Tetrahedron 67 (2011) 4731–4741

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regiospecific synthesis of quercetin *O*-β-D-glucosylated and *O*-β-D-glucuronidated isomers

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ARTICLE INFO

Article history:
Received 6 November 2010
Received in revised form 27 March 2011
Accepted 30 March 2011
Available online 8 April 2011

ABSTRACT

Quercetin, the polyphenolic compound, which has the highest daily intake, is well known for its protective effects against aging diseases and has received a lot of attention for this reason. Both quercetin 3-*O*-β-D-glucuronide and quercetin 3′-*O*-β-D-glucuronide are human metabolites, which, together with their regioisomers, are required for biological as well as physical chemistry studies. We present here a novel synthetic route based on the sequential and selective protections of the hydroxyl functions of quercetin allowing selective glycosylation, followed by TEMPO-mediated oxidation to the glucuronide. This methodology enabled us to synthesize the five *O*-β-D-glucosides and four *O*-β-D-glucuronides of quercetin, including the major human metabolite, quercetin 3-*O*-β-D-glucuronide.

1. Introduction

Quercetin is the flavonoid, which is the most swallowed every day (between 10 and 100 mg per day according food habits) and its main sources are fruits, vegetables, and beverages.[1–4] Quercetin is well known for its protective effects against aging diseases, such as neurodegenerative[5] and cardiovascular diseases[6] as well as cancer both in vitro[7] and in human,[8] as recently demonstrated by the careful analysis of medical data from a cohort of more than 1 80 000 volunteers over 8 years.[9]

The main metabolic pathways in humans and mammals for quercetin are methylation, sulfation, and glucuronidation.[10–14] The relative amount of metabolites varies both in their chemical nature and in their position on the quercetin ring according to the species and of the metabolism phase. All the quercetin-*O*-β-D-glucuronides except quercetin 5-*O*-β-D-glucuronide **14** were found in the incubation of quercetin by human or rat, liver or colon homogenate.[13] While quercetin is one of the most studied polyphenols, with more than 30 000 entries in the Chemical Abstracts, most of its known and potential metabolites are not readily available for pharmacological studies. For glucuronides only quercetin 3-*O*-β-D-glucuronide **10** may be isolated from green beans, which contain it at a maximum level of 15 μg of aglycon per fresh weight in g.[15] We describe here a synthesis of the four on five *O*-glucuronidated isomers of quercetin, including quercetin 3-*O*-β-D-glucuronide **10**, which is the major plasma human metabolite immediately after quercetin ingestion and, which remains the second most important one after quercetin 3′-*O*-β-sulfate.[16] Moreover our synthesis also gives access to the five *O*-glycosylated quercetin isomers. Our approach for the synthesis of *O*-glucuronidated analogues of quercetin is based on a combination of selective quercetin protection allowing alkylation of a specific hydroxyl group combined with the selective transformation of the protected phenol glucoside to the glucuronide by TEMPO mediated primary alcohol oxidation. A preliminary account of this work describing the synthesis of the major human metabolite quercetin 3-*O*-β-D-glucuronide **10** has been previously described.[17]

2. Results and discussion

2.1. Protection of quercetin

The selective protection of each hydroxyl function of quercetin was performed following the Scheme 1 we developed for accessing all the monometylated metabolites of quercetin.[18] Our synthesis was reproduced recently by an independent group.[19] Briefly the free hydroxyl functions of quercetin were, respectively, benzylated using various quantities of benzyl bromide and potassium carbonate in DMF at room temperature leading to a mixture of 3,7,3′,4′-*O*-tetrabenzylquercetin **3** and 3,7,4′-*O*-tribenzylquercetin **4** and, which are readily and routinely separated in a 60% and 20% isolated yield, respectively. Alternatively, the quercetin catechol group was protected using dichlorodiphenylmethane prepared by neat heating at 180 °C with a fair yield (37%).[18,20] A version of this reaction using diphenylether as solvent was recently published leading to an improved 86% yield.[21] Playing with the protected quercetin and the differential reactivity of the hydroxyl function

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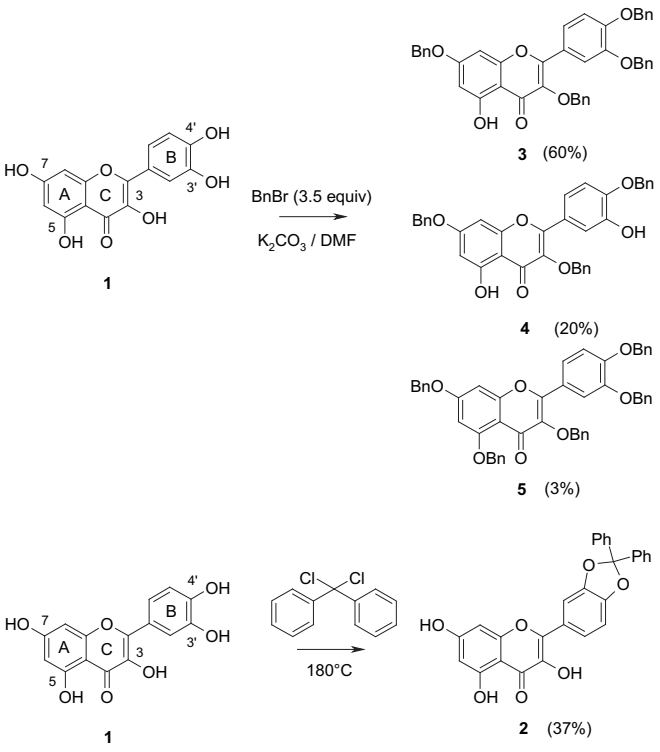
0040-4020/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tet.2011.03.110

3>>7>>5 for the C and A cycle (respectively, 3 and 5,7-positions) and 4′>>3′ for the B cycle allows a specific access to the five phenol positions.



Scheme 1. Protection of quercetin overview.

2.2. Methods of glucuronidation

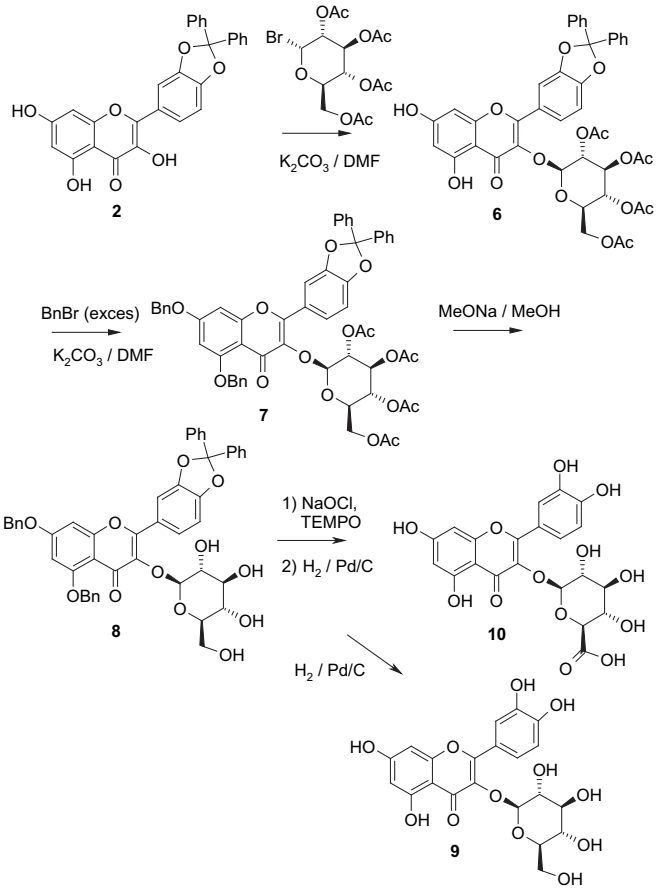
Glucuronidation of phenols is often performed using methyl-2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucuronate, the coupling step being activated by Lewis acids, such as BF_3—etherate.[22] More reactive reagents may be used like methyl-2,3,4-tri-*O*-acetyl-1-*O*-(trifluoroacetimidoyl)-α-D-glucuronate[23] or 2,3,4-tri-*O*-acetyl-α-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate in order to improve the yield.[24] This acidic glucuronidation is usually performed on fully or partially protected phenols.[25,26] If there is no selectivity issue, this Lewis-acid catalyzed glucuronidation may also be performed on unprotected phenols, in which case the deprotection of the acetyl group on the glucose moiety and of the methyl ester are the critical step. Recently, zinc acetate trans-esterification for removing the acyl groups in near neutral conditions and pig liver esterase for the hydrolysis of the ester were introduced in order to avoid the oxidation problem linked to deprotection in basic media.[27] Glucuronidation of phenols may also be obtained under basic condition using methyl acetobromo-α-D-glucuronate. Using lithium hydroxide as a base, morphine-3-glucuronide was obtained in 29% yield.[28] This synthesis has also been applied to the very fragile, unprotected catechin. A mixture of glucuronidated catechins were obtained and were separated by preparative liquid chromatography in tens of milligram quantities.[29] Quercetin glucuronide has also been synthesized in this way; treatment of 4′,7-dibenzylquercetin[30] with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate bromide/silver oxide at 0 °C gave a 52% yield; deprotection was achieved in high yield using Na_2CO_3 in aqueous MeOH.[31,26] The lower temperature increased the yield considerably compared with reaction at room temperature.[26] Finally, glucuronidation of phenols may also be performed enzymatically using pig liver microsomal enzymes in presence of UDP-glucuronic acid. The reaction may be performed on unprotected phenols as described for quercetin itself. A mixture was obtained, which contained all the quercetin glucuronides except the 7 isomer.[32]

We chose an alternative strategy based on the synthesis of the protected quercetin glucoside followed by TEMPO-mediated oxidation of the primary alcohol in carboxylic acid. Several methods have been described in literature for O-glucosylation of phenols.[33–36] For quercetin glucosylation, we chose first to try one protocol reminiscent of our former work for the access to coniferin, the glucoside of coniferyl alcohol (4-(3-hydroxy-1-propenyl)-2-methoxyphenol).[37] In this synthesis the first step consists of condensing 1-bromo-,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosid (abbreviated later as acetobromoglucose) on vanillin in phase transfer conditions using water/dichloromethane as solvents, TDA-1 (tris(2-(2-methoxyethoxy)ethyl)amine) as reagent and potassium carbonate as base. The efficient benzylation of quercetin by benzyl bromide using DMF in the presence of potassium carbonate pushed us to try the same conditions for the reaction of acetobromoglucose. Depending on the hydroxyl position, the former or the latter method is preferred. We observed that the latter method, based on K_2CO_3 and DMF, gives higher yield for the 5,4′ and 3-positions of quercetin, whereas the phase transfer conditions are more suitable for the 3′ and 7-positions.

