ORGANIC LETTERS

2004
Vol. 6, No. 23
4277−4280

# Sugars within a Hydrophobic Scaffold: Glycodendrimers from Polyphenylenes

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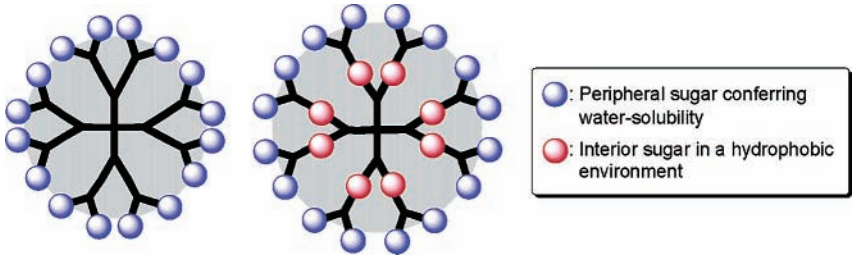
**Received August 27, 2004**

## ABSTRACT




**A new glycodendrimer type has been introduced that is designed on the basis of shape-persistent polyphenylene dendrimers. The sugar installation occurs not only on the dendrimer surface but also within the hydrophobic internal scaffold. The synthesis has been accomplished via both convergent and divergent routes by employing the Schmidt glycosylation and the Diels–Alder reaction. This new glycodendrimer has been found to exhibit water-solubility, while conserving hydrophobicity of the interior environment despite the incorporation of sugars.**

Glycodendrimers attract much interest, not only because of their inherent water solubility but also as synthetic models of glycoconjugates.[1] Thus, incorporation of sugars into dendrimers has been focused primarily at the peripheral sites.[2] On the other hand, the dendrimer interior has attracted little attention as a site for sugar installation, despite the unique microenvironment that it provides. In the present study, a new glycodendrimer type has been prepared on the basis of shape-persistent polyphenylene dendrimers.[3] Thereby, sugar installation occurs not only on the dendrimer surface but also within the hydrophobic internal scaffold. The present paper describes the synthesis via both convergent[4] and divergent[5] routes. Water solubility of the new glycodendrimer and the interior hydrophobicity are also discussed.

The convergent synthesis has been accomplished by the alternating use of the Schmidt glycosylation[6] and the Diels−Alder reaction starting from the peripheral sugar described as follows (Scheme 1). First, the Schmidt glycosylation between 3,4,6-*O*-triacetyl-2-deoxy-2-phthalimido-D-glucopyranosyl trichloroacetimidate (**1**) and 3,4-di(4-hydroxymethylphenyl)-2,5-diphenylcyclopentadienone[3] (**2**) afforded the corresponding $\beta$-glycosyl product **3**; the cyclopentadienone moiety was stable during all of the Schmidt glycosylations described herein employing trimethylsilyl trifluoromethanesulfonate as a catalyst over the temperature range −40 to 0 °C for 30 min in dry dichloromethane. Second, the cyclopentadienone moiety of **3** was applied to the Diels−Alder reaction with *p*-methoxyphenyl 4,6-*O*-diacetyl-2-deoxy-2-phthalimido-3-*O*-propargyl-$\beta$-D-glucopyranoside (**4**) where [4 + 2] cycloaddition occurred with elimination of carbon monooxide[3] to produce **5**. It should be noted that the sugar moieties were found to be stable under the conditions of all Diels−Alder reactions described herein (160 °C, 3−20 h,

(1) See, for example: (a) Kunz, H.; Vondembruch, K. *Methods Enzymol.* **1994**, *247*, 3. (b) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321.

(2) See, for example: (a) Aoi, K.; Itoh, K.; Okada, M. *Macromolecules* **1995**, *28*, 5391. (b) Lindhorst, T. K.; Kieburg, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1953. (c) Jayaraman, N.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Eur. J.* **1997**, *3*, 1193. (d) Zanini, D.; Roy, R. *J. Org. Chem.* **1998**, *63*, 3486.

(3) See, for example: (a) Morgenroth, F.; Müllen, K. *Tetrahedron* **1997**, *53*, 15349. (b) Wiesler, U. M.; Weil, T.; Müllen, K. *Top. Curr. Chem.* **2001**, *212*, 1.

