SYNTHESIS AND PROPERTIES OF A NEW FAMILY OF CYCLODEXTRIN ANALOGUES

S.A. NEPOGODIEV, G. GATTUSO, AND J. F. STODDART
School of Chemistry, University of Birmingham
Edgbaston, Birmingham B15 2TT, UK

ABSTRACT

The chemical synthesis of a series of cyclic oligosaccharides built up from (1→4)-linked alternating D- and L-pyranosidic units is described for the first time. Key intermediates employed were disaccharides representing minimal repeating units. These disaccharides ('monomers') have been prepared in specifically modified forms so that they bear both 'glycosyl donor' (cyanoethylidene group) and 'glycosyl acceptor' (trityloxy group) functions. Polycondensation-cyclisation of these disaccharide monomers, catalysed by $TrClO_4$ under normal conditions of dilution, has led to series of homologous cyclic oligosaccharides with an even number of sugar residues (6, 8, 10, 12, *etc.*) in each case. Cyclic hexa- and octa-saccharides, based on L-rhamnose and D-mannose as the alternating monosaccharides units, have been deprotected to produce analogues of α- and γ-cyclodextrins (CDs) and the X-ray crystal structure of the cyclic octasaccharide has been determined.

1. INTRODUCTION

A large number of chemical modifications have been carried out on the native CDs.[1, 2] With few exceptions, these modifications do not alter the constitution or the configuration of the repeating α-D-glucopyranose residues in the CDs leaving their gross molecular shape essentially the same. Another entry into cyclic oligosaccharides is by total chemical synthesis. Obviously, cyclodextrin analogues, which differ more substantially from the parent CDs, can be obtained by this route. [3] However, taking into account the usual difficulties associated with oligosaccharide synthesis and the problem of efficient macrocyclisation which arises in addition, the chemical synthesis of cyclic oligosaccharides remains something of a challenge. Here, we report a novel cyclo-oligomerisation process which has been applied to the construction of α-(1→4)-linked cyclic oligosaccharides containing either mannose or rhamnose residues or a combination of them so that adjacent units have the opposite D- and L-configurations.

2. RESULTS AND DISCUSSION

2.1. Synthetic Strategy

The chemical synthesis of cyclic oligosaccharides implies the intramolecular glycosylation of linear oligosaccarides incorporating both glycosyl donor and acceptor functions. Provided that the target cyclic molecule is symmetrical, a laborious construction of a long-chain linear precursor can be overcome by using oligomerisation, prior to cyclisation, in a one-pot synthesis (Fig. 1).

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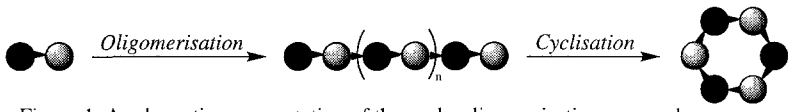

Figure 1. A schematic representation of the cyclo-oligomerisation approach to the chemical synthesis of cyclic oligosaccharides

There are several types of glycosyl donor which can be introduced into potential monomers in this kind of process. In fact, only 1,2-*O*-cyanoethylidene derivatives of sugars have been extensively studied in polycondesation reactions, affording polysaccharides.[4] Relying upon the efficiency of this glycosylation methodology, as well as on the appropriate preorganisation of the growing oligosaccharide chains, we have planned the syntheses of cyclic oligosaccharides incorporating saccharides with the α-*manno* configuration, starting from the 'monomers' **1–3** (Fig. 2).

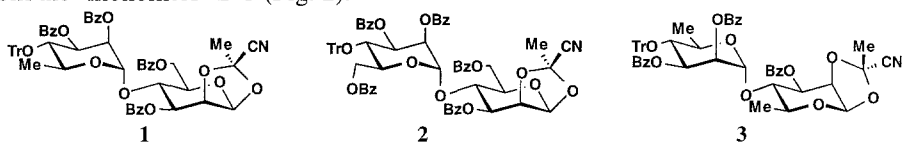

Figure 2. Structures of the disaccharide precursors of the cyclic oligosaccharides

2.2. Construction of the disaccharide precursors and their cyclo-oligomerisation

On account of the structural similarities of the target cyclic oligosaccharides, the syntheses of the disaccharide precursors **1–3** have been performed using a single methodology. The glycosyl donor parts (**6** and **9**) of the monomers **1–3** have been prepared from known compounds **4**[5] and **7**[5] by methanolysis, followed by selective benzoylation (Fig. 3).

