Pergamon

Tetrahedron Letters 43 (2002) 7027–7030

TETRAHEDRON LETTERS

Reducing oligosaccharides via glycal assembly: on the remarkable stability of anomeric hydroxyl groups to global deprotection with sodium in liquid ammonia

Ulrich Iserloh,[a] Vadim Dudkin,[a] Zhi-Guang Wang[a] and Samuel J. Danishefsky[a,b,*]

[a]*Laboratory for Bioorganic Chemistry, The Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10021, USA*

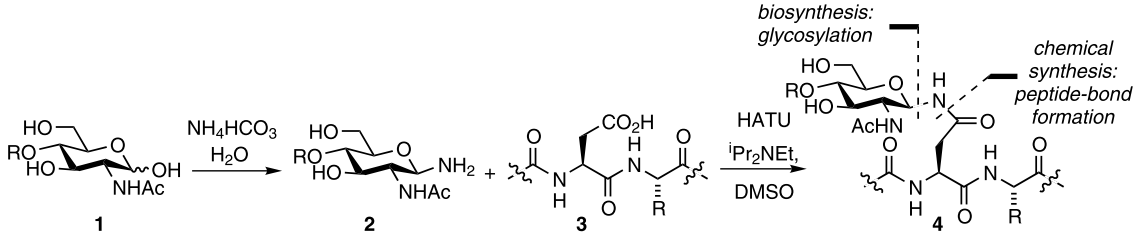
[b]*Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY 10027, USA*

Received 11 July 2002; accepted 26 July 2002

Abstract—Several partially benzylated 1-hydroxy sugars were rapidly deprotected by sodium/liquid ammonia. The terminal hemiketal linkage of the substrates remained intact under these conditions and does not generate ring-opened alditols. Peracetylated glucose and glucosamine derivatives were obtained in 64–79% isolated yields. © 2002 Published by Elsevier Science Ltd.

Glycopeptides are classified on the basis of the attachment mode of an oligosaccharide to the amino acid side-chain of the peptide domain. In *N*-linked glycopeptides (**4**), the asparagine γ-carboxamide is glycosylated with a conserved (high mannose) pentasaccharide core structure.[1] Within the cellular context, this linkage is generated via glycosylation of the asparagine amide side-chain. By contrast, the most promising laboratory approach for synthesizing these compounds involves peptide-bond formation between a glycosylamine (**2**) and the γ-carboxylate of a uniquely disposed aspartate (**3**, Scheme 1).[2] The glycosylamine (**2**) is, in turn, most readily generated via standard Kochetkov–Lansbury amination[3] (NH_4HCO_3/H_2O, 25°C) from the globally deprotected parent saccharide **1**, presenting a free anomeric hydroxy group. Given our interest in synthesizing *N*-linked glycopeptide constructs of complex glycans, we had a need to reach systems such as **2** in the context of structurally challenging oligosaccharides. From the perspective of our laboratory it would be particularly convenient if we could merge the advantages of the glycal route to complex oligosaccharides with the Kochetkov–Lansbury methodology[3] for advancing from oligosaccharides to *N*-linked constructs.

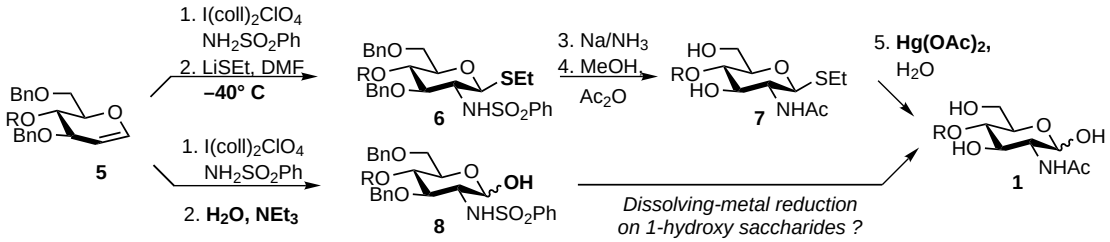
Preparations of generic precursors of the type **1** can be achieved via a number of pathways. One such route, involving the glycal assembly technology,[4] is shown in Scheme 2: glucal **5** was converted into the prototypical 2-*N*-acetylglucose (**1**) via thioglycosides **6** and **7**.[5] In the deprotection of resident benzyl groups, either Pd-mediated hydrogenolysis or dissolving metal conditions have been extensively employed. However, out of concern for the integrity of the terminal hemiketal linkage during Birch-type reductive conditions, such deprotection of the systems of the type **8** had not been attempted.



