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Total synthesis of triazole-linked *C*-glycosyl flavonoids in alternative solvents and environmental assessment in terms of reaction, workup and purification†

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An efficient total synthesis of triazole-linked *C*-glycosyl flavonoids was developed without the use of protective groups in order to promote atom economy, employing alternative solvents, and choosing the least toxic reagents. Aiming to measure the impact of the operation that affects the mass intensity to a greater extent, we envisaged first determining this green metric for the reaction (MI_R), the workup (MI_W), and the purification (MI_P) for each step and then taking advantage of these values to calculate the contributions to the total synthesis.

Introduction

Flavonoids are natural polyphenols largely present in fruits and vegetables and most of them are endowed with antioxidant properties.[1] The addition of a sugar moiety to these compounds may increase their bioavailability by enhancement of their water solubility so that flavonoid-sugars constitute interesting targets with various prospective applications. Indeed, numerous studies have been dedicated to the synthesis of flavonoid glycosides.[2] Various strategies have been developed to prepare flavonoid *O*-glycosides,[2,3] *C*-glycosides,[2b,4] or mixed *O*,*C*-glycosides.[2] Other kinds of linkages have also been proposed to connect the flavones and the carbohydrate as, for instance, unsaturated carbon bridge,[5] or triazole.[6] In the latter approach, the copper(I) catalysed azide–alkyne cycloaddition reaction[7] was employed for the chemical ligation of propargylated isoflavones[6a] or perbenzylated flavonol[6b] and the alkyl azide containing 2,3-unsaturated pyranoside moiety[6a] or deoxy-azido sugars[6b] (Fig. 1). In both cases, the suitably protected azide-functionalised carbohydrate was obtained through a large number of steps, and the protecting groups were not removed after the cycloaddition.

In this context, our project aimed at developing an environmentally friendly method for the synthesis of a new class of molecules in which the structural elements necessary for the antioxidant activity are maintained[1] and a hydrolytically stable *C*-glycoside unit is linked by a 1,2,3-triazole ring. The antioxidant activity of flavonoids by trapping radicals has been extensively studied and these studies have shown, in particular, that the hydroxyl functions at positions 3 and 5, associated with the carbonyl in position 4, induce maximum efficiency.[8]

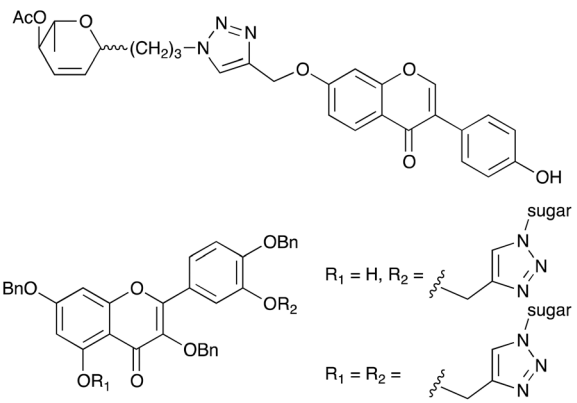

Fig. 1 Chemical structures of previously reported triazole-linked flavonoid-sugars.[6]

These results therefore guided us in choosing to introduce the sugar unit at position 7 of the flavonoid backbone (Fig. 2).

As our synthetic strategy was guided by the principles of green chemistry[9] and more particularly on the non-use of protective groups in order to promote atom economy, we decided to employ the ketone 7 (Scheme 1) since, as shown by previous work carried out in our research institute, this compound can be prepared in a single step directly from D-glucose.[10] In addition, the ketone function of the *C*-glycoside gave scope for the easy introduction of halogen in its alpha position.

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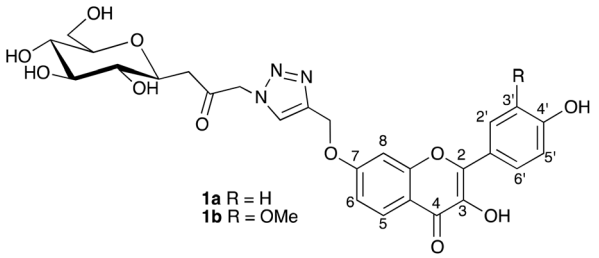


Fig. 2 Chemical structures of the target triazole-linked *C*-glycosyl flavonoids.

To satisfy the principles of green chemistry, we have also favoured the use of alternative solvents, *i.e.* non-toxic or bio-based, and we have chosen the least toxic reagents. Furthermore, each step as well as the total synthesis of the various molecules were assessed using the atom economy (AE),[11] and the mass intensity (MI),[12,13] or its counterpart, the global material economy (GME),[14] that considers all the materials used in the process, the mass intensity being connected to the Sheldon environmental factor *E*:[15]

$$\mathrm{AE} = \frac{\nu_{\mathrm{product}} M_{\mathrm{W}}(\mathrm{Product})}{\sum \nu_{\mathrm{r}} M_{\mathrm{W}}(\mathrm{r})}$$

where $M_{\mathrm{W}}(\mathrm{r})$ is the molecular weight of each reactant and ν_{r} is the corresponding stoichiometric coefficient.

$$\mathrm{MI} = \frac{1}{\mathrm{GME}} = \frac{\text{total mass used in the process}}{m_{\mathrm{product}}}$$

$$E = \frac{\text{mass of waste}}{m_{\mathrm{product}}} = \mathrm{MI} - 1$$

These metrics are increasingly used to evaluate previously described syntheses,[16] or more rarely as tools for comparison and decision in the syntheses in one[17] or more steps.[18]

The process mass intensity was chosen by the American Chemical Society Green Chemistry Institute's Pharmaceutical Roundtable as a high-level metric for evaluating processes[19] and a tool was proposed to evaluate MI for each individual step and for the whole process of a total convergent synthesis (PMI).[20] This tool allows evaluating the relative proportions due to the substrates and reagents, the solvents, and the aqueous phases in the PMI. We propose a complementary approach to highlight the operation that affects to a greater extent the mass intensity and calculated, for each step, the mass intensity for the reaction ($\mathrm{MI_R}$), the workup ($\mathrm{MI_W}$), and the purification ($\mathrm{MI_P}$):

$$\mathrm{MI_R} = \frac{\text{total mass used for the reaction}}{m_{\mathrm{product}}}$$

$$\mathrm{MI_W} = \frac{\text{total mass used for the workup}}{m_{\mathrm{product}}}$$

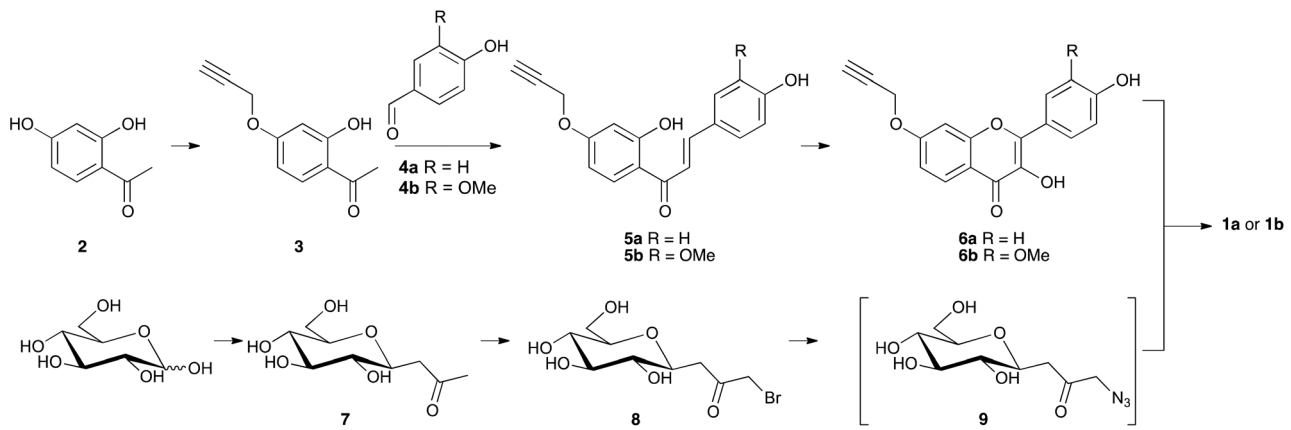
$$\mathrm{MI_P} = \frac{\text{total mass used for the purification}}{m_{\mathrm{product}}}$$

Obviously, the mass intensity MI is the sum of $\mathrm{MI_R}$, $\mathrm{MI_W}$ and $\mathrm{MI_P}$. The related metrics, $\mathrm{PMI_R}$, $\mathrm{PMI_W}$ and $\mathrm{PMI_P}$ were also calculated for each branch as well as for the total synthesis of **1a** and **1b**.

