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Design of Bisphosphonate-Terminated Dendrimers

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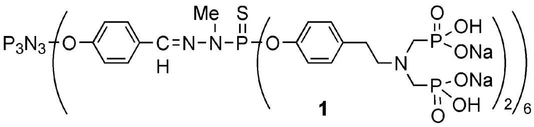
Several new methods for the synthesis of phosphorus dendrimers capped with biologically active azabisphosphonates are reported. Monomers bearing either azido or acetylenic groups were designed as building blocks either for attachment onto the surfaces of classical phosphorus dendrimers or for use in the construction of original dendrimers without the need for use of sensitive dichloro(monomethylhydrazino)thiophosphane.

Introduction

Structural features of dendrimers (their nanometer sizes, perfectly defined structures, topologies, multivalent characters, molecular weights), together with their high density of chemical reactive functions on their outer shells explain their successful use in biology and medicine.[1–8] Among them, phosphorus-containing dendrimers appear to be versatile macromolecules offering a large palette of properties and applications. Those bearing phosphonate end groups are of particular interest. Indeed these dendrimers – such as the first-generation dendrimer **1** – were found to act as new nano-biotools promoting anti-inflammatory and immunosuppresive activation of human monocytes and so show promise as drugs for the treatment of uncontrolled inflammatory process in acute or chronic diseases such as psoriasis, rheumatoid arthritis or autoimmune disorders.[9,10] Moreover, phosphonates grafted onto the surfaces of phosphorus dendrimers display the unexpected property of dramatically and selectively promoting the multiplication of human natural killer (NK) cells, which are a key part of innate immunity.[11,12] The exceptional bioactivity behaviour of these dendrimers prompted us not only to diversify with regard to ways of attaching phosphonates onto the surfaces of known phosphorus dendrimers but also to search for new ways to synthesise phosphorus dendrimers possessing terminal phosphonate groups in order to optimize their properties and to find the best molecule for the applications discussed above.



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Here we report: i) the synthesis of monomers as new building blocks for the construction of dendrimers, ii) the attachment of some of these building blocks onto new or “classical” phosphorus dendrimers developed in our team through “click reactions”, and iii) a strategy of elaboration of original dendrimers which allows the user to avoid the use of toxic methylhydrazine and the preparation of dichloro(methylhydrazino)thiophosphane, which takes place under drastic conditions (–60 °C). This paper focuses on the preparation of analogues of the dendrimer **1**, which appeared to be the most efficient dendrimer for the biomedical applications discussed above. However, the strategies used can be extended to dendrimers of higher generations, as is illustrated below.

Results and Discussion

Various building blocks were prepared for the above goals. Firstly, acetylenic moieties or azido groups were introduced at the level of the core through the formation of the hexafunctionalized compounds **3**–**5** (Scheme 1). Secondly, monomers bearing either an acetylenic group, as in compounds **6**, or an azido unit, as in compounds **8**, were prepared for grafting onto the surfaces of dendrimers (Scheme 2).

The high-yield syntheses of the cores **3** and **4** involve nucleophilic substitution between hexachlorocyclotriphosphazene – $(N_3P_3)Cl_6$ – and phenols substituted in their *para* positions either with $O(CH_2)_2Cl$ or with CH_2OH groups; the terminal chlorine or OH groups were then converted into azido groups. Notably, the use of a phenol bearing a halogen allows the one-step transformation into the corresponding azide **3** (**2a** → **3**), whereas use of the 4-hy-

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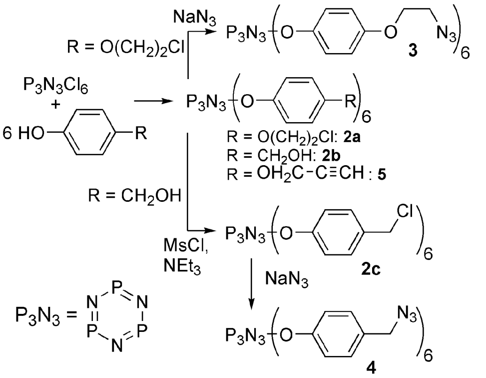
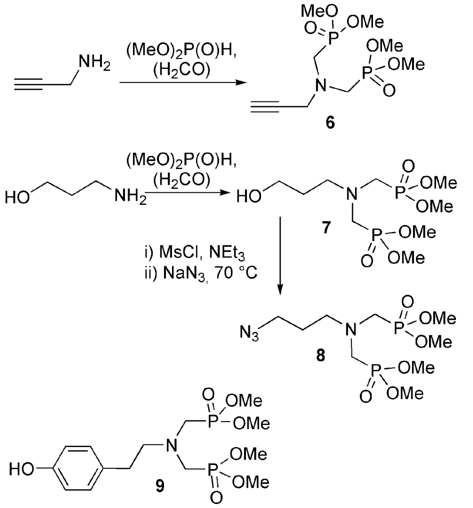


Scheme 1. Synthesis of the azido and acetylenic cores **2a**–**c** and **3**–**5**.



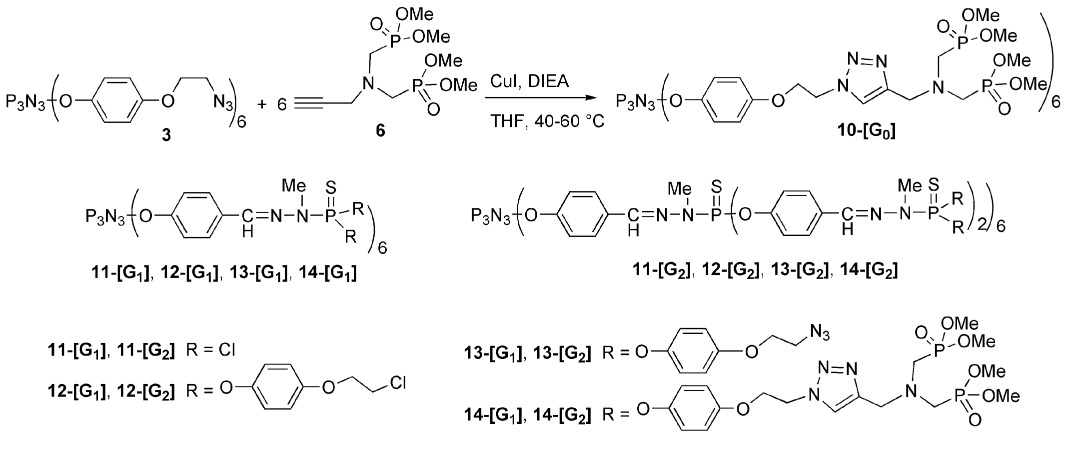
Scheme 2. Synthesis of phosphonate building blocks **6**–**8**.

droxybenzyl alcohol requires two steps to prepare the azido species **4** (**2b** → **2c** → **4**). Grafting of acetylenic units to $(N_3P_3)Cl_6$ also proceeds in a one-step process giving rise to the core **5** (Scheme 1). Kabachnick–Field reactions of either propargylamine or 3-aminopropan-1-ol with the phosphonate $(MeO)_2P(O)H$ and formaldehyde afford the monomers **6** or **7** in high yields. Transformation of the alcohol derivative **7** into the corresponding azide **8** occurs under mild conditions (Scheme 2).

The only previously reported way to introduce an aminobisphosphonate moiety onto the surface of a first-generation phosphorus dendrimer was through a reaction between a terminal $P(S)Cl_2$ group and a phenol such as **9**.[12] A new alternative involves the use of "click chemistry" with dendrimers decorated with azido groups and monomers bearing acetylenic groups.[13–15]

To test this reaction, in a first approach we treated the hexaazido core **3** with the acetylenic aminobisphosphonate **6** (Scheme 3) in the presence of CuI and diisopropylethylamine (DIPEA) as base in THF at 40 °C. Under these conditions the expected dendrimer **10-[G$_0$]** (generation zero), incorporating six azabisphosphonate end groups, was formed. The reaction can be easily monitored by NMR and IR spectroscopy: the disappearance of the N_3 band at 2106 cm^{-1} is observed by IR spectroscopy, whereas ^1H NMR shows the shift of the N methylene signal from 4.33 ppm for **3** to 5.56 ppm in **10-[G$_0$]**, as well as the appearance of characteristic signals due to the CH groups of the triazole units at $\delta = 7.83$ ppm. Moreover, a shielding effect is detected by ^{31}P NMR for the terminal bisphosphonate (δ =25.9 ppm for **6**, 26.5 ppm for **10-[G$_0$]**).