A simple trans-esterification step performed on the four acetate groups using sodium methylate in methanol allows for deprotecting the glycosyl moiety. At this stage the cleavage of the benzyl groups and eventually the diphenylmethane ketal by a simple hydrogenolysis step using palladium on charcoal Pd/C in a THF/EtOH mixture, gave access to the quercetin glucoside. Among the palladium supported on charcoal reagents, palladium hydroxide 30% on charcoal always gave the best yield and was used for all the deprotections. The selective oxidation of the quercetin glucoside with fully protected phenol functions to the corresponding glucuronic acid was performed by NaOCl catalyzed by TEMPO in presence of NaBr, in phase transfer conditions. The cleavage of the benzyl and the ketal groups was achieved as for the glucoside, leading to an analytically pure compound without the need for further purification by chromatography.

2.3. Synthesis of quercetin 3-*O*-β-D-glucoside 9 and glucuronide 10

The synthesis described is an optimized version of the one we published previously but without experimental details.[17] The synthesis of quercetin 3-*O*-β-D-glucuronide **10** starts from compound **2** and proceeds in five steps (Scheme 2): (i) a selective glucosylation of the hydroxyl group in 3-position, (ii) the protection of the remaining 5 and 7 free hydroxyl groups using benzyl bromide, (iii) the deprotection of the glycosyl moiety (iv) the selective oxidation of primary alcohol of quercetin-3-*O*-β-D-glucoside with phenol groups still protected **8** by NaOCl catalyzed by TEMPO and last, (v) the deprotection of the hydroxyl groups of quercetin. The glycosylation coupling is performed directly on **2** as the position 3 is the most reactive on the quercetin A, C cycles. The partially protected glucoside **6** is obtained in 56% yield from **2** (see Table 1, for a comprehensive view of each step yield). The 5 and 7 hydroxyl groups, which did not need protection during the glycosylation step must be protected during the oxidation, which is readily achieved by benzylation. The removal of the acetyl group and the hydrolysis of the methyl ester is performed on the fully protected quercetin 3-*O*-β-D-glucoside, leading to **8**.



Scheme 2. Synthesis of quercetin 3-*O*-β-D-glucoside **9** and quercetin 3-*O*-β-D-glucuronide **10**.

Table 1
Yield of the key steps

Position	Compound, isolated yield (%)									
	Intermediate protection		Glucosylation		Glucoside deprotection		Phenol deprotection		Oxidation[a]	
3	**7**	94	**6**	56	**8**	86	**9**	72	**10**	56
5	—	—	**11**	74	**12**	82	**13**	82	**14**	51
7	**17**	85	**16**	69	**18**	85	**19**	78	**20**	65
3′	**22**	90	**21**	70	**23**	85	**24**	85	**25**	45
4′	**29**	85	**28**	38	**30**	84	**31**	85	—	—

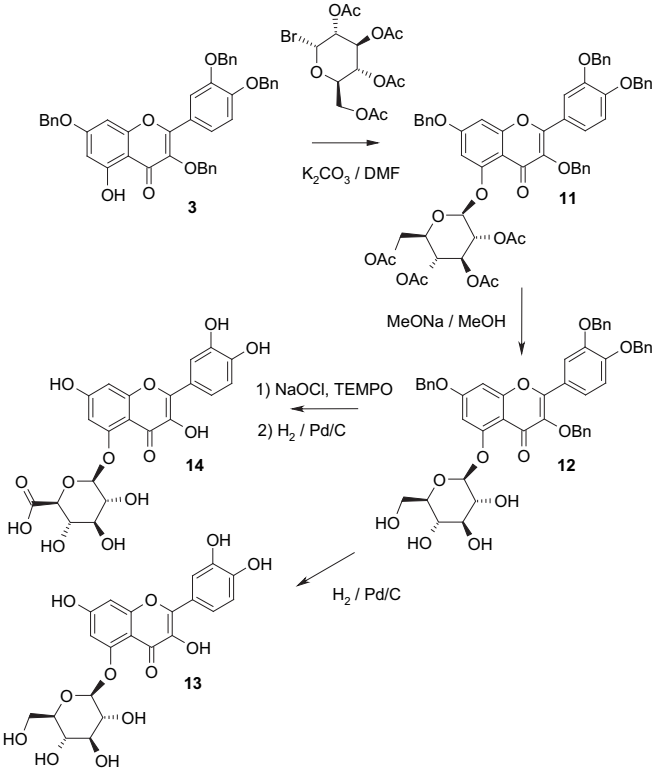
[a] Including the final deprotection step.

The oxidation step proceeded smoothly, yielding 3-*O*-β-D-glucuronide **10** after total deprotection of the hydroxyl protecting group. Direct removal of the hydroxyl protecting group on **8** by H_2 catalyzed by Pd/C yielded the corresponding quercetin 3-*O*-β-D-glucoside **9**. From **2** the glucoside **9** and the glucuronide **10** were obtained in 33% and 25% yield, respectively, on a millimolar scale.

Quercetin 3-*O*-β-D-glucoside **9**, known also as isoquercitrin or isoquercetin, is commercially available and has been previously synthesized several times using variations on the protecting scheme based on benzylation and protection of the catechol by diphenylmethane ketal as described above or obtained during the synthesis of other sugar derivatives at the 3-position.[38–40] Quercetin 3-*O*-β-D-glucoside **9** has been obtained by the total synthesis of the flavanone ring structure using 1-(2′,4′-dibenzyloxy-6′-hydroxyphenyl)-2-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyloxy)ethanone and 3,4-diallyloxybenzoic acid as key intermediates. This last reagent is obtained by condensing the lithiated reagent obtained from 1-bromo-3,4-diallyloxybenzene with carbondioxide, which allows an efficient labeling by ^{13}C on the 2 position of the quercetin ring.[41] To the best of our knowledge, there is only one previous synthesis of quercetin 3-*O*-β-D-glucuronide **10** based on the direct glucuronidation of 4′,7-di-*O*-benzylquercetin[30] by methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate bromide in the presence of silver oxide.[31] This synthesis has been greatly enhanced by using a desiccant (either calcium sulfate or molecular sieves) to obtain strictly anhydrous conditions and operating at 0 °C, which avoids the transacetylation of the free phenol group by the glucuronidation reagent.[26] After optimization the yield was 41% in three steps from the protected 4′,7-dibenzylquercetin. Quercetin 3-*O*-β-D-glucuronide **10** has been also isolated from *Reynoutria sachialinensis*.[42]

2.4. Synthesis of quercetin 5-*O*-β-D-glucoside 13 and glucuronide 14

This protocol must be adapted for the selective glycosylation of the other hydroxyl groups of quercetin on the A ring. For the other hydroxyl groups of quercetin A cycle, which are less reactive than the 3-position, the protocol includes a first protection of the 3 and 7 hydroxyl groups on the C and A cycles, respectively, which are not to be glycosylated. The glycosylation of the 5-position is achieved on the 3,3′,4′,7-tetrabenzylated quercetin **3** (Scheme 3). It proceeds in four steps to give the quercetin-5-*O*-β-D-glucuronide **14**. First, the tetrabenzylated quercetin **3** reacts with acetobromoglucose in the presence of potassium carbonate. Then, the glucoside moiety is deprotected in the same conditions as before. Third, the oxidation of primary alcohol of quercetin 5-*O*-β-D-glucoside with protected phenol groups **12** is performed. Finally, the benzyl groups are cleaved to afford the quercetin 5-*O*-β-D-glucuronide **14**. Cleavage of the benzyl group by H_2, Pd/C on the deprotected glucoside **12** affords quercetin 5-*O*-β-D-glucoside **13**. From **3** the glucoside **13** and glucuronide **14** were obtained in 49% and 25% yield, respectively.

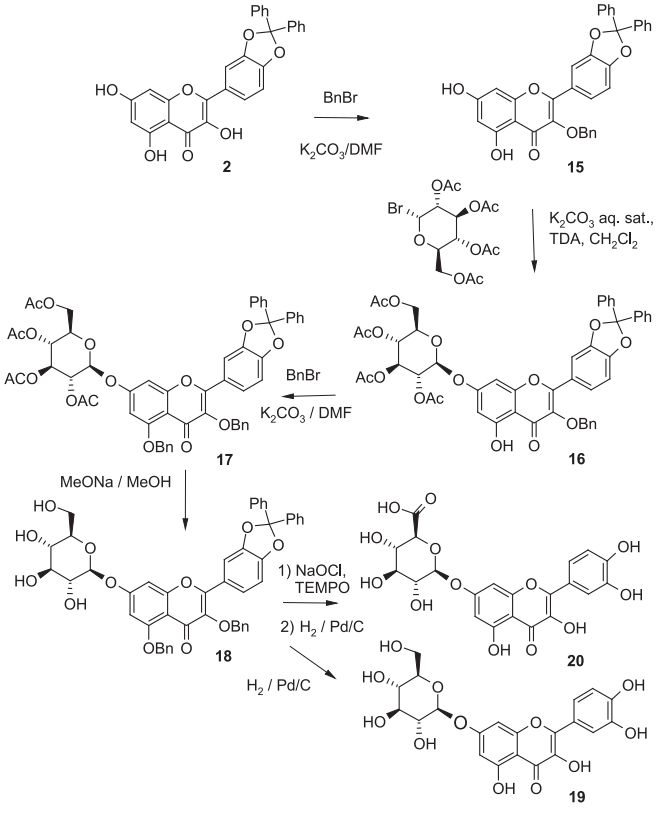


Scheme 3. Synthesis of quercetin 5-*O*-β-D-glucoside **13** and quercetin 5-*O*-β-D-glucuronide **14**.

To the best of our knowledge neither the chemical syntheses or the isolation of quercetin 5-*O*-β-D-glucoside or 5-*O*-β-D-glucuronide have been previously described. 5-*O*-β-D-glucoside quercetin has been isolated from *Leucanthemum vulgare* and from the cocoon shell of the silkworm, *Bombyx mori*.[43,44] 5-*O*-β-D-glucuronide has been isolated from *L. vulgare*.[45]

2.5. Synthesis of 7-*O*-β-D-glucoside 19 and 7-*O*-β-D-glucuronide 20

The preparation of quercetin-7-*O*-β-D-glucuronide **20** is slightly different, since the coupling step is carried out in phase transfer conditions; it starts again from compound **2** whose B cycle is protected by the diphenylmethane ketal and consists of six steps (Scheme 4). First, diphenylmethane ketal protected quercetin **2** reacts with 1 equiv of benzyl bromide so as to protect only the hydroxyl group on position 3. Secondly, the coupling reaction with the glucose moiety proceeds in phase transfer conditions on the 7-position. Thirdly, the last free hydroxyl group on position 5 is protected using benzyl bromide. Fourthly, the glucose moiety is deprotected using sodium methylate. At this stage 7-*O*-β-D-glucoside **19** is obtained in one step by cleaving both diphenylmethane ketal and benzyl protecting groups by H_2, Pd/C. Fifthly, the phenol protected quercetin-7-*O*-β-D-glucoside **18** is oxidized to the corresponding glucuronic acid by TEMPO/NaOCl. Finally, quercetin-7-*O*-β-D-glucuronide **20** is obtained with the last deprotection step that consists in cleaving the benzyl and ketal groups. From **2** the glucoside **19** and glucuronide **20** were obtained in 39% and 32% yield, respectively.

