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Controlled Synthesis of Linear α-Cyclodextrin Oligomers Using Copper-Catalyzed Huisgen 1,3-Dipolar Cycloaddition

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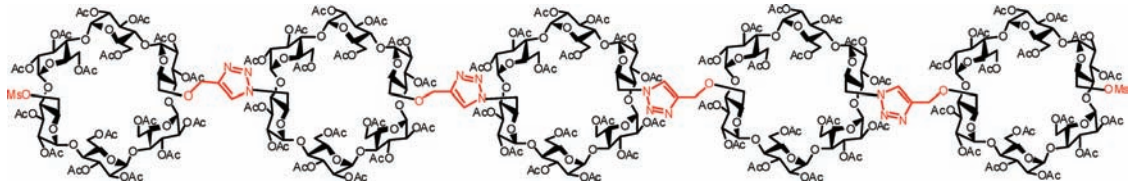
ABSTRACT



The design and efficient synthesis of a novel class of linear oligomers based on cyclodextrins are described. These supramolecules have relatively rigid structures with well-defined topology and sizes, which could provide them with the ability to be used as scaffolds to present bioactive molecules to their receptors as well as host molecules.

Recently, there has been growing interest in cyclodextrin (CD)-based oligomers.[1] Compared to monomeric CDs, the bridged oligomers have more than one binding site which provides them with enhanced binding affinity and specificity. To date, most published works concern CD-based dimers,[2,3] and only a few examples of higher oligomers such as trimers[4] and tetramers[5] have been reported. These host molecules could find vast applications as artificial enzymes, drug carriers, and chemosensors. In an ongoing program of study of carbohydrate−protein interactions, we became interested in scaffolds capable of presenting more than one copy of carbohydrate epitopes to proteins with multiple binding sites. Such scaffolds should be water-soluble with reasonable amounts of rigidity, and their syntheses should be efficient to allow us to prepare large quantities in a few steps. Most importantly, each generated scaffold should be of defined length and be amenable to the synthesis of a library of molecules having a range of molecular sizes, so that the

(1) For a review, see: Sliwa, W.; Girek, T.; Koziol, J. J. *Curr. Org. Chem.* **2004**, *8*, 1445–1462.

(2) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614–1615.

(3) (a) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296–8297. (b) Breslow, R.; Sung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659–9660. (c) Baugh, S. P. D.; Yang, Z.; Leung, D. K.; Wilson, D. M.; Breslow, R. *J. Am. Chem. Soc.* **2001**, *123*, 12488–12494. (d) Wilson, D.; Perlson, L.; Breslow, R. *Bioorg. Med. Chem.* **2003**, *11*, 2649–2653. (e) Yuan, D.-Q.; Immel, S.; Koga, K.; Yamaguchi, M.; Fujita, K. *Chem.—Eur. J.* **2003**, *9*, 3501. (f) Brady, B.; Darcy, R. *Carbohydr. Res.* **1998**, *309*, 237–241. (g) de Jong, M. R.; Engbersen, J. F. J.; Huskens, J.; Reinhoudt, D. N. *Chem.—Eur. J.* **2000**, *6*, 4034–4040. (h) Liu, Y.; Chen, Y.; Liu, S.-X.; Guan, X.-D.; Wada, T.; Inoue, Y. *Org. Lett.* **2001**, *3*, 1657. (i) Liu, Y.; Chen, Y.; Li, L.; Huang, G.; You, C.-C.; Zhang, H.-Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2001**, *66*, 7209–7215. (j) Dong, D.; Baigl, D.; Cui, Y.; Sinaÿ, P.; Sollogoub, M.; Zhang, Y. *Tetrahedron* **2007**, *63*, 2973–2977. Lecourt, T.; Mallet, J.-M.; Sinaÿ, P. *Eur. J. Org. Chem.* **2003**, 4553–4560. (k) Chiu, S.-H.; Myles, S. C.; Garrell, R. L.; Stoddart, J. F. *J. Org. Chem.* **2000**, *65*, 2792.

(4) (a) Leung, D. K.; Atkins, J. H.; Breslow, R. *Tetrahedron Lett.* **2001**, *42*, 6255–6258. (b) Okabe, Y.; Yamamura, M.; Obe, K.; Ohta, K.; Kawai, M.; Fujita, K. *Chem. Commun.* **1995**, 581–582. (c) Liu, Y.; Li, L.; Li, X.-Y.; Zhang, H.-Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 3646–3657. (d) Sasaki, K.; Nagasaka, M.; Kuroda, Y. *Chem. Commun.* **2001**, 2630–2631.

