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Diverse Motifs of Mannoside Clustering on a β-Cyclodextrin Core

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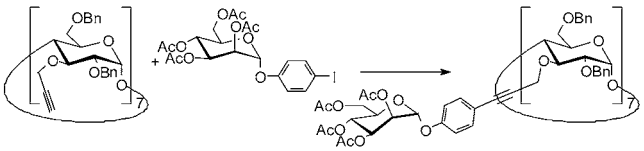
ABSTRACT



A new method for the synthesis of β-cyclodextrin-based cluster mannosides by application of the Sonogashira cross-coupling reaction is described. The method allows for the persubstitution of the β-cyclodextrin at either 2- and 3-positions to give two types of heptavalent clusters, at both 2- and 6-positions to give clusters with 14 mannopyranoside units and at 2-, 3-, and 6-positions to obtain clusters with 21 mannopyranoside ligands.

The construction of site-specific drug delivery systems based on macrocycles with dual function as hosts for the complexation of guest molecules and as lectin ligands has received the attention of several research groups.[1] In particular, those macrocycles that can be used as molecular scaffolds for displaying multivalent arrays of carbohydrate ligands have proven to be the most useful in the development of systems that have enhanced lectin binding affinity due to the so-called glycoside cluster or multivalent effect.[2] There are several examples of macrocyclic scaffolds that have been used for building carbohydrate clusters[1] such as cyclodextrins (CDs),[1] calix[4]arenes,[1a,3] and calix[4]resorcarenes.[1a,4] In particular, it has been demonstrated that the latter type of compounds can deliver guest molecules to polar solid surfaces such as quartz, but also to biological targets such as lectins.

However, the use of CDs as a scaffold of cluster glycosides offers several advantages over other macrocyclic compounds: they are more readily available and affordable, more biocompatible, and have the ability to form inclusion complexes with a large variety of guests in aqueous solution.[5] Two main architectural designs have been used for the construction of CD-based carbohydrate clusters.[1] The most largely focused on strategy takes advantage of the perfunc-

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tionalization of the CDs on their primary face.[6,7] In the case of β-CD, with seven glucosyl units, the most used CD representative, such a strategy has been used for the preparation of clusters with 7[1,6,7] and 14[7a,b] carbohydrate ligands. The second strategy involves the attachment of glycodendrons onto one of the glucosyl residues of the CD providing multivalent monosubstituted β-CD.[8]

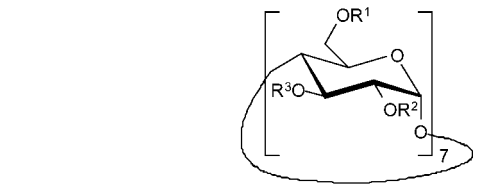
Beyond the primary face the CD torus provides other less explored branching potential by perfunctionalization with carbohydrate appendages at C-2 and C-3, in addition to C-6, giving rise to CD cores with diverse type of clusters differentiated by the number of ligands and their spatial orientation. There is only one reported example of derivatization on the CD secondary face and both the primary and the secondary faces simultaneously obtaining CD-based glycoclusters with seven and fourteen ligands, respectively.[6i] As part of our ongoing project involving both the synthesis and the dual molecular recognition properties as hosts and lectin ligands of glycoclusters based on CD cores,[7] we became interested in exploring new forms of carbohydrate clustering by the β-CD core.

As pointed out elsewhere,[1] the crucial step in the branching of CDs is the attachment of the carbohydrate units onto the CD core. A very high-yielding coupling reaction is required for this purpose to avoid the formation of a mixture of undersubstituted regioisomers from which the separation and purification of the target compound would be a very difficult task. In our case, another key step would be the placement of the functional groups for the coupling of the carbohydrates. On the basis of the known different reactivities of the three types of CD hydroxyl groups in silylation and alkylation reactions,[9] we have introduced propargyl groups at different positions of β-CD. The propargyl groups are the attachment points for the appended glycosides through a Sonogashira cross-coupling reaction.

The Sonogashira reaction[10] has demonstrated its applicability in the construction of multivalent structures, including the preparation of calix[4]arene-based glycoclusters.[3c,11] In our case, in addition to its proven high efficiency, we also have considered that the Sonogashira reaction also provides a method for attaching aryl *O*-mannopyranoside units by cross-coupling reaction of the terminal alkyne groups with 4-iodophenyl α-D-mannopyranoside derivatives. The presence of the bulky hydrophobic aglycon might result in increased affinities toward the mannose-specific lectin Concanavalin A, according to literature results.[12,13]

In an initial stage, we prepared the propargylated CD building blocks (Scheme 1). To obtain the perpropargylated

Scheme 1[a]



[a] Reaction conditions: (a) NaH, propargyl bromide, THF, 0 °C to rt, 24 h, 88%; (b) NaH, propargyl bromide, DMF, 0 °C to rt, 12 h, **4** (88%), **6** (59%); (c) BaO, $Ba(OH)_2 \cdot 8H_2O$, propargyl bromide, DMF−DMSO, 5 days, 37%.