Results and discussion

Synthesis of the flavonol moieties

The synthesis of compound **3** was described using propargyl iodide prepared *in situ* from propargyl bromide and KI[21] or directly propargyl bromide,[22] in acetone with K_2CO_3 as the base. Although the use of *p*-toluenesulfonate as the leaving group is less favourable to the atom economy compared to the use of propargyl bromide (44% *vs.* 56%), we decided to use propargyl *p*-toluenesulfonate since this reagent is less toxic than propargyl bromide. Furthermore, amongst the alternatives to organic solvents, polyethylene glycol dimethyl ether ($\mathrm{PEG(OMe)_2}$) was chosen since it is known to promote nucleophilic substitution and because this linear polymer, available in a wide range of molecular weights, is non-volatile, has low toxicity and high chemical and thermal stability.[23] Therefore, we carried out the reaction in $\mathrm{PEG_{250}(OMe)_2}$ in the presence of



Scheme 1 Synthesis of triazole-linked *C*-glycosyl flavonoids **1a** and **1b** from D-glucose and 2′,4′-dihydroxyacetophenone.

K_2CO_3. The use of non-volatile solvents usually requires extraction steps. Regarding PEG, its solubility properties imply that the products are generally extracted with Et_2O. Compound **3** was thus isolated in 83% yield by extraction with this solvent and purified by recrystallization in EtOH. The mass intensity for the reaction was relatively low (6.2) but the workup (extraction) was problematic since a large amount of Et_2O, a highly hazardous solvent, was necessary to extract the product from $PEG_{250}(OMe)_2$ (Table 1).

This step was optimized and finally, a protocol allowing the precipitation of the propargylated compound in acidic aqueous medium was found, thus avoiding the use of Et_2O and leading to the decrease of MI_W from 28.51 to 8.16 (Table 1 and Fig. 3).

The next reaction was an aldol condensation enabling the synthesis of chalcones **5**. These compounds are conventionally obtained in basic medium after protection of the phenol functional groups.[24] These additional protection–deprotection steps are necessary to maintain sufficient electrophilicity of the aldehyde function but have an impact on the mass intensity of the reaction sequence; that is why the principles of green chemistry recommend avoiding these steps. The aldolisation reaction can also be carried out in acidic medium,[25] but in our case, these conditions only led to low conversions (>8%). Alternatively, pyrrolidine was used in the presence of acetic acid in a benzene–diethyl ether mixture for the synthesis of didehydroparadols from vanillin[26] or, in diethyl ether or THF, for the preparation of diarylheptanoids from different hydroxybenzaldehydes.[27] Since the use of such solvents must be banned, we exploited a pyrrolidine–AcOH mixture for the condensation between 2′-hydroxy-4′-propargyloxyacetophenone (**3**) and 4-hydroxybenzaldehyde, or vanillin, in ethanol or without solvent, which allowed obtaining a mixture of chalcones **5** and flavanones **5′** (Scheme 2). Indeed, *ortho*-hydroxychalcones are known to give rise to an isomerism that can be controlled by the pH, the cyclic flavanone being favoured at pH below ~10 and the chalcone predominating above pH ~ 13.[28]

The reaction without solvent required 5 equiv. of pyrrolidine–AcOH instead of only 1 equiv. in EtOH but was faster, took place at a lower temperature and afforded the *E*-configured chalcones in better yields and lower MI_R (Table 2). After optimizing the reaction conditions, treatment and purification were redesigned to decrease the amount of material used. Initially, these operations were carried out by liquid–liquid extraction, washing (NaCl, $NaHSO_3$) and chromatography, which led to high values of MI_W and MI_P (Table 2).

We found that the compounds could be purified by crystallization (EtOH–H_2O), which significantly reduced these values but also allowed using only water, and AcOEt and EtOH, bio-based solvents for these operations (Fig. 4).

The most straightforward method to prepare 3-hydroxyflavones from chalcones is the Algar–Flynn–Oyamada (AFO) reaction.[29] This base-induced oxidative cyclisation of chalcones occurs in the presence of hydrogen peroxide and sodium hydroxide through a mechanism still debated[30] and affords the flavonol, and often an aurone, so that yields are generally low.[31] Therefore, some modifications of the conventional AFO reaction conditions have been proposed.[32] Among the different protocols tested, the best results were obtained by treating chalcones **5** suspended in an aqueous solution of sodium hydroxide by a 30% hydrogen peroxide solution at

Table 1 Comparison of isolated yields and mass intensities depending on the workup for isolation of **3** after its synthesis in $PEG_{250}(OMe)_2$ as the solvent

Workup by	Yield (%)	MI_R	MI_W	MI_P	MI
Extraction (Et_2O)	83	6.23	28.51	5.58	40.33
Precipitation (HCl aq.)	82	6.19	8.16	4.96	19.31

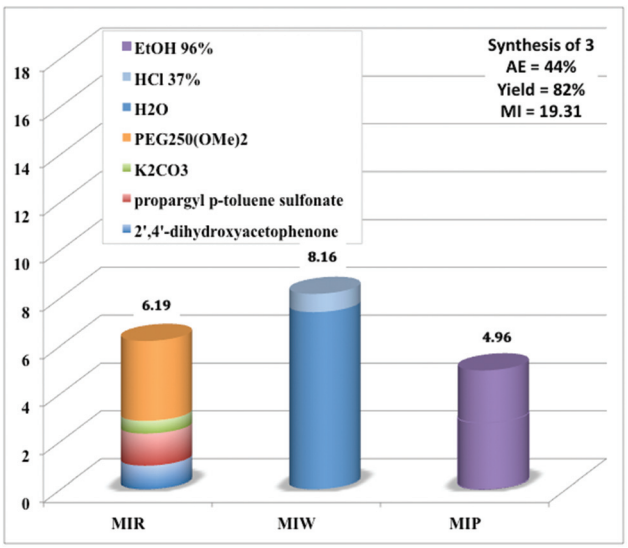
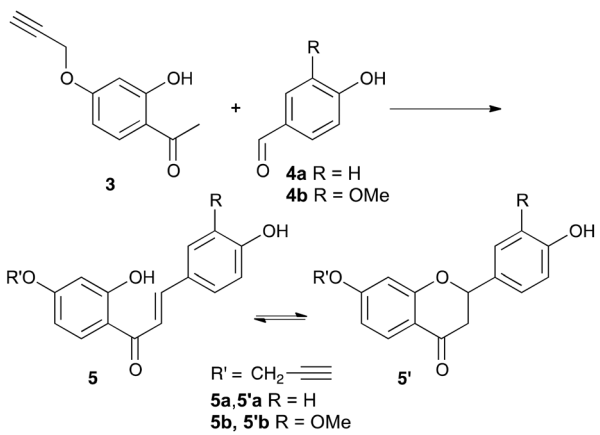


Fig. 3 Amount and nature of reactants and auxiliaries for the synthesis of **3** (g $g_{product}^{-1}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P).



Scheme 2 Synthesis of chalcones **5a** and **5b** and isomerism with flavanone **5′a** or **5′b**.

Table 2 Comparison of isolated yields and mass intensities for the synthesis of **5a** and **5b** in EtOH or without solvent

Aldehyde	Solvent	Temp., time	Yield (%)	MI_R	MI_W	MI_P	MI
4a	EtOH[a]	60 °C, 24 h	80[c]	10.8	110.3	1010.6	1131.7
4a	—[b]	30 °C, 2 h	84[c]	3.9	82.3	965.0	1051
4a	—[b]	30 °C, 2 h	84[d]	3.9	54.6	11.7	70.2
4b	EtOH[a]	60 °C, 24 h	68[c]	11.7	118.2	1222.6	1352.5
4b	—[b]	30 °C, 6 h	80[c]	3.8	143.7	828.0	975.6
4b	—[b]	30 °C, 6 h	71[d]	4.3	57.7	49.5	111.6

[a] 1 equiv. pyrrolidine–AcOH. [b] 5 equiv. pyrrolidine–AcOH. [c] Purification by chromatography. [d] Purification by crystallization.

