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Synthesis of new saccharide azacrown cryptands

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ABSTRACT

New cryptands including bis-azacrown and saccharidic moieties in their structure were prepared in several steps by applying Staudinger–aza-Wittig reaction (SAW). Syntheses have been started from cheap, easily available commercial compounds such as D-glucose, D-cellobiose and D-lactose subsequently transformed into their derivatives in fairly good yields (60–65%) and suitable to give desired final cryptands by direct SAW coupling reactions.

1. Introduction

Supramolecular chemistry is one of the fastest growing and most active fields of chemistry which examines weak and reversible non-covalent interactions between host and guest molecules. These forces include hydrogen bonding, hydrophobic and van der Waals forces, π–π interactions and electrostatic effects. The study of them is very important to understand many biological processes. The development of synthetic receptors capable of forming complexes with specific guests[1] has been significant for host–guest chemistry. Macrocycles are very useful in supramolecular chemistry because they form cavities that can entirely surround guest molecules and can be chemically modified to attune their properties.[2]

Interest in the synthesis of macrocyclic compounds has increased over the last years due to their analytical, industrial and medical applications.[3] It is interesting class of ligands which can form complexes with numerous metal cations, anions and neutral molecules.[4] Very often crown ethers constitute the main part of construction of macrocycles.[5] Preparation of carbohydrate-derived crown ethers has gained special attention because of advantages which are involved with carbohydrate structures.[6] The sugar moieties may be directly incorporated into the crown macrocycle itself or attached to as pendant arms.[7]

Recently, we have described derivatives of carbohydrate azacrown ethers which are efficient receptors for the neutral molecules, such as busulfan, paracetamol, aspirin and *p*-toluenesulfonamide.[8]

These types of compounds have been called pseudocryptands due to their complexing properties which are common for cryptands. On the other hand their structures have not been typical for this type of connection.

Therefore we have decided to prepare closed forms of macrocycles in next step of our study. The present paper describes preparation of new compounds that contain in their structures both two units of saccharides and two molecules of azacrown ethers.

2. Results and discussion

The new cryptands **18**, **19** and **21** were obtained in several steps starting from the commercially available D-glucose, D-cellobiose and D-lactose (Scheme 1).

2.1. Synthesis of starting materials

Azide derivatives of glucose, cellobiose and lactose (**10a**–**c**) were synthesized, as shown in Schemes **2** and **4**, according to a similar method reported previously.[9] The hydroxyl groups of carbohydrate molecules (**1a**–**1c**) were protected by using acetic anhydride in pyridine. Treatment of compounds **2a**–**2c** with 35% solution of hydrogen bromide in acetic acid afforded the corresponding bromo derivatives **3a**–**c** with α-anomeric selectivity.

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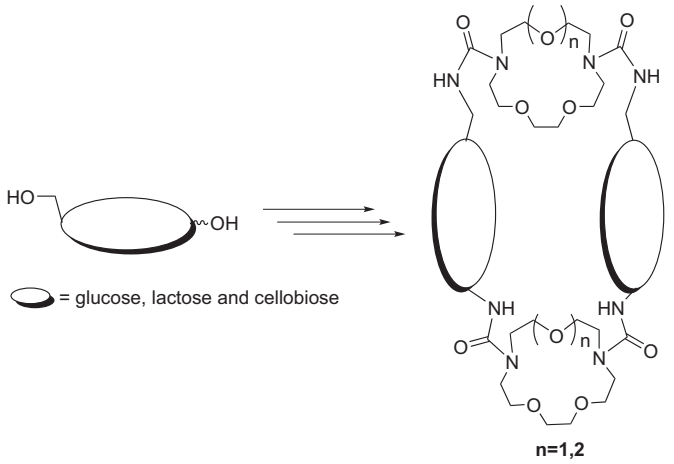
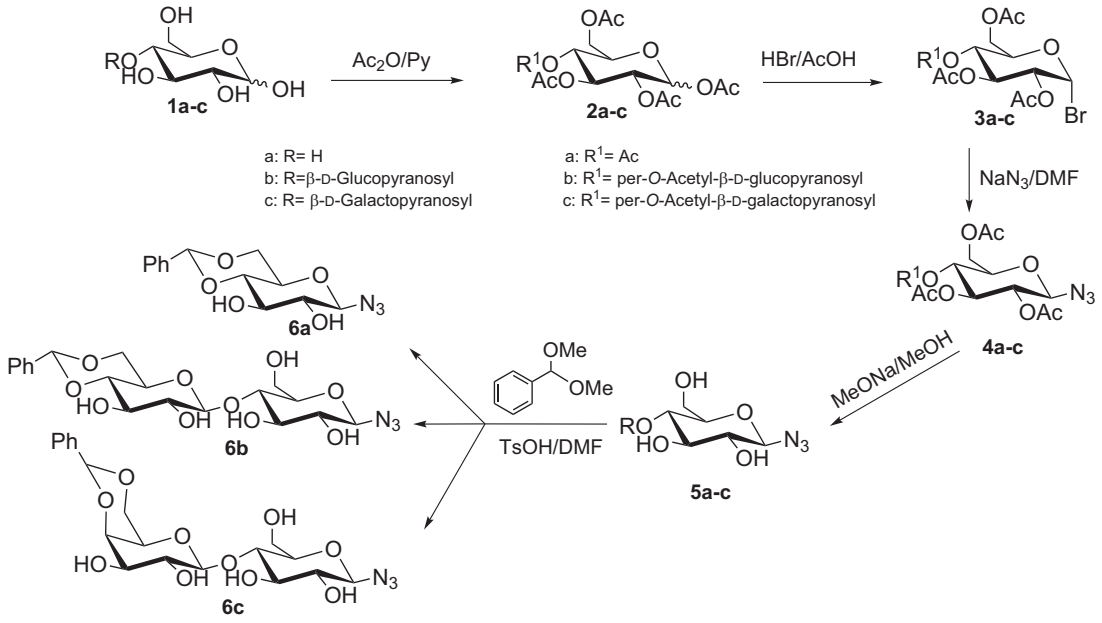


