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C-Glycosides: A Stereoselective Synthesis of α- and β-*C*-Galactosides with Glycosyl Dianions

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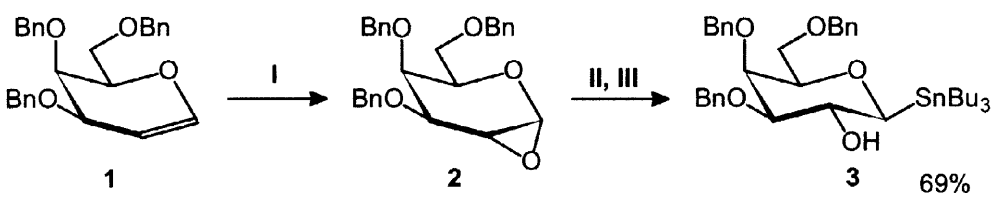
Abstract: α- or β-*C*-galactosides can be obtained from the configurationally stable anomeric glycosyl dianions which are prepared by transmetallation of a tin compound or by reductive lithiation of a chloride. Different electrophiles react selectively at the anomeric center

In previous work the use of glycosyl dianions as synthetic intermediates in the stereoselective synthesis of *C*-glycosides has been demonstrated for glucose [1], glucosamine [2] and galactosamine.[3] Based on the same concept, we present the stereoselective synthesis of α- and β-*C*-galactosides. Only aldehydes were used as electrophiles for the *C*-glycoside synthesis as the conversion of glycosyl dianions with other electrophiles such as cyanides, halides or acyl chlorides resulted only in poor yields of the corresponding *C*-glycosides.

The β-*C*-galactosides were prepared by transmetallation of the β-galactosylstannane **3** and treatment of the generated dianion **4** with electrophiles. The stannane **3** was prepared as outlined in **Scheme 1**.



Scheme 1. Synthesis of the β-galactopyranosylstannane **3**. Reagents and conditions: (I) dimethyldioxirane, acetone/CH_2Cl_2, 0°C, 1h (II) Bu_3SnLi, THF, 0°C, 10 min. (III) $NH_4Cl_{(aq)}$

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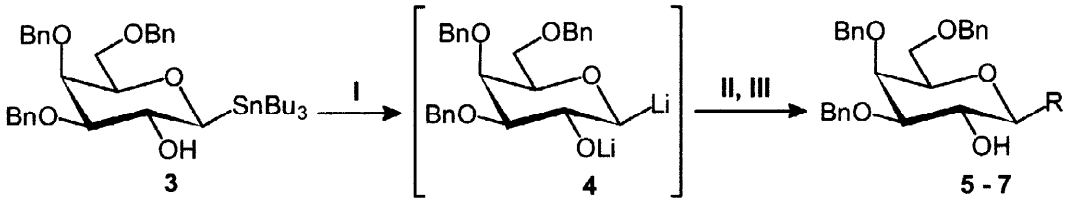
Tribenzylgalactal **1** was converted to the corresponding epoxide **2** with dimethyldioxirane according to a procedure of Danishefsky and co-worker.[4] Reaction of **2** with tributyltinlithium at 0°C followed by workup with a saturated aqueous NH_4Cl solution yielded 69% of stannane **3**.[5] For the transmetallation **3** was dissolved in THF and cooled to -80°C. After the addition of 5 eq. butyllithium, the solution was warmed to -55°C and stirred for 15 min. After the addition of the electrophile the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (**Scheme 2**).



Scheme 2. Synthesis of the β-*C*-galactosides. Reagents and conditions: (I) 5 eq. BuLi, THF, -80°C → -55°C, 15 min (II) electrophile, -55°C, 5 min (III) $NH_4Cl_{(aq)}$.

Treatment of the dianion **4** with deuterated methanol gave the desired compound in 83% yield. The reaction of **4** with benzaldehyde and isobutyraldehyde gave diastereomeric mixtures (ratio 1:1) of **6a/b** and **7a/b** in 77 and 57% yield, respectively (**Table 1**).