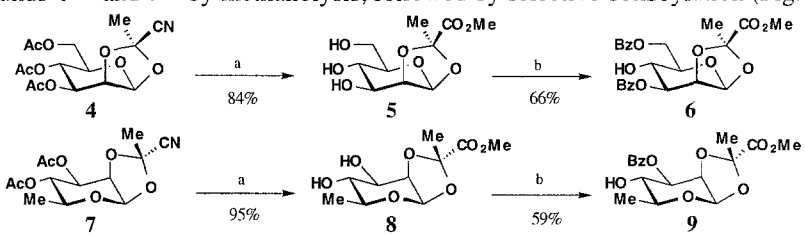

Figure 3. Reagents and conditions: a) MeONa/MeOH, 20°C, 6 h; b)BzCN/Py, 20°C, 17 h.

Selective benzoylation was also used in the first step of the preparation of the glycosyl bromides **12** and **16** (Fig. 4) from commercial L-rhamnose **10** or L-mannose **14**. It gave intermediate 4-hydroxy derivatives which were chloroacetylated and converted into compounds **12** and **16** by a standard bromination procedure. The D-rhamnose[6] derivative **18** has been converted into the bromide **20** using these same two reactions, as well as some additional manipulations with protecting groups at OH-2 and OH-3 as shown in Fig. 4. Coupling of bromides **12**, **16**, and **20**, with alcohols **6** or **9** was accomplished successfully (Fig. 4) using an $AgOSO_2CF_3$–promoted condensation to give the fully-protected disaccharides **13**, **17**, and **21**. These compounds were dechloroacetylated, and successively tritylated by the action of Ph_3CClO_4/collidine to afford the derivatives **22**, **24**, and **26**. The final conversion of methoxycarbonyl groups in **22**, **24**, and **26** to cyano-groups was performed in a two-step procedure involving ammonolysis and dehydration by the action of BzCl/Py (Fig. 5) to afford the desired 'monomers' **1–3**. The structures of these disaccharide derivatives have been confirmed by the presence of characteristic signals for both the cyanoethylidene and trityl groups in their ^{13}C NMR spectra.

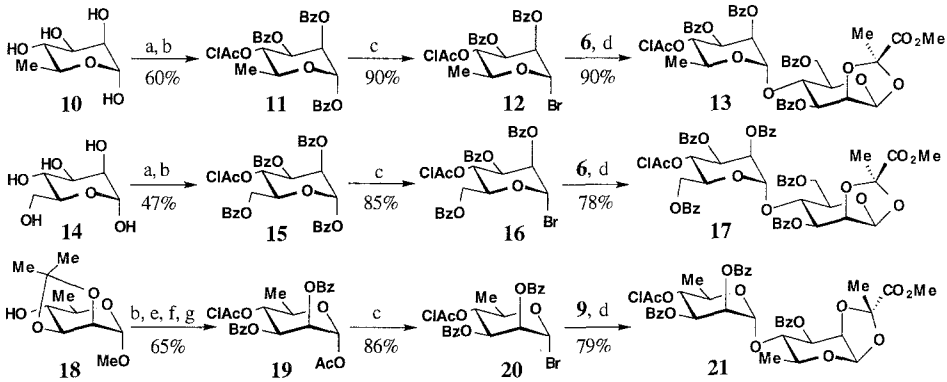

Figure 4. Reagents and conditions: a) BzCl/Py, -30°C, 3 h; b) $ClCH_2COCl/Py/CH_2Cl_2$, 0°C, 1 h; c) $HBr/AcOH/CH_2Cl_2$, 20°C, 8 h; d) AgOTf/collidine/CH_2Cl_2, -30–0 °C, 1-3 h; e) $CF_3COOH/CH_2Cl_2/H_2O$, 20 °C, 3 h; f) BzCl/Py, 20°C, 17 h; g) Ac_2O/H_2SO_4, 20°C, 3 h.

