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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.

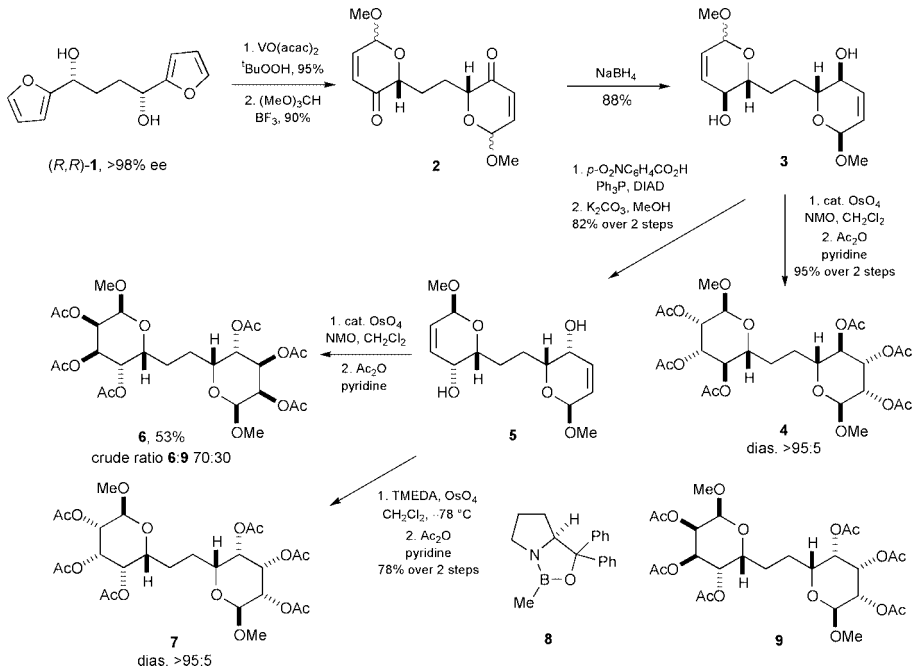
Libraries of stereo- and regioisomeric oligosaccharides and carbohydrate mimetics can probe large areas of conformational space, and can be used to identify unnatural ligands for carbohydrate receptors.[1] *C*-Linked glycosides are a particularly interesting class of carbohydrate mimetic which are resistant to enzymatic degradation, have potential as inhibitors of glycosidases and glycosyl transferases[2] and often have biological activity[3] and conformational properties[4] 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 resolution[6] of *rac*-**1** returned (*R*,*R*)-**1** in 38% yield and 85% ee. An alternative approach[7] 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 $VO(acac)_2$/^{t}BuOOH, and acetalisation, gave the dipyranone **2** as a 75 : 25 mixture of anomers (Scheme 1), which were reduced with $NaBH_4$ to give the separable diols **3**.

The C_2-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. OsO_4–NMO) occurred opposite[8] to the adjacent hydroxy groups to give, after acetylation, the hexaacetate **4** as a > 95 : 5 mixture of diastereoisomers. This two-directional approach[9] 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 to[8] the axial hydroxy groups gave, after acetylation, the protected *C*-linked disaccharides **6** and **9** in 53 and 23% yield respectively. Alternatively, directed[10] 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 diasteroisomer is synthesised is an exceptionally valuable feature of a general synthesis of stereoisomeric analogues.

A two-directional synthetic strategy[9] does not, of course, restrict our approach to the synthesis of C_2-symmetric mim-



Scheme 1

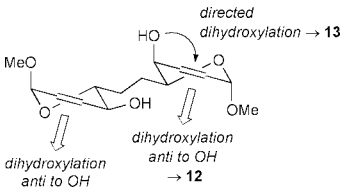
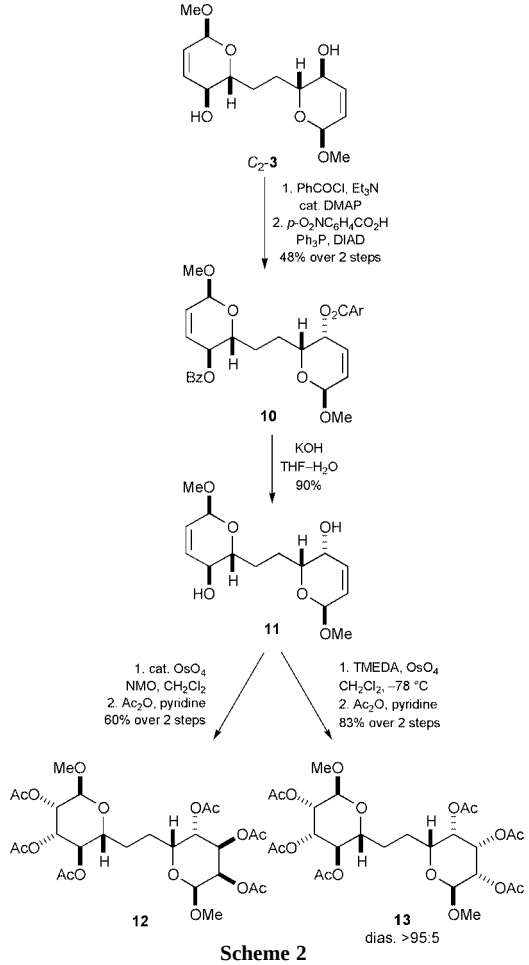


Fig. 1



Scheme 2

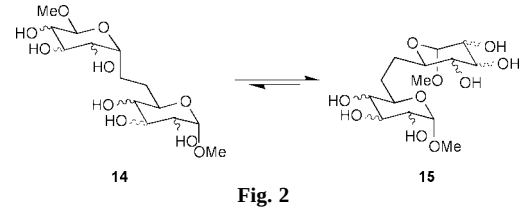


Fig. 2

etics. For example, benzoylation 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 groups[8] (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, OsO_4, CH_2Cl_2, −78 °C) was directed[10] 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→6)- or *C*-β(1→6)-linked disaccharides (see Fig. 2). Although the free *C*-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→6)-linked disaccharides formed from two natural sugars (see Table 1).

Table 1 Classification of *C*-linked disaccharide mimetics

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

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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