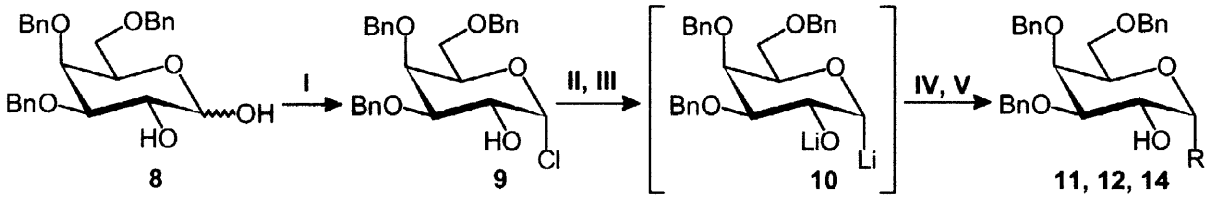
Table 1. Results of β-*C*-glycosylation.

electrophile	product	R	yield %	a : b *
MeOD	**5**	D	83	
PhCHO	**6a/b**	CH(OH)Ph	77	1 : 1
^{i}PrCHO	**7a/b**	CH(OH)^{i}Pr	57	1 : 1

* a is the less polar isomer

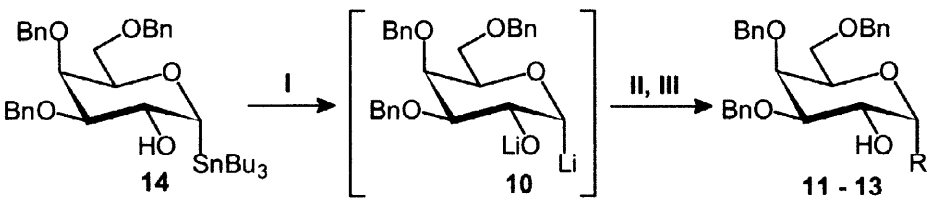
The corresponding α-*C*-galactosides were synthesized by reductive lithiation of chloride **9** which was synthesized from tribenzylgalactose **8** [6] by using a saturated solution of HCl in ether (**Scheme 3**). Contrary to the anomeric chloride of glucose (Ref. 1a) it is not possible to crystallize the galactosylchloride **9** which is also less stable than its glucose analogue. As a result of this **9** was directly converted to dianion **10** using 1.1 eq. butyllithium for deprotonation and 2.2 eq. lithium naphthalenide (LN) for reductive lithiation. After the addition of the electrophile the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The yields of *C*-glycosylation (**Table 2**) were lower than for the glucose analogue (Ref. 1a). The use of deuterated

methanol yielded 53% of the α-deuterated glycitol **11**, 4 % of β-compound **5** and 16% of the corresponding undeuterated glycitol. The reaction of **10** with benzaldehyde gave only 37% of **12a/b** (ratio 1.5:1). The use of tributyltinchloride as electrophile yielded stannane **14** in 35%.



Scheme 3. Synthesis of the α-*C*-galactosides via reductive lithiation of chloride **9**. Reagents and conditions: (I) HCl, Et_2O, 0°C, 2.5 h (II) 1.1 eq. n-BuLi, -90°C, 2 min (III) 2.2 eq. lithium naphthalenide (LN) , -90°C, 5 min (IV) electrophile (V) $NH_4Cl_{(aq)}$.

However, the conversion of stannane **14** via deprotonation and transmetallation with butyllithium followed by the addition of an electrophile resulted in the formation of the corresponding α-*C*-galactosides (**Scheme 4**) in yields similar to those of the β-*C*-galactoside-synthesis (**Table 2**).



Scheme 4. Synthesis of the α-*C*-galactosides via transmetallation of stannane **14**. Reagents and conditions: (I) 5 eq. BuLi, THF, -80°C → -55°C, 15 min (II) electrophile, -55°C, 5 min (III) $NH_4Cl_{(aq)}$.

Table 2. Results of α-*C*-glycosylation via reductive lithiation of chloride **9** [a] and transmetallation of stannane **14** [b].

electrophile	product	R	yield % [a]	a : b *	yield % [b]	a : b *
MeOD	**11**	D	53		94	
PhCHO	**12a/b**	CH(OH)Ph	37	1.5 : 1	77	1 : 1.8
^{i}PrCHO	**13a/b**	CH(OH)^{i}Pr			61	1 : 1.4
Bu_3SnCl	**14**	$SnBu_3$	35			

* a is the less polar isomer

The deuteration yielded 94% of **11** with no β-deuterated glycitol **5** being observed. The reaction of **10** with benzaldehyde and isobutyraldehyde gave the diastereomeric mixtures **12a/b** (ratio 1:1.8) and **13a/b** (ratio 1:1.3) in 77 and 61% yield, respectively.

In summary, we have described a method for the direct and stereoselective synthesis of either α- or β-*C*-galactosides. The galactosyl dianions **4** and **10** are configurationally stable under the conditions described. Although the yields of the α-*C*-glycosylation are moderate, the procedure allows the synthesis of α-*C*-galactosides in a multigram scale.

Acknowledgement

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4 Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

5 In contrast to the synthesis of the β-glucopyranosylstannane described in **Ref. 1b** a solution of the epoxide **2** in THF was added dropwise to a solution of tributyltinlithium in THF at 0°C.

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