



## Note

## Reduction of sugar lactones to hemiacetals with lithium triethylborohydride



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## ABSTRACT

Reduction of ribono-1,4-lactones and gulono-1,4-lactone as well as ribono-1,5-lactone and glucono-1,5-lactones with LTBH (1.2 equiv.) in  $\text{CH}_2\text{Cl}_2$  at 0 °C for 30 min provided the corresponding pentose or hexose hemiacetals in high yields. Commonly used in carbohydrate chemistry protecting groups such as trityl, benzyl, silyl, acetals and to some extent acyls are compatible with this reduction.

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The reduction of sugar lactones to hemiacetals (lactols) plays an important role in the synthesis of modified carbohydrates and nucleosides [1,2]. The commonly used reagents for this transformation include  $\text{NaBH}_4$  [3,4] and organic-soluble metal hydrides [2,5,6].  $\text{LiAlH}_4$  under controlled reaction conditions has also been used for this purpose [7].  $\text{NaBH}_4$  is effective in the reduction of sugar lactones to aldoses. However, it requires aqueous acid conditions to prevent over reduction, which is problematic for nonpolar and/or acid labile compounds [7,8]. Although DIBAL-H is an efficient reagent for this reduction, it often requires low temperature and large excess of the reagent, which is a disadvantage for large scale work [9]. Catalytic reduction of lactones to lactols with generated in situ titanocene(III) hydride, in the presence of silanes as a hydride source, has also been developed [10,11]. This approach was utilized for the large scale preparation of sugar hemiacetals [12].

Although borane-based reagents have been used for the reduction of lactones to lactols and diols [13], reports of reductions of sugar lactones to hemiacetals using borane reagents are sparse. For example, disiamylborane was used for the conversion of 2,3-di-O-acetyl-5-S-acetyl-5-thio-D-arabinono-1,4-lactone to the

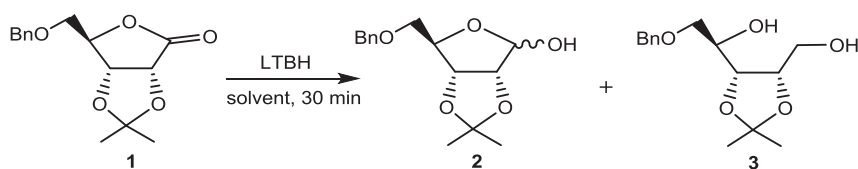
corresponding arabinofuranose [14], and Selectride was employed for the partial reduction of acetyl protected D-galactono-1,4-lactone [15].

Reduction of the pre-constructed sugar lactones to their corresponding hemiacetals and their further coupling with nucleobases are often key steps in the synthesis of important drugs (e.g., anti-cancer gemcitabine [2], anti-HIV 3 TC and dideoxynucleosides [5,16] and others). In our program on developing novel inhibitors of S-ribosylhomocysteine (SRH) hydrolase (LuxS; EC 4.4.1.21), which mediates the interspecies quorum sensing among bacteria [17,18], we recently applied lithium triethylborohydride (LTBH, Super-Hydride®) [19,20] for the reduction of lactam and lactone analogues of SRH to the corresponding azahemiacetals (N,O-acetals) [21] or lactols (O,O-acetals) [22]. Although application of LTBH for the reduction of lactams to cyclic hemiaminals (azahemiacetals) is documented [23,24], the reduction of lactones to the hemiacetals with LTBH is underdeveloped. In his landmark paper from 1980 [25], Brown reported that LTBH, when used in excess (2 equiv.), efficiently reduced esters to alcohols and lactones to diols and this protocol has been used in organic synthesis [19,26]. Herein, we report application of lithium triethylborohydride for the efficient reduction of sugar lactones to hemiacetals.

