 105.4, 108.6, 108.7, 118.1, 124.0, 126.2, 128.4, 129.4, 138.8, 139.7, 147.6, 149.6, 156.1, 156.9, 161.8, 163.8, 172.3, 178.8 (C=O).

4.7.2. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,7-dimethoxy-5-hydroxychromen-4-one 14. Mp 149–151°C [lit.[41] 150°C]. ^{1}H NMR ($CDCl_3$): 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.32 (s, 1H, aromatic H), 6.39 (s, 1H, aromatic H), 7.00 (d, J=8.3 Hz, 1H, aromatic H), 7.36–7.50 (m, 6H, aromatic H), 7.53–7.61 (m, 4H, aromatic H), 7.66 (dd, J=8.2, 1.7 Hz, 1H, aromatic H), 7.68 (d, J=1.7 Hz, 1H, aromatic H). ^{13}C NMR ($CDCl_3$): 55.8 (OCH_3), 60.2 (OCH_3), 92.0, 97.9, 106.0, 108.6, 118.0, 123.9, 123.7, 124.2, 126.2, 128.4, 128.8, 129.4, 131.1, 131.6, 139.0, 139.8, 147.6, 149.4, 155.5, 156.6, 161.9, 165.4, 178.7 (C=O).

Synthesis of compounds **15** and **16**. Potassium carbonate (0.38 g, 2.74 mmol) and benzyl bromide (0.24 mL, 1.99 mmol) were added to a solution of protected quercetin **8** (1.00 g, 1.99 mmol) in DMF (30 mL) under argon. The mixture was stirred at 0°C for 2 h, and then 12 h at room temperature. The resulting mixture was diluted with water (150 mL), extracted with EtOAc (200 mL), then the organic layer was washed with water (150 mL) and dried over $MgSO_4$. The residue resulting from the solvent evaporation was purified by flash column chromatography using a mixture CH_2Cl_2/ EtOAc (95:5) to give two products: a monobenzylether **15** (0.76 g, 64% yield) and a dibenzylether **16** (0.29 g, 21% yield).

4.7.3. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-benzyloxy-5,7-dihydroxychromen-4-one 15. ^{1}H NMR ($CDCl_3$): 4.98 (s, 2H, OCH_2Ph), 6.35 (d, J=2.1 Hz, 1H, aromatic H), 6.40 (d, J=2.1 Hz, 1H, aromatic H), 6.89 (d, J=8.1 Hz, 1H, aromatic H), 7.41–7.48 (m, 11H, aromatic H), 7.60–7.65 (m, 4H, aromatic H), 7.53 (dd, J=8.1, 1.8 Hz, 1H, aromatic H), 7.58 (d, J=1.8 Hz, 1H, aromatic H). ^{13}C NMR($CDCl_3$): 74.7 (OCH_2Ph), 94.2, 99.4, 105.6, 108.3, 109.0, 117.8, 124.1, 124.2, 126.3, 128.1, 128.2, 128.4, 129.0, 129.4, 135.9, 137.8, 147.2, 149.3, 156.9, 157.0, 162.0, 163.2, 178.8 (C=O).

4.7.4. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,7-bisbenzyloxy-5-hydroxychromen-4-one 16. Mp 90–92°C. ^{1}H NMR ($CDCl_3$): 5.08 (s, 2H, OCH_2Ph), 5.12 (s, 2H, OCH_2Ph), 6.47 (d, J=2.1 Hz, 1H, aromatic H), 6.51 (d, J=2.1 Hz, 1H, aromatic H), 6.95 (d, J=8.3 Hz, 1H, aromatic H), 7.18–7.46 (m, 16H, aromatic H), 7.58 (dd, J=8.3, 1.7 Hz, 1H, aromatic H), 7.63 (d, J=1.7 Hz, 1H, aromatic H), 7.65–7.72 (m, 4H, aromatic H). ^{13}C NMR ($CDCl_3$): 70.5 (OCH_2Ph), 74.5 (OCH_2Ph), 93.0, 98.7, 106.2, 108.4, 109.1, 117.9, 124.2, 124.3, 126.3, 127.5, 128.3, 128.5, 128.8, 129.0, 129.5, 135.8, 136.3, 137.3, 139.8, 147.3, 149.3, 156.6, 156.7, 162.1, 164.5, 178.8 (C=O).

Synthesis of compounds **17** and **18**. A solution of compound **13** (200 mg, 0.41 mmol) or **14** (300 mg, 0.61 mmol) in a mixture of acetic acid/water (80:20, 50 mL) was refluxed overnight under stirring. EtOAc (50 mL) and water (50 mL) were then added. The organic layer was washed with an aqueous solution saturated in $NaHCO_3$ (30 mL) and dried over $MgSO_4$. After evaporation of the solvent, the solid obtained was recrystallized from CH_2Cl_2 to afford compound **17** (112 mg) or **18** (170 mg) in a 85% yield.

