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# "Click" Glycodendrimers Containing 27, 81, and 243 Modified Xylopyranoside Termini

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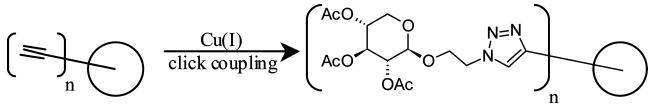


$G_1$-27, $G_2$-81 and $G_3$-243 polyalkynyl dendrimers

$G_1$-27, $G_2$-81 and $G_3$-243 polyxylopyranoside dendrimers

A series of large glycodendrimers containing 27, 81, and 243 terminal modified xylose branches from the first ($G_1$-27) to the third generation ($G_3$-243) were synthesized from 2′-azidoethyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside and alkynyl-terminated dendrimers by "click" chemistry that is confirmed to be an excellent method to obtain large glycodendrimers exemplified by the use of modified xylose. The dendrimers were first characterized by $^1$H NMR, $^{13}$C{$^1$H} NMR, elemental analysis, and IR spectroscopy. The size progression in the series was also demonstrated using both DOSY NMR and size exclusion chromatography (SEC), the latter technique showing the good polydispersity of all the dendrimers. The size measured by dynamic light scattering (DLS) for the dendrimer $G_3$-243 is close to that obtained by the DOSY NMR method.

Agriculture leads to the production of many byproducts. Hemicelluloses obtained from the straw of cereals enable one to get low-cost molecules such as D-xylose and L-arabinose, which can be valorized. After studies leading to the transformation of the above pentoses into products possessing surfactant properties,[1] we are now using them in dendrimer chemistry.[2] Dendrimers are well-defined macromolecules[3] that can be used in various fields of nanosciences such as nanoreactors,[4] molecular micelles,[5] drug vectors,[6] sensors,[7] green catalysts,[8] supramolecular electronics,[9] and light-harvesting devices.[10]

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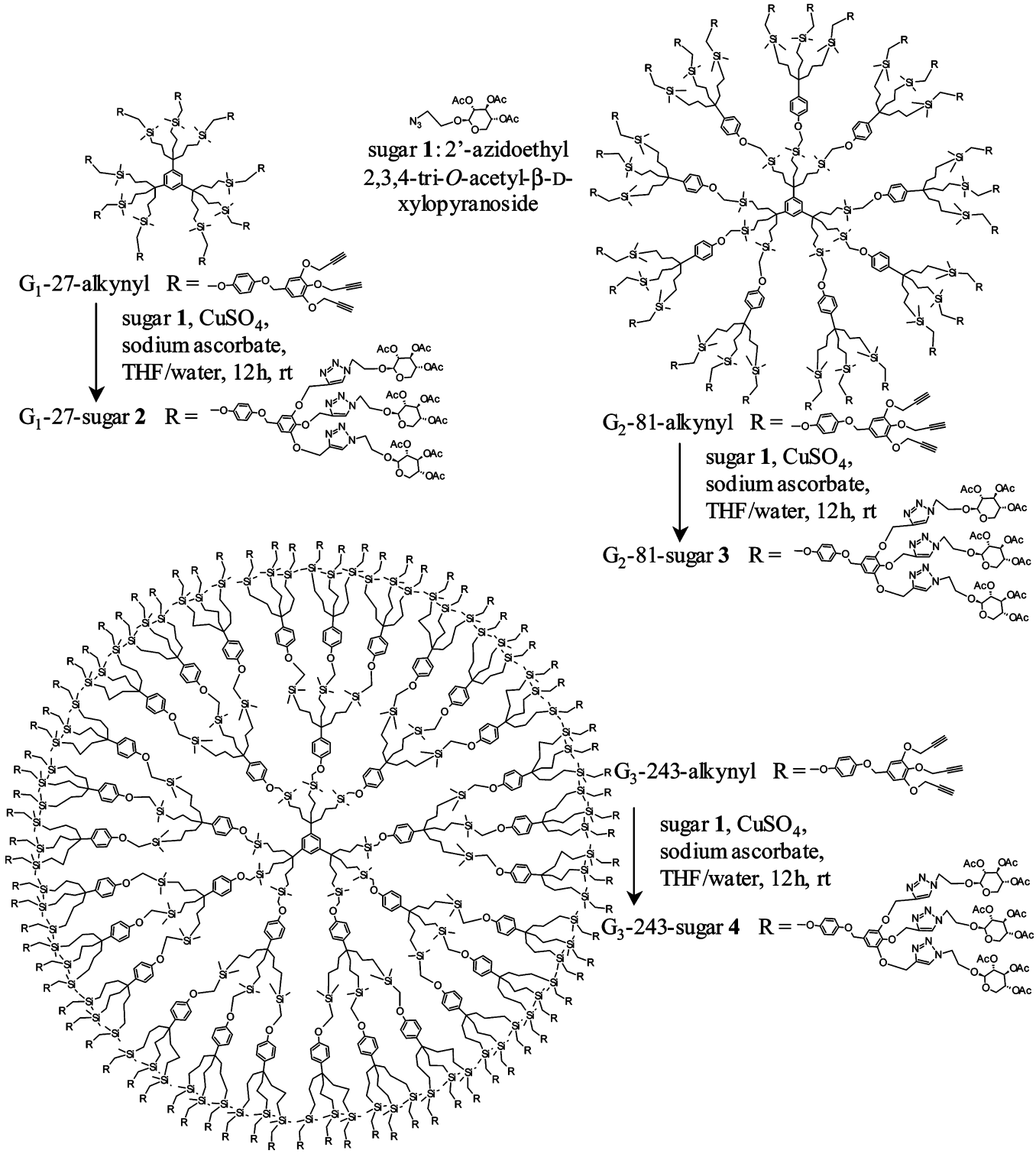
**SCHEME 1. Synthesis of the Polyxylopyranoside Dendrimer Series**






