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

Adeline Molina, Stanislas Czernecki[†] and Juan Xie^{*}

Laboratoire de Chimie des Glucides, CNRS UMR 7613, Université Pierre et Marie Curie,

4 place Jussieu, 75005 Paris, France

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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. © 1998 Elsevier Science Ltd. All rights reserved.

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 lactones⁶⁻⁸ 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 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 ¹H and ¹³C NMR spectra. The Z geometry of the newly formed double bond was established by X-ray diffraction analysis of $2a^{16}$ (Figure 1).





Lactones 1	Reaction time (h)*	C-glycosylidenes 2 (%)	C-glycosides 3 (%)**
1a R1=R4=OBn	15	90	75
R2=R3=H (galacto)			
1b R1=R3=OBn	15	87	76
R2=R4=H (gluco)			
1c R2=R3=OBn	15	28 (9 /1)	_
R1=R4=H (manno)		· ·	
1d R1=NHAc, R4=OBn	2	70	_
R2=R3=H (galacto)			
1e R1=NHAc, R3=OBn	1	70	76
R ₂ =R ₄ =H (gluco)			
1f R2=NHAc, R3=OBn		0	-
R1=R4=H (manno)			

* 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-2enono-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 $(2d^{19} \text{ and } 2e^{15})$ (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 3a¹⁵, 3b³ and amino β -C-glucoside 3e²¹ (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 ¹H 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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- All new compounds described gave satisfactory elemental analysis and spectroscopic data (¹H, ¹³C-NMR) in agreement with their structure.
- 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: C38H40O7, Mr = 608,7, orthorhombic, space group P212121, a = 8.507(3) Å, b = 17.434(2) Å, c = 22.599(4) Å, V = 3352(1) Å³, Z = 4, Dx = 1.21 g/cm³, 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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- 19. The compound 2d was contaminated with some triphenylphosphine oxide.
- 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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