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Efficient synthesis of small-sized phosphonated dendrons: potential organic coatings of iron oxide nanoparticles†

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We report herein the synthesis of biocompatible small-sized phosphonated monomers and dendrons used as functional coatings of metal oxide nanoparticles, more specifically superparamagnetic iron oxides (SPIOs) for magnetic resonance imaging (MRI) and therapy through hyperthermia. The molecules were engineered to modulate their size, their hydrophilic and/or biocompatible character (poly(amido)amine *versus* oligoethyleneglycol), the number of anchoring phosphonate groups (monophosphonate *versus* phosphonic tweezers) and the number of peripheral functional groups for further grafting of dyes or specific vectors. Such a library of hydrophilic phosphonic acids opens new possibilities for the investigation of dendronized nanohybrids as theranostics.

Introduction

Research on inorganic nanoparticles (NPs) is rapidly expanding with a large variety of applications, as well as strategies for their synthesis.[1] Most often, surface modification of the NPs is critical, in particular to avoid their aggregation, make them dispersible in liquid media or derivatize them with functional end groups for further modification. Here again, the exceptional binding properties of phosphonic acids to oxide surfaces have attracted much attention and many examples of decorated magnetic metal oxide NPs using phosphonate terminated molecules have recently emerged in the literature.[2]

Many research groups worldwide are actively developing superparamagnetic iron oxide (SPIO) NPs with the emergence of a vast number of applications in health sciences, including for example combined *in vivo* magnetic resonance imaging (MRI) and optical imaging *via* multimodal NPs based on fluorescent probes conjugated to SPIO NPs,[3] hyperthermic heating of tumours,[4] and drug delivery.[5] In this context, biofunctionalization of the NPs is most often required to avoid aggregation or rapid clearance by the Mononuclear Phagocyte System.[6] For this purpose, appropriate coatings and especially surface modification using molecules derivatized with phosphonic acid groups are being developed. It is also worth noting that bisphosphonate anchors were found to bind more strongly to iron oxide NPs than monophosphonates, thus conferring them higher stability in water at physiological pH.[7]

Among the most common routes to functional phosphonic acids for surface modification are the Michaelis–Arbuzov and Michaelis–Becker reactions,[8] hydrophosphonylation with palladium (Tanaka's[9] or Beletskaya's[10] methods) or with nickel or copper,[11] the Hirao cross-coupling,[12] the phospha-Michael addition,[13] and the Pudovik reaction[14] starting from aldehydes. The Michaelis–Arbuzov reaction,[15] also known as the Arbuzov reaction, is one of the most versatile reactions for the formation of P–C bonds and consists of the reaction of a triester phosphite with an alkyl halide, resulting in the conversion of P(III) to a pentavalent phosphorus species. While elevated temperatures are required for the activation of the transformation, recent data have shown that for some specific substrates this reaction can be advantageously operated at room temperature in the presence of a suitable Lewis acid.[16] Barney *et al.*[17] recently proposed a straightforward synthesis of benzyl or allyl phosphonates from the corresponding alcohols using triethylphosphite and zinc iodide. Benzyl phosphonates esters are usually prepared from benzyl halides and trialkylphosphite *via* an Arbuzov reaction and this procedure is a convenient alternative, although benzylic compounds bearing an electron-withdrawing group are much less reactive. Moreover, such synthetic methodology allows introducing the phosphonate group in the last steps of the synthesis, which is advantageous since the chromatographic

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purification of phosphonate-containing intermediates throughout the whole multistep synthesis is time-consuming.

Dendrimers or dendritic architectures[18] are being developed for biomedical applications due to their precisely defined structure and composition, and high tuneable surface chemistry.[19] A clear input is brought by the dendritic molecules as they are discrete and monodisperse entities in which size, hydrophilicity, molecular weight and biocompatibility can easily be tuned as a function of their generation.[20] Furthermore, a dendritic shell allows versatile and reproducible polyfunctionalization at its periphery which could lead to, multimodal imaging probes through dye or fluorophore grafting, and theranostics through specific drug anchoring. Current studies show that small-sized dendrons may have an impressive future in the functionalization of magnetic nanoparticles[21] due to their highly controlled molecular structure and high tuneability leading to biocompatible, polyfunctional and water-soluble systems. Dendronized iron oxide nanoparticles using a phosphonate or hydroxamic acid anchor were shown to display very good colloidal properties and high relaxivity values.[22] Such anchoring groups induced strong binding,[23] and phosphonic anchors were demonstrated to preserve NPs' magnetic properties.[24]

We recently reported that a dendritic coating (Fig. 1) of magnetic metal oxide nanoparticles increases their effect on water proton relaxation times thus leading to optimized contrast enhancement capacities in MRI.[25]

Therefore, we managed to prepare a library of functional dendritic phosphonic acids either fully PEGylated (Part I) or derived from the poly(amido)amine (PAMAM) family (Part II). In both parts, the generation, the OEG chain length and the number of phosphonic anchors (mono-phosphonate or bisphosphonate tweezers) were varied. Such a library of functional hydrophilic phosphonic acids opens new possibilities for the investigation of dendronized nanohybrids as possible theranostics (Scheme 1).

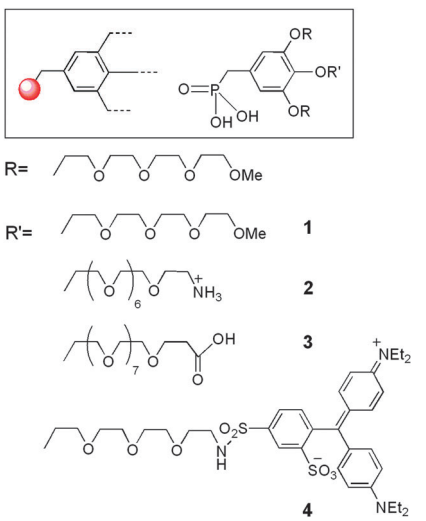
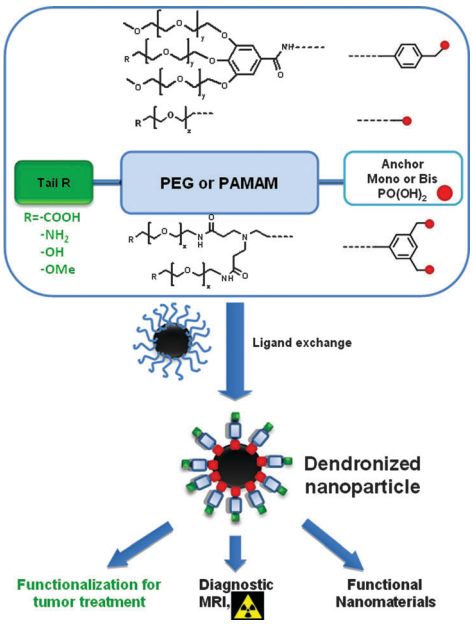


Fig. 1 Structure of phosphonic acid derivatives previously described.[26]



Scheme 1 General structure of synthesized compounds.

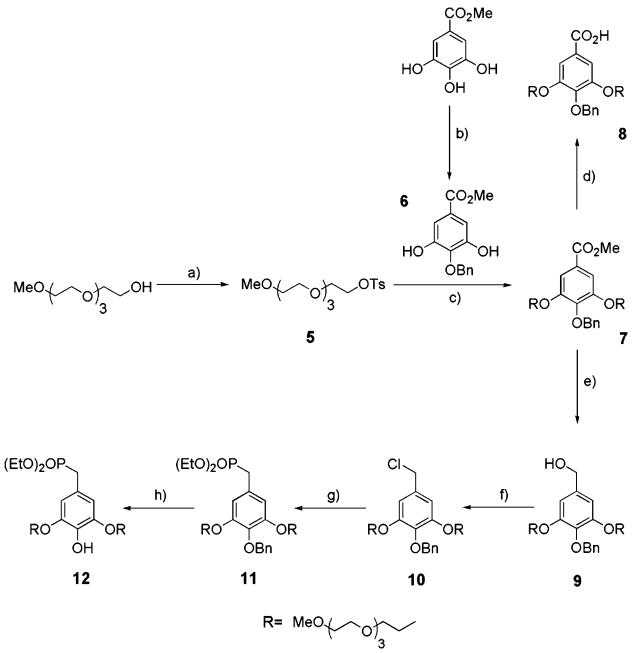
Results and discussion

Part I: PEGylated monomers

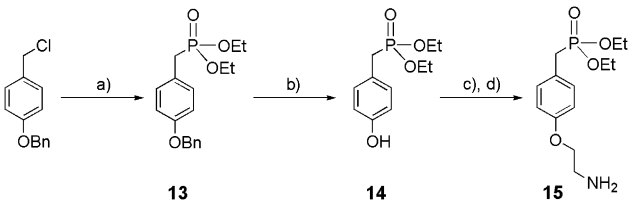
Synthesis of mono-ethylphosphonate. We have previously developed the synthesis of first generation monophosphonate oligoethylene glycol (OEG) gallate dendrons (G_1-P_1-OEG) **1–4** (Fig. 1) bearing a longer functionalized OEG chain in the *para* position for further grafting of biomolecules.[26] These small-sized monomers were obtained from the key intermediate **12** which was obtained in six steps with a 25% overall yield (Scheme 2). First, *para*-benzylated methyl gallate **6** and tosylated tetraethyleneglycol monomethyl ether **5** were obtained in good yields from the commercially available methyl gallate and tetraethyleneoxide monomethyl ether, respectively, following a reported one-step procedure.[27] A Williamson etherification between **5** and **6** in acetone at 60 °C, in the presence of potassium carbonate (K_2CO_3) and potassium iodide (KI), allowed the preparation of ester **7** in 75% yield. Protected ethyl phosphonate **11** was obtained following a three-step sequence: (i) reduction of the ester function by lithium aluminium hydride ($LiAlH_4$) to obtain benzylic alcohol **9** in 90% yield, (ii) treatment of **9** with thionyl chloride ($SOCl_2$) to yield benzyl chloride **10** (70%) and (iii) refluxing **10** at 160 °C in triethyl phosphate ($P(OEt)_3$) to prepare *para*-protected ethyl phosphonate **11** (85%). Finally, phenol deprotection was achieved by hydrogenolysis in the presence of palladium activated on carbon (Pd/C) (10%) which led, after overnight stirring, to ethyl phosphonate **12** in 96% yield.

Finally, monomers **1–4** (Fig. 1) were obtained after deprotection of the phosphonate esters with a large excess of trimethylsilyl bromide (TMSBr).[21]

The synthesis of ethyl phosphonate **15** displaying an ethylamine linker in the *para*-position is highlighted in Scheme 3. The compound was obtained in 4 steps with 54% overall yield.



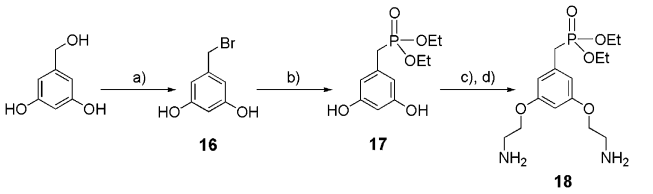
Scheme 2 Synthesis of mono-ethylphosphonate anchor **12**. (a) TsCl, NaOH, THF/H_2O, rt, 24 h, 94%; (b) benzyl bromide, $KHCO_3$, KI, DMF, 30 °C, 4 d, 70%; (c) K_2CO_3, KI, acetone, reflux, 24 h, 75%; (d) NaOH, MeOH/H_2O, reflux, 2 h, 90%; (e) $LiAlH_4$ 1 M in THF, THF, rt, 1 h, 90%; (f) $SOCl_2$, CH_2Cl_2, reflux, 2 h, 70%; (g) $P(OEt)_3$, 160 °C, 3 h, 85%; (h) Pd/C 10%, H_2, EtOH, rt, 16 h, 96%.



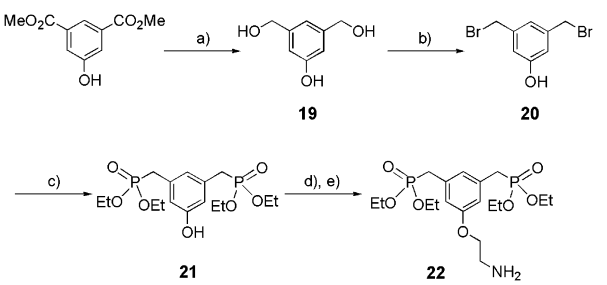
Scheme 3 Synthesis of mono-ethylphosphonate anchor **15**. (a) $P(OEt)_3$, 160 °C, 3 h, 92%; (b) Pd/C 10%, H_2, EtOH, rt, 16 h, 92%; (c) Boc-2-bromoethylamine, K_2CO_3, KI, acetone, reflux, 16 h; (d) TFA, CH_2Cl_2, 0 °C to rt, 16 h, 94%.

First, 4-(benzyloxy) benzyl chloride reacted under reflux with $P(OEt)_3$ to yield **13** (92%). Phenol **14** was obtained after hydrogenolysis in the presence of Pd/C (10%), and was next engaged in an etherification reaction in the presence of Boc-2-bromoethylamine. Subsequent treatment with trifluoroacetic acid (TFA) yielded **15** (94%).