The same sequence of reactions for the introduction of azido groups onto the surfaces was applied to dendrimers of the first and second generations bearing $P(S)Cl_2$ end groups (i.e., dendrimers **11-[G$_1$]** and **11-[G$_2$]**), leading successively to the dendrimers **12-[G$_1$]** and **12-[G$_2$]** and then **13-[G$_1$]** and **13-[G$_2$]**; the latter were successfully treated with the monomer **6** to give the dendrimers **14-[G$_1$]** and **14-[G$_2$]**, incorporating 12 and 24 azabisphosphonate linkages, respectively, thus offering diversity in relation to **1** with regard to the nature of the spacers between the dendrimer backbone itself and the terminal bisphosphonate (Scheme 3). As in the case of the synthesis of **10-[G$_0$]**, reactions can be monitored by NMR spectroscopy. For **14-[G$_1$]**,



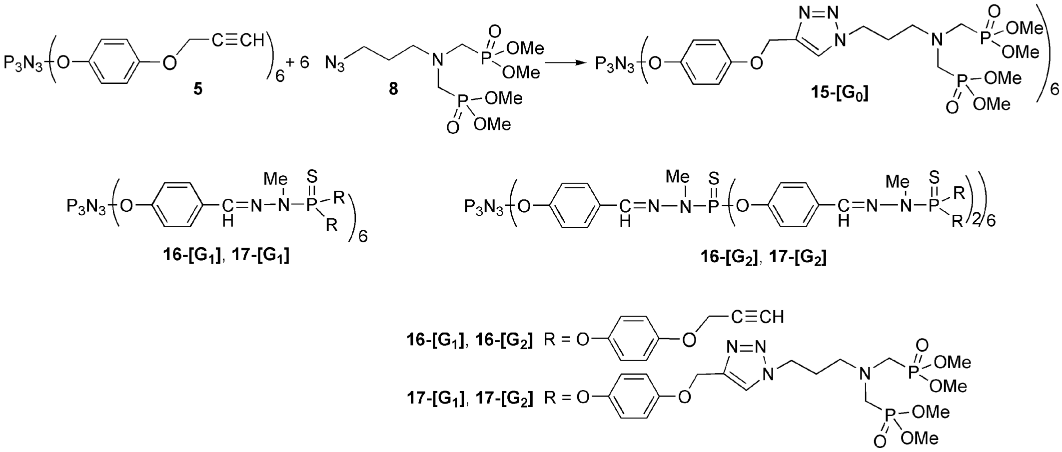
Scheme 3. Synthesis of bisphosphonate-ended dendrimers from the azido dendrimers **3**, **13-[G$_1$]** and **13-[G$_2$]** and the acetylenic azabisphosphonate **6**.

for example, ^{1}H NMR shows the disappearance of the methylene signal (CH_2N_3) at δ = 3.54 ppm (t, $J_{H,H}$ = 4.8 Hz) and the appearance of a triplet ($J_{H,H}$ = 4.8 Hz) at δ = 4.71 ppm, whereas the characteristic signal of the CH group of the triazole appears as a singlet at δ = 7.82 ppm. Moreover, the methylene group connecting the triazole ring and the azabisphosphonate appears as a singlet at δ = 4.15 ppm. ^{31}P NMR spectroscopic data corroborate the presence of terminal phosphonates whereas ^{13}C NMR and IR supply definite confirmation of the formation of the desired dendrimers.

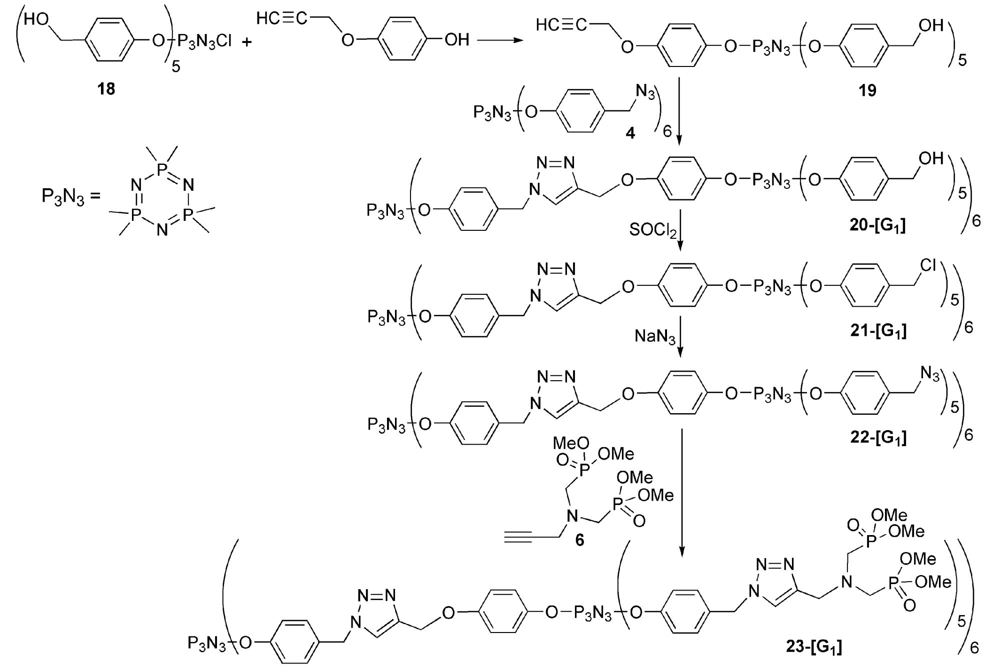
A second general alternative for incorporation of azabisphosphonate units was investigated. It involves the preliminary grafting of acetylenic functions (a type of functional group rarely positioned at the surfaces of phosphorus dendrimers[16,17]) onto the surfaces of dendrimers, followed by treatment of the resulting dendrimers with the multifunctionalized monomer **8** (Scheme 4). As in the first strategy reported above, such an experiment was conducted with two monomers: the hexaacetylenic monomer **5** and the azide **8**. This reaction also takes place under mild conditions, allowing us to isolate the new generation zero dendrimer, **15-[G$_0$]**, bearing spacers different from those in its congener **10-[G$_0$]** on each side of the triazole moieties. This transformation can be monitored by NMR spectroscopy: ^{1}H NMR confirms the total disappearance of the signals due to the methylene acetylenic linkage at 4.68 ppm (d, $J_{H,H}$ = 2.4 Hz, CH_2) and 2.55 ppm (t, $J_{H,H}$ = 2.4 Hz, CH) with the appearance of singlets at 5.13 ppm (CH_2) and at 7.48 ppm (CH, triazole), as well as all signals attributable both to the $(CH_2)_3$ linkage and to the azabisphosphonate fragments. Extension of this method to dendrimers of higher generation first necessitates the synthesis of dendrimers bearing acetylenic units on their outer shells. These dendrimers – **16-[G$_1$]** and **16-[G$_2$]**, prepared through nucleophilic substitution of the terminal $P(S)Cl_2$ groups of dendrimers **11-[G$_1$]** and **11-[G$_2$]** with 4-(prop-2-yn-1-yloxy)phenol in the presence of caesium carbonate – were then allowed to react with the azido monomer **8** to give the new dendrimers **17-[G$_1$]** and **17-[G$_2$]** (Scheme 4). Completion of the reactions was monitored by ^{31}P NMR, which shows a signal at δ = 26.8 ppm in addition to the other unchanged characteristic signals of the phosphorus dendritic backbone. ^{1}H and ^{13}C NMR spectroscopy as well as IR spectroscopy corroborate the full achievement of the sequence of formation and isolation of all the acetylenic- or bisphosphonate-terminated dendrimers.

Except for the formation of the dendrimers of generation zero – **10-[G$_0$]** and **15-[G$_0$]** – the two approaches reported above do not allow the use of monomethylhydrazine for the construction of higher generations to be avoided, the CH=N–N(CH_3)P(S) fragment being present on each generation. Therefore a third general alternative was elaborated. This involves a multistep synthesis as shown in Scheme 5. The three first steps necessitated the design of the AB_5 monomer **18**, obtained through the selective pentasubstitution of the hexachlorocyclotriphosphazene $P_3N_3Cl_6$ with 4-hydroxybenzyl alcohol and nucleophilic substitution of the remaining chlorine atom with 4-(prop-2-yn-1-yloxy)phenol to afford the further AB_5 monomer **19**, which can be treated with the hexa-azido monomer **3** to give the dendrimer **20-[G$_1$]**. In contrast with what is observed with phosphorus dendrimers incorporating P(S)N(CH_3)N=CH– linkages, no fragmentation is detectable by mass spectrometry for such a dendrimer[18] in which the core and the branching points are cyclotriphosphazene units. Introduction of azido groups onto the outer shell then proceeds as above, with the formation of **21-[G$_1$]** (30 terminal chlorines) and then of **22-[G$_1$]**, a dendrimer bearing 30 azido groups. Aminobisphosphonates can be grafted onto **22-[G$_1$]** through [1+3] cycloaddition with the acetylenic monomer **6**, leading to **23-[G$_1$]**.

^{1}H NMR spectroscopy nicely illustrates the dissymmetry of this dendrimer through the AB_5 system present in **19**. Whereas the CH proton of the triazole ring incorporated in the first generation gives a singlet at 8 ppm, those of the triazole units of the second generation appear as two singlets in a 2/3 ratio at δ = 7.71 and 7.78 ppm. This is due to the presence of the cyclotriphosphazene ring used as branching point, allowing a dissymmetric anchoring of the



Scheme 4. Synthesis of bisphosphonate-ended dendrimers from the acetylenic dendrimers **5**, **15-[G$_1$]** and **15-[G$_2$]** and the azido azabisphosphonate **8**.



Scheme 5. Synthesis of phosphorus dendrimers incorporating triazole units in each generation.

five remaining branches as we have already reported.[17] Two singlets at $\delta = 5.54$ and 5.51 ppm are observed for the methylene groups of the $C_6H_4CH_2N$ linkages of the outer shell in the same 2/3 ratio, as well as for the methylene groups of the C–CH_2–N fragments (4.14 and 4.10 ppm), whereas the signals for the NCH_2P groups appear as doublets at 3.13 and 3.16 ppm ($^2J_{H,P} = 10$ Hz).

Several key features can be emphasized with regard to **23-[G$_1$]**: i) it does not contains methylhydrazino units, in marked contrast with the great majority of the known phosphorus dendrimers, ii) each generation incorporates triazole rings, iii) on moving from the first generation to the second the number of triazole rings is multiplied by five (six for the first generation, thirty for the second), and iv) it illustrates the versatility of azide reactivity towards phosphorus compounds, leading either to Staudinger-type reactions[19–22] with removal of N_2 or to [1+3] cycloaddition with retention of the N_3 framework.

Conclusions

New strategies for the synthesis of phosphorus dendrimers and new methods for their incorporation on their surfaces of biologically active bisphosphonates are reported, thus expanding the potential to diversify not only their biomedical applications but also their involvement in the design of hybrid organic-inorganic materials.[23] Uses of all the dendrimers reported here for these applications are under active investigation.

