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An improved synthesis of 3,6-anhydro-D-glucal and a study of its unusual chemical reactivity

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ABSTRACT

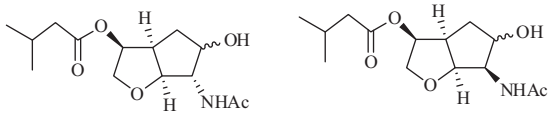
6-*O*-Tosyl-D-glucal **1** upon treatment with excess $LiAlH_4$ unexpectedly gave 3,6-anhydro-D-glucal **2** as a major product in good yield. A crystal structure was obtained. Reaction of the anhydride **2** with *N*-iodosuccinimide (NIS) in excess methanol resulted in the formation of diastereomeric 2-deoxy-2-iodoglycosides. Addition of ceric (IV) ammonium nitrate and thiophenol to a solution of **2** in acetonitrile gave a mixture of 2-deoxy and 2,3-unsaturated thioglycosides. Reaction of 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose with the anhydro sugar **2** in the presence of *N*-iodosuccinimide did not give the expected iodoglycoside mixture, but instead gave an unusual 1,4:3,6-dianhydride **7** as the major product.

1. Introduction

Anhydro sugars have unique properties that allow them to serve both as protecting groups and as reactive materials for the formation of C—C and C—X bonds. Their advantage of easy removal has led to the development of numerous methods for their preparation and their extensive utilization in carbohydrate chemistry.[1–5] These derivatives have been used for the preparation of modified carbohydrates[6] (including C-glycosides),[7] nucleosides,[8] heterocycles,[9] and complex enantiomerically-pure products in which the chirality of the parent sugar is transferred to the target.[6]

Anhydro sugars, as their name implies, are formed by the removal of one or more molecules of water from the corresponding parent sugar. The usual procedure for their synthesis is by activation of one of the hydroxyl groups of the diol or polyol into a leaving group (such as tosylate, triflate, halogen, etc.) while a second hydroxyl group acts as a nucleophile in basic medium. This results in an intramolecular S_N2 closure to form the anhydro ring.[2,3] Milder conditions, such as activation of one of the hydroxyl groups according either to Mitsunobu[7] or Castro[8] protocols, are also used for the preparation of these molecules.

The anhydro sugars are conveniently classified, based on the size of the anhydro ring formed intramolecularly, into sugar oxiranes, oxetanes, tetrahydrofurans and tetrahydropyrans. The stability of the anhydro sugar is a reflection of the size of the cyclic ether formed, with the larger tetrahydrofurans and tetrahydropyrans being more stable.



Furanodictine A **Furanodictine B**

Figure 1. Examples of 3,6-anhydrofuranoses.

The most widely known compounds from the tetrahydrofuran class of anhydro sugars are 3,6-anhydrofuranoses.[6] Furanodictine A and B (Fig. 1) are good examples of this class that show neuronal differentiation activity.[7] 3,6-Anhydro-D- and L-galactoses and their partially methylated derivatives are typical constituents of polysaccharides of red algae.[8] 3,6-Anhydro sugars forming bicyclic nucleosides have shown antiviral activity.[9] The puckering in the bicyclic carbohydrate moiety is believed to cause the molecule to be locked in the proper conformation for biological activity to be observed.[10,11]

Among tetrahydropyran anhydro sugar derivatives, the most common are 3,6-anhydro pyranoses. Methyl-3,6-anhydro-β-D-glucoside has been synthesized by the treatment of methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside with either sodium methoxide or barium hydroxide (Fig. 2). 3,6-Anhydro-D-galactose and 3,6-anhydro-D-mannose were prepared in a similar fashion.[12]

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3,6-Anhydro-D-glucal **2** was earlier synthesized by Tucker et al. from 3,4-di-*O*-acetyl-6-*O*-tosyl-D-glucal using deacidite FF IP (OH–) resin in 66% yield.[13] This paper describes the unexpected synthesis of 3,6-anhydro-D-glucal **2** from 6-*O*-tosyl-D-glucal **1** using excess $LiAlH_4$ in THF as the reagent. With this combination of reagents, an 82% yield of anhydro glycal was realized. Interestingly, the 3,6-anhydro-D-glucal **2** was previously reported as a byproduct (40% yield) from the same reactants when an equimolar amount of lithium aluminum hydride was used, though the structure of this molecule was not fully characterized.[16] The unusual chemical reactivity of the resulting anhydro glycal **2** was also investigated.

There are only a handful of reports detailing the synthesis of dianhydride sugars. They have most often been used in the construction of polymers. The use of smaller anhydro rings, such as oxiranes, gives the dianhydrides enhanced reactivity necessary for the polymerization.[14] Herein we also describe the synthesis of an unusual 1,4:3,6-dianhydrosugar **7** via *N*-iodosuccinimide (NIS) addition to the 3,6-anhydro-D-glucal **2**.

