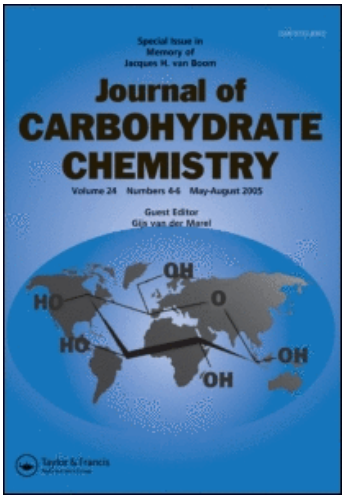

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Nucleophilic Opening of *N*-Carboalkoxy-2,3-anhydro-1-deoxymannojirimycin. A Useful Method for the Syntheses of 2-, 3- and 2,3-Disubstituted 1-Deoxynojirimycin Analogs

Ish K. Khanna[a]; Francis J. Koszyk[a]; Michael A. Stealey[a]; Richard M. Weier[a]; Janet Julien[a]; Richard A. Mueller[a]; Shashidhar N. Rao[a]; Lydia Swenton[a]; Daniel P. Getman[b]; Gary A. DeCrescenzo[b]; Robert M. Heintz[b]

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NUCLEOPHILIC OPENING OF *N*-CARBOALKOXY-2,3-ANHYDRO-1-DEOXYMANNOJIRIMYCIN. A USEFUL METHOD FOR THE SYNTHESES OF 2-, 3- AND 2,3-DISUBSTITUTED 1-DEOXYNOJIRIMYCIN ANALOGS

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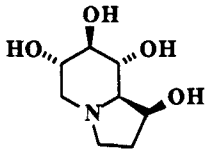
ABSTRACT

A useful methodology for the synthesis of a number of 2-, 3- and 2,3-disubstituted deoxynojirimycin analogs is reported. It has been found that the epoxides in stereoselectively synthesized *N*-carboalkoxy-2,3-anhydro-1-deoxymannojirimycins (**4** and **5**) react with *N*-, *S*- and *F*- nucleophiles to give a mixture of *gluco* and *altro* products. The 3-azido *altro* compound (**12b**) yields the desired *gluco* derivative (**40**) by oxidation, *in situ* epimerization at C-3, followed by stereoselective reduction of the carbonyl group. The azido intermediate (**12a**) affords the 2,3-diazido *gluco* compound (**51**) by double inversion at C-3. Attempts have been made to understand the factors contributing to the opening of epoxides (**4, 5** and **9**) by different nucleophiles.

INTRODUCTION

Polyhydroxylated piperidine, pyrrolidine, and octahydroindolizine (such as castanospermine **1**) alkaloids are potentially useful antiviral agents.[1,2] They are inhibitors of glycosidase activity and are believed to block HIV replication by modifying the glycosylation of the viral envelope protein gp120. *N*-Butyl-1-deoxynojirimycin (**2**) has been evaluated for the treatment of AIDS.[2] In efforts to establish the pharmacophore model and to improve the potency of **2**, structural modifications at positions 2 and 3 have been extensively studied in our laboratories. This paper investigates the ring opening of the 2,3-epoxides (**4** and **5**) with a variety of nucleophiles and expands its utility to the syntheses of a number of 2- and 3-substituted deoxynojirimycin analogs.



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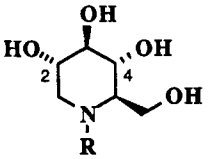
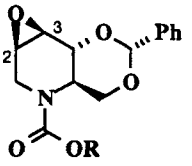


2 R = Bu
3 R = H



4 R = Bn
5 R = *t*-Bu

RESULTS AND DISCUSSION

Stereoselective synthesis of epoxides (4, 5 and 9). The key intermediate **4** needed for our studies was routinely prepared on a multi-gram scale in a regio- and stereoselective fashion from 1-deoxynojirimycin (**3**) as illustrated in Scheme I. The synthesis of the diol **7** and its regioselective tosylation at C-2 has been described previously from these laboratories.[3] Treatment of the tosylate **8** with sodium hydride (4 molar equivalents) in anhydrous tetrahydrofuran (25 °C, 8 h) gave the desired epoxide **4** (75%). The other epoxides (**5, 9 - 11**) investigated in our studies were prepared from **4** by hydrogenolysis (Pd/C, H_2) followed by acylation or alkylation of the resulting intermediate **9** (see experimental).

Nucleophilic opening of the epoxides 4 and 5. On heating a solution of **4** in 2-methoxyethanol with sodium azide and ammonium chloride for 36 h at 120 °C, two products **12a** and **12b** (Table 1), were isolated in yields of 44 and 40%, respectively. The diastereomers were readily separable on a multi-gram scale by chromatography (silica gel, hexane/ethyl acetate 8:2). The configurations of the C-2 and C-3 substituents were assigned by ^1H NMR on the basis of the proton splitting patterns.[17] Hasegawa and coworkers have also reported[7] the opening of the epoxide **5** with azide, yielding results similar to those observed by us.