β-CD derivative at C-2, the heptakis(2,6-di-*O*-*tert*-butyldimethylsilyl) β-CD **1**[14a] was treated with propargyl bromide in the presence of sodium hydride in THF leading to compound **2** in 88% yield. Formation of compound **2** involved the in situ migration of the TBDMS groups from O-2 to O-3 positions.[14b,c] The synthesis of the per(3-*O*-propargyl) β-CD derivative **4** (55% yield) was carried out by reaction of per(2,6-di-*O*-benzyl) β-CD **3**[15] with sodium hydride and propargyl bromide in DMF. To obtain the

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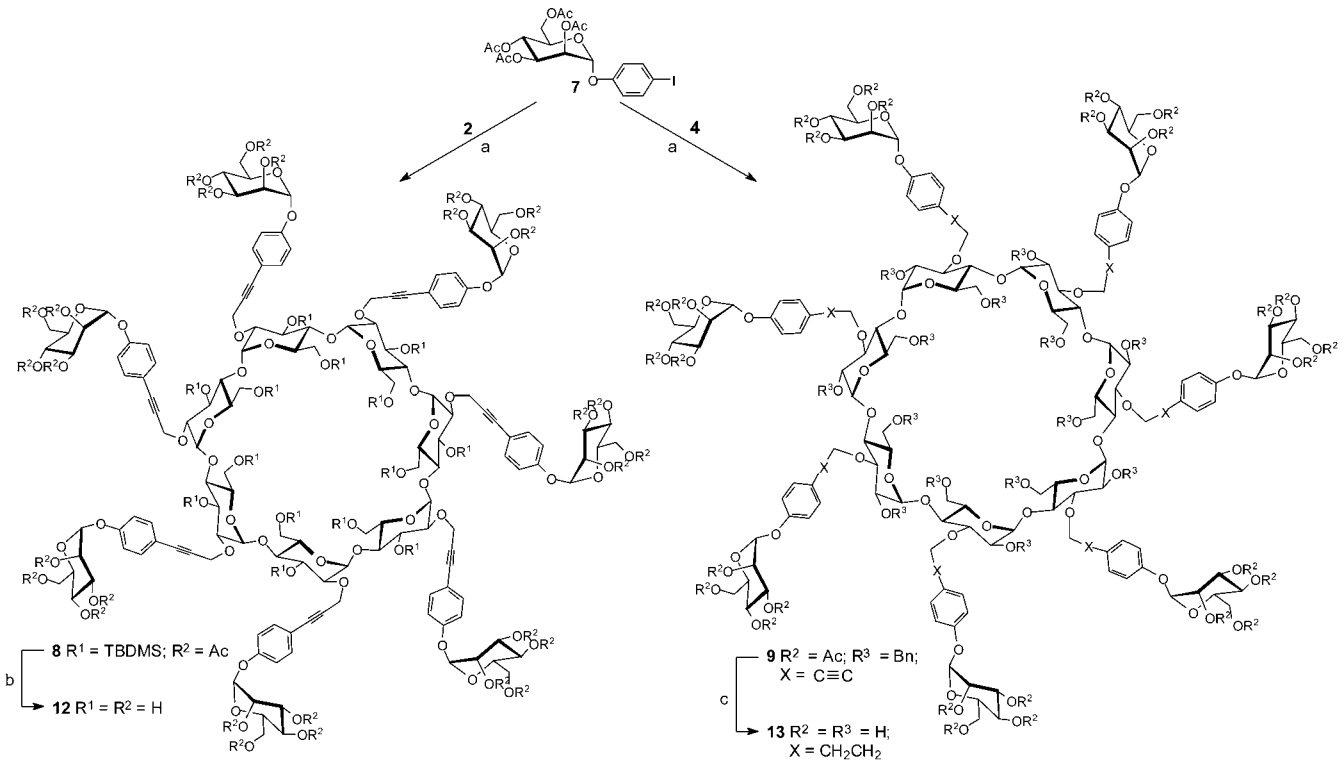
Scheme 2[a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$, CuI, piperidine, 75 °C, 1 h, then Ac_2O−Py (1:1), 24 h, 60% (**8**), 66% (**9**); (b) TBAF, THF, reflux, 5 h, then NaOMe, MeOH, 12 h, 98%; (c) H_2, Pd/C, AcOH, 15 h, then NaOMe, MeOH, 12 h, 98%.

