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Deoxygenation/dimerization of sugar derivatives with $BF_3{\cdot}Et_2O$–Et_3SiH: synthesis of a β-isonucleoside

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ABSTRACT

Lewis acid-Et_3SiH induced deoxygenation of anomeric carbon of sugars generates tetrahydrofuran derivatives, accompanied by hitherto unknown dimeric products. If the reagent addition steps are reversed, tetrahydrofuran derivatives are obtained as the sole products, while only the dimeric products are isolated if Et_3SiH is excluded. One of the deoxygenated products has been transformed into a β-isonucleoside.

Self-glycosylation reaction for the generation of disaccharides is scarcely reported. Formation of di-D-fructose dianhydrides via acid catalyzed dimerization[1] of D-fructose, sucrose or inulin through a fructosyl oxocarbenium cation and in situ glycosylation into the respective disaccharide has been demonstrated by Mellet and García Fernández group.[2] Very recently, a report by Uriel et al.[3] disclosed the use of self-glycosylation for stereoselective formation of disaccharides from mannose-derived orthoesters by treatment with $BF_3{\cdot}Et_2O$. The role of $BF_3{\cdot}Et_2O$ for the cleavage of acetonide protection and as promoter in glycosylation reaction in a tandem manner has been clearly revealed in these reactions. It appeared that during the self-glycosylation reaction occurring through oxocarbenium ion, in situ addition of a hydride donor that could act in the presence of the Lewis acid to reduce the double bond would prevent glycosylation and generate solely 3-hydroxytetrahydrofuran derivatives (deoxygenated products), which could be transformed to bioactive isonucleosides[4–7] via nucleophilic displacement of 3-OH group by nucleobases (Fig. 1). However, if glycosylation and hydride addition compete with each other, the reaction could afford both deoxygenated and dimerized products. This realization has encouraged us to exploit this strategy for the stereoselective preparation of D-glucose-based chiral 3-hydroxytetrahydrofuran derivatives and di-D-glucose 1,2′:1′,2-dianhydrides (dimeric products), and the results are described herein.

The starting sugar based precursor **5** was derived from 3-*O*-benzyl xylose,[8] whereas **6** and **9** were obtained from the corresponding dihydroxymethyl derivatives[9,10] via benzylation. Compounds **7**,[11] **8**,[12] **10**,[13] and **11**[14] were prepared following the literature methods. For the deoxygenation of the anomeric carbon, the starting synthons (type **A**, Scheme 1) **5–11** (Table 1) were treated with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$.[15,16] Interestingly, treatment of $BF_3{\cdot}Et_2O$ at first followed by Et_3SiH (Method I)[17] furnished the normal tetrahydrofuran derivatives (type **B**) **12**, **14**, **16**, **18**, **20**, **22**, and **24** (27–45% yields) along with the hitherto unknown dimeric products (type **C**) **13**, **15**, **17**, **19**, **21**, **23,** and **25** (32–38% yields) (Table 1). However, reversal of the addition schedule to employ Et_3SiH first and then $BF_3{\cdot}Et_2O$ ensured exclusive formation of the deoxygenated products in 67–78% yields (Method II).[17] On the other hand,

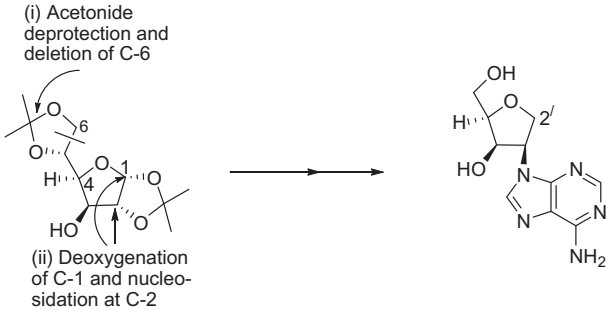

Figure 1. A strategy to generate isonucleosides.