Scheme I

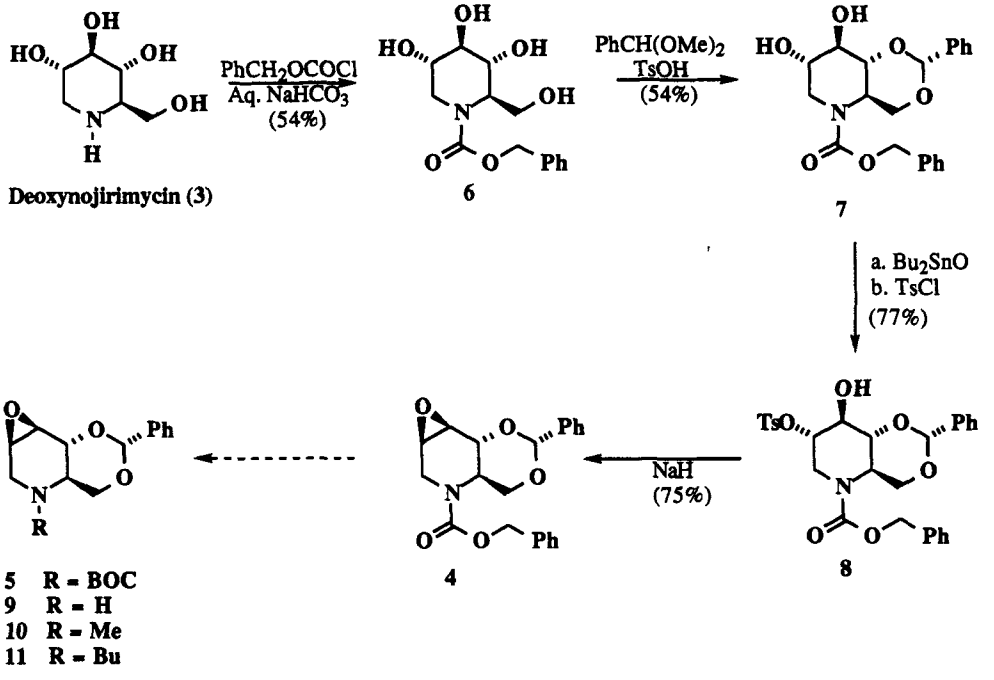
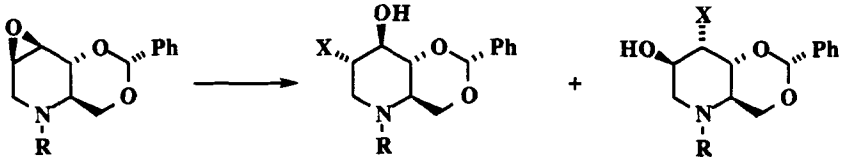


Table 1. Studies on Nucleophilic Opening of Epoxides 4 and 5



Epoxide	Nucleophilic Agent	Diastereomeric Ratio Products (a/b)	Chem Yield (a + b, %)[a]
4 (R = Cbz)	NaN_3	**12a/12b** = 52/48	84
4 (R = Cbz)	i-$Pr_2NH/3HF$	**13a/13b** = 74/26	50
5 (R = BOC)	NaSMe	**14a/14b** = 64/36	73
5 (R = BOC)	NaSPh	**15a/15b** = 58/42	96
4 (R = Cbz)	$Me_2NCH_2CH_2NH_2$	**16a/16b** = 0/100	76
4 (R = Cbz)	$H_2N(CH_2)3CH_3$	**17a/17b** = 0/100	72[b]

a. combined isolated yields; b. based on conversion of starting material.

In the course of our studies, the epoxide opening was tried with other nucleophiles as shown in Table 1. The ratio of the *gluco* to *altro* products in the epoxide opening reaction seems to depend on the nucleophile chosen and the conditions used. On heating a mixture of **4** and diisopropylamine trihydrogenfluoride[5] (5 molar equiv, 125 °C, 70 h), the C_2-F derivative with the *gluco* configuration was formed preferentially (**13a/13b** = 2.8). The reaction of sulfur nucleophiles with epoxide **4** is much faster but also causes removal of the Cbz group. For example, on heating a mixture of **4** in DMF with NaSMe (5 equiv, 90 °C, 1 h), the non-carbamate *gluco* product **22a** was preferentially formed (**22a/22b** = 1.8, combined chemical yield = 90%). The reaction of **4** with 1 molar equiv of NaSMe (65 °C, 24 h) was slower and gave the deprotected epoxide **9** (19%) in addition to a complex mixture of C-2 and C-3 opened products with or without the presence of Cbz group, suggesting that the opening of the epoxide ring in **4** was competing with the cleavage of Cbz group. For a better comparison with other nucleophiles, it was desirable that the epoxide opening be carried out under conditions which would not cleave the carbamate group. The reactions of sulfur nucleophiles (NaSMe and NaSPh) with the *N*-BOC protected epoxide **5** (2-methoxy ethanol, 5 equiv NaSR, reflux, 1 h) proved useful. Under these conditions, the *N*-BOC was not cleaved and the reaction favored formation of the *gluco* products (**14a/14b** = 1.8 and **15a/15b** = 1.4). The nucleophilic opening of the epoxide **4** with amines, (e.g., $H_2N(CH_2)_3CH_3$, $Me_2NCH_2CH_2NH_2$) behaved very differently, giving mainly the C-3 opened *altro* products.

