

PHOSPHORUS CONTAINING DENDRIMERS:
SURFACE CHEMISTRY AND APPLICATIONS

Final Technical Report

by

J.P. Majoral, A.M. Caminade, and D. Prévôté
(August 1997)

United States Army

EUROPEAN RESEARCH OFFICE OF THE U.S. ARMY

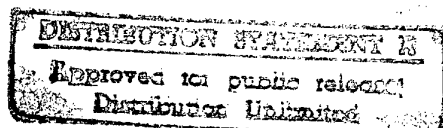
London England

CONTRACT NUMBER N68171-96-C-9026

Jean-Pierre Majoral

Approved for Public Release; distribution unlimited

DTIC QUALITY INSPECTED 4



19970911 087

FERROUS SCRAP IS NOT A CRITICAL MATERIAL -- IMPORTANT, YES; ESSENTIAL YES; SIGNIFICANT, YES; BUT NOT CRITICAL. I SAY THAT NOT TO MINIMIZE THE IMPORTANCE OF SCRAP AS A MAJOR RAW MATERIAL IN IRON AND STEELMAKING. RATHER, SCRAP IS IN SUCH ABUNDANCE THROUGHOUT OUR NATION, AND IS SO READILY AVAILABLE IN SUCH QUANTITIES THAT NOTHING SO UBIQUITOUS CAN BE CRITICAL BY DEFINITION. THE CRITICAL FACT OF SCRAP IRON IS ITS NEED FOR A MARKET.

SCRAP IS AVAILABLE TO BE MADE INTO NEW STEEL, BUT THERE ARE FEW USES FOR SCRAP OTHER THAN TO BE RECYCLED INTO THAT NEW IRON AND STEEL. THUS, SCRAP IS NOT A CRITICAL MATERIAL BUT A MARKET IS CRITICAL FOR THAT MATERIAL.

THE OPPORTUNITIES TO EXPAND THE RECOVERY OF IRON AND STEEL DISCARDS ARE TREMENDOUS AS ARE THE BENEFITS OF SUCH EXPANSION, AND BOTH WILL BE REALIZED WHEN IRON AND STEEL-MAKERS INCREASE THEIR DEMAND FOR SCRAP TO CHARGE THEIR MELTING FURNACES.

THE RESERVOIR OF IRON AND STEEL DISCARDS IN THE UNITED STATE IS ENORMOUS -- HUNDREDS OF MILLIONS OF TONS OF MATERIAL THAT WILL BECOME EITHER AN ASSET OR A LIABILITY TO OUR ECONOMY -- THAT REPRESENT AN INCREDIBLE CONSERVATION POTENTIAL OR A CONSERVATION DISASTER -- DEPENDING ON THE CHOICE MADE FOR METALLICS IN FUTURE STEELMAKING.

IF WE ARE NOT ABLE TO RECOVER THESE METALLIC UNITS FOR RECYCLING INTO NEW PRODUCTS, BY DEFAULT THEY BECOME BOTH AN ECONOMIC AND SOCIAL LIABILITY TO THE JURISDICTIONS IN WHICH THEY ARE LOCATED. WHEN VACANT CITY LOTS AND COUNTRY ROADSIDES BECOME THE DUMPING GROUNDS FOR DERELICT AUTOMOBILES, UNWANTED REFRIGERATORS AND THE LIKE, CITIZENS GENERALLY DEMAND ACTION BY THEIR LOCAL GOVERNMENT TO "GET RID OF THE JUNK." THE RESULT IS AN EXPENDITURE OF TAX DOLLARS TO DISPOSE OF WHAT COULD BE, BUT BY CHOICE IS NOT, AN INDUSTRIAL RAW MATERIAL.

THE ROLE FOR OBSOLETE SCRAP BEGINS WITH THE COLLECTOR, WHO TRANSPORTS IT TO THE SCRAP PLANT FOR PROCESSING AND THEN SHIPMENT AS A PREPARED PRODUCT TO STEEL MILLS AND FOUNDRIES. IN THIS SCENERIO, SCRAP IS TRANSFORMED INTO AN ECONOMIC AND ENVIRONMENTAL ASSET. CERTAINLY IT MAKES MORE SENSE IF SCRAP CAN BE HANDLED THROUGH THE PRIVATE SECTOR GENERATING JOBS, MAKING EXPENDITURES FOR GOODS AND SERVICES, EARNING PROFITS, AND PAYING TAX REVENUES, RATHER THAN BEING A DRAIN ON OUR TAX DOLLARS WHEN IT IS MERELY DISPOSED OF, NOT RECYCLED. HOW COULD ANYONE DISAGREE.

BUT IN REGARD TO THE TOPIC FOR THIS MORNING, IN ADDITION TO CONSERVING ONE AND ONE HALF MILLION TONS OF IRON ORE, EPA FOUND THAT WHEN ONE MILLION TONS OF SCRAP IRON ARE USED TO MAKE NEW STEEL, AIR POLLUTION EFFLUENTS ARE REDUCED 86 PERCENT -- 208 MILLION POUNDS; WATER POLLUTION IS REDUCED 76 PERCENT

Summary

The synthesis of phosphorus containing dendrimers is described up to the fifth generation (96 terminal groups). The surface chemistry of these dendrimers allows the grafting of various functionalities such as phosphate (6 O-P(O)(OEt)₂ groups), aminophosphate (up to 96 N-P(O)(OEt)₂ groups), aminophosphite (up to 96 N-P(OEt)₂ groups), functionalized phosphonate (up to 96 HC(OH)P(O)(OR)₂ (R = Et, (CH₂)₁₁CH₃), up to 96 HC(N-Pr)P(O)(OEt)₂, or up to 48 CH=CH-P(O)(OEt)₂, phosphorus ylide (6 C(O)CH=P(Ph)₃), carboxylic acid (up to 24 CH=CH-C(O)OH), and tetraazamacrocyclic (up to 12 cyclam). These surface functionalities have been chosen due to the wellknown properties of the corresponding monomers and/or polymers in various areas such as adhesives, flame retardants, fuel additives, sequestering agents...

Key words

dendrimers, surface functionalities, phosphate, aminophosphate, aminophosphite, functionalized phosphonate, phosphorus ylide, carboxylic acid, tetraazamacrocyclic

Table of Contents

A- Introduction	1
B- Results	2
I - Synthesis of dendrimers	2
II - Anchorage of phosphorus groups	3
II - 1 - Anchorage of aminophosphate groups	3
II - 2 - Anchorage of aminophosphite groups	3
II - 3 - Anchorage of phosphate groups	5
II - 4 - Anchorage of phosphorus ylide groups	5
II - 5 - Anchorage of phosphonate groups	6
II - 5 - a - Addition to terminal aldehyde groups	6
II - 5 - b - Addition to terminal imino groups	7
II - 5 - c - Horner-Wadsworth-Emmons reaction on terminal aldehyde groups	8
III - Acid terminated dendrimers	8
IV - Grafting of tetraazamacrocycles	9
C - Conclusion	12
D - Literature Cited	13

List of Appendixes:

List of Participating Scientific Personnel

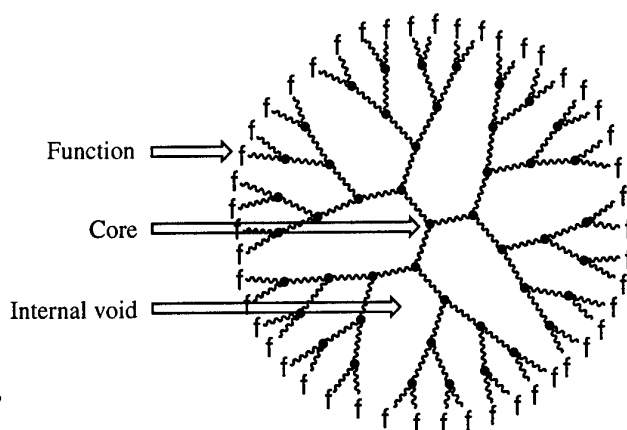
Publications issued from this report:

I - Phosphate, phosphite, ylide and phosphonate terminated dendrimers
Prévôté, D.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* (in press).

II - Application of the Horner-Wadsworth-Emmons reaction to the functionalization of dendrimers: Synthesis of amino acid terminated dendrimers
Prévôté, D.; Le Roy-Gourvenec, S.; Caminade, A.M.; Masson, S.; Majoral, J.P. *Synthesis* (accepted).

A - Introduction

Dendrimers^[1] constitute a new class of macromolecules whose size, shape, and molecular weight are rigorously controlled. Furthermore, their highly branched structure which induce the formation of internal voids and the occurrence of all the reactive functions on the surface make dendrimers unique among polymers.



Fourth Generation of a Dendrimer

The synthesis of organic dendrimers and silicon containing dendrimers are well explored areas, which now come out to the study of properties and applications of these compounds. Concerning phosphorus containing dendrimers, the expertise of our research group is unrivalled in the world (60% of all the papers ever published to date in this field come from our group)^[2]. The methods of synthesis of phosphorus containing dendrimers we have developed present several significant advantages: cheap industrially available starting materials, quantitative yields, possibility to check easily the construction of the dendrimer by ^{31}P NMR, solubility in several common organic solvents, and stability towards hydrolysis and bases.

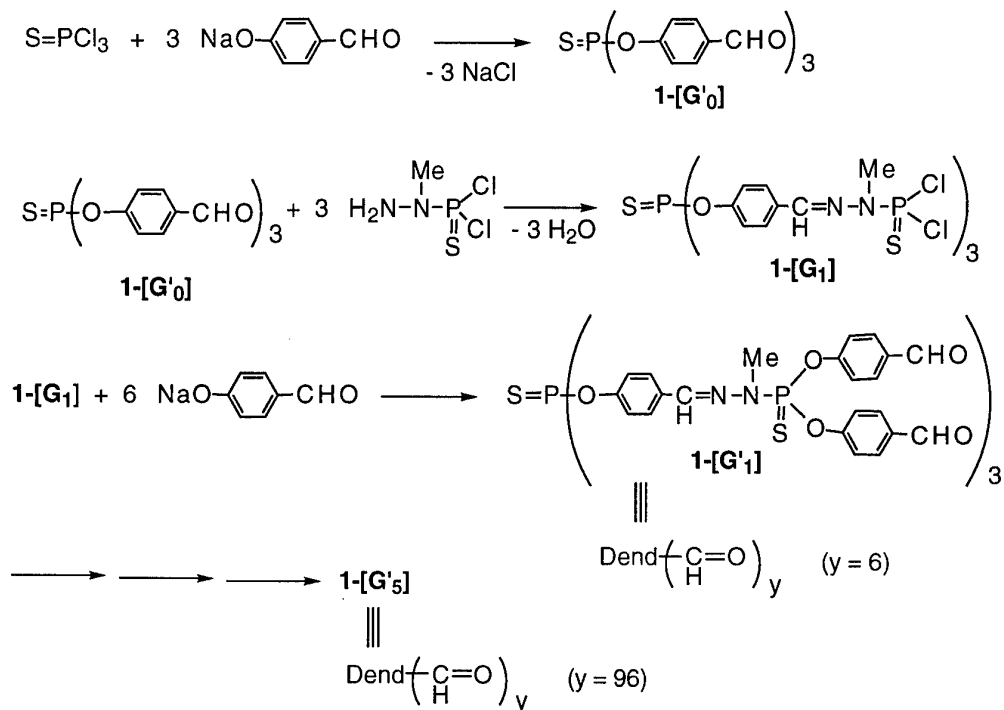
The objectives of the present study was to take advantage of the large number of reactive functions located on the surface of dendrimers to graft various new functional groups susceptible to bring properties in several fields, mainly adhesives, flame retardant, additives, or sequestering agents. For this purpose, we have tried to graft several types of phosphorus containing groups such as phosphates, aminophosphates, aminophosphites, phosphorus ylides, with emphasis on functionalized phosphonates, whose properties of the monomers and/or corresponding polymers are well known in most of the fields evoked above, and in many other fields. The grafting of carboxylic acids and tetraazamacrocycles should also induce properties in the field of adhesives and sequestering agents.

The present report describes only fruitful experiments. All unsuccessful attempts which have been included in the four interim reports are not included in this final report. All the dendrimers described have been isolated and fully characterized by NMR (^{31}P , ^1H , and ^{13}C), IR, elemental analyses, in some cases by mass spectrometry, and by X-ray diffraction for a small molecule.

B - Results

I - Synthesis of dendrimers

Dendrimers from generation 0 to generation 5 were prepared by the repetition of a two steps procedure: nucleophilic substitution of chlorine by hydroxybenzaldehyde, and Schiff condensation reaction (Scheme 1, Table 1, Figure 1).



Scheme 1

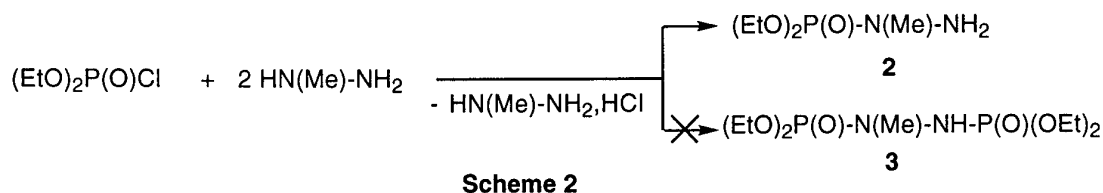
Generation n =	1	2	3	4	5
(Cl)	1-[G₁]	1-[G₂]	1-[G₃]	1-[G₄]	1-[G₅]
Number (CHO)	1-[G'₁]	1-[G'₂]	1-[G'₃]	1-[G'₄]	1-[G'₅]
Number of Cl or CHO	6	12	24	48	96
Molecular weight (terminal Cl)	909	2389	5349	11269	23108
Molecular weight (terminal CHO)	1423	3417	7405	15381	31331

Table 1: Some characteristic data concerning dendrimers **1-[G₁]** – **1-[G₅]** (terminal P-Cl bonds) and **1-[G'₁]** – **1-[G'₅]** (terminal CHO groups).

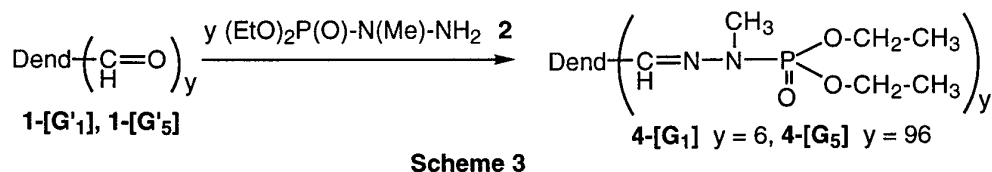
II - Anchorage of phosphorus groups

II - 1 - Anchorage of aminophosphate groups

The strategy investigated for the grafting of aminophosphate groups consists of the reaction of dendrimers **1-[G'₁]** and **1-[G'₅]** (generations 1 and 5, respectively) with a new phospho monohydrazide **2** (Scheme 3). Compound **2** is prepared by reacting the chlorophosphonate (EtO)₂P(O)Cl with methylhydrazine (Scheme 2).



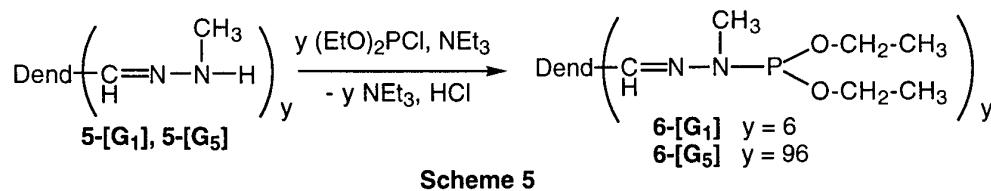
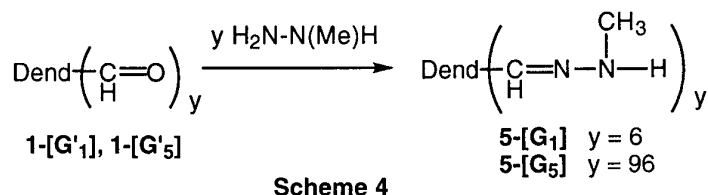
The reaction of formation of **2** is performed at low temperature (-80°C) to avoid the formation of a by-product such as **3** which can be formed via condensation of **2** with (EtO)₂P(O)Cl.



The new dendrimers **4-[G₁]** and **4-[G₅]** possessing 6 or 96 terminal aminophosphate groups respectively are obtained as white powders (Figure 1).

II - 2 - Anchorage of aminophosphite groups

Grafting of aminophosphite groups was successfully performed by reacting dendrimers **5-[G₁]** and **5-[G₅]** possessing 6 and 96 terminal N(CH₃)H groups respectively with the chlorophosphite (EtO)₂PCl (Scheme 5, Figure 1). Arborols **5-[G₁]** and **5-[G₅]** were easily prepared by reacting **1-[G'₁]** and **1-[G'₅]** with methylhydrazine (Scheme 4).

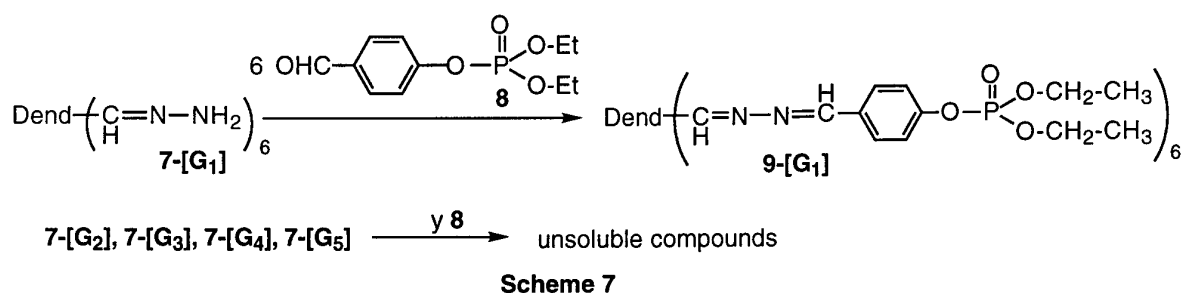
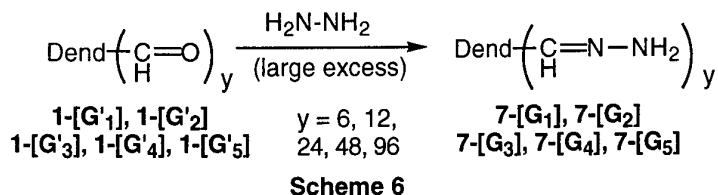


Dendrimers **6-[G₁]** and **6-[G₅]** are sensitive to hydrolysis and oxidation. Cleavage of the terminal nitrogen-phosphorus bond allows to recover **5-[G₁]** and **5-[G₅]** with the formation of (EtO)₂P(O)H.

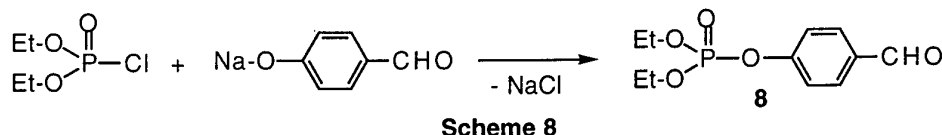
II - 3 - Anchorage of phosphate groups

The formation of a dendrimer possessing terminal phosphate groups involves

- i) the preparation of dendrimers having terminal NH₂ groups 7-[G₁] - 7-[G₅] (Scheme 6)
- ii) the synthesis of a new ligand (EtO)₂P(O)OC₆H₄CHO 8 (Scheme 8)
- iii) the reaction of 7-[G₁] - 7-[G₅] with 8 to give dendrimers 9-[G₁] - 9-[G₅] (Scheme 7).



Derivative 8 is prepared as follows:

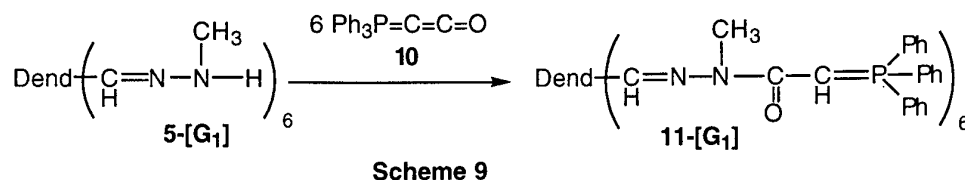


The dendrimer 9-[G₁] (72% yield) incorporates six terminal phosphate groups. Unfortunately the reaction of 1-[G'₅] with 96 equivalents of 8 affords insoluble material. Therefore, such a condensation reaction was attempted with 8 and dendrimers of generation 2 (7-[G₂]) 3 (7-[G₃]) or 4 (7-[G₄]). In all cases insoluble powders were obtained and characterizations were not possible.

It appears that the introduction in the framework of the molecule of CH=N-N=CH sequences dramatically reduces the solubility of the resulting products preventing from rigorous characterization.

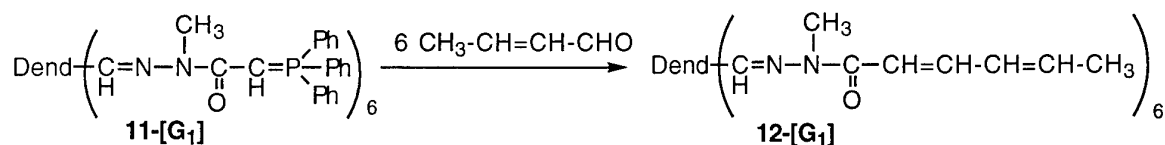
II - 4 - Anchorage of phosphorus ylide groups

Addition of terminal NH groups of the dendrimer 5-[G₁] on the carbon carbon double bond of the cumulene Ph₃P=C=C=O 10 was undertaken (Scheme 9).



