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A NEW APPROACH TO C-GLYCOSIDE CONGENERS: METAL CARBENE MEDIATED METHYLENATION OF ALDONOLACTONES.

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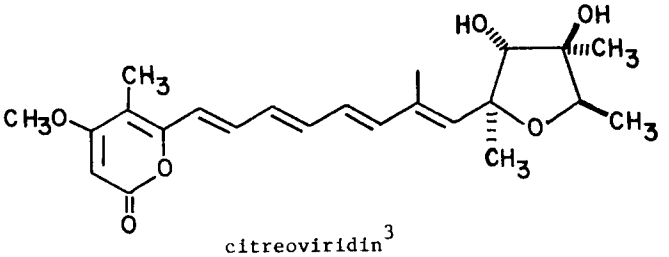
Abstract: *Versatile intermediates for the synthesis of C-glycosides and oxygen heterocycles are readily available through titanium mediated methylenation of aldonolactones.*

Carbohydrate derivatives wherein carbon residues are bonded to the anomeric carbon atom, or C-glycosides, are complex functionalized furanoid and pyranoid heterocycles.[1] Given the large number of naturally occurring biologically active compounds which contain furanoid and pyranoid rings, and the unique biological properties of many naturally occurring C-glycosides and C-nucleosides, the development of new methodologies for the synthesis of C-glycosides is a practical area of investigation and the synthesis of C-glycosides should continue to attract the interests of synthetic chemists for many years to come.

In connection with a project directed toward carbohydrate based syntheses of the naturally occurring mycotoxins aurovertin B[2] and citreoviridin[3], an efficient method was sought for converting a carbohydrate lactone into a furanoid or pyranoid ring which would have a methyl group and a second alkyl group both adjacent to the ring oxygen. An important requirement was that the technique should be readily compatible with asymmetric centers adjacent to the reactive site.



citreoviridin[3]

A convenient approach to this goal was envisioned to lie along the pathway illustrated in Figure 1. Conversion of the aldonolactone to the exocyclic enol ether would provide a practical intermediate for the subsequent alkylation step. Previous synthetic approaches to unsaturated sugars of this type have involved multistep processes culminating with an elimination reaction for the formation of the double bond.[4] We have found that the conversion may be directly achieved using the titanium carbene complex 2.[5,6] (Chart 1) While several

Figure 1.

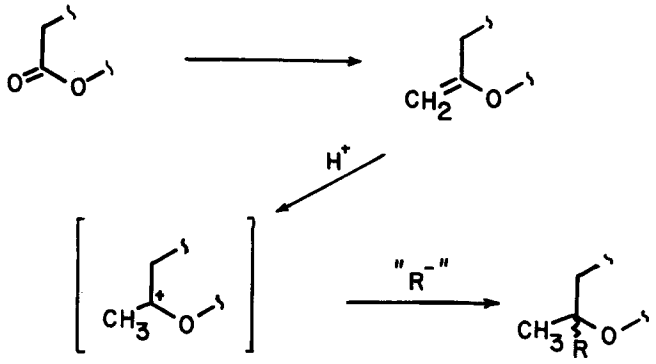
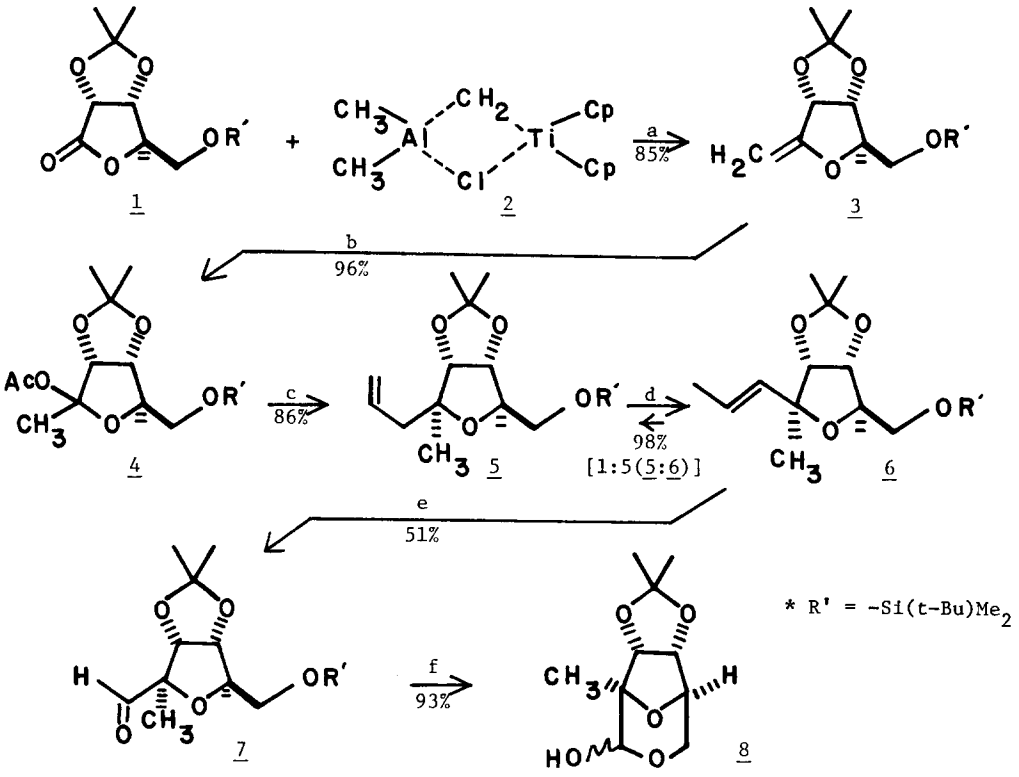


