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A new entry to 4,6-*O*-benzylidene glucal from phenyl 1-seleno-α-D-mannopyranoside

Helen M. I. Osborn,[a,b,*] Paul Meo[a] and Rajdeep K. Nijjar[a]

[a]*School of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK*
[b]*School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AJ, UK*

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Abstract—The two-step synthesis of 4,6-*O*-benzylidene glucal, in 59% overall yield, from phenyl 1-seleno-α-D-mannopyranoside is described.

1. Introduction

Glycals (1,2-anhydro sugars) have found widespread use and application within synthetic carbohydrate programmes. In particular, they have been exploited within Danishefsky's solution[1] and solid phase[2] glycal assembly approaches to complex oligosaccharides and within the synthetically useful Ferrier rearrangement methodology.[3] 3,4,6-Per-*O*-acetylated glycals are generally prepared in excellent yields from per-*O*-acetylated bromopyranosides, via zinc catalysed reductive elimination.[4] 4,6-*O*-Benzylidene glucal was originally prepared in low yield by benzylidene protection of the C-4, C-6 hydroxyl pair within the acid sensitive free glucal.[5] However, improved methods for entry to this target, from methyl, thiophenyl or sulfone glycosides, have subsequently been reported.[6] We herein report a complementary two-step protocol that allows access to 4,6-*O*-benzylidene glucal from phenyl 1-seleno-α-D-mannopyranoside. This approach is expected to be particularly attractive to researchers who utilise phenyl 1-seleno glycosides as intermediates for carbohydrate assembly within their laboratories.

2. Results and discussion

As part of a programme directed towards the synthesis of *C*-linked glycosides using a carbon-Ferrier reaction,[7] we wished to access allylic glycal **1**. Retrosynthetic analysis of target glycal **1** (Fig. 1) suggested that 4,6-*O*-benzylidene glucal **3** would be a suitable precursor and the opportunity arose for developing a new entry to this generally useful intermediate.

Our approach develops a method described by Horton and Weckerle[8] for the synthesis of methyl-2-deoxy-3-ulose mannopyranoside from methyl 2,3;4,6-di-*O*-benzylidene mannopyranoside. This reaction proceeds via elimination of benzaldehyde after abstraction of the more sterically accessible axial proton at C-3. We rationalised that if an anomeric substituent could be incorporated, which both assisted removal of the C-1 anomeric proton, thus initiating eliminative loss of benzaldehyde from the 2,3-*O*-benzylidene acetal, and that itself could be readily removed under basic conditions, then direct entry to 4,6-*O*-benzylidene protected glycals could be developed. Since phenyl 1-selenopyranosides are common intermediates for oligosaccharide synthesis,[9]

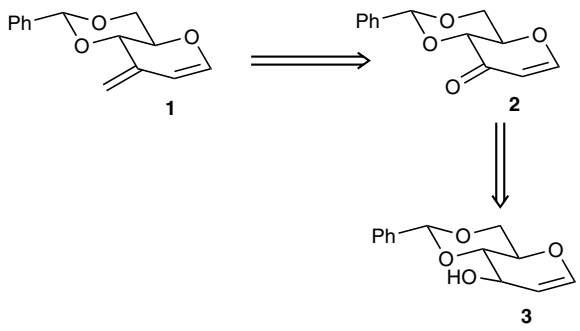

Figure 1.

* Corresponding author. Fax: +44 (0) 118 931 6331; e-mail: h.m.i.osborn@rdg.ac.uk

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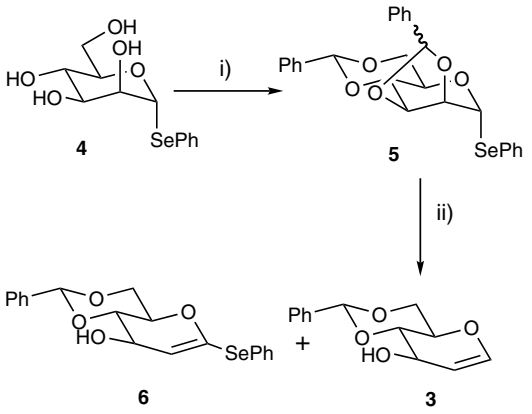

