Glycosidase Inhibitors: Synthesis of Enantiomerically Pure Aza-Sugars from Schiff Base Amino Esters via Tandem Reduction-Alkenylation and Osmylation

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Nitrogen-in-the-ring "aza-sugars" have been synthesized in enantiomerically pure form from the amino acid L-alanine in excellent overall yield. The O'Donnell's Schiff base of L-alanine methyl ester **9a** was converted to aza-sugar L-fuco-1-deoxy-nojirimycin, **18**, and to the epimer L-gulo-1-deoxy-nojirimycin, **20**, in eight steps. The overall yields were 20 and 29%, respectively. The methodology for the efficient generation of silyl- and benzyl-protected (*E*)-3-lithio-2-propen-1-ols, and the use of these alkenyllithiums with iBu_5Al_2H as nucleophiles in the *threo*-selective tandem reduction−alkenylation of the Schiff base esters is described. Osmium-catalyzed *cis*-oxygenation of the resulting olefin products was selective for the *galacto* (*fuco*) amino polyols in all cases for the acyclic olefins, and was *gulo*-selective for the cyclic D-4,5-dihydropyridine pivalate, **17c**. TEMPO-NaOCl was selective for oxidation of the primary position of the acyclic Schiff bases, and allowed for minimal protection/deprotection of the intermediates. The resulting *N*-benzhydryl heterocycles were easily deprotected with H_2−Pd at atmospheric pressure.

Introduction

Glycosidases (glycosylhydrolases) are ubiquitous enzymes that are involved not only in the degradation of carbohydrate foodstuffs[1] but also in the processing of eucaryotic glycoproteins[2] and glycolipids.[3] These enzymes are essential for normal cellular development of all organisms. Glycosidases can be classified in various ways: according to their function, by their location in the organism, or by their mechanistic characteristics.[4] Inhibitors of glycosylhydrolases have provided mechanistic insight into these enzymes and have proven to be important tools for the elucidation of metabolic pathways to the various glycoforms of glycoproteins and glycolipids.[5]

Nojirimycin was isolated from a fermentation broth in 1966[6] (Figure 1). The more stable reduction product, 1-deoxy-nojirimycin was initially obtained from nojirimycin by catalytic hydrogenation of the natural product. Subsequently, both nojirimycin and 1-deoxy-nojirimycin were isolated from other microorganisms and plants. By 1970 nojirimycin and 1-deoxy-nojirimycin were known to possess glucosidase inhibitory activity.[7] Significant inhibition of glucoamylase, microbial α- and β-glucosidases, mammalian intestinal oligo- and disaccharidases were subsequently reported.[8] Efforts have focused on structural and stereochemical modifications of 1-deoxy-nojirimycin for development of antihyperglycemic drugs[9] and have led to glycosidase inhibitors selective for particular enzymes. "Aza-sugars" or "nitrogen-in-the-ring" sugar analogues can be predicted to possess activity against glycosidases specific for the parent sugars in many cases.[15]

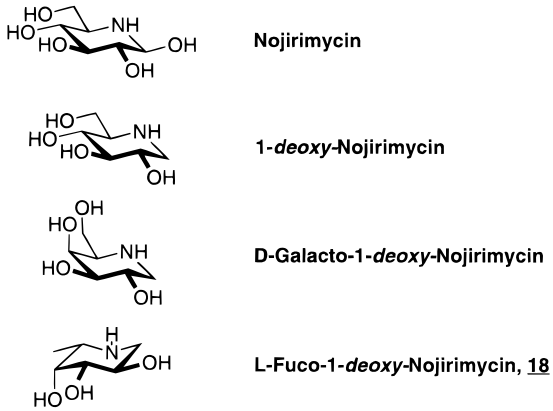

Figure 1. Aza-sugars.

The first synthesis of 1-deoxy-nojirimycin appeared in 1968 by Inouye et al.,[10] required 10 steps and proceeded in 22% overall yield. Later, Ganem et al.[11] synthesized 1-deoxy-nojirimycin and the *manno*-epimer from the

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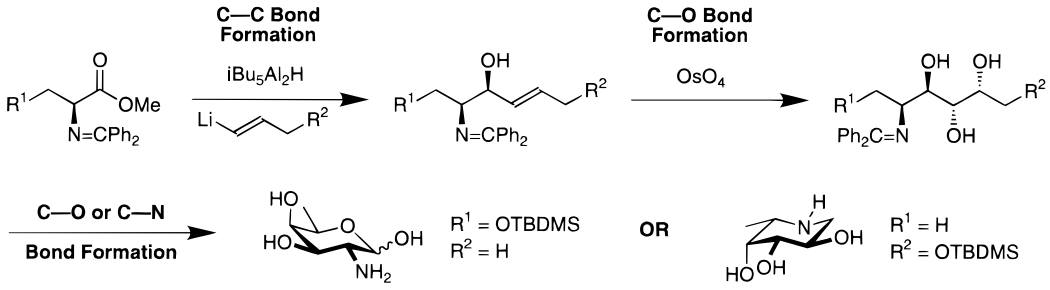


Figure 2. Synthetic approach.

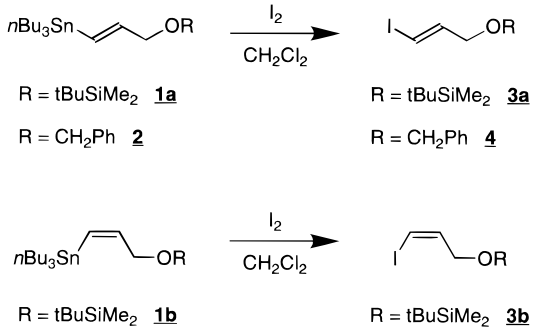
corresponding methyl glycosides in six steps and 28% overall yield. Alteration of fucose expression[12] has been achieved with azafucose, first synthesized by Fleet, et al.[13] in 15 steps from α-D-methylglucoside. Other approaches from acyclic and cyclic chiral precursors have also been employed,[14−18] and Nishimura has reviewed various synthetic approaches to this class of compounds.[19]

Tandem C−C/C−O Approach from α-Amino Acids. Benzophenone imine-protected esters of α-amino acids (O'Donnell's Schiff bases) have been converted to unsaturated *β*-amino alcohols via tandem reduction−alkenylation (C−C bond formation)[20,21] (Figure 2). Due to the pseudosymmetry[22] of fucose (6-deoxy-galactose), exchange of $-CH_3$ for $-CH_2OH$ in the amino acid component (alanine vs serine) and $-CH_2OH$ for $-CH_3$ in the alkenyllithium component ($LiCH{=}CHCH_3$ vs $LiCH{=}CHCH_2{-}$OTBDMS) can provide access to D-fucosamine or L-azafucose from an L-amino acid with the same stereoselective two-step reaction sequence.

Selection of suitable functional group protection was crucial for the efficient execution of this approach. The benzophenone Schiff base protecting group masks the acidic $-NH_2$ protons in the C−C bond formation step and also promotes chelation-controlled delivery of Grignards and alkyllithiums to provide *threo*-selectivity. The imine lone pair is similar to pyridine in terms of basicity and metal-complexing ability[23] and is an important stereochemical control element in the tandem reduction−alkenylation reaction by virtue of its steric bulk and at the same time is a steric hurdle that inhibits enolization of the imino ester.[24]

***threo* Addition of Functionalized Alkenyllithiums (C−C Bond Formation).** Generation of a suitably protected 3-oxygenated-(*E*)-1-lithiopropene species in hydrocarbon solvent was somewhat problematic. Hydroalumination[25] of propargyl alcohol was unsuccessful due to multiple additions to the triple bond, and hydroboration with catechol borane[26] did not yield any identifiable products from the resulting black syrup. Therefore, we explored hydrostannylation[27] methods used by Seebach et al.[28] and Jung et al.[29] The (*E*)-vinylstannanes **1a** and **2** were obtained as the predominant products (Scheme 1). Subsequent iodine−tin exchange was easily accomplished with I_2 in CH_2Cl_2 at room temperature with

Scheme 1. *cis*- and *trans*-Iodoalkenes



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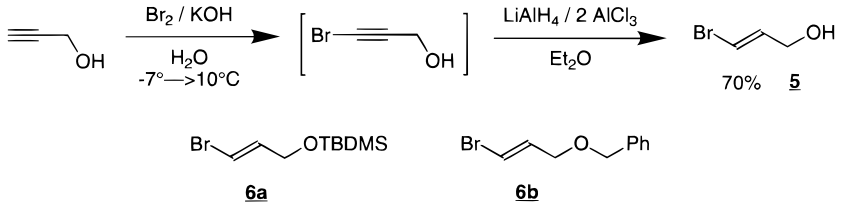
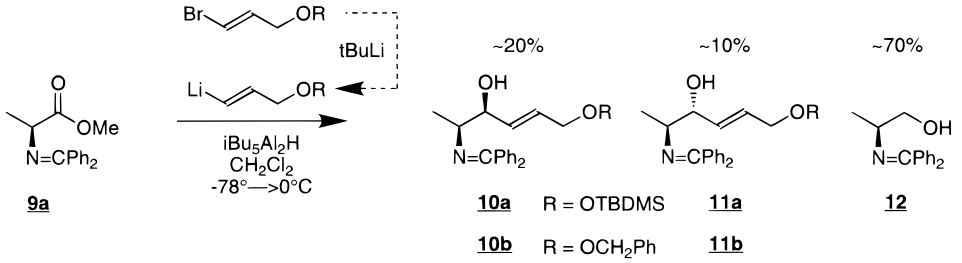
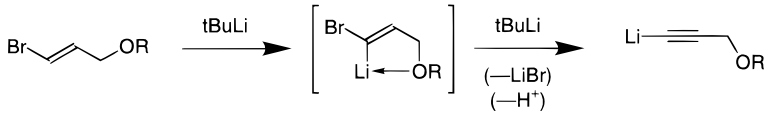
Scheme 2. *trans*-Bromoalkenes



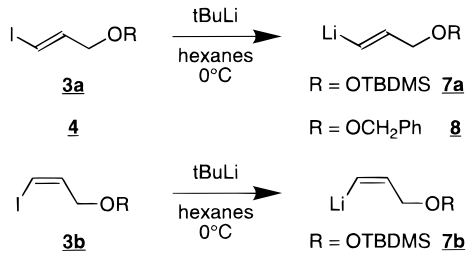
Scheme 3. Li−Br and Li−I Exchange Reactions



c.f. **Seebach & Neumann**[32]



c.f. **Peterson & Polt**[24]



apparent retention of configuration, and the (*E*)-iodoalkenes **3a** and **4** were purified by vacuum distillation. Similarly, the (*Z*)-iodoalkene **3b** was obtained from the minor (*Z*)-hydrostannylation product **1b** in good yield.

