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Total synthesis of high loading capacity PEG-based supports: evaluation and improvement of the process by use of ultrafiltration and PEG as a solvent†

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The present work deals with the total synthesis of high loading capacity PEG supports with attention focused on improving the greenness of all the steps. The systematic calculation of green metrics offers an opportunity to evaluate the greenness and then to improve the process. To evidence such an improvement, the evaluation of the optimized processes was compared with that of the classical ones.

Introduction

Modern chemical syntheses should be based upon green chemistry principles.[1] First, the optimization of atom economy[2] has to steer the design of chemical modifications. Second, the reaction conditions have to be optimized in order to strongly decrease the waste, expressed by the environmental factor.[3] Third, the use of non-toxic reagents and reaction media has to be preferred.

Solvents constitute the major part of waste, up to 80%,[4] and are often hazardous and toxic. Although in some cases solvent-free processes can be developed,[5] a strong need for organic solvent substitutes still remains. Alternatives include aqueous media,[6] PEGs,[7] ionic liquids[8] or supercritical fluids.[9]

Polyethylene glycols (PEGs) are currently employed as organic polymer soluble supports for both synthesis and catalyst immobilization.[10] Their use as drug vectors has been receiving growing interest in pharmaceutical and biomedical areas.[11] The main advantages of using PEGs are related to their non-toxicity and their solubility properties allowing easy recovery.[12] In particular, we have shown that coupling PEG supported synthesis and ultrafiltration allowed the preparation and purification of various heterocycles without the use of organic solvents.[13] A major drawback of these soluble polymers is the low loading capacities, *i.e.* the number of functional groups per gram of polymer: *e.g.* 1 mmol g^{-1} for PEG_{2000}, 0.58 mmol g^{-1} for PEG_{3400}, and 0.32 mmol g^{-1} for PEG_{6000}. The increase of loading capacity of PEGs through chemical modification to reach values similar to those of the widely used, commercially available, insoluble Merrifield resin (1–4 mmol g^{-1}) or OH-functionalized Wang resin (0.4–2 mmol g^{-1}) has been receiving much attention.[14]

In the present work we describe the synthesis of new high loading capacity branched PEG-based polymers starting from the commercially available pentaerythritol. Our strategy relies on reactions with high or even total atom economy and on the use of green media, such as water or PEG. The impact of the processes was assessed using green metrics:

– The atom economy (AE),[2] which allows one to choose a synthetic pathway that maximizes the incorporation of reagent and substrate atoms in the product. This metric, however, cannot be used to evaluate the material economy of the reaction.

– The reaction mass efficiency (RME, eqn (A)),[15] which is the percentage of the mass of the reactants that remains in the product taking into account the experimental conditions (excess of reagents and yields).

$$\mathrm{RME} = \frac{\text{mass of product}}{\text{mass of reactants}} \qquad (A)$$

– The mass intensity (MI),[15,16] or its counterpart, the global material economy (GME, eqn (B)),[17] that considers all the materials used in the process (extraction, washing, separation, recrystallisation, chromatographic support if not recycled, *etc.*).

$$\mathrm{GME} = \frac{1}{\mathrm{MI}} = \frac{\text{mass of product}}{\text{mass of react.} + \text{auxiliaries}} \qquad (B)$$

We showed[17,18] that, for any synthetic sequence, RME and GME are directly proportional to the atom economy, which

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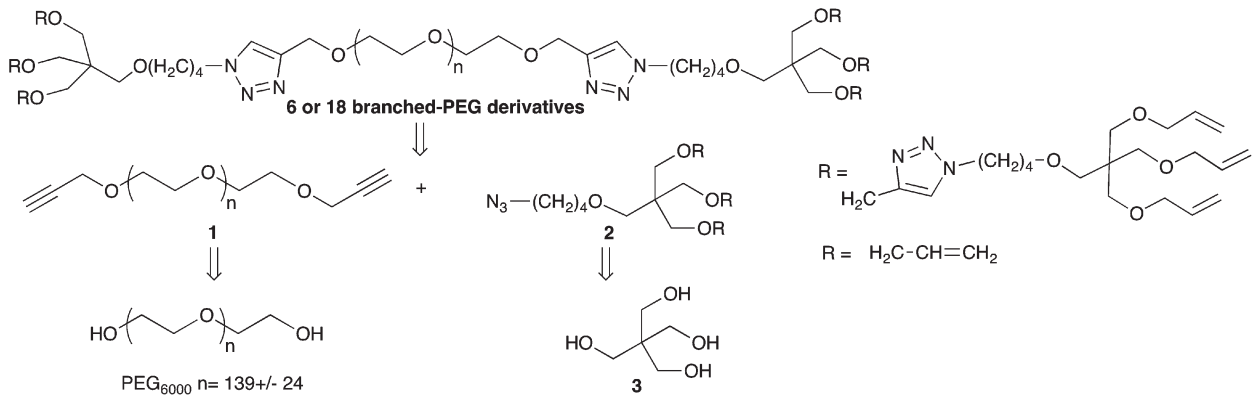


Scheme 1 Retrosynthesis of the targeted PEG derivatives.

means that the choice of high atom economy reactions is crucial. However, it is worth noting that also the yields of the reactions and the excess of the reactants greatly affect RME and, consequently, GME. Moreover, the amounts of the auxiliaries, particularly solvents and chromatographic supports, are very important because they lead to very low GME values. Therefore, from the above-mentioned definitions, it appears that GME < RME < AE. The efficiency of a given reaction is high especially when RME is close or even equal to AE. Similarly, the greenness of a reaction, based on mass economy, is high especially when GME is close to RME and AE.

Besides the above metrics, in the present work we have calculated the very popular Sheldon *E*-factor. There is a simple relationship between the latter metric and MI (eqn (C)).

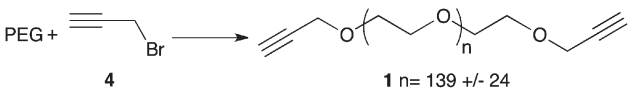
$$E = \frac{\text{mass of waste}}{\text{mass of products}} = \text{MI} - 1 \qquad (C)$$

Strategy

The design of high loading capacity PEGs was based on the copper catalysed 1,3-dipolar azide–alkyne cycloaddition (CuAAC),[19] a 100% atom economy reaction occurring with high yield and selectivity, which are the prerequisites for click chemistry.[20] We chose to prepare dipropargylated PEG **1** from commercially available PEG_{6000} and the azide derivatives **2** starting from pentaerythritol **3** (Scheme 1). This approach was applied to the synthesis of PEGs bearing 6 or 18 functions at their terminal extremities. In the general formula **2**, the R group could be an allyl substituent that allowed the synthesis of 6-branched hydroxy PEG derivatives with 100% atom economy and high yield. On the other hand, for the preparation of 18-branched PEGs, the R group was a three-branched chain obtained *via* CuAAC involving a tripropargylated pentaerythritol derivative.

Synthesis of dipropargylated PEGs 1

The synthesis of low molecular weight bis-alkynylated PEG **1** was previously performed by reacting PEG with propargyl bromide (**4**) in the presence of *t*BuOK in anhydrous THF[21] or toluene.[22] Alternatively, preparations using water as the solvent and NaOH as the base in the presence of tetrabutylammonium hydrogen sulfate were reported.[23] In most cases, the dipropargylated polymers were isolated by chromatography. Applying the anhydrous conditions to PEG_{6000}, we observed the formation of allenes as by-products. Hence, we carried out the alkylation of PEG_{6000} under aqueous conditions using NaOH as the base. At 40 °C, the conversion of PEG was complete after 12 h, as judged by ^{1}H NMR and MALDI TOF analyses, and no chromatography was required since dipropargylated PEG **1** could be isolated using standard precipitation procedures[12] in 96% yield (Scheme 2). However, although the atom economy of the reaction was high (AE = 0.96) and the purification of the product required no chromatography, this efficient preparation using water as the solvent was not fully satisfactory from the standpoint of green chemistry. Indeed, organic solvents, *e.g.* dichloromethane and diethyl ether, were still required for extraction, precipitation, and washing. Therefore, we used ultrafiltration, a membrane process that allows separation of molecules on the basis of their molecular weight, to isolate PEG **1** in similar yield (95%) by forcing the aqueous solution through a regenerated cellulose membrane with a molecular size cutoff of 1000.



Scheme 2 Synthesis of bis-alkynylated PEG **1**.

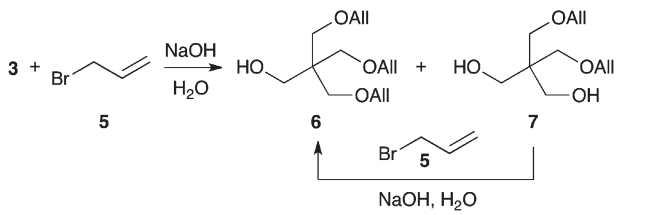
Consequently, the *E* factor was dramatically reduced from 23.5 to 11.7. Moreover, water is the only solvent used in the process. If the amount of water used in the work-up is not included in the calculation of the *E*-factor, as suggested by Sheldon,[24] then the value of *E* falls to 1.3. However, for the ACS Green Chemistry Institute Pharmaceutical Roundtable, water used in chemical and biosynthetic processes must be integrated in the green metrics since it could involve significant capital, energy, and direct environmental impacts.[25]

Synthesis of PEG_{6000} with 6 branches

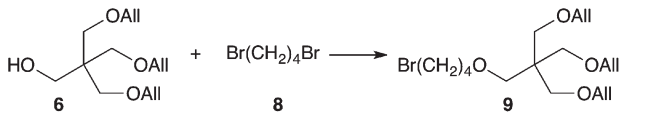
Starting from pentaerythritol **3**, we prepared the triallylated pentaerythritol **6** using aqueous conditions and sodium hydroxide as a base (Scheme 3).[26] Although it is the simplest way to form the ether bond, the atom economy of the reaction is only 0.41, since 3 equivalents of NaBr are produced as waste. The reaction afforded the tri- and di-allylated products **6** and **7** that have to be separated by flash chromatography. We improved the total yield of **6** to 75% by reacting **7** with 2 equivalents of allyl bromide (**5**) under the previously described conditions.[27] The reaction mass efficiency (RME) of the reaction was then raised from 0.18 to 0.22. However, due to the use of an appreciable amount of solvents to convert **7** into **6**, the *E* factor was not greatly affected (without the recovery of compound **7**, $E = 289$; with the recovery of **7** to prepare **6**, $E = 285$).

