Carbohydrate Research 421 (2016) 25–32

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Sugar-based novel chiral macrocycles for inclusion applications and chiral recognition

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ARTICLE INFO

Article history:
Received 12 September 2015
Received in revised form 10 December 2015
Accepted 13 December 2015
Available online 23 December 2015

Keywords:
Macrocycle
Click reaction
Template assisted
Benzyl ammonium perchlorate
Phenylalanine
Chiral recognition

ABSTRACT

A convergent template assisted synthesis of sugar-based chiral macrocycles has been achieved. The host–guest inclusion studies have revealed significant interactions of the synthesized macrocycle with primary over secondary ammonium salt. The chiral macrocyle also discriminates between D- and L-phenylalanine methyl ester hydrochlorides as revealed by ^{1}H NMR spectral studies on the mixture of the host and the guest molecules.

1. Introduction

Sugar-based macrocycles are of immense importance owing to their ease of accessibility from natural resources, multifunctional nature, presence of geometrical constraints and also due to the chiral nature of the sugar which provides key specificities in molecular recognition processes.[1,2] Like naturally occurring sugar-based macrocycles, their synthetic counterparts are also interesting because of their complex structure and synthetic challenges. They have diverse applications as supramolecular architectures,[3] medicines,[4] biomimetic receptors,[5] molecular pores,[6] chiral recognition agents,[7] *etc.*

Recently, some sugar-based macrocycles with triazole linkage have been synthesized involving copper catalyzed alkyne-azide cycloaddition reaction (CuAAC).[8–14] These types of macrocycles find great applications as inclusion hosts and as pharmacophores.[15] In the course of C_n-symmetric synthesis, cyclodimerization/cyclooligomerization of azido-alkyne sugars or synthesis of carbohydrate-peptide hybrids has been reported using glucopyranosides and furanosides.[8,9,16,17] The synthesis of C_n-symmetric macrocycles is a challenging task often due to insufficient product yield and to overcome the problem, different approaches utilizing π-π stacking, π-donor/π-acceptor interactions, hydrogen bonding of non-metallic templates like simple aromatic compounds have been tried.[4,9,11,16,18–21]

In the present work, we have designed and developed a simple and facile template assisted synthesis of chiral sugar-based macrocycles which are homodimer of azido-alkyne sugars derived from 2,5-anhydro-D-mannitol (Fig. 1). Interestingly, one of the synthesized macrocycles exhibited appreciable interaction with the primary ammonium salt, *i.e.* benzyl ammonium perchlorate over dibenzyl ammonium perchlorate salts and also showed chiral discrimination between L- and D-phenylalanine methyl ester hydrochlorides.

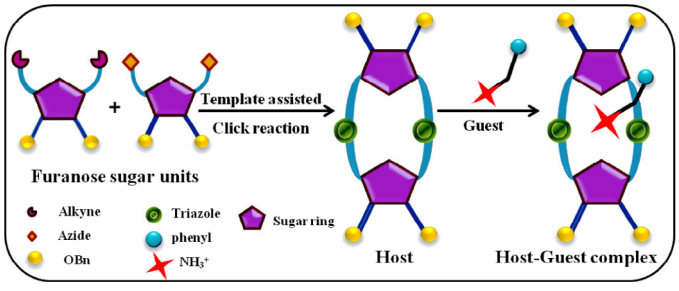

Fig. 1. Template assisted synthesis of chiral sugar-based macrocycles and their interaction with ammonium ion.

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http://dx.doi.org/10.1016/j.carres.2015.12.006
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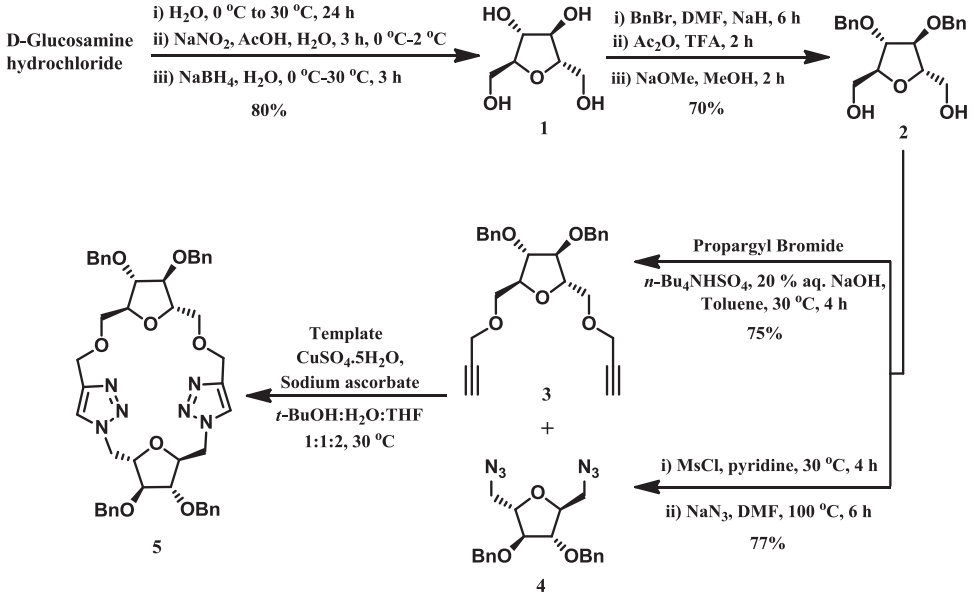

Scheme 1. Synthesis of macrocycle **5**.

