Synthesis of C_2-symmetric Glycophanes Through a 'Click Chemistry' Approach

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Abstract: The synthesis of C_2-symmetric glycophanes incorporating two triazole linkers has been achieved in seven steps from 3,4,6-tri-*O*-acetyl-D-glucal in good overall yields. The intermolecular Cu(I)-mediated Huisgen reaction was used for the ring closure key-step to give almost exclusively 24-, 26-, and 32-membered chiral macrocycles without significant polymerization. Target compounds however had low solubility in water, precluding investigation of their recognition behaviour in this medium.

Keywords: carbohydrate, Ferrier reaction, Huisgen cycloaddition, click chemistry, glycophane.

INTRODUCTION

Glyco-cyclophanes [1], or more concisely glycophanes [2], are a family of neutral and chiral synthetic sugar-based macrocycles that display hydrophobic cavities and are of interest in molecular recognition [3]. Like their cyclophane parents [4] some water-soluble glycophanes are endowed with interesting complexing behaviors which make them potential receptors for small, neutral organic guests [5]. The 'click chemistry' approach independently initiated by the groups of Meldal and Sharpless [6], *i.e.* the copper(I)-catalyzed modern version of the Huisgen-type azide-alkyne cycloaddition [7] to give preferentially if not exclusively the 1,4-regio-isomer, was recently used for the highly convergent synthesis of cyclodextrin analogues [8]. The inertia of the 1,2,3-triazole ring towards basic and acid hydrolysis [9] as well as towards metabolic degradation makes it an attractive connecting unit in the fields of supramolecular [10] and peptide chemistry [11], drug design [12], and materials science [13]. In connection with our previous syntheses of 22- and 23-membered electron-rich cage-like molecules by Glaser oxidative homocoupling of bridged disaccharides [14] and larger glycophanes [15], we report here the syntheses of small symmetric cage-like molecules by a click chemistry approach [16].

RESULTS AND DISCUSSION

Taking advantage of previous works in the laboratory [17], we decided to explore a new approach based on a Ferrier rearrangement for the glycosylation key-step. The stereoselective boron trifluoride-catalyzed allylic rearrangement [18] of tri-*O*-acetyl-D-glucal **1** with ω-bromo-alcohols in dichloromethane below +4°C led mainly if not exclusively to α-anomers **2** and **3** ($J_{1\text{-}2} \leq 2$ Hz) in good to excellent yields. The Zemplén deprotection [19] of esters **2** and **3** yielded diols **4** and **5** almost quantitatively. Nucleophilic azide displacement of bromine in hot DMF afforded diols **6** and **7** which were reacted with trityl chloride to afford protected alcohols **8** and **9** in 58 and 85% yield respectively over 3 steps. Almost quantitative *O*-propargylation on the remaining hydroxyl group at C-4 could be performed either by phase-transfer catalysis [20] or through a classical Williamson reaction [21] (NaH/THF) to give protected azido-alkyne precursors **10** and **11** Scheme **1**.

Gratifyingly, the Cu(I)-catalyzed cycloaddition of **10** and **11** at the concentration of 6×10^{-3} M in toluene in the presence of DBU as a base afforded cyclic dimers **12** and **13** in fair yields. In contrast with similar macrocycle formations reported by Bodine *et al.*, [5e] no traces of trimers or higher oligomers could be detected by ESI-MS in the crude mixture. However, formation of a significant amount of **13b**, resulting from iodine addition on the triazole ring [22], occurred during the preparation of **13a**. Although very little is known about the exact nature of the mechanism of Cu(I)-catalyzed alkyne-azide coupling [23], optimized reaction conditions [24] could avoid the formation of by-product **13b** Scheme **2**.

We next explored the synthesis of a larger glycophane by reversing the relative positions of azide and alkyne substituents on the sugar, *i.e.* the propargyl group being introduced at the anomeric position and the azido group grafted at *O*-4 *via* a longer arm. The synthesis of compound **19** obtained this way is shown in Scheme **3**.

(1-Prop-2-ynyl)-2,3-dideoxy-α-D-*erythro*-hex-2-*eno*pyranoside **15** [25], readily obtained by known procedures from tri-*O*-acetyl-D-glucal in 91% yield over two steps, was protected as a trityl ether to give sec. alcohol **16** (92%) which was reacted under phase-transfer conditions with an excess of 1-chloro-2-(2'-chloroethoxy)ethane [26] to afford chloroalkyl ether **17** in excellent yield. Nucleophilic azide dis-

