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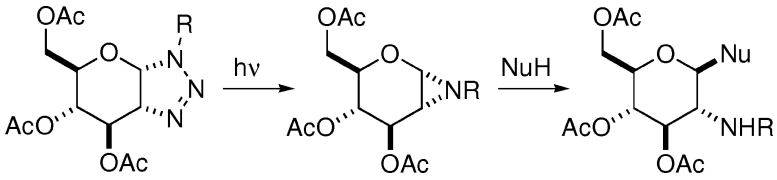

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A Surprising Dipolar Cycloaddition Provides Ready Access to Aminoglycosides

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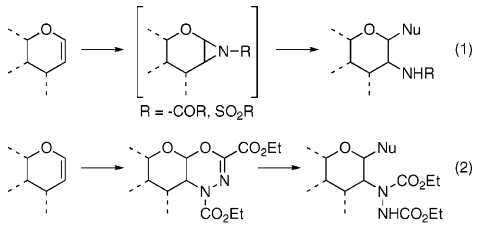
As appreciation for the biological importance of carbohydrates has increased, so have efforts to develop methods for the synthesis of biologically relevant oligosaccharides, glycoconjugates, and analogues thereof.[1] Among the more challenging synthetic targets are aminoglycosides and their derivatives. Despite apparent similarity, hexoses and 2-deoxy-2-aminohexoses pose very different synthetic challenges, the aminosugars proving more difficult to prepare or transform.[1] Aminoglycosides are typically synthesized by one of two approaches: modification of glucose or glucosamine,[2] or introduction of a nitrogen substituent into a glycal derivative.[3−5] The former method requires extensive protecting-group manipulation, while the latter has fewer embodiments. We describe here an approach to installing a nitrogen substituent at C2 of glycals that is both novel and operationally simple.

Among the existing methods for the direct introduction of a nitrogen substituent at C2 of a glycal, the most extensively studied are: (1) iodosulfonamidation followed by aziridine generation (eq 1).[3a−c,4] (2) aziridine generation via a stoichiometric (nitrido)Mn(V) oxidant (eq 1).[3d,4] and (3) oxazoline generation via *C2*-sulfonium intermediates.[5,6] With the exception of dialkyl azodicarboxylate hetero-Diels−Alder reactions (eq 2),[7] methods that rely on cycloaddition for introduction of the nitrogen functionality are largely absent despite the prevalence of nitrogen-containing dipoles. In the course of synthesizing aminoglycoside inhibitors of chitin synthase, we began exploring dipolar cycloadditions that could lead to subsequent aziridine generation.

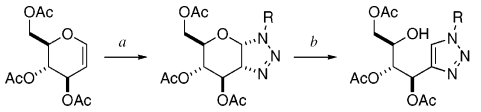


After extensive experimentation, we have found that glycals with electron-withdrawing protecting groups undergo efficient cycloaddition with electron-rich azides and that the cycloadducts can be transformed to semi-stable aziridines which react with nucleophiles under mild conditions to afford diverse aminoglycoside products.[8−10]

Tri-*O*-acetyl-D-glucal (**1**) readily engages in dipolar cycloadditions with alkyl azides, such as benzyl azide, 3,5-dimethoxybenzyl azide, and 1-adamantyl azide, at elevated temperature.[11] Judicious choice of solvent is critical to the outcome of the reaction. If the cycloaddition is carried out at high temperature in trimethyl- or triethylorthoformate, the unstable triazoline intermediates (**2a**−**c**) can be isolated in good yield with little or no purification. In all other solvents the triazoline undergoes elimination to afford the corresponding triazole (Scheme 1).[12]

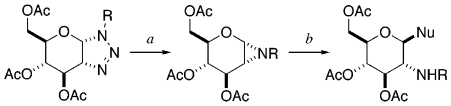
Similarly, all efforts to convert isolated triazolines **2a**−**c** to a reactive aziridine in the presence of a nucleophile and acid or Lewis

Scheme 1. Synthesis of Triazolines from Tri-*O*-acetyl-D-glucal



[a] RN_3 $CH(OEt)_3$, reflux, 24−36 h. [b] acid, base, or Lewis acid. DMB = 3,5-dimethoxybenzyl.

