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Synthesis of dissymmetric phosphorus dendrimers using an unusual protecting group

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Abstract

The presence of an azido group directly linked to phosphorus functionalized monomeric species allows the synthesis of neutral or polycationic original phosphorus dendrimers of reduced symmetry bearing branches of different generations on the core.

Keywords: phosphorus dendrimers; dissymmetric dendrimers; azides; functionalization.

Introduction

Design and applications of dendrimers represent some of the most important developments in macromolecular chemistry, as a new class of highly branched polymers for which, size, internal and external topologies, molecular weight, shape, and charges can be precisely controlled[1]. They are generally prepared *via* step-by-step procedures (divergent synthesis from a core or convergent ones).[2] Physicochemical and biological properties of the dendrimers are related to their structure and anatomy such as generations and surface characteristics. Within numerous dendrimer types described up-to-date, phosphorus dendrimers are among the most useful architectures which can be tailored at will for various uses [3]. Indeed, the rich organophosphorus chemistry allows the development of sophisticated ways of preparation of phosphorus dendrimers or related macromolecular species, and consequently a number of applications in

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different fields ranging from biology, nanomedicine, nanosciences in general and nanomaterials in particular as well as in the field of catalysis [4]. Some examples of the synthesis of topological subclasses of phosphorus dendrimers by blocking partially the branches growth sites of the core [5] or by modifying stepwise their functionalization were reported [6].

It is also possible to modify the dendrimer topology by growing branches of different generations on the core [7]. The potential consequence of the topology alteration is the change of the distribution and density of functional groups on the periphery of dendrimers[8] resulting in drastic changes in dendrimer interactions with various biological systems such as cells, proteins, blood serum, DNA, etc.[9] As an example, the influence of the dendrimers topology on their activity towards immune cells was recently reported by Caminade et al.[10] Interestingly, there are also evidences of the smaller toxicity of low-generation of dissymmetric dendrimers in comparison with symmetric ones[11]. Consequently, obtaining dissymmetric phosphorus dendrimers represents an interesting objective for pharmaceutical applications by developing new synthetic procedures of preparation of phosphorus dendrimers with potential lower toxicity issue.

Dissymmetric dendrimers are generally obtained by using classical protecting groups, often at the level of the core, which need additional reagents for the deprotection and further purification step [12]. The synthesis can be simplified by introducing a temporary protecting group resistant to one of the reactions comprising typical dendrimer synthesis.[13] In particular, azido group linked to a phosphorus atom can be considered as a pseudo-halogen when reacted with phenols,[14] thus this function could be considered also as a protecting group, easily removed by phenols, without adding any deprotecting agent. Despite its potential utility, this method has never been used for the synthesis of dendrimers. In this study, we report the useful and tunable phosphorus azides-based synthesis of original dissymmetric phosphorus dendrimers bearing branches of different generations on the core.

Results and discussion

The synthesis of phosphorus dendrimers[15,16] consists of two orthogonal reactions repeating consecutively: (a) the reaction of dichlorothiophosphate fragments on the periphery of the growing branch with 4-hydroxybenzaldehyde (intermediate generation); (b) the reaction of aldehydes with dichlorothiophosphomethylhydrazide to form the Schiff base stabilized by the aromatic and thiophosphate fragments in vicinity (increasing generation).

Herein, our simple strategy is based on the functionalization of the thiophosphate unit –P(S)< as a core, which allows to conduct iterative synthesis of three structurally independent branches