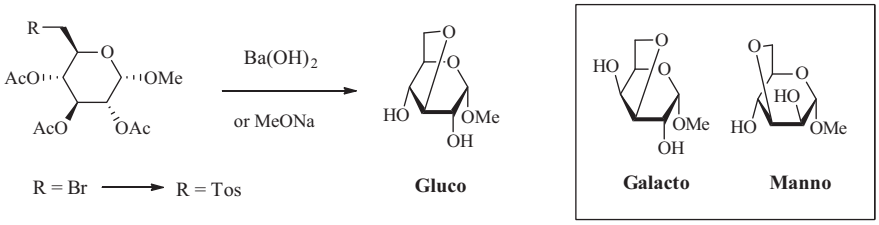
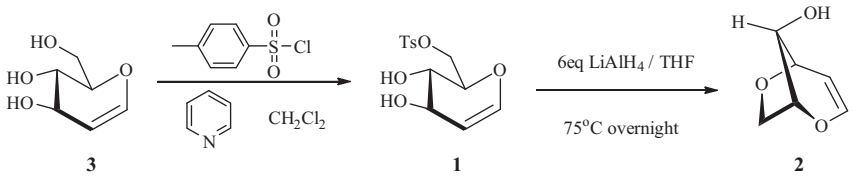


Figure 2. Preparation of 3,6-anhydropyranoses.



Scheme 1. Synthesis of 3,6-anhydro-D-glucal.

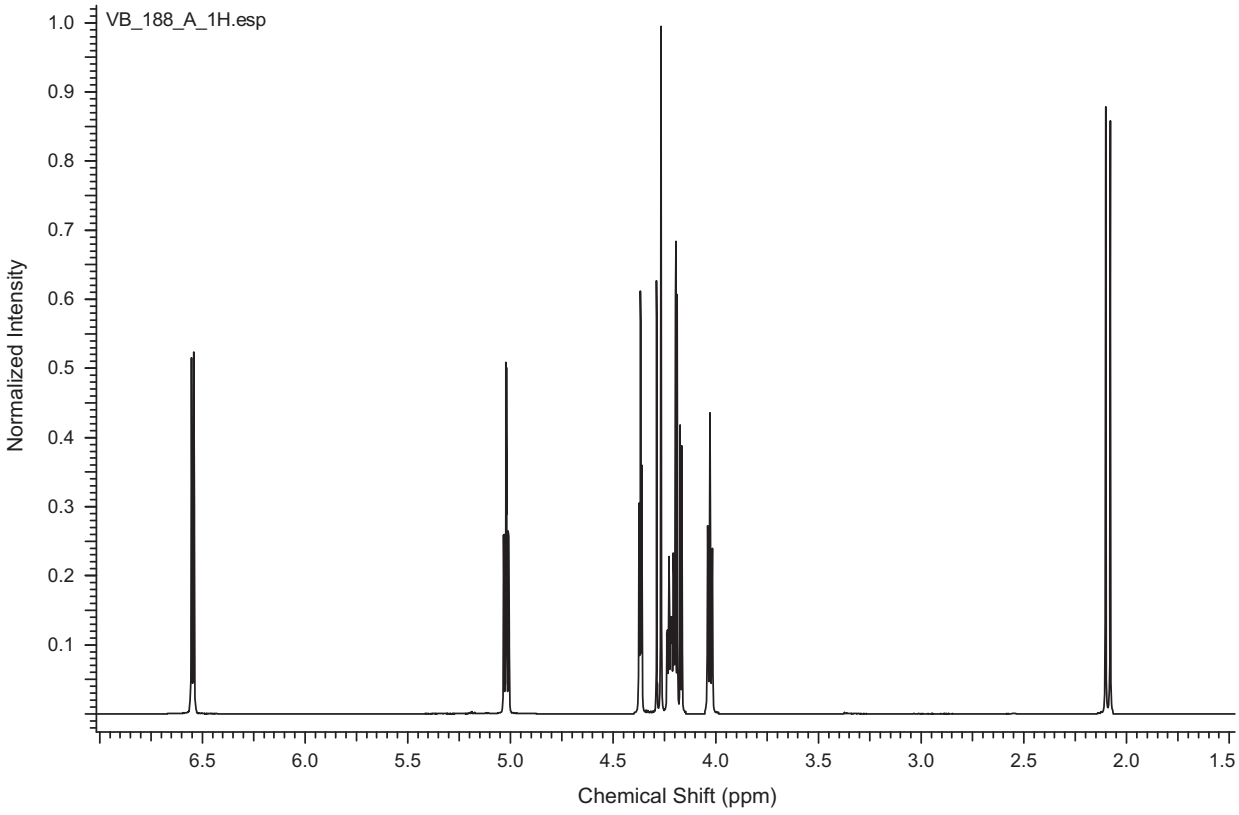


Figure 3. ^1H NMR (500 MHz, $CDCl_3$) of compound **2**.

