First phosphorous D-xylose-derived glycodendrimers

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ABSTRACT

Phosphorous glycodendrimers have been prepared in quantitative yields by grafting xylose-derived moieties on phosphorous dendrimers involving hydrazone units. These dendrimers could be hydrophobic or amphiphilic, respectively, with acetylated or unprotected sugar moieties.

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For several years now, we have been involved in a research programme dedicated to the valorization of pentoses especially D-xylose or L-arabinose, now readily accessible from wheat straw and bran.[1] We have previously transformed pentoses into amphiphilic structures.[2] Since a short time, we have studied the possibility to synthesize some glycodendrimers involving pentose moieties by grafting pentose-derived moieties on phosphorous dendrimers. Glycodendrimers have been recently developed for potential use in micellar enantioselective catalysis[3] or in pharmaceutical field or in nanotechnology.[4]

Phosphorous starting dendrimers involving hydrazone units were prepared as previously described using a two step route (Scheme 1).[5]

Substitution of the chloride atoms of $PSCl_2$ unit could be attempted by amines,[6] phenolic entities branched on specific pesticides,[7] organometallic[8] or fluorophoric moieties.[9] To our knowledge, no sugar entities have been grafted on such dendrimers to give phosphorous glycodendrimers that urge us to publish our study.

At first, we attempted the direct coupling of 2,3,4-tri-O-acetyl-D-xylopyranose[10] or 2′-hydroxyethyl-2,3,4-tri-O-acetyl-β-D-xylopyranoside[11] with **GC1** without success. Such result is not surprising, since no reaction with alcohols had occurred with **GC1** (or higher generations), whereas numerous reactions with phenols were successful, as indicated above. So, we decided to prepare the triacetylated phenolic derivative of xylose **1** by glycosylation of peracetylated xylose in the presence of a Lewis acid, $BF_3.Et_2O$ (Scheme 2).[12] This compound was obtained in a moderate yield as a mixture of two conformers and engaged in coupling reactions with phosphorous dendrimers **GC1**, **GC2** and **GC3**.

The reacting conditions were applied on **GC1** using the protocol described in Scheme 3 and the reactions were followed by ^{31}P NMR spectroscopy. In fact, two different peaks are observed: one corresponding to the core P atom and the other to the P1 atom (Scheme 3). In **GC1**, the chemical shifts of P core and P1 are, respectively, 62.75 and 8.55 ppm. When substitution of one Cl or two Cl occurred, the chemical shift of P core is not modified while the chemical shifts of P1 are, respectively, 68.5 or 63.5 ppm.

At first, nitrogen-containing bases such as Et_3N, TMEDA or DBU in different ratios with respect to the Cl atoms (respectively, 2, 1.25 and 1.25) were used in THF or CH_2Cl_2. Temperatures were adjusted at room temperature or allowed to rise from 0 °C to rt and reaction times varied from 5 to 12 h. Unfortunately, each reaction led to mono- and disubstitution adducts with degradation products of starting phosphorous dendrimer proved by many ^{31}P NMR signals.

Next, inorganic bases such as NaH, K_2CO_3 and Cs_2CO_3 were used under different conditions: with NaH (2 equiv/Cl atom), the disubstitution compound is observed but always with degradation products of **GC1**. No influence of the temperature has also been proved by maintaining this one at 0 or −10 °C during the entire reaction. The addition of 2 equiv of K_2CO_3 per chloride atom led exclusively to the formation of the monosubstitution adduct with few degradation products. Finally, reactions with Cs_2CO_3 were achieved at various temperatures (0 °C to rt), this inorganic base being more soluble in organic solvents than most carbonates such as potassium carbonate. These reactions led to disubstitution and degradation products but ^{31}P NMR spectra seemed to be cleaner than previously observed. So, we explored the possibility of using a large excess of this base in the presence of **GC1** at first and next, the nucleophilic species **1** was added. This experiment was concluding because only the disubstitution compound was observed without degradation of the starting material.

We also developed a protocol of purification of the glycodendrimer **GX1**[13] involving only filtration and extraction steps: Excess of Cs_2CO_3 is eliminated by centrifugation and the glycodendrimer is purified from xyloside **1** traces by precipitation in a mixture of Et_2O/pentane (1:1) and obtained with 96% yield. Grafting of 12 xyloside entities was confirmed by the ^{1}H NMR spectroscopy.

