

Concise methods for the synthesis of 2-aminosugars

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ABSTRACT

Over the last decade, advances in the stereoselective synthesis of 2-aminosugars from glycols have led to more concise methods of obtaining natural products and glycoconjugates. This review highlights some recent methods for the synthesis of 2-aminosugars that should facilitate access to significant quantities of homogeneous material for structural and functional studies in glycobiology.

The presence of 2-aminosugars in nearly every class of glycoconjugates and a number of natural products has inspired the development of synthetic methods for the construction of 2-aminoglycosides.¹ While naturally occurring 2-aminosugars are readily available commercially, with exception of D-glucosamine hydrochloride, they are rather expensive and not practical starting materials for multi-step syntheses. Therefore, there has been considerable interest in devising novel methods for the synthesis of 2-aminosugars from glycols², which are easily accessible on large scale from less costly monosaccharides such as D-glucose or D-galactose.

The pioneering work of Lemieux and Ratcliffe, demonstrated that azidonitration could be performed on tri-*O*-acetyl-D-galactal (**1**) to afford the corresponding azidonitrates **2** and **3** in very good yield (~80%) with excellent stereoselectivity (Figure 1A).³ Unfortunately, azidonitration of tri-*O*-acetyl-D-glucal (**4**) gives azidonitrates **5** and **6** with very poor stereoselectivity, due to lack of substrate direction at C-4 (Figure 1B).⁴ These 2-azidoglycosyl nitrates could be efficiently converted to the corresponding anomeric halides and used a glycosyl donors under Koenigs Knorr conditions for the synthesis of 2-*N*-

acetamido- β -D-pyranosides.⁵ The use of azide at C-2 of the pyranoside provides a non-participating group for glycosylation reactions affording the β -glycoside as the

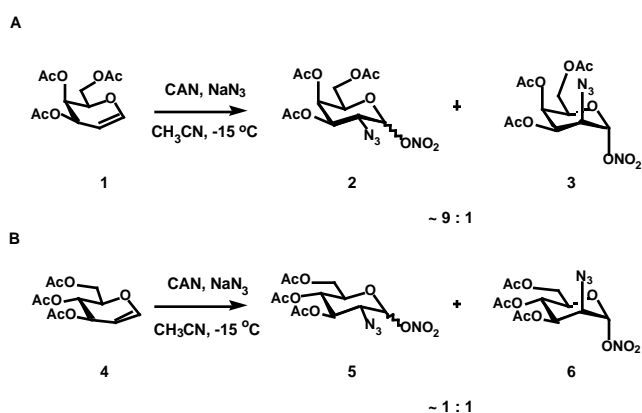


Figure 1. Azidonitration of glycols.

¹ (a) Banoub, J. *Chem. Rev.* **1992**, 92, 1167-1195. (b) Knapp, S. *Chem. Soc. Rev.* **1999**, 28, 61-72.

² Danishefsky, S. J.; Bilodeau, M.T. *Angew. Chem. Int. Ed.* **1996**, 35, 1380-1419.

³ Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, 57, 1244-1251.

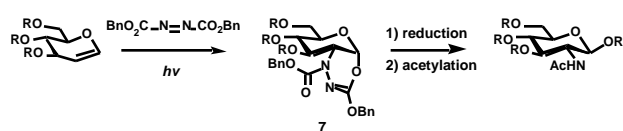
⁴ (a) Kinzy, W.; Schmidt, R. R. *Tetrahedron Lett.* **1987**, 28, 1981-1984. (b) Paulsen, H.; Lorentzen, J. P. *Carbohydr. Res.* **1984**, 133, C1-C4.

major product. This approach has been the most widely used method for the synthesis of 2-*N*-acetamido- β -D-pyranosides, particularly for the synthesis of *N*-acetylgalactosamine β -linked to hydroxyl side chain of

⁵ Review of glycosylation methods: Nicolau, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **2001**, 40, 1576-1624.

serine or threonine in *O*-linked glycoproteins.⁶

Fitzsimmons and LeBlanc Cycloaddition



Danishefsky and Griffith Sulfonamidoglycosylation

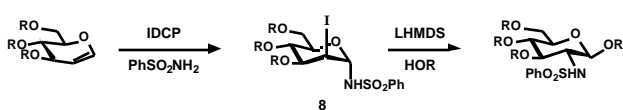


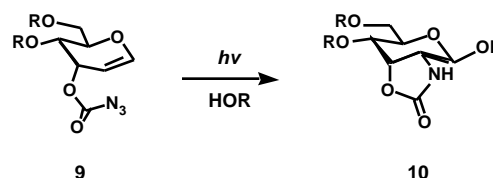
Figure 2. Synthesis of 2-aminosugars by photoinduced [4 + 2] cycloaddition and sulfonamidoglycosylation.