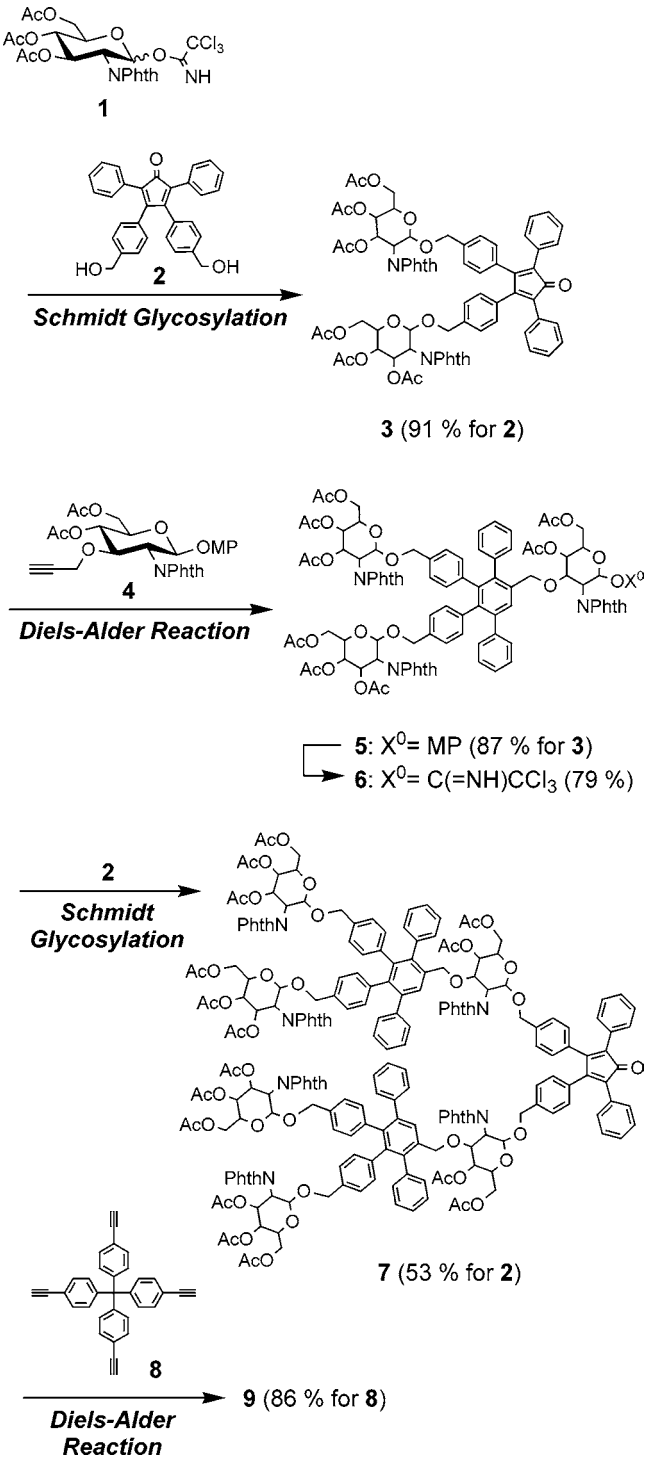
(4) Frechet, J. M. J.; Hawker, C. J. *Comprehensive Polymer Science*, 2nd Supplement; Pergamon: Oxford, England, 1996; pp 140−206.

(5) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Syntheses, Perspectives*; VCH: Weinheim, Germany, 1996.

(6) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

10.1021/ol048282l CCC: $27.50 
**Published on Web 10/12/2004**

**Scheme 1.** Convergent Synthetic Route




diphenyl ether under argon). After the anomeric *p*-methoxyphenyl(MP)-oxy group of **5** was converted to trichloroacetimidate,[7] the activated glycosyl donor **6** was subjected to the Schmidt glycosylation with **2** to afford the corresponding *β*-glycosyl product **7**. A second generation dendrimer **9** (Scheme 3a), which is a precursor of the glycodendrimer **18**, was then obtained by the Diels−Alder reaction between **7** and the tetra(4-ethynylphenyl)methane core (**8**).[3]