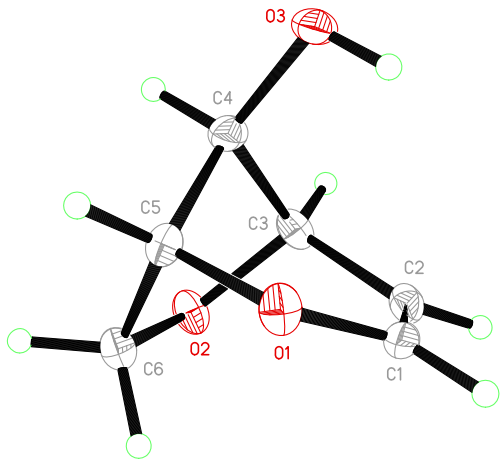


Figure 4. ORTEP representation of compound **2**.

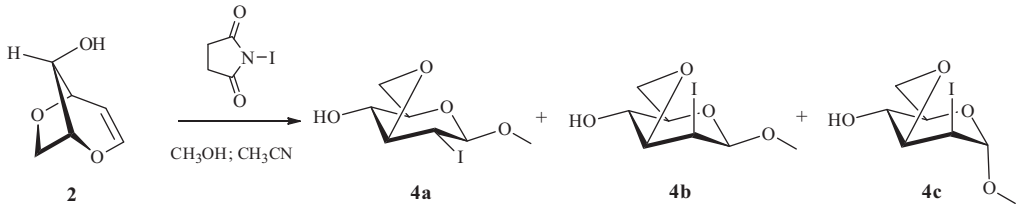
2. Results and discussion

3,4,6-Tri-*O*-acetyl-D-glucal was deacetylated using Zemplen conditions to give D-glucal **3** in 98% yield.[15] The resulting D-glucal **3** was selectively tosylated at the primary hydroxyl using *p*-toluenesulfonyl chloride in a mixture of pyridine and dichloromethane.[5] The 6-*O*-tosylated-D-glucal **1** was obtained in 56% isolated yield. Treatment of **1** with three equivalents of $LiAlH_4$ in THF did not produce the anticipated 6-deoxy-D-glycal, as previously reported, but instead gave the 3,6-anhydro sugar **2** in 82% yield (Scheme 1).[16]

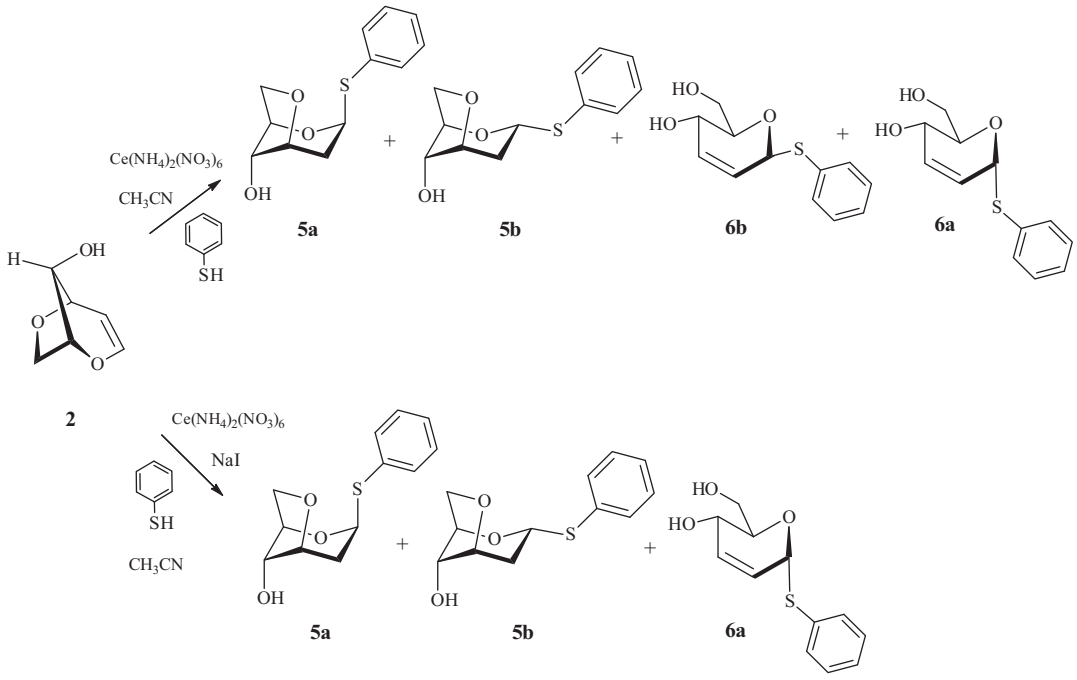
Structural assignments for **2** were based on 1D and 2D ^1H and ^{13}C NMR experiments (Fig. 3). The proposed bridged structure was supported by the observation of long range coupling between the vinylic proton at C2 and the bridgehead proton at C4 (W-coupling) in the proton NMR. In the ^1H–^1H-COSY (Supporting materials), coupling between H4 and H6 and H6′ was also seen, while in the ^1H NMR the H6 and H6′ peaks only appeared as broad doublets of doublets. X-ray quality crystals were obtained and the structure of the molecule was established unambiguously (Fig. 4).

