A synthetic route to pyranoid epoxy-*exo*-glycals from D-glucose

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Dedicated to Prof. Julio Álvarez-Builla on the occasion of his 65th birthday

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Abstract
A synthetic route to a pyranose derived epoxy-*exo*-glycal has been developed from D-glucose. An attempted, one-pot bromination-elimination-oxirane formation, protocol that had worked well on furanoses, resulted only in the generation of 2-bromo-*C*-1-methyl pyranoid glycals.

Keywords: Glycals, *exo*-glycals, bromination, epoxy-*exo*-glycal, pyranoses

Introduction

Our group has been interested in the synthesis of unsaturated anomeric derivatives (**1**–**3**, Figure 1),[1-5] and we have reported novel synthetic entries to glycals **1**,[6] *exo*-glycals **2**,[7] and *C*-1 glycals **3**.[8] In this context, we have been interested in the chemistry of epoxy-*exo*-glycal **4** (Figure 2), and we have demonstrated its usefulness in the synthesis of substituted *exo*-glycals,[9] highly functionalized *C*-1 glycals[10] and, by way of its transformation to epoxy-halo-*exo*-glycals **5** (Figure 2), the preparation of carbohydrate templates,[11] and that of polyfunctionalized furanose derivatives.[12]

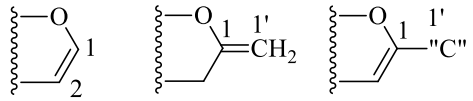


Figure 1. Unsaturated anomeric sugar derivatives **1**–**3**.

In this manuscript, we report a synthetic protocol for the preparation of the pyranosidic sibling of **4**, epoxy-*exo*-glycal **6b** (Figure 2).

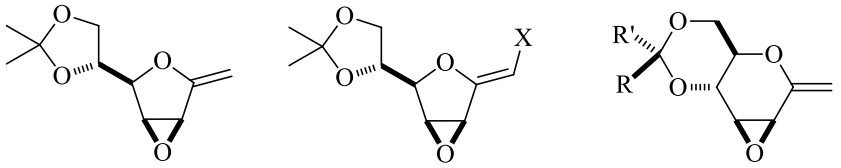
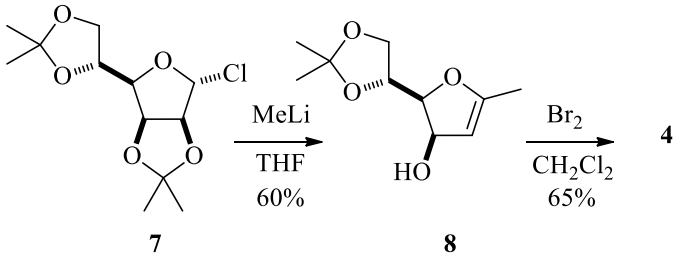


Figure 2. Furanose-derived epoxy-*exo*-glycal **4**, halo-*exo*-glycal **5**, and pyranose-derived epoxy-*exo*-glycals **6**.

Results and Discussion

Our synthetic route to epoxy-*exo*-glycal **4** demanded only four steps and permitted its preparation in a respectable 33% yield from D-mannose. The preparation relied in two synthetic processes described in our laboratory: *i)* the reaction of *manno*furanosyl chloride **7** with MeLi,[8b] and *ii)* the one-pot three step transformation of *C*-1 methyl glycal **8** into **4**[7,11b] (Scheme 1).

