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A Short and Highly Efficient Synthesis of L-Ristosamine and L-*epi*-Daunosamine Glycosides

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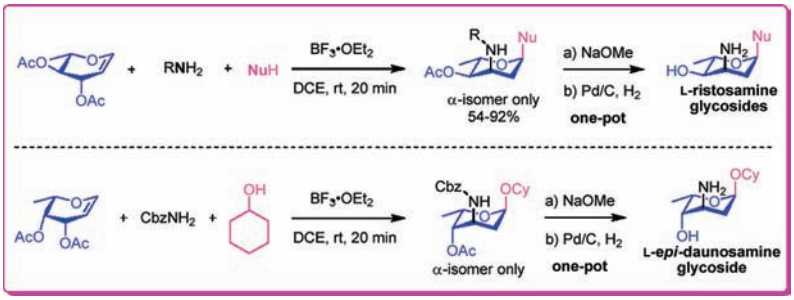
ABSTRACT



A highly efficient synthesis of L-ristosamine and L-*epi*-daunosamine glycosides *via* $BF_3 \cdot OEt_2$ promoted tandem hydroamination/glycosylation of 3,4-di-*O*-acetyl-6-deoxy-L-glucal and L-galactal has been developed. The new method proceeds in a completely stereocontrolled manner within a short reaction time. Preparation of a library of L-ristosamine and L-*epi*-daunosamine glycosides with potential biochemical applications, by varying each component, exemplified the generality of the reaction.

Partially deoxygenated unbranched amino sugars are important components of several classes of effective pharmaceutical compounds with demonstrated antibiotic and anticancer activity.[1] Among those commonly encountered are the 3-amino-2,3,6-trideoxyhexoses, e.g., L-daunosamine, L-*epi*-daunosamine, L-ristosamine, L-acosamine, L-vancosamine, and nocardicylins (Figure 1).[2] It has been well established that the sugar moieties are essential for the biological activity of these antibiotics. L-Daunosamine and related analogues constitute carbohydrate moieties of the anthracycline family of antitumor antibiotics.[3] L-Ristosamine is part of the carbohydrate appended to the ristomycins, members of the vancomycin antibiotic family that cause platelet aggregation and which are used to diagnose variants of von Willebrand disease.[4] On account of their biological importance and commercial nonavailability, development of an expedient stereoselective approach to synthesize 3-amino-2,3,6-trideoxysugars and their unbranched sugars has attracted considerable interest in the synthetic community.[5]

Synthesis of aminoglycosides, in particular 2-deoxyamino glycosides and their derivatives, remains a remarkable

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(4) (a) Sweeney, J. D.; Hoernig, L. A.; Fitzpatrick, J. E. *Am. J. Hematol.* **1989**, *32*, 190. (b) Zhou, L.; Schmaier, A. H. *Am. J. Clin. Pathol.* **2005**, *123*, 172.

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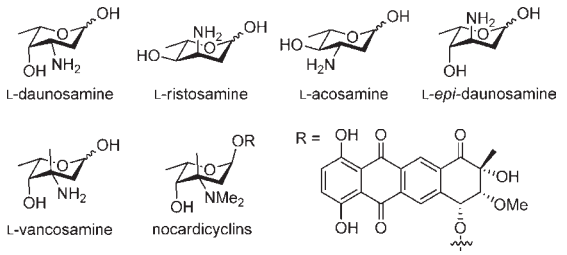


Figure 1. Natural products containing 3-amino-2,3,6-trideoxysugars.

challenge due to the absence of neighboring participating groups at C-2 which usually dictate the stereochemical outcome at the anomeric position. Consequently, such reactions always result in a mixture of anomers. A wide variety of approaches to racemic and asymmetric syntheses of daunosamine, ristosamine, and their unbranched analogs have been reported from both sugar and nonsugar precursors.[5] Recently, Lowary and co-workers developed an alternative method which involves a photoinduced acylnitrene aziridination reaction, and subsequent hydrogenolytic aziridine ring-opening furnishes 2,3,6-trideoxy-3-aminohexopyranoses.[5h] Riera et al. utilized reagent-controlled stereoselective epoxidation and organometallic addition in a stereodivergent approach to synthesize four

