ORGANIC LETTERS

2001
Vol. 3, No. 25
4019−4022

Trehalose-Based Octopus Glycosides for the Synthesis of Carbohydrate-Centered PAMAM Dendrimers and Thiourea-Bridged Glycoclusters

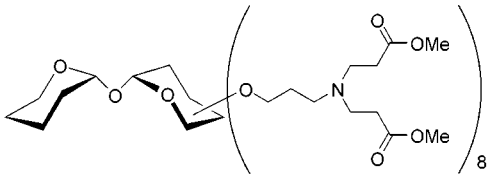
Michael Dubber and Thisbe K. Lindhorst*

Institut für Organische Chemie, Christian-Albrechts-Univeristät zu Kiel, Otto-Hahn-Platz 4, D-24098 Kiel, Germany

tklind@oc.uni-kiel.de

Received September 7, 2001

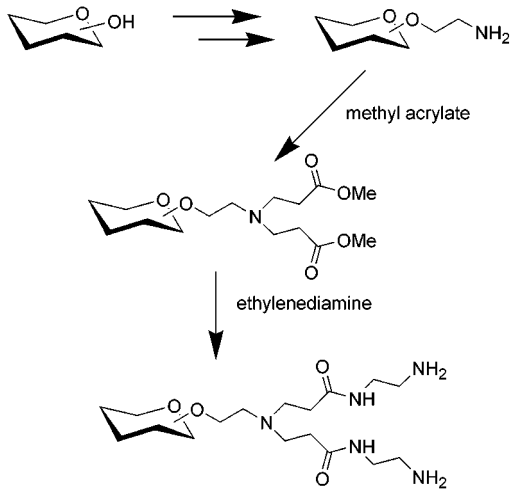
ABSTRACT



The nonreducing disaccharide trehalose was modified into an octa-amino-functionalized core molecule to serve in the synthesis of carbohydrate-centered PAMAM glycodendrimers and thiourea-bridged glycoclusters.

After numerous routes for the synthesis of dendrimers have been elaborated in recent years, today's dendrimer research emphasizes the development of useful applications of functional dendrimers.[1] Early on, PAMAM (polyamido amine) dendrimers[2] became interesting molecules in transfection, as it was shown that they are able to transfer DNA into eukaryotic cells.[3] To synthesize core-modified PAMAM dendrimers, which might have advantageous properties compared to their promising original counterparts, we have recently introduced carbohydrate-centered analogues.[4] First, D-glucose was transformed into its per-aminoethyl-functionalized derivative, which was then submitted to the iterative reaction sequence for the construction of PAMAM genera-

Scheme 1. Synthetic Approach to Carbohydrate-Centered PAMAM Dendrimers[a]



[a] This method has been successful with D-glucose.[4]

(1) (a) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci*. **1998**, *23*, 1−56. (b) Vögtle, F.; Fischer, M. *Angew. Chem.* **1999**, *111*, 934−955; *Angew. Chem., Int. Ed*. **1999**, *38*, 884−905. (c) Hecht, S.; Fréchet, J. M. J. *Angew. Chem.* **2001**, *113*, 76−94; *Angew. Chem., Int. Ed.* **2001**, *40*, 74−91.

