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AN UNUSUAL RING CONTRACTION OF SILYL GLUCOPYRANOSIDES TO SILYL GLUCOFURANOSIDES

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Abstract. Attempts to esterify the C-4 hydroxyl group of *tert*-butyldimethylsilyl 2-azido-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranoside led to an unexpected ring contraction affording the 5-*O*-acyl-α-D-furanoside derivative. Acylation at low temperature in the presence of a catalytic amount of Lewis acid afforded the desired pyranoside structure.

Key words: rearrangement, ring contraction, pyranoside, furanoside, acylation

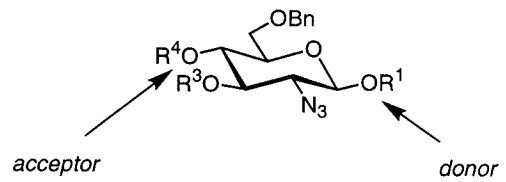
INTRODUCTION

Both 2,6-disulfo- and 2,3,6-trisulfo-2-amino-2-deoxy-D-glucopyranose (D-GlcNS6S and D-GlcNS3S6S) are constituents of heparin, a prominent member of the glycosaminoglycan family. The α-D-GlcNS6S and α-D-GlcNS3S6S residues in heparin are 1→4 glycosidically linked to uronic acid residues, including, α-L-idopyranuronic acid (α-L-IdoAp) and β-D-glucopyranuronic acid (β-D-GlcAp), and their 2-sulfo derivatives.[1] Heparin regulates a number of important biological phenomena by interacting with a diverse group of proteins.[2] For example, heparin inhibits the serine protease thrombin by binding to serine protease inhibitors antithrombin III and heparin cofactor II, causing an inhibition of blood coagulation.[3]

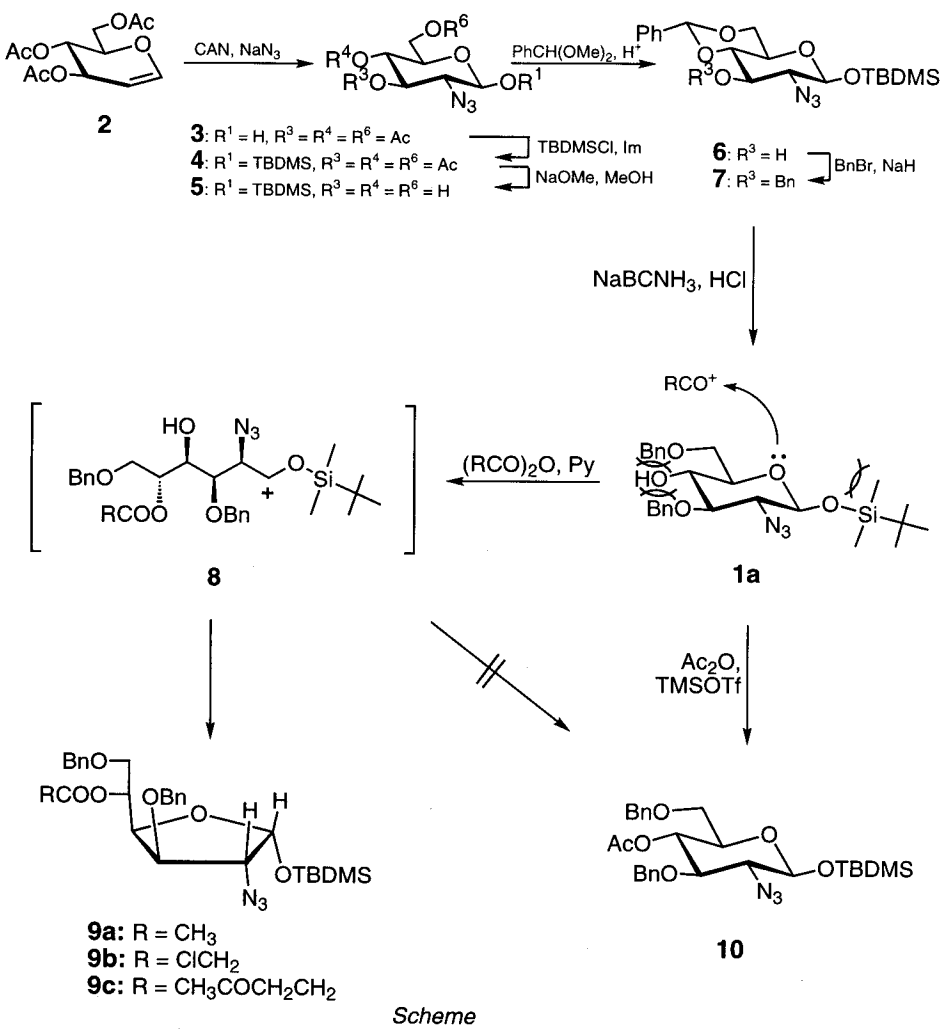
Oligosaccharide sequences, corresponding to protein binding sites, within this polydisperse glycosaminoglycan, are the targets of our synthetic program. Recently, we reported our approach for the synthesis of a differentially protected, potentially universal L-IdoAp-glycosyl-donor and/or -acceptor.[4] We have devised a comparable strategy for the synthesis of its partner D-GlcN-glycosyl-acceptor **1a** and/or -donor **1b** (see *Scheme*).

