Synthesis of Readily Modifiable Cyclodextrin Analogues via Cyclodimerization of an Alkynyl−Azido Trisaccharide

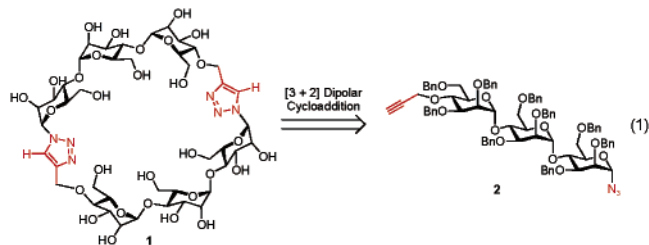Kyle D. Bodine, David Y. Gin, and Mary S. Gin*

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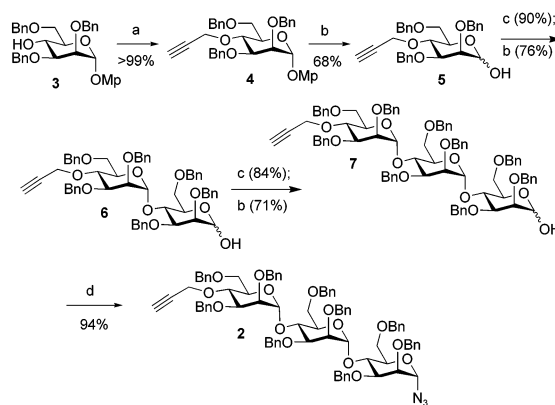Received November 1, 2003; E-mail: mgin@scs.uiuc.edu

Cyclodextrins (CDs) have found widespread use in supramolecular chemistry due to their ability to bind hydrophobic molecules within their cavities while dissolved in polar solvents such as water. Functionalized cyclodextrins have found applications as molecular reactors,[1] enzyme mimics (catalysts),[2] molecular machines,[3] and electrode surface modifiers.[4] Often a key feature of these systems is a cyclodextrin that has been selectively modified to display necessary functional groups in specific positions on the macrocycle. Indeed, differences in reactivity between the secondary hydroxyl groups on one face of β-CD and the primary hydroxyl groups on the other face, in conjunction with the geometric constraints of the macrocycle, have allowed the selective substitution at one,[5] two,[5,6] three,[5,7] or four[8] positions about the macrocycle. Even with these promising advances, the selective placement of different functional groups about the cyclodextrin macrocycle remains challenging, thus limiting the full potential of cyclodextrins as functional materials.

An alternative approach to selectively modified cyclodextrin macrocycles is the stepwise synthesis of cyclodextrins and cyclodextrin analogues from sugar residues that bear different functional groups.[9] Toward this goal, both stepwise oligosaccharide synthesis followed by cycloglycosylation,[10] as well as cyclooligomerization of mono-,[11] di-,[9] and trisaccharides[12] to give synthetic cyclooligosaccharides has been reported. Despite these remarkable synthetic efforts, disadvantages include long synthetic sequences, low cyclization yields, anomeric mixtures, and for cyclooligomerizations, mixtures of macrocycles of different sizes that are difficult to separate.

Our interest in macrocycles with selectively positioned functionality led us to consider the synthesis of cyclodextrin analogues from already-functionalized sugar units. However, we set out to streamline the synthesis by targeting a cyclodimerization reaction of appropriately substituted trisaccharides. The ligation reaction that we chose to investigate is the [3 + 2] Huisgen cyclization of an azide with an alkyne to form a triazole.[13] This reaction is chemoselective and high-yielding, and the precursors are otherwise stable to many reaction conditions. Herein we report the highly convergent preparation of macrocycle 1, a cyclodextrin analogue that exhibits association characteristics with the hydrophobic fluorophore 8-anilino-1-naphthalenesulfonate that are similar to those of β-CD.

The trisaccharide used to test our strategy (2) consists of 1,4-linked mannose units protected as 2,3,6-tribenzyl ethers, with an anomeric azide and a 4-propargyl ether at the opposing termini.