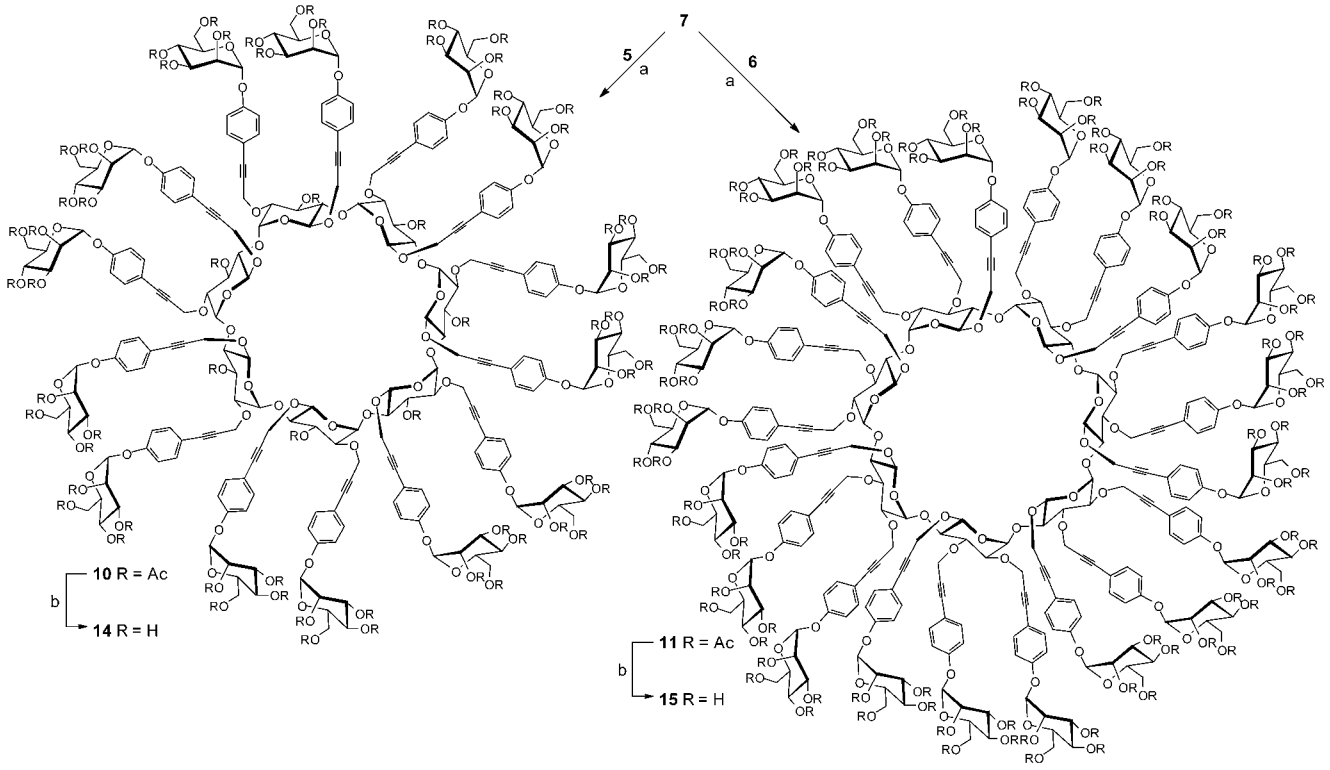
perpropargylated derivatives on both faces of the CD torus, we performed both the regioselective perpropargylation at C-2,6 and the ful perpropargylation of *β*-CD. Reaction of *β*-CD with propargyl bromide in the presence of BaO and $Ba(OH)_2 \cdot 8H_2O$ in a mixture of DMF and DMSO afforded the per(2,6-di-*O*-propargyl) *β*-CD (**5**) in 37% yield. Finally, treatment of *β*-CD with propargyl bromide and sodium hydride in DMF gave the per(2,3,6-tri-*O*-propargyl) *β*-CD (**6**) in 59% yield.

Cross-coupling reaction of propargylated CDs **2** and of **4**−**6** with 4-iodophenyl α-D-mannopyranoside derivative **7** (Schemes 2 and 3) was carried out at 75 °C in piperidine using $Pd(PPh_3)_4$ and CuI in catalytic amounts.[16] The reaction was kept for 1 or 2 h, and then the crude products were treated with acetic anhydride, pyridine, and DMAP. Protected mannosylated CDs **8**−**11** were isolated in 60−75% yields. Removal of the silyl and acetyl groups of **8** (Scheme 2) by sequential treatment with TBAF and NaOMe gave the secondary face-branched *β*-CD with seven mannopyranosyl units **12** in 98% yield. Deprotection of glycoCDs **10** and **11** (Scheme 3) under Zemplen conditions furnished the 14-mer and 21-mer mannose clusters based on both *β*-CD faces **14** and **15** in almost quantitative yields.

