Expeditious Synthesis of Azasugars by the Double Reductive Amination of Dicarbonyl Sugars

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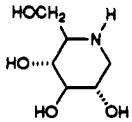
Polyhydroxylated pyrrolidines and piperidines were prepared by the double reductive amination of dicarbonyl sugars with primary amines and $NaCNBH_3$ in MeOH. Stereocontrol in these reactions depended on the nature of the amine and dicarbonyl sugar. For example, 5-keto-D-fructose (**7**) gave three pyrrolidine stereoisomers, with the N-alkylated 2,5-anhydro-2,5-imino-D-glucitol predominating. Under similar reaction conditions with benzhydrylamine, 5-keto-D-glucose (**20**) afforded a 96:4 mixture of piperidines favoring D-gluco **25A**, whereas 5-keto-D-mannose (**6**) produced a 67:33 mixture enriched in D-manno isomer **40**. This method allowed for the direct and relatively short synthesis of 1-deoxynojirimycin (DNJ, **1**) and 1-deoxymannojirimycin (DMJ, **5**) and N-alkylated derivatives thereof. Similar reactions with O-protected 5-keto-D-glucose derivatives **21** and **22** were less stereoselective and lower yielding.

Azasugars such as **1** and **2** constitute an important class of natural and unnatural products because of their ability to inhibit glycohydrolases, enzymes responsible for the cleavage of glycosidic bonds.[1,2] Since they are charged at physiological pH, the azasugars are thought to associate with acidic amino acid residues at the active site.[1,2] Inhibition of glycohydrolases could be of therapeutic value for the treatment of viral infections,[3] cancer,[4] diabetes,[5] and obesity.[5]



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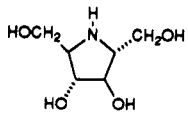

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Paulsen and co-workers[6] prepared 1-deoxynojirimycin (**1**) before it had been isolated from natural sources and was shown to be an enzyme inhibitor.[1,2] The Paulsen synthesis of **1** entailed reduction of an azide followed by intramolecular reductive amination via catalytic hydrogenation with platinum, which proceeded with excellent stereocontrol. Since then, a large number of synthetic routes to **1** and related piperidines have appeared,[7] including those involving enzymatic transformations as key steps. Generally, final ring closure has been achieved through intramolecular N-alkylations or reductive aminations effected by hydrogen and a noble metal catalyst (e.g., Pd or Pt). Alternatively, in a few cases, stereocontrolled intramolecular reductive aminations have employed soluble hydride sources such as $Me_2NH{\cdot}BH_3$ and $NaCNBH_3$.[7d,8,9]

An especially important pyrrolidine azasugar is 2,5-anhydro-2,5-imino-D-mannitol (**2**).[10,11] Other pyrrolidine

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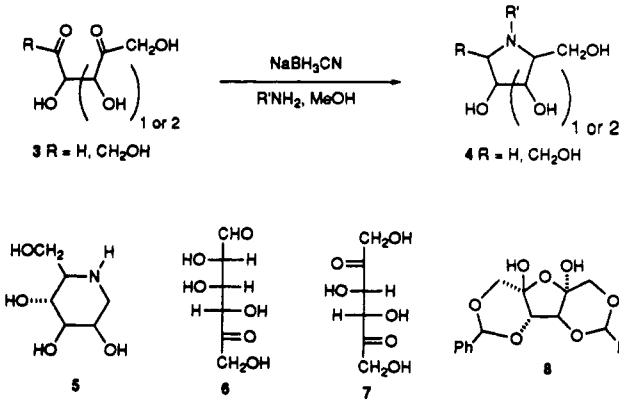
azasugars have also been found in nature or have been prepared synthetically.[1,2] The enzyme inhibition mediated by **2** and related structures is thought to arise from conformational resemblance to a half-chair transition state involved in glycoside cleavage.[2b] Additionally, bicyclic alkaloids such as the indolizidine castanospermine[12] and the pyrrolizidine alexine[13] are potent and selective glycohydrolase inhibitors.

We have reported the direct preparation of five- and six-membered-ring azasugars in one step from benzhydrylamine and suitable dicarbonyl sugars using $NaCNBH_3$, as shown by the conversion of **3** to **4**.[14] Other groups have described related examples of ring closure using bis-electrophiles (e.g., dimesylates) to generate pyrrolidine azasugars,[15] and recently Zou and Szarek have used a protected dicarbonyl sugar as the starting material for a double reductive amination.[16] Advantages associated with the use of dicarbonyl sugars are that no protecting groups on the hydroxyls are needed, N-alkylated products are obtained directly, and there is considerable stereocontrol in certain cases. This method may be biomimetic, as **1** and 1-deoxymannojirimycin (**5**) appear to be formed in *Streptomyces subrutilus* by a series of enzymatic transformations involving 5-keto-D-mannose (**6**) as the key intermediate.[17] Dicarbonyl sugars are also postulated intermediates in the biosynthesis of the important inositol class of cyclitol derivatives.[18] We here present a full account of our work in this area, emphasizing the preparative utility of this method.

Results and Discussion

The preparation of piperidines and pyrrolidines by double reductive aminations using a soluble hydride source is well-established.[19] In reactions of 2,6-diones, the *cis*-2,6-dialkylpiperidines are formed preferentially.[19b]

Pyrrolidine Azasugars. 5-Keto-D-fructose (D-*threo*-2,5-hexodiulose, **7**) is the most accessible 1,4- (or 2,5-)



dicarbonyl sugar,[20] as it is prepared by the microbial oxidation of fructose.[21] Dicarbonyl sugar **7** exists as a dimer in DMSO-d_6 and in the solid state.[22] In D_2O, the sugar adopts the form of a hydrated β-pyranose, and some of the acyclic form can be detected upon heating.[22] Little use has been made of **7** synthetically, apart from the preparation of 4(1*H*)-pyridazones upon treatment with hydrazines.[23] The synthesis of protected 5-keto-D-fructose hydrate **8** from D-mannitol has been reported.[24]

Although **7** is only sparingly soluble in MeOH, it dissolves as it reacts in that solvent upon treatment with primary amines and $NaCNBH_3$, yielding the desired pyrrolidine ring skeleton in modest to good yields. Reactions of **7** with a variety of amines are listed in Table 1. The pH of the reaction was adjusted to 5–7 when necessary by the addition of acetic acid dropwise.[25] A large number of amines were useful substrates for this reaction; exceptions were tritylamine and 1-aminoadamantane.

Three stereoisomers form in the double reductive amination of **7** with primary amines: those related to D-glucitol (**A**), D-mannitol (**B**), or L-iditol (**C**). The relative assignment of their configuration was made by inspection of the ^{13}C NMR spectra. Glucitol isomer **A** is the only one of the three that has six distinct sugar-derived carbon resonances. Alternatively, mannitol **B** and iditol **C** are differentiated by the fact that every carbon of **C** is upfield of the corresponding carbons in **B**, expected for cis ring substitution.[26] Statistically, a 2:1:1 mixture of **A**:**B**:**C** was expected. However, glucitol isomer **A** generally predominated as 60-90% of the total pyrrolidine product.

Entry 1 of Table 1 lists the reaction of **7** with benzhydrylamine to give a mixture of **9A**/**9B**/**9C**. An approximate ratio of 86:8:6 was determined by ^{13}C NMR. Compounds **9B** (4%) and a 92:8 mixture of **9A** and **9C** (64%) were readily separated by chromatography. The enriched sample of **9A** thus obtained was recrystallized to give pure

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(10) The azasugars and dicarbonyl sugars employed in this paper are named using trivial carbohydrate nomenclature. These compounds are also referred to as derivatives of their respective heterocyclic ring systems. For example, 2,5-anhydro-2,5-imino-D-mannitol is also known as (3*R*,4*R*)-dihydroxy-(2*R*,5*R*)-bis(hydroxymethyl)pyrrolidine (DHDP). The more correct carbohydrate name for 5-keto-D-fructose is D-*threo*-2,5-hexodiulose.

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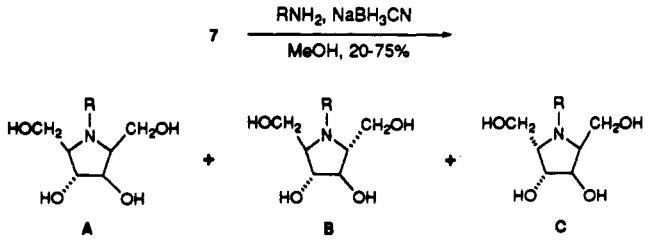
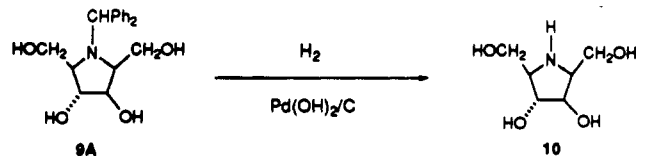


Table 1. Reaction of 5-Keto-D-fructose (7) with Various Amines

entry	amine	compd no.	A:B:C[a]	yield (%)
1	Ph_2CHNH_2	9	86:8:6	68
2	(*R*)-α-MeCH(Ph)NH_2	11	79:19:2	50
3	(*S*)-α-MeCH(Ph)NH_2	12	92:8:0	15
4	4-FPhNH_2	13	60:30:10	25
5	$C_{18}H_{37}NH_2$	14	78:19:3	54
6	$HO(CH_2)_3NH_2$	15	57:39:4	26
7	4-FPh$(CH_2)_2NH_2$	16	76:12:12	31

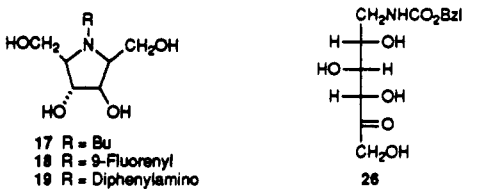
[a] Ratios estimated by ^{13}C NMR peak height measurements of carbons at the identical positions in each diastereomer, except for **13** in which each diastereomer was obtained separately.

9A with good (40–65%) recovery. The benzhydryl groups of **9A** and **9B** were hydrogenolyzed using palladium hydroxide to afford 2,5-anhydro-2,5-imino-D-glucitol (**10**) and **2**. Compound **10**, first reported in our preliminary paper,[14a] is an azasugar which resembles α-fructofuranose and has been demonstrated to be a potent inhibitor of glycohydrolase enzymes.[7cc] We have prepared **10** by this method on a reasonably large scale (30 g) as a crystalline, nonhygroscopic solid (mp 139–142.5 °C).



Entries 2–7 in Table 1 show several further examples of this reaction. As product ratios were determined by NMR integration or chemical isolation, these values can only be considered in a qualitative sense. Interestingly, there is only a minor difference in the amount of the **A** isomer formed upon reaction of **7** with (*R*) and (*S*)-PhCH(Me)NH_2 (entries 2 and 3). All of the products of the reaction of 4-fluoroaniline (entry 4) were separated by chromatography and are the first *N*-aryl pyrrolidine azasugars that appear to have been prepared.

In the reactions of butylamine, 9-fluorenamine, and 1,1-diphenylhydrazine with **7**, glucitol isomers **17-19** were obtained stereochemically pure after chromatography and recrystallization. Although reactions of this type offered no additional information about the relative abundance of minor stereoisomers, they did allow for the ready preparation of N-substituted derivatives of **10** *in a single chemical step, without the need for protecting group manipulations*. As in the case of the preparation of aryl derivatives **13**, the use of **7** in synthesis allowed for the preparation of N-substituted azasugars (e.g., **18** and **19**) which would be difficult to obtain otherwise.



The only reducing agent that consistently worked well in the reductive amination of **7** was $NaBH_3CN$. The use of $NaBH(OAc)_3$[27] was unsuccessful in THF and 1,2-dichloroethane, possibly due to the insolubility of **7** in these solvents. Catalytic conditions using hydrogen and noble metal catalysts were unsuccessful, even though numerous reaction conditions (modifying pH, solvent, and temperature) and reagents (Pt, Pd, Ra-Ni) were employed. No reaction occurred under neutral conditions when using noble metal catalysts, whereas under basic conditions there was clear imine formation (typical browning reactions of sugars), but no observed formation of the desired pyrrolidine products. We primarily used methanol as solvent, but water can be used as well.