Temptative extension of this type of reaction to higher generations (5-[G₂], 5-[G₃]) led only to insoluble materials.

Terminal ylide groups of **11-[G₁]** remain very reactive. For example, a Wittig reaction can be performed by reacting **11-[G₁]** with crotonaldehyde CH₃CH=CH-CHO affording dendrimer **12-[G₁]** (Scheme 10).

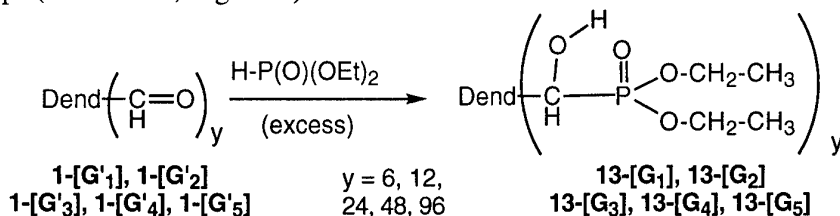


Scheme 10

II - 5 - Anchorage of phosphonate groups

II - 5 - a - Addition to terminal aldehyde groups

Several tries were performed to graft in good yields phosphonate groups on the terminal aldehyde groups (Scheme 11, Figure 1).



Scheme 11

This type of reaction was done in several conditions. After several attempts, the best method was the following one: the dendrimer was dissolved in a mixture of [(EtO)₂P(O)H, NEt₃], at room temperature, the phosphonate acting as reagent and solvent. This experiment gave the best results and allowed us to graft from 6 to 96 phosphonates groups (see Table 2).

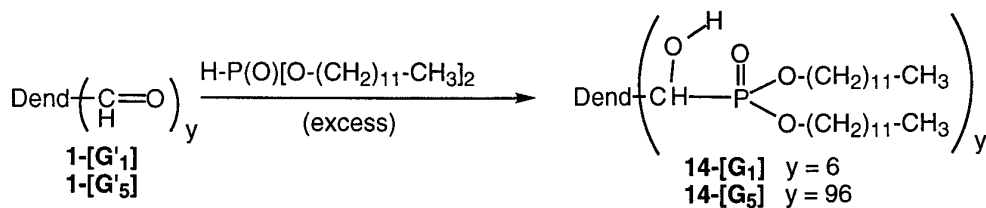
Generation n =	1	2	3	4	5
Compound	13-[G₁]	13-[G₂]	13-[G₃]	13-[G₄]	13-[G₅]
Number of terminal phosphonate groups -CH(OH)-P(O)(OEt) ₂	6	12	24	48	96
Molecular weight	2252	5074	10719	22010	44589

Table 2: Characteristic data concerning dendrimers with -CH(OH)-P(O)(OEt)₂ terminal groups.

It should be mentioned the interest of this reaction which leads to phosphonate end groups but also to secondary alcohols end groups which should be of help for adhesive properties.

The same type of addition reaction was performed with another phosphonate $(C_{12}H_{25}O)_2P(O)H$ to avoid problems of solubility encountered with $(EtO)_2P(O)H$: compound with 96 $CH(OH)-P(O)(OEt)_2$ groups start to be poorly soluble in common organic solvents and NMR data were collected in CD_3OD .

The grafting of $(C_{12}H_{25}O)_2P(O)$ groups was undertaken on dendrimers **1-[G'₁]** and **1-[G'₅]** (Table 3) in the same experimental conditions than that used with $(C_2H_5O)_2P(O)H$ and afforded compounds now easily soluble in CH_2Cl_2 or $CHCl_3$ (Scheme 12, Figure 1).



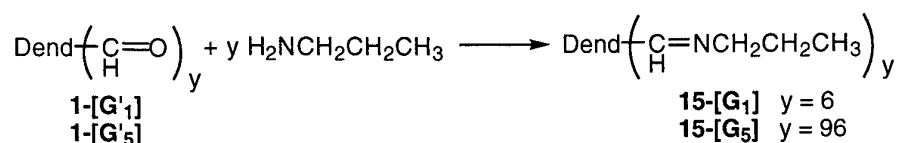
Scheme 12

Generation n =	1	5
Compound number	14-[G₁]	14-[G₅]
Number of terminal phosphonate groups $CH(OH)-P(O)(OC_{12}H_{25})_2$	6	96
Molecular weight	3935	7152

Table 3: Dendrimers with terminal $CH(OH)-P(O)(OC_{12}H_{25})_2$ groups

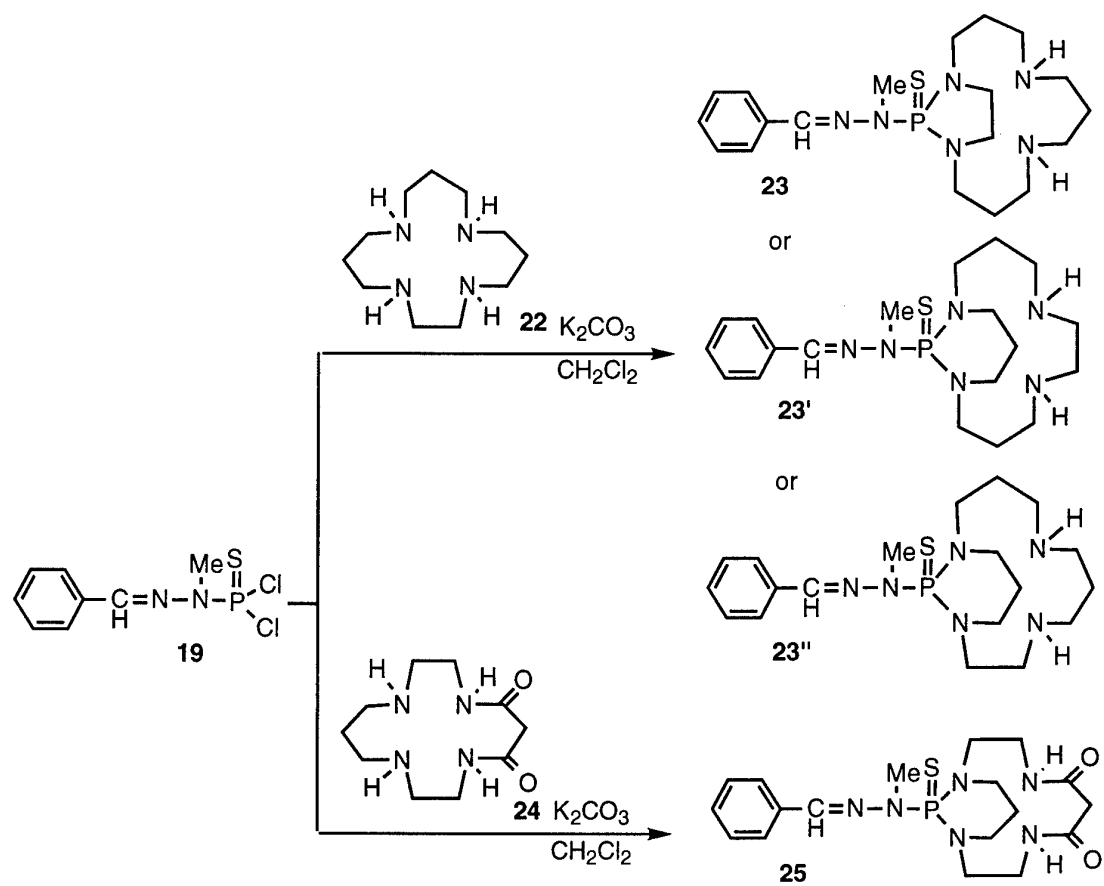
II - 5 - b - Addition to terminal imino groups

New dendrimers with terminal imino groups were prepared as follows (Scheme 13):



Scheme 13

Dendrimers **15-[G₁]** and **15-[G₅]** possessing 6 or 96 terminal imino groups respectively were further reacted with $(EtO)_2P(O)H$ again used as solvent. This reaction allowed to obtain new dendrimers **16-[G₁]** and **16-[G₅]** arising from oxidative addition of the P-H bond on imine functions (Scheme 14, Table 4, Figure 1).



Scheme 18

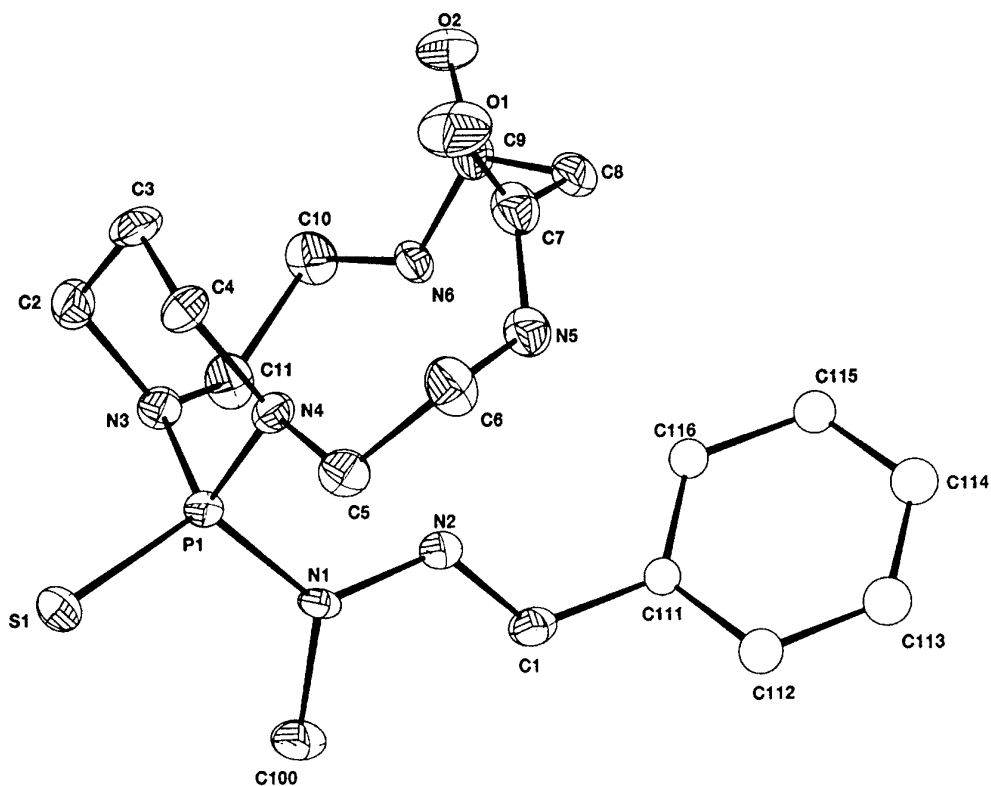
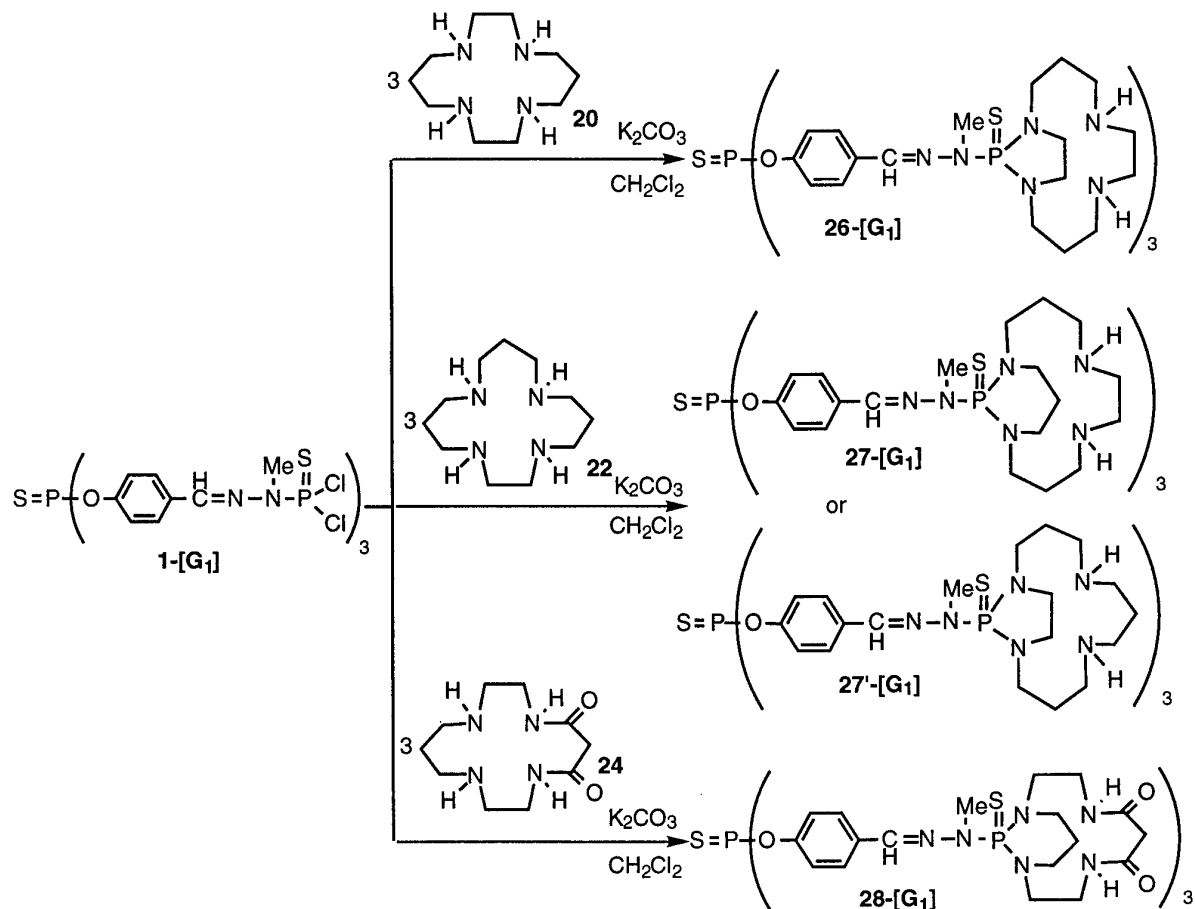


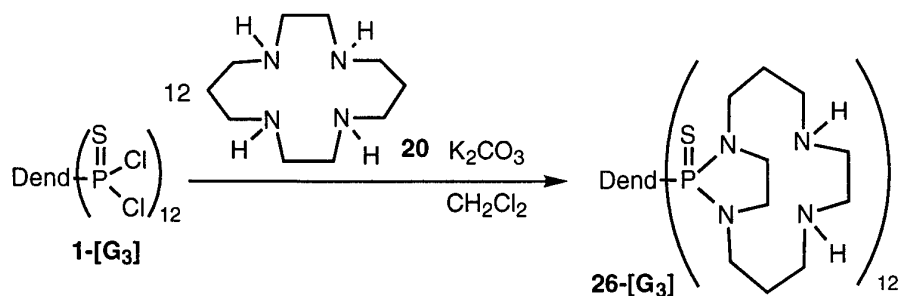
Figure 2: Structure of macrocycle 25 determined by X-ray diffraction studies

Such experiments were extrapolated to the reaction of the dendrimer of generation 1, **1-[G₁]** with macrocycles **20**, **22** and **24** (Scheme 19). The expected tris macrocyclic species **26-[G₁]**, **28-[G₁]** (or **28'-[G₁]**), and **29-[G₁]** were obtained in 64-70% yield. Here also NMR data did not allowed us to choose between the two possible forms **28-[G₁]** or **28'-[G₁]**.



Scheme 19

We have already demonstrated that the reactivity of functional groups grafted on the surface of dendrimers of high generations is similar to those of the same functional groups anchored at the periphery of the dendrimer of generation 1. Therefore, the anchorage of 12 units of macrocycle **20** on the surface of the dendrimer of generation 3, **1-[G₃]** (12 terminal P(S)Cl_2 groups) was attempted, and allowed to isolate dendrimer **26-[G₃]**. Remarkably, no cross linking reactions are detected (Scheme 20).



Scheme 20

C - Conclusion

We have succeeded in grafting various functional groups on the surface of phosphorus containing dendrimers, up to the fifth generation in most cases (up to 96 terminal functional groups). The nature of the terminal groups strongly influence the solubility of dendrimers. Thus, the first generation with 6 $\text{CH}(\text{OH})\text{P}(\text{O})[\text{O}(\text{CH}_2)_{11}\text{CH}_3]_2$ end groups is soluble in pentane (the fifth is not), whereas dendrimers with $\text{CH}(\text{OH})\text{P}(\text{O})(\text{OEt})_2$ end groups are soluble in methanol, and dendrimers with $\text{CH}=\text{CH}-\text{C}(\text{O})\text{OLi}$ end groups (not isolated) are soluble in water. Other common solvents usable, depending on the nature of the end groups, are toluene, benzene, ether, dichloromethane, chloroform, tetrahydrofuran, dioxane, or acetonitrile.

All the dendrimers isolated possess terminal end groups which confer to these macromolecules the expected properties mainly in the field of adhesives, flame retardants, additives, or sequestering agents. Furthermore, it is clear that the procedures experimented for this work should be extended to other types of functional groups to be grafted on the surface, but also in the internal cavities of some of the internally functionalized dendrimers we now develop in the group.

It should be also emphasized that, as we have received the authorization to publish from the US Army Office, most of this work will appear in two papers: the work concerning all phosphorus end groups (excluding vinylphosphonates) is in press in the *Journal of Organic Chemistry*^[3a], and the work concerning the Wadsworth-Horner-Emmons reaction, which has been extended to other functional groups, is accepted as a feature article in *Synthesis*^[3b].

D - Literature Cited

- [1] – for reviews on dendrimers, see for example:
- (a) Tomalia, D. A.; Naylor, A. M.; Goddard III, W. A. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.
 - (b) Tomalia, D. A.; Durst, H.D. in *Topics in Current Chemistry*, vol. 165; *Supramolecular Chemistry I: Directed Synthesis and Molecular Recognition*; Weber, E., Ed.; Springer Verlag: Berlin, Heidelberg, **1993**, 193-313.
 - (c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2413.
 - (d) Moorefield, C. N.; Newkome, G. R. in *Advances in Dendritic Molecules*, Newkome, G. R., Ed.; JAI Press, Greenwich CT, USA **1994**, vol. 1, p 1.
 - (e) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 876.
 - (f) Fréchet, J.M.J.; Hawker, C.J. in: *Comprehensive Polymer Science*, 2nd suppl. **1996**, chapter 3, 71.
 - (g) Newkome, G.R.; Moorefield, C.N.; Vögtle, F. in: *Dendritic molecules*, VCH Weinheim **1996**.
- [2] -
- (a) Launay, N.; Caminade, A.M.; Lahana, R.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1589.
 - (b) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 3282.
 - (c) Galliot, C.; Prévoté, D.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 5470.
 - (d) Slany, M.; Bardají, M.; Casanove, M.J.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764.
 - (e) Caminade, A.M.; Majoral, J.P. *Main Group Chemistry News* **1995**, *3*, 14.
 - (f) Launay, N.; Galliot, C.; Caminade, A.M.; Majoral, J.P. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1149.
 - (g) Kraemer, R.; Galliot, C.; Mitjaville, J.; Caminade, A.M.; Majoral, J.P. *Heteroatom. Chem.* **1996**, *7*, 149.
 - (h) Caminade, A.M.; Slany, M.; Launay, N.; Lartigue, M.L.; Majoral, J.P. *Phosphorus, Sulfur and Silicon* **1996**, *109-110*, 517.
 - (i) Launay, N.; Slany, M.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* **1996**, *61*, 3799.
 - (j) Majoral, J.P.; Caminade, A.M. *Actu. Chim.* **1996**, *13*.
 - (k) Lartigue, M.L.; Slany, M.; Caminade, A.M.; Majoral, J.P. *Chemistry Eur. J.* **1996**, *2*, 1417.
 - (l) Slany, M.; Caminade, A.M.; Majoral, J.P. *Tetrahedron Lett.* **1996**, *37*, 9053.
 - (m) Bardají, M.; Kustos, M.; Caminade, A.M.; Majoral, J.P.; Chaudret B. *Organometallics* **1997**, *16*, 403.
 - (n) Larré, C.; Caminade, A.M.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 596.
 - (o) Slany, M.; Bardaji, M.; Caminade, A.M.; Chaudret, B.; Majoral, J.P. *Inorg. Chem.* **1997**, *36*, 1939.
 - (p) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Organomet. Chem.* **1997**, *529*, 51.

[3] - Publications issued from this report

(a) Phosphate, phosphite, ylide and phosphonate terminated dendrimers

Prévôté, D.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* (in press).

(b) Application of the Horner-Wadsworth-Emmons reaction to the functionalization of dendrimers: Synthesis of amino acid terminated dendrimers

Prévôté, D.; Le Roy-Gourvenec, S.; Caminade, A.M.; Masson, S.; Majoral, J.P. *Synthesis* (accepted).