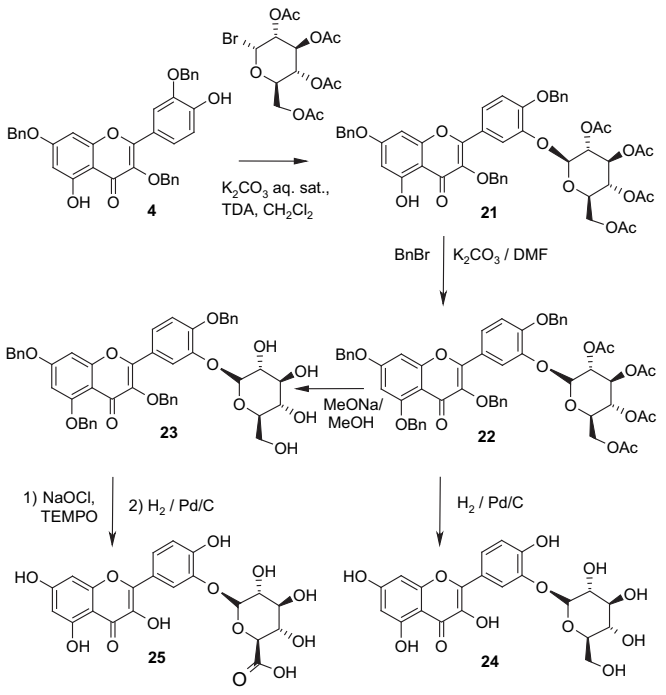


Scheme 4. Synthesis of quercetin-7-*O*-β-D-glucoside **19** and quercetin-7-*O*-β-D-glucuronide **20**.

Quercetin-7-*O*-β-D-glucuronide **20** has previously been obtained in a mixture with quercetin-4′-*O*-β-D-glucuronide,[46] although in low yields, by the direct glucuronidation of 3′,4′,4,5-tetrabenzoylquercetin, with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in presence of silver carbonate, due to the well-documented migration of the acyl or benzoyl protecting group under basic conditions. Quercetin-7-*O*-β-D-glucoside **19** has been synthesized directly from the diphenylmethane ketal protected quercetin **2** without protecting the 3-position, using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, potassium carbonate as base and TMEA (tris[2-(2-methoxyethoxy)ethyl]amine) as transfer reagent.[20] The overall yield for the three steps from B-ring protected quercetin **2** was 15%. Quercetin-7-*O*-β-D-glucoside **19** has also been synthesized from 3′,4′,4,5-tetrabenzoylquercetin using the more reactive perbenzoylated-D-glucopyranosyl-(*N*-phenyl)trifluoro-acetimidate promoted by BF_3—Et_2O.[47] Quercetin-7-*O*-β-D-glucoside **19** has also been isolated from *Gossipyum hirsutum* flowers[48] and from the mixture of isomers obtained by quercetin glucosylation by UDP-glucose (uridinediphosphoglucose) catalyzed by *Arabidopsis thaliana* glycosyltransferase expressed in *E*scherichia *coli* strain.[49]

2.6. Synthesis of quercetin 3′-*O*-β-D-glucoside 24 and 3′-*O*-β-D-glucuronide 25

The quercetin 3′-*O*-β-D-glucuronide **25** is prepared using phase transfer conditions for the coupling step with acetobromoglucose, as discussed earlier. This synthesis consists of five steps (Scheme 5). Starting from the tribenzylated quercetin **4**, the coupling reaction is carried out. As before, it should be noted that position 5 is not protected but as it is not reactive, it is not affected by the glycosylation step, all the more so as this latter relies on phase transfer conditions. Position 5 is then protected with a benzyl group and as usual. Then the deprotection of the glucoside moiety is carried out in the same conditions as before. For the 3′ position also, quercetin 3′-*O*-β-D-glucoside **24** is obtained in one step by deprotecting phenol groups by H_2, Pd/C. The synthesis ends with the selective oxidation of primary alcohol and deprotection of the hydroxyl groups to yield quercetin 3′-*O*-β-D-glucuronide **25**. From **4** the glucoside **24** and glucuronide **25** were obtained in 46% and 24% yield, respectively.



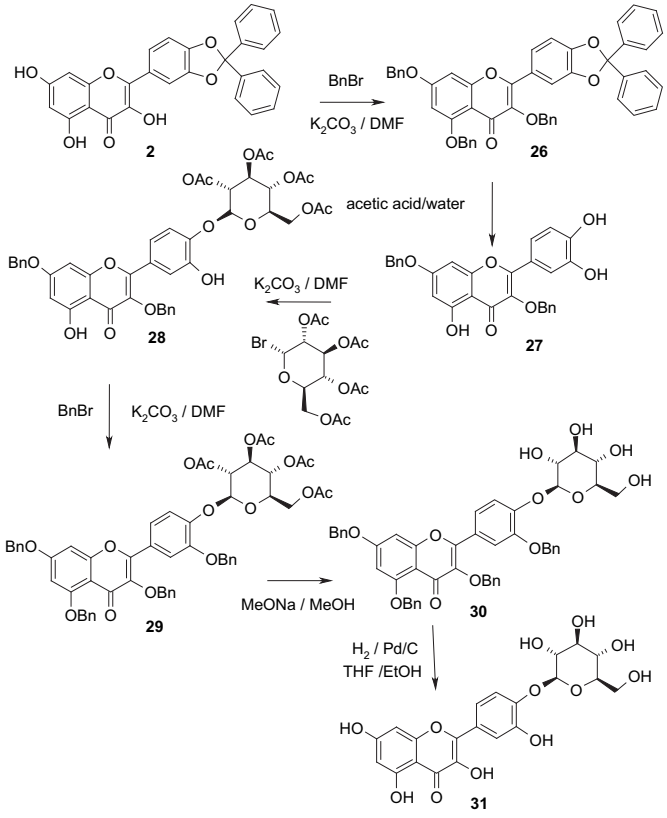
Scheme 5. Synthesis of quercetin 3′-*O*-β-D-glucoside **24** and quercetin 3′-*O*-β-D-glucuronide **25**.

Quercetin 3′-*O*-β-D-glucuronide **25** has been obtained by glucuronidation of protected 4′,7-di-*O*-benzylquercetin[30] using methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate

under Lewis-acid activation by BF_3—Et_2O.[26] The yield in three steps from protected 4′,7-di-*O*-benzylquercetin was 11%. It must be pointed out that the authors observed a reversal with the same substrate when the alkylation was performed under basic conditions, leading quercetin 3-*O*-β-D-glucuronide. Quercetin 3′-*O*-β-D-glucoside **24** was obtained from tribenzyl 3,4′,7 quercetin[50,51] using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, potassium carbonate as base and TMEA (tris[2-(2-methoxyethoxy)ethyl]amine) as transfer reagent.[20] The overall yield for the three steps from 3,7,4′-tribenzylquercetin obtained in 40% yield from quercetin was 18%. Quercetin 3′-*O*-β-D-glucoside **24** was also obtained in the mixture along with quercetin-7-*O*-β-D-glucoside **19** from a natural source or by quercetin glucosylation with UDP-glucose glycosyltransferase.[48,49]

2.7. Access to quercetin 4′-*O*-β-D-glucoside 31 and attempted oxidation to quercetin 4′-*O*-β-D-glucuronide

The preparation of quercetin-4′-*O*-β-D-glucoside **31** proceeds in six steps and starts from compound **2** (Scheme 6). First, all the A and C cycle hydroxyl groups are protected using 3.5 equiv of BnBr. Then, Cycle B is deprotected using a mixture of acetic acid/water (80:20). This deprotection step also allows to free the hydroxyl group on position 5. Nonetheless, as this hydroxyl group is not very reactive, it does not affect the coupling step with acetobromoglucose. The glycosylation step is achieved using potassium carbonate in DMF. Benzyl bromide is again added to the reaction mixture to protect positions 5 and 3′. The synthesis is completed with the same steps as before: the deprotection of the glucoside moiety followed by the cleavage of the benzyl groups to afford 4′-*O*-β-D-glucoside quercetin **31**. Using the conditions we used for all the four other deprotected quercetin glucosides, the selective oxidation of primary alcohol of phenol protected quercetin 4′-*O*-β-D-glucoside **30** did not occurred.



Scheme 6. Synthesis of quercetin 4′-*O*-β-D-glucoside **31**.

We tested this step several times using different methods but we could not obtain the corresponding acid. An almost identical failure to oxidize a phenol glucoside using TEMPO-mediated oxidation has been reported by Wang et al.[24]

As mentioned in the above paragraph describing the access to quercetin-7-*O*-β-D-glucuronide **20**, quercetin 4′-*O*-β-D-glucuronide was previously obtained in mixture with the 7-glucuronide though in low yield by the direct glucuronidation of 3′,4′,4,5-tetrabenzoylquercetin.[46] Alternatively, treatment of quercetin by 2,3,4,6-tetra-*O*-acetyl-α-glucopyranosyl bromide using the Koenigs—Knorr conditions yielded a mixture of 3 and 4′-*O*-β-D-glucuronide, which were separated by chromatography.[52,53] [2-^{13}C] labeled quercetin 4-*O*-β-D-glucoside has been obtained by the total synthesis of the flavanone structure using 3-benzyloxy-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucospyranosyloxy)benzoic acid as a key intermediate.[54] Quercetin 4′-*O*-β-D-glucoside **31** was isolated from the leaves of *Camelia pachysandra* Hu[55] and from the mixture obtained by glycosylation of quercetin by UDP catalyzed by glycosyltransferase.[49]

2.8. Spectroscopic data

Tables 2 and 3 summarizes the ^{1}H and ^{13}C NMR data for the complete quercetin-*O*-β-D-glucosides substitution pattern and for the four quercetin-*O*-β-D-glucuronides (3,5,7,3′) synthesized in this work along with values from the literature. The homogenous series we synthesized clearly show the trend in chemical shift in function of the position of the substitution and the nature of sugar moiety, glucoside or glucuronide. It also shows that some ^{13}C spectra have been misattributed even in recent papers (see, for example, the ^{13}C NMR spectrum of quercetin 4′-*O*-β-D-glucopyranoside in Ref. 55).