Piperidine Azasugars. The preparation of 5-keto-D-glucose (D-*xylo*-hexos-5-ulose, **20**, see Scheme 1) has been reported previously.[28-31] Ferrier and Tyler described a two-step synthesis of the hydrated tetrabenzoate derivative of 5-keto-D-glucose (viz. **21**).[32] Since Helferich had claimed to have deacylated corresponding tetraacetate **22** to give **20**,[29] we attempted to prepare **20** via this method. Hydrated tetrabenzoate (**21**) and tetraacetate (**22**) derivatives of 5-keto-D-glucose were prepared by the Ferrier procedure with minor modifications.[32] ^1H NMR spectra (D_2O) of these compounds revealed the hydrated ring-closed β anomer, attributed to an unfavorable 1,3-diaxial interaction between the 1- and 5-OH groups in the α anomer. In addition, 15–30% of the ring-opened dicarbonyl form was observed in $CDCl_3$. Attempted deacylation of **21** and **22** under a number of alkaline or acidic conditions led only to intractable product mixtures,[29] possibly due to aldol or elimination chemistry. We then prepared 5-keto-D-glucose (**20**) by a two-step procedure.. First, monoketal **23** was oxidized with dibutyltin oxide and bromine[33,34] to give ketone **24**, which was followed by hydrolysis of the isopropylidene group with Dowex-50WX8 resin providing **20**.[28,31]

Double reductive amination of **20** with benzhydrylamine afforded a 96:4 mixture of D-glucitol:L-iditol isomers (**25A**:**25B**; 70%). Removal of the benzhydryl group by hydrogenolysis, treatment with Dowex-50WX8 ion-exchange resin, and recrystallization afforded pure **1** without any of the corresponding L-iditol isomer detected, in an overall conversion from **23** of 25-35%.[35]

Bayer researchers[7c,d] have reported a route in which aminosorbose derivative **26** underwent stereoselective reductive amination using noble metal catalysts and soluble hydride reagents, with formation of only traces of

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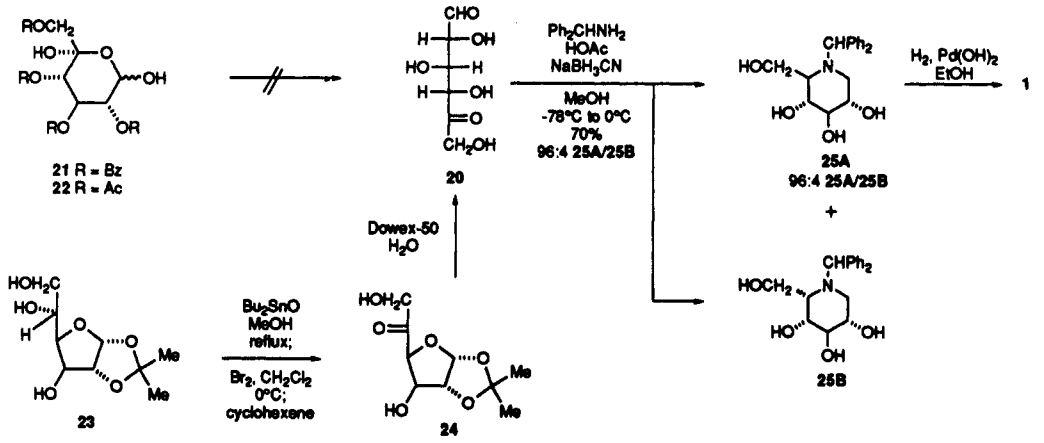
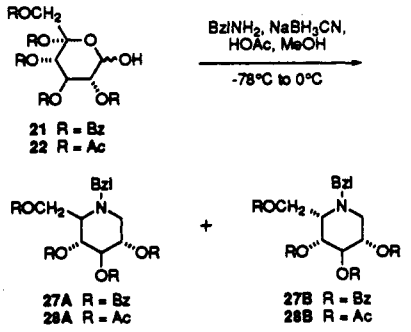
(33) Tsuda, Y.; Hanajima, M.; Matshuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2344.
(34) Use of nBu_2SnO: Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839. See also: David, S.; Thieffry, A. *J. Chem. Soc., Perkin 1* **1979**, 1568.

Scheme 1



the L-iditol diastereomer. Tsuda and co-workers reported the preparation of nojirimycin from **24** involving formation of the C–N bond at C5 first by conversion of **24** to an oxime,[36] a modification of the initial work of Inouye and colleagues.[7a] Oxime reduction with aluminum hydride reagents was poorly stereoselective and dependent on the oxime configuration. Lack of stereocontrol in this case contrasts markedly to that observed in the reductive amination of 5-keto-D-glucose (**20**), in which the first C–N bond formation occurs at C1 (see below). Unlike reactions of **20**, reductive aminations of **21** and **22** resulted in complex product mixtures (Scheme 2), and the overall yields (ca. 30%) and stereoselectivity were poor (ca. 1:2 for **27A**:**27B** and 1:1 for **28A**:**28B**).[37]

Scheme 2

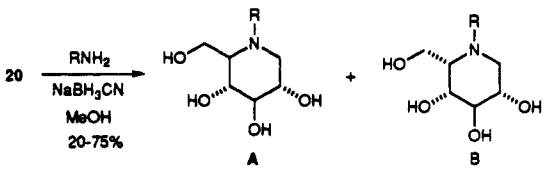


Reaction of **20** with several primary amines resulted in the formation of the expected N-substituted 1-deoxynojirimycin products directly, as seen in Table 2. The D-glucitol product typically predominated over the L-iditol isomer in a ratio of >95:5. Exceptions were in the reaction of **20** with (*S*)-PhCH(Me)NH_2 (entry 4) where a 75:25 mixture of the D-glucitol and L-iditol isomers formed and also when **20** was reductively aminated with 1,1-diphenylhydrazine (entry 6) which gave a 60:40 ratio of D-glucitol and L-iditol isomers. When 4-fluoroaniline was used, *N*-aryl-1-deoxynojirimycin **35A** was formed in a yield of only 35%. The 1-amino-1-deoxyglucitol derivative **36** was also produced as an approximately 1:1 mixture of isomers with respect to the newly formed stereocenter at C5, indicating that the first reductive amination of **20** had occurred at the aldehyde carbon. In the reductive amination of **20** with butylamine, a small amount (10%) of **37** was also isolated.

The synthesis of 1-deoxymannojirimycin (**5**) was also achieved by preparation and reaction of 5-keto-D-mannose (D-*lyxo*-hexos-5-ulose, **6**; Scheme 3). As for 5-keto-D-glucose (**20**), the known mannoside **38**[38,39] was oxidized to give ketone **39**, which was treated with Dowex 50WX8 ion-exchange resin to afford previously undescribed **6**. Reductive amination of **6** with benzhydrylamine as for **20** resulted in a 2:1 mixture of **40** and **41** (45% overall yield), which were separated by chromatography. Compound **40** was then converted to **5** by hydrogenolysis.

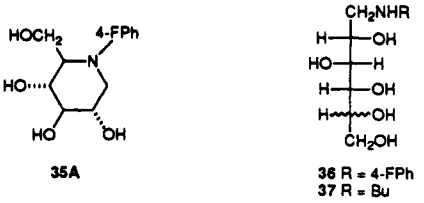
To probe the role of the C-4 hydroxyl group in directing the stereochemical outcome of the reduction at C-5 in reactions of **6** and **20** we prepared 4-hydroxy-5-ketohexanal

Table 2. Reaction of 5-Keto-D-glucose (20) with Various Amines



entry	amine	compd no.	A:B[a]	yield (%)
1	Ph_2CHNH_2	**25**	>95:5	70
2	$Ph_2CHCH_2NH_2$	**29**	>95:5	73
3	(*R*)-α-MeCH(Ph)NH_2	**30**	>95:5	79
4	(*S*)-α-MeCH(Ph)NH_2	**31**	75:25	53
5	$C_4H_9NH_2$	**32**	>95:5	55
6	Ph_2NNH_2	**33**	60:40	39
7	$C_{12}H_{25}NH_2$	**34**	>95:5	27
8	4-FPhNH_2	**35**	>95:5	35

[a] Ratios were determined by integration of key ^1H NMR resonances of mixtures, except for **31** and **33** in which the isomers were chromatographically separated.



(35) The final Dowex ion-exchange treatment was needed in order that the ^1H NMR chemical shifts of our synthetic **1** would match with the most reliable literature values, possibly to remove small amounts of coordinated palladium.

(36) (a) Tsuda, Y.; Okuno, Y.; Iwaki, M.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2673. (b) Stasik et al. (Stasik, B.; Beaupere, D.; Uzan, R.; Demailly, G.; Morin, C. *C. R. Acad. Sci Ser. C. Paris* **1990**, *311*, 521) describe a related synthesis in which the oxime group is constrained in a rigid bicyclic system.

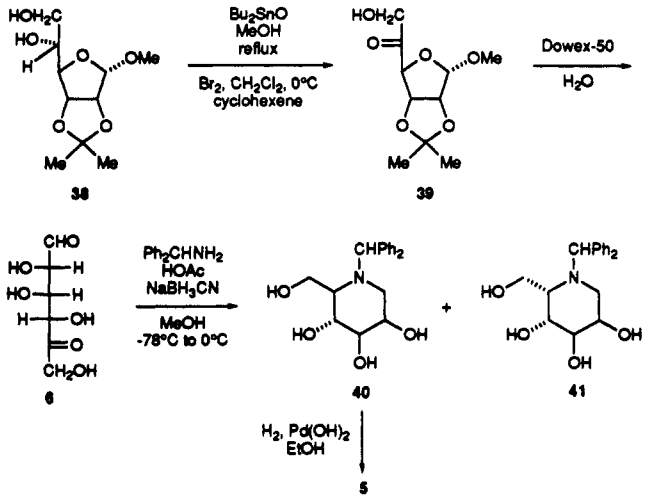
(37) Compounds **28A** and **28B** were previously prepared by an alternative synthetic route: Natsume, M.; Wada, M. *Chem. Pharm. Bull.* **1975**, *23*, 2567.

(38) Holy, A. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2969.

(39) Randall, M. H. *Carbohydr. Res.* **1969**, *11*, 173.

(42, Scheme 4).[40] Commercially available 2-methyl-2-cyclopenten-1-one was reduced with $NaBH_4$ in the presence of $CeCl_3$[41] to provide cyclopentenol 43,[42] which was ozonolyzed[43] to keto aldehyde 42. Unlike the corresponding reductive aminations of 20, reactions of 42 proceeded in poor yield (19%) and piperidines 44 and 45 were formed in roughly equal amounts. However, since 20 exists in the β-pyranose form[31] whereas 42 is present as furanose 46 (C5 at δ 221.6 and 217.2 by ^{13}C NMR for two anomers), it could be that compound 42 is not a suitable model substrate.[44]

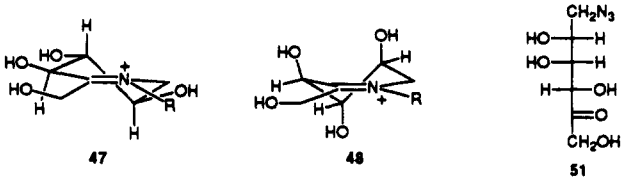
Scheme 3



38 39 6 40 41 5

Mechanistic Analysis

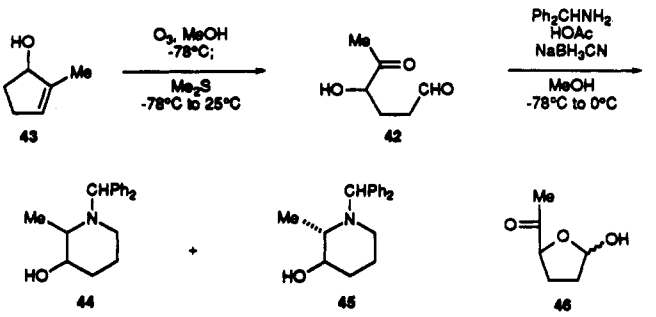
If reaction of 5-keto-D-glucose (20) to give azasugars proceeds by initial reductive amination at the aldehydic carbon, then the resulting amine undergoes an intramolecular condensation with the 5-keto group to form a cyclic iminium species which is reduced in the stereodetermining step. This intermediate cyclic iminium species can be envisioned to exist in half-chair conformations bearing equatorial (47) or axial (48) substituents. Reactions of 5-keto-D-fructose (7) involve reduction aminations of two ketones which both form stereocenters and are more difficult to analyze.



47 48 51

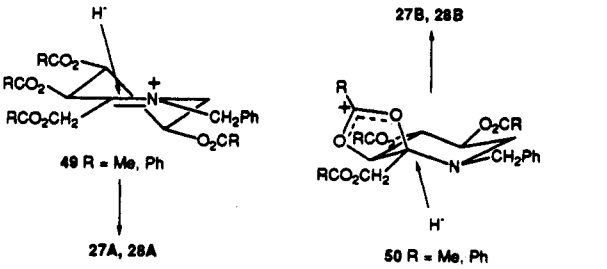
Stevens and co-workers have probed the stereocontrol of nucleophilic additions to six-membered-ring iminium ions.[45] In standard cases involving an equatorial orientation of substituents, axial hydride delivery occurs pre-

Scheme 4



43 42 44 45 46

cluding formation of a boat conformation in the transition state. Thus, if the intermediate formed from 20 existed in conformation 47 it would undergo axial addition of hydride to give the observed D-glucitol product. This rationale cannot, however, be applied to the reaction of O-acylated 5-ketoglucose derivatives 21 and 22 via hydride attack as in 49 because nearly equal mixtures of stereoisomers are formed with these substrates. However, anchimeric assistance[46] via 50 may be responsible for the diminished stereocontrol observed.



Although there are many examples of hydroxyl-directed reactions mediated by $M^+B(OAc)_3H^-$ in which a covalent boron adduct is presumed to deliver hydride,[47] little is known about such reactions involving $NaCNBH_3$.[48] It is conceivable that one or more of the hydroxyls, such as that on C4, could direct hydride delivery.[49] The $^2H_3$ conformer 48 may also play a role; the C4 hydroxyl of 48 is oriented in such a manner as to be more likely to interact with and perhaps direct an oncoming hydride reagent. Conformer 48 would not experience the repulsive $A_{1,2}$ strain found in 47,[50] and may be stabilized by the allylic effect,[51,52] the tendency of electronegative substituents to prefer pseudoaxial orientations in cyclohexene rings. Evidence that hydroxyl group configuration is important can be

(40) For a related synthesis of piperidines from cyclopentene derivatives, see ref 19c.

