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Short Synthesis of Diamide-Linked Sucrose Macrocycles

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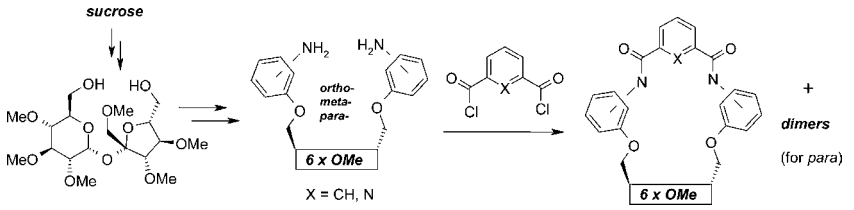
ABSTRACT



A convenient route to macrocyclic diamide-linked macrocyclic derivatives with a sucrose scaffold is presented. Reaction of sucrose based amines (*o*- and *m*-) with acid dichlorides afforded the monomeric macrocycles in excellent yields, while reaction of the *p*-amines also provided dimeric products.

Carbohydrates are convenient and easily accessible starting platforms for the preparation of chiral macrocyclic receptors.[1] Such macrocyclic derivatives based upon sugar scaffolds have been extensively used as chiral catalysts in asymmetric synthesis (asymmetric epoxidation of chalcones,[2] Michael addition,[2c,e,3] and Darzens reactions[2c,e,g,3c,4]). They have also been investigated as fluorescent molecular sensors for cations[5] and anions.[6]

Recently we have demonstrated the synthesis of such receptors with a sucrose scaffold. The C-6 and C-6′ positions in 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (**1**)[7] were connected *via* a bridge providing a range of macrocyclic derivatives (**2a**–**c**).[8] Macrocyclic derivatives with higher symmetry (e.g., **3**)[9] are also available (Figure 1). Compounds of type **2** showed significant enantioselectivity in the complexation of an α-phenylethylammonium cation.[8c]

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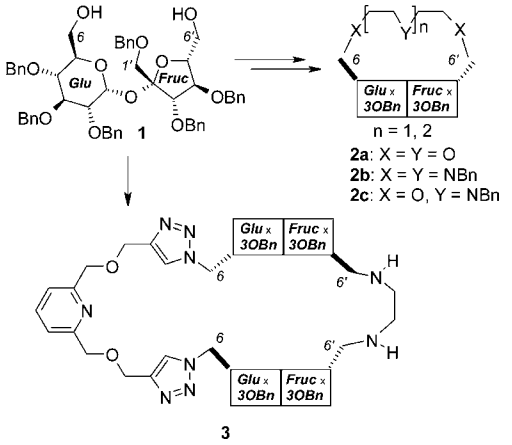
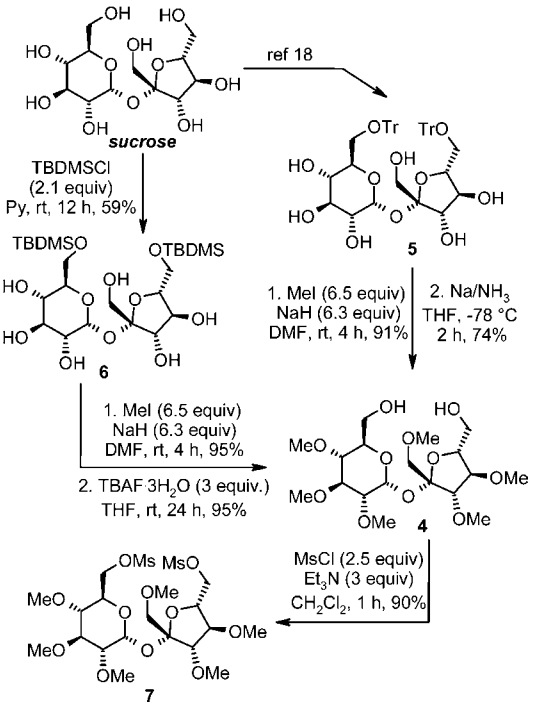