The next step, the reaction of **6** with dibromobutane **8** (Scheme 4), was first carried out in DMF using NaH as the base. An excess of dibromobutane up to 15 equiv. was required to reach 62% conversion at 60 °C (Table 1, entry 1), but under these conditions **9** was isolated in only 24% yield and compound **10** was formed (30% isolated yield) as a by-product (Fig. 1). Unfortunately, the use of THF as the solvent gave only 19% conversion and 17% isolated yield (Table 1, entry 2). Due to the large excess of dibromobutane, the reaction mass efficiency was low (0.065 in the best case, *i.e.* in DMF). To improve such a metric and to avoid DMF, we investigated aqueous conditions in the presence of NaOH and a lower excess of dibromobutane. We were delighted to observe that the addition of TBAB as a phase transfer catalyst enhanced the yield to 73% (Table 1, entry 4). A by-product identified as compound **11** (Fig. 1) was isolated in 4% yield. Under these conditions RME was greatly improved and consequently the *E* factor was largely reduced (Table 1). It is worth noting that although the change of base from NaH to NaOH always implies a slight decrease of the atom economy, NaOH is more common and cheaper than NaH as a base; moreover, it leads to water as waste while hydrogen is formed when NaH is used.

Various conditions were then tested to prepare the azido derivative **12** (Scheme 5, Table 2). We first carried out the reaction under classical conditions with DMF as the solvent. Using 1.1 equiv. of NaN_3 at 25 °C, we isolated **12** in 91% yield after 24 h and in 98% yield at 60 °C after 12 h. As it has been reported that organic azides could be prepared by microwave-assisted nucleophilic substitution of halogenated compounds in water in the absence of any phase-transfer catalyst,[28] we tried this protocol to prepare **12**. Under these conditions, no conversion of **9** was observed. The addition of 10% TBAB under microwave activation allowed us to obtain **12** in 96% yield on a 0.3 mmol scale. Although the yield and RME were not improved (Table 2), we prefer the second method, which uses H_2O instead of DMF as the solvent. However, the *E*-factor remained high and a new method had to be investigated. Amongst the alternatives to organic solvents, PEG was chosen because it is known to promote nucleophilic substitution by acting as a phase transfer catalyst.[7a] Therefore, we carried out the reaction in PEG_{400} (Table 2, entry 5) and after 2 h compound **12** was isolated in 98% yield by extraction with Et_2O. Furthermore, after extraction, PEG_{400} was recycled 2 more times affording **12** in similar high yields. This simple procedure was successfully scaled up to the transformation of 200 mmol (80 g) of **9**. The *E* factor was largely reduced



Scheme 3 Synthesis of triallylated pentaerythritol **6**.



Scheme 4 Preparation of compound **9**.

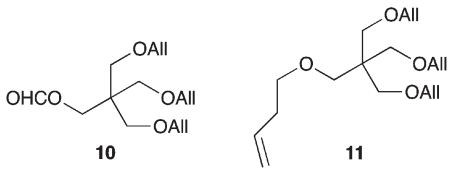
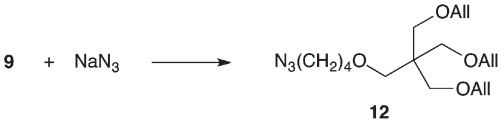


Fig. 1 By-products isolated during the preparation of **9**.



Scheme 5 Preparation of azido derivative **12**.

Table 1 Optimization of conditions for the synthesis of compound **9**

Entry	Solvent (additive)	Base	**8** (equiv.)	Temperature	Time	Conversion (%)	Yield (%)	AE	RME	*E*
1	DMF	NaH	15	60 °C	72 h	62	24	0.79	0.065	818
2	THF	NaH	15	60 °C	48 h	19	17	0.79		
3	H_2O	NaOH	4	85 °C	24 h	22	20	0.76		
4	H_2O (TBAB)	NaOH	4	85 °C	12 h	80	73	0.76	0.31	275

(Table 2) and could be further reduced by multiple recycling of PEG_{400}.

Coupling of dipropargylated PEG **1** with a slight excess of azido derivative **12** was accomplished by the use of $CuSO_4$–sodium ascorbate in water–THF. The triazole-linked polymer **13** (Fig. 2) was isolated by extraction with CH_2Cl_2, washing with an aqueous NH_4Cl–NH_3 solution, in order to remove the copper salts, and precipitation with Et_2O or by ultrafiltration. Atom economy (100%), yield (96 or 95% recovered yield, respectively) and RME (0.91 or 0.90, respectively) were excellent for that reaction (Table 3). Analysis of **13** by ^1H NMR and MALDI-TOF MS showed a complete conversion of **1** into the 1,4-disubstituted triazole derivatives **13**.[29] The residual copper, assayed by atomic absorption, was 835 ppm when **13** was isolated by extraction, washing and precipitation, and 1500 ppm when the purification was carried out by ultrafiltration.

The washing steps, necessary to remove most of the copper salts, dramatically increased the *E* factor, which reached the value of 44. Using an ultrafiltration work-up process not only reduced this metric to 22, but also allowed one to replace the extraction solvents with water.

At this stage it was interesting to test the use of copper turnings. Indeed, the protocol using copper turnings, whose catalytic activity was already established,[30] proved to be very advantageous in providing products containing only traces of the metal.[31] Applied to our PEG derivatives that are good ligands for cations, this method allowed us to isolate **13** by ultrafiltration (95% yield) containing only 220 ppm of copper (ICP MS analysis). Moreover, the copper turnings could be recycled at least 3 times without loss of activity.[32]

Due to a smaller excess of compound **12** ($\varphi_{1,2}$ = 1.14 *vs.* 1.5 in the precedent protocol), RME was enhanced up to 0.936 and even 0.942 since a small amount of the excess of **12** could be recovered. This was interesting because **12** was an advanced intermediate, though such removal required the use of dichloromethane as a washing solvent, which led to a reduction of the global material economy, and consequently an increase of the *E*-factor from 55 to 60. The copper turnings protocol had however a great advantage since water was the only solvent used (except for the partial removal of the excess of one of the reactants).

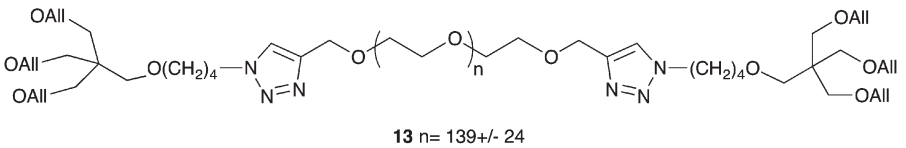
In order to install hydroxyl functions on modified PEG **13**, we chose to exploit another reaction with a total atom economy, the thiol–ene addition.[33] Hence, 2-mercaptoethanol (**14**) was photochemically (λ = 254 nm) added to the allyl groups of **13** in ethanol to give polymer **15** in 94% isolated yield by precipitation from the crude reaction mixture (Fig. 3). The moderate RME (0.76) and *E*-factor (18) were due to a large excess of 2-mercaptoethanol **14** (4.6 equiv.) used to boost the yield. Indeed, when 2 or 4 equiv. of **14** were used, the conversions were 90 and 95% respectively.

In summary, polymer **15** with 6 connection points was prepared by a convergent synthesis with two parallel sequences and a point of convergence (see below for the evaluation of this synthesis by green chemistry metrics). The loading capacity of **15** is 0.8 mmol per gram of support while that of PEG_{6000} is only 0.32 mmol g^{-1}. Then we decided to apply this strategy to the preparation of a support bearing 18 alcohol functions.

Table 2 Comparison of solvents in the synthesis of azido derivative **12**

Entry	Solvent (additive)	Temp. (°C)	Time (h)	Yield (%)	AE	RME	*E*
1	DMF	25	24	91			
2	DMF	60	12	98	0.77	0.75	60.9
3	H_2O	120[a]	1	0			
4	H_2O (TBAB)	120[a]	1	96	0.77	0.69	28.9
5	PEG_{400}	60	2	98	0.77	0.75	7.9
6	PEG_{400} [b]	60	2	96			6.3
7	PEG_{400} [c]	60	2	99			5.8

[a] Microwaves activation. [b] First recycling. [c] Second recycling.



13 n= 139+/- 24

Fig. 2 Structure of polymer **13**.

Table 3 Comparison of catalyst, solvent and work-up for the synthesis of **13**

Entry	**12** (equiv.)	Catalyst (equiv.)	Conditions	Work-up	Yield (%)	AE	RME	*E*
1	1.5	$CuSO_4$–NaAsc (0.5 : 1.05)	THF–H_2O 4 h, 20 °C	Precipitation	96	1	0.912	44
2	1.5	$CuSO_4$–NaAsc (0.5 : 1.05)	THF–H_2O 4 h, 20 °C	Ultrafiltration	95	1	0.903	22
3	1.14	Cu (2.6)[a]	H_2O 26 h, 70 °C	Ultrafiltration	95	1	0.936 0.942[b]	55 60[b]

[a] Recycled 3 times. [b] After removal of a part of the excess of **12**.

