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A facile synthesis of 4,6-*O*-benzylidene glucal

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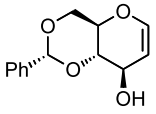
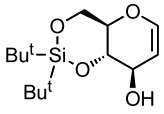
Abstract—4,6-*O*-Benzylidene protected D-glucal, a useful synthetic intermediate, may be accessed from the extremely cheap and readily available starting material α-methyl glucopyranoside, via a simple four-step reaction sequence involving selective triflation and iodide displacement at C-2.

Glycals are extremely useful carbohydrate derivatives, finding uses in oligosaccharide synthesis,[1] for Ferrier rearrangements[2,3] and for many other synthetic purposes as chiral building blocks.[4] Selective 4,6-*O* protection of a glycal is particularly useful since it allows manipulation of the remaining 3-hydroxyl group. Moreover, 4,6-*O*-benzylidene protection is particularly desirable since regioselective reductive cleavage of the benzylidene group,[5] which may be performed at any later point in a synthetic sequence, allows selective access to either the 4- or 6-hydroxyl groups as desired. As part of our ongoing investigations into the use of Tebbe/Claisen methodology for the synthesis of *C*-glycosides[6] we sought easy access to large quantities of 4,6-*O*-benzylidene protected glucal **1**.[7] Although the corresponding 4,6-*O*-silyl protected compound **2**[8] is readily available in four steps from glucose pentaacetate, by a sequence finally involving treatment of D-glucal with di-*tert*butylsilylditriflate, the corresponding 4,6-*O*-benzylidene material **1** is only available via a protracted reaction sequence;[9] attempts at simple 4,6-*O*-benzylidene protection of D-glucal are messy and very low yielding (best yields ~30%) due to the acid sensitivity of the enol ether functionality. To this end we sought an alternative approach to the useful building block **1**, preferably from cheap and readily available starting materials.



1



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Introduction of unsaturation by reductive elimination is the most commonly used method of glycal synthesis,[10] and is compatible with cyclic acetal protection. However the conventional route, which involves selective protection of the 4- and 6-hydroxyls, followed by installation of a bromide or chloride at the anomeric centre, and reductive elimination is protracted, and so an alternative approach was sought. The strategy adopted involved an attempt to perform the reductive elimination reaction in the reverse sense, by the introduction of a halogen selectively at C-2. α-Methyl glucopyranoside **3** was a particularly attractive starting material, due to a combination of its cost,[11] and also the ease by which 4,6-*O*-benzylidene protection may be achieved. To this end **3** was treated with benzyaldehyde dimethyl acetal and camphor sulfonic acid at 60°C under reduced pressure on a rotary evaporator to give the 4,6-benzylidene protected glycoside **4**[12] in 83% yield. Introduction of a halogen at C-2 required selective conversion of OH-2 into a leaving group and this was achieved by selective triflation[13] of the 2-hydroxyl group of **4**; a transformation that required the use of precise reaction conditions. Reaction[14] of **4** with 1.1 equiv. of triflic anhydride at −30°C in dichloromethane, in the presence of pyridine, gave the desired 2-*O*-triflate **5**[15] in an excellent 85% yield, together with a small amount of the di-triflate **6** (ratio of **5** to **6**: 20 to 1). Introduction of iodine at C-2 was then attempted by nucleophilic substitution of triflate **5** with iodide. Although introduction of iodide by displacement of C-2 triflates is well precedented for sugar lactones,[16] it is notable that there are only a few examples of the introduction of a halogen substituent by nucleophilic substitution at C-2 of pyranosides[17] since, for example, the direct displace-

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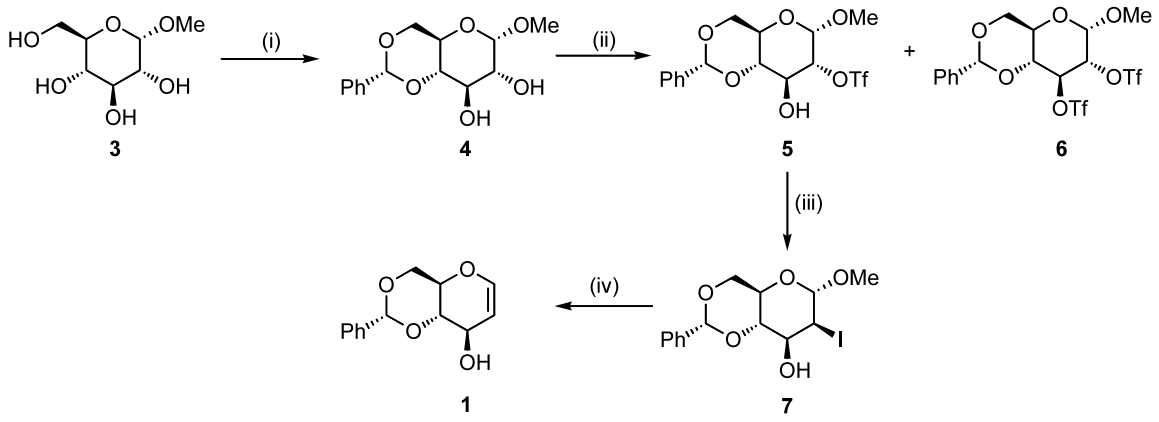