Experimental Section

Methods and Materials: NMR spectra were recorded with Bruker ARX 250, DPX 300, AV 300, AV 400 or AV 500 spectrometers. All spectra were measured at 25 °C in the indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The signals in the spectra are described as s (singlet), d (doublet), t (triplet), m (multiplet), br. (broad resonances), and C_{tz} (triazole signals). References for NMR chemical shifts are H_3PO_4 (85%) for ^{31}P NMR, and $SiMe_4$ for ^{1}H and ^{13}C NMR spectroscopy. Signal attribution was carried out with the aid of two-dimensional experiments when necessary (COSY, HSQC). The numbering used for NMR signals assignment in shown in Figure 1. Fourier transformed infrared (FTIR) spectra were obtained with a Perkin–Elmer Spectrum 100 FT-IR spectrometer on neat samples (ATR FT-IR). Mass spectrometry was carried out with a Thermo Fisher DS QII (DCI/NH_3), a Neromag R10–10 (FAB) and an Applied Biosystems Voyager System 4243 (MALDI). Either protonated molecular ions $[M + H]^+$ or sodium adducts $[M + Na]^+$ were used for empirical formula confirmation.

Chemicals were purchased from Aldrich, Acros, Fluka and Strem and were used without further purification, except for $P_3N_3Cl_6$, which was recrystallized from hexanes. Organic solvents were dried and distilled by routine procedures. Purifications by flash column chromatography were performed with silica gel 60 (43–63 µm). TLCs were performed on silica gel 60 F254 plates and detection was carried out either under UV light or with molybdate solution followed by heating.

Compound 2a: Cs_2CO_3 (38 mmol) was added to an acetone (dry, 60 mL) solution of 4-(2-chloroethoxy)phenol (19 mmol) and $P_3N_3Cl_6$ (2.88 mmol), and the mixture was stirred at 40 °C until the reaction was complete (monitored by ^{31}P NMR). Inorganic salts were filtered through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography (eluent: pentane/CH_2Cl_2 3:7). White powder; yield 75% (2.152 g, 2.16 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.85$ (d, $J = 9.0$ Hz, 12 H, H^2), 6.72 (d, $J = 9.0$ Hz, 12 H, H^3), 4.20 (t, $J = 5.7$ Hz, 12 H, OCH_2), 3.82 (t, $J = 5.7$ Hz, 12 H, CH_2Cl) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 155.2$ (C^4), 144.7 (C^1),

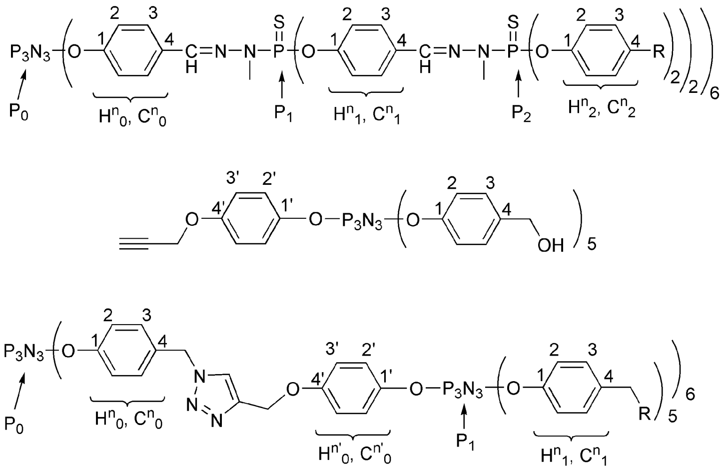


Figure 1. Numbering used for assignment of NMR signals.

122.0 (C^2), 115.4 (C^3), 68.6 (CH_2O), 42.1 (CH_2Cl) ppm. ^{31}P{^{1}H} NMR (101 MHz, CDCl$_3$): δ = 9.9 ppm. MS (FAB): m/z = 1163 [M]$^+$. $C_{48}H_{48}Cl_6N_3O_{12}P_3$ (1164.6): calcd. C 49.51, H 4.15, N 3.61; found C 49.38, H 4.14, N 3.54.

Compound 3: NaN$_3$ (0.6 mmol) was slowly added to a DMF (dry, 5 mL) solution of compound **2a** (0.5 mmol), and the reaction mixture was stirred and heated at 70 °C overnight. The reaction mixture was then allowed to cool to room temp., distilled water (5 mL) was added, and a white precipitate appeared. The aqueous phase was decanted and the precipitate was dissolved in CH$_2$Cl$_2$. The organic phase was then washed with brine, dried with MgSO$_4$ and concentrated to give the azide derivative **3**, which was further purified by silica gel flash chromatography (eluent: pentane/CH$_2$Cl$_2$ 7:3). Waxy, white solid; yield 85% (0.512 g, 0.425 mmol). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.86 (d, J = 8.8 Hz, 12 H, H^2), 6.74 (d, J = 8.8 Hz, 12 H, H^3), 4.12 (t, J = 4.8 Hz, 12 H, OCH_2), 3.61 (t, J = 4.8 Hz, 12 H, CH_2N$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 155.3 (C^4), 144.7 (m, C^1), 122.0 (C^2), 115.2 (C^3), 67.5 (OCH_2), 50.2 (CH_2N$_3$) ppm. ^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$): δ = 9.85 ppm. IR (neat): $\tilde{\nu}$ = 2106 (N$_3$) cm^{-1}. MS (FAB): m/z = 1204 [M + 1]$^+$. $C_{48}H_{48}N_{21}O_{12}P_3$ (1204.0): calcd. C 47.89, H 4.02, N 24.43; found C 47.86, H 4.00, N 24.39.

Compound 2b: Cs$_2$CO$_3$ (38 mmol) was added to a THF (dry, 60 mL) solution of 4-hydroxybenzyl alcohol (19 mmol) and P$_3$N$_3$Cl$_6$ (2.88 mmol), and the mixture was stirred at 40 °C until reaction was complete (monitored by ^{31}P NMR). Inorganic salts were filtered through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography (eluent: CHCl$_3$/MeOH 9:1). White powder; yield 83% (2.088 g, 2.39 mmol). ^{1}H NMR (400 MHz, [D$_8$]THF): δ = 7.18 (d, J = 8.4 Hz, 12 H, H^3), 6.90 (d, J = 8.4 Hz, 12 H, H^2), 4.57 (d, J = 6.0 Hz, 12 H, CH_2OH), 4.38 (t, J = 6.0 Hz, 6 H, CH$_2$$OH$) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_8$]THF): δ = 150.1 (C^1), 136.2 (C^4), 127.2 (C^3), 120.4 (C^2), 63.3 (CH_2OH) ppm. ^{31}P{^{1}H} NMR (162 MHz, [D$_8$]THF): δ = 9.1 ppm. IR (neat): $\tilde{\nu}$ = 3200 (br., OH) cm^{-1}. $C_{42}H_{42}N_3O_{12}P_3$ (873.7): calcd. C 57.74, H 4.85, N 4.81; found C 57.68, H 4.83, N 4.72.

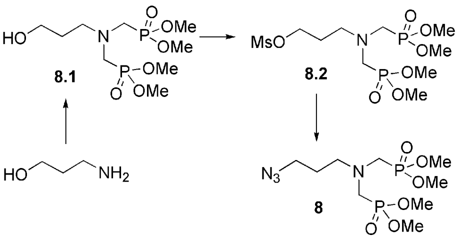
Compound 2c: SOCl$_2$ was added to a cooled (ice bath) round-bottomed flask containing compound **2b** (1 mmol) until complete dissolution. The reaction mixture was stirred overnight. Excess SOCl$_2$ was removed under vacuum line with use of toluene as co-solvent, and the crude product was used for the next step without further purification. White powder; yield 93% (0.915 g, 0.93 mmol). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.24 (d, J = 8.4 Hz, 12 H, H^3), 6.93 (d, J = 8.4 Hz, 12 H, H^2), 4.58 (s, 12 H, CH_2Cl) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 150.2 (m, C^1), 134.3 (C^4), 129.9 (C^3), 121.2 (C^2), 45.6 (CH_2Cl) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, CDCl$_3$): δ = 8.7 ppm. $C_{42}H_{36}Cl_6N_3O_6P_3$ (984.4): calcd. C 51.25, H 3.69, N 4.27; found C 51.10, H 3.62, N 4.19.

Compound 4: NaN$_3$ (0.6 mmol) was slowly added to a DMF (dry, 5 mL) solution of the chloride derivative **2c** (0.5 mmol), and the reaction mixture was stirred at room temp. overnight. Distilled water (5 mL) was then added to the reaction mixture and a white precipitate appeared. The aqueous phase was decanted and the precipitate was dissolved in CH$_2$Cl$_2$. The organic phase was washed with brine, dried with MgSO$_4$ and concentrated to give the azide derivative **4**, which was further purified by silica gel flash chromatography (eluent: pentane/CH$_2$Cl$_2$ 8:2). Waxy, white solid; yield 89% (0.456 g, 0.445 mmol). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.17 (d, J = 8.7 Hz, 12 H, H^3), 6.99 (d, J = 8.7 Hz, 12 H, H^2), 4.33 (s, 12 H, CH_2N$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 150.4 (m, C^1), 132.3 (C^4), 129.4 (C^3), 121.3 (C^2), 54.1 (CH_2N$_3$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, CDCl$_3$): δ = 8.4 ppm. IR (neat): $\tilde{\nu}$ = 2090 (N$_3$) cm^{-1}. MS (FAB): m/z = 1023 [M]$^+$. $C_{42}H_{36}N_{21}O_6P_3$ (1023.8): calcd. C 49.27, H 3.54, N 28.73; found C 49.18, H 3.51, N 28.67.