Appendixes

List of Participating Scientific Personnel

- Dr. Jean-Pierre Majoral (20 %)
- Dr. Anne-Marie Caminade (20 %)
- Miss Delphine Prévoté (80 %)

Phosphate-, Phosphite-, Ylide-, and Phosphonate-Terminated Dendrimers

Delphine Prévôté, Anne-Marie Caminade,* and Jean Pierre Majoral*

Laboratoire de Chimie de Coordination du CNRS, 205, route de Narbonne, 31077 Toulouse Cedex 4, France

Received January 30, 1997^o

Many types of tri- and tetracoordinated phosphorus derivatives have been grafted on the surface of dendrimers, starting from aldehyde terminal functions. Depending on the solubility of the resulting phosphorylated dendrimers, these experiments have been carried out on generation 1 (six end groups) for phosphate- (4-[G₁]), phosphinite- (6-[G₁]), and ylide-terminated (11-[G₁]) dendrimers and up to generation 5 (96 end groups) for aminophosphate- (8-[G₁], 8-[G₅]), aminophosphite (10-[G₁], 10-[G₅]), and functionalized phosphonate-terminated (14-[G₁]-14-[G₅], 15-[G₁], 15-[G₅], 17-[G₁], 19-[G₁], 19-[G₅]) dendrimers. Most of the phosphonate-terminated dendrimers present an unexpected long-range phosphorus-phosphorus coupling constant through seven bonds (3.8 < ⁷J_{PP} < 4.5 Hz).

Introduction

Tetracoordinated organophosphorus derivatives such as phosphates and phosphonates offer a wide range of applications as pesticides, insecticides, herbicides, catalysts, lubricants, adhesives, flame retardants, etc. For many uses, these compounds are grafted on polymers or are polymerized themselves. Owing to their potential applications, we decided to graft several types of tetracoordinated organophosphorus derivatives on a new class of monodisperse and highly branched polymers, namely dendrimers.¹ Our efforts were first directed toward the grafting of phosphates and then mainly toward the grafting of phosphonates, since both types of compounds generally have similar properties, but differ in that phosphonates have a different solubility and a greater stability toward hydrolysis. We have also grafted on dendrimers several other types of organophosphorus derivatives such as aminophosphates, phosphinites, aminophosphites, and even ylides.

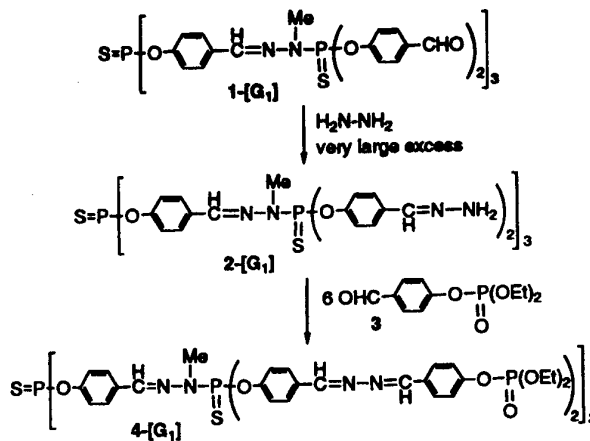
Results and Discussion

The family of dendrimers we used is built from P(S)-Cl₃ as core by the repetition of two reactions, which creates OC₆H₄CH=NN(Me)P(S) linkages.² These compounds possess 6, 12, 24, 48, or 96 terminal functions for generations 1, 2, 3, 4, or 5, respectively. These functions are either Cl or benzaldehyde groups, the latter being the starting groups for the synthesis of all the organophosphorus-terminated dendrimers described in this paper (Figure 1).

* To whom correspondence should be addressed. Fax: (33) 5 61 55 30 03. E-mail: majoral@lcc-toulouse.fr or caminade@lcc-toulouse.fr.
^o Abstract published in *Advance ACS Abstracts*, XXXXXXXX YY, ZZZZ.

(1) For reviews on dendrimers, see, for example: (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. (b) Tomalia, D. A.; Durst, H. D. In *Topics in Current Chemistry*; Weber, E., Ed.; Springer Verlag: Berlin, Heidelberg, 1993; Vol. 165, p 193. (c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem.* **1994**, *106*, 2507; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2413. (d) Moorefield, C. N.; Newkome, G. R. In *Advances in Dendritic Molecules*; Newkome, G. R., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 1, p 1. (e) Caminade, A.-M.; Majoral, J.-P. *Main Group Chem. News* **1995**, *14*. (f) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 876. (g) Majoral, J.-P.; Caminade, A.-M. *Acta Chim.* **1996**, *4*, 13. (h) Fréchet, J. M. J.; Hawker, C. J. In *Comprehensive Polymer Science*: 1996; 2nd Suppl., Chapter 3, p 71.

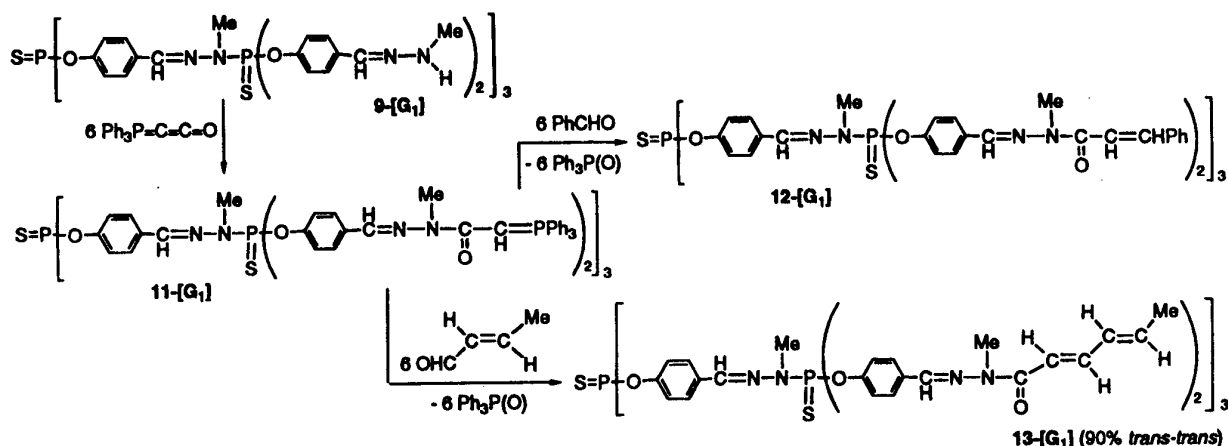
Scheme 1



In first attempts, we tried to graft phosphate groups in two steps from the dendrimer 1-[G₁]. The first step is a condensation with hydrazine, used in very large excess, to afford compound 2-[G₁].^{2d,f} The second step is another condensation, with the phosphate 3, easily obtained by reaction of hydroxybenzaldehyde sodium salt with (EtO)₂P(O)Cl (Scheme 1). The synthesis of dendrimer 4-[G₁] is monitored by ³¹P NMR, which shows a slight deshielding of the signal corresponding to the (EtO)₂P(O)R moieties on going from 3 (δ³¹P = -7 ppm) to 4-[G₁] (δ³¹P = -6.7 ppm). Additional proofs of the condensation reaction are given by ¹H NMR, with the total disappearance of signals corresponding to CHO and NH₂ groups. Furthermore, ¹³C NMR indicates the presence of two very close singlets (δ¹³C = 160.5 and 160.8 ppm) corresponding to the azine -CH=NN=CH- linkages of the dendrimer 4-[G₁].

(2) (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1589. (b) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3282. (c) Slany, M.; Bardaji, M.; Casanove, M. J.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764. (d) Launay, N.; Slany, M.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **1996**, *61*, 3799. (e) Lartigue, M. L.; Slany, M.; Caminade, A. M.; Majoral, J. P. *Chem. Eur. J.* **1996**, *2*, 1417. (f) Bardaji, M.; Kustos, M.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *Organometallics* **1997**, *16*, 403. (g) Slany, M.; Caminade, A. M.; Majoral, J. P. *Tetrahedron Lett.* **1996**, *37*, 9053.

Scheme 5



deed, the higher reactivity of tricoordinated phosphorus precludes the specificity of the reaction on the NHMe group of methylhydrazine, which is observed with tetra-coordinated phosphorus. However, another strategy can be applied, for instance, to graft hydrazinophosphites, in two steps. The first step is the condensation of 1-[G_n] with methylhydrazine, which affords dendrimers 9-[G_n].^{2b-d} The second step consists of grafting (EtO)₂-P-Cl in the presence of NEt₃, which yields the hydrazonophosphite-terminated dendrimers 10-[G_n] (Scheme 4, Figure 1). These reactions have been applied to generation 1 (10-[G₁]: 6 N-P(OEt)₂ end groups) and generation 5 (10-[G₅]: 96 N-P(OEt)₂ end groups) in the same conditions. Both compounds are particularly characterized by the appearance of a new singlet in ³¹P NMR (δ³¹P = 139 ppm, NP(OEt)₂) and by the shielding of the terminal NMe groups in ¹³C NMR on going from 9-[G_n] (δ¹³C = 34.0 ppm, -NMeH) to 10-[G_n] (δ¹³C = 28.4 ppm, -NMeP^{III}).

All the experiments described above allow to bind phosphorus groups to the dendrimer by means of O or N linkages; we have thus isolated dendrimers with phosphate (OP(O)(OR)₂), phosphinite (OPR₂), aminophosphate (NP(O)(OR)₂), or aminophosphite (NP(OR)₂) end groups. In previous papers, we already described the use of carbon-phosphorus bonds to graft phosphines (CH₂-PR₂).^{2c,f,g} It appeared interesting to extend this work to the grafting of other types of phosphorus derivatives with C-P bonds, particularly ylides and phosphonates because of their numerous applications in different fields.

Dendrimers 9-[G_n] may be used as the starting material for the grafting of ylides. Indeed, it is known that triphenylphosphoranylidene ethenone Ph₃P=C=C=O undergoes the addition of compounds with acidic hydrogens, such as alcohols, thiols, or amines, to the C=C bond.³ Application of this type of addition to dendrimer 9-[G₁] affords the ylide-terminated dendrimer 11-[G₁] (Scheme 5). This compound is characterized in particular by the presence of the signal of the ylide moieties in ³¹P NMR (δ³¹P = 18.3 ppm), whereas ¹³C NMR displays the presence of amido groups (δ¹³C = 170.3 ppm, d, ²J_{CP} = 26.8 Hz) and a slight deshielding of the signal corresponding to the NMe end groups (δ¹³C = 26.8 ppm). In view of the widespread use of ylides in organic chemistry, it would have been interesting to synthesize higher generations of dendrimers with ylide end groups; thus,

we tried to obtain the same type of compound from the second generation 9-[G₂]. Unfortunately, the corresponding ylide-terminated dendrimer 11-[G₂] was found to be insoluble in water and in a variety of organic solvents.

However, we decided to test the reactivity of the first generation 11-[G₁] in the Wittig reaction, toward benzaldehyde and crotonaldehyde. Benzaldehyde reacts at room temperature to afford compound 12-[G₁] in quantitative yield as crude product (Scheme 5). The reaction is monitored by ³¹P NMR, which indicates the total disappearance of the ylide signal on behalf of the appearance of the signal corresponding to Ph₃P(O) (δ³¹P = 24 ppm). After removal of the triphenylphosphine oxide, ¹H NMR indicates a slight deshielding of the signal corresponding to the CH₃NCO groups, but the signals of the CH=CH linkages are overlapped by the aromatic signals and did not allow us to determine the geometry of the ethylenic linkage. However, ¹³C NMR indicates the formation of both cis and trans isomers; indeed, each carbon atom of the CH₃NC(O)CH=CH- linkages gives two close singlets, approximately in a 1:3 ratio, whereas for all the other parts of the dendrimer 12-[G₁], each carbon gives a single set of signals. According to the known tendency of stabilized ylides to give predominantly trans isomers in the Wittig reaction,⁴ we tentatively assign the largest signals to the trans isomer.

This assignment is corroborated by the study of the reaction of crotonaldehyde (trans isomer) with 12-[G₁] (Scheme 5). In this case also, ¹³C NMR displays the formation of two isomers, characterized by the presence of two signals for each carbon atom of the CH₃NC(O)-CH=CHCH=CHMe linkages in an approximate 1:9 ratio. The attribution of these signals to the cis-trans and trans-trans isomers, respectively, is unambiguous in this case owing to ¹H two-dimensional NMR experiments. Indeed, two doublets in a 1:9 ratio are observed for the H_d protons of the CH_d-CH_eCH_b-CH_cMe linkages: δ ¹H = 6.80 (d, ³J_{HdHc} = 10.0 Hz), and 7.12 (d, ³J_{HdHc} = 15.0 Hz) ppm. The value of the coupling constants allows us to attribute unambiguously the former signals to the minor cis-trans isomer and the latter to the major trans-trans isomer.

The last type of phosphorus derivatives we tried to graft on dendrimers is phosphonates. In all cases, the

(4) Johnson, A. W.; Kaska, W. C.; Starzewski, K. A. O.; Dixon, D. A. In *Ylides and imines of phosphorus*; Johnson, A. W., Ed.; John Wiley & Sons, Inc.: New York, 1993; Chapter 8.

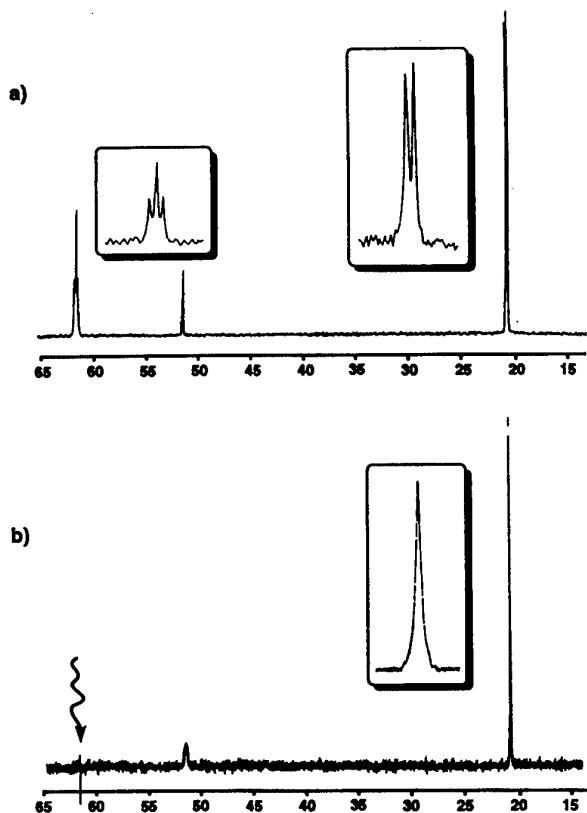


Figure 2. (a) $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of dendrimer 14-[G₁]. (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of dendrimer 14-[G₁] with selective irradiation of the signal at $\delta = 62$ ppm.

method of synthesis we used consists of the addition of P-H bonds on polar double bonds of the dendrimer. In our first attempts, we tried to graft phosphonate groups by addition of diethyl phosphite to the aldehyde functions of dendrimer 1-[G₁] in several conditions, using THF as solvent. It is well known that this type of reaction is catalyzed by bases,⁵ thus, we used either CsF, NEt₃, or DBU as catalysts, heating for several days at 65 °C. In all cases, we observed only a partial reaction, even after heating for 2 weeks (when CsF is used), or a degradation (when DBU is used). On the other hand, when a large excess of diethyl phosphite is used without solvent, and in the presence of CsF as catalyst under heating, the reaction with 1-[G₁] goes to completion. However, the resulting α -hydroxy methylphosphonate-terminated dendrimer 14-[G₁] is difficult to purify in these conditions, both from CsF and from the large excess of diethyl phosphite.

We also tried to use NEt₃ as catalyst (20–40%) without solvent, the dendrimer 1-[G₁] being dissolved in the mixture Et₃N/(EtO)₂P(O)H. In these conditions, the reaction proceeds rapidly and quantitatively at room temperature, and the resulting phosphonate-terminated dendrimer 14-[G₁] is more easily purified (Scheme 6). However, the ^{31}P NMR spectrum of compound 14-[G₁] appears surprisingly complex. Indeed, beside the singlet corresponding to the phosphorus of the core (δ $^{31}\text{P} = 51.8$ ppm, P₀), we observed two signals centered at $\delta = 21.3$ ppm, corresponding to P(O)(OEt)₂, and three signals centered at $\delta = 62.0$ ppm, corresponding to the phospho-

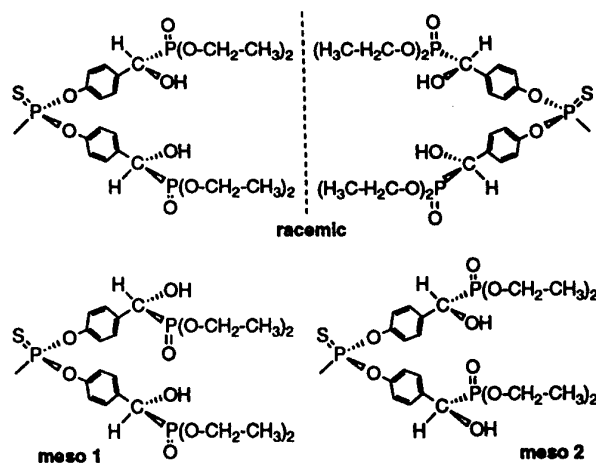
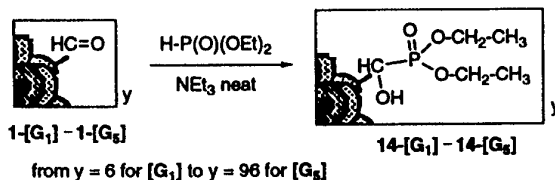


Figure 3. Racemic and meso forms for each branch of dendrimers 14-[G_n].

Scheme 6



rus of the first generation P₁ (Figure 2a). At first glance, these signals could be due to the formation of three diastereoisomers (one racemic and two meso forms) for each branch of the dendrimer, as the addition of PH groups to aldehydes creates chiral carbon centers (Figure 3). However, the relative intensity for each set of signals (1:2:1 for $\delta = 62.0$ ppm and 1:1 for $\delta = 21.3$ ppm) and the line separation seems to be in agreement with the presence of a triplet and a doublet, with a coupling constant of 3.9 Hz, which should correspond to the coupling of P₁(S) with P(O) through seven bonds! This surprising result prompted us to verify this hypothesis by selective phosphorus-decoupling NMR experiments. The selective irradiation of the signal at $\delta = 62.0$ ppm clearly induces the transformation of the signal at $\delta = 21.3$ ppm from a doublet to a singlet (Figure 2b). Furthermore, the selective irradiation of the signal at $\delta = 21.3$ ppm also transforms the signal at $\delta = 62.0$ ppm to a singlet. These experiments confirm the existence of the $^7J_{\text{PP}}$ coupling constant in compound 14-[G₁]. Very few coupling constants through so many bonds have been reported in the literature, most of them concerning through-space couplings,⁶ which are unlikely for compound 14-[G₁] for steric reasons. However, a phosphorus-phosphorus coupling constant over seven bonds has already been measured for a compound whose structure is closely related to that of 14-[G₁]: the analysis of the outer ^{13}C satellites in the ^{31}P NMR spectrum of (EtO)₂P(O)CH₂C₆H₄CH₂P(O)(OEt)₂ gave $^7J_{\text{PP}} = 7.8$ Hz, a value attributed to a large π -electron contribution.⁷ The value directly obtained in the case of 14-[G₁] ($^7J_{\text{PP}} = 3.9$ Hz) compares well with these data.

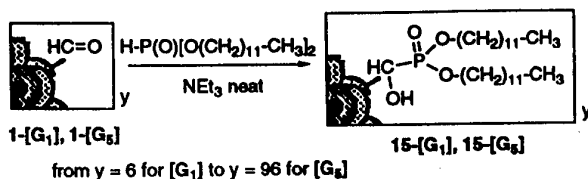
(6) (a) Szalontai, G.; Bakos, J.; Toth, I.; Heil, B. *Magn. Reson. Chem.* **1987**, *25*, 761. (b) Pastor, S. D.; Hyun, J. L.; Odorisio, P. A.; Rodebaugh, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 6547. (c) Pastor, S. D.; Shum, S. P.; DeBellis, A. D.; Burke, L. P.; Rodebaugh, R. K.; Clarke, F. H.; Rihs, G. *Inorg. Chem.* **1996**, *35*, 949 and references cited therein. (7) Ernst, L. J. *Chem. Soc., Chem. Commun.* **1977**, 375. (b) Ernst, L. *Org. Magn. Reson.* **1977**, *1*, 35.

(5) See, for instance, Abramov, V. S. *Zh. Obshch. Khim.* **1957**, *27*, 169; (*Chem. Abstr.* **1957**, *51*, 12878e).

Phosphate-Terminated Dendrimers

J. Org. Chem. E

Scheme 7



The grafting of phosphonate groups can be extended to higher generations without any problem of solubility. We have carried out this reaction under the same conditions for all the generations from 1 to 5 and, thus, isolated dendrimers 14-[G₁]-14-[G₅], with up to 96 phosphonate end groups (Scheme 6). In all cases, we observed a doublet in the ³¹P NMR spectra at $\delta = 21$ ppm ($3.8 < {}^7J_{PP} < 4.5$ Hz) for the P(O)(OEt)₂ groups, whereas the signal at $\delta = 62$ ppm becomes a broad singlet for generations higher than 2, presumably due to the formation of an increasing number of stereoisomers. The full transformation of the aldehyde groups in alcohol for all compounds is characterized in ¹H NMR by the total disappearance of the singlet of the aldehyde groups on behalf of the appearance of a doublet at ca. 5 ppm corresponding to the C*HOH groups. The presence of chiral carbon atoms also complicates the ¹H and ¹³C NMR spectra for all generations, as this renders the CH₂CH₃ groups diastereotopic. This is clearly seen in ¹³C NMR spectra by the presence of two distinct doublets at ca 63-65 ppm corresponding to the OCH₂CH₃ groups.