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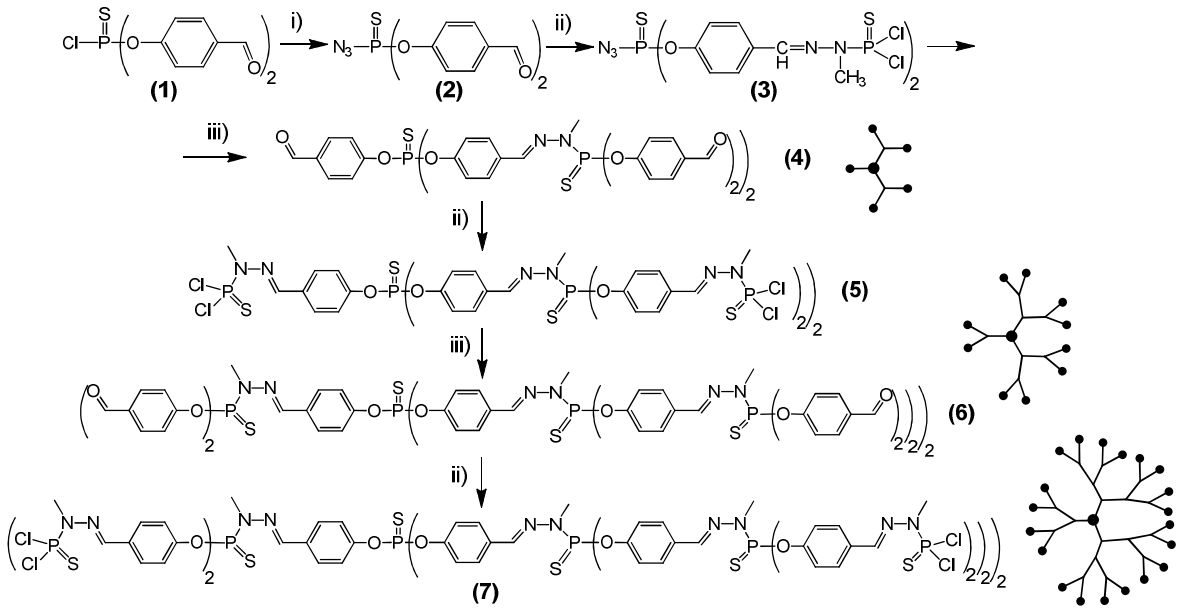
for the construction, for instance, of dissymmetric dendrimers. One of the branch growth sites was temporarily blocked by an azido group to make it unavailable for the generation increasing reaction. The strong advantage of the proposed strategy is the specific nucleophilic substitution of N_3 of >P(S)-N_3 with phenol groups and its stability towards the reaction with amines and hydrazides allowing the construction of tunable dissymmetric assemblages. All further reactions at the branches proceeded identically with the same conversion efficiency, independently of the branch generation. In order to exemplify this approach, we decided to construct dissymmetric phosphorus dendrimers bearing two branches of the generation N and one branch of the generation (N-1) from the –P(S)< core.

Scheme 1



i) NaN_3, acetone; ii) H_2N-N(CH_3)-P(S)Cl_2, THF; iii) 4-hydroxybenzaldehyde, Cs_2CO_3, THF.

As shown in the Scheme 1, the synthesis of dissymmetric dendrimers **(7)** began from the disubstituted core **(1)** which has been prepared in one step synthesis by reacting P(S)Cl_3 with two equivalents of 4-hydroxybenzaldehyde.[17] Then, the remaining >P-Cl fragment of **(1)** was substituted to the P-N_3 by the action of NaN_3 to form the derivative **(2)** quantitatively.[17] Next is the condensation of amino group of dichlorothiophosphomethylhydrazide (2 eq.) with **(2)** (1 eq.) to afford the Schiff base **(3)** in 95% yield. No condensation of dichlorothiophosphomethylhydrazide with >P-N_3 has been observed. This strategy prevents the fast reaction of **(1)** with the amino group of dichlorophosphomethylhydrazide that does not allow

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the construction of tunable dissymmetric dendrimers: both >P-Cl and the two aldehyde groups react with dichlorothiophosphomethylhydrazide.

Topologically, the compound **(3)** is a dendron of the generation 1 (G1) bearing azide group in the focal point. The phosphorus atoms in the core (P_0) and on the periphery (P_1) are clearly discerned in the ^{31}P NMR spectra (chemical shifts of 58.9 and 63.0 ppm, respectively). The next step is the reaction of **(3)** with 4-hydroxybenzaldehyde (3 eq.) leading to **(4)** in 97% yield by the substitution of the both P-Cl fragments on the periphery (63.0 to 60.2 ppm) and P-N_3 fragment in the focal point (58.9 to 51.5 ppm), as expected. Thus, in the structure of the dendrimer (**4**), there appear two types of aldehyde groups. The ^1H NMR signals of these aldehydes (9.99 and 10.03 ppm) have the ratio of the integral intensities of 4:1, as it is expected from the structure of **(4)** (Fig S1 in the ESI). It is clear from these data that the azide group linked to the phosphorus atom plays the role of a protecting group, directly removed by a phenolate. With the objective to obtain the next generation of **(4),** the reaction of phosphorohydrazide (5 eq.) was carried out to form dissymmetric dendrimer **(5)** with 90.4 % yield bearing one branch of generation 1 and two branches of generation 2 (G1-P(S)-$(G2)_2$). The P_0 atom in the structure of **(5)** behaves as a dendrimer core by analogy with fully symmetric phosphorus dendrimers,[15] with its chemical shift (52.2 ppm) being not drastically changed in the course of further reactions. Repeating these two reactions – condensation of 4-hydroxybenzaldehyde (10 eq.) with **(5)** leading to the dissymmetric dendrimers (**6,** 75% yield) and addition of H_2N-N(CH_3)-P(S)Cl_2 (10 eq.) - affords **(7)** bearing one branch of the generation 2 and two branches of the generation 3 (G2-P(S)-$(G3)_2$, 98% yield). Chemical shifts of the peripheral phosphorus atoms depend on the nature of the terminal groups (aldehyde or P(S)Cl_2) and alternate upon iterative synthesis, as described for fully symmetric analogs.[15] The evolution of $^{31}P\{^1H\}$ signals of the dissymmetric dendrimers through the synthetic stages is presented in the Fig. S2 (ESI). The dissymmetric dendrimers **(5)** and **(7)** have 10 and 20 P-Cl fragments, respectively, on the periphery. These fragments are available for further chemical modifications. In order to exemplify the functionalization of dendrimers **(5)** and **(7)** the corresponding cationic amino-terminated dendrimers under non-protonated and protonated forms **(8a,b)** and **(9a,b)** have been prepared (Scheme 2). The protonated dendrimers **(8b)** and **(9b)** have been prepared in order to increase the water solubility of these nanoparticles and to study their complexation with therapeutic nucleic acids (*vide infra*).