Mechanistic discussions on the opening of epoxides 4 and 5. The results on the nucleophilic opening of epoxides **4** and **5** are not easy to explain, mainly because of the limitations involved in addressing the transition state. Molecular mechanics calculations[4,15] performed on **4** (Figure 1) reveal that the benzylidine exists in a chair while the piperidine has a distorted or skewed-boat conformation. It is well established that in general the epoxides derived from cyclohexane or pyranose ring systems react with nucleophiles to give *trans*-diaxial products.[8] However, in conformationally rigid, unsymmetrical epoxides, exceptions to the above rule, yielding diequatorial products, have been reported.[9] The regiochemistry of ring opening in substituted cyclohexene oxides has been studied[18] and is influenced by the reaction conditions (chelation and non-chelation) and the nucleophile chosen. Szmuszkovicz and coworkers reported[10] that the ring opening of a 2,3-epoxide derived from *N*-carbobenzoxypiperidine (**18**) with secondary amines gives the *trans*-diaxial products. On the other hand, as reported by Hasegawa and coworkers,[7] the reaction of epoxide **5** with azide gives a mixture of diastereomers with the diequatorial product favored over the *trans*-diaxial product by a ratio of approximately 2/1. It was suggested that the azide attacked C-2 preferentially because it was less hindered.

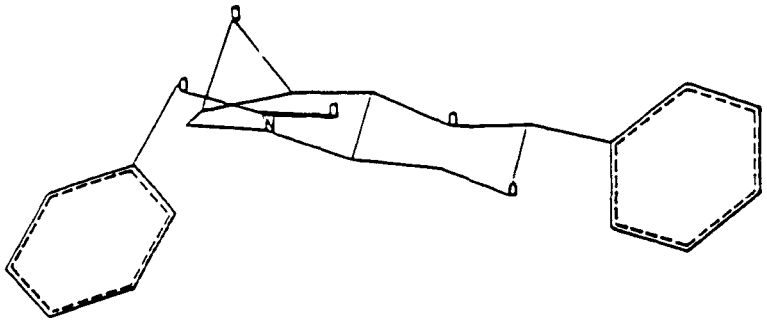
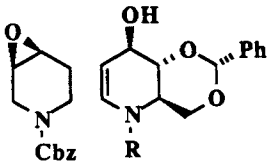


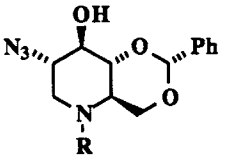
Figure 1. Computer graphics illustration of the energy optimized[6] structure 4

The results from Table 1 clearly indicate that the nucleophilic opening of epoxide **4** with primary amines (such as $Me_2NCH_2CH_2NH_2$ and $NH_2(CH_2)_3CH_3$) shows a strong preference for *altro*- products. These reactions, consistent with the Furst-Plattner rule,[8] are stereoelectronically controlled S_N2 reactions, yielding mainly the *trans*-diaxial products **16b** and **17b**, respectively. The epoxide opening reactions with NaN_3, NaSMe and NaSPh show some preference for *gluco* products (diequatorial attack). These charged nucleophiles (N_3^- and RS^-) may be solvated and would therefore generate bulkier reactive species than the neutral amines. The outcome of epoxide opening, in these cases, may be dictated by the size of the nucleophile and its ability to solvate. In the formation of fluoro derivatives (**13a/13b**), the epoxide cleavage is acid catalysed (HF/i-Pr_2NH) and it would be reasonable to assume that the reaction is an S_N1 type as both F^- and i-Pr_2NH are also weak nucleophiles.

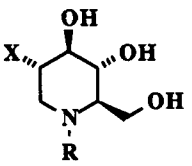
The reaction of epoxide **4** with carbon nucleophiles was also examined. For example, treatment of **4** with $Me_2Cu(CN)Li$ (2 molar equiv, -70 to 0 °C in 1 h and then 0 °C for 5 h) involves carbamate-induced complexation with the organometallic reagent, resulting in a directed deprotonation - epoxide opening to yield **19** (13%). Using an excess of $Me_2Cu(CN)Li$ (6 equiv), a mixture of **19** (15%) and **20** (19%) was isolated. Similarly, the reaction of $Me_2Cu(CN)Li$ (2 equiv, -50 to 25 °C for 4 h and then 25 °C for 18 h) with epoxide **9** gave the unexpected product **10** (28%). The mechanism for this unusual reaction is unclear and requires further investigation. However, these studies indicate that the epoxide is fairly stable to attack by carbon nucleophiles under these reaction conditions. This is further evident from the reaction of the *N*-alkyl epoxide **11** with $Me_2Cu(CN)Li$ in the absence or the presence of Lewis acid (BF_3-Et_2O), which resulted mainly in the recovery of starting material.



