Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 1715–1725
Carbohydrate RESEARCH

Synthesis of new polyether glycodendrons as oligosaccharide mimetics

Katharina Elsner, Mike M. K. Boysen* and Thisbe K. Lindhorst*

Otto Diels Institute of Organic Chemistry, Christiana Albertina University of Kiel, Otto-Hahn-Platz 4, D-24098 Kiel, Germany

Received 5 March 2007; received in revised form 25 April 2007; accepted 6 May 2007
Available online 18 May 2007

Dedicated to Professor Dr. Joachim Thiem on the occasion of his 65th birthday

Abstract—Divalent and tetravalent glycomimetics based on polyether glycodendrons have been prepared. The branched scaffolds were decorated with galactose moieties on one hand and were elaborated into new glycodendrons of a 'mixed' type on the other, carrying both galactose and mannose moieties as biologically important sugar epitopes. All synthesized glycodendrons possess a focal point that can be employed for further derivatization and functionalization.

Keyword: Glycomimetics; Glycodendrimers; Mixed glycodendrons

1. Introduction

To mimic the complex and hyperbranched structure of oligosaccharides occurring on cell surfaces,[1] glycodendrimers and glycodendrons serve as valuable tools.[2] Their preparation is thought to be rather facile and highly flexible; however, the synthesis of such multivalent neoglycoconjugates does not always live up to expectations, as it can be laborious and limited to small scale synthesis.[3]

We have recently introduced a new class of aliphatic polyether glycodendrimers,[4] which can be easily prepared even in gram quantities. Our approach was based on chemistry reported by Fréchet and co-workers for the synthesis of aromatic polyether dendrimers.[5] This efficient strategy involves a sequence of repetitive Williamson etherifications with 3-chloro-2-chloromethyl-1-propene (methallyldichloride) and hydroboration–oxidation of the double bond with 9-BBN resulting in a convergent dendrimer synthesis.[6] Methallyldichloride serves as an activated alkenyl dihalogenide, possessing two leaving groups in allylic positions and yielding a single product no matter whether an S_N2 or S_N2' mechanism is operative. Polyether glycodendrimers are chemically robust, soluble in aqueous media and insensitive to pH changes. Furthermore, in case of possible enzymatic degradation in vivo, they lead only to nontoxic fragments.

This approach has allowed us the synthesis of glycodendrons containing two, four and eight α-mannosyl units, respectively. These compounds are of interest in a biological context and potentially also in material science. In our current studies, we are interested in further developing this chemistry regarding sugar decoration of the aliphatic polyether scaffold. We report here the extension of the polyether glycodendron chemistry to the incorporation of galactose moieties and to the synthesis of glycodendrons of a 'mixed' type, involving the scaffolding of both, mannosyl and galactose residues.

2. Results and discussion

Among many different protecting groups isopropylidene ketals have proved to be ideally compatible with the nec-

* Corresponding authors. Addresses: Institute of Organic Chemistry, Leibniz University of Hannover, Schneiderberg 1B, D-30167 Hannover, Germany (M.M.K.B.). Otto Diels Institute of Organic Chemistry, Christiana Albertina University of Kiel, Otto-Hahn-Platz 4, D-24098 Kiel, Germany; Tel.: +49 431 8802023; fax: +49 431 8807410 (T.K.L.); e-mail addresses: Mike.Boysen@oci.uni-hannover.de; tklind@oc.uni-kiel.de

