A New Route to 3-Amino Sugars. A Concise Synthesis of L-Daunosamine and D-Ristosamine Derivatives

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An asymmetric aldol strategy has been developed for the synthesis of L-daunosamine and D-ristosamine derivatives starting from noncarbohydrate precursors. Lithium and boron enolate mediated aldol reactions of **12** with *O*-TBS lactaldehyde gave non-Evans *syn* and Evans *syn* aldol products, respectively, with high selectivity. The chemical efficiency of the lithium enolate reactions were higher than the corresponding reactions with the boron enolates. Curtius rearrangement of lactone acids **23** and **26** gave the corresponding *N*-BOC amino lactones **30** and **32** in 64% and 62%, respectively, with complete retention of configuration. Lactone **30** was converted by a two-step sequence to *N*-benzoyldaunosamide **40**. The overall yield for the amino sugar **40** was 18% over six steps. Similarly, lactone **32** was converted to *N*-benzoylristosamide **42** with an overall yield of 18% starting from **12**.

Introduction

A number of clinically important anthracycline antibiotics contain a 3-aminohexose unit as part of their structure. L-Daunosamine[2] (**1**, 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) is the glycosidic component of naturally occurring anthracyclines daunomycin (**2a**), adriamycin (**2b**), and carminomycin (**2c**) (Figure 1).[3] L-Acosamine (**3**, 3-amino-2,3,6-trideoxy-L-*arabino*-hexose) was isolated from the antibiotic actinoidin,[4] and L-ristosamine (**4**, 3-amino-2,3,6-trideoxy-L-*ribo*-hexose) is a component of glycoprotein ristomycin.[5] The anthracycline antibiotics have attracted attention because of their bioactivity against a wide range of experimental and human tumors.[6] Adriamycin[7] exhibits impressive activity against solid tumors, especially toward soft tissues and bone sarcomas. Additionally, daunomycin, adriamycin, and their analogs have shown a strong effect on HIV-reverse transcriptase,[8] although their activity against HIV-infected human cells has been rather limited.[9] The relative stereochemistry of the functional groups in natural and unnatural amino sugars has a large impact on the activity profile of the anthracycline antibiotics,[10] especially with regards to the suppression of toxic side effects.[11]

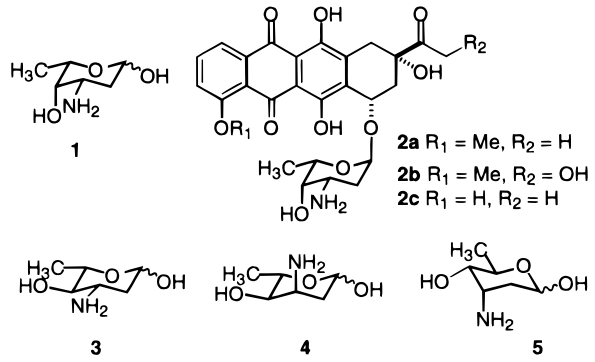

Figure 1.

Since their discovery in the 1960s, the amino sugar components of anthracyclines have been popular targets in the synthetic community. Numerous racemic[12] and asymmetric syntheses[13,14] of daunosamine, ristosamine[15−17] along with their fluoro[18] and branched[19] analogs have been reported in the literature. Critical to the development of new methods for the synthesis of 3-amino sugars is the control of the relative as well as the absolute stereochemistry of the amino alcohol functions at the C-3 and C-4 positions. Traditionally, approaches to 3- amino sugars have relied on naturally occurring D- and L-carbohydrates as starting materials. Recently, more

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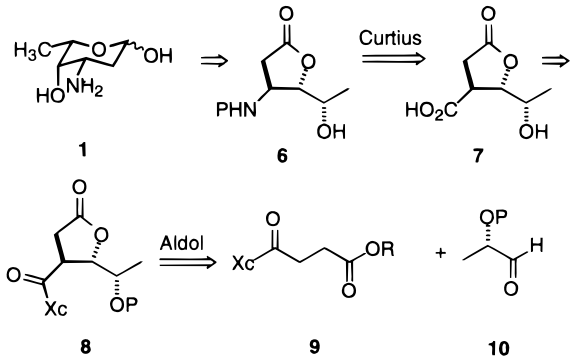
attention has been focused on developing new methods starting from noncarbohydrate precursors. We have been exploring the diastereoselective aldol reactions of desymmetrized succinates in the context of natural product synthesis.[20] The aldol reaction of desymmetrized succinates in conjunction with the Curtius rearrangement seemed an attractive method for the installation of the amino functionality in 3-amino sugars. Our synthetic strategy is shown retrosynthetically in Scheme 1 using daunosamine as an example.

The key features of our synthetic strategy are (1) the regio- and diastereoselective *syn* aldol reaction of a desymmetrized chiral succinate with an *O*-protected lactaldehyde (**9** + **10** to **8**) and (2) the Curtius rearrangement of the acid **7** with retention of configuration to an advanced intermediate **6**. Further adjustments in the oxidation state of **6** leads to the target amino sugar. The generality of the methodology can be gleaned by the ease with which one can control the relative as well as the absolute stereochemistry of the aldol products by a simple change of the auxiliary and by the nature of the metal used for enolate generation. Additionally other amino sugars such as D-ristosamine (**5**), the C-5 epimer of daunosamine, can also be prepared using the same methodology by using the (*R*)-*O*-protected lactaldehyde. As can be seen from the disconnection, high degree of stereoselection in aldol and Curtius reactions are essential for a successful execution of our strategy.

Scheme 1



Results and Discussion

Our synthesis starts with the attachment of the C-4 succinate side chain to the chiral auxiliary. Deprotonation of the auxiliary[21] **11** with *n*-BuLi at −78 °C followed by acylation with 3-carbomethoxypropionyl chloride furnished the desymmetrized succinate **12** in excellent yield

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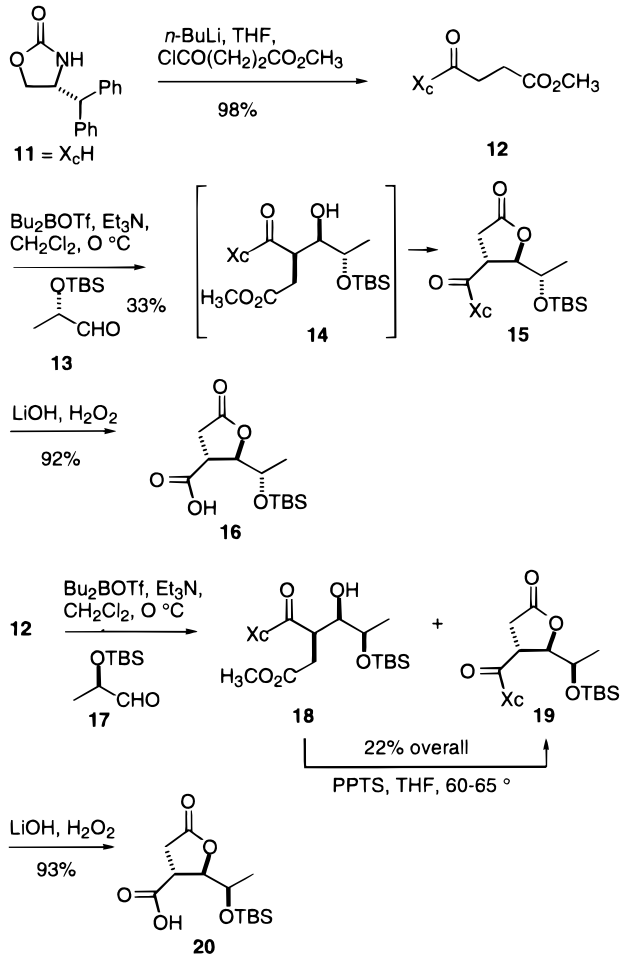
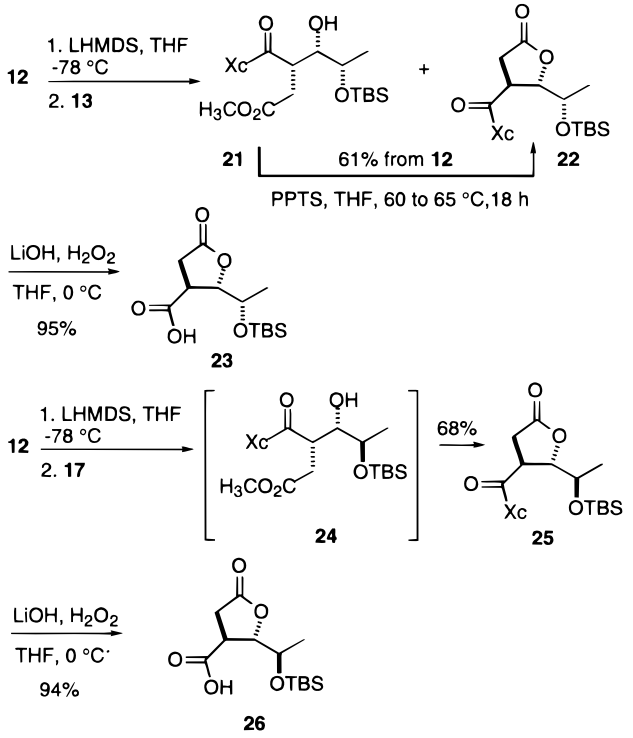
Scheme 2



