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Dendrimers bearing three types of branching functions

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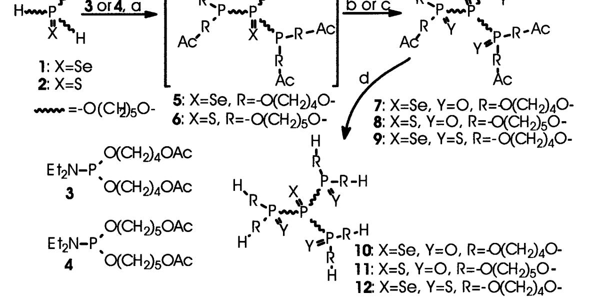
Abstract—Selective *t*-butylperoxy-trimethylsilane oxidation of phosphites, having labile seleno- and thiophosphate groups, to corresponding phosphates has been accomplished. This key reaction has been successfully applied to the synthesis of dendrimers possessing three different (P=Se, P=O and P=S) branching units within the same molecule. © 2002 Elsevier Science Ltd. All rights reserved.

Dendrimers, perfectly ordered, monodisperse macromolecules exhibiting iterative architecture (branching of branches) are one of the major themes in chemistry today.[1] Their synthesis with precisely tuned structural components like core, branches and surface terminal groups affords material possessing particular physical properties and applications.[1] To the best of our knowledge, only one example of a dendrimer built of two types of repeat branching elements has been described.[2]

On the other hand, amidophosphite reagents enabled the convenient synthesis of the large diversity of biologically relevant phosphates and their analogs.[3]

Recently, we have developed a methodology for the synthesis of phosphorus-based dendrimers involving chemistry of trivalent phosphorus derivatives.[4,5] As a continuation of our efforts, we now report a highly efficient synthesis of new heteroorganic dendrimers having different chalcogen atoms bound to a branching phosphorus at different 'layers' of a dendrimer. Additionally, we wish to demonstrate that 2,4,6-collidine trifluoroacetate (COLT) is a remarkably good activator[6] of phosphoroamidites, thus it can be used instead of expensive tetrazole, as a reagent in a dendrimer growth phosphitylation step.

The dendrimer building units, tris(5-hydroxypentyl) selenophosphate (**1**), tris(5-hydroxypentyl) thiophosphate (**2**), bis(4-acetoxybutoxy)-*N*,*N*-diethylaminophosphine (**3**) and bis(5-acetoxypentoxy)-*N*,*N*-diethylaminophosphine (**4**) were prepared in high yield from appropriate alkanediol monoacetates,[7] as described previously.[4,5] The core triols **1** and **2** reacted readily with phosphoroamidites **3** and **4** (3.4 equiv., 1 h, rt), in the presence of 2,4,6-collidine trifluoroacetate[8] (COLT) (6 equiv.) or tetrazole (6 equiv.), to afford the corresponding trisphosphite intermediates **5** and **6**, respectively (Scheme 1), which were not isolated from the reaction medium. At this point we faced the challenge to find an oxidant for the generation of the oxyphosphoryl functions in **5** and **6** without affecting the labile thiophosphate and/or the especially sensitive selenophosphate group,[9] present in the molecule. The first choice oxidant seemed to be *t*-BuOOH, which was successfully used for the selective conversion of the ribonucleotide 3′-phosphite, 2′-thiophosphate derivatives into the corresponding 3′-phosphate esters.[10] However, the oxidation of **5** and **6** with *t*-BuOOH produced a low yield of **7** and **8** accompanied by by-products



Scheme 1. (a) Tetrazole or COLT, dichloromethane; (b) *t*-$BuOOSiMe_3$; (c) S_8; (d) K_2CO_3, methanol, water.

Keywords: dendrimers; phosphorus compounds; chalcogens; oxidation; pyridinium salts.

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(apparently, the skeleton of the forming dendrimers was damaged), as detected by $^{31}P\{^1H\}$ NMR. Recently, we have shown that *t*-butylperoxy–trimethylsilane[11] quantitatively oxygenated a selenophosphate dendrimer of generation 3 into its phosphate derivative but a thiophosphate-based dendrimer remained intact.[5] Surprisingly, the addition of *t*-BuOOSiMe$_3$ (3.7 equiv., 2 h at 0°C, then 10 h at rt) to crude **5** and **6** resulted in exclusive oxidation of P(III) phosphorus atoms at peripheral branching, providing the first generation dendrimers **7** and **8**, in high isolated yields.[12] It appears, that even in the case of 'small' dendritic molecules, outer phosphite nucleophilic centers are much more accessible for the bulky peroxide than nucleophilic selenium in the core. Addition of elemental sulfur (6 equiv., 12 h at rt) to the crude **5** furnished dendrimer **9** in 92% overall yield.[12] Cleavage of terminal acetates in **7**, **8** and **9** using K$_2$CO$_3$ in methanol afforded polyalcohols **10**, **11** and **12** in quantitative yield. It is noteworthy that dendrimers **7** and **8** were obtained in virtually the same good yield regardless of the phosphitylation activator (tetrazole or COLT) used.