2. Result and discussion

2.1. Synthesis

The synthesis of chiral sugar-based macrocycles **5** and **7** has been illustrated in Schemes 1 and 2. The 2,5-anhydro-D-mannitol (**1**) was synthesized from commercially available D-glucosamine hydrochloride in 80% overall yields in three steps, which was again converted to the partially benzylated furanoside, *i.e.* 3,4-di-*O*-benzyl-2,5-anhydro-D-mannitol (**2**) *via* its perbenzylation, partial acetolysis followed by deacetylation using NaOMe-methanol in 70% overall yields following literature procedure.[22] In a parallel set of reactions, compound **2** was converted to 3,4-di-*O*-benzyl-1,6-di-*O*-propargyl-2,5-anhydro-D-mannitol (**3**) using propargyl bromide and *N*-*tetra*-butyl ammonium hydrogen sulphate as phase transfer catalyst in 75% yields and to 1,6-diazido-3,4-di-*O*-benzyl-2,5-anhydro-D-mannitol (**4**) by mesylation using MsCl-pyridine followed by azidation with NaN_3 in DMF in 77% yields (Scheme 1).

The synthesis of macrocycle **5** was attempted through cycloaddition reaction between sugar alkyne **3** and azide **4** using conventional click condition,[23] *i.e.* in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in *t*-butanol-water-THF (1:1:2; 1 mL/100 mg of equimolar mixture of compounds **3** and **4**). The reaction led to the formation of a complex mixture and even after repeated column-chromatography the desired macrocycle **5** was obtained only in 6% yield in 28 h (entry 1, Table 1). To improve the yield, the click reaction was performed under the same condition in the presence of ethylene diamine dihydrochloride as template to assist the macrocyclization, but it does not lead to any improvement in the efficiency of the reaction (entry 2, Table 1). The use of *S*-phenyl ethyl ammonium acetate as template instead of ethylene diamine dihydrochloride in macrocyclization reaction resulted in threefold improvement in the yield of compound **5** along with the decrease in the reaction time (entry 3, Table 1). The improvement in yield of macrocycle formation could be due to the pre-organization of the azide and the alkyne substrates by virtue of the interaction of ammonium ion of the template with different hydrogen bond acceptor sites of both the sugar units **3** and **4** as well as with the resulted triazole ring of the macrocycle **5**. In addition, the interaction of phenyl group of the template with the benzyl groups of two sugar moieties *via* π-π stacking may also helps in holding the two reacting sugar units in closer proximity. The yield of macrocyclization affording compound **5** was further improved by sixfold with respect to entry 1 and almost 1.7 fold with respect to entry 3 in Table 1 by carrying out the reaction at 20 times higher dilution of *t*-butanol-water-THF (1:1:2 ratio), *i.e.* at 20 mL solvent/100 mg of equimolar mixture of compounds **3** and **4** (entry 4, Table 1). The enhancement in yield at higher dilution may be attributed to the enhancement of the opportunity for intramolecular azide-alkyne coupling over intermolecular coupling.[24] Thus, in a typical reaction an equimolar mixture of sugar alkyne **3** and azide **4**, $CuSO_4.5H_2O$, sodium ascorbate, *S*-phenyl ethyl ammonium acetate salt and *t*-butanol-water-THF (1:1:2) was stirred at 30 °C for 6 h. On completion, the reaction mixture was dried under reduced pressure and the product was extracted with chloroform. The residue obtained by removal of solvent was purified by silica gel column chromatography to afford the pure macrocycle **5** as off-white solid in 30%

Table 1
Optimization of macrocyclisation reaction for the synthesis of macrocycle **5**

Entry	Solvent/100 mg of equimolar mixture of compds. **3** and **4**	Template	Reaction time (h)	Yield (%)
1	1 mL	–	28	6
2	1 mL	$ClH_3\overset{+}{N}$ $\overset{+}{N}H_3Cl^-$	28	6
3	1 mL	$\overset{+}{N}H_3\bar{O}Ac$ (*S*)	15	18
4	20 mL	$\overset{+}{N}H_3\bar{O}Ac$ (*S*)	6	30
5	20 mL	$\overset{+}{N}H_3\bar{O}Ac$ (*R*)	6	28