Compound 5: Cs$_2$CO$_3$ (38 mmol) was added to a THF (dry, 60 mL) solution of 4-(prop-2-yn-1-yloxy)phenol[24] (19 mmol) and P$_3$N$_3$Cl$_6$ (2.88 mmol), and the mixture was stirred at 40 °C until the reaction was complete (monitored by ^{31}P NMR). Inorganic salts were filtered off through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography (eluent: pentane/ethyl acetate 7:3). White powder; yield 95% (2.785 g, 2.736 mmol). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 6.84 (m, 24 H, H^{2,3}), 4.68 (d, J = 2.4 Hz, 12 H, OCH_2), 2.55 (t, J = 2.4 Hz, 6 H, C≡CH) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 154.5 (C^4), 144.8 (m, C^1), 121.9 (C^2), 115.5 (C^3), 78.5 (C≡CH), 75.8 (C≡CH), 56.2 (OCH_2) ppm. ^{31}P{^{1}H} NMR (101 MHz, CDCl$_3$): δ = 9.8 ppm. MS (FAB): m/z = 1017 [M]$^+$. $C_{54}H_{42}N_3O_{12}P_3$ (1017.9): calcd. C 63.72, H 4.16, N 4.13; found C 63.58, H 4.10, N 4.06.

Compound 6: A solution of propargylamine (30 mmol) and paraformaldehyde (60 mmol, in H$_2$O solution) in THF (20 mL) was introduced into a two-necked flask fitted with a condenser. Dimethyl hydrogen phosphonate (60 mmol) was then added dropwise, and the reaction mixture was heated at 70 °C until the reaction was complete (monitored by ^{31}P{^{1}H} NMR). After evaporation of THF, $CHCl_3$ was added and the organic phase was washed with NaOH (0.1 N), to extract excess dimethyl hydrogen phosphonate, and dried with $MgSO_4$. The crude residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH 98:2). Pale yellow oil; yield 76% (6.822 g, 22.80 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.81 (d, *J* = 10.5 Hz, 12 H, PO*CH*$_3$), 3.77 (d, *J* = 2.1 Hz, 2 H, C*CH*$_2$N), 3.14 (d, *J* = 10.5 Hz, 4 H, N*CH*$_2$P), 2.30 (t, *J* = 2.1 Hz, 1 H, C≡*CH*) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 77.0 (*C*≡CH), 74.6 (*HC*≡C), 52.5 (d, *J* = 6.7 Hz, PO*CH*$_3$), 48.8 (dd, *J* = 162.7, *J* = 11.6 Hz, NCH_2P), 45.5 (t, *J* = 8.6 Hz, C*CH*$_2$N) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 25.9 ppm. MS (DCI/NH_3): *m*/*z* = 300.0 $[M + H]^+$. $C_9H_{19}NO_6P_2$ (299.2): calcd. C 36.13, H 6.40, N 4.68; found C 36.06, H 6.34, N 4.61.

Compound 8.2: A solution of compound **8.1**[25] (see Scheme 6, 14 mmol) and Et_3N (84 mmol) in dry CH_2Cl_2 was cooled in an ice bath. MsCl (70 mmol) was then added dropwise. The reaction mixture was stirred at room temp. until the reaction was complete (monitored by TLC and ^{31}P{^{1}H} NMR). NH_4Cl (aq) was added and the organic compounds were extracted with CH_2Cl_2. The organic phase was washed with brine and dried with $MgSO_4$, and the solvents were evaporated. The crude residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH 99:1). Pale yellow oil; yield 65% (3.615 g, 9.10 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.37 (t, *J* = 6.4 Hz, 2 H, MsO*CH*$_2$), 3.80 (d, *J* = 10.4 Hz, 12 H, PO*CH*$_3$), 3.18 (d, *J* = 8.8 Hz, 4 H, N*CH*$_2$P), 3.05 (s, 3 H, *Ms*O), 2.95 (t, *J* = 6.4 Hz, 2 H, CH_2*CH*$_2$N), 1.95 (q, *J* = 6.4 Hz, 1 H, CH_2*CH*$_2$$CH_2$) ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 26.7 ppm. $C_{10}H_{25}NO_9P_2S$ (397.3): calcd. C 30.23, H 6.34, N 3.53; found C 30.06, H 6.29, N 3.46.



Scheme 6. Synthesis of **8**.

Compound 8: NaN_3 (4.5 mmol) was added to a solution of **8.2** (3 mmol) in H_2O (10 mL), and the reaction mixture was stirred at 60 °C overnight. The aqueous phase was extracted with ethyl acetate and the organic phase was washed with brine, dried with $MgSO_4$ and concentrated to give the azide derivative as a pale yellow oil; yield 90% (0.929 g, 2.70 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (d, *J* = 10.8 Hz, 12 H, PO*CH*$_3$), 3.40 (t, *J* = 6.9 Hz, 2 H, N_3CH_2), 3.18 (d, *J* = 8.7 Hz, 4 H, N*CH*$_2$P), 2.90 (t, *J* = 6.9 Hz, 2 H, CH_2*CH*$_2$N), 1.77 (q, *J* = 6.9 Hz, 2 H, CH_2*CH*$_2$$CH_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 53.9 (t, *J* = 6.6 Hz, CH_2*CH*$_2$N), 52.6 (d, *J* = 6.7 Hz, PO*CH*$_3$), 49.4 (dd, *J* = 156.4, *J* = 6.6 Hz, NCH_2P), 49.0 (N_3*CH*$_2$$CH_2$), 27.0 ($CH_2$*CH*$_2$$CH_2$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 26.9 ppm. IR (neat): $\tilde{\nu}$ = 2095 (N_3) cm^{-1}. MS (DCI/NH_3): *m*/*z* = 345.1 $[M + H]^+$. $C_9H_{22}N_4O_6P_2$ (344.2): calcd. C 31.40, H 6.44, N 16.28; found C 31.17, H 6.41, N 16.15.

Dendrimer 10-[G$_0$]: DIPEA (2 equiv. per azide) and CuI (0. 1 equiv. per azide) were added to a degassed THF solution of dendrimer **3** (0.1 mmol) and alkyne **6** (1.1 equiv. per azide). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h, monitored by IR, ^{31}P{^{1}H} NMR, ^{1}H NMR). On completion, THF was evaporated, the residue was dissolved in $CHCl_3$, the organic phase was washed with water and brine and dried with $MgSO_4$, and the solvents were evaporated. The crude product was obtained as a white foam and excess starting material was removed by flash chromatography (eluent: CH_2Cl_2/MeOH 95:5). White foam; yield 75% (0.225 g, 0.075 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (s, 6 H, *CH*$_{tz}$), 6.75 (d, *J* = 8.8 Hz, 12 H, H^2), 6.60 (d, *J* = 8.8 Hz, 12 H, H^3), 4.76 (t, *J* = 5.0 Hz, 12 H, CH_2*CH*$_2$N), 4.28 (d, *J* = 5.0 Hz, 12 H, O*CH*$_2$$CH_2$), 4.13 (s, 12 H, C*CH*$_2$N), 3.72 (d, *J* = 10.8 Hz, 72 H, PO*CH*$_3$), 3.21 (d, *J* = 10.4 Hz, 24 H, N*CH*$_2$P) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 154.9 (C^4), 144.8 (m, C^1), 143.3 (C$_{tz}$), 124.9 (*CH*$_{tz}$), 121.8 (C^2), 115.1 (C^3), 66.9 (O*CH*$_2$$CH_2$), 52.8 (d, *J* = 6.9 Hz, PO*CH*$_3$), 51.1 (t, *J* = 8.1 Hz, C*CH*$_2$N), 49.7 (CH_2*CH*$_2$N), 49.0 (dd, *J* = 159.4, *J* = 9.5 Hz, NCH_2P) ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 26.4 [PO(OCH_3)$_2$], 9.4 (P$_0$) ppm. MS (MALDI): *m*/*z* = 3021 $[M + Na]^+$. $C_{102}H_{162}N_{27}O_{48}P_{15}$ (2999.1): calcd. C 40.85, H 5.44, N 12.61; found C 40.72, H 5.42, N 12.48.

General Procedure for the Synthesis of the First and Second Generations of Dendrimers – 12-[G$_1$] and 12-[G$_2$]: Cs_2CO_3 (13.2 or 26.4 mmol) was added to a THF (dry, 20 mL) solution of dendrimer **11-[G$_1$]** or **11-[G$_2$]** (0.5 mmol) and 4-(2-chloroethoxy)phenol (6.6 or 13.2 mmol), and the reaction mixture was stirred at 40 °C until the reaction was complete (12–36 h, monitored by ^{31}P{^{1}H} NMR). Inorganic salts were filtered through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography in pentane/ethyl acetate (7:3).

Dendrimer 12-[G$_1$]: White foam; yield 87% (0.602 g, 0.174 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.4 Hz, 12 H, H$^3{}_0$), 7.59 (s, 6 H, *CH*=N), 7.10 (d, *J* = 9.0 Hz, 24 H, H$^2{}_1$), 7.00 (d, *J* = 8.4 Hz, 12 H, H$^2{}_0$), 6.79 (d, *J* = 9.0 Hz, 24 H, H$^3{}_1$), 4.12 (t, *J* = 5.1 Hz, 24 H, O*CH*$_2$), 3.77 (t, *J* = 5.1 Hz, 24 H, *CH*$_2$Cl) 3.24 (d, *J* = 10.2 Hz, 18 H, *CH*$_3$NP$_1$) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.6 (C$^4{}_1$), 151.2 (br. s, C$^1{}_0$), 144.6 (d, *J* = 7.2 Hz, C$^1{}_1$), 138.4 (d, *J* = 14.3 Hz, *CH*=N), 132.3 (C$^4{}_0$), 128.3 (C$^3{}_0$), 122.4 (d, *J* = 4.3 Hz, C$^2{}_1$), 121.4 (C$^2{}_0$), 115.4 (C$^3{}_1$), 68.4 (O*CH*$_2$), 41.9 (*CH*$_2$Cl), 33.1 (d, *J* = 11.2 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.2 (P$_1$), 8.5 (P$_0$) ppm. $C_{144}H_{144}Cl_{12}N_{15}O_{30}P_9S_6$ (3461.4): calcd. C 49.97, H 4.19, N 6.07; found C 49.72, H 4.14, N 5.99.