(41) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(42) (a) Funk, R. L.; Vollhardt, K. P. C. *Synthesis* **1980**, 118. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.

(43) Paukstelis, J. V.; Macharia B. W. *J. Org. Chem.* **1973**, *38*, 646.

(44) The preference for the furanose form in 6-deoxy-5-keto-D-glucose has been demonstrated, showing the importance of the 6-hydroxyl group in this system for stabilizing the pyranose ring: Kiely, D. E.; Talhouk, J. W.; Riordan, J. M.; Gray, K. J. *J. Carbohydr. Chem.* **1983**, *2*, 427.

(45) (a) Stevens, R. V. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T.; Academic Press: San Diego, 1984; pp 275–298. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289 and references cited therein.

(46) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

(47) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Baumberger, F.; Vasella, A.; Schauer, R. *Helv. Chim. Acta* **1988**, *71*, 429.

(48) For examples of hydroxyl-directed reactions of borohydrides, see: (a) Lansbury, P. T.; Bieron, J. F.; Klein, M. *J. Am. Chem. Soc.* **1966**, *88*, 1477. (b) Akhtar, M.; Marsh, S. *J. Chem. Soc. C* **1966**, 937. (c) Yamada, S.; Koga, K. *Tetrahedron Lett.* **1967**, 1711. (d) Weissenberg, M.; Krinsky, P.; Glotter, E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 565. (e) Watanabe, H.; Kawanishi, T.; Miyamoto, K.; Kubodera, N.; Sasahara, K.; Ochi, K. *Steroids* **1992**, *57*, 444.

(49) For a recent review on internally-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(50) (a) $A_{1,2}$ strain: Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) For a recent example in piperidines, see ref 9b.

(51) (a) Ferrier, R. J.; Sankey, G. H. *J. Chem. Soc. C* **1966**, 2345. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1967**, 1417. (c) Lessard, J.; Tan, P. V. M.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. (d) Dodziuk, H. *Carbohydr. Res.* **1979**, *70*, 19. (e) Abraham, R. J.; Gottschalck, H.; Paulsen, H.; Thomas, W. A. *J. Chem. Soc.* **1965**, 6268. (f) For a specific example, see: Barili, P. L.; Berti, G.; D'Andrea, F.; Gaudiosi, A. *Carbohydr. Res.* **1991**, *212*, C5. It is not clear whether the effects attendant to cyclohexenes would also apply to charged cyclic iminium species.

seen in the 67:33 ratio observed for reductive amination of **6**, compared to the 96:4 ratio seen for **20**. Additionally, when azido ketone **51** was subjected to reductive amination under conditions of *catalytic hydrogenation* the manno product was observed almost exclusively, revealing a discrepancy between the soluble hydride and catalytic methods.[7r,s,x,dd]

Conclusions

Dicarbonyl sugars are useful substrates for the construction of pyrrolidine and piperidine azasugars. Key advantages for this method are brevity due to a lack of protecting group manipulations and the generally high degree of stereocontrol. Using this method, we have effected direct and efficient syntheses of 1-deoxynojirimycin (**1**), 1-deoxymannojirimycin (**5**), 2,5-anhydro-2,5-imino-D-glucitol (**10**), and related N-alkyl derivatives. This methodology could also be applied to the preparation of modified azasugars, such as 1,3-dideoxy-3-(halogeno)-nojirimycin compounds, by manipulation of **23** prior to oxidation. In principle, many different dicarbonyl sugars could be utilized as a reductive amination substrate to prepare a large number of structurally diverse azasugars.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 90, 300, 360, or 400 MHz while ^{13}C NMR spectra (both broad band and DEPT) were recorded at 100 MHz. Unless indicated otherwise for NMR analysis, $CDCl_3$, acetone-d_6, DMSO-d_6, or CD_3OD were used with tetramethylsilane as the internal standard, and D_2O was used with 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid (TSP), sodium salt as the internal standard. Abbreviations for NMR assignments are as follows: s, singlet; d, doublet; t, triplet; bs, broad singlet; br, broad; exc, exchangeable. Chemical-ionization mass spectra (CI-MS) were recorded with either methane or ammonia as the reagent gas. Fast atom bombardment mass spectra (FAB-MS) and high-resolution mass determinations were obtained at 8 keV and 2 mA. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN) or at the R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ. Melting points were measured in open capillary tubes with a Thomas-Hoover apparatus and are corrected. 5-Keto-D-fructose (**7**) was obtained from Schweitzerhall (South Plainfield, NJ, formerly Chemical Dynamics).

***N*-Benzhydryl-2,5-anhydro-2,5-imino-D-glucitol (9A) and *N*-Benzhydryl-2,5-anhydro-2,5-imino-D-mannitol (9B).** A suspension of **7** (50 g, 280 mmol) in MeOH (400 mL) was reacted with $NaBH_3CN$ (40 g, 476 mmol). A slurry of benzhydrylamine (42.0 mL, 234 mmol) in MeOH (120 mL) was treated with sufficient HOAc to bring the pH to 6–7 and was then added to the solution containing **7** over a 0.5-h period. An additional portion of $NaBH_3CN$ (20 g, 235 mmol) was added, and the mixture was stirred for 6 h at reflux. The solvent was then removed, the residue was treated with 10% Na_2CO_3 (ca. 100 mL), and the product was extracted 4× with $CHCl_3$. The $CHCl_3$ layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was then purified by preparative HPLC ($CHCl_3$/MeOH/NH_4OH, 88:11:1) to give ca. 50 g of the target compound (65%). Recrystallization from EtOAc gave 21.3 g (43% recrystallization recovery, 28% yield) of white needles (first crop), mp 152.5–154.5 °C. Recrystallization of this material on a smaller scale (ca. 1 g) resulted in a 65% recovery: ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.73 (q, J = 4.3, 4.0 Hz, 1 H), 3.03 (ddd, J = 6.3, 4.5, 0.3 Hz, 1 H), 3.92–3.99 (m, 2H), 4.16 (t, J = 5.4 Hz, exc, 1 H), 4.58 (t, J = 4.9 Hz, 1 H), 4.85 (d, J = 4.2 Hz, 1H), 4.87 (d, J = 4.9 Hz, 1H), 5.06 (s, 1 H), 7.14–7.35 (m, 6 H), 7.39–7.48 (m, 4 H): ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.5 (C-1), 61.0 (C-6), 64.0 (C-2), 68.8 (C-5)), 71.7 (Ph_2CH), 76.4 (C-3), 76.9 (C-4), 126–128 (8 C's), 142.7, 143.1; $[\alpha]^{22}_D$ 25.8° (*c* 1.2, MeOH). Anal. Calcd for $C_{19}N_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; O, 19.43. Found: C, 69.21; H, 7.03; N, 4.19; O, 19.61.

During the chromatography a faster moving material was rechromatographed under the same conditions and recrystallized (MeOH/CH_2Cl_2/pentane) to give 0.7 g of white crystals of **9B**: mp 172–179 °C; CI-MS (NH_3) *m/e* 330 (M + 1, 40%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.0–3.2 (m, 6H), 3.84 (br d, J = 4 Hz, 2 H), 4.58 (br s, exc, 2 H), 5.20 (m, Ph_2CH and 2OH's, 3 H), 7.1–7.4 (m, 8 H), 7.51 (d, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.9 ($2CH_2$, C-1, C-6), 67.0 (CH), 70.3 (2 CH, C-2, C-3), 79.1 (2 CH, C-3, C-4), 126–129.5 (8 CH), 143.2, 144.1. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; O, 19.43. Found: C, 68.79; H, 7.00; N, 4.14; O, 19.45.

2,5-Anhydro-2,5-imino-D-glucitol (10). A mixture of compound **9A** (8.40 g, 25.5 mmol) and 20% $Pd(OH)_2$/C (0.42 g) in MeOH (100 mL) was set shaking on a Parr apparatus under hydrogen (60 psig) overnight. This solution was then filtered and concentrated. Hexane (ca. 300 mL) was added, and the solvent was then removed from a white solid, which was washed with hexane (ca. 200 mL). The product was recrystallized from EtOH/CH_3CN to give 3.79 g (91%) of white needles of **10**: mp 139–142.5 °C; IR (KBr) 3100–3400, 2700–3000, 1420, 1367, 1317 cm^{-1}; CI-MS (NH_3) *m/e* 164 (M + 1, 100%); ^{1}H NMR (400 MHz, D_2O) δ 4.06 (dd, J = 4.8, 2.9 Hz, 1 H), 3.81 (dd, J = 5.0, 2.9 Hz, 1 H), 3.55–3.74 (m, 4 H), 3.25 (q, J = 5.0, 2.9 Hz, 1 H), 2.94 (q, J = ca. 4, 5 Hz, 1 H); ^{13}C NMR (100 MHz, D_2O) δ 62.9 (C-1), 63.4 (C-2), 65.0 (C-6), 67.4 (C-5), 80.1 (C-3), 81.9 (C-4); $[\alpha]^{22}_D$ 27.6 (*c* 1.3, MeOH). Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58; O, 39.22. Found: C, 44.21; H, 8.13; N, 8.54; O, 38.94.

2,5-Anhydro-2,5-imino-D-mannitol (2). A solution of compound **9B** (300 mg, 0.91 mmol) was dissolved in MeOH (10 mL) and treated with 20% $Pd(OH)_2$/C (60 mg). This suspension was shaken at 50 psig hydrogen on a Parr apparatus overnight. The solution was then filtered, and the filtrate was concentrated. The residue was triturated with hexane three times and then recrystallized from MeOH/ether/hexane to give **2** as a white powder (74 mg, 50%), whose physical properties compared favorably to those reported in the literature:[11] ^{13}C NMR (100 MHz, D_2O) δ 64.4 (C-2,5), 64.7 (C-1,6), 80.5 (C-3,4).

***N*-[(*R*)-α-Methylbenzyl]-2,5-anhydro-2,5-imino-D-glucitol and Related Sugar Diastereomers (11).** A solution of **7** (214 mg, 1.2 mmol) and (*R*)-PhCH(Me)NH_2 (129 μL, 1.0 mmol) in MeOH (20 mL) was adjusted to a pH of 6–7 by the addition of HOAc. $NaBH_3CN$ (168 mg, 2 mmol) was added, and the solution was set at reflux. After 6 h, the solution was cooled and 5 mL of 1 N NaOH was added. Because the product was soluble in water, the solution was concentrated to dryness and then the residue was purified on silica gel ($CHCl_3$/MeOH/NH_4OH, 90:9.5:0.5; broad band taken to minimize fractionation) to give **11** as a yellow oil assigned as a 79:19:2 mixture of **11A**:**11B**:**11C** by ^{13}C NMR analysis (90 mg, 34%). As in all cases in which ^{13}C NMR was used for the purposes of estimating product ratios, similar carbons in each structure (e.g., C-2 of one vs C-2 of the others) were used for comparison purposes. In this manner, inaccuracies resulting from differences in delay times were minimized: ^{13}C NMR (75 MHz, DMSO-d_6) δ nonaromatic resonances for **11A** 16.3, 50.3, 55.7, 62.35, 62.4, 77.6, 77.9; for **11B** 20.2, 55.7, 63.1, 70.3, 80.6; assigned for **13C** 59.0, 62.7, 77.0; MS (CI) *m/e* 268 (M + 1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (d, 3 H, major diastereomer), 1.39 (d, 3 H, minor diastereomer), 2.47 (m, ca. 0.2 H), 2.7 (m, ca. 0.8 H), 2.8–3.05 (m, ca. 2 H), 3.2–3.4 (m, 3 H), 3.54–3.8 (m, 2H), 3.9 (q, ca. 0.8 H), 4.15 (q, ca. 0.2 H), 4.3–5.0 (br m, 4H, exc). The presence of 0.4 mol equiv of MeOH was confirmed by a 1.2H singlet at δ 3.18. Anal. Calcd for $C_{14}H_{21}NO_4$·0.4MeOH·0.1H_2O: C, 61.34; H, 8.15; N, 4.97; H_2O, 0.64. Found: C, 61.42; H, 7.89; N, 5.25; H_2O, 0.49.

(52) The conformational preference in cyclohexenes for equatorial substitution is considerably weaker that that in cyclohexanes: (a) Anet, F. A. L. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH Publishers: New York, 1989; pp 1–45. (b) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternak, Th. *Helv. Chim. Acta* **1970**, *53*, 739.

