# Convergent synthesis and inclusion properties of novel $C_n$-symmetric triazole-linked cycloglucopyranosides†

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**We present a convergent synthetic approach based on CuAAC to three carbon-linked cycloglucopyranosides displaying two, four, and six sugar residues, respectively, and triazole rings as inter-glycosidic spacers. The term with the largest cavity proved to serve as the host of 8-anilino-1-naphthalene-sulfonate.**

Cyclodextrins (CDs), macrocyclic oligosaccharides composed of six or more (α1,4)-linked D-glucopyranoside units, have been extensively used as molecular receptors due to their ability to bind hydrophobic molecules into their nanometric cavities while dissolved in polar solvents.[1] However, the development of CD-based functional materials has been hampered by the difficulty of modifying natural CDs by introducing functional groups in specific positions of the macrocycle.[2] Consequently, intense research has been carried out on the synthesis of CD analogues whose sugar residues are duly and selectively functionalized.[3] Toward this goal, the oligosaccharide synthesis followed by intramolecular glycosylation,[4] as well as cyclooligomerization of mono-,[5] di-,[3] and trisaccharides,[6] has been reported. Other methods involved the cyclization of functionalized mono- and oligosaccharides by the formation of various types of linkages, such as thioureido,[7] amide,[8] diethynyl,[9] thioether,[10] carbamate,[5] phosphodiester.[11] Following the growing popularity aroused during the last decade by the quintessential click reaction represented by the copper-catalyzed azide–alkyne cycloaddition (CuAAC),[12] this powerful ligation means was conveniently exploited by Vasella,[9] Gin,[13] Chen[14] and their co-workers to synthesize CD analogues of varied sizes from acyclic glycooligomers having an azido group at one end and a terminal alkyne group at the other hand. Consequently all cyclic oligosaccharides thus prepared featured two or more 1,4-disubstituted triazole rings as spacers. In some cases, however, *O*-glycosidic bonds holding the sugar moieties were also present due to the use of acyclic *O*-glycosides as precursors. We would like to report here on our CuAAC-based approach to structurally defined cyclooligomers displaying alternant triazole and *C*-glucoside moieties as shown by the general structure **D** in Fig. 1. The carbon–carbon bond between the sugar and triazole ring

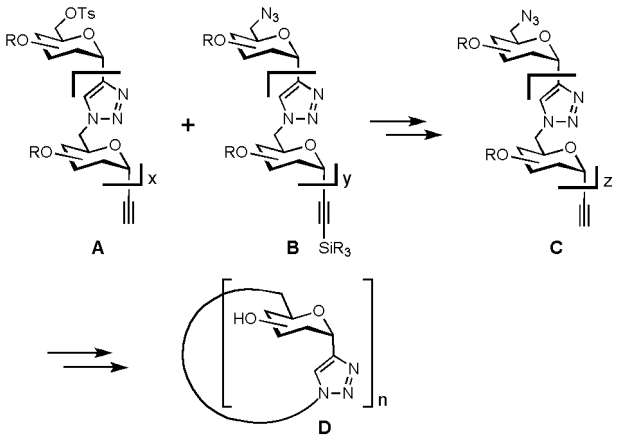


**Fig. 1** Modular approach to triazole-linked cyclic oligoglycosides.

served to ensure high stability toward chemical and enzymatic degradation. Our approach is based on a convergent strategy involving the copper-catalyzed coupling of an alkyne **A** with azide **B** leading to *C*-oligoglycoside **C** that in turn *via* intramolecular CuAAC leads to the target triazole-linked cyclooligomer **D**. This modular strategy aimed at providing synthetic CD analogues with varied cavity sizes, this being a key property for specific applications in molecular recognition processes.

The access to the initial *C*-glucoside building blocks **4** and **6** featuring orthogonally protected functional groups was established starting from the α,β-glucopyranosyl acetate **1** (Scheme 1). Thus treatment of **1** with excess tributylstannyl trimethylsilyl acetylene and TMSOTf afforded the trimethylsilyl protected ethynyl *C*-glycoside **2** displaying a TMS ketene acetal functionality at C6. Compound **2** was transformed into the key intermediate **3** by basic treatment and this was activated to form the *O*-tosyl derivative **4**. Alternatively the ethynyl group of **3** was protected with the robust *tert*-butyldimethylsilyl group to give **5** which in turn was transformed *via* tosylation and azidation into the azide **6**.