3. Conclusion

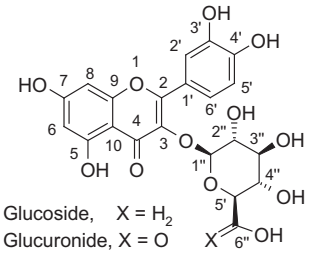
We describe a robust set of protection and deprotection steps allowing to specifically access the five phenol functions of quercetin without risking migration during alkylation of the free positions. The deprotection is particularly mild under neutral conditions and yields pure glucosides and glucuronides without further purification. TEMPO-mediated oxidation proved to be efficient for all the glucosides except the one in the 4′ position. This synthesis may be extended easily to flavones and flavanones bearing fewer hydroxyl groups. Combined with our previous synthesis of all *O*-methylated quercetin metabolites[18] it opens the way for the synthesis of widely distributed quercetin double metabolites.[13,16] The intermediate we described during the synthesis may also be used for regioselectively accessing other labile derivatives of quercetin.

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 Eurisotop (Saint-Aubin, France). Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under argon before use. Dimethylformamide (DMF) was distilled under reduced 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 spectra were recorded on a Bruker (Wissembourg, France) AM 300 spectrometer (300 MHz, for ^{1}H and ^{13}C, respectively) using $CDCl_3$, CD_3OD or DMSO-d_6 as solvents and TMS as internal standard; chemical shifts and *J* values are given in parts per million and hertz, respectively. Fast atom bombardment (FAB) mass spectra were measured on a JEOL Mass Station 700 spectrometer at

Table 2
^{1}H NMR and ^{13}C NMR of the 5 quercetin *O*-β-D-monoglucosides (300 MHz, δ ppm, CD_3OD or DMSO-d_6, see Experimental part)



Compound	**9** (this work)	**9** (lit.[41]; see also[48])	**13** (this work)	**13** (lit.[44])	**19** (this work)	**19** (lit.[20]; see also[48])	**24** (this work)	**24** (lit.[20]; see also[48])	**31** (this work)	**31** (lit.[54]; see also[49,56])
Glucoside position	3	3	5	5	7	7	3′	3′	4′	4′
H6	6.15	6.08	6.77	6.75	6.37	6.42	6.29	6.19	6.21	6.20
H8	6.33	6.27	6.61	6.62	6.58	6.76	6.55	6.49	6.47	6.45
H2′	7.70	7.61	7.63	7.65	7.64	7.72	7.85	7.96	7.88	7.71
H5′	6.75	6.76	6.88	6.88	6.86	6.90	6.89	6.97	7.01	7.25
H6′	7.57	7.47	7.50	7.52	7.49	7.55	7.57	7.84	7.31	7.62
H1″	5.23	5.14	4.78	4.78	4.98	5.07	4.75	4.78	4.86	4.85
H2″	3.18–3.78	3.10–3.66	3.28–3.68		3.12–3.67	3.16–3.52	3.15–3.77	3.15–3.37	3.12–3.79	3.17–3.51
H3″	3.18–3.78	3.10–3.66	3.28–3.68		3.12–3.67	3.16–3.52	3.15–3.77	3.15–3.37	3.12–3.79	3.17–3.51
H4″	3.18–3.78	3.10–3.66	3.28–3.68		3.12–3.67	3.16–3.52	3.15–3.77	3.15–3.37	3.12–3.79	3.17–3.51
H5″	3.18–3.78	3.10–3.66	3.28–3.68		3.12–3.67	3.16–3.52	3.15–3.77	3.15–3.37	3.12–3.79	3.17–3.51
H6″	3.18–3.78	3.10–3.66	3.28–3.68		3.12–3.67	3.16–3.52	3.15–3.77	3.15–3.37	3.12–3.79	3.17–3.51
C2	159.0	158.9	147.3	147.7	147.7	147.4	150.7	151.1	146.9	146.2
C3	135.6	135.6	137.2	137.2	136.0	136.0	136.4	136.6	136.6	136.7
C4	179.4	179.4	171.7	171.7	175.1	175.7	178.2	179.0	176.3	176.4
C5	162.9	162.9	158.5	158.4	160.1	160.0	161.1	161.4	161.0	161.0
C6	99.9	99.8	103.1	103.1	99.0	98.7	99.7	99.3	98.7	98.6
C7	165.9	165.9	162.5	162.4	162.1	162.3	161.9	161.5	164.7	164.4
C8	94.7	94.7	97.4	97.3	94.6	94.1	94.7	94.6	93.9	93.9
C9	158.4	158.6	157.1	157.1	157.4	157.4	156.6	157.0	156.7	156.6
C10	105.7	105.6	106.4	106.3	104.9	104.2	106.0	106.2	103.9	103.4
C1′	123.0	122.9	122.0	122.0	120.1	121.8	123.1	123.0	124.0	125.4
C2′	117.6	117.5	115.7	115.6	115.9	115.3	116.9	116.6	116.9	116.2
C3′	145.7	145.8	145.1	145.0	144.7	144.8	157.1	156.8	147.8	147.1
C4′	149.8	149.8	143.5	143.5	147.4	147.4	146.6	146.3	146.7	146.7
C5′	116.0	115.9	114.7	114.7	115.1	115.7	116.1	117.0	115.8	115.5
C6′	123.2	123.4	119.6	119.5	122.0	119.9	124.0	124.2	120.4	119.9
C1″	104.3	104.4	103.9	103.9	100.1	99.8	103.1	103.5	102.1	101.7
C2″	75.7	75.7	73.7	73.7	72.9	73.5	73.9	74.1	73.0	73.6
C3″	78.3	78.1	75.7	75.7	75.9	76.4	76.7	76.8	77.2	77.6
C4″	71.2	71.2	69.7	69.7	69.3	69.6	69.9	70.4	70.5	70.1
C5″	78.1	78.3	77.5	77.5	77.0	77.2	77.9	78.1	76.7	76.3
C6″	62.5	62.5	60.8	60.8	61.0	60.7	61.3	61.5	61.1	61.0

the École Normale Supérieure (Paris, France). ESI mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. Microanalyses were performed by the CNRS 'Service Central d'Analyse' (Vernaison, France).

4.2. Synthesis of quercetin 3-*O*-β-D-glucuronide 10

4.2.1. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,5,7-trihydroxy-4H-chromen-4-one ***2***[18,21]. A mixture of quercetin **1** (3.00 g, 8.87 mmol) and dichlorodiphenylmethane (4.3 ml, 22.5 mmol) was intimately mixed, and then heated at 180 °C for 10 min. The crude reaction 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 2 (1.62 g, 39% yield). Mp 222–224 °C (lit.[21] 218–219 °C; lit.[18] 222–224 °C). ^{1}H NMR (DMSO-d_6): 6.20 (d, *J*=1.9 Hz, 1H), 6.47 (d, *J*=1.9 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 1H), 7.44–7.58 (m, 10H), 7.79 (dd, *J*=8.3, 1.6 Hz, 1H), 7.81 (d, *J*=1.6 Hz, 1H). ^{13}C NMR (DMSO-d_6): 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, 146.7, 147.6, 156.2, 160.7, 164.2, 177.8. Elemental analysis: calculated for $C_{28}H_{18}O_7$ C, 72.10; H, 3.89; O, 24.09. Observed C, 71.83; H, 3.74; O, 23.89.

4.2.2. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-5,7-dihydroxy-4H-chromen-4-one ***6***. Catechol-protected quercetin **2** (1.00 g, 2.14 mmol), acetobromoglucose (1.76 g, 4.29 mmol) and potassium carbonate (593 mg, 4.29 mmol) were dissolved in 20 ml of DMF under argon and the mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with 150 ml of EtOAc and was washed with water (2×75 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product obtained was purified by flash column chromatography using a mixture of EtOAc/Petroleum ether (30:70) as eluent. (956 mg, 56% yield). ^{1}H NMR ($CDCl_3$): 1.91 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 3.76 (m, 1H), 4.15 (m, 2H), 5.00–5.28 (m, 3H), 5.59 (d, *J*=7.5 Hz, 1H), 6.25 (d, *J*=2.0 Hz, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 6.94 (d, *J*=8.3 Hz, 1H), 7.64 (dd, *J*=8.3, 1.7 Hz, 1H), 7.57 (d, *J*=1.7 Hz, 1H), 7.32–7.63 (m, 10H). ^{13}C NMR ($CDCl_3$): 20.2, 20.6, 20.9, 62.0, 67.2, 68.5, 70.0, 71.1, 94.1, 99.1, 99.3, 105.3, 108.3, 109.2, 117.9, 123.1, 124.7, 126.2, 126.3, 128.4, 129.3, 133.7, 139.7,

Table 3
^{1}H NMR and ^{13}C NMR of quercetin *O*-β-D-monoglucuronides (300 MHz, δ ppm, CD_3OD)

Compound	**10** (this work)	**10** (lit.[15]; see also[42])	**14** (this work)	**20** (this work)	**25** (this work)	**25** (lit.[26])
Glucuronide position	3	3	5	7	3′	3′
H6	6.22	6.18	6.64	6.42	6.22	6.15
H8	6.42	6.37	6.90	6.62	6.42	6.39
H2′	7.73	7.63	7.73	7.69	7.91	8.03
H5′	6.76	6.84	6.88	6.85	6.95	6.95
H6′	7.64	7.63	7.64	7.61	7.79	7.89
H1″	5.38	5.31	5.02	5.12	5.15	4.92
H2″	3.48–3.85	3.47–3.75	3.55–3.70	3.25–3.73	3.35–3.83	3.52–3.70
H3″	3.48–3.85	3.47–3.75	3.55–3.70	3.25–3.73	3.35–3.83	3.52–3.70
H4″	3.48–3.85	3.47–3.75	3.55–3.70	3.25–3.73	3.35–3.83	3.52–3.70
H5″	3.48–3.85	3.47–3.75	3.78	4.08	4.28	4.04
C2	159.2	159.0	159.4	162.0	151.6	
C3	135.7	135.4	138.7	137.7	136.7	
C4	179.4	179.2	176.3	177.4	176.9	
C5	163.0	162.9	159.7	162.9	161.9	
C6	99.9	99.9	105.0	100.4	98.7	
C7	166.0	166.0	164.8	164.3	164.3	
C8	94.7	94.8	99.0	95.7	94.2	
C9	158.5	158.4	148.7	157.6	156.8	
C10	105.7	105.6	107.6	106.3	104.1	
C1′	122.7	122.8	121.5	122.0	121.7	
C2′	118.1	117.2	116.3	116.3	116.6	
C3′	145.9	145.9	145.7	146.2	147.2	
C4′	149.8	149.9	146.3	148.7	149.1	
C5′	116.2	116.0	115.8	116.1	115.7	
C6′	122.8	123.5	124.0	123.9	122.0	
C1″	104.3	104.3	105.3	105.1	103.9	
C2″	75.6	75.4	74.7	74.5	73.5	
C3″	78.1	77.6	77.2	77.4	76.4	
C4″	73.4	72.8	73.5	73.2	71.7	
C5″	77.7	77.0	76.8	76.5	75.5	
C6″	172.3	172.1	173.8	174.8	170.8	

139.8, 147.2, 149.4, 156.7, 157.1, 161.9, 163.0, 169.7, 170.2, 170.9, 177.4. HR-FABMS (*m*/*z*): observed, 819.1920; calculated for $C_{42}H_{36}O_{16}Na$, 819.1901 $[M+Na]^+$.