Scheme 1. Reagents and conditions: (i) $PhCH(OMe)_2$, *p*-TsOH, DMF, 50 °C, 69%; (ii) 2 equiv *n*-BuLi, THF, −40 °C.

we considered phenyl 1-seleno-α-D-mannopyr- anoside to be a useful starting material for this strategy. To test this hypothesis, phenyl 1-seleno-2,3;4,6-di-*O*-benzylidene pyranoside **5** was prepared from tetrol **4**[10] using benzaldehyde dimethyl acetal and *p*-TsOH at 50 °C under reduced pressure (Scheme 1). The fully protected di-*O*-benzylidene acetal **5** was produced as a 1:1 mixture of benzylidene diastereoisomers at O-2 and O-3 in 69% yield. In our initial studies, the mixture of diastereoisomers was subsequently treated with 2 equiv of *n*-BuLi at −40 °C to facilitate removal of the C-1 anomeric proton and potentially initiate elimination of benzaldehyde. This allowed access to a separable mixture of the desired product **3** and the intermediate glycal **6** in a 1:1 ratio, with a total yield of 60%. Formation of the intermediate glycal **6** suggested that there was insufficient base present to effect complete conversion as the reaction of the second equivalent of *n*-BuLi with the liberated benzaldehyde competes with the desired transformation.

However, further studies illustrated that glycal **6** could be converted to the desired glycal product **3** in 89% yield upon exposure to two further equivalents of *n*-BuLi, at −40 °C. In subsequent reactions, deprotonation, elimination and removal of the phenyl selenide substituent were effected in one pot by simply treating the di-*O*-benzylidene acetal **5** with four equivalents of *n*-BuLi at −40 °C. The desired glycal **3** was then obtained in an excellent 85% yield.

3. Conclusion

In summary, we have developed an efficient, high yielding, two-step strategy for entry to the synthetically useful 4,6-*O*-benzylidene glucal, from a common carbohydrate intermediate. The incorporation of this glycal within our carbon-Ferrier protocol is currently under investigation.

4. Experimental

The melting points of all solid products were determined using an Electrothermal digital heated metal block apparatus. All melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Frequencies of absorption maxima are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded at 250 MHz on a Bruker DPX-250 FT-NMR spectrometer, using $CDCl_3$ as an internal standard unless stated otherwise. Correlations between protons were determined using correlation spectroscopy (COSY) while proton–carbon correlations were determined using heteronuclear correlation spectroscopy (HETCOR). Multiplicities of carbon atoms (methyl, methylene, methine or quaternary) were determined using broadband decoupled carbon spectra and distortionless enhancement by polarisation transfer (DEPT) carbon spectra. All chemical shifts (δ_H values) are quoted in units of parts per million (ppm). The following abbreviations are used: s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet). All coupling constants (*J* values) are expressed in hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on the spectrometer described above at 62.5 MHz and the external reference provided by the $CDCl_3$ solvent. The chemical shifts (δ_C values) are quoted in units of ppm. Low- and high-resolution mass spectrometry data were recorded by the School of Chemistry's mass spectrometry service using a Fisons VG Autospec. Low resolution mass spectra were also recorded at the School of Chemistry using a Micromass Platform LC/MS. In addition, high-resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service, Swansea, using a Finnigan MAT900XLT. Molecular ions and fractions from molecular ions are reported as mass/charge (*m*/*z*) ratios. Optical activities were determined using a Perkin–Elmer 341 polarimeter at a wavelength of 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was performed using silica gel 60 (Merck) using head pressure by means of bellows. TLC analysis was performed using Merck aluminium backed plates, coated with 0.2 mm silica 60 F_{254}. Visualisation of the compounds on TLC plates was achieved using 254 nm UV light or by using an acid dip (EtOH/H_2SO_4, 25:1). All chemicals were obtained from Sigma–Aldrich, BDH, Fluka or Lancaster chemical suppliers and were used as received, unless stated otherwise. For reactions requiring anhydrous conditions, anhydrous solvents were used, with glassware oven-dried prior to use and the procedures carried out under a nitrogen atmosphere.