As a result of the Sonogashira reaction, the spacer arms that separate the mannopyranosyl units from the CD core in clusters **12**, **14**, and **15** consist of linear and rigid *para*-prop-1-ynylphenyl groups. Compound **9** (Scheme 2) was not easy to de-O-benzylate without affecting the carbon−carbon triple bonds, despite the different attempted conditions (Na/NH_3, $TMSOTf/Ac_2O$; $EtSH/BF_3$; $FeCl_3$). Compound **9** was then subjected to hydrogenolysis and hydrogenation (Pd/C and acetic acid) to afford the secondary face-substituted *β*-CD **13** (70% yield) with seven mannopyranoside units bound to the CD torus through the more flexible *para*-propylphenyl spacer groups. To our knowledge, compound **13** is the first permannosylated *β*-CD at the 3-position. Because of the low reactivity of the hydroxyl group at C-3 the 3-position is not easily available for modification.[9] The mannosylated CDs **8**−**15** were characterized by NMR spectroscopic techniques with INEPT, COSY, HMQC, and HMBC experiments and MALDI-TOF mass spectrometry. Measurements of the NMR data were performed at 80 °C to avoid broadening of the signals. However, while the ^1H NMR spectra of compounds **8**−**11** displayed an improvement of the resolution of the signals for the mannopyranosyl protons, the broadening of the signals for the CD protons still was very significant. The ratios of the integrals for the signals of the mannopyranoside

(16) **General Procedure for the Synthesis of 8−11.** To a degassed solution of 4-iodophenyl mannoside derivative **7** (2−3 equiv per propargyl group) and the propargylated CDs **2**−**5** (0.03−0.06 mmol) in anhydrous piperidine (4−6 mL) were added $Pd(PPh_3)_4$ (10% of **7**) and CuI (10% of **7**). The solution was heated at 75 °C under an argon atmosphere for 1 to 2 h. The piperidine was removed by evaporation under vacuum. The residue was treated with Ac_2O−pyridine (1:1, 12−20 mL). Conventional workup gave a crude product that was purified by column chromatography on silica gel giving **8**−**11**.

Scheme 3 [a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$, CuI, piperidine, 75 °C, 1 h, then Ac_2O−Py (1:1), 24 h, 75%; (b) NaOMe, MeOH, 12 h, 98%.

anomeric protons and for the signals of the anomeric protons belonging to the CD core are in accordance with the structures of the products. A useful fact for the assignment of the ^{13}C NMR signals is the lower intensity and the slight broadening of the signals corresponding to the CD moiety, probably due in part to the lack of flexibility of the cyclodextrin torus. The ^{13}C NMR spectra of **8**−**15** show carbon signals at 156.5−115.0 ppm revealing the presence of the phenyl groups on the CD torus. The signals corresponding to the mannopyranose carbon atoms appear at identical chemical shifts independently of the number of appended carbohydrate units 7, 14, and 21. Thus, ^{13}C NMR spectra of **8**−**11** and **12**−**15** display two anomeric carbon signals at 100.7−97.1 (C-1) and 99.1−95.6 ppm (C-1′). In addition, the signals corresponding to the terminal sp carbons at 75.4−74.0 ppm for propargylated CDs **2** and **4**−**6** shift downfield to 86.2−83.8 ppm for mannosylated CDs **8**−**12**, **14**, and **15** as a result of the cross-coupling reaction. Unlike that for compounds **8**−**12**, **14**, and **15**, the ^{13}C NMR spectrum of the CD permannosylated at the 3-position **13** does not show presence of sp carbons. Instead, the spectrum reveals signals corresponding to the two carbons of the ethylene linker that resulted after the hydrogenation of the triple bonds.

In conclusion, we describe herein an efficient method for the synthesis of β-CD-based cluster mannosides by application of the Sonogashira cross-coupling reaction. This strategy allows for persubstitution of the β-CD either at 2- and 3-positions to give two types of heptavalent clusters, both simultaneously at 2- and 6-positions to give a cluster with 14 mannopyranoside units and at 2-, 3-, and 6-positions to obtain a cluster with 21 mannopyranoside ligands. We are currently investigating the double functionality of these cluster compounds as molecular hosts and lectin ligands.

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Supporting Information Available: NMR and MALDI-TOF MS data for compounds **2**, **4**−**6**, and **8**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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