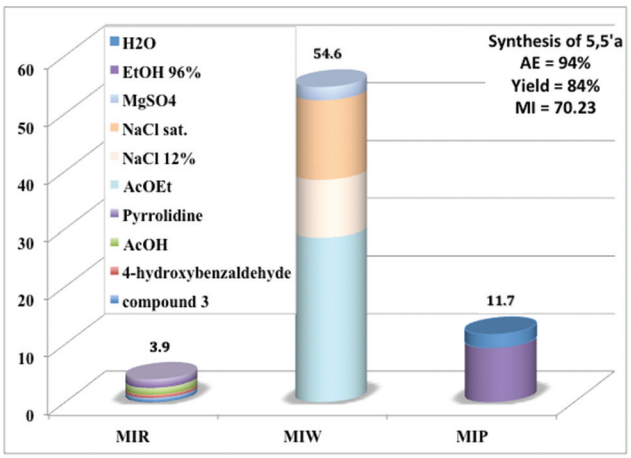


Fig. 4 Amount and nature of reactants and auxiliaries for the synthesis of **5**, **5'a** (g $g_{product}^{-1}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P). For **5**, **5'b**, see ESI.†

room temperature. A meticulous analysis of all the products of the reaction has shown that the benzoic acids **10** and **11a** or **11b** were formed up to approximately 16% with flavonol **6a** or **6b** respectively (Fig. 5).

Formation of these by-products can be explained by the oxidation of 3-hydroxyflavones formed through a mechanism similar to that of the oxygenolysis of these compounds in basic medium.[33] Therefore, to separate flavonols and the acid **10** that precipitate together during the acidification of the reaction medium, while **11** remained in solution, we realized a liquid–liquid extraction (EtOAc–$NaHCO_3$ aq.). The mass intensity increased significantly since the low solubility of flavonols

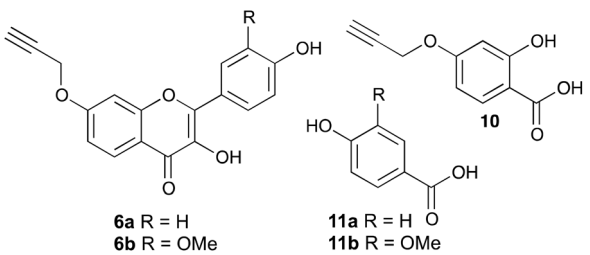


Fig. 5 Structures of 3-hydroxyflavone **6a** or **6b** and of by-products **10**, **11a** and **11b**.

in ethyl acetate led to the use of large volumes of this solvent (Table 3). We then opted for solid–liquid extraction to recover pure compounds.

This new protocol has proved effective since flavonol **6a** was recovered in a similar yield (65%) and **6b** in a greater yield (64%) compared with liquid–liquid extraction (Table 3). In addition, the MI_P were divided by about 5.5 (**6a**) and 7.9 (**6b**) which has resulted in greatly reducing the mass intensities (Table 3 and Fig. 6).

Evaluation of whole sequences for the syntheses of 6a and 6b

PMI_R, PMI_W and PMI_P of the linear sequence (**2** → **6**, Fig. 7) can be calculated from the mass intensities, the

Table 3 Comparison of isolated yields and mass intensities for the purification of flavonols **6a** and **6b** by liquid–liquid extraction (LLE) or solid–liquid extraction (SLE)

Flavonol	Purification	Yield (%)	MI_R	MI_W	MI_P	MI
6a	LLE	65	18.4	81.9	626.5	726.8
	SLE	65	18.4	81.9	113.9	214.3
6b	LLE	61	24.7	87.1	913.3	1025.2
	SLE	64	23.5	82.7	116.0	222.2

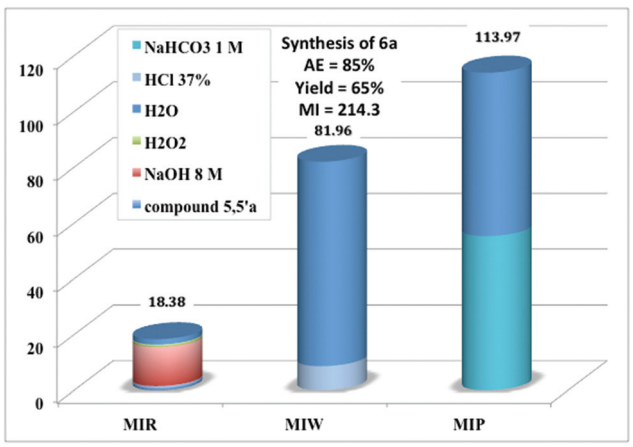


Fig. 6 Amount and nature of reactants and auxiliaries for the synthesis of **6a** (g $g_{product}^{-1}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P). For **6b**, see ESI.†

$$2 \xrightarrow[\varepsilon_1]{MI^{(1)}} 3 \xrightarrow[\varepsilon_2]{MI^{(2)}} 5 \xrightarrow[\varepsilon_3]{MI^{(3)}} 6$$

Fig. 7 Synthesis of **6** through a linear three-step sequence, each step *i* occurring in a yield of ε_i and a mass intensity $MI^{(i)}$.

yields of each step and the molecular weights M_W of the compounds:

$$PMI_R^{2\to6} = \frac{M_W(3)}{\varepsilon_2\varepsilon_3 M_W(6)}\left(MI_R^{(1)} - 1\right) + \frac{M_W(5)}{\varepsilon_3 M_W(6)}\left(MI_R^{(2)} - 1\right) + MI_R^{(3)}$$

$$PMI_W^{2\to6} = \frac{M_W(3)}{\varepsilon_2\varepsilon_3 M_W(6)}MI_W^{(1)} + \frac{M_W(5)}{\varepsilon_3 M_W(6)}MI_W^{(2)} + MI_W^{(3)}$$

$$PMI_P^{2\to6} = \frac{M_W(3)}{\varepsilon_2\varepsilon_3 M_W(6)}MI_P^{(1)} + \frac{M_W(5)}{\varepsilon_3 M_W(6)}MI_P^{(2)} + MI_P^{(3)}$$

$$PMI^{2\to6} = PMI_R^{2\to6} + PMI_W^{2\to6} + PMI_P^{2\to6}$$

As shown by this analysis (Table 4), the global mass intensities were 336.44 for **6a** and 409.84 for **6b**, PMI_R accounting for only 8% in both cases (Fig. 8).

Synthesis of the sugar moiety

The first step in this sequence was Lubineau's reaction[10] involving a Knoevenagel condensation[34] between the unprotected D-glucose and pentanedione in an aqueous medium. This quantitative reaction, whose by-products are sodium acetate, CO_2 and H_2O, has an atom economy of 60%. Using more concentrated conditions with respect to the original process, and optimizing the workup, we obtained a mass intensity of 24.52 (Fig. 9).

We recently described[35] a modification of the original synthesis of the bromo derivatives **8**[36] by using L-proline and Br_2 in EtOH. We envisaged replacing bromine, a reagent with acute toxicity (categories 1, 2, 3), by polymer-bound pyridinium tribromide, whose toxicity is lower. Although the use of the supported-reactive allowed avoiding treatment with sodium bisulfite since the brominating agent was removed from the medium by simple filtration, MI_W was higher mainly due to the volume of ethanol required to wash the resin (Table 5).

The recovery of compound **8** in a pure form was crucial for the success of the next synthetic step. Unfortunately, using both methods, chromatography was necessary to isolate **8**

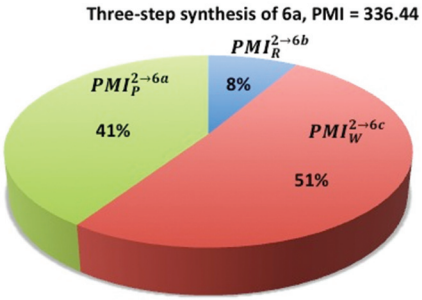


Fig. 8 Composition by mass of the material used for the synthesis of **6a** (g $g_{product}^{-1}$) for the reaction (PMI_R), the workup (PMI_W) and the purification (PMI_P). For **6b** see ESI.†

since it could not be purified by other techniques. This led to a very high mass intensity (Table 5 and Fig. 10), which was lower with method B, therefore the latter method was adopted for the total synthesis.