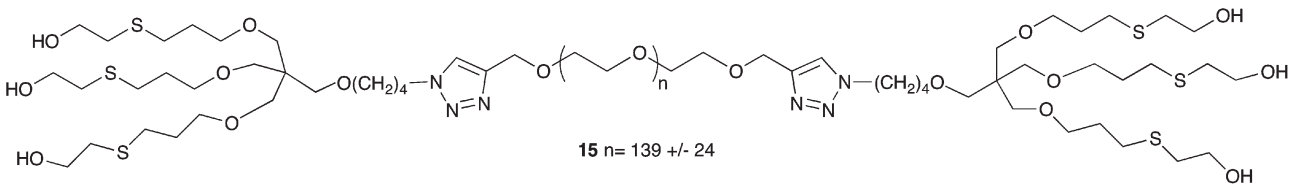


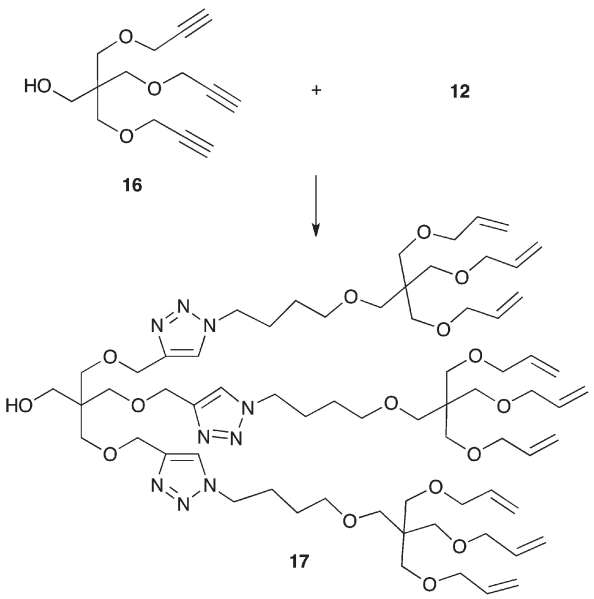
Fig. 3 Polymer **15** with 6 connection points having a loading capacity of 0.8 mmol g^{-1}.

Synthesis of PEG_{6000} with 18 branches

For the preparation of PEG with 18 branches we planned to prepare compound **17** (Scheme 6) using the copper(I) catalysed cycloaddition between **12** and tripropargylated pentaerythritol **16**.[34] The preparation of the latter compound has been previously described starting from pentaerythritol (**3**) and propargyl bromide (**4**) in H_2O–DMSO (71% yield calculated on the basis of propargyl bromide).[35] These conditions induce a low value for RME (0.10) due to a high stoichiometric ratio between pentaerythritol and propargyl bromide (φ_1 = 5.01) as well as a high stoichiometric ratio between sodium hydroxide and propargyl bromide (φ_2 = 5.68). In order to increase the mass efficiency of the reaction, we rather choose to work with a small excess of propargyl bromide (3.85 mol mol^{-1} of **3**, which corresponds to a stoichiometric ratio of 1.28) and a small excess of sodium hydroxide (1.33 equiv.). Under our conditions, the yield based on propargyl bromide is reduced from 71% to 35%, whereas the yield based on pentaerythritol is enhanced from 14 to 45%. Finally, RME was increased by 50% (RME = 0.15).

Tripropargylated pentaerythritol **16** and the azido derivative **12** were coupled in the presence of $CuSO_4$–sodium ascorbate in water–THF affording **17** in 59% yield after chromatography (Scheme 6). Notwithstanding the yield, RME remained moderate (RME = 0.43) thanks to a total atom economy and a limited excess of one of the reagents (1.49 equiv.). The high value of the *E* factor (*E* = 798) was related to the chromatography step, which involved solvents and silica gel. This high value prompted us to change the method or to improve the purification step. A first assay to prepare **18** from **17** by addition of dibromobutane in water under the same conditions developed for the preparation of **9** gave poor results, since **18** was isolated in only 33% yield due to degradation during the purification step. Then, we decided to by-pass the preparation of **17** by grafting the spacer earlier in the synthetic sequence and we were pleased to obtain **20** in 85% yield through the coupling of **16** with dibromobutane in water (Fig. 5). As for the preparation of the allylated derivative **9**, some elimination occurred, giving rise to **21** in 4% yield. Dibromobutane was used in excess (4 equiv.), but the recovery by distillation of a part of this excess allowed us to increase RME from 0.22 up to 0.36, an acceptable value for a reaction with an atom economy of 0.76.

The copper-catalysed cycloaddition between **12** and **20** to form **18** (Fig. 4) proceeded to completion in 1.5 h using a stoichiometric amount of $CuSO_4$–NaAsc (relative to alkyne functions) in H_2O–THF (Table 4, entry 1). Since chromatography



Scheme 6 Synthesis of compound **17** through CuAAC.

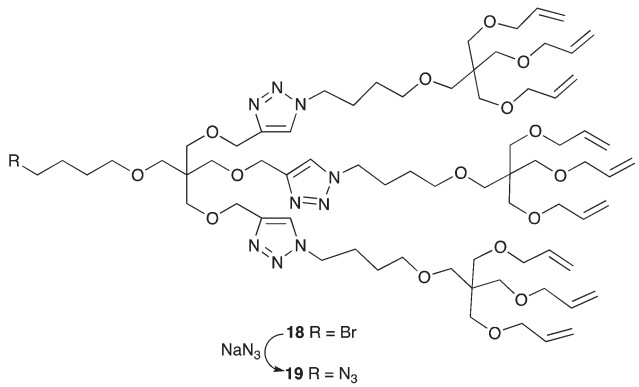


Fig. 4 Synthesis of **19** from **18**.

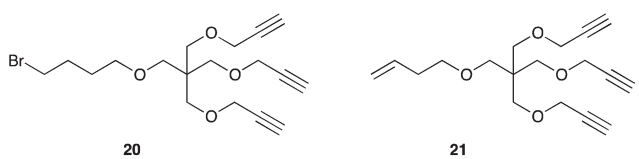


Fig. 5 Structures of compounds **20** and **21**.

Table 4 Optimisation of the synthesis of **18** by CuAAC between **12** and **20**

Entry	**12** (equiv.)	Catalyst (equiv. per alkyne)	Time (h)	Solvent	Isolated yield (%)	RME	*E*
1	1.3	$CuSO_4$–NaAsc (1 : 1)	1.5	H_2O–THF (3 : 1)	50		
2	1	$CuSO_4$–NaAsc (0.1 : 0.1)	5	H_2O–THF (3 : 1)	96		
3	1	$CuSO_4$–NaAsc (0.033: 0.033)	24	H_2O–THF (1 : 3)	96		
4	1	$CuSO_4$–NaAsc (0.033: 0.033)	0.5	H_2O–PEG_{400} (1 : 7)	99	0.99	9.8
5	1	Cu turnings (1.3)	25	H_2O–PEG_{400} (1 : 6)	98	0.97	12.5

was necessary to remove the excess of azido derivative **12**, compound **18** was isolated in only 50% yield due to some decomposition on silica gel. Hence we tried to reduce the amount of **12** and copper salts. We found that when the stoichiometric ratio between the reactants was respected and when 0.1 or even 0.033 equiv. of copper were used, the reaction was complete in 5 or 24 h, respectively (Table 4, entries 2 and 3). Almost pure **18** (^{1}H NMR analysis) was isolated by simple extraction and washing with an aqueous NH_4Cl–NH_3 solution to remove most of the copper.

Due to the excellent results obtained in reactions carried out by us (**9** → **12**) and by others,[36] we were encouraged to test a mild protocol using aqueous PEG_{400} as the solvent. Using 1 equivalent of **12** and a catalytic amount of copper (0.033 equiv. per alkyne) allowed us to get a very clean and rapid reaction with **20** in H_2O–PEG_{400} (1 : 7) (Table 4, entry 4). In order to avoid the washing step with ammonia, we also tried copper turnings as the catalyst. The reaction took place in H_2O–PEG_{400} (1 : 6) and compound **18** was isolated by simple extraction in almost quantitative yield (Table 4, entry 5), the copper content in the isolated compound being 910 ppm (atomic absorption analysis). In reactions performed in H_2O–PEG_{400}, RME values were excellent (0.97 and 0.99). When using copper(II), the *E* factor was reduced to 9.8.

The following nucleophilic substitution step was also performed in PEG_{400} and a simple extraction allowed us to isolate **19** in 97% yield (Fig. 4, Table 5). For comparison, the reaction was also conducted in DMF. A yield of 93% was obtained but the transformation required 12 h while it was complete after 2.5 h in PEG, confirming the efficiency of this solvent for nucleophilic substitutions.[7a] PEG_{400} was recycled 3 times and similar high yields were obtained. Excellent values of RME (0.91) and the *E*-factor (between 3.1 and 3.8 according to the number of times PEG can be recycled) were obtained for that reaction with an atom economy of 0.93.

The dipropargylated PEG **1** was then reacted with the azido derivative **19** to obtain **22** (Scheme 7). When $CuSO_4$–sodium ascorbate was used as the catalyst, the reaction took place in 2 : 1 THF–H_2O in 3 h at room temperature. 2.3 equiv. of **19**, with respect to alkyne function, were necessary to reach a total conversion (^{1}H NMR and MALDI-TOF analyses). PEG **22** was isolated in 91% yield by extraction with CH_2Cl_2, washing with an aqueous NH_4Cl–NH_3 solution followed by precipitation with Et_2O. The copper content of the polymer was determined at 240 ppm by atomic absorption. We also tried to purify **22** by ultrafiltration of the aqueous solution, but we were not able to remove all the excess of azido derivative **19** from PEG **22** by this technique. The calculation of green metrics gave RME and *E* values of 0.66 and 31, respectively. Use of copper turnings as the catalyst allowed us to carry out the reaction in THF–H_2O[37] using only 1.25 instead of 2.3 equiv. of azido derivative **19** per alkyne function. Purification by ultrafiltration allowed recovering **22** in 91% yield containing 1000 ppm of copper (atomic absorption analysis). These new conditions also led to a high RME value (0.93) and would lead to an extremely low value of the *E* factor (3.0) if H_2O was excluded from the calculation. The actual value of 319, which is high compared to 3, must be correlated to the fact that water is the major part of the waste.

