ORGANIC LETTERS

2000
Vol. 2, No. 8
1093−1096

Synthesis of Carbamate-Containing Cyclodextrin Analogues

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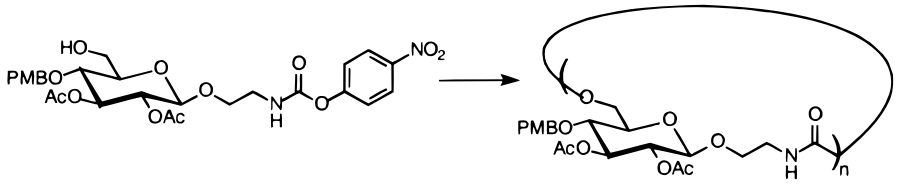
Received February 10, 2000

ABSTRACT



The one-pot cyclooligomerization of a saccharide-derived *p*-nitrophenyl carbamate monomer was developed to generate a series of novel carbamate-containing cyclodextrin analogues. The "transcarbamoylation" occurs by initial base-induced activation to the isocyanate, followed by polycondensation/cyclization of the isocyanato alcohol. In the presence of NaH, only cyclized oligomers were observed, suggesting the importance of Na^+ in promoting the efficiency of the cyclization process. The facile deprotection of the oligomers was achieved.

Since their discovery in 1891, cyclodextrins (CDs) have attracted considerable interest, particularly in the field of supramolecular chemistry, as a result of their ability to form inclusion complexes with a wide range of substrates.[1] Because of these remarkable inclusion properties, CDs have found numerous applications.[1d] For example, immobilized CDs have been employed for the separation of compounds based on their selective retention of guest molecules, and mobile CDs have been used as delivery systems.[1e] However, most of the applications of CDs make use of their ability to modify the chemical and physical properties of guest molecules. Thus, CDs have been used to both increase and decrease the availability of drugs by changing their solubilities upon complexation. Additionally, CDs have been used to stabilize active substances from degradation and to bind and catalyze reactions.[1f]

A large number of chemical modifications have been made to native CDs in order to fine-tune them for specific applications, for example, as enzyme mimics, and to alter their binding characteristics to tailor them for specific guest molecules.[1g] The complexation characteristics of CDs are dictated by the internal cavity size and shape, which in native CD is somewhat fixed by the α(1 → 4) linked glucopyranosyl units within the backbone. As derivatizations at the C2, C3, and C6 hydroxyl groups of native CD have a limited effect on the cavity shape, analogues of CDs that have configurationally and/or constitutionally modified backbones are of particular interest in the development of organic hosts with different complexation properties.[2−8] Despite the synthetic challenge that these targets pose, a variety of cycloglycans have been prepared by a total synthetic approach (stepwise

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(2) Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1989**, *192*, 131−146.

(3) Kuyama, H.; Nukada, T.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1993**, *34*, 2171−2174.

(4) Collins, P. M.; Ali, M. H. *Tetrahedron Lett.* **1990**, *31*, 4517−4520.

(5) (a) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1919−1958. (b) Ashton, P. R.; Brown, C. L.; Menzer, S.; Nepogodiev, S. A.; Stoddart, J. F.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 580−591.

(6) (a) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463−471. (b) Penadés, S.; Coterón, J. M. *J. Chem. Soc., Chem. Commun.* **1992**, 683−684.

(7) (a) Dumont, B. D.; Joly, J.-P,; Chapleur, Y. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1123−1126. (b) Haslegrave, J. A.; Stoddart, J. F.; Thompson, D. J. *Tetrahedron Lett.* **1979**, *24*, 2279−2282. (c) Pietraszkiewicz, M.; Jurczak, J. *J. Chem. Soc., Chem. Commun.* **1983**, 132−133. (d) Kanakamma, P. P.; Mani, N. S.; Nair, V. *Synth. Commun.* **1995**, *25*, 3777−3787. (e) Ellinghaus, R.; Schroder, G. *Liebigs Ann. Chem.* **1985**, 418−420.

