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Octopus glycosides: multivalent molecular platforms for testing carbohydrate recognition and bacterial adhesion

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ABSTRACT

Multivalency of carbohydrate–protein interactions is critical for cell adhesion, including attachment of bacteria to their host cells. To investigate specific parameters of multivalency effects, a variety of multivalent glycoconjugates has been designed according to different mimetic approaches. Some 15 years ago, carbohydrates were elaborated as multivalent scaffold molecules for the preparation of carbohydrate-centred 'octopus glycosides' as well as of other carbohydrate-centred glycoconjugates. The beginning of this research is reported from a historical perspective and a selection of interesting applications is highlighted.

1. Introduction

Over many years, it has been our interest to investigate multivalency effects in carbohydrate recognition, employing artificially designed multivalent glycomimetics in solution.[1] This work has been inspired by the importance of multivalency in carbohydrate–protein interactions[2] on the one hand. On the other hand, it was driven by the motivation to access multivalent glycoconjugates or branched oligosaccharides, respectively, much faster than it would be possible by the synthesis of natural oligosaccharide structures. Certainly, it has to be kept in mind that the properties of structural mimetics can be different from those of the natural material. But, carbohydrate mimetics allow systematic alteration of specific structural characteristics and features and thus, testing of carbohydrate mimetics can effectively supplement investigations with natural glycoconjugates.

In order to achieve multivalent glycomimetic architectures, we first used non-carbohydrate dendritic scaffold molecules for functionalization with carbohydrates to furnish, what we called 'glycodendrimers',[3] simultaneously with the research group of René Roy.[4] Concomitantly, we and others started testing such glycodendrimers as inhibitors of bacterial adhesion, in particular of type 1 fimbriae-mediated adhesion of bacterial cells to surfaces (vide infra).[5–8] However, when we realized, that simple glycodendrimers were no especially potent inhibitors of bacterial adhesion per se,[5] we looked for alternative ways of carbohydrate clustering, assuming that the nature of the multivalent scaffold can be critical for affinity and the inhibitory potency of the corresponding multivalent glycoconjugates. This consideration has inspired the idea to use carbohydrates as multivalent scaffold molecules instead of, for example, PAMAM dendrimers.[9]

2. A new type of carbohydrate clustering

We published a first paper about using carbohydrates as multivalent scaffold, entitled 'A new type of carbohydrate clustering: synthesis of a pentavalent glycocluster based on a carbohydrate core'.[10] Here, we started from simple allyl α-D-glucoside (**1**) which was carried on in a Williamson etherification to give the per-allylated glucoside **2**, which can be regarded as first versatile carbohydrate scaffold (Scheme 1). Further functionalization of **2** could be easily achieved by multiple radical addition of thiols to the double bonds of the molecule. Thus, irradiation of the penta-allylated glucoside with cysteamine hydrochloride in MeOH gave the pentaamine **3**, which was obtained in the form of its penta-hydrochloride.

At the time, we referred to the latter reaction as to the 'well-known photoaddition reaction of cysteamine hydrochloride to allyl groups',[10] citing the work of Lee and Lee back in 1974.[11] Today, the addition of thiols such as cysteamine to double bonds is called the

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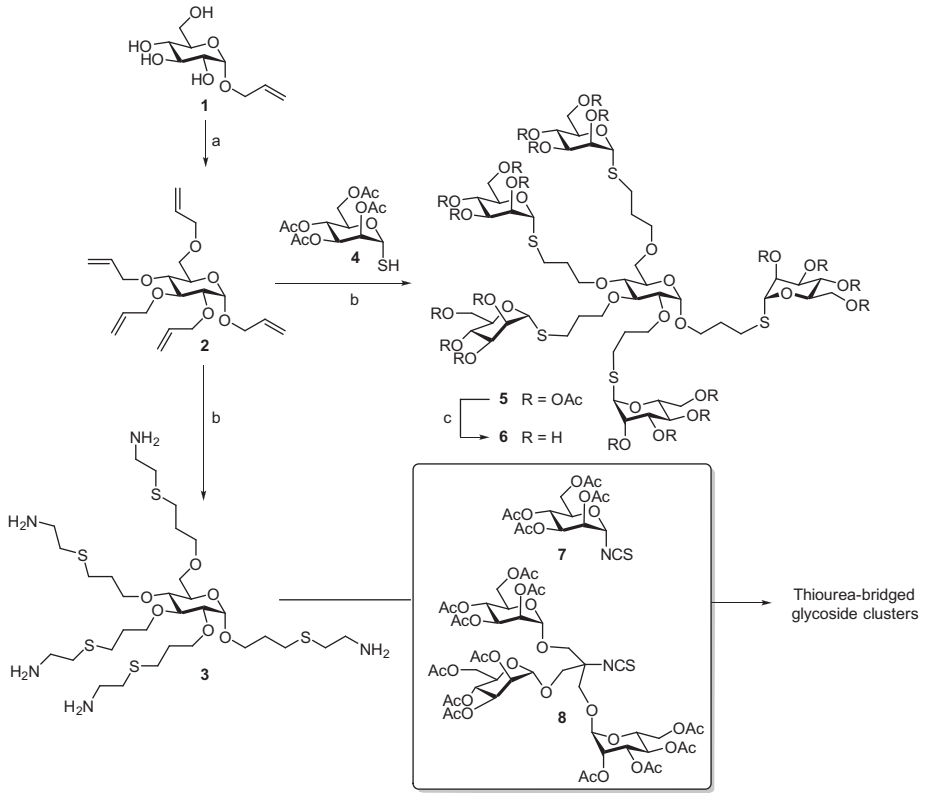