Table 5 Comparison of solvents for the nucleophilic substitution affording **19**

Entry	Solvent	Time (h)	Isolated yield (%)	RME	*E*
1	DMF	12	93	—	—
2	PEG_{400}	2.5	97	0.91	3.8
3	PEG_{400} (1st recycling)	2.5	96	0.91	3.3
4	PEG_{400} (2nd recycling)	2.5	99	0.91	3.2
5	PEG_{400} (3rd recycling)	2.5	98	0.91	3.1

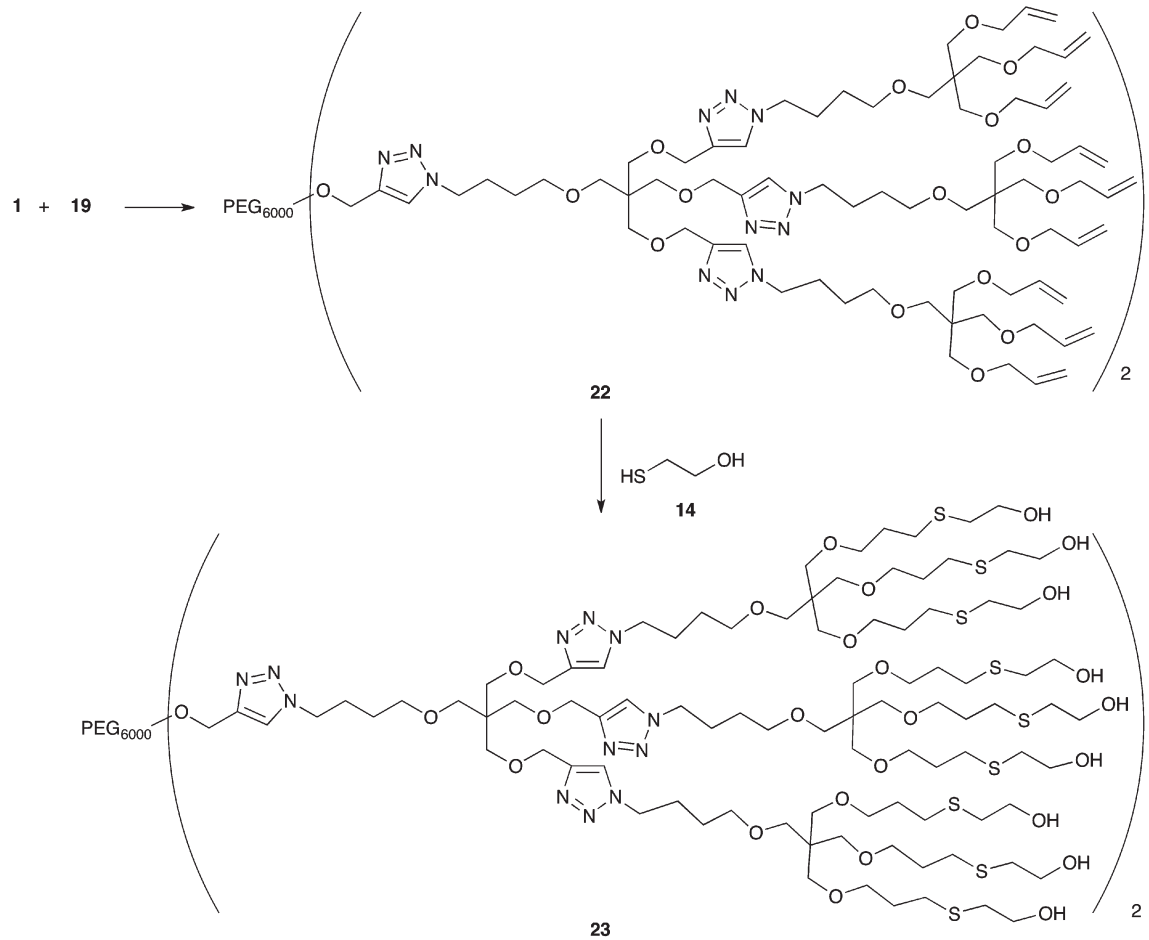
Finally, the radical addition of an excess of 2-mercaptoethanol (φ = 4.97 to reach complete conversion) to **22** was carried out in ethanol–H_2O by irradiating the solution at λ = 254 nm for 14 h to give the polyol **23** (Scheme 7) in 98% isolated yield by precipitation from the reaction mixture. Under these conditions we found RME = 0.64 and *E* = 10.8, that are acceptable values for such a reaction.

The loading capacity of polymer **23** with 18 connection points is 1.71 mmol g^{-1}, which corresponds to an increase of 534% compared to PEG_{6000}. It was prepared by a convergent synthesis with three parallel sequences and two points of convergence.

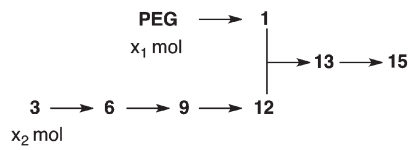
Evaluation of the total synthesis of 15

This is a convergent synthesis with two parallel sequences and one point of convergence (Scheme 8).

Table 6 gathers the green metrics of all the steps. Two of them gave unsatisfactory *E*-factors due to a chromatographic purification in the work-up of these two steps. However, we succeeded in replacing DMF as a solvent and NaH as a base by carrying out these transformations under aqueous conditions using NaOH as a green base. The other steps were optimized to reduce the impact of the processes. Particularly interesting was the use of ultrafiltration to purify large molecules and also



Scheme 7 Synthesis of **23** with 18 connection points having a loading capacity of 1.71 mmol g^{-1} through thiol–ene addition of 2-mercaptoethanol **14**.



Scheme 8 Synthesis of **15**.

Table 6 Yields and green metrics for each step of the synthesis of **15**

Reaction	Yield (%)	AE (%)	RME[a] (%)	GME (%)	*E*
PEG → **1**	96	96	77	7.88[b]	11.72[b]
3 → **6**	75	41	22	0.3	285
6 → **9**	73	76	31	0.4	275
9 → **12**	98	77	75	15	5.8[c]
1 + **12** → **13**	95	100	94	1.7[d]	55[b,d]
13 → **15**	94	100	76	5	18.7

[a] RME values were systematically calculated according to (a) the classical method, *i.e.* by adding the mass of reactants used, and (b) the method that we have developed recently. Both methods gave strictly the same results allowing the checking of the data.[17] [b] Purification by ultrafiltration. [c] After 2 cycles. [d] Method with copper turnings.

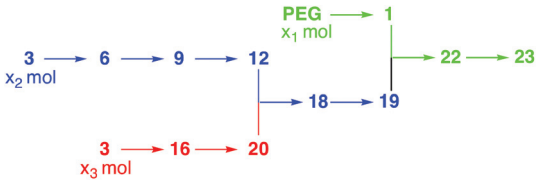
the use of PEG as a solvent both for the substitution reaction with NaN_3 and the copper-catalyzed cycloaddition.

We have recently developed a new algorithm to evaluate any whole synthesis.[17] By using this methodology, we found that the global reaction mass efficiency (GRME) of the total synthesis of **15**, starting from PEG_{6000} and pentaerythritol, was 41% for an overall atom economy of 84%. The overall yield calculated from PEG_{6000} was equal to 85% (see ESI† for details of the calculation).

Evaluation of the total synthesis of 23

This is a convergent synthesis with three parallel sequences and two points of convergence (Scheme 9).

The sequences PEG → **1** and **3** → **12** have been described in the previous synthesis. We greatly improved the synthesis of **16** in terms of waste production but it still retained a chromatography step, enhancing dramatically the *E*-factor. Use of ultrafiltration for purification and PEG as the solvent allowed us to decrease the environmental impact of the next steps. By using our methodology, we found that the global reaction mass efficiency of the total synthesis of **23**, starting from PEG_{6000} and pentaerythritol, was GRME = 24% for an overall atom economy of 71% and an overall yield of 86% from PEG_{6000} (Table 7).



Scheme 9 Synthesis of **23**.

Table 7 Yields and green metrics for each step of the synthesis of **23**

Reaction	Yield (%)	AE (%)	RME[a] (%)	GME (%)	*E*
3 → 16	45	41	15	0.2	409
16 → 20	85	76	36	0.4	222
12 + 20 → 18	99	100	99	9.2	9.8
18 → 19	98	93	91	24[b]	3.1[b]
1 + 19 → 22	91	100	86	0.3	319[c]
22 → 23	99	100	64	8.4	10.8

[a] RME values were systematically calculated according to (a) the classical method, *i.e.* by adding the mass of reactants used, and (b) the method that we have developed recently. Both methods gave strictly the same results allowing the checking of the data. [b] After 3-fold recycling of PEG. [c] Most of the waste is water.

Conclusions

The aim of this work was the synthesis of high loading capacity polymers by implementing methods of green chemistry. The choice of reactions with high atom economy, such as CuAAC and thiol–ene coupling, and optimization of the reaction conditions to increase the yields and reduce the excess of reagents allowed us to increase significantly the reaction mass efficiency (RME) of the different steps. Replacement of solvents, traditionally used in organic synthesis, by recyclable alternative media such as PEG_{400} together with the use of purification methods such as ultrafiltration of aqueous media, where possible, also contributed to the eco-compatible synthesis. The new polymer featuring 6 connection points has a loading capacity of 0.80 mmol g^{-1} whereas that with 18 connection points has a loading capacity of 1.71 mmol g^{-1}, which correspond to an increase of 250% and 534%, respectively, with respect to the starting PEG_{6000}. These loading capacities are comparable to those displayed by most of the commercially available insoluble resins such as the Merrifield or Wang resins.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature with Bruker spectrometers (250, 300, or 360 MHz). Chemical shifts are reported in parts per million (ppm) *vs.* Me_4Si for ^{1}H-NMR and ^{13}C-NMR. Signals were assigned thanks to ^{1}H–^{1}H COSY and gradient-HMQC experiments. Mass spectra were recorded in positive mode on a Finnigan MAT 95 S spectrometer using electrospray ionization except for MALDI-TOF which were performed at the Service de Spectrométrie de Masse IMAGIF/ICSN – CNRS (Gif-sur-Yvette, France) with a Perseptive Voyager DE-STR MALDI time-of-flight mass spectrometer (Perseptive Biosystems) using 2,5-dihydroxybenzoic acid as the matrix. Spectra of the compounds were compared to commercial PEG_{6000} (found for the central peak 6209, $HOCH_2CH_2(OCH_2CH_2)_{139}OH$, [M + Na]).