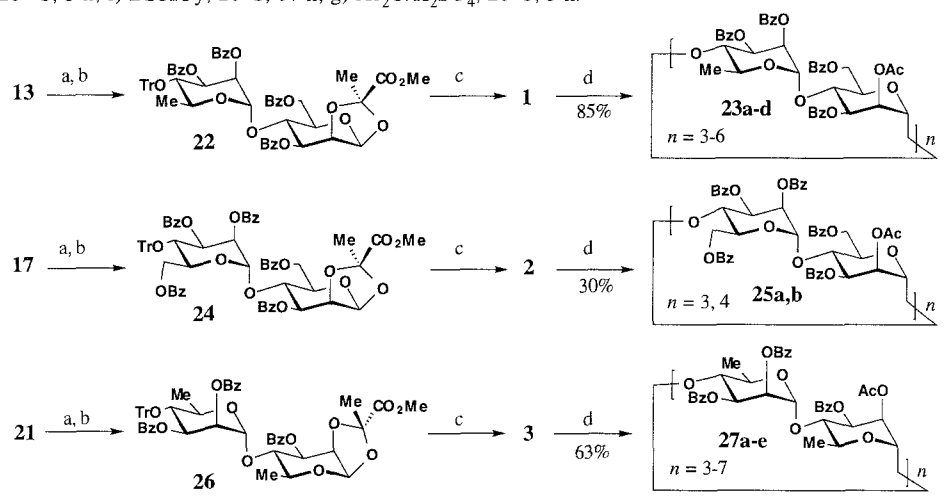

Figure 5. Reagents and conditions: $(NH_2)_2CS/MeCN/H_2O$, 20°C, 20 h; b) $TrClO_4$/collidine/ CH_2Cl_2, 20°C, 5 h, c) NH_3/MeOH, 20°C, 17 h, then BzCl/Py, 20°C, 18 h; d) $TrClO_4/CH_2Cl_2$, 20°C, 40 h, concentration of the disaccharide substrate and $TrClO_4$ = 0.01M.

The crucial cyclo-oligomerisation reactions of the disaccharide monomers **1**-**3** have been carried out under identical conditions (Fig. 5, d) involving activation of the glycosyl donor (1,2-*O*-cyanoethylidene group) by $TrClO_4$ using moderately dilution conditions. As the carbocation intermediates generated in these reactions are extremely sensitive to moisture, it was important to use ultra-dry conditions to avoid chain breaking and the formation of linear oligomers. The overall yields of cyclic products varied from 85 down to 30%, depending on the structure of the disaccharide monomers. The ratio between homologous cyclic compounds was also different. Thus, the major products in the case of the cyclo-oligomerisation of **1**, were the cyclohexa- and cycloocta-saccharides **23a** and **23b**, separated in 34 and 31% yields, respectively, whereas **3** produced the analogous compounds **27a** and **27b** in only 14 and 17% yields, respectively, and starting from **2**, less than 10% of each of **25a** and **25b**.

The symmetrical structures of the newly formed cyclic oligosaccharides are obvious from both their ^1H and ^{13}C NMR spectra which, according to the C_n symmetry of the compounds, showed only *one* set of signals, corresponding to the disaccharide repeating units. The reactions proceeded stereospecifically and, as a consequence, in the anomeric region of the ^{13}C NMR spectra, there are only *two* signals, which can be assigned to the C-1 of α-rhamnosyl and the C-1 of α-mannosyl residues. The precise determination of the ring size of the synthetic cyclic oligosaccharides was accomplished by LSIMS and MALDI-TOFMS (Table 1). The combination of mass-spectrometry and NMR spectroscopy seems to provide comprehensive evidence for the cyclic structure of products obtained by the cyclo-oligomerisation of **1-3**.