(5) For recent syntheses of 3-amino-2,3,6-trideoxyhexoses, see: (a) Matsushima., Y.; Kino., J. *Eur. J. Org. Chem.* **2010**, 2206. (b) Shi, W.; Coleman, R. S.; Lowary, T. L. *Org. Biomol. Chem.* **2009**, *7*, 3709. (c) Fan, E.; Shi, W.; Lowary, T. L. *J. Org. Chem.* **2007**, *72*, 2917. (d) Doi, K.; Shibata, K.; Kinbara, A.; Takahashi, T. *Chem. Lett.* **2007**, *36*, 1372. (e) Friestad, G. K.; Jiang, T.; Mathies, A. K. *Org. Lett.* **2007**, *9*, 777. (f) Matsushima, Y.; Kino, J. *Tetrahedron Lett.* **2006**, *47*, 8777. (g) Hayman, C. M.; Larsen, D. S.; Simpson, J.; Bailey, K. B.; Gill, G. S. *Org. Biomol. Chem.* **2006**, *4*, 2794. (h) Matthew, T. M.; Peng, T.; Christopher, M. H.; Robert, S. C.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 8059. (i) Parker, K. A.; Chang, W. *Org. Lett.* **2005**, *7*, 1785. (j) Parker, K. A.; Chang, W. *Org. Lett.* **2003**, *5*, 3891. (k) Trost, B. M.; Jiang, C. H.; Hammer, K. *Synthesis* **2005**, 3335. (l) Ginesta, X.; Pasto, M.; Pericas, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001. (m) Brimble, M. A.; Davey, R. M.; McLeod, M. D.; Murphy, M. *Aust. J. Chem.* **2003**, *56*, 787. (n) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749. (o) Liberek, B.; Dabrowska, A.; Frankowski, R.; Matuszewska, M.; Smiatacz, Z. *Carbohydr. Res.* **2002**, *337*, 1803. (p) Saotome, C.; Ono, M.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 4137. (q) Davey, R. M.; Brimble, M. A.; Mcleod, M. D. *Tetrahedron Lett.* **2000**, *41*, 5141. (r) Effenberger, F.; Roos, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1085. (s) Davies, S. G.; Smyth, G. D.; Chippindale, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089. (t) Szechner, B.; Achmatowicz, O.; Badowska-Roslonek, K. *Pol. J. Chem.* **1999**, *73*, 1133. (u) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem.—Eur. J.* **1999**, *5*, 2648. (v) Daley, L.; Roger, P.; Monneret, C. *J. Carbohydr. Chem.* **1997**, *16*, 25. (w) Colinas, P. A.; Bravo, R. D. *Org. Lett.* **2003**, *5*, 4509. (x) Colinas, P. A.; Nicolás, A. N.; Bravo, R. D. *J. Carbohydr. Chem.* **2008**, *27*, 141. (y) Sibi, M.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864. Sibi *et al.* provide an extensive list of references to earlier syntheses.

(6) (a) Lorpitthaya, R.; Xie, Z. Z.; Sophy, K. B.; Kuo, J. L.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 588. (b) Gorityala, B. K.; Lorpitthaya, R.; Bai, Y.; Liu, X.-W. *Tetrahedron* **2009**, *65*, 5844. (c) Yang, R. L.; Pasunooti, K. K.; Li, F.; Liu, X.-W.; Liu, C.-F. *J. Am. Chem. Soc.* **2009**, *131*, 13592. (d) Ding, F. Q.; William, R.; Gorityala, B. K.; Ma, J. M.; Wang, S. M.; Liu, X.-W. *Tetrahedron Lett.* **2010**, *51*, 3146. (e) Lorpitthaya, R.; Xie, Z. H.; Sophy, K. B.; Kuo, J. L.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 588. (f) Lorpitthaya, R.; Xie, Z. Z.; Kuo, J. L.; Liu, X.-W. *Chem.—Eur. J.* **2008**, *14*, 1561. (g) Lorpitthaya, R.; Sophy, K. B.; Kuo, J. L.; Liu, X.-W. *Org. Biomol. Chem.* **2009**, *7*, 1284.

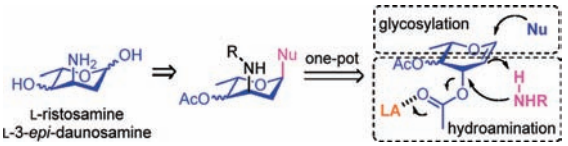


Figure 2. Our synthetic strategy.