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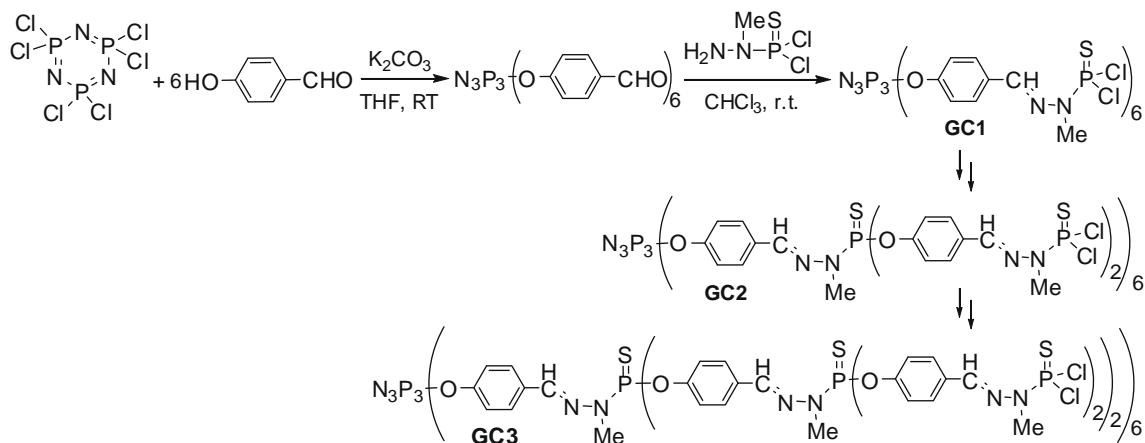
Scheme 1. Synthesis of phosphorous starting dendrimers.
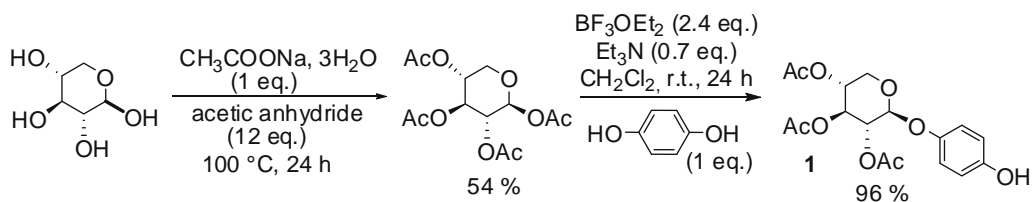
Scheme 2. Preparation of *para*hydroxyphenyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside, **1**.
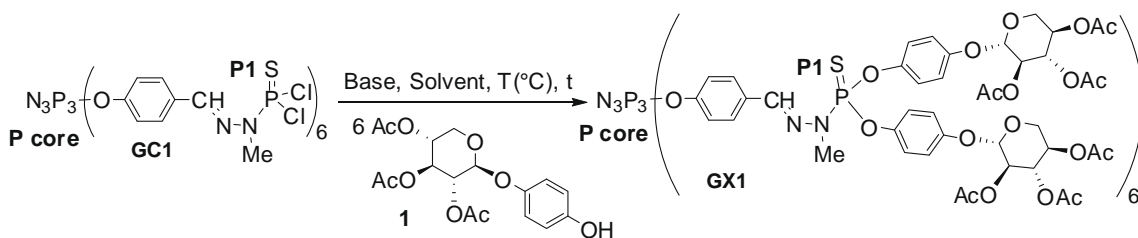
