Novel, Stereoselective Synthesis of 2-Amino Saccharides

J. Du Bois, Craig S. Tomooka, Jason Hong, and Erick M. Carreira*

Arnold and Mabel Beckman Laboratory for Chemical Synthesis California Institute of Technology Pasadena, California 91125

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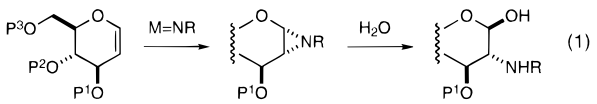
Available methods for the preparation of 2-amino sugars are few in number despite the ubiquity of such structures in nature.[1] Recent, pioneering work by Danishefsky, Fitzsimmons, and Leblanc has led to the development of two distinct methodologies for the conversion of carbohydrate glycals to the corresponding 2-amino products.[2,3] These protocols have found widespread use in the construction of complex amine-containing polysaccharides, as most recently highlighted in Danishefsky's elegant synthesis of the MBr1 antigen.[4] Neither method, however, involves direct, transition metal-promoted amination of glycal substrates (eq 1).[5] Herein, we report a process which



(1)

employs a novel, easily prepared manganese nitrido complex that, upon activation with trifluoroacetic anhydride, serves as a reactive nitrogen transfer agent.[6] This methodology offers two attractive and important features: (1) the glycal is used as the limiting reagent and (2) the products isolated are conveniently protected as the *N*-trifluoroacetylamide derivatives.[7] Additionally, it represents the first example of a metal-mediated glycal amination reaction.

We considered developing manganese reagents for glycal amination based on our finding that easily accessible salen-derived nitrido manganese complexes, when reacted with trifluoroacetic anhydride, transferred a CF_3CON unit to electron-rich silyl enol ethers.[6,8] Initial attempts to aminate tri-*O*-benzylglucal using (saltmen)Mn(N)[9] were, however, unsuccessful. The failure of this reaction was attributed to the greatly diminished reactivity of this carbohydrate-derived olefin compared to unfunctionalized vinyl ethers.[10] As a result, we speculated that the reactive manganese species was being consumed in side-reactions which occurred at a rate faster than the desired alkene amination step. This problem could be circumvented by maintaining a high concentration of the glycal relative to the activated manganese complex, thereby allowing the rate of CF_3CON transfer to effectively compete with other deleterious reaction pathways. In practice, this was accomplished by slowly adding the (saltmen)Mn(N) reagent to a solution containing both glycal and trifluoroacetic anhydride (TFAA).[11] As shown in Table 1, application of these conditions with (saltmen)Mn(N) and various glycals successfully afforded *N*-trifluoroacetylated 2-amino sugars.

The requisite glycal starting materials were constructed to incorporate a variety of commonly employed carbohydrate protecting groups, each of which proved tolerant to the mild conditions of the reaction (Table 1).[12,13] *N*-Trifluoroacetylamino alcohol products were isolated following chromatography on silica gel and were formed with high levels of diastereoselectivity at C-2 (with the exception of entry 7).[14] The stereochemical outcome at C-2 in this reaction process is controlled by the proximal stereocenter at C-3 (*cf.*, entries 1, 3, 7). The product yields from the pyranoid glycals (entries 1-7) ranged from 60 to 75% while the more reactive furanoid starting materials (entries 8, 9) proved to be even more effective substrates (80% yields) for this reaction. We speculated that the product amino alcohols resulted from hydrolytic opening in the workup of either a labile intermediate aziridine or oxazoline generated under the reaction conditions. To this end, we have isolated oxazoline **11** (derived from glycal **10**) which, under mildy acidic conditions, could be opened to the *N*-protected amino alcohol **9** (Scheme 1). As confirmation of our structural assignment of **11**, we have demonstrated that **9** may be converted back to the oxazoline upon treatment with methanesulfonyl chloride (Et_3N, CH_2Cl_2, 90%). For the six-membered ring glycals, both the putative aziridine and oxazoline products have eluded isolation.

We reasoned that if an aziridine or oxazoline was an intermediate on the reaction pathway, then it might be possible

(1) (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (b) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443. (c) Danishefsky, S. J.; Roberge, J. Y. *Pure Appl. Chem.* **1995**, *67*, 1647. (d) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167. (e) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(2) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526. (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.