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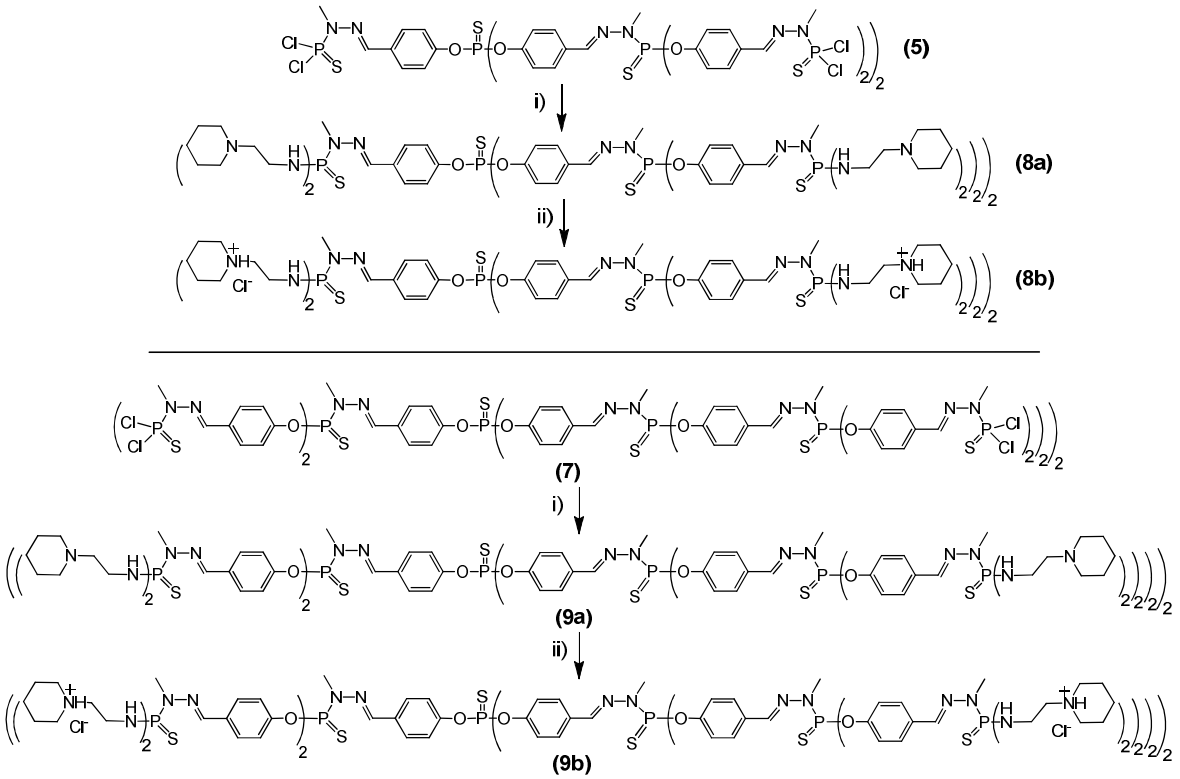
Scheme 2



i) 1-(2-Aminoethyl)piperidine, DIPEA, THF; ii) HCl/Et_2O, THF.

Amino-derivatives of the dissymmetric phosphorus dendrimers were obtained by the reaction of the dendrimers **(5)** and **(7)** with a primary amine in the presence of an organic base (diisopropylethylamine, DIPEA). As an example, 1-(2-aminoethyl)piperidine has been chosen for the modification of the dendrimers' periphery. Recently, we have shown that cationic phosphorus dendrimers bearing tertiary amines on the periphery are biocompatible and highly efficient carriers for the delivery of nucleic acids into cells [18–21]. The grafting of amines onto the periphery of dendrimers resulted in the shifting of the ^{31}P NMR signals corresponding to the peripheral phosphorus atoms from 63.0 to 68.2 ppm (Fig. S3 in the ESI). Neutral amino-modified dendrimers **(8a)** and **(9a)** have been obtained in high yields (83-85%). Water-soluble cationic dendrimers **(8b)** and **(9b)** were obtained by the protonation of neutral dendrimers **(8a)** and **(9a)** in the organic medium with HCl solution in Et_2O. The quantity of HCl used was calculated to protonate 90% of amines on the dendrimer periphery. Nevertheless, despite of being incompletely protonated, cationic dendrimers are well soluble in water. Considering the pK values of ethylpiperidine (~11.3), we can assume that immediately after dissolving in water, remaining amino groups are ionized by water protons. Thus, cationic dendrimers can be

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considered fully protonated. ^{31}P NMR data confirmed the integrity of the dendrimer architecture after the protonation. The full chemical structure of the compound (**9b**) is shown in Figure 1.