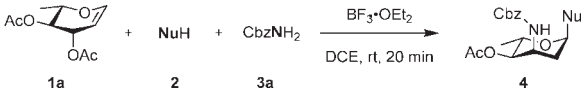
diastereomeric 3-amino-2,3,6-trideoxysugars.[51] In another multistep synthesis, the sequence of asymmetric dihydroxylation and a regio-reversed Wacker oxidation *via* the application of silicon-tethered vinyl addition under tin-free thiyl radical conditions accomplished the synthesis of L-daunosamine derivatives.[5e]

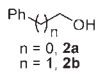
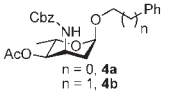
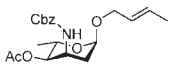
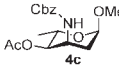
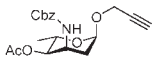
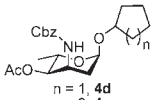
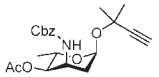
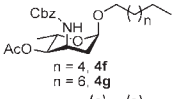
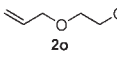
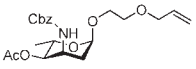
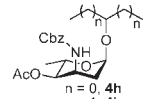
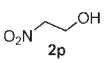
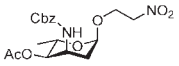
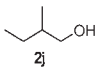
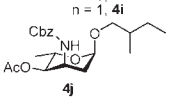
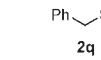
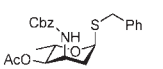
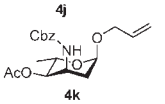
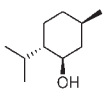
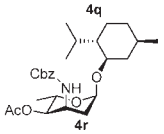
However, most of the reported approaches suffer from drawbacks such as an excessive number of synthetic steps, low yields, poor stereoselectivity, and long reaction times. In continuation of our efforts to develop a reliable method to prepare aminosugars with potential biological activity,[6] we wish to report a direct and stereospecific synthesis of 3-amino-2,3,6-trideoxyhexoses that include L-ristosamine and L-*epi*-daunosamine glycosides. We envisaged a rapid assembly of 3-amino-2,3,6-trideoxyhexoses *via* a three-component reaction of 3,4-di-*O*-acetyl-6-deoxy-L-glucal with two (*N*- and *O*-, or *S*-containing) nucleophiles in a one-pot manner. Our synthetic strategy involves regio- and stereoselective tandem hydroamination/glycosylation on the protected glycal scaffold (Figure 2). To demonstrate the versatility of the present method, it was applied for facile synthesis of L-ristosamine and L-*epi*-daunosamine glycosides in a three-step reaction sequences.

In our initial study, a mixture of 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**1a**), benzyl alcohol (**2a**), and benzyl carbamate (**3a**) in DCE was subjected to treatment with 2.2 equiv of $BF_3 \cdot OEt_2$ at room temperature under a nitrogen atmosphere for 20 min, to afford **4a** in 87% yield with exclusive stereospecificity (Table 1, entry 1). The exclusive formation of pure diastereomers allowed easy purification of the desired product by SiO_2 flash column chromatography. Chemical structure determination and stereochemical characterization of **4a** was achieved by extensive and detailed 1D and 2D NMR studies.[7] The J_{H1-H2a} of 3.2 Hz for anomeric proton H-1 signal at δ 4.93 in ^{1}H NMR is diagnostic for α-linked glycosides. The stereochemistry at the C-3 position is assigned by NOESY experiment. The correlation for N−H/H-5 and no correlation for H-1/N−H or H-1/H-3 indicate that the newly introduced sulfonamido group and glycosyl acceptor are in a *cis* diaxial configuration, adopting $^1C_4$ conformation in solution. With this gratifying preliminary result, our attention was directed to investigating the substrate scope by varying the nucleophiles. A diverse set of primary, secondary, tertiary alcohols (**2b**−**2p**) and thiol (**2q**) worked well as nucleophiles to provide the desired *N*-benzyloxycarbonyl-L-ristosamine glycosides with exclusive stereoselectivity

(7) See Supporting Information, pp S32−S36.