Glycodendrimers are already a rich family, with large possibilities of potential applications. The chirality of sugar allows for their use in enantioselective catalysis,[11] and the supramolecular interaction between sugars and proteins such as lectins,[12] for example, provides potential applications in nanomedicine.[13] With these perspectives, we report here the synthesis of a series of large glycodendrimers containing from 27 ($G_1$) to 243 ($G_3$) modified xylopyranoside termini by Cu(I)-catalyzed Huisgen cycloaddition.[14] The D-xylose was functionalized[15] to introduce the azido group, and the "click" cycloaddition was carried out using the corresponding

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alkynyl-terminated dendritic core[16] to yield the glycodendrimers with 27, 81, and 243 terminal branches.

We recently published the polyalkynyl-terminated dendrimers shown in Scheme 1, and we now report "click" reactions between these dendrimer cores[16] and the known 2′-azidoethyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside,[15] including the syntheses and characterizations of large sugar-terminated dendrimers containing $3^n$ sugar termini ($n = 3-5$) shown in Scheme 1.

$Cu^I$-"catalyzed" Huisgen 1,3-dipolar cycloaddition reaction of the polyalkynyl dendritic cores with the modified azido sugar, **1**, was carried out in the presence of a stoichiometric amount of $Cu^I$ [14] in a homogeneous THF/water mixture yielding the glycodendrimers $G_1$-27-xylopyranoside, **2**, $G_2$-81-xylopyranoside, **3**, and $G_3$-243-xylopyranoside, **4**, under the same reaction conditions (Scheme 1).[17]

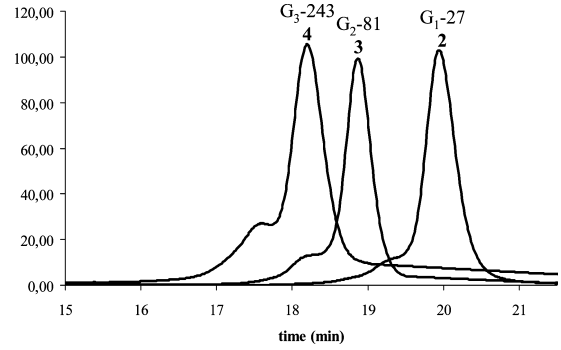
This set of dendrimers was purified by flash column chromatography followed by precipitations (see the Experimental Section). All these functionalized dendrimers were characterized by SEC, $^1H$, $^{13}C\{^1H\}$, and DOSY NMR, IR, elemental analysis, plus DLS for the largest dendrimer $G_3$-243-xylopyranoside, **4** (hydrodynamic diameter in $CH_2Cl_2$ at 25 °C of 7.1 ± 0.9 nm (Table 1)), and MALDI TOF mass spectrometry for the smallest dendrimer $G_1$-27-xylopyranoside, **2**.