Evaluation of whole sequences for the syntheses of 8

The global atom economy of the synthesis of **8** from D-glucose was 57% and the global yield was 54%. The PMI were calcu-

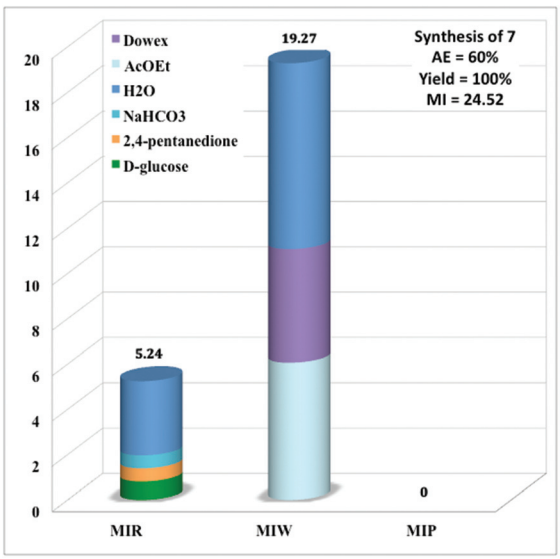


Fig. 9 Amount and nature of reactants and auxiliaries for the synthesis of **7** (g $g_{product}^{-1}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P).

Table 4 Yields and green metrics for each step of the synthesis of **6a** and **6b** and for the whole sequence

Step	2 → 3	3 → 5a	3 → 5b	5a → 6a	5b → 6b	2 → 6a	2 → 6b
AE (%)	44	94	94	85	86	49	52
Yield (%)	82	84	71	65	64	45	37
MI_R	6.18	3.90	4.33	18.38	23.49	28.48	34.87
MI_W	8.16	54.60	57.69	81.96	82.72	171.21	178.91
MI_P	4.96	11.72	49.52	113.97	116.01	136.75	196.05
MI	19.31	70.23	111.55	214.32	222.23	336.44	409.84
E	18.31	69.23	110.55	213.32	221.23	335.44	408.84

Table 5 Comparison of isolated yields and mass intensities for the synthesis of **8** using Br_2 (method A) or polymer-bound pyridinium tribromide (method B)

Method	Yield (%)	MI_R	MI_W	MI_P	MI
A (Br_2)	61	13.11	5.03	1775.19	1793.34
B (polymer bound reagent)	54	16.11	19.76	1190.70	1226.57

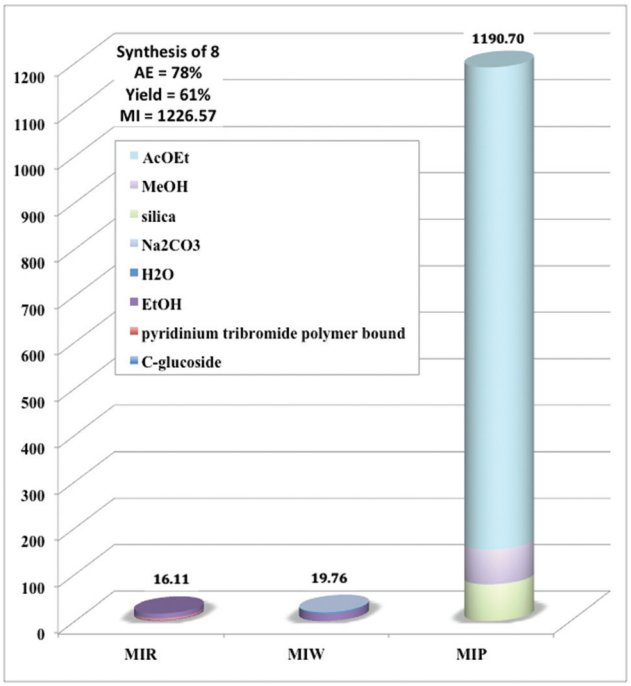


Fig. 10 Amount and nature of reactants and auxiliaries for the synthesis of **8** (g $g_{product}^{-1}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P).

lated from the molecular weights M_W, the yields of the second step (ε'_2) and the mass intensities $M^{(1)}$ and $M^{(2)}$ of the two steps:

$$PMI_R^{glc\rightarrow 8} = \frac{M_W(7)}{\varepsilon'_2 M_W(8)}\left(MI_R^{(1')} - 1\right) + MI_R^{(2')}$$

$$PMI_W^{glc\rightarrow 8} = \frac{M_W(7)}{\varepsilon'_2 M_W(8)} MI_W^{(1')} + MI_W^{(2')}$$

$$PMI_P^{glc\rightarrow 8} = \frac{M_W(7)}{\varepsilon'_2 M_W(8)} MI_P^{(1')} + MI_P^{(2')}$$

$$PMI^{glc\rightarrow 8} = PMI_R^{glc\rightarrow 8} + PMI_W^{glc\rightarrow 8} + PMI_P^{glc\rightarrow 8}$$

As expected from the large value of MI_P for the bromination step, the PMI for the two-step synthesis of **8** from D-glucose was very high (1258.36) with most of the mass used for the purification in the second step, showing that chromatography should be avoided if possible. This high value should nevertheless be lowered by recycling the solvent used for the chromatography but to the detriment of higher energy expenditure (Fig. 11).

Synthesis of the triazole-linked *C*-glycosyl flavonoids 1a and 1b

PEG_{2000} proved to be an excellent solvent for carrying out, in a one-pot procedure, the nucleophilic substitution of bromine derivatives by sodium azide and the copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition.[35] We applied this method for the synthesis of triazole-linked flavonoid-sugars **1a** and **1b** (Fig. 1, R = H or OMe respectively). CuI or the $CuSO_4$/Na ascorbate catalytic system was investigated as the Cu(I) source (Table 6).

The two catalyst systems have been found effective in this transformation, the $CuSO_4$/Na ascorbate system giving slightly better results in terms of yield but also lower mass intensities. As in most of the preceding steps, the major part of the mass required for the preparation of **1a** or **1b** was not used for carrying out the reaction but for treatment. This was achieved by simple operations of precipitation and washings and afforded pure **1a** or **1b** without the need of further purification, allowing for $MI_P = 0$ in all cases (Table 6).

Evaluation of whole sequences for the syntheses of 1a and 1b

1a and **1b** were obtained from D-glucose and 2′,4′-dihydroxyacetophenone *via* convergent syntheses with two parallel sequences and one point of convergence. The global atom economies (GAE), the global reaction mass efficiencies (GRME), *i.e.* the percentage of the mass of the reactants that

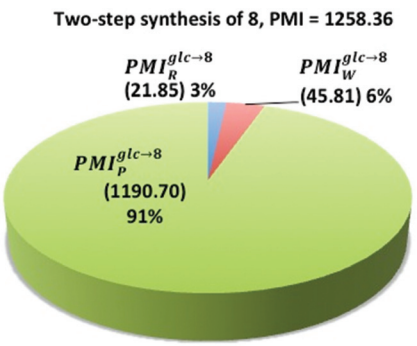


Fig. 11 Composition by mass of the material used for the synthesis of **8** (g $g_{product}^{-1}$) for the reaction (PMI_R), the workup (PMI_W) and the purification (PMI_P).