Scheme 1 [a]

[a] (a) NaH, HCCCH₂Br, DMF; (b) CAN, 4:1 MeCN/H₂O; (c) Ph₂SO, Tf₂O, 3:1 PhMe/CH₂Cl₂; **3**; Et₃N; (d) Ph₂SO, Tf₂O, 3:1 PhMe/CH₂Cl₂; TMSN₃; Et₃N.

Trisaccharide **2** was prepared by sequential dehydrative glycosylation of mannosides derived from the common intermediate **3**[10b] (Scheme 1). The terminal alkyne was installed by C4-*O*-alkylation of **3** (NaH, HCCCH₂Br) to afford propargyl ether **4** in >99% yield. Anomeric deprotection (CAN, H₂O) afforded the hemiacetal **5** (68%, 9:1 α:β) which then served as an appropriate donor for sulfoxide-mediated dehydrative glycosylation.[14] Thus, hemiacetal **5** was activated with Ph₂SO and Tf₂O at −45 °C in the absence of a triflic acid scavenger, allowing for glycosylation of the C-4 hydroxyl in **3** to give the disaccharide in 90% yield with complete α-selectivity.[15] Oxidative removal of the 4-methoxyphenyl acetal as before afforded hemiacetal **6** in 76% yield. A second iteration of glycosylation with C-4 nucleophile **3** and removal of the anomeric protecting group gave the final hemiacetal **7** in 60% yield for the two-step sequence. Glycosylation of trimethylsilyl azide under the same dehydrative coupling conditions furnished the trisaccharide **2** in 94% yield.

A critical feature of our synthetic strategy for the formation of macrocycle **1** is the preferred cyclodimerization over unproductive linear oligomerization. Thus, trisaccharide **2** was subjected to a variety of [3 + 2] cycloaddition conditions. While cyclodimerization was observed upon simply heating a solution of **2** in toluene, we found these conditions to be sluggish and to lead to the formation of multiple products. Decomposition could be suppressed by using copper catalysts, a number of which have been shown to promote the Huisgen cycloaddition of alkynes and azides.[16] After surveying the efficiency of reaction with a variety of Cu(I) sources (CuSO₄, sodium ascorbate; CuSO₄, Cu⁰ powder; CuI·P(OEt)₃; CuI), additives (DBU, tris(triazolyl)amine), and solvents (DMF/H₂O, CH₃CN, toluene), we were pleased to discover that treatment of trisaccharide **2** with CuI and DBU in toluene at 50 °C afforded the desired cyclodimer in 80% yield, with the corresponding cyclotrimer formed in 15% yield (eq 1). Transfer hydrogenolysis to remove the 18 benzyl groups (NH₄HCO₂, Pd/C, 50 °C) effected quantitative
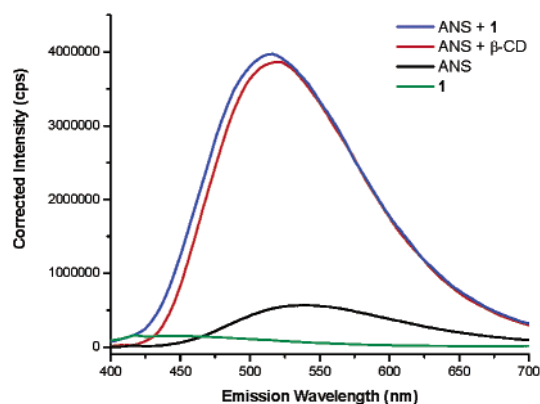
conversion to the desired macrocycle **1**, which was purified by dialysis to remove excess salts.
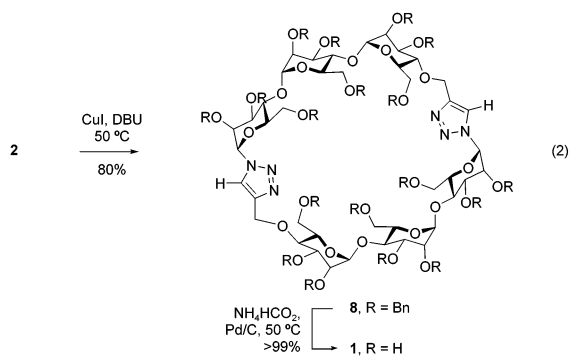
This synthetic protocol offers a facile, highly convergent method for the preparation of cyclodextrin-like macrocycles with differentially functionalized starting materials; however, there are distinct differences between macrocycle **1** and β-CD. First, where β-CD comprises seven sugar residues, macrocycle **1** has six sugar residues and two triazole rings. Second, cyclodextrins contain glucose residues, whereas the sugars in macrocycle **1** are derived from mannose. This difference in C2-stereochemistry of the pyranose rings precludes hydrogen-bonding between secondary hydroxyl groups on adjacent residues of **1**, which should result in diminished structural rigidity relative to the cyclodextrins.[17] In light of these differences, it is imperative to determine whether macrocycle **1** displays a propensity for forming inclusion complexes analogous to those of β-CD in order to assess its potential utility in supramolecular systems.