Dendrimer 12-[G$_2$]: White foam; yield 79% (3.182 g, 0.395 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (m, 54 H, H$^3{}_0$, H$^3{}_1$, CH=N$_0$, *CH*=N$_1$), 7.18 (d, *J* = 7.8 Hz, 24 H, H$^2{}_1$), 7.08 (d, *J* = 8.7 Hz, 48 H, H$^2{}_2$), 6.88 (d, *J* = 7.8 Hz, 12 H, H$^2{}_0$), 6.78 (m, 48 H, H$^3{}_2$), 4.10 (d, *J* = 5.7 Hz, 48 H, O*CH*$_2$), 3.72 (d, *J* = 5.7 Hz, 48 H, *CH*$_2$Cl), 3.24 (d, *J* = 10.2 Hz, 36 H, *CH*$_3$NP$_2$), 3.20 (d, *J* = 12.6 Hz, 18 H, *CH*$_3$NP$_1$) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.6 (C$^4{}_2$), 151.2 (d, *J* = 7.0 Hz, C$^1{}_1$, C$^1{}_0$), 144.5 (d, *J* = 7.0 Hz, C$^1{}_2$), 139.1 (d, *J* = 12.9 Hz, *CH*=N$_1$), 138.4 (d, *J* = 14.0 Hz, CH=N$_2$), 132.4 (C$^4{}_1$), 132.1 (C$^4{}_0$), 128.3 (br. s, C$^3{}_1$, C$^3{}_0$), 122.4 (d, *J* = 4.4 Hz, C$^2{}_2$), 121.8 (d, *J* = 4.4 Hz, C$^2{}_1$), 121.4 (br. s, C$^2{}_0$), 115.4 (C$^3{}_2$), 68.4 (O*CH*$_2$), 41.9 (*CH*$_2$Cl), 33.1 (d, *J* = 12.5 Hz, *CH*$_3$NP$_2$), 32.9 (d, *J* = 12.5 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.3 (P$_2$), 62.3 (P$_1$), 8.5 (P$_0$) ppm. $C_{336}H_{336}Cl_{24}N_{39}O_{66}P_{21}S_{18}$ (8055.1): calcd. C 50.10, H 4.20, N 6.78; found C 50.00, H 4.17, N 6.66.

General Procedure for the Synthesis of Azide Derivatives 13-[G$_1$] and 13-[G$_2$]: NaN_3 (6.6 or 13.2 mmol) was slowly added to a DMF (dry, 5 mL) solution of the corresponding chloride derivative **12-[G$_1$]** or **12-[G$_2$]** (0.5 mmol), and the reaction mixture was stirred and heated overnight at 70 °C. The reaction mixture was then allowed to cool at room temp., distilled water (5 mL) was added, and a white pre-

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cipitate appeared. The aqueous phase was decanted and the precipitate was dissolved in CH_2Cl_2. The organic phase was washed with brine, dried with $MgSO_4$ and concentrated to give the azide derivative. If necessary, silica gel flash chromatography was performed.

Dendrimer 13-[G_1]: White foam; yield 92% (1.628 g, 0.460 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 12 H, H^3_0), 7.60 (s, 6 H, *CH*=N), 7.10 (d, *J* = 9.0 Hz, 24 H, H^2_1), 7.01 (d, *J* = 8.4 Hz, 12 H, H^2_0), 6.79 (d, *J* = 9.0 Hz, 24 H, H^3_1), 4.05 (t, *J* = 4.8 Hz, 24 H, O*CH*$_2$), 3.54 (t, *J* = 4.8 Hz, 24 H, *CH*$_2$N$_3$) 3.25 (d, *J* = 10.2 Hz, 18 H, *CH*$_3$NP$_1$) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.7 (C^4_1), 151.2 (br. s, C^1_0), 144.6 (d, *J* = 6.8 Hz, C^1_1), 138.4 (d, *J* = 14.2 Hz, *CH*=N), 132.3 (C^4_0), 128.3 (C^3_0), 122.4 (d, *J* = 4.5 Hz, C^2_1), 121.4 (C^2_0), 115.3 (C^3_1), 67.4 (O*CH*$_2$), 50.1 (*CH*$_2$N$_3$), 33.1 (d, *J* = 12.0 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.3 (P_1), 8.5 (P_0) ppm. IR (neat): ṽ = 2097 (N_3) cm^{-1}. $C_{144}H_{144}N_{51}O_{30}P_9S_6$ (3540.2): calcd. C 48.86, H 4.10, N 20.18; found C 48.61, H 4.01, N 20.09.

Dendrimer 13-[G_2]: White foam; yield 88% (3.614 g, 0.440 mol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (m, 42 H, H^3_1, CH=N$_0$, *CH*=N$_1$), 7.56 (d, *J* = 8.4 Hz 12 H, H^3_0), 7.19 (d, *J* = 7.8 Hz, 24 H, H^2_1), 7.08 (d, *J* = 9.0 Hz, 48 H, H^2_2), 6.88 (d, *J* = 8.4 Hz 12 H, H^2_0), 6.79 (m, 48 H, H^3_2), 4.02 (d, *J* = 4.5 Hz, 48 H, O*CH*$_2$), 3.51 (d, *J* = 4.5 Hz, 48 H, *CH*$_2$N$_3$), 3.24 (d, *J* = 10.4 Hz, 36 H, *CH*$_3$NP$_2$), 3.20 (d, *J* = 11.2 Hz, 18 H, *CH*$_3$NP$_1$) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.6 (C^4_2), 151.2 (d, *J* = 7.1 Hz, C^1_1,C^1_0), 144.5 (d, *J* = 7.0 Hz, C^1_2), 138.9 (br. s, *CH*=N$_1$), 138.4 (d, *J* = 13.6 Hz, CH=N$_2$), 132.4 (C^4_1), 132.1 (C^4_0), 128.3 (br. s, C^3_1, C^3_0), 122.4 (d, *J* = 4.3 Hz, C^2_2), 121.8 (C^2_1), 121.4 (C^2_0), 115.3 (C^3_2), 67.3 (O*CH*$_2$), 50.1 (*CH*$_2$Cl), 33.1 (d, *J* = 12.5 Hz, *CH*$_3$NP$_2$), 32.9 (d, *J* = 12.9 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.4 (P_2), 62.3 (P_1), 8.5 (P_0) ppm. IR (neat): ṽ = 2095 (N_3) cm^{-1}. $C_{336}H_{336}N_{111}O_{66}P_{21}S_{18}$ (8212.7): calcd. C 49.14, H 4.12, N 18.93; found C 48.99, H 4.06, N 18.86.

General Procedure for the Synthesis of Dendrimers 14-[G_1] and 14-[G_2] by "Click Chemistry": DIPEA (2 equiv. per azide) and CuI (0.1 equiv. per azide) were added to a degassed THF solution of dendrimer **13-[G_1]** or **13-[G_2]** (0.1 mmol) and alkyne **6** (1.1 equiv. per azide). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h, monitored by IR, ^{31}P{^{1}H} NMR, ^{1}H NMR). On completion, THF was evaporated, the residue was dissolved in $CHCl_3$, the organic phase was washed with water and brine and dried with $MgSO_4$, and the solvents were evaporated. The crude products were obtained as white foams and excess starting material was removed by washing with THF.

Dendrimer 14-[G_1]: White foam; yield 85% (0.606 g, 0.085 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 12 H, *CH*$_{tz}$), 7.65 (d, *J* = 8.5 Hz, 12 H, H^3_0), 7.64 (s, 6 H, *CH*=N), 7.10 (d, *J* = 9.2 Hz, 24 H, H^2_1), 7.01 (d, *J* = 8.5 Hz, 12 H, H^2_0), 6.76 (d, *J* = 9.2 Hz, 24 H, H^3_1), 4.71 (t, *J* = 4.8 Hz, 24 H, CH$_2$*CH*$_2$N), 4.27 (d, *J* = 4.8 Hz, 24 H, O*CH*$_2$CH$_2$), 4.15 (s, 24 H, C*CH*$_2$N), 3.75 (d, *J* = 10.4 Hz, 144 H, PO*CH*$_3$), 3.23 (d, *J* = 10.0 Hz, 18 H, *CH*$_3$NP$_1$), 3.17 (d, *J* = 10.4 Hz, 48 H, N*CH*$_2$P) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.3 (C^4_1), 151.3 (br. s, C^1_0), 144.7 (d, *J* = 7.5 Hz, C^1_1), 143.4 (C_{tz}), 138.4 (br. s, *CH*=N), 132.3 (C^4_0), 128.3 (C^3_0), 124.7 (*CH*$_{tz}$), 122.4 (d, *J* = 3.8 Hz, C^2_1), 121.4 (C^2_0), 115.3 (C^3_1), 66.7 (O*CH*$_2$CH$_2$), 52.8 (d, *J* = 7.1 Hz, PO*CH*$_3$), 51.0 (t, *J* = 8.3 Hz, C*CH*$_2$N), 49.6 (CH$_2$*CH*$_2$N), 49.0 (dd, *J* = 159.4, *J* = 9.3 Hz, NCH$_2$P), 33.1 (d, *J* = 11.7 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.4 (P_1), 26.5 [PO(OCH$_3$)$_2$], 8.4 (P_0) ppm. $C_{252}H_{372}N_{63}O_{102}P_{33}S_6$ (7130.6): calcd. C 42.45, H 5.26, N 12.38; found C 42.41, H 5.22, N 12.33.