Compound **2** was subjected to a series of different glycal addition reactions. Treatment of compound **2** with NIS in the presence of methanol led to the formation of a mixture of β-*gluco*-, β-*manno*-, and α-*manno*-2-deoxy-2-iodo-*O*-methylglycosides (**4a**, **4b,** and **4c**) in a ratio of 5.2:1.5:1 with an overall yield of 93% (Scheme 2).[17] None of the α-gluco diastereomer was detected in the mixture.

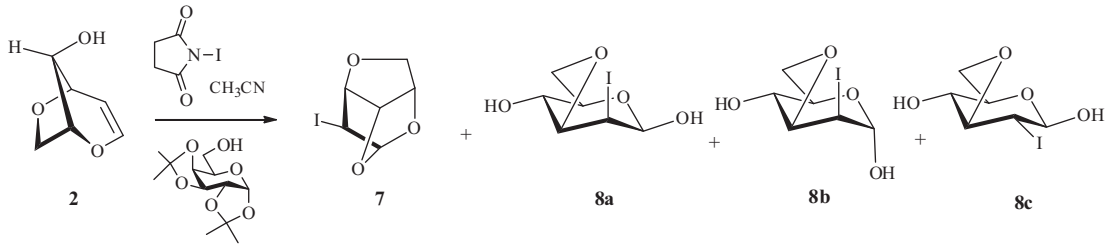
Treatment of **2** with thiophenol in the presence of a catalytic amount of ceric (IV) ammonium nitrate (CAN) gave a mixture of α- and β-2-deoxy sugars (**5a** and **5b**) in a ratio 1.85:1 with a 65% yield. Also formed in the reaction was an α-, β-mixture of the Ferrier rearranged adducts (**6a** and **6b**) with a 35% yield in a ratio of 2.5:1, formed upon the breakdown of the anhydride ring (Scheme 3).[18]



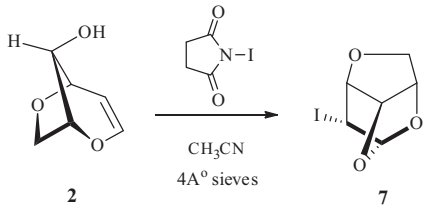
Scheme 2. Synthesis of 2-deoxy-2-iodo-*O*-methylglycosides.



Scheme 3. Addition of thiophenol to **2** in the presence and absence of CAN.



Scheme 4. Synthesis of 1,4:3,6-dianhydride **7** from **2** in the presence of DIPG.



Scheme 5. Synthesis of 1,4:3,6-dianhydride **7** from **2** in the absence of DIPG.

When the anhydro sugar **2** was reacted with thiophenol and a catalytic amount of ceric (IV) ammonium nitrate in the presence of sodium iodide, a reagent known to enhance α-selectivity, a mixture of α- and β-2-deoxy sugars (**5a** and **5b**) was again obtained in this reaction (34%), but only the α-adduct **6b** from the Ferrier rearrangement was isolated (65%) (Scheme 3).[19]

Because of the success of the NIS addition with methanol, attempts were made to synthesize disaccharides from the anhydro sugar donor. Compound **2** was treated with an equimolar amount of 1,2:3,4-di-*O*-isopropylidine-D-galactopyranose (DIPG) in the presence of *N*-iodosuccinimide to give 2-deoxy-2-iodo-1,4:3,6-dianhydride **7** as the major product (48%).[8] An inseparable mixture of 2-deoxy-2-iodo sugars (**8a**, **8b,** and **8c**) was also formed in low yield, and residual starting materials were isolated (~20%) (Scheme 4). When the same reaction was repeated in the absence of 1,2:3,4-di-*O*-isopropylidine-D-galactopyranose and in the presence of 4 Å molecular sieves, **7** was obtained in a much higher yield of 76% (Scheme 5).