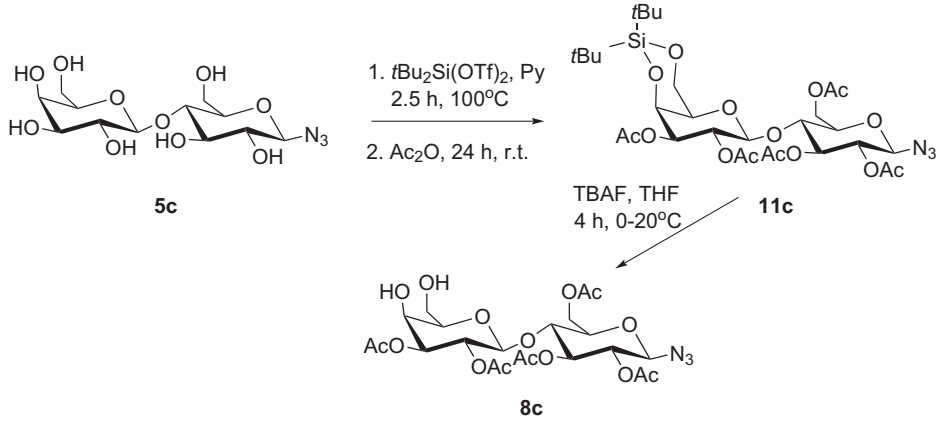
Scheme 1. General strategy for the synthesis of cryptands.

Then compounds **3a**–**c** were converted without purification into azido derivatives (**4a**–**c**) applying excess of sodium azide in DMF at 80 °C.[10] The removal of ester protecting groups included a catalytic amount of sodium metoxide in methanol at room temperature (Zemplén conditions).[11] Compounds **5a**–**c** were reacted with α,α-dimethoxybenzaldehyde in the presence of catalytic amount of *p*-toluenesulfonic acid to protect the hydroxyl groups either at positions 4 and 6 (glucose (**6a**) derivative) or at positions 4′ and 6′ (cellobiose (**6b**) and lactose (**6c**) derivatives) (Scheme 2).[12]

Compounds **6a**–**b** were obtained in good yields (60–65%) whereas that of **6c** was much lower (40%). Therefore we were looking for a more efficient method for protecting selectively positions 4′ and 6′ in lactose. To protect the above-mentioned two hydroxyl groups of compounds **5c** was used di-*tert*-butylsilyl bis(-trifluoromethanesulfonate).[13] Silylation of lactose derivative (**5c**) with 1.1 equiv of tBu$_2$Si(OTf)$_2$ in pyridine provided a mixture of three products. After acetylation of this crude mixture, the expected product **11c** was obtained in 38% yield (Scheme 3). Then, reaction of **11c** with a TBAF·3H$_2$O resulted in a cleavage of the tBu$_2$Si(OTf)$_2$ group and gave 2,3,6,2′,3′-penta-*O*-acetyl-1-azido-β-D-lactose (**8c**).[14]



Scheme 2. Synthesis of **6a**–**c** for preparation of the target macrocycles.



Scheme 3. Synthesis of the lactose derivative **8c**.