(3) (a) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (b) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889. (c) Fitzsimmons, B. J.; Leblanc, Y.; Chan, N.; Rokach, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229.

(4) Park, T. K.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488.

(5) Lemieux has reported both nitrosochlorination and azidonitration of glycals, see: (a) Lemieux, R. U.; James, K.; Nagabhushan, T. L. *Can. J. Chem.* **1973**, *51*, 48 and references therein. (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. For other methods for the synthesis of amino sugars from glycals, see: (c) Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119. (d) Kozlowska-Gramsz, E.; Descotes, G. *Can. J. Chem.* **1982**, *60*, 558. (e) Lafont, D.; Descotes, G. *Carbohydr. Res.* **1988**, *175*, 35.

(6) Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915.

(7) The *N*-trifluoroacetyl protecting group may be cleaved under either mild hydrolytic or reductive conditions, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons Ltd.: New York, 1991; pp 353−354.

(8) Aziridination of *cis*-cyclooctene with a porphyrin manganese nitride and TFAA has been demonstrated, see: Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073. Elegant work describing olefin aziridination reactions with PhI=NTs has been reported, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328 and references therein.

(9) (saltmen)Mn(N) = nitrido[*N*,*N*′−(1,1,2,2-tetramethyl)ethylenebis-(salicylideneaminato)]manganese(V). This complex may be readily prepared on 20 g scale in one step by reacting *N*,*N*′−(1,1,2,2-tetramethyl)bis-(salicylideneamino)ethane (H_2saltmen) with $Mn(OAc)_2 \cdot 4H_2O$ followed by treatment with NH_4OH and Clorox bleach, see ref 6.

(10) AM1 calculations performed with the SPARTAN program package (Wavefunction, Inc., Irvine, CA) show that the HOMO of tri-*O*-benzylglucal is lower in energy than that of 3,4−dihydro−2*H*−pyran. We have found that CF_3CON may be transferred to 3,4-dihydro-2*H*-pyran (45−50% yield) following a previously described protocol (ref 6). Under identical conditions, no reaction was observed when tri-*O*-benzylglucal was employed as the substrate.

(11) An analogous, slow addition procedure is typically used for intermolecular cyclopropanation reactions, see: Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787.

(12) For general references for the preparation of glycals, see: (a) Collins, P. M.; Ferrier, R. J. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; John Wiley & Sons Ltd.: New York, 1995; pp 316−341. (b) Roth, W.; Pigman, W. *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963 Vol. 2, pp 405−408. (c) Fraser-Reid, B.; Radatus, B.; Tam, S. Y.-K. *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1980; Vol. 8, pp 219−225. (d) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825.

(13) For leading references for the preparation of furanoid glycals, see: (a) Yokoyama, M.; Ikuma, T.; Obara, N.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3243 and references therein. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

(14) The stereochemistry was determined by analysis of ^{1}H coupling constants and ^{1}H difference NOE experiments; see Supporting Information for details.

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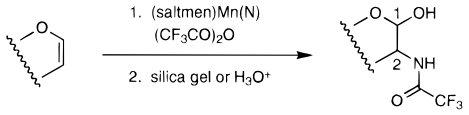
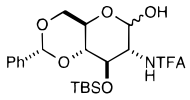
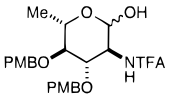
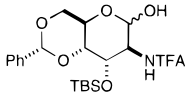
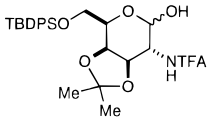
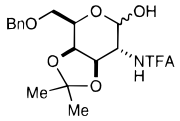
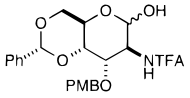
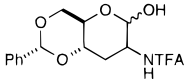
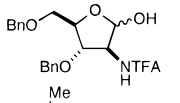
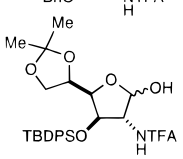
Table 1. Preparation of *N*-Trifluoroacetyl 2-Amino Sugars