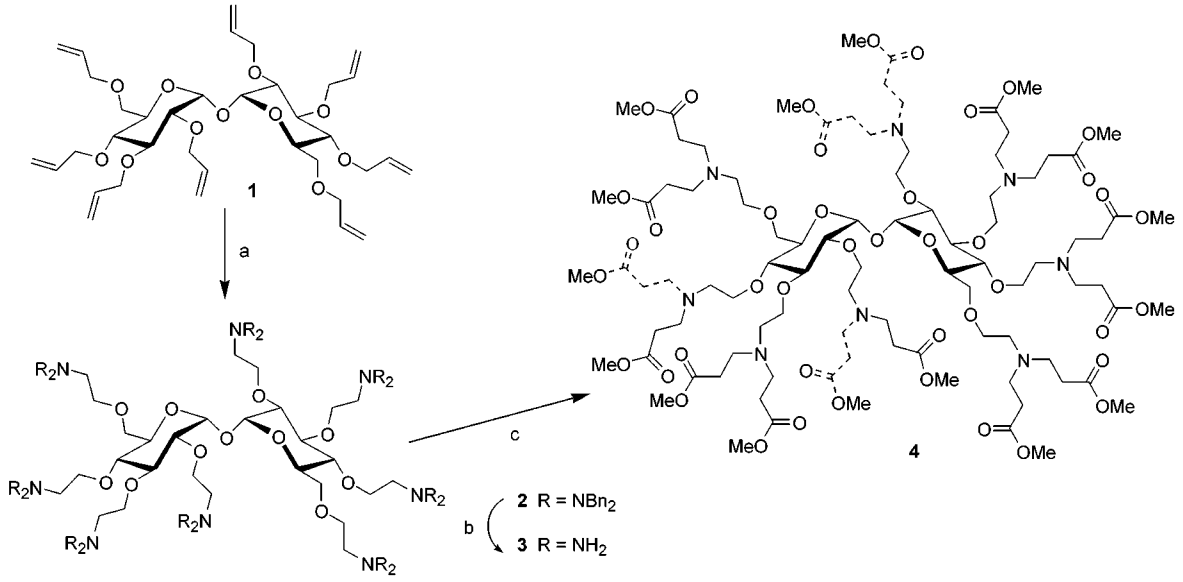
(2) Tomalia; D. A.; Baker, H.; Dewald, J. R. *Polym. J.* **1985**, *17*, 117−132.

(3) Tang, M. X.; Redemann, C. T.; Szoka, F. C. *Bioconjugate Chem.* **1996**, *7*, 703−714.

(4) Dubber, M.; Lindhorst, Th. K. *Chem. Commun.* **1998**, 1265−1266.

10.1021/ol016717o CCC: $20.00
Published on Web 11/14/2001

Scheme 2[a]



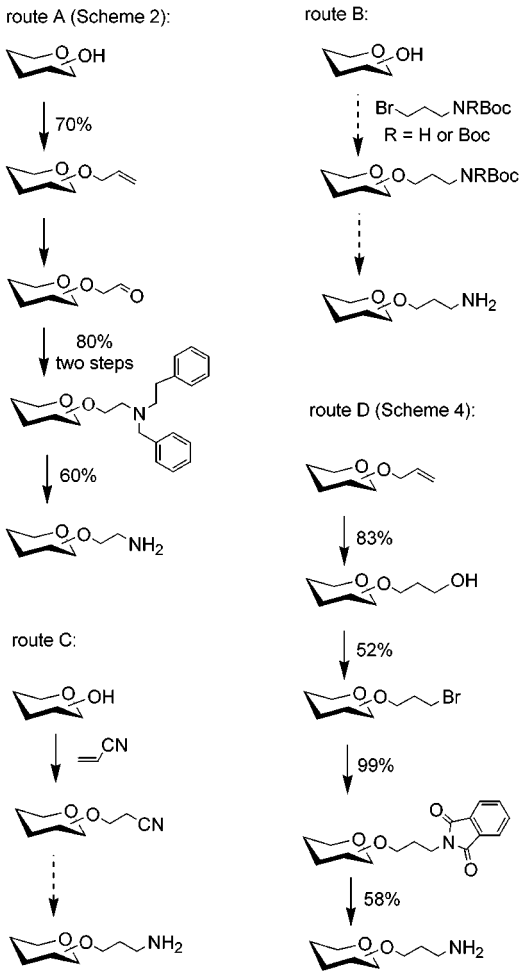
[a] Key: (a) CH_2Cl_2−MeOH 5:1, $NaHCO_3$, O_3, 15 min, −78 °C, then PPh_3, 12 h, then dibenzylamine, $NaBH(OAc)_3$, CH_2Cl_2, 80%; (b) Pd−C, NH_4CO_2, MeOH, reflux, 60%; (c) methyl acrylate, MeOH, led to a polydisperse mixture of structurally defect molecules.

