

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 mimetic which are resistant to enzymatic degradation, have potential as inhibitors of glycosidases and glycosyl transferases² and often have biological activity³ and conformational properties⁴ 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 D- and L-hexoses, and C-linked trisaccharides which are potential ligands for cell surface proteins.⁵

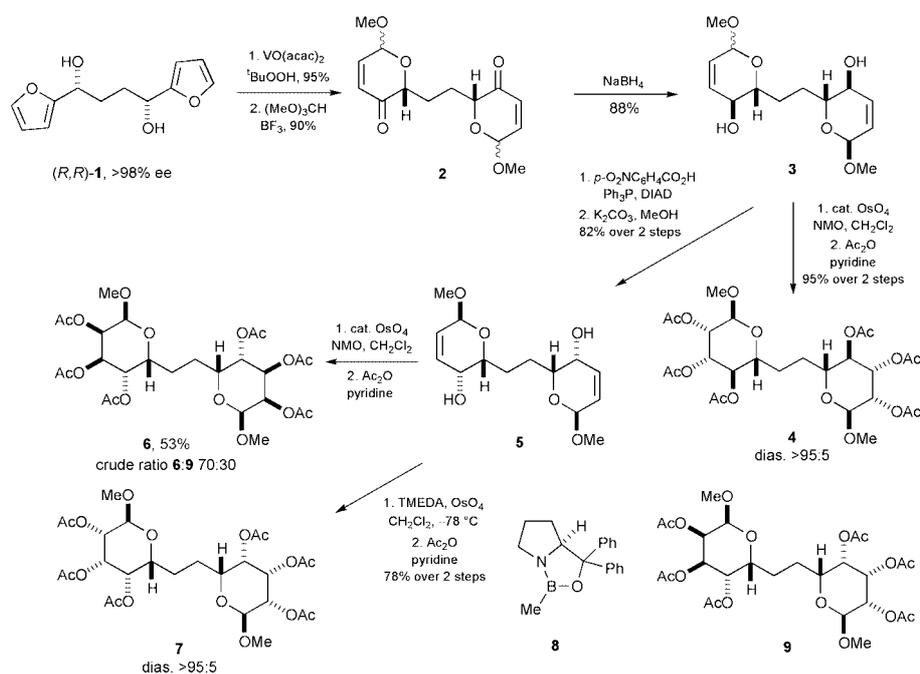
In this communication, we describe the preparation of some C-linked analogues of some (1→6)-linked disaccharides from the racemic difuryl diol *rac*-**1**, prepared by unselective reduction of the corresponding diketone. Sharpless kinetic resolution⁶ of *rac*-**1** returned (*R,R*)-**1** in 38% yield and 85% ee. An alternative approach⁷ involved asymmetric reduction of the

corresponding diketone using borane–dimethyl sulfide complex and 10 mol% of Corey's CBS catalyst **8** 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/tBuOOH, 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 opposite⁸ to the adjacent hydroxy groups to give, after acetylation, the hexaacetate **4** as a >95:5 mixture of diastereoisomers. This two-directional approach⁹ 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 mimetic in which C-6 of the 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 to⁸ the axial hydroxy groups gave, after acetylation, the protected C-linked disaccharides **6** and **9** in 53 and 23% yield respectively. Alternatively, directed¹⁰ 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