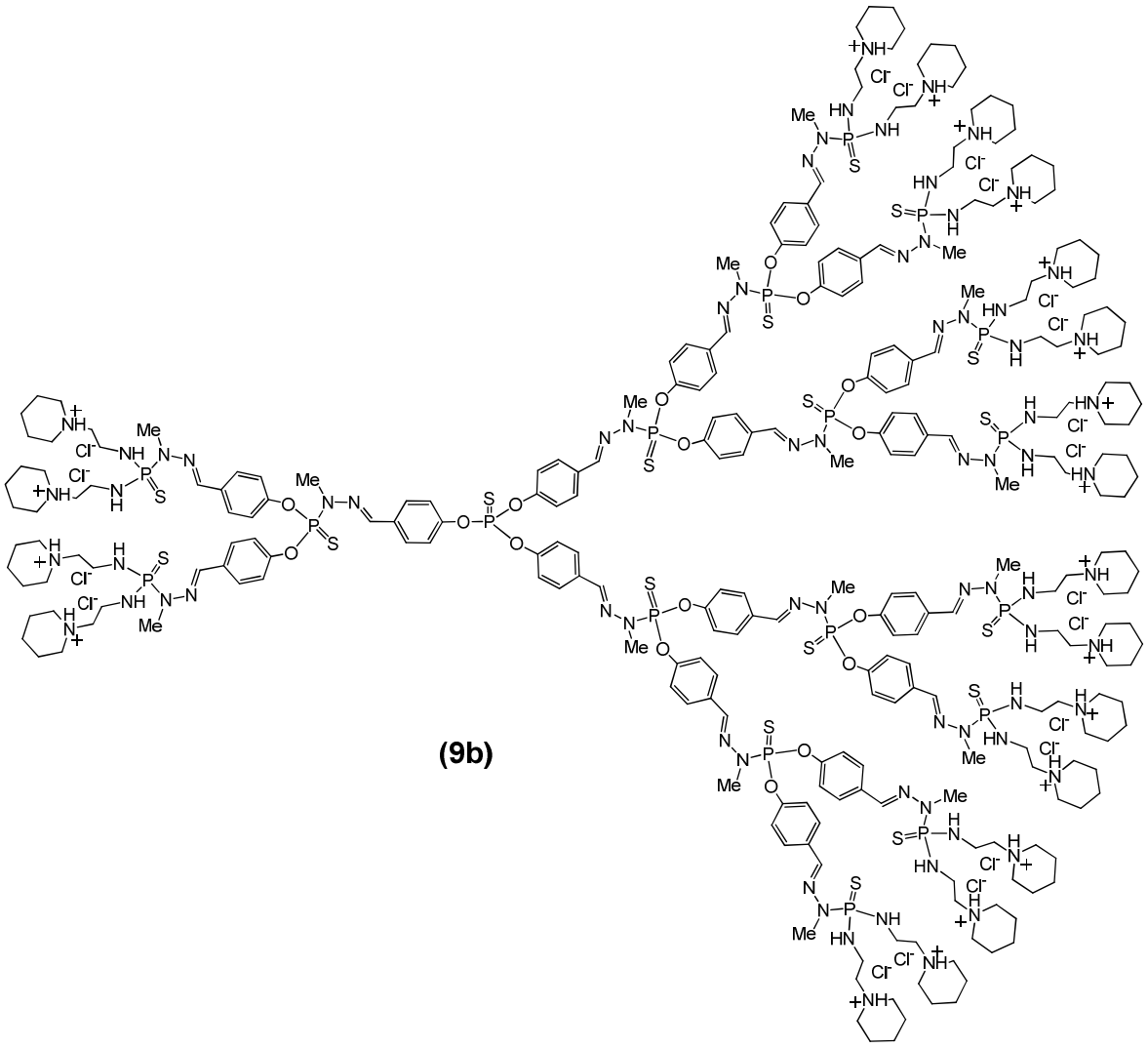

Fig. 1. Chemical structure of the amino-modified dissymmetric dendrimer G2-P(S)-$(G3)_2$, protonated form **(9b)**.

Conclusions

In summary, an original strategy of the synthesis of dissymmetric phosphorus dendrimers was reported, using an azide group as unusual protecting group. On one side, the core has an aminothiophosphate, and on the other side a thiophosphate, both functions being linked through a methylhydrazinophenol. This work is a new facet of the use of phosphorus azides. Up to now, two major reactions of phosphorus azides were outlined. The first one consists on the use of active synthons bearing phosphorus azide unit for the preparation, *via* Staudinger reaction, of monomers, macrocycles, dendrimers etc. bearing P=N-P=S, or P=N-P=N-P=S linkages[6,22] within

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their structures. The second one illustrated the possibility *via* irradiation of P-N_3 units to form transient phosphorus nitrenes *via* a Curtius type rearrangement[23] or unprecedented P≡N triple bond species which afford unusual cyclodiphosphazene four membered rings[24].