(5) (a) Jiang, T.; Li, M.; Lawrence, D. S. *J. Org. Chem.* **1995**, *60*, 7293–7297. (b) Breslow, R.; Zhang, X.; Xu, R.; Maletic, M.; Merger, R. *J. Am. Chem. Soc.* **1996**, *118*, 11678–11679. (c) Lecourt, T.; Blériot, Y.; Auzély-Velty, R.; Sollogoub, M. *Chem. Commun.* **2010**, *46*, 2238–2240.

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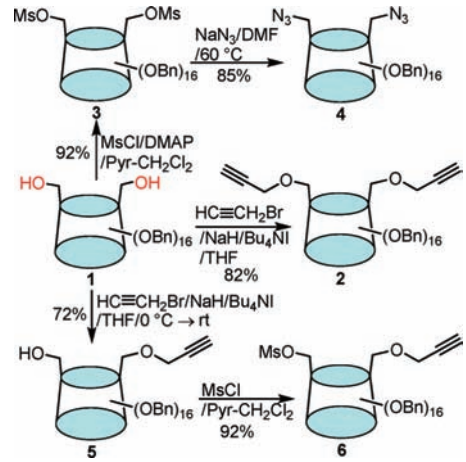
presented carbohydrate epitopes can effectively interact with proteins that have binding sites spanning 10−80 Å apart. Although protein or polymer-based scaffolds can be used for such a purpose, they are either difficult to modify or they do not have predefined lengths. CD-based oligomers came to our attention as they meet all of the aforementioned criteria: CDs[6] are cyclic oligosaccharides formed by six to eight D-glucopyranosyl units which are linked together via a series of α(1,4)-glycosidic linkages—their tubular, bidimensional structure provides them with a relatively rigid skeleton. All CD molecules are water-soluble and have low toxicity, which is compatible with biological systems. By adopting the shape of a truncated cone, the macrocycles have a large unit diameter (8.7 Å for α-CD and 11.7 Å for γ-CD at the narrow end). If we develop efficient chemistry for their construction, we might be able to easily generate linear structures of 10−80 Å length. As an example, if we join two CD monomers together via their primary face, we can quickly generate scaffolds of length greater than 18−24 Å in just one coupling step (Figure 1).

Figure 1. (a) Dimensions of dimeric CDs from α-, β-, or γ-CD (left). (b) Structure of C_2 symmetrical $6^A,6^D$-diol (**1**) of α-CD used for synthesis (right).

The copper-catalyzed Huisgen 1,3-dipolar cycloaddition[7,8] was chosen as the key reaction for linking our monomers because of its high efficiency and high functional group tolerability. In designing synthetic targets, we also took into consideration our characterization methods, which should be reliable, because we are dealing with highly complex CD oligomers. Multisubstituted CDs typically have quite complex NMR spectra.[9] When linked together, CD oligomers would be expected to be even more complex. We considered that if we designed strategies to synthesize CD oligomers with C2 symmetry, the complexity of the NMR spectra of synthesized oligomers would be significantly reduced, thus facilitating the structural determination.

On the basis of the above two considerations, the $6^A,6^D$-disubstituted α-CD derivative (**1**) was chosen as the starting material because it had the desired C2 symmetry (Figure 1). The diol can be readily prepared in large amounts from perbenzylated α-CD via DIBAL-H mediated reductive debenzylation.[10] Treatment of diol (**1**) with 5 equiv of propargyl bromide and 3 equiv of sodium hydride in anhydrous THF under the catalysis of tetrabutylammonium iodide (Scheme 1) provided the desired $6^A,6^D$-dipropargylated

Scheme 1. Synthesis of α-CD Building Blocks



compound **2** in high yield (82%). Similarly, using methanesulfonyl chloride as the reagent, we obtained the $6^A,6^D$-dimesylated intermediate **3** in excellent yield (92%) using conventional conditions. A subsequent displacement of both mesylates with sodium azide in anhydrous DMF furnished the corresponding $6^A,6^D$-diazide **4** in 85% yield. The NMR spectra of all compounds **2**−**4** revealed the expected C2 symmetry. Starting from diol **1**, a selective monopropargylation was also performed using conditions similar to those for **2** (Scheme 1) but with controlled amounts of propargyl bromide (1.2 equiv); the desired monopropargylated alcohol **5** was obtained in very good yield (72%) and selectivity. A subsequent mesylation of the remaining hydroxyl group in **5** provided the unsymmetrical mesylate **6** in excellent yield (92%).