3. Conclusion

In summary, good yields of 3,6-anhydro-D-glucal **2** have been obtained from 6-*O*-tosyl-D-glucal **1** via reaction with excess lithium aluminum hydride. The resulting anhydro glycal was studied under a variety of reaction conditions. Iodoglycosylation of **2** with methanol gave good yields of a mixture of 2-deoxy-2-iodomethylglycosides **4a**–**c**, but attempts to use the primary hydroxyl sugar donor 1,2:3,4-diisopropylidine-D-galactopyranose gave the dianhydro sugar **7** and iodohydrins **8a**–**c**. These observed products may result due to the steric hindrance present in the anhydroglycal reactant or in the transition state for the reaction. Alternatively, unfavorable dipole–dipole interactions in the transition state for the sugar nucleophile approaching the glycal double bond may be responsible for the observed products. β-Anomers were favored over α-anomers by a ratio of ~4:1. Furthermore, the formation of **7** is favored because the intramolecular attack by the bridgehead hydroxyl group is anticipated to be faster entropically than is the attack by the solvated nucleophiles. The small methanol nucleophile and adventitious water can more easily access the double bond and mixtures of product resulted from their attack. In those cases where the DIPG was excluded and freshly powdered and activated 4 Å molecular sieves were added, only the dianhydro sugar **7** was obtained. Further reactions with **2** are ongoing.

4. Experimental section

4.1. General methods

Melting points (mp) were recorded on a Mel-Temp melting point apparatus (Laboratory Devices, Inc., USA) and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Inova (500 MHz) spectrometer. NMR samples were dissolved in $CDCl_3$, and chemical shifts were reported in ppm relative to the residual non-deuterated solvent ($CHCl_3$ as δ = 7.26 ppm). ^{1}H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublet of doublets; m = multiplet), coupling constant, and assignment. ^{13}C NMR spectra were recorded on a Varian Inova (125 MHz) spectrometer. The samples were dissolved in $CDCl_3$, and chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ as δ = 77.0 ppm). ^{1}H and ^{13}C NMR spectra were measured at room temperature and the chemical shifts are reported in parts per million, unless otherwise noted. ^{1}H NMR assignments were done using gCOSY and ^{13}C NMR assignments were done using gHMQC. Elemental analysis was performed at Robertson Microlit Laboratories Inc., Ledgewood, NJ. High resolution and low resolution mass spectra (HRMS and LRMS) were obtained at the Mass Spectrometry Lab, University of Illinois, Champaign-Urbana, IL and are reported in *m*/*z* (electrospray ionization). X-ray crystallographic data for compound **2** was deposited at the Cambridge Crystallographic Data Center (CCDC); deposition number CCDC 988697.[20] Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated aluminum sheet 60 F_{254} (Analtech, # 157017). Silica gel (particle size 40–63 μm, 230–400 mesh Silicycle Siliflash P60) was used for flash column chromatography. Preparative thin-layer chromatographic separations were carried out on 2000 μm silica gel coated glass plate 60 F_{254} (Analtech). Rotary evaporation was performed using a Buchi R-114 rotary evaporator. Unless otherwise noted, non-aqueous reactions were carried out in oven-dried (125 °C) glassware under nitrogen. Dry CH_3CN, THF, and methanol were purchased from Pharmco-Aaper products, Inc. All other commercially available reagents were used as received.

4.2. 6-*O*-*p*-Toluenesulfonyl-D-*arabino*-hex-1-enitol (1)

To a solution of D-glucal (7.6 g, 52.5 mmol) in anhydrous pyridine was added dropwise a solution of *p*-toluenesulfonyl chloride (15.02 g, 78.8 mmol) in anhydrous CH_2Cl_2 at 0 °C upon vigorous stirring. The reaction was terminated after 3 h by the addition of water, followed by washing with saturated $CuSO_4$ (3 × 30 mL), water (5 × 30 mL), and brine (1 × 30 mL). The organic extracts were dried under anhydrous $MgSO_4$ and concentrated in vacuo to yield crude **1**. Although the compound was synthesized earlier,[13]

no spectroscopic data was reported. The product was purified by flash chromatography using 3%, 4%, and 5% CH_3OH in $CHCl_3$ mixtures to give 8.18 g (56% yield) of **1** as a colorless oily mass which crystallized upon freezing: R_f (1:20 $CH_3OH/CHCl_3$): 0.46; mp 50–51 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, 2H, J = 6.3 Hz, Ar), 7.35 (d, 2H, J = 7.9 Hz, Ar), 6.24 (d, 1H, $J_{1,2}$ = 6.1, $J_{1,3}$ = 1.8 Hz, H-1), 4.74 (dd, 1H, $J_{2,1}$ = 6.3, $J_{2,3}$ = 2.2 Hz, H-2), 4.47 (dd, 1H, $J_{6,6'}$ = 11.25, $J_{6,5}$ = 4 Hz, H-6), 4.28 (dd, 1H, $J_{6,6'}$ = 11.45, $J_{6',5}$ = 2.5 Hz, H-6′), 4.26 (d, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 3.91 (ddd, 1H, $J_{5,4}$ = 9.75, $J_{5,6}$ = 3.9, $J_{5,6'}$ = 2 Hz, H-5), 3.76 (dd, 1H, $J_{4,3}$ = 8.3, $J_{4,5}$ =8.3 Hz, H-4), 3.09 (s, 1H, 4-OH), 2.45 (s, 3H, $PhCH_3$), 2.23 (s, 1H, 3-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.19 (CH, Ar), 143.99 (C-1), 132.61, 129.93, 128.02 (CH, Ar), 103.04 (C-2), 75.7 (C-5), 69.57 (C-3), 69.35 (C-4), 67.92 (C-6), 21.66 ($PhCH_3$).