RESULTS AND DISCUSSION

Azidonitration[5] of 3,4,6-tri-*O*-acetyl-D-glucal **2** afforded **3**. Next the anomeric hydroxyl group was protected as its *tert*-butyldimethylsilyl (TBDMS) ether **4** and the acetyl groups removed under Zemplen conditions providing **5**. Glycosidic compounds carrying an unprotected hydroxyl group at the 4-position are usually prepared by 4,6-*O*-benzylidenation **6**, protection at the 3-position and then regioselective ring-opening of the corresponding benzylidene derivative **7** using sodium cyanoborohydride in the presence of hydrogen chloride.[6] Following this reaction sequence it should be easy to elaborate an acceptor **1a** having an unprotected 4-hydroxyl group for the ensuing glycosidation reactions with uronic acid donors.



1a: R^1 = TBDMS, R^3 = Bn or Bz, R^4 = H (*acceptor*)
1b: R^1 = trichloroacetimidyl, R^3 = Bn or Bz, R^4 = acyl (*donor*)



Scheme

Attempts to prepare the precursor of the glycosyl donor **1b** (R^1= trichloroacetimidate) through the esterification of the C-4 hydroxyl group surprisingly led to an unexpected ring contraction (**1a** to **9**).[7] The resulting α-furanoside derivatives **9a-c** were obtained in excellent yields in pyridine when using either acetic, chloroacetic or levulinic anhydrides as acylating agents. None of the desired C-4-esterified pyranoside products were detected. ^{1}H-NMR data clearly indicated the presence of a furanoside ring and its anomeric configuration. This assignment was based on the downfield shift of the *ddd* observed for the H-5 signal at a δ of > 5.0 ppm. The small (< 7 Hz), $J_{2,3}$- and $J_{3,4}$-values are inconsistent with a pyranoside structure in a $^4C_1$-conformation. The large $J_{1,2}$ value of > 7.2 Hz demonstrates the nearly *synperiplanar* relationship of the α-furanoside.[8]

This unusual ring contraction is probably due to the specific surroundings of both the pyranoside and the glycosidic *O*-atoms in **1a**. A silicon atom with an empty d-orbital is attached to the glycosidic *O*-atom engaging its lone electron pairs. Thus, the glycosidic *O*-atom has insufficient nucleophilicity to attract an external electrophile, such as acyl cation. The pyranoside oxygen, however, should have no trouble donating a lone electron pair for interaction with an electron deficient species. Furthermore, in **1a** the steric hindrance at C-4-hydroxyl group and the presence of a bulky TBDMS-group may serve to increase this regioselection. The resulting endocyclic cleavage affords a resonance stabilized silyl oxocarbenium cation **8**,[9] which in turn collapses in a presence of a 4-hydroxyl group to the furanoside product **9**. Recently, similar ring contractions have been observed by others during the glycosidation of a C-4-acceptors, in flexible 3-deoxypyranosides.[10]

Acylation of **1a** with acyl anhydride in the presence of catalytic amount TMSOTf at -40°C affords the desired 4-*O*-acyl-β-D-pyranoside **10** in moderate yield.