18 19 R = Cbz
20 R = COMe



24 R = Bu

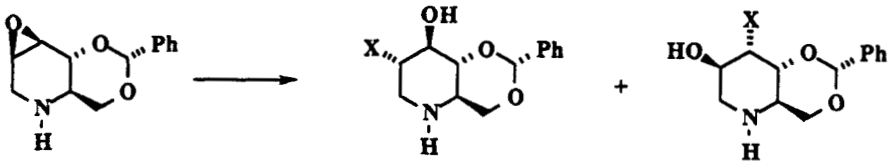


25 X = N_3, R = H
26 X = N_3, R = Bu
27 X = F, R = H
28 X = SMe, R = H
29 X = SMe, R = Bu

Nucleophilic opening of the epoxide 9. The role of *N*-substitution in the epoxide cleavage was also studied using the non-carbamate epoxide **9** (Table 2). The reaction of **9** with sodium azide and ammonium chloride in 2-methoxyethanol (120 °C, 24 h) gave mainly the C-3 opened *altro* product (**21a/21b** = 16/84). Similar results were also obtained from the reaction of **9** with sodium thiomethoxide (**22a/22b** = 19/81). This change in the stereochemical outcome of a nucleophilic attack on carbamate *vs* non-carbamate epoxides (**4** and **5** *vs* **9**) was unexpected, and the following attempts have been made to rationalize these results. It was anticipated that, with the removal of the carbamate group, the epoxide **9** would have a conformation different from **4**. However, molecular mechanics calculations done on **9** (overlap of **4** and **9** is shown in Figure 2) indicate that there is no significant difference in their conformations and thus the epoxide opening should favor similar product distributions. *Ab initio* calculations[11] performed on the intermediates (**23a**, **23b**, **23c** and **23d**) suggest that **23d** with the NH flipped into the *axial* position is the lowest energy conformer and is stabilized by electrostatic attraction between the NH and the negatively charged oxygen at C-3, the interatomic distance (N---H---O) for **23d** being 2.6 Å. The isomer **23d** is 5 kcals/mole lower in energy compared to **23c** and is 9.5 and 14 kcals/mole lower in energy compared to **23a** and **23b**, respectively. On the other hand, in the case of *N*-carbamate epoxides (**4** and **5**), there is electrostatic repulsion between the polarized carbamate oxygens and the oxygen anion at C-2. These polar and hydrogen bonding differences between carbamate (**4** and **5**) and non-carbamate (**9**) epoxides, may favor different transition states for the two epoxides and hence explain the experimental results.

Synthesis of 2-substituted 1-deoxynojirimycin derivatives.[16] The compound **12a** was used to synthesize 1-deoxynojirimycin derivatives **25** and **26** by a three-step sequence involving hydrolysis of the carbamate group (3.5% NaOH in EtOH/H_2O 1/1, 70 °C, 18 h, 93%, intermediate **21a**), reductive amination (e.g., PrCHO, $NaCNBH_3$, MeOH, AcOH, 25 °C, 20 h, 88%, intermediate **24**) followed by acid hydrolysis [CF_3CO_2H/H_2O (4/1), 25 °C, 60 - 75%] of the intermediates **21a** and **24**. The fluoro intermediate **13a** was converted directly to the deoxynojirimycin derivative **27** by catalytic hydrogenation (Pd/C, 50 psi, H_2, 50 °C, 35%). On the other hand, the thiomethyl

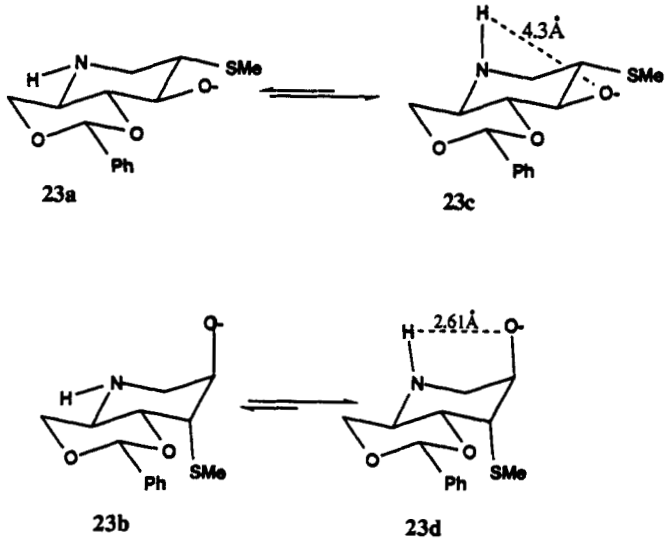
Table 2. Studies on the Nucleophilic Opening of Epoxide 9