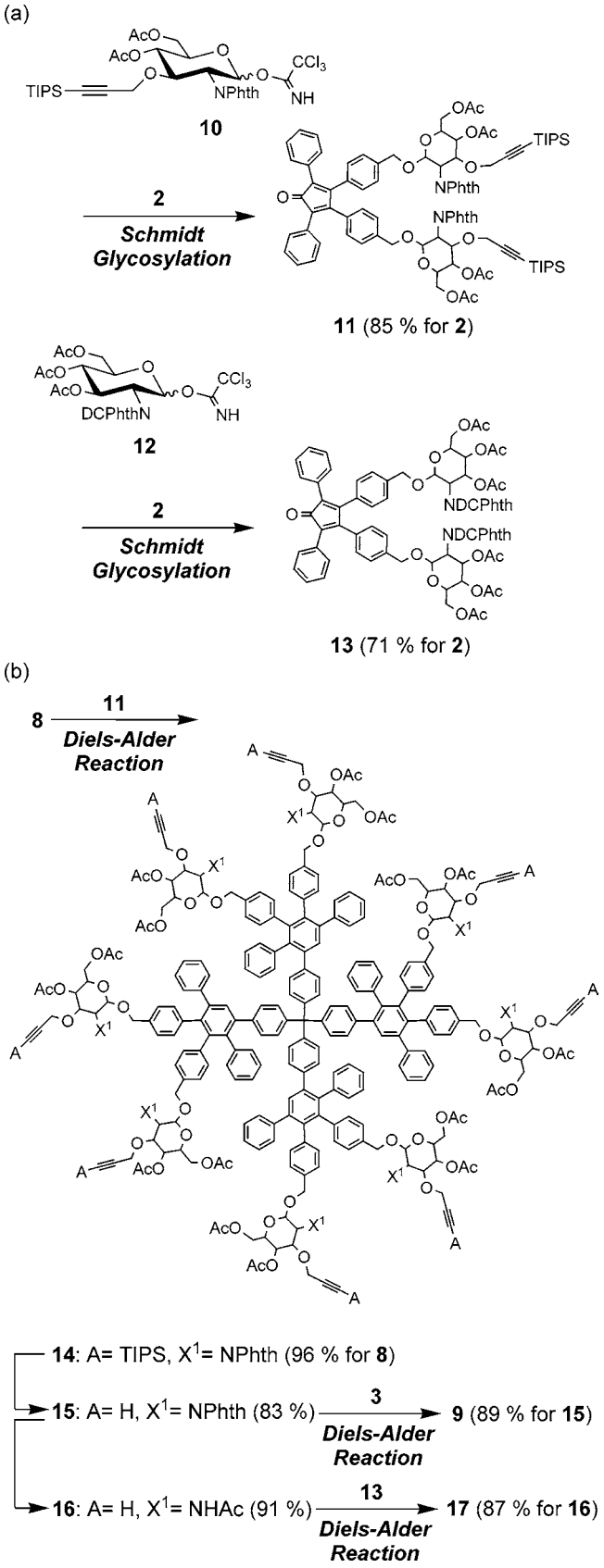
(7) Lergenmüller, M.; Ito, Y.; Ogawa, T. *Tetrahedron* **1998**, *54*, 1381.

On the other hand, the divergent synthesis of the dendrimer **9** was also achieved. The $AB_2$ building block **11** was prepared by the Schmidt glycosylation of **2** with 4,6-*O*-diacetyl-2-deoxy-2-phthalimido-3-*O*-(1-triisopropylsilylpropargyl)-D-glucopyranosyl trichloroacetimidate (**10**), where the cyclopentadienone moiety and the ethynyl group correspond to the A- and B-functions, respectively (Scheme 2a). The dendrimer was divergently constructed starting from the core by employing the Diels−Alder reaction as follows (Scheme 2b). First, the tetra(4-ethynylphenyl)methane core (**8**) was subjected to the Diels−Alder reaction with the $AB_2$ building blocks **11** to give the first generation dendrimer **14**; the triisopropylsilyl(TIPS)-protected ethynyl groups were stable during the present Diels−Alder reaction.[3] After the TIPS groups were removed with *n*-$Bu_4NF$ in THF (**14** to **15**), the first generation dendrimer carrying eight ethynyl groups at the periphery, **15**, was subjected to the Diels−Alder reaction with the end-capping blocks **3** to afford the second generation dendrimer **9**. Spectroscopic data such as $^1H$ NMR, $^{13}C$ NMR, $^1H-^1H$ COSY, $^1H-^{13}C$ COSY, and MALDI-TOF mass spectra indicated that both the convergent and the divergent routes lead to the identical dendrimer **9**. The glycodendrimer **18** (Scheme 3a) was finally obtained from **9** by O-deacetylation with methylamine and N-dephthaloylation with ethylenediamine under reflux in methanol quantitatively.