4.2.3. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-5,7-bisbenzyloxy-4H-chromen-4-one ***7***. To a solution of compound **6** (700 mg, 0.88 mmol) in DMF (20 ml), potassium carbonate (300 mg, 2.2 mmol) and benzyl bromide (0.26 ml, 2.2 mmol) were added under argon. The reaction mixture was agitated vigorously at room temperature for 16 h. The resulting mixture was diluted with 100 ml of AcOEt and was washed with water (2×75 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated (807 mg, 94% yield). Mp 126–129 °C. ^{1}H NMR ($CDCl_3$): 1.99 (s, 3H), 2.03 (s, 6H), 2.12 (s, 3H), 3.62 (m, 1H), 3.97 (d, *J*=3.0 Hz, 2H), 5.06 (s, 2H), 5.28 (s, 2H), 5.06–5.31 (m, 3H), 5.77 (d, *J*=7.5 Hz, 1H), 6.44 (d, *J*=2.2 Hz, 1H), 6.55 (d, *J*=2.2 Hz, 1H), 6.96 (d, *J*=8.3 Hz, 1H), 7.67 (dd, *J*=8.3, 1.7 Hz, 1H), 7.59 (d, *J*=1.7 Hz, 1H), 7.28–7.62 (m, 20H). ^{13}C NMR ($CDCl_3$): 20.3, 20.7, 20.9, 61.2, 68.3, 70.5, 70.7, 71.5, 71.6, 72.9, 93.8, 98.2, 98.8, 108.2, 109.0, 109.7, 117.6, 124.2, 124.3, 126.3, 126.4, 126.6, 127.6, 127.8, 128.3, 128.5, 128.6, 128.8, 129.3, 135.6, 135.9, 136.3, 139.8, 140.0, 147.2, 148.9, 154.2, 158.6, 159.7, 162.9, 169.5, 170.1, 170.5, 172.7. HR-FABMS (*m*/*z*): observed, 999.2864; calculated for $C_{56}H_{48}O_{16}Na$, 999.2840 $[M+Na]^+$.

4.2.4. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-β-D-glucopyranosyloxy-5,7-bisbenzyloxy-4H-chromen-4-one ***8***. Compound **7** (500 mg, 0.51 mmol) was dissolved in 40 ml of a mixture of MeOH/THF (50:50). A solution of sodium methylate, prepared from 10 mg of sodium metal in methanol (10 ml) was added. When the deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained for 30 min, then the resin was filtered. The MeOH was eliminated by vacuum evaporation, at room temperature (356 mg, 86% yield). Mp 137–139 °C. ^{1}H NMR ($CDCl_3$): 3.20 (m, 1H), 3.33–3.68 (m, 5H), 4.81 (d, *J*=6.7 Hz, 1H), 5.01 (s, 2H), 5.17 (s, 2H), 6.33 (d, *J*=2.2 Hz, 1H), 6.49 (d, *J*=2.2 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 7.12–7.77 (m, 22H). ^{13}C NMR ($CDCl_3$): 62.4, 70.1, 70.5, 70.7, 74.0, 76.0, 93.8, 98.4, 105.4, 108.1, 109.1, 109.5, 117.9, 123.9, 124.2, 126.3, 126.5, 126.7, 127.6, 127.8, 128.3, 128.5, 128.6, 128.8, 129.4, 135.4, 136.0, 137.6, 139.6, 139.6, 147.0, 149.3, 155.1, 158.7, 159.7, 163.4, 174.1. HR-FABMS (*m*/*z*): observed, 831.2400; calculated for $C_{48}H_{40}O_{12}Na$, 831.2417 $[M+Na]^+$.

4.2.5. Quercetin 3-O-β-D-glucopyranoside ***9***[41,48]. A suspension of **8** (50 mg, 0.06 mmol) in a mixture of EtOH (20 ml) and THF (20 ml) was treated with palladium hydroxide (30%, 30 mg) under a hydrogen flow for 12 h. The reaction mixture was then filtered on Celite and rinsed with EtOH (30 ml). The residue obtained after evaporation of the solvent was purified on C18 column using a mixture of MeOH/H_2O (30:70). (20 mg, 72% yield). ^{1}H NMR (CD_3OD): 3.18–3.78 (m, 6H), 5.23 (d, *J*=7.7 Hz, 1H), 6.15 (d, *J*=2.0 Hz, 1H), 6.33 (d, *J*=2.0 Hz, 1H), 6.75 (dd, *J*=8.6, 2.0 Hz, 1H), 7.57 (d, *J*=8.6 Hz, 1H), 7.70 (d, *J*=2.0 Hz, 1H). ^{13}C NMR (CD_3OD): 62.5, 71.2, 75.7, 78.1, 78.3, 94.7, 99.9, 104.3, 105.7, 116.0, 117.6, 123.0, 123.2, 135.6, 145.7, 149.8, 158.4, 159.0, 162.9, 165.9, 179.4. HR-FABMS (*m*/*z*): observed, 487.0848; calculated for $C_{21}H_{20}O_{12}Na$, 487.0852 $[M+Na]^+$.

4.2.6. Quercetin 3-O-β-D-glucuronide ***10***[15,17,42]. To a solution of compound **8** (50 mg, 0.06 mmol) in CH_2Cl_2 were added 1 ml of solution saturated in potassium carbonate, 1.5 mg of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), 5 mg of potassium bromide and 2.0 mg tetrabutylammonium bromide. Then 10 mL of a solution of 5.5% NaOCl were added dropwise. After 1 h the resulting mixture was diluted with 30 ml of AcOEt and 30 ml of water. The precipitate thus formed was filtered off. The solid obtained was dissolved in a mixture of EtOH (20 ml) and THF (20 ml), and was treated with palladium hydroxide (30%, 30 mg) under a hydrogen flow for 12 h.

The reaction mixture was then filtered on Celite and rinsed with EtOH (30 ml). The residue obtained after evaporation of the solvent was purified by chromatography on C18 column (LC-SPE) using a mixture of MeOH/H_2O (40:60) as eluent. (16 mg, 56% yield). ^{1}H NMR (CD_3OD): 3.48–3.85 (m, 4H), 5.38 (d, J=7.2 Hz, 1H), 6.22 (d, J=2.0 Hz, 1H), 6.42 (d, J=2.0 Hz, 1H), 6.76 (dd, J=8.4, 2.0 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.73 (d, J=2.0 Hz, 1H). ^{13}C NMR (CD_3OD): 73.4, 75.6, 77.7, 78.1, 94.7, 99.9, 104.3, 105.7, 116.2, 118.1, 122.7, 122.8, 135.7, 145.9, 149.8, 158.5, 159.2, 163.0, 166.0, 172.3, 179.4. HR-FABMS (m/z): observed, 479.0779; calculated for $C_{21}H_{19}O_{13}$, 479.0826 $[M+H]^+$.

4.3. Synthesis of quercetin 5-*O*-β-D-glucuronide 14

4.3.1. 3,7-Bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-5-hydroxyl-4H-chromen-4-one ***3***[18,50]. To a solution of quercetin **1** (5.00 g, 14.79 mmol) in DMF (40 ml), potassium carbonate (7.14 g, 51.77 mmol) and benzyl bromide (6.19 ml, 51.77 mmol) were added under argon. The reaction mixture was agitated vigorously at room temperature for 16 h. The resulting mixture was diluted with 200 ml of AcOEt and was washed with water (2×150 ml). The residue obtained after evaporation of the solvent was purified by flash column chromatography using CH_2Cl_2 as eluent, to afford **3** (5.88 g, 60% yield), **4** (1.69 g, 20% yield) and **5** (0.33 g, 3% yield), respectively. Mp 140–142 °C (lit.[18] 140–142 °C; lit.[50] 128 °C). ^{1}H NMR ($CDCl_3$): 4.96 (s, 2H), 5.01 (s, 2H), 5.12 (s, 2H), 5.25 (s, 2H), 6.44 (d, J=2.1 Hz, 1H), 6.46 (d, J=2.1 Hz, 1H), 6.96 (d, J=8.7 Hz, 1H), 7.21–7.45 (m, 20H), 7.54 (dd, J=8.7, 2.1 Hz, 1H), 7.72 (d, J=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 70.4, 70.8, 71.0, 74.3, 93.0, 98.5, 106.1, 113.6, 115.2, 122.6, 123.4, 127.2, 127.4, 127.6, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 135.8, 136.05, 136.7, 136.9, 137.4, 148.2, 151.1, 156.2, 156.7, 162.0, 164.4, 178.8. Elemental analysis: calculated for $C_{43}H_{34}O_7$ C, 77.94; H, 5.14; O, 16.92. Observed C, 77.97; H, 5.16; O, 16.95.

4.3.2. 3,7-Bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-5-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-4H-chromen-4-one ***11***. Compound **3** (1.00 g, 1.51 mmol), (1.24 g, 3.02 mmol) of acetobromoglucose and (417 mg, 3.02 mmol) of potassium carbonate were dissolved in 20 ml of DMF under argon. The mixture was agitated for 6 h. The reaction mixture was diluted with 150 ml of EtOAc and was washed with water (2×75 ml). The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue obtained was purified by flash column chromatography using a mixture of CH_2Cl_2/EtOAc (85:15) as eluent. (1.10 g, 74% yield). Mp 104–107 °C. ^{1}H NMR ($CDCl_3$): 1.96 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.15 (s, 3H), 3.76 (m, 1H), 4.15 (m, 2H), 4.93 (s, 2H), 5.05 (s, 2H) 5.09 (s, 2H), 5.19 (s, 2H), 5.49–5.11 (m, 3H), 4.83 (d, J=7.5 Hz, 1H), 6.59 (d, J=2.0 Hz, 1H), 6.85 (d, J=2.0 Hz, 1H), 6.94 (d, J=8.3 Hz, 1H), 7.59 (dd, J=8.3, 1.7 Hz, 1H), 7.72 (d, J=1.7 Hz, 1H), 7.18–7.55 (m, 20H). ^{13}C NMR ($CDCl_3$): 20.2, 20.7, 22.5, 61.1, 66.3, 67.2, 70.3, 71.1, 74.3 93.1, 98.7, 106.7, 110.7, 114.8, 115.9, 121.8, 123.9, 126.1, 127.2, 127.4, 127.9, 128.1, 128.3, 128.4, 128.4, 128.7, 128.8, 129.0, 129.3, 135.7, 135.9, 136.4, 137.5, 139.3, 145.5, 147.8, 156.7, 162.0, 164.4, 169.5, 169.8, 170.2, 178.8. ESI-MS (m/z): observed, 993.1; calculated for $C_{57}H_{53}O_{16}$, 993.33 $[M+H]^+$.

