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Glycosidic bond hydrolysis in septanosides: a comparison of mono-, di-, and 2-chloro-2-deoxy-septanosides

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ABSTRACT

A kinetic study of the hydrolytic stabilities of mono-, di-, and 2-chloro-2-deoxy septanosides, under acid-catalysis, is reported herein. A comparison of mono- and diseptanosides, shows that the glycosidic bond in the disaccharide is more stable than the monosaccharide. Further the glycosidic bond at the reducing end hydrolyzes almost twice as faster than that of the non-reducing end of the disaccharide. 2-Chloro-2-deoxy septanoside is found to be the most stable and its glycosidic bond hydrolysis occurs at elevated temperatures only. The orientation of the *exo*-cyclic hydroxymethyl group and the inductive effect are suggested to play a role in the rates of hydrolysis.

1. Introduction

Hydrolytic stabilities of glycosidic bonds play a major role in manifold chemical and biological functions of sugars.[1,2] Differences in the rates of hydrolysis of anomeric and epimeric furanosides and pyranosides were studied in detail.[3–9] Factors, such as, steric interactions, field, and electronic effects control the rate of hydrolysis.[10–12] On the other hand, the hydrolytic stabilities of the glycosidic bond in seven-membered ring sugars, namely, septanoside are not known in great detail currently. Peczuh and co-workers showed that the rate of hydrolysis of methyl-α-septanoside was much faster than pyranoside analogues, under an acid-catalyzed condition,[13,14] as a result of structural flexibility of the seven-membered ring systems. It was observed that an α-anomer hydrolyzed 2 times faster than the β-anomer, which contradicted the results in case of α/β-pyranosides. The hydrolytic stabilities of seven carbon analogues of pyranosides, namely, 4-*C*-hydroxymethyl-linked mono- and disaccharides were studied by us previously.[15] An outcome of the study was that the glycosidic bond of such *hepto*-pyranosides was more stable at the reducing end than the non-reducing end of the disaccharide, in comparison to the corresponding pyranoside disaccharides. In continuation of an interest on hydrolytic stabilities, we undertook acid-catalyzed hydrolysis of the glycosidic bond in septanosides. The study herein focuses on three closely-related septanosides, namely, *n*-pentyl septanoside, α-1,7-linked diseptanoside, and 2-chloro-2-deoxy septanoside.

2. Results and discussion

2.1. Synthesis of *n*-pentyl α-D-*glycero*-D-*galacto*-septanoside

Synthesis of *n*-pentyl septanoside was initiated from a hydroxyl glycal ether, or an oxyglycal.[16,17] A cyclopropanation of oxyglycal **I** was performed using in situ generated dichlorocarbene. The carbene addition afforded **2**, as a single diastereomer, in a good yield. Reaction of *n*-pentanol with **1**, using K_2CO_3 and 18-C-6 (cat.) in PhMe, for 48 h afforded chloro-oxepine **2**, in 82% yield (Scheme 1). In the ^{1}H NMR spectrum of **2**, the anomeric proton resonated at 5.29 as a singlet, whereas in the ^{13}C NMR spectrum, the anomeric carbon resonated at 99.4 ppm, and signals at 122.7 and 152.6 ppm confirmed C-2 and C-3 of the chloro-vinyl ether moiety, respectively. Mass spectral analysis further confirmed the constitution of **2**. Chloro-oxepine **2** was subjected to $RuCl_3$–$NaIO_4$-mediated oxidation to afford 2,3-diketo derivative **3**, in 70% yield. Appearance of a signal at 204.8 ppm in the ^{13}C NMR spectrum confirmed the presence of the ketone moiety in **3**, with concomitant absence of peaks at 122.7 and 152.6 ppm confirming to C-2 and C-3 of the chloro-vinyl moiety oxidized to a ketone moiety in **3**. Reduction of **3**, using $NaBH_4$/MeOH led to diol **4**, in 89% yield. The reduction was diastereoselective and only a single diastereomer was isolated. In the ^{1}H NMR spectrum of **4**, the anomeric proton resonated at 4.98 ppm as a doublet with $J_{1,2}$ = 4.4 Hz, indicating a *cis*-relationship between H-1