Despite the fact that azides display a versatile reactivity, their use as a protecting group sensitive to phenols but not to hydrazines opens new perspectives in the synthesis domain, as illustrated here with the design of original dissymmetric dendrimers. The first species of this topological group bearing two branches of generation 2 or 3 and one branch of generation 1 or 2 at the core and dichlorohydrazidothiophosphate fragments on the periphery were synthesized. Using these dendrimers as precursors, water-soluble polycationic dissymmetric dendrimers were obtained with good overall yield. It should be noted that the reported approach can be extended to another phosphorus core with different branching degree (cyclotriphosphazene). For example, a penta-substituted core, penta(4-formylphenoxy)chlorocyclo(triphosphazene)[5], can be also converted into an azide derivative[25] that would lead to dissymmetric dendrimers.

Dissymmetric phosphorous dendrimers can be used in molecular biology and nanomedicine[26,27] as therapeutics *per se* or as carriers of biologically active molecules (*i.e.*, nucleic acids) into cells. The future research will help to investigate the potential of the reported synthetic methodology and the use of these phosphorus dendrimers for organic chemistry and nanomedicine[28].

Experimental

All manipulations were carried out using standard dry argon-high vacuum technique. Organic solvents were dried and distilled prior to use. Dichlorothiophosphomethylhydrazine was obtained as described elsewhere[15,16] and used without further purification as 0.2 M solution on $CHCl_3$. Compounds (**1**) and (**2**) were synthesized according to published procedures[17], as well as compound (**3**)[29] [Caution: It is strongly recommended to apply standard safety precautions while treating phosphorus azides because of their explosive nature]. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using AV300PAS, AV400PAS, AV400LIQ spectrometers (Bruker, Germany). The attribution of the NMR signals of the dendrimer branches was made by analogy with Refs. [15,16], the attribution of the NMR signals of the amines on the periphery was made by analogy with Refs.[21,30]. To assign the ^{13}C NMR signals, Jmod, HMBC, HBQC NMR experiments were additionally done, if necessary. The atom numbering used for the signals attribution is given in Fig. 2. Protonated dendrimers were characterized only by $^{31}P\{^1H\}$ NMR to ensure the integrity of structure. Unfortunately, mass spectrometry could not be used to prove the

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purity of these dendrimers because of spontaneous rearrangements in the phosphorhydrazone structure during the analysis.[31]

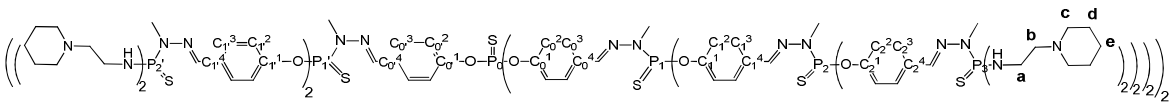

Fig. 2. Atom numbering used for the NMR signals attribution.

O,O-bis(4-((2-(bis(formylphenyloxy)phosphorothioyl)-2-(methylhydrazono)methyl)phenyl)-O-(4-formylphenyl)-phosphorothioate (dissymmetric dendrimer G0′-P(S)-(G1′)$_2$ (4). 4-Hydroxybenzaldehyde (805.2 mg, 6.6 mmol) was stirred with Cs_2CO_3 (2 g, 9 mmol) in THF (40 mL) overnight at room temperature. Then, the solution of **(3)** (700 mg, 1.04 mmol) in 10 mL THF was added dropwise at 0 °C, the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was filtered, the filtrate was evaporated to oil, and the product **(4)** was purified by the silica gel column chromatography (eluent 25% THF/CH_2Cl_2, Rf 0.9), re-precipitated in 60 mL pentane as white powder. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (d, J = 10.8, 6 H, CH_3NNP_1), 7.30 (dd, J = 8.7, 1.5, 4 H, $C_0{}^3H$), 7.41 (dd, J = 8.4, 1.2, 8 H, $C_1{}^3H$), 7.45 (dd, J = 8.5, 1.4, 2 H, $C_{0'}{}^3H$), 7.69 (c, 2 H, $C_0{}^4$-CH), 7.73 (d, J = 8.5, 4 H, $C_0{}^2H$), 7.91 (d, J = 8.5, 8 H, $C_1{}^2H$), 7.97 (d, J = 8.4, 2 H, $C_{0'}{}^2H$), 9.99 (s, 4 H, $C_1{}^4$-CHO), 10.03 (s, 1H, $C_{0'}{}^4$-CHO). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 32.3 (d, J = 13.5, CH_3NP_1), 121.6 (d, J = 5.0, $C_0{}^3$), 121.8 (d, J = 5.1, $C_{0'}{}^3$), 122.0 (d, J = 5.0, $C_1{}^3$), 128.5 (m, $C_{0'}{}^2$), 131.5 (m, $C_1{}^2$) 131.7 (m, $C_0{}^2$), 132.5 (m, $C_{0'}{}^4$), 133.7 (m, $C_1{}^4$), 134.1 (m, $C_0{}^4$), 139.2 (d, J = 13.9, CH=NNP$_1$), 151.2 (d, J = 8.0, $C_0{}^1$), 154.8 (d, J = 7.5, $C_{0'}{}^1$), 155.1 (d, J = 8.0, $C_1{}^1$), 190,6 (s, $C_{0'}{}^4$-CHO), 190.7 (s, $C_1{}^4$-CHO). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 51.5 (m, P_0), 60.2 (s, P_1).