Scheme 3. Couplings of *para*hydroxyphenyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **1** with **GC1**.
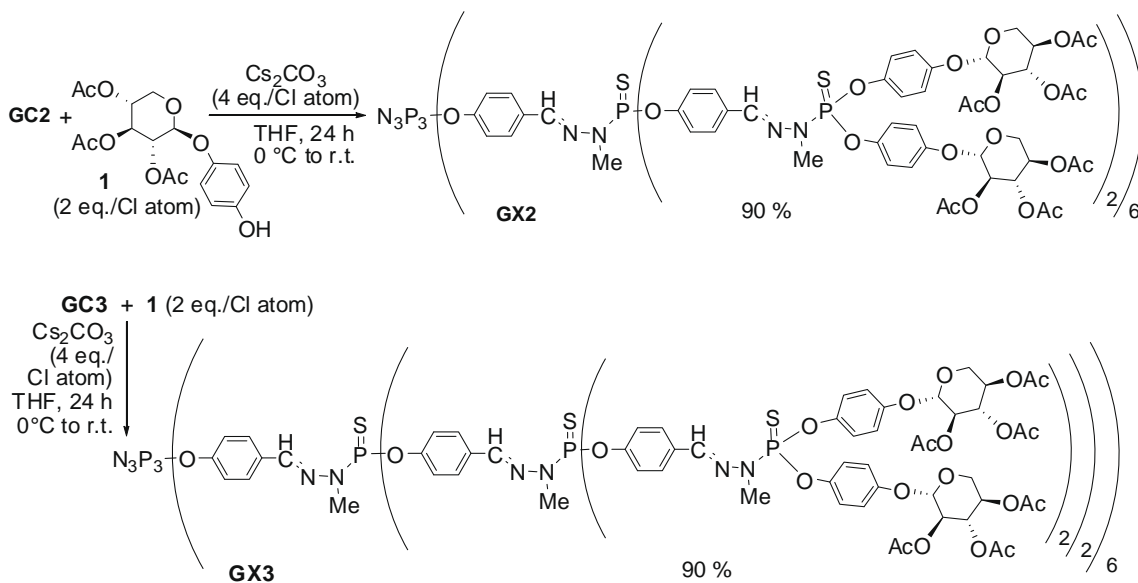
Scheme 4. Couplings of *para*hydroxyphenyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **1** with **GC2** and **GC3**.
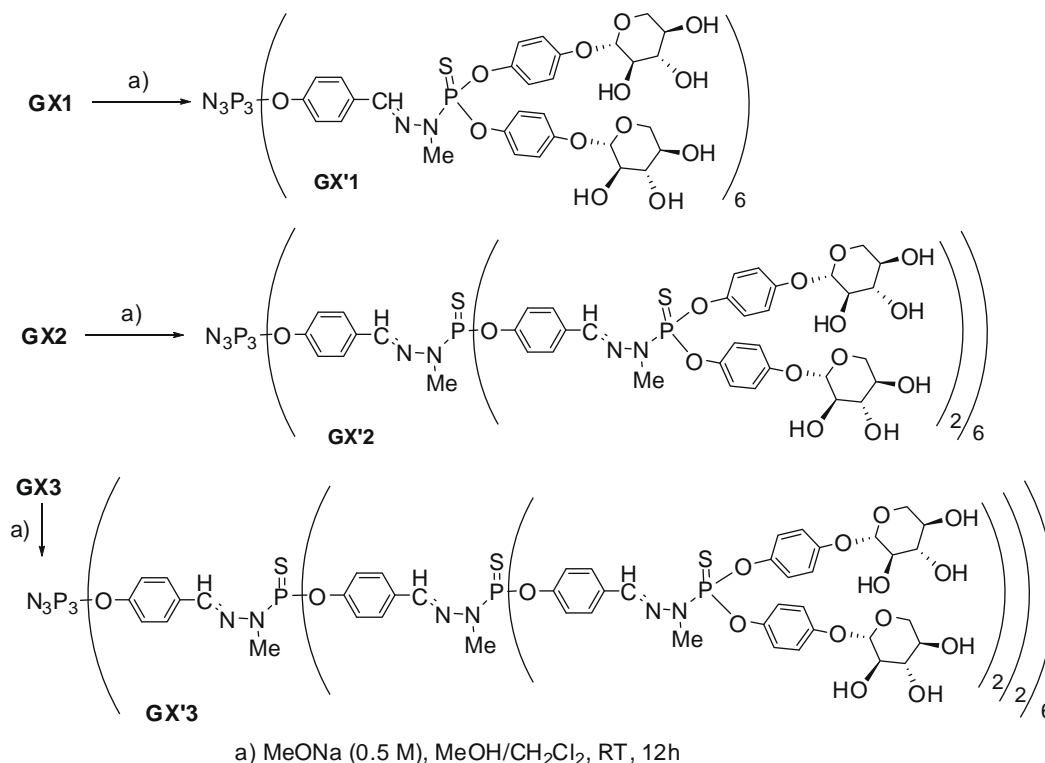
Scheme 5. Hydrolysis of glycodendrimers **GX1**, **GX2** and **GX3**.