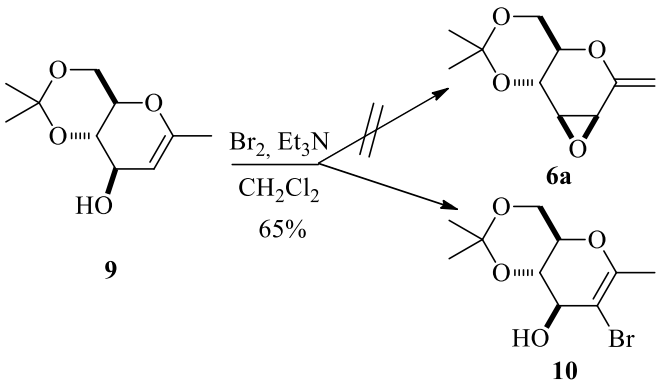


Scheme 1. Synthesis of furanosidic epoxy-*exo*-glycal **4** from furanosyl chloride **7**.

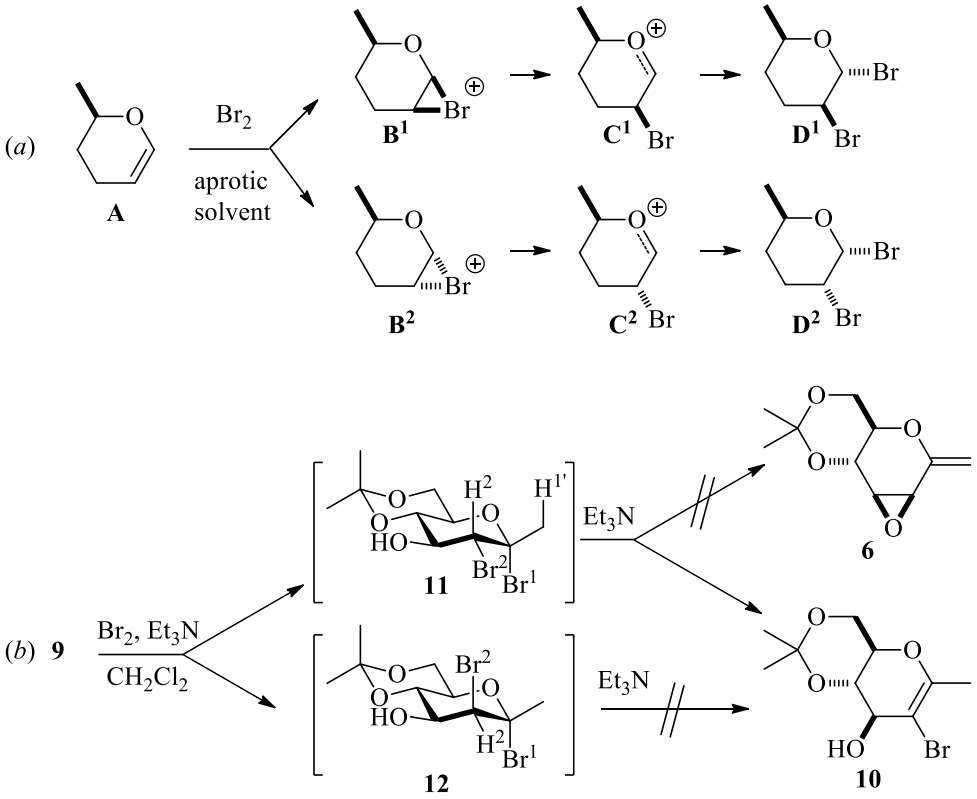
By analogy, we decided to explore a synthetic route to **6a**, which would include a related one-pot three step (bromination-elimination-oxirane formation) procedure. Accordingly, *C*-1 methyl glycal **9**[8b] was treated with bromine and triethylamine in CH_2Cl_2. However, the resulting product was 2-bromo-*C*-1 glycal **10**, rather than the sought epoxy-*exo*-glycal **6a** (Scheme 2).

This attempted protocol for the preparation compound **6a** had relied on some insight in the electrophilic bromination of glycals, as follows. The electrophilic addition of halogens to cyclic enol ethers was first investigated by Lemieux and Fraser-Reid,[13] who proposed a general mechanism involving the initial formation of carbenium ions which, upon nucleophilic attack by halide ion, gave mainly the products of thermodynamic control. Later on, it was shown that the

product formation is under kinetic control and that the stereoselectivity depends on the solvent polarity,[14] the structure of the enol ether, and the halogen.[15]



Scheme 2. Attempted synthesis of epoxy-*exo*-glycal **6a** from *C*-1 methyl glycal **9**.