Scheme 1. *Reagents and conditions*: (i) $PhCH(OMe)_2$, CSA, DMF, 240 mbar, 60°C, 83%; (ii) Tf_2O, pyridine, CH_2Cl_2, −30°C, 85%, **5**:**6**, 20:1; (iii) Bu_4NI, toluene, 80°C, 83%; (iv) Zn, H_2PtCl_6, AcOH:CH_2Cl_2, 3:1, 69%.

ment of 2-*O*-tosylates does not normally occur with charged nucleophiles.[18] Once again, precise reaction conditions had to be employed[19] and in particular the choice of solvent proved to be crucial for the success of this transformation.[20] After screening several sets of reaction conditions, it was found that treatment of **5** with tetra-*n*-butyl ammonium iodide in toluene with heating to 80°C produced the desired iodide **7**[21] in 83% yield. Finally reductive elimination of iodide **7** was achieved by treatment with zinc in acetic acid[22] with dichloromethane as a co-solvent, in the presence of a catalytic amount of platinic chloride[23] to yield the desired glucal **1**,[24] in a satisfactory 69% yield (Scheme 1).

In conclusion this short reaction sequence, involving selective triflation of OH-2, introduction of iodine, and reductive elimination, provides an efficient synthesis of this important chiral building block from an extremely cheap starting material. In addition, since 2-iodo glycosides such as **7** may readily be reduced, this sequence of selective triflation and iodide displacement would in principle also give ready access to 2-deoxy glycosides. Studies into the use of glycal **1** for the synthesis of a variety of *C*-glycosides, *C*-glycosyl amino acids, and *C*-oligosaccharides, and also into use of the reaction sequence of selective triflation, iodide displacement, and reduction in order to access 2-deoxy oligosaccharides, are currently in progress, and the results will be reported in due course.

