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C-Glycosides: A Stereoselective Synthesis of α-*C*-Galactosamines with a Glycosyl Dianion

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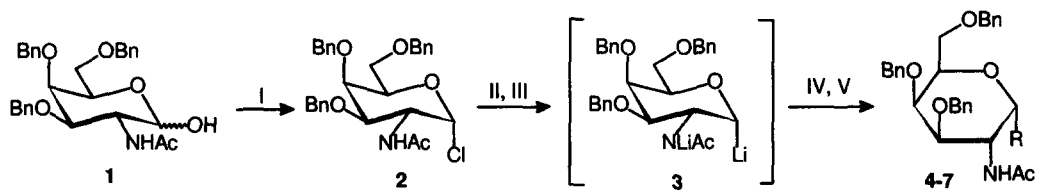
Abstract: α-*C*-glycosides of the galactosamine can be obtained from the configurationally stable α-glycosyl dianion which can be prepared by reductive lithiation of the chloride. Different electrophiles react selectively at the anomeric center.

During the last years *C*-glycosides have achieved growing interest due to their biological potential and their synthetic applications.[1] Despite the importance of 2-acetamido-2-deoxy-galactosides in biological systems, only a few syntheses of their *C*-glycosides are reported.[2,3]

In previous work, the synthesis of *C*-glycosides with glycosyl dianions was reported for glucose [4] and glucosamine.[5] Herein we present the synthesis of α-*C*-galactosamines using this dianion strategy. Only carbon dioxide and aldehydes were used as electrophiles for the *C*-glycoside synthesis as the conversion of the glucosamine dianion with other electrophiles such as cyanides, halides and acyl chlorides gave poor yields of the corresponding *C*-glycosides.

As outlined in **Scheme 1**, the synthesis started out with **1** which was obtained from 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose [6] by hydrogenolysis and subsequent reaction with acetic anhydride. After recrystallization from methanol **1** was treated with thionyl chloride to give the corresponding chloride **2**.



Scheme 1. Synthesis of the the α-*C*-glycosides. Reagents and conditions: (I) $SOCl_2$, $CHCl_3/PhCH_3$ 1:1, rt, 20 min (II) 1.2 eq n-BuLi, THF, -90°C, 1 min, (III) 2.2 eq lithium naphthalenide (LN), -90°C, 10 min (IV) 1.5 eq electrophile, 1 min, -90°C (V) NH_4Cl_{aq}.

The dianion intermediate **3** was obtained from **2** by deprotonation with butyllithium and reductive lithiation with lithium naphthalenide. Treatment of the dianion **3** with deuterated methanol gave the desired

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compound **4** in 75% yield. This deuteration experiment showed an α:β ratio of approximately 25:1. Only 2-3% of the nondeuterated compound were found. The reaction of **3** with benzaldehyde and isobutyraldehyde gave diastereomeric mixtures of **5 a/b** (ratio 1.8:1) and **6 a/b** (ratio 1.6:1) in 72 and 75% yield, respectively. The heptonic acid **7** was obtained by the reaction of **3** with carbon dioxide in 86% yield after column chromatography (**Table 1**).

Table 1. Results of *C*-glycosylation.

electrophile	product	R	yield %	a : b
MeOD	**4**	D	75	
PhCHO	**5a/b**	CH(OH)Ph	72	1.8 : 1
iPrCHO	**6a/b**	CH(OH)iPr	75	1.6 : 1
CO_2	**7**	COOH	86	

As determined by ^{1}H NMR spectra[7], the conformations of products **5-7** deviate from the usual $^4C_1$ chair. This was also observed by *Urban et al.* [2] who synthesized α-*C*-galactosamines promoted by samarium diiodide. Although all α-*C*-glycosides display a solution conformation deviating from the $^4C_1$ chair, the X-ray structure analysis of one of these compounds revealed that the $^4C_1$ conformation is preferred in the solid state.

The attempt to synthesize the β-*C*-galactosamines in analogy to the β-*C*-glucosamines resulted in the formation of a trianion so that after the addition of the electrophile the benzyl protecting group at C-3 was alkylated along with the C-1.[8]

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7 The coupling constant between H-2 and H-3 is approx. 3 Hz, in contrast to approx 10 Hz in the usual $^4C_1$-conformation. The coupling constant between H-1 and H-2 is approx. 2 Hz.

8 The alkylated benzyl ether was determined by NMR spectroscopy using a HMBC spectrum.