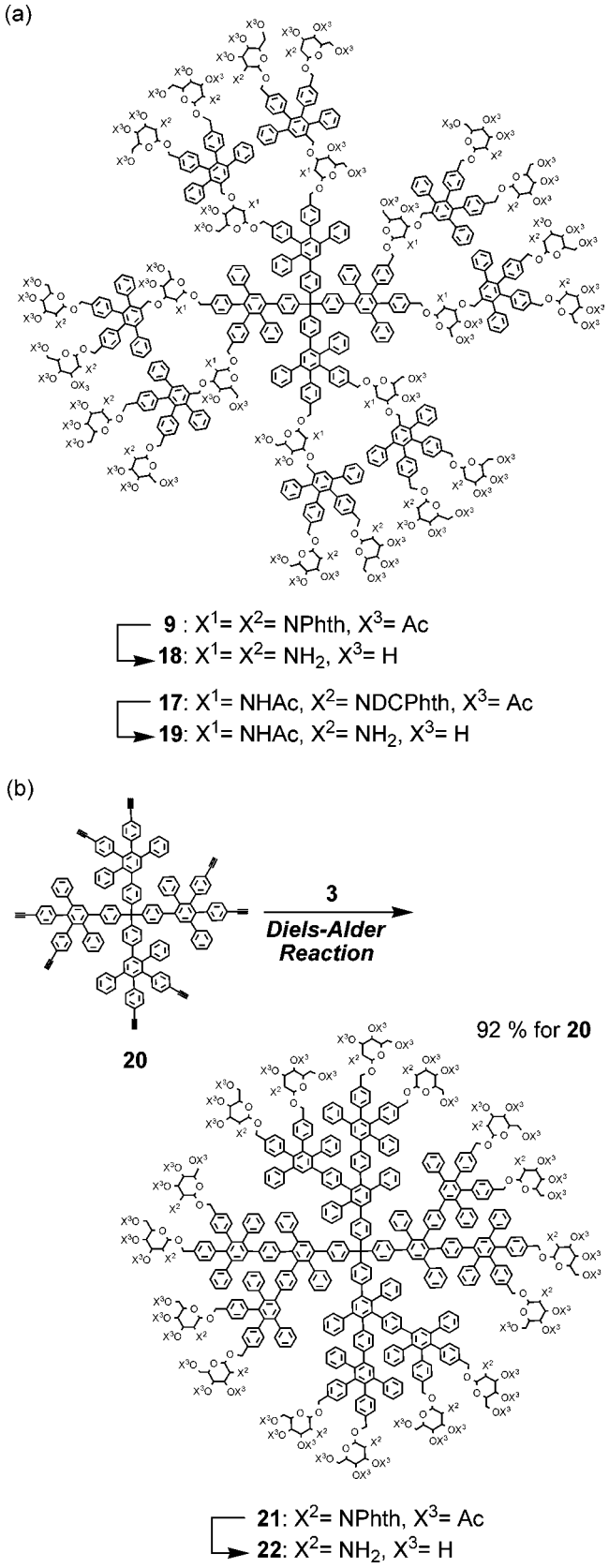
Synthesis of the other new glycodendrimer, which is composed of two different sugar layers, also has been accomplished via the divergent route. Thereby, the phthalimido groups of the first generation dendrimer **15** were converted to the acetamido groups (**16**) in advance (Scheme 2b), so that the following Diels−Alder reaction with the end-capping block **13** afforded the second generation dendrimer **17** (Scheme 3a); **13** was prepared by the Schmidt glycosylation of **2** with 3,4,6-*O*-triacetyl-2-deoxy-2-(4,5-dichlorophthalimido)-D-glucopyranosyl trichloroacetimidate (**12**) (Scheme 2a). The glycodendrimer **19** was finally obtained by removal of the protecting groups; the 4,5-dichlorophthaloyl (DCPhth) groups were cleaved off selectively at room temperature with retention of the *N*-acetyl groups of the internal sugar moieties (Scheme 3a).[7] In addition, a hitherto known type of glycodendrimer that possesses sugar moieties just at the periphery also has been prepared from a shape-persistent polyphenylene dendrimer[3] (Scheme 3b). The Diels−Alder reaction between a first generation polyphenylene dendrimer **20**[3] and **3** has afforded a second generation dendrimer **21**, followed by deprotection to give the glycodendrimer **22**.