Synthesis of bis-amino mono-ethylphosphonate. The synthetic route of the key intermediate **18** for the preparation of dendritic ethyl phosphonate is reported in Scheme 4. Benzyl bromide **16** was obtained in 84% yield from the commercially available 3,5-dihydroxybenzyl alcohol after its activation with triphenyl phosphine (PPh_3) and tetrabromomethane (CBr_4). Compound **16** was immediately converted to its corresponding ethyl phosphonate **17** after refluxing for 2 hours in $P(OEt)_3$. An etherification reaction between **17** and Boc-2-bromoethylamine, followed by the deprotection of the two amine functions in the presence of TFA, provided **18** as a ditrifluoroacetate salt (59% yield over 2 steps).



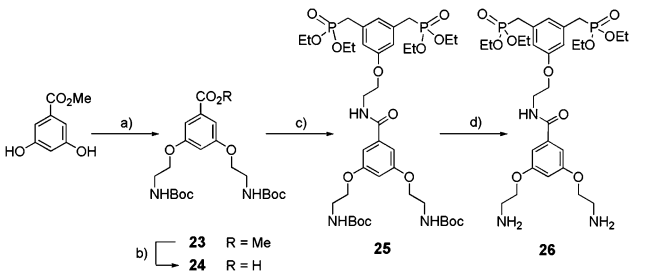
Scheme 4 Synthesis of mono-ethylphosphonate anchor **18**. (a) CBr_4, PPh_3, THF, 0 °C at rt, 2 h, 88%; (b) $P(OEt)_3$, 160 °C, 2 h, 75%; (c) Boc-2-bromoethylamine, K_2CO_3, KI, acetone, reflux, 16 h, 65%; (d) TFA, CH_2Cl_2, 0 °C to rt, 16 h, 95%.



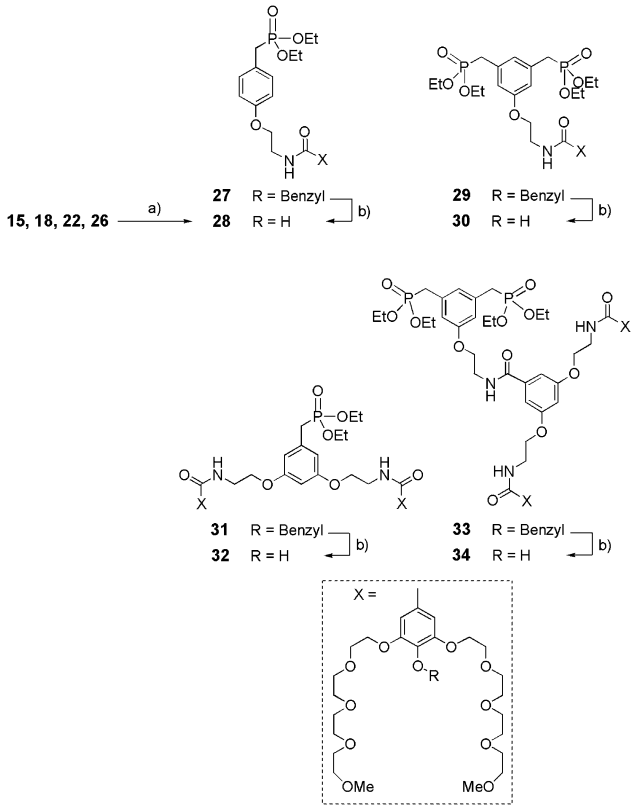
Scheme 5 Synthesis of bis-ethylphosphonate anchor **22**. (a) $LiAlH_4$ 1 M in THF, THF, reflux, 3 h, 94%; (b) HBr in acetic acid 30%, acetic acid, rt, 24 h, 96%; (c) $P(OEt)_3$, 160 °C, 2 h, 95%; (d) Boc-2-bromoethylamine, K_2CO_3, KI, acetone, reflux, 16 h, 76%; (e) TFA, CH_2Cl_2, 0 °C to rt, 16 h, 88%.

Synthesis of mono-amino bis-ethylphosphonate tweezers. The synthesis of tweezers **22** is detailed in Scheme 5. Its precursor **21** was obtained in three steps (reduction, bromination, and phosphorylation), with 86% overall yield, starting from the commercially available dimethyl-5-hydroxyisophthalate. Amine **22** was then easily prepared from **21** by Williamson etherification in the presence of Boc-2-bromoethylamine followed by the treatment with TFA (67% over 2 steps).

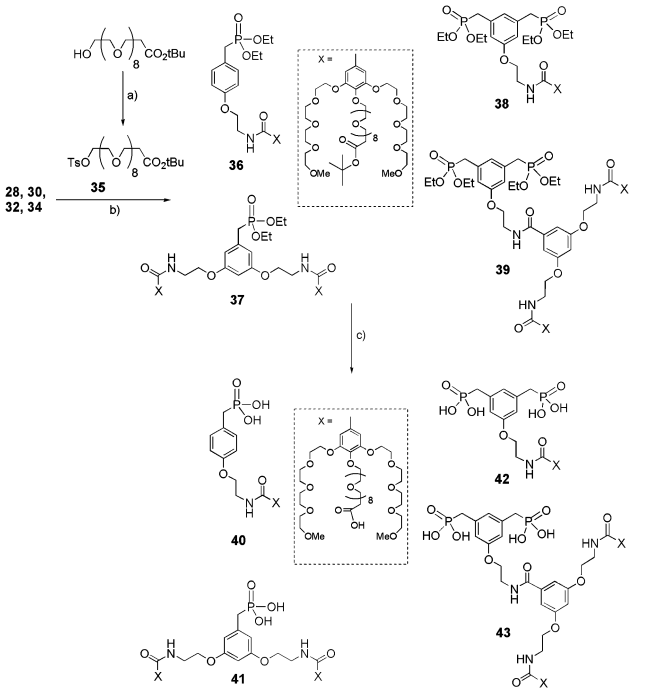
Synthesis of bis-amino bis-ethylphosphonate tweezers. Bis-ethyl phosphonate **26** was obtained following the synthetic route depicted in Scheme 6. Synthesis of the carboxylic acid intermediate **24** was accomplished in two steps starting from 3,5-dihydroxybenzoic acid methyl ester: etherification in acetone with Boc-2-bromoethylamine under basic conditions (**23**) (65%) followed by saponification by sodium hydroxide (NaOH) (86%). A peptide coupling between amine **22** and acid **24** in the



Scheme 6 Synthesis of bis-ethylphosphonate anchor **26**. (a) Boc-2-bromoethylamine, K_2CO_3, KI, acetone, reflux, 16 h, 65%; (b) NaOH, MeOH/H_2O, reflux, 2 h, 86%; (c) **22**, BOP, DIPEA, CH_2Cl_2, rt, 24 h, 65%; (d) TFA, CH_2Cl_2, 0 °C to rt, 16 h, 98%.



Scheme 7 Synthesis of dendritic ethylphosphonates **28–34**. (a) **8**, BOP, DIPEA, CH_2Cl_2, rt, 24 h, (70–85%); (b) Pd/C 10%, H_2, EtOH, rt, 16 h, (75–85%).



Scheme 8 Synthesis of dendritic and functional phosphonic acids **40–43**. (a) TsCl, NEt_3, CH_2Cl_2, rt, 24 h, (85%); (b) **35**, K_2CO_3, KI, acetone, reflux, 16 h, (70–90%); (c) TMSBr, CH_2Cl_2, rt, 16 h, (85–95%).

presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and *N*,*N*-diisopropylethylamine (DIPEA) led to **25** with 65% yield. Finally, Boc removal by TFA yielded **26** as a di-trifluoroacetate salt (98%).

Synthesis of dendritic mono- and bis-ethylphosphonates. The synthetic route to phenolic intermediates **28**, **30**, **32**, **34** is described in Scheme 7. Amines **15**, **18**, **22** or **26** underwent a peptide coupling type reaction with carboxylic acid **8** (obtained by saponification of **7** with NaOH, Scheme 2) in the presence of BOP and DIPEA to obtain benzylated compounds **27**, **29**, **31** or **33** (70–85%) respectively. Finally, hydrogenolysis in the presence of Pd/C led to the corresponding ethyl phosphonates **28**, **30**, **32** or **34**, respectively, with 75 to 85% yield.

Synthesis of COOH-functionalized dendritic phosphonic acids. Refluxing in concentrated hydrochloric acid (HCl) is an easy route for conversion of phosphonate esters into their acid analogues. However, for sensitive products requiring milder reaction conditions, McKenna's method[28] using bromotrimethylsilane (TMSBr) remains an efficient method which allows the obtention of trimethylsilyl phosphonate ester intermediates that hydrolyze *in situ* into phosphonic acids, in protic medium (water or alcohol).

In order to achieve the synthesis of phosphonic acids **40–43** bearing a long functionalized oligoethylene glycol chain in the *para* position, the first step was the synthesis of the common intermediate **35** (Scheme 8), which was obtained in good yield starting from the commercially available hydroxy-dPEG®$_8$-*t*-butylester.[29] **35** then underwent a Williamson reaction with ethylphosphonates **28**, **30**, **32** or **34** in acetone at 60 °C in the presence of K_2CO_3 and KI to yield the corresponding dendritic ethyl phosphonates **36–39** in 70–90% yield. Treatment of **36**, **37**, **38** or **39** with a large excess of TMSBr generated a phosphonic acid function at the focal point and converted the terminal *tert*-butyl ester group into its corresponding carboxylic acid. This step allowed the obtention of compounds **40–43** in 85–95% yields.

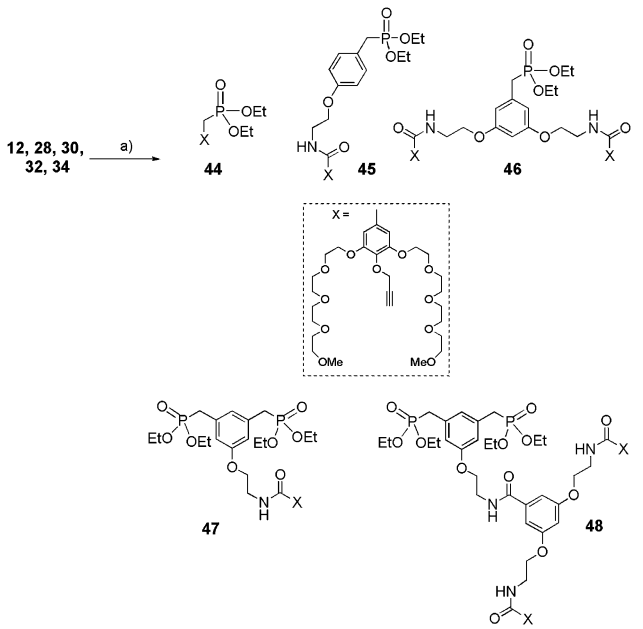
Synthesis of dye-functionalized dendritic phosphonic acids *via* click chemistry. Phenols **12** and **28**, **30**, **32**, **34** were subjected to an etherification reaction in acetone at reflux in the presence of propargyl bromide (Scheme 9).

The corresponding acetylenic derivatives **44–48** were engaged in click reactions with azide-derivatized Patent Blue VF Dye (Scheme 10).

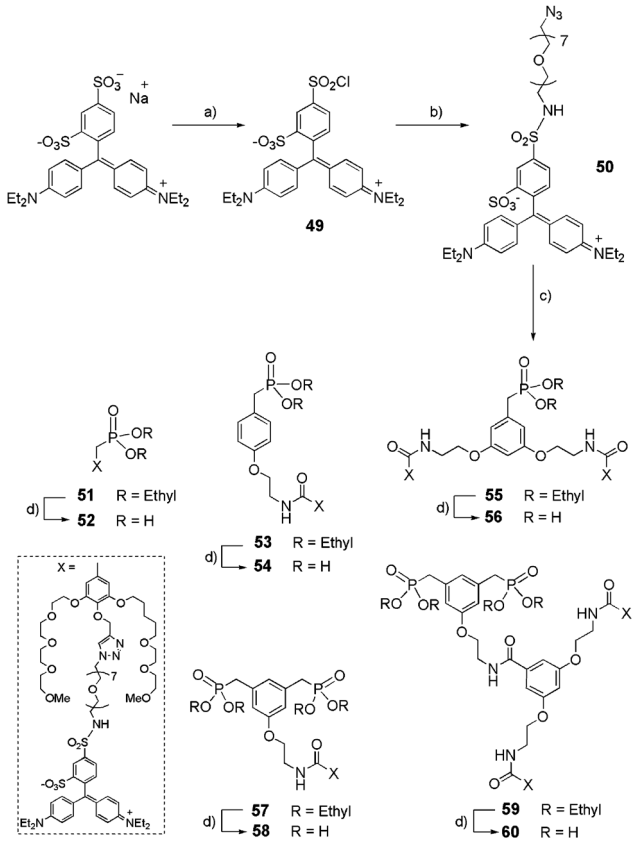
Patent Blue VF was first converted into sulfonyl chloride **49** by treatment with phosphoryl chloride ($POCl_3$) for 3 days and was used without further purification. The reaction between the commercially available OEGylated azide and sulfonyl chloride **49** led to the preparation of sulfonamide **50** in a moderate 50% yield. The click reaction between propargyl derivatives **44–48**, and **50**, in the presence of copper(II) sulphate ($CuSO_4{\cdot}5H_2O$) and sodium ascorbate, gave ethyl phosphonates **51**, **53**, **55**, **57**, **59** in 50–85% yields, which were then deprotected with an excess of TMSBr to yield their phosphonic acid derivatives **52**, **54**, **56**, **58**, and **60** (90–95% yield).

