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β-Selective Glycosylations with Masked D-Mycosamine Precursors

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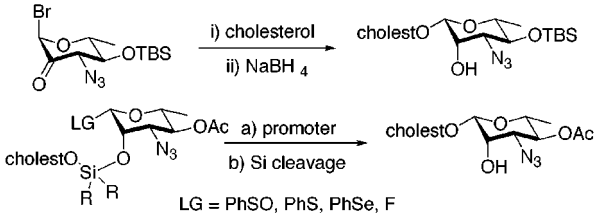
ABSTRACT



Both an intramolecular aglycon delivery (IAD) method and an intermolecular S_N2 displacement method were examined for β-selective glycosylations of cholesterol with D-mycosamine. An anomeric sulfoxide, sulfide, selenide, and fluoride were all successfully used as glycosyl donors in IAD reactions. The α-bromo ketone 19 was synthesized from protected mycosamine and employed in an intermolecular S_N2 glycosylation reaction. Both routes were successful for the model alcohol, cholesterol.

The mycosamine residue is present in a large number of macrolide antibiotics,[1] and stereoselective glycosylation is generally the last challenge in a macrolide total synthesis. Mycosamine is a difficult substrate with which to form β-glycosides because of the axial orientation of the alcohol at C2. Nicolaou's group solved this problem in their synthesis of amphotericin B[2] by using a mycosamine donor with an equatorial acetate at C2 and then inverting the stereochemistry through deprotection, oxidation, and subsequent reduction. Although effective, the overall process required four steps and proceeded in only 14% yield.[3] In conjunction with a macrolide total synthesis project, we sought to develop a method that would allow us to form mycosamine glycosides with high β-selectivity, in high yield, and under conditions mild enough for a sensitive macrolide aglycon.

The synthesis of β-mannosides has been an area of active research in recent years and has been extensively reviewed.[4] Two methods immediately seemed appropriate for glycosylation with mycosamine. An intramolecular aglycon delivery (IAD) method developed by Stork[5] looked attractive since it requires only two steps to achieve a completely β-selective glycosylation and has been successful even with hindered glycosyl acceptors. An intermolecular S_N2 displacement method pioneered by Lichtenthaler[6] also looked attractive since it uses mild, basic conditions to achieve the same overall transformation. In this paper we detail our efforts to implement both the Stork and Lichtenthaler methods for β-selective glycosylations with D-mycosamine. Cholesterol was selected as the glycosyl acceptor since, as a moderately hindered secondary alcohol, it resembles a typical protected macrolide aglycon.

D-Mycosamine can be obtained by acidolysis[7] of nystatin A (Scheme 1). For our purposes we required the amine at C3 protected as an azide and the hydroxyls at C2 and C4 differentially protected. Both of these requirements were met by first converting the C3 amine to an azide with TfN_3,[8] hydrolyzing the mycosamine moiety, and then forming an acetonide between the C1 and C2 hydroxyls. Next the

(1) Schaffner, C. P. *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984.
(2) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1998**, *110*, 4696−4705.
(3) The first step proceeded in 40% yield on the basis of 50% recovered aglycon.
(4) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491 and references therein.
(5) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248.
(6) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728−6734.
(7) Dutcher, J. D.; Young, M. B.; Sherman, J. H.; Hibbits, W. E.; Walters, D. R. *Antibiotics Annual, 1956−1957*; Medical Encyclopedia, Inc.: New York, 1956; p 866.