(Scheme 2). With the appropriate substrate in hand, our attention was directed toward the boron-mediated asymmetric aldol condensation reaction using the protocol developed by Evans.[22] Key to the success of the aldol strategy was obtaining high levels of regio- and diastereoselectivities. Thus, deprotonation and subsequent enolate formation has to take place on the α-carbon of the imide carbonyl rather than the ester function to ensure high regioselectivity.[23] Support for this mode of reactivity comes from literature precedents[24] as well as work from our laboratory.[20a] The boron enolate was generated by treating a CH_2Cl_2 solution of **12** with freshly prepared dibutylboron triflate at 0 °C, followed by the addition of triethylamine. A solution of freshly prepared aldehyde was added slowly at −78 °C, and the reaction was allowed to warm to rt over 24 h. To our surprise, the aldol reaction using either (*S*)- or (*R*)-*O*-TBS lactaldehyde[25] was sluggish. A rather moderate chemical yield (∼30%) was obtained in either case with recovery of the

Scheme 3



starting material. The aldol products were formed with high *syn* selectivity. Additionally, the aldol products from the two different aldehydes behaved differently with regard to the lactonization process. The aldol adduct **14** from (*S*)-*O*-TBS-lactaldehyde **13** possessing a (2*R*,3*R*,4*S*)-configuration underwent cyclization to form **15** during silica gel chromatography. In contrast, the aldol adduct **18** derived from (*R*)-*O*-TBS-lactaldehyde **17** possessing the (2*R*,3*R*,4*R*)-configuration was obtained as an inseparable mixture with the lactone **19**. Complete lactonization of this substrate was accomplished with a catalyst (PPTS) by heating the reaction to 60−65 °C. The slower lactonization rate associated with this all *syn* configuration aldol adduct **18** is presumably because of steric reasons. A similar observation was also made in our previous work.[26] The chiral auxiliary was easily removed (>90% yield) from the lactones by hydrolysis[22] using $LiOH/H_2O_2$. The absolute stereochemistry of the aldol adducts and lactones were assigned based on their conversion to natural products of known configuration (*vide infra*).

The low chemical yield in the boron-mediated aldol condensation led us to examine reactions with the more reactive lithium enolates.[27] We were delighted to find that the lithium enolate mediated aldol condensation gave a satisfactory chemical yield as well as high diastereoselectivity (Scheme 3). Treatment of a THF solution of **12** with LHMDS at −78 °C furnished the lithium enolate which was immediately reacted with a freshly prepared (*S*)- or (*R*)-*O*-TBS-lactaldehyde solution. The aldol reactions were highly *syn* selective with the absolute stereochemistry (non-Evans *syn*) opposite to that obtained from the boron-mediated aldol reaction (Evans *syn*). The aldol adduct **24** resulting from reaction between **12** and the (*R*)-*O*-TBS-lactaldehyde **17** underwent

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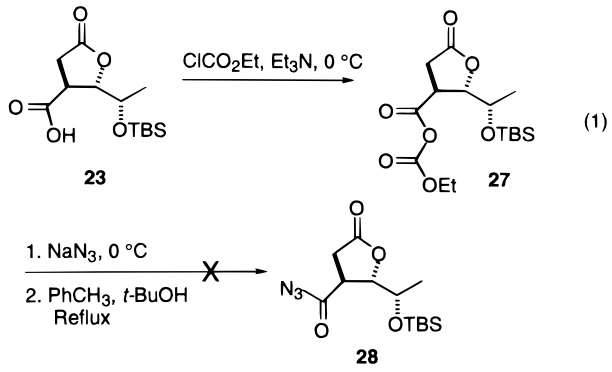
lactonization easily providing the product **25** in an isolated yield of 68%. A minor diastereomer **19** was also isolated in 5% yield, along with the unreacted starting material (6%) and cleaved chiral auxiliary (14%). The isolation of *ca.* 14% of chiral auxiliary from lithium aldol reaction was bothersome since it lowered the overall chemical yield and made the chromatographic purification difficult. Examples of chiral auxiliary cleavage during enolate formation have been reported in the literature.[28] A set of control experiments were conducted to evaluate the thermal stability of the lithium enolate derived from compound **12**. The enolate was generated at −78 °C according to the standard protocol and then stirred at two different temperatures for 10 min before it was quenched. The extent of decomposition was readily accessed by ^{1}H-NMR integration of relevant protons in the starting material **12** and auxiliary **11**. At −78 °C, only 3% cleavage was detected. While at 0 °C, significant amounts of auxiliary (21%) was observed. Other amide bases were also tested in the aldol reactions. LDA gave similar result as LHMDS, whereas NaHMDS gave the cleaved chiral auxiliary **11** (65%) as the major product. Thus aldol reactions with **12** were conducted at −78 °C using LHMDS as the base.

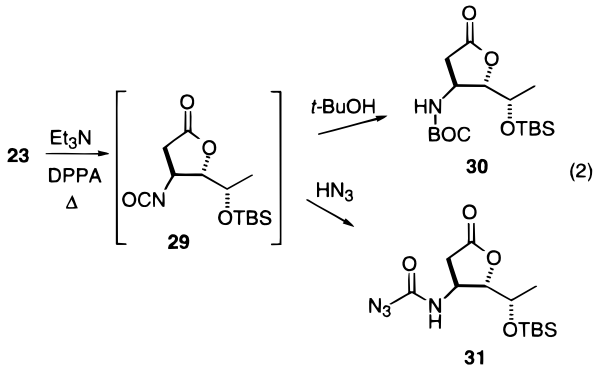
Aldol reaction of **12** with the (*S*)-*O*-TBS lactaldehyde **13** gave an inseparable mixture of adduct **21** and the corresponding lactone **22**. Additionally, a minor diastereomer **15** (5%), recovered starting material (8%), and cleaved chiral auxiliary in 15% yield were also obtained from the reaction. Treatment of the mixture of **21** and **22** with PPTS in THF at 60−65 °C gave the desired lactone **22** in 61% yield. A new compound was also detected on TLC analysis of the PPTS-catalyzed lactonization reaction. This new compound was separated in 3% yield. ^{1}H-NMR, ^{13}C-NMR, and elemental analysis indicated that it was another isomer of the lactone. A large coupling constant for C3-H and C4-H ($^3J_{H_3,H_4} = 8.9$ Hz) suggested a *cis* relationship and the compound was tentatively assigned the (3*S*,4*R*) configuration.[29]

The lactones **22** and **25** were hydrolyzed using the same procedure as before to acids **23** and **26**, respectively, in high yields. Compounds **16** and **26** exhibited identical ^{1}H- and ^{13}C-NMR spectra and opposite optical rotation indicating that they are enantiomeric. Compound **20** and **23** also displayed the same behavior and were enantiomers to each other as well. The assignment of *syn vs anti* stereochemistry in aldol reactions was supported by ^{1}H-NMR analysis of the lactone products and was further corroborated by the absolute configuration of the target natural products. The observed opposite facial selectivities of boron and lithium enolate aldol reactions is precedented in the work of Pridgen *et al.*[30] In their work, the boron-mediated aldol reaction of an α-(halomethyl)-*N*-acylimides furnished the Evans *syn* adduct exclusively. In contrast, the lithium aldol gave a non-Evans *syn* product as a major compound along with a minor *anti* isomer. The diastereoselectivity observed in our work can be explained by using a three-point chelated chair transition state postulated by Pridgen[31] and thus account for the non-Evans *syn* selectivity in the case of strongly coordinating enolate counterion (*e.g.* Li^+, Zn^{2+}, Sn^{4+}).

The next key step in our synthesis was the preparation of the amino lactones using the Curtius rearrangement.[32] A procedure[33] utilizing ethyl chloroformate and sodium azide failed to produce any amine product starting from either **23** or **27**. Only a mixed anhydride **27** was detected by NMR and IR (1784, 1720, 1697 cm^{-1}) analysis (eq 1). Apparently, acyl azide **28** was not formed through azide displacement which may be explained by the low solubility of the substrate and/or the azide.