N-(S)-(α-Methylbenzyl)-2,5-anhydro-2,5-imino-D-glucitol and Related Sugar Diastereomers (12). To a suspension of **7** (428 mg, 2.4 mmol) in MeOH (35 mL) was added (S)-PhCH(Me)NH_2 (258 μL, 2 mmol). The pH was adjusted to 7 by addition of HOAc, and $NaBH_3CN$ (336 mg, 4 mmol) was added. The solution was refluxed for 3 h, the solvent was removed, and the residue was treated with a minimal volume (ca. 2 mL) of 10% aqueous Na_2CO_3. The product was extracted 5× with $CHCl_3$, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel ($CHCl_3$/MeOH/NH_4OH, 80:18:2) to give **12** as a yellow oil assigned as a 92:8 mixture of **12A**:**12B** by ^1H NMR integration (210 mg, 40%): CI-MS (NH_3) *m/e* 268 (M + 1, 72); ^1H NMR (360 MHz, DMSO-d_6) δ 1.34 (d, 3 H, major diastereomer), 1.40 (d, 3 H, minor diastereomer), 2.7 (m, 1 H), 3.02–3.16 (m, 2 H), 3.24 (m, 1 H), 3.4 (m, 2 H), 3.54 (q, 1 H), 3.81 (q, 1 H), 4.02 (m, PhCH), 4.18 (m, exc), 4.38 (m, exc), 4.78 (m, exc), 4.81 (m, exc); ^{13}C NMR (100 MHz, DMSO-d_6) δ resonances for **12A** 18.3, 58.2, 59.7, 60.4, 62.0, 64.0, 75.5, 76.7, 126.7 (4C), 127.7, 128.4, 142.2; selected resonances for minor diastereomer assigned **12B** 20.6, 57.8, 60.9, 69.6, 80.4, 143.7; $[\alpha]^{22}_D$ −3.9° (*c* 0.8, MeOH). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24; O, 23.94. Found: C, 61.64; H, 8.00; N, 5.09; O, 23.95.

This material (100 mg) was dissolved in 1:1 HOAc/MeOH (ca. 5 mL) and treated with 20% $Pd(OH)_2/C$ (100 mg). The suspension was shaken on a Parr apparatus overnight (55 psig H_2) and then filtered through Celite and concentrated. Examination of the ^{13}C NMR revealed a ca. 9:1 mixture of **10** and D-mannitol diastereomer **2**.

N-(4-Fluorophenyl)-2,5-anhydro-2,5-imino-D-mannitol (13B) and Related Sugar Diastereomers. A solution of 4-fluoroaniline (30 g, 0.27 mol) and HOAc (15.46 mL) in MeOH (100 mL) was added to **7** (57.7 g, 0.324 mol) in MeOH (350 mL). To this suspension was added $NaBH_3CN$ (32.0 g, 0.5 mol), and the tan mixture was heated at reflux overnight, cooled, and then concentrated. The residue was dissolved in water (ca. 200 mL) and treated with Dowex 50W-X8 cation-exchange resin (500 mL). After being stirred for 2 h, the resin and solution were added to a column with a bed of additional resin (150 mL), and the supernatant was eluted. The resin was then washed with water (ca. 500 mL) and eluted with 1 N NH_4OH. Fractions containing the products were concentrated under reduced pressure and then purified on two Waters Prep 500 HPLC columns (hexane/iPrOH/NH_4OH, 65:34:1). The fastest eluting material was recrystallized from iPrOH/hexane to give 4.9 g of white needles of **13B** (7%): mp 140.5–142.5 °C; MS (FAB) *m/e* 258 (M + 1); IR 3395, 3261, 2927, 2892 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.32 (m, 1 H), 3.50 (m, 2 H), 3.62 (m, 1 H), 3.70 (m, 2 H), 4.0 (m, 1 H), 4.1 (m, 1 H), 4.54 (t, 1 H, exc), 4.82 (t, 1 H, exc), 5.04 (d, 1 H, exc), 5.22 (d, 1 H, exc), 6.72 (dd, 2 H), 7.0 (t, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 58.6 (C-1), 60.2 (C-6), 64.6 (2 CH), 65.0, 75.1, 113.2 and 113.3 (2 CH's, F splitting), 114.8 and 115.0 (2 CH's, F splitting), 114.9, 153.3, and 155.6 (CF, F splitting); $[\alpha]^{20}_D$ +8.4° (*c* 1.2, MeOH). Anal. Calcd for $C_{12}H_{16}FNO_4$: C, 56.03; H, 6.27; F, 7.38; N, 5.44. Found: C, 55.90; H, 6.21; F, 7.37; N, 5.32.

The middle eluting component was recrystallized twice from iPrOH/hexane to give stereochemically pure (>99%) **13A** (4.9 g, 7%) as determined by NMR spectral analysis: mp 153 °C (softening), 198 °C (browning), 205–207 °C (melting with decomposition); MS (FAB) *m/e* 258 (M + 1, 65); IR (KBr) 3389, 3336, 2929, 2829, 1514, 1343 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.50 (br s, 4 H), 3.70 (m, 2 H), 4.11 (d, 2 H), 4.87 (t, 2 H, exc), 5.32 (d, 2 H), 6.95 (m, 2 H), 7.01 (t, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 57.9 (2 CH_2's), 68.8 (C-2, C-5), 78.3 (C-3, C-4), 113.6 and 113.7 (2 CH's, F coupling), 115.3 and 115.5 (2 CH's, F coupling), 142.1, 152.5, and 154.8 (CF); $[\alpha]^{20}_D$ −10.5° (*c* 1.2, MeOH). Anal. Calcd for $C_{12}H_{16}FNO_4$: C, 56.03; H, 6.27; F, 7.38; N, 5.44. Found: C, 56.12, H, 6.37; F, 7.18; N, 5.26.

The slowest eluting component was recrystallized from iPrOH/hexane to give a 1.45-g sample of ca. 98% stereochemically pure iditol isomer **13C** (2%): mp 195 °C (browning), 211–213 °C; MS (FAB) *m/e* 258 (M + 1); ^1H NMR (400 MHz, DMSO-d_6) δ 3.39 (dd, 2 H), 3.54 (m, 2 H), 3.78 (br s, 2 H), 4.18 (t, 2 H, exc), 4.38 (t, 2 H), 5.20 (d, 2 H, exc), 6.61 (m, 2 H), 7.00 (t, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 56.5 (2 CH's), 59.3 (C-2, C-5), 61.9 (C-3, C-4), 113.9 and 114.0 (2 CH's, F coupling), 115.0 and 115.2 (2 CH's, F coupling), 142.0, 152.7 and 155.0 (CF, F coupling); $[\alpha]^{20}_D$ −18.2° (*c* 1.0, MeOH). Anal. Calcd for $C_{12}H_{16}FNO_4$: C, 56.03; H, 6.27; F, 7.38; N, 5.44. Found: C, 56.04; H, 6.36; F, 7.23; N, 5.34.

N-Stearyl-2,5-anhydro-2,5-imino-D-glucitol and Related Sugar Diastereomers (14). A suspension of stearylamine (11.0 g, 40.8 mmol) and HOAc (2.34 mL, 40.9 mmol) in MeOH (300 mL) was heated at reflux to effect dissolution. The solution was cooled to ambient temperature, reacted with **7** (8.7 g, 49.1 mmol) and $NaBH_3CN$ (5.22 g, 81.6 mmol), and heated at reflux (18 h). The solution was concentrated, and 10% aqueous $NaHCO_3$ (ca. 100 mL) was added. The product was extracted 2× with CH_2Cl_2, and the extracts were combined, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil which was purified by preparative HPLC ($CHCl_3$/MeOH/ NH_4OH, 88:11:1). The first fraction that contained product (3.6 g) was found to consist of a 62:31:7 mixture of the glucitol/mannitol/iditol diastereomers by ^{13}C NMR analysis. The second fraction that emerged (6.2 g) was recrystallized from MeOH/water and determined to be an 88:12 mixture of the glucitol/mannitol diastereomers: mp 85–93 °C; MS (FAB) *m/e* 416 (M + 1); the weighted average of the two fractions was 78:19:3; ^1H NMR (400 MHz, DMSO-d_6) δ 0.82 (t, 3 H), 1.18–1.5 (m, 32 H), 2.4–2.7 (m, 3 H), 2.8 (m, 1 H), 3.3–3.6 (m, 4 H), 3.8 (m, 2 H), 4.15 (br t, ca. 0.9 H, exc, glucitol OH), 4.36 (d, ca. 0.1 H, exc, mannitol OH), 4.48 (br t, ca. 0.9 H, exc, glucitol OH), 4.66–4.70 (m, ca. 2H, exc), 4.82 (d, ca. 0.1 H, exc, mannitol OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ resonances for **14A** 54.3, 60.0, 61.7, 66.4, 71.4, 76.0, 76.6; resonances for **14B** 46.50, 59.69, 69.24, 78.80. Anal. Calcd for $C_{24}H_{49}NO_4$: C, 69.35; H, 11.88; N, 3.37; O, 15.40. Found: C, 68.84; H, 11.92; N, 3.29; O, 15.35.

N-(3-Hydroxypropyl)-2,5-anhydro-2,5-imino-D-glucitol and Related Sugar Diastereomers (15). A suspension of **7** (24 g, 0.135 mol) in MeOH (350 mL) was treated with 3-hydroxypropylamine (8.6 mL, 0.112 mol) and HOAc (6.9 mL, 0.121 mmol) in MeOH (50 mL). $NaBH_3CN$ (12.6 g, 0.2 mol) was added, and the mixture was refluxed for 3 h. The solution was concentrated, and the residue was dissolved in water (ca. 100 mL) and treated with Dowex 50WX8 resin (400 g). After sitting overnight, this suspension was passed over a column of 100 g of resin, and the combined resin was washed with water (1 L). The column was eluted with 1 N NH_4OH (1.5 L), and fractions containing the product were lyophilized to give a brown oil which was purified on two Waters Prep 500 HPLC columns ($CHCl_3$/MeOH/NH_4OH, 65:33:2) to yield **15** as a ca. 57:39:4 mixture of glucitol/mannitol/iditol isomers by analysis of ^{13}C NMR (6.4 g, 26%); $[\alpha]^{20}_D$ −7.7° (*c* 1.9, MeOH); MS (FAB) *m/e* 222 (M + 1, 100), 190 (M − CH_2OH, 40); ^1H NMR (400 MHz, DMSO-d_6) δ 1.49 (br m, 2 H), 2.48–2.90 (m, 2 H), 3.3–3.5 (br m, 6 H), 3.5-3.7 (3 H), 3.8–4.9 (5 H, OH's); ^{13}C NMR (100 MHz, DMSO-d_6) resonances for glucitol δ 51.5, 60.1, 61.9, 66.8, 71.8, 76.1, 76.8; resonances for mannitol 54.3, 59.6, 69.1, 78.7; resonances for iditol 45.7, 51.5, 63.3, 76.3; common resonances 30.9, 58.7. Anal. Calcd for $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33; O, 36.16. Found: C, 47.87; H, 8.88; N, 6.06; O, 37.14.

N-(4-Fluorophenethyl)-2,5-anhydro-2,5-imino-D-glucitol Tosylate and Related Sugar Diastereomers (16). 4-Fluorophenethylamine hydrochloride (10 g, 57.0 mmol) was dissolved into water and treated with 1 N NaOH until the pH was ca. 10. This solution was extracted with $CHCl_3$ (3×), dried ($MgSO_4$), filtered, and concentrated to a clear oil which was dissolved in MeOH (ca. 300 mL) and reacted with HOAc (3.4 mL, 59.4 mmol), **7** (12.2 g, 68.3 mmol), and $NaBH_3CN$ (6.24 g, 0.1 mol). This solution was refluxed for 5 h under N_2 and then cooled and added to ca. 500 g of Dowex 50WX8 resin. After sitting overnight, the slurry was added to a column with 150 g of the resin and then eluted with water (150 mL) and 1 N NH_4OH (ca. 4 L). Fractions containing product were lyophilized to give a brown oil which was purified by preparative HPLC (iPrOH/hexane/NH_4OH, 65:34:1) to give **16** as a yellow oil. The bulk of this material was dissolved into iPrOH, filtered through a Millipore filter, treated with *p*-TsOH, and precipitated with hexane. The solid was recrystallized from iPrOH/Et_2O and then from CH_3CN/Et_2O to give, after drying at 65 °C, 5.3 g of **16** as a white solid (ca. 76:12:12 mixture of glucitol/mannitol/iditol isomers by ^{13}C NMR analysis): mp 121.5–125 °C; $[\alpha]^{20}_D$ +9.0° (*c* 1.1, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ key resonances only 7.1–7.2 (m, 4 H), 7.3 (m, 2 H), 7.51 (d, 2 H), 9.4 (ca. 0.75, exc), 9.7 (ca. 0.25 H, exc); ^{13}C

NMR (100 MHz, DMSO-d_6) key resonances for **16A** δ 28.6, 56.1, 57.0, 59.5, 70.1, 74.7, 74.9, 75.2; key resonances for **16B** 29.9, 57.1, 71.6; key resonances for **16C** 29.9, 59.6, 69.4; $[\alpha]^{20}_D$ 9.1° (*c* 1.0, MeOH). Anal. Calcd for $C_{14}H_{20}FNO_4 \cdot C_7H_8O_3S$: C, 55.13; H, 6.17; N, 3.06; F, 4.15; S, 7.01. Found: C, 55.07; H, 6.14; N, 3.02; F, 4.08; S, 6.87.

