Rapid access to rare natural pyranosides using 1,2-diacetal protected intermediates

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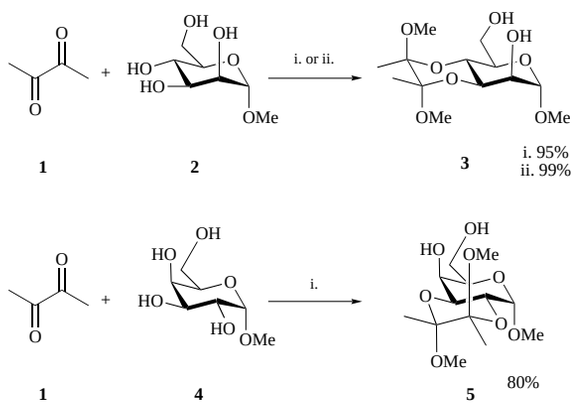
The synthesis of six rare methylpyranosides from common manno- and galacto-pyranoside starting materials has been achieved by the expedient use of 1,2-diacetal protecting group methodology highlighting its compatibility with a number of other common synthetic procedures.

The use of 1,2-diacetals as protecting groups for *trans*-1,2-diols has been shown to be a particularly useful method for the efficient construction of complex, biologically significant oligosaccharides.[1] Recently, several parameters for the design and exploitation of these 1,2-dione reagents for the direct protection of *trans*-1,2-diols have been established.[2] Although relatively few 1,2-diones are effective in these reactions, they have proved to be a versatile and powerful new protecting group protocol. The high selectivity for *trans*-1,2-diols, in the presence of other polyols, rapidly leads to protected monosaccharides amenable for further synthetic manipulation. The additional tuning effect on the latent glycosidation reactivity of these 1,2-diacetal protected building blocks in oligosaccharide assembly further enhances their synthetic utility.[3]

In this work we describe the high yielding, selective protection reaction of methyl-α-D-mannopyranoside and methyl-α-D-galactopyranoside with butane-2,3-dione, affording the corresponding butane-2,3-diacetal (BDA) intermediates which may be further manipulated in the expedient synthesis of some rare monosaccharides using a range of standard synthetic procedures. These reactions take place with no degradation or loss of the 1,2-diacetal protecting group.



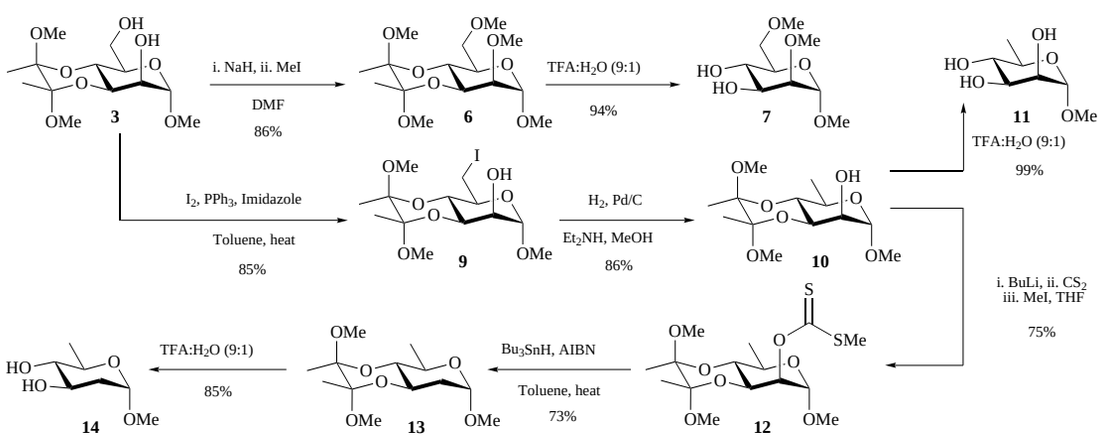
1 **2** **3** **1** **4** **5**

Scheme 1 i, cat. CSA, $CH(OME)_3$, MeOH, heat; ii, cat. $BF_3{\cdot}OEt_2$, $CH(OMe)_3$, MeOH, room temp.

Typically the BDA intermediates such as **3** and **5** may be prepared by the direct reaction of butane-2,3-dione **1**, which is both cheap and commercially available, with the parent monosaccharide in the presence of catalytic camphorsulfonic acid (CSA) and trimethyl orthoformate in boiling methanol (Scheme 1).[2] The protection reaction may also be carried out at room temperature in high yield using boron trifluoride–diethyl ether as a Lewis acid (Scheme 1). The highly crystalline BDA products need little further purification. The protection of the *trans*-1,2-diol in monosaccharide **2** in the presence of a *cis*-1,2-diol pair and 1,3-related pair makes this high yielding, selective process highly attractive. The single step BDA procedure also eliminates several steps from conventional approaches to this level of protecting group selectivity.[4]