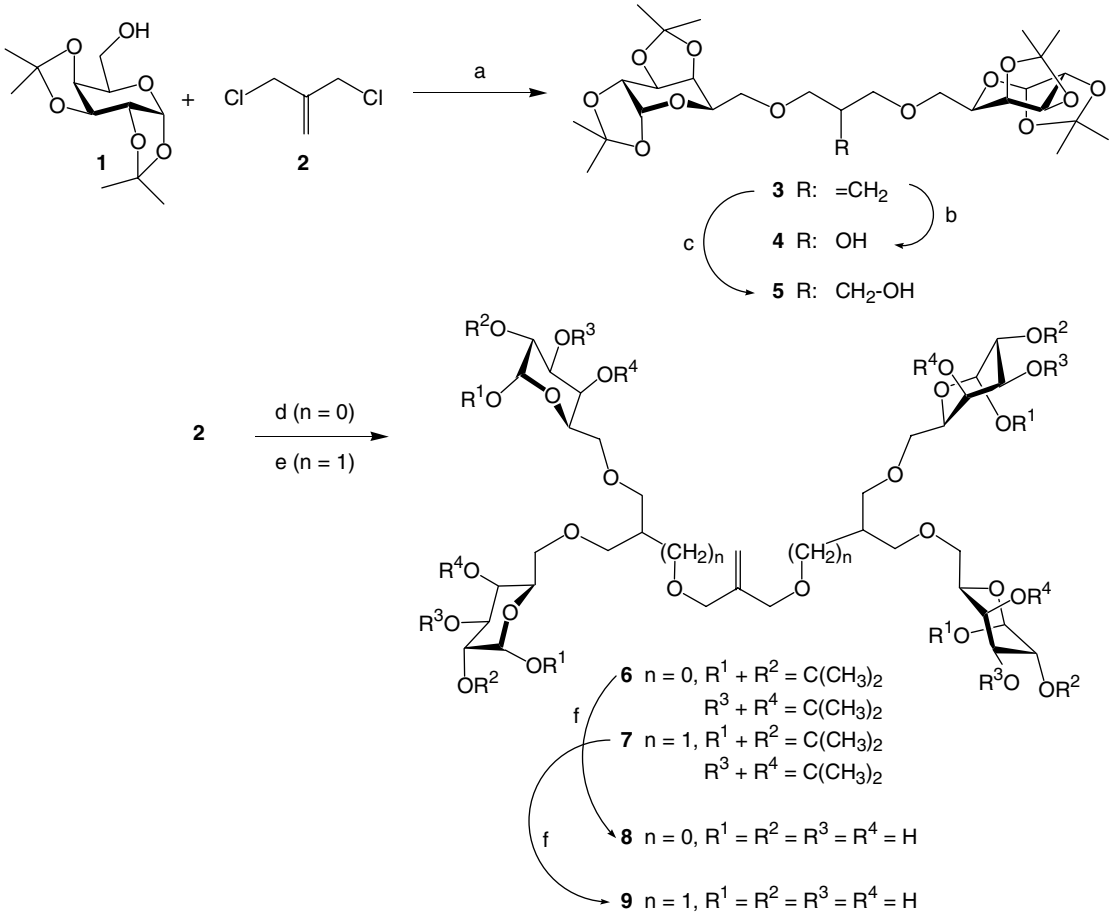
0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.05.005

essary reaction steps involved in the dendron construction.[7] Therefore, to produce polyether glycodendrimers with galactose termini, 1,2:3,4-di-*O*-isopropylidene-galactose (**1**)[8] was employed. In the second part of this work, galactose derivative **1** was scaffolded, together with 2,3:4,6-di-*O*-isopropylidene-protected 2-hydroxyethyl mannoside **14**, to obtain polyether glycodendrons of a mixed type. This approach leads to glycomimetics in which mannose is attached to the scaffold molecule via its anomeric centre, whereas galactose is linked via its 6-position. It has to be kept in mind that the biological activity of 6-linked glycomimetics is not guaranteed and that 6-O-linked galactose does not necessarily mimic a galactose moiety, but might rather resemble another three-dimensional assembly of hydroxyl groups.

2.1. Synthesis of galactos-6-yl glycodendrons

1,2:3,4-Di-*O*-isopropylidene-galactose **1** was deprotonated with NaH in dry THF at the 6-OH group and then reacted with methallyldichloride (MDC, **2**) to give alkene **3** (Scheme 1) with two galactos-6-yl residues in 95% yield. There are two options for further derivatization of the double bond at the focal point of dimer **3**. Ozonolysis followed by reductive workup yields the secondary alcohol **4** with concomitant loss of one carbon, while submission to a hydroboration–oxidation protocol leads to primary alcohol **5**. Ozonolysis of **3** followed by reductive work-up with sodium borohydride proceeded with ease yielding the corresponding alcohol **4** in a quantitative reaction. Without any purification, this product was etherified with MDC, leading to the galactose-decorated polyether glycodendron of the next generation (**6**) as the single product in excellent yield. Deprotection of **6** employing TFA–water yielded the hydrophilic glycocluster **8**, after purification by GPC.

On the other hand, hydroboration of **3**, employing 9-BBN followed by oxidation and hydrolysis with NaOH and H_2O_2 led to **5** in 87% yield, which was in turn subjected to Williamson etherification using MDC (**2**) to yield glycodendron **7** as a more flexible analogue of tetramer **6**. Again, formation of by-products resulting from



Scheme 1. Synthesis of galactos-6-yl glycodendrons **8** and **9**. Reagents and conditions: (a) NaH, THF, 60 °C, 16 h, 95%; (b) (1) O_3; (2) $NaBH_4$, MeOH–CH_2Cl_2 (1:1), −60 °C to rt, 16 h, quant.; (c) 9-BBN, THF, 60 °C, 2 h, NaOH, H_2O_2, 0 °C→rt, 16 h, 87%; (d) **4**, NaH, THF, 60 °C, 16 h, 90%; (e) **5**, NaH, dry THF, 60 °C, 16 h, 54%; (f) TFA–water (9:1), 15 min, rt, 75%; (g) TFA–water (9:1), 15 min, rt, 73%.