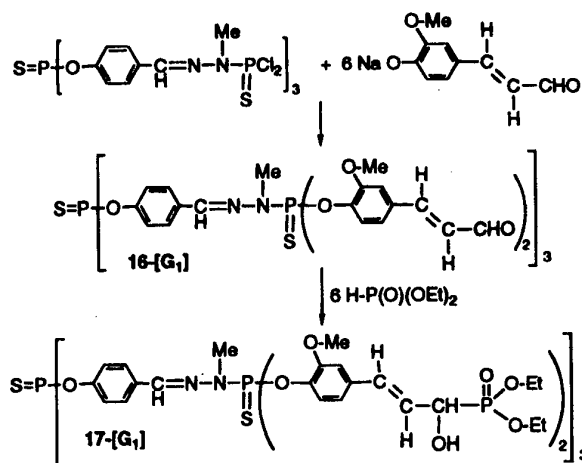
The facility of the synthesis of dendrimers 14-[G₁]-14-[G₅] incited us to try to extend this reaction to other phosphonates and to other end groups on the dendrimers. For instance, the long chain phosphonate HP(O)(O(CH₂)₁₁-CH₃)₂ also reacts with dendrimers 1-[G₁] and 1-[G₅] to afford dendrimers 15-[G₁] and 15-[G₅] (Scheme 7). These compounds possess the same spectral characteristics already noted for dendrimers 14-[G₁]-14-[G₅], in particular, a ${}^7J_{PP} = 3.8$ Hz is clearly observed on the ³¹P NMR spectrum of 15-[G₁]. The presence of several long-chain hydrocarbons modifies the solubility of the dendrimer: for instance, compound 15-[G₁] is soluble in pentane, whereas none of the dendrimers we already synthesized is.

We also tried the addition of phosphonates on a dendrimer with α,β -unsaturated aldehydes as end groups, 16-[G₁]. This compound is obtained in THF at 40 °C by reacting 6 equiv of the sodium salt of 4-hydroxy-3-methoxycinnamaldehyde with (S)P[OC₆H₄CH=NN(Me)P(S)Cl₂]₃ (Scheme 8). Addition of HP(O)(OEt)₂ on 16-[G₁] affords dendrimer 17-[G₁], which possesses six unsaturated alcohol-phosphonate end groups. In this case, no phosphorus-phosphorus coupling constant through nine bonds is observed on the ³¹P NMR spectrum of 17-[G₁]. ¹H NMR shows the total disappearance of the CHO groups on behalf of the appearance of a doublet of doublet at $\delta = 4.6$ ppm (${}^2J_{HP} = 13.4$ Hz, ${}^3J_{HH} = 5.0$ Hz) corresponding to C*HOH. As expected, no reaction occurred on the CH=CH bonds.

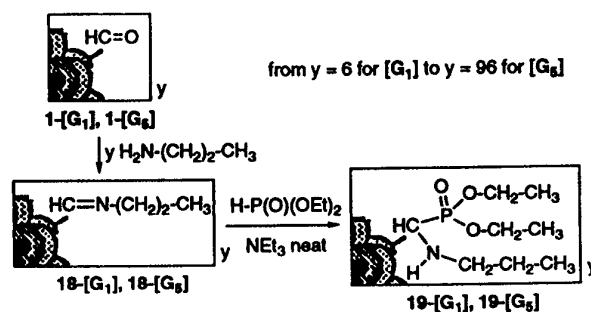
IR spectra of compounds 14-[G₁]-14-[G₅], 15-[G₁], 15-[G₅], and 17-[G₁] exhibit classical $\nu_{OH} \approx 3270$ cm⁻¹, demonstrating the presence of a hydrogen bond between hydroxyl and phosphoryl groups.

Finally, we also tried to add phosphonates to imine terminal functions, as it is known that this type of reaction proceeds approximately under the same condi-

Scheme 8



Scheme 9



tions as the addition to aldehydes.⁸ For this purpose, we synthesized first the imine-terminated dendrimers 18-[G₁] and 18-[G₅], easily obtained by condensation of propylamine with dendrimers 1-[G₁] and 1-[G₅], respectively (Scheme 9). Addition of HP(O)(OEt)₂ on dendrimers 18-[G₁] and 18-[G₅] at room temperature affords dendrimers 19-[G₁] and 19-[G₅], respectively. In this case also, the phosphorus-phosphorus coupling constant through seven bonds (${}^7J_{PP} = 4.5$ Hz) is clearly observed on the ³¹P NMR spectra of both generations. The reaction has gone to completion, as demonstrated by the total disappearance of the imine functions ($\delta = 8.20$ ppm) in ¹H NMR. The addition to the imine bonds is chemoselective; no reaction occurs on the hydrazone functions of the skeleton of the dendrimer, either in this experiment or in all the previous cases.

Conclusion

We have experimented with several strategies to graft tri- and tetracoordinated phosphorus derivatives on dendrimers of generation one-five, depending on the solubility of the resulting dendrimer. It can be inferred from all these experiments that the solubility of the dendrimers depends essentially on the type of substituents grafted on the surface. Indeed, azinephosphate, azinephosphinite, and ylide linkages on the periphery dramatically reduce the solubility of dendrimers possessing more than six end groups. On the other hand, the grafting of long-chain hydrocarbons increases the solubility of the dendrimer in organic solvents. However, it can

(8) See, for instance: (a) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528. (b) Caccamese, S.; Failla, S.; Finocchiaro, P.; Hägele, G.; Principato, G. *J. Chem. Res., Synop.* **1992**, 242.

be pointed out that each end group seems to behave independently as far as the reactivity is concerned. Moreover, the reactivity of the ylide-terminated dendrimer with aldehydes follows the rules elaborated for classical Wittig reactions in organic chemistry.

The phosphonate-terminated dendrimers appears to be very interesting, as all of them remain soluble in common organic solvents, even for high generations. Furthermore, the addition reaction we used allows several variations, both in the nature of the phosphonate to be grafted and in the nature of the polar double bond on the surface of the dendrimer. It is also worth noting that this reaction creates additional functions on the surface on the dendrimer, besides the phosphonate groups: alcohols or secondary amines groups, whose reactivity should be interesting to investigate. Furthermore, these compounds possess a rare and unexpected long-range phosphorus-phosphorus coupling constant through seven bonds for the (S)POC₆H₄CHRP(O)(OR')₂ linkages (R = OH, NHPr; R' = Et, (CH₂)₁₁CH₃).

To summarize, this work clearly demonstrates for the first time that it is possible to anchor to the surface of dendritic molecules a large variety of phosphorus groups (phosphates, phosphites, hydrazonophosphates, hydrazonophosphites, phosphorus ylides, and phosphonates (from 6 to 96 units), each of them having potentially a great interest in different fields. Indeed, biologically important phosphates are known (nucleotides, phospholipides, nucleosides, polyphosphates, phosphate sugars);^{9,10} phosphite monomers are used in some catalytic processes (acrylonitrile dimerization) and in the well-known Arbusov rearrangement,¹¹ while phosphorus ylides play a key role in Wittig reactions.¹¹ Moreover, phosphonate monomers have found wide applications in general organic synthesis¹²⁻¹⁴ (Horner-Wadsworth-Emmons condensation, Diels-Alder reactions, Michael additions, etc.), and they can be used as versatile intermediates for the preparation of a number of heterocycles.¹⁴

Work is in progress to study the properties of these new terminated dendrimers in some of the areas reported above and to extend the scope of reactions developed in this paper to other types of phosphorus derivatives.

Experimental Section

General Methods. All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. ¹H, ³¹P{¹H}, and ¹³C{¹H} NMR spectra were recorded on Bruker AC 200 or WM 250 or AMX 400 spectrometers, using CDCl₃ as solvent, except where noted. ³¹P NMR chemical shifts are reported in ppm relative to 85% H₃PO₄. Coupling constants (*J*) are reported in Hz.

Synthesis of Compound 3. To a solution of 4-hydroxybenzaldehyde sodium salt (0.500 g, 3.47 mmol) in THF (10 mL) was added (EtO)₂P(O)Cl (0.500 mL, 3.47 mmol). The resulting mixture was stirred for 1 h at room temperature and then filtered to give an oil that was used without further purification.

3: colorless oil; 70% yield (0.627 g); ³¹P NMR δ -7.0; ¹H NMR δ 1.04 (t, *J* = 7.0, 6H), 3.92 (q, *J* = 7.0, 2H), 3.96 (q, *J* = 7.0, 2H), 7.08 (dd, *J* = 8.5, 2H), 7.58 (dd, *J* = 8.5, 2H), 9.65 (s,

1H); ¹³C NMR δ 15.6 (d, *J* = 6), 64.6 (d, *J* = 6), 120.2 (d, *J* = 5), 131.3, 132.9, 155.0 (d, *J* = 7), 190.4.

Synthesis of Phosphate-Terminated Dendrimer 4-[G₁]. To a solution of 0.200 g of dendrimer 2-[G₁] (0.133 mmol) in THF (10 mL) was added phosphate **3** (0.206 g, 0.798 mmol). The resulting mixture was stirred overnight at room temperature and then evaporated to dryness to give a yellow powder. This powder was washed with pentane/ether (1/1).

4-[G₁]: yellow powder; 72% yield (0.282 g); ³¹P NMR δ -6.7, 52.0, 61.2; ¹H NMR δ 1.33 (m, 36H), 3.36 (d, *J* = 9.8, 9H), 4.19 (m, 24H), 7.26-7.78 (m, 63H), 8.56 (br s, 12H); ¹³C NMR δ 15.9 (d, *J* = 6), 32.8 (d, *J* = 16), 64.6 (d, *J* = 6), 120.2 (d, *J* = 5), 121.3, 121.7 (d, *J* = 4), 128.3, 129.8, 129.9, 130.6, 131.2, 138.4 (d, *J* = 14), 150.5 (d, *J* = 9), 152.5 (d, *J* = 9), 152.7 (d, *J* = 9), 160.5, 160.8. Anal. Calcd for C₁₃₂H₁₄₄N₁₈O₃₃P₁₀S₄: C, 53.77; H, 4.92; N, 8.55. Found: C, 53.63; H, 4.89; N, 8.47.

Synthesis of Compound 5. To a solution of 4-hydroxybenzaldehyde (0.250 g, 2.047 mmol) in THF (10 mL) were added triethylamine (0.285 mL, 2.047 mmol) and then diphenylchlorophosphine (0.367 mL, 2.047 mmol). The resulting mixture was stirred for 1 h at room temperature and then filtered and evaporated to dryness to give a pale yellow paste. This compound was used without further purification.

5: yellow paste; 83% yield (0.520 g); ³¹P NMR δ 112.3; ¹H NMR δ 7.0-7.8 (m, 14H), 9.87 (s, 1H); ¹³C NMR δ 118.8 (d, *J* = 13), 128.5 (d, *J* = 7), 130.0, 130.5 (d, *J* = 23), 131.7, 132.1, 139.5 (d, *J* = 17), 155.5 (d, *J* = 9), 190.8.

Synthesis of Phosphinite-Terminated Dendrimer 6-[G₁]. To a solution of dendrimer 2-[G₁] (0.177 g, 0.117 mmol) in dichloromethane (10 mL) was added a solution of compound **5** (0.215 g, 0.702 mmol) in CH₂Cl₂ (4 mL) in the presence of molecular sieves (4 Å). The resulting mixture was stirred overnight at room temperature and then filtered and evaporated to dryness to give a yellow powder very sensitive to oxidation.

6-[G₁]: yellow powder; 64% yield (0.242 g); ³¹P NMR δ 52.5, 61.6, 111.5; ¹H NMR δ 3.30 (d, *J* = 10.5, 9H), 7.20-7.80 (m, 123H), 8.60 (br s, 12H); ¹³C NMR δ 32.9 (d, *J* = 12), 118.8 (d, *J* = 11), 120.9, 121.6, 128.4, (d, *J* = 7), 128.7, 129.8, 130.0 (d, *J* = 13), 130.6, 131.5, 131.7, 138.4 (d, *J* = 14), 140.0 (d, *J* = 17), 151.2 (d, *J* = 8), 152.4 (m), 161.00. Anal. Calcd for C₁₈₀H₁₄₄N₁₈O₁₅P₁₀S₄: C, 66.78; H, 4.48; N, 7.79. Found: C, 66.51; H, 4.36; N, 7.65.

Synthesis of Compound 7. To a solution of 0.31 mL (5.83 mmol) of methylhydrazine in THF (10 mL) was slowly added a solution of 0.42 mL (2.92 mmol) of chloro diethyl phosphite in THF (10 mL) at -90 °C. This mixture was allowed to slowly warm to room temperature. After filtration, the solvent was eliminated under vacuum to give a pale-yellow oil. This compound was used without further purification.

7: yellow oil; 70% yield (0.372 g); ³¹P NMR δ 8.7; ¹H NMR δ 0.97 (t, *J* = 7.0, 6H), 2.57 (d, *J* = 8.8, 3H), 3.67 (q, *J* = 7.0, 2H), 3.77 (q, *J* = 7.0, 2H), 3.98 (br s, 2H); ¹³C NMR δ 15.8 (d, *J* = 6), 40.3 (d, *J* = 11), 62.4 (d, *J* = 6).

General Procedure for the Synthesis of Aminophosphate-Terminated Dendrimers 8-[G₁] and 8-[G_n]. To a solution of 0.250 g of 1-[G_n] (*n* = 1, 0.176 mmol; *n* = 5, 0.008 mmol) in THF (10 mL) was added an excess of (EtO)₂P(O)-NMeNH₂ (*n* = 1, 0.385 g, 2.11 mmol; *n* = 5, 0.280 g, 1.54 mmol) in the presence of molecular sieves (4 Å). The resulting mixture was stirred for 2 days at room temperature and then evaporated to dryness to give an oil. Addition of pentane precipitated the oil to give a white powder. Pentane was eliminated via cannula, and the powder was dried under vacuum. This powder was then washed with ether.

8-[G₁]: white powder; 65% yield (0.275 g); ³¹P NMR δ 2.8, 52.7, 62.6; ¹H NMR δ 1.3 (br t, *J* = 7.3, 36H), 3.2 (d, *J* = 7.3, 18H), 3.4 (d, *J* = 10.4, 9H), 4.0 (m, 24H), 7.1-7.8 (m, 45H); ¹³C NMR δ 15.9 (d, *J* = 7), 31.9 (d, *J* = 10), 32.9 (d, *J* = 13), 63.4 (d, *J* = 6), 121.5 (d, *J* = 5), 127.6, 128.3, 132.6, 136.7, (d, *J* = 15), 138.3 (d, *J* = 14), 150.7 (d, *J* = 8), 151.0 (d, *J* = 9). Anal. Calcd for C₂₆₆H₁₃₂N₁₈O₂₇P₁₀S₄: C, 47.88; H, 5.52; N, 10.47. Found: C, 47.79; H, 5.46; N, 10.24.

8-[G₅]: white powder; 15% yield (0.056 g); ³¹P NMR δ 2.7, 62.6 (br s); ¹H NMR δ 1.25 (br s, 576 H), 3.18 (d, *J* = 6.4, 288H), 3.33 (d, *J* = 10, 279 H), 4.05 (m, 384H), 7.14-7.65 (m, 945H);

(9) Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(10) Klachburn, G. M.; Peree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. *Chem. Scripta* **1986**, *26*, 21.

(11) *Methoden der Organischen Chemie (Houben-Weyl E1)*; Regitz, M., Ed.; Georg Thieme Verlag: Stuttgart, 1982.

(12) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.

(13) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(14) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

Phosphate-Terminated Dendrimers

J. Org. Chem. G

^{13}C NMR δ 16.0 (d, $J = 7$), 32.0 (d, $J = 10$), 32.9 (d, $J = 14$), 63.4 (d, $J = 6$), 121.5 (d, $J = 3$), 127.6, 128.1, 132.0, 132.5, 136.8 (d, $J = 15$), 138–140 (m), 150.7 (d, $J = 7$), 151.2 (m). Anal. Calcd for $\text{C}_{1898}\text{H}_{2472}\text{N}_{378}\text{O}_{477}\text{P}_{190}\text{S}_4$: C, 48.36, H, 5.29; N, 11.24. Found: C, 48.17; H, 5.14; N, 11.07.

General Procedure for the Synthesis of Aminophosphate-Terminated Dendrimers 10-[G_n] and 10-[G₅]. To a solution of 0.120 g of dendrimer 9-[G_n] ($n = 1$, 0.075 mmol; $n = 5$, 0.0035 mmol) in THF (10 mL) were added chlorodiethylphosphine ($n = 1$, 130 μL , 0.90 mmol; $n = 5$, 98 μL , 0.677 mmol) and triethylamine ($n = 1$, 126 μL , 0.90 mmol; $n = 5$, 100 μL , 0.677 mmol). The resulting mixture was stirred for 2 h at room temperature and then filtered and evaporated to dryness to give a white powder, very sensitive to oxidation.

10-[G₁]: white powder; 40% yield (0.070 g); ^{31}P NMR δ 52.5, 62.8, 139.2; ^1H NMR δ 1.22 (t, $J = 7.0$, 36H), 2.93 (d, $J = 1.0$, 18H), 3.33 (d, $J = 10.4$, 9H), 3.71–3.85 (m, 24H), 7.15–7.77 (m, 45H); ^{13}C NMR δ 16.7 (d, $J = 6$), 28.4, 32.9 (d, $J = 13$), 59.7 (d, $J = 17$), 121.4 (d, $J = 4$), 126.9, 128.3, 132.5, 132.6, 133.3 (d, $J = 28$), 138.2 (d, $J = 12$), 149.9 (d, $J = 7$), 150.9 (d, $J = 8$). Anal. Calcd for $\text{C}_{99}\text{H}_{132}\text{N}_{18}\text{O}_{21}\text{P}_{10}\text{S}_4$: C, 49.87; H, 5.75; N, 10.90. Found: C, 49.73; H, 5.71; N, 10.72.

10-[G₅]: white powder; 64% yield (0.102 g); ^{31}P NMR δ 62.6, 62.7, 138.6; ^1H NMR δ 1.15–1.27 (m, 576H), 2.85 (d, $J = 1.87$, 288H), 3.25 (d, $J = 11.6$, 279H), 3.70–3.86 (m, 384H), 7.11–7.60 (m, 945H); ^{13}C NMR δ 16.7 (d, $J = 5$), 28.4, 32.9 (d, $J = 12$), 59.6 (d, $J = 17$), 121.3 (d, $J = 3$), 121.6 (d, $J = 6$), 126.9, 128.0, 132.0, 132.6, 133.2 (d, $J = 28$), 138.3–140.0 (m), 149.9 (d, $J = 7$), 151.1 (d, $J = 9$). Anal. Calcd for $\text{C}_{1898}\text{H}_{2472}\text{N}_{378}\text{O}_{477}\text{P}_{190}\text{S}_4$: C, 49.99; H, 5.47; N, 11.62. Found: C, 49.76; H, 5.32; N, 11.51.

Synthesis of Ylide-Terminated Dendrimer 11-[G₁]. To a solution of (triphenylphosphoranyl)ethenone (0.120 g, 0.397 mmol) in THF (7 mL) was added 9-[G₁] (0.105 g, 0.066 mmol) in THF (5 mL) at room temperature. The resulting mixture was stirred for 24 h at room temperature and then evaporated to dryness. The resulting powder was washed with 3×10 mL of THF/ether/pentane (1/2/2).

11-[G₁]: yellow powder; 78% yield (0.175 g); ^{31}P NMR δ 18.3, 52.8, 62.6; ^1H NMR δ 3.3 (s, 18H), 3.3 (d, $J = 11.5$, 9H), 4.2 (br d, $J = 25$, 6H), 7.1–7.7 (m, 135H); ^{13}C NMR δ 26.8, 32.4 (d, $J = 13$), 32.5 (d, $J = 12.7$), 120.9 (d, $J = 4$), 126.7, 127.5, 128.0 (d, $J = 12$), 129.7 (d, $J = 13$), 131.1, 132.4 (d, $J = 10$), 133.3, 134.3, 137.5 (d, $J = 14$), 149.6 (d, $J = 7$), 150.4 (d, $J = 8$), 170.3 (d, $J = 12$); IR (KBr) 1663 cm^{-1} ($\nu_{\text{C}=\text{O}}$). Anal. Calcd for $\text{C}_{192}\text{H}_{168}\text{N}_{18}\text{O}_{15}\text{P}_{10}\text{S}_4$: C, 67.71; H, 4.97; N, 7.40. Found: C, 67.62; H, 4.87; N, 7.01.

Reaction of Dendrimer 11-[G₁] with Aldehydes. To a solution of 0.211 mg (0.062 mmol) of dendrimer 11-[G₁] in THF (10 mL) was added benzaldehyde (0.040 mL, 0.37 mmol) or crotonaldehyde (0.031 mL, 0.37 mmol). The resulting mixture was stirred overnight at room temperature (benzaldehyde) or for 1 week at 40 $^{\circ}\text{C}$ (crotonaldehyde). The solvent was evaporated under vacuum to give a yellow powder that was washed with 3×10 mL of THF/ether/pentane (1/2/2).