4.1. Phenyl 2,3:4,6-*O*-benzylidene-1-seleno-α-D-mannopyranoside 5

Phenyl 1-seleno-α-D-mannopyranoside **4**[10] (1.073 g, 3.5 mmol) was dissolved in anhydrous DMF (40 ml). To this were added benzaldehyde dimethyl acetal (1.3 ml, 8.75 mmol) and *p*-toluene sulfonic acid (40 mg), and the reaction mixture placed on a rotary evaporator at 50 °C. After 3 h, TLC analysis showed the reaction to be complete. The reaction mixture was quenched by the addition of satd $NaHCO_3$ (50 ml), extracted with DCM (2 × 50 ml) and washed with brine (50 ml). The organic fractions were collected, dried over $MgSO_4$, filtered and concentrated in vacuo to afford a

white solid. This was suspended in a minimum amount of hexane and the ensuing white solid filtered off to afford **5** (1.191 g, 69%) as a mixture of diastereoisomers. Mp 174–178 °C; ν_{max}/cm^{-1} 2929 (C–H stretch), 2878 (CH_3 stretch), 1461 (CH_3, C–C ring stretch), 1406 (C–C ring stretch), 746 (C–H aromatic bend), 694 (C–H aromatic bend); δ_H (250 MHz; $CDCl_3$) 7.63–7.56 (4H, m, ArH), 7.47–7.33 (11H, m, ArH), 6.34 (1H, s, PhC*H*), 6.18 (1H, s, H-1), 5.67 (1H, s, PhC*H*), 4.71 (1H, dd, *J* 5.0, 8.0, H-4), 4.50 (1H, d, *J* 5.0, H-3), 4.30–4.21 (2H, m, H-2, H-6), 4.28 (1H, dd, *J* 8.0, 9.5, H-5), 3.83 (1H, t, *J* 11.5, H-6); δ_C (62.5 MHz; $CDCl_3$) 138.87 (ArC), 137.41 (ArC), 135.10 (ArCH), 129.74 (ArCH), 129.63 (ArCH), 128.86 (ArCH), 128.76 (ArCH), 128.694 (ArCH), 128.48 (ArC), 126.71 (ArCH), 126.43 (ArCH), 103.56 (Ph*C*H), 102.43 (Ph*C*H), 81.67 (C-1), 78.09 (C-5), 77.08 (C-3), 75.58 (C4), 68.81 (C-6), 63.75 (C-2); *m/z* (CI) 497 ($M+H^+$, 19%), 390 (25), 339 (49), 233 (44), 105 (100). Found 497.0855. $C_{26}H_{25}O_5Se$ requires 497.0867.

4.2. 4,6-*O*-Benzylidene-1,2-dideoxy-D-*arabino*-hex-1-enitol 3 and phenyl 4,6-*O*-benzylidene-1,2-dideoxy-1-seleno-D-*arabino*-hex-1-enitol 6

Phenyl 2,3:4,6-*O*-benzylidene-1-seleno-α-D-mannopyranoside **5** (500 mg, 1 mmol) was dissolved in anhydrous THF (25 ml) and cooled to −40 °C. *n*-BuLi (0.8 ml, 2 mmol, 2.5 M) was added to the reaction mixture with the temperature maintained at −40 °C. After TLC analysis confirmed complete consumption of starting material satd ammonium chloride (20 ml) was added and the mixture extracted with ethyl acetate (3 × 20 ml) and washed with brine (2 × 40 ml). The organic fractions were collected and dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude product was subjected to column chromatography using silica gel (hexane/ethyl acetate [1:1]) to afford **3** (70 mg, 30%) as a white solid and **6** (117 mg, 30%) as a yellow oil.