Copper concentrations were determined at 324.8 nm on a spectrometer AAS novAA400 with a C_2H_2–air flame (fuel flow at 50 L h^{-1}), equipped with a burner of 10 mm and a lamp M-HCL. A certified solution of Cu in HNO_3 (Copper RS NORMEX, Carlo Erba) was diluted in distillated water to give a stock solution at 1000 ppm Cu that was used to prepare standard solutions for calibration. Samples were dissolved in a 1% aq. solution of HNO_3 at 1 mg mL^{-1}. Three replicates were recorded for each sample (SD for all samples were <4%). ICP-MS measurements were performed at the Laboratoire d'Analyses Nucléaires Isotopiques et Elémentaires at CEA-Saclay, France.

Bis propargylated PEG_{6000} 1

To a solution of PEG_{6000} (40 g; 6.47 mmol) in THF (30 mL) was added an aqueous solution of sodium hydroxide (5.34 g; 133 mmol in 11 mL of water) under stirring. After 5 min, propargyl bromide solution 80 wt% in toluene (4.3 mL; 38.6 mmol) was added and the mixture was stirred at 40 °C for 12 h. After cooling to r.t., THF was evaporated.

Purification by extraction and precipitation. The aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with an aqueous saturated solution of KH_2PO_4 until pH 6 was reached (2 × 40 mL), and then with water (40 mL), dried over sodium sulfate (10 g), and filtered. The CH_2Cl_2 phase was concentrated to 80 mL, cooled to 0 °C, and dry Et_2O (450 mL) was slowly added under vigorous stirring. The precipitate was recovered by filtration and washed with Et_2O (200 mL) affording compound **1** as a white powder (39.0 g; 96%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.44 (t, 2 H, J = 2.5 Hz), 3.43–3.85 (m, 560 H, PEG), 4.20 (d, 4 H, J = 2.5 Hz); **^{13}C NMR** (91 MHz, $CDCl_3$). δ 58.5 ($OCH_2C{\equiv}CH$), 69.2, 70.6 (OCH_2, PEG), 76.7 (${\equiv}CH$), 79.8 ($C{\equiv}CH$), MALDI-TOF MS: found for the central peak (n = 139): 6285 [M + Na].

Purification by ultrafiltration. The aqueous solution was diluted with water (160 mL), filtered on a PVDF membrane (47 mm, 0.45 μm) and the ultrafiltration was performed in Amicon 8200 stirred cells fitted with Amicon Ultracell PL Membrane Disks, molecular weight cutoff 1000, under 3.8 bar pressure. After the first ultrafiltration, the retentate (40 mL) was diluted with water (120 mL), and the solution was ultrafiltrated again. The operation was repeated once to afford, after freeze drying, 38.5 g of **1** as a white powder (95%).

Pentaerythritol triallyl ether 6

To a solution of pentaerythritol **3** (103.4 g; 0.759 mol) in aqueous sodium hydroxide (122 g; 3.05 mol in 250 mL water) was slowly added allyl bromide **5** (368.4 g; 3.04 mol). The mixture was heated at 70 °C for 12 h. After cooling to room temperature, the biphasic mixture was decanted and

separated. The aqueous layer was extracted with diethyl ether (200 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen phosphate (200 mL), brine (200 mL), dried over sodium sulfate (25 g), filtered and concentrated under vacuum. Purification by column chromatography (petroleum ether–ethyl acetate: 5/1 then 3/1) afforded first compound **6** as a colorless oil (109 g; 56%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.90 (t, 1 H, J = 6.0 Hz, CH_2OH), 3.50 (s, 6 H, C_qCH_2O), 3.73 (d, 2 H, J = 6.0 Hz, CH_2OH), 3.96 (dt, 6 H, J = 5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.15 (dq, 3 H, J = 10.5 Hz, J = 1.5 Hz, $CH_2CH{:}CH_2$), 5.25 (dq, 3 H, J = 17.5 Hz, J = 1.5 Hz, $CH_2CH{:}CH_2$), 5.83–5.92 (m, 3 H, $CH_2CH{:}CH_2$). **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ 44.8 (C_q), 65.9 (CH_2OH), 70.8 (CH_2OAll), 72.3 ($OCH_2CH{:}CH_2$), 116.5 ($OCH_2CH{:}CH_2$), 134.7 ($OCH_2CH{:}CH_2$).

Eluted second was compound **7**. Colorless oil. (41 g; 25%). Spectral data were in accordance with those previously reported.[38] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.65 (br s, 2 H, CH_2OH), 3.50 (s, 4 H, C_qCH_2O), 3.68 (s, 4 H, CH_2OH), 3.96 (dt, 4 H, J = 5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.18 (dq, 2 H, J = 10.5 Hz, J = 1.5 Hz, $CH_2CH{:}CH_2$), 5.25 (dq, 2 H, J = 17.5 Hz, J = 1.5 Hz, $CH_2CH{:}CH_2$), 5.83–5.92 (m, 2 H, $CH_2CH{:}CH_2$).

Following the same procedure, compound **6** was obtained from compound **7** (41 g; 0.19 mol) using 2 equivalents of sodium hydroxide (15.2 g; 0.38 mol) in water (30 mL) and allyl bromide (46 g; 0.38 mol). Purification by flash chromatography (petroleum ether–AcOEt: 5/1) afforded **6** (36.5 g). The two batches were brought together to yield 145.5 g (75%).

Compound 9

Method in DMF. To a solution of compound **6** (430 mg; 1.68 mmol) in dry DMF (3.5 mL) was added NaH (60% in mineral paraffin) (135 mg; 3.36 mmol) at 0 °C in three portions over a period of 15 min under stirring. Dibromobutane (1.0 mL; 8.4 mmol) was added and the mixture was heated at 60 °C for 72 h. After cooling to room temperature, the mixture was diluted in diethyl ether (10 mL), quenched with water (3 mL), neutralized with an aqueous saturated solution of KH_2PO_4 (5 mL), washed with brine (3 × 5 mL), dried over Na_2SO_4 (1.5 g) and concentrated under vacuum. Flash chromatography of the residue (petroleum ether–AcOEt: 95/5) afforded first compound **9** (155 mg; 24%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.64–1.68 (m, 2 H, $Br(CH_2)_2CH_2$), 1.90–1.93 (m, 2 H, $BrCH_2CH_2$), 3.38–3.43 (m, 12 H, $BrCH_2$, OCH_2), 3.92 (dt, 6 H, J = 5.0 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.12 (dq, 3 H, J = 10.5 Hz, J = 1.5 Hz, $CH_2CH{:}CH_2$), 5.26 (dq, 3 H, J = 17.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.81–5.90 (m, 3 H, $OCH_2CH{:}CH_2$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 28.5 ($Br(CH_2)_2CH_2$), 30.2 ($BrCH_2CH_2$), 34.1 ($BrCH_2$), 45.7 (C_q), 69.6 (C_qCH_2OAll), 70.0 (C_qCH_2O), 70.6 (OCH_2CH_2), 72.6 ($OCH_2CH{:}CH_2$), 116.4 ($OCH_2CH{:}CH_2$), 135.5 ($OCH_2CH{:}CH_2$). **IR** (NaCl) n: 3079, 2910, 1646, 646 cm^{-1}. **MS:** (ESI + m/z): $[M + 23]^+$: 415.1. **HRMS** (ES+) Calcd for $C_{18}H_{31}BrO_4Na$: 413.1298; Found: 413.1305. **Anal.** Calcd for $C_{18}H_{31}BrO_4$: C, 55.24; H, 7.98. Found: C, 54.98; H, 7.81.

Eluted second was compound **7** (142 mg; 30%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.45 (s, 6 H, CH_2OAll), 3.93 (dt, 6 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 4.25 (s, 2 H, OCH_2C_q), 5.14 (dq, 3 H, J = 10.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.24 (dq, 3 H, J = 17.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.82–5.91 (m, 3 H, $OCH_2CH{:}CH_2$), 8.07 (s, 1 H, CHO). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 44.4 (C_q), 63.6 (C_qCH_2O), 68.9 (C_qCH_2OAll), 72.3 ($OCH_2CH{:}CH_2$), 116.5 ($OCH_2CH{:}CH_2$), 134.9 ($OCH_2CH{:}CH_2$), 161.1 (CHO). **IR** (NaCl): 3080, 2868, 1725 cm^{-1}. **MS:** (ES+): $[M + 23]^+$: 307.1.