***N*-Butyl-2,5-anhydro-2,5-imino-D-glucitol Perchlorate (17).** A suspension of **7** (25 g, 140 mmol), $BuNH_2$ (11.56 mL, 113 mmol), $NaBH_3CN$ (12.6 g, 200 mmol), and HOAc (7.5 mL, 131 mmol) in MeOH (50 mL) was heated at reflux for 18 h. This solution was then added to Dowex 50WX8 ion-exchange resin (400 mL) in water (100 mL). After 2 h, this slurry was passed over a column containing 100 mL of resin, which was eluted with 1 L of water followed by 1 N NH_4OH (500 mL) and 0.5 N NH_4OH (ca. 500 mL). The basic eluants containing the product were combined and lyophilized. The resulting oil was purified on two preparative HPLC columns ($CHCl_3$/MeOH/NH_4OH, 70:28:2), and the product was converted to the perchlorate salt by treatment with 70% $HClO_4$ in iPrOH and trituration with ether. This solid was recrystallized from iPrOH/ether to give 10.45 g (30%) of a white solid of **17**: mp 101.5–103.5 °C; FAB-MS *m/e* 220 (M + 1); IR (KBr) 3378, 2964, 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, 3 H), 1.32 (m, 2 H), 1.7 (m, 2 H), 3.16 (m, 1 H), 3.3 (m, 2 H), 3.6 (m, 1 H), 3.7 (d, 2 H), 3.8–3.9 (m, 3 H), 4.0 (br s, 1 H), 5.08 (br s, 1 H, exc), 5.21 (br s, 1 H, exc), 5.7 (d, 1 H, exc), 5.78 (d, 1 H, exc); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.6 (CH_3), 19.3 (CH_2), 25.1 (CH_2), 54.8 (CH_2), 56.7 (C-1), 59.5 (C-6), 69.7 (C-2), 74.7 (CH), 74.9 (CH), 75.2 (C-4); $[\alpha]^{20}_D$ 23.5° (*c* 1.1, MeOH). Anal. Calcd for $C_{10}H_{21}NO_4 \cdot HClO_4$: C, 37.56; H, 6.93; N, 4.38; O, 40.03. Found: C, 37.41; H, 6.97; N, 4.28; O, 39.76.

***N*-(9-Fluorenyl)-2,5-anhydro-2,5-imino-D-glucitol (18).** A suspension of **7** (15.26 g, 86 mmol), 9-fluorenamine hydrochloride (14.98 g, 69 mmol), and $NaBH_3CN$ (8.96 g, 140 mmol) in MeOH (200 mL) was heated at reflux for 24 h. The solvent was then evaporated, and the residue was treated with 10% aqueous Na_2CO_3, and the product was extracted into $CHCl_3$ (3 vol). The combined organics were dried ($MgSO_4$), filtered, and concentrated, and the product was purified on two Waters Prep 500 HPLC columns ($CHCl_3$/MeOH/NH_4OH, 88:11:1) to give a tan solid of **18** which was further recrystallized twice from water (7.5 g, 33%): 158.5–160 °C; CI-MS (CH_4) 328 (M + 1); ^1H NMR (400 MHz, DMSO-d_6) δ 2.7–3.0 (br s, 2 H), 3.1 (br, 1 H), 3.2 (br s, 1 H), 3.4 (br s, 1 H), 3.5 (br s, 1 H), 3.87 (dm, 2 H), 4.05 (br s, 1 H, exc), 4.6 (br s, 1 H, exc), 4.78 (d, 1 H, exc), 5.0 (d, 1 H, exc), 5.18 (s, 1 H, exc), 7.22–7.40 (m, 4 H), 7.62 (d, 1 H), 7.7–7.9 (m, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.4 (CH_2), 61.4 (CH_2), 62.5 (CH), 64.9 (CH), 69.3 (CH), 75.8 (CH), 75.9 (CH), 119.6, 119.9 (2CH), 125.3, 125.3 (2CH), 126.7, 126.9 (2CH); 127.7, 127.8 (2CH); 139.1, 140.0 (2C); 144.7, 146.2 (2C); the resonances at δ 69.3 and 62.5 were broad suggesting hindered rotation; $[\alpha]^{20}_D$ –64.4° (*c* 1.1, MeOH). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; O, 13.55. Found: C, 69.54; H, 6.41; N, 4.18; O, 13.52.

***N*-(Diphenylamino)-2,5-anhydro-2,5-imino-D-glucitol (19).** A solution of **7** (12.84 g, 72 mmol), 1,1-diphenylhydrazine hydrochloride (13.24 g, 60 mmol), and $NaBH_3CN$ (7.68 g, 120 mmol) in MeOH (250 mL) was refluxed for 10 h. The solvent was removed, and the residue was treated with 10% aqueous Na_2CO_3 and extracted into $CHCl_3$ (3×). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The resultant purple tacky solid was purified on two Waters preparative HPLC columns and recrystallized from water to give 2.0 g of **19** (10%): mp 148.5–150.5 °C; CI-MS (CH_4) *m/e* 331 (M + 1, 60), 330 (M, 95), 299 (M – CH_2OH, 10), 169 (Ph_2N, 100); ^1H NMR (400 MHz, DMSO-d_6) δ 2.92 (br s, 1 H), 3.2 (m, 1 H), 3.32–3.52 (m, 3 H), 3.64–3.8 (m, 2 H), 3.83 (br s, 1 H), 4.4 (t, 1 H, exc), 4.77 (t, 1 H, exc), 4.81 (d, 1 H, exc), 4.87 (d, 1 H, exc), 6.5–7.5 (m, 10 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 57.1 (C-1), 60.6 (C-6), 65.5 (C-2), 69.4 (CH), 73.8 (CH), 76.1 (C-5), 113.5, 118, 126.5, 129–133, 138; the resonances in the aromatic region were very broad; $[\alpha]^{22}_D$ 40.0° (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48; O, 19.37. Found: C, 65.23; H, 6.77; N, 8.35; O, 19.65.

2,3,4,6-Tetra-*O*-acetyl-5-hydroxy-β-D-glucopyranose (22). Glucose pentaacetate (5.00 g, 12.8 mmol) and *N*-bromosuccinimide (3.42 g, 19.2 mmol) in CCl_4 (200 mL) was brought to reflux for 16 h using a 250W IR heat lamp.[32] The reaction mixture was then cooled and filtered, and the filtrate was washed with water, dried (Na_2SO_4), and concentrated to provide a yellow foam which was purified on flash silica gel (2:1 hexanes/EtOAc) to provide 2.40 g (40%) of the 5-bromo derivative: FAB-MS *m/e* 411/413 (MH^+ – HOAc), 389 (MH^+ – HBr); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.07 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.14 (s, 3 H), 4.31 (d, *J* =12.5 Hz, 1 H), 4.59 (d, *J*=12.3 Hz, 1 H), 5.26 (m, 2 H), 5.57 (t, *J* =9.9 Hz, 1 H), 6.23 (d, *J* =8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.3–20.9 (O_2CCH_3), 65.5 (C-6), 68.1, 69.2, 70.9 (C-2, C-3, C-4), 91.3 (C-1), 95.8 (C-5), 168.2–169.6 (C=O ester). To a solution of this material (12.0 g, 0.026 mol) in a water–acetone mixture (1:5, 600 mL) was added silver(I) oxide (23.7 g, 0.102 mmol), and the resulting mixture was stirred for 18 h. After the addition of a small amount of decolorizing charcoal, the mixture was filtered, and the precipitate was washed 3× with CH_2Cl_2. The washings and the filtrate were combined, the layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated to afford 6.57 g (74%) of **22** as a yellow foam: CI-MS (NH_3) *m/e* 364 (M + NH_4), 347 (M + 1), 287 (M – OAc, 100); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 4.04 (d, *J* = 11.8 Hz, 1 H, H-6), 4.15 (d, *J* = 11.9 Hz, 1 H, H-6), 5.00 (t, *J* = 9.0 Hz, 1 H, H-2 or H-3), 4.90–5.20 (br s, 1 H, OH), 5.22 (t, *J* = 9.9 Hz, 1 H, H-4), 5.29 (d, *J* = 7.9 Hz, 1 H, H-1), 5.52 (t, *J* = 9.9 Hz, 1 H, H-2 or H-3); ^1H NMR (D_2O) δ 2.21 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.18 (d, *J* = 11.9 Hz, 1 H, H-6), 4.38 (d, *J* = 11.9 Hz, 1 H, H-6), 5.16 (dd, *J* = 9.6, 8.1 Hz, 1 H, H-2 or H-3), 5.40 (d, *J* = 9.9 Hz, 1 H, H-1 or H-4), 5.49 (d, *J* = 8.1 Hz, 1 H, H-1 or H-4), 5.62 (t, *J* = 9.8 Hz, 1 H, H-2 or H-3); ^{13}C NMR ($CDCl_3$) δ 20.0–20.9 (O_2CCH_3), 64.8 (C-6), 69.5, 69.6, 73.0 (C-2, C-3, C-4), 90.7 (C-1), 169.4–171.6 (C=O ester), 194.0 (C=O aldehyde), 197.5 (C=O ketone); ^{13}C NMR (D_2O) δ 22.8–23.3 (O_2CCH_3), 64.5 (C-6), 72.5, 73.3, 79.6 (C-2, C-3, C-4), 92.6 (C-1), 97.7 (C-5), 175.3, 175.4, 175.7, 175.9 (C=O ester).

1,2-*O*-Isopropylidene-5-keto-α-D-glucofuranose (24). A suspension of 1,2-*O*-isopropylidene-α-D-glucofuranose (**23**; 10.0 g, 45.4 mmol) and dibutyltin oxide hemihydrate (25.1 g, 97.6 mmol) in MeOH (250 mL) was heated at reflux. After 1.5 h, the reaction was concentrated to provide a white solid, which was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C, and a solution of Br_2 (2.58 mL, 45.0 mmol) in CH_2Cl_2 (60 mL) was added over 5 min. After 10 min, the reaction mixture was concentrated and dried to a solid which was washed with hexanes to remove tin-containing species and then dissolved in $CHCl_3$. This solution was filtered and then subjected to chromatography on flash silica gel to provide 4.71 g (48%) of desired ketosugar **24** as a pale yellow-green solid whose spectral properties were identical to those reported by Tsuda.[33]

5-Keto-D-glucose (20). To a solution of **24** (4.60 g, 21.1 mmol) in water (46 mL) was added Dowex 50W-X8 beads (23 g). This suspension was stirred at 25 °C for 36 h and filtered, and the filtrate was lyophilized to provide 4.12 g of **20** as a pale pink foam. The ^1H NMR in D_2O indicated that this material was a mixture of interconverting forms with the β-pyranose predominating (70%): CI-MS (NH_3) *m/e* 196 [M + H_2O]; ^1H NMR (D_2O) δ 3.12 (t, *J* = 8.8 Hz, 1 H, H-2 or H-3), 3.40 (br t, *J* = 9.9 Hz, 2 H, H-6), 3.51 (d, *J* = 11.8 Hz, 1 H, H-4), 3.57 (t, *J* = 10.1 Hz, 1 H, H-2 or H-3), 4.83 (d, *J* = 8.2 Hz, 1 H, H-1); ^{13}C NMR (D_2O) δ 66.3, 73.0, 75.0, 77.2, 94.5, 100.0.

***N*-Benzhydryl-1-deoxynojirimycin (25A).** To a solution of benzhydrylamine (3.29 g, 0.0180 mol) and HOAc (1.08 g, 0.0180 mol) in MeOH (100 mL) at –78 °C was added 5-keto-D-glucose (**20**) (4.00 g, 0.0225 mol) in MeOH (100 mL) and $NaBH_3CN$ (2.82 g, 0.0449 mol). The reaction mixture was stirred at –78 °C for 2 h, warmed to ambient temperature, and concentrated after 20 h. Saturated aqueous Na_2CO_3 solution was added, the solution was extracted 3× with $CHCl_3$, and the extracts were combined, dried (Na_2SO_4), and concentrated to afford a yellow foam. Chromatographic purification on flash silica gel (5%–10% MeOH/$CHCl_3$) afforded **25A** as 4.06 g (69%) of a pale yellow foam: ^1H NMR (acetone-d_6) δ 1.85 (br t, *J* = 10.5 Hz, 1 H, H-1ax), 2.38 (br d, *J* = 9.2 Hz, 1 H, H-5), 2.93 (dd, *J* = 11.3, 4.3 Hz, 1 H, H-1eq), 3.06 (br t, *J* = 8.1 Hz, 1 H, H-3 or H-4), 3.51 (br m, 2 H, H-2 and H-3 or H-4), 3.67 (br t, *J* = 5.5 Hz, 1 H, 6-OH), 3.83 (br d, *J* = 4.5 Hz, 1 H, OH), 3.95 (br d, *J* = 10.1 Hz, 1 H, H-6),

3.99 (br d, J = 4.8 Hz, 1 H, OH), 4.11 (br s, 1 H, OH), 4.22 (br d, J = 11.5 Hz, 1 H, H-6), 5.71 (s, 1 H, C*H*Ph$_2$), 7.10–7.42 (m, 10 H); ^{13}C NMR (acetone-d_6) δ 52.5 (C-6), 60.9 (C-1), 65.1 (C-5 or *C*HPh$_2$) 65.2 (C-5 or *C*HPh$_2$), 71.1, 72.7, 79.8 (C-2, C-3, C-4), 127.2, 127.9, 128.7, 128.8, 131.2, 139.4, 143.8; CI-MS (CH_4) m/e 330 (M + 1), 312, 298, 262, 167; HRMS calcd for $C_{19}H_{23}NO_4$ (M^+) 329.162 708, found 329.165 146.