The approach to the first cyclooligomer was commenced by the CuI-catalyzed coupling of the ethynyl *C*-glucoside **4** with the azide **6** under microwave assisted conditions (Scheme 2). This reaction was completed after 15 min heating at 80 °C. The replacement of the OTs group of the crude product **7** was carried out by treatment with $NaN_3$ in DMF to give compound **8** in good isolated yield. The removal of the silyl group from **8** under standard desilylating conditions afforded the triazole-linked disaccharide **9** featuring an azide at C6 and an anomeric *C*-ethynyl group at the opposing terminus.

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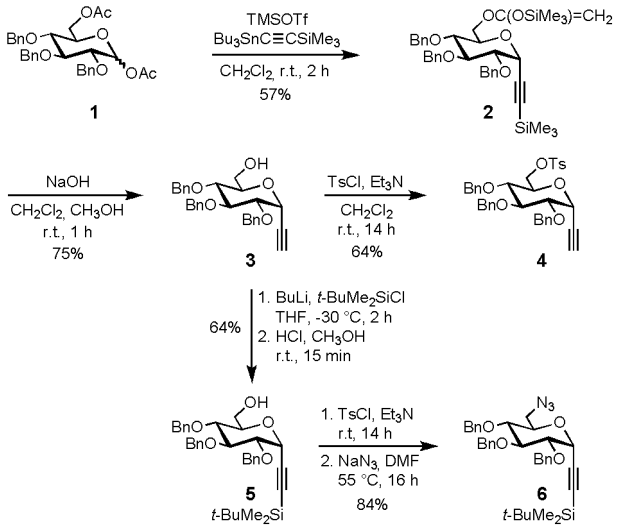
† Electronic supplementary information (ESI) available: Syntheses, characterization data and NMR spectra of all new compounds. See DOI: 10.1039/c0cc04127k