Method in water. To a suspension of triallyl pentaerythritol **6** (78.0 g; 0.304 mol) in an aqueous solution of sodium hydroxide (120 g; 3.0 mol in 250 mL water) were added dibromobutane (145 mL, 1.21 mol) and TBAB (9.7 g; 0.03 mol). The mixture was heated under stirring at 85 °C for 12 h. After cooling to room temperature, the two layers were separated. The aqueous layer was extracted with diethyl ether (200 mL). The combined organic layers were washed with a saturated aqueous solution of KH_2PO_4 (100 mL) and water (100 mL), dried over sodium sulfate (25 g), filtered and concentrated to give a yellow oil from which 180 g (0.83 mol) of dibromobutane was recovered by distillation (bp 38 °C at 0.6 mbar). Flash chromatography (petroleum ether–Et_2O: 9/1) of the residue afforded first compound **11** (3.4 g; 4%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.30 (qt, 2 H, J = 6.5 Hz, 1.5 Hz, $CH_2CH_2CH{:}CH_2$), 3.44 (m, 10 H, OCH_2CH_2, C_qCH_2O), 3.93 (dt, 6 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.00 (dq, 1 H, J = 10.5 Hz, J = 1.5 Hz, $CH_2CH_2CH{:}CH_2$), 5.06 (dq, 1 H, J = 17.5 Hz, J = 1.5 Hz, $CH_2CH_2CH{:}CH_2$), 5.14 (dq, 3 H, J = 10.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.24 (dq, 3 H, J = 17.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.76–5.91 (m, 4 H, $OCH_2CH{:}CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 34.2 ($CH_2CH_2CH{:}CH_2$), 45.6 (C_q), 69.5 (CH_2OAll), 69.8 (C_qCH_2O), 70.8 ($C_qCH_2OCH_2$), 72.4 ($OCH_2CH{:}CH_2$), 116.1 ($CH_2CH_2CH{:}CH_2$), 116.2 ($OCH_2CH{:}CH_2$), 135.4 ($OCH_2CH{:}CH_2$), 135.8 ($CH_2CH_2CH{:}CH_2$). **MS:** (ES+): $[M + 23]^+$: 333.3. **Anal.** Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.46; H, 9.76.

Eluted second was compound **9** (86.8 g; 73%).

Compound 12

Method in DMF. To a solution of compound **9** (7.83 g; 20.0 mmol) in DMF (20 mL) was added sodium azide (1.43 g; 22.0 mmol). The mixture was stirred and heated at 60 °C for 12 h. After cooling to room temperature, diethyl ether (65 mL) was added and the organic layer was washed with brine (5 × 50 mL) and water (45 mL). The organic layer was dried over sodium sulfate (8 g), filtered and concentrated to afford compound **12** as a colorless oil (6.95 g; 98%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.61–1.66 (m, 4 H, $N_3CH_2(CH_2)_2$), 3.27 (t, 2 H, J = 6.5 Hz, N_3CH_2), 3.37–3.48 (m, 10 H, C_qCH_2O, OCH_2CH_2), 3.93 (dt, 6 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.11–5.27 (dq, 6 H, J = 10.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.27 (dq, 3 H, J = 17.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.82–5.91 (m, 3 H, $OCH_2CH{:}CH_2$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.0 ($N_3CH_2CH_2$), 26.9 (OCH_2CH_2), 45.5 (C_q), 51.4 (N_3CH_2), 69.5 (CH_2OAll), 69.8 ($C_qCH_2OCH_2$), 70.7 (C_qCH_2O), 72.4 ($OCH_2CH{:}CH_2$), 116.2 ($OCH_2CH{:}CH_2$), 135.4 ($OCH_2CH{:}CH_2$). **IR** (NaCl): 3079, 2868, 2096, 1646 cm^{-1}. **MS:** (ES+): $[M + 23]^+$: 376.2. **HRMS** (ES+):

Calcd for $C_{18}H_{31}N_3O_4Na$: 376.2207. Found: 376.2218. **Anal.** Calcd for $C_{18}H_{31}N_3O_4$: C, 61.17; H, 8.84; N, 11.89; O, 18.11. Found: C, 61.12; H, 8.62; N, 11.71; O, 18.11.

Method in PEG_{400}. To a solution of compound **9** (80 g; 204.4 mmol) in PEG_{400} (200 mL) was added sodium azide (14.6 g; 224.4 mmol). The mixture was stirred and heated at 60 °C for 2 h. After cooling to room temperature, compound **12** was extracted with diethyl ether (200 mL). The organic layer was washed with water (150 mL), dried over sodium sulfate (25 g), filtered and concentrated to afford compound **12** as a colorless oil (71.1 g; 98%). An analytical sample was obtained by flash chromatography (petroleum ether–Et_2O: 9/1).

Method in water under microwave activation. Compound **9** (177 mg; 0.45 mmol), TBAB (14 mg; 0.04 mmol), sodium azide (44 mg; 0.677 mmol) and water (1 mL) were placed in a microwave reactor (CEM discovery). The reactor was then sealed and irradiated at 120 °C for 1 h (power 100 watt). After cooling to room temperature, compound **12** was extracted with diethyl ether (2 × 2 mL). The organic layer was dried over sodium sulfate (0.5 g), filtered and concentrated to afford compound **12** as a slightly yellow oil (153 mg; 96%).

PEG_{6000} with 6 allyl functions (13)

Method with $CuSO_4$–AscNa. To a solution of bispropargylated PEG **1** (3.00 g; 0.48 mmol) and azido derivative **12** (508 mg; 1.4 mmol) in a mixture of THF–H_2O (6 mL/4.5 mL) were successively added a 1 M aqueous solution of $CuSO_4{\cdot}5H_2O$ (500 μL) and a 1 M aqueous solution of sodium ascorbate (1 mL). After 4 h, THF was removed under vacuum.

Purification by extraction/precipitation. The aqueous solution was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed twice with a mixture of a saturated aqueous solution of ammonium chloride (10 mL) and a 28% aqueous solution of ammonia (3 mL) for 30 min, water (20 mL), dried over sodium sulfate (4 g) and filtered. The CH_2Cl_2 phase was concentrated to 5 mL and Et_2O (40 mL) was added over 30 min under vigorous stirring at 0 °C and polymer **13** was filtered. The white powder was washed with Et_2O (20 mL) to afford **13** (3.20 g; 96%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.53–1.60 (m, 4 H, OCH_2CH_2), 1.92–2.01 (m, 4 H, NCH_2CH_2), 3.40–3.44 (m, 20H, C_qCH_2O, OCH_2CH_2), 3.57–3.75 (m, 560 H, PEG), 3.93 (dt, 12 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 4.37 (t, 4 H, J = 7.5 Hz, NCH_2), 4.68 (s, 4 H, O-CH_2-C_q:CH), 5.12 (dq, 6 H, J = 10.5 Hz, 1.5 Hz, $OCH_2CH{:}CH_2$), 5.23 (dq, 6 H, J = 17.5 Hz, 1.5 Hz, $OCH_2CH{:}CH_2$), 5.81–5.92 (m, 6 H, $OCH_2CH{:}CH_2$), 7.55 (s, 2 H, O-CH_2-C_q:CH). **^{13}C NMR** (63 MHz, $CDCl_3$): δ 26.4 (OCH_2CH_2), 27.4 (NCH_2CH_2), 45.5 (C_q), 50.1 (NCH_2), 65.2 (O-CH_2-C_q:CH), 69.3 (C_d), 69.6 (C_qCH_2OAll), 70.7 (OCH_2, PEG), 72.2 ($OCH_2CH{:}CH_2$), 116.0 ($OCH_2CH{:}CH_2$), 122.3 (O-CH_2-C_q:CH), 135.3 ($OCH_2CH{:}CH_2$), 145.3 (O-CH_2-C_q:CH). **MALDI-TOF MS**: found for the central peak: 6990 [M + Na].

Purification by ultrafiltration. The aqueous solution was diluted with water (30 mL), filtered on a PVDF membrane (47 mm, 0.45 μm) and the ultrafiltration was performed in Amicon 8050 stirred cells fitted with Amicon Ultracell PL Membrane Disks, molecular weight cutoff 1000, under 3.8 bar pressure. After the first ultrafiltration, the retentate (10 mL) was diluted with water (30 mL), and the solution was ultrafiltrated again to afford, after freeze drying, 3.17 g of **13** as a powder (95%).

Method with copper turnings. A mixture of bispropargylated PEG **1** (715 mg; 0.11 mmol), azido derivative **12** (92 mg; 0.26 mmol), copper turnings (38 mg; 0.60 mmol), and water (1.4 mL) was stirred at 70 °C for 26 h. The copper turnings were removed and the aqueous solution was diluted with water (20 mL), filtered on a PVDF membrane (47 mm, 0.45 μm) and the ultrafiltration was performed in Amicon 8050 stirred cells fitted with Amicon Ultracell PL Membrane Disks, molecular weight cutoff 1000, under 3.8 bar pressure. After the first ultrafiltration, the retentate (5 mL) was diluted with water (20 mL), and the solution was ultrafiltrated again to afford, after freeze drying of the retentate, 0.755 g of **13** as a white powder (95%). The PVDF membrane was washed with CH_2Cl_2 (3 mL). Concentration of the solution allowed recovering 3.5 mg of the azido derivative **12**. Concentration of the ultrafiltration filtrate allowed recovering 2 mg of the azido derivative **12**.

PEG_{6000} with 6 alcohol functions (15)

Polymer **13** (0.34 g; 0.049 mmol) was dissolved in ethanol (0.5 mL) by heating at 60 °C in a quartz tube equipped with a stirring bar. After cooling to room temperature, mercaptoethanol (96 μL; 1.37 mmol) was added. The mixture was submitted to UV irradiation (254 nm) under stirring for 14 h then diluted with 2 mL of ethanol, placed at −14 °C for 30 min. The white solid was then filtered and washed with diethyl ether (2 × 3 mL) affording compound **15** as a white solid (0.34 g; 94%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.54–1.63 (m, 4 H, $OCH_2CH_2(CH_2)_2$), 1.77–1.85 (m, 12 H, $SCH_2CH_2CH_2$), 1.94–2.02 (m, 4 H, NCH_2CH_2), 2.58 (t, 12 H, J = 7.0 Hz, $SCH_2CH_2CH_2$), 2.70 (t, 12 H, J = 6.0 Hz, SCH_2CH_2OH), 3.34 (s, 16 H, C_qCH_2O), 3.40–3.46 (m, 28 H, OCH_2CH_2, CH_2OH), 3.63–3.71 (m, 560 H, PEG), 4.37 (t, 4 H, J = 7.0 Hz, NCH_2), 4.54 (s, 4 H, O-CH_2-C_q:CH), 7.61 (s, 2 H, O-CH_2-C_q:CH). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.2 ($OCH_2CH_2(CH_2)_2$), 27.2 (NCH_2CH_2), 28.4 ($SCH_2CH_2CH_2$), 29.6 ($SCH_2CH_2CH_2$), 34.6 (SCH_2CH_2OH), 45.1 (C_q), 49.8 (NCH_2), 60.6 (CH_2OH), 64.4 (O-CH_2-C_q:CH), 69.3 (C_qCH_2O), 70.2 (OCH_2, PEG), 122.4 (O-CH_2-C_q:CH), 144.7 (O-CH_2-C_q:CH). **MALDI-TOF MS**: found for the central peak: 7458 [M + Na].