Scheme 3. *(a)* Bromination of glycals with bromine in aprotic solvents, and *(b)* genesis of 2-bromo-1-*C*-methyl glycal **10** from *C*-1-methyl glycal **9**.

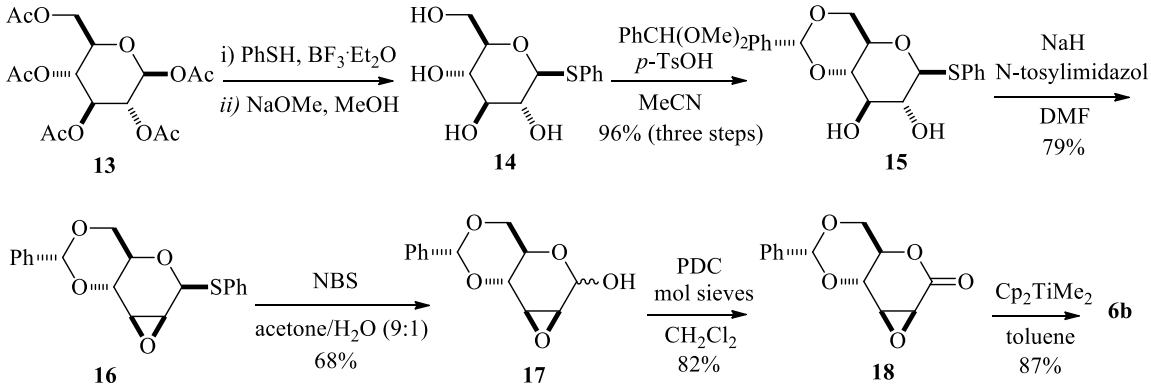
Recent studies on bromine addition to glycals in aprotic solvents[16] (a system closely related to ours) have established that the reaction is a two-step process involving an electrophilic

addition (**A→B**, Scheme 3a) after which, an irreversibly formed bromo oxocarbenium ion (**C**) suffers an axial attack by the nucleophile (**C→D**, Scheme 3a), which is governed by the stereoelectronic α-anomeric effect.[17] For that reason, both *cis* and *trans* adducts **D^1** and **D^2** are observed.

According to these observations, two compounds (**11** and **12**) could arise by bromination of **9** (Scheme 3b). The former could experience Br^1 elimination either from H^2 to give compound **10**, or from $H^{1'}$ to generate the $\Delta^{1,1'}$ unsaturation in **6**, a process that might be followed by nucleophilic substitution to furnish the $\Delta^{2,3}$ oxirane.[18] Conversely, no Br^1 elimination could take place from H^2 in dibromo derivative **12**, since H^2 and Br^1 are not in an antiperiplanar disposition, nor could $\Delta^{2,3}$ oxirane formation be expected either, owing to the *cis*-relationship between the C3-OH and Br^2.

According to this, the observed reaction pathway might have involved bromination *anti*- to the C3-OH group to give intermediate **11** which, subsequently undergoes Br^1 elimination from H^2 to generate the tetrasubstituted olefin, **10**.[19]

After this initial setback, we devised an alternative route to **6b** from commercially available β-D-glucose pentaacetate **13**. Thus, sequential $BF_3{\cdot}Et_2O$ catalyzed thioglycosidation,[20] and Zemplen deacetylation,[21] led to tetraol **14**.[22] Subsequent 4,6-*O*-benzylidene acetal formation on **14** yielded phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **15**[23] in 96% yield (three steps). Oxirane formation from diol **15** was then conveniently performed by double deprotonation of the diol, followed by selective tosylation at *O*-2 (with the assistance of *N*-tosylimidazole[18a]) and spontaneous displacement of the resulting leaving group.[24] The ensuing thioglycoside, **16**, was submitted to NBS-mediated hydrolysis[25] to give hemiacetal **17**. Finally, oxidation (PDC, CH_2Cl_2, 82%) of hemiacetal **17** followed by methylenation of the resulting lactone, **18**, with the Petasis reagent[26] yielded the sought epoxy-*exo*-glycal, **6b**.