4.7.5. 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-methoxychromen-4-one 17. Mp 271–273°C [lit.[44] 273–276°C]. ^{1}H NMR ([D_6]DMSO): 3.75 (s, 3H, OCH_3), 6.14 (s, 1H, aromatic H), 6.32 (s, 1H, aromatic H), 6.87 (d, J=8.3 Hz, 1H, aromatic H), 7.48 (d, J=8.3 Hz, 1H, aromatic H), 7.59 (s, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 60.5 (OCH_3), 94.7, 99.8, 105.8, 116.4, 116.5, 122.4, 122.9, 139.5, 146.4, 149.9, 157.9, 158.3, 163.0, 165.8, 179.9 (C=O). MS *m/z* 316 ($M^{+\cdot}$) 315, 301, 284, 270, 229, 228, 166, 141, 137, 110. HRMS ($C_{16}H_{12}O_7$) calcd: 316.0583; found 316.0587. $C_{16}H_{12}O_7$, 1.5H_2O (343.29): calcd C 55.98, H 4.40; found C 56.12, H 4.12.

4.7.6. 2-(3,4-Dihydroxyphenyl)-5-hydroxy-3,7-methoxychromen-4-one 18. Mp 238–240°C [lit.[41] 235°C]. ^{1}H NMR ([D_6]DMSO): 3.79 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.32 (s, 1H, aromatic H), 6.58 (s, 1H, aromatic H), 6.90 (d, J=8.3 Hz, 1H, aromatic H), 7.55 (d, J=8.3 Hz, 1H, aromatic H), 7.64 (s, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 56.5 (OCH_3), 60.5 (OCH_3), 93.1, 98.9, 106.7, 116.4, 116.5, 122.4, 122.8, 139.7, 146.5, 150.1, 158.2, 158.3, 162.8, 167.3, 180.1 (C=O). MS (EI, 70 eV) *m/z* 330 ($M^{+\cdot}$) 329, 316, 312, 301, 287, 256, 244, 203, 151, 135. HRMS ($C_{17}H_{14}O_7$) calcd: 330.0740; found 330.0739. $C_{17}H_{14}O_7$, 1.25H_2O (352.81): calcd C 57.87, H 4.71; found C 57.40, H 4.13.

4.8. Synthesis of 7-*O*-methylquercetin

4.8.1. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-benzyloxy-5-hydroxy-7-methoxychromen-4-one 19. Potassium carbonate (0.15 g, 1.1 mmol) and methyl iodide (0.056 mL, 0.9 mmol) were added to a solution of **15** (500 mg, 0.9 mmol) in DMF (30 mL). Stirring was maintained for 6 h. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (100 mL), then the organic layer was washed with water (50 mL) and dried over $MgSO_4$. After removal of the solvent, the product was purified by flash column chromatography with a mixture of EtOAc/petroleum ether (20:80 to 50:50) as eluent to provide **19** (307 mg, 60% yield). Mp 134–136°C. ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H, OCH_3), 5.02 (s, 2H, OCH_2Ph), 6.34 (d, J=2.3 Hz, 1H, aromatic H), 6.37 (d, J=2.3 Hz, 1H, aromatic H), 6.94 (d, J=8.3 Hz, 1H, aromatic H), 7.12–7.21 (m, 5H, aromatic H), 7.32 (dd, J=8.3, 1.8 Hz, 1H, aromatic H), 7.40–7.46 (m, 6H, aromatic H), 7.52 (d, J=1.8 Hz, 1H, aromatic H), 7.61–7.66 (m, 4H, aromatic H). ^{13}C NMR ($CDCl_3$): 55.8 (OCH_3), 74.4 (OCH_2Ph), 92.1, 97.9, 106.0, 108.4, 109.0, 117.8, 124.1, 124.3, 126.3, 128.2, 128.4, 128.9, 129.4, 136.2, 137.3, 139.8, 147.3, 149.3, 156.6, 162.0, 165.4, 178.8 (C=O).

4.8.2. 2-(3,4-Dihydroxyphenyl)-3,5-dihydroxy-7-methoxychromen-4-one 20. 10% Palladium hydroxide (0.12 mmol) was added to a stirred solution of **17** (0.7 g,

1.21 mmol) in EtOH/THF (1:2, 20 mL) under a hydrogen flow. The suspension was stirred overnight and then the solution was filtered through a plug of Celite® and eluted with EtOH (20 mL). The filtrate was concentrated under vacuum and the crude resulting solid was directly dissolved in a mixture of acetic acid/water (80:20, 30 mL). The deprotection of the catechol ring was performed as previously described for the quercetin derivatives **17** and **18** to give **20** (311 mg, 80% yield). Mp 283–285°C [lit.[45] 280–285°C]. ^{1}H NMR ([D_6]DMSO): 3.84 (s, 3H, OCH_3), 6.32 (d, J=2.0 Hz, 1H, aromatic H), 6.67 (d, J=2.0 Hz, 1H, aromatic H), 6.89 (d, J=8.3 Hz, 1H, aromatic H), 7.57 (d, J=8.3 Hz, 1H, aromatic H), 7.72 (s, 1H, aromatic H). ^{13}C NMR ([D_6]DMSO): 56.0 (OCH_3), 91.8, 97.4, 105.4, 115.2, 115.6, 120.0, 121.8, 136.0, 145.1, 147.8, 158.5, 160.3, 164.8, 166.3, 175.9 (C=OMS *m/z* 316 ($M^{+\cdot}$) 315, 301, 287, 273, 259, 242, 227, 182, 167,137, 123, HRMS ($C_{16}H_{12}O_7$) calcd: 316.0583; found 316.0578. $C_{16}H_{12}O_7$, $1.25H_2O$ (338.78): calcd C 56.72, H 4.31; found C 56.49, H 3.97.

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