2,2-Bis(prop-2-ynyloxy)propan-1-ol (16)

To a solution of pentaerythritol (100 g; 0.73 mmol) in DMSO (250 mL) was added, under stirring, sodium hydroxide (117 g; 2.92 mol) in water (250 mL). The mixture was cooled to 0 °C and propargyl bromide (315 mL; 2.82 mol; 80% in toluene) was slowly added. The mixture was then stirred at room temperature for 24 h. The mixture was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen phosphate (200 mL), brine (200 mL), dried over sodium sulfate (100 g), filtered and concentrated under vacuum. Purification by flash chromatography (petroleum ether–AcOEt: 3/2) afforded

compound **16** as a colorless oil (82.7 g; 45%). Spectral data were in accordance with those previously reported.[30]

Compound 17

To a solution of **16** (116 mg; 0.46 mmol) and **12** (732 mg; 2.07 mmol) in THF (5 mL) were successively added under stirring a 1 M aqueous solution of $CuSO_4{\cdot}5H_2O$ (1.2 mL) and a 1 M aqueous solution of sodium ascorbate (2.8 mL). After 20 h compound **17** was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed three times with a mixture of a saturated aqueous solution of ammonium chloride (10 mL) and a 28% aqueous solution of ammonia (3 mL) for 30 min, water (10 mL) and brine (10 mL), dried over sodium sulfate (4 g), filtered and concentrated. Compound **17** was obtained as a colorless oil (361 mg; 60%) after flash chromatography (CH_2Cl_2–MeOH: 95/5). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.41–1.60 (m, 6 H, OCH_2CH_2), 1.91–2.00 (m, 6 H, NCH_2CH_2), 3.34–3.40 (m, 30 H, C_qCH_2O), 3.51 (s, 6 H, OCH_2CH_2), 3.62 (s, 2 H, CH_2OH), 3.91 (dt, 18 H, J = 5.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 4.36 (t, 6 H, J = 7.5 Hz, CH_2N), 4.56 (s, 6 H, OCH_2C_q:CH), 5.08–5.13 (dq, 9 H, J = 10.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 5.18–5.26 (dq, 9 H, J = 17.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 5.78–5.91 (m = 9 H, OCH_2CH:CH_2), 7.53 (s, 3 H, OCH_2C_q:CH). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.6 (OCH_2CH_2), 27.5 (NCH_2CH_2), 45.3 (C_q), 45.5 (C_q), 50.3 (CH_2N), 64.7 (CH_2OH), 65.2 (OCH_2C_q:CH), 69.5 (C_qCH_2O), 70.0 (C_qCH_2O), 70.6 (OCH_2CH_2), 72.4 (OCH_2CH:CH_2), 116.2 (OCH_2CH:CH_2), 122.6 (OCH_2C_q:CH), 135.3 (OCH_2CH:CH_2), 145.3 (OCH_2C_q:CH). **IR** (NaCl): 3400, 3079, 3012, 2868, 1645, 1094 cm^{-1}. **MS:** (ES+): $[M + 23]^+$: 1333.6, $[M/2 + 23]^+$: 666.9. **Anal.** Calcd for $C_{68}H_{111}N_9O_{16}$: C, 62.31; H, 8.54; N, 9.62; O, 19.53. Found: C, 61.91; H, 8.46; N, 9.51; O, 19.35.

Compound 20

To a suspension of tripropargylated pentaerythritol **16** (82.0 g; 0.328 mol) in aqueous sodium hydroxide (131 g; 3.28 mol in 250 mL of water) were added dibromobutane (155 mL; 1.30 mol) and TBAB (10.0 g; 0.03 mol). The mixture was heated at 85 °C under stirring for 12 h. After cooling to room temperature, the two layers were separated. The aqueous layer was extracted once with diethyl ether (200 mL). The organic layer was washed with a saturated aqueous solution of KH_2PO_4 (100 mL) and water (100 mL), dried over sodium sulfate (25 g), filtered and concentrated to give a yellow oil from which dibromobutane (190 g) was recovered by distillation (bp 38 °C at 0.6 mbar). Flash chromatography (petroleum ether–Et_2O: 9/1) of the residue afforded first compound **21** (4.0 g; 4%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.30 (qt, 2 H, J = 6.5 Hz, 1.5 Hz, CH_2CH:CH_2), 2.40 (t, 2 H, J = 2.5 Hz, ≡C*H*), 3.41 (s, 2 H, C_qCH_2O), 3.45 (t, 2 H, J = 6.5 Hz, OCH_2CH_2), 3.52 (s, 6 H, C_qCH_2O), 4.12 (d, 6 H, J = 2.5 Hz, $OCH_2C{\equiv}CH$), 4.98–5.10 (m, 2 H, CH_2CH:CH_2), 5.75–5.89 (m, 1 H, CH_2CH:CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 34.2 (CH_2CH:CH_2), 45.1 (C_q), 58.8 ($OCH_2C{\equiv}CH$), 69.2 (C_qCH_2O), 69.3 (C_qCH_2O), 70.8 (OCH_2CH_2), 74.1 (≡*C*H), 80.2 (*C*≡CH) 116.2 (CH_2CH:CH_2), 135.7 (CH_2CH:CH_2). **MS:** (ES+): $[M + 23]^+$: 327.3. **Anal.** Calcd for $C_{18}H_{26}BrO_4$: C, 71.03; H, 7.95; O, 21.03. Found: C, 70.98; H, 8.07; O, 21.01.

Eluted second was compound **20** as a colorless oil (107.7 g; 85%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.67–1.71 (m, 2 H, OCH_2CH_2), 1.92–1.97 (m, 2 H, $BrCH_2CH_2$), 2.40 (t, 2 H, J = 2.5 Hz, ≡C*H*), 3.39 (s, 2 H, C_qCH_2O), 3.41–3.47 (m, 4 H, $BrCH_2CH_2$, OCH_2CH_2), 3.51 (s, 6 H, C_qCH_2O), 4.12 (d, 6 H, J = 2.5 Hz, $OCH_2C{\equiv}CH$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 28.3 (OCH_2CH_2), 30.0 ($BrCH_2CH_2$), 34.0 ($BrCH_2CH_2$), 45.0 (C_q), 58.8 ($OCH_2C{\equiv}CH$), 69.2 (C_qCH_2O), 69.4 (C_qCH_2O), 70.4 (OCH_2CH_2), 74.2 (≡CH), 80.4 (*C*≡CH). **IR** (NaCl): 3292, 2876, 2116, 1091, 642 cm^{-1}. **MS** (ES+): 409.4. **HRMS** (ES+): Calcd for $C_{18}H_{25}BrO_4Na$: 407.0828. Found: 407.0832. **Anal.** Calcd for $C_{18}H_{25}BrO_4$: C, 56.11; H, 6.54. Found: C, 56.33; H, 6.31.

Compound 18

Method with $CuSO_4$–AscNa. To a solution of compound **20** (23.4 g; 60.7 mmol) and compound **12** (64.4 g; 182.2 mmol) in PEG_{400} (130 mL) at 0 °C were successively added, under stirring, a 1 M aqueous solution of $CuSO_4{\cdot}5H_2O$ (1.51 g; 6.07 mmol) and a 1 M aqueous solution of sodium ascorbate (2.41 g; 12.1 mmol). After 30 min, compound **18** was extracted with diethyl ether (2 × 200 mL). The organic layer was washed twice with a mixture of a saturated aqueous solution of ammonium chloride (50 mL) and a 28% aqueous solution of ammonia (15 mL) for 30 min, water (100 mL) and brine (100 mL), dried over sodium sulfate (50 g) and filtered. Evaporation of the solvent afforded compound **18** as a slightly orange oil (87.3 g; 99%) that was used in the next step without further purification. An analytical sample was obtained by flash chromatography (petroleum ether–AcOEt: 3/7). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.53–1.68 (m, 8 H, $OCH_2CH_2(CH_2)_2$), 1.83–2.03 (m, 8 H, $BrCH_2CH_2$, NCH_2CH_2), 3.34–3.47 (m, 42 H, $BrCH_2$, OCH_2CH_2, C_qCH_2O), 3.92 (dt, 18 H, J = 5.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 4.36 (t, 6 H, J = 7.5 Hz, NCH_2), 4.56 (s, 6 H, OCH_2C_q:CH), 5.11–5.27 (dq, 9 H, J = 10.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 5.27 (dq, 9 H, J = 17.5 Hz, J = 1.5 Hz, OCH_2CH:CH_2), 5.82–5.93 (m = 9 H, OCH_2CH:CH_2), 7.56 (s, 3 H, OCH_2C_q:CH). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.4 (OCH_2CH_2), 27.3 (NCH_2CH_2), 28.0 (OCH_2CH_2), 29.7 ($BrCH_2CH_2$), 33.8 ($BrCH_2$), 45.2 (C_q), 50.0 (NCH_2), 65.0 (OCH_2C_q:CH), 69.2 (C_qCH_2O), 69.7 (C_qCH_2O), 70.3 (OCH_2CH_2), 72.3 (OCH_2CH:CH_2), 116.2 (OCH_2CH:CH_2), 122.6 (OCH_2C_q:CH), 135.3 (OCH_2CH:CH_2), 145.3 (OCH_2C_q:CH). **IR** (NaCl): 3400, 3079, 3012, 2868, 1645, 1094 cm^{-1}. **MS:** (ES+): $[M + 23]^+$: 1468.8, $[M/2 + 23]^+$: 745.9. **HRMS** (ES+): Calcd for $C_{72}H_{118}BrN_9O_{16}Na_2$: 744.8832. Found: 744.8823. **Anal.** Calcd for $C_{72}H_{118}BrN_9O_{16}$: C, 59.82; H, 8.23; N, 8.72; O, 17.71. Found: C, 59.79; H, 7.99; N, 8.77; O, 17.47.

