A Mild Procedure for Cleavage of 1,6-Anhydro Sugars

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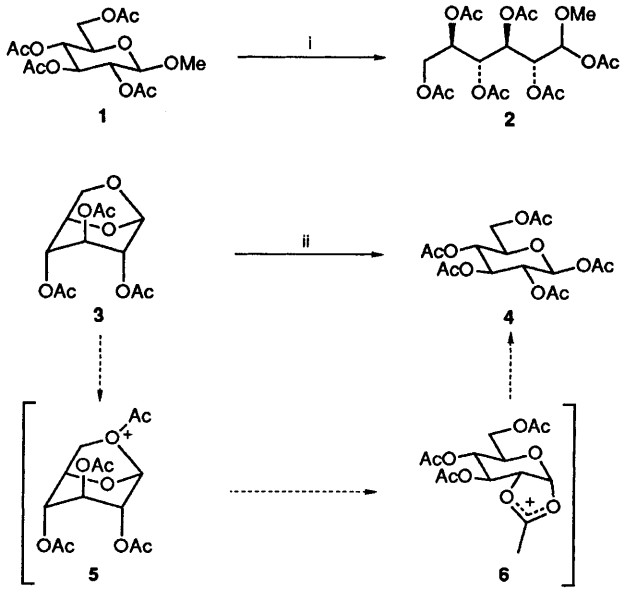
Acetolysis of 1,6-anhydro sugars can be achieved by treatment with acetic anhydride and triethylsilyl trifluoromethanesulphonate at 0 °C for 5–15 minutes, under which conditions a wide variety of protecting groups are unaffected, and even the trisulphonate is cleaved, albeit in six hours.

1,6-Anhydro sugars[1] are popular starting materials for carbohydrate-based syntheses of natural products in this[2] and other laboratories.[3] Their caged bicyclic skeletons ensure that a high degree of steric-approach control occurs in their reactions, and the existence of the internal acetal means that two fewer protecting groups are needed than with their pyranoside counterparts. However, the value of these advantages can be compromised when it subsequently becomes necessary to cleave the sturdy acetal linkage, as may be judged from continuing efforts to develop protocols for this task.[4] In this manuscript we describe a new, mild procedure that is applicable to a wide variety of substrates.

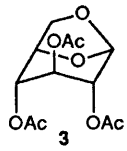
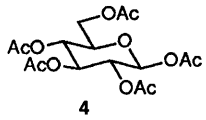
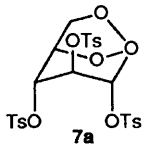
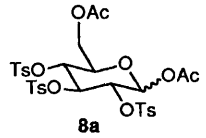
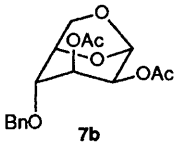
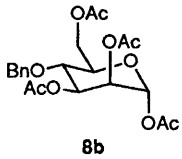
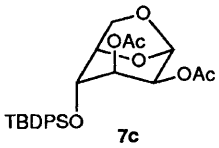
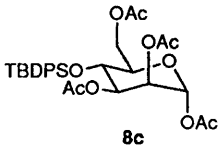
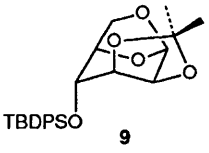
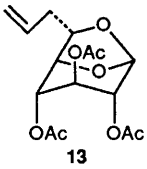
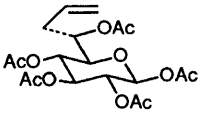
Our investigations were prompted by the report by Angibeaud and Utille that acetolysis of the methyl glucoside **1** in the presence of triethylsilyl trifluoromethanesulphonate at 0 °C, led to the acylal **2** in nearly quantitative yield.[5] Although β-D-glucose pentacetate **4** was not observed in their reactions, the response of 1,6-anhydro systems to this reaction medium was of interest to us, and the triacetate **3** was our first test substrate. Acetolysis was complete within 5 min to give β-D-glucose pentacetate **4** in 88% yield. The reaction undoubtedly involves the cationic species **5** and **6** as key intermediates.