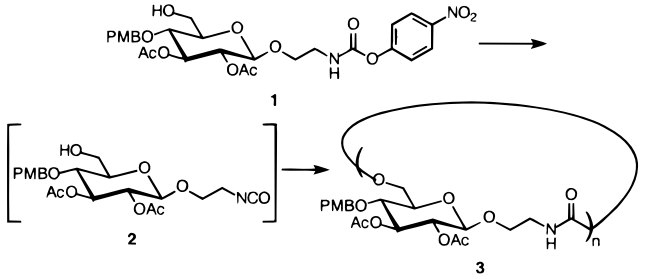
10.1021/ol005648v CCC: $19.00
Published on Web 03/24/2000

preparation of a linear precursor followed by cyclization) and by a one-pot polycondensation/cyclization approach (using a "monomer" to generate a variety of macrocycles).[2−5]

The incorporation of nonsaccharide components within the backbone has also been employed to access a variety of constitutional CD analogues with profound changes in the cavity shape. These include the "glycophanes"[6] that incorporate aromatic components and others that utilize crown ether units[7] and butadiyne units.[8]

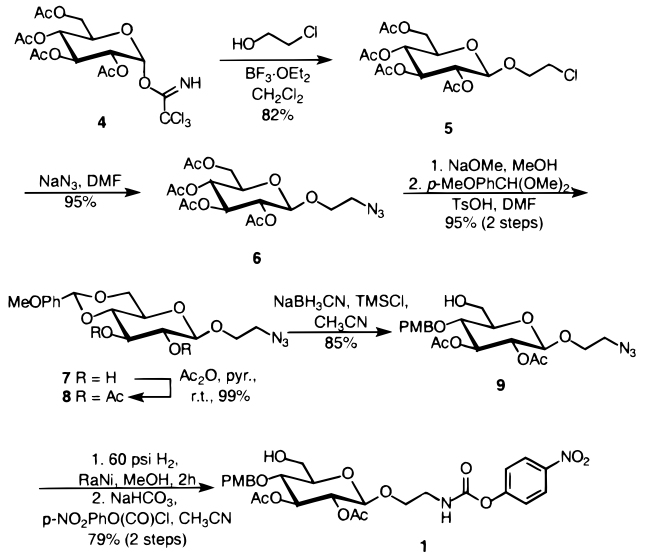
Herein, we report the synthesis of a series of novel carbamate-containing CD analogues **3** from isocyanato alcohol monomer **2**, which is generated in situ from the activated carbamate monomer **1** (Scheme 1).

Scheme 1. Synthesis of the Carbamate-Containing CD Analogues **3**



In monomer **1**, the *p*-nitrophenyl carbamate acts as a stable isocyanate precursor. Access to this carbamate was obtained by glycosylation of the fully acetylated glucopyranosyl trichloroacetimidate **4** with 2-chloroethanol to give the 2-chloroethyl glycoside as the β-anomer **5** in 82% yield (Scheme 2). Subsequent displacement of chloride with NaN_3 afforded the 2-azidoethyl glycoside **6** in 95% yield.[9] The 2-azidoethyl glycoside **6** was deacetylated and benzylidenated

Scheme 2. Synthesis of Monomer **1**

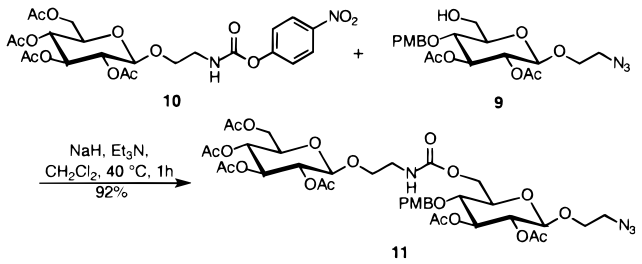


with *p*-methoxybenzaldehyde dimethyl acetal. Reacetylation of **7** at the C2 and C3 positions gave **8**. Regioselective reduction of the benzylidene at the C6 position was achieved using the conditions of Johansson and Samuelsson to afford alcohol **9**.[10] Finally, azide reduction and carbamoylation with *p*-nitrophenyl chloroformate gave the desired saccharide-bound *p*-nitrophenyl carbamate **1**. The heterogeneous conditions of Choy and co-workers were used for the carbamoylation,[11] as the activated carbamate could be isolated and purified in good yield with minimal base-induced decomposition.[12]