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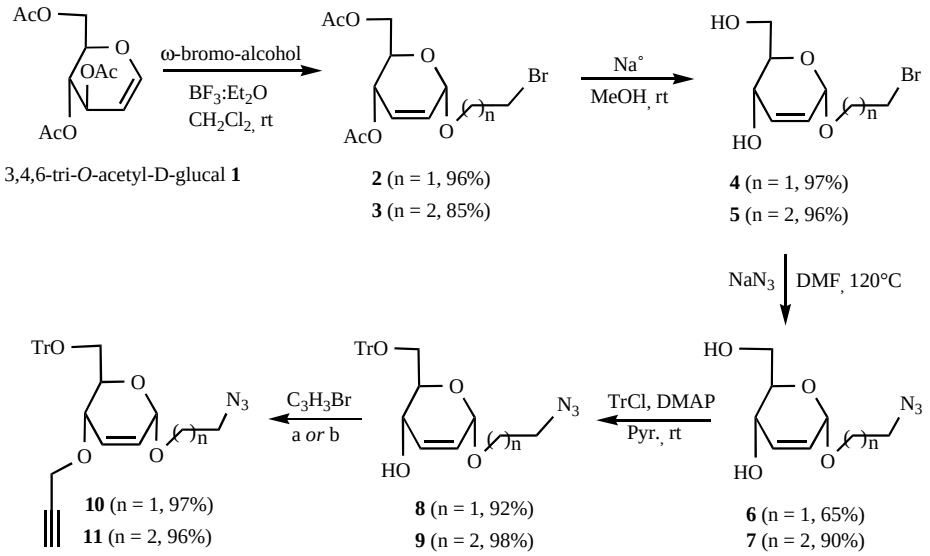
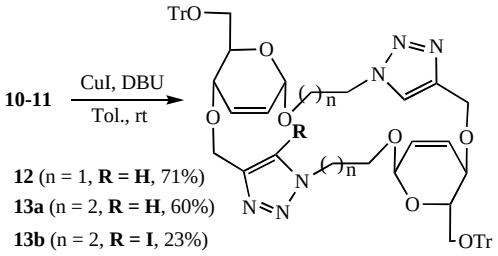


Scheme 1. Synthesis of azido-alkynes **10** and **11** from tri-*O*-acetyl-D-glucal **1**; a: aq. NaOH, Tol., NBu_4HSO_4, < 4°C; b: NaH, THF, 0°C.

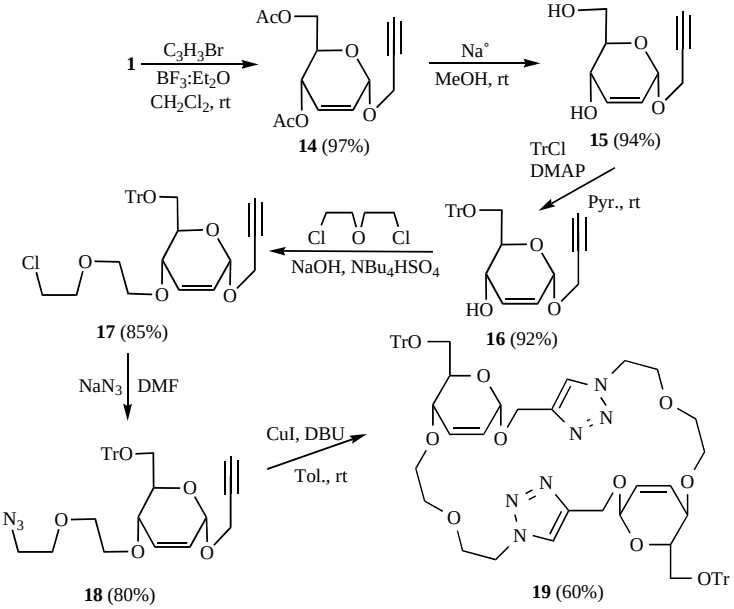
placement of the chlorine atom in hot DMF afforded azido-alkyne precursor **18** which was cyclized in the presence of CuI and DBU-excess to yield glycophane **19** in fair yield. Like glycophanes **12** and **13a**, the ^{1}H-NMR spectrum of this 32-membered macrocycle displayed a C_2-symmetry in $CDCl_3$ solution at 27°C [27].



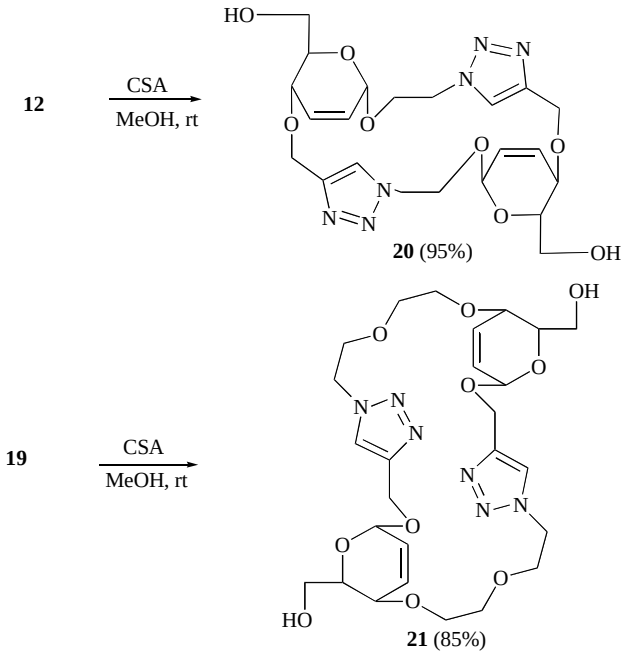
Scheme 2. Synthesis of glycophanes **12** and **13** *via* tandem dimerization-macrocyclization of **10** and **11**.

