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A convenient new route to protected and free 2,6-anhydro-D-glycero-D-gulo-heptoses (1-formyl-β-D-glucopyranosides)

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Abstract—A new and efficient process has been developed for the synthesis of 1-formyl-β-D-glucopyranosides from D-glucose.

C-Glycosides, in which the *exo*-anomeric oxygen atom is replaced by a methylene group, have been the subject of considerable interest in carbohydrate chemistry and biochemistry. A wide variety of applications[1] have been developed from this class of compounds including their use as synthetic intermediates for organic synthesis as well as inhibitors of glycosidases and glycosyltransferases. In addition they are used as models in enzymatic and metabolic studies, since it has been shown that the conformational differences between the *O*- (or *N*-) and *C*-linked analogues are minimal.[2] A number of reliable methods have been developed for the synthesis of *C*-linked disaccharides.[3] For example, the coupling between 1-formyl-*C*-glycosides and another sugar moiety or an aglycone residue was investigated for the formation of C–C bonds at the anomeric position.[4] Many syntheses of these highly-coveted *C*-glycosylaldehydes have been previously described[5] but they often afford an α/β anomeric mixture thus limiting their utilisation. Moreover, in most cases, yields are modest and, for the preparation of the most used aldehyde that is formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside,[5e–g,k,l] they are calculated from 2,3,4,6-tetra-*O*-benzyl-D-glucopyrolactone, which is commercially expensive and not readily available.

In line with our recent interest in indium-mediated stereoselective syntheses of *C*-linked glycosides and *C*-disaccharides under Barbier-type conditions in water,[4d,6] we needed to synthesise formyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside and formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside. In this communication, we wish to report a new and general method for the preparation of these two compounds from D-glucose along with the corresponding unprotected derivative.

Our approach towards the synthesis of sugar aldehydes is described in Scheme 1. It is based on the utilisation of β-*C*-glucosidic ketone **1**, which was recently prepared by our group[7] in one-step from D-glucose (96% yield). Indeed, to the best of our knowledge, this reaction constitutes the most efficient way to selectively form a C–C bond at the anomeric position of a pyranose. In our strategy described herein towards various protected formyl glucopyranosides, we postulated that, after appropriate alcohol protection, enolisation of the resulting ketone **2** using thermodynamic conditions then oxidative cleavage of the more substituted double bond, would furnish the desired aldehyde **6**.

We started our study with the preparation of formyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside **6a**.[5c] After acetylation of **1** (Ac_2O, pyridine, 91% yield) to give **2a**,[8] enolisation was performed under various conditions. We first carried out the reaction using the conditions described by Cazeau et al. with the Me_3SiCl–NaI–NEt_3 reagent.[9] The reaction proceeds very well at room temperature but the major product obtained was the less substituted enoxysilane **4a**. However, when triethylamine was replaced by pyridine, the reaction led only to the thermodynamic compound **3a**. With this base, the reaction was slower and was performed at 52 °C for 36 h to achieve complete

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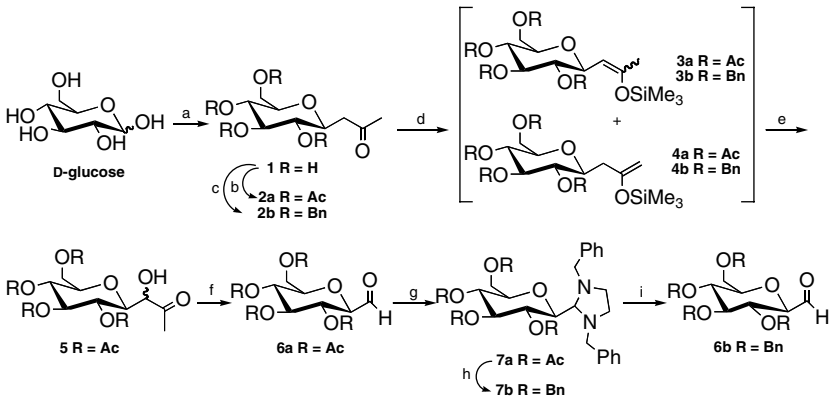