Despite their well-deserved reputation for explosive decomposition, a method based on 1-haloacetylenes[30] also worked quite well in our hands. Bromination of distilled propargyl alcohol with potassium hypobromide at −5 °C gave 1-bromo-propargyl alcohol in good yield, which was subjected without purification to reduction with "Cl_2AlH" ($LiAlH_4 + 2\ AlCl_3$) (Scheme 2). Only the (*E*)-isomer **5** was obtained in 70% yield on a 30-gram scale. A similar $LiAlH_4/AlCl_3$ reduction protocol of 1-iodo-propynol at various temperatures resulted only in reductive removal of iodine. Standard protection protocols yielded the benzyl-protected bromoalkene **6b** and the TBDMS-protected bromoalkene **6a**.

Reduction−alkenylation in Et_2O or THF has been shown to result in a dramatic decrease in the stereoselectivity of the iBu_5Al_2H/R−Li addition sequence. Preparation of the lithio-alkenes in nonpolar solvents such as hexane or toluene was crucial for preserving the chelation control in this step. At the outset it was not clear whether the presence of oxygen substitution on the alkenyllithium would permit stereoselective reduction−alkenylation of the Schiff base substrates with these functionalized nucleophiles.

When the oxygen-substituted bromides **6a** and **6b** were treated with tBuLi in hexanes, and subsequently added to the reaction vessel with the iBu_5Al_2H·**9a** at −78 °C, only poor yields (∼20%) of the corresponding alcohols **10a** and **11a** or **10b** and **11b** were isolated, and a great deal of the reduction product **12** was observed (Scheme 3). Seebach and Neumann[31] reported some time ago that bromoallylic alcohols in THF undergo facile lithiation with nBuLi at the olefinic position α to the bromine. Geminal elimination of LiBr then led to a vinylcarbene, which rearranged to propargyl alcohol.[32] Use of the corresponding iodides proved to be a much more practical solution in this case.

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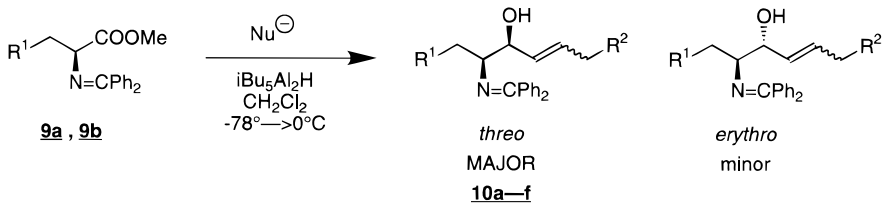

Figure 3. Reductive alkenylation provides *threo* products.

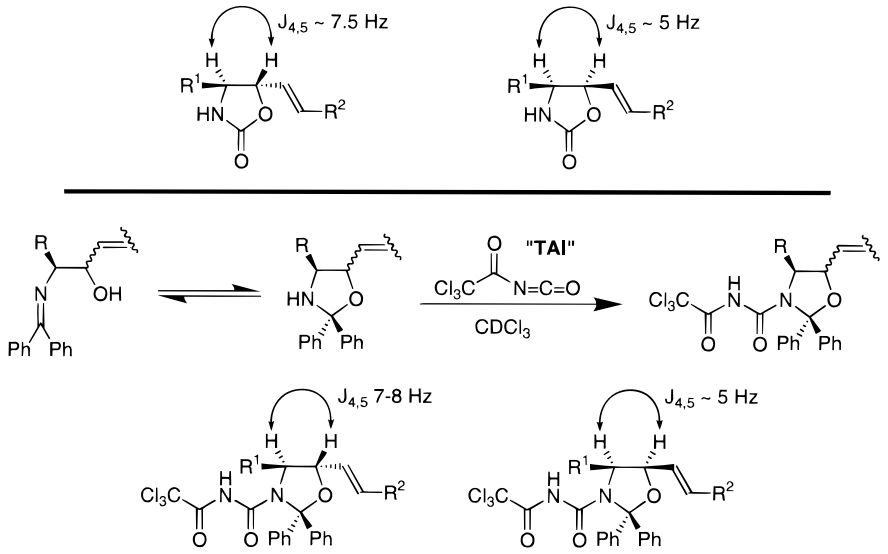

Figure 4. "TAI" simplifies stereochemical assignment.

Table 1. Reductive Alkenylation Yields

#	Schiff base	Nu⊖	Solvent	R^1	R^2	*threo* Product	Isolated Yield
1	**9a**	**7a**	CH_2Cl_2 hexanes	-H	-OTBDMS	**10a**	70%
2	**9a**	**8**	CH_2Cl_2 hexanes	-H	$-OCH_2Ph$	**10b**	60%
3	**9b**	**7a**	CH_2Cl_2 hexanes	-OTBDMS	-OTBDMS	**10c**	89%
4	**9a**	**7b**	CH_2Cl_2 hexanes	-H	-OTBDMS	**10d**	90%
5	**9b**	Li	$PhCH_3$	-OTBDMS	-H	**10e**	70%
6	**9a**	Li	$PhCH_3$	-H	-H	**10f**	70%

In contrast to the bromides, iodoalkenes **3a**, **3b**, and **4** underwent rapid Li−I exchange with tBuLi in hexanes to provide stable solutions of **7a**, **7b**, and **8**, which could be stored and handled in the usual fashion.[33] Treatment of Schiff base **9a** or **9b** with iBu_5Al_2H (1:1 mixture of iBu_2AlH + iBu_3Al)[34] at −78 °C in CH_2Cl_2, followed by addition of a lithiopropene provided the *threo* amino alcohols **10a**−**10f** in excellent yield and selectivity (>20:1) (Figure 3). Yields for several reaction partners studied are depicted in Table 1. In every case studied, the reduction product corresponding to **12** was also observed, but if the iBu_5Al_2H was added slowly with a syringe pump, the amount of this byproduct was only 5−10%. The *threo* selectivity and chemical yields did not suffer from introduction of the oxygen atom into the alkenyllithium substrates.

Initially, the stereochemical configuration of several amino alcohols was determined following a two-step method, which involved removal of the Schiff base with aqueous HCl and isolation of the β-amino alcohol, followed by cyclization to the oxazolidin-2-one (cyclic carbamate, Figure 4) with carbonyldiimidazole or another phosgene equivalent. With care, the $J_{4,5}$ coupling constant of the cyclic carbamate could then be related to the *erythro*/*threo* identity of the amino alcohol.[35] This procedure was less than satisfactory due to the time involved as well as to the uncertainty in the observed ratios following manipulation of the Schiff base and amino alcohol products.

Trapping of the cyclic oxazolidine form of the crude β-hydroxy Schiff bases with the very reactive trichloroacetylisocyanate (TAI)[36] proved to be a rapid and convenient way to examine the pertinent $J_{4,5}$ coupling constants. In addition to causing a difference in chemical shift between the *erythro* and *threo* forms, the observed $J_{4,5}$ coupling constant seemed to be consistently larger for the *threo* products (Figure 4). The TAI reaction was complete within seconds, was quantitative, and was normally performed in the NMR tube just prior to measurement; and without any of the isolation and purification steps required in the previous method. Proton integration of *erythro*/*threo* mixtures was then performed without the complication introduced by the

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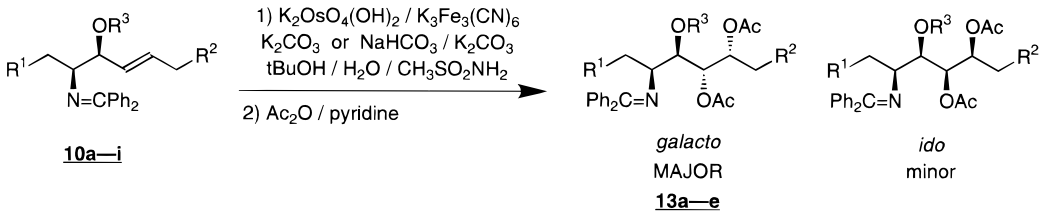

Figure 5. Osmylation provides *galacto* amino polyol acetates.