CHART 1: Dialkylation of Ribonic Acid 1,4-Lactone.*



a) $THF/C_7H_8/-40\ ^{o}C$; b) HOAc/ 25 ^{o}C/1 hr.; c) $CH_2{=}CHCH_2Si(CH_3)_3/ZnBr_2/CH_2Cl_2$;
d) $(PhCN)_2PdCl_2/C_7H_8$; e) OsO_4/N-methylmorpholine oxide, then $NaIO_4$/dioxane;
f) $Bu_4N^+\ F^-$/THF.

bond forming processes, including concerted additions, could be applied to these versatile substrates, one efficient method for the desired second alkylation relies on the ready availability of electrophiles of type I (Figure 1). This electrophile is alkylated in good yield by allyltrimethylsilanes.[7]

A specific example of the overall process is illustrated in Chart 1. Treatment of the protected D-ribonolactone 1[8] with the titanium carbene complex 2 in THF afforded the enol ether 3[9] (85%, $[\alpha]_D^{25}$= -111 ($CHCl_3$)). Direct methods for alkylation of this enol ether, for example using protic acids in the presence of allyltrimethylsilane, were not as satisfactory as the following two step approach. This enol ether was converted to the acetate 4,[9] a single isomer,[10] in 96% yield (HOAc/25°C/1 hr.; $[\alpha]_D^{25}$= -25.5 ($CHCl_3$)). Subsequent treatment of this acetate (1 mmol) with allyltrimethylsilane (4 mmol) and zinc bromide (2.5 mmol, CH_2Cl_2, 25°C, 1 hr.) afforded the allylic, bis-alkylated C-glycoside 5[9] (86%, $[\alpha]_D^{25}$= +6.7 ($CHCl_3$)).

It is interesting to note that Kozikowski reports that 1-O-acetyl-2,3-O-isopropylidene-5-O-t-butyldiphenylsilyl-D-ribo-pentofuranose affords in neat trimethylallylsilane with ZnBr an equimolar mixture of C-glycosidic products. In contrast, the closely analogous but anomerically methylated substrate 4 yields only one isomer under the same conditions. NMR and TLC analysis of the crude product gives no indication of a second isomer. Apparently the added methyl group significantly improves the stereoselectivity of this reaction. The stereochemistry of the product was established by olefin isomerization ($PdCl_2$:$(PhCN)_2$, benzene, 80°C) to afford the alkene 6[9] and cleavage (OsO_4/N-methylmorpholine oxide/acetone, then $NaIO_4$/dioxane) which provided aldehyde 7[9] [^{1}H-NMR (CCl_4) 9.4 (s, 1H, CHO)] in 50% overall yield from 5. Deprotection of the aldehyde (93%, Bu_4N-F, THF) provided the isomeric lactols 8,[9] as evidenced by the loss of the aldehyde proton resonance, and the presence of two new singlets in the ^{13}C-NMR spectrum (93 and 97 ppm) appropriate for the hemiacetal carbon. The cisoid relationship of the allyl group and the hydroxymethyl side chain in 5 is therefore confirmed.

The process offers an effective solution to the challenge of bis-alkylation at the anomeric carbon in carbohydrate rings. In just three steps, two carbon-carbon bonds are introduced at the lactone carbonyl carbon. The intermediate enol ethers should prove to be versatile substrates for the development of other practical allylation processes. Lehmann has demonstrated that enol ethers of this type are novel substrates for glycosidase enzymes,[4] and the successful application of the titanium reagent 2 to aldonolactones should greatly facilitate the synthesis of these and other potentially enzyme inhibitory molecules. Finally, it is important to note that the presence of the methyl group at the anomeric site enhances the stereoselectivity for alkylation with allyltrimethylsilane. Yields are comparable to yields reported earlier in cases involving less substituted electrophilic nuclei.[7]

Summary. Aldonolactones may be alkylated using the titanium carbene complex 2. The resulting enol ethers are of value as potential substrates for glycosidase enzymes. A high yield two step process for alkylation of these enol ethers was described. The products and procedures are relevant to the synthesis of mycotoxins, including citreoviridin and aurovertin B.

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References and Notes

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6. We are grateful to Professor Grubbs for helpful advice concerning the preparation and handling of this reagent.
7. For examples of previous uses of allylsilanes for alkylation at an anomeric carbon, see Kozikowski, A.P.; Sorgi, K.L. Tetrahedron Lett. 1982, 2281-2284. Danishefsky, S.; Kerwin, J.F., Jr. J. Org. Chem. 1982, 47, 3083-3085.
8. Prepared in 95% yield by silylation (DMF, imidazole, t-butyldimethylchlorosilane) of the corresponding alcohol. The alcohol was prepared according to Hough, L.; Jones, J.K.N.; Mitchell, D.L. Can. J. Chem. 1958, 36, 1720.
9. Elemental analysis (combustion or mass spectrometric), and magnetic resonance spectroscopy (proton and carbon 13) were consistent with the indicated structure for this molecule. Optical rotations were measured in ethanol free chloroform.
10. We have not as yet been able to prepare the anomer of this acetate. Therefore the stereochemistry of this intermediate remains open to speculation. However, comparison of the NMR spectrum for this intermediate with the spectra for other intermediates in this series and consideration of the probable mode of formation for this molecule indicate we are dealing here with the beta anomer.

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