

## **C-Glycosides: A Stereoselective Synthesis of $\alpha$ - and $\beta$ -C-Galactosides with Glycosyl Dianions**

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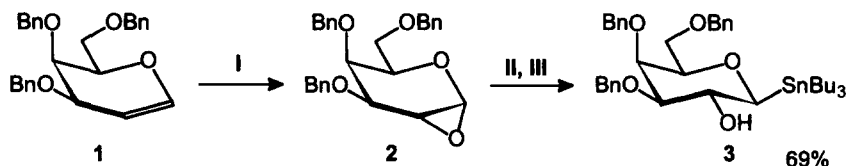
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**Abstract:**  $\alpha$ - or  $\beta$ -C-galactosides can be obtained from the configurationally stable anomeric glycosyl dianions which are prepared by transmetalation of a tin compound or by reductive lithiation of a chloride. Different electrophiles react selectively at the anomeric center  
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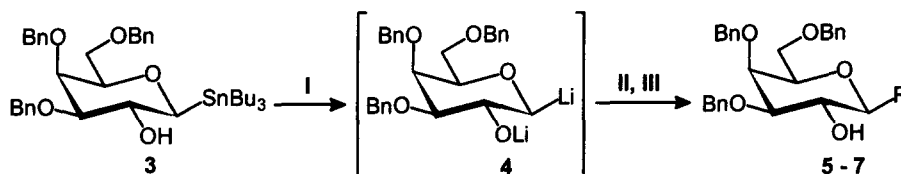
In previous work the use of glycosyl dianions as synthetic intermediates in the stereoselective synthesis of C-glycosides has been demonstrated for glucose<sup>1</sup>, glucosamine<sup>2</sup> and galactosamine.<sup>3</sup> Based on the same concept, we present the stereoselective synthesis of  $\alpha$ - and  $\beta$ -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  $\beta$ -C-galactosides were prepared by transmetalation of the  $\beta$ -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  $\beta$ -galactopyranosylstannane **3**. Reagents and conditions: (I) dimethyldioxirane, acetone/ $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 1 h (II)  $\text{Bu}_3\text{SnLi}$ , THF,  $0^\circ\text{C}$ , 10 min. (III)  $\text{NH}_4\text{Cl}_{(\text{aq})}$

Tribenzylgalactal **1** was converted to the corresponding epoxide **2** with dimethyldioxirane according to a procedure of Danishefsky and co-worker.<sup>4</sup> Reaction of **2** with tributyltinlithium at 0°C followed by workup with a saturated aqueous NH<sub>4</sub>Cl solution yielded 69% of stannane **3**.<sup>5</sup> 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<sub>4</sub>Cl solution (**Scheme 2**).



**Scheme 2.** Synthesis of the  $\beta$ -C-galactosides. Reagents and conditions: (I) 5 eq. BuLi, THF, -80°C  $\rightarrow$  -55°C, 15 min (II) electrophile, -55°C, 5 min (III) NH<sub>4</sub>Cl<sub>(aq)</sub>.

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**).

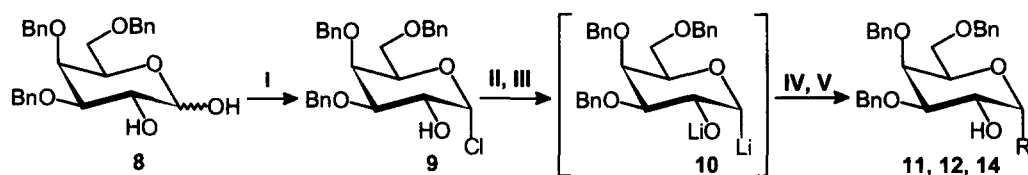
**Table 1.** Results of  $\beta$ -C-glycosylation.

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

\* a is the less polar isomer

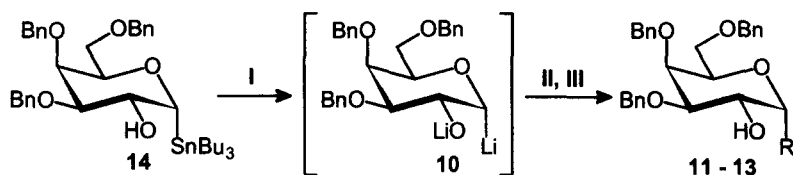
The corresponding  $\alpha$ -C-galactosides were synthesized by reductive lithiation of chloride **9** which was synthesized from tribenzylgalactose **8**<sup>6</sup> by using a saturated solution of HCl in ether (**Scheme 3**). Contrary to the anomeric chloride of glucose (Ref. 1a) it is not possible 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<sub>4</sub>Cl 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  $\alpha$ -deuterated glycitol **11**, 4 % of  $\beta$ -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  $\alpha$ -C-galactosides via reductive lithiation of chloride **9**. Reagents and conditions: (I) HCl, Et<sub>2</sub>O, 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<sub>4</sub>Cl<sub>(aq)</sub>.

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



**Scheme 4.** Synthesis of the  $\alpha$ -C-galactosides via transmetalation 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<sub>4</sub>Cl<sub>(aq)</sub>.

**Table 2.** Results of  $\alpha$ -C-glycosylation via reductive lithiation of chloride **9** [a] and transmetalation of stannane **14** [b].

electrophile	product	R	yield % [a]	a : b *	yield % [b]	a : b *
MeOD	<b>11</b>	D	53		94	
PhCHO	<b>12a/b</b>	CH(OH)Ph	37	1.5 : 1	77	1 : 1.8
<sup>i</sup> PrCHO	<b>13a/b</b>	CH(OH) <sup>i</sup> Pr			61	1 : 1.4
Bu <sub>3</sub> SnCl	<b>14</b>	SnBu <sub>3</sub>	35			

\* a is the less polar isomer

The deuteration yielded 94% of **11** with no  $\beta$ -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  $\alpha$ - or  $\beta$ -C-galactosides. The galactosyl dianions **4** and **10** are configurationally stable under the conditions described. Although the yields of the  $\alpha$ -C-glycosylation are moderate, the procedure allows the synthesis of  $\alpha$ -C-galactosides in a multigram scale.

### Acknowledgement

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### References

- <sup>1</sup> a) Wittmann, V.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1091-1093. b) Frey, O.; Hoffmann, M.; Wittmann, V.; Kessler, H.; Uhlmann, P.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 2060-2069. c) Lesimple, P.; Beau, J. M. *Bioorg. Med. Chem.* **1994**, *2*, 1319-1330.
- <sup>2</sup> a) Hoffmann, M.; Kessler, H. *Tetrahedron Lett.* **1994**, *35*, 6067-6070. b) Hoffmann, M.; Burkhardt, F.; Hessler, G.; Kessler, H. *Helv. Chim. Acta* **1996**, *79*, 1519-1532. c) Hoffmann, M.; Kessler, H. *Tetrahedron Lett.* **1997**, *38*, 1903-1906.
- <sup>3</sup> Burkhardt, F.; Kessler, H. *Tetrahedron Lett.* **1998**, *39*, 255-256.
- <sup>4</sup> Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.
- <sup>5</sup> In contrast to the synthesis of the  $\beta$ -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.
- <sup>6</sup> Wu, E.; Wu, Q. *Carbohydr. Res.* **1993**, *250*, 327-333.