Table 2. Osmylation Selectivities and Yields

#	Schiff base	R^1	R^2	R^3	*galacto*/*ido* ratio[a]	*galacto* product	isolated yield[b] (%)
1	**10a**	−H	−OTBDMS	−H	6:1	**13a**	60
2	**10b**	−H	$-OCH_2Ph$	−H	4:1	**13b**	52
3	**10e**	−OTBDMS	−H	−H	6:1	**13c**	60
4	**10g**	−OTBDMS	−H	−OAc	3:1	**13c**	60
5	**10h**	−H	−OTBDMS	−OPiv	9:1	**13d**	50[c]
6	**10j**	−OTBDMS	−OTBDMS	−OPiv	6:1	**13e**	43

[a] ^{1}H NMR of crude acetate mixture. [b] Isolated as acetates. [c] +20% recovered starting material.

Schiff base-oxazolidine tautomerism. As determined by ^{1}H NMR of the crude TAI-mixtures, the reduction−alkenylation methodology provided amino alcohols **10a**−**10f** with excellent stereoselectivity (>20:1 *threo*:*erythro*) (Table 1).

Oxygenation of the Olefin (C−O Bond Formation). The well-known Stork/Kishi empirical rules for substrate-controlled delivery of OsO_4 to allylic systems ("inside alkoxy effect")[37] was of great predictive value in the stereoselective introduction of the diol to the *threo* products **10**.[38] The exact mechanism of the osmylation ([2 + 2] vs [3 + 2] mechanism), the role of additional ligands, and the origin of such π-facial differentiation in oxygenated allylic systems have been debated extensively.[39] Kinetic isotope data on the reaction has been subjected to differing interpretation.[40] Stereoelectronic arguments and the role of Os−substrate complexation have been advanced.[41] Houk suggested σ-acceptors would occupy antiperiplanar ("outside") or eclipsed ("inside") position and the best σ-donor would be anti to the electrophile to facilitate olefin HOMO-electrophile LUMO interactions.[42] Most workers have concluded that sterics have a strong influence on the reaction, and the use of substrate-controlled delivery of OsO_4 with chiral substrates is both predictable and useful.[43]

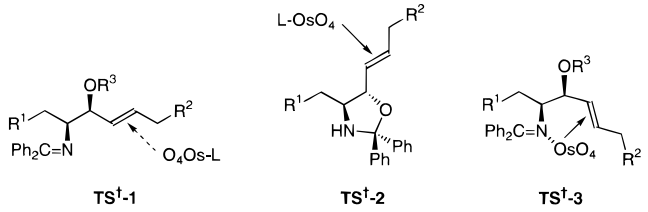

Figure 6. Osmylation geometries.

The osmylation conditions of Yamamoto, et al.,[44] modified by the addition of 1 equiv of $CH_3SO_2NH_2$ as described by Sharpless and Gobel[45] were explored (Figure 5 and Table 2). A mixture of diastereomeric *galacto* (major) and *ido* (minor) configurations was obtained after acylation of the crude diol or triol mixtures. Both OsO_4 and $K_2OsO_2(OH)_2$ (potassium osmate) were used as catalysts and gave identical results. The reactions did not reach completion without the addition of $CH_3SO_2NH_2$. The substitution of potassium glycolate for $CH_3SO_2NH_2$ had a strongly inhibitory effect on the reaction rate, essentially stopping the reaction entirely. The addition of pyridine, normally required for this reaction, also had a negative effect on the rate. The basic character of the aqueous medium was suitable for the acid-sensitive imine substrates, but the substitution of $NaHCO_3/K_2CO_3$ for K_2CO_3 was superior (vide infra).

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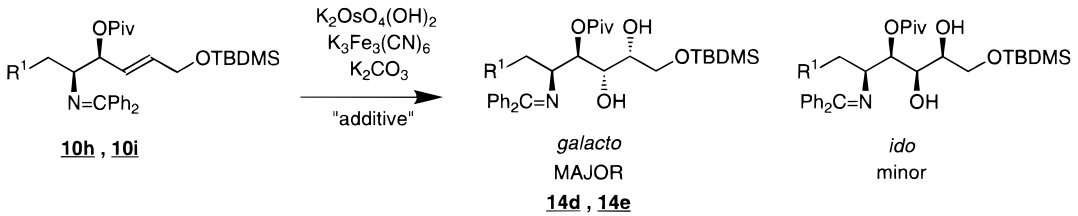

Figure 7. Osmylation of pivalates provides *galacto* amino polyols with selective protection.

Table 3. Osmylation Additive Effects on *galacto* Selectivity

#	Schiff base	R^1	additive	*galacto*/*ido* ratio[a]	*galacto* product	isolated yield[b] (%)
1	**10h**	−H	none	9:1	**14d**	50
2	**10h**	−H	$(DHQ)_2$−PHAL	14:1	**14d**	60
3	**10i**	−OTBDMS	none	6:1	**14e**	43−50
4	**10i**	−OTBDMS	quinuclidine	9:1	**14e**	69
5	**10i**	−OTBDMS	$(DHQD)_2$−PHAL	8−9:1	**14e**	60
6	**10i**	−OTBDMS	$(DHQ)_2$−PHAL	11−20:1	**14e**	54−60
7	**10i**	−OTBDMS	$NaHCO_3$	>20:1	**14e**	67

[a] ^{1}H NMR of crude alcohol mixture. [b] Isolated as alcohol.

Acylation of **10e** provided the imine **10g**, which gave a poorer 3:1 *galacto* mixture still favoring **13c** (entry 4). Pivalylation of **10a** with pivaloyl chloride, pyridine, and DMAP yielded compound **10h** in 89% yield. Osmylation of this pivalate with 1.2 mol % $K_2OsO_2(OH)_2$ in the presence of 1 equiv of $MeSO_2NH_2$ yielded 20% of recovered starting material and 50% of the desired *galacto* isomer **13e** (entry 5). The *galacto*-*ido* selectivity was improved to 9:1. These results can be rationalized by the oxygenation of the cyclic oxazolidine tautomer[46] in entries 1, 2, and 3, which may oxygenate more selectively than the open-chain compound (**TS†-1** vs **TS†-2**, Figure 6). Upon O-acylation, this cyclic structure no longer exists, eliminating **TS†-2** as a possibility. The increased steric bulk of the pivalate would be expected to enhance the selectivity. Another possibility is that the imine itself could have directed the osmylation reaction intramolecularly via **TS†-3**. This possibility was appealing given the strong negative effect that pyridine had on the reaction rate. The effect of bulky, sp^3-hybridized amine ligands on the reaction was explored next.

Several researchers have used chiral amines for reagent-controlled osmylation of chiral substrates in an effort to enhance or override natural substrate reactivity with various degrees of success.[47] The chiral dimeric $(DHQ)_2$−PHAL ligand[48] was added (3 mol %) to the reaction mixture with **10h**, and resulted in an increased chemical yield of the *galacto* product (50 → 60%), and an increase in stereoselectivity (9:1 → 14:1, Entries 1 and 2, Table 3). The C-4 protons (i.e., CH bearing the *O*-pivaloyl group) for the *galacto* and *ido* diol isomers could be easily distinguished in the crude ^{1}H NMR spectra (5.00 vs 5.10 ppm), and quantified by integration for these compounds. When substrate **10i** was osmylated in the absence of a chiral auxiliary it provided a 6:1 mixture of diastereomers (entry 3), and as expected in the presence of the $(DHQ)_2$−PHAL ligand the stereoselectivity was improved (11−20:1, entry 6). However, **10i** and the pseudo-enantiomeric $(DHQD)_2$−PHAL also resulted in increased selectivity, (8−9:1, entry 5). Achiral quinuclidine increased the selectivity to 9:1 in a similar fashion (entry 4). This result indicates that, to the extent that the substrate imine complexed with OsO_4,[49] it did not aid in the stereoselectivity of diol formation and that it was unlikely that intramolecular delivery of OsO_4 had occurred. It is possible that the interaction between OsO_4 and the Schiff base nitrogen may unfavorably compete with the stereoelectronic effects of the allylic ester moiety, and the presence of tertiary amines may preclude such participation.

Since Schiff base alcohols exist predominantly in the cyclic oxazolidine form, the question as to which form is the actual reactive species must be considered. Clearly, this complication is eliminated by the protection of the allylic alcohol group prior to osmylation (substrates **10g**, **10h**, and **10i**). All of the substrates studied gave the same anti selectivity (*galacto* product), and these results can be rationalized by the models proposed by Stork,[39b] Kishi,[39a,c] Vedejs,[39e] or Houk[39d,44b] for the osmylation transition state (Figure 7). The pivaloyl group that enhances selectivity must be *opposite to the osmium reagent* during the initial attack.

Finally, it should be pointed out that substitution of a $NaHCO_3/K_2CO_3$ mixture for K_2CO_3 (entry 7) slowed the rate of base-catalyzed pivalate migration from its initial position on the allylic OH to the newly formed OH groups introduced by osmylation. This transesterification reduced the isolated yield of *galacto* products, thus reducing the observable stereoselectivity. Performing the osmylation at a slightly lower pH (i.e., with $NaHCO_3/K_2CO_3$) slowed the rate of the transesterification without appreciably slowing the rate of osmylation.