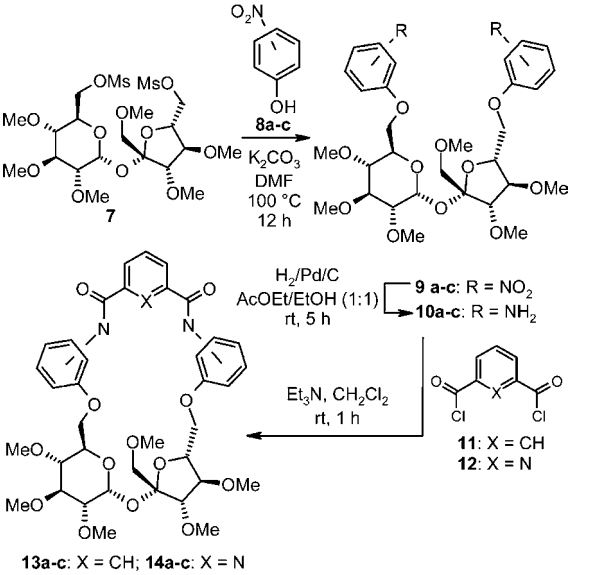
Figure 1. Macrocyclic receptors containing a sucrose scaffold.

In this paper we report on the synthesis of sucrose-derived macrocyclic derivatives containing isophthalic and 2,6-pyridinedicarbonate amide groupings. Macrocyclic compounds with such aromatic platforms play an important role in supramolecular chemistry,[10] as receptors for anions,[11] ion pairs,[12] zwitterions (e.g., dopamine[12c]),

Scheme 1. Synthesis of Dimesylate **7**



Scheme 2. Synthesis of Sucrose-Based Macrocyclic Diamides



and amino acid derivatives.[13] The anion-complexing properties of these amides have been exploited in the templated syntheses of catenane,[14] rotaxane,[14a,15] and pseudorotaxane[16] systems.

Macrocyclic diamides are usually synthesized from isophthalic and 2,6-pyridinedicarboxylic acids (or isophthaloyl and 2,6-pyridinedicarbonyl dichlorides) in combination with other building blocks, such as polyethylene glycol

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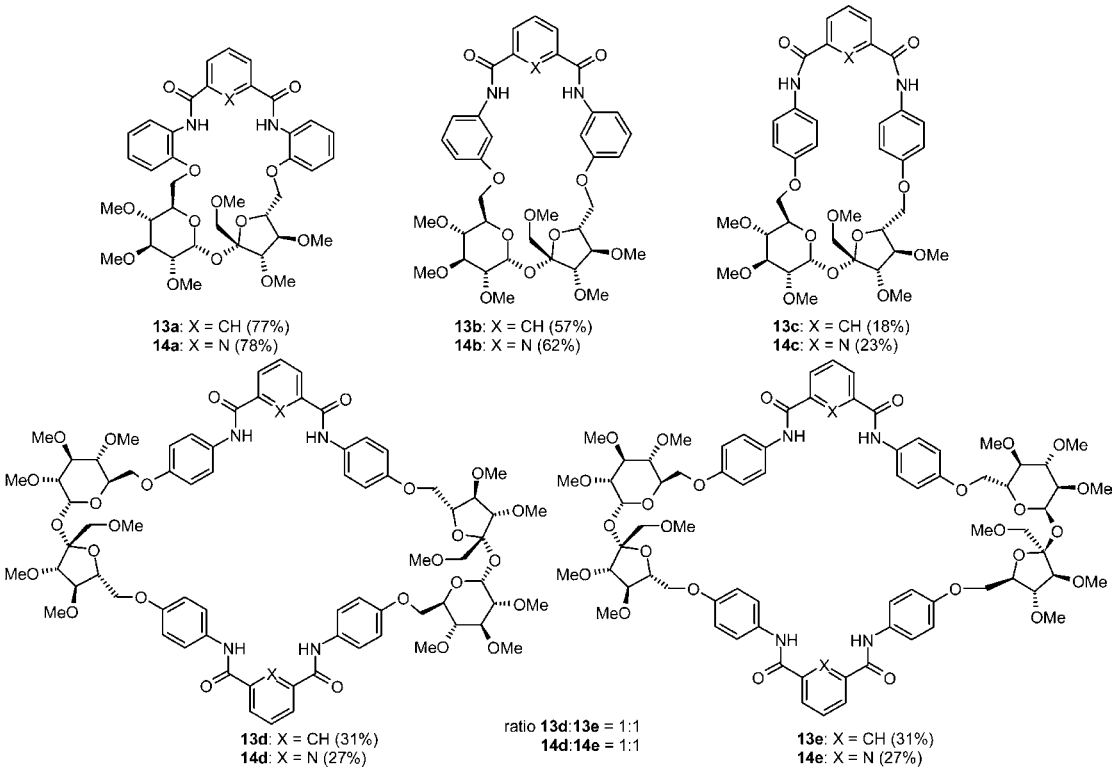

Figure 2. Macrocyclic diamides **13a**–**e** and **14a**–**e**.