Initially, we tested reduction of lactones to hemiacetals with LTBH with readily available 5-O-benzyl-2,3-O-isopropylidene-D-ribo-1,4-lactone [12] **1** (Scheme 1). Thus, treatment of **1** with

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**Scheme 1.** Reduction of the protected ribono-1,4-lactone **1** with LTBH.

1.0 equiv. or 1.1 equiv. of LTBH ( $\text{CH}_2\text{Cl}_2/0^\circ\text{C}/30\text{ min}$ ) showed about 90–95% conversion to the ribofuranose **2** with ~5–10% of substrate **1** remaining unchanged ( $^1\text{H NMR}$ ; Table 1, entries 1 and 2). However, treatment of **1** with 1.2 equiv. of LTBH gave a complete conversion to hemiacetals **2** ( $\alpha/\beta$ , 1:4) without noticeable detection of the peaks for the lactone **1** and diol **3** on the  $^1\text{H NMR}$  spectra of the crude reaction mixture (entry 3, see SI Section). Effect of different ratios of LTBH to lactone **1** as well as temperature, reaction time and solvent are summarized in Table 1. Briefly, increasing the ratio of LTBH to 1.5 equiv. still gives **2** as a sole product (entry 4). However, reduction with 2.5 equiv. of LTBH led to the substantial formation of diol **3** (entry 5). Yet, even when the reduction was carried out for longer time (up to 22 h) hemiacetals **2** was still isolated although in lower yields. Interestingly, temperature did not have a significant effect on the reduction of lactone **1** to hemiacetals **2** and similar results were obtained at  $-78^\circ\text{C}$ ,  $0^\circ\text{C}$ , or r.t. (entries 4, 6 and 7). Additionally, reduction of **1** in other solvents (toluene or chloroform) did not affect the reduction (entries 8 and 9) with the exception of THF which gave substantially lower yield (entry 10).

In order to investigate the reaction profile for the conversion of lactone **1** to lactol **2** and diol **3**, reduction of **1** was performed using 1.2 equiv (see Fig. S1 in SI section) and 2.5 equiv. of LTBH (see Fig. S2 in SI section). In both cases complete conversion of lactone **1** to lactol **2** was observed in less than 5 min. In the reaction with 1.2 equiv. of LTBH no diol **3** was detected even after 1 h. Reduction of **1** with 2.5 equiv. of LTBH was completed within 1 min showing exclusive formation of lactol **2**. Longer reaction time showed a slow disappearance of lactol **2** with increasing formation of diol byproduct **3** [0.5 h, **2** (72%)/**3** (28%); 2 h, **2** (65%)/**3** (35%)].

To probe the generality of the reduction of sugar lactones to the corresponding hemiacetals with LTBH, several  $\gamma$ - and  $\delta$ -lactones were tested (Table 2). Thus, reduction of 2,3-*O*-isopropylidene-ribo-1,4-lactones with trityl (**4**), benzoyl (**6**) or acetyl (**8**) protection at 5-hydroxyl provided the corresponding hemiacetals **5**, **7**, and **9** (entries 2–4). The trityl and benzoyl protection groups were found to be stable under these reducing conditions. Reduction of the 5-*O*-acetyl lactone **8** yielded also substantial amount of 2,3-*O*-isopropylidene- $\alpha/\beta$ -D-ribofuranose as a result of the reduction of an acetyl ester. However, reduction with 1.1 equiv. of LTBH and

shorter reaction time (10 min) provided hemiacetals **9** in 70% yield (entry 4). Reduction of 2,3,5-tri-*O*-acetyl lactone **10** gave hemiacetals **11** but in low yield (30%, entry 5). Conversion of 2,3-*O*-isopropylideneribono-1,4-lactone **12** to ribose **13** required an increased amount of LTBH (1.6 equiv.; entry 6). Reduction of the 3,5-*O*-TBDMS-2-deoxy-D-ribo-1,4-lactone **14** also proceeded efficiently to give the 2-deoxyribose product **15** when 1.5 equiv. of LTBH was used (entry 7). However, reduction of 5-*O*-TBDMS-2,3-dideoxy-D-ribo-1,4-lactone **16** yielded both the 2,3-dideoxyribose **17** and the corresponding diol byproduct (entry 8). Moreover, reduction of D-ribo-1,5-lactone **18** efficiently produced the corresponding ribopyranose derivative **19** in 88% yield (entry 9).