9 **21a/22a** **21b/22b**

Nucleophilic Agent	Diastereomeric Ratio Products (a/b)	Chem Yield (a + b,%)[a]
NaN_3	**21a/21b** = 16/84	57
NaSMe	**22a/22b** = 19/81	45

a. isolated yield



23a **23c**

23b **23d**

deoxynojirimycin derivative **28** was synthesized from **22a** using solvolytic conditions (95% EtOH, cat. TsOH, 98%). The *N*-butyl analog (**29**) was synthesized from **28** by using a reductive amination procedure (PrCHO, $NaCNBH_3$, MeOH, AcOH, 25 °C, 20 h, 63%).

The syntheses of 2-amino, 2-alkylamino and 2-acylamino derivatives (**35 - 38**) of *N*-butyl-1-deoxynojirimycin were accomplished by starting from the 2-azido intermediate

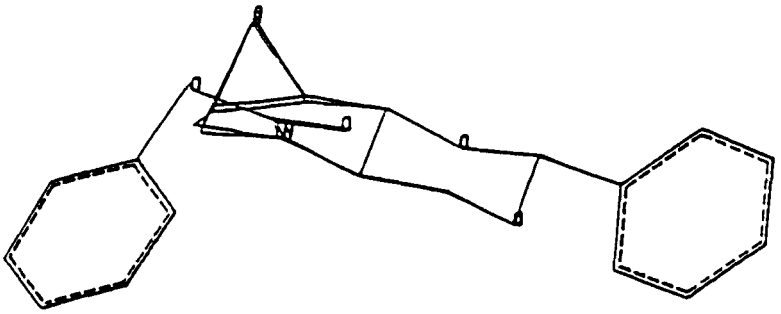


Figure 2. Overlap of the energy optimized structures 4 and 9

24 (Scheme II). The catalytic reduction of the azido group (Pd/C, H_2, 5 psi), followed by alkylation or acylation, gave the key intermediates (**30** - **34**), which were deprotected to the desired analogs (**35** - **38**). Syntheses and applications of 2-amino derivatives of deoxynojirimycin have also been reported by Nippon Shinyaku and Bayer in the patent literature.[14]

Synthesis of 3-substituted 1-deoxynojirimycin derivatives. The 3-amino-1-deoxynojirimycin derivative **44** was synthesized by starting with the 3-azido *altro* intermediate **12b** (Scheme III). Swern oxidation of the C-2 hydroxyl of **12b** (DMSO - trifuoroacetic anhydride, -70 to -30 °C in 4 h, -30 °C for 1 h) followed by equilibration with NEt_3 (-70 to 25 °C in 1 h, 25 °C for 20 h) yielded the thermodynamically more stable, all equatorially substituted compound **39** in 86% yield. The reduction of the 2-keto group of **39** to the 2-hydroxyl yields a mixture of *gluco* (**40**) and *manno* (**41**) compounds (see Table III). With sodium borohydride, essentially a 1:1 mixture of stereoisomers was obtained whereas with the bulkier DIBAL-H, the *gluco* isomer predominates (86:14). The reduction of **39** with lithium methylborohydride[12] as well as with Yamamoto's reagent[13] gave lower isolated yields of the product.

The 3-amino-1-deoxynojirimycin derivative **44** was synthesized from the 3-azido intermediate **40** in the same manner as for the 2-amino analog. The sequence involved hydrolysis of the carbamate group in **40** ($EtOH/H_2O$, NaOH, 75 °C, 20 h, 91%) and reduction of the resulting azide (**42**) using catalytic hydrogenation (4% Pd/C, 5 psi, H_2, 93%), followed by acid cleavage (CF_3CO_2H/H_2O, 22 °C, 24 h, 32%) of the benzylidine group in **43**.

Synthesis of 2,3-disubstituted 1-deoxynojirimycin derivatives. The 2,3-diamino compound **56** was synthesized from the intermediate **12a**. The displacement