A number of small molecules are known to form inclusion complexes with cyclodextrins.[18] We chose to investigate the interaction of 8-anilino-1-naphthalenesulfonate (ANS) with macrocycle **1** as complexation with β-CD is readily detected by changes in the fluorescence of the ANS dye (Figure 1). In aqueous solutions, the fluorescence of ANS is largely quenched (black curve).[19] Addition of an excess of β-CD leads to an increase in the fluorescence intensity and a slight blue shift as the bound ANS encounters a more hydrophobic environment (red curve).[20] Addition of a similar excess of **1** to a solution of ANS resulted in similar changes in the fluorescence intensity (blue curve), indicating that macrocycle **1** is able to serve as host to inclusion of ANS in a manner similar to β-CD. It should be noted that macrocycle **1** displays weak fluorescence, which may account for the increased intensity of the

ANS + **1** fluorescence relative to that of ANS + β-CD. Simple solvent effects were ruled out by addition of mannose to ANS, which displayed fluorescence identical to that of ANS alone (superimposable with black curve). An association constant of 38 ± 10 M^{-1} was determined for ANS + **1** by fluorescence titration,[21] which is comparable to that of β-CD (71 ± 4 M^{-1}).[22] While this suggests that ANS associates similarly within the cavities of **1** and β-CD, further studies will be necessary to determine the generality of such host−guest interactions for **1**.[23]

In conclusion, we have demonstrated a convergent strategy for the synthesis of β-cyclodextrin analogues, exemplified by the preferential cyclodimerization of trisaccharide **2** via a [3 + 2] dipolar cycloaddition of the alkyne and azide functional groups. The resultant oligosaccharide macrocycle retains the binding propensity of cyclodextrins, as demonstrated by the similar ANS association constants measured for macrocycle **1** and β-cyclodextrin. This new synthetic strategy opens up new avenues for modular preparation of functionally diverse cyclodextrin analogues that are otherwise inaccessible. Efforts toward such selectively modified cyclodextrin analogues are currently underway.

Supporting Information Available: Experimental procedures for all compounds and for fluorescence studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Figure 1. Fluorescence emission spectra of ANS (0.1525 mM) in the presence and absence of β-cyclodextrin (21.12 mM) and macrocycle **1** (21.11 mM). All solutions were 0.1 M aqueous sodium phosphate buffer (pH 7.40), λ_{ex} = 365 nm.

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(23) A ¹H NMR spectrum of a 1:1 mixture of **1** and ANS in D₂O displayed complexation induced shifts (CIS) for both compounds. Those for ANS were of different magnitude and occasionally different direction compared to the CIS of ANS with β-CD. This highlights that the specific structure of the complex of ANS + **1** is distinct from that of ANS + β-CD. Further studies to explore the solution structure of **1** and its complexes are currently underway.

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