Dissymmetric dendrimer G1-P(S)-(G2)$_2$ (5). Dissymmetric dendrimer **(4)** (0.9 g, 0.825 mmol) was dissolved in THF (30 mL), then 2 g anhydrous Na_2SO_4 was added, the reaction mixture was cooled to 0 °C, and the solution of dichlorothiophosphomethylhydrazine (0.2 M in $CHCl_3$, 4.13 mmol, 20.6 mL) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C, then 30 min at room temperature. The reaction was followed by the disappearance of the aldehyde signal in the ^{1}H NMR. The solution of the product was recovered by filtration, evaporated to oil, the product **(5)** was precipitated in 60 mL pentane as white powder. Yield 90.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (d, J = 13.5, 3 H, $CH_3NNP_{1'}$), 3.50 (d, J = 13.8, 6 H, CH_3NNP_1), 3.53 (d, J = 13.7, 12 H, CH_3NNP_2), 7.30 (d, J = 1.5, 2 H, $C_0{}^3H$), 7.32 (dd, J = 3.1, 1.5, 4 H, $C_1{}^3H$), 7.35 (d, J = 1.7, 1 H, $C_{0'}{}^3H$), 7.68 (br. s, 6 H, CH=NNP$_1$, CH=NNP$_2$), 7.72 (m, 5

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H, $C_{0'}{}^2H$, $C_1{}^2H$), 7.75 (br. s, 1 H, CH=NNP$_2$), 7.80 (m, 2 H, $C_0{}^2H$). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 31.8 (d, J = 19.1, CH_3NNP_2), 33.1 (d, J = 19.1, CH_3NNP_1, $CH_3NNP_{1'}$), 121.8 (m, $C_0{}^3$, $C_1{}^3$, $C_{0'}{}^3$), 128.4 (d, J = 18.1, $C_{0'}{}^2$), 128.8 (m, $C_0{}^2$, $C_1{}^2$), 131.4-132.8 (m, $C_0{}^4$, $C_{0'}{}^4$ $C_1{}^4$), 140.3 (d, J = 19.1, CH=NNP$_2$), 140.6 (m, CH=NNP$_1$, CH=NNP$_{1'}$), 151.9 (m, $C_0{}^1$, $C_1{}^1$, $C_{0'}{}^1$). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 52.2 (m, P_0), 61.8 (s, P_1), 62.96 (s, P_2), 63.04 (s, $P_{1'}$).

Dissymmetric dendrimer G1′-P(S)-(G2′)$_2$ (6). 4-Hydroxybenzaldehyde (350 mg, 2.9 mmol) was stirred with Cs_2CO_3 (1.3 g, 4 mmol) in THF (30 mL) overnight at room temperature. Then, the solution of **(5)** (500 mg, 0.26 mmol) in 10 mL THF was added dropwise at 0 °C, the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered, the filtrate was evaporated to oil, and the product **(6)** was precipitated in 60 mL pentane as white powder. Yield 75%. ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (m, 21 H, CH_3NNP_1, $CH_3NNP_{1'}$, CH_3NNP_2), 7.25 (d, J = 8.7, 5 H, $C_1{}^3H$, $C_{0'}{}^3H$), 7.30 (d, J = 7.6, 2 H, $C_0{}^3H$), 7.36 (d, J = 8.7, 10 H, $C_2{}^3H$, $C_{1'}{}^3H$), 7.63 (m, 6 H, CH=NNP$_1$, CH=NNP$_2$), 7.70 (s, 1 H, CH=NNP$_{1'}$), 7.77 (d, J = 8.7, 3 H, $C_0{}^2H$, $C_{0'}{}^2H$), 7.85 (d, J = 8.7, 14 H, $C_1{}^2H$, $C_{1'}{}^2H$, $C_2{}^2H$), 9.93 (s, 2 H, $C_{1'}{}^4$-CHO), 9.94 (s, 8 H, $C_2{}^4$-CHO). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 33.1 (d, *J* = 3.2, $CH_3NP_{1'}$), 32.9 (d, *J* = 3.1, CH_3NP_1), 33.0 (d, *J* = 3.1, CH_3NP_2), 121.6 (d, *J* = 3.5, $C_0{}^3$), 121.8 (d, *J* = 4.8, $C_{0'}{}^3$), 121.9 (d, *J* = 5.0, $C_1{}^3$), 122.0 (m, $C_{1'}{}^3$, $C_2{}^3$), 128.4 (m, $C_0{}^2$, $C_{0'}{}^2$, $C_{1'}{}^2$), 131.4 (m, $C_1{}^2$, $C_2{}^2$), 131.8 (s, $C_1{}^4$), 132.4 (s, $C_{0'}{}^4$), 132.7 (s, $C_{0'}{}^4$), 133.7 (m, $C_{1'}{}^4$, $C_2{}^4$), 138.8 (d, J = 14.2, CH=NNP$_1$), 139.3 (d, J = 14.2, CH=NNP$_{1'}$), 139.5 (d, J = 14.2, CH=NNP$_2$), 151.2 (d, J = 8.0, $C_0{}^1$), 151.3 (d, J = 7.9, $C_{0'}{}^1$), 151.6 (d, J = 7.1, $C_1{}^1$), 155.1 (m, $C_{1'}{}^1$, $C_2{}^1$), 190.6 (s, $C_{1'}{}^4$-CHO), 190.7 (s, $C_2{}^4$-CHO). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 52.5 (s, P_0), 60.17 (s, P_1), 60.22 (s, P_2), 62.1 (s, $P_{1'}$).