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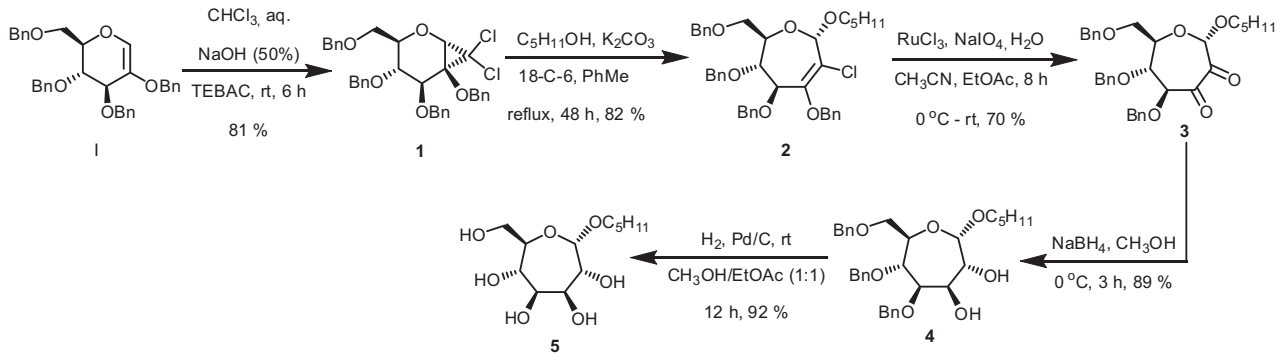


Scheme 1.

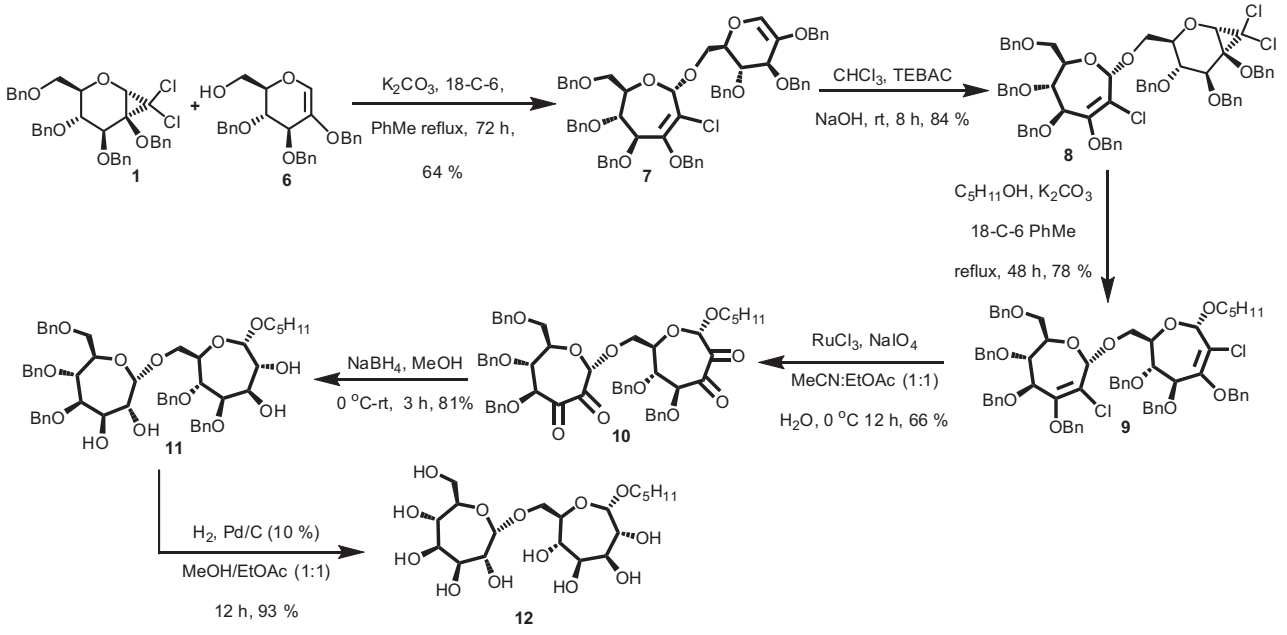
and H-2, whereas, in the ^{13}C NMR spectrum, the presence of a signal at 97.9 ppm corresponded to the anomeric carbon. The protecting groups in **4** were deprotected (Pd/C, H_2) to secure free hydroxyl groups containing D-*glycero*-D-*galacto*-septanoside derivative **5**, in 92% yield. In the ^1H NMR spectrum of **5**, a doublet at 4.91 ppm ($J_{1,2}$ = 3.2 Hz) corresponded to the anomeric proton, whereas, H-3 resonated at 4.00 ppm ($J_{2,3}$ = 6.8 Hz, $J_{3,4}$= 3.2 Hz), indicating a *cis*-relationship between H-3 and H-4, as well as, a *trans*-relationship between H-2 and H-3. The signal at 96.7 ppm in the ^{13}C NMR spectrum corresponded to the anomeric carbon. Mass spectrum further confirmed the constitution of **5**.

