α-C-Glycopyranosides from Lewis Acid Catalysed Condensations of Acetylated Glycals and Enol Silanes

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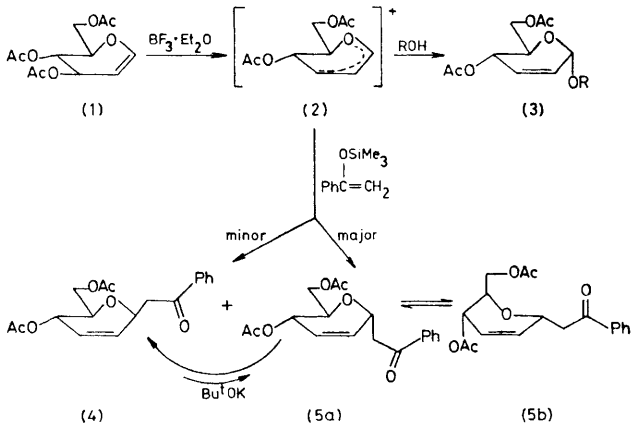
Summary Acetylated glycals undergo Lewis acid-catalysed condensations with enol silanes in virtually quantitative yields to form C-glycopyranosides in which the thermodynamically unfavourable α-'anomers' are formed predominantly.

THE development of routes to functionalized C-glycopyranosides is an area of interest in our laboratory and we have investigated methods based on enone photoalkylation,[1] sigmatropic rearrangements,[2] and Wittig olefinations[2] with varying degrees of success with respect to efficiency, yield, and stereoselectivity. We have sought improvements in these areas and, in view of recent reports,[3–6] we report herein some of our recent results.

Lewis acid-catalysed reactions at the anomeric centres of sugars are thought to involve the formation of glycosyl oxo-carbonium ions and these intermediates may be trapped with a variety of nucleophiles including activated arenes[7] and enol ethers.[8] The allyl-oxo-carbonium ion (**2**) has long been recognized as the intermediate in the Ferrier reaction[9] for preparation of *O*-glycosides (**3**) from acetylated glycals (**1**). We therefore sought to trap intermediate (**2**) for the preparation of unsaturated *C*-glycopyranosides (Scheme 1).

Results of the reactions of 1-trimethylsilyloxystyrene with 'triacetyl glucal'† (**1**) shown in the Table reveal an extremely high dependence upon the various reaction parameters. Thus overall yields were affected by changes in temperature (entries 1 and 2, 6 and 7), catalyst (entries 1 and 4, 8 and 9), and solvent (entries 1 and 5, 1 and 8). It was hoped that use of acetonitrile (entries 8 and 9) would have led to a substantial increase in the proportion of the α-anomers since the intermediate nitrilium ion [C(1)–N^+≡CMe][10] would be obliged to adopt a β-orientation because of the reverse anomeric effect.[11] However the α/β ratio is seen to be the same in entries 1 and 9, and in view of the ease of operation involved, we prefer the conditions of entry 1.



SCHEME 1

Compounds (**4**) and (**5**)‡ were readily separated chromatographically. Previously,[1,2] we had found that *C*-glycopyranosides obeyed Hudson's rules of isorotation, and on this basis alone the assignment of structures to (**4**) and (**5**) would have been reversed. However, the γ-effect rule[12] of ^{13}C n.m.r. spectroscopy has been found to be a more discriminating tool for distinguishing between such epimers.[2] Accordingly the isomer in which C(5) is more shielded was assigned as (**5**).

TABLE. Lewis acid-catalysed reaction of (**1**) with CH_2=C(OSiMe_3)Ph

Entry	Solvent	Catalyst	*T*/°C	*t*/h	(**5**) : (**4**)	% Yield
1[a]	CH_2Cl_2	$BF_3.EtO_2$	−40 to 0	0·5	4 : 1	99
2	"	"	−78	2·5	—	< 1
3	"	$AlCl_3$	−40 to 0	1	7 : 3	92
4	"	$CF_3SO_3SiMe_3$[b]	23	0·3	7 : 3	75
5	THF[c]	$BF_3.Et_2O$	−40 to 23	5·0	—	< 1
6	"	$AlCl_3$	−40 to 0	18	—	—
7	"	"	23	36	7 : 3	77
8	CH_3CN	$BF_3.Et_2O$	−45 to 0	0·75	—	< 1
9	"	$AlCl_3$	−45 to 10	1	4 : 1	97

[a] A solution of compound (**1**) (1 mmol) and the enol silane (1·5 mmol) in CH_2Cl_2 (15 ml) was cooled to −40 °C under argon and practical grade $BF_3.Et_2O$ (1·4 mmol) was added *via* a syringe. The mixture was allowed to warm to 0 °C when a bright yellow colour developed. This colour disappeared upon the usual work-up. [b] See reference 7. [c] Tetrahydrofuran.

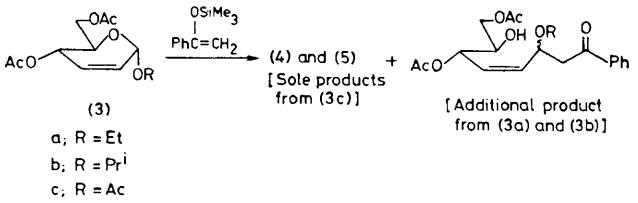
† 3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol.

‡ For (**4**) $[\alpha]_D^{20}$ + 111·3°; ^1H n.m.r.: δ 4·86 ($J_{1,2}$ 1·1 Hz, 1-H) and 3·79 ($J_{4,5}$ 8·7 Hz, 5-H); ^{13}C n.m.r.: 68·024 (C-5). For (**5**) $[\alpha]_D^{20}$ 35·7°; ^1H n.m.r.: δ 4·95 ($J_{1,2}$ 2·3 Hz, 1-H) and 4·05 ($J_{4,5}$ 3·3 Hz, 5-H); ^{13}C n.m.r.: 73·293 (C-5). The value of $J_{4,5}$ for (**4**) indicates that this anomer is in the $^4C_1$ conformation with the C(1) substituent equatorially oriented. This is to be expected since these molecules should not display an anomeric effect. The $J_{4,5}$ value for (**5**) suggests conformational mobility between $^4C_1$ and $^1C_4$ forms.

In our earlier study, it had been found that with *C*-glycopyranosides possessing an activated methylene group at the anomeric carbon, the β-anomers were thermodynamically favoured.[2] For the present study we established that the epimers (**4**) and (**5**) were not interconverted when placed separately in the reaction medium of entry 1. We then found that treatment of the major product (**5**) with potassium t-butoxide (strong base was found necessary) in benzene for six hours led to a predominance of the minor product (**4**). This equilibrium study therefore shows that these Lewis acid-catalysed condensations are kinetically controlled.

Other acetylated glycals have also been found to react with 1-trimethylsilyloxystyrene to give comparable products. However, with 2-acetoxy-analogues a complex mixture of intractable material was obtained. Reaction of (**1**) with 1-trimethylsilyloxycyclohexene gave the expected α/β mixture in 95% isolated yield.

Alkyl hex-2-enopyranosides are also sources of allyl-oxocarbonium ions[13] and their potential for *C*-alkylation was therefore investigated. As indicated in Scheme 2 the



SCHEME 2

reaction of the alkyl glycosides (**3a**) or (**3b**) gave mixtures of acyclic as well as cyclic products, indicating that both C(1)–O bonds of these glycosides are amenable to cleavage. However with the *O*-acetyl analogue (**3c**), cleavage of the C(1)–O(5) bond was completely suppressed, cyclic compounds (**4**) and (**5**) being the only products.

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