Part II: PAMAM-OEG dendrons

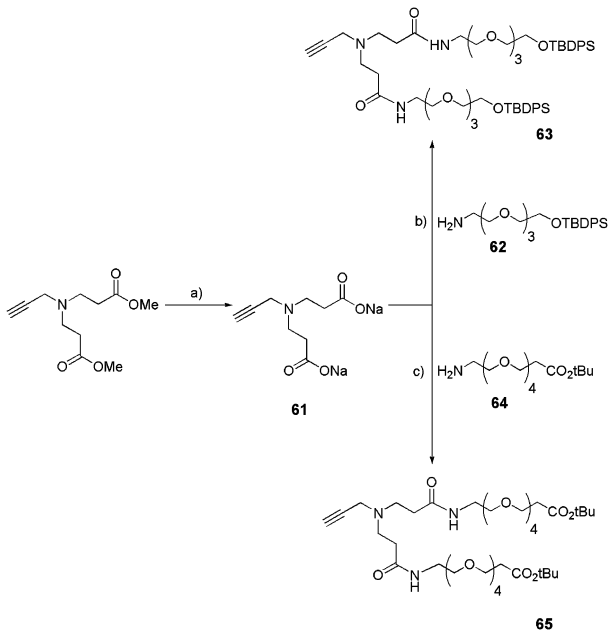
Another design of our small-size dendrons was based on a small poly(amido)amine structure. Precisely, alkyne monomer



Scheme 9 Synthesis of acetylenic derivatives **44** to **48**. (a) Propargyl bromide in xylene 80%, K_2CO_3, KI, acetone, reflux, 2 h, (80–90%).



Scheme 10 Synthetic route to dye-functionalized dendritic phosphonic acids **52**, **54**, **56**, **58** and **60**. (a) Patent Blue VF, $POCl_3$, rt, 3 d, 90%; (b) azido-dPEG™$_7$-amine, NEt_3, 4-DMAP, CH_2Cl_2/DMF, 0 °C to rt, 16 h, 50%; (c) **44**, **45**, **46**, **47** or **48**, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, DMSO/H_2O, rt, 16 h, (50–85%); (d) TMSBr, CH_2Cl_2, rt, 16 h, (90–95%).



Scheme 11 Introduction of functional OEG chains into a poly(amido)-amine monomer.[22c] (a) TMSONa 1 M, CH_2Cl_2, rt, 16 h, quant; (b) *N*,*N*′-diisopropylcarbodiimide (DIC), hydroxybenzotriazole (HOBt), DMF, 60 °C, 24 h, 70%; (c) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), HOBt, DIPEA, CH_3CN, rt, 16 h, 67%.

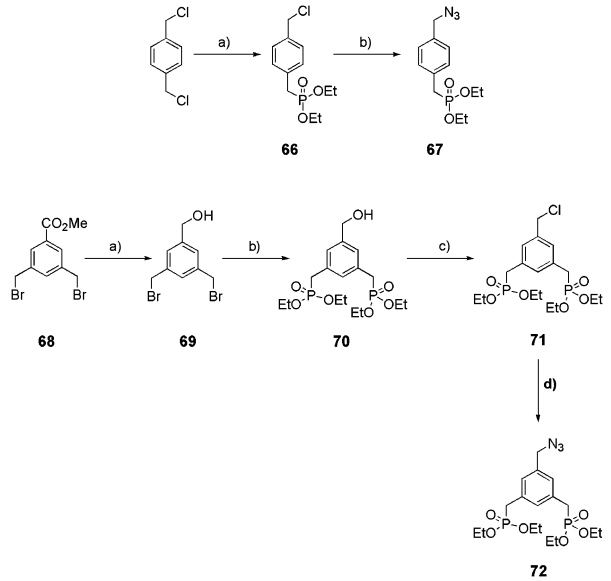
61 was synthesized following a reported procedure (Scheme 11).[30] After deprotection of the two methyl esters by sodium trimethylsilanolate (TMSONa), functionalized OEG chains (**62** or **64**) were introduced into the monomer by a peptide coupling reaction as shown in Scheme 11 to yield bifunctional acetylenic conjugates (**63** or **65**). The OEG chains were chosen for their tunable length and possible derivatization.

In parallel, two azide-derivatized ethylphosphonate precursors displaying one (**67**) or two (**72**) phosphorus anchors were synthetized (Scheme 12). The mono-ethylphosphonate precursor **67** was obtained in a two-step sequence starting from commercially available 1,4-bis(chloromethyl)benzene whereas the bis-ethylphosphonate anchor **72** was obtained in a four-step procedure starting from methyl-3,5-dibromomethylbenzoate **68** [22c,30,31] (Scheme 12).

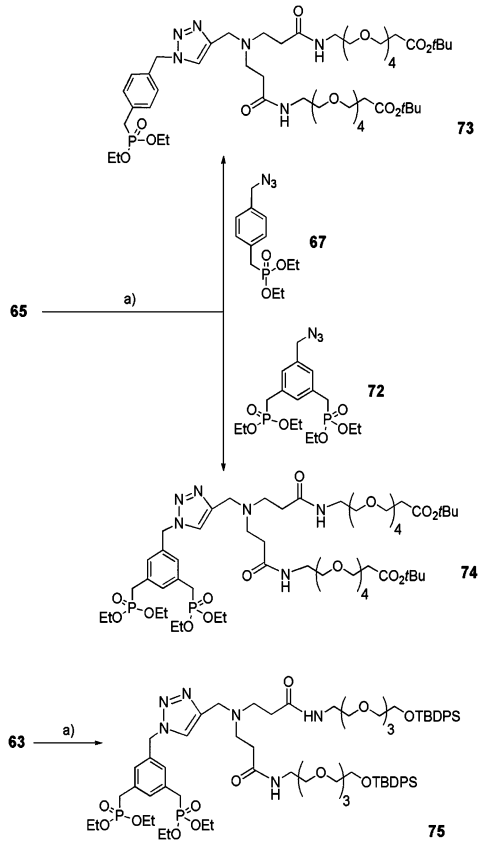
Acetylenic PAMAM monomers **63** and **65** underwent the click reaction catalyzed by Cu(II)$SO_4{\cdot}5H_2O$ in the presence of sodium ascorbate as the reducing agent with either azide **67** or **72** (Scheme 13) to yield mono-(**73**) or bis-ethylphosphonates **74** and **75**.

Part III: linear phosphonates

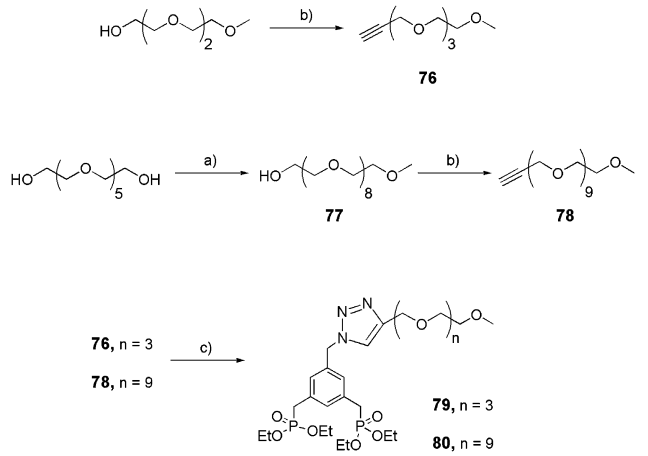
Linear aromatic bis-ethyl phosphonates were successfully prepared *via* the click reaction (Schemes 14 and 15).[32] Discrete short (**76**) or long (**78**)[33] alkyne-derivatized OEG arms were obtained quantitatively starting from their alcohol counterparts in the presence of propargylbromide and potassium *tert*-butoxide (*t*BuOK) in THF. They were then reacted with azide **72** following the same procedure described for **74–75** (Scheme 13) to yield linear bis-ethyl phosphonates **79** and **80,** respectively (Scheme 14).



Scheme 12 Synthesis of mono- and bis-ethylphosphonate azide precursors **67** and **72**. For precursor **67**: (a) $P(OEt)_3$, 120 °C, 2 h, 48%; (b) NaN_3, CH_3CN, reflux, 16 h, 95%. For precursor **72**: (a) DIBALH, toluene, 3 h, 0 °C, 90%; (b) $P(OEt)_3$, 2 h, 140 °C, quant; (c) $SOCl_2$, $CHCl_3$, 1 h, reflux, quant; (d) NaN_3, CH_3CN, reflux, 16 h, quant.



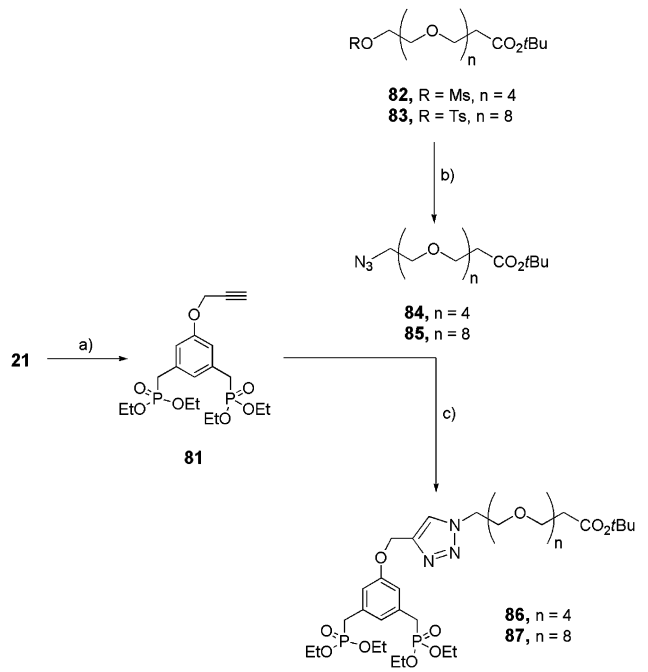
Scheme 13 Coupling between PAMAM monomers **63** or **65** and mono or bisphosphonate precursors **67** and **72** *via* click reaction. (a) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, THF/H_2O (4 : 1), rt, 16 h (**73**: 60%, **74**: 75%, **75**: 62%).



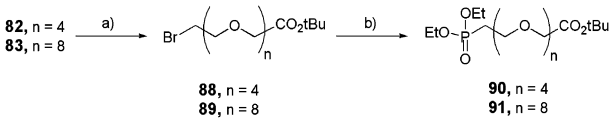
Scheme 14 Synthesis of linear bis-ethylphosphonates **79** and **80**. (a) TsO-PEG_3-Me,[25] KOH, THF, reflux, 18 h, 65%; (b) propargylbromide, *t*BuOK, THF, rt, 1 week; (c) **72**, $CuSO_4{\cdot}5H2O$/sodium ascorbate, THF/H_2O (4 : 1), rt, 16 h (**79**: 65%, **80**: 61%).

Functionalized and linear bis-ethyl phosphonates **86** and **87** were similarly (*via* click reaction) prepared starting from the azide-OEG arm **84** and **85** and the alkyne-derivatized aromatic bis-ethyl phosphonate **81** (Scheme 15).

Activated alcohols **82** and **83**[34] were quantitatively transformed into their azide derivatives **84** and **85** respectively *via* a nucleophilic substitution in the presence of sodium azide (NaN_3) in acetone, under reflux. In parallel, phenol **21** reacted with propargylbromide under basic conditions to obtain



Scheme 15 Synthesis of functional bis-ethylphosphonates **86** and **87**. (a) Propargylbromide, K_2CO_3, 18-crown-6, acetone, reflux, 16 h, 84%; (b) NaN_3, acetone, reflux, 16 h (**84** see ref. 30, **85**: quant); (c) **72**, $CuSO_4{\cdot}5H_2O$/sodium ascorbate, THF/H_2O (4 : 1), rt, 16 h (**86**: 32%, **87**: 69%).



Scheme 16 Synthesis of linear and functional mono-ethylphosphonates **90** and **91**. (a) LiBr, acetone, reflux, 16 h (**88**: 72%, **89**: 70%); (b) $P(OEt)_3$, reflux, 2 h (**90**: quant, **91**: 92%).