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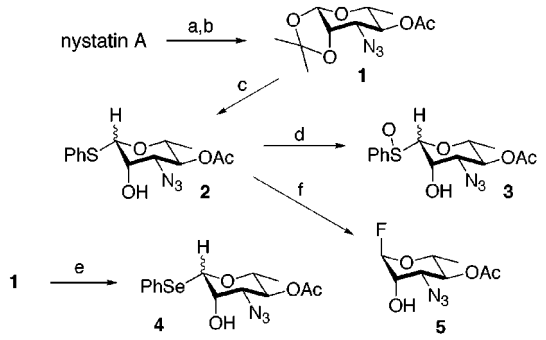
Scheme 1. Preparation of Mycosamine Donors[a]

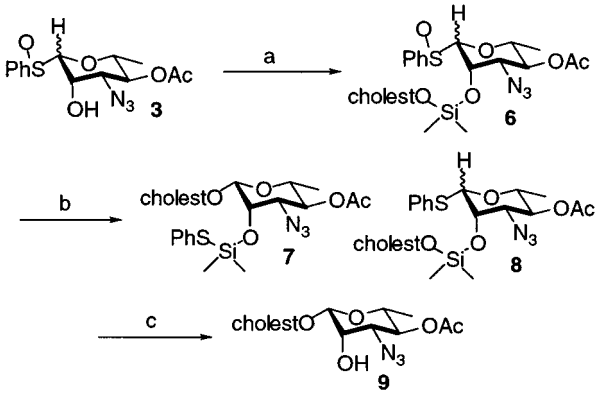


[a] (a) i. TfN_3, DMAP, $CuSO_4$ (cat.), DMSO; ii. H_2SO_4, wet acetone; iii. 2,2-dimethoxy propane, 56% overall; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2; (c) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 88%, (3.2:1, equatorial to axial sulfide); (d) OXONE, MeOH, pH 7 buffer, 21% of axial sulfoxide, 64% of equatorial, 12% starting material; (e) PhSeH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 85%, (3:1, equatorial to axial selenide); (f) DMTSF, 4 Å molecular sieves, THF, (38%).

hydroxyl at C4 was protected as an acetate.[9] Reaction with thiophenol and $BF_3{\cdot}OEt_2$ gave sulfide **2** as an inseparable mixture of diastereomers. Similarly, treatment of **1** with phenylselenol and $BF_3{\cdot}OEt_2$ gave selenide **4** as a mixture of diastereomers. Oxidation of **2** with buffered Oxone gave sulfoxide **3** while reaction of **2** with DMTSF[10] gave fluoride **5**.

Investigation of the IAD method began with sulfoxide **3** (Scheme 2). Silylation followed by addition of cholesterol

Scheme 2. Sulfoxide Glycosylations[a]



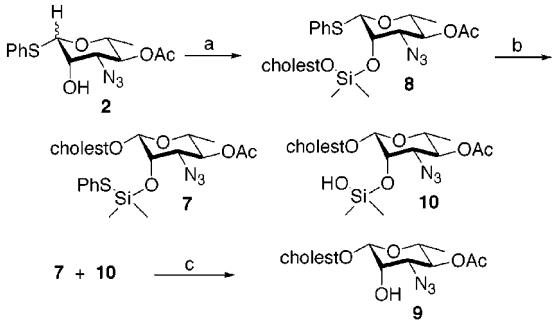
[a] (a) Me_2SiCl_2, imidazole, DMAP, DMF, then cholesterol, 60% for axial sulfoxide, 84% for equatorial; (b) Tf_2O, 2,6-di-*tert*-butylpyridine, 4 Å molecular sieves, CH_2Cl_2; (c) HF·pyr, pyridine, THF, 51% from **6** for axial sulfoxide, 46% from **6** for equatorial.

gave tethered product **6**. Treatment of **6** with Tf_2O in CH_2Cl_2 gave **7** and **8**, which were inseparable by column chromatography. Sulfide **8** is the product of simple reduction of sulfoxide **6**. Desilylation of **7** and **8** using HF·pyridine gave glycosylated product **9** as one diastereomer. Both axial and equatorial sulfoxides **6** gave similar results, with a 31−39% yield of **9** from cholesterol. The stereochemistry and connectivity of coupled product **9** were proven by NOE analysis.

A significant amount of sulfoxide **6** was converted to sulfide **8** during the glycosylation reaction. This unexpected side reaction led us to examine other glycosyl donors: anomeric sulfides, selenides, and fluorides.