Glycophanes **12** and **19** could be easily deprotected by treatment with camphor sulphonic acid (CSA) in MeOH at room temperature [16b] to yield diols **20** and **21** Scheme **4**.

However in our hands deprotection of **13a** under the same conditions (*i.e.* a catalytic amount of CSA in a CH_2Cl_2/MeOH mixture at rt) failed, leading only to polar degradation products [28]. The target compounds **20** and **21** displayed very low solubility in water, precluding an investigation of their complexing behaviour in this medium. However, preliminary NMR investigations using known protocols [29] showed no measurable extraction of amino acids (*e.g.* L-valine, glycine methyl esters as their ammonium perchlorate salts) by these glycophanes from D_2O. One may assume that the cavity of such dimers is too small to accept even a small guest and that the two triazole spacers provide a too rigid macrocycle which would adopt an extended conformation. Thus, a conformational search of host **20** pro-

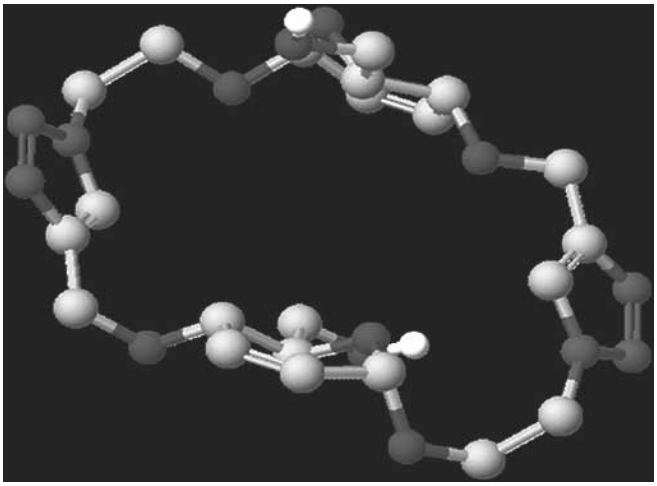


Scheme 3. Synthesis of glycophane **19** from 3,4,6-tri-*O*-acetyl-D-glucal.



Scheme 4. Deprotection of glycophanes **12** and **19** by CSA in MeOH at rt.

a



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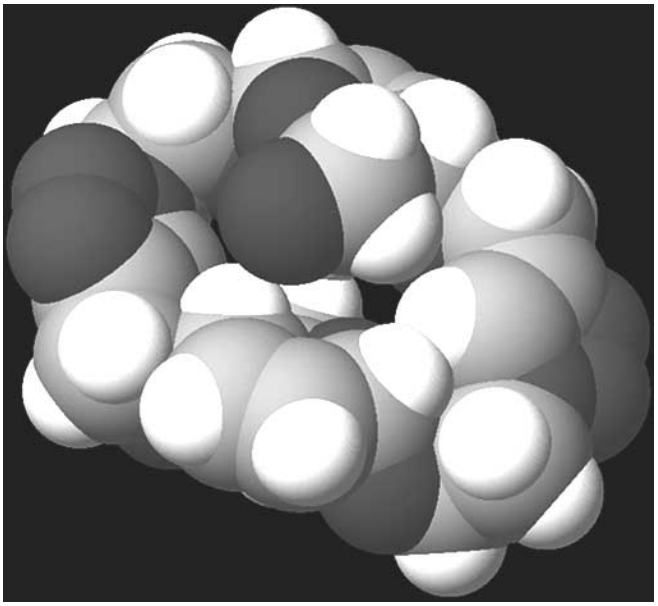

Fig. (1). Low energy conformer of glycophane **20**.

vided a low energy conformer family [30] such as the one depicted in Fig. (**1**). It exhibits a C_2-symmetry and a rectangular shape: the distance between the CH of the two triazole rings in this model is about 7.7 Å and the smallest distance between the two sugar rings is around 3.2 Å. This may be compared with the 5.0 Å cavity diameter of α-cyclodextrin. A CPK representation of our model clearly shows that the cavity should be sterically closed on both sides by the two primary hydroxyl groups of the sugars.

CONCLUSION

In summary, the convergent synthesis of three C_2-symmetric glycophanes incorporating two triazole linkers was readily achieved in seven steps from 3,4,6-tri-*O*-acetyl-D-glucal in good overall yield (34-41%). The intermolecular Cu(I)-mediated Huisgen 1,3-dipolar cycloaddition of azido-alkyne precursors afforded only dimers with 24-, 26-, or 32-membered macrocycles in good yield without significant polymerization. The deprotection of the trityl ethers by CSA in methanol was obtained in good yields for only two of these three glycophanes. No complexing ability towards amino acids as their methyl ester salts was observed for these macrocycles in $CDCl_3$ mainly due to their small, non-circular cavity. Tri- or tetrameric water-soluble structures [5e] would likely be far better complexing agents but their synthesis needs a stepwise approach which is currently underway.

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SUPPLEMENTARY MATERIAL

Supplementary material can be viewed at www.bentham.org/loc

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