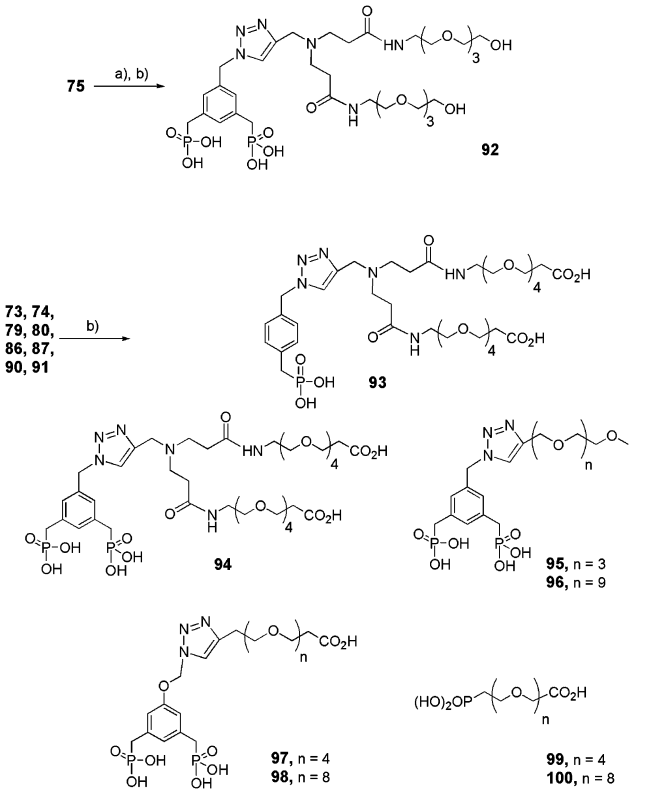
alkyne-derivatized bisphosphonate **81** which underwent the Cu(II) catalyzed Huisgen 1,3-dipolar cycloaddition in the presence of **84** or **85** and sodium ascorbate as the reducing agent, to obtain **86** (34%) and **87** (71%), respectively, in moderate yields.

Aliphatic and hydrophilic monophosphonates were prepared in a two-step sequence starting from the activated alcohols **82** and **83** (Scheme 16). Once transformed into their corresponding halides **88** and **89**, respectively, they underwent the second step of the Michaelis–Arbuzov reaction in the presence of $P(OEt)_3$ to obtain ethylphosphonates **90** and **91** quantitatively.

The final deprotection of the previously mentioned mono- or bis-ethylphosphonates (Schemes 13–16) was achieved in the presence of TMSBr, which allowed the simultaneous deprotection of *tert*-butyl esters of compounds **73**, **74**, **86**, **87**, **90** and **91**, whereas a two-step sequence was necessary to yield hydroxy-functionalized bis-phosphonic acid **92** (Scheme 17).

Proof of concept of dendronized iron oxide nanoparticles. Designing and synthesizing hybrid materials is of utmost importance since such materials can display strong versatility and adaptability in biomedical applications due to an appropriate organic coating. Aqueous suspensions of dendronized iron oxide nanoparticles (NPs), synthesized by co-precipitation (leading to naked NPs in water) or by thermal decomposition (NPs *in situ* coated by oleic acid in an organic solvent), have been obtained after functionalization of NPs with either phosphonic acid **1**, **2**, **3**,[21a,c,22b,25,26a] **4**, **58**, **60**,[26b] **92**,[22c] **93** [21c] or **94** [22c] (Fig. 2). Different grafting strategies have been optimized depending on the NPs synthetic method.[21a,24a,b] The size distribution, the colloidal stability in isoosmolar media (Fig. 3), the surface complex nature as well as the preliminary biokinetic studies performed with optical imaging, and the contrast enhancement properties evaluated through *in vitro* and *in vivo* MRI experiments, have been compared as a function of the nature of both organic shell and NPs.[22a–c,25,26a,b] All functionalized NPs displayed good colloidal stability in water; however, the ones bearing a peripheral carboxylic acid function gave the best results in iso-osmolar media.[22]

Whereas the grafting rates were similar, the nature of the surface complex depended on the NPs synthetic method. The *in vitro* contrast enhancement properties were better than commercial products (Table 1), with a better performance of the NPs synthesized by co-precipitation.[25] On the other hand, the NPs synthesized by thermal decomposition were more efficient *in vivo*. However, all of our previously reported studies[21,22,24–26] clearly highlighted that the dendritic organic coating impacts the nanoobject aggregation state, thus influencing the bioelimination speed and importance of the hepato-biliary *versus* urinary



Scheme 17 Final deprotection step of functional dendritic and linear mono- and bis-ethyl phosphonates. (a) TBAF, THF, rt, 16 h; (b) TMSBr, CH_2Cl_2, rt, 2–4 h (**92**: 75%, **93**: 98%, **94**: 91%, **95**: 98%, **96**: 99%, **97**: 98%, **98**: 97%, **99**: 83%, **100**: 99%).

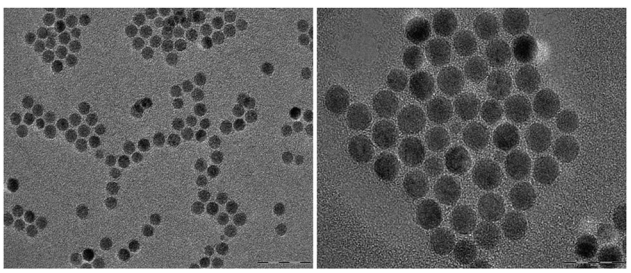


Fig. 2 TEM images of dendronized iron oxides NPs@**94** of 10 nm.[22c]

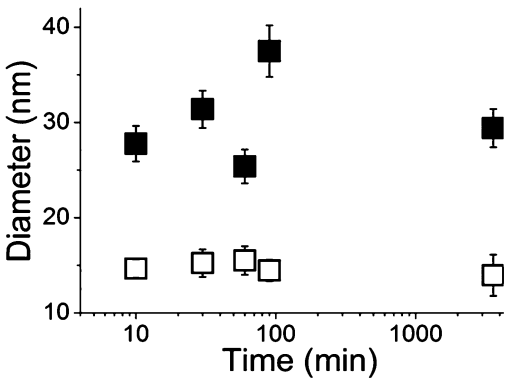


Fig. 3 Evolution of the size distribution of NP@**94** (■) and NP@**94** diluted (□) in sodium chloride medium (0.15 M NaCl) after 24 h.[22c]

Table 1 *In vitro* relaxivity studies (1.5 T, room temperature) of dendronized nanoparticles compared to commercially available polymer-coated nanoparticles

Compound (company)	Coating agent	D_H (nm)	$r1$ (mM^{-1} s^{-1})	$r2$ (mM^{-1} s^{-1})	$r2/r1$
Sinerem (Guerbet)	Dextran	51–30	9.9	65	6.7
NP@**1**	Dendritic-OEG monophosphonate	30 ± 1.5	6.2	91.2	14.7
NP@**94**	Dendritic-PAMAM bisphosphonate	30 ± 1.5	7.7	53.8	7.0

elimination pathway: NPs covered with small dendrons are more rapidly and completely eliminated within 24 hours post intravenous injection, predominantly by urinary elimination.

Conclusions

The chemistry of phosphonates and related multifunctional hybrids has witnessed an exponential growth, due to the potential applications of these compounds in medicine and nanobiomaterial research. A variety of discretely sized hydrophilic dendritic or linear phosphonic acids useful for the functionalization of metal oxide nanoparticles have been synthesized with high yields. A number of them were successfully grafted onto iron or manganese oxide nanoparticles through a ligand exchange method to afford stable and biocompatible nano-colloids, the bioelimination of which was mainly renal. This library of phosphonates may stimulate the development of advanced hybrid materials for better *in vivo* performance and sensitivity.

Experimental

General

All reactions were performed under an argon atmosphere. All the solvents, dichloromethane (CH_2Cl_2), tetrahydrofurane (THF), acetonitrile (CH_3CN), toluene, acetone, ethanol (EtOH), methanol (MeOH), chloroform ($CHCl_3$), dimethylformamide (DMF), ethyl acetate (EtOAc), and cyclohexane (CH), were of HPLC grade (chromasolv®, Sigma-Aldrich) further purified in a solvent system containing drying columns or dried over 4 Å molecular sieves. All commercially available reagents were used without further purification. Flash column chromatography was performed on silica gel (high-purity grade, 230–400 mesh, 40–63 μm, Sigma-Aldrich) according to a standard technique. Nuclear magnetic resonance spectra (^1H, ^{13}C and ^{31}P) were recorded on a Bruker spectrometer (300 MHz). Chemical shifts for ^1H and ^{13}C spectra are recorded in parts per million and are calibrated to solvent residual peaks (for example: $CHCl_3$: ^1H 7.26 ppm, ^{13}C 77.16 ppm; MeOH: ^1H 3.31 ppm, ^{13}C 49.00 ppm) according to ref. 35. Multiplicities are indicated by s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet) and m (multiplet). Coupling constants, *J*, are reported in Hertz. Exact mass was obtained through Matrix Assisted Laser Desorption Ionization Time Of Flight mass spectrometry (MALDI-TOF MS).

The experimental section is composed of the syntheses of phosphonated anchors and final compounds. All the other syntheses are described in the ESI† (^1H, ^{13}C, ^{31}P, Maldi-TOF, see ESI†).

Part I: amino or hydroxy-bearing mono- or bi-phosphonates

Compound 12. Palladium activated on carbon 10% (0.4 g, 0.75 mmol) was added to a solution of **11** (2.0 g, 2.6 mmol) dissolved in ethanol (30 mL). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 95 : 5) to afford **12** (2.5 mmol, 96%). Pale yellow oil. Spectroscopic data of **12** have already been reported in the literature.[29]

Compound 15. (2-Bromo-ethyl) carbamic acid *tert*-butyl ester (1.4 g, 6.3 mmol, 3 equiv.), K_2CO_3 (0.87 g, 6.3 mmol, 3 equiv.) and KI (0.05 g, 0.4 mmol, 0.2 equiv.) were added to a solution of **14** (0.5 g, 2.1 mmol) in acetone (25 mL). The mixture was stirred for 72 h at 65 °C, filtered over Celite and concentrated under reduced pressure. The resulting crude product was diluted in CH_2Cl_2 (50 mL) and washed twice with an aqueous saturated solution of $NaHCO_3$ and with brine. After drying over $MgSO_4$, filtration and evaporation of the solvent, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 95/5) to afford the protected amine as yellow oil in 63% yield. Trifluoroacetic acid (1.1 mL, 13 mmol, 10.0 equiv.) was added dropwise at 0 °C to a solution of Boc-protected amine (0.5 g, 1.3 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight at room temperature, and then the volatiles were evaporated. The crude product was dissolved in a mixture of CH_2Cl_2/MeOH (9/1) (20 mL) and was washed with NaOH 1 N (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **15** (1.97 mmol, 94%), which was used without further purification. White foam. ^1H NMR (300 MHz, CD_3OD) δ 7.20 (dd, J = 2.7 and 8.0 Hz, 2H, Ar-2,6-*H*), 6.85 (d, J = 8.0 Hz 2H, Ar-3,5-*H*), 4.02 (m, 6H, OCH_2CH_2NH and $PO(OCH_2CH_3)_2$), 3.08 (m, 4H, OCH_2CH_2NH and Ar^1CH_2P), 1.21 (t, J = 7.0 Hz, 6H, $PO(OCH_2CH_3)_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 157.8 (J = 3.3 Hz) (Ar), 130.7 (J = 6.6 Hz) (Ar), 123.6 (J = 9.3 Hz) (Ar), 114.6 (J = 2.7 Hz) (Ar), 70.0 (OCH_2), 62.0 (J = 6.6 Hz) (CH_2CH_3), 41.4 (CH_2NH_2), 32.5 (J = 138.9 Hz) (*C*H-P), 16.3 (J = 6.1 Hz) (CH_2CH_3); ^{31}P NMR (81 MHz, CD_3OD) δ 26.81. MS (MALDI-TOF) m/z calculated for $C_{13}H_{23}NO_4P$: 288.13, obtained: 288.19.