12-[G₁]: pale yellow powder; 66% yield (0.097 g); ^{31}P NMR δ 52.9, 62.2; ^1H NMR δ 3.32 (d, $J = 14.1$, 9H), 3.42 (s, 18H), 7.2–7.8 (m, 87H); ^{13}C NMR δ 27.3, 27.6, 32.4 (d, $J = 12$), 116.8, 117.0, 121.3 (d, $J = 6$), 121.7 (d, $J = 6$), 127.9, 128.1, 128.3, 128.4, 128.6, 131.9, 132.0, 137.5 (d, $J = 12$), 137.6, 139.2, 142.2, 142.5, 151.0 (d, $J = 9$), 151.3 (d, $J = 7$), 166.3, 167.0. IR (KBr) 1663 cm^{-1} ($\nu_{\text{C}=\text{O}}$). Anal. Calcd for $\text{C}_{126}\text{H}_{114}\text{N}_{18}\text{O}_{15}\text{P}_{10}\text{S}_4$: C, 63.79; H, 4.84; N, 10.63. Found: C, 63.52; H, 4.71; N, 10.49.

13-[G₁]: pale yellow powder; 63% yield (0.08 g); ^{31}P NMR δ 52.9, 62.2; ^1H NMR (400 MHz, ^2D) δ 1.80–1.90 (m, 12H, $\text{CH}=\text{CHCH}_3$), 3.30–3.40 (m, 27H, P_1NCH_3 , $\text{C}(\text{O})\text{NCH}_3$), 6.05 (m, (6 \times 0.1)H, *cis,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 6.13 (dq, $^3J_{\text{HaHb}} = 15.1$, $^3J_{\text{HaHc}} = 6.6$ (6 \times 0.9)H, *trans,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 6.31 (m, (6 \times 0.9)H, *trans,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 6.54 (m, (6 \times 0.1)H, *cis,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 6.80 (d, $J_{\text{HcHd}} = 10.0$, (6 \times 0.1)H, *cis,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 7.12 (d, $J_{\text{HcHd}} = 15.0$, (6 \times 0.9)H, *trans,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 7.37 (dd, $J_{\text{HcHd}} = 15.0$, $J_{\text{HcHb}} = 10.1$, (6 \times 0.9)H, *trans,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$), 7.20–7.80 (m, 45H, $\text{CH}=\text{N}$, C_6H_4 and *cis,trans*- $\text{CH}_d-\text{CH}_c\text{CH}_b-\text{CH}_a\text{Me}$); ^{13}C NMR δ 18.5, 27.4, 27.9, 32.9 (d, $J = 13$),

114.7, 117.8, 121.4 (d, $J = 4$), 121.6 (d, $J = 5$), 128.0, 128.3, 130.3, 130.4, 132.2, 137.1, 137.2 (d, $J = 11$), 138.2, 138.3, 142.7, 143.6, 151.0 (d, $J = 7$), 151.2 (d, $J = 9$), 166.6, 167.5; IR (KBr) 1663 cm^{-1} ($\nu_{\text{C}=\text{O}}$). Anal. Calcd for $\text{C}_{108}\text{H}_{114}\text{N}_{18}\text{O}_{15}\text{P}_{10}\text{S}_4$: C, 60.15; H, 5.33; N, 11.69. Found: C, 59.97; H, 5.27; N, 11.60.

General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 14-[G₁]–14-[G₅]. To 0.200 g of dendrimer 1-[G_n] ($n = 1$, 0.140 mmol; $n = 2$, 0.058 mmol; $n = 3$, 0.027 mmol; $n = 4$, 0.013 mmol; $n = 5$, 0.0064 mmol) were added triethylamine ($n = 1$, 30 μL ; $n = 2$, 50 μL ; $n = 3$, 50 μL ; $n = 4$, 140 μL ; $n = 5$, 140 μL) and diethyl phosphite (the quantity necessary to dissolve 1-[G_n]; $n = 1$, 0.6 mL, $n = 2$, 1.0 mL; $n = 3$, 1.0 mL; $n = 4$, 2.9 mL; $n = 5$, 2.9 mL). The mixture was stirred overnight at room temperature and then evaporated under vacuum to give an oil. Addition of ether/pentane precipitated this oil. The resulting powder was washed with acetonitrile.

14-[G₁]: white powder; 27% yield (0.085 g); ^{31}P NMR δ 21.3 (d, $J_{\text{PP}} = 3.9$, P(O)), 51.8 (s, P₀), 62.0 (t, $J_{\text{PP}} = 3.9$, P₁); ^1H NMR δ 1.20 (m, 36H), 3.30 (d, $J = 10.3$, 9H), 3.92 (m, 24H), 4.90 (s, 6H), 4.93 (d, $J = 11.5$, 6H), 7.15–7.73 (m, 39H); ^{13}C NMR δ 16.2 (d, $J = 4$), 32.7 (d, $J = 13$), 63.0 (d, $J = 10$), 63.2 (d, $J = 8$), 69.8 (d, $J = 160$), 121.0, 121.3, 128.2, 132.5, 133.8, 138.2 (d, $J = 12$), 150.0 (d, $J = 7$), 150.9 (d, $J = 6$); IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{90}\text{H}_{120}\text{N}_6\text{O}_{33}\text{P}_{10}\text{S}_4$: C, 48.00; H, 5.37; N, 3.73. Found: C, 47.81; H, 5.28; N, 3.61.

14-[G₂]: white powder; 19% yield (0.079 g); ^{31}P NMR (CH_2Cl_2) δ 20.8 (d, $J = 4.0$), 51.7, 61.4, 61.8 (t, $J = 4.0$); ^1H NMR (CD_3OD) δ 1.23 (m, 72H), 3.32 (d, $J = 10.3$, 27H), 3.98 (m, 48H), 5.04 (d, $J = 13.0$, 12H), 7.23–7.76 (m, 93H); ^{13}C NMR (CD_3OD) δ 17.3 (d, $J = 3$), 34.1 (d, $J = 13$), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 165$), 122.6, 123.3, 129.7, 130.2 (d, $J = 4$), 134.0, 136.3, 141.2 (d, $J = 12$), 151.3, 152.0 (d, $J = 4$); IR (KBr) 3272 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{204}\text{H}_{264}\text{N}_{18}\text{O}_{69}\text{P}_{22}\text{S}_{10}$: C, 48.32; H, 5.25; N, 4.97. Found: C, 48.27; H, 5.19; N, 4.85.

14-[G₃]: white powder; 18% yield (0.052 g); ^{31}P NMR (CH_2Cl_2) δ 21.2 (d, $J = 3.8$), 52.3, 62.2 (br s); ^1H NMR (CD_3OD) δ 1.21 (m, 144H), 3.22 (m, 63H), 4.00 (m, 96H), 5.03 (d, $J = 12.6$, 24H), 7.23–7.67 (m, 201H); ^{13}C NMR (CD_3OD) δ 17.3, 34.2 (d, $J = 10$), 64.7 (d, $J = 8$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 123.2, 130.3 (m), 134.1, 136.3, 140.5 (m), 151.0, 152.1 (d, $J = 4$); IR (KBr) 3271 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{432}\text{H}_{552}\text{N}_{42}\text{O}_{141}\text{P}_{46}\text{S}_{22}$: C, 48.40; H, 5.19; N, 5.49. Found: C, 48.23; H, 5.11; N, 5.37.

14-[G₄]: white powder; 18% yield (0.052 g); ^{31}P NMR (CH_2Cl_2) δ 21.2 (d, $J = 4.3$), 62.2 (br s); ^1H NMR (CD_3OD): δ 1.21 (m, 288H), 3.26 (m, 135H), 4.00 (m, 192H), 5.03 (d, $J = 12.7$, 48H), 7.25–7.67 (m, 417H); ^{13}C NMR (CD_3OD) δ 17.3, 34.0 (m), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 130.2, 133.7–134.0 (m), 136.3, 140.0–141.5 (m), 152.1 (d, $J = 5$); IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{888}\text{H}_{1128}\text{N}_{90}\text{O}_{285}\text{P}_{94}\text{S}_{46}$: C, 48.46; H, 5.16; N, 5.73. Found: C, 48.23; H, 5.03; N, 5.61.

14-[G₅]: white powder; 22% yield (0.059 g); ^{31}P NMR (CH_2Cl_2) δ 21.3 (d, $J = 4.5$), 62.4 (br s); ^1H NMR (CD_3OD) δ 1.20 (m, 576H), 3.25 (m, 279H), 4.05 (m, 384H), 5.03 (d, $J = 13.2$, 96H), 7.23–7.67 (m, 849H); ^{13}C NMR (CD_3OD) δ 17.3, 34.0 (m), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 130.2, 133.8–134.1 (m), 136.3, 140.0–141.0 (m), 151.0, 152.1; IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{1800}\text{H}_{2280}\text{N}_{186}\text{O}_{573}\text{P}_{190}\text{S}_{94}$: C, 48.48; H, 5.15; N, 5.84. Found: C, 48.51; H, 5.09; N, 5.78.

General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 15-[G₁] and 15-[G₅]. To 0.200 g of dendrimer 1-[G_n] ($n = 1$, 0.140 mmol; $n = 5$, 0.0064 mmol) were added dilauryl phosphite ($n = 1$, 0.775 mL, 1.68 mmol; $n = 5$, 0.682 mL, 1.5 mmol) and then triethylamine ($n = 1$, 20 μL ; $n = 5$, 100 μL). The resulting mixture was stirred for 3 days at room temperature (for 15-[G₁]) or for 5 days at room temperature then for 2 days at 45 $^{\circ}\text{C}$ (for 15-[G₅]). Evaporation under vacuum gave an oil that was washed several times with acetonitrile to give a white powder.

15-[G₁]: white powder; 16% yield (0.089 g); ^{31}P NMR δ 21.2 (d, $J = 3.8$), 51.8, 62.2 (t, $J = 3.8$); ^1H NMR δ 0.85 (t, $J = 5.0$, 36H), 1.22 (br s, 216 H), 1.40–1.55 (m, 24H), 3.30 (d, $J = 9.8$,

9H), 3.80–3.95 (m, 24H), 4.60 (br s, 6H), 4.95 (d, $J = 6.5$, 6H), 7.16–7.74 (m, 39H); ^{13}C NMR δ 13.9, 22.5, 25.2, 28.9, 29.2, 29.4, 29.5, 30.3, 30.4, 31.7, 32.9 (d, $J = 12$), 66.9 (d, $J = 8$), 67.2 (d, $J = 7$), 70.0 (d, $J = 159$), 121.0, 121.4, 128.2, 132.5, 133.7, 137.9, 150.0, 151.0 (d, $J = 9$); IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{210}\text{H}_{390}\text{N}_6\text{O}_{33}\text{P}_{10}\text{S}_4$: C, 64.10; H, 9.22; N, 2.14. Found: C, 64.25; H, 9.34; N, 2.07.

15-[G₅]: white powder; 27% yield (0.123 g); ^{31}P NMR δ 21.3, 62.6 (m); ^1H NMR δ 0.84 (br s, 576H), 1.21 (br s, 3456H), 1.50 (br s, 384H), 2.87 (br s, 96H), 3.27 (br s, 279H), 3.90 (br s, 384H), 4.95 (br s, 96H), 7.17–7.65 (m, 849H); ^{13}C NMR δ 13.9, 22.5, 25.2, 28.9, 29.2, 29.5, 30.3, 31.7, 32.5 (m), 66.5 (d, $J = 7$), 67.1 (d, $J = 7$), 71.3, 121.0, 121.7, 128.1, 132.0, 133.9, 137.6–139.4 (m), 149.9 (d, $J = 7$), 151.2 (d, $J = 7$); IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{3720}\text{H}_{6120}\text{N}_{186}\text{O}_{573}\text{P}_{190}\text{S}_{94}$: C, 62.47; H, 8.62; N, 3.64. Found: C, 62.73; H, 8.80; N, 3.52.

Synthesis of Dendrimer 16-[G₁]. To 0.300 g (0.33 mmol) of (S)[P(OC₆H₄CH=NN(Me)P(S)Cl₂)₃] in THF (30 mL) was added 0.420 g (2.27 mmol) of 4-hydroxy-3-methoxycinnamaldehyde sodium salt. The resulting mixture was stirred for 5 days at 40 °C and then centrifuged. The solution was evaporated to dryness to give a powder that was washed twice with pentane/ether (1/1).

16-[G₁]: yellow powder; 48% yield (0.278 g); ^{31}P NMR δ 52.7, 62.0; ^1H NMR δ 3.40 (d, $J = 9.9$, 9H), 3.73 (s, 18H), 6.51 (dd, $J = 16.0$, 7.0, 6H), 7.00–7.34 (m, 33H), 7.55 (d, $J = 16.0$, 6H), 9.54 (d, $J = 7.0$, 6H); ^{13}C NMR δ 32.5 (d, $J = 12$), 55.9, 111.7, 121.1, 121.5, 122.3, 128.2, 131.7, 132.6, 137.9 (d, $J = 15$), 142.3 (d, $J = 8$), 150.6 (d, $J = 8$), 151.3 (d, $J = 6$), 151.9, 193.4; IR (KBr) 1677 cm^{-1} (ν_{CHO}). Anal. Calcd for $\text{C}_{84}\text{H}_{78}\text{N}_6\text{O}_{21}\text{P}_4\text{S}_4$: C, 57.33; H, 4.47; N, 4.78. Found: C, 57.18; H, 5.48; N, 4.71.

Synthesis of Phosphonate-Terminated Dendrimer 17-[G₁]. To 0.280 g (0.160 mmol) of dendrimer 16-[G₁] were added triethylamine (30 μL) and diethyl phosphite (the quantity necessary to dissolve 16-[G₁]: 0.5 mL). The mixture was stirred overnight at room temperature and then evaporated under vacuum to give an oil that was washed with acetonitrile to give a powder.

17-[G₁]: yellow powder; 18% yield (0.074 g); ^{31}P NMR δ 21.3, 52.3, 62.1; ^1H NMR δ 1.28 (m, 36H), 2.62 (br s, 6H), 3.40 (d, $J = 10.0$, 9H), 3.75 (s, 18H), 4.13 (m, 24H), 4.61 (dd, $J = 13.4$, 5.0, 6H), 6.21 (d, $J = 15.7$, 6H), 6.67 (dd, $J = 15.7$, 5.0, 6H), 6.86–7.67 (m, 33H, C₆H₄); ^{13}C NMR δ 16.5 (d, $J = 6$), 32.7 (d, $J = 12$), 56.0, 63.2 (d, $J = 6$), 69.3 (d, $J = 162$), 110.7, 119.1, 121.3, 122.2, 124.1, 128.3, 133.0, 134.3, 137.4 (d, $J = 16$), 139.9, 150.8 (d, $J = 8$), 151.2 (d, $J = 6$); IR (KBr) 3270 cm^{-1} (ν_{OH}). Anal. Calcd for $\text{C}_{108}\text{H}_{144}\text{N}_6\text{O}_{39}\text{P}_{10}\text{S}_4$: C, 50.12; H, 5.61; N, 3.25. Found: C, 50.01; H, 5.49; N, 3.21.

General Procedure for the Synthesis of Imine-Terminated Dendrimers 18-[G₁] and 18-[G_n]. To a solution of 0.250 g of 1-[G_n] ($n = 1$, 0.176 mmol; $n = 5$, 0.008 mmol) in THF (10 mL) was added propylamine ($n = 1$, 0.180 mL, 2.112 mmol; $n = 5$, 0.130 mL, 1.530 mmol) in the presence of molecular sieves (4 Å). The mixture was stirred at room

temperature for 24 h and then filtered and evaporated to dryness. The resulting powder was washed with ether.

18-[G₁]: white powder; 61% yield (0.179 g); ^{31}P NMR δ 52.4, 61.9; ^1H NMR δ 0.90 (t, $J = 6.7$, 18H), 1.67 (m, 12H), 3.35 (d, $J = 10$, 9H), 3.51 (m, 12H), 7.26–7.70 (m, 39H), 8.20 (s, 6H); ^{13}C NMR δ 11.7, 23.8, 32.9 (d, $J = 14$), 63.2, 121.4 (d, $J = 4$), 128.3, 129.2, 132.4, 133.5, 138.4 (d, $J = 14$), 151.0 (d, $J = 7$), 152.0 (d, $J = 9$), 159.3; IR (KBr) 1647 cm^{-1} ($\nu_{\text{C-N}}$). Anal. Calcd for $\text{C}_{84}\text{H}_{98}\text{N}_{12}\text{O}_9\text{P}_4\text{S}_4$: C, 60.42; H, 5.79; N, 10.06. Found: C, 60.31; H, 5.67; N, 9.95.

18-[G₅]: white powder; 46% yield (0.130 g); ^{31}P NMR δ 61.9, 62.5; ^1H NMR δ 0.86 (br s, 288H), 1.61 (br s, 192H), 3.28 (br s, 279H), 3.47 (br s, 192H), 7.21–7.65 (m, 849H), 8.15 (s, 96H); ^{13}C NMR δ 11.7, 23.8, 32.8 (m), 63.2, 121.4 (d, $J = 4$), 121.7, 128.1, 129.1, 131.9, 133.5, 138–139 (m), 151.2 (d, $J = 5$), 151.9 (d, $J = 6$), 159.3; IR (KBr) 1647 cm^{-1} ($\nu_{\text{C-N}}$). Anal. Calcd for $\text{C}_{1704}\text{H}_{1896}\text{N}_{282}\text{O}_{188}\text{P}_{94}\text{S}_{94}$: C, 58.01; H, 5.42; N, 11.20. Found: C, 57.88; H, 5.33; N, 11.06.

General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 19-[G₁] and 19-[G_n]. To 0.130 g of dendrimer 18-[G_n] ($n = 1$, 0.078 mmol; $n = 5$, 0.0037 mmol) was added diethyl phosphite (the quantity necessary to dissolve 18-[G_n]: $n = 1$, 0.6 mL; $n = 5$, 2.0 mL) and then triethylamine ($n = 1$, 30 μL ; $n = 5$, 150 μL). This mixture was stirred overnight at room temperature and then evaporated to dryness. Dendrimer 19-[G₁] was purified by extraction with pentane/toluene. Dendrimer 19-[G₅] was purified by washings with pentane, ether, and then acetonitrile.

19-[G₁]: white powder; 11% yield (0.022 g); ^{31}P NMR δ 23.5 (d, $J = 4.5$), 52.6, 62.5 (t, $J = 4.5$); ^1H NMR δ 0.83 (t, $J = 7.3$, 18H), 1.08 (t, $J = 7.0$, 18H), 1.21 (t, $J = 7.0$, 18H), 1.40 (m, 12H), 2.11 (s, 6H), 2.41 (m, 12H), 3.34 (d, $J = 10.4$, 9H), 3.70–4.08 (m, 30H), 7.15–7.77 (m, 39H); ^{13}C NMR δ 11.5, 16.1 (d, $J = 7$), 16.2 (d, $J = 6$), 22.7, 32.8 (d, $J = 13$), 49.7 (d, $J = 16$), 60.2 (d, $J = 153$), 62.6 (d, $J = 7$), 62.8 (d, $J = 8$), 121.1 (d, $J = 3$), 121.4, 128.2, 129.4 (d, $J = 6$), 132.5, 133.0 (d, $J = 4$), 138.2 (d, $J = 15$), 149.9 (d, $J = 7$), 150.9 (d, $J = 8$); IR (KBr) 3300 cm^{-1} (ν_{NH}). Anal. Calcd for $\text{C}_{108}\text{H}_{162}\text{N}_{12}\text{O}_{27}\text{P}_{10}\text{S}_4$: C, 51.92; H, 6.53; N, 6.73. Found: C, 51.80; H, 6.50; N, 6.62.

19-[G₅]: white powder; 24% yield (0.043 g); ^{31}P NMR δ 22.9 (d, $J = 4.5$), 62.1; ^1H NMR δ 0.77 (br s, 288H), 1.03 (br s, 288H), 1.18 (br s, 288H), 1.45 (br s, 192H), 2.3–2.4 (m, 288H), 3.30 (br s, 279H), 3.85–4.00 (m, 480H), 7.15–7.65 (m, 849H); ^{13}C NMR δ 11.4, 16.0 (d, $J = 5$), 16.2 (d, $J = 5$), 21.2–22.0 (m), 32.6–33.0 (m), 49.3–49.5 (m), 59.5 (d, $J = 160$), 62.9 (m), 121.2–121.6 (m), 128.0, 129.7, 131.5–131.9 (m), 138.1–139.1 (m), 150.1–150.3 (m), 151.1; IR (KBr) 3300 cm^{-1} (ν_{NH}). Anal. Calcd for $\text{C}_{2088}\text{H}_{2982}\text{N}_{282}\text{O}_{477}\text{P}_{190}\text{S}_{94}$: C, 51.67; H, 6.13; N, 8.14. Found: C, 51.32; H, 6.05; N, 8.06.

Acknowledgment. Thanks are due to CNRS and the US Navy for financial support.