Diphenylphosphoryl azide (DPPA) has been established as a reagent of choice for the preparation of acyl azides from carboxylic acids.[34] As has been established in the literature, the conversion of an acid to the corresponding amino compound requires refluxing an equimolar mixture of the carboxylic acid, DPPA, and triethylamine in the presence of an alcohol (eq 2). When **23** was first refluxed with triethylamine and DPPA for 1 h and then with *t*-BuOH for 12 h, a consistent 32% chemical yield of **30** was obtained along with significant amounts of carbamoyl azide **31**.[35]



We found that the formation of carbamoyl azide **31** was significantly suppressed when the reaction was carried

(28) (a) D'Souza, A. A.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans 1* **1995**, 1. (b) Reference 27b.

(29) This minor isomer most likely arises from an *anti* aldol product. The absolute stereochemistry of the product is unknown at the present time. mp 65−67 °C; R_f 0.15 (65:35 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.61 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 2.45 (dd, J = 17.7, 9.1 Hz, 1H), 3.28 (dd, J = 17.7, 10.5 Hz, 1H), 3.71 (dq, J = 6.6, 2.0 Hz, 1H), 4.19 (ddd, J = 10.5, 9.1, 8.9 Hz, 1H), 4.33 (dd, J = 9.5, 8.6 Hz, 1H), 4.48 (dd, J = 9.5, 2.8 Hz, 1H), 4.78 (d, J = 6.7 Hz, 1H), 4.97 (dd, J = 8.9, 2.0 Hz, 1H), 5.24 (ddd, J = 8.6, 6.7, 2.8 Hz, 1H), 7.19−7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 168.3, 153.9, 139.5, 138.3, 129.4, 128.9, 128.8, 128.5, 128.0, 127.5, 83.9, 69.4, 66.2, 58.4, 52.6, 42.9, 32.1, 25.8, 18.0, 17.5, −4.5, −4.6; IR (CH_2Cl_2) 3082, 1793, 1701 cm^{-1}; $[\alpha]^{25}_D = -52.5°$ (*c* 1.00, CH_2Cl_2). Anal. calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.13; H, 6.74; N, 2.72.

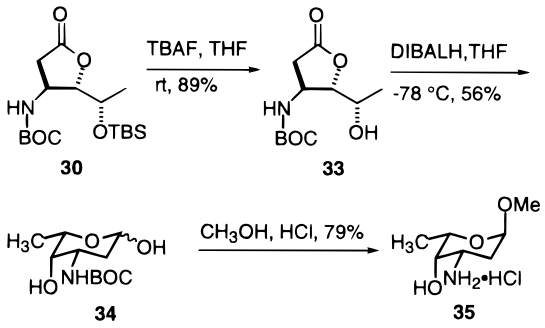
(30) (a) Abdel-Magid, A. F.; Lantos, I.; Pridgen, L. N. *Tetrahedron Lett.* **1984**, *25*, 3273. (b) Abdel-Magid, A. F.; Pridgen, L. N.; Eggelston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595.

(31) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107.

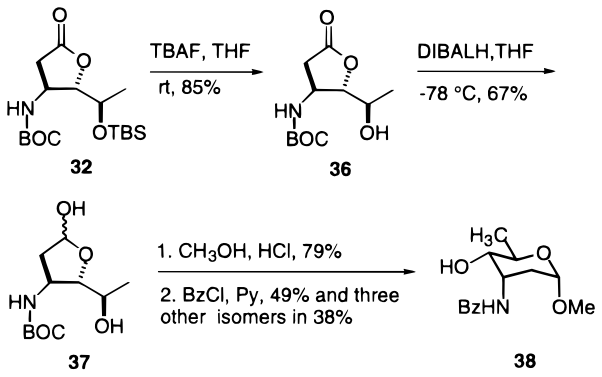
(32) (a) Buchler, C. A.; Pearson, D. E. *Survey of Organic Synthesis*; Wiley-Interscience: New York, 1970; pp 494−503. (b) Smith, P. A. S. *Org. React.* **1946**, *3*, 337.

(33) (a) Wienstock, J. *J. Org. Chem.* **1961**, *26*, 3511. (b) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

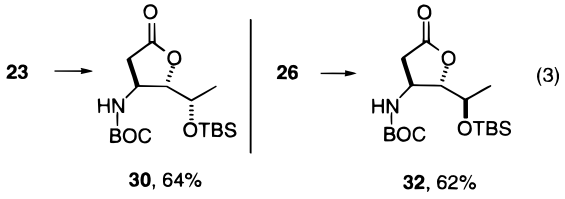
Scheme 4



Scheme 5



out in a mixed solvent with equal amounts of toluene and *t*-BuOH at an elevated temperature (120 °C). The chemical yield of the desired amino lactone **30** increased dramatically to over 60%, besides the chromatographic purification was also much easier. Thus, a solution of **23** or **26** in toluene and *t*-BuOH was treated with Et_3N at room temperature and then immediately heated to reflux in a preheated oil bath at 120 °C. DPPA was then added. The yellow solution was maintained at reflux for an additional 12 h period. After removal of solvent and subsequent silica gel column purification, the carbamates **30** and **32** were isolated in 64% and 62% yields, respectively (eq 3).



With the key amino lactone intermediates **30** and **32** at hand, the synthesis of L-daunosamine (Scheme 4) and D-ristosamine derivatives (Scheme 5) was completed as described below. Desilylation of **30** with TBAF at room temperature furnished the known hydroxy lactone **33**.[13pp] The γ-lactone to δ-lactone isomerization[36] has been observed in several cases. The rate of this isomerization was slow, and if chromatographic purification was conducted immediately after the reaction, a clean γ-lactone **33** could be obtained. However, the presence of small amount of δ-lactone isomer did not interfere with further transformations.

The amino alcohol **33** has been converted to L-methyl α-daunosamine hydrochloride (**35**) by Davies and Smyth in two steps in an overall yield of 36%.[13pp] We were able to make marginal improvement in the chemical yield for these two steps (overall 44%). Thus, the hydroxy lactone **33** was reduced by DIBALH in THF at −78 °C to give the lactol **34** as a complex mixture in 56% yield. Small amounts of the starting material and over-reduction product were also formed. Hauser *et al.*[13bb] encountered similar problems in their approach to duanosamine. The over-reduction and sluggish lactone reduction were attributed to the low solubility of the substrate. Etherification of the mixture of lactols **34** in methanolic hydrogen chloride gave **35** in 79% yield. It is of interest to note that signals for a minor isomer (identity unknown) was also observed in the NMR spectrum of **35**. The ^1H NMR and analytical data for **35** was in excellent agreement with that reported in the literature.[37] Thus, a seven-step total synthesis of L-methyl α-daunosamine hydrochloride was accomplished in 14% overall yield.

A parallel synthesis of D-ristosamine derivative was also carried out (Scheme 5). Thus, TBAF deprotection of **32** followed by DIBALH reduction yielded **37** in 57% yield as a complex mixture. Methanolic HCl treatment did not produce a solid as expected, rather a mixture of hydrochloride salts was isolated as a syrup. Although DL-methyl α-ristosamine hydrochloride[13cc] and L-α-ristosamine hydrochloride[16n] have been described as white solids in the literature, there is still confusion about the exact physical nature of ristosamine and its hydrochloride salt because of their extreme hygroscopic nature.[38] To confirm the structure of the compounds from our synthesis, the hydrochloride salt was reacted with benzoyl chloride to form the known D-methyl *N*-benzoyl-α-ristosamide (**38**)[17b] in 49% isolated yield. Therefore, an eight-step synthesis of D-methyl *N*-benzoyl-α-ristosamide (**38**) was achieved in 7.8% yield. Three other isomers were also isolated during the conversion of **37** to **38** in 38% chemical yield with an isomeric ratio of 1:1.8:1.9. Analysis of the proton and carbon NMR indicated that these were furanose and pyranose isomers of the parent ristosamide.[39]

To improve the overall yield in the conversion of the lactones **30** and **32** to the target amino sugars, an alternate reduction and deprotection sequence was devised. The DIBALH reduction of **30** gave the lactol **39** in 67% yield as a mixture of anomers in the ratio of 2.9/1 (Scheme 6). The double deprotection of the *O*-TBS and *N*-BOC groups in **39** was carried out by trifluoroacetic acid to yield the trifluoroacetate salt of daunosamine. Without purification, this salt was converted to the benzoate using BzCl to afford the L-*N*-benzoyl-daunosamide **40** as a mixture of anomeric pyranosides and furanosides, mp 146−149 °C, $[\alpha]^{25}_D = -87.8$ to −61.5° (*c* 0.50, EtOH), (lit.[13i] mp 152 °C, $[\alpha]^{25}_D = -108°$ (*c* 0.50, EtOH)). The ratios of isomers are pyranose/furanose = 3.4:1, and α-pyranose/β-pyranose = 1.1:1.[40] Thus, a six-step total synthesis of L-*N*-benzoyldaunosamide (**40**) was achieved in 18% overall yield.

(34) (a) Shioiri, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Ninomiya, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(35) (a) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull. Tokyo* **1974**, *23*, 855. (b) Csuk, R.; Schabel, M. J.; Scholz, Y. V. *Tetrahedron: Asymmetry* **1996**, *7*, 3505.