All of the present glycodendrimers were found to exhibit good solubility in weakly acidic aqueous solutions (e.g., acetate buffer, pH < 4.0), as well as in dimethyl sulfoxide, as a result of the amino sugar moieties at the periphery. In contrast to the hydrophilic dendrimer surface, the interior environment of the glycodendrimers was revealed to be hydrophobic by employing 8-anilino-naphthalene-1-sulfonic acid ammonium salt (ANS) as a fluorescent probe.[8] ANS was added to aqueous solutions (acetate buffer, 100 mM, pH 3.6) of **18**, **19**, and **22**, adjusting the concentrations to be $2.1 \times 10^{-5}$ M for ANS and $2.2 \times 10^{-5}$ M for the

**Scheme 2.** Divergent Synthetic Route




**Scheme 3.** Polyphenylene-Based Glycodendrimers




glycodendrimer. Fluorescence spectroscopy measurements allowed the observation of a remarkable hypsochromic shift (from 520 to 470 nm) and hyperchromic effect on the fluorescence of ANS for all solutions containing the glyco-

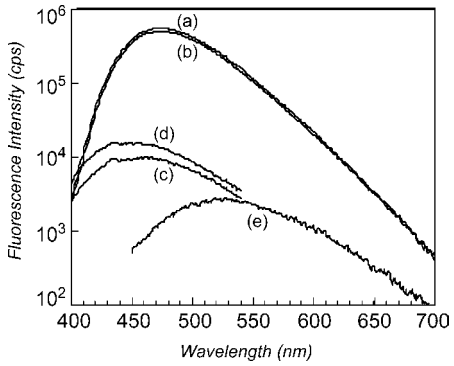



**Figure 1.** Fluorescence spectra of aqueous solutions of (a) ANS with **18**, (b) ANS with **22**, (c) **18** only, (d) **22** only, and (e) ANS only. The concentrations of ANS and the glycodendrimer are adjusted to be $2.1 \times 10^{-5}$ M and $2.2 \times 10^{-5}$ M, respectively. The excitation wavelength was 370 nm.

dendrimers; the peak fluorescence intensity is ca. $10^2$ times higher than that of an aqueous solution containing ANS only (Figure 1; data for **19** not shown). This phenomenon is typically observed for ANS when its nonradiative relaxation, the dominant process for relaxation in water, is suppressed as a result of a decrease in the polarity of the environment around ANS.[8] The experimental results described herein suggest that ANS is accommodated inside the glycodendrimers **18** and **19** (possessing internal sugar moieties), as well as within **22** (which possesses only hydrophobic phenylene moieties in its interior). Even with the sugar incorporation of **18** and **19**, hydrophobicity of the dendrimer interior environment is conserved.

In conclusion, a new glycodendrimer type that incorporates sugar moieties within a hydrophobic scaffold has been introduced. Such interior sugar moieties are very unique and reminiscent of an active center situated inside a hydrophobic pocket of natural enzymes.[9] It is expected that the interior sugar moieties will form inherently stable hydrogen bonds with a guest and may eventually lead to molecular recognition. In this regard, further investigation, especially in terms of the guest selectivity of the present glycodendrimer as host, is in progress.

**Supporting Information Available:** Synthetic procedure for **4** and **10** and spectroscopic data of **3**, **5**, **7**, **9**, **11**, **13**, **14**, **17**, **18**, **19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.* **2001**, *101*, 3793.