Scheme 1. Reagents and conditions: (a) pentan-2,4-dione, $NaHCO_3$, H_2O (**1**, 96%); (b) Ac_2O, pyridine (**2a**, 91%); (c) Ag_2O, BnBr, DMF (**2b**, 30–45%); (d) TMSCl, pyridine, NaI, CH_3CN/pentane (1.2/1); (e) i. dimethyldioxirane, K_2CO_3, acetone; ii. HCl, H_2O/THF (**5**); (f) $NaIO_4$, THF/H_2O (**6a**); (g) *N*,*N*-dibenzylethylene diamine, toluene (**7a**, 68% from **2a**); (h) i. NaOMe, MeOH; ii. NaH, BnBr, DMF (**7b**, 90%); (i) Dowex-H^+ resin, H_2O/THF (1/1) (**6b**, 94%).

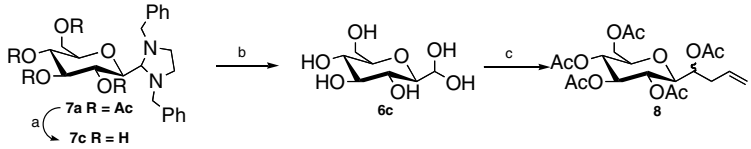
conversion. The reaction carried out in the biphasic acetonitrile–pentane medium allowed us to obtain rapid (12 h at 52 °C) and more reproducible results.

The resulting enoxysilane **3a** was then directly engaged (without purification) in an oxidation reaction with ozone at −78 °C in DCM. Under these conditions, modest yields of the aldehyde were obtained (40–50%). These results were improved by performing the oxidation in two steps. The enoxysilane was first transformed into α-hydroxyketone **5** by a freshly prepared solution of dimethyldioxirane.[10] Further treatment of **5** with sodium metaperiodate in THF–water provided the desired β-D-linked glucosyl aldehyde **6a**. Due to its instability and to achieve better purification by column chromatography, the product was protected and stored as aminal **7a**, which was obtained in 68% overall yield from **2a**. Deprotection with Dowex-H^+ resin led quantitatively to **6a**, which can be used directly without further purification.

The synthesis of formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **6b** was more challenging since obtaining *O*-benzylated ketone **2b** directly from **1** proved to be non-trivial. Indeed, the classical benzylation method (NaH, DMF, BnBr) led to complex mixtures whereas under milder conditions no reaction was observed. Only the utilisation of Ag_2O in DMF allowed us to obtained the desired compound **2b**. This reaction required large excess (8 equiv) of the expensive Ag_2O and gave **2b** in 30–45% yield. Nevertheless, **2b** could be obtained by an alternative but longer four-step sequence in 83% yield from **2a**. Ketone **2a** was protected with ethylene glycol in toluene, deacetylated (NaOMe in MeOH), benzylated with NaH in DMF and the cyclic ketal was deprotected (TFA/H_2O). Compound **2b** was then submitted to the enolisation conditions described above[11] but the reaction was not as regioselective as for **2a** and led to the formation of the thermodynamic product **3b** and the kinetic adduct **4b** in a ratio of 90/10. For these reasons, we decided not to pursue this way and formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **6b** was prepared in a three-step procedure from aminal **7a**. After deacetylation (NaOMe in MeOH) and benzylation with NaH in DMF, **7b** was obtained in 90% yield over two steps. Deprotection of the aminal with Dowex-H^+ resin led to β-D-linked glucosyl aldehyde **6b**, which was isolated in 94% yield after purification by column chromatography.

The synthesis of aminal **7a** also allowed us to prepare the free aldehyde **6c**.[5h] This was achieved by simple acetate deprotection (NaOMe in MeOH) to **7c**, directly followed by removal of the aminal function (Dowex-H^+ resin). For proof of our obtaining aldehyde **6c**, its hydrated form was allowed to react in a mixture of water and THF (1/1) in the presence of allyl bromide and indium. After acetylation of the reaction mixture, **8** was obtained in 85% yield over four steps (Scheme 2).