Cyclization (C−N Bond Formation). The base-stable methoxymethyl (MOM) group was initially chosen

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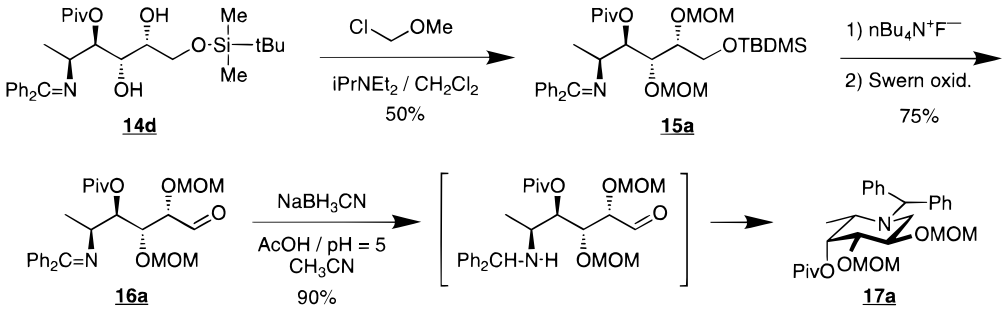
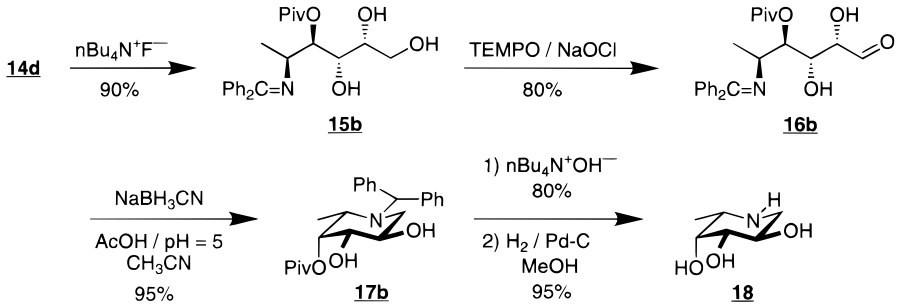
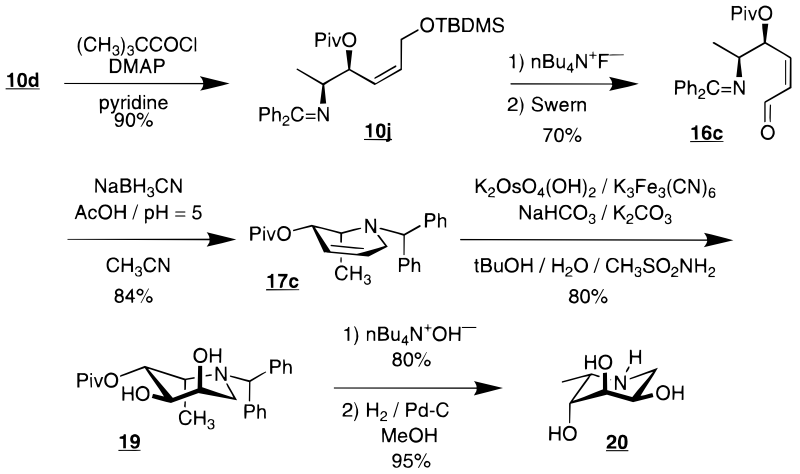
Scheme 4. Reductive Amination with MOM Protection (*fuco*-Norjirimycin)



Scheme 5. Selective Oxidation of "Nearly Naked Triol"



Scheme 6. Reductive Amination of Enal (*gulo*-Norjirimycin)



for protection of the newly formed diol. (Scheme 4) Treatment of diol **14d** with MOM-Cl in CH_2Cl_2 and Hünig's base in the normal fashion resulted in rapid acetal formation at one hydroxyl, but proceeded slowly to the desired fully protected amino tetrol **15a**. Desilylation and Swern oxidation proceeded smoothly to the aminofucose derivative **16a**. While the cyclization protocol was successful, protection of the vicinal diol system was not very efficient.

The reduction of benzophenone imines to the corresponding *N*-benzhydrylamines with $NaBH_3CN$ at pH 7 works well when a reducible aldehyde is not present. At this pH, the aldehyde of **16a** is selectively attacked. By running this same reaction under acidic conditions (pH 5), the resulting iminium ion was reduced selectively in the presence of the aldehyde. This led to rapid cyclization and further reduction (reductive amination) to the protected aza-fucose **17a**. Given the problems involved in MOM protection, we abandoned this approach for a more adventurous route that omitted protection and deprotection of the 2,3-diol functionality entirely. (Scheme 5).

Fluoride-catalyzed desilylation of **14d** proceeded to give the crystalline triol **15b**. Without purification, the nearly-naked triol was subjected to oxidation with TEMPO/NaOCl[50] to provide the fucose derivative **16b**. This compound could be isolated, but the best yields were obtained when it was immediately subjected to the next reaction. Reduction of this intermediate at pH 5 as before led to imine reduction and cyclization to produce the aza-fucose diol **17b**. Saponification of the pivalate and hydrogenolysis of the *N*-benzhydryl protection was straightforward, leading to L-fuco-1-deoxy-nojirimycin,[13] **18** in excellent yield.

To illustrate a slightly different approach to aza-sugars, the geometric isomer, **10d**, was converted to L-gulo-1-deoxy-nojirimycin in seven steps (Scheme 6). Pivaloylation led to the compound **10j**, which was deprotected and oxidized to enal **16c** in excellent yield. Reductive amination as before provided the unsaturated pi-

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peridine **17c**. Osmylation led to diol **19** possessing the *gulo* configuration. Deprotection as before led to the epimeric L-gulo-deoxy-nojirimycin, **20**.

Conclusions

Stereoselective tandem reduction−alkenylation of O'Donnell's Schiff bases, followed by pivaloylation and osmylation of the resulting allylic *threo* amino alcohols is a chemically efficient and stereoselective approach to aza-sugars (1-deoxy-norjirimycins) of the *galacto* configuration. In summary, the synthesis of L-fuco-1-deoxy-nojirimycin, **18**, was accomplished in eight steps from the Schiff base **9a** in 20% yield. Similarly, L-gulo-1-deoxy-nojirimycin, **20**, was synthesized from the same starting material in 29% yield in 8 steps by varying only the olefin geometry in the starting material and the order of the chemical operations. This work demonstrates the synthetic utility inherent in amino acid-based acyclic stereocontrol facilitated by the benzophenone Schiff bases and appropriately functionalized organometallics. This work illustrates a powerful approach to amino polyols and related complex natural products.

Experimental Section

General Methods. All air- and moisture-sensitive reactions were performed under an argon atmosphere in flame-dried reaction flasks using modified Schlenk methods. All solvents were dried over the standard drying agents and freshly distilled prior to use. For flash chromatography, 400−230 mesh silica gel 60 was employed. All compounds described were characterized by IR as well as ^{1}H (250 or 300 MHz for 1-D spectra, COSY were obtained at 500 MHz) and ^{13}C NMR spectroscopy (62.9 MHz). Optical rotations were measured using the Na-D line. Elemental analyses (CHN) were performed by Desert Analytics, Tucson, AZ.

(*E*)-1-*tert*-Butyldimethylsilyloxy-3-iodo-2-propene (3a), (*Z*)-1-*tert*-Butyldimethylsilyloxy-3-iodo-2-propene (3b). *O*-*tert*-butyldimethylsilylpropynol (20.0 g, 117 mmol), nBu_3-SnH (63.2 mL, 153 mmol, 1.3 equiv) and AIBN (150 mg) were stirred and heated at 110−130 °C for 2 h.[28,29] The mixture was distilled in vacuo. An excess of nBu_3SnH can be separated as the first fraction (65−70 °C, 0.4 mmHg). The second fraction (100−130 °C) yielded 53.68 g (99%) of a mixture of vinylstannanes ((*E*)-**1a**:(*Z*)-**1b**:terminal 69:16:15). The mixture of vinylstannanes (53.68 g, 116 mmol) was dissolved in 700 mL of CH_2Cl_2, and a solution of I_2 in CH_2Cl_2 (32.41 g, 1.1 equiv in 900 mL of CH_2Cl_2) was added dropwise at rt until the solution remained brown. The mixture was washed with saturated $Na_2S_2O_3$ and H_2O and dried over K_2CO_3. The solvent was removed, and the crude product was purified by Kugelrohr distillation. The first fraction (58−61 °C, 0.4 mmHg) yielded 21.0 g of vinyliodides ((*E*)-**3a**:(*Z*)-**3b**:terminal 3:1:1) and the second (61−65 °C, 0.4 mmHg) yielded *E*-enriched vinyliodides ((*E*)-**3a**:(*Z*)-**3b**:terminal 8:1:1). Total yield was 84%. A second distillation through a 2-cm column provided reasonably pure **3a**. The product was stored in a brown reagent bottle under argon at low temperature (−20 °C) in the dark (freezer) with a piece of copper wire.

***E*-3a:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.58 (dt, J = 14.3, 4.4 Hz, 1H), 6.27 (dt, J = 14.5, 1.8 Hz, 1H), 4.09 (dd, J = 4.7, 1.8 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

***Z*-3b:** 4.22 (dd, J = 5.3, 1.8 Hz, 2H).

Terminal isomer: 4.15 (t, J = 1.8 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 136.69 (C3), 106.06 (C2), 63.24 (C1), 25.80 (^{t}Bu), −5.40 (SiMe).

(*E*)-1-Benzyloxy-3-iodo-2-propene (4). Prepared from $PhCH_2OCH_2CCH$ (**2** → **4**) by following the same procedure used for the TBDMS-protected vinyliodide **3a**. The product (105 °C, 0.5 mmHg) was obtained in 80% yield as an 8:1 mixture of *E*- and *Z*-isomers.

4: ^{1}H NMR (250 MHz, $CDCl_3$) δ *E*-isomer 7.39−7.25 (m, 5H), 6.66 (dt, J = 14.6, 5.7 Hz, 1H), 6.40 (dt, J = 14.6, 1.5 Hz, 1H), 4.51 (s, 2H), 3.95 (dd, J = 5.6, 1.5 Hz, 2H); *Z*-isomer: 4.22 (dd, J = 5.3, 1.8 Hz, 2H); terminal isomer 4.15 (t, J = 1.8 Hz, 2H).