4.3.3. 3,7-Bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-5-β-D-glucopyranosyloxy-4H-chromen-4-one ***12***. Compound 11 (800 mg, 0.81 mmol) was dissolved in 40 ml of a mixture of MeOH/THF (50:50). A solution sodium methylate, prepared from 10 mg of sodium metal in methanol (15 ml), was added at room temperature. When the deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained for 30 min, then the resin was filtered. The MeOH was eliminated by vacuum evaporation, at room temperature. (540 mg, 82% yield). Mp 137–139 °C. ^{1}H NMR ($CDCl_3$): 3.20 (m, 1H), 3.70–3.93 (m, 5H), 4.95 (d, J=6.8 Hz, 1H), 4.73 (s, 2H), 4.89 (s, 4H), 5.03 (s, 2H), 6.34 (d, J=1.5 Hz, 1H), 6.67 (d, J=1.5 Hz, 1H), 6.72 (d, J=8.8 Hz, 1H), 7.34 (dd, J=8.8 Hz, 1.4 Hz, 1H), 7.60 (d, J=1.4 Hz, 1H), 7.08–7.34 (m, 20H). ^{13}C NMR ($CDCl_3$): 61.2, 69.1, 70.5, 70.7, 72.9, 74.0, 75.8, 96.3, 101.7, 103.3, 109.7, 113.1, 114.6, 121.9, 123.4, 127.1, 127.3, 127.6, 127.7, 127.9, 128.2, 128.3, 128.5, 128.6, 128.7, 135.7, 136.7, 136.8, 137.0, 139.5, 148.0, 150.5, 153.3, 157.4, 158.5, 162.8, 174.5. HR-FABMS (m/z): observed, 847.2742; calculated for $C_{49}H_{44}O_{12}Na$, 847.2730 $[M+Na]^+$.

4.3.4. Quercetin 5-O-β-D-glucopyranoside ***13***[44]. Compound **13** was synthesized according to the procedure reported for **9**. (82% yield). ^{1}H NMR (DMSO-d_6): 3.28–3.68 (m, 6H), 4.78 (d, J=6.7, 1H), 6.61 (d, J=2.2 Hz, 1H), 6.77 (d, J=2.2 Hz, 1H), 6.88 (d, J=8.5 Hz, 1H), 7.50 (d, J=8.5 Hz, 1H), 7.63 (s, 1H). ^{13}C NMR (CD_3OD): 60.8, 69.7, 73.7, 75.7, 77.5, 97.4, 103.1, 103.9, 106.4, 114.7, 115.7, 119.6, 122.0, 137.2, 143.5, 145.1, 147.3, 157.1, 158.5, 162.5, 171.7. HR-FABMS (m/z): observed: 465.1036; calculated for $C_{21}H_{21}O_{12}$, 465.1033 $[M+H]^+$.

4.3.5. Quercetin 5-O-β-D-glucuronide ***14***. Compound **14** was synthesized according to the procedure reported for **10**. (51% yield). ^{1}H NMR (CD_3OD): 3.55–3.70 (m, 3H), 3.78 (m, 1H), 5.02 (d, J=6.7 Hz, 1H), 6.64 (d, J=2.2 Hz, 1H), 6.90 (d, J=2.2 Hz, 1H), 6.88 (d, J=8.5 Hz, 1H), 7.64 (d, J=8.5 Hz, 1H), 7.73 (s, 1H). ^{13}C NMR (DMSO-d_6): 73.5, 74.7, 76.8, 77.2, 99.0, 105.0, 105.3, 107.6, 115.8, 116.3, 121.5, 124.0, 138.7, 145.7, 146.3, 148.7, 159.4, 159.7, 164.8, 173.8, 176.3. HR-FABMS (m/z): observed: 479.0809; calculated for $C_{21}H_{19}O_{13}$: 479.0826 $[M+H]^+$.

4.4. Synthesis of quercetin-7-*O*-β-D-glucuronide 20

4.4.1. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3-benzyloxy-5,7-dihydroxy-4H-chromen-4-one ***15***. Compound **15** was prepared by benzylation of compound **2** under standard conditions (1.1 equiv of benzyl bromide and 1.5 equiv of potassium carbonate in DMF at room temperature for 12 h). (65% yield). Mp 124–126 °C. ^{1}H NMR ($CDCl_3$): 4.98 (s, 2H), 6.35 (d, J=2.1 Hz, 1H), 6.40 (d, J=2.1 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 7.41–7.48 (m, 10H), 7.60–7.65 (m, 5H), 7.53 (dd, J=8.1, and 1.8 Hz, 1H), 7.58 (d, J=1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): 74.7, 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. Elemental analysis: calculated for $C_{35}H_{24}O_7$ C, 75.53; H, 4.35; O, 20.12. Observed C, 75.53; H, 4.59; O, 19.63.

4.4.2. 2-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-3-benzyloxy-5-hydroxyl-7-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-4H-chromen-4-one ***16***. To a solution of compound **15** (500 mg, 0.9 mmol) and TDA (0.25 g, 1.73 mmol), in 40 ml of aqueous solution saturated in K_2CO_3, acetobromoglucose (553 mg, 1.35 mmol) dissolved in CH_2Cl_2 (30 ml) were added under argon. The mixture reaction was agitated for 24 h. The aqueous layer was extracted with CH_2Cl_2 (60 ml). The organic layer was washed successively with NaOH 0.5% (50 ml), water (50 ml), and 50 ml of HCl 2% (neutral pH). The residue obtained after evaporation of the solvent was purified by flash column chromatography using a mixture of Petroleum ether/EtOAc (70:30) as eluent (550 mg, 69% yield). Mp 104–106 °C. ^{1}H NMR ($CDCl_3$): 2.01 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 3.93 (m, 1H), 4.23 (m, 2H), 5.01 (s, 2H), 5.12–5.38 (m, 3H), 5.19 (d, J=7.0 Hz, 1H), 6.41 (d, J=2.2 Hz, 1H), 6.50 (d, J=2.2 Hz, 1H), 6.87 (d, J=8.3 Hz, 1H), 7.54 (dd, J=8.3, 1.7 Hz, 1H), 7.46 (d, J=1.7 Hz, 1H), 7.06–7.60 (m, 15H). ^{13}C NMR ($CDCl_3$): 20.5, 20.6, 20.6, 21.0, 61.3, 68.2, 70.9, 72.4, 72.6, 74.4, 95.1, 98.1, 99.5, 107.3, 108.4, 108.9, 124.0, 124.2, 126.2, 127.4, 128.2, 128.3, 128.4, 128.9, 129.4, 133.8, 139.7, 147.2, 149.4, 156.6, 157.0, 161.9, 162.7, 169.5, 169.9, 170.3, 170.9, 174.4. ESI-MS (m/z): observed, 887.2; calculated for $C_{49}H_{43}O_{16}$, 887.25 $[M+H]^+$.

4.4.3. 2-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-3,5-bisbenzyloxy 7-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-4H-chromen-4-one

17. Compound **17** was prepared by benzylation of compound **16** under standard conditions (1.3 equiv of benzyl bromide and 1.5 equiv of potassium carbonate in DMF at room temperature for 12 h). (85% yield). Mp 92–96 °C. ^{1}H NMR ($CDCl_3$): 1.99 (s, 3H), 2.02 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 3.92 (m, 1H), 4.18 (m, 2H), 5.01 (s, 2H), 5.06 (s, 2H), 5.11–5.36 (m, 3H), 5.17 (d, *J*=7.0 Hz, 1H), 6.37 (d, *J*=2.2 Hz, 1H), 6.47 (d, *J*=2.2 Hz, 1H), 6.87 (d, *J*=8.3 Hz, 1H), 7.54 (dd, *J*=8.3, 1.7 Hz, 1H), 7.46 (d, *J*=1.7 Hz, 1H), 7.06–7.60 (m, 20H). ^{13}C NMR ($CDCl_3$): 20.3, 20.4, 20.6, 20.9, 61.9, 68.2, 70.5, 72.1, 72.4, 72.7, 94.1, 98.2, 99.3, 108.3, 109.2, 117.9, 124.0, 124.2, 126.2, 127.4, 128.2, 128.3, 128.4, 128.9, 129.4, 133.7, 137.3, 139.7, 147.2, 149.4, 156.6, 157.0, 162.0, 162.9, 169.6, 170.2, 170.3, 170.9, 177.4. HR-FABMS (*m*/*z*): observed, 999.2852; calculated for $C_{56}H_{48}O_{16}Na$: 999.2840 $[M+Na]^+$.

4.4.4. 2-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-3,5-bisbenzyloxy 7-β-D-glucopyranosyloxy-4H-chromen-4-one ***18***. Compound **17** (500 mg, 0.51 mmol) was dissolved in 40 ml of a mixture MeOH/THF (50:50). A solution of sodium methylate prepared from 10 mg of sodium metal in methanol (10 ml) was added at room temperature. When the deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained for 30 min, then the resin was filtered. The MeOH was eliminated by vacuum evaporation, at room temperature. (350 mg, 85% yield). Mp 140–144 °C. ^{1}H NMR ($CDCl_3$): 3.15 (m, 1H), 3.28–3.62 (m, 5H), 4.76 (d, *J*=6.7 Hz, 1H), 5.05 (s, 2H), 5.12 (s, 2H), 6.33 (d, *J*=2.2 Hz, 1H), 6.43 (d, *J*=2.2 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 7.12–7.77 (m, 22H). ^{13}C NMR ($CDCl_3$): 61.4, 68.9, 70.2, 71.7, 72.1, 73.4, 76.0, 94.8, 98.4, 107.4, 108.7, 109.1, 117.9, 123.9, 124.2, 126.3, 126.3, 126.6, 127.6, 127.8, 128.4, 128.5, 128.6, 128.8, 129.4, 136.0, 137.7, 139.6, 147.0, 149.3, 155.1, 158.7, 159.7, 162.7, 173.1. HR-FABMS (*m*/*z*): observed, 831.2403; calculated for $C_{49}H_{40}O_{12}Na$, 831.2417 $[M+Na]^+$.