Scheme 1.

* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01551-4



Scheme 2.

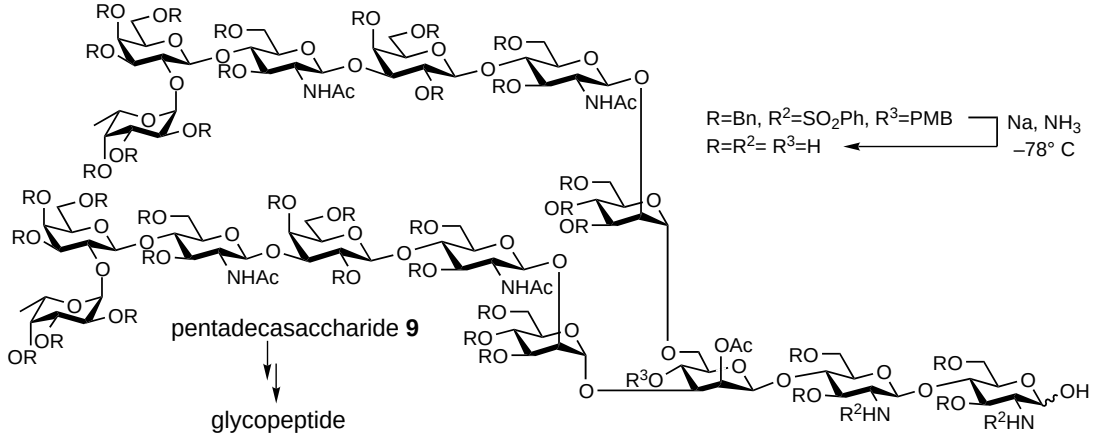
Rather, we resorted to iodosulfonamidation[6] of glucal **5**, followed by LiSEt-induced rearrangement at –40°C giving rise to a protected thioglycoside intermediate (**6**). This type of system was subjected to dissolving metal reduction. After *N*-acetylation, deprotected thioglycoside **7** is hydrolysed in the presence of Hg(II) salts to introduce the required anomeric hydroxyl group.

In this letter, we report the important finding that, in fact, deprotection of partially benzylated mono- and disaccharides containing free anomeric hydroxyl-groups under dissolving metal conditions is entirely possible. Happily, the terminal hemiketal linkage remains intact and ring-opened alditol products are not produced. This capability obviates the need for more complex protocols for accomplishing the overall transformation of synthetic glycals to Kochetkov–Lansbury precursors.

We note at the outset that these studies were occasioned by a recent isolated case in 2001.[7] During the synthesis of pentadecasaccharide **9**, 37 benzyl groups and two sulfonamido groups were removed in a single massive deprotection step (1. Na/NH_3, 2. Ac_2O, 46%; Scheme 3). While the product was obtained in 46% yield, we deemed this result promising. Based on this precedent, we proceeded to evaluate the scope of the method in the context of simpler model structures, featuring either a 1,2-dihydroxy or a 1-hydroxy-2-amino-based functionality in their reducing domains.