To test the efficiency of Huisgen cycloaddition on synthesized CD monomers, we subjected a 6-monoazido derivative of α-CD (**9**)[11] to react with the $6^A,6^D$-dipropargylated α-CD (**2**) (Scheme 2). The azide **9** was obtained

(6) Szeitli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, 1988.

(7) For reviews, see: (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. (b) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278–308. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015. (d) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.

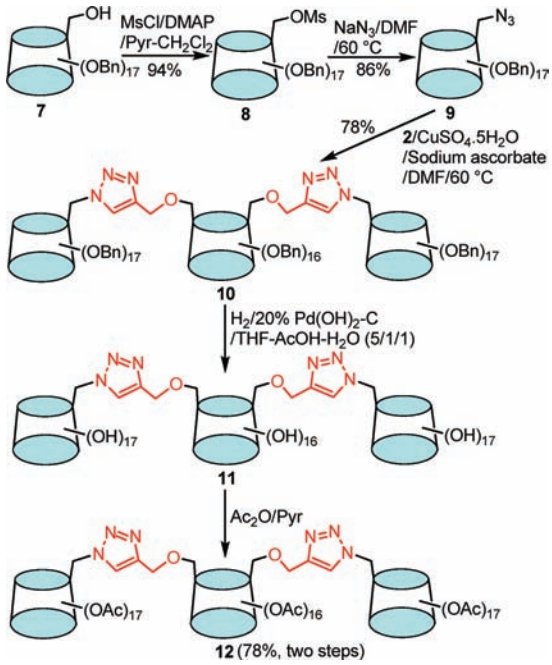
(8) (a) Pérez-Balderas, F.; Ortega-Munõz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951–1954. (b) Maisonneuve, S.; Fang, Q.; Xie, J. *Tetrahedron* **2008**, *64*, 8716–8720. (c) Aime, S.; Gianolio, E.; Arena, F.; Barge, A.; Martina, K.; Heropoulos, G.; Cravotto, G. *Org. Biomol. Chem.* **2009**, *7*, 370–379. (d) Cravotto, G.; Mendicuti, F.; Martina, K.; Tagliapietra, S.; Robaldo, B.; Barge, A. *Synlett* **2008**, 2642–2646.

(9) (a) Ward, S.; Zhang, P.; Ling, C.-C. *Carbohydr. Res.* **2009**, *344*, 808–814. (b) Ling, C.-C.; Coleman, A. W.; Miocque, M. *Carbohydr. Res.* **1992**, *223*, 287–291. (c) Rawal, G. K.; Rani, S.; Ward, S.; Ling, C.-C. *Org. Biomol. Chem.* **2010**, *8*, 171–180.

(10) (a) Pearce, A. J.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3610–3612. (b) Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sinaÿ, P. *Chem.—Eur. J.* **2004**, *10*, 2960–2971. (c) Rawal, G. K.; Rani, S.; Ling, C.-C. *Tetrahedron Lett.* **2009**, *50*, 4633–4636.

(11) Guieu, S.; Sollogoub, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7060–7063.

Scheme 2. Synthesis of Unfunctionalized α-CD Trimer



from the 6-monool **7** via intermediate mesylate **8** (94% yield) using conditions analogous to the literature,[11] in 81% yield over two steps. The monoazide (**9**) was used in 5 equiv excess (2.5 equiv per alkyne), and the cycloaddition was carried out in a mixture of DMF−H_2O, using the $CuSO_4$•H_2O/sodium ascorbate system to generate in situ the required Cu(I) catalyst; after heating the reaction mixture at 60 °C for 2 days, the linear trimer (**10**) was isolated in 78% yield and in pure form by chromatography on silica gel.

The trimer **10** has a C2 symmetry, and nine types of α-glucopyranosyl units are found in the structure. The NMR spectra of **10** are extremely complex; in the 1D ^{1}H NMR, the characteristic triazole proton was found to be hidden inside the aromatic peaks. Therefore, we relied on 2D experiments to confirm its structure. Indeed, when analyzing the 2D GCOSY and 2D HSQC NMR spectra of **10** in $CDCl_3$ (400 MHz), we observed nine anomeric signals for both ^{1}H and ^{13}C nuclei, confirming that the synthesized trimer had the correct structure and symmetry (see Supporting Information). Two sets of H-6a and H-6b protons of the glucopyranosyl units were directly attached to the triazole ring formed. Because of its strong deshielding effects, we observed two largely deshielded protons at δ 5.39 and 4.10 ppm, both attached to the same carbon resonating at δ 50.33 ppm, and these correlated to two pairs of H-6a's and H-6b's that were directly attached to the triazole units.