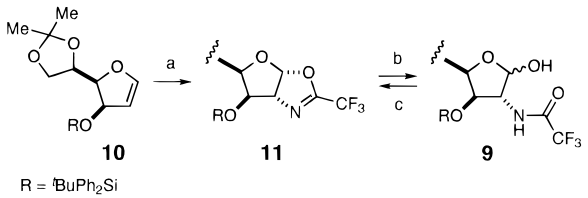
entry	major product	selectivity(C–2)[a]	yield
1		7:1	75%
2		7:1	60%
3		7:1	68%
4[b]		15:1	64%
5[b]		15:1	62%
6		6:1	66%
7		1:1	70%
8[c]		13:1	80%
9[c]		10:1	80%

[a] Stereoselectivity at C-2 determined by ^{1}H and ^{19}F NMR spectroscopies of both the lactol product and the corresponding lactone obtained upon oxidation (PCC, CH_2Cl_2). [b] A higher yield of the desired product was obtained if 1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine was utilized. [c] Starting materials were combined in CH_2Cl_2 at −78 °C, and the solution was warmed slowly to 23 °C.

to trap *in situ* either of these electrophilic species with an appropriate nucleophile. This was demonstrated using galactal **12** (Scheme 2). In the event, a solution of (saltmen)Mn(N) was added to a mixture of TFAA and **12** (CH_2Cl_2, 23 °C) followed by cooling to −78 °C and sequential treatment with thiophenol and BF_3·OEt_2. Under these conditions, thioglycoside **13** was isolated solely as the β-epimer with *trans* 1,2 stereochemistry.[15] Generation of the *trans* product **13** supports the intermediacy of either aziridine **14** or oxazoline **15** in this reaction sequence.[16] The single-step preparation of **13** from **12** allows immediate access to 2-amino thioglycosides, whose versatility and importance in glycosidation reactions have been elegantly displayed by Kahne, Nicolaou, and others.[17−19]

(15) The *trans* 1,2 configuration was established on the basis of an observed 10.7 Hz coupling constant, see: Griffith, D. A. Ph.D. Dissertation, Yale University, New Haven, CT, 1993.

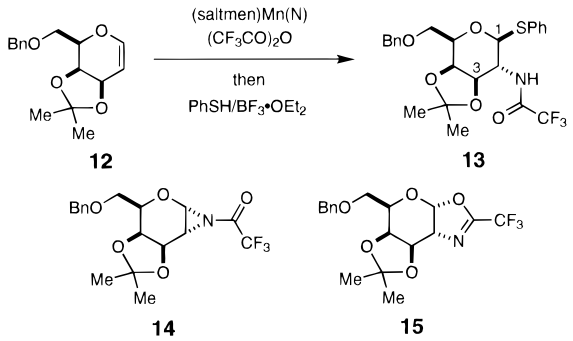
Scheme 1[a]



R = ^{t}BuPh$_2$Si

[a] Key: (a) (saltmen)Mn(N), $(CF_3CO)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine; (b) aqueous AcOH, THF, 80% (two steps); (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 90%.

Scheme 2



Methodology for the construction of 2-amino-2-deoxy monosaccharides from glycal precursors has been described. This work represents the first example of a metal-mediated amination reaction of this important class of alkene substrates. Activation of (saltmen)Mn(N) with TFAA and transfer of the CF_3CON group to give *N*-trifluoroacetyl-protected amine products is efficient in both chemical yield (60−80%) and product stereoselectivity. Moreover, it has been demonstrated that an intermediate in this reaction process can be coupled *in situ* with PhSH to give a functionalized 2-amino sugar suitable for subsequent glycosidation reactions. Successful extension of this latter reaction to include other coupling partners should provide direct methods for the synthesis of complex 2-amino carbohydrate-derived natural products.

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Supporting Information Available: General experimental procedures for the preparation of amino alcohols **1**−**9** are included along with spectral and analytical data for both the starting glycals and the *N*-trifluoroacetylamino alcohol products (14 pages). See any current masthead page for ordering and Internet access instructions.

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(16) In reactions with unfunctionalized olefins, we have isolated and characterized products whose spectra are consistent with those of aziridines (Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira E. M. Unpublished results).

(17) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239 and references therein.

(18) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.

(19) (a) Fukase, K.; Kinoshita, I.; Kanoh, T.; Nakai, Y.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897 and references therein. (b) For a comprehensive review on glycosylation methods, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.