1-Deoxynojirimycin (1). A mixture of **25A** (1.00 g, 3.06 mmol) and 20% Pd(OH)$_2$/C (0.20 g) in MeOH (40 mL) was hydrogenated (60 psig) in a Parr apparatus for 24 h. The suspension was filtered through Celite, and the filtrate was concentrated to a light gray foam, which was washed with hexanes, dissolved in water (10 mL), and stirred over Dowex 50W-X8 ion-exchange beads (100 mL) for 2 h. The beads were then washed with 1 N NH_4OH (ca. 300 mL), and lyophilization afforded 0.49 g (99%) of 1 as a white foam. The ^{1}H NMR spectrum of the material was identical to that of an authentic sample (Sigma). Recrystallization from EtOH/CH_3CN gave 1 as very light tan crystals: mp 198–201 °C (lit.[7c] mp 198–202 °C). The HCl salt of 1 was recrystallized from EtOH/CH_3CN to afford fine white crystals: mp 210.5–211 °C (lit.[7k,x] mp 205, 206 °C). The ^{1}H NMR and ^{13}C NMR spectra of the HCl salt were identical to those of an authentic sample (Genzyme).

***N*-Benzyl-2,3,4,6-tetrabenzoyl-1-deoxynojirimycin (27A/27B).** A solution of **21** (0.10 g, 0.163 mmol) in MeOH (1.0 mL) was added to $NaBH_3CN$ (0.021 g, 0.327 mmol) at −78 °C, followed by addition of a 1.24 M solution of benzylamine acetate in MeOH (0.2 mL, 0.147 mmol). The reaction was stirred at −78 °C for 1 h, at 0 °C for 1 h, and then at ambient temperature for 22 h. The reaction mixture was poured into saturated aqueous Na_2CO_3 and then extracted 3× with $CHCl_3$. The extracts were combined, dried (Na_2SO_4), and concentrated to provide a yellow oil. Purification by preparative thin-layer chromatography (1% MeOH/$CHCl_3$) provided an inseparable mixture of **27A** and **27B** in a 1:2 ratio as 0.03 g (27%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$) gluco isomer **27A** δ 2.57 (br t, J = 10 Hz, 1 H, H-1ax), 3.22 (br d, J = 10 Hz, 1 H, H-5), 3.39 (br d, J = 10 Hz, 1 H, H-1eq), 3.64 (d, J = 12 Hz, 1 H, CH_2Ph), 4.29 (d, J = 12 Hz, 1 H, CH_2Ph), 4.47 (br d, J = 12 Hz, 1 H, H-6), 4.86 (d, J = 12 Hz, 1 H, H-6), 5.43 (m, 1 H, H-2), 5.73 (m, 1 H, H-4), 5.82 (t, J = 10 Hz, 1 H, H-3), 7.05–7.60 (m, 20 H), 7.80–8.15 (m, 5 H); ido isomer **27B** δ 3.20 (br t, J = 10.8 Hz, 1 H, H-1ax), 3.28 (dd, J = 10, 3 Hz, 1 H, H-1eq), 3.90 (m, 1 H, H-5), 4.05 (AB quartet, J = 12 Hz, 2 H, CH_2Ph), 4.72 (dd, J = 12, 2 Hz, 1 H, H-6), 4.90 (dd, J = 12, 5 Hz, 1 H, H-6), 5.50 (m, 1 H, H-2), 5.69 (dd, J = 10, 3 Hz, 1 H, H-4), 6.19 (t, J = 10 Hz, 1 H, H-3), 7.05–7.60 (m, 20H), 7.78–8.15 (m, 5H); the presence of the small 3-Hz coupling for H-4 supports the iditol assignment; FAB-MS (thio) m/e 670 (M + H); HRMS calcd for $C_{41}H_{35}NO_8$ (M^+) 669.223 692, found 669.232 284.

***N*-Benzyl-2,3,4,6-tetraacetyl-1-deoxynojirimycin (28A/28B).** This reaction was conducted in the same manner as for **27A/27B** using **22** (0.10 g, 0.275 mmol) in MeOH (1.0 mL), $NaBH_3CN$ (0.035 g, 0.550 mmol), and the 1.24 M solution of benzylamine acetate in MeOH (0.2 mL, 0.272 mmol) at −78 °C to provide *N*-benzyl-2,3,4,6-tetraacetyl-1-deoxynojirimycin (**28A**, 0.15 g, 13%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.20 (br t, J = 10.8 Hz, 1 H, H-1ax), 2.73 (br d, J = 9.6 Hz, 1 H, H-5 or H-1eq), 3.06 (dd, J = 11.5, 4.6 Hz, 1 H, H-5 or H-1eq), 3.44 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.08 (d, J = 13.8 Hz, 1 H, CH_2Ph), 4.18 (dd, J = 12.8, 3.6 Hz, 1 H, H-6), 4.37 (dd, J = 13.8, 2.7 Hz, 1 H, H-6), 4.99 (m, J = 14.7, 9.3 Hz, 1 H, H-2), 5.05 (dd, J= 9.1 Hz, 1 H, H-3 or H-4), 5.19 (dd, J = 9.3 Hz, 1 H, H-3 or H-4), 7.22–7.40 (m, 5 H); the two large couplings (>9 Hz) for H-4 indicate the gluco configuration; CI-MS (NH_3) m/e 422 (M + H); HRMS calcd for $C_{21}H_{27}NO_8$ (M^+) 421.17367, found 421.17547. In addition, 0.14 g (12%) of the iditol isomer (**28B**) was isolated as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.81 (br t, J = 11.0 Hz, 1 H, H-1ax), 2.98 (dd, J = 12.3, 5.4 Hz, 1 H, H-1eq), 3.51 (br s, 1 H), 3.87 (d, J = 13.4 Hz, 1 H), 3.98 (d, J = 13.4 Hz, 1 H), 4.34 (d, J = 9.5 Hz, 1 H, H-6), 4.51 (dd, J = 12.0, 6.5 Hz, 1 H), 5.02 (m, J = 14.7, 9.3 Hz, 1 H, H-2), 5.17 (dd, J = 9.8, 5.8 Hz, 1 H, H-4), 5.29 (t, J = 9.4 Hz, 1 H), 7.34 (m, 5H); CI-MS (NH_3) m/e 422 (M + H); HRMS calcd for $C_{21}H_{27}NO_8$ (M^+) 421.173 667, found 421.175 430.

***N*-(2,2-Diphenylethyl)-1-deoxynojirimycin (29A).** A solution of 2,2-diphenylethylamine (0.62 g, 3.14 mmol) and HOAc (0.18 mL, 3.14 mmol) in MeOH (18 mL) was added to 5-keto-D-glucose (**20**; 0.70 g, 3.93 mmol) in MeOH (18 mL) at −78 °C, followed by addition of $NaBH_3CN$ (0.49 g, 7.86 mmol). After 2 h at −78 °C followed by 18 h at ambient temperature, the reaction was concentrated and 10% aqueous Na_2CO_3 was added followed by extraction 3× with $CHCl_3$. The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and concentrated to a yellow foam which was purified on silica gel (5% MeOH/$CHCl_3$ to 7.5% MeOH/$CHCl_3$) giving 0.79 g (73%) of **29A** as a colorless foam; ^{1}H NMR (CD_3COCD_3) δ 2.05 (t, J = 12.6 Hz, 1 H, H-1ax), 2.13 (m, 1 H, H-5), 2.65 (br m, 1 H, exc), 2.74 (dd, J = 13.1, 5.0 Hz, 1 H, H-1eq), 2.95–3.30 (m, 4 H, H-3 or H-4 or H-5, N*C*H_2CHPh$_2$), 3.60–3.75 (m, 4 H), 3.92 (br s, 1 H, exc), 3.97 (br s, 1 H exc), 4.28 (dd, J = 10.0, 5.0 Hz, CH_2*C*HPh$_2$), 7.11 (m, 2 H), 7.22 (m, 4 H), 7.31 (d, J = 7.6 Hz, 2 H), 7.35 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (CD_3COCD_3) δ 50.1 (*C*HPh$_2$), 57.7, 58.6, 60.2 (C-1, C-6, *C*H_2CHPh$_2$), 68.3, 70.4, 71.9 (C-2, C-3, C-4), 80.4 (CH, C-5), 126.9, 127.0, 128.9, 129.0, 129.2, 129.2, 144.9, 145.1; ^{1}H NMR (DMSO-d_6) δ 1.83 (t, J = 10.6 Hz, 1 H, H-1ax), 2.00 (br m, 1 H, H-5), 2.71 (dd, J = 13.5, 4.8 Hz, 1 H, H-1eq), 2.88 (br m, 2 H, H-3 and H-4), 3.00 (br s, 1 H, H-5), 3.47 (m, 1 H, H-2), 3.73 (dd, J = 13.2, 10.4 Hz, 2 H, *C*H_2CHPh$_2$), 4.09 (t, J = 4.9 Hz, 1 H, exc), 4.23 (m, 1 H, CH_2*C*HPh$_2$), 4.59 (d, J = 4.5 Hz, 1 H, exc), 4.63 (d, J = 3.7 Hz, 1 H, exc), 4.67 (d, J = 3.7 Hz, 1 H, exc), 7.14 (m, 2 H), 7.28 (m, 6 H), 7.36 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 48.5 (CHPh$_2$), 57.4, 59.7 (C-1, C-6, and *C*H_2CHPh$_2$), 67.7, 69.2, 70.7, 79.1 (C-2, C-3, C-4, C-5), 125.9, 126.0, 127.9, 128.1, 128.2, 128.3, 144.1, 144.7 (C); $[\alpha]^{25}_D$ −30.0° (*c* 1.00, MeOH); FAB-MS (thio) m/e 344 (M + 1); HRMS calcd for $C_{21}H_{27}NO_8$ (M + 1) 344.186 183; obsd 344.185 699.

***N*-[(*R*)-α-Methylbenzyl]-1-deoxynojirimycin (30A).** This reaction was performed in the same manner as for **29A** using (*R*)-(+)-α-Ph(Me)NH_2 (0.27 g, 2.25 mmol) and HOAc (0.13 mL, 2.25 mmol) in MeOH (12 mL), 5-keto-D-glucose (**20**; 0.50 g, 2.81 mmol) in MeOH (12 mL), and $NaBH_3CN$ (0.35 g, 5.61 mmol). After the reaction was worked up, the resultant foam was dissolved in water (20 mL) followed by the addition of Dowex 50W-X8 beads (25 g). After 2 h, this suspension was filtered and the beads were washed with 1 N NH_4OH (300 mL). Lyophilization of the washes afforded **30A** as 0.48 g (79%) of a cream colored solid: mp 197.5–199.5 °C; ^{1}H NMR (CD_3OD) δ 1.32 (d, J = 6.9 Hz, 3 H, CH_3), 2.03 (t, J = 10.6 Hz, 1 H, H-1ax), 2.44 (br d, J = 9.2 Hz, 1 H, H-5), 2.54 (dd, J = 11.0, 4.7 Hz, 1 H, H-1eq), 3.10 (t, J = 8.8 Hz, 1 H, H-3 or H-4), 3.20 (br m, 1 H, H-2), 3.37 (t, J = 9.0 Hz, 1 H, H-3 or H-4), 3.95 (dd, J = 11.9, 3.1 Hz, 1 H, H-6), 4.07 (br d, J = 11.9 Hz, 1 H, H-6), 4.50 (q, J = 6.7 Hz, 1 H, C*H*Me), 7.18 (t, J = 7.1 Hz, 1 H), 7.29 (t, J = 7.4 Hz, 2 H), 7.47 (d, J = 7.6 Hz, 2H); ^{1}H NMR (DMSO-d_6) δ 1.21 (d, J = 6.7 Hz, 3 H, CH_3), 1.85 (t, J = 10.4 Hz, 1 H, H-1ax), 2.25–2.30 (m, 2 H, H-1eq, H-5), 2.85–3.15 (m, 3 H, H-2, H-3, H-4), 3.69 (m, 1 H, H-6), 3.92 (br d, J = 6.8 Hz, 1 H, H-6), 4.44 (br q, 2 H, C*H*Me, 1 H exc), 4.54 (d, J = 4.4 Hz, 1 H, exc), 4.67 (d, J = 4.1 Hz, 1 H, exc), 4.73 (d, J = 5.4 Hz, 1 H, exc), 7.19 (t, J =7.2 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.42 (d, J = 7.5 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 10.4 (CH_3), 51.4 (C-1), 55.0 (C-5), 61.2 (C-6), 66.8, 71.7, 73.0, 81.3 (C-2, C-3, C-4, CHMe), 127.8, 129.2, 129.5 (CH), 146.3 (C); $[\alpha]^{25}_D$ −18.3° (*c* 0.869, MeOH); HRMS calcd for $C_{14}H_{21}NO_4$ 267.147 058, obsd 267.147 064.