Although the reaction of *p*-nitrophenyl carbamates with amines to form ureas is, in most cases, facile and well-documented, their reaction with stoichiometric amounts of alcohols proceeds with lower yields while requiring harsher conditions that involve prior activation to the isocyanate.[13] Lewis acids such as chlorosilanes may be used in the presence of base to quantitatively cleave the activated carbamate to its isocyanate; however, the presence of Et_3N alone will often readily generate the isocyanate to varying extents of conversion.[14]

Our oligomerization conditions for monomer **1** were developed from optimization of the parallel reaction between model compounds **9** and **10** (Scheme 3). It is worth noting

Scheme 3. Model Reaction between **9** and **10**



that protection of the C4 hydroxyl group as the PMB ether in both monomers **1** and **9** was necessary, as it prevented

(8) (a) Burli, R.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 485−493. (b) Burli, R.; Vasella, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1852−1853. (c) Burli, R.; Vasella, A. *Helv. Chim. Acta* **1997**, *80*, 1027−1052. (d) Burli, R.; Vasella, A. *Helv. Chim. Acta* **1997**, *80*, 2215−2237.

(9) This two-step route avoids the use of the explosive 2-azidoethanol as the glycosyl acceptor. Glycosylations using 2-hydoxyethyl carbamic acid esters as glycosyl acceptors led to the predominant formation of the undesired α anomer.

(10) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(11) Choy, N.; Moon, K. Y.; Park, C.; Son, Y. C.; Jung, W. H.; Choi, H.; Lee, C. S.; Kin, C. R.; Kim, S. C.; Yoon, H. *Org. Prep. Proced. Int.* **1996**, *28*, 173−177.

(12) When soluble base conditions were used, the product underwent base-induced decomposition during purification, resulting in lowered yields.

(13) (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055−4058. (b) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 2583−2586. (c) Koh, H. J.; Kim, O. S.; Lee, H. W.; Lee, I. *J. Phys. Org. Chem.* **1997**, *10*, 725−730. (d) Umezawa, S.; Takagi, Y.; Tsuchiya, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1411−1415. (e) Fukuda, Y.; Kitasato, H.; Sakai, H.; Suami, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 880−886.

(14) (a) Greber, G.; Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 941. (b) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781. (c) Chong, P. Y.; Janicki, S. J.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515−8521 and references therein.

acetyl migrations originating from C2 and C3, thereby allowing us to maintain the position of the free alcohol at C6. Reaction between **9** and **10** with the use of both NaH and Et_3N in CH_2Cl_2, afforded carbamate **11** in 92% yield, the reaction reaching completion within 1 h. In addition to increasing the nucleophilicity of the alcohol, the NaH plays an important role in driving the reaction to completion by precipitating the byproduct *p*-nitrophenol out of solution as the phenolate salt.

Polycondensation of monomer **2** produced a series of low molecular weight cyclized oligomers **3**, linear growth being terminated by intramolecular cyclization. The formation of these oligomers is apparent from the MALDI mass spectrum (Figure 1) in which the MW of each successive oligomer

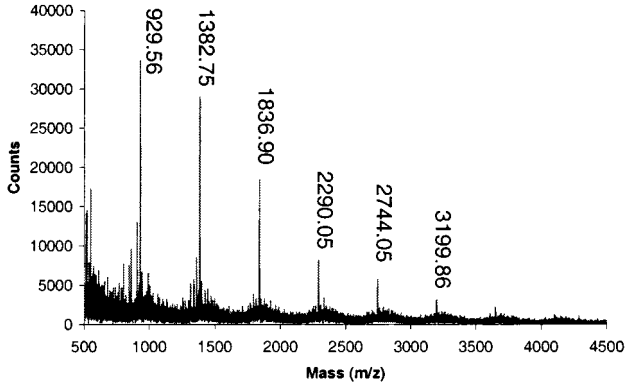


Figure 1. MALDI mass spectrum of cyclized oligomers **3** obtained by cyclooligomerization of monomer **1**. All masses correspond to $(M + Na)^+$, for example, the peak at 929.56 corresponds to the cyclic 2-mer (MW = 906.3).

increases by 453 mass units (corresponding to a monomer unit).