Application of the Horner-Wadsworth-Emmons Reaction to the Functionalization of Dendrimers: Synthesis of Amino Acid Terminated Dendrimers

Delphine Prévôté,^a Sylvie Le Roy-Gourvenec,^b

Anne-Marie Caminade,^{*,a} Serge Masson,^{*,b} Jean Pierre Majoral^{*,a}

^a *Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse Cedex 4, France. fax: (33) 5 61 55 30 03 . e-mail: caminade@lcc-toulouse.fr or majoral@lcc-toulouse.fr*

^b *Laboratoire de Chimie Moléculaire et Thioorganique, Université de Caen-Institut des Sciences de la Matière et du Rayonnement (ISMRA), 6 Bd du Maréchal Juin, 14050 Caen, France. fax: (33) 2 31 45 28 77. e-mail: masson@ismra.unicaen.fr*

Abstract:

The Horner-Wadsworth-Emmons reaction of the first, third and fourth generation of aldehyde terminated dendrimers **1-[G_n]** (**n** = 1: 6 CHO, **n** = 3: 24 CHO, **n** = 4: 48 CHO groups, respectively) with phosphonates unsubstituted at the carbon α to the phosphoryl group **2a-i** affords in moderate yield dendrimers bearing various α, β -unsaturated functional groups on the surface, including amino acid derivatives.

Key words: Dendrimer, arborol, phosphonate, Horner-Wadsworth-Emmons reaction, amino-acid

The design of highly branched macromolecules with well defined structure and constitution, namely dendrimers¹ gives rise to an increasing interest in several fields of chemistry, including biochemistry. For instance, natural amino acids have been included several times in the skeleton of dendritic structures, or grafted on the surface. In previous examples, amino acids such as α,ω -diamino carboxylic acids (mainly lysine) were used as building blocks in divergent syntheses up to the tenth generation.² Later, oligonucleotides were used in convergent syntheses.³ Small lysine dendrimers have also been a support for the grafting of peptides,⁴ carboranes and peptides,⁵ or α -thiosialosides⁶ onto the surface, whereas poly(ethylene oxide) has been grafted to the core.⁷ Several antibodies have also been linked to the surface of organic dendrimers such as PAMAM dendrimers.⁸

All the above-mentioned papers deals with the use of "oligomeric" amino acids; in contrast, only one series of reports concerns the synthesis of dendrimers possessing monomeric amino acids on the surface. They were obtained by the modification of poly (propylene imine) dendrimer end-groups with bulky amino acids, which resulted in a "dendritic box" able to encapsulate small molecules.⁹ We recently described the synthesis of phosphorus containing dendrimers possessing either PCl_2 or aldehyde end-groups¹⁰ and the grafting on the surface of various types of functional groups.¹¹ Pursuing our investigations in the field of functionalized dendrimers, it appeared interesting to try to graft natural amino acids onto the surface. Amino acid could be grafted directly by a Schiff reaction with the aldehyde end-groups, but the resulting imine bonds would be too sensitive to hydrolysis. In order to get amino acids firmly bounded to the dendrimers, we decided to use the Horner-Wadsworth-Emmons reaction¹² which creates a carbon carbon double bond, starting from the phosphonylated amino acids of general formula $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{S})[\text{amino acid}]$ that we recently described.¹³

To demonstrate the versatility of the Horner-Wadsworth-Emmons reaction applied to dendrimers, we carried out preliminary experiments with the first (**1-[G₁]**), third (**1-[G₃]**), or fourth (**1-[G₄]**) generation of the dendrimer (6, 24, or 48 aldehyde end-groups, respectively) and with the salts of the ester, phosphonate, thioamide, and carboxylic acid derivatives of phosphonates **2a-e**. Subsequent reactions were carried out with the salts of the amino acid derivatives of phosphonates **2f-i**. Two different synthetic procedures have been applied,

depending on the absence or presence of carboxylic acid on compounds **2**. In the former case, one equivalent of sodium hydride is added to the phosphonates **2a-d** to afford the corresponding phosphonate salts. Then, the dendrimer is added to this salt, used *in situ* and stirred overnight. All these experiments are carried out with the first generation of the dendrimer **1-[G₁]** (Scheme 1). This procedure affords dendrimers **3a-[G₁]** – **3d-[G₁]** in quantitative yield as crude products, and in moderate yield after workup (see Table 1).

All these compounds have been characterized by ³¹P, ¹H, and ¹³C NMR (Table 1), IR, and elemental analyses. The reaction induces a slight deshielding of the signal corresponding to the external phosphorus (P₁) of the dendrimer, from 60.1 ppm for **1-[G₁]** to 60.9-61.4 ppm for **3a-[G₁]** – **3d-[G₁]**. Furthermore, the formation of the carbon carbon double bond is unambiguously proved by the total disappearance of the aldehyde signals on ¹H and ¹³C NMR, and IR spectra, and by the appearance of new signals corresponding to the HC=CH linkage. Indeed, two new doublets appears in the ¹H NMR spectrum of compound **3a-[G₁]** at $\delta = 6.34$ and 7.61 ppm (³J_{HH} = 16 Hz), corresponding to CH=CH-CO and CH=CH-CO, respectively. The value of the coupling constant indicates a *E*-configuration for all the HC=CH linkages. The formation of the alkene moieties is also confirmed by the ¹³C NMR spectrum, with the appearance of two singlets at $\delta = 118.4$ (CH=CH-CO) and 143.3 ppm (CH=CH-CO). A similar trend is observed for dendrimer **3b-[G₁]** which possesses six unsaturated phosphonate functions. In this case, the ¹H NMR spectrum is slightly complicated by the presence of the phosphonate moieties. Indeed, the signal corresponding to CH=CH-P(O) appears as a doublet of doublet, with two equivalent coupling constants ($\delta = 6.15$ ppm, ²J_{HP} = ³J_{HH} = 17.3 Hz), whereas the signal corresponding to CH=CH-P(O) appears as a single doublet ($\delta = 7.47$ ppm, ³J_{HH} = 17.3 Hz). The formation of the carbon carbon double bond is also demonstrated by the presence of two doublets in the ¹³C NMR spectrum at $\delta = 113.9$ ppm (¹J_{CP} = 191 Hz) for CH=CH-P(O) and $\delta = 147.3$ ppm (²J_{CP} = 7 Hz) for CH=CH-P(O).

The above mentioned data indicate for both compounds **3a-[G₁]** and **3b-[G₁]** the unique formation of the *E* isomer of the double bond. A different behaviour is observed for compounds **3c-[G₁]** and **3d-[G₁]**. Indeed, beside the expected signals corresponding to the *E* isomers, several other signals appear in the ¹H and ¹³C NMR spectra of both compounds, as already

observed in some cases for alkene bonds obtained by Wittig reactions on dendrimers.^{11c} For example, the ¹H NMR spectrum of **3c**-[**G**₁] displays a AB system at $\delta = 6.20$ and 6.26 ppm, with $^3J_{\text{HH}} = 12.0$ Hz. The smaller value of the coupling constant and the shielding of the signals indicate the formation of the *Z* isomer.¹³ Integration of these signals compared to that of the *E* isomer gives approximately 10/90 for the *Z/E* ratio. Both isomers are also detected on the ¹³C NMR spectrum of **3c**-[**G**₁]. The signal corresponding to the *Z* isomer appears at higher field than for the *E* isomer ($\delta = 124.9$ and 126.0 ppm for *Z* and *E* CH=CH-C(S), respectively; $\delta = 128.0$ and 140.4 ppm for *Z* and *E* CH=CH-C(S), respectively). The same behaviour is observed for dendrimer **3d**-[**G**₁]. In this case, integration of the *Z* and *E* signals of the alkene bond in ¹H NMR indicates the formation of a higher proportion of *Z* isomer (30/70 for the *Z/E* ratio). Obviously, isomers of compounds **3c**-[**G**₁] and **3d**-[**G**₁] cannot be purified, as both *E* and *Z* isomers are linked to the same dendrimer.

All these experiments have been extended to the third **1**-[**G**₃] or fourth **1**-[**G**₄] generation of the dendrimer which possesses 24 or 48 aldehyde end groups (Scheme 2, Figure 1). These reactions are slightly slower than for the first generation and need two days at room temperature to go to completion. The reactions are monitored by ³¹P NMR which indicates the total disappearance of the signal of the external phosphorus (P_3 : $\delta = 60.1$ ppm for **1**-[**G**₃]; P_4 : $\delta = 60.0$ ppm for **1**-[**G**₄]) on behalf of a new singlet slightly deshielded (P_3 : $\delta = 60.9$ ppm for **3d**-[**G**₃]; P_4 : $\delta = 61.0$ - 61.4 ppm for **3a**-[**G**₄] – **3c**-[**G**₄]). The reaction of all the aldehyde groups is confirmed by ¹H and ¹³C NMR, and IR spectra with the total disappearance of the signals corresponding to these linkages. Furthermore, beside the signals corresponding to the skeleton of the dendrimer, ¹H and ¹³C NMR spectra display signals characteristic of the CH=CH-R moieties, as already seen for the first generation (Table 1). Dendrimers **3a**-[**G**₄] and **3b**-[**G**₄] possess a all-*E* configuration, as noted for **3a**-[**G**₁] and **3b**-[**G**₁], whereas a mixture of *E* and *Z* configuration is observed for **3c**-[**G**₄] and **3d**-[**G**₃]. The *Z/E* ratio seems to depend on the generation used for compounds **3d** (*Z/E* \cong 30/70 for **3d**-[**G**₁]; 50/50 for **3d**-[**G**₃]) but not for compounds **3c** (*Z/E* \cong 10/90 for **3c**-[**G**₁] and **3c**-[**G**₄]). It must be noted that the precision of the technique used, ¹H NMR, is hampered by the occurrence of signals of

the *E* CH=CH linkage within the area corresponding to the C₆H₄ and CH=N signals of the dendrimer skeleton.

After these preliminary experiments, we have tried to apply the same procedures to phosphonates bearing acid or amino acid substituents **2e-i**. In these cases, two equivalents of base are required: one reacts with the carboxylic acid, the other creates the carbanion α to the phosphonate. A first attempt was carried out with phosphonate **2f** (glycine derivative) and two equivalents of sodium hydride. The reaction with the first generation is slow and necessitates to be heated. In this case, the monitoring by ³¹P NMR indicates the partial cleavage of the skeleton of the dendrimer, thus compound **3f-[G₁]** is extremely difficult to isolate in these conditions. We encountered analogous problems with the salt of phosphonate **2g** (alanine derivative) obtained by reaction with one equivalent of triethylamine, and one equivalent of sodium hydride. To overcome these problems, we decided to use two equivalents of butyllithium, which should give a more reactive carbanion. The reaction is carried out first with dendrimer **1-[G₁]** and the simplest acid derivative of phosphonate **2e** in tetrahydrofuran (Scheme 3). A yellow precipitate is observed when the reaction has gone to completion, and no phosphorus derivative remains in solution. The precipitate is solubilized in water and checked by ³¹P NMR. It contains the water soluble dendrimer with six CH=CH-COOLi end groups, and (EtO)₂P(O)OLi. In order to separate the dendrimer from (EtO)₂P(O)OLi, formic acid is slowly added. A precipitate appears rapidly, and the mixture is acidified up to pH = 3-4. This value allows to maximize the amount of dendrimer **3e-[G₁]** which precipitates; lower pH values precipitates also (EtO)₂P(O)OH and induces the cleavage of the skeleton of the dendrimer. Compound **3e-[G₁]** thus obtained is soluble in several organic solvents such as tetrahydrofuran. This compound is characterized by all the techniques already used for the other dendrimers, and particularly by ¹H NMR, which indicates the formation of only one isomer for all the CH=CH bonds. The value of the chemical shift (two doublets at δ = 6.56 and 7.74 ppm) and the value of the coupling constant (³J_{HH} = 16 Hz) correspond to the *E* isomer.

The use of two equivalents of butyl lithium has been extended then to the reaction involving the phosphonate derivatives of glycine (**2f**), L-alanine (**2g**), L-phenylalanine (**2h**), L-methionine

(2i), and dendrimer **1-[G₁]** (Scheme 3). In all cases, water soluble dendrimers with HC=CHC(S)NHCHR'COOLi end groups (R' = H, Me, CH₂Ph, CH₂CH₂SMe) are obtained but not isolated, then acidified to give in moderate yields dendrimers **3f-[G₁]** – **3i-[G₁]**. These dendrimers which possess six HC=CHC(S)NHCHR'COOH end groups are soluble in THF. ¹H and ¹³C NMR spectra of compounds **3f-[G₁]** – **3i-[G₁]** indicate in all cases the formation of both *E* and *Z* isomers of the carbon carbon double bonds. The presence of isomers is also detected on the level of N-H groups. The *Z/E* ratio, measured by integration of ¹H NMR spectra, is similar in all cases, roughly 10/90 (see Table 1 and Scheme 3). These compounds are stable in solution or as powders, provided the solvent is not totally eliminated. Indeed, the total removal of last traces of solvents causes the dendrimer to become impossible to solubilize again in organic solvents or in water. This phenomenon, which has not been observed for dendrimers **3a-e**, is presumably due to the formation of inter- and intra-molecular hydrogen bonds between NH and COOH groups.

The extension of the reaction to the third and fourth generation of the dendrimer has been carried out with the dilithium salts of phosphonates **2e-i** in THF (Scheme 3). The dendrimer precipitates very often before the reaction has gone to completion. This can be seen easily when a sample of this precipitate is dissolved in water and checked by ³¹P NMR. Beside the signal at δ = 61.0-61.4 ppm, corresponding to the phosphorus of the external layer (P₃ or P₄) linked to two OC₆H₄CH=CHC(S)NHCHR'COOLi moieties, another singlet at δ = 60.5 ppm, corresponding to the external phosphorus linked to one OC₆H₄CHO and one OC₆H₄CH=CHC(S)NHCHR'COOLi moieties is observed. However, the reaction can be continued in heterogeneous conditions. In these conditions, the reaction rate is slower, but nevertheless the reaction goes to completion after several days. A work up similar to the one used for the first generation allows to isolate dendrimers **3e-[G₃]**, **3f-[G₄]**, **3g-[G₃]**, **3h-[G₄]**, and **3i-[G₄]** (Figure 1). The absence of any signal corresponding to the CHO groups in ¹H and ¹³C NMR, as well as in IR spectra confirms that all the branches of the dendrimer have reacted. ¹H NMR spectra indicate the formation of both *E* and *Z* isomers of the CH=CH bond for all the dendrimers having thioamide functions. A higher proportion of *Z* isomer is generally observed for the third and fourth generation than for the first generation (compare *Z/E* = 15/85

for **3g**-[G₃], **3i**-[G₄], and 35/65 for **3f**-[G₄], **3h**-[G₄], to $Z/E = 10/90$ for **3f**-[G₁] – **3i**-[G₁]).

The reasons of the variations observed for the Z/E ratio, particularly for the amino acid derivatives which differ only by one substituent in γ position relative to the reactive site (compounds **2f-i**) are not fully understood. One may presume that steric crowding plays a role, as the Z proportion increases in most cases with the generation. Electronic effects also influence the Z/E ratio, as Z isomers are observed only when thioamide substituents are linked to the phosphonate (compounds **2c-d**, **2f-i**). Furthermore, the nature of the base used to generate the phosphonate salt is also an important factor. Indeed, the Z/E ratio measured for dendrimer **3g**-[G₁] generated from the reaction of **2g** with one equivalent of triethylamine and one equivalent of sodium hydride is 30/70, whereas the Z/E ratio measured for the same dendrimer generated from the reaction of **2g** with two equivalents of butyllithium is 10/90.

The presence of chiral amino acids on the surface of dendrimers could have induced interesting optical rotation properties, as we have already shown for dendrimers terminated with chiral methyl benzyl amine.¹⁴ Unfortunately, the formation of both E and Z isomers of the double bond for compounds **3f**-[G_n] – **3i**-[G_n] precludes any study in this field. However, this paper demonstrates that the use of the Horner-Wadsworth-Emmons reaction constitutes a new way of grafting various functional groups on the surface of dendrimers.

Experimental Section

General

All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. ¹H, ³¹P and ¹³C NMR spectra were recorded on Bruker AC 80 and AC 200 spectrometers. ³¹P NMR chemical shifts are reported in ppm relative to 85% H₃PO₄. The numbering used for NMR is depicted on Scheme 4. Dendrimers **1**-[G₁] – **1**-[G₄]¹⁰ and phosphonates **2c**, **2d**, **2f-2i**¹³ are synthesized according to published procedures. Phosphonates **2a**, **2b**, **2e** are purchased from Aldrich. Satisfactory elemental analyses were obtained for all new compounds.

General procedure for the synthesis of dendrimers 3a-[G₁] – 3d-[G₁], 3d-[G₃], and 3a-[G₄] – 3c-[G₄]:

To a solution of phosphonate **2a-d** (0.420 mmol) in THF (5 mL) was added NaH (0.420 mmol, 10 mg). The resulting mixture was stirred for 30 min. at room temperature. After evolution of H₂, a solution of dendrimer **3-[G_n]** (**n** = 1, 0.070 mmol, 100 mg; **n** = 3, 0.0175 mmol, 130 mg; **n** = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at room temperature and stirred overnight (**1-[G₁]**) or for two days (**1-[G₃]**, **1-[G₄]**), then the solution was evaporated to dryness. The resulting powder was washed with water to eliminate (EtO)₂P(O)ONa and to afford compounds **3a-[G₁]**, **3b-[G₁]**, **3a-[G₄]**, and **3b-[G₄]** which were obtained as white powders. Compounds **3c-[G₁]**, **3d-[G₁]**, **3c-[G₄]**, and **3d-[G₃]** were recovered as yellow powders after purification by column chromatography on silica gel (eluent THF).

General procedure for the synthesis of dendrimers with carboxylic acid end groups 3e-[G₁] – 3i-[G₁], 3e-[G₃], 3g-[G₃], 3f-[G₄], 3h-[G₄], and 3i-[G₄]:

To a solution of phosphonate (0.420 mmol) in THF (5 mL) were added 2 equivalents of butyllithium 1.6 M (0.840 mmol, 530 μ L) at - 60°C. The resulting solution was stirred for 30 min. at this temperature. A solution of dendrimer **1-[G_n]** (**n** = 1, 0.070 mmol, 100 mg; **n** = 3, 0.0175 mmol, 130 mg; **n** = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at this temperature, then the mixture was allowed to warm up to room temperature and stirred overnight (**1-[G₁]**) or for two days (**1-[G₃]**, **1-[G₄]**). A yellow precipitate appeared. A small sample of the precipitate was dissolved in water and checked by ³¹P NMR. If only one signal appeared for the phosphorus of the external layer (P₁ for [**G₁]**, P₃ for [**G₃]**, P₄ for [**G₄]**), all the precipitate was isolated by centrifugation and dissolved in water. If two signals appeared for the phosphorus of the external layer, the reaction has not gone to completion. In this case, the sample was thrown away and a small amount of butyllithium (10 % of the initial quantity) was added to the heterogeneous mixture, which was stirred for two days more. Then, another small sample of the precipitate was taken, dissolved in water and

checked by ^{31}P NMR, to verify that the reaction has gone to completion. The precipitate was then isolated by centrifugation and dissolved in water. In all cases, formic acid was added dropwise to lower the pH from 9 to 3-4 (the use of more acidic conditions induced the cleavage of the dendrimer). A yellow precipitate appeared at acidic pH; it was recovered by centrifugation. This precipitate was then washed with ether and afforded dendrimers **3e-[G₁]** – **3i-[G₁]**, **3e-[G₃]**, **3f-[G₄]**, **3g-[G₃]**, **3h-[G₄]**, and **3i-[G₄]** as yellow powders.

References

- (1) For reviews on dendrimers see for example : (a) Tomalia, D. A.; Naylor, A. M.; Goddard III, W. A. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.
 (b) Tomalia, D. A.; Durst, H. D. in *Topics in Current Chemistry*, Vol. 165, Weber, E. Ed.; Springer Verlag: Berlin, Heidelberg, **1993**; p 193.
 (c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem.* **1994**, *106*, 2507; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2413.
 (d) Moorefield, C. N.; Newkome, G. R. in *Advances in Dendritic Molecules*, Vol. 1, Newkome, G. R. Ed.; JAI Press: Greenwich CT, USA **1994**, p 1.
 (e) Caminade, A.-M.; Majoral, J.-P. *Main Group Chemistry News* **1995**, *3*, 14.
 (f) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 876.
 (g) Majoral, J.-P.; Caminade, A.-M. *Act. Chim.* **1996**, *4*, 13.
 (h) Fréchet, J. M. J.; Hawker, C. J. in *Comprehensive Polymer Science*, 2nd suppl., **1996**, chap. 3, pp 71.
 (i) Newkome, G.R.; Moorefield, C.N.; Vögtle, F. in *Dendritic Molecules*, VCH, Weinheim, **1996**
- (2) (a) Denkewalter, R. G.; Kolc, J. F.; Lukasavage, W. J.; C. A. **1984**, 100, 103907p (US patent 4,410,688).
 (b) Denkewalter, R. G.; Kolc, J.; Lukasavage, W. J. C. A. **1985**, 102, 79324q (US patent 4,289,872).