2.2. Synthesis of *n*-pentyl α-1,7-linked diseptanoside

Following synthesis of monosaccharide **5**, effort was undertaken to synthesize diseptanoside. The synthesis was initiated using 6-hydroxy oxyglycal **6** in the ring-opening reaction of **1**, in the presence of K_2CO_3 and 18-C-6 (cat.), which afforded **7**, in 64% yield (Scheme 2). In the ^1H NMR spectrum of **7**, the anomeric proton at the non-reducing end appeared as a singlet at 5.36 ppm, whereas H-1 of the reducing end resonated as a singlet at 6.27 ppm. In the ^{13}C NMR spectrum, the anomeric carbon, C-2, and C-3 nuclei of the non-reducing end resonated at 99.6, 122.7, and 152.6 ppm, respectively. The C-2 of the reducing end moiety resonated at 136.8 ppm. Mass spectrum further confirmed the composition of **7**.

Cyclopropanation of **7**, through in situ generated dichlorocarbene ($CHCl_3$, NaOH, and triethyl benzyl ammonium chloride (cat.)) afforded **8**, in 84% yield (Scheme 2). The chloro-vinyl group present in the non-reducing end of disaccharide **7** was not affected in this reaction. In the ^1H NMR spectrum of **8**, the anomeric proton of the chloro-oxepine ring appeared as a singlet at 5.44 ppm, whereas the absence of a proton signal at 6.27 ppm confirmed cyclopropanation at the reducing end of the sugar moiety. In the ^{13}C NMR spectrum of **8**, C-1 and C-2 of the non-reducing end resonated at 100.1 and 122.2 ppm, respectively. The presence of a resonance at 153.2 ppm indicated that the double bond in the oxepine ring was not affected during the reaction. Mass spectral analysis further confirmed the composition of **8**.

The *gem*-dichloro-1,2-cyclopropane **8** reacted with *n*-pentanol, in the presence of K_2CO_3 and 18-C-6 (cat.) in PhMe, to afford 1,7-linked dichloro-oxepine **9**, in 78% yield. In ^1H NMR spectrum, the presence of two distinct singlets at 5.27 and 5.46 ppm indicated two anomeric protons of two chloro-oxepine rings of **9**. HSQC NMR analysis confirmed that resonance at 5.46 ppm corresponded to H-1 of the non-reducing end, whereas 5.27 ppm indicated H-1 of the reducing end. The presence of signals at 100.3 and 99.7 ppm corresponded to anomeric nuclei of C-1′ and C-1, respectively,



Scheme 2.