ACKNOWLEDGMENTS

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7. General procedure for the acylation of **5**.
   To a pyridine (10 mL) solution of **1a** (1 mmol) in an ice-water bath, acylating agent (1.6 mmol), was added and the mixture was stirred for 16-48 hr at room temperature. The solution was evaporated and the residue chromatographed (hexanes/ethyl acetate) to give **9** (80-95% yield).

8. Selected ^{1}H NMR data (500 MHz, $CDCl_3$, δ ppm, *J* Hz were determined by decoupling experiments).
1a: 0.14 (s, 6H, 2 Si*Me*), 0.94 (s, 9H, t-*Bu*), 2.61 (d, 1H, *J* =2.1, O*H*), 3.23 (dd, 1H, $J_{2,3}$ = 10, $J_{3,4}$= 9.5, H-3), 3.33 (dd, 1H, $J_{1,2}$ = 7.6, $J_{2,3}$ = 10, H-2), 3.40-3.46 (m, 1H, H-5), 3.65 (ddd, 1H, $J_{3,4}$=$J_{4,5}$ = 9.5, H-4), 3.70-3.77 (m, 2H, 2xH-6), 4.70 (d, 1H, H-1), 4.60, 4.57 (2d, 2H, PhCH_2), 4.93, 4.78 (2d, 2H, PhCH_2), 7.22-7.40 (m, 10H, arom.*H*).

9a: 0.18 (s, 6H, 2 Si*Me*), 0.95 (s, 9H, t-*Bu*), 2.00 (s, 3H, CH_3CO), 3.34-3.40 (m, 2H, H-2, H-4), 3.42-3.56 (m, 3H, H-3, 2xH-6), 4.48, 4.52 (2d, 2H, PhCH_2), 4.55 (d, 1H, $J_{1,2}$=7.2, H-1), 4.60, 4.80 (2d, 2H, PhCH_2), 5.03 (m, 1H, H-5), 7.20-7.40 (m, 10H, arom.*H*).

9b: 0.15 (s, 6H, 2 Si*Me*), 0.92 (s, 9H, t-*Bu*), 3.35-3.43 (m, 2H, H-2, H-6b), 3.51-3.55 (m, 3H, H-3, H-4, H-6a), 3.57, 3.62 (2d, 2H, Cl CH_2 CO), 4.47 (s, 2H, PhCH_2), 4.58 (d, 1H, $J_{1,2}$=7.3, H-1), 4.60, 4.84 (2d, 2H, PhCH_2), 5.04 (ddd, 1H, $J_{5,6a}$=3.3, $J_{4,5}$=5.8, $J_{5,6b}$=7.3, H-5), 7.22-7.40 (m, 10H, arom.*H*).

9c: 0.18 (s, 6H, 2 Si*Me*), 0.92 (S, 9H, t-*Bu*), 2.12 (s, 3H, *Me* of Lev), 2.28-2.42 (m, 2H, CH_2 of Lev), 2.52-2.65 (m, 2H, CH_2 of Lev), 3.34-3.40 (m, 2H, H-2, H-6b), 3.48-3.56 (m, 3H, H-3, H-4, H-6a), 4.48, 4.52 (2d, 2H, PhCH_2), 4.54 (d, 1H, $J_{1,2}$=7.4, H-1), 4.80 (d, 2H, PhCH_2), 5.00 (m, 1H, H-5), 7.20-7.40 (m, 10H, arom.*H*).

10: 0.20 (s, 6H, 2Si*Me*), 0.92 (s, 9H, t-*Bu*), 1.98 (s, 3H, CH_3 CO), 3.40 (dd, 1H, $J_{1,2}$=7.6, $J_{2,3}$=9.2, H-2), 3.44 (dd, 1H, $J_{2,3}$=9.2, H-3), 3.50 (dd, 1H, $J_{5,6b}$=3.4, $J_{6a,6b}$=11, H-6b), 3.52-3.60 (m, 2H, H-5, H-6a), 4.38, 4.42 (2d, 2H, PhCH_2), 4.56 (d, 1H, H-1), 4.59-4.73 (2d, 2H, PhCH_2), 5.24 (dd, 1H, $J_{4,5}$=9.2, H-4), 7.22-7.40 (m, 10H, arom.*H*).

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