Dissymmetric dendrimer G2-P(S)-(G3)$_2$) (7). Dissymmetric dendrimer **(6)** (0.4 g, 0.145 mmol) was dissolved in THF (30 mL), then 2 g anhydrous Na_2SO_4 was added, the reaction mixture was cooled to 0 °C, and the solution of dichlorothiophosphomethylhydrazine (0.2 M in $CHCl_3$, 1.45 mmol, 7.36 mL) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C, then 30 min at room temperature. The reaction was followed by the disappearance of the aldehyde signal in the ^1H NMR. The solution of the product was recovered by filtration, evaporated to oil, the product **(7)** was precipitated in 60 mL pentane as white powder. Yield 98%. ^1H NMR (400 MHz, $CDCl_3$) δ 3.34-3.42 (m, 21 H, CH_3NNP_1, $CH_3NNP_{1'}$, CH_3NNP_2), 3.42-3.51 (m, 30 H, $CH_3NNP_{2'}$, CH_3NNP_3), 7.23-7.26 (m, 17 H, $C_0{}^3H$, $C_1{}^3H$, $C_{0'}{}^3H$, $C_2{}^3H$, $C_{1'}{}^3H$ $C_{2'}{}^3H$, $C_3{}^3H$), 7.63-7.68 (m, 17 H, CH=NNP$_1$, CH=NNP$_{1'}$, CH=NNP$_2$, CH=NNP$_{2'}$, CH=NNP$_3$), 7.68-7.82 (m, 17 H, $C_0{}^2H$, $C_1{}^2H$, $C_{0'}{}^2H$, $C_2{}^2H$, $C_{1'}{}^2H$ $C_{2'}{}^2H$, $C_3{}^2H$). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 31.8 (d, J = 13.2, CH_3NNP_1, $CH_3NNP_{1'}$, CH_3NNP_2), 33.1 (d, J = 13.0, $CH_3NNP_{2'}$, CH_3NNP_3), 128.3 (m, $C_0{}^3$, $C_{0'}{}^3$), 128.5 (m, $C_1{}^3$, $C_2{}^3$, $C_{1'}{}^3$), 128.7 (m, $C_{2'}{}^3$, $C_3{}^3$), 131.5 (m, $C_{2'}{}^4$,

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C_3^4), 132.1 (m, C_1^4, $C_{1'}^4$, C_2^4), 132.7 (s, $C_{0'}^4$, C_0^4), 138.7 (d, J = 11.1, CH=NNP$_1$), 138.8 (d, J = 11.4, CH=NNP$_{1'}$), 139.0 (d, J = 11.8, CH=NNP$_2$), 140.7 (d, J = 18.8, CH=NNP$_{2'}$, CH=NNP$_3$), 151.2 (m, C_0^1, $C_{0'}^1$, C_1^1), 151.5 (m, $C_{1'}^1$, C_2^1), 151.9 (d, J = 7.3, $C_{2'}^1$, C_3^1). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 52.4 (m, P_0), 61.7 (s, P_1), 61.8 (s, P_2), 62.1 (s, $P_{1'}$), 63.0 (s, $P_{2'}$, P_3).