We began by examining sulfide **2** (Scheme 3). Silylation followed by addition of cholesterol gave tethered product

Scheme 3. Sulfide Glycosylations[a]



[a] (a) Me_2SiCl_2, imidazole, DMAP, DMF, then cholesterol, 76%; (b) MeOTf, 2,6-di-*tert*-butylpyridine, 4 Å molecular sieves, CH_2Cl_2; (c) PPTS, wet MeOH, CH_2Cl_2, 61% from **8**.

8.[11] Several reagents were evaluated as intramolecular glycosylation promoters. Treatment of **8** with DMTSF[12] gave cholesterol as the only identifiable product. Reaction with dimethyl sulfate gave back recovered starting material, but treatment with the more reactive methyl triflate gave coupled products **7** and **10** in good yield. Desilylation was then effected with PPTS in MeOH to give **9** as one diastereomer in 46% overall yield from cholesterol.

Although the dimethylsilyl tether had served our purposes thus far, we found that forming a diisopropylsilyl tether proceeded in higher yield and gave cleaner tethered products. Both tethers gave similar results in IAD reactions.

Anomeric selenides are reportedly activated under very mild conditions.[13] Silylation of selenide **4** (Scheme 4) with $(i\text{-Pr})_2Si(OTf)_2$ followed by addition of cholesterol gave **11** in excellent yield. Although AgOTf proved to be an ineffective glycosylation promoter, reaction of **11** with MeOTf gave an excellent yield of coupled product **12**. This material was then desilylated to give **9** as one diastereomer in 75−83% overall yield from cholesterol.

Anomeric fluorides also are good glycosylation substrates since they are activated under a variety of reaction condi-

(8) Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567−3569. Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chem. Acta* **1991**, *74*, 2073−2076. Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032.

(9) A TBS protecting group was not robust enough for the chemistry to follow.

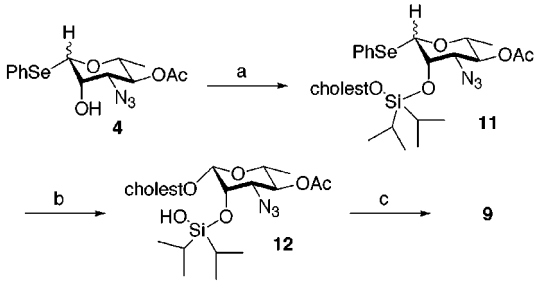
(10) Blomberg, L.; Norberg, T. *J. Carbohydr. Chem.* **1992**, *11*, 751−760. Meerwein, H.; Zenner, K.-F.; Gipp, R. *Liebigs Ann. Chem.* **1965**, *688*, 67−77.

(11) The axial isomer could not be separated from impurities.

(12) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235−244.

(13) Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269−3276.

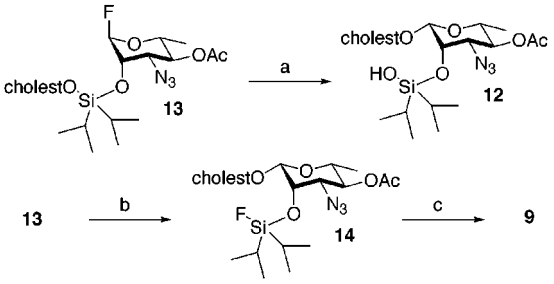
Scheme 4. Selenide Glycosylations[a]



[a] (a) $(i\text{-Pr})_2Si(OTf)_2$, pyridine, DMF, then cholesterol, 96%; (b) MeOTf, 2,6-di-*tert*-butylpyridine, 4 Å molecular sieves, CH_2Cl_2, 75% for axial selenide, 83% for equatorial; (c) TBAF, THF, quantitative.

tions[14] but, unlike bromides or chlorides, are stable and isolable intermediates. Fluoride **13** was prepared from **5** in 98% yield using the procedure described for selenide **11** (Scheme 5). Treatment of **13** with $Ce(ClO_4)_3$ gave coupled