Table 6 Yields and mass intensities for the one pot S_N-CuAAC between **8** and **6a** or **6b** using $CuSO_4$/NaAsc or CuI as catalysts in PEG_{2000}–H_2O (3.3/1) at 60 °C

Flavonol	Catalyst	Yield (%)	MI_R	MI_W	MI_P	MI
6a	$CuSO_4$–NaAsc	91	5.87	202.72	0	208.60
	CuI	88	6.30	210.23	0	216.53
6b	$CuSO_4$–NaAsc	90	5.94	212.86	0	218.80
	CuI	85	6.38	224.06	0	230.45

remains in the product taking into account the experimental conditions (excess of reagents and yields), and the global mass intensities (PMI^{TS}) were calculated using a previously described algorithm[14] (Table 7). Furthermore, we also calculated the PMI for the reactions (PMI_R^{TS}), the workups (PMI_W^{TS}) and the purifications (PMI_P^{TS}) using the following equations:

$$PMI_R^{TS} = \frac{m_8}{m_1}(PMI_R^{(glc\rightarrow 8)} - 1) + \frac{m_6}{m_1}(PMI_R^{(2\rightarrow 6)} - 1) + PMI_R^{(6+8\rightarrow 1)}$$

$$PMI_W^{TS} = \frac{m_8}{m_1}PMI_W^{(glc\rightarrow 8)} + \frac{m_6}{m_1}PMI_W^{(2\rightarrow 6)} + PMI_W^{(6+8\rightarrow 1)}$$

$$PMI_P^{TS} = \frac{m_8}{m_1}PMI_P^{(glc\rightarrow 8)} + \frac{m_6}{m_1}PMI_P^{(2\rightarrow 6)} + PMI_P^{(6+8\rightarrow 1)}$$

m_6 and m_8 are the masses of **6a** or **6b** and **8** used in the final step to get a mass m_1 of **1a** or **1b**.

GRME and GME are directly proportional to the atom economy, so that the choice of high atom economy reactions is of high importance. In the case of the total syntheses of **1a** and **1b**, AE is, in particular, impacted by the choice of propargyl tosylate as the reactant in the first step of the preparation of **8** (AE = 44%), choosing a reagent leading to improved atom economy could be done to the detriment of toxicology considerations. The yield of the reactions and the excess of the reactants greatly affect GRME and GME. This latter metric is also very dependent on auxiliaries used (solvents, aqueous phases for washing, chromatography supports, drying agents, *etc.*). For the synthesis of triazole-linked flavonoid-sugars, the values of GRME indicate that 18 and 14% of the reactant mass ends up in the final products **1a** and **1b** respectively. When the process is considered as a whole, only 0.083 (**1a**) and 0.066% (**1b**) of the total mass used is incorporated into the product as indicated by the GME values. The total mass (PMI^{TS}) is used to (i) implement the reactions (PMI_R^{TS}, 3%), (ii) carry out the workup (PMI_W^{TS}, 44%) and (iii) purify the compounds (PMI_P^{TS}, 48%).

Table 7 Yields and green metrics for the total syntheses of **1a** and **1b**

Product	**1a**	**1b**
GAE (%)	47	48
Yield from D-glucose (%)	45	32
Yield from **2** (%)	41	33
GRME (%)	18	14
PMI_R^{TS} (% of MI^{TS})	35.46 (3%)	44.54 (3%)
PMI_W^{TS} (% of MI^{TS})	333.70 (28%)	363.38 (24%)
PMI_P^{TS} (% of MI^{TS})	836.93 (69%)	1111.55 (73%)
PMI^{TS}	1206.10[a]	1519.48[a]
GME (= $1/PMI^{TS}$) (%)	0.083	0.066

[a] PMI^{TS} values were systematically calculated according to the method previously described[14] or by addition of PMI_R^{TS}, PMI_W^{TS}, and PMI_P^{TS}. Both methods gave strictly the same results allowing the checking of the data.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers. Chemical shifts (δ) in ppm, are given relative to tetramethylsilane for ^1H NMR and relative to the CD_3OD or d_6-DMSO resonances at 49.00 and 39.52 ppm, respectively for ^{13}C NMR. Signals were assigned on the basis of ^1H–^1H COSY, HSQC and HMBC experiments. HRMS spectra were recorded in positive or negative mode with a microtof-QII spectrometer (Bruker) using electrospray ionization. IR spectra were recorded on an FT/IR Jasco 4100 equipped with diamond ATR. Elemental analyses were performed at the service central de microanalyses du CNRS at Gif-sur-Yvette, France.

2′-Hydroxy-4′-propargyloxyacetophenone (3)

2′,4′-Dihydroxyacetophenone (10.551 g, 69.34 mmol) was dissolved in PEG_{250} (35 mL) and heated at 60 °C. K_2CO_3 in the powder form (5.751 g, 41.61 mmol) was slowly added and the mixture was stirred for 15 min. Propargyl *p*-toluenesulfonate (12.0 mL, 69.34 mmol) was added and the mixture was stirred at 60 °C for 2 days. Water (70 mL) and HCl 37% (7 mL) were added and the crude product precipitated upon cooling. The product was collected by filtration and washed with water (10 mL). The crude product was recrystallized with ethanol 96% (31 mL). Crystals were collected by filtration and washed with cold ethanol 96% (20 mL). The filtrate was concentrated and a second recrystallization with ethanol 96% (7.0 mL) afforded crystals that were collected by filtration and washed with cold ethanol 96% (10 mL). The two crops afforded **3** as white needles (10.816 g, 56.9 mmol, 82%); m.p. 71–73 °C, EtOH 96% (lit. 102–103 °C, EtOH;[21] 65 °C, ligroin;[22a] 71.2–71.5 °C, AcOEt).[22h] Spectral data were in accordance with those previously reported. Elemental analysis: calculated for $C_{11}H_{10}O_3$: C 69.46%, H 5.30%, O 25.24%. Found: C 69.40%, H 5.28%, O 25.28%.

General procedure for synthesis of chalcone–flavanone 5, 5′

Acetic acid (1.5 mL, 26.2 mmol) was added to pyrrolidine (2.15 mL, 26.2 mmol) cooled with a bath of ice and water. After a few minutes, the mixture was warmed at 30 °C. Then, compound **3** finely ground (997.7 mg, 5.25 mmol) and hydroxybenzaldehyde (4-hydroxybenzaldehyde (**4a**) or vanillin (**4b**) (5.25 mmol)) were added. The mixture was stirred at 30 °C for 2 h (**4a**) or 6 h (**4b**).

2′,4-Dihydroxy-4′-propargyloxychalcone (5a) and 4′-hydroxy-7-propargyloxyflavanone (5′a). After cooling at r.t., ethyl acetate (20 mL) and a solution of NaCl 12% (12 mL) were added. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with $NaCl_{sat}$ (15 mL), $NaHSO_{3sat}$ (15 mL, vigorous stirring for 4 h) and $NaCl_{sat}$ (15 mL). The organic layer was dried over $MgSO_4$ (3 g) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (cyclohexane–acetone 8 : 2 then 7 : 3) to give **5a–5′a** (1.0 : 0.5) as a solid (1.30 g, 84%) or by crystallization: after dissolution in hot ethanol 96% (3.5 mL), water (2 mL) was added and the mixture **5a–5′a** precipitated upon