While azidonitration is an extremely useful method for introduction of nitrogen at C-2 of the pyranose ring, amination and glycosylation remain two separate steps requiring the conversion of the azidonitrate into a suitable glycosyl donor for glycosylation. In the late 1980's to early 1990's two elegant methods were developed by Fitzsimmons/LeBlanc⁷ and Danishefsky/Griffith⁸ to couple amination with glycosylation into a more concise sequence of synthetic manipulations (Figure 2). The approach taken by Fitzsimmons and LeBlanc involves a photoinduced [4 + 2] cycloaddition of dibenzyl azodicarboxylate ($\text{BnO}_2\text{C-N=N-CO}_2\text{Bn}$, DBAD) with glycals to stereoselectively introduce nitrogen at C-2. The resulting cycloadducts (**7**) could then be used directly as donors for glycosylation reactions. Raney Ni deprotection of nitrogen followed by acetylation affords 2-*N*-acetamido- -pyranosides. An alternative approach taken by Danishefsky and Griffith utilizes the stereoselective iodoglycosylation of glycals with iodonium di-*sym*-collidine perchlorate (IDCP) and benzene sulfonamide to afford 2-iodo- -sulfonamidopyranoside (**8**). Treatment of **8** with lithium hexamethyldisilazide (LHMDS) generates the intermediate sulfonylaziridine that is attacked from the β -face of the anomeric carbon with nucleophilic acceptor. Deprotection of the sulfonamide followed by acetylation provides 2-*N*-acetamido- -pyranosides in good yields. The utility of the sulfonamidoglycosylation methodology has been demonstrated in the total synthesis of the natural product

chitinase inhibitor, allosamidin⁹ and more recently in the total chemical synthesis of an *N*-linked glycopeptide¹⁰.

Both of the approaches described above have provided novel methods for allowing the amination and glycosylation of glycals in two steps. Two recent approaches by Rojas¹¹ and Nicolau¹² have reduced the task of amination and glycosylation into one step by tethering the source of nitrogen donor (Figure 3). Rojas' photo amidoglycosylation takes advantage of intramolecular delivery of nitrogen from allal C-3 azidoformate (**9**) in the presence of the alcohol acceptor, which affords 2-*N*-acetamido- -alloypyranosides (**10**) stereoselectively. The recent develop of IBX-mediated oxidation methodology by Nicolau and coworkers allowed the application of this methodology to 2-aminosugars syntheses.¹³ The reaction of glycal C-3 urethanes (**11**) with IBX in the presence of water provides the protected forms of the 2-aminosugars (**12**) in a single step. While this method is extremely useful for generating libraries of aminosugars, the reaction provides 2-aminopyranosides with free reducing ends and does not allow access to glycosides. The intramolecular amination of glycals allows for excellent stereoselectivities for the synthesis of aminosugars. However, tethered approaches are somewhat limited to introducing nitrogen *cis* to hydroxy functionality.

Rojas Photo Amidoglycosylation



Nicolau IBX-mediated method

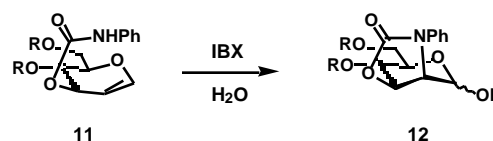


Figure 3. Tethered approaches for the synthesis of 2-aminosugars.

⁶ (a) Schwarz, J. B.; Kuduk, S. D.; Chen, X-T.; Williams, L. J.; Sames, D.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 2662-2673. (b) Herzner, H.; Reipen, T.; Shultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495-4537.

⁷ (a) LeBlanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995-3000. (b) LeBlanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889-2892. (c) Fitzsimmons, B. J.; LeBlanc, Y.; Chan, N.; Rokach, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229-5231.

⁸ Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811-5819.

⁹ (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863-5864. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526-9538.

¹⁰ (a) 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. (b) Wang, Z-G.; Zhang, X.; Live, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3652-3656.

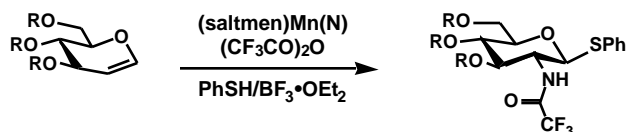
¹¹ Kan, C.; Long, C. M.; Moushumi, P.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381-384.

¹² Nicolau, K. C.; Baran, P.S.; Zhong, Y.L.; Vega, J.A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525-2529.