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14. Anhydrous pyridine (1.69 ml, 21.0 mmol) and then triflic anhydride (0.97 ml, 5.76 mmol) were added to anhydrous dichloromethane (30 ml) at −30°C, and the mixture stirred under an atmosphere of argon. Methyl glycoside **4** (1.479 g, 5.24 mmol) was dissolved in DCM (70 ml) and added to the reaction mixture via cannular. After 3 h, TLC (petrol:ethyl acetate, 4:1) indicated consumption of starting material ($R_f = 0.0$) and formation of a single product ($R_f = 0.4$). The reaction mixture was quenched by dropwise addition of water (2 ml), and concentrated in vacuo. The residue was taken up in dichloromethane (150 ml) and washed with water (2×150 ml), then dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by flash column chromatography (petrol:ethyl acetate, 4:1) to give the desired mono-triflate **5** and di-triflate **6** as a 20:1 mixture (combined yield of 85%), which could be recrystallised from ether/petrol to give the pure mono-triflate **5** (1.677 g, 77%) as a white crystalline solid.
15. (a) Data for **5**: mp 101–105°C (ether/petrol) [lit. 110–111°C];[15b] $[\alpha]_D^{21} = +81.2$ (*c* 0.91, $CHCl_3$) [lit. $[\alpha]_D^{23} = +73.3$ (*c* 0.51];[13a] δ_H (400 MHz, $CDCl_3$) 2.90 (1H, d, $J_{H\text{-}3,OH}$ 3.1 Hz, OH-3), 3.48 (3H, s, OCH_3), 3.51–3.55 (1H, m, H-4), 3.74 (1H, at, *J* 10.4 Hz, H-6), 3.80–3.89 (1H, m, H-5), 4.21–4.27 (1H, m, H-3), 4.32 (1H, dd, $J_{5,6'}$ 4.8 Hz, $J_{6,6'}$ 10.0 Hz, H-6′), 4.70 (1H, dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.3 Hz, H-2), 4.97 (1H, d, H-1), 5.54 (1H, s, $PhCHO_2$), 7.38–7.51 (5H, m, 5×Ar-H); (b) Tsuda, Y.; Nishimura, M.; Kobayashi, T.; Sato, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1991**, *39*, 2883–2887.
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19. Triflate **5** (2.55 g, 6.15 mmol) was dissolved in anhydrous toluene (80 ml), and tetra-*n*-butylammonium iodide (6.73 g, 18.46 mmol) was added. The mixture was stirred at 80°C under an atmosphere of argon for 4 h, when TLC (petrol:ethyl acetate, 4:1) indicated the consumption of starting material ($R_f = 0.4$) and formation of a major product ($R_f = 0.3$). The reaction mixture was concentrated in vacuo, and the residue taken up in ether (150 ml). The solution was washed with sodium thiosulphate (100 ml of a 10% aqueous solution) and water (100 ml) and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and the residue purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford iodide **7** (2.00 g, 83%) as a white crystalline solid.
20. No reaction occurred in ether, acetone, or DMF below 80°C. Although displacement did occur in DMF above 80°C, reductive elimination of the product was observed producing iodine, which in turn cleaved the 4,6-*O*-benzylidene protecting group. Addition of co-reductants was not able to suppress this benzylidene cleavage.
21. (a) Data for **7**: mp 94–96°C (ethyl acetate/petrol) [lit. 98–99 ($CHCl_3$/petrol)];[21b] $[\alpha]_D^{25} = +8.3$ (*c* 1.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.73 (1H, br s, OH-3), 3.32 (1H, dd, $J_{2,3}$ 4.1 Hz, $J_{3,4}$ 8.5 Hz, H-3), 3.39 (3H, s, OCH_3), 3.83–3.97 (m, H-4, H-5, H-6), 4.27 (1H, dd, $J_{5,6'}$ 2.5 Hz, $J_{6,6'}$ 8.2 Hz, H-6′), 4.48 (1H, d, H-2), 5.11 (1H, s, H-1), 5.59 (1H, s, PhCH), 7.35–7.90 (5H, m, 5×Ar-H); (b) Wood, K. R.; Kent, R. W.; Fisher, D. *J. Chem. Soc. C* **1966**, 912–913. δ_C (100.6 MHz, $CDCl_3$) 36.1 (d, C-2), 55.3 (q, $O\underline{C}H_3$), 64.1 (d), 66.0 (d, C-3), 68.6 (t, C-6), 81.3 (d), 102.2 (d, Ph$\underline{C}$H), 103.7(d, C-1), 126.3, 128.4, 129.3 (3×d, Ar-$\underline{C}$H), 137.0 (s, Ar-$\underline{C}$).
22. Alternative reduction conditions were also attempted; transmetallation with MeLi or the use of Zn in EtOH gave only low yields of product and in the latter case a major side product was identified as the 2-deoxy methyl glycoside. Notably no cleavage of the 4,6-*O*-benzylidene was observed in the acetic acid/dichloromethane solvent system.
23. To a solution of iodide **7** (2.70 g, 6.89 mmol) in dichloromethane (40 ml) was added zinc (4.50 g, 68.9 mmol), hydrogen hexachloroplatinate(IV) hydrate (28 mg, 0.069 mmol), and then acetic acid (15 ml). The mixture was stirred under an atmosphere of argon for 1 h until TLC (petrol:ethyl acetate, 2:1) showed consumption of starting material ($R_f = 0.5$) and formation of a major product ($R_f = 0.3$). The reaction mixture was diluted with dichloromethane (40 ml), sonicated for 2 min, and filtered through Celite®. The solution was washed with water (2×75 ml), and sodium bicarbonate (2×75 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo and purified by flash column chromatography (petrol:ethyl acetate, 3:1) to give glucal **1** (1.11 g, 69%) as a white crystalline solid.
24. Data for **1**: mp 134–138°C (ethyl acetate/petrol) [lit. 142–143°C (diethyl ether/hexane)];[7] $[\alpha]_D^{25} = -17.0$ (*c* 1.0, $CHCl_3$) [lit. $[\alpha]_D^{27} = -20$ (*c* 1.0, $CHCl_3$)];[7] δ_H (400 MHz, $CDCl_3$) 2.48 (1H, br s, OH), 3.78–3.85 (2H, m, H-4, H-5), 3.89–3.96 (1H, m, H-6), 4.38 (1H, dd, $J_{5,6'}$ 5.1 Hz, $J_{6,6'}$ 10.4 Hz, H-6′), 4.49–4.52 (1H, m, H-3), 4.77 (1H, dd, *J* 2.0 Hz, 6.4 Hz, H-2), 5.60 (1H, s, PhCH), 6.33–6.35 (1H, m, H-1), 7.36–7.54 (5H, m, 5×Ar-H).