4.4.5. Quercetin 7-O-β-D-glucopyranoside ***19***[20,48]. Compound **19** was synthesized according to the procedure reported for **9**. (78% yield). ^{1}H NMR (DMSO-d_6): 3,12–3.67 (m, 6H), 4.98 (d, *J*=6.7 Hz, 1H), 6.37 (d, *J*=2.2 Hz, 1H), 6.58 (d, *J*=2.2 Hz, 1H), 6.86 (d, *J*=8.5 Hz, 1H), 7.49 (dd, *J*=8.5, 1.7 Hz, 1H), 7.64 (d, *J*=1.7 Hz, 1H). ^{13}C NMR (CD_3OD): 61.0, 69.3, 72.9, 75.9, 77.0, 94.6, 99.0, 100.1, 104.9, 115.1, 115.9, 120.1, 122.0, 136.0, 144.7, 147.4, 147.7, 157.4, 160.1, 162.1, 175.1. HR-FABMS (*m*/*z*): observed, 465.1040; calculated for $C_{21}H_{21}O_{12}$, 465.1033 $[M+H]^+$.

4.4.6. Quercetin-7-O-β-D-glucuronide ***20***. Compound **20** was synthesized according to the procedure reported for **10**. (65% yield) ^{1}H NMR (CD_3OD): 3.25–3.73 (m, 3H), 4.08 (d, *J*=9.2 Hz, 1H), 5.12 (d, *J*=6.7 Hz, 1H), 6.42 (d, *J*=2.2 Hz, 1H), 6.62 (d, *J*=2.2 Hz, 1H), 6.85 (d, *J*=8.5 Hz, 1H), 7.61 (dd, *J*=8.5, 1.8 Hz, 1H), 7.69 (d, *J*=1.8 Hz, 1H). ^{13}C NMR (CD_3OD): 73.2, 74.5, 76.5, 77.4, 95.7, 100.4, 105.1, 106.3, 116.1, 116.3, 122.0, 123.9, 137.7, 146.2, 148.7, 157.6, 162.0, 162.9, 164.3, 174.8, 177.4. HR-FABMS (*m*/*z*): observed: 479.0797; calculated for $C_{21}H_{19}O_{13}$, 479.0826 $[M+H]^+$.

4.5. Synthesis of quercetin 3′-*O*-β-D-glucuronide 25

4.5.1. 3,7-Bisbenzyloxy-2-(4-benzyloxyphenyl)-5-hydroxy-4H-chromen-4-one ***4***[20,26,50]. Compound **4** was prepared by benzylation of quercetin under classical conditions (3.5 equiv of benzyl bromide and 3.5 equiv of potassium carbonate in DMF at room temperature for 12 h). (20% yield). Mp 150–152 °C (lit.[50] 148–150 °C; lit.[26] 155 °C). ^{1}H NMR ($CDCl_3$): 5.03 (s, 2H), 5.12 (s, 2H), 5.18 (s, 2H), 6.41 (d, *J*=2.1 Hz, 1H), 6.50 (d, *J*=2.1 Hz, 1H), 6.94 (d, *J*=8.7 Hz, 1H), 7.21–7.47 (m, 15H), 7.70 (dd, *J*=8.7, 2.1 Hz, 1H), 7.72 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 70.4, 71.02, 74.04, 93.02, 98.72, 106.1, 111.6, 115.1, 121.9, 123.8, 127.5, 127.9, 128.2, 128.3, 128.6, 128.7, 128.9, 135.7, 135.8, 136.5, 137.6, 145.6, 148.0, 156.3, 156.7, 161.9, 164.4, 178.8. Elemental analysis: calculated for $C_{36}H_{28}O_7$ C, 75.51; H, 4.93; O, 19.56. Observed C, 75.31; H, 5.10; O, 19.43.

4.5.2. 3,7-Bisbenzyloxy-2-(3-(2,3,4,6-tetra-O-acetyl)-β-D-glucopyranosyloxy-4-benzyloxyphenyl)-5-hydroxyl-4H-chromen-4-one ***21***[20]. To a solution of compound **4** (1.00 g, 1.75 mmol) and TDA (0.48 g, 3.5 mmol), in 40 ml of saturated K_2CO_3 aqueous, acetobromoglucose (1.1 g, 2.7 mmol) dissolved in CH_2Cl_2 (40 ml) was added under argon. The mixture reaction was agitated for 24 h. The aqueous layer was extracted with CH_2Cl_2 (60 ml). The organic layer was washed successively with NaOH 0.5% (50 ml), water (50 ml), and 50 ml of HCl 2% (neutral pH). The residue obtained after evaporation of the solvent was purified by flash column chromatography using a mixture of CH_2Cl_2/EtOAc (70:30) as eluent (1.10 g, 70% yield). ^{1}H NMR ($CDCl_3$): 1.96 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 2.13 (s, 3H), 3.12 (m, 1H), 4.07 (m, 2H), 5.05 (s, 2H), 5.12 (s, 2H), 5.18 (s, 2H), 5.05–5.35 (m, 3H), 4.81 (d, *J*=7.5 Hz, 1H), 6.65 (d, *J*=2.0 Hz, 1H), 6.85 (d, *J*=2.0 Hz, 1H), 6.95 (d, *J*=8.3 Hz, 1H), 7.58 (dd, *J*=8.3, 1.7 Hz, 1H), 7.74 (d, *J*=1.7 Hz, 1H), 7.18–7.52 (m, 15H). ^{13}C NMR ($CDCl_3$): 20.8, 20.9, 21.6, 61.9, 68.3, 70.8, 71.1 71.4, 72.1, 72.9, 74.2, 94.0, 99.2, 100.2, 106.2, 114.9, 119.5, 122.8, 124.9, 127.2, 127.4, 127.9, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 135.7, 135.8, 136.4, 137.6, 139.3, 145.6, 147.9, 156.7, 162.0, 164.4, 169.8, 169.9, 170.6, 171.2, 178.9. HR-FABMS (*m*/*z*): observed, 925.2671; calculated for $C_{50}H_{46}O_{16}Na$, 925.2668 $[M+Na]^+$.

4.5.3. 2-(3-(2,3,4,6-Tetra-O-acetyl)-β-D-glucopyranosyloxy-4-benzyloxyphenyl)-3,5,7-tribenzyloxy-4H-chromen-4-one ***22***. Compound **22** was prepared by benzylation of compound **21** under standard conditions (1.3 equiv of benzyl bromide and 1.5 equiv of potassium carbonate in DMF at room temperature for 12 h). (90% yield). ^{1}H NMR ($CDCl_3$): 1.97 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 3.13 (m, 1H), 4.12 (m, 2H), 5.22 (s, 2H), 5.15 (s, 2H), 5.10 (s, 2H) 5.21 (s, 2H), 5.07–5.30 (m, 3H), 4.83 (d, *J*=7.5 Hz, 1H), 6.65 (d, *J*=2.1 Hz, 1H), 6.85 (d, *J*=2.1 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 1H), 7.58 (dd, *J*=8.1, 1.8 Hz, 1H), 7.74 (d, *J*=1.8 Hz, 1H), 7.18–7.52 (m, 20H). ^{13}C NMR ($CDCl_3$): 20.5, 20.6, 20.7, 20.8, 61.0, 66.4, 68.1, 70.5, 70.8, 71.5, 73.1, 74.2, 74.6, 93.9, 98.2, 107.8, 113.7, 117.5, 123.5, 124.0, 127.3, 127.5, 127.7, 128.2, 128.5, 128.7, 128.9, 129.0, 129.2, 129.6, 135.7, 136.4, 137.4, 139.6, 140.3, 146.2, 150.6, 152.7, 159.0, 159.8, 162.9, 169.3, 169.6, 170.3, 170.7, 173.8. ESI-MS (*m*/*z*): observed, 1015.3; calculated for $C_{57}H_{52}O_{16}Na$, 1015.32 $[M+Na]^+$.

4.5.4. 2-(3-β-D-Glucopyranosyloxy-4-benzyloxyphenyl)-3,5,7-tribenzyloxy-4H-chromen-4-one ***23***. Compound **22** (800 mg, 0.81 mmol) was dissolved in 40 ml of a mixture MeOH/THF (50:50). A solution sodium methylate prepared from 10 mg of sodium metal in methanol (15 ml) was added at room temperature. When the deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained for 30 min, then the resin was filtered. The MeOH was eliminated by vacuum evaporation, at room temperature. (565 mg 85% yield). Mp 144–147 °C. ^{1}H NMR ($CDCl_3$): 3.02–3.82 (m, 4H), 4.11 (m, 2H), 4.83 (d, *J*=7.5 Hz, 1H), 5.05 (s, 2H), 5.09 (s, 2H), 5.12 (s, 2H) 5.18 (s, 2H), 6.59 (d, *J*=2.1 Hz, 1H), 6.82 (d, *J*=2.1 Hz, 1H), 6.95 (d, *J*=8.1 Hz, 1H), 7.61 (dd, *J*=8.1, 1.8 Hz, 1H), 7.77 (d, *J*=1.8 Hz, 1H), 7.18–7.52 (m, 20H). ^{13}C NMR ($CDCl_3$): 60.8, 70.5, 71.1, 71.2, 72.7, 73.2, 74.1, 76.7, 77.2, 94.2, 99.1, 100.9, 108.9, 114.2, 115.8, 123.0, 123.2, 126.8, 127.4, 127.7, 128.1, 128.3, 128.5, 128.7, 128.9, 129.1, 136.5, 136.8, 136.9, 138.9, 147.0, 149.8, 154.2, 158.1, 159.1, 163.0, 172.3. HR-FABMS (*m*/*z*): observed 847.2745; calculated for $C_{49}H_{44}O_{12}Na$, 847.2730 $[M+Na]^+$.

4.5.5. Quercetin 3′-O-β-D-glucopyranoside ***24***[20,48]. Compound **24** was synthesized according to the procedure reported for **9**. (85% yield). ^{1}H NMR (DMSO-d_6): 3.15–3.77 (m, 6H), 4.75 (d, *J*=6.7 Hz,

1H), 6.29 (d, *J*=1.9 Hz, 1H), 6.55 (d, *J*=1.9 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 7.57 (d, *J*=8.6 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR (DMSO-d_6): 61.3, 69.9, 73.9, 76.7, 77.9, 94.7, 99.7, 103.1, 106.0, 116.1, 116.9, 123.1, 124.0, 136.4, 146.6, 150.7, 156.6, 157.1, 161.1, 161.9, 178.2. HR-FABMS (*m*/*z*) Observed: 465.1042 calculated for $C_{21}H_{21}O_{12}$: 465.1033 $[M+H]^+$.