Scheme 5. Fluoride Glycosylations[a]



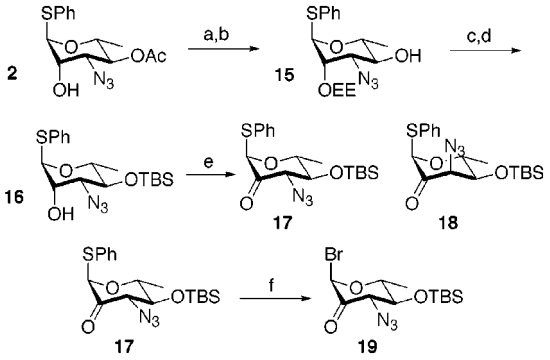
[a] (a) $Ce(ClO_4)_3$, K_2CO_3, 4 Å molecular sieves, Et_2O, 71%; (b) Cp_2ZrCl_2, $AgClO_4$, 4 Å molecular sieves, toluene, 73%; (c) TBAF, THF, quantitative.

product **12** while reaction with $Cp_2ZrCl_2/AgClO_4$, gave fluoride **14**. This transformation can also be achieved using AgOTf in place of $AgClO_4$ although it requires much longer reaction times. The use of AgOTf alone, Yb(OTf), and $SnCl_2/AgClO_4$ all gave back recovered starting material. Fluoride **14** was desilylated to give **9** as one diastereomer in 72% overall yield from cholesterol.

Although several methods were developed to glycosylate mycosamine by the IAD method, none proved to be useful for our total synthesis project due to the extreme acid lability of our macrolide aglycon. Therefore, we turned our attention to the Lichtenthaler[15] methodology for the synthesis of *β*-mannosides. This methodology involves intermolecular S_N2 reaction of an aglycon with an α-bromo ketone followed by diastereoselective reduction to give the required axial alcohol at C2. Lichtenthaler has published several routes to α-ulosyl bromides.[16] None of these methods could be successfully applied to mycosamine; therefore we were forced to develop our own route.

Sulfide **2** was converted in four steps to TBS ether **16** in 85% overall yield (Scheme 6).[17] Oxidation of alcohol **16** gave

Scheme 6. Synthesis of Bromide **19**[a]

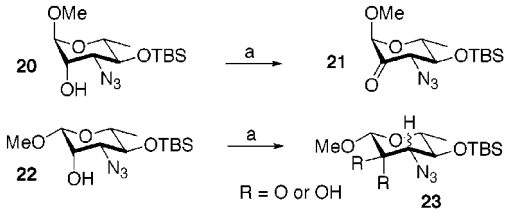


[a] (a) Ethyl vinyl ether, PPTS, CH_2Cl_2; (b) NaOH, MeOH, H_2O; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2; (d) HCl, MeOH, H_2O, 91% from **2**; (e) TFAA, DMSO, tetramethylurea, Et_3N, CH_2Cl_2, 59% of **17** and 18% of **18**; (f) IBr, 4 Å mol. sieves, CH_2Cl_2, quant.

ketone **17** as the major product along with varying amounts of the epimerized product **18**, which could be separated by careful chromatography. Treatment of sulfide **17** with IBr resulted in quantitative conversion to bromide **19**.[18]

With bromide **19** in hand, we examined the Lichtenthaler glycosylation protocol. Initial glycosylation attempts resulted in complex mixtures of products that appeared to be mixtures of diastereomers. Independent synthesis of ketones **21** and **23** revealed why (Scheme 7). Oxidation of alcohol **20** gave

Scheme 7. *β*-ketones Epimerize and Form Hydrates[a]



[a] (a) TFAA, DMSO, tetramethylurea, Et_3N, CH_2Cl_2, 97% of **21** and 100% of **23**.

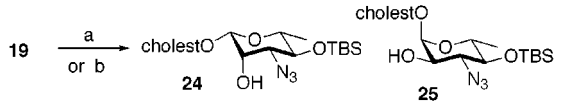
an excellent yield of ketone **21** as one diastereomer. Oxidation of alcohol **22**, however, gave four different products identified as C3 epimers of ketone and ketone hydrate **23**.