Compounds **10**, **11** and **12** were transformed into larger dendrimers[13] of generation 2 and 3, via reiteration of the synthetic strategy shown in Scheme 1. For instance, phosphitylation of the hexol **12** containing both P=Se and P=S groups, with amide **4** (9 equiv.) and COLT (13 equiv.), followed by *t*-BuOOSiMe$_3$ (9.8 equiv.) oxidation, cleanly afforded the second generation dendrimer **13** (Fig. 1A) in 86% isolated yield and high purity (Fig. 1B). The dendrimer growth reactions can be easily monitored by $^{31}P\{^1H\}$ NMR analyses. The presence of oxyphosphoryl, thiophosphoryl and selenophosphoryl functions in one molecule gave very clear spectra compared with fully phosphorylated or thiophosphorylated dendrimer.[4,5] This is due to the occurrence of signals corresponding to P=O, P=S and P=Se in three very distinct areas (Fig. 1C).

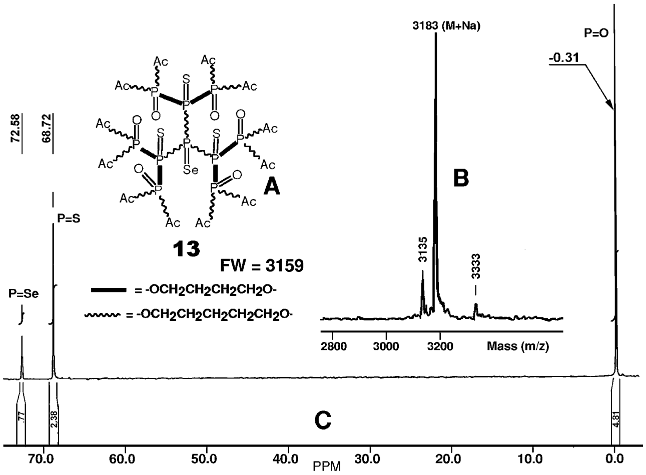

Figure 1. Structure of the second generation dendrimer **13** (A), as well as its MALDI TOF MS and $^{31}P\{^1H\}$ NMR spectra (B) and (C), respectively.

In conclusion, unprecedented oxidation of phosphites to phosphates with preservation of sensitive P=Se and/or P=S functions was accomplished. This key reaction was applied to the synthesis of dendrimers having three different branching units in their framework. Additionally, we have shown that phosphoroamidites **3** and **4** can be advantageously activated by 2,4,6-collidine trifluoroacetate.

Acknowledgements

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12. The dendrimers **7**, **8** and **9** were purified on a short pad of silica gel. Compound **7**: oil, 90%, ($CHCl_3$–acetone 10:1), $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = -0.37$ (3P), 72.69 ($^1J_{PSe} = 942$ Hz, 1P); MALDI TOF MS: calcd for $C_{51}H_{96}O_{27}P_4Se$: M+Na=1367.14. Found: *m/z* 1367. Compound **8**: oil, 90%, ($CHCl_3$–acetone 10:1), $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = -0.53$ (3P), 68.50 (1P); MALDI TOF MS: calcd for $C_{57}H_{108}O_{27}P_4S$: M+Na=1404.41. Found: *m/z* 1405. Compound **9**: 92%, (CCl_4–acetone 10:1), $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 68.61$ (3P), 72.59 ($^1J_{PSe} = 942$ Hz, 1P); MALDI TOF MS: calcd for $C_{51}H_{96}O_{24}P_4S_3Se$: M+Na=1415.34. Found: *m/z* 1416.
13. Analytical data for the third generation dendrimer $(S)P(OCH_2CH_2CH_2CH_2CH_2OP(O)(OCH_2CH_2CH_2CH_2CH_2OP(Se)(OCH_2CH_2CH_2CH_2CH_2OP(S)(OCH_2CH_2CH_2CH_2OAc)_2)_2)_2)_3$: NMR ($CDCl_3$) δ_H 1.40–1.52 [m, γ-$CH_2{}^{0,1,2}$ (superscripts refer to the sphere number), 42H], 1.64–1.75 (m, β-$CH_2{}^{0,1,2,3}$, 180H), 2.04 (s, Ac, 72H), 3.98–4.11 (m, α-$CH_2{}^{0,1,2,3}$, 180H) ppm; δ_C 20.8 (Ac), 21.4 (m, γ-$CH_2{}^{0,1,2}$), 24.7 (β'-$CH_2{}^3$), 26.5 (d, $^3J_{CP} = 7.7$ Hz, β-$CH_2{}^3$), 29.2–29.8 (m, β-$CH_2{}^{0,1,2}$), 63.6 (α'-$CH_2{}^3$), 67.5 (d, $^2J_{CP} = 5.3$ Hz, α-$CH_2{}^3$), 67.7–68.3 (m, α-$CH_2{}^{0,1,2}$), 170.9 (C=O) ppm; δ_P −0.26 (3P, 1st sphere), 68.67 (13P, core and 3rd sphere), 72.65 (6P, $^1J_{PSe} = 942$ Hz, 2nd sphere) ppm; FT-IR (neat): $\nu = 2957$ (C–H), 1739 (C=O), 1469 (C–H), 1366 (C–H), 1245 (C–H), 1014 (P=O), 993 (C–O), 835 (P–O–C) cm^{-1}; MALDI TOF MS: calcd for $C_{249}H_{474}O_{117}P_{22}S_{13}Se_6$: M+Na=6935.41. Found: *m/z* 6935.