Conversion of Pent-4-enyl Glycosides into Glycosyl Bromides

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The unique features of pent-4-enyl glycosides for chemospecific (a) protection and (b) activation of the anomeric centre have been exploited for the preparation of glycosyl bromides under such mild conditions that oxidizable and acid sensitive protecting groups are not affected, and in such excellent yields that the product can be used *in situ* for saccharide coupling.

Glycosyl halides[1] have been prototype glycosyl donors for 80 years, and myriad saccharide couplings during that time have so revealed their strengths[2] that for many investigators, they are regarded as the substrates of first resort for oligosaccharide syntheses,[3] or for any process requiring glycosyl donors.[4,5] Nevertheless, their use is not without its failings. Of various glycosyl halides, the bromides show the best compromise between reactivity and stability; but preparation of these derivatives usually employs hydrogen bromide, which is clearly inapplicable for acid-sensitive substrates, and problematic for complex oligosaccharides, where intersaccharide bonds may suffer acid-induced cleavage. A modern alternative route to glycosyl bromides has been by reaction of thioglycosides with bromine.[6] In this manuscript, we present yet another alternative, which allows rapid, non-acidic, efficient routes to these favoured substrates.

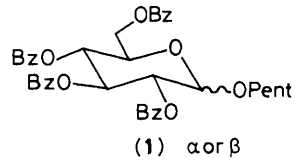
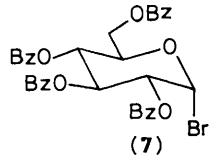
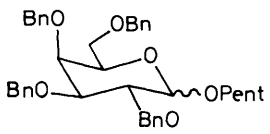
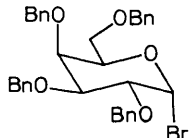
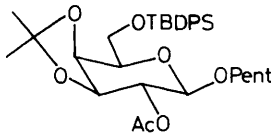
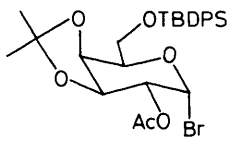
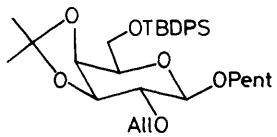
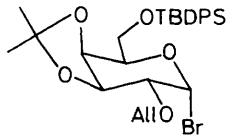
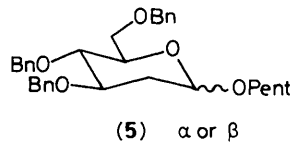
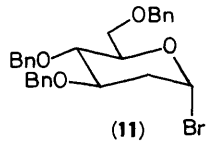
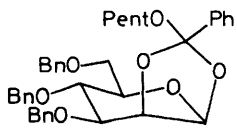
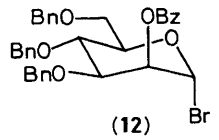
We have recently shown that the pent-4-enyl group provides chemospecific activation for the anomeric centre, enabling hydrolysis under non-acidic conditions[7] and direct saccharide coupling to take place,[8] the latter process being highly responsive to the character of the C-2 substituent.[9]

Treatment of the pent-4-enyl glycosides, (**1**)—(**5**) (Table 1) with bromine in methylene chloride at 0 °C, caused rapid formation of a single product in each case.† Evaporation of the solvent and ^{1}H n.m.r. analysis established the products as the α-glycosyl bromides (**7**)—(**12**). Four noteworthy conclusions can be drawn from Table 1. (a) Comparison of entry (i) with entries (ii) and (iii) shows that even where the pent-4-enyl glycone is 'disarmed' by a C-2 ester,[9] addition of bromine across the double bond does not compete with oxidative deglycosidation. (b) From entries (ii), (v), and (vi) it is clear that glycosyl bromide formation occurs faster than oxidation of benzylic protecting groups. (Of course, prolonged treatment with bromine will lead to the formation of benzaldehyde). (c) From entry (iv), the allyl protecting group survives the bromination. (d) Entries (iii), (iv), and (v) show that acid labile protecting groups [in (iii) and (iv)] or acid sensitive substrates [in (v)] are tolerated very well.