Scheme 2. Transformation of Triazolines to Aminoglycosides



[a] hν, $(CH_3)_2CO$, 10−12 h. [b] NuH (Chart 1), $Sc(OTf)_3$.

acid led, at best, to poor yields of the corresponding aminoglycoside derivatives accompanied by extensive elimination to triazole. In the case of **2c**, small amounts of the aziridine (**4c**) could be generated thermally, although this intermediate could not be intercepted. Attempts at photochemical generation of aziridine **4b** from triazoline **2b** led only to cycloreversion. Fortunately, triazoline **2a** underwent clean, quantitative photochemical conversion to the corresponding aziridine, **4a**, provided the photolysis was carried out in acetone (Scheme 2).[13,14] The intermediate aziridine was not isolated or purified, although photolysis in acetone-d_6 allowed the acquisition of a clean ^{1}H NMR spectrum consistent with the proposed aziridine intermediate.[15]

More importantly, solutions of the aziridine generated in acetone could be transferred directly to solutions of nucleophile in THF containing an appropriate Lewis acid. Again, careful selection of reagent (Lewis acid) was critical. In the presence of 0.2 equiv of $Sc(OTf)_3$ and 2−3 equiv of nucleophile, aziridine **4a** underwent clean reaction with a range of nucleophiles to afford the corresponding aminoglycoside derivatives (**5**−**15**, Scheme 2, Chart 1) possessing exclusively the β-configuration.[15,16]

While all reactions were carried out in pure dry solvents, no efforts were made to exclude oxygen or water; despite this, good to excellent yields of almost all aminoglycosides were realized. Among the notable successes are the reactions with a secondary alcohols (**7**, **10**), a nitrogen nucleophile (**11**), and more complex alcohols (**12**−**14**). The preparation of **14** bodes well for developing iterative versions of this reaction.

Two notable exceptions to the generally good yields are the reactions of **4a** with BnSH and glycine methyl ester. The former gives only moderate yields of the adduct, while reaction with the latter provides none of the desired product. In each case, the remaining material is a mixture of the products of aziridine hydrolysis and condensation with the enol tautomer of acetone.[17] This observation led us to expose the crude aziridine to $Sc(OTf)_3$ in the

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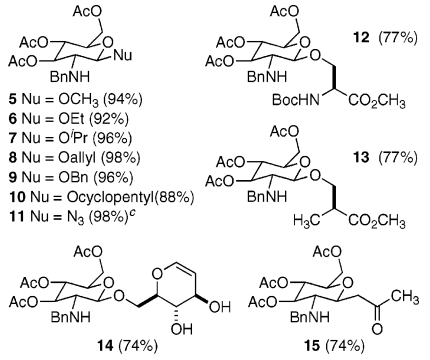
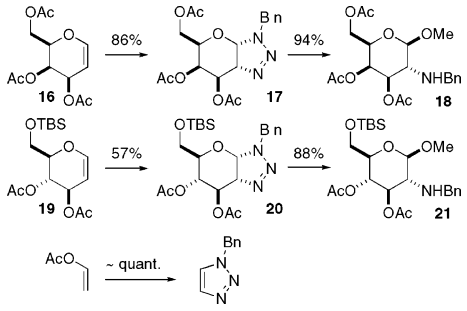
Chart 1. Adducts of **4a** and Various Nucleophiles[a−c]



[a] 2−3 equiv of NuH, 0.2 equiv of $Sc(OTf)_3$, THF, 2−3 h. [b]Yields for aziridine formation and opening. [c]2 equiv of $TMSN_3$, 1 h, $Sc(OTf)_3$ omitted.

Scheme 3. Expansion of Substrate Scope[a]



absence of added nucleophile. Under these conditions, the acetone-derived *C*-glycoside (**15**) could be isolated in good yield (74%).

With regard to the glycal and azide components, matching the electronic character of the components is essential. Glycal **1** failed to undergo cycloaddition with electron-deficient azides such as TsN_3 or $BocN_3$. Condensation of BnN_3 with tri-*O*-benzyl glucal was similarly ineffective under our conditions, as was reaction with dihydropyran. While alkynes react readily with numerous azides, alkene/azide cycloadditions most commonly involve either an electron-rich azide/electron-poor alkene pair or an electron-rich alkene/electron-poor azide pair.[18] The reaction of **1** and BnN_3 appears to fall into the former category, suggesting that **1** acts as an electron-deficient alkene despite the fact that enol ethers are typically regarded as nucleophilic/electron rich. (While unusual, this is entirely consistent with the requirement for the C3/C4 acetate groups; vide infra.)

In contrast, and as expected on the basis of the reactivity of **1**, tri-*O*-acetyl-D-galactal (**16**) undergoes ready cycloaddition with benzyl azide to form triazoline **17**; subsequent photolysis and ring opening efficiently provide the corresponding methylglycoside (**18**, 94%; Scheme 3; conditions as Scheme 2). Equally important, serial replacement of the acetate groups has revealed that although the C3/C4 acetates are required, 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-D-glucal (**19**) reacts with benzyl azide to form triazoline **20** in moderate (57%) yield.[19] Subsequent photochemical ring contraction and opening cleanly afford methyl glycoside **21** (88%). A final observation suggests further expansion of the substrate scope: benzyl azide and vinyl acetate react readily under our standard conditions, although rapid in situ elimination leads to formation of *N*-benzyltriazole as the only isolable product. Thus, while the issue of elimination must be addressed, the methodology can be extended to acyclic alkenes.