Compound 18. (2-Bromo-ethyl)carbamic acid *tert*-butyl ester (3.1 g, 13.9 mmol, 2.4 equiv.), K_2CO_3 (4.8 g, 34.6 mmol, 6 equiv.) and KI (0.2 g, 1.1 mmol, 0.2 equiv.) were added to a solution of **17** (1.5 g, 5.8 mmol) in acetone (120 mL). The mixture was stirred for 72 h at 65 °C, filtered over Celite and evaporated

under reduced pressure. The resulting crude product was diluted in CH_2Cl_2 (100 mL) and washed twice with an aqueous saturated solution of $NaHCO_3$ and with brine. After drying over $MgSO_4$, filtration and evaporation of the solvent, the crude product was purified by chromatography (SiO_2, CH_2Cl_2/MeOH 100 to 98/2) to afford the protected diamine as yellow oil in 65% yield. 2.4 mL of trifluoroacetic acid (27.4 mmol, 20.0 equiv.) was then added dropwise to a solution of protected diamine (0.75 g, 1.4 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then the volatiles were evaporated. Compound **18** was obtained as a salt (1.3 mmol, 95%) and was used without further purification. White foam. ^{1}H NMR (300 MHz, CD_3OD) δ 6.55 (t, J = 2.3 Hz, 2H, Ar-2,4-*H*), 6.42 (m, 1H, Ar-6-*H*), 4.11 (t, J = 5.0 Hz, 4H, OCH_2CH_2NH), 3.98–3.87 (m, 4H, $PO(OCH_2CH_3)_2$), 3.23–3.20 (m, 4H, $OCH_2CH_2NH_2$), 3.11 (d, J = 21.8 Hz, 2H, $ArCH_2P$), 1.18 (t, J = 7.0 Hz, 6H, $PO(OCH_2CH_3)_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 158.8 (J = 2.6 Hz) (Ar), 133.5 (J = 8.8 Hz) (Ar), 108.7 (J = 6.6 Hz) (Ar), 99.6 (J = 3.3 Hz) (Ar), 63.5 (OCH_2), 61.9 (J = 7.1 Hz) (CH_2CH_3), 38.2 (CH_2NH_2), 31.8 (J = 137.8 Hz) (*C*H-P), 14.8 (J = 6.0 Hz) (CH_2CH_3); ^{31}P NMR (81 MHz, CD_3OD) δ 27.24. MS (MALDI-TOF) m/z calculated for $C_{15}H_{27}NaN_2O_{13}P$: 369.17, obtained: 369.12; calculated for $C_{15}H_{27}Na_2N_2O_{13}P$: 392.17, obtained: 392.15.

Compound 22. (2-Bromo-ethyl)carbamic acid *tert*-butyl ester (1.1 g, 4.95 mmol, 1.3 equiv.), K_2CO_3 (2.1 g, 15.2 mmol, 4 equiv.) and KI (0.1 g, 0.4 mmol, 0.1 equiv.) were added to a solution of **21** (1.5 g, 3.8 mmol) in acetone (40 mL). The mixture was stirred for 48 h at 65 °C, filtered over Celite and evaporated under reduced pressure. The resulting crude product was diluted in CH_2Cl_2 (100 mL) and washed twice with an aqueous saturated solution of $NaHCO_3$ and with brine. After drying over $MgSO_4$, filtration and evaporation of the solvent, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98/2 to 95/5) to afford the (Boc-amino) derivative as a white solid (76%). The compound (1.2 g, 2.2 mmol) was then dissolved in anhydrous CH_2Cl_2 (30 mL) at 0 °C and trifluoroacetic acid (2 mL, 22.0 mmol, 10.0 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature, and then the volatiles were evaporated. The crude product was dissolved in CH_2Cl_2 (20 mL) and was washed with NaOH 1 N (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **21** (1.9 mmol, 88%) as a white foam, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (m, 3H, Ar-2,4,6-*H*), 5.25 (br s, 2H, $OCH_2CH_2NH_2$), 4.03–3.92 (m, 10H, $PO(OCH_2CH_3)_2$ and OCH_2CH_2NH), 3.10 (d, J = 21.7 Hz, 4H, $ArCH_2P$), 3.02 (m, 2H, OCH_2CH_2NH), 1.25 (t, J = 7.1 Hz, 12H, $PO(OCH_2CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 (J = 2.8 Hz) (Ar), 133.1 (J = 6.0 Hz) (Ar), 123.8 (J = 6.8 Hz) (Ar), 114.5 (J = 5.0 Hz) (Ar), 70.0 (OCH_2), 62.1 (J = 7.0 Hz) (CH_2CH_3), 41.5 (CH_2NH_2), 33.5 (J = 138.2 Hz) (*C*H-P), 16.5 (J = 2.7 Hz) (CH_2CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ 26.24. MS (MALDI-TOF) m/z calculated for $C_{18}H_{34}NO_7P_2$: 438.17, obtained: 438.18; calculated for $C_{18}H_{34}NaO_7P_2$: 460.17, obtained: 460.16.

Compound 26. Trifluoroacetic acid (780 μL, 8.0 mmol) was added dropwise to a solution of **25** (0.4 g, 0.4 mmol) in CH_2Cl^2 (15 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then the volatiles were evaporated. The compound **26** was obtained as a salt (0.39 mmol, 98%) and was used without further purification. White foam. ^{1}H NMR (300 MHz, CD3OD) δ 8.74 (m, 1H, $Ar^1OCH_2CH_2NH$), 8.55 (m, 4H, $Ar^2OCH_2CH_2NH_2$), 6.95 (m, 2H, Ar^1-2,6-*H*), 6.85–6.78 (m, 3H, Ar^2-2,4,6-*H*), 6.69 (m, 1H, Ar^1-4-*H*), 4.21 (m, 2H, $Ar^1OCH_2CH_2NH$), 4.05–3.90 (m, 12H, $Ar^2OCH_2CH_2NH$ and $PO(OCH_2CH_3)_2$), 3.78 (m, 2H, $Ar^1OCH_2CH_2NH$), 3.58–3.50 (m, 4H, $Ar^2OCH_2CH_2NH$), 3.08 (d, J = 22.0 Hz, 4H, Ar^1CH_2P), 1.25 (t, J = 7.0 Hz, 12H, $PO(OCH_2CH_3)_2$); ^{13}C NMR (75 MHz, CD3OD) δ 167.8 (*C*ONH), 158.7 (Ar), 136.2 (Ar), 132.5 (Ar), 123.3 (Ar), 114.1 (J = 4.9 Hz) (Ar), 105.8 (Ar), 104.4 (Ar), 65.6 (OCH_2-CH_2NH), 63.8 ($OCH_2CH_2NH_2$), 61.9 (J = 3.3 Hz) (CH_2CH_3), 38.8 ($CH_2NHCOAr$), 38.2 (CH_2NH_2), 31.4 (J = 147.8 Hz) (*C*H-P), 14.8 (J = 2.7 Hz) (CH_2CH_3); ^{31}P NMR (81 MHz, CD_3OD) δ 27.41. MS (MALDI-TOF) m/z calculated for $C_{29}H_{48}N_3O_{14}P_2$: 660.27, obtained: 660.24; calculated for $C_{29}H_{48}NaN_3O_{14}P_2$: 682.27, obtained: 682.22.

General procedure for the conversion of phosphonate ester to phosphonic acid by TMSBr (McKenna's method[28]) (40–43)

TMSBr (10.0 equiv. per ethyl phosphonate and *tert*-butyl ester function) was added dropwise to a solution of ethyl phosphonate (**36–39**) in CH_2Cl_2 at 0 °C. After stirring overnight at room temperature, the volatiles were evaporated and MeOH was added to the crude product, and then evaporated. The phosphonic acid was obtained without further purification.

Compound 40. Starting from **36** (0.13 g, 0.10 mmol) and TMSBr (0.26 mL, 2 mmol, 20 equiv.), **40** was obtained (0.09 mmol, 93%) as an orange oil. ^{1}H NMR (300 MHz, CD_3OD) δ 7.307.25 (m, 4H, Ar^1-2,6-*H* and Ar^2-2,6-*H*), 6.97 (d, J = 8.3 Hz, 2H, Ar^1-3,5-*H*), 4.31–4.18 (m, 8H, $Ar^1OCH_2CH_2NH$ and Ar^2OCH_2-CH_2O), 3.93 (m, 6H, OCH_2CH_2O), 3.85–3.50 (m, 56H, OCH_2-CH_2O), 3.41 (s, 6H, $OCH_2CH_2OCH_3$), 3.12 (d, J = 21.3 Hz, 2H, Ar^1CH_2P), 2.63 (t, 2H, J = 6.1 Hz, $Ar^2OCH_2CH_2COOH$); ^{13}C NMR (75 MHz, CD_3OD) δ 171.8 (*C*OOH), 167.8 (NH*C*O), 157.2 (Ar), 151.8 (Ar), 140.4 (Ar), 130.1 (J = 6.0 Hz) (Ar), 128.5 (Ar), 124.3 (J = 9.3 Hz) (Ar), 113.8 (Ar), 106.1 (Ar), 71.8 (PEG), 71.0 (PEG), 69.9 (PEG), 69.8 (PEG), 69.7 (PEG), 69.6 (PEG), 69.4 (PEG), 69.3 (PEG), 68.9 (PEG), 68.2 (PEG), 65.8 (OCH_2CH_2NH), 65.6 (CH_2CH_2COO), 57.2 (OCH_3), 50.1, 39.0 ($CH_2NHCOAr$), 33.9 (CH_2COO), 32.8 (J = 135.5 Hz) (*C*H-P); ^{31}P NMR (81 MHz, CD_3OD) δ 25.32. MS (MALDI-TOF) m/z calculated for $C_{53}H_{90}NaNO_{26}P$: 1210.55 obtained: 1220.57; calculated for $C_{61}H_{106}KNO_{26}P$: 1226.55, obtained: 1226.58.

Compound 41. Starting from **37** (0.1 g, 0.04 mmol) and TMSBr (0.16 mL, 1.2 mmol, 30 equiv.), **41** was obtained (0.034 mmol, 86%) as an orange oil. ^{1}H NMR (300 MHz, CD_3OD) δ 7.28 (s, 4H, Ar^2-2,6-*H*), 6.62 (t, 2H, J = 2.0 Hz, Ar^1-2,6-*H*), 6.51 (t, J = 2.0 Hz, 1H, Ar^1-4-*H*), 4.30–4.25 (m, J = 4.3 Hz, 12H, $Ar^2OCH_2CH_2O$), 4.20 (t, 4H, J = 5.3 Hz, $Ar^1OCH_2CH_2NH$), 3.95–3.75 (m, 16H, $Ar^1OCH_2CH_2NH$ and OCH_2CH_2O), 3.80–3.55 (m, 108H, OCH_2CH_2O), 3.41 (s, 12H, $OCH_2CH_2OCH_3$), 3.12 (d, J = 21.4 Hz, 2H, Ar^1CH_2P), 2.62 (t, 4H, J = 6.6 Hz, $Ar^2OCH_2CH_2$-COOH); ^{13}C NMR (75 MHz, CD_3OD) δ 172.2 (*C*OOH), 168.2 (NH*C*O), 159.8 (J = 3.3 Hz) (Ar), 152.2 (Ar), 141.1 (Ar), 129.2 (Ar), 108.7 (J = 6.6 Hz) (Ar), 106.4 (Ar), 72.2 (PEG), 71.6 (PEG),

70.3 (PEG), 70.2 v, 70.1 (PEG), 70.0 (PEG), 70.3 (PEG), 69.9 (PEG), 69.5 (PEG), 68.7 (PEG), 66.3 (OCH_2CH_2NH), 66.1 (CH_2CH_2COO), 57.8 (OCH_3), 50.8, 39.5 ($CH_2NHCOAr$), 33.8 (CH_2COO), 32.6 (J = 133.4 Hz) (*C*H-P); ^{31}P NMR (81 MHz, CD_3OD) δ 24.22. MS (MALDI-TOF) m/z calculated for $C_{99}H_{171}NaN_2O_{49}P$: 2223.07 obtained: 2223.09.

Compound 42. Starting from **38** (0.2 g, 0.14 mmol) and TMSBr (0.55 mL, 3 mmol, 30 equiv.), **42** was obtained (0.13 mmol, 94%) as an orange oil. ^{1}H NMR (300 MHz, CD_3OD) δ 7.28 (s, 2H, Ar^2-2,6-*H*), 6.92–6.86 (m, 3H, Ar^1-2,4,6-*H*), 4.35–4.20 (m, 8H, $Ar^2OCH_2CH_2O$ and $Ar^1OCH_2CH_2NH$), 3.92–3.82 (m, 8H, $Ar^1OCH_2CH_2NH$ and OCH_2CH_2O), 3.80–3.53 (m, 54H, OCH_2CH_2O), 3.38 (s, 6H, $OCH_2CH_2OCH_3$), 3.18 (d, J = 21.8 Hz, 4H, Ar^1CH_2P), 2.62 (t, 2H, J = 6.0 Hz, $Ar^2OCH_2CH_2COOH$); ^{13}C NMR (75 MHz, CD_3OD) δ 172.2 (*C*OOH), 167.1 (NH*C*O), 158.8 (Ar), 152.3 (Ar), 141.0 (Ar), 134.8 (J = 6.0 Hz) (Ar), 128.8 (Ar), 123.8 (Ar), 114.3 (Ar), 106.4 (Ar), 72.2 (PEG), 71.7 (PEG), 70.4 (PEG), 70.25 (PEG), 70.15 (PEG), 70.1 (PEG), 70.0 (PEG), 69.95 (PEG), 69.4 (PEG), 68.8 (PEG), 66.3 (OCH_2CH_2NH), 66.1 (CH_2CH_2COO), 57.8 (O*C*H3), 50.8, 39.6 ($CH_2NHCOAr$), 34.6 (CH_2COO), 33.6 (J = 134.5 Hz) (*C*H-P); ^{31}P NMR (81 MHz, CD_3OD) δ 25.19. MS (MALDI-TOF) m/z calculated for $C_{54}H_{94}NO_{29}P_2$: 1282.53, obtained: 1282.46; calculated for $C_{54}H_{93}NaNO_{29}P_2$: 1304.53, obtained: 1304.45.