¹³ Nicolau, K. C.; Zhong, Y.L.; Baran, P.S. *Angew. Chem. Int. Ed.*

The recent advances in synthetic methodology have provided new opportunities for one-pot amination and glycosylation of glycols. The extension of the nitrogen transfer nitridomanganese(V) complexes by Du Bois and Carreira allowed the aziridination of glycols with (saltmen)Mn(N) and trifluoroacetic anhydride (Figure 4).¹⁴ In the presence of acid and water the initial product *N*-trifluoroacetyl aziridine opens to afford the corresponding free reducing sugars. However, treatment of the *N*-trifluoroacetyl aziridine with a Lewis acid and thiophenol affords the thioglycoside in good yield and high stereoselectivities. More recently, the introduction of one-pot acetamidoglycosylation by Gin and coworkers provides direct access to 2-*N*-acetamido- -pyranosides.¹⁵ The reaction of the glycol with first set of reagents results in the formation of an oxazoline intermediate, which upon treatment with acidic resin and alcohol acceptor opens to afford the -glycoside products in good to moderate yield. This is the first method that directly affords the desired 2-*N*-acetamido- -pyranosides from glycols, which should facilitate the synthesis of glycoconjugates containing these monosaccharides.

Du Bois and Carreria Method



Gin Acetamidoglycosylation

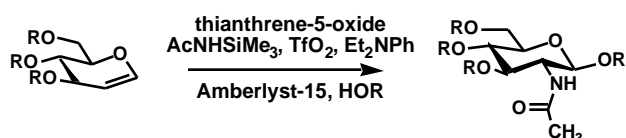


Figure 4. One-pot syntheses of 2-aminosugars from glycols

All of the methods described above either produce 2-*N*-acetamido- -pyranosides or free reducing sugars as the product of the reaction and does not provide access to 2-*N*-acetamido- -pyranosides. Therefore, the synthesis of 2-*N*-acetamido- -pyranosides still rely upon 2-azidoglycosyl donors or non-participating protecting groups on nitrogen. Unfortunately, most of nitrogen protecting groups that have been developed participate in glycosylation reactions and afford the -glycoside as the major product.¹⁶ To convert naturally occurring 2-aminosugars into 2-

2000, 39, 625-628.

¹⁴ Dubois, J.; Tomooka, C. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179-3180.

¹⁵ Bussolo, V. D.; Liu, J.; Huffman, L. G.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 204-207.

¹⁶ Jiao, H.; Hindsgaul, O. *Angew. Chem. Int. Ed.* **1999**, *38*, 346-348 and references therein.

azidosugars, Wong and coworkers have utilized a metal-catalyzed diazo transfer approach to convert amines into azides.¹⁷ However, this methodology is not cost effective for 2-aminosugars other than D-glucosamine and hazardous, because trifluoromethanesulfonyl azide is a potentially explosive reagent. A novel approach by Schmidt and coworkers involve a Michael-type addition to tri-*O*-benzyl-2-nitro-D-galactal (**13**), which provides good / selectivity in the formation of glycosidic linkage.¹⁸ While this approach requires the synthesis of **13** and multiple protecting group manipulations to generate the glyco-amino acid building block required for SPPS, the overall yields of the reaction sequence are very good. The efficiency of this approach was recently demonstrated in the syntheses of various core *O*-linked glycoamino acid building blocks (Figure 5).¹⁹

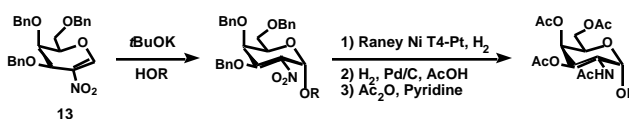


Figure 5. Synthesis of 2-aminosugars by Michael-type addition by Schmidt and coworkers.

Very recently, Kerns and coworkers have utilized the oxazolidinone protecting group between the 3-OH and 2-NH of the pyranose ring to effectively eliminate neighboring group participation in glycosylation reactions.²⁰ This simple and very elegant strategy provides general and useful solution to the synthesis of -linked glycosides of 2-aminosugars.

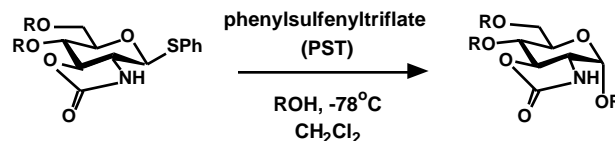


Figure 6. Oxazolidinone protection of 2-aminosugars for synthesis of -linked glycosides.

¹⁷ Alper, P. B.; Hung S.C.; Wong, C-H. *Tetrahedron Lett.* **1996**, *37*, 6029-6032.

¹⁸ (a) Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167-1171. (b) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609-1613.

¹⁹ Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2654-2657.

²⁰ Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, ASAP,

The advances in carbohydrate chemistry highlighted above provide more concise methods for the synthesis of 2-aminosugars. These novel and concise methods should facilitate the synthesis of α - and β -linked 2-*N*-acetamidopyranosides, which are prevalent in a variety of

glycoconjugates and intermediate metabolites of carbohydrate biosynthesis. These methods should provide access to homogeneous material in significant quantities for structural and functional studies to further our understanding of glycobiology.