4.5.6. Quercetin 3′-O-β-D-glucuronide ***25***[26]. Compound **25** was synthesized according to the procedure reported for **10**. (45% yield). ^{1}H NMR (CD_3OD): 3.35–3.83 (m, 3H), 4.28 (d, *J*=9.2 Hz, 1H) 5.15 (d, *J*=6.7 Hz, 1H), 6.22 (d, *J*=2.2 Hz, 1H), 6.42 (d, *J*=2.2 Hz, 1H), 6.95 (d, *J*=8.3 Hz, 1H), 7.91 (s, 1H), 7.79 (d, *J*=8.3 Hz, 1H). ^{13}C NMR (CD_3OD): 71.7, 73.5, 75.5, 76.4, 94.2, 98.7, 103.9, 104.1, 115.7, 116.6, 121.7, 122.0, 136.7, 147.2, 149.1, 151.6, 156.8, 161.9, 164.3, 170.8, 176.9. HR-FABMS (*m*/*z*): observed: 479.0791; calculated for $C_{21}H_{19}O_{13}$, 479.0826 $[M+H]^+$.

4.6. Synthesis of quercetin 4′-*O*-β-D-glucopyranoside 31

4.6.1. 2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-3,5,7-tribenzyloxy-4H-chromen-4-one ***26***[20]. Compound **26** was prepared by benzylation of the compound **2** under classical conditions (3.5 equiv of BnBr and 3.5 equiv of K_2CO_3 in the DMF at room temperature for 12 h). The residue obtained was purified by recrystallization in EtOAc. (90% yield). Mp 120–122 °C. ^{1}H NMR ($CDCl_3$): 5.08 (s, 2H), 5.09 (s. 2H), 5.28 (s, 2H), 6.47 (d, *J*=1.9 Hz, 1H), 6.56 (d, *J*=1.9 Hz, 1H), 6.90 (d, *J*=8.2 Hz, 1H), 7.12–7.25 (m, 2H), 7.37–7.65 (m, 25H). ^{13}C NMR ($CDCl_3$): 70.5, 70.8, 74.2, 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. Elemental analysis: calculated for $C_{49}H_{36}O_7$ C, 79.88; H, 4.92; O, 15.20. Observed C, 78.86; H, 5.07; O, 15.16.

4.6.2. 3,7-Bisbenzyloxy-2-(3,4-dihydroxyphenyl)-5-hydroxy-4H-chromen-4-one ***27***[18]. Compound **26** 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 saturated $NaHCO_3$ aqueous solution (40 ml) and dried over $MgSO_4$. After solvent evaporation, the residue was purified by recrystallization from CH_2Cl_2 to give **27**. (430 mg, 65% yield). Mp 202–204 °C. ^{1}H NMR (DMSO-d_6): 5.01 (s, 2H), 5.21 (s, 2H), 6.43 (d, *J*=2.0 Hz, 1H), 6.75 (d, *J*=2.0 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 7.28–7.46 (m, 11H), 7.55 (d, *J*=2.0 Hz, 1H). ^{13}C NMR (DMSO-d_6): 70.0, 73.3, 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. Elemental analysis: calculated for $C_{29}H_{22}O_7$ C, 72.19; H, 4.60; O, 23.21. Observed C, 72.87; H, 4.57; O, 23.30.

4.6.3. 2-(4-(2,3,4,6-Tetra-O-acetyl)-β-D-glucopyranosyloxy-3,7-dibenzyloxy)-4H-chromen-4-one ***28***. Compound **27** (400 mg, 0.83 mmol), acetobromoglucose (340 mg, 0.83 mmol) and potassium carbonate (115 mg, 0.83 mmol) were dissolved in 15 ml of DMF, under argon. The mixture was agitated for 6 h. The reaction mixture was diluted with 75 ml of EtOAc and was washed with water (2×75 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue obtained was purified by flash column chromatography using a mixture of CH_2Cl_2/EtOAc (85:15) as eluent. (256 mg, 38% yield). ^{1}H NMR ($CDCl_3$): 1.96 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 2.07(s, 3H), 3.75 (m, 1H), 4.16 (m, 2H), 5.05 (s, 2H), 5.13 (s, 2H), 5.14–5.24 (m, 3H), 5.06 (d, *J*=7.5 Hz, 1H), 6.20 (d, *J*=2.0 Hz, 1H), 6.57 (d, *J*=2.0 Hz, 1H), 7.35 (d, *J*=8.3 Hz, 1H), 7.71 (dd, *J*=8.3, 1.7 Hz, 1H), 7.73 (d, *J*=1.7 Hz, 1H), 7.36–7.53 (m, 10H). ^{13}C NMR ($CDCl_3$): 20.4, 20.5, 20.7, 21.2, 61.9, 68.4, 70.3, 71.1, 71.8, 72.3, 74.7, 93.6, 99.2, 100.2, 107.7, 116.2, 116.5, 120.7, 123.3, 127.2, 127.4, 127.6, 127.9, 128.4, 128.5, 129.2, 130.18, 136.4, 136.7, 144.2, 147.3, 148.2, 156.7, 157.6, 162.7, 164.3, 170.0, 173.2. HR-FABMS (*m*/*z*): observed, 835.2193; calculated for $C_{43}H_{40}O_{16}Na$, 835.2206 $[M+Na]^+$.

4.6.4. 2-(4-(2,3,4,6-Tetra-O-acetyl)-β-D-glucopyranosyloxy-3-benzyloxyphenyl)-3,5,7-tribenzyloxy-4H-chromen-4-one ***29***. Compound **29** was prepared by benzylation of compound **28** under classical conditions (2 equiv of benzyl bromide and 2 equiv of potassium carbonate in DMF at room temperature for 12 h). (85% yield). Mp 127–129 °C. ^{1}H NMR ($CDCl_3$): 2.00 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 3.16 (m, 1H), 4.15 (m, 2H), 5.27 (s, 2H), 5.18 (s, 2H), 5.13 (s, 2H), 5.06 (s, 2H), 5.06–5.35 (m, 3H), 4.91 (d, *J*=7.5 Hz, 1H), 6.69 (d, *J*=2.1 Hz, 1H), 6.93 (d, *J*=2.1 Hz, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 7.63 (dd, *J*=8.1 and 1.8 Hz, 1H), 7.79 (d, *J*=1.8 Hz, 1H), 7.18–7.66 (m, 20H). ^{13}C NMR ($CDCl_3$): 20.6, 20.7, 20.8, 20.9, 61.5, 66.9, 68.8, 71.1, 71.5, 72.3, 73.1, 74.7, 74.9, 94.5, 98.8, 108.2, 114.2, 119.0, 124.6, 124.5, 127.9, 128.2, 128.4, 128.6, 128.9, 129.2, 129.3, 129.5, 129.7, 130.0, 136.2, 136.9, 137.9, 139.8, 140.7, 146.8, 151.1, 153.2, 159.5, 160.4, 163.6, 169.9, 170.3, 170.6, 173.5. ESI-MS (*m*/*z*): observed, 993.3; calculated for $C_{57}H_{53}O_{16}$, 993.33 $[M+H]^+$.

4.6.5. 2-(4-O-β-D-Glucopyranosyloxy-3-benzyloxyphenyl)-3,5,7-tribenzyloxy-4H-chromen-4-one ***30***. Compound **29** (250 mg, 0.28 mmol) were dissolved in 40 ml of a mixture MeOH/THF (50:50). A sodium methylate solution, prepared from 10 mg of sodium metal in methanol (7 ml) was added at room temperature. When deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained for 30 min, and then the resin was filtered. The MeOH was eliminated by vacuum evaporation, at room temperature. (173 mg, 84% yield). Mp 142–144 °C. ^{1}H NMR ($CDCl_3$): 4,02–4.23 (m, 4H), 4.12 (m, 2H), 5.27 (d, *J*=7.5 Hz, 1H), 5.0 (s, 2H), 5.14 (s, 2H), 5.16 (s, 2H) 5.20 (s, 2H), 6.53 (d, *J*=2.1 Hz, 1H), 6.61 (d, *J*=2.1 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.60 (dd, *J*=8.1, 1.8 Hz, 1H), 7.69 (d, *J*=1.8 Hz, 1H), 7.29–7.53 (m, 20H). ^{13}C NMR ($CDCl_3$): 61.3, 70.3, 70.5, 70.9, 71.2, 73.7, 74.7, 77.1, 77.3, 96.7, 98.9, 101.1, 112.9, 114.1, 115.4, 120.9, 123.3, 124.1, 127.1, 127.4, 127.9, 128.1, 128.3, 128.4, 128.6, 130.2, 136.3, 136.5, 136.9, 144.2, 148.9, 149.8, 153.2, 156.7, 159.1, 161.4, 173.1. HR-FABMS (*m*/*z*): observed, 847.2742; calculated for $C_{49}H_{44}O_{12}Na$, 847.2730 $[M+Na]^+$.

4.6.6. Quercetin 4′-O-β-D-glucopyranoside ***31***[49,54,56]. Compound **31** was synthesized according to the procedure reported for **9**. (85% yield). ^{1}H NMR (DMSO-d_6): 3.12–3.79 (m, 6H), 4.86 (d, *J*=6.7 Hz, 1H), 6.21 (d, *J*=1.9 Hz, 1H), 6.47 (d, *J*=1.9 Hz, 1H), 7.01 (d, *J*=8.6 Hz, 1H), 7.31 (d, *J*=8.6 Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (DMSO-d_6): 61.1, 70.5, 73.0, 76.7, 77.2, 93.9, 98.7, 102.1, 103.9, 115.8, 116.9, 120.4, 124.0, 136.6, 146.7, 146.9, 147.8, 156.7, 161.0, 164.7, 176.3. HR-FABMS (*m*/*z*): observed, 465.1034; calculated for $C_{21}H_{21}O_{12}$, 465.1033 $[M+H]^+$.

Acknowledgements

The NMR and Mass Spectrometry facilities used in this study are funded by the European Community (FEDER), the Région Nord-Pas de Calais (France), the CNRS, and the Université Lille 1 Sciences et Technologies. Part of this work was funded by the European Contract QLK1-CT-1999-00505 POLYBIND. The authors thank Dr. Séverine Le Gac for her participation to the writing of the manuscript and Dr. Maria van Agthoven for her help with editing this manuscript. The authors thank the Referees for their careful reading of the manuscript.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.03.110. These data include MOL files and InChiKeys of the most important compounds described in this article.

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