Table 1. Substrate Scope Studies for $BF_3 \cdot OEt_2$-Promoted Three-Component α-Selective Tandem Hydroamination/Glycosylation Reaction[a]



entry	Nucleophile	Product[b]	yield[c] (%)	entry	Nucleophile	Product[b]	yield[c] (%)
1	 n = 0, **2a** n = 1, **2b**	 n = 0, **4a** n = 1, **4b**	87 (**4a**) 55 (**4b**)	8	 **2l**	 **4l**	76
2	MeOH **2c**	 **4c**	71	9	 **2m**	 **4m**	62
3	 n = 1, **2d** n = 2, **2e**	 n = 1, **4d** n = 2, **4e**	68 (**4d**) 83 (**4e**)	10	 **2n**	 **4n**	69
4	 n = 4, **2f** n = 6, **2g**	 n = 4, **4f** n = 6, **4g**	81 (**4f**) 73 (**4g**)	11	 **2o**	 **4o**	67
5	 n = 0, **2h** n = 1, **2i**	 n = 0, **4h** n = 1, **4i**	72 (**4h**) 75 (**4i**)	12	 **2p**	 **4p**	68
6	 **2j**	 **4j**	86	13	 **2q**	 **4q**	55
7	 **2k**	 **4k**	72	14	 **2r**	 **4r**	54

[a] See Supporting Information for a detailed experimental procedure. [b] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. [c] Isolated yield.

in good yield as shown in Table 1. Accordingly, facile syntheses of 3-amino-2,3,6-trideoxyhexoses **4b**−**4q** were achieved in moderate to good yields (55−86%) (Table 1, entries 2−13). To further exploit this protocol, L-menthol glucoside **4r** was prepared in 54% yield (Table 1, entry 14).[8] To our delight, in all cases, the desired aminosugars were obtained as pure diastereomers with an α configuration at the C-1 position. The stereochemical outcome can presumably be viewed as a result of stereospecific amination at the C-3 position followed by possible hydrogen bonding between the nitrogen and the incoming *O*-nucleophile (ROH). Additionally, the anomeric effect also favors the formation of the thermodynamically more stable α anomeric product.[9]

Having established the scope for the *O*-nucleophile, we set out to demonstrate the generality of the reaction by using various *N*-nucleophiles. It is noteworthy that the reaction proceeded remarkably well with aromatic and aliphatic sulfonamides. For example, when the reactions were carried out with $NsNH_2$, $TsNH_2$, or $MsNH_2$, the corresponding aminosugars were isolated in high yields with exclusive stereoselectivities (Table 2, entries 1−3, **4rd**, **4rf**, **4rg**, and **4s**). In comparison to sulfonamides, reaction with ethyl carbamate (**3j**) gave the corresponding 3-amino-2,3,6-trideoxyhexoses **4t** in slightly lower yields (Table 2, entry 4). In contrast, reaction of trimethylsilyl azide ($TMSN_3$) with 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**1a**) turned out to be unsuccessful.

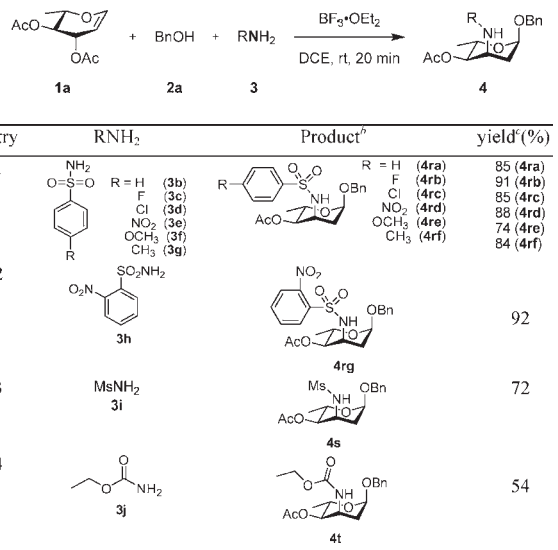
As a final step in the sequence, *N*-benzyloxycarbonyl-L-ristosamine glycosides were converted into the desired free L-ristosamine glycosides. For example, one-pot deprotection of the Cbz and acetyl groups resulted in L-ristosamine derivatives (**5a**) and (**5b**) in 82% and 87% yield, respectively (Scheme 1). Overall, the development of this novel one-pot method is of particular significance for the synthesis of L-ristosamine glycosides **5a** and **5b**, as it is highly superior to previously described routes that normally are comprised of 9 to 11 linear steps.[5h,10] X-ray crystallography

(8) Noguchi, K.; Nakagawa, H.; Yoshiyama, M.; Shimura, S.; Kirimura, K.; Usami, S. *J. Ferment. Bioeng.* **1998**, *85*, 436.