4.3. 3,6-Anhydro-2-deoxy-D-*arabino*-hex-1-enitol (2)

To a solution of **1** (200 mg, 0.33 mmol) in 20 mL of tetrahydrofuran (THF) was added dropwise 0.83 mL of 2.4 M $LiAlH_4$ in THF (2 mmol) at 0 °C. The mixture was refluxed at 73 °C for two days. It was then cooled to 0 °C and neutralized with 15% w/v NaOH and water, and filtered through a Celite@ bed upon dilution with ethyl acetate (EtOAc). The mixture was concentrated in vacuo and the product was purified by flash chromatography using 1:1 mixture of EtOAc/hexanes to give 73 mg (84%) of **2** as a white solid: R_f (1:20 $CH_3OH/CHCl_3$): 0.42; $[\alpha_D]^{22}$ −24.17 (*c* 0.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 5.02 (ddd, 1H, $J_{2,1}$ = 5.25, $J_{2,3}$ = 5.5, $J_{2,4}$ = 1.5 Hz, H-2), 4.36 (br dd, 1H, $J_{5,6}$ = 3.65, $J_{5,6'}$ = 3.65 Hz, H-5), 4.27 (d, 1H, $J_{6',6}$ =11.2 Hz, H-6′), 4.23–4.2 (m, 1H, H-4), 4.18 (dd, 1H, $J_{6,6'}$ = 11.3, $J_{5,6}$ = 4.5 Hz, H-6), 4.03 (br dd, 1H, $J_{3,4}$ = 4.5, $J_{3,2}$ = 5.5 Hz, H-3), 2.09 (d, 1H, $J_{4,-OH}$ = 10.7 Hz, 4-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.53 (C-1), 100.41 (C-2), 76.56 (C-5), 74.71 (C-6), 68.76 (C-3), 66.26 (C-4); Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.15; H, 6.42.

4.4. General procedure for the synthesis of 3,6-anhydro-*O*-glycosides

To a solution of 50 mg (0.39 mmol) of **2** in 5 mL of anhydrous CH_3CN at 0 °C was added 105.5 mg (0.47 mmol) of *N*-iodosuccinimide. To the solution was then added 1.2 equiv of the desired nucleophile and the reaction mixture was stirred at rt overnight. The solvent was evaporated in vacuo and the crude product was purified by preparatory thin-layer chromatography (TLC) using 1:50 $CH_3OH/CHCl_3$ as the solvent.

4.4.1. Methyl-3,6-anhydro-2-deoxy-2-iodo-gluco- and manno-pyranosides (4a, 4b, and 4c)

Data for the mixture of diastereomers: ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.03 (d, 1H, J = 7.8 Hz), 4.72 (s, 1H), 4.47 (dd, 1H, J = 4.4 Hz, J = 3.4 Hz), 4.42–4.44 (m, 1H), 4.39–4.36 (m, 2H), 4.28–4.32 (m, 2H), 4.24 (d, 2H, J = 10.7 Hz), 4.15–4.12 (m, 1H), 4.09–4.06 (m, 3H), 3.96 (dd, 1H, J = 10 Hz, J = 5 Hz), 3.91 (dd, 1H, J = 5 Hz, J = 10 Hz), 3.54 (s, 1H), 3.48 (s, 1H), 3.46 (s, 1H), 2.64 (d, 1H, J = 8.8 Hz), 2.44 (d, 1H, J = 5 Hz), 2.41 (d, 1H, J = 8.8 Hz), 2.04 (d, 1H, J = 5.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.43, 72.81, 69.06, 29.57, 26.60, 20.28; HRMS (ESI): Calcd $C_7H_{11}O_4NaI$ for $(M+Na)^+$: 308.9611. Found: 308.9600.

4.5. General procedure for the synthesis of 2-deoxythioglycosides

To a stirred solution of 50 mg (0.39 mmol) of **2** and 21 mg (0.039 mmol) of $Ce(NH_4)_2(NO_3)_6$ in anhydrous CH_3CN (5 mL) was added a solution of 0.2 mL (1.95 mmol) of PhSH in anhydrous CH_3CN (5 mL) at 0 °C and allowed to stir overnight at rt. The solvent was evaporated in vacuo and the residue was diluted with excess CH_2Cl_2, washed with 10% NaOH, saturated $NaHCO_3$ and saturated NaCl and, dried over anhydrous Na_2SO_4. The organic solvent was evaporated in vacuo and the crude (150 mg) obtained was purified by preparatory TLC using 1:50 $CH_3OH/CHCl_3$ as the solvent to give mixtures of compounds **5a**, **5b** (60 mg) and **6a**, **6b** (33 mg).