Compound 43. Starting from **39** (0.08 g, 0.03 mmol) and TMSBr (0.16 mL, 1.2 mmol, 40 equiv.), **43** was obtained (0.028 mmol, 93%) as an orange oil. ^{1}H NMR (300 MHz, CD_3OD) δ 7.27 (s, 4H, Ar^3-2,6-*H* and Ar^2-4-*H*), 7.11 (d, J = 1.7 Hz, 2H, Ar^2-2,6-*H*), 6.90–6.85 (m, 3H, Ar^1-2,4,6-*H*), 6.82 (m, 1H, Ar^2-4-*H*), 4.30–4.18 (m, 18H, $Ar^1OCH_2CH_2NH$, $Ar^2OCH_2CH_2NH$ and $Ar^3OCH_2CH_2O$), 3.95–3.83 (m, 18H, $Ar^1OCH_2CH_2NH$, $Ar^2OCH_2CH_2NH$ and OCH_2CH_2O), 3.80–3.53 (m, 108H, OCH_2CH_2O), 3.38 (s, 12H, $OCH_2CH_2OCH_3$), 3.12 (d, J = 21.6 Hz, 4H, Ar^1CH_2P), 2.63 (t, 4H, J = 6.6 Hz, $Ar^3OCH_2CH_2COOH$); ^{13}C NMR (75 MHz, CD_3OD) δ 172.1 (*C*OOH), 168.2 (NH*C*O), 159.9 (Ar), 158.8 (Ar), 152.2 (Ar), 140.8 (Ar), 136.2 (Ar), 134.3 (Ar), 129.0 (Ar), 114.3 (Ar), 106.5 (Ar), 105.8 (Ar), 104.5 (Ar), 72.2 (PEG), 71.5 (PEG), 70.3 (PEG), 70.2 (PEG), 70.1 (PEG), 70.0 (PEG), 69.95 (PEG), 69.9 (PEG), 69.4 (PEG), 68.6 (PEG), 66.2 (OCH_2CH_2NH), 65.8 (CH_2CH_2COO), 57.8 (OCH_3), 50.8, 39.4 ($CH_2NHCOAr$), 34.5 (CH_2COO), 34.1 (J = 136.2 Hz) (*C*H-P); ^{31}P NMR (81 MHz, CD_3OD) δ 24.03. MS (MALDI-TOF) m/z calculated for $C_{79}H_{127}N_3O_{34}P_2$: 1723.78, obtained: 1723.46; calculated for $C_{29}H_{53}NaO_{14}P$: 679.31, obtained: 679.24.

General procedure for the conversion of phosphonate ester to phosphonic acid by TMSBr (McKenna's method[28]) (52, 54, 56, 58, and 60)

TMSBr (10.0 equiv. per ethyl phosphonate) was added dropwise to a solution of ethyl phosphonate (**51**, **53**, **55**, **57**, **59**) in CH_2Cl_2 at 0 °C. After stirring overnight at room temperature, the volatiles were evaporated and MeOH was added to the crude product and then evaporated several times. The phosphonic acid was obtained without further purification.

Compound 52. Starting from **51** (0.12 g, 0.07 mmol), **52** was obtained (0.06 mmol, 90%) as a dark yellow-green foam without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.77 (s, 1H, ArTriazole-*H*), 8.54 (d, J = 1.9 Hz, 1H, Ardye-2-*H*), 8.09 (dd, J = 1.7 and 7.9 Hz, 1H, Ardye-6-*H*), 7.62 (d, 4H, J = 8.2 Hz, Ardye-AA′-*H*), 7.52 (d, J = 7.8 Hz, 1H, Ardye-5-*H*), 7.44 (d, 4H, J = 9.4 Hz, Ardye-BB′-*H*), 6.68 (d, J = 2.2 Hz, 2H, Ar^1-2,6-*H*), 5.34 (s, 2H, OCH_2Ar-Triazole-CH_2), 4.89 (t, J = 4.6 Hz, 2H, OCH_2ArTriazole-CH_2), 4.18 (t, J = 4.4 Hz, 4H, $Ar^1OCH_2CH_2$), 4.04 (t, J = 4.6 Hz, 2H, CH_2-CH_2NHO_2), 3.88–3.80 (m, 12H, OCH_2CH_2O and $N(CH_2CH_3)_2$), 3.72–3.50 (m, 50H, OCH_2CH_2O), 3.32 (s, 6H, $OCH_2CH_2OCH_3$), 3.18 (t, J = 5.2 Hz, 2H, $CH_2CH_2NHO_2$), 3.14 (d, J = 22.0 Hz, 2H, Ar^1CH_2P), 1.31 (t, J = 7.1 Hz, 12H, $N(CH_2CH_3)_2$); 13C NMR (75 MHz, CD_3OD) δ 158.5 (J = 3.3 Hz) (Ardye = N), 145.2 (Ar), 142.1 (ArTriazole), 140.6 (Ar), 139.5 (Ar), 139.1 (Ar), 134.2 (Ar), 131.8 (Ar), 129.5 (J = 8.8 Hz) (Ar), 127.6 (ArTriazole), 127.2 (Ar), 127.1 (Ar), 125.8 (Ar), 116.0 (Ar), 107.8 (J = 6.6 Hz) (Ar), 71.9 (OCH2-ArTriazole), 71.0 (PEG), 70.7 (PEG), 70.6 (PEG), 70.5 (PEG), 70.4 (PEG), 68.8 (PEG), 68.6 (PEG), 67.5 (OCH_2CH_2NH), 62.5 (PEG), 60.2 (PEG), 57.2 (OCH_3), 52.2 (ArTriazole-CH_2), 48.4 ($N(CH_2CH_3)_2$), 42.1 (CH_2NHSO_2), 33.9 (J = 138.5 Hz) (*C*H-P), 10.8 ($N(CH_2CH_3)_2$); ^{31}P NMR (81 MHz, CD_3OD) δ 24.09. MS (MALDI-TOF) m/z calculated for $C_{71}H_{112}N_6O_{26}PS_2$: 1559.67, obtained: 1559.56; calculated for $C_{71}H_{111}NaN_6O_{26}PS_2$: 1581.67, obtained: 1581.55.

Compound 54. Starting from **53** (0.11 g, 0.06 mmol), **54** was obtained (0.055 mmol, 94%) as a dark yellow-green foam without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.82 (s, 1H, ArTriazole-*H*), 8.61 (m, 1H, Ardye-2-*H*), 8.18 (m, 1H, Ardye-6-*H*), 7.72–7.52 (m, 9H, Ardye-5-*H*, Ardye-AA′-*H* and Ardye-BB′-*H*), 7.36 (s, 2H, Ar2-2,6-*H*), 7.28 (d, 2H, J = 7.6 Hz, Ar^1-2,6-*H*), 6.97 (d, 2H, J = 7.6 Hz, Ar^1-3,5-*H*), 5.49 (s, 2H, OCH_2ArTriazole-CH_2), 4.95 (m, 2H, OCH_2ArTriazole-CH_2), 4.30 (m, 4H, $Ar^2OCH_2CH_2$), 4.21 (t, 2H, J = 4.7 Hz, $Ar^1OCH_2CH_2NH$), 4.08 (t, J = 4.7 Hz, 2H, $CH_2CH_2NHO_2$), 3.88–3.80 (m, 6H, OCH_2CH_2O and $Ar^1OCH_2CH_2NH$), 3.82–3.50 (m, 58H, OCH_2CH_2O and $N(CH_2CH_3)_2$), 3.38 (s, 6H, $OCH_2CH_2OCH_3$), 3.22 (t, J = 5.2 Hz, 2H, $CH_2CH_2NHO_2$), 3.20 (d, J = 22.0 Hz, 2H, Ar^1CH_2P), 1.38 (t, J = 7.1 Hz, 12H, $N(CH_2CH_3)_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 167.8 (NH*C*O), 157.9 (J = 3.3 Hz) (Ar), 152.1 (Ardye = N), 145.2 (Ar), 142.7 (ArTriazole), 140.6 (Ar), 139.5 (Ar), 138.1 (Ar), 130.8 (J = 8.8 Hz) (Ar), 130.3 (Ar), 128.9 (Ar), 128.1 (ArTriazole), 126.5 (Ar), 124.7 (J = 9.6 Hz) (Ar), 120.1 (Ar), 114.4 (Ar), 106.1 (Ar), 72.1 (OCH_2-ArTriazole), 71.5 (PEG), 70.7 (PEG), 70.6 (PEG), 70.5 (PEG), 70.4 (PEG), 69.4 (PEG), 69.2 (PEG), 68.5 (PEG), 67.8 (PEG), 66.1 (OCH_2CH_2NH), 62.5 (PEG), 60.8 (PEG), 57.8 (OCH_3), 53.2 (ArTriazole-CH_2), 48.6 ($N(CH_2CH_3)_2$), 42.8 (CH_2NHSO_2), 39.4 ($CH_2NHCOAr$), 32.9 (J = 135.1 Hz) (*C*H-P), 11.2 ($N(CH_2CH_3)_2$); ^{31}P NMR (81 MHz, CD_3OD) δ 26.69. MS (MALDI-TOF) m/z calculated for $C_{80}H_{121}N_7O_{28}PS_2$: 1722.74, obtained: 1722.61; calculated for $C_{80}H_{120}NaN_7O_{28}PS_2$: 1744.74, obtained: 1744.63.

Compound 56. Starting from **55** (0.1 g, 0.03 mmol), **56** was obtained (0.028 mmol, 95%) as a dark yellow-green foam without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (s, 2H, ArTriazole-*H*), 8.57 (m, 2H, Ardye-2-*H*), 8.08 (m, 1H, Ardye-6-*H*), 7.62–7.55 (d, 8H, J = 9.2 Hz, Ardye-AA′-*H*), 7.48 (d, 2H, J = 8.0 Hz, Ardye-5-*H*), 7.38–7.30 (m, 8H, Ardye-BB′-*H*), 7.27 (s, 4H, Ar^2-2,6-*H*), 6.53 (m, 2H, Ar^1-2,6-*H*), 6.45 (m, 1H, Ar^1-4-*H*),

5.41 (s, 4H, OCH_2ArTriazole-CH_2), 4.84 (t, J = 4.6 Hz, 4H, OCH_2-ArTriazole-CH_2), 4.22 (m, 8H, Ar^{2}OCH_2CH_2), 4.18–4.11 (m, 4H, Ar^{1}OCH_2CH_2NH), 3.98 (t, J = 4.6 Hz, 4H, CH_2CH_2NHO$_2$), 3.90–3.84 (m, 12H, OCH_2CH_2O, Ar^{1}OCH$_2$CH_2NH), 3.82–3.48 (m, 116H, OCH_2CH_2O and N(CH_2CH$_3$)$_2$), 3.32 (s, 12H, OCH_2-CH_2OCH_3), 3.18 (t, J = 5.0 Hz, 4H, CH$_2$CH_2NHO$_2$), 3.12 (d, J = 21.5 Hz, 2H, Ar^{1}CH_2P), 1.28 (t, J = 7.0 Hz, 24H, N(CH$_2$CH_3)$_2$); ^{13}C NMR (75 MHz, CD$_3$OD) δ 166.7 (NH*C*O), 159.9 (Ar), 152.2 (Ardye = N), 145.7 (Ar), 142.6 (ArTriazole), 140.8 (Ar), 139.7 (Ar), 139.1 (Ar), 138.4 (Ar), 132.2 (Ar), 130.5 (Ar), 128.4 (Ar), 127.8 (ArTriazole), 126.6 (Ar), 124.8 (Ar), 119.1 (Ar), 108.9 (Ar), 106.2 (Ar), 72.1 (O*C*H$_2$-ArTriazole), 71.6 (PEG), 70.7 (PEG), 70.6 (PEG), 70.55 (PEG), 70.5 (PEG), 70.45 (PEG), 70.4 (PEG), 69.5 (PEG), 69.3 (PEG), 68.5 (PEG), 68.2 (PEG), 66.2 (O*C*H$_2$CH$_2$NH), 62.8 (PEG), 60.7 (PEG), 57.8 (O*C*H$_3$), 52.7 (ArTriazole-*C*H$_2$), 48.5 (N(*C*H$_2$CH$_3$)$_2$), 42.8 (*C*H$_2$NHSO$_2$), 39.3 (*C*H$_2$NHCOAr), 33.1 (J = 135.2 Hz) (*C*H-P), 11.2 (N(CH$_2$*C*H$_2$)$_2$); ^{31}P NMR (81 MHz, CD$_3$OD) δ 23.91. MS (MALDI-TOF) m/z calculated for $C_{152}H_{229}N_{14}O_{53}PS_4$: 3259.74, obtained: 3260.41.