Aminomodification of the periphery of the dissymmetric dendrimers

To the ice-cooled solution of the dendrimer **(5)** or **(7)** (0.1 mmol) in 10 mL THF, DIPEA (2.5 eq. per P-Cl fragment, 2.5 or 5 mmol, respectively) and 1-(2-aminoethyl)piperidine (1.05 eq. per P-Cl, 1.05 or 2.1 mmol, respectively) were added dropwise. The reaction mixture was stirred for 3 h at room temperature, and then evaporated to dryness. The solid residue was dissolved in 20 mL CH_2Cl_2, 10 mL 1M K_2CO_3 was added, and the product was extracted 3 times 20 mL CH_2Cl_2. Organic fractions were mixed, dried over $MgSO_4$ and evaporated to oil. The product **(8a)** or **(9a)** was precipitated in 70 mL pentane as white powder which was recovered by filtration and dried.

To obtain the protonated forms **(8b)** or **(9b)**, 1M HCl in Et_2O (0.9 mmol or 1.8 mmol, respectively) was added dropwise to the ice-cooled solution of dendrimer **(8a)** or **(9a)** in 20 mL THF (0.1 mmol). Protonated dendrimers were recovered by filtration as white powders, washed 2 times with 20 mL THF and dried.

Aminomodified dissymmetric dendrimer G1-P(S)-(G2)$_2$ (8a). Yield 85%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 20 H, C_eH_2), 1.51 (m, 40 H, C_dH_2), 2.35 (s, 40 H, C_cH_2), 2.42 (t, *J* = 5.9, 10 H, C_bH_2), 2.87–3.11 (m, 20H, C_aH_2), 3.16 (m, 15 H, $CH_3NNP_{1'}$, CH_3NNP_2), 3.34 (d, *J* = 10.2, 6 H, CH_3NNP_1), 4.00 (m, 10 H, NH), 7.20 (d, *J* = 8.8, 8 H, C_1^3H), 7.24 (d, *J* = 8.5, 4 H, C_0^3H), 7.28 (d, *J* = 9.0, 2 H, $C_{0'}^3H$), 7.45 (s, 4 H, CH=NNP$_2$), 7.49 (s, 2 H, CH=NNP$_1$), 7.60 (m, 8 H, C_1^2H), 7.65 (m, 5 H, C_0^2H, CH=NNP$_{1'}$), 7.75 (m, 2 H, C_1^2H). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 52.5 (m, P_0), 62.6 (m, P_1), 68.2 (m, P_2, $P_{1'}$).

Aminomodified dissymmetric dendrimer G1-P(S)-(G2)$_2$, protonated form (8b). $^{31}P\{^1H\}$ NMR (162 MHz, CD_3OD) δ 53.3 (m, P_0), 62.5 (m, P_1), 69.8 (m, P_2), 69.9 (m, $P_{1'}$).

Aminomodified dissymmetric dendrimer G2-P(S)-(G3)$_2$ (9a). Yield 83%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 40 H, C_eH_2), 1.52 (m, 80 H, C_dH_2), 2.36 (s, 80 H, C_cH_2), 2.42 (t, *J* = 5.7, 20 H, C_bH_2), 2.88–3.10 (m, 40H, C_aH_2), 3.14 (d, *J* = 9.5, 30 H, $CH_3NNP_{2'}$, CH_3NNP_3), 3.33 (m, 21 H, CH_3NNP_1, $CH_3NNP_{1'}$, CH_3NNP_2), 4.03 (m, 20 H, NH), 7.18 (d, *J* = 7.7, 20 H, $C_{1'}^3H$, C_2^3H), 7.26 (d, *J* = 7.6, 10 H, $C_{0'}^3H$, C_1^3H), 7.31 (d, *J* = 6.9, 4 H, C_0^3H), 7.45 (s, 12 H, CH=NNP$_2$, CH=NNP$_{2'}$, CH=NNP$_3$), 7.60 (dd, *J* = 7.8, 3.4, 20 H, $C_{1'}^2H$, C_1^2H), 7.65 (s, 4 H, CH=NNP$_1$), 7.65 (m, 5 H, C_0^2H, CH=NNP$_{1'}$), 7.72 (d, *J* = 6.7, 10 H, $C_{0'}^2H$, C_1^2H), 7.77 (d, *J* =

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6.9, 2 H, $C_0{}^2H$), 7.82 (s, 2 H, CH=NNP$_{1'}$). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 52.3 (m, P_0), 62.6 (m, P_1, $P_{1'}$, P_2), 68.14 (s, P_3), 68.17 (s, $P_{2'}$).

Aminomodified dissymmetric dendrimer G2-P(S)-(G3)$_2$, protonated form (9b). $^{31}P\{^1H\}$ NMR (162 MHz, CD_3OD) δ 52.7 (m, P_0), 61.8 (m, P_1), 62.5 (s, $P_{1'}$, P_2), 69.74 (s, P_3), 69.78 (s, $P_{2'}$).

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Synthesis of dissymmetric phosphorus dendrimers using an unusual protecting group

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We report the synthesis of neutral and polycationic dissymmetric phosphorus dendrimers bearing branches of different generations on the core.