4.5.1. Thiophenyl-3,6-anhydro-2-deoxy-D-glucopyranoside (5a and 5b)

Data for α-anomer (**5b**): R_f (1:50 $CH_3OH/CHCl_3$): 0.84; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.50 (m, 2H, Ar), 7.33–7.24 (m, 3H, Ar), 5.73 (dd, 1H, $J_{1,2}$ = 8.0, $J_{1,2'}$ = 3.2 Hz, H-1), 4.69–4.67 (m, 1H, H-5), 4.59 (dd, 1H, $J_{2,3}$ = 5.4, $J_{3,4}$ = 1.2 Hz, H-3), 4.29–4.26 (m, 1H, H-4), 3.99 (dd, 1H, $J_{6,6'}$ = 9.7, $J_{5,6}$ = 4.4 Hz, H-6), 3.84 (dd, 1H, $J_{6,6'}$ = 9, $J_{5,6'}$ = 5.5 Hz, H-6′), 3.06 (d, 1H, $J_{4,-OH}$ = 10.7 Hz, 4-OH), 2.63 (ddd, 1H, $J_{2,2'}$ = 14.15, $J_{1,2}$ = 8.55, $J_{2,3}$ = 6.3 Hz, H-2), 2.35 (ddd, 1H, $J_{2,2'}$ = 14.1, $J_{1,2'}$ = 3.15, $J_{2',3}$ = 1.3 Hz, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.3, 130.8, 129.1 (CH, Ar), 89.8 (C-1), 85.17 (C-5), 82.9 (C-3), 74.86 (C-6), 71.83 (C-4), 40.6 (C-2); HRMS (ESI): Calcd $C_{12}H_{14}O_3NaS$ for $(M+Na)^+$: 261.0570. Found: 261.0561. Data for β-anomer (**5a**): R_f (1:50 $CH_3OH/CHCl_3$): 0.76; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.50 (m, 2H, Ar), 7.33–7.24 (m, 3H, Ar), 5.66 (dd, 1H, $J_{1,2}$ = 6.8, $J_{1,2'}$ = 1.3 Hz, H-1), 4.69–4.67 (m, 1H, H-5), 4.64 (dd, 1H, $J_{3,4}$ = 5.4, $J_{2,3}$ = 1.2 Hz, H-3), 4.26–4.25 (m, 1H, H-4), 3.82 (dd, 1H, $J_{6,6'}$ = 9.55, $J_{5,6'}$ = 5.7 Hz, H-6′), 3.63 (dd, 1H, $J_{6,6'}$ = 9.5, $J_{5,6}$ = 6.2 Hz, H-6), 2.58 (d, 1H, $J_{4,-OH}$ = 7.4 Hz, 4-OH), 2.5 (ddd, 1H, $J_{2,2'}$ = 14.1, $J_{1,2}$ = 6.35, $J_{2,3}$ = 2 Hz, H-2), 2.17–2.22 (m, 1H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129, 127.78, 127.35 (CH, Ar), 88.41 (C-1), 82.52 (C-5), 82.39 (C-3), 73.16 (C-6), 72.12 (C-4), 40.77 (C-2); HRMS (ESI): Calcd $C_{12}H_{14}O_3NaS$ for $(M+Na)^+$: 261.0570. Found: 261.0561.