The lactones derived from hexoses were also efficiently reduced with LTBH to the corresponding hemiacetals. Thus, reduction of 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone **20** gave gulonofuranose **21** (91%, entry 10). Treatment of trimethylsilyl protected glucono-1,5-lactones **22** with LTBH yielded glucopyranose **23** ( $\alpha/\beta$ , 2:1; entry 11). Analogous reduction of the fully acetylated D-glucono-1,5-lactone **24** provided glucose **25** in low yield due to concomitant reduction of the ester protecting group (entry 12). Attempted reduction of the fully benzoylated glucono-1,5-lactone gave similar results (entry 12, footnote f). However, reduction of glucono-1,5-lactone **26** bearing benzylidene and *tert*-butyldimethylsilyl protection groups proceeded efficiently to give hemiacetals **27** in 80% yield (entry 13). Hence, reduction of sugar lactones with LTBH to lactols appears to have a general character and is clearly compatible with acid-, base- and fluoride-labile protecting groups commonly used in carbohydrate chemistry.

We also performed reduction of several sugar lactones with  $\text{NaBH}_4$  and DIBAL-H, in order to compare LTBH protocol with these commonly used reducing agents. Thus, reduction of **4** or **14** with  $\text{NaBH}_4$  (1.1 equiv.) in EtOH ( $0^\circ\text{C}$ ) after 30 min showed only a small conversion to the lactol products **5** and **15** (~10%) with the unchanged lactones (~80%) and the corresponding diols (~10%) present (TLC,  $^1\text{H NMR}$ ). Increasing the amount of  $\text{NaBH}_4$  (5 equiv.) resulted in the formation of the corresponding diols as the major product (~70%). Reduction of **14** with DIBAL-H in  $\text{CH}_2\text{Cl}_2$  ( $-78^\circ\text{C}$ , 30 min) yielded lactol **15** (90%). However, analogous treatment of 5-

**Table 1**  
Effect of various reaction parameters on reduction of **1** with LTBH<sup>a</sup>.

Entry	Solvent	LTBH (equiv.)	Temperature ( $^\circ\text{C}$ )	Yield <sup>b</sup> <b>2</b> (%)	Yield <sup>b</sup> <b>3</b> (%)	Ratio <sup>b</sup> <b>1:2:3</b>
1	$\text{CH}_2\text{Cl}_2$	1.0	0	90	–	1:9:0
2	$\text{CH}_2\text{Cl}_2$	1.1	0	95	–	1:19:0
3	$\text{CH}_2\text{Cl}_2$	1.2	0	99 (95) <sup>c</sup>	–	0:1:0
4	$\text{CH}_2\text{Cl}_2$	1.5	0	99	–	0:1:0
5	$\text{CH}_2\text{Cl}_2$	2.5	0	40 (34) <sup>c</sup>	60 (55) <sup>c</sup>	0:4:6
6	$\text{CH}_2\text{Cl}_2$	1.5	20	94	–	0:1:0
7	$\text{CH}_2\text{Cl}_2$	1.5	$-78$	95	–	0:1:0
8	Toluene	1.5	0	93	–	0:1:0
9	$\text{CHCl}_3$	1.5	0	95	–	1:19:0
10	THF	1.5	0	30	–	7:3:0

<sup>a</sup> Reduction was performed on 0.15 mmol scale of **1** with 1 M solution of LTBH in THF.

<sup>b</sup> Determined by  $^1\text{H NMR}$  of the crude reaction mixture.

<sup>c</sup> Isolated yield.

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