(*E*)-3-Bromo-2-propene-1-ol (5). Essentially, the procedure of Kruglikova, et al.[30] was used. *CAUTION*: *1-Halopropynes are potentially explosive. Do not heat these compounds. Perform these operations behind a blast shield.* Molecular Br_2 (48.0 g, 300 mmol) was added to a vigorously stirring solution of 45 g KOH in 120 mL of water at −5 °C. The yellow solution was kept at 0 °C and added dropwise to propargyl alcohol (17.83 g, 1.06 equiv; freshly distilled) in 39 mL of H_2O at −7−0 °C. The addition took approximately 3 h. The mixture was warmed to 10 °C and then extracted 4 times with Et_2O. The ether layer was washed with $Na_2S_2O_3$ and dried over K_2CO_3, and the solvent was removed to provide 28.50 g of the crude 1-bromopropyne-3-ol. *DO NOT DISTILL*!

A 2L flask was charged with $LiAlH_4$ (20.3 g, 2.0 equiv) and $AlCl_3$ (53.5 g, 1.0 equiv). Anhydrous Et_2O (270 mL, distilled from K/Na/benzophenone) was carefully added at −5 °C with stirring. The *crude* bromoacetylene (*DO NOT DISTILL*!), prepared in the first step, was added dropwise, and the mixture was refluxed for 4 h. The reaction was quenched with 200 mL of wet Et_2O (H_2O saturated), followed by 20 mL of H_2O and 20 mL of 5% NaOH at −10 °C. An additional 60 mL of H_2O was added to break up the solid mass. The liquid was decanted and extracted three times with Et_2O. The Et_2O layer was dried over K_2CO_3 and the solvent was removed. The crude material was vacuum distilled (67 °C, 84 mmHg) to yield pure bromoalkene **5** (27.7 g, 70% from propargyl alcohol).

5: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.36 (m, 2H), 4.13 (apparent d, 2H), 2.51 (1H, OH).

(*E*)-3-*tert*-Butyldimethylsilyloxy-1-lithio-1-propene (7a). Distilled *E*-TBDMSO−CH_2CH=CH−I, **3a** (4.00 mmol, 1.20 g) and 8 mL of hexane were cooled to 0 °C, and tBuLi (4.8 mL, 1.7 M in pentane, 2.04 equiv) was added dropwise with vigorous stirring. After 30 min at O° C a white precipitate (LiBr) was observed. It is strongly recommended to monitor temperature *inside* the reaction vessel for larger scales.

(*Z*)-3-*tert*-Butyldimethylsilyloxy-1-lithio-1-propene (7b). A solution of **7b** was prepared from *Z*-TBDMSO−CH_2CH=CH−I, **3b** (4.00 mmol, 1.20 g), using the same protocol used to prepare **7a**.

(*E*)-3-Benzyloxy-1-lithio-1-propene (8). A solution of **8** was prepared from *E*-$PhCH_2O-CH_2CH$=CH−I, **4** (4.00 mmol, 1.10 g), using the same protocol used to prepare **7a**.

Methyl *N*-(diphenylmethylene)-L-alaninate (9a), methyl *O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-L-serinate (9b): prepared as previously described.[20b,51]

(*4S,5S,2E*)-5-Amino-*N*-diphenylmethylene-1-*O*-*tert*-butyldimethylsilyl-2-hexen-1,4-diol (10a). Schiff base ester **9a** (22.3 mmol, 6.63 g) and 220 mL of CH_2Cl_2 were cooled to −78° with stirring and 1.1 equiv iBu_5Al_2H (49.0 mL of 0.5 M solution in hexane) was added via syringe pump over 2 h. After the iBu_5Al_2H addition was complete, 3.0 equiv *E*-1-lithio-3-*tert*-butyldimethylsilyloxy-1-propene, **7a** (20.0 g **3a**, 80.2 mL 1.7 M tBuLi, 133 mL of hexanes) was slowly cannulated into the reaction flask. The reaction was stirred overnight at −78 °C and then warmed to rt. After stirring 3 h at rt, the reaction was cooled to 0 °C and quenched by cautious addition of wet ether followed by 20 mL of 1% $NaHCO_3$. The reaction mixture was extracted with Et_2O, dried over K_2CO_3 and filtered through Celite, and the solvent was removed in vacuo. The product was purified via flash chromatography (20% EtOAc/hexanes/0.1%NEt_3) to provide pure **10a** (6.40 g, 70%).

10a: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR (neat) ν_{max} 3315.1, 3048.3, 2937.3 (C−H), 1662.9 (C=C), 1584.3, 1350.0 (C−O); $[\alpha]_D$ 4.4° (c = 0.1, $CHCl_3$).

(*4S,5S,2E*)-5-Amino-*N*-diphenylmethylene-1-*O*-benzyl-2-hexen-1,4-diol (10b). The Schiff base ester **9a** (1.0 mmol,

(51) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663−2666.

Table 4. ^{1}H NMR Data for Acyclic Compounds (250 MHz, $CDCl_3$)

	Chemical Shifts (ppm)												
	10a	**10b**	**10d**	**10h**	**10i**	**13a**	**13b**	**14d**	**14e**	**15a**	**15b**	**16a**	**16c**
H_1	4.13	4.00	4.46	4.17	4.11	3.56	3.47	3.68	3.66	3.62	3.86	9.63	10.14
H'_1	4.13	4.00	4.36	4.17	4.11	3.43	3.39	3.68	3.69	3.62	3.71		
H_2	5.79	5.87	5.72	5.84	5.75	5.13	5.35	3.48	3.46	3.73	3.93	3.88	6.01
H_3	5.51	5.60	5.22	5.64	5.60	5.40	5.43	4.17	4.04	4.01	4.15	4.16	6.29
H_4	3.89	3.92	5.62	5.45	5.44	5.24	5.25	4.94	5.00	5.51	4.94	5.41	6.01
H_5	2.95	3.00	3.56	3.57	3.71	3.64	3.64	3.92	4.00	3.86	3.52	3.94	3.62
H_6	1.19	1.21	1.14	1.13	3.78	0.91	1.19	1.13	3.87	1.1	1.12	1.10	1.08
	Coupling Constants (Hz)												
$J_{H,H}$	**10a**	**10b**	**10d**	**10h**	**10i**	**13a**	**13b**	**14d**	**14e**	**15a**	**15b**	**16a**	**16c**
1,1′			13.8			10.4	10.3				11.3		
1′,2		5.6	5.9	4.3		5.8	6.1				5.7		
1,2	4.5	5.6	5.7	4.3	4.0	5.3	5.2	7.2	6.6	nd	4.4	1.0	7.8
2,3	15.4	15.4	11.2	15.3	15.2	2.7	2.8	0.5	∼0	3.6	nd	2.7	11.4
3,4	7.9	7.7	8.8	6.9	6.4	7.5	7.6	9.5	9.3	3.6	9.6	5.8	9.4
4,5	7.9	4.0	7.6	7.2	nd	4.4	4.5	3.7	3.5	7.3	3.8	5.8	nd
5,6	6.3	6.3	6.7	6.5	nd	nd	6.5	6.3	6.2	6.5	6.6	6.5	6.6

Table 5. ^{13}C NMR Shifts for Acyclic Compounds (62.5 MHz, $CDCl_3$)

	10a	**10b**	**10d**	**10h**	**13a**	**13b**	**14d**	**15a**	**15b**	**16a**	**16c**
C-1	63.0	69.9	73.9	63.0	67.3	68.6	63.8	62.6	65.3	201.7	191.5
C-2	131.2	130.0	nd	129.8	72.6	73.1	70.0	74.9	69.6	82.3	136.4
C-3	134.7	131.7	nd	133.6	73.1	73.4	71.4	76.2	71.1	76.2	139.3
C-4	70.0	72.1	75.0	77.5	70.2	70.1	68.6	78.5	71.6	74.5	73.0
C-5	59.7	59.7	60.1	60.2	55.9	56.9	58.3	57.3	58.4	56.5	59.6
C-6	16.0	16.0	17.9	18.3	17.9	18.5	15.2	18.7	14.9	16.6	17.7

267 mg) and 10 mL of CH_2Cl_2 were cooled to −78° and 1.1 equiv iBu_5Al_2H (2.2 mL of 0.5 M solution in hexane) was added via syringe pump over 15−20 min. After addition was complete, 3.0 equiv (*E*)-1-lithio-3-benzyloxy-1-propene, **8**, was slowly cannulated into the reaction flask. The reaction was stirred for 1 h at −78 °C, then warmed to rt. After stirring 1 h at rt, the reaction was cooled and quenched by adding wet ether (saturated with H_2O) and 1 mL of 1% $NaHCO_3$. The reaction mixture was extracted with Et_2O, dried over K_2CO_3 and filtered through Celite, and the solvent was removed in vacuo. The product was purified via flash chromatography (20% EtOAc/hexanes/0.1%NEt_3) to provide pure **10b** (259 mg, 60%).

10b: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR (neat) ν_{max} 3152.3 (C−H), 2930.2 (C−H), 1645.5 (C═C), 1326.7 (C−O). $[\alpha]_D$ +3.1° (c = 0.1, $CHCl_3$).

(*4S,5S,2E*)-5-Amino-1-*O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-4-*O*-pivaloyl-2-hexen-1,4-diol (10h). The alcohol **10a** (820 mg, 2.0 mmol) and DMAP (48.8 mg, 0.40 mmol) were dissolved in 8 mL of pyridine. Pivaloyl chloride (1.48 mL, 12 mmol) was added dropwise via syringe while stirring the mixture at rt. Stirring was continued until completion (2 days). The mixture was poured into water and ice, and the aqueous solution was extracted 3× with CH_2Cl_2. The organic solution was dried ($MgSO_4$) and filtered through Celite, and the solvent was removed in vacuo. The crude sample was flash chromatographed on SiO_2 (5−10% EtOAc/hexanes) to yield pure **10h** (880 mg, 89%) as a colorless oil.