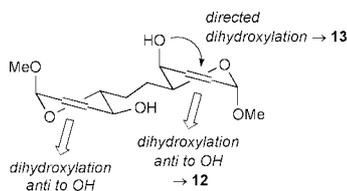
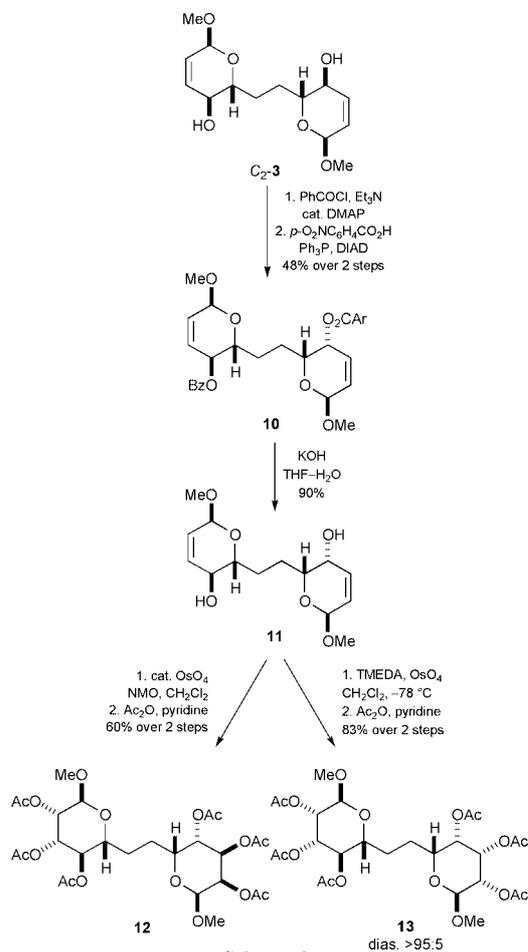


Fig. 1



Scheme 2

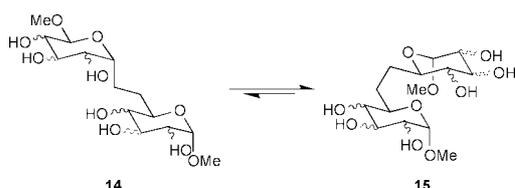


Fig. 2

etics. For example, benzylation of one of the homotopic alcohols of **3**, inversion of the remaining alcohol and hydrolysis, gave **11** in which the dihydropyran rings had been stereochemically differentiated (Scheme 2). Dihydroxylation of **11**, *anti* to both of the hydroxy groups⁸ (Fig. 1) gave the protected carbohydrate mimetic **12**.

More remarkably, the diol **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 **11** has both an axial and an equatorial hydroxy group; the dihydroxylation of **11** under Donohoe's conditions (TMEDA, OsO₄, CH₂Cl₂, -78 °C) was directed¹⁰ by the axial alcohol but occurred *anti* to the equatorial alcohol (Fig. 1) to give, after acetylation, the protected disaccharide mimetic **13** in 83% yield.

The stereoisomeric compounds **4**, **6**, **7**, **9**, **12** and **13** can be considered to be protected versions of either C- α (1 \rightarrow 6)- or C- β (1 \rightarrow 6)-linked disaccharides (see Fig. 2). Although the free C-

Table 1 Classification of C-linked disaccharide mimetics

Compound	Parent α -linked disaccharide(s)	Parent β -linked disaccharide(s)
4	D-Alt- α (1 \rightarrow 6)-D-Man	L-Gal- β (1 \rightarrow 6)-D-Man
6	D-Gal- α (1 \rightarrow 6)-D-Gul	L-Alt- β (1 \rightarrow 6)-D-Gul
7	D-Alt- α (1 \rightarrow 6)-D-Tal	L-Tal- β (1 \rightarrow 6)-D-Tal
9	D-Gal- α (1 \rightarrow 6)-D-Tal or D-Alt- α (1 \rightarrow 6)-D-Gul	L-Alt- β (1 \rightarrow 6)-D-Tal or L-Tal- β (1 \rightarrow 6)-D-Gul
12	D-Gal- α (1 \rightarrow 6)-D-Man or D-Alt- α (1 \rightarrow 6)-D-Gul	L-Alt- β (1 \rightarrow 6)-D-Man or L-Gal- β (1 \rightarrow 6)-D-Gul
13	D-Alt- α (1 \rightarrow 6)-D-Man or D-Alt- α (1 \rightarrow 6)-D-Tal	L-Tal- β (1 \rightarrow 6)-D-Man or L-Gal- β (1 \rightarrow 6)-D-Tal

disaccharides are likely to predominantly populate the conformation **15** which resembles a β -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.^{4b} The conformations **14** mimic α (1 \rightarrow 6)-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 **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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