- (3) Hudson, R. H. E., Damha, M. J., *J. Am. Chem. Soc.* **1993**, 115, 2119.
- (4) (a) Posnett, D. N.; McGrath, H.; Tam, J. P. *J. Biol. Chem.* **1988**, 263, 1719.
(b) Rao, C.; Tam, J. P. *J. Am. Chem. Soc.* **1994**, 116, 6975.
(c) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, 117, 14.
(d) Zhang, L.; Tam, J. P. *J. Am. Chem. Soc.* **1997**, 119, 2363.
- (5) Qualmann, B.; Kessels, M. M.; Musiol, H. J.; Sierralta, W. D.; Jungblut, P. W.; Moroder, L. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 909.
- (6) Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869.
- (7) Chapman, T. M.; Hillyer, G. L.; Mahan, E. J.; Shaffer, K. A. *J. Am. Chem. Soc.* **1994**, 116, 11195.
- (8) (a) Barth, R. F.; Adams, D. M.; Soloway, A. H.; Alam, F.; Darby, M. V. *Bioconjugate Chem.* **1994**, 5, 58.
(b) Capala, J.; Barth, R. F.; Bendayan, M.; Lauzon, M.; Adams, D. M.; Soloway, A. H.; Fenstermaker, R. A.; Carlsson, J. *Bioconjugate Chem.* **1996**, 7, 7.
- (9) (a) Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, 266, 1226.
(b) Jansen, J. F. G. A.; Peerlings, H. W. I.; de Brabander-van den Berg, E. M. M., Meijer, E. W. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1206.
(c) Jansen, J. F. G. A.; Meijer, E. W.; de Brabander-van den Berg, E. M. M. *J. Am. Chem. Soc.* **1995**, 117, 4417.
(d) Jansen, J. F. G. A.; Jansen, R. A. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Adv. Mater.* **1995**, 7, 561.
(e) Stevelmans, S.; Van Hest, J. C. M.; Jansen, J. F. G. A.; Van Boxtel, D. A. F. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, 118, 7398.
- (10) (a) Launay, N.; Caminade, A.M.; Lahana, R.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1589.
(b) Galliot C.; Prévoté D.; Caminade A.M.; Majoral J.P. *J. Am. Chem. Soc.* **1995**, 117, 5470.

- (c) Launay N.; Caminade A.M.; Majoral J.P. *J. Organomet. Chem.* (in press).
- (11) (a) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 3282.
(b) Slany, M.; Bardaji, M.; Casanove, M. J.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764.
(c) Launay, N.; Slany, M.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* **1996**, *61*, 3799.
(d) Lartigue, M.L.; Slany, M.; Caminade, A.M.; Majoral, J.P. *Chem. Eur. J.* **1996**, *2*, 1417.
(e) Slany, M.; Caminade, A.M.; Majoral, J.P. *Tetrahedron Lett.* **1996**, *37*, 9053.
(f) Majoral J.P.; Caminade A.M. *Actu. Chim.* **1996**, *13*.
(g) Bardaji, M.; Kustos, M.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *Organometallics* **1997**, *16*, 403.
(h) Slany M.; Bardaji M.; Caminade A.M.; Chaudret B.; Majoral J.P. *Inorg. Chem.* **1997**, *36*, 1939.
- (12) For reviews on the Horner-Wadsworth-Emmons reaction see for example (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.
(b) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863.
- (13) Le Roy-Gourvennec, S.; Masson, S. *Synthesis*, **1995**, 1393.
- (14) Lartigue, M.L.; Caminade, A.M.; Majoral, J.P. (to be published)

Acknowledgements

Thanks are due to CNRS and US-Navy for financial support.

Table 1:

1

3	Yield %	³¹ P NMR δ (THF)	¹ H NMR, δ, J (Hz)	¹³ C { ¹ H} NMR, δ, J (Hz)
a-[G₁]	35	51.6 (P ₀),	^a 1.31 (t, J = 7.0, 18H, CH ₂ -CH ₃), 3.37 (d, J = 10.5, 9H,	^a 14.3 (s, CH ₂ -CH ₃), 33.0 (d, J = 14, P ₁ -N-CH ₃), 60.5 (s,
		60.9 (P ₁)	P ₁ -N-CH ₃), 4.24 (q, J = 7.0, 12H, CH ₂ -CH ₃), 6.34 (d, J =	CH ₂ -CH ₃), 118.4 (s, CH=CH-CO), 121.5 (d, J = 4, C ₀ ²), 121.9
			16.0, 6H, CH=CH-CO), 7.22 (d, J = 8.1, 12H, C ₁ ² H),	(d, J = 4, C ₁ ²), 128.5 (s, C ₀ ³), 129.4 (s, C ₁ ³), 131.9 (s, C ₁ ⁴),
			7.29 (d, J = 8.3, 6H, C ₀ ² H), 7.47 (d, J = 8.0, 12H, C ₁ ³ H),	132.6 (s, C ₀ ⁴), 138.8 (d, J = 14, CH=N), 143.3 (s, CH=CH-
		7.49 (d, J = 8.1, 6H, C ₀ ² H), 7.61 (d, J = 16.0, 6H,	CO), 151.2 (d, J = 8, C ₀ ¹), 151.9 (d, J = 6, C ₁ ¹), 166.8 (s,	
		CH=CH-CO), 7.72 (s, 3H, CH=N)	C=O)	
a-[G₄]	20	51.7 (P ₀),	^a 1.25 (m, 144H, CH ₂ -CH ₃), 3.30 (d, J = 8.6, 135H, P _{1,4} -	^a 14.1 (s, CH ₂ -CH ₃), 32.8 (d, J = 13, P _{1,4} -N-CH ₃), 60.4 (s,
		61.0 (P ₄),	N-CH ₃), 4.17 (m, 96H, CH ₂ -CH ₃), 6.30 (d, J = 15.9,	CH ₂ -CH ₃), 118.1 (s, CH=CH-CO), 121.7 (d, J = 4, C ₀ ² , C ₁ ² ,
		61.6 (P ₃),	48H, CH=CH-CO), 7.00-7.60 (m, 465H, C ₆ H ₄ , CH=N,	C ₂ ² , C ₃ ² , C ₄ ²), 128.1 (br s, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³), 129.2 (s,
		62.0 (P ₂),	CH=CH-CO)	C ₄ ³), 131.6 (br s, C ₄ ⁴), 131.8 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴), 138.5-
		62.3 (P ₁)		139.0 (m, CH=N), 143.1 (s, CH=CH-CO), 150.5-150.7 (m,
			166.6 (s, C=O)	
b-[G₁]	35	18.1	^a 1.31 (t, J = 7.1, 36H, CH ₂ -CH ₃), 3.35 (d, J = 10.6, 9H,	^a 16.2 (d, J = 7, CH ₂ -CH ₃), 32.9 (d, J = 13, P ₁ -N-CH ₃), 61.7
		(P(O)),	P ₁ -N-CH ₃), 4.01-4.16 (m, 24H, CH ₂ -CH ₃), 6.15 (dd, J =	(d, J = 5, CH ₂ -CH ₃), 113.9 (d, J = 191, CH=CH-P(O)), 121.4
		51.7 (P ₀),	J = 17.3, 6H, CH=CH-P(O)), 7.18-7.77 (m, 39H, C ₆ H ₄ ,	(d, J = 4, C ₀ ²), 121.7 (d, J = 5, C ₁ ²), 128.3 (s, C ₀ ³), 128.9 (s,
		61.1 (P ₁)	CH=N), 7.47 (d, J = 17.3, 6H, CH=CH-P(O))	C ₁ ³), 131.8 (s, C ₀ ⁴), 132.3 (d, J = 4, C ₁ ⁴), 138.7 (d, J = 14,
				CH=N), 147.3 (d, J = 7, CH=CH-P(O)), 151.0 (d, J = 7, C ₀ ¹),
				151.6 (d, J = 7, C ₁ ¹)

Table 1 (Continued):

2

b-[G₄]	37	18.1 (P(O)), 51.7 (P ₀), 61.2 (P ₄), 61.6 (P ₃), 61.7 (br s, P ₂ , P ₁)	^a 1.30 (t, <i>J</i> = 6.8, 288H, CH ₂ -CH ₃), 3.31 (br d, <i>J</i> = 8.4, 135H, P _{1,4} -N-CH ₃), 4.00-4.10 (m, 192H, CH ₂ -CH ₃), 6.13 (dd, <i>J</i> = <i>J</i> = 17.5, 48H, CH=CH-P(O)), 7.19-7.67 (m, 465H, C ₆ H ₄ , CH=N, CH=CH-P(O))	^a 16.2 (d, <i>J</i> = 7, CH ₂ -CH ₃), 32.8 (br d, <i>J</i> = 13, P _{1,4} -N-CH ₃), 61.7 (d, <i>J</i> = 5, CH ₂ -CH ₃), 113.9 (d, <i>J</i> = 192, CH=CH-P(O)), 121.7 (br d, <i>J</i> = 4, C ₀ ² , C ₁ ² , C ₂ ² , C ₃ ² , C ₄ ²), 128.2 (br s, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³), 128.9 (s, C ₄ ³), 131.8 (d, <i>J</i> = 4, C ₄ ⁴), 132.3 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴), 139.0 (br d, <i>J</i> = 14, CH=N), 147.3 (d, <i>J</i> = 5, CH=CH-P(O)), 151.2 (br d, <i>J</i> = 6, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 151.6 (d, <i>J</i> = 7, C ₄ ¹)
c-[G₁]	25	51.6 (P ₀), 61.4 (P ₁)	^a 1.72 (br s, 36H, N-CH ₂ -(CH ₂) ₃), 3.35 (d, <i>J</i> = 10.6, 9H, P ₁ -N-CH ₃), 3.73 (br s, 12H, N-CH ₂), 4.28 (br s, 12H, N-CH ₂), 6.20 (d, <i>J</i> = 12.0, (6*0.1)H, CH=CH-C(S) ^Z), 6.26 (d, <i>J</i> = 12.0, (6*0.1)H, CH=CH-C(S) ^Z), 7.14 (d, <i>J</i> = 15.0, (6*0.9)H, CH=CH-C(S) ^E), 7.50 (d, <i>J</i> = 15.3, (6*0.9)H, CH=CH-C(S) ^E), 7.11-7.75 (m, 39H, C ₆ H ₄ , CH=N)	^a 24.0, 24.6, 25.3 [3s, N-CH ₂ -(CH ₂) ₃], 32.9 (d, <i>J</i> = 13, P ₁ -N-CH ₃), 51.5 (s, N-CH ₂), 51.6 (s, N-CH ₂), 121.4 (d, <i>J</i> = 4, C ₀ ²), 121.6 (d, <i>J</i> = 5, C ₁ ²), 124.9 (s, CH=CH-C(S) ^Z), 126.0 (s, CH=CH-C(S) ^E), 128.0 (s, CH=CH-C(S) ^Z), 128.3 (s, C ₀ ³), 128.6 (s, C ₁ ³), 132.4 (s, C ₀ ⁴), 132.8 (s, C ₁ ⁴), 138.5 (d, <i>J</i> = 14, CH=N), 140.4 (s, CH=CH-C(S) ^E), 150.9 (d, <i>J</i> = 7, C ₁ ¹), 151.0 (d, <i>J</i> = 9, C ₀ ¹), 193.9 (s, C=S ^E), 194.6 (s, C=S ^Z)
c-[G₄]	25	51.6 (P ₀), 61.4 (P ₄), 61.8 (br s, P ₁ , P ₂ , P ₃)	^a 1.65 (br s, 288H, N-CH ₂ -(CH ₂) ₃), 3.28 (d, <i>J</i> = 8.9, 135H, P _{1,4} -N-CH ₃), 3.73 (br s, 96H, N-CH ₂), 4.20 (br s, 96H, N-CH ₂), 6.20 (br s, (96*0.1)H, CH=CH-C(S), CH=CH-C(S) ^Z), 6.91-7.65 (m, 369H, C ₆ H ₄ , CH=N), 6.94 (d, <i>J</i> = 15.0, (48*0.9)H, CH=CH-C(S) ^E), 7.45 (d, <i>J</i> = 15.0, (48*0.9)H, CH=CH-C(S) ^E)	^a 24.2, 25.4, 26.8 [3s, N-CH ₂ -(CH ₂) ₃], 32.9 (m, P _{1,4} -N-CH ₃), 51.6 (s, N-CH ₂), 51.8 (s, N-CH ₂), 121.7 (br s, C ₀ ² , C ₁ ² , C ₂ ² , C ₃ ² , C ₄ ²), 125.5 (s, CH=CH-C(S) ^Z), 126.1 (s, CH=CH-C(S) ^E), 128.3 (br s, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³), 128.8 (s, C ₄ ³), 129.0 (s, CH=CH-C(S) ^Z), 132.1 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴), 132.9 (s, C ₄ ⁴), 140.6 (s, CH=CH-C(S) ^E), 138.9-139.2 (m, CH=N), 151.0 (d, <i>J</i> = 7, C ₄ ¹), 151.3 (d, <i>J</i> = 6, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 193.9 (s, C=S ^Z), 194.6 (s, C=S ^E)

Table 1 (Continued):

d-[G₁]	20	51.6 (P ₀), 61.0 (P ₁)	<i>b</i> 3.22 (d, <i>J</i> = 4.5, 18H, NH-CH ₃), 3.46 (d, <i>J</i> = 10.6, 9H, P ₁ -N-CH ₃), 6.29 (d, <i>J</i> = 12.3, (6*0.3)H, CH=CH-C(S) ^Z), 6.34 (d, <i>J</i> = 12.3, (6*0.3)H, CH=CH-C(S) ^Z), 6.91 (d, <i>J</i> = 15.3, (6*0.7)H, CH=CH-C(S) ^E), 7.23 (d, <i>J</i> = 8.5, 6H, C ₀ ² H), 7.43 (d, <i>J</i> = 8.1, 12H, C ₁ ² H), 7.60 (d, <i>J</i> = 8.1, 12H, C ₁ ³ H), 7.78 (d, <i>J</i> = 15.3, (6*0.7)H, CH=CH-C(S) ^E), 7.88 (d, <i>J</i> = 8.7, 6H, C ₀ ³ H), 7.90 (s, 3H, CH=N), 9.20 (m, (6*0.3)H, NH ^Z), 9.33 (m, (6*0.7)H, NH ^E)	<i>b</i> 34.0 (s, NH-CH ₃), 34.5 (d, <i>J</i> = 13, P ₁ -N-CH ₃), 123.5 (d, <i>J</i> = 4, C ₀ ²), 123.8 (d, <i>J</i> = 3, C ₁ ²), 128.0 (s, CH=CH-C(S) ^Z), 130.4 (s, C ₀ ³), 130.9 (s, C ₁ ³), 132.0 (s, CH=CH-C(S) ^E), 134.0 (s, CH=CH-C(S) ^Z), 135.0 (s, C ₁ ⁴), 135.3 (s, C ₀ ⁴), 140.6 (s, CH=CH-C(S) ^E), 141.5 (d, <i>J</i> = 12, CH=N), 152.2 (d, <i>J</i> = 7, C ₀ ¹), 153.4 (d, <i>J</i> = 8, C ₁ ¹), 196.8 (s, C=S ^Z), 199.3 (s, C=S ^E)
d-[G₃]	20	51.6 (P ₀), 60.9 (P ₃), 61.4 (br s, P ₁ , P ₂)	<i>b</i> 3.30 (d, <i>J</i> = 4.4, 72H, NH-CH ₃), 3.52 (d, <i>J</i> = 9.9, 63H, P ₁₋₃ -N-CH ₃), 6.36 (d, <i>J</i> = 12.8, (24*0.5)H, CH=CH-C(S) ^Z), 6.43 (d, <i>J</i> = 12.8, (24*0.5)H, CH=CH-C(S) ^Z), 6.91-8.00 (m, 201H, C ₆ H ₄ , CH=N), 6.99 (d, <i>J</i> = 15.5, (24*0.5)H, CH=CH-C(S) ^E), 7.72 (d, <i>J</i> = 15.5, (24*0.5)H, CH=CH-C(S) ^E), 9.23 m, (24*0.5)H, NH ^Z), 9.33 (m, (24*0.5)H, NH ^E)	<i>b</i> 34.0 (s, NH-CH ₃), 34.4 (d, <i>J</i> = 13, P ₁₋₃ -N-CH ₃), 123.1 (br s, C ₀ ² , C ₁ ² , C ₂ ²), 123.8 (br s, C ₃ ²), 128.0 (s, CH=CH-C(S) ^Z), 129.4 (s, C ₂ ³), 130.2 (br s, C ₀ ³ , C ₁ ³), 130.9 (s, C ₃ ³), 131.9 (s, CH=CH-C(S) ^E), 134.0 (s, CH=CH-C(S) ^Z), 134.6 (s, C ₃ ⁴), 135.0 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴), 140.6 (s, CH=CH-C(S) ^E), 141.3-141.9 (m, CH=N), 153.6 (d, <i>J</i> = 5, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 196.9 (s, C=S ^Z), 199.3 (s, C=S ^E)
e-[G₁]	15	51.6 (P ₀), 61.0 (P ₁)	<i>b</i> 3.53 (d, <i>J</i> = 10.7, 9H, P ₁ -N-CH ₃), 6.56 (d, <i>J</i> = 16.0, 6H, CH=CH-CO), 7.41 (d, <i>J</i> = 7.4, 12H, C ₁ ² H), 7.49 (d, <i>J</i> = 8.5, 6H, C ₀ ² H), 7.74 (d, <i>J</i> = 8.6, 12H, C ₁ ³ H), 7.74 (d, <i>J</i> = 16.0, 6H, CH=CH-CO), 7.95 (d, <i>J</i> = 8.6, 6H, C ₀ ³ H), 7.98 (s, 3H, CH=N), 8.50 (br s, 6H, OH)	<i>b</i> 32.9 (d, <i>J</i> = 13, P ₁ -N-CH ₃), 119.3 (s, CH=CH-CO), 121.9 (d, <i>J</i> = 4, C ₀ ²), 122.2 (d, <i>J</i> = 5, C ₁ ²), 128.8 (s, C ₀ ³), 129.8 (s, C ₁ ³), 132.7 (s, C ₁ ⁴), 133.6 (s, C ₀ ⁴), 139.9 (d, <i>J</i> = 14, CH=N), 143.4 (s, CH=CH-CO), 151.8 (d, <i>J</i> = 7, C ₀ ¹), 152.5 (d, <i>J</i> = 8, C ₁ ¹), 167.4 (s, CO)

Table 1 (Continued):

4

e-[G₃]	15	51.8 (P ₀), 61.0 (P ₃), 61.5 (P ₂), 61.9 (P ₁)	<i>b</i> 3.53 (d, <i>J</i> = 10.2, 63H, P ₁₋₃ -N-CH ₃), 6.60 (d, <i>J</i> = 16.0, 24H, CH=CH-CO), 7.25-7.96 (m, 201H, C ₆ H ₄ , CH=N, OH), 7.77 (d, <i>J</i> = 16.0, 24H, CH=CH-CO)	<i>b</i> 32.9 (d, <i>J</i> = 13, P ₁₋₃ -N-CH ₃), 119.3 (s, CH=CH-CO), 122.2 (d, <i>J</i> = 4, C ₀ ² , C ₁ ² , C ₂ ² , C ₃ ²), 128.5 (s, C ₀ ³), 128.6 (br s, C ₁ ³ , C ₂ ³), 129.8 (s, C ₃ ³), 132.6 (s, C ₃ ⁴), 133.0 (br s, C ₂ ⁴), 133.1 (s, C ₁ ⁴), 133.6 (s, C ₀ ⁴), 140.2 (d, <i>J</i> = 13, CH=N), 143.5 (s, CH=CH-CO), 152.1 (d, <i>J</i> = 6, C ₀ ¹ , C ₁ ¹ , C ₂ ¹), 152.5 (d, <i>J</i> = 7, C ₃ ¹), 167.4 (s, CO)
f-[G₁]	25	51.6 (P ₀), 61.0 (P ₁)	<i>b</i> 3.52 (d, <i>J</i> = 10.7, 9H, P ₁ -N-CH ₃), 4.43 (d, <i>J</i> = 5.5, 12H, N-CH ₂), 4.60 (d, <i>J</i> = 4.8, 12H, N-CH ₂), 6.35 (d, <i>J</i> = 12.5, (6*0.1)H, CH=CH-C(S) ^Z), 6.44 (d, <i>J</i> = 12.5, (6*0.1)H, CH=CH-C(S) ^Z), 7.17 (d, <i>J</i> = 15.0, (6*0.9)H, CH=CH-C(S) ^E), 7.38 (d, <i>J</i> = 7.7, 12H, C ₁ ² H), 7.48 (d, <i>J</i> = 7.9, 6H, C ₀ ² H), 7.69 (d, <i>J</i> = 8.4, 12H, C ₁ ³ H), 7.90 (d, <i>J</i> = 15.0, (6*0.9)H, CH=CH-C(S) ^E), 7.95 (d, <i>J</i> = 7.7, 6H, C ₀ ³ H), 7.93 (br s, 9H, CH=N, OH), 9.24 (br s, (6*0.9)H, NH ^E), 9.49 (br s, (6*0.1)H, NH ^Z)	<i>b</i> 32.9 (d, <i>J</i> = 12, P ₁ -N-CH ₃), 47.2 (s, N-CH ₂), 121.9 (d, <i>J</i> = 5, C ₀ ²), 122.2 (d, <i>J</i> = 4, C ₁ ²), 127.3 (s, CH=CH-C(S) ^Z), 128.1 (s, CH=CH-C(S) ^E), 128.9 (s, C ₀ ³), 129.5 (s, C ₁ ³), 131.7 (s, CH=CH-C(S) ^Z), 133.5 (s, C ₁ ⁴), 133.7 (s, C ₀ ⁴), 139.9 (d, <i>J</i> = 13, CH=N), 140.4 (s, CH=CH-C(S) ^E), 151.9 (d, <i>J</i> = 9, C ₀ ¹), 152.1 (d, <i>J</i> = 10, C ₁ ¹), 170.3 (s, CO), 195.3 (s, C=S ^E), 196.7 (s, C=S ^Z)
f-[G₄]	10	51.7 (P ₀), 61.0 (P ₄), 61.2 (P ₁ , P ₂), 61.6 (P ₃)	<i>b</i> 3.46 (m, 135H, P ₁₋₄ -N-CH ₃), 4.42 (d, <i>J</i> = 4.2, 96H, N-CH ₂), 4.60 (d, <i>J</i> = 4.2, 96H, N-CH ₂), 6.33 (d, <i>J</i> = 12.5, (48*0.35)H, CH=CH-C(S) ^Z), 6.41 (d, <i>J</i> = 12.5, (48*0.35)H, CH=CH-C(S) ^Z), 7.14 (d, <i>J</i> = 15.2, (48*0.65)H, CH=CH-C(S) ^E), 7.00-7.90 (m, 465H+(48*0.65)H, C ₆ H ₄ , CH=N, CH=CH-C(S) ^E , OH), 9.26 (br s, (48*0.65)H, NH ^E), 9.49 (br s, (48*0.35)H, NH ^Z)	<i>b</i> 32.9 (m, P ₁₋₄ -N-CH ₃), 46.5 (br s, N-CH ₂), 121.6 (br s, C ₀ ² , C ₁ ² , C ₂ ²), 121.9 (br s, C ₃ ²), 122.2 (br s, C ₄ ²), 127.4 (s, CH=CH-C(S) ^Z), 128.4 (s, CH=CH-C(S) ^E), 128.6 (m, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³), 129.5 (br s, C ₄ ³), 131.6 (s, CH=CH-C(S) ^Z), 133.0 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴ , C ₄ ⁴), 140.5 (m, CH=N, CH=CH-C(S) ^E), 150.7 (br s, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 152.0 (d, <i>J</i> = 6, C ₄ ¹), 170.0 (s, CO), 197.5 (s, C=S ^E), 198.4 (s, C=S ^Z)

