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 anomic 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 glycals10 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 anomic sugar derivatives 1–3.](image_url)
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 mannofuranosyl chloride 7 with MeLi, and ii) the one-pot three step transformation of C-1 methyl glycal 8 into 4 (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 was treated with bromine and triethylamine in CH$_2$Cl$_2$. 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, 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,\textsuperscript{14} the structure of the enol ether, and the halogen.\textsuperscript{15}

\textbf{Scheme 2.} Attempted synthesis of epoxy-\textit{exo}-glycal 6\texttextit{a} from C-1 methyl glycal 9.

\textbf{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\textsuperscript{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. For that reason, both cis and trans adducts D1 and D2 are observed.

According to these observations, two compounds (11 and 12) could arise by bromination of 9 (Scheme 3b). The former could experience Br1 elimination either from H2 to give compound 10, or from H1' to generate the Δ1,1' unsaturation in 6, a process that might be followed by nucleophilic substitution to furnish the Δ2,3 oxirane. Conversely, no Br1 elimination could take place from H2 in dibromo derivative 12, since H2 and Br1 are not in an antiperiplanar disposition, nor could Δ2,3 oxirane formation be expected either, owing to the cis-relationship between the C3-OH and Br2.

According to this, the observed reaction pathway might have involved bromination anti- to the C3-OH group to give intermediate 11 which, subsequently undergoes Br1 elimination from H2 to generate the tetrasubstituted olefin, 10.

After this initial setback, we devised an alternative route to 6b from commercially available β-D-glucose pentaacetate 13. Thus, sequential BF3·Et2O catalyzed thioglycosidation, and Zemplen deacetylation, led to tetraol 14. Subsequent 4,6-O-benzylidene acetal formation on 14 yielded phenyl 4,6-O-benzylidene-1-thio-β-D-glucopyranoside 15 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) and spontaneous displacement of the resulting leaving group. The ensuing thioglycoside, 16, was submitted to NBS-mediated hydrolysis to give hemiacetal 17. Finally, oxidation (PDC, CH2Cl2, 82%) of hemiacetal 17 followed by methylenation of the resulting lactone, 18, with the Petasis reagent yielded the sought epoxy-exo-glycal, 6b.

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

Conclusions
Pyranosidic epoxy-\textit{exo}-glycal 6b, can be efficiently prepared from commercially available β-D-glucose pentaacetate 13 in seven steps. The synthetic route from tetraol 14\textsuperscript{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 mixture of phosphomolybdic acid in H2SO4 and camphorsulfonic acid. 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-isopropylidene-2-deoxy-2-bromo-1-C-methyl-D-arabino-hex-1-enitol** (10). To a solution of C-1 methyl glycal 9\textsubscript{8b} (150 mg, 0.53 mmol) and NEt\textsubscript{3} (0.5 mL) in CH\textsubscript{2}Cl\textsubscript{2} (6.5 mL) at 0 °C, was slowly added a solution of Br\textsubscript{2} (0.60 mmol, 1.1 equiv) in CH\textsubscript{2}Cl\textsubscript{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\textsubscript{2}SO\textsubscript{4} (10%). Extraction (CH\textsubscript{2}Cl\textsubscript{2}), drying (Na\textsubscript{2}SO\textsubscript{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%): [α]\textsubscript{D}\textsuperscript{25} +40.0 (c 1.15 in CHCl\textsubscript{3}); \textsuperscript{1}H NMR δ \textdaggerbrace(CDCl\textsubscript{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,); \textsuperscript{13}C NMR δ (CDCl\textsubscript{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\textsuperscript{+}Na), 304 (M\textsuperscript{+2}Na). Anal. Calcd for C\textsubscript{10}H\textsubscript{15}BrO\textsubscript{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\(_3\)CN (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\(_3\)N 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 °C, was added NaH (252 mg, 10.5 mmol, 2.1 equiv) and the resulting 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); \(^1\)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 (2 x), 128.3 (4 x), 130.2 (2 x), 133.6. Anal. Calcd for C\(_{22}\)H\(_{26}\)O\(_7\)S\(_2\) (466.57): C, 56.81; 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\(_4\)S (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\(_2\)O (7 mL) at −15 °C, 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\(_2\)SO\(_4\)) 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%): [α]\(_D\)\(^{21}\) + 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); \(^1\)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\(_2\)Cl\(_2\) (15 mL), containing 4 Å 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 °C, [α]D21 108.4 (c 0.7 in CHCl3); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (50 MHz, CDCl3) δ 48.7, 50.4, 52.1, 52.7, 64.5, 68.9, 77.6, 97.1, 102.8, 126.5, 128.6, 129.7, 136.3, 153.9. API-ES(+) 249.0 (M+H). Anal. Calcd for C13H12O5 (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). Cp2TiMe2 (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%): [α]D21 36 (c 2.5 in CHCl3); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (50 MHz, CDCl3) 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 C14H14O4 (248.07): C, 68.28; H, 5.73. Found: C, 68.14; H, 5.82.

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