TABLE 1. Mass spectrometric data (*m/z* values) for acylated synthetic cyclic oligosaccharides [a]

Compound	**a**, *n = 3*	**b**, *n = 4*	**c**, *n = 5*	**d**, *n = 6*	**e**, *n = 7*
23	2321	3087	3852	4619	
25	2683	3569			
27	1965	2613	3260	3904	4563

[a] All data correspond to $[M+Na]^+$ ions.

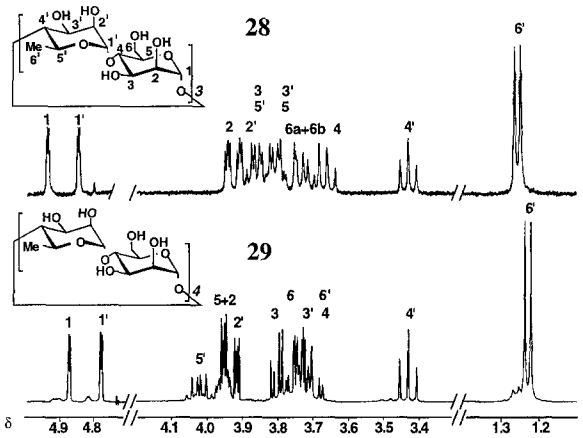

Figure 6. ^1H NMR spectra (400 MHz, D_2O) of the cyclic oligosaccharides **28** and **29**.

Deprotection of the cyclo-oligomerisation products can be achieved by saponification with NaOMe in $MeOH/CH_2Cl_2$, followed by treatment with NaOH in aqueous MeOH. The structures of the 'free' cyclic oligosaccharides **28** and **29** have been analysed by ^1H NMR (Fig. 6) and ^{13}C NMR spectroscopies and confirmed by MALDI-TOFMS data which reveals peaks with *m/z* values of 947 and 1255 corresponding to $[M+Na]^+$ ions arising from the cyclohexa- and cycloocta-saccharides. The latter compound crystallised from aqueous solution as needles that were suitable for X-ray crystallography.

2.3 Crystal structure of cyclo{→4-[α-L-Rha*p*-(1→4)-α-D-Man*p*]$_4$-(1→}

The X-ray crystal structure analysis of the **29** reveals (Fig. 7a) the presence of two crystallographically independent C_4 symmetric molecules in the asymmetric unit. The conformational difference between these molecules is very small and both of them contain the alternating 1,4-linked α-L-rhamnopyranosyl and α-D-mannopyranosyl residues, adopting normal $^1C_4$ and $^4C_1$ chair conformations, respectively. These individual pyranose rings are disposed almost orthogonally towards the plane of the cyclic oligosaccharide. The intra-annular diameter of **29**, measured as a distance between the diametrically opposite glycosidic oxygen atoms is about 11.2 Å. The highly symmetical conformation observed for **29** is in sharp contrast with the much more distorted geometries observed for the closely-related hydrated γ-cyclodextrin.[7] Due to the different natures of the monosaccharide components, both rims of **29** differ significantly in their structures from the

cyclodextrin rims. Whereas the cyclodextrins are characterised by the presence of 'primary' and 'secondary' faces with an intrinsic intramolecular hydrogen bonding network, compound **29** is almost identical on both faces (exluding C-6), and no intramolecular hydrogen bonding has been detected. In contrast, intermolecular hydrogen bonds play an important role in determining the crystal lattice. Both crystallographically independent molecules form discrete stacks (Fig. 7b) that extend *via* a lattice translation (7.92 Å repeat) in the *c* direction. The molecules within each stack are perfectly in register with each other and form large open channels. Stacks of molecules exist in a cubic close-packed array with adjacent stacks which are cross-linked *via* pair of [O–H...O] hydrogen bonds. The space within the intra- and inter-stack cavities, associated with the close-packed arrangement of stacked molecules, is filled by many H_2O molecules.

