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# CONVERSION OF D-MANNOSE INTO 1,5-ANHYDRO-D-ALLITOL-4,6-ACETONIDE; UNUSUAL INTRAMOLECULAR EPOXY ALCOHOL OPENING IN BASE

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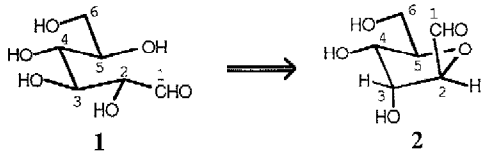
**Abstract**: Treatment of 3-tosyl-D-mannose-4,6-acetonide **9** with sodium borohydride affords an epoxy alcohol **11** which on treatment with base gives 1,5-anhydro-D-allitol-4,6-acetonide **15** by a 6-endo opening of the rearranged epoxy alcohol **13** rather than the product of a 5-exo opening, namely a C-ribose acetonide derivative **14**.

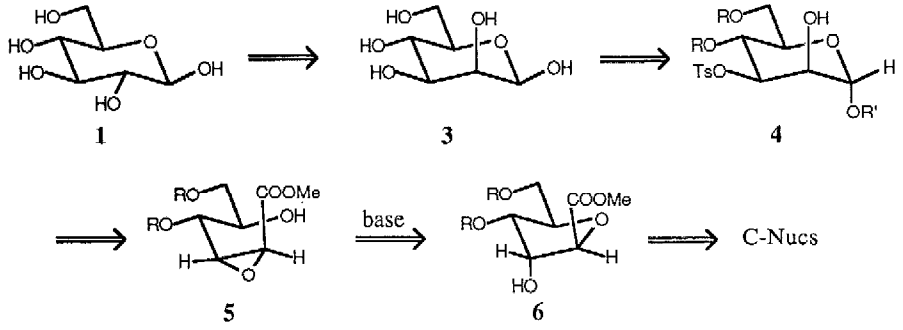
We have been interested for some time in the conversion of readily available, inexpensive six-carbon sugars, e.g., D-glucose, D-glucosamine, etc., directly into a C1-carbon-substituted ribose derivative without removing and re-adding a carbon (i.e., via a 1-haloribose derivative). These C-ribose derivatives have already been converted in good yield to a series of C-nucleosides such as showdomycin and oxazinomycin which are active antitumor antibiotics.[1] Recently we reported a very efficient route to several 2'-deoxy C-nucleosides beginning with D-glucosamine.[2] We report here earlier work on the attempted conversion of D-glucose into such a C1-carbon-substituted ribose via D-mannose. Of special interest is the unusual base-catalyzed cyclization of the epoxy alcohol **13**, which gives the 6-endo product **15** in preference to the 5-exo product **14**.

To convert D-glucose **1** into the 1β-formyl ribose **2**, the stereochemistry of two of the four secondary hydroxyl groups need not be changed (C4 and C5), one must be inverted (C3), and the last (C2) depends on the reaction used to close the five-membered ring. If an internal $S_N2$-type reaction of the C5-hydroxyl on a leaving group at C2 is used, then C2 must be inverted too. Our plan was to convert D-glucose **1** to D-mannose **3** (C2 inversion), prepare a protected 3-tosyl mannopyranoside **4**, cleave the O-C1 bond oxidatively and use an epoxidation (C3