tions, consisting of the addition to methyl acrylate followed by amidation with ethylenediamine (Scheme 1). It has been our goal to extend this concept, exemplified with glucose, to oligosaccharides such as the nonreducing disaccharide trehalose. First, we followed the route, which had been successful with the monosaccharide, comprising perallylation, ozonization, reductive amination with dibenzylamine, and reductive debenzylation (Scheme 2; Scheme 3, route A).[5] Indeed, this procedure furnished the fully aminoethyl-modified trehalose derivative **3** in good yield. However, when **3** was treated with methyl acrylate in MeOH to give the first PAMAM half-generation, a clean product was not obtained. No reaction conditions that led to a structurally perfect, monodisperse product could be discovered. A polydisperse mixture such as **4** (Scheme 2) was obtained instead, showing significant amounts of defects upon mass spectrometric investigation.

Molecular modeling suggested that steric hindrance prevents the synthesis of structurally perfect trehalose-centered dendrimers of the targeted type. We therefore decided to extend the sugar-linked spacers by one methylene group. Thus, the aminopropyl-modified trehalose-centered core molecule **8** (Scheme 4) became our target. Several routes for its synthesis were investigated (Scheme 3, routes B−D) of which the reaction of trehalose with an amino-protected 3-bromo-propylamine (Scheme 3, route B) represents the shortest pathway. However, this approach was not successful in our hands.

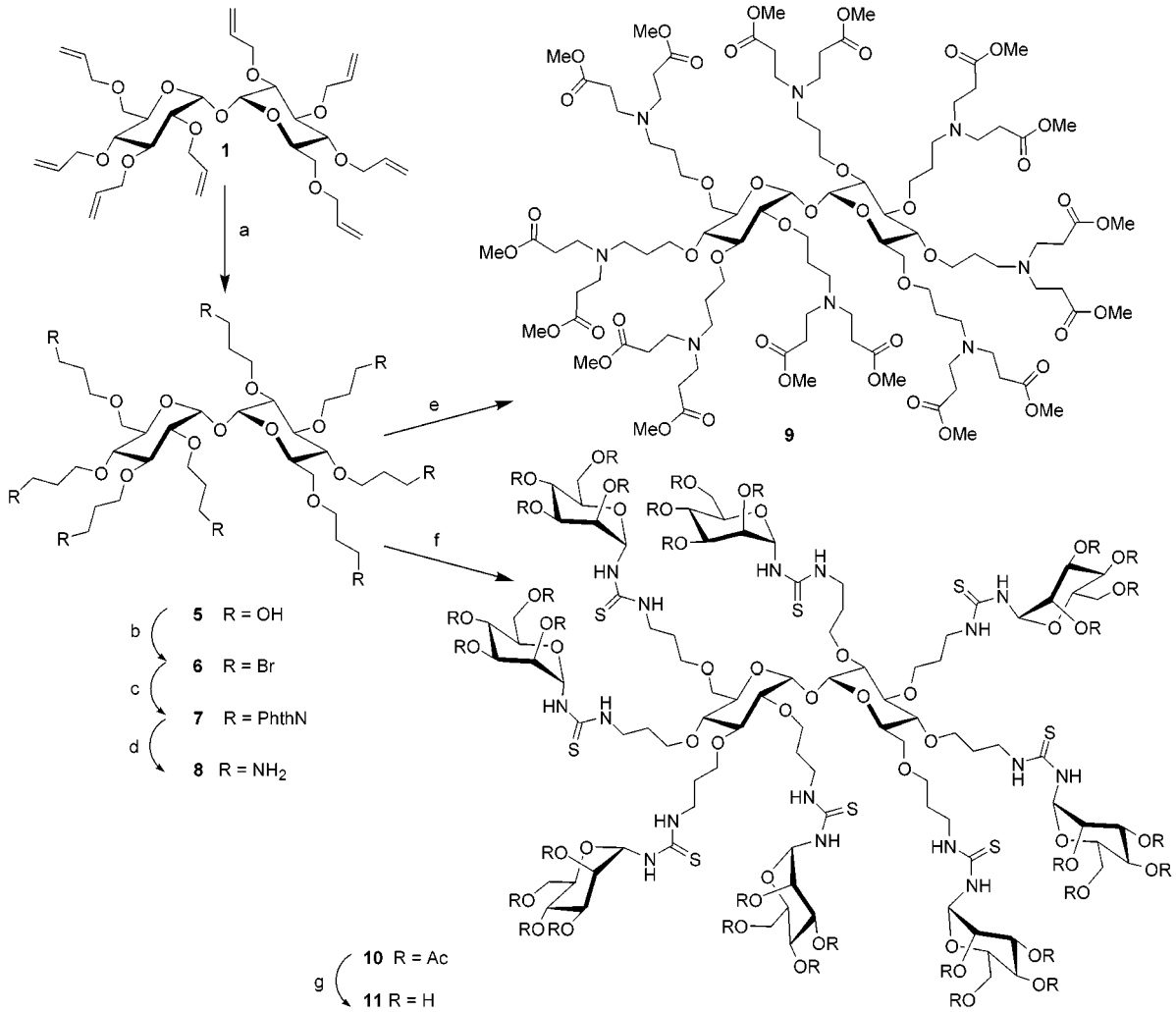
Alternatively, the exhaustive addition to acrylonitrile and subsequent reduction of the resulting oligo-nitrile (Scheme 3, route C) may lead to **8**. While the exhaustive addition of trehalose to acrylonitrile was easily accomplished following