**TABLE 1. Sizes of the Dendrimers by DOSY NMR and DLS**

| | $G_1$-27 | $G_2$-81 | $G_3$-243 |
|---|---|---|---|
| polyalkynyl DOSY[a] | 4.1 | 4.8 | 4.9 |
| polyxylopyranoside DOSY[a] | 4.4 | 5.2 | 8.5 |
| polyalkynyl DLS[b] | / | 6.2 | 6.6 |
| polyxylopyranoside DLS[b] | / | / | 7.1 |

[a] Diameter in nanometers obtained in $CDCl_3$ at 25 °C. [b] Hydrodynamic diameter in nanometers obtained in $CH_2Cl_2$ at 25 °C.

**SCHEME 2. Size Progression in the Polyxylopyranoside Dendrimer Series Observed by SEC[a]**




[a] Side bands at high masses increasing with the generation number are attributed to aggregated dendrimers.[3d]

As can be seen by IR spectroscopy (no visible alkyne or azide vibrating band for all these compounds), there is neither free alkyne branch in these molecules nor excess sugar. SEC indicates the size progression (Scheme 2) from **2** to **4** (retention time of 19.93, 18.85, and 18.18, respectively) and the low polydispersity (1.04 to 1.05). The size progression was also shown by the DOSY NMR data (in $CDCl_3$ at 25 °C: 4.4, 5.2, and 8.5 nm, respectively, for $G_1$-27-xylopyranoside, $G_2$-81-xylopyranoside, and $G_3$-243-xylopyranoside (Table 1)). Table 1 compares the characterizations of the precursor polylalkynyl dendrimers with those of the sugar-terminated dendrimers.

These values demonstrate the increase of the dendrimer size upon coupling the polyalkynyl cores with the sugar (from 4.1 to 4.4 nm for $G_1$-27, from 4.8 to 5.2 for $G_2$-81, and from 4.9 to 8.5 for $G_3$-243 under the same conditions). This increase also appears by DLS for the largest dendrimer $G_3$-243 (from 6.6 to 7.1 nm). These values are rather close to those obtained by the DOSY NMR technique (Table 1).

Moreover, the elemental analyses of the two dendrimers $G_1$-27-sugar **2** and $G_2$-81-sugar **3** are very good for such giant molecules (less than 0.3% difference between calculated and found for both carbon and hydrogen) and not so far for the largest dendrimer $G_3$-243-sugar **4** (MW > 130 000 Da and 0.7% difference between calculated and found for carbon). These results were obtained after more than 1 week under vacuum. After this period, the values obtained were stabilized, which is an indication of the strong encapsulation capacity of these dendrimers.

In this work, we have synthesized three generations of large to giant glycodendrimers containing 27, 81, and 243 xylopyranosides that have been characterized by standard spectroscopic and analytical techniques. The dendrimer size growth from $G_1$-27 to $G_3$-243 and also upon functionalization within each generation was shown using diffusion light scattering (DLS),

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DOSY NMR, and size exclusion chromatography (SEC), with a satisfactory agreement concerning size data among these methods.

## Experimental Section

**General Procedure for "Click" Coupling.** To a solution of polyalkynyl dendrimer[16] (1.0 equiv) in a THF/water 1:1 (v/v) mixture were added 2′-azidoethyl 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranoside **1**[15] (2.0 equiv per branch), $CuSO_4 \cdot 5H_2O$ (4.0 equiv per branch), and sodium ascorbate (8.0 equiv per branch). The mixture was stirred at room temperature under a nitrogen atmosphere for 12 h. The mixture was concentrated, and $CH_2Cl_2$ was added. The organic layer was washed with aqueous ammonium hydroxide until a colorless aqueous layer was obtained and then with water to neutrality. The organic phase was concentrated to dryness in vacuo. The crude product was purified by flash column chromatography with ethyl acetate and then an ethyl acetate/methanol 7:3 (v/v) mixture as eluents. The product obtained was dissolved in minimum $CH_2Cl_2$ and precipitated with excess diethylether and then with excess methanol. Glycodendrimers were obtained as off-white gums in 59, 62, and 51% yield for $G_1$-27, $G_2$-81, and $G_3$-243, respectively.

