SYNTHESIS AND PROPERTIES OF A NEW FAMILY OF CYCLODEXTRIN ANALOGUES

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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 TrClO₄ 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. 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. 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 oligosaccharides 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).
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 polycondensation reactions, affording polysaccharides. 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).

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 and 7 by methanolysis, followed by selective benzoylation (Fig. 3).

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 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 AgOSO₂CF₃-promoted condensation to give the fully-protected disaccharides 13, 17, and 21. These compounds were dechloroacetylated, and successively tritylated by the action of Ph₃CClΟ/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 ¹³C NMR spectra.