Scheme II

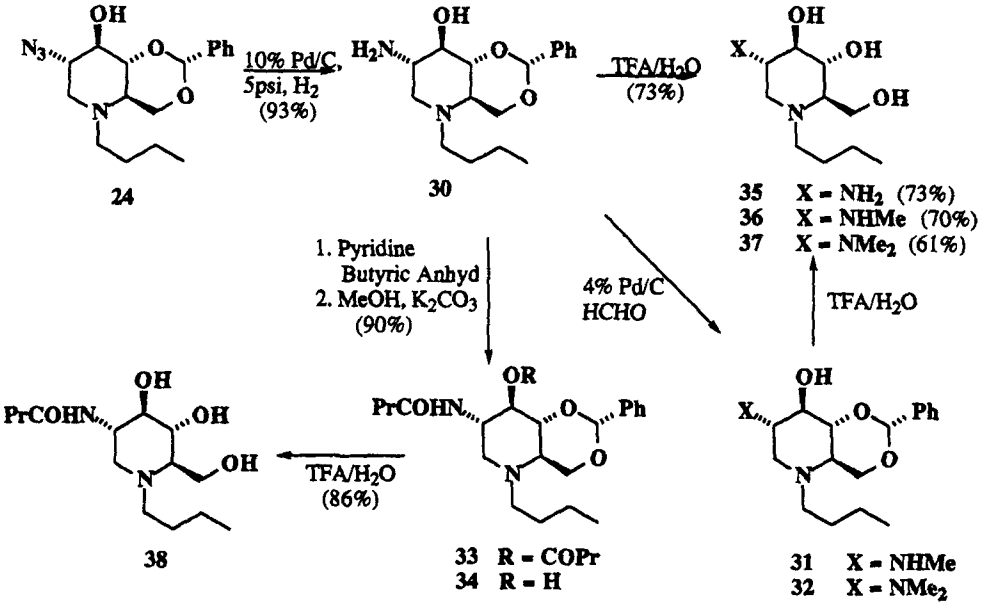
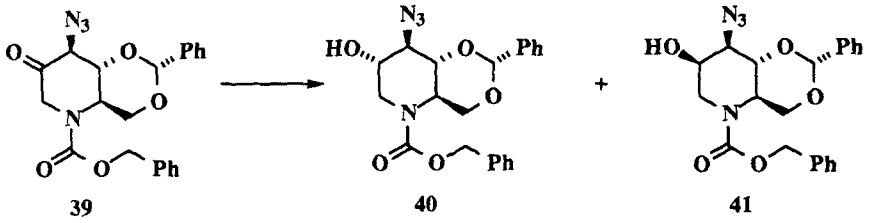


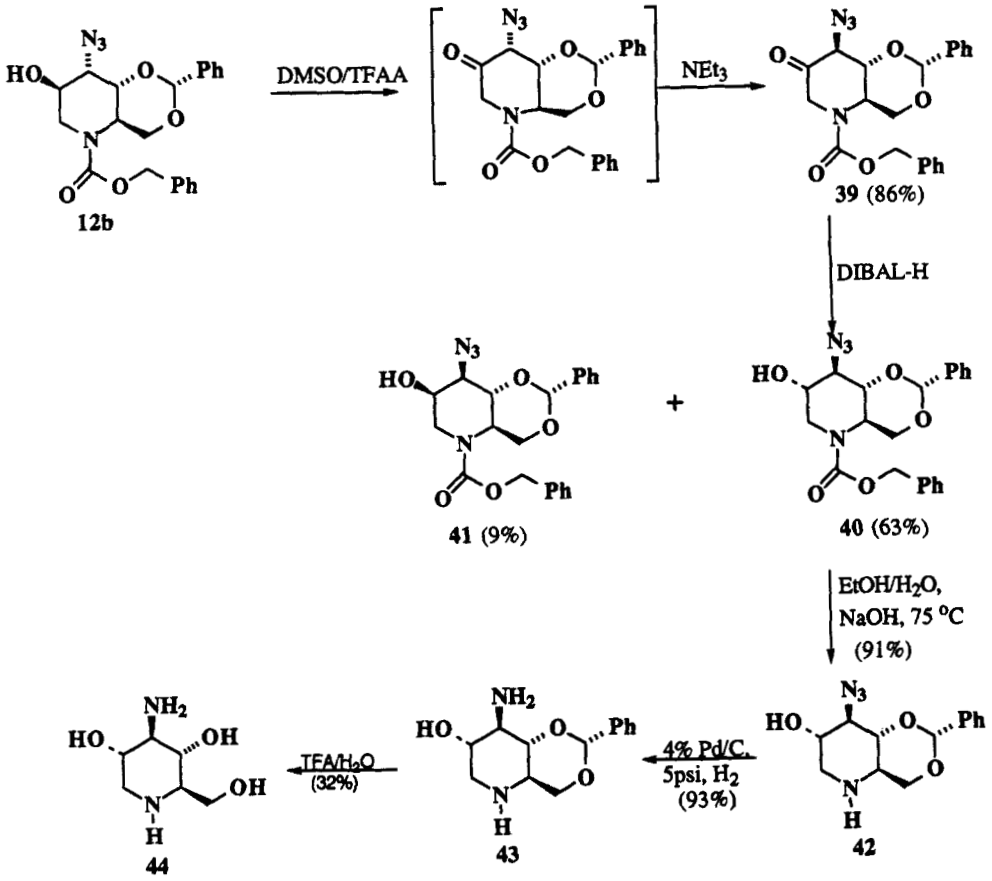
Table 3. Studies on Stereoselective Reduction of 39