10h: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR (neat) ν_{max} 3250.1, 2945.3 (C−H), 1729.5 (C═O), 1345.1, 1215.3 (C−O); $[\alpha]_D$ 5.60 (c = 0.5, $CHCl_3$). Elemental anal.: $C_{30}H_{43}NO_3Si$ theoretical C, 72.98; H, 8.78. Found: C, 73.10; H, 8.72.

(*4S,5S,2Z*)-5-Amino-1-*O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-4-*O*-pivaloyl-2-hexen-1,4-diol (10j). The alcohol **10d** was prepared from **9a** (1.0 mmol, 267 mg) and **7b** by means of the same protocol used to prepare **10a** as a colorless oil (280 mg, 68%) after chromatography (10%−20% EtOAc/hexanes/0.1%NEt_3). The product was immediately treated with $(CH_3)_3CCOCl$ (0.740 mL, 6.0 mmol), 2 mg DMAP in 2.0 mL pyridine for 12 h at rt. Chromatography (30% EtOAc/hexane/0.1%NEt_3) provided pure **10j** as an oil. (280 mg, 0.567 mmol, 83%).

10j: ^{1}H NMR ($CDCl_3$) δ 7.60−7.15 (m, 10H), 5.72 (pseudo q, 1H), 5.61 (pseudo t, J = 8.8 Hz, 1H), 4.46 (ddd, J = 1.7, 5.9, 13.8 Hz, $^1/_2$AB, 1H), 4.36 (ddd, J = 1.8, 5.7, 13.8 Hz, 1/2AB), 3.56 (pseudo q, 1H), 1.14 (d, CH_3), 1.11 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.16 (C═O), 136.67, 135.70, 129.90, 128.49, 128.40, 127.96, 127.72, 125.34 (aromatic), 74.97 (CH−O), 73.94 (CH_2−O), 60.06 (CH−N), 27.19 (tBu), 25.90 (tBu), 17.93 (CH_3), −5.19 ($SiCH_3$); IR (neat) ν_{max} 2956.3 (C−H), 1731.7 (C═O), 1631.3 (C═C), 1352.1 (C−O); $[\alpha]_D$ 7.3 (c = 0.07, $CHCl_3$).

(*4S,5R*)-4-Methyl-5-[(*E*)-1-propen-1-yl]-2-oxazolidinone (see Figure 4). Imino alcohol **10f** (251 mg, 0.90 mmol) was hydrolyzed with 3% HCl in 1 mL THF for 1 h, extracted with CH_2Cl_2 to remove Ph_2C═O, made basic with NaOH, and extracted with CH_2Cl_2. After drying and filtration, solvent was removed in vacuo, a portion (45 mg, 0.39 mmol) was dissolved in 1.5 mL of dry THF, and carbonyldiimidazole (CDI, 91 mg, 0.56 mmol) was added. After stirring for 2 days at rt (TLC), the solvent was removed, and the crude material was purified via flash chromatography (50% EtOAc/hexanes) to yield the pure oxazolidinone (47 mg, 85%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.85 (ddq, J = 15.2, 6.6, 0.7 Hz), 5.51 (m, 1H), 4.41 (pseudo t, J = 7.7 Hz; $J_{4,5}$ = 7.5 Hz determined via decoupling of the 1.24 ppm CH_3); 3.61 (m, 1H), 1.72 (dd, J = 6.6, 1.4 Hz, 3H); 1.24 (d, J = 6.2 Hz, 3H); ^{13}C NMR (APT, $CDCl_3$) δ 132.65, 126.67 (CH═CH), 85.08 (CH−O),54.14 (CH−N), 19.26, 17.76 (Me).

(*4S,5R*)-2,2-Diphenyl-4-methyl-5-[(*E*)-1-propen-1-yl]-*N*-(trichloro-acetylcarbamoyl)-oxazolidine (see Figure 4). The compound was prepared in situ by the addition of one drop of trichloroacetylisocyanate (TAI)[36] to the NMR sample of alcohol **10f** (5 mg in 0.5 mL of $CDCl_3$). The cyclic product was formed instantaneously and quantitatively. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81−7.21 (m, 10H), 5.81 (dq, J = 15.2, 6.4 Hz), 5.61 (ddd, J = 15.2, 7.8, 1.4 Hz, 1H), 4.15 (dq, J = 8.6, 6.1 Hz, 1H), 3.82 (dd, J = 8.2 Hz; $J_{2,3}$ = 8.7 Hz, determined via decoupling of the 1.36 ppm CH_3), 1.73 (dd, J = 6.4, 1.4 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H); ^{13}C NMR (APT, $CDCl_3$) δ 139.56, 138.78 (q aromatic), 133.22 130.42, 130.04, 129.36, 128.89, 128.71, 128.38, 128.27, 128.16, 128.03, 127.78, 126.57 (aromatic), 82.98 (CH−O), 60.00 (CH−N), 17.91, 16.31 (Me).

(4*S*,5*R*)-2,2-Diphenyl-4-(*tert*-butyldimethylsiloxymethyl)-5-[(*E*)-1-propen-1-yl]-*N*-(trichloroacetylcarbamoyl)-oxazolidine (see Figure 4). The compound was prepared in situ by the addition of one drop of trichloroacetylisocyanate (TAI)[36] to the NMR sample of alcohol **10e** (5 mg in 0.5 mL of $CDCl_3$). The cyclic product was formed instantaneously and quantitatively as judged by NMR. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54−7.17 (m, 10H), 5.82 (dq, J = 15.4, 6.5 Hz, 1H), 5.64 (ddd, J = 15.3, 7.4, 1.5 Hz, 1H), 4.35 (apparent t, J = 7.7 Hz, 1H), 4.16 (ddd, J = 8.2, 5.9, 3.5 Hz, 1H), 3.94 (m, 1H, $^1/_2$ AB), 3.82 (dd, J = 10.3, 5.9 Hz, 1H), 1.72 (dd, J = 6.3, 1.3 Hz, 3H), 0.75 (s, 9H), −0.05 (s, 6H); ^{13}C NMR (APT, $CDCl_3$) δ 139.83, 138.67 (q aromatic), 132.15, 130.32, 130.04, 129.22, 128.83, 128.69, 128.24, 128.15, 127.77, 127.72, 127.56 (aromatic), 79.25 (CH−O), 64.66 (CH_2−O), 60.96 (CH−N), 25.76 (tBu), 17.85 (Me), −5.39 (SiMe), −5.54 (SiMe).

Procedure A: Catalytic Dihydroxylation in the Absence of a Chiral Auxiliary. A flask was charged with 5 mL of water, 5 mL of *tert*-butyl alcohol, 0.98 g of $K_3Fe(CN)_6$ (3 mmol), 0.42 g K_2CO_3 (3 mmol), 10.8 mg of $K_2OsO_2(OH)_4$ (3 mol %), and 95 mg of $MeSO_2NH_2$. The mixture was stirred at rt until both phases were clear. The olefin (1 mmol) was added, and the heterogeneous mixture was vigorously stirred at rt until the substrate was consumed (TLC). Na_2SO_3 (2.3 g) was added, and the mixture was stirred for 20 min. The phases were separated, and the aqueous layer was extracted 3× with $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered through Celite, and dried in vacuo to give a crude mixture of diastereomeric triols.

2,3,4-Tri-*O*-acetyl-5-amino-1-*O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-5-deoxy-L-galactitol (13a). Compound **10a** was oxidized following procedure A. Without purification, the crude product mixture was dissolved in 2 mL of pyridine, a catalytic amount of DMAP was added, and the mixture was cooled to 0 °C. Two milliliters of Ac_2O were added dropwise. The reaction was allowed to stand in the refrigerator overnight. Solvent was removed in vacuo, and the mixture of **13a** and the *ido*-isomer (6:1) was separated by gradient flash chromatography.

13a: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR (neat) ν_{max} 2953.1 (C−H), 1740.1 (C=O), 1365.3, 1262.1, 1250.1, 1212.3 (C−O). $[\alpha]_D$ +5.4° (c = 0.4 $CHCl_3$). Elemental anal.: calcd for $C_{31}H_{43}NO_7Si$ C, 65.35; H, 7.61. Found C, 65.39; H, 7.65.

Procedure B: Catalytic Dihydroxylation in the Presence of a $(DHQ)_2PHAL$ [or $(DHQD)_2PHAL$]. A container was charged with 5 mL of H_2O, 5 mL of *tert*-butyl alcohol, $K_3Fe(CN)_6$ (0.98 g, 3 mmol), K_2CO_3 (0.42 g, 3 mmol), $K_2OsO_2(OH)_4$ (4.3 mg, 1.2 mol %), and $MeSO_2NH_2$ (95 mg, 1 mmol) and $(DHQ)_2PHAL$ (23.8 mg, 3 mol %). The mixture was stirred at rt until both phases were clear and then added to the olefin (1 mmol). The heterogeneous mixture was vigorously stirred at rt until consumption of starting material (TLC). Solid Na_2SO_3 (2.3 g) was added, and the mixture was stirred for 20 min. Two phases were separated and the aqueous layer extracted 3× with $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered through Celite, and dried in vacuo to give a crude mixture of diastereomeric triols.