Table 1 (Continued):

g-[G₁]	43	51.6 (P ₀), 61.3 (P ₁)	<i>b</i> 1.44 (d, <i>J</i> = 7.2, 18H, CH-CH ₃), 3.36 (d, <i>J</i> = 8.6, 9H, P ₁ -N-CH ₃), 5.24 (m, 6H, CH-CH ₃), 6.17 (d, <i>J</i> = 12.3, (6*0.1)H, CH=CH-C(S) ^Z), 6.26 (d, <i>J</i> = 12.3, (6*0.1)H, CH=CH-C(S) ^Z), 6.72-7.83 (m, 45H, C ₆ H ₄ , CH=N, OH), 6.97 (d, <i>J</i> = 15.3, (6*0.9)H, CH=CH-C(S) ^E), 7.75 (d, <i>J</i> = 15.3, (6*0.9)H, CH=CH-C(S) ^E), 9.17 (d, <i>J</i> = 7.4, (6*0.9)H, NH ^E), 9.35 (d, <i>J</i> = 7.4, (6*0.1)H, NH ^Z)	<i>b</i> 17.2 (s, CH-CH ₃), 33.4 (d, <i>J</i> = 13, P ₁ -N-CH ₃), 54.4 (s, CH), 122.0 (d, <i>J</i> = 4, C ₀ ²), 122.4 (d, <i>J</i> = 5, C ₁ ²), 128.2 (s, CH=CH-C(S) ^Z), 128.4 (s, CH=CH-C(S) ^E), 129.3 (s, C ₀ ³), 129.9 (s, C ₁ ³), 131.9 (s, CH=CH-C(S) ^Z), 133.7 (s, C ₁ ⁴), 134.0 (s, C ₀ ⁴), 140.7 (d, <i>J</i> = 13, CH=N), 141.1 (s, CH=CH-C(S) ^E), 151.9 (d, <i>J</i> = 7, C ₀ ¹), 152.3 (d, <i>J</i> = 8, C ₁ ¹), 174.6 (s, CO), 194.9 (s, C=S ^E), 198.0 (s, C=S ^Z)
	40	51.9 (P ₀), 60.6-61.7 (m, P ₁ , P ₂ , P ₃)	<i>b</i> 1.61 (d, <i>J</i> = 7.0, 72H, CH-CH ₃), 3.50 (d, <i>J</i> = 9.6, 63H, P ₁₋₃ -N-CH ₃), 5.41 (m, 24H, CH-CH ₃), 6.32 (d, <i>J</i> = 12.6, (24*0.15)H, CH=CH-C(S) ^Z), 6.42 (d, <i>J</i> = 12.6, (24*0.15)H, CH=CH-C(S) ^Z), 7.04-7.96 (m, 225H, C ₆ H ₄ , CH=N, OH), 7.11 (d, <i>J</i> = 15.3, (24*0.85)H, CH=CH-C(S) ^E), 7.90 (d, <i>J</i> = 15.3, (24*0.85)H, CH=CH-C(S) ^E), 9.30 (d, <i>J</i> = 6.6, (24*0.85)H, NH ^E), 9.45 (d, <i>J</i> = 7.3, (24*0.15)H, NH ^Z)	<i>b</i> 17.2 (s, CH-CH ₃), 33.0 (br d, <i>J</i> = 12, P ₁₋₃ -N-CH ₃), 53.7 (br s, CH), 122.3 (d, <i>J</i> = 5, C ₀ ² , C ₁ ² , C ₂ ² , C ₃ ²), 127.2 (s, CH=CH-C(S) ^Z), 128.3 (s, CH=CH-C(S) ^E), 128.8 (br s, C ₀ ³ , C ₁ ³ , C ₂ ³), 129.6 (s, C ₃ ³), 131.9 (s, CH=CH-C(S) ^Z), 133.2 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴), 133.5 (br s, C ₃ ⁴), 139.9-140.5 (m, CH=N), 140.8 (s, CH=CH-C(S) ^E), 150.9 (d, <i>J</i> = 6, C ₀ ¹), 151.9 (d, <i>J</i> = 8, C ₁ ¹ , C ₂ ¹), 152.3 (d, <i>J</i> = 6, C ₃ ¹), 173.7 (br s, CO), 194.7 (s, C=S ^E), 197.5 (s, C=S ^Z)
h-[G₁]	20	51.6 (P ₀), 61.0 (P ₁)	<i>b</i> 3.30-3.37 (m, 12H, CH ₂ Ph), 3.51 (d, <i>J</i> = 10.6, 9H, P ₁ -N-CH ₃), 5.56 (m, 6H, CH), 6.28 (d, <i>J</i> = 12.2, (6*0.1)H, CH=CH-C(S) ^Z), 6.38 (d, <i>J</i> = 12.2, (6*0.1) H, CH=CH-C(S) ^Z), 7.17 (d, <i>J</i> = 15.3, (6*0.9)H, CH=CH-C(S) ^E), 7.92 (d, <i>J</i> = 15.3, (6*0.9)H, CH=CH-C(S) ^E), 7.04-7.97 (m, 45H, C ₆ H ₄ , CH=N, OH), 9.20 (br s, (6*0.9)H, NH ^E), 9.40 (br s, (6*0.1)H, NH ^Z)	<i>b</i> 32.9 (d, <i>J</i> = 13, P ₁ -N-CH ₃), 36.5 (s, CH ₂ Ph), 59.4 (s, CH-CO), 121.9 (d, <i>J</i> = 4, C ₀ ²). 122.2 (d, <i>J</i> = 5, C ₁ ²), 126.9 (s, CH=CH-C(S) ^E), 127.1 (s, CH=CH-C(S) ^Z), 128.3 (s, C ₀ ³), 128.5 (s, C ₁ ³), 128.8 (s, <i>p</i> -C ₆ H ₅), 129.5 (s, <i>o</i> -C ₆ H ₅), 129.9 (s, <i>m</i> -C ₆ H ₅), 131.6 (s, CH=CH-C(S) ^Z), 133.6 (s, C ₁ ⁴), 133.7 (s, C ₀ ⁴), 137.8 (s, <i>i</i> -C ₆ H ₅), 139.9 (d, <i>J</i> = 12, CH=N), 140.7 (s, CH=CH-C(S) ^E), 151.9 (d, <i>J</i> = 8, C ₀ ¹), 152.1 (d, <i>J</i> = 6, C ₁ ¹), 173.2 (s, CO), 194.6 (s, C=S ^E), 198.0 (s, C=S ^Z)

Table 1 (Continued):

6

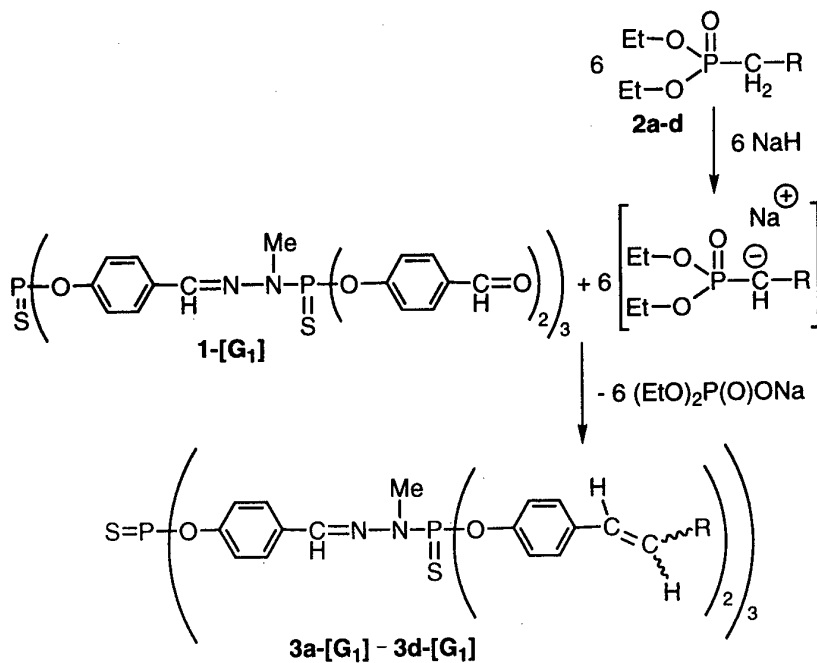
h-[G₄]	10	51.6 (P ₀), 61.4 (P ₄), 61.9 (br s, P ₁ , P ₂ , P ₃)	3.20-3.54 (m, 231H, CH ₂ Ph, P ₁₋₄ -N-CH ₃), 5.70 (m, 48H, CH), 6.26 (d, J = 12.0, (48*0.35)H, CH=CH-C(S) ^Z), 6.36 (d, J = 12.0, (48*0.35)H, CH=CH-C(S) ^Z), 7.00-7.94 (m, 657H+(96*0.65)H, C ₆ H ₄ , CH=N, OH, CH=CH-C(S) ^E , CH=CH-C(S) ^E), 9.14 (br s, (48*0.65)H, NH ^E), 9.50 (br s, (48*0.35)H, NH ^Z)	b 32.9 (d, J = 14, P ₁₋₄ -N-CH ₃), 36.5 (br s, CH ₂ Ph), 58.9 (s, CH-CO), 121.6 (br s, C ₀ ² , C ₁ ²), 122.2 (br s, C ₂ ² , C ₃ ² , C ₄ ²), 127.0 (s, CH=CH-C(S) ^E), 127.9 (s, CH=CH-C(S) ^Z), 128.6 (br s, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³ , C ₄ ³ , p-C ₆ H ₅), 129.5 (s, o-C ₆ H ₅), 129.9 (s, m-C ₆ H ₅), 131.5 (s, CH=CH-C(S) ^Z), 133.0 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴ , C ₄ ⁴), 137.4 (s, i-C ₆ H ₅), 138.5-142.8 (m, CH=N, CH=CH-C(S) ^E), 150.6 (m, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 152.0 (d, J = 7, C ₄ ¹), 172.2 (br s, CO), 194.8 (s, C=S ^E), 196.0 (s, C=S ^Z)
i-[G₁]	15	51.6 (P ₀), 61.0 (P ₁)	2.17 (s, 18H, SCH ₃), 2.10-2.51 (2m, 12H, CH-CH ₂), 2.70 (t, J = 7.5, 12H, CH ₂ S), 3.53 (d, J = 10.6, 9H, P ₁ -N-CH ₃), 5.55 (m, 6H, CH-CH ₂), 6.35 (d, J = 12.0, (6*0.1)H, CH=CH-C(S) ^Z), 6.43 (d, J = 12.5, (6*0.1)H, CH=CH-C(S) ^Z), 7.15 (d, J = 15.0, (6*0.9) H, CH=CH-C(S) ^E), 7.38 (d, J = 7.9, 12H, C ₁ ² H), 7.48 (d, J = 8.0, 6H, C ₀ ² H), 7.68 (d, J = 7.8, 12H, C ₁ ³ H), 7.90 (d, J = 15.0, (6*0.9)H, CH=CH-C(S) ^E), 7.95 (d, J = 7.6, 6H, C ₀ ³ H), 7.88 (br s, 9H, CH=N, OH), 9.34 (d, J = 5.6, (6*0.9)H, NH ^E), 9.52 (d, J = 6.4, (6*0.1)H, NH ^Z)	b 14.9 (s, SCH ₃), 30.5 (s, CH ₂ S), 32.0 (s, CH-CH ₂), 32.9 (d, J = 12, P ₁ -N-CH ₃), 57.6 (s, CH-CH ₂), 121.9 (d, J = 4, C ₀ ²), 122.2 (d, J = 5, C ₁ ²), 126.9 (s, CH=CH-C(S) ^Z), 128.3 (s, CH=CH-C(S) ^E), 128.9 (s, C ₀ ³), 129.5 (s, C ₁ ³), 131.7 (s, CH=CH-C(S) ^Z), 133.5 (s, C ₁ ⁴), 133.7 (s, C ₀ ⁴), 140.0 (d, J = 13, CH=N), 140.7 (s, CH=CH-C(S) ^E), 151.8 (d, J = 8, C ₀ ¹), 152.1 (d, J = 7, C ₁ ¹), 173.2 (br s, CO), 195.1 (s, C=S ^E), 198.5 (s, C=S ^Z)

Table 1 (Continued):

7

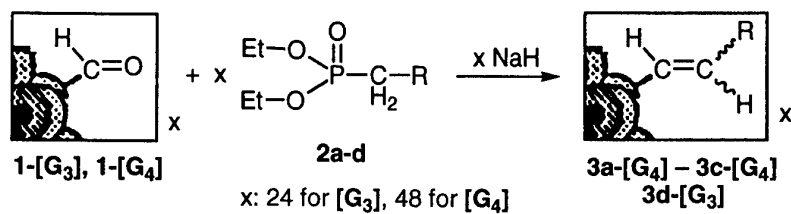
i-[G₄]	10	51.6 (P ₀), 61.0 (P ₄), 61.6 (P ₁ , P ₂ , P ₃)	2.15 (br s, 144H, SCH ₃), 2.32 (m, 96H, CH-CH ₂), 2.66 (m, 96H, CH ₂ S), 3.51 (d, J = 6.5, 135H, P ₁₋₄ -N-CH ₃), 5.53 (m, 48H, CH-CH ₂), 6.35 (m, (96*0.15)H, CH=CH-C(S)Z, CH=CH-C(S)Z), 7.04-7.86 (m, 465+(96*0.85)H, C ₆ H ₄ , CH=N, OH, CH=CH-C(S)E, CH=CH-C(S)E), 9.40 (br s, (48*0.85)H, NH ^E), 9.50 (br s, (48*0.15)H, NH ^Z)	b 14.9 (s, SCH ₃), 30.6 (m, CH ₂ S), 31.0 (m, CH-CH ₂), 32.9 (m, P ₁₋₄ -N-CH ₃), 57.0 (m, CH-CH ₂), 121.6 (m, C ₀ ² , C ₁ ² , C ₂ ² , C ₃ ²), 122.2 (br s, C ₄ ²), 127.0 (s, CH=CH-C(S)Z), 128.6 (br s, CH=CH-C(S)E, C ₀ ³ , C ₁ ³ , C ₂ ³ , C ₃ ³), 129.5 (br s, C ₄ ³), 131.5 (s, CH=CH-C(S)Z), 133.1 (br s, C ₀ ⁴ , C ₁ ⁴ , C ₂ ⁴ , C ₃ ⁴ , C ₄ ⁴), 140.8 (m, CH=N, CH=CH-C(S)E), 150.7 (d, J = 7, C ₀ ¹ , C ₁ ¹ , C ₂ ¹ , C ₃ ¹), 152.0 (br s, C ₄ ¹), 168.3 (br s, CO), 195.0 (s, C=S ^E), 198.5 (s, C=S ^Z)
--------------------------	----	---	--	--

a in CDCl₃*b* in THF D₈*Z* Z-isomers*E* E-isomers



3 (% of Z isomer)	a-[G ₁] (0)	b-[G ₁] (0)	c-[G ₁] (10)	d-[G ₁] (30)
R				

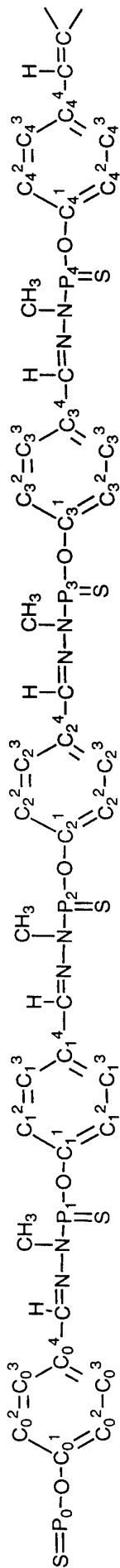
Scheme 1



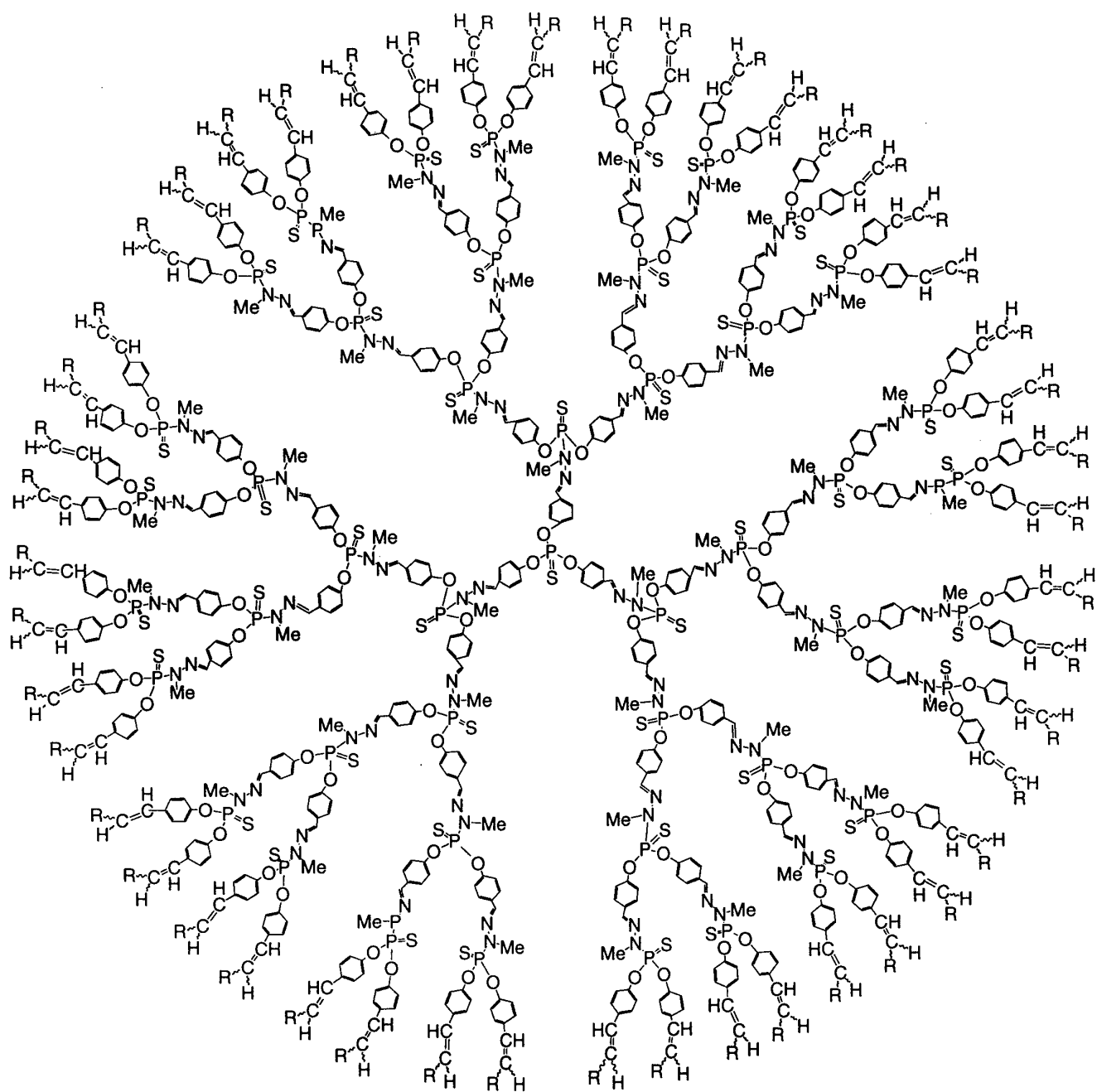
3 (% of Z isomer)	a-[G ₄] (0)	b-[G ₄] (0)	c-[G ₄] (10)	d-[G ₃] (50)
R				

Scheme 2

Numbering used for NMR:



Scheme 4



1-[G₄]

Figure 1