Dendrimer 14-[G_2]: White foam; yield 79% (1.216 g, 0.079 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 24 H, CH$_{tz}$), 7.61 (m, 54 H, H^3_0, H^3_1, CH=N$_0$, *CH*=N$_1$), 7.20 (d, *J* = 8.8 Hz, 24 H, H^2_1), 7.05 (d, *J* = 8.4 Hz, 48 H, H^2_2), 6.91 (m, 12 H, H^2_0), 6.76 (d, *J* = 8.4 Hz, 48 H, H^3_2), 4.69 (m, 48 H, CH$_2$*CH*$_2$N), 4.26 (m, 48 H, O*CH*$_2$CH$_2$), 4.15 (s, 48 H, C*CH*$_2$N), 3.75 (d, *J* = 11.2 Hz, 288 H, PO*CH*$_3$), 3.25 (d, *J* = 9.6 Hz, 54 H, *CH*$_3$NP$_1$, *CH*$_3$NP$_2$), 3.16 (d, *J* = 10.4 Hz, 96 H, N*CH*$_2$P) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.2 (C^4_2), 151.2 (d, *J* = 7.0 Hz, C^1_1, C^1_0), 144.5 (d, *J* = 7.1 Hz, C^1_2), 143.3 (C_{tz}), 139.2 (br. s, *CH*=N$_1$), 138.5 (d, *J* = 17.7 Hz, CH=N$_2$), 132.4 (C^4_1), 132.1 (C^4_0), 128.3 (C^3_1, C^3_0), 124.7 (*CH*$_{tz}$), 122.5 (d, *J* = 5.4 Hz, C^2_2), 121.8 (C^2_1), 121.3 (C^2_0), 115.2 (C^3_2), 66.7 (O*CH*$_2$CH$_2$), 53.8 (d, *J* = 7.0 Hz, PO*CH*$_3$), 51.1 (t, *J* = 8.0 Hz, C*CH*$_2$N), 50.0 (CH$_2$*CH*$_2$N), 49.0 (dd, *J* = 159.4, *J* = 9.3 Hz, NCH$_2$P), 33.1 (d, *J* = 12.3 Hz, *CH*$_3$NP$_2$), 33.0 (d, *J* = 12.0 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.5 (P_2), 62.5 (P_1), 26.4 [PO(OCH$_3$)$_2$], 8.4 (P_0) ppm. $C_{552}H_{792}N_{135}O_{210}P_{69}S_{18}$ (15393.4): calcd. C 43.07, H 5.19, N 12.28; found C 42.89, H 5.12, N 12.19.

Dendrimer 15-[G_0]: DIPEA (2 equiv. per azide) and CuI (0. 1 equiv. per azide) were added to a degassed THF solution of dendrimer **5** (0.10 mmol) and azide **8** (1.1 equiv. per alkyne). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h , monitored by IR, ^{31}P{^{1}H} NMR, ^{1}H NMR). On completion, THF was evaporated, the residue was dissolved in $CHCl_3$, the organic phase was washed with water and brine and dried with $MgSO_4$, and the solvents were evaporated. The crude product was obtained as a white foam and excess starting material was removed by flash chromatography (eluent: CH_2Cl_2/MeOH 95:5). White foam; yield 72% (0.222 g, 0.072 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 6 H, *CH*$_{tz}$), 6.81 (m, 24 H, $H^{2,3}$), 5.13 (s, 12 H, O*CH*$_2$C), 4.48 (t, *J* = 7.2 Hz, 12 H, N$_{tz}$*CH*$_2$CH$_2$CH$_2$), 3.77 (d, *J* = 10.5 Hz, 72 H, PO*CH*$_3$), 3.15 (d, *J* = 8.7 Hz, 24 H, N*CH*$_2$P), 2.85 (t, *J* = 7.2 Hz, 12 H, CH$_2$*CH*$_2$NCH$_2$), 2.06 (m, 12 H, CH$_2$*CH*$_2$CH$_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.2 (C^4), 144.5 (C^1), 143.5 (C_{tz}), 123.6 (*CH*$_{tz}$), 121.8 (C^2), 115.3 (C^3), 62.3 (O*CH*$_2$C), 53.7 (t, *J* = 7.3 Hz, CH$_2$*CH*$_2$N), 52.6 (d, *J* = 6.3 Hz, PO*CH*$_3$), 49.5 (dd, *J* = 157.0, *J* = 6.6 Hz, N*CH*$_2$P), 47.7 (N$_{tz}$*CH*$_2$CH$_2$), 28.4 (CH$_2$*CH*$_2$CH$_2$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 26.8 [PO(OCH$_3$)$_2$], 9.7 (P_0) ppm. $C_{108}H_{174}N_{27}O_{48}P_{15}$ (3083.3): calcd. C 42.07, H 5.69, N 12.27; found C 42.03, H 5.62, N 12.22.

General Procedure for the Synthesis of Dendrimers 16-[G_1] and 16-[G_2]: Cs_2CO_3 (13.2 or 26.4 mmol) was added to a THF (dry, 20 mL) solution of the dendrimer **11-[G_1]** or **11-[G_2]** (0.5 mmol) and 4-(prop-2-yn-1-yloxy)phenol (6.6 or 13.2 mmol), and the reaction mixture was stirred at 40 °C until the reaction was complete (12–36 h, monitored by ^{31}P{^{1}H} NMR). Inorganic salts were filtered through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography in pentane/ethyl acetate (7:3).

Dendrimer 16-[G_1]: White foam; yield 91% (1.441 g, 0.455 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.7 Hz, 12 H, H^3_0), 7.57 (s, 6 H, *CH*=N), 7.11 (d, *J* = 8.7 Hz, 24 H, H^2_1), 7.02 (d, *J* = 8.7 Hz, 12 H, H^2_0), 6.86 (d, *J* = 8.7 Hz, 24 H, H^3_1), 4.60 (d, *J* = 2.4 Hz, 24 H, O*CH*$_2$C), 3.24 (d, *J* = 10.2 Hz, 18 H, *CH*$_3$NP$_1$), 2.50 (t, *J* = 2.4 Hz, 12 H, *HC*≡C) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.0 (C^4_1), 151.2 (br. s, C^1_0), 144.8 (d, *J* = 7.5 Hz, C^1_1), 138.4 (d, *J* = 13.6 Hz, *CH*=N), 132.3 (C^4_0), 128.2 (C^3_0), 122.3 (d, *J* = 4.5 Hz, C^2_1), 121.4 (C^2_0), 115.7 (C^3_1), 78.4 (HC≡*C*), 75.8 (*HC*≡C), 56.2 (O*CH*$_2$), 33.1 (d, *J* = 12.1 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ = 64.0 (P_1), 8.4 (P_0) ppm. $C_{156}H_{132}N_{15}O_{30}P_9S_6$ (3168.0): calcd. C 59.15, H 4.20, N 6.63; found C 59.10, H 4.10, N 6.55.

Dendrimer 16-[G$_2$]: White foam; yield 77% (2.875 g, 0.385 mmol). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.61 (m, 42 H, H^{3}_{0}, H^{3}_{1}, CH=N$_0$), 7.54 (s, 12 H, *CH*=N$_1$), 7.17 (d, *J* = 7.5 Hz, 24 H, H^{2}_{1}), 7.09 (m, 48 H, H^{2}_{2}), 6.85 (m, 60 H, H^{3}_{2}, H^{2}_{0}), 4.57 (d, *J* = 2.4 Hz, 48 H, O*CH*$_2$C), 3.23 (d, *J* = 10.2 Hz, 36 H, *CH*$_3$NP$_2$), 3.18 (d, *J* = 10.5 Hz, 18 H, *CH*$_3$NP$_1$), 2.48 (t, *J* = 2.4 Hz, 24 H, *HC*≡C) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 154.9 (C^{4}_{2}), 151.2 (d, *J* = 7.1 Hz, C^{1}_{1}, C^{1}_{0}), 144.7 (d, *J* = 7.1 Hz, C^{1}_{2}), 139.0 (br. s, *CH*=N$_1$), 138.4 (d, *J* = 13.6 Hz, CH=N$_2$), 132.4 (C^{4}_{1}), 132.1 (C^{4}_{0}), 128.3 (br. s, C^{3}_{1}, C^{3}_{0}), 122.4 (d, *J* = 4.4 Hz, C^{2}_{2}), 121.8 (d, *J* = 4.4 Hz, C^{2}_{1}), 121.5 (br. s, C^{2}_{0}), 115.6 (C^{3}_{2}), 78.4 (HC≡*C*), 75.8 (*HC*≡C), 56.2 (O*CH*$_2$), 33.1 (d, *J* = 12.5 Hz, *CH*$_3$NP$_2$), 32.9 (d, *J* = 12.4 Hz, *CH*$_3$NP$_1$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, CDCl$_3$): δ = 64.1 (P$_2$), 62.4 (P$_1$), 8.6 (P$_0$) ppm. $C_{360}H_{312}N_{39}O_{66}P_{21}S_{18}$ (7468.3): calcd. C 57.90, H 4.21, N 7.31; found C 57.37, H 4.15, N 7.24.

General Procedure for the Synthesis of Dendrimers 17-[G$_1$] and 17-[G$_2$]: DIPEA (2 equiv. per alkyne) and CuI (0.1 equiv. per alkyne) were added to a degassed THF solution of dendrimer **16-[G$_1$]** or **16-[G$_2$]** (0.1 mmol) and azide **8** (1.1 equiv. per alkyne). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h , monitored by IR, ^{31}P{^{1}H} NMR, ^{1}H NMR). On completion, THF was evaporated, the residue was dissolved in CHCl$_3$, the organic phase was washed with water and brine and dried with MgSO$_4$, and the solvents were evaporated. Crude products were obtained as white foams and excess starting material was removed by washing with THF.