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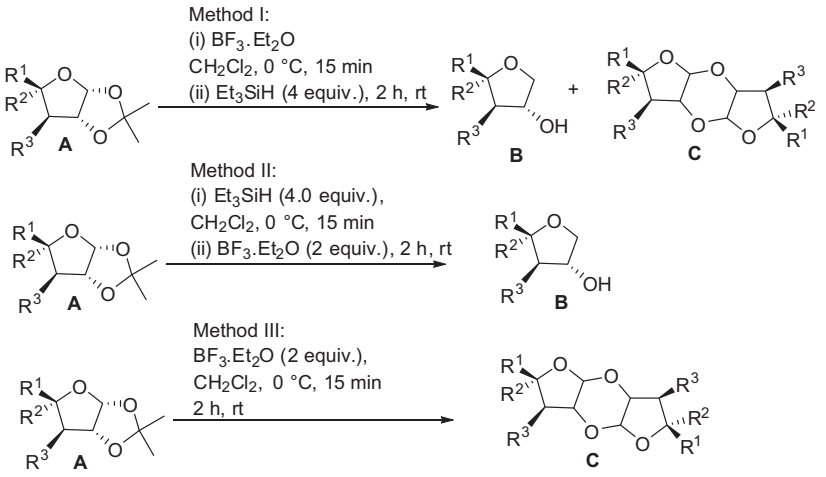
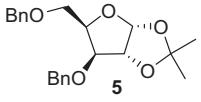
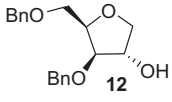
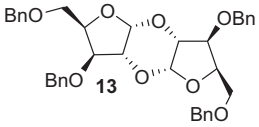
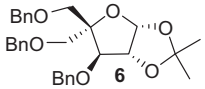
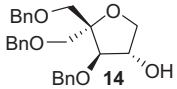
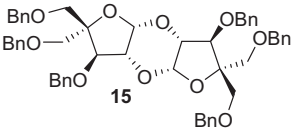
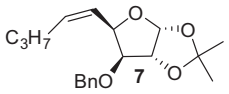
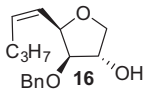
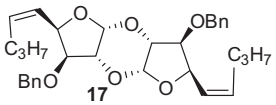
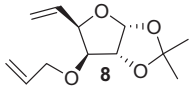
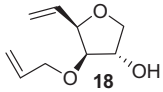
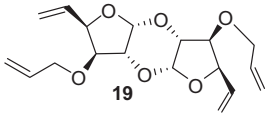
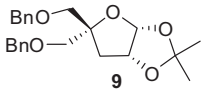
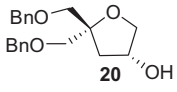
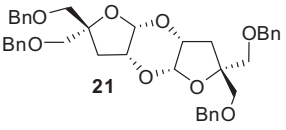
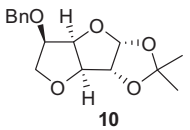
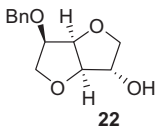
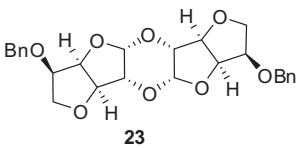
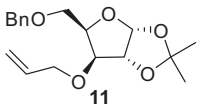
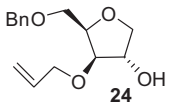
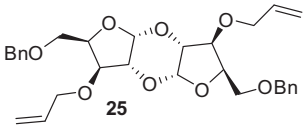


Scheme 1. Deoxygenation of anomeric carbon and dimerization of sugar.

Table 1
Reaction of sugar derivatives with $BF_3{\cdot}Et_2O$–Et_3SiH

Entry	Starting sugar	Deoxygenated product	Yield (%)		Dimeteric product	Yield (%)	
			Method I	Method II		Method I	Method II
1	 **5**	 **12**	42	78	 **13**	33	75
2	 **6**	 **14**	27	67	 **15**	37	72
3	 **7**	 **16**	35	72	 **17**	35	80
4	 **8**	 **18**	38	72	 **19**	36	78
5	 **9**	 **20**	42	75	 **21**	32	73
6	 **10**	 **22**	45	71	 **23**	36	79
7	 **11**	 **24**	44	69	 **25**	38	70

the use of $BF_3{\cdot}Et_2O$ as the sole reagent furnished the dimeric products exclusively in 70–80% yields (Method III).[17] All the products were characterized by ^1H and ^{13}C NMR besides MS analyses.[18] The presence of an extra CH_2 signal ($\sim\delta$ 70.0) and absence of the anomeric carbon signal in the ^{13}C NMR spectra, coupled with the absence of signals for isopropylidene methyl and the anomeric proton in the ^1H NMR spectra of the deoxygenated products indicated the successful reduction of the anomeric position. However,