These CD analogues are structurally interesting with potential utility in host−guest chemistry. The cyclic 2-mer, 3-mer, and 4-mer are isolable from the reaction mixture and have been purified (by silica gel flash chromatography) and fully characterized. The high degree of symmetry of these protected cyclized oligomers was apparent from their NMR spectra. Each oligomer gave rise to one set of pyranoside signals, corresponding to the repeating monomer unit. Connectivities were established by COSY NMR spectra, and molecular compositions were confirmed by HRMS−FAB. The 2-mer showed no broadened signals in the ^1H NMR spectrum, and the appearance of the NH signal as a dd indicates a fairly conformationally restricted structure. On the other hand, both the 3-mer and 4-mer showed some signal broadening, as well as some asymmetry at 20 °C.[15] When the temperature was elevated to 50 °C, these signals coalesced and/or sharpened to some degree, suggesting that line broadening is the result of slow-equilibrating conformers

(15) The NMR spectra of the 3-mer and 4-mer at 50 °C are very similar with similar chemical shifts and almost identical coupling constants for H_1, H_2, and H_3.

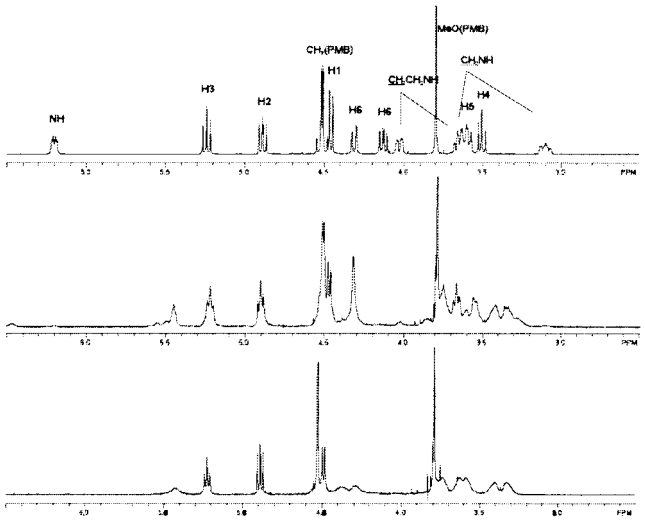


Figure 2. ^1H NMR specta (in $CDCl_3$) of (a) cyclic 2-mer at 20 °C, (b) cyclic 3-mer at 20 °C, and (c) cyclic 3-mer at 50 °C.

(Figure 2). Increasing the ring size of the cyclic oligomer is expected to increase the degree of conformational flexibility; therefore, this observation is not surprising.[16]

Although less entropically favored, cyclization of the larger oligomers was observed. We believe that this tendency toward cyclization may be due to coordination (perhaps of the O atoms within the backbone) with Na^+ ions, which structurally preorganizes the oligomer for cyclization. In support of this, the same reaction in the absence of NaH led to the formation of the linear oligomers, although the more entropically favored cyclization of the smaller oligomers was also observed (Figure 3).[17]

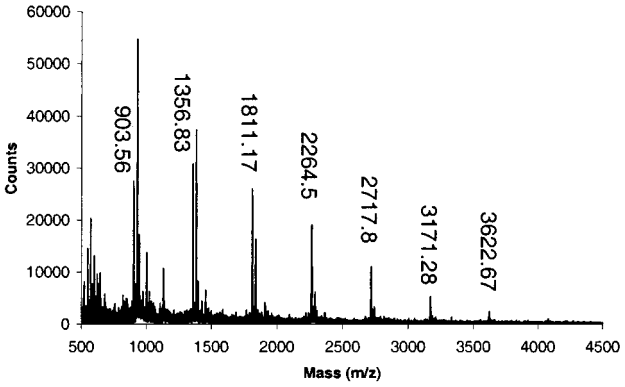
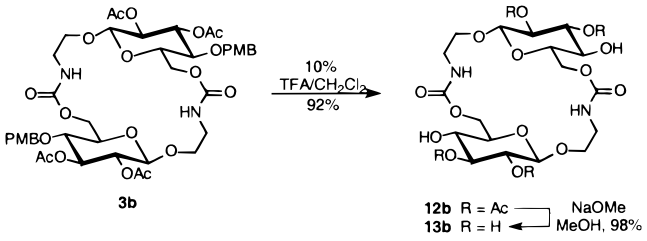


Figure 3. MALDI mass spectrum of the result of the reaction in the absence of NaH. Although cyclized oligomers **3** are observed at low MW, the uncyclized counterparts appear to dominate at and beyond the 4-mer. All masses correspond to $(M + Na)^+$.[17]

Our deprotection sequence was performed on the isolated cyclic 2-mer **3b** to evaluate its efficiency for these systems.