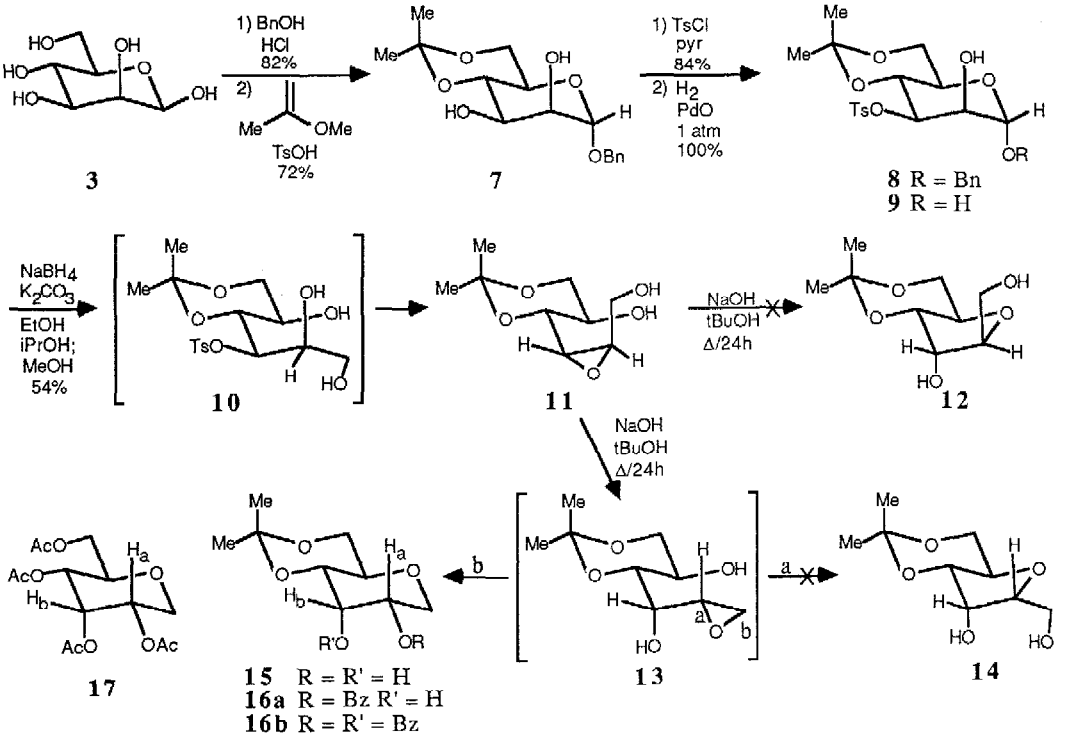

**1** **2**

inversion) to give the 2,3-epoxy ester **3**, followed by intramolecular opening of **5** at C2 to give the ribose 1β-ester **6** and from it the desired C-nucleosides. We now report our studies in this area, including a necessary modification of the basic idea which utilized the primary alcohols corresponding to the esters shown below. In particular, we report a selective cyclization of an epoxy alcohol, in which a 6-endo cyclization is favored over a 5-exo cyclization.




The preparation of a substituted mannose derivative such as **4** was relatively straightforward. The conversion of the very inexpensive D-glucose **1** into D-mannose **3** is known.[3] Preparation of benzyl mannopyranoside (87%) and formation of the acetonide **7** (72%) followed known chemistry in the methyl mannopyranoside series.[4] Selective tosylation of the equatorial hydroxyl[4] was easily accomplished to give the tosylate **8**. Hydrogenolysis of the benzyl group over freshly prepared palladium oxide produced the 3-tosyl mannose-4,6-acetonide **9** in excellent yield. Several attempts (e.g., bromine in water, etc.) to oxidize **9** to give the corresponding lactone or the open hydroxy ester failed. Therefore we were forced to change our original plan and instead reduce the lactol to a diol and then proceed with the cyclization to the tetrahydrofuran. This change would require an eventual re-oxidation of the primary alcohol to either the acid or the corresponding aldehyde (possibly more useful than the acid or ester for conversion to C-nucleosides).[1] Treatment of **9** with $NaBH_4$ in a 1:1 mixture of EtOH and iPrOH containing a catalytic amount of amount of $K_2CO_3$, followed by stirring in methanol and chromatography on silica gel, gave a nearly quantitative crude yield of the epoxy diol **11** (purified yield 54%). This compound is presumably produced by cyclization of the initially-formed triol tosylate **10**. The key cyclization step was carried out by heating a solution of **11** in *t*-butanol with 0.5 N NaOH at 75-105° C for 24 h. Flash chromatography gave a good yield (80%) of not the desired product **12** but rather the rearranged product **15**. Presumably direct cyclization to **12** is slow due to the strain associated with forming the trans trioxaindane ring system.[5] Instead a reversible Payne rearrangement[6] occurs in base to convert **11** into the isomeric epoxy diol **13**. Opening of the epoxide at bond **a** would lead to the 1α-C-substituted ribose derivative **14** which would not have necessarily doomed this approach, since if C2 is to undergo an additional inversion (due to the Payne rearrangement), one could possibly use a 3-tosyl D-glucose derivative to produce the correct stereochemistry at C1. However this reaction path is disfavored, again perhaps due to the strain of the trans

