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Stereoselective Preparations of Ribofuranosyl Chlorides and Ribofuranosyl Acetates. Solvent Effects and Stereoselectivity In the Reaction of Ribofuranosyl Acetates with Trimethylallylsilane.

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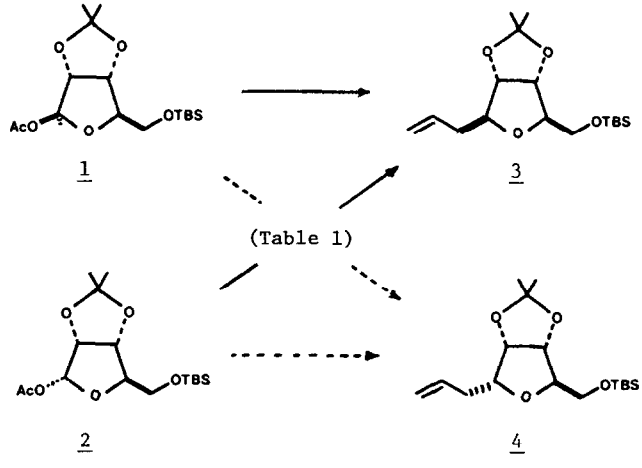
Abstract: The preparation of pure samples of each anomer of 2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-D-ribofuranosyl chloride and the preparation of each corresponding furanosyl acetate is described. The reaction of these acetates with an allylsilane and zinc bromide is not stereospecific, but shows good stereoselectivity in some solvents.

The influence of starting material geometry upon product geometry, or the lack of such influence, is a matter which should be investigated in any asymmetric reaction. In connection with our interest in the stereoselective synthesis of C-glycosides this test of stereospecificity in the reaction of furanosyl acetates was carried out.[1,2] Kozikowski and Sorgi first observed that a β-acetate similar to 1, with neat trimethylallylsilane and zinc bromide, afforded an equimolar mixture of diastereomeric products similar to 3 and 4.[2e] (Figure 1) The purpose of this study was to prepare pure samples of each starting material, to test whether such processes are indeed stereospecific, and to determine how the reaction conditions and starting material structure might influence stereochemical outcome.

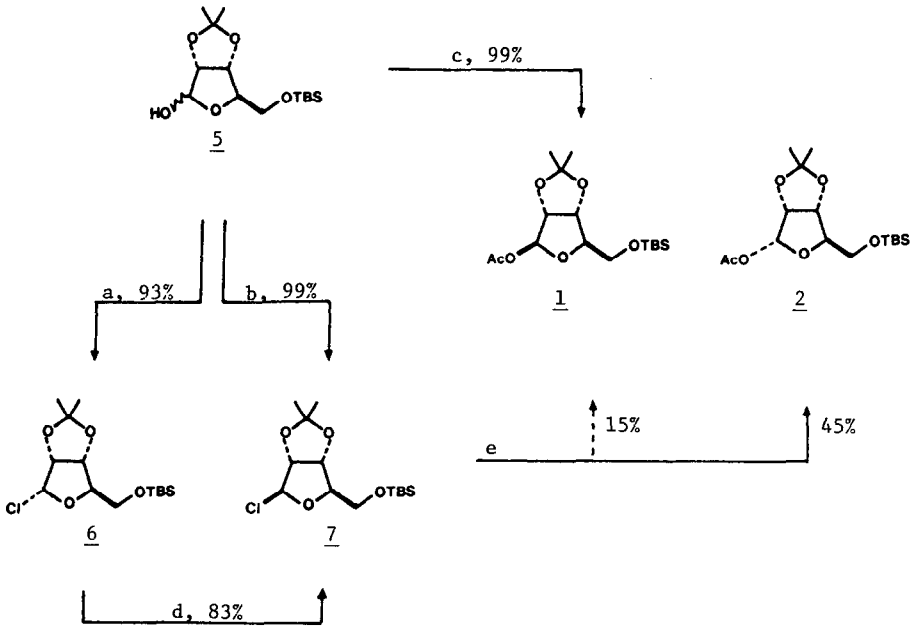
Figure 1.



The required pure samples of anomeric ribofuranosyl acetates 1 and 2 were prepared as illustrated in Chart 1. It is particularly notable that the preparation of the α-ribofuranosyl chloride 6 ($J_{1,2}$ = 4.2 Hz; $[\alpha]_D^{25}$ = 56°, c 0.015, CCl_4) is entirely stereoselective when carried out with hexamethylphosphorus triamide[3] at -78 °C and only a single anomer of the chloride is produced. The neat α-chloride 6 is converted to the β-chloride 7 ($J_{1,2}$ = 0.0 Hz; $[\alpha]_D^{25}$ = -44°, c 0.016, CCl_4) in good yield by heating at 90 °C for 30 hours. Alternatively, the β-chloride may be obtained directly from the lactol. (CCl_4/Ph_3P; THF; 67°C) By these methods either anomeric chloride is therefore available as a single isomer and in good yield for the first time. The β-acetate 1 ($J_{1,2}$ = 0.0 Hz; $[\alpha]_D^{25}$ = -101°, c 0.0186, CCl_4) is easily prepared directly from the lactol 5 (Ac_2O, pyridine). The α-acetate 2 ($J_{1,2}$ = 4.5 Hz; $[\alpha]_D^{25}$ = -10.8°, c 0.0141, CCl_4) is prepared from the β-chloride via a predominant S_N2 pathway[4,5] in the presence of silver acetate in benzene. The ratio of esters produced in this last reaction is 3/1 and the small amount of β-acetate which is formed is removed by flash chromatography on silica gel with 5% ethyl acetate - toluene. Stereochemical assignments on all compounds were based on comparisons of 360 MHz NMR spectra and the results of difference N.O.E. experiments.