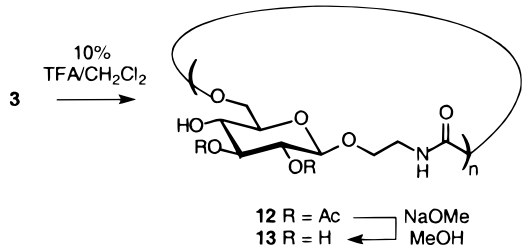
Facile removal of the PMB groups was achieved using Kahne's conditions (10% TFA/CH_2Cl_2) to afford **12b** in 92% yield.[18] Following this, Zemplén deacetylation provided the fully deprotected 2-mer **13b** in 98% yield (Scheme 4).

Scheme 4. Deprotection of the Cyclic 2-Mer **3b**



The same deprotection sequence was then performed on the oligomeric mixture **3** (Scheme 5). PMB ether deprotection proceeded cleanly to produce oligomers **12** with the MALDI mass spectrum shown in Figure 4a, each successive oligomer being separated by 333 units (corresponding to the mass of a C4-deprotected monomer unit). Final deacetylation afforded the fully deprotected oligomers **13** (Figure 4b).

Scheme 5. Deprotection of the CD Analogues **3**



In conclusion, we have developed a facile one-pot polycondensation/cyclization approach to access novel carbamate-containing cyclodextrin analogues. This cyclooligmerization involves the activation of a saccharide-derived *p*-nitrophenyl carbamate to the isocyanato alcohol. Facile deprotection of the oligomers was also achieved.

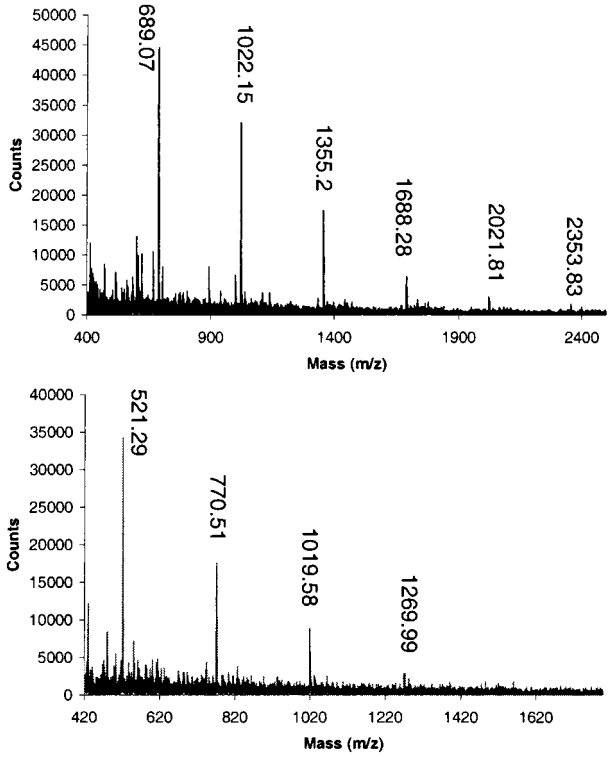


Figure 4. (a) MALDI mass spectrum of the C4-deprotected CD analogues **12**. (b) MALDI mass spectrum of the fully deprotected CD analogues **13**. All masses correspond to $(M + Na)^+$.

Acknowledgment. We gratefully acknowledge the NIH, PRF, American Heart Association, UIUC Research Board, and Critical Research Initiatives Program for financial support. We also extend special thanks to Professor Jeffrey Moore for useful suggestions. All mass spectra were obtained by the UIUC Mass Spectrometry Lab.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is free of charge via the Internet at http://pubs.acs.org.

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(16) Our observed line broadening and temperature dependence of the spectra is similar to that observed in Vasella's cyclic hybrids of 2,2′-bipyridine and acetylenosaccharides (ref 8a).

(17) The uncyclized oligomers have molecular weights 26 units lower than their cyclic counterparts because the *p*-nitrophenyl carbamate is hydrolyzed on workup to the amines.

(18) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524.