6/5 ring system and the molecule chooses to open at bond **b** to furnish the 1,5-anhydro-D-allitol derivative **15**. The structure was determined by its spectral data, especially the high field $^1$H NMR spectra of **15** in several solvents and of its mono- and dibenzoates **16ab**, which showed the chemical shifts and coupling constants expected for the allitol derivatives. In addition, the acetonide of **15** was removed and the tetraol peracetylated to give **17**, the high field $^1$H NMR spectrum of which was helpful in assigning the structure of this series of compounds. In particular, the coupling constants observed for the protons at C2 and C3, $H_a$ and $H_b$, respectively, in compounds **15-17** indicated




that these were all 1,5-anhydro-D-allitol derivatives.[7] In most unbiased cases, 5-exo cyclization of an intermediate such as **13** to give a molecule such as **14** is preferred over the 6-endo cyclization seen here which gives **15**.[8] The exact reasons for this unusual preference are not fully known at this time, although it probably involves the extra strain inherent in the trans perhydrotrioxaindane system present in both **12** and **14** vs. the trans trioxadecalin **15**.[5]

In summary, we report a very efficient route from D-mannose to an anhydro-D-allitol derivative, a process which features an unusual intramolecular epoxide opening.

**Acknowledgement**: We thank the National Institutes of Health (AI26692 and GM47228) for generous financial support.

## References and Notes


1. For reviews of C-nucleoside syntheses, see: a) James, S. R. *J. Carbohydr., Nucleosides, Nucleotides* **1979**, *6*, 417; b) Buchanan, J. G. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 243; c) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.
2. Jung, M. E.; Trifunovich, I. D.; Gardiner, J. M.; Clevenger, G. L. *J. Chem. Soc., Chem. Commun.* **1990**, 84.
3. D-glucose is easily epimerized to a separable mixture of D-glucose and D-mannose. For examples, see: Bílik, V.; Babor, K. *Chem. Zvesti* **1983**, *37*, 791; Abe, Y.; Takizawa, T.; Kunieda, T. *Chem. Pharm. Bull.* **1980**, *28*, 1324. Obviously commercially available D-mannose could be used as starting material to shorten the route by one step.
4. For example, see: Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.
5. MM2 calculations indicate that **15** has a strain energy of 27.2 kcal/mol while **12** and **14** both have strain energies significantly higher (**12**: 33.6 kcal/mol; **14**: 34.2 kcal/mol). One would expect that the transition states leading to these compounds would show similar differences in energy and thus formation of **15** would be greatly favored over formation of **12** or **14**.
6. a) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819. b) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67. c) Koizumi, N.; Ishiguro, M.; Yasuda, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1401. d) Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763. e) Bulman Page, P. C.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1988**, 356.
7. $H_a$ appeared as a clean ddd, with *J*'s of 2.5-2.8, 5.4-6.3, and 10.1-10.9 Hz, depending on the derivative, while $H_b$ appeared as a broad dd, with both *J*'s in the range of 2.2-2.8 Hz. Clearly this pattern is consistent with $H_a$ being axial and $H_b$ being equatorial, namely the allitol structure.
8. Nicolaou has reported that similar substituted epoxy alcohols give predominately the product of a 5-exo cyclization rather than that of a 6-endo cyclization. He also developed a clever way to favor 6-endo cyclizations over 5-exo ones, by placing a vinylic substituent at the terminus of the epoxy alcohol to direct attack at the allylic position to give the tetrahydropyran (6-endo) in preference to the tetrahydrofuran (5-exo) product. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.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