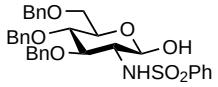
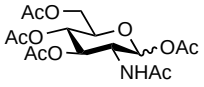
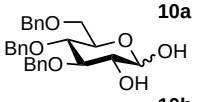
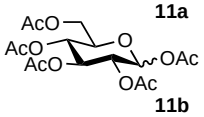
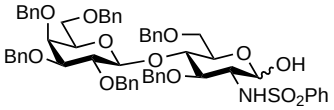
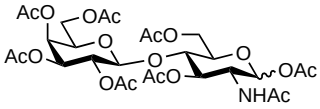
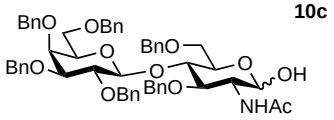
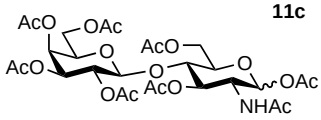
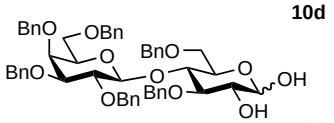
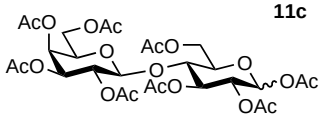
The preparation of test substrates **10a**–**10e** was carried out along established routes, starting from commercially available tribenzylglucal or hexabenzyllactal (Table 1). Following iodosulfonamidation with IDCP/NH_2SO_2Ph, the resulting intermediates were directly subjected to hydrolysis (H_2O/Et_3N) to provide sulfonamides **10a** and **10c** in good yield.[6] The corresponding 1,2-dihydroxy saccharides **10b** and **10e** were prepared by DMDO-mediated glycal-epoxidation, followed by exposure of the oxiranes to an aqueous $ZnCl_2$ solution. With ample quantities of compounds **10** in hand, we began investigating the effect of reaction time in Birch-type deprotections (ammonia/sodium at –78°C). Reactions were quenched with solid NH_4Cl, concentrated in vacuo and peracetylated, prior to analysis by LCMS for any traces of ring-opened alditols. *Interestingly*, *the anomeric linkage of amides* ***10a***, ***10c***, *and* ***10d*** *proved very robust and survived the Birch-type conditions for at least 60 min*. In contrast, 1,2-dihydroxy saccharides **10b** and **10e** were less stable and generated about 15% of alditols over the course of 60 min. In these cases, a 10–20 min reaction time was sufficient to achieve complete deprotection without observable hemiketal reductive opening. For the purposes of obtaining accurate yields the fully deprotected products were subjected to direct peracetylation followed by silica gel chromatography. The yields for peracetylated materials **11a**–**11d** were in the range of 64–79%. All products exhibited satisfactory LRMS data and spectral properties as previously described in the literature.[8]

In summary, free anomeric hydroxy-groups in carbohydrate–hemiketal linkages are stable to sodium–ammonia debenzylation conditions. Since it can well be assumed that any free aldehydes at the sugar terminus would be rapidly reduced, the success of these reactions



Scheme 3.

Table 1.

Deprotection substrate	Peracetylated product	Time[a]	Yield[b]
D-glucal derivatives			
 **10a**	 **11a**	60 min	64%
 **10b**	 **11b**	20 min	75%
D-lactal derivatives			
 **10c**	 **11c**	60 min	76%
 **10d**	 **11c**	60 min	72%
 **10e**	 **11d**	20 min	79%

[a] Reaction time for dissolving metal reduction. Reactions were performed by the addition of saccharide **1**, dissolved in THF, to a stirred solution of Na (6 equiv per benzyl-group) in NH_3 at –78° C. After quenching and workup, the crude solid was peracetylated for analysis. [b] Isolated yield by column chromatography.

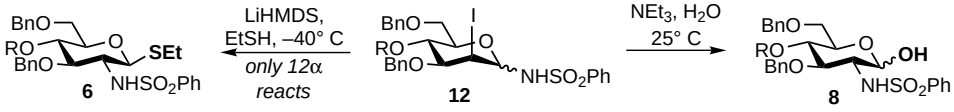
underscores the dominance of the closed hemiacetal form (or its corresponding alkoxide) under these conditions. This route to glycal-derived 1-hydroxy sugars presents several major advantages in terms of simplicity over the thioglycoside route described above: the moisture sensitive LiSEt-mediated rearrangement of iodosulfonamide **12** (Scheme 4) into thioglycoside (**6**) can now be circumvented and replaced with a much simpler protocol utilizing aqueous triethylamine (**12**→**8**). Toxic Hg(II)-salts are no longer required in the route shown here. Moreover, both anomers of **12** are efficiently utilized in this protocol to give **8**, whereas progression to a generic type **6** system is only possible with the *trans*-diaxial iodosulfonamide. The streamlined synthesis allows for increased efficiency, which is paramount for producing required quantities of glycosyl amines (**2**) en route to *N*-linked glycopeptides and, eventually, *N*-linked glycoproteins. Applications of these findings will be disclosed shortly.