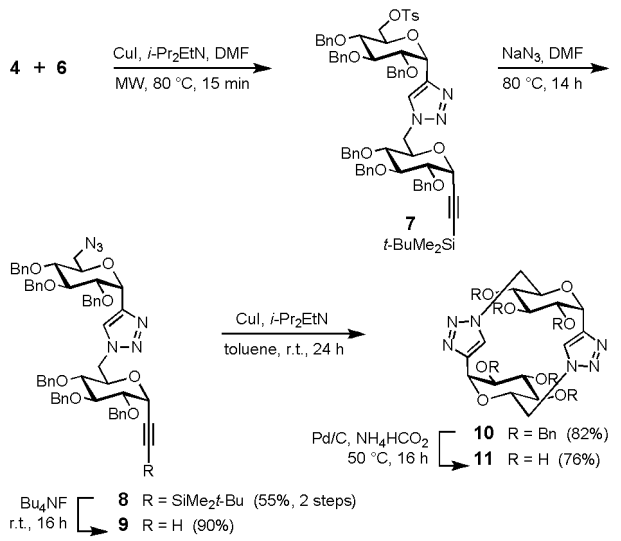
 



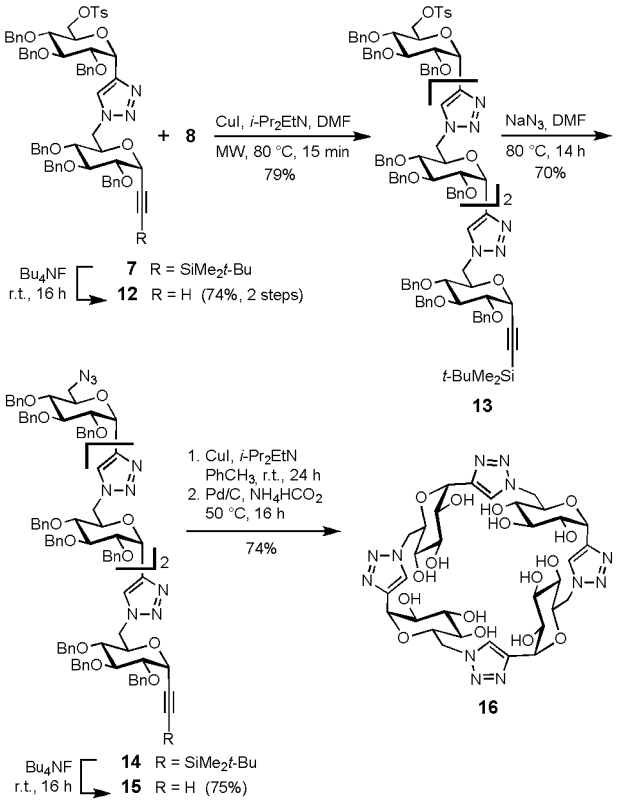

**Scheme 1**

Copper-catalyzed intramolecular cycloaddition in **9** ($10^{-3}$ M in toluene at room temperature) was preferred over unproductive linear oligomerization to give the $C_2$-symmetric cyclodimer **10** in excellent isolated yield. Debenzylation of the sugar residues of this compound by catalytic hydrogenation furnished the free hydroxy triazole-linked cyclodiglucopyranoside **11**.

A second cyclooligomer with a larger cavity was targeted by a similar convergent route with the use of linear oligomers obtained in the previous approach as starting building blocks (Scheme 3). To this end the disaccharide **7** was desilylated to give the ethynyl *C*-glucoside **12** and this was coupled with the azide **8** under the previously established CuI-catalyzed and microwave assisted conditions. The cycloaddition afforded the linear triazole-linked tetraglucoside **13** which was transformed into the key intermediate **15** *via* azidation by nucleophilic displacement of the *O*-tosyl group by $NaN_3$ and removal of the silyl protective group by fluoride ion. Finally, the intramolecular CuAAC of **15** and debenzylation of the crude




**Scheme 2**

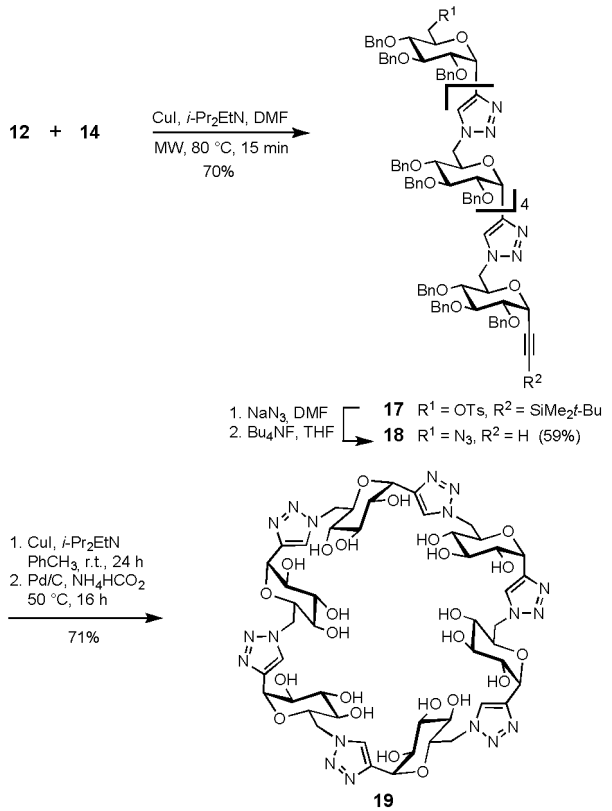



**Scheme 3**

product furnished the $C_4$-symmetric triazole-linked cyclotetraglucopyranoside **16** in good isolated yield.