Data for **3**: mp 140–143 °C, [Lit.[5a] 142–143]; $[\alpha]_D^{20} = -15.8$ (*c* 0.83, $CHCl_3$), {lit.[5a] $[\alpha]_D^{22} = -19$ (*c* 0.6, $CHCl_3$)}; ν_{max}/cm^{-1} (nujol) 3166 (O–H stretch) 2715 (ArCH stretch), 1635 (C=C stretch), 1406 (C–C ring stretch), 746 (C–H aromatic bend), 694 (C–H aromatic bend); δ_H (250 MHz; $CDCl_3$) 7.46–7.40 (2H, m, ArH), 7.33–7.27 (3H, m, ArH), 6.26 (1H, dd, *J* 1.5, 6.0, H-1), 5.52 (1H, s, PhC*H*), 4.69 (1H, dd, *J* 2.0, 6.0, H-2), 4.44–4.41 (1H, m, H-3), 4.29 (1H, dd, *J* 4.5, 10.0, H-6), 3.89–3.68 (3H, m, H-4, H-5, H-6); δ_C (62.5 MHz; $CDCl_3$) 144.58 (C-1), 137.41 (ArC), 129.73 (ArCH), 128.79 (ArCH), 126.62 (ArCH), 103.93 (C-2), 102.25 (Ph*C*H), 81.14 (C-4), 68.74 (C-6, C-5), 67.0 (C-3); *m/z* (CI) 235 ($M+H^+$, 100%), 129 (71), 105 (51), 85 (25). Found $M+H^+$ 235.0979. $C_{13}H_{15}O_4$ requires 235.0970.

Data for **6**: $[\alpha]_D^{20} = -10.0$ (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (nujol) 3411 (O–H stretch), 3061, 2955, 2930, 2859 (ArCH stretch), 1734, 1575, 1494, 1474, 1455, 1437, 1380, 1297, 1176, 1077, 1020, 915, 736, 699, 688; ^1H NMR (250 MHz; $CDCl_3$) 7.49–7.39 (4H, m, ArH), 7.30–7.22 (6H, m, ArH), 5.49 (1H, s, PhCH), 5.05 (1H, d, *J* 2.5, H-2), 4.45–4.41 (1H, m, H-3), 4.26 (1H, dd, *J* 5.0, 10.5, H-6), 3.90 (1H, dd, *J* 5.0, 10.0, H-5), 3.79–3.70 (2H, m, H-4, H-6); ^{13}C NMR (62.5 MHz; $CDCl_3$) 147.31 (C-1), 137.24 (ArC), 133.66 (ArCH), 129.82 (ArCH), 129.79 (ArCH), 128.80 (ArCH), 128.45 (ArCH), 126.64 (ArCH), 109.68 (C-2), 102.23 (PhCH), 80.51 (C-4), 70.74 (C-5), 68.47 (C-6), 68.45 (C-3); *m/z* (CI) 390 (M^+, 2 %), 338 (2), 316 (51), 85 (25). Found M^+ 390.0352. $C_{19}H_{18}O_4Se$ requires 390.0370.

4.3. Direct entry to 4,6-*O*-Benzylidene-1,2-dideoxy-D-*arabino*-hex-1-enitol 3

Phenyl 2,3:4,6-*O*-benzylidene-1-seleno-α-D-mannopyranoside **5** (500 mg, 1 mmol) was dissolved in anhydrous THF (25 ml) and cooled to −40 °C. *n*-BuLi (1.6 ml, 4 mmol, 2.5 M) was added to the reaction mixture, with the temperature maintained at −40°C. After TLC analysis confirmed the reaction to be complete, satd ammonium chloride (20 ml) was added and the mixture extracted with ethyl acetate (3 × 20 ml) and washed with brine (2 × 40 ml). The organic fractions were collected and dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude product was subjected to column chromatography using silica gel (hexane/ethyl acetate [1:1]) to afford **3** (199 mg, 85 %) as a white solid with spectroscopic data identical to that reported above.

Acknowledgements

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