Scheme 3



(5) Dubber, M.; Lindhorst, Th. K. *Carbohydr. Res.* **1998**, *310*, 35−41.

Scheme 4[a]



[a] Key: (a) 9-BBN, THF, then NaOH, H_2O_2, 83%;[8] (b) CBr_4, PPh_3, THF, 63%; (c) KPhthN, DMF, 99%; (d) NH_2NH_2, THF, 58%; (e) methyl acrylate, MeOH, 94%; (f) 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl isothiocyanate, CH_2Cl_2, 4 h, 41%; (g) NaOMe, MeOH, 87%.

a procedure of Newkome,[6] reduction of the resulting octanitrile led to complex product mixtures. Due to the sensitivity of the intraglycosidic bond in trehalose, standard reduction protocols, which are also applied in dendrimer chemistry,[7] were not applicable. Milder procedures, on the other hand, always led to the formation of secondary amines as side products, which could not be separated from the product.

Finally, we envisaged utilizing hydroxypropyl-functionalized trehalose **5**, which we have recently described in the context of glycocluster synthesis.[8] The octa-ol **5** can be easily obtained by hydroboration of octa-*O*-allyl-trehalose **1** (Scheme 4). An Appel reaction[9] is suited to convert **5** into its bromo-functionalized analogue **6** in sufficient yield. Subsequent Gabriel synthesis[10] finally gave the desired octa-*O*-aminopropyl-modified trehalose derivative to be used as a core molecule in PAMAM synthesis. Even though route D is the longest of a collection of four alternatives, it proved to be very convenient for this purpose.

When **8** was used as the core molecule in PAMAM synthesis, the first half-generation trehalose-centered dendrimer was obtained as a monodisperse product without structural defects (Scheme 4).

We will eventually evaluate the construction of higher dendrimer generations. Here, we also demonstrate that **8** can be favorably used for the synthesis of glycoclusters. As carbohydrate clusters form crucial ligands in numerous biological recognition processes[11] such as in the mannose-

(6) Newkome, G. R.; Lin, X.; Young, J. K. *Synlett* **1992**, 53−54.

(7) (a) Moors, R.; Vögtle, F. *Chem. Ber.* **1993**, *126*, 2133−2135. (b) Wörner, C.; Mülhaupt, R. *Angew. Chem.* **1993**, *105*, 1367−1369, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1306−1308. (c) de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem.* **1993**, *105*, 1370; *Angew. Chem., Int. Ed.* **1993**, *32*, 1308.