(PEG) reagents,[14b,c,15b,d,f–h,j] chiral 1,2-diamines,[13] calix-[4]arenes,[11c,12b,14a,15c] and calix[4]diquinones.[12d,14d,15i]

Our synthesis of sucrose-based macrocyclic derivatives of this type was initiated from 1′,2,3,3′,4,4′-hexa-*O*-methylsucrose (**4**). These protecting groups were selected because they are stable to a range of conditions (e.g., catalytic hydrogenation). Moreover, the NMR spectra of the complex macrocyclic products might be simpler than those of their per-*O*-benzyl analogs. Therefore we reasoned that application of hexa-*O*-methylsucrose (**4**) in the model synthesis of macrocyclic diamides would be preferable in comparison to 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (**1**).

Synthon **4** was prepared for the first time by Sachinvala et al. in a rather long and tedious synthesis from free sucrose.[17] We offer now an alternative and more convenient method for the preparation of **4** from either 6,6′-ditrityl[18] or 6,6′-disilyl[19] sucroses (**5** and **6** respectively). Per-*O*-methylation of either **5** or **6** with methyl iodide followed by deprotection of the 6,6′-hydroxyl groups afforded the diol **4** in good overall yield (Scheme 1).

This diol **4** was converted into the mesylate **7** which was then applied as starting material for the preparation of the target macrocycles. Its condensation with 2 equiv of the proper nitro-phenol **8a**–**c** (*o*-, *m*-, *p*- respectively) provided the expected 6,6′-di-*O*-nitrophenyl-1′,2,3,3′,4,4′-hexa-*O*-methylsucroses **9a**–**c** in 85–90% yields.

Hydrogenation of these intermediates afforded the respective diamines **10a**–**c** in excellent (91–96%) yield (Scheme 2). These diamines were used for the preparation of the macrocyclic bis-amides under high dilution conditions.

Condensation of *o*-diamine **10a** with isophthaloyl or 2,6-pyridinedicarbonyl dichlorides (**11** and **12** respectively) afforded the expected macrocyclic derivatives **13a** or **14a** in 77% and 78% yields (Figure 2). These excellent yields of cyclization can be explained by assuming that there is good preorganization of the molecule substrate.

Reaction of the *m*-diamine **10b** with reagent **11** or **12** proceeded analogously, although the corresponding diamides **13b** and **14b** were formed in lower yields (57% and 62% respectively).

Condensation of the *p*-diamine **10c** with acid dichloride **11** or **12** under the same conditions was, however, more complex. The expected monomeric product **13c** was formed in low yield (18%) in the reaction with **11**, and the main one consisted of a mixture of two isomeric dimers

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with *C*2-symmetry (**13d/13e**) obtained in 62% overall yield. Reaction of **10c** with dichloride **12** proceeded analogously affording the monomeric product **14c** (23%) and a 1:1 mixture of the dimeric products **14d/14e** (54%; Figure 2).

Although these dimers could not be isolated in pure form, the proportions of **13d:13e** and **14d:14e** were estimated as 1:1 based on integration of aromatic signals in the ^{1}H NMR spectrum.

The relative orientations of the amino groups in the energetically accessible conformations of substrates **10a**−**c** define the direction of macrolactamization. For compound **10c**, conformations of the monoamide where the second amine is close to the remaining acid chloride must have low populations, reducing the probability of formation of dilactams **13c** and **14c**; thus, 2:2-cyclization becomes dominant.

In conclusion, the work presented herein describes the synthesis of macrocyclic diamides **13**−**14** containing the sucrose subunit. The starting material for the macrocyclization is prepared in a relatively small number of steps, making this an efficient synthesis of such macrocycles.

The presence of sucrose and isophthalic or 2,6-pyridinedicarbonate amide in these scaffolds makes them promising receptors.

It is worth pointing out that the sucrose *p*-diamine (**10c**) upon reaction with an acid dichloride (**11** or **12**) afforded only small amounts of the desired monomer; the main products were dimers (with *C*2-symmetry) which could be distinguished by NMR.

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Supporting Information Available. Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.