In order to test the compatibility of protecting groups with the reaction conditions, we examined the two mannosan derivatives **7b** and **c** (Table 1). Excellent results were obtained



Scheme 1 *Reagents and conditions*: i, $Et_3SiOSO_2CF_3$ (1 equiv.), Ac_2O, 0 °C, quantitative yield; ii, $Et_3SiOSO_2CF_3$ (cat.), Ac_2O, 0 °C, 5 min, 88% yield

Table 1 Acetolysis of some 1,6-anhydro sugars by acetic anhydride and triethylsilyl trifluoromethanesulphonate[a]

Entry	Substrate	Product	Yield (%)
1	 **3**	 **4**	88
2[b]	 **7a**	 **8a**	87[c]
3[d]	 **7b**	 **8b**	80
4[d]	 **7c**	 **8c**	95
5	 **9**	Complex mixture	
6	 **13**	 **14**	85

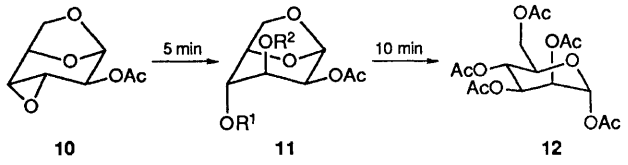
[a] Typical experimental procedure. The anhydro sugar is dissolved in Ac_2O and cooled to 0 °C with stirring under argon. Two drops (~20–30 μl) of triethylsilyl trifluoromethanesulphonate are added to the solution. The reaction is followed by TLC and generally requires 5–15 min for completion. A solution of saturated sodium bicarbonate is then added and after being stirred for 30 min, the aqueous mixture is extracted three times with ethyl acetate. The organic extracts are combined and washed with saturated sodium hydrogen carbonate solution followed by brine. The mixture is then dried over sodium sulphate, filtered and the solvents removed under reduced pressure. Percolation through silica gel removes any trace of acetic anhydride affording clean product. [b] This reaction required 6 hours for completion; Ts = *p*-tolylsulphonyl. [c] β:α = 3:1. [d] TBDPS = *tert*-butyldiphenylsilyl.

in each case, the yields of the products **8b** and **c**† being 80 and 95%, respectively. The survival of the silyl ether in the product **8** is particularly noteworthy.

In the light of these results, we examined the *O*-isopropylidine derivative **10** in the hope that acetolysis would lead first to **7c** and thence to **8c**. However a complex mixture of products was obtained.

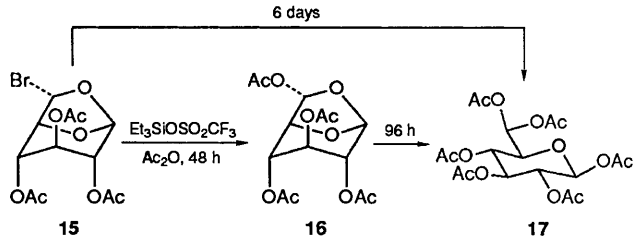
On the other hand the dianhydroaltrose **10** (Scheme 2) reacted in the expected way, the oxirane ring being cleaved first to give mannosan triacetate **11**, while prolonged acetolysis gave α-D-mannose pentacetate **12**.

† Satisfactory elemental and spectroscopic analyses were obtained.



10 **11** **12**

Scheme 2



15 **16** **17**

Scheme 3

In the case of the branch-chain sugar **13** (Table 1), there were no complications arising from the alkenic residue, judging from the isolation of a single isomer of the pentaacetate **14**† in 85% yield.

The glycosyl bromide **15** (Scheme 3), whose efficient preparation has been described by Ferrier[6] was of particular interest since its solvolysis is uncharacteristically difficult for an α-bromo ether. Indeed it required 48 h and two equivalents of trifluoromethanesulphonate for the starting material to be consumed, a 3:1 mixture of the replacement and cleavage products, **16** and **17**, respectively, being obtained. It required a further 96 h for complete acetolysis to give **17**. The overall yield of the latter was 65%.

The case of tritosylate **7a** is especially noteworthy since the published attempts at hydrolysis have all met with failure.[7]

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