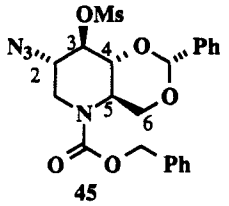
Reducing Agent	Conditions	Relative Yield (40/41)	Chem Yield (40+41, %)
$NaBH_4$	THF/MeOH (4/1), -15 - 0 °C, 30 min	52/48	67
$LiBH_3Me$	-70 to -20 °C, 3 h	37/63	20
Yamamoto Reagent[a]	0 - 5 °C, 5 h	85/15	26
DIBAL-H (1M soln in toluene)	-70 °C, 4 h	86/14	86

a. see reference 13

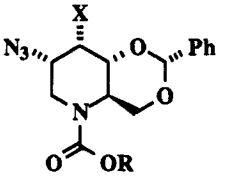
Scheme III



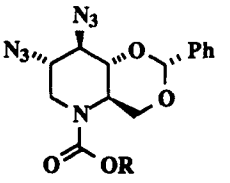
reaction of its C-3 mesylate **45** with cesium acetate (18-crown-6, toluene, reflux, 72 h) gave the *talo* derivative **46** in 52% yield. The reaction of **46** with sodium methoxide in methanol (reflux, 18 h) gave a mixture of the C-3 hydroxyl derivatives **47** and **48** in 57 and 35% yields, respectively. The second inversion of their mesylates **49** and **50** with sodium azide (DMF, 110 °C, 30 h) gave the 2,3-diazido *gluco* compounds **51** and **52**, respectively. The intermediates **51** and **52** were hydrolyzed ($EtOH/H_2O$, reflux, 20 h, 68%) to remove the carbamate group and the resulting compound **53** was alkylated to give **54** (PrCHO, $NaCNBH_3$, MeOH, AcOH, 25 °C, 18 h, 94%). Reduction of the azide groups (10% Pd/C, H_2, 5 psi, 73%) followed by acid catalyzed deprotection of the benzylidine group of **55** (CF_3CO_2H/H_2O, 22 °C, 18 h, 43%) gave the targeted 2,3-diamino compound **56**.



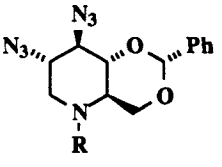
45



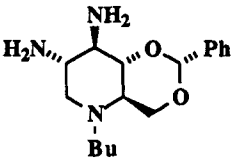
46 X = OAc, R = Bn
47 X = OH, R = Bn
48 X = OH, R = Me
49 X = OMs, R = Bn
50 X = OMs, R = Me



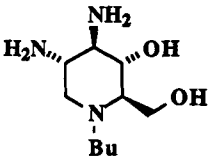
51 R = Bn
52 R = Me



53 R = H
54 R = Bu



55



56

CONCLUSIONS

The results reported herein demonstrate a convenient method for the introduction of polar substituents (N_3, F, SR, NR_2) at position C-2 and/or C-3 using stereoselectively synthesized epoxides (**4**, **5** and **9**). The resulting intermediates have been utilized for the syntheses of a number of 2- and 3-substituted 1-deoxynojirimycin analogs. The stereochemical opening of epoxides (**4**, **5** and **9**) by charged nucleophiles seems to be influenced by the substituents on the piperidine nitrogen. This is apparent from the observed reversal in diastereomeric preference during the reactions of azide and thiolate ions with the carbamate protected (**4**, **5**) *vs* the unprotected (**9**) epoxides. The nucleophile chosen and the reaction conditions used also determine the stereochemical outcome of the epoxide opening reaction. The biological activity of these and several other analogs will be published elsewhere.

EXPERIMENTAL SECTION

General. All NMR spectra were measured in 5-mm o.d. tubes (Wilmad - 535) in $CDCl_3$, DMSO-d_6, D_2O or MeOH-d_4 (Merck Isotopes) solution at 20 °C. NMR spectra were collected on either a General Electric QE-300 or Varian VXR-400 at 300 or 400 MHz for ^1H (75 or 100 MHz for ^{13}C). NOE difference spectra and 2-dimensional NMR spectra were measured on the VXR-400. The chemical shifts (δ) are referenced to tetramethylsilane

(TMS, d = 0.00 ppm) and expressed in ppm. Infrared spectra were recorded on a Perkin-Elmer Model 681 grating spectrophotometer in $CHCl_3$ or using KBr pellets; frequencies are expressed in cm^{-1}. Melting points were determined on a Thomas Hoover capillary melting point apparatus. DSC measurements were performed on a Dupont Model 912 Dual DSC system and run under nitrogen. Mass spectra were obtained on either a Finnigan-MAT Model 4500 or a Finnigan-MAT 8430 system. Micoranalyses (C,H,N) were performed by the Microanalytical Group at G. D. Searle & Co.