2,3,4-Tri-*O*-acetyl-5-amino-1-*O*-benzyl-*N*-diphenylmethylene-5-deoxy-L-galactitol (13b). Compound **10b** (150 mg, 0.388 mmol) was oxidized following procedure A. Without purification, the crude product mixture was dissolved in 2 mL of pyridine. A catalytic amount of DMAP was added, and the mixture was cooled to 0 °C. Two milliliters of Ac_2O were added dropwise. The reaction was complete within 3 h. Solvent was removed in vacuo, and the mixture of **13b** and the *ido*-isomer (4:1) was separated by gradient flash chromatography (5−20% EtOAc/hexanes) to yield pure **13b** (110 mg, 52%) and pure *ido*-isomer (28 mg, 13%) as a colorless oil.

13b: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR (neat) ν_{max} 2983.1 (C−C), 1745.1 (C=O), 1665.8 (aromatic), 1358.7, 1261.3 (C−O).

3,4,5-Tri-*O*-acetyl-2-amino-1-*O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-2-deoxy-D-galactitol (13c). Procedure A. A mixture of $K_3Fe(CN)_6$ (0.49 g, 1.5 mmol, 3 equiv), K_2CO_3 (0.21 g, 1.5 mmol, 3 equiv), and $K_2OsO_2(OH)_4$ (5.6 mg, 3 mol %) in 6.7 mL of H_2O was prepared. Compound **10e** (204.8 mg, 0.50 mmol) was dissolved in 3 mL of tBuOH and added to the aqueous solution. The mixture was stirred vigorously at rt. After 24 h the reaction was complete (TLC). Na_2SO_3 (0.375 g) was added, and the mixture was stirred for 20 min. The phases were separated, and the aqueous layer was extracted with three portions of $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered through Celite, and dried in vacuo. Without purification the mixture was dissolved in 1 mL of pyridine, catalytic amount of DMAP was added, and the mixture was chilled to 0 °C. One milliliter of Ac_2O was added dropwise. The reaction was complete in 3 h. Solvent was removed, and the mixture of **13c** and the *ido*-isomer was separated by flash chromatography (5−25% EtOAc/hexanes) to yield pure **13c** (170 mg, 60%) and pure *ido*-isomer (28 mg, 9.8%) as colorless oils.

13c: ^{1}H NMR (250 MHz, $CDCl_3$) δ −0.07 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.84 (s, 9H, tBu), 1.09 (d, 3H, J = 6.4 Hz, CH_3), 1.85 (s, 3H, Ac), 1.97 (s, 3H, Ac), 2.06 (s, 3H, Ac), 3.65−3.69 (m, 1H, unresolved, CH−N), 3.72−3.85 (m, 2H, unresolved, CH_2O), 5.13 (dq, 1H, J = 3.65, 6.5 Hz, C(5)H−OAc), 5.20 (dd, 1H, J = 3.6, 7.0 Hz, C(4)H−OAc), 5.39 (dd, 1H, J = 3.3, 7.0 Hz, C(3)H−OAc), 7.23−7.58 (m, 10H, unresolved); ^{13}C NMR ($CDCl_3$) δ −5.48 (CH_3Si), 16.6 (CH_3), 20.84 (acetate CH_3), 20.97 (acetate CH_3), 21.06 (acetate CH_3), 25.85 (tBu), 63.43 (CH_2O), 63.62 (CH_3−N), 68.22 (CH−OAc), 70.54 (CH−OAc), 72.93 (CH−OAc),127.94, 128.22, 128.51, 128.62, 128.71, 130.04 (aromatic CH), 135.92 (q aromatic), 140.20 (q aromatic), 169.85 (acetate C=O), 170.00 (acetate C=O), 170.25 (acetate C=O); IR (neat) ν_{max} 3058.0, 3023.9, 2928.1, 2856.9, 1742.2, 1698.9, 1625.0, 1578.1 cm^{-1}; MS (CI) 570 (MH^+), 512 (MH − $(CH_3)_3$CH), 424 (MH − TBDMS−OMe), 364 (MH − (TBDMS−OMe) − CH_3COOH), 338 (TBDMS−OCH_2=N=CPh_2), 280 (338 − $(CH_3)_3CH$); $[\alpha]_D$ +2.15° (c = 0.04, $CHCl_3$).

***ido*-Isomer:** ^{1}H NMR ($CDCl_3$) δ −0.05 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.86 (s, 9H, tBu), 1.23 (d, 3H, J = 6.4 Hz, CH_3), 3.63−3.70 (m, 1H, unresolved, CH−N), 3.74−3.77 (m, 2H, unresolved, CH_2−O), 4.89 (quintet, 1H, J = 6.6 Hz, C(5)H−OAc), 5.25 (dd, 1H, J = 3.6, 6.9 Hz, CH−OAc), 5.50 (dd, 1H, J = 3.6, 7.0 Hz), 7.20−7.62 (m, 10H, unresolved, aromatic); ^{13}C NMR ($CDCl_3$) δ −5.5 (CH_3Si), 16.42 (CH_3), 20.41 (CH_3COO), 20.92 (2 CH_3COO), 25.80 (tBu), 63.35 (CH_2O), 63.65 (CH−N), 69.15 (CH−OAc), 70.76 (CH−OAc), 73.15 (CH−OAc), 127.99, 128.17, 128.29, 128.40, 128.62 (aromatic CH), 130.14 (q aromatic), 167.75 (CH_3COO), 169.95 (2 CH_3COO).

5-Amino-1-*O*-*tert*-butyldimethylsilyl-*N*-diphenylmethylene-4-*O*-pivaloyl-5-deoxy-L-galactitol (14d). From **10h** using procedure A. Provided a colorless oil.

14d: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5); IR ν_{max} 3500.0 (OH), 2957.3, 2930.2, 2856.9 (C−H), 1732.3 (C=O), 1151.7 (C−O); $[\alpha]_D$ +37.6°. Elemental anal.: calcd for $C_{30}H_{45}N_5Si$ C, 71.53; H, 9.00. Found C, 71.58; H, 9.06.

5-Amino-*N*-diphenylmethylene-4-*O*-pivaloyl-5-deoxy-L-galactitol (15b). (TBAF Deprotection of *tert*-Butyldimethylsilyl group.) The *tert*-butyldimethylsilyl group (TBDMS) was deprotected under standard conditions.[52] Diol **14d** (1 mmol) was dissolved in THF (4 mL), $nBu_4N^+F^-$, (TBAF), (1.1 mmol) was added as a 1.0 M solution in THF, and the mixture stirred at rt to completion (2−3 h). The solvent was removed in vacuo to provide a colorless oil. Normally, the resulting triol **15b** was carried on to the oxidation step without purification. In one case the residue was purified via flash chromatography on silica gel (6% MeOH/CH_2Cl_2) to provide crystalline triol **15b**.

15b: White crystals, mp 92−94 °C (recrystallized from hexane/EtOAc); ^{13}C NMR ($CDCl_3$) δ 177.13 (C=O), 138.63 (q aromatic), 134.69 (q aromatic), 130.90, 128.60, 128.56, 128.31, 127.66 (aromatic), 71.59 (CH−O), 71.09 (CH−O), 69.60 (CH−O), 65.32 (CH_2−O), 58.38 (CH−N), 38.80 (q Bu), 27.04 (tBu), 14.95 (Me); IR ν_{max} 3213.4−3425.1 (broad, OH), 1732.2 (C=O), 1274.2 (C−O); $[\alpha]_D$ +51.3° (c = 1, $CHCl_3$).

(52) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

(*4S,5S,2Z*)-5-Amino-*N*-diphenylmethylene-4-pivaloyloxyhex-2-en-1-al (16c) (Swern Oxidation). Oxalyl chloride (28 μL, 0.32 mmol) and 0.55 mL of dry CH_2Cl_2 were mixed in a flask under an argon atmosphere. The mixture was cooled to −65 °C ($CHCl_3$, solid CO_2) and DMSO (40 μL, 0.56 mmol) in 110 μL of CH_2Cl_2 was added. The reaction was stirred for 2 min at −65 °C and 100 mg (∼0.26 mmol) of the crude alcohol resulting from the desilylation of **10j** (see procedure for **14d → 15b**, above) in 0.22 of mL of CH_2Cl_2 was added. The reaction was stirred at −65 °C for 15 min, and 154 μL of NEt_3 was added. After stirring for an additional 10 min, the mixture was allowed to warm to rt and quenched with 6 mL of water. The mixture was extracted 2× with $CHCl_3$. The combined $CHCl_3$ extracts were subsequently washed with 3% $NaHCO_3$ and dried ($MgSO_4$), and the solvent was removed in vacuo to provide the crude aldehyde **16c** as an oil (87 mg, 70% for both steps).

16c: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5).

(*2S,3R,4R,5S*)-5-Amino-*N*-diphenylmethylene-2,3-bis-methoxymethoxy-4-pivaloyloxy-1-hexanal or 5-Amino-*N*-diphenylmethylene-2,3-bis-*O*-methoxymethyl-4-*O*-pivaloyl-5,6-dideoxy-L-galactose (16a). Aldehyde **16a** was prepared from **15a** by desilylation (see procedure for **14d → 15b**), and Swern oxidation (see procedure for **10j → 16c**) to provide a colorless oil in 75% yield.

16a: ^{1}H NMR (Table 4); ^{13}C NMR (Table 5).