(9) (a) Bussolo, V. D.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383. (b) Bussolo, V. D.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299.

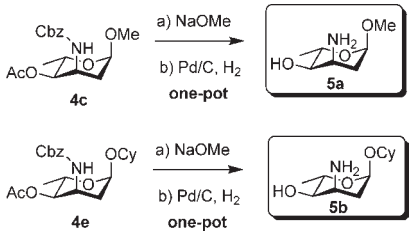
(10) (a) Sztaricskai, F.; Hornyak, U.; Konaromi, I.; Gyula, B. G.; Pelyvis, I. F. *Bioorg. Med. Chem. Lett.* **1992**, *3*, 235. (b) Kovacs, I.; Herczegh, P.; Sztaricskai, F. *Tetrahedron* **1991**, *47*, 7837. (c) Sztaricskai, F.; Pelyvas, I.; Szilagyi, L.; Bognar, R. *Carbohydr. Res.* **1978**, *65*, 193. (d) Claudio, F. C.; Grasselli, P.; Fantoni, G. P. *J. Org. Chem.* **1983**, *48*, 909.

Table 2. Scope of the Nitrogenic Nucleophiles[a]



[a] See Supporting Information for a detailed experimental procedure. [b] All products were characterized by IR, HRMS, ^{1}H NMR, and ^{13}C NMR. [c] Isolated yield.

Scheme 1. Synthesis of L-Ristosamine Glycosides **5a** and **5b**



analysis of L-ristosamine derivative **5b** further confirmed the structure and stereochemical outcome of the tandem hydroamination/glycosylation (Figure 3).

To prepare another diastereomeric 3-amino-2,3,6-trideoxyhexose, L-*epi*-daunosamine, the starting 3,4-di-*O*-acetyl-6-deoxy-L-galactal (**1b**) was synthesized from L-fucose according to a literature reported procedure.[11] Intermediary carbamate protected L-*epi*-daunosamine (**4u**) was obtained in 79% yield *via* a three-component reaction involving benzyl carbamate ($CbzNH_2$) (**3a**), cyclohexanol (**2e**), and 3,4-di-*O*-acetyl-6-deoxy-L-galactal (Scheme 2). Similarly, removal of the acetyl group by treating **4u** with NaOMe in methanol, followed by direct removal of the Cbz group through treatment with Pd/C under H_2, provided cyclohexyl L-*epi*-daunosamine (**5c**) in 83% yield with exclusive stereo- and

(11) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955.

(12) Other efficient syntheses of daunosamine and its derivatives from commercially available achiral or noncarbohydrate precursors range from five to nine steps with 7−34% overall yield.

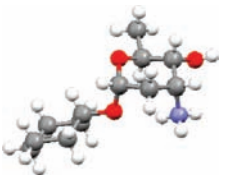
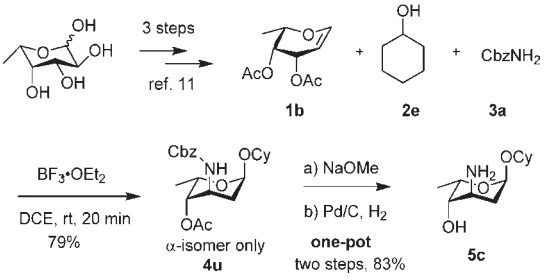


Figure 3. X-ray structure of L-ristosamine derivative **5b**; red (O); blue (N); Cl^- is omitted for clarity.

Scheme 2. Synthesis of L-*epi*-Daunosamine Derivative (**5c**)



regioselection. The spectroscopic data (^{1}H and ^{13}C NMR, IR) and optical rotation of **5c** were identical to those reported in the literature.[5e,12]

In summary, a stereocontrolled one-pot $BF_3 \cdot OEt_2$-promoted hydroamination/glycosylation on glycal scaffolds to synthesize 3-amino-2,3,6-trideoxyhexoses has been developed that circumvents the problem of lack of stereoselectivity, and thus laborious isolation of pure diastereomeric products, associated with previously reported strategies. Other attractive features of this multicomponent reaction are a simple and practical experimental procedure and its adaptability for the synthesis of a diverse set of aminosugars. The synthetic utility of this novel method has been further illustrated in a concise and highly expedient synthesis of L-ristosamine and L-*epi*-daunosamine glycosides. Thus, the present methodology represents an attractive entry to aminosugars, and its further application is underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.