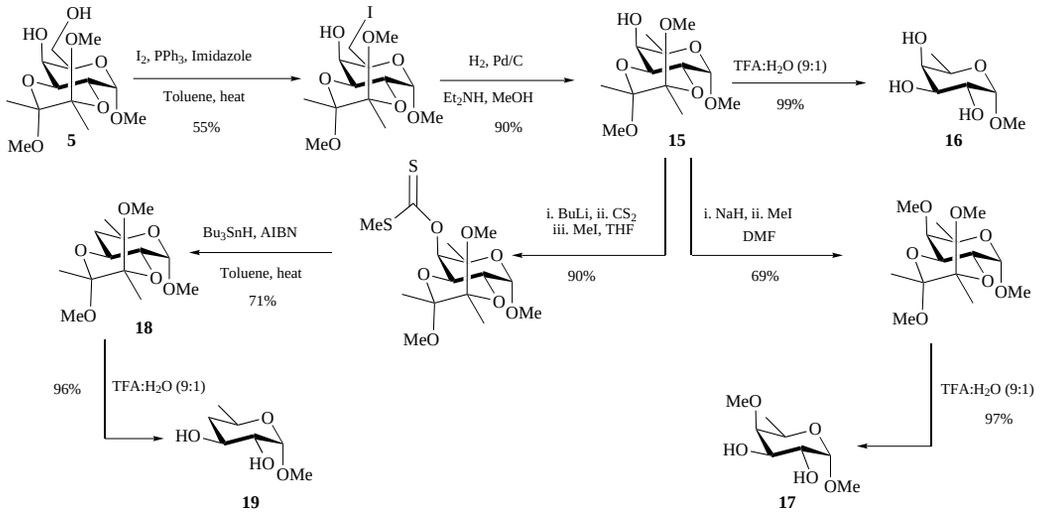
These BDA protected intermediates were subjected to several standard synthetic manipulations in the synthesis of some monosaccharide targets. The protected monosaccharide **3** was readily permethylated using sodium hydride and methyl iodide (Scheme 2). Deprotection of the diacetal **6** in quantitative yield, using trifluroacetic acid and water (9:1) at room temperature yielded methyl curamicoside **7**, a component of everinomycin C **8** (Fig. 1) which is a member of the orthosomycin family of antibiotics.[5] These antibiotics feature several unusual monosaccharide components (Fig. 1) which were readily synthesised using this diacetal methodology. An added attractive aspect to the deprotection process was the volatility of the reaction by-products, leaving evaporation as the only purification process necessary.

Returning to the synthetic manipulations, selective iodination of the 6-hydroxy of **3** was possible by the procedure of Garegg and Samuelsson[6] allowing catalytic hydrogenation to convert the *manno*-configuration of **9** to a BDA protected rhamnopyranoside intermediate **10** (Scheme 2). Deprotection yielded methyl-α-D-rhamnopyranoside **11**, the unnatural rhamnose configuration, which is the main constituent of the



3 **6** **7** **11** **9** **10** **12** **13** **14**

Scheme 2



Scheme 3

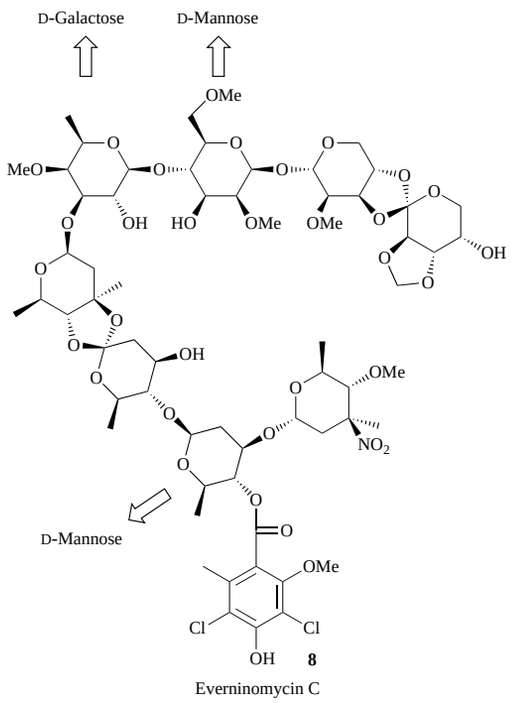


Fig. 1

A-band lipopolysaccharide from the mutant *Pseudomonas aeruginosa*.[7] The intermediate **10** was also converted to the xanthate ester **12** which on treatment with the conditions of Barton and McCombie yielded the 2-deoxygenated material **13**.[8] Hydrolysis of the diacetal yielded the 2-deoxyrhamnose structure **14** (Scheme 2) which is also a monosaccharide subunit found in certain orthosomycin antibiotics.[5]

The BDA protected galactose intermediate **5** proved equally as versatile in the synthesis of three further monosaccharides (Scheme 3). Once again it was available by the straightforward, single step BDA protection of the parent monosaccharide **4** using the conditions illustrated (Scheme 1).[2] Deoxygenation of the 6-position *via* iodination and hydrogenation led to the *fuco*-configured intermediate **15**. Deprotection yielded the rarer D-configured methylfucopyranoside **16** in quantitative yield, giving a monosaccharide 350 times as expensive as the starting D-galactopyranoside **4** in four steps. Returning to intermediate **15**, methylation of the 4-hydroxy followed by deprotection yielded the 4-*O*-methylfucopyranoside **17** which is also found in everninomycin C (Fig. 1).

As a final synthetic example of the BDA method, formation of the xanthate ester at the 4-position of **15** by reaction of the alkoxide with carbon disulfide followed by methyl iodide allowed the Barton–McCombie deoxygenation of the secondary position to take place. Direct access to this doubly deoxygenated pyranoside **18** *via* this method failed due to the difficulties in the breakdown of primary xanthates. The sequential deoxygenation strategy was therefore adopted. Deprotection of the diacetal unit under the standard conditions led to diol **19** which is an intermediate in Mitsunobu's Grahamimycin A synthesis.[9]

In conclusion, the protection pattern achieved rapidly by the use of 1,2-diacetal methodology allows facile interconversion of cheap monosaccharides to rarer, expensive or commercially unavailable targets. The application of the method in the total synthesis of more structurally complex natural products is currently under investigation and will be reported in due course. The high yields obtained in the protection and deprotection of the BDA unit suggest that this may prove to be a versatile and strategic protecting group for use in synthesis.

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