(36) References 13g, m, bb, ii, uu.

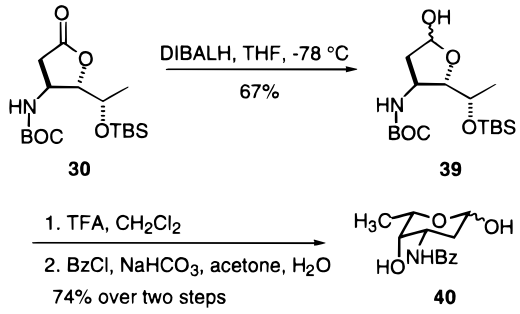
(37) Arcamone, F.; Cassinelli, G.; Franrecchi, G.; Mondelli, R.; Orezzi, P.; Penco, S. *Gazz. Chim. Ital.* **1970**, *100*, 949.

(38) (a) Boganr, R.; Sztaricskai, F.; Munk, M. E.; Tamas, J. *J. Org. Chem.* **1974**, *39*, 2971. (b) Reference 16j.

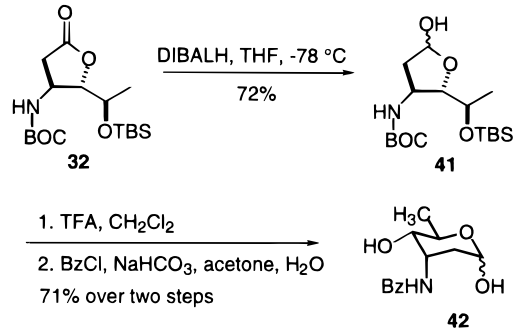
(39) The identity of each isomer was not established.

(40) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans 1* **1982**, 885.

Scheme 6



Scheme 7



A similar transformation starting with lactone **32** gave D-*N*-benzoyl ristosamide (**42**) as an anomeric mixture in 18% overall yield over 6 steps from **12** (Scheme 7). The ratios for furanoside/pyranoside are 1.7/1, and α-furanose/*β*-furanose = 1.2/1, mp 103−107 °C, $[\alpha]^{25}_D$ = 43.8 to 41.2° (*c* 1.00, EtOH), (lit.[17a] mp 128−129 °C, $[\alpha]^{23}_D$ = 13.5° (*c* 1.00, EtOH), and lit.[17b] mp 135−137 °C, [α] = 15.6 to 9.8° (*c* 1.00, EtOH)).

It has been reported that the *N*-benzoyl derivatives **40** and **42** (Scheme 6, 7) exist in solution as α- and *β*-anomers of furanosides and pyranosides.[40] In particular, L-*N*-benzoyldaunosamide (**40**) exists as an α-pyranose (100%), while L-*N*-benzoyl ristosamide (**42**) exists as a mixture of α- and *β*-furanose anomers in a ratio of α/*β* = 57/43. In our synthesis we obtained a mixture of furanose and pyranose anomers for both amino sugars **40** and **42**. This observation most likely is a result of our reaction conditions. The benzoylated sugars **40** and **42** were liberated from double deprotection of the corresponding lactones by a strong acid, TFA. Furthermore, when the pure α-pyranoside **38** was demethylated by refluxing in HOAc/H_2O as described in literature,[17a,b] **42** was produced as a mixture of four isomers. The isomer composition from this experiment was identical to the one obtained from the conversion of **41** to **42**. It is known that acid promotes anomerization; in some cases a base can be added to the reaction to prevent anomerization from trace amounts of free acid.[14a] Therefore, the differences in physical properties of the target compounds from our synthesis and those from the literature can be rationalized by the presence of different isomeric ratios. Nevertheless, NMR data for the major isomers were in excellent agreement with that reported in the literature. Satisfactory elemental analyses were also obtained for **40** and **42**.

Conclusion

An asymmetric aldol strategy has been developed for the synthesis of L-daunosamine and D-ristosamine derivatives starting from noncarbohydrate precursors. The overall yields for these two amino sugars were 18% and 18%, respectively. Lithium- and boron-mediated aldol reactions were examined, and the former was found to be more effective in terms of chemical efficiency. The two reactions provided products of opposite absolute stereochemistry. An experimental modification of the Curtius procedure was developed for the installation of the amino functionality. The aldol-Curtius protocol developed in this work is amenable to the synthesis of other amino sugars such as acosamine and tolyposamine[41] when appropriate *anti* aldol condensation reaction conditions are employed. Work along these lines is underway.

Experimental Section

For general experimental procedures see ref 42. **(−)-(*R*)-3-(1-Oxo-3-carbomethoxypropyl)-4-(diphenylmethyl)oxazolidin-2-one (12).** To a flame-dried 250 mL three-necked flask was added a solution of (*R*)-4-(diphenylmethyl)oxazolidin-2-one (**11**) (6.64 g, 26.25 mmol) dissolved in freshly distilled THF (80 mL) under N_2. The solution was cooled to −78 °C in a dry ice/acetone bath. *n*-BuLi (1.6 M, 17.2 mL, 27.6 mmol) was added in a dropwise fashion *via* syringe over a period of 10 min at −78 °C. This red solution was further stirred at −78 °C for 10 min. 3-Carbomethoxypropionyl chloride (3.4 mL, 27.6 mmol) was added slowly over 5 min. The light yellow solution was stirred at −78 °C for 15 min and at 0 °C for 30 min. The reaction was quenched with saturated NH_4Cl (30 mL) at 0 °C. The solvent was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed successively with H_2O (40 mL) and brine (40 mL) and dried with anhydrous $MgSO_4$ and filtered. Evaporation of solvent resulted in a yellow oil. Purification of the crude compound by flash column chromatography (eluted with 20% EtOAc in hexane) gave a white solid (9.44 g, 25.72 mmol, 98%): mp 80−82 °C; R_f 0.60 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.59 (t, *J* = 6.3 Hz, 2H), 3.05−3.13 (m, 1H), 3.17−3.25 (m, 1H), 3.70 (s, 3H), 4.41 (dd, *J* = 9.2, 2.9 Hz, 1H), 4.46 (dd, *J* = 9.2, 7.3 Hz, 1H), 4.70 (d, *J* = 5.4 Hz, 1H), 5.30 (ddd, *J* = 7.3, 5.4, 2.9 Hz, 1H), 7.07−7.36(m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.4, 172.2, 153.8, 139.8, 138.2, 129.6, 129.2, 128.9, 128.6, 128.2, 127.3, 65.0, 56.1, 51.7, 50.3, 30.4, 27.6; IR ($CDCl_3$) 1784, 1737, 1703 cm^{-1}; $[\alpha]^{25}_D$ = −145.3° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.42; H, 5.95; N, 4.07.

General Procedure for the Boron-Mediated Aldol Condensation of 12 with 2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propanal. To a flame-dried two necked 25 mL flask under N_2 was added **12** (0.507 g, 1.38 mmol) in CH_2Cl_2 (3 mL) and cooled to 0 °C in an ice bath. 1.0 M Dibutylboron triflate solution in CH_2Cl_2 (1.52 mL, 1.52 mmol) was added slowly over a period of 5 min, and the resultant brownish solution was stirred for another 5 min. Freshly distilled triethylamine (0.24 mL, 1.79 mmol) was then added dropwise while maintaining the temperature at 0 °C. The pale yellow solution was stirred at 0 °C from 45 min to 1 h. The boron enolate solution was then cooled to −78 °C. Freshly prepared (*R*)- or (*S*)-*O*-TBS-lactaldehyde (0.389 g, 2.07 mmol) in 1.5 mL of CH_2Cl_2 was added dropwise over 10 min. The reaction mixture was warmed gradually to 0 °C over a period of 24 h. The progress of the reaction was monitored by TLC. The reaction was quenched slowly by the addition of pH = 7 buffer (1.0 mL), MeOH (1.5 mL), and MeOH/30% H_2O_2 = 2/1 (1.5 mL). The cloudy mixture was stirred at 0 °C for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (4 × 5 mL). The combined extracts were dried over Na_2SO_4 and filtered,

(41) Guanti, G.; Banfi, L.; Narisano, E.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 2221.

(42) ^{1}H and ^{13}C NMR were recorded on JEOL-GSX instruments. IR spectra were recorded on a Mattson Instruments, 2020 Galaxy series FT-IR spectrophotometer. Optical rotations were recorded on a JASCO-DIP-370 instrument. For typical experimental protocols, see: Gaboury, J. A.; Sibi, M. P. *J. Org. Chem.* **1993**, *58*, 2173.

and the solvent was evaporated to dryness under reduced pressure. Flash chromatography furnished pure aldol product and the recovered starting material.