This grafting method was extended to dendrimers of second and third generation **GC2** and **GC3** in quantitative yields (Scheme 4).[14] As for **GX1**, we also observed by ^{31}P NMR besides the signals corresponding to the internal structure, an intermediate singlet at about 68.5 ppm, corresponding to the monosubstitution on the terminal groups, which disappears to give a new singlet at 63.5 or 64.5 ppm, corresponding to the full substitution (**GX2** or **GX3**, respectively).

In order to obtain amphiphilic glycodendrimers, we engaged **GX1**, **GX2** and **GX3** into deprotection reactions. Classical conditions for hydrolysis of acetate groups on sugar derivatives (MeONa in MeOH/CH$_2$Cl$_2$)[2e] have been used during a short time to avoid the decomposition of the starting materials (Scheme 5).[15] Indeed, the P–O linkages might be sensitive to these drastic conditions. However, ^{31}P NMR displays a single signal for each phosphorous layer confirming the integrity of the structure. The hydrolysis of all the acetate groups is shown by ^{1}H NMR by the total disappearance of the acetate signal.

In conclusion, we prepared the first phosphorous glycodendrimers derived from D-xylose in very good yields through an easy purification process. The potential of using these macromolecules in asymmetric synthesis or micellar catalysis, especially for amphiphilic compounds, is currently under study.

References and notes

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12. *Preparation of parahydroxyphenyl-2,3,4-tri-O-acetyl-β-D-xylopyranoside* **1**: 1,2,3,4-tri-O-acetyl-β-D-xylopyranoside (2 g, 6.29 mmol) and the hydroquinone (693 mg, 6.29 mmol, 1 equiv) were dissolved in CH$_2$Cl$_2$ (20 mL) under argon. Triethylamine (0.63 mL, 4.40 mmol, 0.7 equiv) and BF$_3$·OEt$_2$ (1.9 mL, 15.08 mmol, 2.4 equiv) were then successively added dropwise. After 24 h stirring at room temperature, the mixture was neutralized with triethylamine until neutral pH was obtained. The crude product was then concentrated under reduced pressure and chromatographed on silica gel (petroleum ether/ethyl acetate: 1:4). The *para*-hydroxyphenyl-2,3,4-tri-O-acetyl-β-D-xylopyranoside **1** was obtained as a beige solid (2.22 g, 96%). Mp 121 °C. [α]$_D$ −34.8 (*c* 1.11 CHCl$_3$). IR (KBr): 3458 (F), 2963(f), 2880 (f), 1775 (F), 1602 (f), 1511 (m), 1442 (f), 1222 (F), 1097 (m) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ 2.18–2.36 (18H), 3.70 (2H), 4.40 (dd, J = 4.6, 11.9 Hz, 2H), 5.16–5.48 (8H), 6.86–7.18 (8H) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 20.7–20.8, 61.9, 62.0, 68.5, 68.5, 70.3, 70.5, 70.8, 71.1, 99.3, 99.9, 116.1, 116.2, 118.3, 118.7, 149.5, 150.1, 152.1, 152.2, 169.5–170.1. HRMS: calcd for [M+Na$^+$] = 391.1005. Found for [M+Na$^+$] = 391.1001 g mol^{-1}. Calcd for C$_{17}$H$_{20}$O$_9$: C, 55.43; H, 5.43. Found for C, 55.27; H, 5.79.
13. *Typical procedure for preparation of phosphorous glycodendrimer* **GX1**: In a Schlenk tube was dissolved the *parahydroxyphenyl-2,3,4-tri-O-acetyl-β-D-xylopyranoside* **1** (236 mg, 0.641 mmol, 24 equiv) in THF (4 mL). After cooling the solution at 0 °C, cesium carbonate (418 mg, 1.283 mmol, 48 equiv) was