Dendrimer 17-[G$_1$]: White foam; yield 89% (0.650 g, 0.089 mmol). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.78 (s, 12 H, *CH*$_{tz}$), 7.65 (m, 18 H, *CH*=N, H^{3}_{0}), 7.09 (d, *J* = 8.7 Hz, 24 H, H^{2}_{1}), 7.01 (d, *J* = 9.0 Hz, 12 H, H^{2}_{0}), 6.87 (d, *J* = 8.7 Hz, 24 H, H^{3}_{1}), 5.10 (s, 24 H, O*CH*$_2$), 4.48 (t, *J* = 6.7 Hz, 24 H, *CH*$_2$N$_{tz}$), 3.78 (d, *J* = 10.5 Hz, 144 H, PO*CH*$_3$), 3.24 (d, *J* = 10.3 Hz, 18 H, *CH*$_3$NP$_1$), 3.17 (d, *J* = 9.0 Hz, 48 H, N*CH*$_2$P), 2.85 (t, *J* = 6.7 Hz, 24 H, CH$_2$*CH*$_2$N), 2.07 (m, 24 H, CH$_2$*CH*$_2$CH$_2$) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 155.8 (C^{4}_{1}), 151.2 (br. s, C^{1}_{0}), 144.4 (d, *J* = 7.5 Hz, C^{1}_{1}), 143.5 (C$_{tz}$), 138.7 (d, *J* = 13.5 Hz, *CH*=N), 132.2 (C^{4}_{0}), 128.3 (C^{3}_{0}), 123.5 (*CH*$_{tz}$), 122.3 (d, *J* = 4.4 Hz, C^{2}_{1}), 121.4 (C^{2}_{0}), 115.4 (C^{3}_{1}), 62.3 (O*CH*$_2$), 53.6 (t, *J* = 7.4 Hz, CH$_2$*CH*$_2$N), 52.6 (m, PO*CH*$_3$), 49.5 (dd, *J* = 157.0, *J* = 6.8 Hz, NCH$_2$P), 47.7 (N$_{tz}$*CH*$_2$CH$_2$), 33.1 (d, *J* = 12.0 Hz, *CH*$_3$NP$_1$), 28.4 (CH$_2$*CH*$_2$CH$_2$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, CDCl$_3$): δ = 64.4 (P$_1$), 26.8 [PO(OCH$_3$)$_2$], 8.5 (P$_0$) ppm. $C_{264}H_{396}N_{63}O_{102}P_{33}S_{6}$ (7298.9): calcd. C 43.44, H 5.47, N 12.09; found C 43.22, H 5.41, N 11.99.

Dendrimer 17-[G$_2$]: White foam; yield 76% (1.195 g, 0.076 mmol). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.78 (s, 24 H, CH$_{tz}$), 7.62 (m, 54 H, H^{3}_{0}, H^{3}_{1}, CH=N$_0$, *CH*=N$_1$), 7.17 (m, 24 H, H^{2}_{1}), 7.07 (m, 48 H, H^{2}_{2}), 6.87 (m, 60 H, H^{3}_{2}, H^{2}_{0}), 5.07 (s, 48 H, O*CH*$_2$), 4.46 (m, 48 H, *CH*$_2$N$_{tz}$), 3.76 (m, 288 H, PO*CH*$_3$), 3.23–3.12 (m, 150 H, *CH*$_3$NP$_1$, *CH*$_3$NP$_2$, N*CH*$_2$P), 2.83 (m, 48 H, CH$_2$*CH*$_2$N), 2.04 (m, 48 H, CH$_2$*CH*$_2$CH$_2$) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 155.7 (C^{4}_{2}), 151.2 (d, *J* = 7.1 Hz, C^{1}_{1}, C^{1}_{0}), 144.5 (d, *J* = 7.1 Hz, C^{1}_{2}), 143.5 (C$_{tz}$), 139.0 (br. s, *CH*=N$_1$, CH=N$_2$), 132.4 (C^{4}_{1}), 132.1 (C^{4}_{0}), 128.4 (C^{3}_{1}, C^{3}_{0}), 123.6 (*CH*$_{tz}$), 122.4 (d, *J* = 4.4 Hz, C^{2}_{2}), 121.8 (d, *J* = 4.4 Hz, C^{2}_{1}), 121.4 (br. s, C^{2}_{0}), 115.4 (C^{3}_{2}), 62.3 (O*CH*$_2$), 53.7 (t, *J* = 7.7 Hz, *CH*$_2$NCH$_2$), 52.7 (m, PO*CH*$_3$), 49.5 (dd, *J* = 157.0, *J* = 6.8 Hz, NCH$_2$P), 47.7 (N$_{tz}$*CH*$_2$CH$_2$), 33.2 (d, *J* = 12.0 Hz, *CH*$_3$NP$_2$, *CH*$_3$NP$_1$), 28.5 (CH$_2$*CH*$_2$CH$_2$) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, CDCl$_3$): δ = 64.5 (P$_2$), 62.5 (P$_1$), 26.8 [PO(OCH$_3$)$_2$], 8.4 (P$_0$) ppm. $C_{576}H_{840}N_{135}O_{210}P_{69}S_{18}$ (15730.1): calcd. C 43.98, H 5.38, N 12.02; found C 43.71, H 5.22, N 11.85.

Dendrimer 18: Cs$_2$CO$_3$ (31.68 mmol) was added to a THF (dry, 60 mL) solution of 4-hydroxybenzyl alcohol (15.84 mmol) and P$_3$N$_3$Cl$_6$ (2.88 mmol), and the mixture was stirred at 40 °C until the reaction was complete (monitored by ^{31}P{^{1}H} NMR). Inorganic salts were filtered through a Celite® pad and the residual solution was evaporated. The crude product was purified by silica gel flash chromatography in CHCl$_3$/MeOH (95:5); yield 60% (1.358 g, 1.728 mmol). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.35 (d, *J* = 8.7 Hz, 4 H, H^3), 7.28 (d, *J* = 8.7 Hz, 4 H, H^3), 7.27 (d, *J* = 8.7 Hz, 2 H, H^3), 7.12 (d, *J* = 8.7 Hz, 4 H, H^2), 6.92 (d, *J* = 8.7 Hz, 4 H, H^2), 6.87 (d, *J* = 8.7 Hz, 2 H, H^2), 4.63 (s, 10 H, *CH*$_2$OH), 4.49 (br. s, 3 H, OH), 4.42 (m, 2 H, OH) ppm. ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]acetone): δ = 149.2 (m, C^1), 148.8 (d, *J* = 9.7 Hz, C^1), 140.2 (d, *J* = 2.6 Hz, C^4), 139.8 (C^4), 139.6 (C^4), 127.8 (C^3), 127.75 (C^3), 120.8 (m, C^2), 120.5 (m, C^2), 63.2 (*CH*$_2$OH), 63.1 (*CH*$_2$OH) ppm. ^{31}P{^{1}H} NMR (121.5 MHz, [D$_6$]acetone): δ = 22.5 (dd, *J* = 81.0, 85.0 Hz, P$_0$), 7.2 (2 × d, *J* = 81.0, 85.0 Hz, P$_0$) ppm. $C_{35}H_{35}ClN_{3}O_{10}P_{3}$ (786.0): calcd. C 53.48, H 4.49, N 5.35; found C 53.42, H 4.48, N 5.33.

Dendrimer 19: Cs$_2$CO$_3$ (1.65 mmol) was added to a THF (dry, 60 mL) solution of compound **18** (1.5 mmol) and 4-(prop-2-ynyloxy)phenol (1.65 mmol), and the mixture was stirred at 40 °C until the reaction was complete (monitored by ^{31}P NMR). Inorganic salts were filtered through a Celite® pad and the residual solvent was removed. The crude product was purified by silica gel flash chromatography (CHCl$_3$/MeOH 95:5); yield 79% (1.064 g, 1.185 mmol). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.28 (d, *J* = 8.4 Hz, 4 H, H^3), 7.24 (d, *J* = 8.4 Hz, 6 H, H^3), 6.9 (m, 10 H, H^2), 6.89 (s, 4 H, $H^{2',3'}$), 4.79 (d, *J* = 2.4 Hz, 2 H, *CH*$_2$C≡CH), 4.64 (m, 10 H, *CH*$_2$OH), 4.45 (t, *J* = 5.7 Hz, 3 H, OH), 4.38 (t, *J* = 5.7 Hz, 2 H, OH), 3.11 (t, *J* = 2.4 Hz, 1 H, C≡*CH*) ppm. ^{13}C{^{1}H} NMR (75 MHz, [D$_8$]THF): δ = 154.9 ($C^{4'}$), 149.5 (m, C^1), 144.8 (m, $C^{1'}$), 139.2 (C^4), 139.1 (C^4), 127.3 (C^3), 127.2 (C^3), 121.7 (m, $C^{2'}$), 120.5 (m, C^2), 115.2 ($C^{3'}$), 78.8 (*C*≡CH), 75.7 (C≡*CH*), 63.3 (*CH*$_2$OH), 63.2 (*CH*$_2$OH), 55.7 (*CH*$_2$C≡CH) ppm. ^{31}P{^{1}H} NMR (162 MHz, [D$_6$]acetone): δ = 9.3 (m, P$_0$) ppm. MS (DCI/NH$_3$): *m*/*z* = 898.2 [M + H]$^+$. $C_{44}H_{42}N_{3}O_{12}P_{3}$ (897.7): calcd. C 58.87, H 4.72, N 4.68; found C 58.61, H 4.61, N 4.60.