(−)-(3*R*,4*R*,5*R*)-3-[[(*R*)-*N*-[2-oxo-4-(diphenylmethyl)oxazolidinyl]]carbonyl]-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (19). The general procedure described above was used. **12** (0.550 g, 1.5 mmol) was reacted with (*R*)-*O*-TBS-lactaldehyde **17** which gave an inseparable mixture of the aldol adduct and lactone. This mixture was subjected to PPTS-catalyzed (15 mg) cyclization with THF as a solvent at 60−65 °C for 12 h. Purification by chromatography gave **19** (0.1860 g, 0.3356 mmol, 22%, 2 steps) as a white foam; R_f 0.52 (65:35 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.18 (d, J = 6.3 Hz, 3H), 2.02 (dd, J = 18.0, 5.5 Hz, 1H), 2.76 (dd, J = 18.0, 10.3 Hz, 1H), 4.00 (dq, J = 6.3, 2.7 Hz, 1H), 4.16 (ddd, J = 10.3, 5.5, 4.2 Hz, 1H), 4.36−4.42 (m, 2H), 4.59−4.64 (m, 2H), 5.33 (ddd, J = 7.4, 6.3, 4.4 Hz, 1H), 7.11−7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 171.1, 153.2, 139.0, 137.7, 129.3, 129.1, 128.8, 128.6, 128.3, 127.5, 83.3, 69.4, 66.1, 56.7, 52.0, 41.3, 32.5, 25.8, 19.1, 17.9, −4.5, −4.9; IR ($CDCl_3$) 1782, 1703 cm^{-1}; $[\alpha]^{25}_D$ = −45.1° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H,7.12; N, 2.67. Found: C, 66.47; H, 7.13; N, 2.74.

(−)-(3*R*,4*R*,5*S*)-3-[[(*R*)-*N*-[2-Oxo-4-(diphenylmethyl)oxazolidinyl]]carbonyl]-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (15). Aldol condensation of **12** (0.507 g, 1.38 mmol) with (*S*)-*O*-TBS-lactaldehyde gave **15** (0.2352 g, 0.4497 mmol, 33%) as a white foam: mp 49−51 °C; R_f 0.70 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.07 (d, J = 6.3 Hz, 3H), 1.80 (dd, J = 18.2, 6.4 Hz, 1H), 2.86 (dd, J = 18.2, 11.0 Hz, 1H), 4.02 (dq, J = 6.3, 3.3 Hz, 1H), 4.28 (ddd, J = 11.0, 6.4, 4.4 Hz, 1H), 4.34−4.42 (m, 2H), 4.67 (d, J = 7.5 Hz, 1H), 4.76 (dd, J = 4.4, 3.3 Hz, 1H), 5.33 (ddd, J = 7.5, 4.8, 2.4 Hz, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 171.3, 153.0, 138.9, 137.7, 129.4, 129.1, 128.9, 83.1, 68.8, 66.0, 56.6, 51.9, 39.5, 33.4, 25.7, 19.7, 17.9, −4.5, −4.9; IR ($CDCl_3$) 1782, 1703 cm^{-1}; $[\alpha]^{25}_D$ = −62.1° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.45; H, 6.93; N, 2.62.

(−)-(3*S*,4*S*,5*S*)-3-[[(*R*)-*N*-[2-Oxo-4-(diphenylmethyl)oxazolidinyl]]carbonyl]-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (22). In a flame dried three-necked 250 mL round bottom flask under N_2 was placed **12** (11.19 g, 30.51 mmol). THF (60 mL) was added, and it was stirred at rt to form a clear solution. The solution was then cooled to −78 °C in a dry ice/2-propanol bath. A solution of LHMDS (5.36 g, 32.04 mmol) in THF (30 mL) was added against the glass wall of the flask at a rate of 0.81 mL/min by a syringe pump. The resultant yellow solution was further stirred at −78 °C for 10 min. A solution of (*S*)-*O*-TBS-lactaldehyde **13** (8.60 g, 45.77 mmol) in THF (10 mL) was added at a rate of 0.57 mL/min by a syringe pump. The reaction was further stirred at −78 °C for 10 min. (TLC analysis indicated completion of the reaction). The reaction was quenched subsequently with HOAc (1.7 mL) and saturated NH_4Cl (10 mL) at −78 °C. It was further stirred at −78 °C for 10 min and warmed to rt. The bulk of the solvent was removed in vacuo. The mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with 10% citric acid (2 x 50 mL), H_2O (100 mL), and brine (100 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated. Purification of the crude product by flash chromatography, eluting with a solvent gradient from 15% to 40% EtOAc in hexane, gave a 4.7/1 mixture of lactone and aldol adduct (10.97 g), along with **15** (0.7793 g, 1.49 mmol, 5%), starting material **12** (0.8995 g, 8.0%), and cleaved chiral auxiliary **11** (1.1205 g, 4.42 mmol, 15%). The lactone and aldol adduct mixture (10.97 g) was dissolved in THF (50 mL) with PPTS (1.0 g), and the solution was refluxed for 18 h. At this point, TLC analysis indicated lactone cyclization was completed, but a new compound in a small amount appeared. The reaction mixture was filtered through a pad of silica gel, and the solvent was evaporated. Purification of the crude mixture by flash chromatography, eluted with 20% EtOAc in hexane, afforded **22** (9.7330 g, 18.61 mmol, 61%) along with a minor lactone[29] (0.4112 g, 0.7862 mmol, 3%): mp 172−174 °C; R_f 0.52 (65:35 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 9H), 1.09 (d, J = 6.4 Hz, 3H), 2.72 (dd, J = 17.4, 9.0 Hz, 1H), 2.80 (dd, J = 17.4, 3.0 Hz, 1H), 3.49 (dd, J = 1.8, 1.5 Hz, 1H), 4.02 (dq, J = 6.4, 1.5 Hz, 1H), 4.06 (ddd, J = 9.0, 3.0, 1.8 Hz, 1H), 4.41 (dd, J = 9.7, 8.6, Hz, 1H), 4.48 (dd, J = 9.7, 3.1 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 5.32 (ddd, J = 8.6, 6.8, 3.1 Hz, 1H), 7.11−7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 171.7, 153.5, 138.9, 137.5, 129.4, 129.3, 129.0, 128.3, 128.2, 127.4, 84.9, 70.2, 65.7, 56.7, 51.0, 42.6, 30.3, 25.8, 20.0, 17.9, −4.5, −4.7; IR (CH_2Cl_2) 1807, 1687 cm^{-1}; $[\alpha]^{25}_D$ = −54.7° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.67; H, 7.26; N, 2.65.

(−)-(3*S*,4*S*,5*R*)-3-[[(*R*)-*N*-[2-Oxo-4-(diphenylmethyl)oxazolidinyl]]carbonyl]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (25). Lithium-mediated aldol condensation of **12** (4.13 g, 11.247 mmol) with (*R*)-*O*-TBS lactaldehyde **17** gave **25** (4.0 g, 7.648 mmol, 68%), **19** (0.2739 g, 0.5238 mmol, 5%), starting material **12** (0.2519 g, 6.1%), and cleaved chiral auxiliary **11** (0.3927 g, 1.552 mmol, 14%): mp 132−134 °C; R_f 0.45 (65:35 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.09 (s, 9H), 0.97 (d, J = 6.4 Hz, 3H), 2.40 (dd, J = 18.0, 3.8 Hz, 1H), 2.91 (dd, J = 18.0, 10.5 Hz, 1H), 4.02 (dq, J = 6.4, 2.2 Hz, 1H), 4.16 (dd, J = 2.6, 2.2 Hz, 1H), 4.38−4.42 (m, 2H), 4.51 (ddd, J = 10.5, 3.8, 2.6 Hz, 1H), 4.67 (d, J = 7.1 Hz, 1H), 5.31−5.39 (m, 1H), 7.10−7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.1, 139.1, 137.9, 129.3, 129.1, 128.9, 84.3, 68.8, 65.7, 56.6, 51.7, 38.1, 33.3, 25.8, 19.0, 17.9, −4.8, −4.9; IR (CH_2Cl_2) 1799, 1682 cm^{-1}; $[\alpha]^{25}_D$ = −42.9° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.32; H, 7.13; N, 2.57.

General Procedure for the Hydrolysis of Removing the Chiral Auxiliary. To a 250 mL round bottom flask was placed **25** (4.0 g, 7.648 mmol) in 75 mL of THF/H_2O = 4/1 under N_2. The solution was cooled to 0 °C in an ice bath. 30% H_2O_2 (3.2 mL) was added dropwise over 10 min to the solution, followed by the addition of LiOH (0.30 g) in H_2O (15 mL) in 10 min. The temperature of the reaction was maintained at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of Na_2SO_3 (3.8 g) in H_2O (23 mL) was added. The organic solvent was removed in vacuo. The remaining aqueous mixture was extracted with CH_2Cl_2 (4 × 40 mL) to remove the chiral auxiliary. The organic layers were dried with anhydrous Na_2SO_4, and solvent was evaporated to give recovered auxiliary **12** (1.8382 g, 7.266 mmol, 95%). The aqueous solution was cooled to 0 °C and neutralized with 6 M HCl carefully to pH = 3−4. This cloudy mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried with anhydrous Na_2SO_4. Evaporation of the solvent to dryness furnished a clear oil **26** (2.07 g, 7.189 mmol, 94%).