***N*-[(*S*)-α-Methylbenzyl]-1-deoxynojirimycin (31A).** A solution of (*S*)-(−)-α-methylbenzylamine (0.27 g, 2.25 mmol) and HOAc (0.13 mL, 2.25 mmol) in MeOH (12 mL) was added to 5-keto-D-glucose (**20**; 0.50 g, 2.81 mmol) in MeOH (12 mL) at −78 °C. To this solution was added $NaBH_3CN$ (0.35 g, 5.61 mmol), and the reaction was stirred at −78 °C for 2 h and then slowly warmed to ambient temperature. After 20 h of stirring, the solvent was removed to give a white foam which was dissolved in water (20 mL). Dowex 50W-X8 resin (20 g) was added, and this suspension was stirred for 2 d, filtered, and then washed with 1.0 N NH_4OH (350 mL), and the basic washings were lyophilized to provide 0.52 g of a white solid which was purified on flash silica gel (90:9:1 to 85:14:1 $CHCl_3$/MeOH/NH_4OH) to provide 0.08 g (13%) of iditol isomer **31B** as a cloudy film: ^{1}H NMR (CD_3OD) δ 1.38 (d, J = 6.7 Hz, 3 H, CH_3), 2.43 (br t, J = 9.7 Hz, 1 H, H-1ax), 2.75 (dd, J = 12.8, 3.3 Hz, 1 H, H-5), 3.28–3.43 (m, 3 H, H-1eq, H-2 and H-3), 3.75 (dd, J = 9.0, 5.5 Hz, 1H,

H-4), 3.83–3.92 (m, 2 H, H-6), 3.98 (q, J = 6.5 Hz, 1 H, *CH*MePh), 7.20 (t, J = 7.0 Hz, 1H), 7.29 (t, J = 7.4 Hz, 2 H), 7.35 (d, J = 7.5 Hz); ^{13}C NMR (CD_3OD) δ 22.0 (CH_3), 50.8 (C-1), 57.9 (C-6), 60.7, 61.7, 71.5, 73.5, 76.8 (C-2, C-3, C-4), 128.1, 128.2, 129.6, 147.6; $[\alpha]^{25}_D$ –52.9° (*c* 0.82, CH_3OH); FAB-MS (thio) *m/e* 290 (M + Na), 268 (M + H); HRMS calcd for $C_{14}H_{21}NO_4$ 267.147 058, obsd 267.146 790. Compound **31A** was isolated as 0.24 g (40%) of a white solid: ^{1}H NMR (CD_3OD) δ 1.49 (d, J = 6.9 Hz, 3 H, CH_3), 1.73 (t, J = 10.7 Hz, 1 H, H-1ax), 2.04 (br d, J = 9.0 Hz, 1 H, H-5), 2.92 (br dd, J = 9.0 Hz, 1 H, H-3 or H-4), 3.18 (dd, J = 11.0, 4.5 Hz, 1 H, H-1eq), 3.38 (dd, J = 9.1 Hz, 1 H, H-3 or H-4), 3.35–3.50 (br m, 1 H, H-2), 3.95 (d, J = 12.1 Hz, 1 H, H-6), 4.19 (d, J = 11.9 Hz, 1 H, H-6), 4.46 (q, J = 6.9 Hz, 1 H, *CH*MePh), 7.15–7.40 (m, 5 H, aromatic H); the two large couplings for H-4 (>9 Hz) indicate the gluco configuration; ^{13}C NMR (CD_3OD) δ 19.6 (CH_3), 51.4 (C-1), 56.4 (C-5), 59.6 (C-6), 65.9 (CHMePh), 71.4, 72.5, 80.5 (C-2, C-3, C-4), 128.2, 129.0, 129.7, 140.2. $[\alpha]^{25}_D$ –13.5° (*c* 0.78, CH_3OH); FAB-MS (thio) *m/e* 268 (M + H); HRMS calcd for $C_{14}H_{21}NO_4$ 267.147 058, obsd 267.146 820.

***N*-Butyl-1-deoxynojirimycin (32A).** This reaction was performed under the same conditions as for **31A** using butylamine (0.35 mL, 3.50 mmol) and HOAc (0.20 mL, 3.50 mmol) in MeOH (19.5 mL), 5-keto-D-glucose (**20**; 0.78 g, 4.38 mmol) in MeOH (19.5 mL), and $NaBH_3CN$ (0.55 g, 8.76 mmol). After lyophilization of the product from the Dowex 50W-X8 resin, the ninhydrin-positive fractions were combined and purified by column chromatography on flash silica gel (80:19:1–70:28:2 $CHCl_3$:MeOH:NH_4OH). *N*-Butyl-1-deoxynojirimycin (**32A**) was isolated as 0.42 g (55%) of a cream-colored powder: ^{1}H NMR (D_2O) δ 0.91 (t, J = 7.3 Hz, 3 H, CH_3), 1.29 (sextet, J = 7.3 Hz, 2 H, CH_2CH_3), 1.47 (br m, 2 H, NCH_2CH_2), 2.24 (br dd, J = 8.6, 2.4 Hz, 1 H, H-5), 2.29 (t, J = 11.2 Hz, 1 H, H-1ax), 2.61 (br m, 1 H, NCH_2CH_2), 2.75 (br m, 1 H, NCH_2CH_2), 3.03 (dd, J = 11.4, 4.9 Hz, 1 H, H-1eq), 3.26 (t, J = 9.2 Hz, 1 H, H-3 or H-4), 3.39 (t, J = 9.5 Hz, 1 H, H-3 or H-4), 3.35 (td, J = 10.0, 5.0 Hz, 1 H, H-2), 3.87 (AB quartet, J = 12.8, 2.3 Hz, 2 H, H-6); ^{13}C NMR (D_2O) δ 16.1 (CH_3), 23.0 (CH_2CH_3), 27.9 ($CH_2CH_2CH_3$), 54.6 (NCH_2 or C-1), 58.1-(NCH_2 or C-1), 60.4 (C-6), 67.9, 71.7, 73.0, 81.0 (C-2, C-3, C-4, C-5); $[\alpha]^{25}_D$ –19.1° (*c* 1.00, MeOH); FAB-MS (thio) *m/e* 238 (M + 23), 220 (M + 1), 202, 188; HRMS calcd for $C_{10}H_{21}NO_4$ (M + 1) 220.154 883, obsd 220.156 937. Further elution provided monoreductive amination–monoreduction product (**37**) as a tan solid (1:1 diastereomeric mixture, 90 mg, 10%): ^{1}H NMR (D_2O) δ 0.76 (t, J = 7.3 Hz, 3 H, Me), 1.20 (sextet, J = 7.3 Hz, 2 H, CH_2CH_3), 1.40 (pentet, J = 7.5 Hz, 2 H, NCH_2CH_2), 2.65 (m, 3 H, NCH_2CH_2, H-1), 2.77 (m, J = 6.0 Hz, 1 H, H-1), 3.44-3.72 (m, 5 H), 3.64 (m, 1 H); ^{13}C NMR (D_2O) δ 15.8 (CH_3), 22.4 (CH_2CH_3), 32.2, 32.3 ($CH_2CH_2CH_3$), 50.8 (NCH_2 or C-1), 52.8, 53.2 (NCH_2 or C-1), 65.5, 65.6 (CH_2OH), 71.2, 71.6, 72.9, 73.5, 73.7, 73.8, 74.4, 75.1 (C-2, C-3, C-4, C-5); $[\alpha]^{25}_D$ –10.9° (*c* 1.00, MeOH); CI-MS (NH_3) *m/e* 238 (M + H), 220 (M – 17); HRMS calcd for $C_{10}H_{24}NO_5$ 238.165 448, obsd 238.164 508.

***N*-(*N,N*-Diphenylamino)-1-deoxynojirimycin (33).** A solution of 1,1-diphenylhydrazine hydrochloride (0.99 g, 4.49 mmol) in MeOH (25 mL) was added to a solution of 5-keto-D-glucose (**20**; 1.00 g, 5.61 mmol) in MeOH (25 mL) at -78 °C, followed by addition of $NaBH_3CN$ (0.706 g, 11.2 mmol). The reaction mixture was stirred at –78 °C for 2 h and then slowly warmed to ambient temperature. After 66 h the reaction mixture was partially concentrated to a purple-pink residue to which was added saturated aqueous $NaHCO_3$. This solution was extracted 3× with $CHCl_3$, and the extracts were combined, dried (Na_2SO_4), and concentrated to provide a purple foam which was purified on flash silica gel (5% to 7.5% MeOH/$CHCl_3$) to provide 0.58 g total (39%) of two materials (0.29 g each) highly enriched (>90%) in either **33A** or **33B**. The iditol isomer **33B** was a white foam: ^{1}H NMR (CD_3COCD_3) δ 2.79 (dd, J = 11.5, 1.5 Hz, 1 H, H-1ax), 2.87 (dd, J = 11.6, 2.0 Hz, 1 H, H-1eq), 3.25 (br m, 1 H, H-5), 3.68 (t, J = 5.4 Hz, 1 H, exc), 3.91 (br m, 1 H, H-3 or H-4), 4.05 (m, J = 5.9, 2.9 Hz, 2 H, H-6), 4.11 (br m, 1 H, H-2), 4.21 (d, J = 3.7 Hz, 1 H, H-3 or H-4), 4.60 (d, J = 7.8 Hz, 1 H, exc), 4.83 (d, J = 6.6 Hz, 1 H, exc), 6.92 (br t, 2 H), 7.20 (d, J = 7.8 Hz, 4 H), 7.28 (t, J = 7.7 Hz, 4 H); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 1 H, 1H, exc), 1.89 (dd, J = 10.0, 2.0 Hz, 1 H, exc), 2.82 (br d, J = 10.5 Hz, 1 H, H-1), 3.04 (d, J = 11.7 Hz, 1 H, H-1), 3.15 (br s, 1 H, H-5), 3.81 (br s, 1 H, H-2, H-3, or H-4), 3.94 (t, J = 10.9 Hz, 1 H, H-6), 3.99 (br s, 1 H, H-2, H-3, or H-4), 4.27 (br s, 1 H, H-2, H-3, or H-4), 4.60 (br d, J = 10.3 Hz, 1 H, H-6), 4.71 (br d, J = 12.2 Hz, 1H, exc), 5.22 (s, 1 H, exc), 7.06 (m, 2 H), 7.18 (m, 4 H), 7.29 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 52.9 (C-1), 59.6 (C-5), 64.8 (C-6), 67.7, 71.7, 76.7 (C-2, C-3, C-4), 129.5; $[\alpha]^{25}_D$ +128.7° (*c* 1.00, MeOH); mass spectrum FAB-MS (thio) *m/e* 353 (M + 23), 331 (M + H), 330 (M+); HRMS calcd for $C_{18}H_{22}N_2O_4$ 330.157 957, obsd 330.156 967. In addition, the glucitol isomer **33A** was isolated as a colorless glass: ^{1}H NMR (CD_3COCD_3) δ 2.15 (t, J = 10.3 Hz, 1 H, H-1ax), 2.67 (br m, 1 H, H-5), 3.05 (m, 2 H, H-1eq, H-3 or H-4), 3.64 (m, 2 H, H-3 or H-4, 1 H, exc), 3.71 (br m, 1 H, H-2), 3.99 (br d, J = 4.2 Hz, 1 H, H-6), 4.04 (br m, 2 H, H-6, 1 H, exc), 4.16 (br s, 1 H, exc), 4.34 (br s, 1 H, exc), 6.58–7.65 (br m, 10 H); ^{13}C NMR ($CDCl_3$) δ 54.2 (C-1), 60.3 (C-6), 66.2 (C-5), 68.8, 70.5, 78.4 (C-2, C-3, C-4), 114.7, 119.8, 127.2, 128.9, 129.2, 129.6, 140.6, 149.1 (CH), 140.6, 149.1 (aromatic C-1); $[\alpha]^{25}_D$ –115.5° (*c* 0.87, MeOH); FAB-MS (thio) *m/e* 331 (M + H); HRMS calcd for $C_{18}H_{22}N_2O_4$, 330.157 957, obsd 330.156 281.

***N*-Dodecyl-1-deoxynojirimycin (34A).** This reaction was performed as for **33** using dodecylamine (0.92 g, 4.94 mmol) and HOAc (0.28 mL, 4.94 mmol) in MeOH (27.5 mL), 5-keto-D-glucose (**20**; 1.10 g, 6.17 mmol) in MeOH (27.5 mL), and $NaBH_3CN$ (0.78 g, 12.3 mmol). After reaction workup, the product was purified twice on flash silica gel (85:14:1–75:23:2 $CHCl_3$:MeOH:NH_4OH) affording 0.44 g (27%) of **34A** as a white solid: ^{1}H NMR (DMSO–D_2O) δ 0.74 (br t, J = 6.3 Hz, 3 H, CH_3), 1.12 (br s, 18 H, $(CH_2)_9$), 1.30 (br s, 2 H, CH_2CH_2N), 2.03 (br s, 2 H, H-1ax and NCH_{2a}), 2.68 (br s, 1 H, H-1eq or H-5), 2.77 (br d, 1 H, H-1eq or H-5), 2.88 (t, J = 8.8 Hz, 1 H, H-3 or H-4), 3.01 (t, J = 9.1 Hz, 1 H, H-3 or H-4), 3.19 (br m, 2 H, H-2 and NCH_{2b}), 3.50 (d, J = 10.9 Hz, 1 H, H-6), 3.61 (d, J = 10.4 Hz, 1 H, H-6); ^{1}H NMR (DMSO–DCl) δ 0.84 (br d, J = 6.6 Hz, 3 H, CH_3), 1.24 (br s, 18 H, $(CH_2)_9$), 1.63 (br s, 2 H, NCH_2CH_2), 2.90 (br t, J = 11.1 Hz, 1 H, H-1ax), 3.00 (br d, J = 10.0 Hz, 1 H, H-1eq), 3.10 (br m, 1 H, H-5), 3.25 (br t, J = 8.6 Hz, 3 H, NCH_2, H-3 or H-4), 3.42 (br t, J = 9.3 Hz, 1 H, H-3 or H-4), 3.67 (br m, 1 H, H-2), 3.80 (br d, J = 12.3 Hz, 1 H, H-6), 3.90 (br d, J = 12.6 Hz, 1 H, H-6); ^{13}C NMR (DMSO–D_2O) δ 13.9 (CH_3), 22.0, 22.1, 25.9, 28.4, 28.6, 28.7, 28.9, 31.2 (CH_2), 52.2, 53.0, 54.2 (C-1, C-6, $NCH_2(CH_2)_9$), 65.6, 65.8, 67.1, 75.9 (C-2, C-3, C-4, C-5); $[\alpha]^{25}_D$ –9.8° (*c* 1.00, MeOH); HRMS calcd for $C_{18}H_{37}NO_4$ 331.272 259, obsd 331.270 126.