Acknowledgements

This work was supported by grants from the National Institutes of Health (CA-28824). A postdoctoral fellowship is gratefully acknowledged by U.I. (NIH F32 CA88478-02).

References

1. (a) Montreuil, J.; Vliegenthart, J. F. G.; Schachter, H. In *Glycopeptides*; Neuberger, A.; Van Deenen, L. L. M., Series Eds.; Elsevier: New York, 1995; Vol. 29a; (b) Rudd, P. M.; Wormald, M. R.; Stanfield, R. L.; Huang, M.; Mattsson, N.; Speir, J. A.; DiGennaro, J. A.; Fetrow, J. S.; Dwek, R. A.; Wilson, I. A. *J. Mol. Biol.* **1999**, *293*, 351–366; (c) Wormald, M. R.; Dwek, R. A. *Structure* **1999**, *7*, R155–R160.
2. Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–601.



Scheme 4.

3. (a) Likhosherstov, L. M.; Novikova, O. S.; Derevitskaja, V. A.; Kochetkov, N. K. *Carbohydr. Res.* **1986**, *146*, C1–C5; (b) Cohen-Anisfeld, S. T.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 10531.
4. Review: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419.
5. Wang, Z.-G.; Zhang, X.; Live, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3652–3656.
6. Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819.
7. Wang, Z.-G.; Zhang, X.; Visser, M.; Live, D.; Zatorski, A.; Iserloh, U.; Lloyd, K. O.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1728–1732.
8. *Representative procedure*: Liquid NH_3 (15 mL) was condensed at −78°C into a 2-neck flask (25 mL) equipped with stir bar and dewar-type condenser (all equipment oven-dried, then cooled under a stream of argon). Solid sodium (47 mg, 2.0 mmol, 42 equiv.) was added, and the resulting deep blue solution was stirred for 10 min. A solution of disaccharide **10c** (53 mg, 51 μmol) in THF (1 mL) was added, and the reaction was continued to stir for 60 min at −78°C. Upon removing the cold finger, solid NH_4Cl (300 mg, 5.6 mmol) was added and the suspension was vigorously stirred until the blue color disappeared. The reaction vessel was subsequently removed from its cooling bath, warmed to 25°C, and the resulting white solid was dried in vacuo for 30 min. Pyridine (6 mL) and DMAP (5 mg) were added to the 2-neck flask, followed by Ac_2O (4 mL). After stirring the reaction at 25°C for 15 h, EtOAc (25 mL) was added, followed by washing of the combined organic phases with sat. $NaHCO_3$, H_2O and brine. After drying over Na_2SO_4 and concentrating in vacuo, the resulting white solid was chromatographed over silica (100% EtOAc) to yield octaacetate **11c** as a mixture of α/β-anomers (26.8 mg, 39.5 μmol, 76%). For characterization data of peracetylated materials, see: (a) **11a**: Kretzschmar, G.; Stahl, W. *Tetrahedron* **1998**, *54*, 6341–58 and Bamford, M. J.; Pichel, J. C.; Husman, W.; Patel, B.; Storer, R.; Weir, N. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1181–85; (b) **11b**: Shimizu, H.; Brown, J. M.; Homans, S. W.; Field, R. A. *Tetrahedron* **1998**, *54*, 9489–9506; (c) **11c**: Range, G.; Krähmer, R.; Welzel, P.; Müller, D.; Herrmann, G. F.; Kragl, U.; Wandrey, C.; Markus, A.; v. Heijenoort, Y.; v. Heijenoort, J. *Tetrahedron* **1997**, *53*, 1695–1706; (d) **11d**: Wang, R.; Steensma, D. H.; Takaoka, Y.; Yun, J. W.; Kajimoto, T.; Wong, C.-H. *Bioorg. Med. Chem.* **1997**, *5*, 661–672.