(+)-(3*R*,4*R*,5*S*)-3-Carboxyl-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (16). Following the general hydrolysis procedure, **15** (0.3517 g, 0.67 mmol) gave **16** (0.1762 g, 0.62 mmol, 92%) as a clear oil: R_f 0.36 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.18 (d, J = 6.4 Hz, 3H), 2.75 (dd, J = 18.1, 10.5 Hz, 1H), 2.87 (dd, J = 18.1, 5.3 Hz, 1H), 3.44 (ddd, J = 10.5, 5.3, 3.9 Hz, 1H), 4.13 (dq, J = 6.4, 2.4 Hz, 1H), 4.58 (dd, J = 3.9, 2.4 Hz, 1H), 9.26 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 175.2, 84.9, 68.9, 38.2, 31.7, 31.0, 25.8, 19.3, 17.9, −4.7, −4.9; IR (neat) 3500−3200, 1780, 1720 cm^{-1}; $[\alpha]^{25}_D$ = 17.8° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found: C, 54.54; H, 8.11.

(−)-(3*S*,4*S*,5*R*)-3-Carboxyl-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoic Acid γ-Lactone (26). Using the general hydrolysis procedure, **25** (4.0 g, 7.648 mmol) gave **26** (2.07 g, 7.189 mmol, 94%) as a clear oil, which was the enantiomer of **16**; $[\alpha]^{25}_D$ = −17.6° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found: C, 53.99; H, 8.03.

(−)-(3*R*,4*R*,5*R*)-3-Carboxyl-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]Hexanoic Acid γ-Lactone (20).

Using the general hydrolysis procedure, **19** (0.186 g, 0.3556 mmol) gave **20** (0.0952 g, 0.3307 mmol, 93%) as a clear oil: R_f 0.52 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H), 2.81 (dd, J = 18.1, 10.1 Hz, 1H), 2.88 (dd, J = 18.1, 6.5 Hz, 1H), 3.32 (ddd, J = 10.1, 6.5, 5.0 Hz, 1H), 4.03 (dq, J = 6.4, 2.6 Hz, 1H), 4.59 (dd, J = 5.0, 2.6 Hz, 1H), 9.10 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 175.1, 84.3, 69.2, 41.4, 31.5, 25.8, 19.3, 18.0, −4.2, −4.8; IR (neat) 3477−3036, 1774, 1720 cm^{-1}; $[\alpha]^{25}_D$ = −6.7° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found: C, 54.25; H, 8.01.

(+)-(3*S*,4*S*,5*S*)-3-Carboxyl-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]Hexanoic Acid γ-Lactone (23). Using the general hydrolysis procedure, **22** (0.9858 g, 1.88 mmol) gave **23** (0.5128 g, 1.79 mmol, 95%) as a clear oil, which was enantiomer of **20**: $[\alpha]^{25}_D$ = 6.9° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found: C, 53.84; H, 8.07.

General Procedure for the Curtius Rearrangement. To a flame-dried two-necked 25 mL round bottom flask, equipped with a condenser, was placed **26** (1.00 g, 3.49 mmol) in 8 mL of toluene (dry) and 8 mL of *t*-BuOH (dried over Na) under N_2. Freshly distilled triethylamine (0.56 mL, 4.02 mmol) was added dropwise with fast stirring at rt over 5 min. This solution was immediately heated to reflux in a preheated oil bath at 120 °C. DPPA (0.83 mL, 3.84 mmol) was then added dropwise in 2 min. The resultant yellow solution was maintained at reflux for 12 h. The solvent was removed in vacuo. Purification of the crude product by flash chromatography (elution with 10−15% EtOAc) yielded **32** as a colorless oil (0.7752 g, 2.17 mmol, 62%).

(+)-(3*S*,4*S*,5*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-hexanoic Acid γ-Lactone (30). Following the general Curtius rearrangement procedure, **23** (0.1004 g, 0.351 mmol) gave **30** (0.0802 g, 0.2246 mmol, 64%) as a colorless oil: R_f 0.35 (65:35 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.43 (s, 9H), 2.28 (dd, J = 16.7, 1.9 Hz, 1H), 2.99 (dd, J = 16.7, 8.6 Hz, 1H), 4.05−4.14 (m, 1H), 4.14−4.26 (m, 2H), 4.91 (d, J = 5.0 Hz, 1H); ^{1}H NMR (400 MHz, C_6D_6) δ −0.08 (s, 3H), −0.02 (s, 3H), 0.85 (s, 9H), 1,00 (d, J = 6.4 Hz, 3H), 1.39 (s, 9H), 1.79 (dd, J = 18.1, 2.5 Hz, 1H), 2.67 (dd, J = 18.1, 9.1 Hz, 1H), 3.77 (dq, J = 6.4, 1.3 Hz, 1H), 3.89 (dd, J = 1.3, 1.3 Hz, 1H), 4.10 (dddd, J = 9.1, 6.7, 2.5, 1.3 Hz, 1H), 4.39 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 155.2, 89.9, 80.5, 69.3, 50.1, 35.8, 28.4, 25.9, 19.8, 18.0, −4.2, −4.7; ^{13}C NMR (100 MHz, C_6D_6) δ 174.2, 154.9, 89.5, 79.2, 69.3, 49.4, 35.1, 28.1, 25.6, 19.5, 17.8, −4.7, −5.0; IR (neat) 3360 (br), 1793, 1707 cm^{-1}; $[\alpha]^{25}_D$ = 10.70° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.51; H, 8.85; N, 3.83.

(−)-(3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-hexanoic Acid γ-Lactone (32). Using Curtius procedure described above, **26** (1.0 g, 3.49 mmol) gave **32** (0.7752 g, 2.17 mmol, 62%) as a colorless oil; R_f 0.35 (80:20-hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 1.25 (d, J = 6.7 Hz, 3H), 1.43 (s, 9H), 2.32 (d, J = 17.9, Hz, 1H), 2.98 (dd, J = 17.9, 8.7 Hz, 1H), 4.06 (dq, J = 6.7, 2.4 Hz, 1H), 4.18 (dd, J = 2.5, 2.4 Hz, 1H), 4.31−4.48 (m, 1H), 4.93 (d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 154.9, 89.7, 80.5, 68.9, 47.3, 36.8, 28.4, 25.8, 19.4, 17.9, −4.8, −5.0; IR (neat) 3365, 1793, 1707 cm^{-1}; $[\alpha]^{25}_D$ = −24.5° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.43; H, 8.86; N, 3.76.

General Procedure for the Silicon Deprotection. The amino lactone **32** (0.7752 g, 2.17 mmol) was dissolved in THF (4 mL) under N_2. The solution was cooled to 0 °C in an ice bath. 1.0 M TBAF (2.2 mL, 2.2 mmol) was added dropwise over 10 min. The ice bath was removed, and the resultant yellow solution was stirred at rt for 16 h. The solvent was evaporated, and purification of the resultant yellow crude product by flash chromatography (eluted with 50% EtOAc) yielded **36** (0.4507 g, 1.84 mmol, 85%) as a white solid.

(+)-(3*S*,4*S*,5*S*)-3-[*N*-[*tert*-Butyloxycarbonyl)amino]-4,5-dihydroxyhexanoic Acid γ-Lactone (33). Deprotection of **30** (1.12g, 3.14 mmol) gave **33** (0.6847 g, 2.79 mmol, 89%) as a white solid: mp 105−107 °C; R_f 0.27 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.4 Hz, 3H), 1.49 (s, 9H), 2.43 (dd, J = 18.2, 5.0 Hz, 1H), 2.75 (bs, 1H), 2.99 (dd, J = 18.2, 8.8 Hz, 1H), 3.98 (m, 1H), 4.20 (dd, J = 3.9, 3.1 Hz, 1H), 4.33 (m, 1H), 5.18 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 155.4, 89.2, 80.6, 67.7, 49.4, 35.5, 28.5, 19.2; IR (neat) 3580−3200 (br), 1780, 1693 cm^{-1}; $[\alpha]^{25}_D$ = 8.6° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.92; H, 7.56; N, 5.54.

