A general, two-directional synthesis of C-(1→6)-linked disaccharide mimetics: synthesis from non-carbohydrate based starting materials

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The enantiomerically enriched diol 1,4-di(furan-2-yl)butane-1,4-diol (R,R)-1, synthesised either by Sharpless kinetic resolution or asymmetric reduction of the corresponding diketone, was a key intermediate in the stereodivergent synthesis of diastereoisomeric C-(1→6)-linked disaccharides. Two-directional stereoselective functionalisation steps, for example syn- and/or anti-selective dihydroxylation reactions, were exploited in the stereoselective synthesis of five diastereoisomeric C-linked disaccharides.

Libraries of stereo- and regioisomeric oligosaccharides and carbohydrate mimetics can probe large areas of conformational space, and can be used to identify unnatural ligands for carbohydrate receptors.1 C-Linked glycosides are a particularly interesting class of carbohydrate mimic which are resistant to enzymatic degradation, have potential as inhibitors of glycosidases and glycosyl transferases and often have biological activity and conformational properties which are similar to natural oligosaccharides. Established methods for the preparation of stereoisomeric C-linked di- and trisaccharides often rely on the separation of the stereoisomers which result from unselective functionalisation reactions; this approach has been exploited in the synthesis of C-linked analogues of disaccharides formed from α- and β-hexoses, and C-linked trisaccharides which are potential ligands for cell surface proteins.5

In this communication, we describe the preparation of some C-linked analogues of some (1→6)-linked disaccharides from the racemic difuryl diol rac-1, prepared by unselective reduction of the corresponding diketone. Sharpless kinetic resolution of rac-1 returned (R,R)-1 in 38% yield and 85% ee. An alternative approach involved asymmetric reduction of the corresponding diketone using borane–dimethyl sulfide complex and 10 mol% of Corey’s CBS catalyst to give the diol 1 as a 85:15 mixture of diastereoisomers in 80% yield; (R,R)-1 had > 98% ee. Oxidative ring expansion of the furan rings of (R,R)-1, using VO(acac)2/PhMeO2H, and acetalisation, gave the dipyranone 2 as a 75:25 mixture of anomers (Scheme 1), which were reduced with NaBH4 to give the separable diols 3.

The C2-symmetric diol 3 was a key intermediate in our divergent synthesis of C-linked disaccharides. For example, dihydroxylation of both of the alkenes of 3 under Upjohn conditions (cat. OsO4–NMO) occurred opposite to the adjacent hydroxy groups to give, after acetylation, the hexaacetate 4 as a > 95:5 mixture of diastereoisomers. This two-directional approach is very efficient indeed; in just two steps, six new stereogenic centres have been introduced in the reaction sequence 2→4 with almost complete stereocontrol. The di-THP 4 is a protected C-linked disaccharide mimic in which C-6 of one of the rings has been replaced with a methoxy group.

In a similar manner, the diastereomeric diol 5, synthesised by Mitsunobu inversion of 3 and hydrolysis, was converted into the protected C-linked disaccharides 6 and 7. Hence, double dihydroxylation of 5 opposite to the axial hydroxy groups gave, after acetylation, the protected C-linked disaccharides 6 and 9 in 53 and 23% yield respectively. Alternatively, directed double dihydroxylation of 5 under Donohoe’s reaction conditions gave, after acetylation, the hexaacetate 7 in 78% yield. The ability to choose at a late stage which diastereoisomer is synthesised is an exceptionally valuable feature of a general synthesis of stereoisomeric analogues.

A two-directional synthetic strategy9 does not, of course, restrict our approach to the synthesis of C2-symmetric mim-

Scheme 1

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both of the hydroxy groups \( \text{8 (Fig. 1)} \) gave the protected alcohols of \( \text{ethics. For example, benzoylation of one of the homotopic alcohols of \( \text{3, inversion of the remaining alcohol and hydrolysis, gave \text{11 in which the dihydroxypolymer was stereochemically differentiated (Scheme 2). Dihydroxylation of \text{11, anti to both of the hydroxy groups}^6 \text{Fig. 1) gave the protected carbohydrate mimic \text{12.}} \)

More remarkably, the diol \text{11 could be elaborated in a two-directional fashion such that the stereochemical outcome of dihydroxylation was different in each of the rings. The diol \text{11 has both an axial and an equatorial hydroxy group; the dihydroxylation of \text{11 under Donohoe's conditions (TMEDA, OsO}_4, \text{CH}_2\text{Cl}_2, -78 \degree \text{C}) was directed}^{10} \text{by the axial alcohol but occurred} \text{anti to the equatorial alcohol (Fig. 1) to give, after acetylation, the protected disaccharide mimic \text{13} in 83% yield.} \)

The stereoisomeric compounds \( \text{4, 6, 7, 9, 12 and 13 can be considered to be protected versions of either C-\( \alpha \)-linked or C-\( \beta \)-linked disaccharides (see Fig. 2). Although the free C-disaccharides are likely to predominantly populate the conformation \text{15 which resembles a \( \beta \)-linked disaccharide formed from a D and an L sugar (see Table 1), higher energy conformations can often be stabilised by complexation with a carbohydrate receptor.}^{46} \text{The conformations \text{14 mimic \( \alpha \)-linked disaccharides formed from two natural sugars (see Table 1).} \)

We believe that our work is the first synthesis of C-linked disaccharides entirely from non-carbohydrate based precursors, though Vogel has reported the use of a non-carbohydrate based template to introduce one of the sugar rings.\(^{11}\) Most other syntheses rely on the coupling of sugar derivatives.\(^{12–15}\) A particular merit of our approach, which makes it amenable to the synthesis of libraries of stereoisomeric carbohydrate mimetics, is that several diastereomeric C-linked disaccharides may be prepared by minor variation of a general reaction sequence. There are 136 possible stereoisomeric carbohydrate mimetics \text{14 (ignoring anomers); we have reported the stereoselective synthesis of five of these mimetics, and their enantiomers could have been synthesised by using the enantiomeric reagent in the enantioselective step.} \)

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**Notes and references**