Method with copper turnings. A mixture of compound **20** (0.77 g–2.00 mmol) and compound **12** (2.13 g–6.03 mmol), copper turnings (0.5 g–7.86 mmol), water (1.2 mL), and PEG_{400} (8.4 g) was stirred at r.t. for 17 h and then at 60 °C for 8 h. The copper turnings were removed and the solution was extracted with Et_2O (2 × 12.5 mL), washed with water (5 mL) and brine (1 mL), dried over sodium sulfate (1 g), filtered and concentrated. Compound **18** was obtained as an oil (2.82 g – 97%).

Compound 19

To a solution of compound **18** (20.0 g; 13.8 mmol) in PEG_{400} (16 mL) was added sodium azide (0.99 g; 15.2 mmol). The mixture was heated at 60 °C under stirring for 2.5 h and then cooled to room temperature. Compound **19** was extracted with diethyl ether (2 × 20 mL). The organic layer was washed once with water (20 mL), dried over sodium sulfate (5 g) and filtered. Evaporation of diethyl ether afforded compound **19** as a slightly orange viscous oil (19.1 g; 98%) that was used in the next step without further purification. An analytical sample was obtained by flash chromatography (petroleum ether–AcOEt: 3/7). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.52–1.67 (m, 10 H, OCH_2CH_2, $N_3CH_2CH_2$), 1.91–2.03 (m, 6 H, NCH_2CH_2), 3.27 (t, 2 H, J = 6.5 Hz, N_3CH_2), 3.32–3.52 (m, 40 H, OCH_2CH_2), 3.92 (dt, 18 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 4.36 (t, 6 H, J = 7.5 Hz, NCH_2CH_2), 4.56 (s, 6 H, $OCH_2C_q{:}CH$), 5.11–5.27 (dq, 9 H, J = 10.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.11 (dq, 9 H, J = 10.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.24 (dq, 9 H, J = 17.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 5.79–5.92 (m = 9 H, $OCH_2CH{:}CH_2$), 7.56 (s, 3 H, $OCH_2C_q{:}CH$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.0 (OCH_2CH_2), 26.5 (OCH_2CH_2), 26.7 ($N_3CH_2CH_2$), 27.4 (NCH_2CH_2), 45.4 (C_q), 50.1 (NCH_2CH_2), 51.2 ($N_3CH_2CH_2$), 65.1 ($OCH_2C_q{:}CH$), 69.3 (C_qCH_2O), 69.8 (C_qCH_2O), 70.4 (OCH_2CH_2), 72.3 ($OCH_2CH{:}CH_2$), 116.2 ($OCH_2CH{:}CH_2$), 122.6 ($OCH_2C_q{:}CH$), 135.3 ($OCH_2CH{:}CH_2$), 145.3 ($OCH_2C_q{:}CH$). **IR** (NaCl): 3400, 3079, 2096, 1645, 1094 cm^{-1}. **MS:** (ES+): $[M + 23]^+$: 1429.8, $[M/2 + 23]^+$: 726.4. **HRMS** (ES+): Calcd for $C_{72}H_{118}N_{12}O_{16}Na_2$: 726.4287. Found: 726.4291. **Anal.** Calcd for $C_{72}H_{118}N_{12}O_{16}$: C, 61.43; H, 8.45; N, 11.94; O, 18.18. Found: C, 61.31; H, 8.41; N, 11.68; O, 18.15.

Compound 22

Method with $CuSO_4$/AscNa. To a solution of propargylated PEG **1** (20.0 g; 3.2 mmol) and compound **19** (20.0 g; 14.2 mmol) in THF (35 mL) and water (35 mL) were successively added, under stirring, $CuSO_4{\cdot}5H_2O$ (0.80 g; 3.2 mmol) and sodium ascorbate (1.27 g; 6.4 mmol). After 3 h, THF was evaporated and the aqueous phase was extracted with dichloromethane (3 × 60 mL). The combined organic layers were washed twice with a mixture of a saturated aqueous solution of ammonium chloride (50 mL) and a 28% aqueous solution of ammonia (15 mL) for 30 min, water (100 mL), dried over sodium sulfate (20 g), and filtered. The volume of the organic phase was reduced to 40 mL and compound **22** was precipitated under vigorous stirring at 0 °C by addition of Et_2O (250 mL). The precipitate was recovered by filtration and washed with Et_2O (100 mL) affording compound **22** as a white powder (26.4 g; 91%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.51–1.61 (m, 16 H, OCH_2CH_2), 1.92–2.01 (m, 16 H, NCH_2CH_2), 3.36–3.46 (m, 80 H, OCH_2CH_2), 3.57–3.75 (m, 560 H, PEG), 3.93 (dt, 36 H, J = 5.5 Hz, J = 1.5 Hz, $OCH_2CH{:}CH_2$), 4.35 (t, 16 H, J = 7.0 Hz, NCH_2CH_2), 4.54 (s, 12 H, $OCH_2C_q{:}CH$), 4.67 (s, 4 H, $OCH_2C_q{:}CH'$), 5.10 (dq, 18 H, J = 10.5 Hz, 1.5 Hz, $OCH_2CH{:}CH_2$), 5.23 (dq, 18 H, J = 17.5 Hz, 1.5 Hz, $OCH_2CH{:}CH_2$), 5.81–5.91 (m = 18 H, $OCH_2CH{:}CH_2$), 7.56 (s, 6 H, $OCH_2C_q{:}CH$), 7.60 (s, 2 H, $OCH_2C_q{:}CH$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.7 (OCH_2CH_2), 27.6 (NCH_2CH_2), 45.5 (C_q), 50.2 (NCH_2CH_2), 64.8 ($OCH_2C_q{:}CH$), 65.2 ($OCH_2C_q{:}CH$), 69.5 (C_qCH_2O), 70.0 (PEG-CH_2-O), 70.7 (OCH_2, PEG), 72.4 ($OCH_2CH{:}CH_2$), 116.2 ($OCH_2CH{:}CH_2$), 122.5 ($OCH_2C_q{:}CH$), 122.7 ($OCH_2C_q{:}CH$), 135.3 ($OCH_2CH{:}CH_2$), 145.3 ($OCH_2C_q{:}CH$). **MALDI-TOF MS**: found for the central peak: 9097 [M + Na].

Method with copper turnings. A mixture of bispropargylated PEG **1** (324 mg; 51.7 μmol), azido derivative **12** (176 mg; 125 μmol), copper turnings (233 mg; 3.6 mmol), water (0.5 mL), and THF (1 mL) was stirred at r.t. for 22 h and then at 60 °C for 2.5 h. The copper turnings were removed and the aqueous solution was diluted with water (20 mL), filtered on a PVDF membrane (47 mm, 0.45 μm) and the ultrafiltration was performed in Amicon 8050 stirred cells fitted with Amicon Ultracell PL Membrane Disks, molecular weight cutoff 1000, under 3.8 bar pressure. After the first ultrafiltration, the retentate (5 mL) was diluted with water (20 mL), and the solution was ultrafiltrated again to afford, after freeze drying, 430 mg of **22** as a white powder (91%).

Compound 23

Compound **22** (0.50 g; 0.056 mmol) was dissolved in ethanol (1 mL) by heating at 60 °C in a quartz tube equipped with a magnetic stirrer. After cooling to room temperature, mercaptoethanol **14** (0.35 mL; 5 mmol) was added. The mixture was submitted to UV irradiation at 254 nm under stirring for 14 h then diluted with 1 mL of ethanol, placed at −14 °C for 30 min. The white solid was then filtered and washed with diethyl ether (2 × 3 mL) affording compound **23** as a white powder (0.57 g; 99%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.50–1.63 (m, 16 H, OCH_2CH_2), 1.75–1.85 (m, 36 H, $SCH_2CH_2CH_2$), 1.92–2.00 (m, 16 H, NCH_2CH_2), 2.58 (t, 36 H, J = 7.0 Hz, $SCH_2CH_2CH_2$), 2.70 (t, 36 H, J = 5.5 Hz, SCH_2CH_2OH), 3.34 (s, 64 H, C_qCH_2O), 3.40–3.46 (m, 52 H, OCH_2CH_2), 3.63–3.71 (m, 590 H,$(OCH_2CH_2)_{140}O$, PEG, CH_2OH), 4.37 (t, 16 H, J = 7.0 Hz, NCH_2CH_2), 4.54 (s, 12 H, $OCH_2C_q{:}CH$), 4.66 (s, 4 H, $OCH_2C_q{:}CH$), 7.61 (s, 8 H, $OCH_2C_q{:}CH$). **^{13}C NMR** (91 MHz, $CDCl_3$): δ 26.9 (OCH_2CH_2), 27.7 (NCH_2CH_2), 28.9 ($SCH_2CH_2CH_2$), 30.2 ($SCH_2CH_2CH_2$), 35.4 (SCH_2CH_2OH), 45.7 (C_q), 50.4 (NCH_2CH_2), 61.0 (SCH_2CH_2OH), 65.3 ($OCH_2C_q{:}CH$), 69.7–69.9 (OCH_2CH_2), 70.8 (OCH_2, PEG), 122.9 ($OCH_2C_q{:}CH$), 145.4 ($OCH_2C_q{:}CH$). **MALDI-TOF MS**: found for the central peak: 10 503 [M + Na].

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