cooling. The product was collected by filtration and washed with cold ethanol 96% (5 mL). The filtrate was concentrated and a second precipitation with ethanol 96% (2.0 ml) and water (1 mL) afforded a product that was collected by filtration and washed with cold ethanol 96% (5 mL). The two crops afforded **5a–5′a** as a solid (1.30 g, 84%); ν_{max} (neat)/cm^{-1} 1671 ($\nu_{C=O}$), 3208 (ν_{OH}), 3288 ($\nu_{\equiv C-H}$); δ_H (360 MHz, d$_6$-DMSO), **5a:** 3.65 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 4.92 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–C*H*$_2$), 6.56 (d, $J_{3',5'}$ = 2.5 Hz, 1 H, H-3′), 6.60 (dd, $J_{3',5'}$ = 2.5 Hz, $J_{5',6'}$ = 9.0 Hz, 1 H, H-5′), 6.84 (d, $J_{2,3}$ = $J_{5,6}$ = 9.0 Hz, 2 H, H-3 and H-5), 7.77 (d, $J_{2,3}$ = $J_{5,6}$ = 9.0 Hz, 2 H, H-2 and H-6), 7.77 (d, $J_{\alpha,\beta}$ = 15.5 Hz, 1 H, H-α), 7.81 (d, $J_{\alpha,\beta}$ = 15.5 Hz, 1 H, H-β), 8.27 (d, $J_{5',6'}$ = 9.0 Hz, 1 H, H-6′); **5′a:** 2.67 (dd, $J_{2,3a}$ = 3.0 Hz, $J_{3a,3b}$ = 17.0 Hz, 1 H, H-3a), 3.20 (dd, $J_{2,3b}$ = 13.0 Hz, $J_{3a,3b}$ = 17.0 Hz, 1 H, H-3b), 3.62 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 4.88 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–C*H*$_2$), 5.51 (dd, $J_{2,3a}$ = 3.0 Hz, $J_{2,3b}$ = 13.0 Hz, 1 H, H-2), 6.65 (d, $J_{6,8}$ = 2.5 Hz, 1 H, H-8), 6.69 (dd, $J_{6,8}$ = 2.5 Hz, $J_{5,6}$ = 8.5 Hz, 1 H, H-6), 6.80 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8.5 Hz, 2 H, H-3′ and H-5′), 7.34 (d, $J_{2',3'}$ = $J_{3',5'}$ = 8.5 Hz, 2 H, H-2′ and H-6′), 7.73 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-5); δ_C (90.6 MHz, d$_6$-DMSO), **5a:** 55.9 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 78.8 (H*C*≡C), 102.0 (C-3′), 107.6 (C-5′), 114.4 (C-1′), 115.9 (C-3 and C-5), 117.3 (C-α), 125.7 (C-1), 131.4 (C-2 and C-6), 132.4 (C-6′), 145.0 (C-β), 160.5 (C-4), 163.5 (C-4′), 165.3 (C-2′), 192.0 (C=O); **5′a:** 43.1 (C-3), 55.9 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 78.8 (H*C*≡C), 79.3 (C-2), 102.0 (C-8), 110.2 (C-6), 114.9 (C-10), 115.2 (C-3′ and C-5′), 128.0 (C-5), 128.3 (C-2′ and C-6′), 129.1 (C-1′), 157.7 (C-4′), 163.0 (C-9), 163.4 (C-7), 190.4 (C-4); HRMS (ESI): calculated for $[C_{18}H_{14}O_4 + H]^+$: 295.0965. Found: 295.0950. Calculated for $[C_{18}H_{14}O_4 + Na]^+$: 317.0784. Found: 317.0767.

4-Hydroxy-3-methoxy-4′-propargyloxychalcone (5b) and 4′-hydroxy-3′-methoxy-7-propargyloxyflavanone (5′b). After cooling at r.t., ethyl acetate (10 mL), acetone (10 mL) and a solution of NaCl 12% (12 mL) were added. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with $NaCl_{sat}$ (15 mL), $NaHSO_{3sat}$ (15 mL, vigorous stirring for 4 h) and $NaCl_{sat}$ (15 mL). The organic layer was dried over $MgSO_4$ (3 g) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (cyclohexane–acetone 8 : 2 then 7 : 3) to give **5b–5′b** (1.0 : 0.4) as a yellow solid (1.36 g, 80%) or by recrystallization: the crude product was dissolved in hot ethanol 96% (59 mL) and the mixture **5b–5′b** precipitated upon cooling. The product was collected by filtration and washed with cold ethanol 96% (5 mL). The filtrate was concentrated and a second precipitation with ethanol 96% (5.4 mL) and water (1 mL) afforded a product that was collected by filtration and washed with cold ethanol 96% (5 mL). The two crops afforded **5b–5′b** as crystals (1.21 g, 71%); ν_{max} (neat)/cm^{-1} 1604 ($\nu_{C=O}$), 1661 ($\nu_{C=O}$), 3276 ($\nu_{\equiv C-H}$); δ_H (360 MHz, d$_6$-DMSO), **5b:** 3.66 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 3.88 (s, 3 H, 3-OC*H*$_3$), 4.92 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–C*H*$_2$), 6.57 (d, $J_{3',5'}$ = 2.5 Hz, 1 H, H-3′), 6.61 (dd, $J_{3',5'}$ = 2.5 Hz, $J_{5',6'}$ = 9.0 Hz, 1 H, H-5′), 6.84 (d, $J_{5,6}$ = 8.0 Hz, 1 H, H-5), 7.31 (dd, $J_{2,6}$ = 2.0 Hz, $J_{5,6}$ = 8.0 Hz, 1 H, H-6), 7.55 (d, $J_{2,6}$ = 2.0 Hz, 1 H, H-2), 7.77 (d, $J_{\alpha,\beta}$ = 15.0 Hz, 1 H, H-α), 7.83 (d, $J_{\alpha,\beta}$ = 15.0 Hz, 1 H, H-β), 8.31 (d, $J_{5',6'}$ = 9.0 Hz, 1 H, H-6′), 9.75 (s, 1 H, 4-OH), 13.62 (s, 1 H, 2′-OH); **5′b:** 2.68 (dd, $J_{2,3a}$ = 3.0 Hz, $J_{3a,3b}$ = 17.0 Hz, 1 H, H-3a), 3.25 (dd, $J_{2,3b}$ = 13.0 Hz, $J_{3a,3b}$ = 17.0 Hz, 1 H, H-3b), 3.63 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 3.79 (s, 3 H, 3′-OC*H*$_3$), 4.89 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–C*H*$_2$), 5.50 (dd, $J_{2,3a}$ = 3.0 Hz, $J_{2,3b}$ = 13.0 Hz, 1 H, H-2), 6.67 (d, $J_{6,8}$ = 2.5 Hz, 1 H, H-8), 6.69 (dd, $J_{6,8}$ = 2.5 Hz, $J_{5,6}$ = 8.5 Hz, 1 H, H-6), 6.80 (d, $J_{5',6'}$ = 8.0 Hz, 1 H, H-5′), 6.93 (dd, $J_{2',6'}$ = 2.0 Hz, $J_{5',6'}$ = 8.0 Hz, 1 H, H-6′), 7.13 (d, $J_{2',6'}$ = 2.0 Hz, 1 H, H-2′), 7.73 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-5), 9.11 (s, 4′-OH); δ_C (90.6 MHz, d$_6$-DMSO); **5b:** 55.86 (3-OC*H*$_3$), 55.92 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 78.9 (H*C*≡C), 102.0 (C-3′), 107.6 (C-5′), 111.8 (C-2), 114.3 (C-1′), 115.6 (C-5), 117.4 (C-α), 124.8 (C-6), 126.1 (C-1), 132.5 (C-6′), 145.4 (C-β), 148.1 (C-3), 150.2 (C-4), 163.5 (C-4′), 165.4 (C-2′), 192.0 (C=O); **5′b:** 43.2 (C-3), 55.7 (3′-OC*H*$_3$), 55.9 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 78.8 (H*C*≡C), 79.5 (C-2), 102.0 (C-8), 110.3 (C-6), 111.2 (C-2′), 114.9 (C-10), 115.2 (C-5′), 119.7 (C-6′), 128.0 (C-5), 129.6 (C-1′), 146.9 (C-4′), 147.6 (C-3′), 163.0 (C-9), 163.4 (C-7), 190.4 (C-4); HRMS (ESI): calculated for $[C_{19}H_{16}O_5 + H]^+$: 325.1071. Found: 325.1071. Calculated for: $[C_{19}H_{16}O_5 + Na]^+$: 347.0890. Found: 347.0887; Elemental analysis: calculated for $C_{19}H_{16}O_5$: C 70.36%, H 4.97%, O 24.66%. Found: C 70.14%, H 5.08%, O 24.84%.