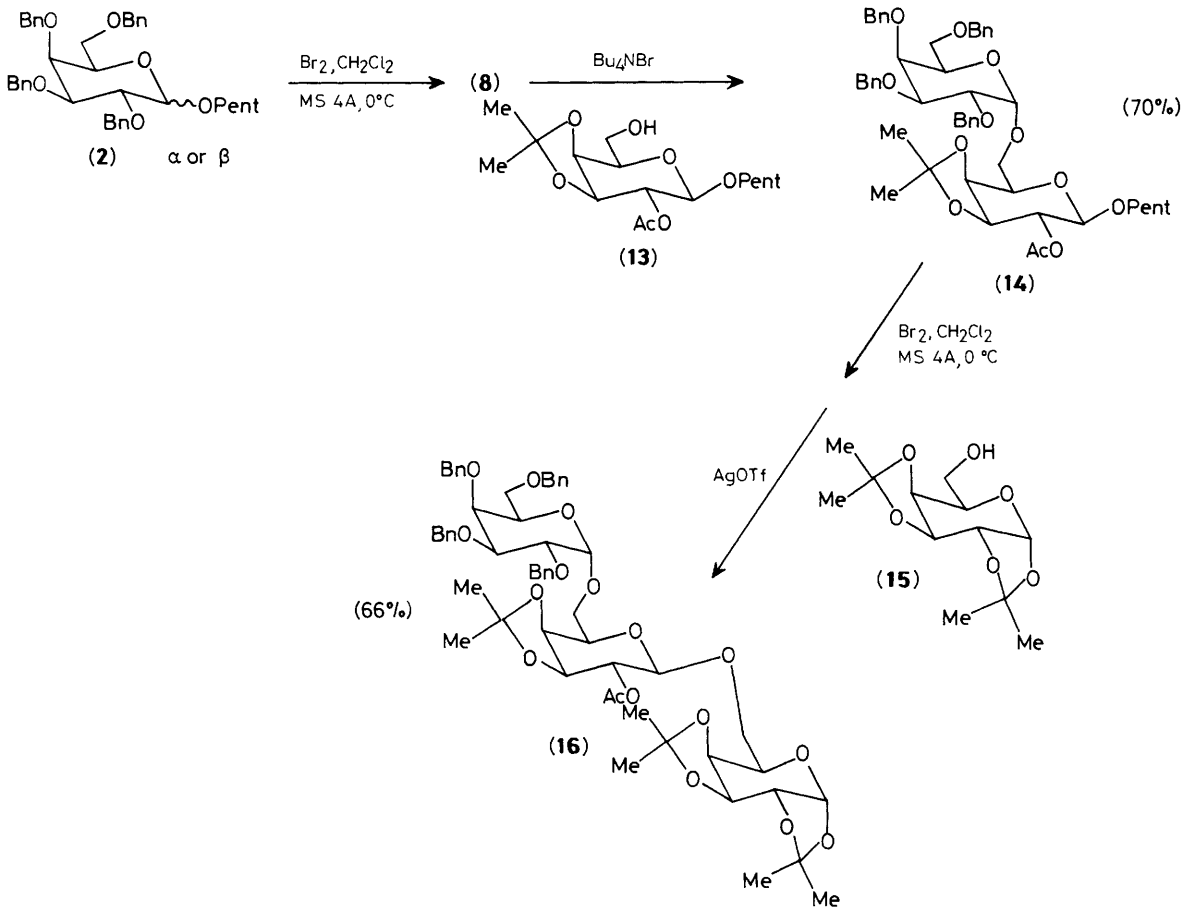
The results in Table 1 are particularly advantageous in cases where direct use of pent-4-enyl glycosides in saccharide coupling reactions is sluggish, or when the stereodirecting influences of a C-2 ester are required. In this regard, an attractive experimental feature of this process is that it is not necessary to isolate the reactive glycosyl bromide. For example, after the brominolysis of (**2**) to (**8**) was complete (t.l.c.), a solution of the glycosyl acceptor (**13**) and tetra-n-butylammonium bromide [10] in methylene chloride was added. After five days, the disaccharide (**14**) was obtained in 70% yield, and repetition of the process using (**15**) as a glycosyl acceptor with silver trifluoromethanesulphonate (AgOTf) as the promoter[11] led to the trisaccharide (**16**) in 66% yield.

† 2-Bromomethyltetrahydrofuran has been identified as a product of the reaction. The stereochemistry of this product is now being investigated.

Table 1. Formation of glycosyl bromides from pent-4-enyl glycosides.[a]

Entry	Substrate[b]	Product
(i)	 (**1**) α or β	 (**7**)
(ii)	 (**2**) α or β	 (**8**)
(iii)	 (**3**)	 (**9**)
(iv)	 (**4**)	 (**10**)
(v)	 (**5**) α or β	 (**11**)
(vi)	 (**6**)	 (**12**)

[a] A stirred solution of the pent-4-enyl glycoside in dichloromethane was cooled to 0 °C and protected from light. A dilute dichloromethane solution of bromine (1 equiv.) was added dropwise and the solvent was immediately removed *in vacuo* at 40 °C. In all cases, the yields of isolated bromides were >90%, and the structures were verified by ^{1}H and ^{13}C n.m.r. [b] Compounds (**2**) and (**3**) were obtained from D-galactose penta-acetate by reaction with pent-4-en-1-ol in $SnCl_4$, followed by separation of anomers (where necessary), deacetylation, and differential protection by standard methods. Pent = pent-4-enyl Bn = $PhCH_2$, Bz = PhCO, All = allyl, TBDPS = Bu^tPh_2Si.



Scheme 1

The results in Scheme 1 demonstrate that the pent-4-enyl residue serves as a protecting group for the anomeric centre, which allows ready formation of glycosyl bromides. The products are obtained in such purity and high yields that they can be used *in situ* to forge α- or β-selective linkages by standard carbohydrate methodology.‡

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‡ An invention disclosure has been filed for the processes described in this Communication.