

## **C-Glycosides: A Stereoselective Synthesis of $\alpha$ -C-Galactosamines with a Glycosyl Dianion**

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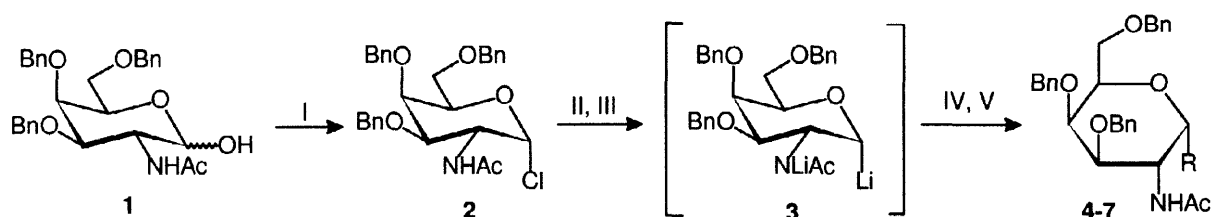
Received 22 September 1997; accepted 31 October 1997

**Abstract:**  $\alpha$ -C-glycosides of the galactosamine can be obtained from the configurationally stable  $\alpha$ -glycosyl dianion which can be prepared by reductive lithiation of the chloride. Different electrophiles react selectively at the anomeric center.  
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During the last years C-glycosides have achieved growing interest due to their biological potential and their synthetic applications.<sup>1</sup> Despite the importance of 2-acetamido-2-deoxy-galactosides in biological systems, only a few syntheses of their C-glycosides are reported.<sup>2,3</sup>

In previous work, the synthesis of C-glycosides with glycosyl dianions was reported for glucose<sup>4</sup> and glucosamine.<sup>5</sup> Herein we present the synthesis of  $\alpha$ -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<sup>6</sup> 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  $\alpha$ -C-glycosides. Reagents and conditions: (I)  $\text{SOCl}_2$ ,  $\text{CHCl}_3/\text{PhCH}_3$  1:1, rt, 20 min (II) 1.2 eq n-BuLi, THF,  $-90^\circ\text{C}$ , 1 min, (III) 2.2 eq lithium naphthalene (LN),  $-90^\circ\text{C}$ , 10 min (IV) 1.5 eq electrophile, 1 min,  $-90^\circ\text{C}$  (V)  $\text{NH}_4\text{Cl}_{\text{aq}}$ .

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

compound **4** in 75% yield. This deuteration experiment showed an  $\alpha:\beta$  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	<b>4</b>	D	75	
PhCHO	<b>5a/b</b>	CH(OH)Ph	72	1.8 : 1
iPrCHO	<b>6a/b</b>	CH(OH)iPr	75	1.6 : 1
CO <sub>2</sub>	<b>7</b>	COOH	86	

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

The attempt to synthesize the  $\beta$ -C-galactosamines in analogy to the  $\beta$ -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.<sup>8</sup>

#### Acknowledgement.

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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- <sup>7</sup> The coupling constant between H-2 and H-3 is approx. 3 Hz, in contrast to approx 10 Hz in the usual <sup>4</sup>C<sub>1</sub>-conformation. The coupling constant between H-1 and H-2 is approx. 2 Hz.
- <sup>8</sup> The alkylated benzyl ether was determined by NMR spectroscopy using a HMBC spectrum.