Data for dendrimer $G_1$-27, **2**, $C_{612}H_{795}O_{261}N_{81}Si_9$: MW 13 715.09 $g \cdot mol^{-1}$; yield 59%; off-white gum; $\delta_H$ (300 MHz, $CDCl_3$, 25 °C, TMS) 0.05 (s, 54H, Si−C*H*$_3$), 0.60 (s, 18H, $CH_2-CH_2-CH_2-$Si), 1.15 (s, 18H, $CH_2-CH_2-CH_2-$Si), 1.66 (s, 18H, $CH_2-CH_2-CH_2-$Si), 1.90−2.04 (m, 243H, C*H*$_3$ sugar), 3.31 (m, 27H, $H_{5a}$ sugar), 3.46 (s, 18H, Si−C*H*$_2$−O), 3.92−3.99 (2m, 27H + 27H, $H_2 + H_4$ sugar), 4.03 (m, 27H, $H_{5e}$ sugar), 4.45−4.55 (m, 27H + 54H, $H_{1\beta} + H_{2'}$ sugar), 4.85−4.89 (m, 18H + 54H, O−C*H*$_2-C_{Ar}$ + $H_{1'}$ sugar), 5.08−5.16 (m, 27H + 54H, $H_3$ sugar + O−C*H*$_2-C_{triazole}$), 6.77−7.00 (m, 57H, $H_{Ar}$), 7.88 (s, 27H, $H_{triazole}$); $\delta_C$ (75.5 MHz, $CDCl_3$, 25 °C, TMS) −4.5 ($CH_3$), 14.2 ($CH_2$), 17.8 ($CH_2$), 20.6 ($CH_3$), 20.7 ($CH_3$), 20.8 ($CH_3$), 42.4 ($CH_2$), 44.3 (C), 49.7 ($CH_2$), 50.0 ($CH_2$), 60.9 ($CH_2$), 62.0 ($CH_2$), 62.1 ($CH_2$), 63.0 ($CH_2$), 63.0 ($CH_2$), 67.4 ($CH_2$), 67.5 ($CH_2$), 68.8 (CH), 70.5 (CH), 71.2 (CH), 71.3 ($CH_2$), 100.5 (CH), 100.6 (CH), 107.0 (CH), 114.8 (CH), 115.5 (CH), 116.2 (CH), 124.5 (CH), 125.1 (CH), 133.6 (C), 137.1 (C), 143.7 (C), 144.5 (C), 152.3 (C), 152.5 (C), 156.1 (C), 169.5 (C), 169.9 (C), 170.0 (C); no more azide or alkyne absorption in IR spectroscopy; *m*/*z* (MALDI-TOF) for $C_{612}H_{795}O_{261}N_{81}Si_9$-NaCu 13 801 $[M + NaCu]^+$, found 13 801. Anal. Calcd $C_{612}H_{795}O_{261}N_{81}Si_9$: C, 53.59; H, 5.84. Found: C, 53.29; H, 5.78. DOSY NMR gives $D = 1.85 \times 10^{-10}$ $m^2 \cdot s^{-1}$ in chloroform at 25 °C, which corresponds to a diameter of 4.4 nm; SEC shows the low polydispersity (1.04).

Data for dendrimer $G_2$-81, **3**, $C_{1935}H_{2541}O_{792}N_{243}Si_{36}$: MW 42 888.36 $g \cdot mol^{-1}$; yield 62%; off-white gum; $\delta_H$ (300 MHz, $CDCl_3$, 25 °C, TMS) 0.05−0.12 (s, 54H + 162H, Si−C*H*$_3$), 0.60 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.15 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.66 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.90−2.04 (m, 729H, C*H*$_3$ sugar), 3.31 (m, 81H, $H_{5a}$ sugar), 3.38 (s, 54H, outer Si−C*H*$_2$−O), 3.47 (s, 18H, inner Si−C*H*$_2$−O), 4.04−4.07 (2m, 81H + 81H, $H_2 + H_4$ sugar), 4.19 (m, 81H, $H_{5e}$ sugar), 4.45−4.55 (m, 81H + 162H, $H_{1\beta} + H_{2'}$ sugar), 4.85−4.89 (m, 54H + 162H, O−C*H*$_2-C_{Ar}$ + $H_{1'}$ sugar), 5.08−5.16 (m, 81H + 162H, $H_3$ sugar + O−C*H*$_2-C_{triazole}$), 6.77−7.00 (m, 201H, $H_{Ar}$), 7.88 (s, 81H, $H_{triazole}$); $\delta_C$ (62.9 MHz, $CDCl_3$, 25 °C, TMS) −4.6 ($CH_3$), 14.2 ($CH_2$), 17.8 ($CH_2$), 20.6 ($CH_3$), 20.7 ($CH_3$), 20.8 ($CH_3$), 42.4 ($CH_2$), 44.3 (C), 50.0 ($CH_2$), 60.9 ($CH_2$), 62.1 ($CH_2$), 63.1 ($CH_2$), 67.4 ($CH_2$), 67.5 ($CH_2$), 68.8 (CH), 70.5 (CH), 71.2 (CH), 71.4 ($CH_2$), 100.6 (CH), 107.0 (CH), 114.9 (CH), 115.6 (CH), 116.2 (CH), 124.5 (CH), 125.1 (CH), 133.6 (C), 137.2 (C), 143.7 (C), 144.5 (C), 152.3 (C), 152.5 (C), 156.1 (C), 169.5 (C), 169.9 (C), 170.0 (C); no more azide or alkyne absorption in IR spectroscopy. Anal. Calcd for $C_{1935}H_{2541}O_{792}N_{243}Si_{36}$: C, 54.19; H, 5.97. Found: C, 54.14; H, 5.92%. DOSY NMR gives $D = 1.55 \times 10^{-10}$ $m^2 \cdot s^{-1}$ in chloroform at 25 °C, which corresponds to a size of 5.2 nm; SEC shows the low polydispersity (1.04).