In summary, we have reported an efficient strategy for the preparation of synthetically useful 1-formyl-β-D-glucopyranosides from D-glucose. Indeed, only five steps from D-glucose were required to synthesise formyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside in 59% overall yield. The use of this new protocol also allowed us to prepare formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (nine steps, 50% overall yield from D-glucose)



Scheme 2. Reagents and conditions: (a) NaOMe, MeOH (**7c**); (b) Dowex-H^+ resin, H_2O/THF (1/1) (**6c**); (c) i. allyl bromide, In, H_2O/THF (1/1); ii. Ac_2O, pyridine (**8**, 85% over four steps).

and 1-formyl-β-D-glucopyranoside (eight steps, 50% overall yield from D-glucose). Further applications of the above method for the synthesis of *C*-disaccharides will be presented in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.034. This contains a typical procedure for the preparation of compounds **2a**, **5**, **7a**, **7b**, **8** and their ^{1}H, ^{13}C and elemental analysis data. ^{1}H data for **3a**, ^{1}H and ^{13}C data for **6a**, **6c**. Procedure for the preparation of aldehydes **6a**, **6b** and **6c**.

References and notes

1. (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983; (b) BeMiller, J. N.; Yadav, M. P.; Kalabokis, V. N.; Myers, R. W. *Carbohydr. Res.* **1990**, *200*, 111; (c) Schmidt, R. R.; Dietrich, H. *Angew. Chem., Int. Ed.* **1991**, *30*, 1328; (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55; (e) Wang, J.; Kovac, P.; Sinay, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1998**, *308*, 191; (f) Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* **1999**, *5*, 1384.
2. (a) Wu, T. C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819; (b) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H. S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160, and references cited therein.
3. Recent reviews: (a) Postema, H. D. *Tetrahedron* **1992**, *48*, 8545; (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995; (c) Du, Y.; Lindhart, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913.
4. (a) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1844; (b) Dondoni, A.; Boscarato, A.; Zuurmond, H. *Tetrahedron Lett.* **1996**, *37*, 7587; (c) Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114; (d) Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206.
5. (a) Dettinger, H.-M.; Kurz, G.; Lehmann *J. Carbohydr. Res.* **1979**, *74*, 301; (b) Reed, L. A.; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 6468; (c) Martin, O. R.; Khamis, F. E.; Prahlada Rao, S. *Tetrahedron Lett.* **1989**, *30*, 6143; (d) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. *Tetrahedron Lett.* **1992**, *33*, 737; (e) Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7319; (f) Lasterra Sanchez, M. E.; Michelet, V.; Besnier, I.; Genêt, J.-P. *Synlett* **1994**, 705; (g) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404; (h) Petrusova, M.; BeMiller, J. N.; Krihnova, A.; Petrus, L. *Carbohydr. Res.* **1996**, *295*, 57; (i) Dent, B. R.; Furneaux, R. H.; Gainsford, G. J.; Lynch, G. P. *Tetrahedron* **1999**, *55*, 6977; (j) Zhu, Y.-H.; Vogel, P. *Synlett* **2001**, 79; (k) Labéguère, F.; Lavergne, J.-P.; Martinez, J. *Tetrahedron Lett.* **2002**, *43*, 7271; (l) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13.
6. Lubineau, A.; Canac, Y.; Le Goff, N. *Adv. Synth. Catal.* **2002**, *344*, 319.
7. Rodrigues, F.; Canac, Y.; Lubineau, A. *Chem. Commun.* **2000**, 2049.
8. Riemann, I.; Papadopoulos, M. A.; Knorst, M.; Fessner, W.-D. *Aust. J. Chem.* **2002**, *55*, 147.
9. Cazeau, P.; Buboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089.
10. Prepared according to: Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
11. The reaction was carried out at room temperature since degradation was observed with heating at 52 °C.