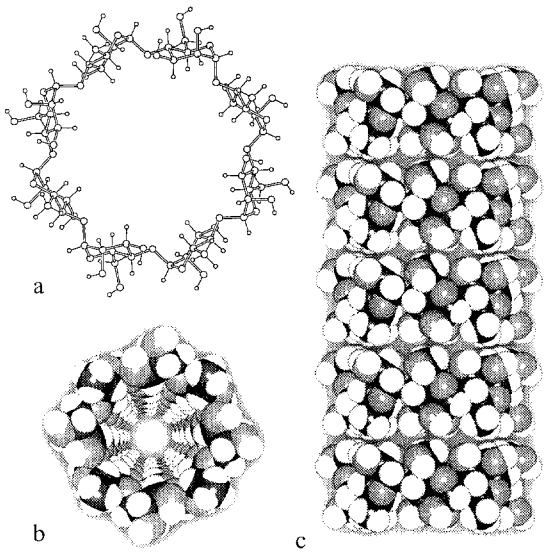

Figure 7. (a) Ball-and-stick representations of the solid state structure of **29** in a plan view; discrete stacks of **29** in a space-filling representation – (b) a view looking down one of the stacks, and (c) a side-on view of the stack.

2.4. **Molecular modelling**

Since we had solid state structural information available for **29,** we decided to carry out some molecular simulations, based on the semi-empirical method AM1, with the objective of comparing theoretical and experimental data for this cyclic oligosaccharide. The data for the calculated structure of **29** and solid state structure discussed above demonstrate the relatively close correspondence between most of their geometrical and physical characteristics. This high degree of correlation allows us to use computational methods to predict the structures of other cyclic hexa- and octa-saccharides, as well as one decasaccharide, listed in Table 2. As the saccharides in these three series differ only by the substituents at C-6, it is not surprising that cyclic oligosaccharides of the same size showed very similar conformational features. Thus, intra-annular diameters of cyclic hexa- and octa-saccharides, which have cylindrical shapes, were 8.3 Å and 11.4 Å, respectively. The space-filling molecular models of cyclic DL rhamno-oligosaccharides are shown in Fig. 8.

TABLE 2. Synthetic cyclic oligosaccharides used for semi-empirical simulations.

cyclo{→4-[α-L-Rha*p*-(1→4)-α-D-Man*p*]$_3$-(1→}	(**28**)
cyclo{→4-[α-L-Rha*p*-(1→4)-α-D-Man*p*]$_4$-(1→}	(**29**)
cyclo{→4-[α-L-Man*p*-(1→4)-α-D-Man*p*]$_3$-(1→}	(**30**)
cyclo{→4-[α-L-Man*p*-(1→4)-α-D-Man*p*]$_4$-(1→}	(**31**)
cyclo{→4-[α-D-Rha*p*-(1→4)-α-L-Rha*p*]$_3$-(1→}	(**32**)
cyclo{→4-[α-D-Rha*p*-(1→4)-α-L-Rha*p*]$_4$-(1→}	(**33**)
cyclo{→4-[α-D-Rha*p*-(1→4)-α-L-Rha*p*]$_5$-(1→}	(**34**)

32 **33** **34**

Figure 8. Space-filling representations of **32** (n = 3), **33** (n = 4), and **34** (n = 5).

3. CONCLUSION

A number of homologous cyclic oligosacharides with even numbers of sugar units in their rings have been synthesised by using disaccharide precursors playing the roles of 'monomers' in polycondensation–cycloglycosylation processes. The success of these syntheses results from *i)* the efficiency of the glycosylation procedure, *ii)* the similarities of the constitutions of the synthetic cyclic oligosaccharides to those of the cyclodextrins giving the advantage of the desired helical preorganisation of the linear chain prior to cyclisation, and *iii)* the α-D-*manno*-configurations of the newly-formed intersaccharide bonds which are relatively easy to construct. The yields of the cyclic oligosaccharides are not the same in the reactions of the different 'monomers', but cyclic products predominate very much in the cases of **1** and **3**. The low yield of cyclic oligosaccharides from **2** can be explained in terms of the low reactivity of the 4-*O*-trityl group in mannose (not 6-deoxymannose) structures. In the solid state, the cyclic oligosaccharide **29** forms nanotubes with a diameter of *ca.* 1 nm.

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