(14) (a) Hosono, S.; Kim, W.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4−5. (b) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189−4192. (c) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567−3570. (d) Hosono, S.; Kim, W.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett*, **1995**, *36*, 4443−4446. (e) Kim, W.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 7797−7800. (f) Barrena, I.; Echarri, R.; Castillon, S. *Synlett* **1996**, 675−676.

(15) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728−6734.

Thus, there are two problems with the Lichtenthaler procedure as it pertains to β-selective glycosylations with mycosamine: (1) the product ketones readily form hydrates and (2) the product ketones are very prone to epimerization. We reasoned that if the S_N2 displacement and $NaBH_4$ reduction could be run sequentially in one pot in the absence of water, these problems would be avoided. Initial one-pot procedures (Scheme 8) using CH_2Cl_2 as solvent were

Scheme 8. Intermolecular Glycosylation[a]

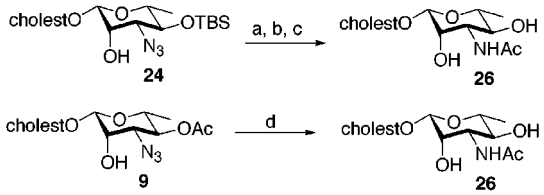


[a] (a) Cholesterol, Ag_2CO_3, 3 Å molecular sieves, THF, then MeOH, $NaBH_4$, 82%, (14:1, **24**:**25**); (b) cholesterol, Ag_2CO_3, AgOTf, 3 Å molecular sieves, then DMAP, MeOH, $NaBH_4$, 95%, (7:1, **24**:**25**).

successful but proceeded very slowly and gave only an ~30% yield of coupled product **24**. Changing the solvent to THF resulted in a more rapid reaction, and coupled products **24** and **25** were obtained in 82% yield as a 14:1 mixture of diastereomers favoring **24**. AgOTf proved to be a very effective promoter of this reaction, resulting in rapid conversion even under dilute conditions at −78 °C although with only a 7:1 diastereoselectivity. Other silver salts ($AgSiO_4$, AgOAc, and AgOTs) were ineffective promoters that showed no conversion of starting materials.

Turning to deprotection (Scheme 9), the azide group of **24** was reduced to the corresponding amine and acetylated

Scheme 9. Deprotection[a]



[a] (a) Propanedithiol, Et_3N, MeOH; (b) Ac_2O, MeOH, 79% from **24**; (c) TBAF, THF, 80%; (d) i. propanedithiol, Et_3N, MeOH, 40 °C; ii. Ac_2O, MeOH, 90%.

to aid in purification, and then the TBS protecting group was cleaved with TBAF to give **26** in 63% overall yield. Azide **9** was reduced in a similar fashion and then acetylated to give **26** in 90% overall yield.

In summary, two methods have been developed for the β-selective glycosylation of cholesterol with D-mycosamine. These methods are an extension of previous methods used for formation of β-mannosides and should allow the attachment of β-D-mycosamine to a wide range of alcohols.

Acknowledgment. Financial support from the National Institutes of Health (GM 43854) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all numbered compounds except **7**, **10**, and **20**−**23**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Lichtenthaler, F. W.; Klares, U.; Szurmai, Z.; Werner, B. *Carbohydr. Res.* **1998**, *305*, 293−303. Lichtenthaler, F. W.; Metz, T. W. *Tetrahedron Lett.* **1997**, *38*, 5477−5480. Lichtenthaler, F. W.; Jarglis, P.; Hempe, W. *Liebigs Ann. Chem.* **1983**, 1959−1972.

(17) The TBS protecting group is necessary since both C4 acetates and benzoates are eliminated upon oxidation of the C2 alcohol.

(18) This product decomposes upon exposure to SiO_2; therefore, following an aqueous workup, it is used directly in the next step.