Compound 58. Starting from **57** (0.22 g, 0.11 mmol), **58** was obtained (0.10 mmol, 98%) as a dark yellow-green foam without further purification. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.78 (s, 1H, ArTriazole-*H*), 8.55 (m, 1H, Ardye-2-*H*), 8.11 (m, 1H, Ardye-6-*H*), 7.70–7.50 (m, 9H, Ardye-5-*H*, Ardye-AA′-*H* and Ardye-BB′-*H*), 7.30 (s, 2H, Ar^2-2,6-*H*), 6.88 (m, 3H, Ar^1-2,4,6-*H*), 5.51 (s, 2H, OCH_2ArTriazole-CH_2), 4.91 (m, 2H, OCH$_2$ArTriazole-CH_2), 4.30 (m, 4H, Ar^{2}OCH_2CH_2), 4.26 (m, 2H, Ar^{1}OCH_2CH_2NH), 4.04 (m, 2H, CH_2CH$_2$NHO$_2$), 3.90–3.82 (m, 6H, OCH$_2$CH_2O and Ar^{1}OCH$_2$CH_2NH), 3.82–3.50 (m, 58H, OCH$_2$CH_2O and N(CH_2-CH_3)$_2$), 3.31 (s, 6H, OCH$_2$CH$_2$OCH_3), 3.21 (d, J = 22.0 Hz, 4H, Ar^{1}CH_2P), 3.19 (m, 2H, CH$_2$CH_2NHO$_2$), 1.32 (m, 12H, N(CH$_2$-CH_3)$_2$); ^{13}C NMR (75 MHz, CD$_3$OD) δ 167.8 (NH*C*O), 158.8 (Ar), 152.1 (Ardye = N), 142.7 (ArTriazole), 140.4 (Ar), 139.5 (Ar), 138.3 (Ar), 133.2 (Ar), 131.1 (Ar), 130.4 (Ar), 128.9 (Ar), 128.1 (Ar), 127.5 (ArTriazole), 126.2 (Ar), 123.7 (Ar), 123.3 (Ar), 120.2 (Ar), 114.8 (Ar), 106.2 (Ar), 72.1 (O*C*H$_2$-ArTriazole), 71.5 (PEG), 70.7 (PEG), 70.6 (PEG), 70.5 (PEG), 70.4 (PEG), 69.4 (PEG), 69.2 (PEG), 68.5 (PEG), 67.8 (PEG), 66.1 (O*C*H$_2$CH$_2$NH), 62.5 (PEG), 60.9 (PEG), 57.8 (O*C*H3), 53.8 (ArTriazole-*C*H2), 48.4 (N(*C*H$_2$CH$_3$)$_2$), 42.6 (*C*H$_2$NHSO$_2$), 39.5 (*C*H$_2$NHCOAr), 33.8 (J = 135.1 Hz) (*C*H-P), 11.2 (N(CH$_2$*C*H$_3$)$_2$); ^{31}P NMR (81 MHz, CD$_3$OD) δ 24.21. MS (MALDI-TOF) m/z calculated for $C_{81}H_{123}NaN_7O_{31}P_2S_2$: 1838.72, obtained: 1838.64.

Compound 60. Starting from **59** (0.2 g, 0.06 mmol), **60** was obtained (0.058 mmol, 98%) as a dark yellow-green foam without further purification. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.82 (m, 2H, Ardye-2-*H*), 8.58 (s, 2H, ArTriazole-*H*), 8.14 (m, H, Ardye-6-*H*), 7.72–7.47 (m, 18H, Ardye-5-*H*, Ardye-AA′-*H* and Ardye-BB′-*H*), 7.31 (s, 4H, Ar3-2,6-*H*), 7.11 (m, 2H, Ar2-2,6-*H*), 6.95–6.88 (m, 3H, Ar^1-2,4,6-*H*), 6.75 (m, 1H, Ar^2-4-*H*), 5.48 (s, 4H, OCH_2ArTriazole-CH_2), 4.91 (m, 4H, OCH$_2$ArTriazole-CH_2), 4.30–4.15 (m, 14H, Ar^{1}OCH_2CH$_2$NH, Ar^{2}OCH_2CH$_2$NH and Ar^{2}OCH_2-CH$_2$), 4.02 (m, 4H, CH_2CH$_2$NHO$_2$), 3.85–3.70 (m, 14H, OCH$_2$-CH$_2$O, Ar^{1}OCH$_2$CH_2NH and Ar^{2}OCH_2CH$_2$NH), 3.75–3.45 (m, 116H, OCH$_2$CH$_2$O and N(CH_2CH$_3$)$_2$), 3.34 (s, 12H, OCH$_2$CH$_2$OCH_3), 3.22–3.12 (m, 8H, CH$_2$CH_2NHO$_2$ and Ar^{1}CH_2P), 1.32 (m, 24H, N(CH$_2$CH_3)$_2$); 13C NMR (75 MHz, CD$_3$OD) δ 167.8 (NH*C*O), 159.9 (Ar), 158.6 (Ar), 151.9 (Ardye = N), 145.0 (Ar), 142.2 (ArTriazole), 140.0 (Ar), 139.5 (Ar), 138.3 (Ar), 135.5 (Ar), 133.4 (Ar), 131.8 (Ar), 130.1 (Ar), 128.3 (Ar), 127.9 (ArTriazole), 126.2 (Ar), 119.3 (Ar), 114.1 (Ar), 105.5 (Ar), 104.2 (Ar), 71.5 (O*C*H$_2$-ArTriazole), 71.3 (PEG), 70.7 (PEG), 70.6 (PEG), 70.5 (PEG), 70.4 (PEG), 69.4 (PEG), 69.2 (PEG), 68.5 (PEG), 67.8 (PEG), 66.8 (O*C*H$_2$CH$_2$NH), 62.1 (PEG), 60.2 (PEG), 57.1 (O*C*H$_3$), 53.2 (ArTriazole-*C*H$_2$), 48.4 (N(*C*H$_2$CH$_3$)$_2$), 42.3 (*C*H$_2$NHSO$_2$), 38.8 (*C*H$_2$NHCOAr), 33.8 (J = 135.1 Hz) (*C*H-P), 10.7 (N(CH$_2$*C*H$_3$)$_2$); ^{31}P NMR (81 MHz, CD$_3$OD) δ 25.11. MS (MALDI-TOF) m/z calculated for $C_{163}H_{243}N_{15}O_{58}P_2S_4$: 3530.95, obtained: 3530.84.

Part II: click-chemistry with phosphonates

Compound 67. Sodium azide (0.9 g, 13.9 mmol) was added to a solution of **66** (1.92 g, 6.94 mmol) in CH$_3$CN (35 mL) and the resulting mixture was refluxed for 16 h. The solvent was then removed under pressure and the residue dissolved in water. The aqueous phase was washed with EtOAc and the organic layer was dried over MgSO$_4$, filtered and concentrated *in vacuo* to yield **67** (6.56 mmol, 95%) as yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35–7.25 (m, 4H, Ar), 4.32 (s, 2H, CH$_2$N$_3$), 4.01 (qt, 4H, J = 6.99 Hz, CH_2CH$_3$), 3.20 (d, 4H, J = 21.7 Hz, CH_2PO(OEt)$_2$), 1.25 (dd, 3H, J = 7.02 and 6.99 Hz, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.8 (J = 3.84 Hz, C Ar next to CH$_2$N$_3$), 131.8 (J = 9.27 Hz, C Ar next to CH$_2$PO(OEt)$_2$), 130.0 (J = 6.54 Hz, CH Ar next to CH$_2$PO(OEt)$_2$), 128.2 (J = 2.72 Hz, CH Ar next to CH$_2$N$_3$), 61.9 (J = 6.54 Hz, *C*H$_2$CH$_3$), 54.1 (CH$_2$N$_3$), 34.1, 32.3 (d, J = 136.9 Hz, *C*H$_2$PO(OEt)$_2$), 16.1 (J = 6.54 Hz, CH$_3$); ^{31}P NMR (81 MHz, CDCl$_3$) δ 26.48; MS (MALDI-TOF) m/z calculated for $C_{12}H_{18}N_{303}P$ 283.11, obtained $[M + H]^+$ = 284.13.

Compound 72. The preparation procedures and analytical data are similar to those reported in the literature.[22c]

Compound 81. Propargylbromide (2.1 mL, 19 mmol) was added to a solution of **21** (6.2 g, 16 mmol) and K$_2$CO$_3$ (22.0 g, 160 mmol) in acetone (150 mL). A pinch of 18-crown-6 was added and the resulting mixture was refluxed for 16 h. The solvent was then removed *in vacuo* after filtration. The crude product was dissolved in CH$_2$Cl$_2$ and the organic phase was washed with water, brine, dried over MgSO$_4$, filtered and concentrated *in vacuo* to yield **81** (13.4 mmol, 84%). Colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.85–6.83 (m, 3H, H Ar), 4.67 (d, 2H, J = 2.19 Hz, CH$_2$ alkyne), 4.02 (qt, 8H, J = 6.99 Hz, CH_2CH$_3$), 3.14, 3.06 (d, 2H, J = 21.93 Hz, CH_2PO(OEt)$_2$), 2.50 (dd, 1H, J = 2.43 and 2.40 Hz, H alkyne), 1.25 (dd, 12H, J = 4.59 and 7.02 Hz, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.6 (C Ar next to alkyne), 133.1 (J = 11.45 Hz, C Ar next to CH$_2$PO(OEt)$_2$), 124.4 (J = 13.09 Hz, CH Ar next to CH$_2$PO(OEt)$_2$), 114.8 (J = 8.72 Hz, CH Ar next to alkyne), 78.3 (C alkyne), 75.4 (CH alkyne), 61.9 (J = 7.63 Hz, *C*H$_2$CH$_3$), 55.7 (CH$_2$ alkyne), 34.5, 32.6 (J = 137.46 Hz, *C*H$_2$PO-(OEt)$_2$), 16.2 (J = 5.45 Hz, CH$_3$); ^{31}P NMR (81 MHz, CDCl$_3$) δ 26.63; MS (MALDI-TOF) m/z calculated for $C_{19}H_{30}O_7P_2$ 432.14, obtained $[M + H]^+$ = 434.12, $[M + Na]^+$ = 455.09.

Bisphosphonic acid anchors final deprotection

The pegylated PAMAM dendrons were deprotected in the last step to give the bisphosphonic acid anchors necessary for

grafting onto nanoparticles. For dendron **75**, two steps were necessary to get the OH-functionalized bisphosphonic acid **92**. On the other hand, for dendrons **73**, **74**, **79**, **80**, **86**, **87**, **90** and **91**, one step was enough to deprotect both of the esters and obtain COOH-functionalized bisphosphonic acids **93–100**.

Compound 92. A solution of tetrabutylammonium fluoride (TBAF, 1 M) in THF (1.6 mL, 0.17 mmol) was added to a solution of **75** (0.85 g, 0.58 mmol) in THF (6 mL). The reaction mixture was stirred for 16 h at room temperature and quenched with acetic acid (140 μL). The solvent was then removed *in vacuo*. The crude product was directly purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 90 : 10–80 : 20) to yield the corresponding protected dialcohol (0.53 mmol, 75%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 2H, NH), 7.59 (s, 1H, H triazole), 7.20–7.11 (m, 3H, H Ar), 5.48 (s, 2H, CH_2N next to triazole), 4.00 (qt, 8H, J = 7.23 Hz, CH_2CH$_3$), 3.81–3.51 (m, 30H, PEG, NCH_2 PAMAM, CH_2N PAMAM), 3.52 (q, 4H, J = 5.25 and 10.53 Hz, CH_2OH), 3.14, 3.07 (d, 2H, J = 21.93 Hz, CH_2PO(OEt)$_2$), 2.75 (dd, 4H, J = 6.36 and 6.57 Hz, CONHCH_2), 2.41 (dd, 4H, J = 6.36 and 6.33 Hz, CH_2CONH), 1.23 (t, 12H, J = 7.02 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (CONH), 143.0 (J = 6.50 Hz, C Ar next to triazole), 134.4 (J = 11.91 Hz, C Ar next to $CH_2PO(OEt)_2$), 132.0 (J = 13.00 Hz, CH Ar next to $CH_2PO(OEt)_2$), 130.4 (C alkyne), 127.0 (J = 9.21 Hz, CH Ar next to triazole), 122.3 (CH alkyne), 72.1 (*C*H_2CH$_2$OH), 70.0 (PEG), 69.9 (PEG), 69.6 (PEG), 69.5 (PEG), 69.3 (PEG), 61.7 (J = 7.05 Hz, *C*H_2CH$_3$), 60.8 (CH_2OH), 53.2 (CH_2N next to triazole), 48.9 (NCH_2 PAMAM), 47.4 (CH_2N PAMAM), 38.7 (CH_2CONH), 33.9, 32.1 (d, J = 136.54 Hz, *C*H_2PO(OEt)2), 33.3 (CONHCH_2), 16.2 (J = 5.96 Hz, CH_3). An excess of bromotrimethylsilane (TMSBr, 2 mL, 15.3 mmol) was then added at room temperature to a solution of bisphosphonate ester (0.51 g, 0.52 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 2 h then quenched with MeOH. The solvent was evaporated under vacuum to give **92** (0.51 mmol, quant) without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.33 (s, 1H, H triazole), 7.27–7.21 (m, 3H, H Ar), 5.66 (s, 2H, CH_2N next to triazole), 5.66 (s, 2H, CH_2N PAMAM), 3.69–3.38 (m, 32H, PEG, NCH_2 PAMAM, CH_2OH), 3.19, 3.12 (d, 2H, J = 21.93 Hz, CH_2PO(OH)$_2$), 2.86 (m, 4H, CONHCH_2), 2.67 (m, 4H, CH_2CONH); ^{13}C NMR (75 MHz, CD_3OD) δ 171.9 (CONH), 136.7 (C Ar next to triazole), 134.2 (C Ar next to $CH_2PO(OH)_2$), 132.3 (CH Ar next to $CH_2PO(OH)_2$, C alkyne), 129.1 (CH Ar next to triazole, CH alkyne), 73.1 (*C*H_2CH$_2$OH), 70.9 (PEG), 70.8 (PEG), 69.9 (PEG), 61.9 (CH_2OH), 54.6 (CH_2N next to triazole), 50.86 (NCH_2 PAMAM), 47.5 (CH_2N PAMAM), 40.3 (CH_2CONH), 35.5, 33.7 (d, 4H, J = 134.18 Hz, *C*H_2PO(OH)$_2$), 29.9 (CONHCH_2); ^{31}P NMR (81 MHz, CD_3OD) δ 25.76; MS (MALDI-TOF) m/z calculated for $C_{34}H_{60}N_6O_{16}P_2$ 870.35, obtained $[M + H]^+$ = 871.31.