There are 50 benzyl groups present in trimer **10**, and it was a concern whether we could completely remove all of them by hydrogenation. We proceeded to carry out a catalytic hydrogenation experiment in a mixture of THF−AcOH−H_2O using 20% $Pd(OH)_2$ as catalyst. After 3 days, all benzyl groups were removed in a clean manner without complications. The intermediate **11** was characterized in its fully acetylated form (**12**, 78% yield over two steps).

With the help of 2D ^{1}H−^{1}H GCOSY and ^{1}H−^{13}C HSQC NMR experiments, we observed unambiguously nine sets of anomeric signals of compound **12**; these corresponded to the expected nine pairs of glucopyranosyl units. Eight anomeric protons appeared in the δ 4.95−5.20 ppm region as doublets, and the remaining one was more distinct from others, resonating more downfield at δ 5.63 ppm. This signal should correlate to the anomeric protons of the glucopyranosyl pairs next to the units that contain the triazole rings. Geometrically, these anomeric protons are close to the triazoles, thus they could be deshielded by the triazole rings (see Supporting Information). Due to the absence of benzyl protons, the triazole proton was now observed clearly at δ 7.67 ppm as a singlet.

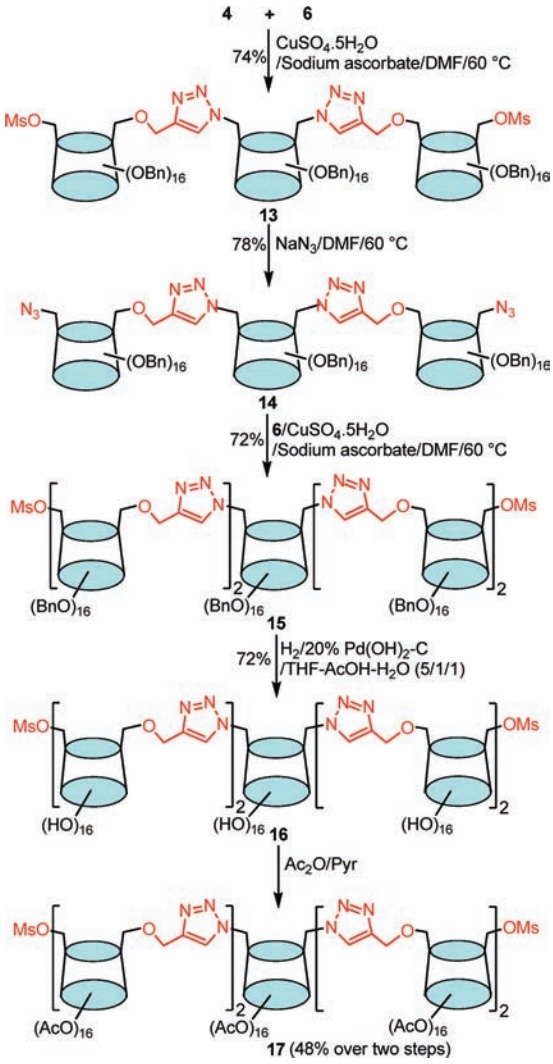
The success of our synthesis of trimer **10** and the subsequent clean removal of benzyl groups were very encouraging. However, certain structural features of **10** did not meet our original goals which required reactive functional groups to be present in the scaffold so that sugar epitopes could be introduced regioselectively. Additionally, the structure of **10** did not permit expandability.

To achieve our original goals, we decided to alter our strategy by using a heterobifunctional α-CD as the reagent. Thus, the symmetric diazide **4** and unsymmetric monomer **6** with a reactive mesylate were chosen as starting materials in the revised strategy. The mesylate in **6** would serve as a handle to allow future derivatizations. As illustrated in Scheme 3, we reacted the diazide **4** with compound **6** under the same conditions as **10**. A new trimer **13** with two reactive mesylates was obtained in one step and in 74% yield after chromatography on silica gel. The mesylate proved to be compatible with the Huisgen 1,3-dipolar cycloaddition conditions. It is worth mentioning that we could obtain trimer **13** in gram quantities. Compound **13** has NMR features similar to compound **10**; the two mesylates appear as a singlet resonating at δ 2.76 ppm in $CDCl_3$. The high-resolution ESI-QTOF MS results confirmed that **13** had the correct *m*/*z* 2530.0504 $(M + 3Na)^{3+}$ (mass accuracy: 2.7 ppm).