(−)-(3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino[-4,5-dihydroxyhexanoic Acid γ-Lactone (36). Using the procedure for *O*-TBS deprotection, **32** (0.7752 g, 2.17 mmol) gave **36** (0.4507 g, 1.84 mmol, 85%) as a white solid: mp 108−110 °C; R_f 0.26 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 2.45 (dd, J = 18.2, 5.9 Hz, 1H), 2.82 (bs, 1H), 3.00 (dd, J = 18.2, 8.8 Hz, 1H), 3.93−4.05 (m, 1H), 4.11−4.17 (m, 1H), 4.32−4.43 (m, 1H), 4.91 (d, J = 7.1 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 155.5, 89.0, 81.0, 68.2, 48.6, 35.7, 28.4, 19.0; IR (neat) 3600−3200 (br), 1780, 1701 cm^{-1}; $[\alpha]^{25}_D$ = −24.5° (*c* 0.40, CH_2Cl_2). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.77; H, 7.63; N, 5.50.

General Procedure for the DIBALH Reduction. In a flame-dried 10 mL round bottom flask was placed **36** (0.0998 g, 0.407 mmol) in THF (3.0 mL) under N_2. It was stirred at rt to form a clear solution. Then it was cooled to −78 °C in a dry ice/acetone bath. 1.0 M DIBALH in hexane (1.4 mL, 1.4 mmol) was added slowly over 10 min with a fast stirring. When the reaction was stirred at −78 °C for 1.5 h, it was quenched with CH_3OH/H_2O = 4/1 (2.0 mL) at −78 °C and further stirred at −78 °C for 5 min. The mixture was warmed to rt. A solution of saturated $NaHCO_3$ (0.5 mL) was added. The mixture was filtered through a pad of celite. The filter cake was washed thoroughly with acetone, and the solvent was evaporated. The residue was purified by silica gel column (eluted with benzene/acetone = 5/3) to give **37** (0.0673 g, 0.272 mmol, 67%) as a complex mixture.

(−)-L-*N*-(*tert*-Butyloxycarbonyl)daunosamide (34). Following the general DIBALH reduction procedure (purification by the elution with benzene/acetone = 4/3), **33** (0.1964 g, 0.80 mmol) gave **34** as a complex mixture (0.1098 g, 56%): IR (neat) 3616−3115 (br), 1716, 1691 cm^{-1}; $[\alpha]^{25}_D$ = −64.7° (*c* 1.00, CH_3OH, 2 h). Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.26; H, 8.28; N, 5.32.

(+)-D-*N*-(*tert*-Butyloxycarbonyl)ristosamide (37). DIBALH reduction of **36** (0.0998 g, 0.407 mmol) gave an isomeric mixture of **37** (0.0673 g, 0.272 mmol, 67%) as an oil: IR (neat) 3649−3095 (br), 1710, 1692 cm^{-1}; $[\alpha]^{25}_D$ = 17.2−15.18° (*c* 0.90, CH_3OH, 3 h). Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.25; H, 8.30; N, 5.26.

(+)-[4*S*,5*S*,5-(1*S*)]-2-Hydroxy-4-[*N*-(*tert*-butyloxycarbonyl)amino]-5-[1-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]tetrahydrofuran (39). DIBALH reduction of (using 2.5 equiv of DIBALH for the reaction and 20% EtOAc in hexane for chromatography purification) **30** (60 mg, 0.1681 mmol) furnished **39** as a clear oil (40.6 mg, 0.1131 mmol, 67%) as a mixture of two isomers in a ratio of 2.9:1 by NMR integration; R_f 0.24 (80:20 hexane:ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) major isomer: δ 0.03 (s, 3H), 0.11 (s, 3H), 0.96 (s, 9H), 1.14 (d, J = 6.3 Hz, 3H), 1.41 (s, 9H), 1.67 (ddd, J = 13.4, 13.2, 1.5 Hz, 1H), 1.96 (ddd, J = 13.4, 8.6, 4.6 Hz, 1H), 3.85 (dq, J = 6.3, 3.9 Hz, 1H), 4.00 (m, 1H), 4.21 (m, 1H), 5.29 (dd, J = 13.2, 4.6 Hz, 1H), 5.45 (d, J = 2.2 Hz, 1H); minor isomer: δ 0.02 (s, 3H), 0.18 (s, 3H), 0.91 (s, 9H), 1.16 (d, J = 6.7 Hz, 3H), 1.54 (s, 9H), 1.29−1.36 (m, 1H), 2.08−2.14 (m, 1H), 3.91−3.97 (m, 1H), 4.09−4.14 (m, 1H), 4.37−4.46 (m, 1H), 5.29 (m, 1H), 5.45 (b, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ major isomer: 155.2, 98.2, 89.5, 78.7, 51.6, 39.9, 28.2, 25.8, 20.1, 18.0, −4.6, −4.8; minor isomer: 155.2, 98.5, 89.8, 78.8, 51.5, 42.3, 28.2, 25.8, 19.4, 17.9, −4.7, −4.9; IR (neat) 3120−3556 (br), 1720, 1693 cm^{-1}; $[\alpha]^{25}_D$ = 39.5° (*c* 1.00, CH_2Cl_2); HRMS *m*/*z* calcd for $C_{17}H_{35}NO_5Si$ $[MH]^+$ 362.2363, obsd 362.2364.

**(+)-[4*S*,5*S*,5-(1*R*)]-2-Hydroxy-4-[*N*-(*tert*-butyloxycarbonyl)amino]-5-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy-

]ethyl]tetrahydrofuran (41). DIBALH reduction (using 2.5 equiv of DIBALH for reaction, and 20% EtOAc in hexane for chromatography purification) of **32** (0.1004 g, 0.28 mmol) furnished **41** as a clear oil (0.0727 g, 0.2025 mmol, 72%) as a mixture of two isomers in a ratio of 8.5:1 by NMR integration; R_f 0.21 (80:20 hexane:ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) major isomer: δ 0.02 (s, 3H), 0.05 (s, 3H), 0.94 (s, 9H), 1.18 (d, J = 6.4 Hz, 3H), 1.41 (s, 9H), 1.67 (ddd, J = 13.3, 4.2, 1.4 Hz, 1H), 1.97 (ddd, J = 13.3, 8.6, 4.2 Hz, 1H), 3.79 (dq, J = 6.4, 3.0 Hz, 1H), 3.93 (dd, J = 3.0, 3.0 Hz, 1H), 4.32 (dddd, J = 8.8, 8.6, 3.0, 1.4 Hz, 1H), 5.24 (dd, J = 4.2, 4.2 Hz, 1H), 5.35 (d, J = 8.8 Hz, 1H); minor isomer: δ 0.04 (s, 3H), 0.11 (s, 3H), 0.97 (s, 9H), 1.27 (d, J = 6.0 Hz, 3H), 1.42 (s, 9H), 1.65 (dd, J = 10.7, 4.7 Hz, 1H), 2.32−2.37 (m, 1H), 3.76−3.86 (m, 1H), 3.87−3.90 (m, 1H), 4.40−4.60 (m, 1H), 5.15−5.18 (m, 1H), 5.56−5.59 (b, 1H); ^{13}C NMR (100 MHz, C_6D_6) major isomer: δ 155.0, 98.8, 89.9, 78.8, 69.3, 50.1, 40.5, 28.2, 25.8, 20.2, 18.0, −4.7, −5.0; minor isomer: 155.0, 98.4, 88.0, 78.8, 69.3, 54.1, 46.0, 28.4, 25.9, 20.4, 17.4, −4.5, −4.8; IR (neat) 3500−3220 (br), 1728, 1687 cm^{-1}; $[\alpha]^{25}_D$ = 20.6° (*c* 1.00, CH_2Cl_2); HRMS *m*/*z* calcd for $C_{17}H_{35}NO_5Si$ $[MH]^+$ 362.2363, obsd 362.2364.

(−)-Methyl 3-Amino-2,3,6-trideoxy-α-L-*lyxo*-pyranoside Hydrochloride ((−)-L-*O*-Methyl-α-daunosamine Hydrochloride) (35). In a 10 mL round bottom flask was placed **34** (52 mg, 0.2105 mmol). A 2.0 mL volume of methanolic HCl was added at rt. The solution was stirred at rt for 6 h. The solvent was removed by an aspirator (connected with a drying tube) to give a light yellow solid. The solid was dissolved in 0.5 mL of CH_3OH (dry), and **35** was precipitated out as a white solid by the addition of anhydrous ethyl ether (4.0 mL) (32.9 mg, 0.167 mmol, 79%): mp 187−190 °C; ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.36 (d, J = 6.6 Hz, 3H), 2.42 (dd, J = 12.3, 1.5 Hz, 1H), 2.49 (dd, J = 12.3, 12.3 Hz, 1H), 3.25 (s, 3H), 3.91 (dq, J = 6.6, 0.8 Hz, 1H), 4.28 (ddd, J = 12.3, 5.0, 2.8 Hz, 1H), 4.50 (dd, J = 2.8, 0.8 Hz, 1H), 4.83 (dd, J = 3.3, 1.5 Hz, 1H), 10.5 (bs, 2H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 97.7, 67.0, 66.4, 54.3, 47.9, 29.2, 17.2; IR (KBr) 3452−3281, 3066−2777 cm^{-1}; $[\alpha]^{25}_D$ = −139.4° (*c* 0.48, CH_3OH), lit.[37] mp 188−90 °C, $[\alpha]_D$ = −140° (*c* 1.0, CH_3OH)).