Scheme 4. Synthesis of pyranosidic epoxy-*exo*-glycal **7b** from β-D-glucose pentaacetate.

Conclusions

Pyranosidic epoxy-*exo*-glycal **6b**, can be efficiently prepared from commercially available β-D-glucose pentaacetate **13** in seven steps. The synthetic route from tetraol **14**[22] to **6b** takes place in a synthetically useful 37% yield. An alternative approach featuring a one-pot three steps transformation, which had worked well for us in related furanose systems, led to 2-bromo C-1 methyl derivative **10** instead. This route provides access to compound **6b**, which is now under study in our laboratory.

Experimental Section

General. All reactions were performed in dry flasks fitted with glass stoppers or rubber septa under a positive pressure of Ar, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred by syringe or stainless steel cannula. Optical rotations were determined for solutions in chloroform. Flash column chromatography was performed using 230–400 mesh silica gel. Thin-layer chromatography was conducted on Kieselgel 60 F254 (Merck). Spots were observed first under UV irradiation (254 nm) then by charring with a solution of 20 % aqueous H_2SO_4 (200 mL) in AcOH (800 mL). Anhydrous $MgSO_4$ or Na_2SO_4 were used to dry organic solutions during workup, and evaporation of the solvents was performed under vacuum using a rotary evaporator. Solvents were dried and purified using standard methods. Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 50 MHz, respectively. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.25 ppm). Elemental analyses were carried out at the *Centro Nacional de Química Orgánica "Manuel Lora Tamayo", Juan de la Cierva 3, 28006 Madrid,* with a Heraeus CHN-O-rapid elemental analyzer.

1,5-Anhydro-4,6-*O*-isopropyliden-2-deoxy-2-bromo-1-*C*-methyl-D-arabino-hex-1-enitol (10). To a solution of *C*-1 methyl glycal **9**[8b] (150 mg, 0.53 mmol) and NEt_3 (0.5 mL) in CH_2Cl_2 (6.5 mL) at 0 ºC, was slowly added a solution of Br_2 (0.60 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL). The mixture was then allowed to warm to room temperature and, after TLC examination showed no starting material remaining, was treated with an aqueous solution of $Na_2S_2O_3$ (10%). Extraction (CH_2Cl_2), drying (Na_2SO_4), and evaporation of the organic layers led to a residue that was chromatographed (hexane/ethyl acetate, 95:5) to yield compound **10** (96 mg, 65%): $[\alpha]_D^{25}$ +40.0 (*c* 1.15 in $CHCl_3$); ^1H NMR δ (□$CDCl_3$, 300 MHz) 1.45 (s, 3 H), 1.54 (s, 3 H), 1.96 (d, *J* = 1.6 Hz, 3 H), 3.73 (m, 1 H), 3.83 (t, *J* = 10.1 Hz, 1 H), 3.90 (dd, *J* = 7.0, 10.2 Hz, 1 H), 3.98 (dd, *J* = 5.0, 10.2 Hz, 1 H), 4.29 (dq, *J* = 1.6, 7.0 Hz, 1 H,); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 19.4, 19.5, 29.3, 61.7, 69.5, 71.1, 73.1, 100.1, 100.2, 151,5; API-ES(+) 302 (M^++Na), 304 (M^++2+Na). Anal. Calcd for $C_{10}H_{15}BrO_4$ (278.02): C, 43.03; H, 5.42. Found: C, 42.79; H, 5.32.