To exploit fully the potential of our methodology, we decided to convert the mesylates to azides, to allow the incorporation of two additional α-CD monomers and obtain a longer pentamer.

Treatment of **13** with sodium azide in DMF at 60 °C overnight afforded diazide **14** in 78% yield. Using the same conditions as established for **10**, we reacted **14** with 2 equiv of **6** at 60° for three days, and we isolated the major product by column chromatography on silica gel in 72% yield. A series of NMR experiments were carried out to study the isolated compound. Both ^{1}H and ^{13}C NMR spectra of the isolated product were extremely complex, due to severe overlap. Using a series of 1D and 2D experiments, we were able to determine that the isolated compound was indeed a single compound with features of the expected pentamer **15**. For example, only one type of mesylate was found at δ 2.77

Scheme 3. Synthesis of Functionalized α-CD Trimer and Pentamer



ppm, which integrated to six protons. Using MALDI-TOF mass spectrometry, we observed a peak with *m*/*z* of 12487 (100%), which corresponds to the $[M + Na]^+$ peak of the synthesized pentamer.

The pentamer has over 80 benzyl groups in total, which appeared to pose a tremendous challenge for the deprotection step. We considered this step to be critical to test the viability of our methodology. Thus, compound **15** was subjected to the same catalytic hydrogenation conditions as before. After 7 days, the intermediate **16** was fully acetylated to afford compound **17** in 48% yield over two steps. The structure of acetylated pentamer **17** was unambiguously confirmed by NMR and mass spectrometry. For example, in the 600 MHz ^{1}H NMR of **17** in $CDCl_3$ (Figure 2), we observed two types of triazole proton and 1 type of mesyl group at δ 7.70, 7.69,

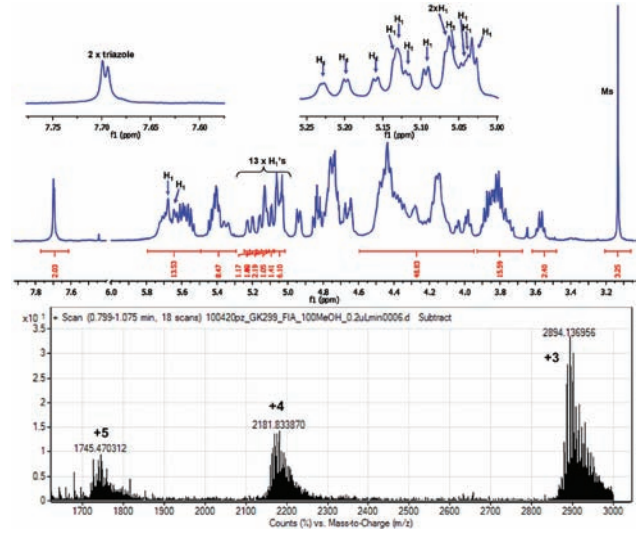


Figure 2. 1D ^{1}H NMR and high-resolution ESI-QTOF mass spectra of pentamer **17**.

and 3.13 ppm, respectively; we also observed 15 anomeric protons in the δ 5.00−5.80 ppm region with the help of a series of 2D experiments. Finally, the high-resolution ESI-QTOF mass spectrometry results revealed a peak with *m*/*z* 2899.8040, which correlated with the triple charged $(M + 3Na)^{3+}$ (mass accuracy: 3.4 ppm) of **17** with the correct isotope patterns.

In conclusion, we have developed a viable strategy to obtain a new class of linear oligomer of the cyclodextrins. These molecules have a well-defined shape and molecular sizes. The reported methodology allows expandability and the incorporation of other functional groups. We believe that these supramolecular structures could find application in numerous areas such as for use as scaffolds to present important biomolecules for molecular recognition or as artificial enzymes. The cavities found in the molecules could provide an ability to form inclusion complexes with potential guests with high affinities. We are currently conducting a systematic study on the synthesis and structural study of this class of molecules.

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Supporting Information Available: Experimental procedures and related analytical data for compounds **2**−**6** and **8**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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