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Stereocontrolled Synthesis of β-C-Glycosides and Amino β-C-Glycosides by Wittig Olefination of Perbenzylated Glyconolactones Derivatives

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Abstract: Wittig olefination of perbenzylated glyconolactones afforded stereoselectively the Z-C-glycosylidenes which were transformed to the corresponding β-C-glycosides and amino β-C-glycosides by hydrogenation followed by acetylation.

The important biological roles played by cell-surface carbohydrates and aminosugars have stimulated much effort in the preparation of their nonhydrolysable derivatives, C-glycosides and amino C-glycosides. The Wittig reaction has been widely employed for the synthesis of C-glycosides and amino C-glycosides by reaction of ylides with lactols followed by Michael cyclisation.[1-3] However, a mixture of α/β anomers was often obtained, with the α anomer as the major product.[4,5] The sugars olefinated at the anomeric center, which can be prepared by the Wittig reaction of the ylide on the sugar lactones[6-8] or by using titanium-based reagents,[9] represent valuable synthons in the synthesis of various C-glycosides because the enolether function can be easily transformed. Although several examples have been reported to prepare the alkenyl ether from lactones, these procedures are often lacking in good stereoselectivity.[8,10] Furthermore, few functionalized C-glycosides or amino C-glycosides have been directly prepared by this way,[11,12] especially in the case of 2-amino-2-deoxy lactones. We report herein an efficient method for the stereoselective preparation of β-C-glycosides and amino β-C-glycosides by the Wittig olefination of sugar lactones and further reduction of the double bond.

The reaction of the readily available perbenzylated galactonolactone **1a**[13] and gluconolactone **1b**[14] with 2 equivalents of ethoxycarbonylmethylene-(triphenyl)phosphorane at reflux in toluene afforded in good yields the olefins **2a**[15] and **2b**[15] (Table 1). The condensation proceeded with total stereocontrol, a single isomer was obtained as demonstrated by ^{1}H and ^{13}C NMR spectra. The *Z* geometry of the newly formed double bond was established by X-ray diffraction analysis of **2a**[16] (Figure 1).

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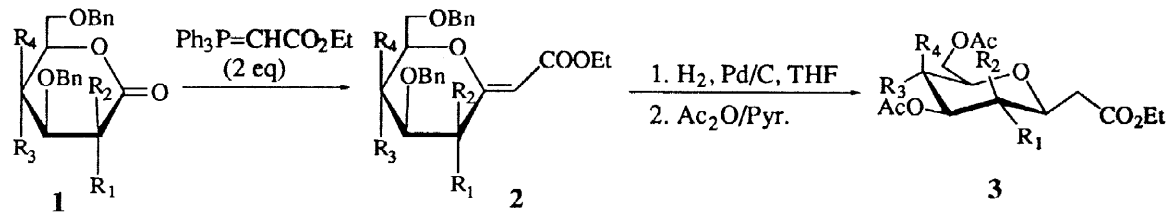
Table 1. Formation of C-glycosylidenes and further transformation to β-C-glycosides



Lactones **1**	Reaction time (h)*	C-glycosylidenes **2** (%)	C-glycosides **3** (%)**
1a R_1=R_4=OBn R_2=R_3=H (galacto)	15	90	75
1b R_1=R_3=OBn R_2=R_4=H (gluco)	15	87	76
1c R_2=R_3=OBn R_1=R_4=H (manno)	15	28 (9 /1)	–
1d R_1=NHAc, R_4=OBn R_2=R_3=H (galacto)	2	70	–
1e R_1=NHAc, R_3=OBn R_2=R_4=H (gluco)	1	70	76
1f R_2=NHAc, R_3=OBn R_1=R_4=H (manno)		0	–

* All the Wittig condensations were conducted under reflux in toluene except compound **1e** (in THF).

** The β-C-glycosides **3** were obtained as peracetylated derivatives.

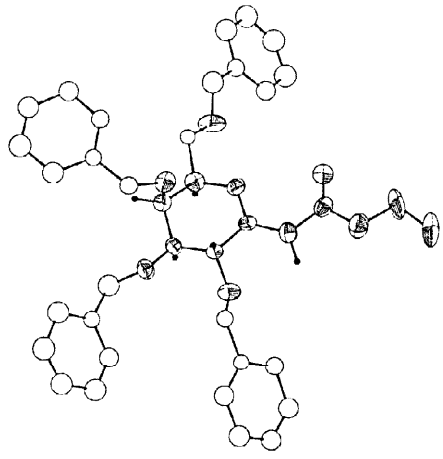


Figure 1. Perspective view of **2a**.

In the case of mannonolactone **1c**,[17] the condensation could not be completed without decomposition of the starting material, mainly by β-elimination to the (known) 2,4,6-tri-*O*-benzyl-3-deoxy-D-erythro-hex-2-enono-1,5-lactone. A mixture of two C-glycosylidenes **2c** (28 %) were obtained in a ratio of 9:1.

The extension of this reaction to 2-acetamido-2-deoxy glyconolactones has also been realized. The reaction of 2-acetamido 2-deoxy galactonolactone **1d**[18] and gluconolactone **1e**[18] proceeded also stereoselectively, giving a single isomer (**2d**[19] and **2e**[15]) (Table 1). For the compound **2e**, the *Z* configuration was established by the observation of an Overhauser effect between NHAc and H-2 : irradiation of NH enhanced the signal of H-2; irradiation of H-2 enhanced both signals of NH and acetyl H. Consequently, a *syn* relationship was demonstrated between NHAc and the ethylenic hydrogen atom. However, the 2-acetamido 2-deoxy mannonolactone **1f**[20] failed to react under these conditions : no reaction occurred in refluxing THF and total decomposition was observed in refluxing toluene.

The C-glycosylidenes are good precursors of C-glycosides. For exemple, hydrogenation (over Pd/C in THF) of compounds **2a, 2b** and **2e** followed by classical acetylation afforded stereoselectively the corresponding acetylated β-C-glycosides **3a**[15], **3b**[3] and amino β-C-glucoside **3e**[21] (Table 1), which are thermodynamically more stable. The β configuration at the anomeric position was confirmed by the large coupling constant between H-3 and H-4 ($J_{3,4}$ = 9.3 to 9.9 Hz) which was observed in the ^{1}H NMR spectra.

In conclusion, this easy performed sequence provides an efficient method for the stereoselective preparation of β-C-glycosides and amino β-C-glycosides from sugar lactones in good yield. The application of this method to other ylides and the transformation of C-glycosylidenes to other sugar derivatives are under investigation.

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References and Notes

† Deceased on October 20, 1997.

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16. X-ray analysis of **2a** : Crystal size, 0.1 x 0.1 x 0.8 mm. All data were obtained on Enraf Nonius CAD4. Crystal data: $C_{38}H_{40}O_7$, *Mr* = 608,7, orthorhombic, space group $P2_12_12_1$, a = 8.507(3) Å, b = 17.434(2) Å, c = 22.599(4) Å, V = 3352(1) Å^3, Z = 4, Dx = 1.21 g/cm^3, F(000) = 1296.38 and m(MoKa) = 0.08 cm^{-1}. Of the 3362 independent reflections collected, 1558 reflections with $I > 3.0s(I)$ were used for the structure determination. The final refinement converged with R = 0.072 and Rw = 0.060 for 262 parameters. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.
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20. The compound **2f** was obtained by catalytic hydrogenation over Raney Ni of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy glucono-1,5-lactone in the presence of acetic anhydride, results to be published.
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