A third cyclooligomer featuring six triazole-linked glucopyranose fragments was prepared as well involving as a first step the standard copper-catalyzed coupling of the alkyne **12** with the azide **14** (Scheme 4). Also in this case the linear oligosaccharide **17** thus obtained was transformed into the azido and ethynyl functionalized compound **18** that in turn underwent the desired intramolecular CuAAC without any substantial linear oligomerization. The crude product was liberated of the benzyl protective groups to give the target $C_6$-symmetric triazole-linked cyclohexaglucopyranoside **19** in good yield. NMR spectra of cyclooligomers **11**, **16**, and **19** supported their $C_n$-symmetry as in all cases a single signal at 7.7–8.0 ppm corresponding to the H5 of the triazole ring and a single set of signals corresponding to the seven protons of the glucopyranose moiety were observed (see ESI†). Moreover, the ESI/Q-TOF HRMS data confirmed the authenticity of all products. It is worth pointing out that in all cases the intramolecular high yield CuAAC reaction occurring in the ultimate precursors to these compounds indicated a curved topology favorable to cyclization in preference to linear oligomerization.

Having established a convergent route to the cyclooligomers **11**, **16**, and **19**, it can be realized that lower and higher homologues can be equally prepared by using the appropriate building blocks shown in Schemes 1–3. Thus, we addressed the main issue regarding the application of CDs and synthetic analogues, that is their ability to serve as host of organic molecules. To this aim we examined the potential of




**Scheme 4**

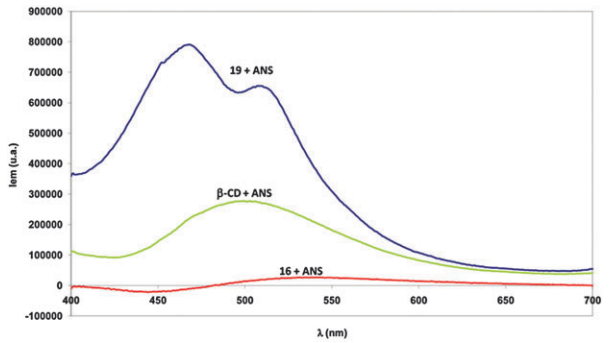



**Fig. 2** Fluorescence emission spectra ($\lambda_{ex}$ = 365 nm) of phosphate buffer solutions (pH 7.22) of ANS (0.15 mM) in the presence of β-CD, **16** and **19** (21 mM).

compounds **11**, **16**, and **19** to form inclusion complexes with the fluorescent probe 8-anilino-1-naphthalene-sulfonate (ANS), a typical model guest of β-CD and synthetic macrocyclic oligosaccharides.[7,13a,14] In fact, it is well known[15] that the fluorescence yield of ANS strongly increases when this dye is complexed in hydrophobic sites not accessible to polar solvents. As expected, in aqueous solutions the fluorescence of ANS was quenched (see Fig. S1 in ESI†), whereas the addition of excess **19** led to a hypsochromic shift and a remarkable enhancement of the fluorescence intensity, much larger than that observed for β-CD (Fig. 2). On the other hand, **11** (data not shown) and **16** (Fig. 2) did not cause a significant increase in the fluorescence of ANS, very likely due to their smaller cavities that prevented the complexation. An association constant of 22.5 ± 1.3 $M^{-1}$ was determined (see Fig. S2 in ESI†) for **19** + ANS by fluorescence titration (reported[16] $K_{as}$ for β-CD + ANS: 71 ± 4 $M^{-1}$).

The binding properties of **16** were evaluated by $^1$H NMR spectroscopy using racemic phenylalanine hydrochloride as the guest, according to a procedure developed for α-CD.[17] Upon addition of increasing amounts of amino acid to a $D_2O$ solution of **16** (pD 2.0), a small downfield shift for the H3 sugar proton signal was observed ($\Delta\delta \approx 0.05$ ppm).[18] In the case of α-CD a $\Delta\delta$ value of 0.10 ppm was reported.[17] Therefore, it appears that cyclotetramer **16** and cyclohexamer **19** showed complexation properties similar to those displayed by α- and β-cyclodextrins, respectively.

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18 When the $^1$H NMR spectra recorded by adding individual D- and L-Phe hydrochloride were compared, a very small difference in the chemical shift [$\Delta(\delta_L - \delta_D) = 0.01$ ppm] was observed only for the proton linked to the stereocenter of the guest (see Fig. S3 in ESI†).


 