(8) Dubber, M.; Lindhorst, Th. K. *J. Org. Chem.* **2000**, *65*, 5275−5281.

(9) Appel, R. *Angew. Chem.* **1975**, *87*, 863−874; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.

(10) Gabson, M. S.; Bradshaw, R. W. *Angew. Chem.* **1968**, *80*, 986−996; *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919−929.

(11) *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbour Laboratory Press: Spring Harbor, Plainview, NY, 1999.

specific adhesion of *Escherichia coli* bacteria to their host cells,[12] the synthesis of multivalent glycoligands[13] forms an interesting field of glycobiology.[14]

Thiourea bridging is an especially successful technique in glycocluster synthesis.[15] When **8** was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl isothiocyanate, the octavalent thiourea-bridged mannose cluster **10** was obtained in a clean reaction and easily deprotected to give the free glycocluster **11**.

In conclusion, we found a versatile way to transfer trehalose into an octa-amino-functionalized core molecule, which can be employed in various ways. Two possibilities, the syntheses of trehalose-centered dendrimers and glycoclusters, are demonstrated in this contribution. The potential of the research presented herein will invite the use of the described chemistry also for applications in a different context such as that recently shown with the glucose-centered predecessor of **8**.[16]

Acknowledgment. We thank Dr. R. Esfand for the helpful discussions. We are indebted to Dr. V. Sinnwell and to Dr. C. Wolff for performing the NMR experiments. Support of this work by FCI and Karl-Ziegler-Stiftung is gratefully acknowledged.

Supporting Information Available: Full experimental details, ^{1}H NMR as well as ^{13}C NMR spectroscopic data, and MALDI-TOF-MS data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016717O

(12) Lindhorst, Th. K.; Kieburg, C.; Krallmann-Wenzel, U. *Glycoconjugate J.* **1998**, *15*, 605−613.

(13) (a) Roy, R. *TIGG* **1996**, *8*, 79−99. (b) Roy, R. *Curr. Opin. Struct. Biol.* **1996**, *6*, 692−702. (c) Zanini, D.; Roy, R. In *Carbohydrate Mimics, Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; pp 385−415. (d) Roy, R. *Carbohydr. Eur.* **1999**, *27*, 34−41. (e) Jayaraman, N.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Eur. J.* **1997**, *3*, 1193−1199. (f) Ashton, P. R.; Hounsell, E. F.; Jayaraman, N.; Nilsen, T. M.; Spencer, N.; Stoddart, J. F. *J. Org. Chem.* **1998**, *63*, 3429−3437. (g) Turnbull, W. B.; Pease, A. R.; Stoddart, J. F. *ChemBioChem* **1998**, *1*, 70−74. (h) Kitov, P. I.; Sadowska, J. M. M.; Mulvey, G.; Amstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669−672. (i) Fan, E.; Zhang, Z.; Minke, W. E.; Hou, Z.; Verlinde, C. L. M. J.; Hol, W. G. J. *J. Am. Chem. Soc.* **2000**, *122*, 2663−2664.

(14) (a) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321−327. (b) Kiessling, L. L.; Pohl, N. L. *Chem. Biol.* **1996**, *3*, 71−77. (c) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem.* **1998**, *110*, 2908−2953; *Angew. Chem., Int. Ed.* **1998**, *37*, 2754−2794. (d) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357−2364.

(15) (a) Lindhorst, Th. K.; Kieburg, C. *Angew. Chem.* **1996**, *108*, 2083−2086; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1953−1956. (b) Pagé, D.; Roy, R. *Bioconjugate Chem.* **1997**, *8*, 714−723. (c) Ortiz-Mellet, C.; Benito, J. M.; García Fernández, J. M.; Law, H.; Chmurski, K.; Defaye, J.; O'Sullivan, M. L.; Caro, H. N. *Chem. Eur. J.* **1998**, *4*, 2523−2531.

(16) de Santiago, R.; Fernández-Mayoralas, A.; García-Junceda, E. *J. Mol. Catal. B: Enzym.* **2000**, *11*, 71−79.