Phenyl 1-thio-β-D-glucopyranoside (14). This compound was prepared from D-glucose, according to Wang and co-workers, ref. 22.

Phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (15). A solution of phenyl 1-thio-β-D-glucopyranoside **14**[22] (10 g, 36.7 mmol) in CH_3CN (150 mL) was treated with benzaldehyde dimethyl acetal (8.25 mL, 55.0 mmol, 1.5 equiv) and *p*-toluenesulfonic acid monohydrate (2.79 g, 14.7 mmol, 0.4 equiv), and kept with stirring at room temperature overnight. After that time, no starting material was detected by TLC and Et_3N was then added to reach neutral pH. Then evaporation of the solvent, and chromatography (hexane/ethyl acetate, 1:1) yielded compound **15** (12.70 g, 96%) whose ^{1}H NMR data were in agreement with those in the reported in the literature[22]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (m, 3 H), 3.65 (m, 2 H), 3.77 (br s, 2 H), 4.24 (dd, *J* = 4.0, 10.4 Hz, 1 H), 4.55 (d, *J* = 9.6 Hz, 1 H), 5.42 (s, 1 H), 7.23 (m, 6 H), 7.40 (m, 4 H). API-ES(+) 383.1 (M^++Na).

Phenyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (16). To a solution of diol **15** (1.8 g, 5 mmol) in dry DMF (40 mL) at 0 ºC, was added NaH (252 mg, 10.5 mmol, 2.1 equiv) and the solution was maintained with stirring at room temperature (30 min). *N*-tosylimidazole (1.3 g, 5.5 mmol, 1.1 equiv) was then added to the reaction mixture, which was kept with stirring for one additional hour. The resulting solution was poured onto ice/water and extracted with ethyl ether/toluene. The organic layer was then dried ($MgSO_4$) and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexane/ethyl acetate, 8:2) to yield epoxide **16** (1,36 g, 79%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.26 (dt, *J* = 4.8, 9.9 Hz, 1 H), 3.38 (d, *J* = 3.6 Hz, 1 H), 3.68 (d, *J* = 10.0 Hz, 1 H), 3.71 (t, *J* = 10.6 Hz, 1 H), 4.20 (dd, *J* = 4.8, 10.6 Hz, 1 H), 5.27 (s, 1 H), 5.40 (s, 1 H), 7.21–7.50 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.6, 54.5, 63.1, 67.8, 73.6, 76.1, 101.4, 125.2, 127.4 (2 x), 127.8 (2x), 128.3 (4 x), 130.2 (2 x), 133.6. Anal. Calcd for $C_{22}H_{26}O_7S_2$ (466.57): C, 56.63; H, 5.62. Found: C, 56.81; H, 5.49. API-ES(+) 343.0 (M^++H), 365.0 (M^++Na). Anal. Calcd for $C_{19}H_{18}O_4S$ (342.09): C, 66.65; H, 5.30, S 9.36. Found: C, 66.81; H, 5.49, S, 9.21.

2,3-Anhydro-4,6-*O*-benzylidene-D-mannopyranose (17). A solution of thiopyranoside **21** (136 mg, 0.39 mmol), in (9:1) acetone/H_2O (7 mL) at –15 ºC, was treated with NBS, (90 mg, 0.50 mmol, 1.3 equiv). The resulting solution was allowed to warm to room temperature and kept with stirring (1 h). The solution was then treated with an aqueous $NaHCO_3$ solution, and extracted with ethyl acetate and brine. The organic layer was then dried (Na_2SO_4) and concentrated under vacuum to give a residue that was chromatographed (hexane/ethyl acetate, 6:4) to yield hemiacetal **17** as one single anomer (66.4 mg, 68%): $[\alpha]_D^{21}$ + 48.2 (*c* 0.4 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.91 (t, *J* = 9.8 Hz, 1 H), 4.08 (dt, *J* = 4.6, 9.0 Hz, 1 H), 4.12 (d, *J* = 3.4 Hz, 1 H), 4.33 (d, *J* = 3.4 Hz, 1 H), 4.35 (m, 2 H), 4.55 (m, 1 H), 5.58 (s, 1 H), 5.65 (s, 1 H), 7.27–7.66 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.6, 67.1, 67.5, 72.6, 73.0, 83.8, 101.1, 125.3, 127.4 (2 x), 128.2 (2 x), 130.5. API-ES(+) 251.0 (M^++H). Anal. Calcd for $C_{13}H_{14}O_5$ (250.08): C, 62.39; H, 5.64. Found: C, 62.35; H, 5.75.