Scheme 1. Reagents and conditions: (a) allyl chloride, NaH, TBABr, 76%. (b) *hν* (254 nm), MeOH, 97% (**3**), 67% (**5**). (c) NaOMe, MeOH, 79%.

'thiol-ene coupling'[12] and in the era of 'click reactions' it is considered as 'click chemistry beyond metal-catalysed cycloaddition'.[13]

In a later paper we have extended this work together with the groups of Ortiz Mellet and García Fernández and used thioglycosides such as **4** to access carbohydrate-centred thioglycoside clusters, for example **5** leading to **6** after de-O-acetylation (Scheme 1).[14] Another reaction of the 'click type',[15] namely thiourea-bridging,[16] was used to convert the pentaamine **3** and NCS-functionalized carbohydrates (e.g., **7**) or carbohydrate clusters (e.g., **8**), respectively, into the corresponding cluster glycosides.[10,14]

The pentavalent carbohydrate core introduced by us, was a little later employed by Kitov et al.,[17a] for the design of an extremely powerful pentavalent inhibitor of the bacterial AB_5 Shiga-like toxin.[17] In this work, glucose was employed as penta-allyl ether and modified by addition of thioglycolic acid and subsequent chain elongation of the radial arms to yield what was called a decameric 'starfish' molecule (Fig. 1).

3. Carbohydrate-centred dendrimers

Next, we have employed carbohydrates as core molecules in various other fields, such as for the synthesis of carbohydrate-centred PAMAM dendrimers.[18] This idea was attractive, as core molecules for PAMAM dendrimer synthesis are typically bi- and trivalent,[9] whereas a core valency of 5 is difficult to realize. Thus, the penta-allylated glucoside **2** was converted into the penta-amine **10** in a reaction sequence of ozonolyis and reductive amination with dibenzylamine leading to **9**, followed by catalytic transfer hydrogenation of the *N*-benzyl protecting groups using ammonium formate as the hydrogen source (Scheme 2). It is interesting to note that reductive amination with benzyl amine (instead of dibenzyl amine), leading to **12**, finally resulted in an inseparable mixture after the terminal debenzylation step, comprising bicyclic by-products as depicted in Scheme 2.[19] This finding was hardly recognized by NMR analysis but mass spectrometry gave the critical hint.

The carbohydrate-centred pentaamine **10** was carried on as core molecule for synthesis of PAMAM-type dendrimers. The reaction sequence consisting of Michael-analogue addition to methyl acrylate and amidolysis using an excess of ethylenediamine in MeOH led to the carbohydrate-centred PAMAM dendrimer of the first generation **11**.

Sometime later we could extend this work to the synthesis of carbohydrate-centred dendrimers on trehalose.[20] Thus, when trehalose was employed as the carbohydrate core en route to PAMAM-type dendrimers (or for preparation of trehalose-centred carbohydrate clusters, respectively), the resulting products we named 'octopus glycosides' owing to the eight functional groups of the non-reducing core carbohydrate. With trehalose, one initial step furnished the per-O-allylated derivative **13** (Scheme 3), which was converted into the respective octaamine according to a synthetic route different from that leading to the allyl glucoside **2** (Scheme 2). Instead of ozonolysis, hydroboration was performed to yield the octa-*O*-(3-hydroxylpropyl)-modified sugar **14**. The following bromination was achieved in an Appel reaction to yield **15**, and then nucleophilic substitution with potassium phthalimide (Gabriel synthesis) led to **16**, hydrazinolysis to the desired octopus-type octaamine **17**.

4. Pride and prejudice of carbohydrate chemistry

The basis for the herein summarized work on the modification of carbohydrates as core molecules for multivalent targets was laid with our research published in *Carbohydrate Research* in 1998, entitled 'Synthesis of octopus glycosides'.[21] We have intended to develop this kind of chemistry into a rather general tool for the