Dendrimer 20-[G$_1$]: DIPEA (2 equiv. per azide) and CuI (0.1 equiv. per azide) were added to a degassed THF solution of dendrimer **4** (0.1 mmol) and alkyne **19** (1.1 equiv. per azide). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h , monitored by IR, ^{31}P{^{1}H} NMR, ^{1}H NMR). On completion, THF was evaporated, the residue was dissolved in CHCl$_3$, the organic phase was washed with water and brine and dried with MgSO$_4$, and the solvents were evaporated. The crude product was obtained as a white foam and excess starting material was removed by flash chromatography (eluent: THF/MeOH 6:4). White foam; yield 62% (0.397 g, 0.062 mmol). ^{1}H NMR (300 MHz, [D$_8$]THF): δ = 8.1 (s, 6 H, *CH*$_{tz}$), 7.19 (d, *J* = 8.4 Hz, 24 H, H^{3}_{1}), 7.18 (d, *J* = 8.4 Hz, 36 H, H^{3}_{1}), 7.14 (d, *J* = 8.8 Hz, 12 H, H^{3}_{0}), 6.93–6.86 (m, 72 H, H^{2}_{1}, H^{2}_{0}), 6.80 (m, 24 H, $H^{2',3'}_{0}$), 5.57 (s, 12 H, *CH*$_2$N$_{tz}$), 5.17 (s, 12 H, *CH*$_2$O), 4.64 (m, 12 H, OH), 4.58 (d, *J* = 5.6 Hz, 24 H, *CH*$_2$OH), 4.57 (d, *J* = 5.6 Hz, 36 H, *CH*$_2$OH), 4.57 (m, 18 H, OH) ppm. ^{13}C{^{1}H} NMR (75 MHz, [D$_8$]THF): δ = 155.6 ($C^{4'}_{0}$), 150.3 (m, C^{1}_{0}), 149.5 (m, C^{1}_{1}), 144.4 (m, $C^{1'}_{0}$), 144.0 (C$_{tz}$), 139.1 (C^{4}_{1}), 132.8 (C^{4}_{0}), 129.3 (C^{3}_{0}), 127.4 (C^{3}_{1}), 127.3 (C^{3}_{1}), 124.0 (*CH*$_{tz}$), 121.8 ($C^{2'}_{0}$), 121.1 (C^{2}_{0}), 120.5 (C^{2}_{1}), 115.1 ($C^{3'}_{0}$), 63.3 (*CH*$_2$OH), 63.27 (*CH*$_2$OH), 61.9 (*CH*$_2$O), 52.6 (*CH*$_2$N$_{tz}$) ppm. ^{31}P{^{1}H} NMR (162 MHz, [D$_6$]acetone): δ = 8.9 (s, P$_0$), 9.3 (m, P$_1$) ppm. MS (MALDI): *m*/*z* = 6432 [M + Na]$^+$. $C_{306}H_{288}N_{39}O_{78}P_{21}$ (6410.3): calcd. C 57.34, H 4.53, N 8.52; found C 57.12, H 4.51, N 8.41.

Dendrimer 21-[G$_1$]: SOCl$_2$ was added to a cooled (ice bath) round-bottomed flask containing dendrimer **20-[G$_1$]** (0.04 mmol) until complete dissolution. The reaction mixture was stirred overnight. Excess $SOCl_2$ was removed under a vacuum line with use of toluene as co-solvent and the crude product was used for the next step without further purification. White foam. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (s, 6 H, CH_{tz}) 7.20 (2 × d, $J = 8.4$ Hz, 60 H, $H^3{}_1$), 7.04 (d, $J = 8.4$ Hz, 12 H, $H^3{}_0$), 6.89 (d, $J = 8.4$ Hz, 60 H, $H^2{}_1$), 6.85–6.75 (m, 36 H, $H^2{}_0$, $H^{2',3'}{}_0$), 5.45 (s, 12 H, CH_2N_{tz}), 5.11 (s, 12 H, CH_2O), 4.55, 4.54, 4.52 (3 × s, 60 H, CH_2Cl) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 155.4$ ($C^{4'}{}_0$), 150.3 (m, $C^1{}_0$, $C^1{}_1$), 144.3 (m, $C^{1'}{}_0$, C_{tz}), 134.2 ($C^4{}_1$), 131.8 ($C^4{}_0$), 129.9 ($C^3{}_1$), 129.3 ($C^3{}_0$), 123.5 ($C_{tz}H$), 122.0 ($C^{2'}{}_0$), 121.3 ($C^2{}_0$), 121.1 ($C^2{}_1$), 115.1 ($C^{3'}{}_0$), 62.2 (CH_2O), 53.3 (CH_2N_{tz}), 45.7, 45.6 (2 × s, CH_2Cl) ppm. $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): $\delta = 8.3$ (s, P_0), 8.8 (m, P_1) ppm.

Dendrimer 22-[G$_1$]: NaN_3 (1.6 mmol) was slowly added to a DMF (dry, 5 mL) solution of dendrimer **21-[G$_1$]** (0.05 mmol), and the reaction mixture was stirred and heated overnight at 70 °C. The reaction mixture was then allowed to cool at room temp., distilled water (5 mL) was added, and a white precipitate appeared. The aqueous phase was decanted and the precipitate was dissolved in CH_2Cl_2. The organic phase was then washed with brine, dried with $MgSO_4$ and concentrated to give the azide derivative. White foam; yield 87% (0.311 g, 0.0435 mmol). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (s, 6 H, CH_{tz}), 7.14 (m, 60 H, $H^3{}_1$), 7.04 (d, $J = 9.0$ Hz, 12 H, $H^3{}_0$), 6.98 (m, 72 H, $H^{2'}{}_0$, $H^2{}_1$), 6.86 (d, $J = 9.0$ Hz, 12 H, $H^{3'}{}_0$), 6.77 (d, $J = 9.0$ Hz, 12 H, $H^2{}_0$), 5.45 (s, 12 H, CH_2N_{tz}), 5.10 (s, 12 H, CH_2O), 4.31, 4.30, 4.29 (3 × s, 60 H, CH_2N_3) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 155.5$ ($C^{4'}{}_0$), 150.3 (m, $C^1{}_0$, $C^1{}_1$), 144.3 (m, $C^{1'}{}_0$), 144.2 (C_{tz}), 132.3 ($C^4{}_1$), 131.8 ($C^4{}_0$), 129.4 ($C^3{}_1$), 129.2 ($C^3{}_0$), 123.3 ($C_{tz}H$), 121.9 ($C^{2'}{}_0$), 121.2 ($C^2{}_0$, $C^2{}_1$), 115.4 ($C^{3'}{}_0$), 62.3 (CH_2O), 54.1, 54.05 (2 × s, CH_2N_3), 53.2 (CH_2N_{tz}) ppm. $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): $\delta = 8.3$ (s, P_0), 8.6 (m, P_1) ppm. IR (neat): $\tilde{\nu} = 2092$ (N_3) cm^{-1}. $C_{306}H_{258}N_{129}O_{48}P_{21}$ (7160.7): calcd. C 51.33, H 3.63, N 25.23; found C 51.11, H 3.57, N 25.12.

Dendrimer 23-[G$_1$]: DIPEA (2 equiv. per azide) and CuI (0.1 equiv. per azide) were added to a degassed THF solution of dendrimer **22-[G$_1$]** (0.05 mmol) and alkyne **6** (1.1 equiv. per azide). The reaction mixture was stirred at 40 °C until the reaction was complete (12–24 h, monitored by IR, $^{31}P\{^1H\}$ NMR, ^1H NMR). On completion, THF was evaporated, and the crude residue was directly purified by silica gel flash chromatography; yield 88% (0.710 g, 0.044 mmol). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.99$ (s, 6 H, CH_{tz0}), 7.78 (s, 18 H, CH_{tz1}), 7.71 (s, 12 H, CH_{tz1}), 7.15 (m, 12 H, $H^3{}_0$), 7.08 (m, 60 H, $H^3{}_1$), 6.91 (m, 12 H, $H^2{}_0$), 6.86 (m, 72 H, $H^{2'}{}_0$, $H^2{}_1$), 6.77 (m, 12 H, $H^{3'}{}_0$), 5.57, 5.54, 5.51 (3 × s, 72 H, CH_2N_{tz0}, CH_2N_{tz1}), 5.13 (s, 12 H, CH_2O), 4.14 (s, 36 H, $C_{tz1}\mathit{CH}_2N$), 4.10 (s, 18 H, $C_{tz1}CH_2N$), 3.75–3.68 (m, 360 H, $PO\mathit{CH}_3$), 3.16, 3.13 (2 × d, $J = 10.0$ Hz, 120 H, NCH_2P) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 155.7$ ($C^{4'}{}_0$), 150.4 (m, $C^1{}_0$, $C^1{}_1$), 144.2 (m, $C^{1'}{}_0$), 143.9, 143.8 (C_{tz}), 132.1 (m, $C^4{}_1$, $C^4{}_0$), 129.5 ($C^3{}_0$), 129.2, 129.1 (2 × s, $C^3{}_1$), 124.0, 123.9 (2 × s, CH_{tz}), 121.9 ($C^{2'}{}_0$), 121.2 (2 × s, $C^2{}_0$, $C^2{}_1$), 115.5 ($C^{3'}{}_0$), 62.3 (CH_2O), 53.2 (CH_2N_{tz}), 52.8 (d, $J = 6.9$ Hz, $PO\mathit{CH}_3$), 51.2 (t, $J = 8.8$ Hz, $C_{tz}CH_2N$), 49.0 (dd, $J = 159.5$, $J = 9.2$ Hz, NCH_2P) ppm. $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): $\delta = 26.4$ [s, $PO(OCH_3)_2$] 8.4 (s, P_0), 8.5 (m, P_1) ppm. $C_{576}H_{828}N_{159}O_{228}P_{81}$ (16136.6): calcd. C 42.87, H 5.17, N 13.80; found C 42.16, H 5.06, N 13.59.

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