Data for dendrimer $G_3$-243, **4**, $C_{5904}H_{7779}O_{2385}N_{729}Si_{117}$: MW 130 408.18 $g \cdot mol^{-1}$; yield 51%; off-white gum; $\delta_H$ (300 MHz, $CDCl_3$, 25 °C, TMS) 0.05−0.12 (m, 54H +162H + 486H, Si−C*H*$_3$), 0.60 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.15 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.66 (s, 18H + 54H + 162H, $CH_2-CH_2-CH_2-$Si), 1.90−2.04 (m, 2187H, C*H*$_3$ sugar), 3.30−3.47 (m, 18H + 54H + 162H + 243H, inner Si−C*H*$_2$−O + outer Si−C*H*$_2$−O + $H_{5a}$ sugar), 3.9−4.2 (3m, 3 × 243H, $H_2 + H_4 + H_{5e}$ sugar), 4.45−4.55 (m, 243H + 486H, $H_{1\beta} + H_{2'}$ sugar), 4.85−4.89 (m, 162H + 486H, O−C*H*$_2-C_{Ar}$ + $H_{1'}$ sugar), 5.08−5.16 (m, 243H + 486H, $H_3$ sugar + O−C*H*$_2-C_{triazole}$), 6.77−7.00 (m, 633H, $H_{Ar}$), 7.88 (s, 243H, $H_{triazole}$); $\delta_C$ NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS) −4.4 ($CH_3$), 14.6 ($CH_2$), 17.9 ($CH_2$), 20.7 ($CH_3$), 20.8 ($CH_3$), 20.8 ($CH_3$), 42.4 ($CH_2$), 44.3, 49.7 ($CH_2$), 50.0 ($CH_2$), 61.0 ($CH_2$), 62.0 ($CH_2$), 62.2 ($CH_2$), 63.1 ($CH_2$), 67.4 ($CH_2$), 67.5 ($CH_2$), 68.8 (CH), 70.5 (CH), 71.2 (CH), 71.8 ($CH_2$), 100.5 (CH), 100.6 (CH), 107.0 (CH), 114.8 (CH), 115.6 (CH), 116.3 (CH), 124.5 (CH), 125.6 (CH), 134.1 (C), 137.2 (C), 143.8 (C), 144.5 (C), 152.3 (C), 152.5 (C), 156.1 (C), 169.9 (C), 170.0 (C), 170.1 (C); no more azide or alkyne absorption in IR spectroscopy. Anal. Calcd for $C_{5904}H_{7779}O_{2385}N_{729}Si_{117}$: C, 54.38; H, 6.01. Found: C, 53.65; H, 6.35. DOSY NMR gives $D = 9.5 \times 10^{-11}$ $m^2 \cdot s^{-1}$ in chloroform at 25 °C, which corresponds to a size of 8.5 nm; DLS gives a size of 7.1 ± 0.9 nm in dichloromethane at 25 °C; SEC shows the low polydispersity (1.05).

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**Supporting Information Available:** General data, spectroscopic data including $^1H$ NMR, $^{13}C\{^1H\}$ NMR, IR and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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