(+)-Methyl 3-Benzamido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside ((+)-D-*O*-Methyl-α-3-benzamidoristosamide) (38). In a 10 mL round bottom flask was placed **37** (66.4 mg, 0.2688 mmol). Methanolic HCl (2.0 mL) was added at rt. The solution was stirred at rt for 6 h. The solvent was removed by an aspirator connected with a drying tube to give a light yellow solid. The crude reaction mixture (0.0499 g, 0.2532 mmol) was dissolved in pyridine (2.0 mL). To this solution was added benzoyl chloride (0.03 mL, 0.26 mmol). After the reaction was stirred at rt for 1 h, pyridine was removed in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with 10% citric acid and H_2O (5 mL), and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo to furnish a brown oil. This crude product was purified by preparative TLC (eluted with 50% EtOAc in hexane) to yield **38** (32.7 mg, 0.1234 mmol, 49%) as a clear oil. R_f 0.36 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 7.2 Hz, 3H), 2.01 (ddd, J = 14.6, 3.0, 1.2 Hz, 1H), 2.13 (ddd, J = 14.6, 4.0 4.0 Hz, 1H), 3.44 (s, 3H), 3.54 (ddd, J = 9.6, 3.2, 2.5 Hz, 1H), 3.79 (dq, J = 9.6, 7.2 Hz, 1H), 4.05 (d, J = 2.5 Hz, 1H), 4.64 (dddd, J = 6.4, 4.0, 3.2, 3.0 Hz, 1 H), 4.79 (dd, J = 4.0, 1.2 Hz, 1H), 7.25−7.79 (m, 5H), 7.96 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 133.5, 132.0, 128.7, 127.2, 98.1, 74.8, 64.8, 55.3, 48.4, 33.3, 17.5; IR (neat) 3431, 1655 cm^{-1}; $[\alpha]^{25}_D$ = 122.8° (*c* 0.86, benzene), lit.[17a] $[\alpha]^{22}_D$ = 122.5° (*c* 1.4, benzene). Another fraction (25.7 mg, 0.969 mmol, 38%), a mixture of the other three isomers, was also isolated in a ratio of 1:1.8:1.9 (NMR integration on OCH_3 peaks). R_f 0.24 (50:50 hexane: ethyl acetate); $[\alpha]^{25}_D$ = 8.1° (*c* 1.00, benzene).

General Benzoylation Procedure. A mixture of **41** (0.0430 g, 0.1198 mmol) was dissolved in CH_2Cl_2 (2.0 mL), and trifluoroacetic acid (0.2 mL) was added dropwise at rt. The solution was stirred at rt for 1.5 h. The solvent and acid were removed in a fumehood using an aspirator. The residue was dissolved in H_2O (1.0 mL). $NaHCO_3$ (53 mg, 0.5990 mmol) and a solution of benzoyl chloride (0.015 mL, 0.1318 mmol) in acetone (1.0 mL) were added subsequently. This solution was stirred at rt for 6 h. The solvent was evaporated and the aqueous layer was extracted with EtOAc (5 × 3 mL). The organic extract was evaporated and the crude product was purified by preparative TLC to give **42** as a white solid (0.0213 g, 0.0849 mmol, 71%).

3-Benzamido-2,3,6-trideoxy-L-*lyxo*-hexose (*N*-Benzoyl-L-daunosamine) (40). Following the general benzoylation procedure, **39** (33.3 mg, 0.0921 mmol) gave **40** as a white solid (17.1 mg, 0.0681 mmol, 74%). This product is a mixture of four isomers in a ratio of pyranose/furanose = 3.4/1, and α-pyranose/β-pyranose = 1.1:1: mp 146−149 °C; R_f 0.24 (93:7 CH_2Cl_2:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ for the β-pyranose: 1.13 (d, J = 6.3 Hz, 3H), 1.59 (dd, J = 12.7, 4.3, 2.0 Hz, 1H), 1.74 (dd, J = 12.7, 12.4, 9.7 Hz, 1H), 3.46 (bd, 1H), 3.54 (dq, J = 6.3 Hz. 1H), 4.02 (m, J = 12.4, 4.3 Hz, 1H), 4.67 (ddd, J = 9.7, 6.3, 2.0 Hz, 1H), 4.75 (d, J = 6.2 Hz, 1H), 6.51 (d, J = 6.4 Hz, 1H), 7.43−7.97 (m, 4H), 8.04 (d, J = 7.9 Hz, 1H); for the α-pyranose: 1.08 (d, J = 6.7 Hz, 3H), 1.44 (dd, J = 12.5, 5.1, 4.4 Hz, 1H), 1.99 (dd, J = 12.9, 12.5, 2.2 Hz, 1H), 3.46 (bd, 1H), 3.54 (m, 1H), 4.04 (m, J = 6.7 Hz, 1H), 4.37 (m, J = 12.9, 5.1 Hz, 1H), 4.75 (d, J = 6.2 Hz, 1H), 5.14 (ddd, J = 4.4, 3.3, 2.2 Hz, 1H), 6.09 (d, J = 3.3 Hz, 1H), 7.43−7.97 (m, 4H), 7.97 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) for the β-pyranose δ 164.1, 135.3, 131.6, 128.8, 128.0, 94.8, 71.5, 67.4, 50.2, 33.6, 17.8; for the α-pyranose 166.3, 135.1, 131.7, 128.7, 128.0, 90.9, 68.7, 66.0, 46.2, 30.9, 17.7; IR (KBr) 3500−3121 (br), 1647, 1604 cm^{-1}; $[\alpha]^{25}_D$ = −87.8 to −61.8° (*c* 0.50, EtOH, 3 h), lit.[13i] mp 152 °C, $[\alpha]^{25}_D$ = −108° (*c* 0.50, EtOH). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 61.97; H, 6.74; N, 5.22.

3-Benzamido-2,3,6-trideoxy-D-*ribo*-hexose (*N*-Benzoyl-D-ristosamine) (42). Lactol **38** (44 mg, 0.166 mmol) was dissolved in HOAc (1.0 mL) and H_2O (1.0 mL). This solution was heated to reflux in an oil bath for 1.5 h. It was evaporated to dryness to yield a light yellow solid, which was purified *via* chromatography (eluted with EtOAc) to yield **42** as a white solid. This solid was a mixture of four isomers in the ratio of furanose/pyranose = 1.7/1, and α-furanose/β-furanose = 1.2/1: mp 103−107 °C; R_f 0.32 (93:7 CH_2Cl_2:CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) for the β-furanose: δ 1.08 (d, J = 6.0 Hz. 3H), 2.01−2.04 (m, 2H), 3.68 (m, 2H), 4.59 (d, J = 2.8 Hz, 1H), 5.40 (bs, 1H), 6.37 (d, J = 4.9 Hz, 1H), 7.42−7.89 (m, 4H), 8.57 (d, J = 7.9 Hz, 1H); for the α-furanose: δ 1.16 (d, J = 6.3 Hz. 3), 1.76 (ddd, J = 13.2, 5.0, 2.2 Hz, 1H), 2.31 (ddd, J = 13.2, 9.2, 5.2 Hz, 1H), 3.63 (ddq, J = 6.3, 4.5, 4.4 Hz, 1H), 3.88 (dd, J = 5.3, 4.5 Hz, 1H), 4.39 (dddd, J = 9.2, 7.8, 5.3, 5.0 Hz, 1H), 4.69 (d, J = 4.4 Hz, 1H), 5.40 (bs, 1H), 6.37 (d, J = 4.9 Hz, 1H), 7.42−7.89 (m, 4H), 8.41 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) for the β-furanose: δ 166.6, 134.8, 131.8, 128.8, 127.9, 97.8, 86.2, 67.2, 50.3, 40.9, 19.7; for the α-furanose: 166.4, 134.9, 131.8, 128.9, 127.3, 97.5, 87.7, 68.3, 50.3, 41.0, 19.6; IR (KBr) 3500−3100 (br), 1641, 1601 cm^{-1}; $[\alpha]^{25}_D$ = 43.8−41.2° (*c* 1.00, EtOH, 1.0 h), lit.[17a] mp 128−129 °C, $[\alpha]^{23}_D$ = 13.5° (*c* 1.00, EtOH), and lit.[17b] mp 135−137 °C, $[\alpha]$ = 15.6−9.8° (*c* 1.00, EtOH). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 61.72; H, 6.52; N, 5.22. Compound **42** (21.3 mg, 0.0849 mmol, 71%) was also obtained from **41** (43 mg, 0.1198 mmol) following the general benzoylation procedure.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for selected compounds (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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