4′-Hydroxy-7-propargyloxyflavonol 6a. 8 M NaOH (3.78 mL, 30.2 mmol) was added to compounds **5a–5′a** (500 mg, 1.69 mmol). Then, H_2O_2 30% (870 μL, 8.52 mmol) was slowly added and the reaction mixture was stirred at r.t. for 25 min, the mixture was then cooled in an ice bath and HCl 37% (2.5 mL) mixed with crushed ice (5 mL) was slowly added. After precipitation, the mixture was filtered and washed with water (20 mL). The crude product was vigorously stirred with a solution of 1 M $NaHCO_3$ (10 mL). The mixture was centrifuged (5000 rpm, 15 min) and the supernatant removed. The solid was again vigorously stirred with a solution of 1 M $NaHCO_3$ (8 mL) and then centrifuged (5000 rpm, 15 min). The supernatant was removed and the precipitate was suspended in water (20 mL) and filtered and dried in a desiccator to give **6a** as a solid (341 mg, 65%); ν_{max} (neat)/cm^{-1} 1592 ($\nu_{C=O}$), 3273 ($\nu_{\equiv C-H}$), 3402 (ν_{OH}), 3488 ($\nu_{H\text{-bonded OH}}$); δ_H (360 MHz, d$_6$-DMSO) 3.67 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 4.99 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–C*H*$_2$), 6.94 (d, $J_{2',3'}$ = $J_{5',6'}$ = 9.0 Hz, 2 H, H-3′ and H-5′), 7.07 (dd, $J_{6,8}$ = 2.0 Hz, $J_{5,6}$ = 9.0 Hz, 1 H, H-6), 7.31 (d, $J_{6,8}$ = 2.0 Hz, 1 H, H-8), 8.01 (d, $J_{5,6}$ = 9.0 Hz, 1 H, H-5), 8.08 (d, $J_{2',3'}$ = $J_{5',6'}$ = 9.0 Hz, 2 H, H-2′ and H-6′), 9.21 (s, 1 H, 3-O*H*), 10.04 (s, 1 H, 4′-O*H*); δ_C (90.6 MHz, d$_6$-DMSO) 56.2 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 79.0 (H*C*≡C), 101.5 (C-8), 114.6 (C-6), 115.5 (C-3′ and C-5′), 115.7 (C-10), 122.1 (C-1′), 126.2 (C-5), 129.3 (C-2′ and C-6′), 137.5 (C-3), 145.6 (C-2), 156.0 (C-9), 159.0 (C-4′), 161.2 (C-7), 172.0 (C-4); HRMS (ESI): calculated for $[C_{18}H_{12}O_5 + H]^+$: 309.0757. Found: 309.0750. Calculated for: $[C_{18}H_{12}O_5 + Na]^+$: 331.0577. Found: 331.0566.

4′-Hydroxy-3′-methoxy-7-propargyloxyflavonol 6b. 5 M NaOH (5.5 mL, 27.5 mmol) was added to compounds **5b–5′b** (500 mg, 1.54 mmol). Then, H_2O_2 30% (790 μL, 7.73 mmol)

was slowly added and the reaction mixture was stirred at r.t. for 1.25 hours, the mixture was then cooled in an ice bath and HCl 37% (2.3 mL) mixed with crushed ice (5 mL) was slowly added. After precipitation, the mixture was filtered and washed with water (20 mL). The crude product was vigorously stirred with a solution of 1 M $NaHCO_3$ (10 mL). The mixture was centrifuged (5000 rpm, 15 min) and the supernatant removed. The solid was again vigorously stirred with a solution of 1 M $NaHCO_3$ (8 mL) and then centrifuged (5000 rpm, 15 min). The supernatant was removed and the precipitate was suspended in water (20 mL) and filtered and dried in a desiccator to give **6b** as a solid (335 mg, 64%); ν_{max} (neat)/cm^{-1} 1601 ($\nu_{C=O}$), 3289 ($\nu_{\equiv C-H}$), 3490 ($\nu_{H\text{-bonded OH}}$); δ_H (360 MHz, d_6-DMSO) 3.70 (t, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 1 H, *H*C≡C), 3.86 (s, 3 H, 3′-OCH_3), 4.99 (d, $J_{HC\equiv C,HC\equiv C-CH_2}$ = 2.5 Hz, 2 H, HC≡C–CH_2), 6.95 (d, $J_{5',6'}$ = 8.5 Hz, 1 H, H-5′), 7.08 (dd, $J_{6,8}$ = 2.5 Hz, $J_{5,6}$ = 9.0 Hz, 1 H, H-6), 7.35 (d, $J_{6,8}$ = 2.5 Hz, 1 H, H-8), 7.73 (dd, $J_{2',6'}$ = 2.0 Hz, $J_{5',6'}$ = 8.5 Hz, 1 H, H-6′), 7.80 (d, $J_{2',6'}$ = 2.0 Hz, 1 H, H-2′), 8.00 (d, $J_{5,6}$ = 9.0 Hz, 1 H, H-5), 9.30 (s, 1 H, 3-O*H*), 9.71 (s, 1 H, 4′-O*H*); δ_C (90.6 MHz, d_6-DMSO) 55.9 (3′-O*C*H$_3$), 56.3 (HC≡C–*C*H$_2$), 78.5 (HC≡*C*), 79.0 (H*C*≡C), 101.6 (C-8), 111.8 (C-2′), 114.6 (C-6), 115.6 (C-10), 115.7 (C-5′), 121.5 (C-6′), 122.4 (C-1′), 126.2 (C-5), 137.6 (C3), 145.4 (C-2), 147.4 (C-3′), 148.6 (C-4′), 155.9 (C-9), 161.2 (C-7), 171.9 (C-4); HRMS (ESI): calculated for $[C_{19}H_{14}O_6 + H]^+$: 339.0863. Found: 339.0850. Calculated for: $[C_{19}H_{14}O_6 + Na]^+$: 361.0683. Found: 361.0670.

3′-(β-D-Glucopyranosyl)-2′-propanone (7). Prepared as previously described,[10] the volumes of solvents were optimized: a solution of D-glucose (2.50 g, 13.87 mmol), 2,4-pentanedione (1.75 g, 17.52 mmol), and $NaHCO_3$ (1.75 g, 20.83 mmol) in water (10 mL) was refluxed overnight, then cooled to r.t. and treated with Dowex 50 X-8 200 H^+ to reach pH 5 (15.30 g). The resin was filtered, rinsed with H_2O (25 mL) and the aqueous solution was washed with AcOEt (20 mL) and concentrated to afford 7 (3.05 g, 100%). Data were in accordance with those previously described.[10]

1′-Bromo-3′-(β-D-glucopyranosyl)-2′-propanone (8). To a solution of 7 (2.00 g, 9.08 mmol) in ethanol (20.2 mL) was added pyridinium tribromide polymer-bound (5.905 g, 11.81 mmol) and the mixture was stirred on an orbital shaker at r.t. for 2 h. The resin was filtered and washed with ethanol (3 × 10 mL). Water (1 mL) was added to the filtrate and the mixture was stirred for 15 min. A solution of Na_2CO_3 (1.4 M) was slowly added until pH = 6 (3.9 mL). The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica = 116 g, AcOEt–MeOH 9.5 : 0.5 (800 mL) then 9 : 1 (1 L)) affording compound **8** as a white solid (1.480 g, 4.95 mmol, 54%). Data were in accordance with those previously described.[35,36]

General procedure for triazole-linked *C*-glycosyl flavonoid synthesis

1′-Bromo-3′-(β-D-glucopyranosyl)-2′-propanone (7) was dissolved in molten PEG_{2000} (2.0 g $mmol^{-1}$ of flavonoid) at 60 °C. After dissolution, sodium azide, water (0.29 mL $mmol^{-1}$ of flavonoid), the source of Cu(I) ($CuSO_4{\cdot}5H_2O$ 0.05 eq. and sodium ascorbate 0.1 eq.; CuI 0.05 eq.) and flavonoid were added and the mixture was stirred at 60 °C overnight. The reaction mixture was then dissolved in water, acidified with 1 M HCl (pH ∼ 3.5) and kept in the fridge for one day. The solution was filtered through a PVDF membrane (0.45 μm) and the precipitate was washed with water and dried in a desiccator.