2,3-Anhydro-4,6-*O*-benzylidene-D-mannono-1,5-lactone (18). To a solution of compound **17** (88 mg, 0.35 mmol) in dry CH_2Cl_2 (15 mL), containing 4 A molecular sieves, was added pyridinium dichromate (PDC, 376 mg, 1.0 mmol, 3 equiv) and the resulting mixture kept with stirring at room temperature overnight. Once the starting material disappeared (TLC) the mixture

was diluted with ethyl ether, filtered over Celite, and the resulting solution concentrated under vacuum. The resulting residue was then purified by flash chromatography (hexane/ethyl acetate, 9:1) to yield lactone **18** (71.2 mg, 82%): m. p. 330–333 ºC, $[\alpha]_D^{21}$ + 108.4 (*c* 0.7 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, *J* = 3.6 Hz, 1 H), 3.79 (d, *J* = 3.6 Hz, 1 H), 3.82 (t, *J* = 9.9 Hz, 1 H), 4.24 (d, *J* = 9.2 Hz, 1 H), 4.42 (dd, *J* = 4.8, 10.6 Hz, 1 H), 4.65 (dt, *J* = 4.8, 9.8 Hz, 1 H), 5.61 (s, 1 H), 7.29–7.56 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.4, 52.9, 65.3, 68.0, 76.4, 100.0, 126.3, 128.6, 129.7, 136.3, 153.9. API-ES(+) 249.0 (M^++H). Anal. Calcd for $C_{13}H_{12}O_5$ (248.07): C, 62.90; H, 4.87. Found: C, 62.81; H, 4.76.

1,5-Anhydro-2,3-anhydro-4,6-*O*-benzylidene-1'-*C*-methylene-D-manno-hex-1-enitol (6b). Cp_2TiMe_2 (30 mg, 0.15 mmol, 2.1 equiv) was added to a solution of lactone **18** (19 mg, 0.07 mmol) in toluene (9 mL) and the resulting mixture heated at reflux overnight. Evaporation of the solvent and chromatography (Hexane/EtOAc 8:2) of the resulting residue gave epoxy-*exo* glycal **6b** (14.1 mg, 87%): $[\alpha]_D^{21}$ + 3.6 (*c* 2.5 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (d, *J* = 4.4, Hz, 1 H), 3.71 (d, *J* = 4.6 Hz, 1 H), 3.73 (t, *J* = 10.2 Hz, 1 H), 4.10 (d, *J* = 9.0 Hz, 1 H), 4.23 (dd, *J* = 5.1, 10.2 Hz, 1 H), 4.31 (dt, *J* = 4.9, 10.0 Hz, 1 H), 4.50 (d, *J* = 1.6 Hz, 1 H), 4.67 (d, *J* = 1.5 Hz, 1 H), 5.57 (s, 1 H), 7.28–7.57 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.1, 52.7, 64.5, 68.9, 77.6, 97.1, 102.8, 126.5, 128.6 (2 x), 129.6 (2 x), 137.1, 151.6. API-ES(+) 247 (M^++H). Anal. Calcd for $C_{14}H_{14}O_4$ (248.07): C, 68.28; H, 5.73. Found: C, 68.14; H, 5.82.

Acknowledgements

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