***N*-(4-Fluorophenyl)-1-deoxynojirimycin (35A).** A solution of 4-fluoroaniline (0.43 mL, 4.58 mmol) and HOAc (0.26 mL, 4.58 mmol) in MeOH (25 mL) at –78 °C was added to **20** (1.02 g, 5.73 mmol) in MeOH (25 mL) at –78 °C, followed by addition of $NaBH_3CN$ (0.72 g, 11.5 mmol). After 1 h at –78 °C, and 23 h at ambient temperature, the mixture was concentrated to a beige foam, stirred with $CHCl_3$ (100 mL) to remove unreacted aniline, and then dissolved in water (75 mL) and stirred over Dowex 50W-X8 resin (10 g). After 2.5 h, the suspension was filtered and the beads were poured onto a column of the Dowex resin (15 g). The column was eluted with water (250 mL) and then with 1 N NH_4OH solution (250 mL). Fractions containing ninhydrin-positive components were combined and purified by chromatography on flash silica gel (95:4.5:1–75:23:2 $CHCl_3$:MeOH:NH_4OH) to provide two products. Compound **35A** was isolated as 0.41 g (35%) of a cream colored solid: ^{1}H NMR (D_2O) δ 2.70 (m, J = 11.0 Hz, 2 H, H-1ax, H-5), 3.04 (dd, J = 11.4, 5.0 Hz, 1 H, H-1eq), 3.25 (dd, J = 12.5, 2.4 Hz, 1 H, H-6), 3.32 (t, J = 9.2 Hz, 1 H, H-3 or H-4), 3.50 (t, J = 9.4 Hz, 1 H, H-3 or H-4), 3.56–3.70 (m, 2 H, H-2, H-6), 7.02 (t, J = 8.8 Hz, 2 H), 7.19 (dd, J = 9.0, 5.0 Hz, 2 H); ^{13}C NMR (D_2O) δ 60.2 (C-1 or C-6), 62.6 (C-1 or C-6), 68.2 (C-5), 72.1, 72.9, 81.0 (C-2, C-3, C-4), 118.8 (d, J = 22.8 Hz), 129.6 (d, J = 8.7 Hz), 148.0 (d, J = 2.7 Hz), 163.2 (d, J = 242.5 Hz); $[\alpha]^{25}_D$ +4.0° (*c* 1.00, MeOH); FAB-MS (thio) *m/e* 276 $(M + H_2O)^+$, 258 $(MH)^+$; HRMS calcd for $C_{12}H_{16}FNO_4$ 257.106 336, obsd 257.104 552. Compound **36** was isolated as 0.17 g (22%) of a cream-colored solid: ^{1}H NMR (D_2O) δ 3.09–3.22 (m, 2 H, H-1), 3.34 (t, J = 4.3 Hz, 1 H, H-1), 3.37 (t, J = 4.3 Hz, 1 H, H-1), 3.61–3.88 (m, 10 H), 3.98 (m, 2 H), 6.85 (m, 2 H), 7.04 (t, J = 9.0 Hz); ^{13}C NMR (D_2O) δ 49.5 (C-1), 50.2 (C-1), 65.5 (C-6), 72.2, 73.4, 73.5, 73.8, 74.0, 74.1, 74.4, 74.9 (C-2, C-3, C-4, C-5), 118.4, 118.6, 118.8, 118.9, 146.8, 159.3 (d, J = 240.3 Hz); $[\alpha]^{25}_D$ –8.5° (*c* 0.98, MeOH); CI-MS (NH_3) *m/e* 276 (M + H), 258 (M – 17); HRMS calcd for $C_{12}H_{18}FNO_5$ 275.116 901, obsd 275.118 469.

Methyl 2,3-*O*-Isopropylidene-5-keto-α-D-mannofuranoside (39). A suspension of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**38**; 2.0 g, 8.53 mmol) and dibutyltin oxide hemihydrate (4.72 g, 18.4 mmol) in MeOH (100 mL) was heated under argon at reflux for 1.5 h. The mixture was cooled and concentrated affording a white solid which was dissolved in CH_2Cl_2 (200 mL). This solution was cooled to 0 °C, and Br_2 (1.50 g, 9.39 mmol) in CH_2Cl_2 (20 mL) was added dropwise over a 5-min period. After a total of 10 min cyclohexene was added dropwise until the reaction decolorized. The mixture was then concentrated to give a pale green oil. Purification on flash silica gel ($CHCl_3$ to 1:1 $CHCl_3$/EtOAc to EtOAc) provided 1.98 g (75%) of ketosugar **39** as a waxy white solid: IR (KBr) 3453, 3402, 1729 cm^{-1}; ^1H NMR δ 1.28 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.96 (t, J = 5.0 Hz, 1 H, exc), 3.35 (s, 3 H, OCH_3), 4.48 (d, J = 4.7 Hz, 1 H, H-2 or H-3), 4.52 (d, J = 5.4 Hz, 1 H, H-2 or H-3), 4.59 (m, 2 H, H-6), 5.01 (dd, J = 5.7, 4.2 Hz, 1 H, H-4), 5.04 (s, 1 H, H-1); $[\alpha]^{25}_D$ −2.1 (*c* 1.00, CH_2Cl_2); HRMS calcd for $C_{10}H_{16}O_6$ 232.094 688, obsd 232.092 529.

5-Keto-D-mannose (6). To a solution of **39** (1.44 g, 6.20 mmol) in water (20 mL) was added Dowex 50W-X8 resin (6.8 g). This suspension was stirred at 25 °C for 24 h and then filtered and lyophilized to provide 1.31 g of a pale pink foam. The ^1H NMR in D_2O indicated that this material was a complex mixture of interconverting forms.

***N*-Benzhydryl-1-deoxymannojirimycin (40).** A solution of benzhydrylamine (0.55 g, 3.02 mmol) and HOAc (0.18 g, 3.02 mmol) in MeOH (50 mL) at −78 °C was added to 5-keto-D-mannose (**6**; 0.74 g, 3.79 mmol) in MeOH (50 mL) by cannulation, followed by addition of $NaBH_3CN$ (0.48 g, 7.58 mmol). The resulting mixture was stirred at −78 °C for 1 h and then warmed to ambient temperature. After 48 h, the reaction mixture was concentrated and treated with saturated aqueous K_2CO_3 solution and extracted with 3× with chloroform. The organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a lemon yellow foam. Purification on silica gel gave 0.15 g (15%) of the L-gulo isomer **41** as a colorless glass: ^1H NMR (CD_3COCD_3) δ 2.77 (m, 2 H), 3.55–3.60 (m, 2 H), 3.62–3.75 (m, 2 H), 3.85 (m, 1 H), 3.90 (m, 2 H), 3.96 (m, 1 H), 4.08–4.17 (m, 2 H), 5.43 (s, 1 H), 7.12–7.22 (m, 2 H), 7.22–7.35 (m, 4 H), 7.55 (d, J = 7.9 Hz); FAB-MS (thio) *m/e* 352 (M + Na), 330 (M + H), 298 (M − CH_2-OH). Further elution provided 0.29 g (29%) of **40** as a colorless glass: IR (KBr) 3389, 3387 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 2.80 (m, J = 8.1, 3.5 Hz, 1 H, H-5), 2.90 (dd, J = 12.0, 8.4 Hz, 1 H, H-1), 3.51 (d, J = 6.6 Hz, 1 H, exc), 3.64 (br s, 1 H, exc), 3.72 (br t, J = 5.1 Hz, 1 H, exc), 3.85 (br t, J = 4.5 Hz, 1 H, exc), 3.89 (br s, 2 H, H-6), 4.03 (m, 3 H, H-2, H-3), 5.43 (s, 1 H, C*H*Ph_2), 7.12–7.35 (br m, 6 H, aromatic H), 7.50 (br d, J = 7.1 Hz, 2 H, aromatic H), 7.56 (d, J = 7.5 Hz, 2 H, aromatic H); $[\alpha]^{25}_D$ +4.0° (*c* 1.00, MeOH); FAB-MS (thio) *m/e* 352 (M + Na), 330 (MH), 298 (M − CH_2OH); HRMS calcd for $C_{19}H_{23}NO_4$ 329.162 708, obsd 329.160 263.

1-Deoxymannojirimycin (5). To an ice-cooled solution of **40** (0.0143 g, 0.0435 mmol) was added 20% $Pd(OH)_2$/C (0.100 g). This mixture was shaken on a Parr hydrogenation apparatus at 50 psig for 30 h, filtered through Dicalite, and concentrated to provide a waxy white solid which was dissolved in water (80 mL). This solution was stirred with Dowex 50W-X8 resin (0.5 g) for 1 h, filtered, and then washed with 0.5 N NH_4OH solution which was concentrated on a rotary evaporator and lyophilized to afford **5** (7 mg, 100%) as a white powder. This material was stirred with HCl/MeOH and then concentrated to provide **5** as the corresponding HCl salt whose ^1H NMR and mass spectrum were identical to that of an authentic sample (Sigma). The comparison of **5** with authentic material also confirmed our assignment of the manno stereochemistry for **40**.

4-Hydroxy-5-oxo-1-hexanal (42). A solution of cyclopentenol **43** (0.47 g; 4.79 mmol) in MeOH (14 mL) was cooled to −78 °C, and ozone was bubbled through the reaction mixture. When it developed a blue color, ozone bubbling was continued for another 45 min. The mixture was purged with nitrogen (1 h), and then dimethyl sulfide (3.0 g, 49.0 mmol) was added. The solution was warmed to ambient temperature and stirred overnight. The reaction mixture was concentrated on a rotary evaporator to provide a lemon yellow oil. Chromatography on flash silica gel (1:1 hexanes:ethyl acetate) afforded 0.35 g (56%) of **42** as a very pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.89–2.02 (m, 4 H, H-2, H-3), 2.09 (m, 1 H, H-2 or H-3), 2.19 (s, 3 H, CH_3), 2.21–2.31 (m, 2 H, H-2 or H-3), 2.26 (s, 3 H, CH_3), 2.32-2.45 (m, 1 H, H-2 or H-3), 3.40–4.15 (br s, 1 H, exc), 4.50 (t, J = 8.0 Hz, 1 H), 4.63 (dd, J = 8.6, 4.8 Hz, 1 H), 5.64 (t, J = 2.8 Hz, 1 H, H-1), 5.73 (t, J = 2.2 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 28.2/28.3 (C-6), 28.9/29.3 (C-2 or C-3), 34.5/35.5 (C-2 or C-3), 85.3/86.7 (C-4), 101.9/102.1 (C-1), 221.6/217.2 (C-5); CI-MS (NH_3) *m/e* 130 (M + NH_4 − H_2O); HRMS calcd for $C_6H_{10}O_3$ − H (M − 1), 129.055 169, obsd for (M − 1) 129.054 810.

***cis*- and *trans*-*N*-Benzyhydryl-5-hydroxy-6-methylpiperidine (44/45).** A solution of benzhydrylamine (0.33 g, 1.78 mmol) and HOAc (0.11 g, 1.78 mmol) in MeOH (10 mL) was added to a solution of **42** (0.29 g, 2.23 mmol) in MeOH (10 mL) at −78 °C, followed by the addition of $NaBH_3CN$ (0.28 g, 4.46 mmol). The mixture was stirred at −78 °C for 1 h and then slowly warmed to ambient temperature. After 16 h, the reaction mixture was concentrated to a white foam. To this residue was added saturated aqueous Na_2CO_3 solution which was extracted with chloroform. The organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a yellow oil which was purified twice on flash silica gel columns ($CHCl_3$ to 3% MeOH/$CHCl_3$; 5% hexanes–$CHCl_3$ to $CHCl_3$). Fractions which contained the faster moving product were combined and purified on a tapered silica gel preparative TLC plate (1% MeOH/$CHCl_3$) to provide 0.05 g (8%) of one of the diastereomers as a colorless glass: CI-MS (CH_4) *m/e* 282 (M + H). In the same manner, fractions containing a slower moving material afforded 0.07 g (11%) of the other diastereomer as a cream color film: CI-MS (CH_4) *m/e* 282 (M + H).

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Supplementary Material Available: Key ^1H and ^{13}C NMR spectra (50 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.