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First example of 5/6-O-linked pseudosaccharides: synthesis of bicyclic nucleosides containing azido or extended carbohydrate moiety

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Abstract—Treatment of the D-glucose-derived substrate **1** with sodium hydride in tetrahydrofuran provided 3,6-anhydro monosaccharide **2**, along with the 5,6-ether linked pseudodisaccharide **3**, and pseudotrisaccharide **4**. However, reaction of **1** with sodium ethoxide in ethanol afforded **2** as the sole product, elaborated to the bicyclic azidonucleosides **9** and **16**. Acetylated bicyclic nucleosides **17**–**19** with extended carbohydrate residues have been synthesized from **3**.

Keywords: Pseudosaccharides; Synthesis; Azido bicyclic nucleosides; Carbohydrate; D-Glucose

1. Introduction

Bicyclic nucleosides[1] are derived by the replacement of the natural furanose sugar moiety with a bicyclic ring structure. Such replacement results in the diminution of the conformational freedom of the nucleosides.[2] A plethora of conformationally restricted bicyclic nucleosides have been synthesized for potential antiviral, antitumor, and other biological activities. Bicyclic nucleosides have been encountered in natural sources too. Among them, the most notable are the griseolic acids[3] (having furano-furan skeleton), which are known to inhibit the 3′,5′-cyclic nucleotide phosphodiesterase. Other bicyclic nucleosides such as ezomycins, quantamycin, and malayamycins (all with furanopyran skeleton) are antibiotics having interesting properties.[4] The common structural motif present in some of these products is an extended carbohydrate moiety. The fact that the location of such structural features in the nucleosides imparts various antibiotic properties encouraged researchers to take up programs on the synthesis of conformationally restricted glycotriazole-tethered nucleoside/nucleotide analogues,[5] which have not been adequately explored so far. Keeping this in mind, we took up the synthesis of glucose-derived bicyclic nucleosides with azido functionality at C-2′ and C-5′. In the process, we could also synthesize the hitherto unknown 5,6-ether linked pseudosaccharides and characterize a representative member unequivocally through X-ray crystallographic structure determination. It is pertinent to mention here that a 5,4-ether linked disaccharide has been identified as a structural element of the exotoxin of *Bacillus thuringiensis* and synthesized by Prystaš and Šorm,[6] while 6,6′-ether linked disaccharides have been synthesized by Ikegami's group[7] and by Haines[8] to establish the structure of a natural product[9] having antidiabetic activity.

2. Results and discussion

2.1. Synthesis of pseudosaccharides 2–4 from 1

We initially treated the glucose-derived precursor **1**[10] with sodium hydride in tetrahydrofuran, hoping to

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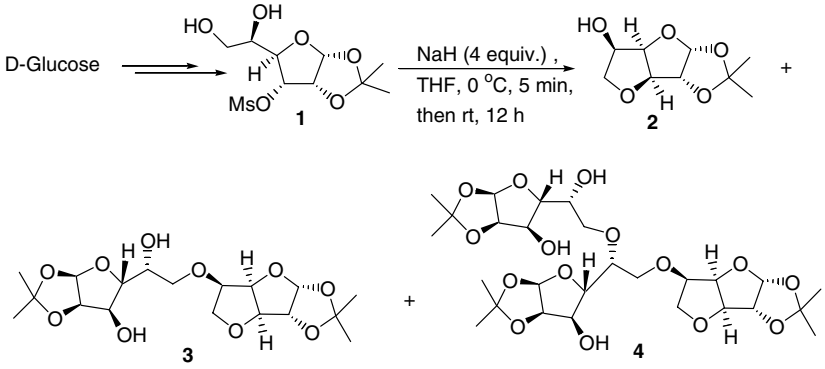
produce the fused bis-tetrahydrofuran (the skeleton present in furanodictines[11]) analogue **2**.[12] Interestingly, the reaction mixture yielded (Scheme 1), in addition to **2**, the hitherto unknown pseudodisaccharide **3** and pseudotrisaccharide **4** (both 5,6-ether linked). On the other hand, treatment of **1** with sodium ethoxide in ethanol furnished **2** as the sole product (in 76% yield). Previous workers[6–8] used the reaction of an appropriate sugar alkoxide with a suitable sugar–iodide/–tosylate/–triflate to obtain 5,4- and 6,6′-ether linked disaccharides. The present transformation, however, differs in having an internal functional group migration, which precedes the coupling step.

Formation of products **2**–**4** was found to depend on the concentration of the starting material **1** (Table 1). As the concentration of **1** increases, the yields of **2** and **3** decrease with simultaneous increase in the yield of **4**.

The occurrence of these products suggested that the nucleophilic attack of the C-6 hydroxyl group in **1** occurred in two different ways. Intramolecular attack on C-3 (bearing mesyl group) resulted in the formation of the cyclic product **2**. On the other hand, an intramolecular transfer of the mesyl functionality from C-3 to C-6 through the nucleophilic attack of the C-6 hydroxyl group (or stepwise migration of the mesyl group via C-5) produced the non-isolable intermediate **5a**, which could also lead to epoxide **5b** (Fig. 1). Either of these intermediates upon reaction with the hydroxyl group of **2** could have generated **3**, which subsequently yielded **4** after reaction with another molecule of **5a** or **5b**. The possible formation of the C-5 epimer of **5b** through the attack of C-6 OH on the C-5 mesylate could be ruled out from the structure of product **3**.

The presence of signals for four methyl groups and two anomeric centers together with other expected signals in the ^{1}H and ^{13}C NMR, and the location of a peak at m/z 427 $(MNa)^{+}$ in the mass spectrum of **3** proved helpful for deducing the gross structure. Finally, the structure and relative stereochemistry were established from an X-ray analysis (Fig. 2), which showed that there are two molecules in the asymmetric unit with equivalent geometries. With **4**, the location of the molecular ion peak m/z: 629 $(M+Na)^{+}$ in the mass spectrum coupled with the preliminary analysis of the NMR spectra suggested the coupling of another molecule of monoacetonide glucose. Almost all the NMR signals of **3** were repeated, pointing to the presence of this moiety in **4**. Due to the close chemical shifts of virtually all proton and carbon signals assigned to the two monocyclic units, an unambiguous structure assignment was difficult. However, starting from the anomeric proton signals of the two furanoside units, analysis of the ^{1}H–^{1}H COSY spectrum revealed that the two H-3 signals resonated at 4.14 ppm. These were coupled to the two OH doublet signals located at δ 3.15 and δ 3.27, ruling out an ether linkage involving either of the hydroxyl groups. This



Scheme 1. One-pot generation of pseudosaccharides **2**, **3**, and **4** from **1**.

Table 1. Concentration dependent formation of **2**, **3**, and **4** from **1**

1 $\xrightarrow[\text{THF, 0 °C, 5 min, then rt,12 h}]{\text{4 molar equiv. NaH,}}$ **2** + **3** + **4**

1 g[a] (mmol)	THF (mL)	Concn (mM)	**2** g[a] (%)[b]	**3** g[a] (%)[b]	**4** g[a] (%)[b]
0.25 (0.84)	250	3.36	0.068 (40)	0.108 (32)	—
2.0 (6.71)	75	89.5	0.474 (35)	0.758 (28)	0.122 (3)
5.0 (16.8)	50	336.0	1.080 (32)	1.550 (23)	0.506 (5)

[a] Amount taken/isolated.
[b] Isolated yield.