added followed, after 10 h stirring, by the **GC1** dendrimer (49 mg, 0.027 mmol). The resulting mixture was stirred at room temperature during 14 h. Cesium salts were eliminated by centrifugation and the floating solution was evaporated under reduced pressure to give a yellow solid. This one was washed by a mixture Et$_2$O/pentane (1:1) and isolated by centrifugation. Phosphorous glycodendrimer **GX1** was therefore obtained as a yellow powder (150.5 mg, 96%). Mp 133 °C. IR (KBr): 3417 (F), 1755 (F), 1643 (f), 1501 (m), 1222 (F), 1183 (m) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ 2.03 (s, 108H), 3.22 (d, J = 10.13 Hz, 18H), 3.50 (dd, J = 7.9, 11.9 Hz, 12H), 4.28 (dd, J = 4.7, 11.9 Hz, 12H), 4.90–5.28 (48H), 6.80–7.15 (60H), 7.51–7.69 (18H) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 20.6–20.7, 33.0 (d, J = 12.17 Hz), 61.9, 68.4, 70.1, 70.7, 98.9, 117.8, 121.3, 122.4, 128.3, 132.2, 138.7 (d, J = 6.9 Hz), 145.8, 151.2, 153.9, 169.3–169.9 ppm. ^{31}P NMR (101.5 MHz, CDCl$_3$): δ 8.52, 63.49 ppm. Calcd for C$_{252}$H$_{276}$N$_{15}$O$_{114}$P$_9$S$_6$: C, 52.09; H, 4.79; N, 3.62; S, 3.31. Found for C, 52.02; H, 4.84; N, 3.72; S, 3.19.

14. *Phosphorous glycodendrimer* **GX2**: Similar procedure as for phosphorous glycodendrimer **GX1** with *para*hydroxyphenyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **1** (243 mg, 0.660 mmol, 48 equiv), cesium carbonate (430 mg, 1.320 mmol, 96 equiv) and the **GC2** dendrimer (65 mg, 0.014 mmol). Phosphorous glycodendrimer **GX2** was obtained as a yellow powder (160 mg, 90%). Mp 145 °C. IR (KBr): 3418 (F), 1757 (f), 1642 (m), 1501 (f), 1265 (m), 1224 (m) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ 2.05 (s, 216H), 3.10–3.38 (54H), 3.50 (dd, J = 7.9, 11.9 Hz, 24H), 4.28 (dd, J = 4.7, 11.9 Hz, 24H), 4.90–5.28 (96H), 6.80–7.15 (132H), 7.51–7.69 (54H) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 21.2, 33.5, 62.3, 68.9, 70.6, 71.2, 99.2, 118.3, 121.8, 122.2, 122.9, 128.6, 132.5, 132.8, 139.1–139.4, 146.1, 151.7, 153.3, 169.3–169.9 ppm. ^{31}P NMR (101.5 MHz, CDCl$_3$): δ = 8.76, 62.99, 64.55 ppm. Calcd for C$_{552}$H$_{600}$N$_{39}$O$_{234}$P$_{21}$S$_{18}$: C, 51.99; H, 4.74; N, 4.28; S, 4.53. Found for C, 51.24; H, 4.80; N, 4.32; S, 4.25. *Phosphorous glycodendrimer* **GX3**: Similar procedure as for phosphorous glycodendrimer **GX1** with *para*hydroxyphenyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **1** (197 mg, 0.535 mmol, 96 equiv), cesium carbonate (343 mg, 1.054 mmol, 192 equiv) and the **GC3** dendrimer (69 mg, 0.006 mmol). Phosphorous glycodendrimer **GX3** was obtained as a yellow powder (135 mg, 90%). Mp 150 °C. IR (KBr): 3415 (F), 1757 (F), 1642 (f), 1501 (m), 1266 (F), 1225 (m) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ 1.85–2.04 (432H), 3.07–3.40 (126H), 3.04-3.58 (48H), 4.16 (dd, J = 3.5, 11.4 Hz, 48H), 4.86–5.28

(192H), 6.67–7.23 (276H), 7.46–7.80 (126H) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 21.6–21.7, 33.0, 61.9, 68.4, 70.2, 70.7, 98.2, 117.8, 121.8, 122.5, 128.3, 132.3, 140.0, 146.1, 151.2, 154.3, 169.3–169.9 ppm. ^{31}P NMR (101.5 MHz, CDCl$_3$): δ 8.26, 62.16, 64.55 ppm. Calcd for C$_{1152}$H$_{1248}$N$_{87}$O$_{474}$P$_{45}$S$_{42}$: C, 51.94; H, 4.72; N, 4.57; S, 5.06. Found for C, 51.32; H, 4.61; N, 4.77; S, 4.45.