In conclusion, we have discovered a new route to aminoglycosides based on the formation of triazolines from a readily available glycal precursor followed by efficient formation and ring-opening of the corresponding aziridine. The approach is operationally simple, with no purification required after the initial cyclization and mild conditions for the formation of the aminoglycoside product. This methodology complements existing methods, and there is clear potential for development of iterative reaction protocols, expansion of substrate scope and extension to solid-phase synthesis.

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Supporting Information Available: Complete experimental and spectroscopic details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 1999. For recent reviews: (b) Dwek, R. A.; Butters, T. D. *Chem. Rev.* **2002**, *102*, 283. (c) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357. (d) Dove, A. *Nat. Biotechnol.* **2001**, *19*, 913. (e) Kobata, A. *Glycoconjugate J.* **2001**, *17*, 443. (f) Koeller, K. M.; Wong, C.-H. *Nat. Biotechnol.* **2000**, *18*, 835.

(2) For reviews of aminoglycoside synthesis and associated protecting group manipulations, see: (a) Banoub, J.; Boullanger, P.; LaFont, D. *Chem. Rev.* **1992**, *92*, 1167. (b) Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann.* **1997**, 791.

(3) (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863. (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (d) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. For earlier work on glycal aziridination, see: (e) Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119-X. (f) Koslowska-Gamsz, E.; Descotes, G. *Can. J. Chem.* **1982**, *60*, 558-X. (g) Lafont, D.; Descotes, G. *Carbohydr. Res.* **1988**, *175*, 35.

(4) Nucleophilic ring opening of such bicyclic aziridines has clear precedent in the ring opening of the analogous epoxides. See: Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(5) (a) Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204. (b) Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789. (c) Liu, J. Di Bussolo, V.; Gin, D. Y. *Tetrahedron Lett.* **2003**, *44*, 4015.

(6) For halo- and azidonitration of glycals, see: (a) Lemieux, R. U.; Nagabushan, T. L. *Can. J. Chem.* **1968**, *46*, 401. (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. For a recent modification, see: (c) Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. J. *Carbohydr. Res.* **2000**, *328*, 61.

(7) (a) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokacht, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (b) Fitzsimmons, B. J.; Leblanc, Y.; Rokacht, J. *J. Am. Chem. Soc.* **1987**, *109*, 285. (c) Fitzsimmons, B. J.; Leblanc, Y.; Chan, N.; Rokacht, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229.

(8) For reviews of azide cycloadditions, see: (a) Sha, C.-K.; Mohanakrishnan, A. K. *Chem. Heterocycl. Comput.* **2002**, *59*, 623. (b) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 771.

(9) For a review of triazolines as aziridine equivalents, see: Semenov, V. P. *Russ. J. Org. Chem.* **1996**, *32*, 1576 (*Zh. Org. Khim.* **1996**, *32*, 1627).

(10) For recent work on the intramolecular cyclization of carbamoyl- and azidoglycals, see: (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, 124, 2233 and references therein. (b) Churchill, D. G.; Rojas, C. M. *Tetrahedron Lett.* **2002**, *43*, 7225 and references therein.

(11) While we have encountered no problems in this respect, CAUTION should always be used when heating solutions of azides.

(12) We believe the acid- and base-lability of the triazoline lead to the requirement for trialkyl orthoformate as a non-basic acid-scavenging solvent.

(13) For early examples of the photochemical generation of aziridines from triazolines, see: (a) Scheiner, P. *J. Org. Chem.* **1967**, *32*, 2022. (b) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988. (c) Scheiner, P. *Tetrahedron* **1968**, *24*, 2757.

(14) The solvent specificity and requirement for a quartz reaction vessel are evidence that acetone serves both as solvent and triplet sensitizer for aziridine formation. For a previous example of sensitized photochemical conversion of a triazoline to an aziridine, see ref 12b.

(15) See Supporting Information for experimental details and ^1H NMR spectra.

(16) C2 configurations were assigned based on X-ray crystallographic analysis of **4b**. The C1 configuration was assigned based on 1H coupling constants.

(17) Formation of the acetone adduct could also proceed through *O*-alkylation of acetone followed by rearrangement. We thank Prof. C. Rojas (Barnard College) for bringing this possibility to our attention. See: Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720.

(18) For examples and discussion, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298.

(19) Loss of the TBS group during the cycloaddition accounts for the majority of material loss. Optimization is currently under way in the context of identifying an appropriate silyl linker for solid-phase synthesis.

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