Triazole-linked *C*-glycosyl flavonoid 1a. From **6a** (50.0 mg, 0.162 mmol), **8** (53.3 mg, 0.178 mmol), NaN_3 (12.1 mg, 0.186 mmol) and $CuSO_4{\cdot}5H_2O$ (2 mg, 8 μmol) and Asc·Na (3.2 mg, 16.2 μmol) as a solid (84 mg, 91%) or CuI (1.5 mg, 8 μmol) (81 mg, 88%); ν_{max} (neat)/cm^{-1} 1604 ($\nu_{C=O}$), 1730 ($\nu_{C=O}$), 3260 (ν_{OH}), 3485 ($\nu_{H\text{-bonded OH}}$); δ_H (400 MHz, d_6-DMSO) 2.63 (dd, $J_{1'',1'''a}$ = 9.0 Hz, $J_{1'''a,1'''b}$ = 15.5 Hz, 1 H, H-1‴a), 2.89 (dd, $J_{1'',1'''b}$ = 3.5 Hz, $J_{1'''a,1'''b}$ = 15.5 Hz, 1 H, H-1‴b), 2.95 (m, 1 H, H-2″), 3.03–3.21 (m, 3 H, H-3″, H-4″, H-5″), 3.42 (m, 1 H, H-6″a), 3.54 (td, $J_{1'',1'''b}$ = 3.5 Hz, $J_{1'',2''}$ = $J_{1'',1'''a}$ = 9.0 Hz, 1 H, H-1″), 3.68 (m, 1 H, H-6″b), 4.46 (t, $J_{6''a,6''\text{-}OH}$ = $J_{6''b,6''\text{-}OH}$ = 5.0 Hz, 1 H, 6″-O*H*), 4.90 (d, $J_{4'',4''\text{-}OH}$ = 4.5 Hz, 1 H, 4″-O*H*), 4.95 (d, $J_{3'',3''\text{-}OH}$ = 3.5 Hz, 1 H, 3″-O*H*), 5.17 (d, $J_{2'',2''\text{-}OH}$ = 5.0 Hz, 1 H, 2″-O*H*), 5.35 (s, 2 H, H-6‴), 5.56 (s, 2 H, H-3‴), 6.95 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8.5 Hz, 2 H, H-3′ and H-5′), 7.09 (dd, $J_{6,8}$ = 2.0 Hz, $J_{5,6}$ = 9.0 Hz, 1 H, H-6), 7.44 (d, $J_{6,8}$ = 2.0 Hz, 1 H, H-8), 7.99 (d, $J_{5,6}$ = 9.0 Hz, 1 H, H-5), 8.09 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8.5 Hz, 2 H, H-2′ and H-6′), 8.14 (s, 1 H, H-4‴), 9.17 (s, 1 H, 3-O*H*), 10.04 (s, 1 H, 4′-O*H*); δ_C (100.6 MHz, d_6-DMSO) 43.2 (C-1‴), 58.6 (C-3‴), 61.3 (C-6″), 61.8 (C-6‴), 70.4 (C-4″), 73.8 (C-2″), 75.8 (C-1″), 77.9 (C-3″), 80.9 (C-5″), 101.2 (C-8), 114.8 (C-6), 115.4 (C-3′ and C-5′ and C-10), 122.1 (C-1′), 126.1 (C-5), 126.2 (C-4‴), 129.3 (C-2′ and C-6′), 137.5 (C-3), 141.8 (C-5‴), 145.5 (C-2), 156.2 (C-9), 158.9 (C-4′), 162.1 (C-7), 172.0 (C-4), 201.6 (C-2‴); HRMS (ESI): calculated for $[C_{27}H_{27}N_3O_{11} + H]^+$: 570.1718. Found: 570.1718. Calculated for $[C_{27}H_{27}N_3O_{11} + Na]^+$: 592.1538. Found: 592.1545; $[\alpha]_D^{24}$ = −10.9 (*c* = 0.25, DMSO).

Triazole-linked *C*-glycosyl flavonoid 1b. From **6b** (50.3 mg, 0.149 mmol), **8** (66.4 mg, 0.222 mmol), NaN_3 (15.0 mg, 0.231 mmol) and $CuSO_4{\cdot}5H_2O$ (1.8 mg, 7.3 μmol)–NaAsc (2.9 mg, 14 μmol) as a solid (80 mg, 90%) or from **6b** (50.2 mg, 0.148 mmol), **8** (77.6 mg, 0.259 mmol), NaN_3 (17.2 mg, 0.265 mmol) and CuI (1.4 mg, 7.4 μmol) (76 mg, 85%); ν_{max} (neat)/cm^{-1} 1596 ($\nu_{C=O}$), 1732 ($\nu_{C=O}$), 3279 (ν_{OH}); δ_H (400 MHz, d_6-DMSO) 2.63 (dd, $J_{1'',1'''a}$ = 9.0 Hz, $J_{1'''a,1'''b}$ = 15.5 Hz, 1 H, H-1‴a), 2.89 (dd, $J_{1'',1'''b}$ = 3.5 Hz, $J_{1'''a,1'''b}$ = 15.5 Hz, 1 H, H-1‴b), 2.95 (m, 1 H, H-2″), 3.03–3.20 (m, 3 H, H-3″, H-4″, H-5″), 3.42 (m, 1 H, H-6″a), 3.53 (td, $J_{1'',1'''b}$ = 3.5 Hz, $J_{1'',2''}$ = $J_{1'',1'''a}$ = 9.0 Hz, 1 H, H-1″), 3.68 (m, 1 H, H-6″b), 3.87 (s, 3 H, 3′-OCH_3), 4.45 (t, $J_{6''a,6''\text{-}OH}$ = $J_{6''b,6''\text{-}OH}$ = 5.0 Hz, 1 H, 6″-O*H*), 4.89 (d, $J_{4'',4''\text{-}OH}$ = 4.0 Hz, 1 H, 4″-O*H*), 4.94 (d, $J_{3'',3''\text{-}OH}$ = 3.0 Hz, 1 H, 3″-O*H*), 5.16 (d, $J_{2'',2''\text{-}OH}$ = 5.0 Hz, 1 H, 2″-O*H*), 5.35 (s, 2 H, H-6‴), 5.56 (s, 2 H, H-3‴), 6.96 (d, $J_{5',6'}$ = 8.5 Hz, 1 H, H-5′), 7.09 (dd, $J_{6,8}$ = 2.0 Hz, $J_{5,6}$ = 9.0 Hz, 1 H, H-6), 7.48 (d, $J_{6,8}$ = 2.0 Hz, 1 H, H-8), 7.75 (dd, $J_{2',6'}$ = 2.0 Hz, $J_{5',6'}$ = 8.5 Hz, 1 H, H-6′), 7.81 (d, $J_{2',6'}$ = 2.0 Hz, 1 H, H-2′), 7.99 (d, $J_{5,6}$ = 9.0 Hz, 1 H, H-5), 8.14 (s, 1 H, H-4‴), 9.20 (s, 1 H, 3-O*H*), 9.66 (s, 1 H, 4′-O*H*); δ_C 100.6 MHz, d_6-DMSO) 43.2 (C-1‴), 55.9 (3′-O*C*H$_3$), 58.6 (C-3‴), 61.3 (C-6″), 61.8 (C-6‴), 70.4 (C-4″), 73.8 (C-2″), 75.8

(C-1″), 77.9 (C-3″), 80.9 (C-5″), 101.3 (C-8), 111.7 (C-2′), 114.7 (C-6), 115.4 (C-10), 115.6 (C-5′), 121.6 (C-6′), 122.4 (C-1′), 126.1 (C-5), 126.2 (C-4‴), 137.6 (C-3), 141.8 (C-5‴), 145.3 (C-2), 147.4 (C-3′), 148.5 (C-4′), 156.2 (C-9), 162.1 (C-7), 172.0 (C-4), 201.6 (C-2‴); HRMS (ESI): calculated for $[C_{28}H_{29}N_3O_{12} + H]^+$: 600.1824. Found: 600.1822. Calculated for $[C_{28}H_{29}N_3O_{12} + Na]^+$: 622.1643. Found: 622.1626; $[\alpha]_D^{25} = -12.4$ (c = 0.25, DMSO).

Conclusions

We have described the total synthesis of a new class of products without the use of protective groups with overall yield of 41 (**1a**) and 33% (**1b**) from 2′,4′-dihydroxyacetophenone. These syntheses were performed mainly using alternative solvents such as water or PEG, or bio-based solvents, either for the synthesis steps, workup or purification and the least toxic reagents were preferred. Each step was optimized to decrease the mass intensity related to the three operations of the process (reaction, workup and purification). We proposed for the first time such an analysis and a method to calculate these metrics for a linear or convergent synthesis from the values obtained for the individual steps. The analysis revealed that for the synthesis of **1a** and **1b** the biggest part of the material used was dedicated to the workups and purifications, this was particularly dramatic when chromatography was necessary. The nature of the auxiliary substances used for these operations should thus be considered as recently highlighted by Jessop.[37]

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