4.5.2. Thiophenyl-2,3-dideoxy-D-glucopyranoside (6a and 6b)

Data for α-anomer (**6a**): R_f (1:50 $CH_3OH/CHCl_3$): 0.19; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2H, Ar), 7.26–7.33 (m, 3H, Ar), 6.0 (dd, 1H, $J_{1,2}$ = 10.2 Hz, $J_{2,3}$ = 2 Hz, H-2), 5.98 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.74 (dd, 1H, $J_{3,4}$ = 1.2 Hz, $J_{2,3}$ = 2.7 Hz, H-3), 4.32 (dd, 1H, $J_{3,4}$ = 2 Hz, $J_{4,5}$ = 8.75 Hz, H-4), 4.03–4.07 (m, 1H, H-5), 3.86–3.92 (m, 2H, H-6,6′), 1.85 (d, 1H, $J_{4,-OH}$ = 7.3 Hz, 4-OH), 1.82 (dd, 1H, $J_{6,-OH}$ = 6.35 Hz, $J_{6',-OH}$ = 6.4 Hz, 6-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.77, 129.03, 127.32 (CH, Ar), 131.72 (C-1), 127.12 (C-2), 83.61 (C-3), 71.88 (C-5), 64.29 (C-4), 62.91 (C-6); HRMS (ESI): Calcd $C_{12}H_{14}O_3NaS$ for $(M+Na)^+$: 261.0561. Found: 261.0561. Data for β-anomer (**6b**): R_f (1:50 $CH_3OH/CHCl_3$): 0.19; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2H, Ar), 7.26–7.33 (m, 3H, Ar), 5.88 (dd, 1H, $J_{1,2}$ = 2 Hz, $J_{2,3}$ = 1.9 Hz, H-2), 5.86 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 1.4 Hz, H-1), 4.72–4.78 (m, 1H, H-4), 4.54–4.60 (m, 1H, H-5), 4.11–4.16 (m, 2H, H-6,6′), 2.18–2.24 (m, 4-OH, 6-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.10, 132.5, 131.69 (CH, Ar), 131.62 (C-1), 128.84 (C-2), 81.74 (C-3), 79.74 (C-5), 63.40 (C-4), 62.75 (C-6); HRMS (ESI): Calcd $C_{12}H_{14}O_3NaS$ for $(M+Na)^+$: 261.0561. Found: 261.0561.

4.6. General procedure for the preparation of the dianhydrosugar

To 100 mg (0.78 mmol) of **2** in 10 mL of CH_3CN was added 210 mg (0.94 mmol) of *N*-iodosuccinimide in the presence of 4 Å molecular sieves, and allowed to stir overnight at rt. The solvent was removed in vacuo and the residue was diluted with excess CH_2Cl_2, washed with 10% $Na_2S_2O_3$, saturated NaCl and dried over anhydrous Na_2SO_4. The organic filtrate was evaporated in vacuo and the crude product (170 mg) was purified by flash chromatography using 2:3 EtOAc/hexanes to give 150 mg (0.61 mmol, 76%) of **7**. In the absence of activated sieves, a mixture of 2-deoxy-2-iodo-hexopyranoses (**8a**–**c**) was also obtained (30%).

4.6.1. 1,4:3,6-Dianhydro-2-deoxy-2-iodo-D-glucopyranose (7)

Data for the dianhydrosugar: R_f (1:50 $CH_3OH/CHCl_3$): 0.9; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (br s, 1H, H-1), 5.09 (dd, 1H, $J_{4,3}$= 4.25, $J_{4,5}$ = 4.5 Hz, H-4), 4.27 (dd, 1H, $J_{5,4}$ = 3.5, $J_{5,6}$ = 3.25 Hz, H-5), 4.18 (dd, 1H, $J_{3,2}$ = 7.0, $J_{3,4}$ = 5.0 Hz, H-3), 4.15 (d, 1H, $J_{6,6'}$ = 10.8 Hz, H-6′), 4.0 (dd, 1H, $J_{2,3}$ = 7.0, $J_{2,1}$ = 2.0 Hz, H-2), 3.94 (dd, 1H, $J_{6,6'}$ =10.7, $J_{5,6}$ = 3.0 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.20 (C-1), 79.87 (C-4), 77.02 (C-5), 73.28 (C-3), 71.30 (C-6), 32.85 (C-2); LRMS (ESI) m/z (rel. intensity) 254.9 $(M+H)^+$ (79).

4.6.2. 3,6-Anhydro-2-deoxy-2-iodo-D-hexopyranose (8a, 8b and 8c)

Data for mixture of diastereomers: R_f 1:50 $CH_3OH/CHCl_3$): 0.12; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 5.68 (d, 1H, J = 5 Hz), 5.38 (s, 1H), 5.02 (dd, 1H, J = 5.4 Hz, J = 4.9 Hz), 4.89 (d, 1H, J = 5 Hz), 4.83 (ddd, 1H, J = 15 Hz, J = 5 Hz, J = 5 Hz), 4.73–4.70 (m, 2H), 4.48 (d, 1H, J = 1.4 Hz), 4.44 (d, 1H, J = 4.9 Hz), 4.40–4.37 (m, 2H), 4.19 (dd, 1H, J = 4.9 Hz, J = 4.4 Hz), 4.14 (d, 1H, J = 5 Hz), 4.09–4.06 (m, 2H), 4.04–3.98 (m, 2H), 3.79–3.76 (m, 2H), 3.62 (dd, 1H, J = 9.5 Hz, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.69, 99.48, 96.06, 90.68, 84.04, 83.32, 82.26, 76.37, 75.55, 71.75, 70.55, 46.57, 46.56, 26.66, 25.12, 23.61, 8.72, 8.71; LRMS (ESI): Calcd $C_6H_9IO_4$: 271.9. Found for $(M+Na)^+$: 294.8.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.03.005.

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20. CCDC 988697 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.