These four reactants, the isomeric acetates (1 and 2) and the corresponding chlorides (6 and 7) are ribofuranosylating reagents. The availability of each isomer of these reactants will allow straightforward tests for stereospecificity of nucleoside forming reactions and other glycosidation reactions which lead to furanoid products.

Chart 1. Preparation of Isomeric Ribosyl Derivatives.



*a) $CCl_4/P(NMe_2)_3$/-78 °C/THF; b) $CCl_4/P(C_6H_5)_3$/67 °C/THF; c) Ac_2O/C_5H_5N; d) 90 °C/neat/24 hr; e) $AgOAc/C_6H_6$/24 °C.

To test the stereospecificity of the C-glycoside preparation which was in question, each of the anomeric acetates was treated with allyltrimethylsilane and zinc bromide under a variety of conditions (Table 1). It was observed that for the β-acetate 1, the use of solvents of high dielectric strength afforded the greatest stereoselectivity. For the β-acetate, the process occurs with predominant retention of stereochemistry in nitromethane, while in neat allyl trimethylsilane retention and inversion are more closely competitive. Products were not interconverted under these reaction conditions.

Notably, more polar solvents, preferably nitromethane, greatly increase the rate and stereoselectivity of this reaction.[6] Previously, good stereocontrol was achieved for this type of reaction only with BF_3-etherate in acetonitrile, and these reagents (in our hands and in accord with previous reports) remove silyl protecting groups at rates competitive with bond formation.[2d,e] The use of nitromethane with $ZnBr_2$ affords good stereocontrol in this furanose system at room temperature and is compatible with silyl protecting groups.[7]

These data show that the stereochemical outcome in the reaction of allyltrimethylsilane and zinc bromide in nitromethane with ribofuranosyl acetates 1 or 2 is only slightly influenced by starting material structure. An important practical observation is that in less polar solvents the influence of starting material geometry is more pronounced. These observations suppport the reasonable expectation that in less polar solvents a non-dissociative pathway is effectively competing with a less stereospecific (but, in this case, stereoselective) dissociative pathway.

The ready availability of the four ribofuranosylating reagents described here should stimulate other investigations of stereospecificity in nucleoside and C-glycoside forming processes.

Table 1. Variation of the Exo/Endo Distribution.[a]

Entry	Acetate	Reaction Conditions		Yield[b]	Ratio (3/4)[c]
		Solvent	Time/Temp(°C)		
1	1	CH_2CHCH_2TMS	1 hr/80°C	92%	2.8/1.0
2	1	$ClCH_2CH_2Cl$	7 hr/25°C	98%	4.0/1.0
3	1	$ClCH_2CH_2Cl$	1.5 hr/60°C	81%	8.4/1.0
4	1	CH_3NO_2	0.3 hr/25°C	84%	16/1.0
5	2	CH_2CHCH_2TMS	5 min/80°C	91%	1.9/1.0
6	2	$ClCH_2CH_2Cl$	3 hr/60°C	87%	4.1/1.0
7	2	CH_3NO_2	0.4 hr/25°C	52%	11/1.0

[a]Entry 2,3,4,6,7: 4 mol-eq allylsilane/2.5 mol-eq $ZnBr_2$/1.0 mol-eq acetate. [b]Combined yield of allylated products. [c]Ratio determined by NMR analysis of unfractionated product.

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References and Notes.

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5. Elemental analyses (combustion or high resolution mass spectra) and spectral data (^{1}H-NMR, ^{13}C-NMR, IR, MS) are consistent with the assigned structure for each new compound.

6. An increase in stereoselectivity with more polar solvents was also observed by Kozikowski, et. al.[2g] and Giannis and Sandhoff[2h].

7. At this time, we prefer not to speculate on the mechanism of this process. These data would support both a dissociative mechanism involving reaction of a cationic anomeric carbon with the allylic silane, or a mechanism involving multiple displacements at the anomeric site. It was found that in nitromethane the endo acetate 2 affords nearly the same ratio of product isomers as the exo acetate 1, and that the endo acetate and exo acetate interconvert in the more polar solvent at a rate comparable to product formation. Starting with either isomer, product formation was faster in polar solvents than in non-polar solvents. Note that with identical reaction mixtures higher temperatures afforded better stereocontrol.

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