(*2S,3R,4R,5S*)-5-Amino-*N*-diphenylmethylene-4-pivaloyloxy-2,3,4-trihydroxy-hexan-1-al or 5-Amino-*N*-diphenylmethylene-2,3-bis-*O*-methoxymethyl-4-*O*-pivaloyl-6-deoxy-L-galactose (16b) (TEMPO Oxidation). Triol **15b** (0.53 mmol, 220 mg) was dissolved in 1.4 mL of CH_2Cl_2, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxide) (1 mol %, 0.8 mg, 320 μL of a solution of 5 mg TEMPO in 2 mL of CH_2Cl_2), 0.87 mL of saturated $NaHCO_3$ containing 5.3 mg of KBr and 7.3 mg of tetrabutylammonium chloride hydrate were added. The mixture was cooled to −5 °C (ice/MeOH). While stirring vigorously a mixture of 1.56 mL of NaOCl (4% solution, Aldrich), 0.76 mL of saturated $NaHCO_3$, and 1.49 mL of brine was added dropwise to the cooled flask. The addition time was 12−15 min. Extension of this addition time resulted in deactivation of the catalyst. At the end of the reaction (TLC) the mixture was diluted with excess CH_2Cl_2, dried ($MgSO_4$), and filtered, and solvent was removed in the dark at 0−10 °C. The unstable crude aldehyde **16b** (210 mg, 96%) was used immediately for the next reaction, and a complete spectral characterization was not done.

***N*-Diphenylmethyl-2,3-*bis*-*O*-methoxymethyl-4-*O*-pivaloyl-L-(−)-1-deoxyfuconojirimycin (17a).** Aldehyde **16a** (90 mg, 0.18 mmol) in 0.52 mL of anhydrous CH_3CN was acidified with glacial HOAc (8−10 equiv) to maintain pH 5−6. Solid $NaBH_3CN$ (12.4 mg, 0.197 mmol) was added to the mixture at once. The reaction was complete in 10 min (TLC). The mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried and evaporated to provide the crude diol (48 mg), which was purified via flash chromatography (50% EtOAc/hexanes) to yield the pure heterocycle **17a** (34 mg, 88%) as a colorless oil.

17a: ^{1}H NMR and ^{13}C NMR (Table 6); IR ν_{max} 2972.7, 2891.7 (C−H), 1730.4 (C═O), 1479.6, 1165.5, 1033.9; $[\alpha]_D$ −55.3° ($CHCl_3$).

***N*-Diphenylmethyl-4-*O*-pivaloyl-L-(−)-1-deoxyfuconojirimycin (17b).** Crude aldehyde **16b** was converted to azafucose **17b** (80% yield) following the same protocol as for **16a → 17a**.

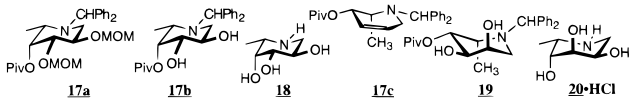
17b: ^{1}H NMR and ^{13}C NMR (Table 6); IR ν_{max} 3443.4 (OH), 2976.5 (C−H), 1728 (C═O), 1165.15 (C−O); $[\alpha]_D$ −41°.

(*2S,3S*)-*N*-Diphenylmethyl-2-methyl-3-pivaloyloxy-D-4,5-tetrahydropyridine (17c). Crude aldehyde **16c** yielded **17c** (85% yield) following the same protocol as for **16a → 17a**.

17c: ^{1}H NMR and ^{13}C NMR (Table 6); IR ν_{max} 2974.6 (C−H), 1728.4 (C═O), 1157.4 (C−O), $[\alpha]_D$ +58.6°.

***N*-Diphenylmethyl-4-*O*-pivaloyl-L-(−)-*gulo*-1-deoxynojirimycin (19).** Cyclic alkene **17c** was converted to azagulose **19** (80% yield) by following the osmylation procedure A. Only the *gulo* isomer **19** was detected in the crude ^{1}H NMR spectrum.

Table 6. ^{1}H NMR and ^{13}C NMR Data for Cyclic Compounds



	17a	17b	18	17c	19	20•HCl
			^{1}H Chemical Shifts (ppm)			
1e	3.05	3.03	2.85	2.99	2.73	2.99
1a	1.93	1.96	2.13	2.75	2.50	2.86
2	3.93	3.86	3.48	5.71	3.58	3.95
3	3.50	3.49	3.26	5.49	3.73	3.80
4	5.26	5.12	3.58	5.49	5.09	3.71
5	2.71	2.81	2.56	3.42	3.34	3.35
6	1.24	1.23	0.87	0.86	0.88	1.07
Ph_2CH	5.22	5.16	—	4.65	4.62	—
			$J_{H,H}$ Coupling Constants (Hz)			
1a,1e	11.6	11.6	13.0	17.2	12.8	12.0
1a,2	8.9	8.6	10.8	nd	9.5	11.5
1e,2	4.3	4.0	5.3	10.0	3.3	5.1
2,3	8.7	7.7	9.8	8.0	3.3	4.4
3,4	3.3	3.3	3.2	nd	10.0	3.2
4,5	2.4	2.0	1.4	~6	5.5	0.5
5,6	6.5	6.5	6.8	6.6	6.8	6.9
			^{13}C Chemical Shifts (ppm)			
C-1	49.6	49.8	49.3	45.5	47.2	43.9
C-2	54.6	65.4	73.2	128.8	69.1	63.9
C-3	65.2	69.1	75.6	128.5	70.8	71.3
C-4	72.7	74.3	68.3	72.7	70.1	70.1
C-5	54.6	54.4	53.6	49.3	51.9	51.7
C-6	15.2	14.4	16.7	4.2	3.7	15.2
Ph_2CH	73.4	74.8	—	71.8	72.9	—

19: White crystals, mp 151−3 °C; ^{1}H NMR and ^{13}C NMR (Table 6); IR ν_{max} 3462.2 (OH), 2992.2 (C−H), 1743.2 (C═O), 1143.3 (C−O); $[\alpha]_D$ −85.40 ($CHCl_3$). Calcd for $C_{27}H_{31}NO_4$ C, 74.80; H, 7.21. Found C, 74.89; H, 7.30.

1-deoxy-L-(−)-Azafucose (L-(−)-1-deoxyfuconojirimycin) (18). Deprotection of Pivalate and Benzhydryl Groups. *N*-Diphenylmethyl-4-pivaloyl-L-azasugar **17b** (313.4 mg, 1 mmol) was dissolved in 10 mL of dioxane and 6.5 mL of H_2O. An aqueous solution of nBu_4NOH (720 μL, 1.1 mmol) was added at 0 °C. The mixture was stirred until completion (TLC, 5% MeOH/CH_2Cl_2), and diluted with excess CH_2Cl_2. The aqueous layer was extracted 3× with CH_2Cl_2. The combined organic phases were washed with brine (H_2O generated an emulsion), dried ($MgSO_4$), and evaporated. When necessary, the crude material was purified via gradient flash chromatography (2−5% MeOH/CH_2Cl_2) to yield a pure *N*-benzhydryl triol (typically 85%), which was submitted to hydrogenolysis in MeOH. A portion of the triol (56.0 mg, 0.179 mmol) was dissolved in 2 mL EtOAc, and the solution was added to an argon-purged flask (omission of argon leads to the N-methylated impurity) with 50 mg of 5% Pd/C catalyst and 50 mL of MeOH in the presence of H_2. Hydrogen was applied via rubber balloon. The mixture was vigorously stirred at rt for 3 h, and then it was filtered and evaporated to dryness. The residue was dissolved in H_2O, acidified with HCl (2 mmol), and washed 2× with hexane to remove diphenylmethane. The aqueous solution was lyophilized, and the crude sample was purified via ion exchange. An aqueous solution (∼1 mL) was taken to pH 9−10 with 1 N NaOH, applied to Dowex (H^+form), washed with H_2O, and eluted with 10 mL of MeOH/H_2O/NH_3 (MeOH: 3 M NH_3:H_2O, 2:5:3 by volume) to yield the pure azasugar **18** (typically 95% for the second step).

18: ^{1}H NMR and ^{13}C NMR (Table 6); $[\alpha]_D$ −50° ($c = 1$, D_2O). Calcd for $C_6H_{12}NO_3$: C, 48.96; H, 8.22. Found: C, 49.01; H, 8.25.

1-deoxy-L-(−)-Azagulose (L-(−)-1-Deoxygulonojirimycin) (20). *N*-Diphenylmethyl-4-pivaloyl-L-azasugar **19** (27 mg, 0.068 mmol) was dissolved in 0.3 mL of dioxane and 0.2 mL of H_2O. An aqueous solution of nBu_4NOH (150 μL) was added at 0 °C. The mixture was stirred until completion (TLC, 5% MeOH/CH_2Cl_2), and the mixture was diluted with an excess of CH_2Cl_2. The aqueous layer was extracted 3× with CH_2Cl_2. The combined organic phases were washed with brine (H_2O generated an emulsion), dried ($MgSO_4$), and evaporated. The crude material was purified via gradient flash chromatography

(2−5% MeOH/CH_2Cl_2) to yield the pure triol as snow-white crystals (mp 147−148 °C). Hydrogenation of 13 mg of this material in 2 mL EtOAc and 50 mL MeOH with 50 mg 5% Pd−C as before yielded 8.0 mg of **20**·HCl after lyophylization.

20·HCl: ^{1}H NMR and ^{13}C NMR (Table 6); $[\alpha]_D$ +13.5° (c = 0.33, H_2O/MeOH 1:1). Calcd for $C_6H_{13}NO_3Cl$: C, 39.46; H, 7.17. Found: C, 39.46; H, 7.22.

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Supporting Information Available: ^{1}H NMR spectra (250 or 300 MHz) are available for olefin **10h**, diol **14d** (crude reaction mixture showing *ido*−*galacto* mixture), *cis*-enal **16c**, and cyclic products **17a**, **17b**, **17c**, **18**, **19**, and **20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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