General procedure for the conversion of phosphonate ester to phosphonic acid by TMSBr (McKenna's method[28]) (93–100)

TMSBr (30 equiv.) was added at room temperature to a solution of bisphosphonate ester **73**, **74**, **79**, **80**, **86**, **87**, **90** or **91** (1 equiv.) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 2 h then quenched with MeOH. The solvent was evaporated under vacuum 3 times to give the desired compound without further purification.

Compound 93. Starting from **73** (0.15 g, 0.14 mmol), compound **93** was obtained (0.13 mmol, 98%). Yellow oil. ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (s, 1H, CH triazole), 7.36 (s, 4H, Ar), 5.68 (s, 2H, CH_2N triazole), 4.66 (s, 2H, CH_2N PAMAM), 3.74 (dd, 4H, J = 6.15 and 5.91 Hz, CH_2CH$_2$COOH), 3.70–3.34 (m, 36H, PEG), 3.25, 3.18 (d, 2H, J = 21.93 Hz, CH_2PO(OH)$_2$), 2.62 (dd, 4H, J = 5.19 and 6.12 Hz, CH_2COOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (COOH), 170.7 (CONH), 135.9 (C Ar next to triazole), 133.7 (J = 2.73 Hz, C Ar next to $CH_2PO(OH)_2$), 133.1 (C triazole), 130.3 (J = 6 Hz, CH Ar next to $CH_2PO(OH)_2$), 128.1 (J = 2.18 Hz, CH Ar next to triazole), 127.3 (CH Ar next to triazole), 127.3 (CH triazole), 70.2 (PEG), 70.1 (PEG), 70.0 (PEG), 69.9 (PEG), 69.0 (CONHCH$_2$*C*H$_2$O), 66.3 (*C*H$_2$CH$_2$COOH), 53.5 (CH_2N PAMAM), 49.9 (CH_2N triazole), 46.4 (NCH_2 PAMAM), 39.1 (CONHCH_2), 34.3 (CH_2COOH), 34.4, 32.9 (J = 133.64 Hz, *C*H_2PO(OH)$_2$), 28.6 (CH_2COOH); ^{31}P NMR (81 MHz, CD_3OD) δ 25.10; MS (MALDI-TOF) m/z calculated for 920.41, obtained $[M + H]^+$ = 921.36.

Compound 94. The preparation procedures and analytical data are reported in the literature.[22c]

Compound 95. Starting from **79** (0.19 g, 0.29 mmol), compound **95** was obtained (0.29 mmol, 98%) as an yellow oil. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (s, 1H, H triazole), 7.31 (m, 3H, H Ar), 5.73 (s, 2H, CH_2N next to triazole), 4.76 (s, 2H, CH_2O next to triazole), 3.73–3.52 (m, 12H, PEG), 3.35 (s, 3H, OCH_3), 3.25, 2.18 (d, 4H, J = 21.93 Hz, CH_2PO(OH)$_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 141.6 (C triazole), 134.0 (J = 10.16 Hz, C Ar next to triazole), 132.8 (C Ar next to $CH_2PO(OH)_2$), 131.7 (J = 11.77 Hz, CH Ar next to $CH_2PO(OH)_2$), 128.2 (J = 8.55 Hz, CH Ar next to triazole), 126.2 (CH triazole), 73.0 (*C*H$_2$OCH$_3$), 72.3 (PEG), 71.2 (PEG), 71.1 (PEG), 69.8 (PEG), 71.0 (PEG), 70.9 (PEG), 70.8 (PEG), 70.7 (PEG), 62.6 (CH_2-OC*H*$_2$CH$_2$O next to triazole), 61.8 (CH_2O next to triazole), 58.8 (OCH_3), 57.0 (CH_2N next to triazole), 36.4, 34.7 (d, J = 131.07 Hz, *C*H_2PO(OH)$_2$); ^{31}P NMR (81 MHz, CD_3OD) δ 25.15; MS (MALDI-TOF) m/z calculated for $C_{19}H_{31}N_3O_{10}P_2$ 523.14, obtained $[M + H]^+$ = 524.03, $[M + Na]^+$ = 545.99, $[M + K]^+$ = 561.94.

Compound 96. Starting from **80** (0.17 g, 0.18 mmol), compound **96** was obtained (0.18 mmol, 99%) as an orange oil. ^{1}H NMR (300 MHz, CD_3OD) δ 8.67 (s, 1H, CH triazole), 7.36 (s, 3H, H Ar), 5.86 (s, 2H, CH_2N next to triazole), 4.84 (s, 2H, CH_2O triazole), 3.77–3.52 (m, 36H, PEG), 3.35 (s, 3H, OCH_3), 3.25, 3.18 (d, 4H, J = 21.93 Hz, CH_2PO(OH)$_2$), 2.57 (t, 2H, J = 6.15 Hz, CH_2COOH); ^{13}C NMR (75 MHz, CD_3OD) δ 141.7 (C triazole), 134.0 (J = 9.09 Hz, C Ar next to triazole), 132.9 (C Ar next to $CH_2PO(OH)_2$), 131.8 (J = 5.34 Hz, CH Ar next to $CH_2PO(OH)_2$), 128.3 (CH Ar next to triazole), 126.4 (CH triazole), 73.0 (*C*H$_2$OCH$_3$), 72.4 (PEG), 71.2 (PEG), 70.9 (PEG), 70.9 (PEG), 62.6 (CH_2OC*H*$_2$CH$_2$O next to triazole), 61.9 (CH_2O next to triazole), 58.9 (OCH_3), 57.0 (CH_2N next to triazole), 36.5, 34.7 (d, J = 130.53 Hz, *C*H_2PO(OH)$_2$); ^{31}P NMR (81 MHz, CD_3OD) δ 25.08; MS (MALDI-TOF) m/z calculated for $C_{31}H_{55}N_3O_{16}P_2$ 787.30, obtained $[M + H]^+$ = 788.13,$[M + Na]^+$ = 810.09.

Compound 97. Starting from **86** (0.68 g, 0.87 mmol), compound **97** was obtained (0.85 mmol, 98%). Yellow oil. ^{1}H NMR

(300 MHz, CD_3OD) δ 8.53 (s, 1H, CH triazole), 6.98 (s, 3H, Ar), 4.79 (dd, 2H, J = 5.04 and 4.62 Hz, OCH_2 triazole), 4.04 (dd, 2H, J = 5.25 and 4.62 Hz, NCH_2 triazole), 3.79–3.64 (m, 16H, PEG), 3.23, 3.16 (d, 4H, J = 21.93 Hz, $CH_2PO(OH)_2$), 2.63 (t, 2H, J = 6.12 Hz, CH_2COOH); ^{13}C NMR (75 MHz, CD_3OD) δ. 173.7 (COOH), 158.7 (C Ar next to triazole), 141.2 (C triazole), 135.5 (J = 12 Hz, C Ar next to $CH_2PO(OH)_2$), 129.0 (CH triazole), 126.1 (J = 6.00 Hz, CH Ar next to $CH_2PO(OH)_2$), 115.9 (CH Ar next to triazole), 71.2 (PEG), 71.1 (PEG), 71.0 (PEG), 69.0 (NCH_2CH_2O next to triazole), 67.4 (OCH_2 next to triazole), 60.3 (NCH_2CH_2O), 54.1 (NCH_2-CH_2O), 52.2 (CH_2CH_2COOH), 35.6 (CH_2COOH), 36.0, 34.3 (J = 133.09 Hz, $CH_2PO(OH)_2$); ^{31}P NMR (81 MHz, $CDCl_3$) δ 25.77; MS (MALDI-TOF) m/z calculated for $C_{22}H_{35}N_3O_{13}P_2$ 611.16, obtained $[M + H]^+$ = 612.12.

Compound 98. Starting from **87** (0.53 g, 0.56 mmol), compound **98** was obtained (0.54 mmol, 97%) as a Burgundy oil. ^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (s, 1H, CH triazole), 6.95 (bs, 3H, Ar), 5.28 (s, 2H, OCH_2 triazole), 4.71 (dd, 2H, J = 4.80 and 4.83 Hz, NCH_2 triazole), 3.99 (dd, 2H, J = 5.04 and 4.80 Hz, NCH_2CH_2O triazole), 3.82–3.66 (m, 26H, PEG), 3.20, 3.13 (d, 4H, J = 21.48 Hz, $CH_2PO(OH)_2$), 2.65 (dd, 2H, J = 6.15 and 6.12 Hz, CH_2COOH);^{13}C NMR (75 MHz, CD_3OD) δ 173.7 (COOH), 158.9 (J = 2.73 Hz, C Ar next to triazole), 135.7 (J = 9.27 Hz, C Ar next to $CH_2PO(OH)_2$), 153.2 (C triazole), 126.0 (J = 6.54 Hz, CH Ar next to $CH_2PO(OH)_2$), 125.4 (CH triazole), 115.9 (CH Ar next to triazole), 71.3 (PEG), 71.1 (PEG), 69.3 (NCH_2CH_2O next to triazole), 67.4 (OCH_2 next to triazole), 60.7 (NCH_2CH_2O), 53.6 (NCH_2CH_2O), 52.2 (CH_2CH_2COOH), 35.6 (CH_2COOH), 36.3, 34.5 (J = 133.0 Hz, $CH_2PO(OH)_2$); ^{31}P NMR (81 MHz, $CDCl_3$) δ 25.79; MS (MALDI-TOF) m/z calculated for $C_{30}H_{51}N_3O_{17}P_2$ 787.26, obtained $[M + H]^+$ = 788.12.

Compound 99. Starting from **90** (0.37 g, 0.84 mmol), compound **99** was obtained (0.69 mmol, 83%). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 3H, $PO(OH)_2$, COOH), 3.78–3.52 (m, 12H, PEG), 2.50 (qt, 2H, J = 4.38 Hz, CH_2COOH), 2.17 (m, 2H, $CH_2PO(OH)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (COOH), 70.5 (PEG), 70.4 (PEG), 70.3 (PEG), 70.2 (PEG), 69.9 (PEG), 66.4 (CH_2CH_2COOH), 51.7 (J = 5.45 Hz, $OCH_2CH_2PO(OH)_2$), 34.7 (CH_2COOH), 28.0, 26.2 (J = 135.27 Hz, $CH_2PO(OH)_2$); ^{31}P NMR (81 MHz, $CDCl_3$) δ 33.18; MS (MALDI-TOF) m/z calculated for $C_{11}H_{23}O_9P$ 330.10, obtained $[M + H]^+$ = 331.11, $[M + Na]^+$ = 353.10.

Compound 100. Starting from **91** (0.09 g, 0.14 mmol), compound **100** was obtained (0.14 mmol, 99%). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 3H, $PO(OH)_2$, COOH), 3.84–3.42 (m, 32H, PEG), 2.55 (m, 2H, CH_2COOH), 2.26 (m, 2H, $CH_2PO(OH)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (COOH), 70.3 (PEG), 70.2 (PEG), 70.1 (PEG), 69.9 (PEG), 69.6 (PEG), 66.4 (CH_2CH_2COOH), 51.7 ($OCH_2CH_2PO(OH)_2$), 34.7 (CH_2COOH), 28.1, 26.3 (J = 135.27 Hz, $CH_2PO(OH)_2$); ^{31}P NMR (81 MHz, $CDCl_3$) δ 29.03; MS (MALDI-TOF) m/z calculated for $C_{19}H_{39}O_{13}P$ 506.21, obtained $[M + H]^+$ = 507.15, $[M + Na]^+$ = 529.12.

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