15. *Typical procedure for preparation of phosphorous glycodendrimer* **GX′1**: To a solution of phosphorous glycodendrimer **GX1** (238 mg, 0.041 mmol) in a MeOH/CH$_2$Cl$_2$ mixture (1:1) (20 ml) was added dropwise a 0.5 M NaOMe solution (1.5 mL, 0.738 mmol, 18 equiv). After 2 hours stirring at room temperature, phosphorous glycodendrimer **GX1′** was precipitated and isolated by centrifugation as a beige powder (170 mg, 96%). Mp 172 °C. IR (KBr): 3409 (F), 1600 (F), 1501 (m), 1185 (F), 1102 (m) cm^{-1}. ^{1}H NMR (250 MHz, D$_2$O): δ 3.27–3.68 (54H), 3.72–4.23 (24H), 4.90–5.15 (12H), 7.10–7.35 (60H), 7.51–7.69 (18H) ppm. ^{13}C NMR (62.9 MHz, D$_2$O): δ 33.8 (d, J = 11.9 Hz), 66.7, 70.5, 74.2, 77.3, 102.8, 118.7, 122.1, 122.9, 129.3, 133.7, 140.3 (d, J = 15.4 Hz), 146.3 (d, J = 6.6 Hz), 152.2, 156.0 ppm. ^{31}P NMR (101.5 MHz, D$_2$O): δ 9.10, 64.33 ppm. *Phosphorous glycodendrimer* **GX′2**: Similar procedure as for phosphorous glycodendrimer **GX′1** with a 0.5 M NaOMe solution (1.05 mL, 0.508 mmol, 36 equiv) and the **GX2** dendrimer (180 mg, 0.014 mmol). Phosphorous glycodendrimer **GX′2** was obtained as a beige powder (136 mg, 100%). Mp 196 °C. IR (KBr): 3408 (F), 1601 (F), 1501 (m), 1186 (m), 1101 (f) cm^{-1}. ^{1}H NMR (250 MHz, D$_2$O): δ 3.25–3.50 (78H), 3.55–3.65 (48H), 3.70–3.90 (24H), 3.95–4.05 (24H), 4.90–5.00 (24H), 7.10–7.45 (132H), 7.80–8.02 (54H) ppm. ^{13}C NMR (62.9 MHz, D$_2$O): δ 33.7–33.9, 66.7, 70.6, 74.3, 77.3, 103.0, 118.8, 122.7, 123.1, 123.2, 129.4, 133.7, 134.0, 140.1–140.4, 146.5 (d, J = 6.9 Hz), 152.5, 156.1 ppm. ^{31}P NMR (101.5 MHz, D$_2$O): δ 9.35, 62.65, 64.64 ppm. *Phosphorous glycodendrimer* **GX′3**: Similar procedure as for phosphorous glycodendrimer **GX′1** with a 0.5 M NaOMe solution (0.9 mL, 0.450 mmol, 72 equiv) and the **GX3** dendrimer (166 mg, 0.006 mmol). Phosphorous glycodendrimer **GX′3** was obtained as a beige powder (125 mg, 100%). Mp 199 °C. IR (KBr): 3408 (F), 1604 (F), 1501 (m), 1187 (f), 1100 (f) cm^{-1}. ^{1}H NMR (250 MHz, D$_2$O): δ 3.25–3.40 (174H), 3.45–4.40 (192H), 4.95–5.05 (48H), 7.10–7.45 (276H), 7.81–8.12 (126H) ppm. ^{13}C NMR (62.9 MHz, D$_2$O): δ 33.5–33.7, 66.4, 70.3, 74.0, 77.0, 102.7, 118.5, 122.2, 122.8–123.0, 129.1–129.2, 133.6–133.7, 140.1–140.6, 146.3, 152.4–152.6, 155.8 ppm. ^{31}P NMR (101.5 MHz, D$_2$O): δ 8.82, 62.92, 64.43 ppm.