Di-*n*-butyltin oxide, diisopropylamine trihydrogenfluoride, sodium azide, *N,N*-dimethylaminoethylamine, butylamine, sodium thiomethoxide, thiophenol, DIBAL-H, Amberlite, IRA-400 (OH) were all commercial products and were used without any further purification. Solvents used were reagent grade or were dried using conventional procedures. The reactions were routinely carried out under an inert atmosphere unless otherwise indicated. Analytical chromatography was performed on EM Reagents 0.25 mm silica gel 60-F plates. Preparative chromatographic separations were carried out on Merck silica gel 60 (230 - 400 mesh).

I. Synthesis of Epoxides

***N*-Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (6).** To a stirred solution of 1-deoxynojirimycin (100 g, 0.61 mol) in saturated aqueous sodium bicarbonate (1000 mL), benzyl chloroformate (95%, 121 g, 0.67 mol) was added dropwise at room temperature. After being stirred at room temperature for 18 h, the solution was extracted once with methylene chloride (300 mL) to remove any unreacted benzyl chloroformate. The aqueous layer was extracted several times with ethyl acetate to give a total of 2.5-3 liters of the extract. The organic layer was dried (Na_2SO_4), filtered and concentrated to give a white solid (98.57 g, 54%): mp 101-102 °C; ^1H NMR (CD_3OD) δ 7.2 - 7.4 (m, 5H), 5.15 (s, 2H), 4.23 (br m, 1H), 4.05 (br d, J = 8 Hz, 1H), 3.87 (dd, J = 6, 4 Hz, 1H), 3.78 - 3.85 (m, 2H), 3.70 - 3.78 (m, 2H), 3.45 (br d, J = 8 Hz, 1H).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.33; H, 6.38; N, 4.58.

4,6-*O*-(*R*-Benzylidene)-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (7). A mixture of **6** (98.5 g, 0.33 mol), benzaldehyde dimethyl acetal (65.5 g, 0.43 mol) and *p*-toluenesulfonic acid (1 g) in a round-bottom flask was dissolved in dimethylformamide (400 mL). The flask was connected to a water aspirator and the reaction was heated at 60-65 °C for 4 h. The reaction mixture was cooled to room temperature and poured into stirred ice-water (1200 mL) containing sodium bicarbonate (14 g). The white solid formed was filtered, washed with cold water and dried. Recrystallization using hexane/ethyl acetate gave **7** (96.2 g, 54%) as a pure white solid: mp 147-148 °C; IR (KBr) 3420, 1715, 1450, 1425, 1395, 1380, 1365, 1090 cm^{-1}; ^1H NMR

(CD_3OD) δ 7.28 - 7.53 (m, 10H), 5.61 (s, 1H), 5.14 (s, 2H), 4.77 (dd, J = 11, 4.6 Hz, 1H), 4.38 (t, J = 11 Hz, 1H), 4.16 (dd, J = 13.4, 4.2 Hz, 1H), 3.5 - 3.7 (complex m, 3H), 3.35 (td, J = 11, 4.6 Hz), 2.97 (dd, J = 13.4, 9.3 Hz, 1H); ^{13}C NMR (CD_3OD) δ 156.7, 139.4, 138.0, 129.9, 129.7, 129.3, 129.2, 129.1, 127.6, 102.8, 81.9, 77.5, 71.5, 70.6, 68.6, 55.9, 50.5; MS (CI, NH_3, *m/z*) 386 (MH^+).

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.15; H, 5.93; N, 3.49.

4,6-*O*-(*R*-Benzylidene)-*N*-benzyloxycarbonyl-1,5-dideoxy-2-*O*-(*p*-toluenesulfonyl)-D-glucitol (8). A mixture of diol **7** (46.3 g, 0.12 mol) and di-*n*-butyltin oxide (31.1 g, 0.125 mol) in methanol (300 mL) was refluxed for 2 h. The methanol was removed, toluene was added and removed under vacuum. The residue was dissolved in methylene chloride (300 mL) and triethylamine (20 mL, 0.144 mmol). After cooling to 0 °C, *p*-toluenesulfonyl chloride (25.2 g, 0.132 mmol) was added. The reaction was stirred at 0 °C for 30 min and then warmed to 20 °C. After being stirred for 3 h, the reaction was quenched by adding saturated aqueous sodium bicarbonate. The organic layer was separated and washed successively with water, 0.5M $KHSO_4$ and water. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give pure **8** (50.27 g, 77%) as a white solid: mp 115-117 °C; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 2H), 7.35 - 7.50 (m, 10H), 7.31 (d, J = 7.8 Hz, 2H), 5.51 (s, 1H), 5.12 (s, 2H), 4.76 (dd, J = 11.4, 4.5 Hz, 1H), 4.38 (ddd, J = 9.3, 7.6, 4.8 Hz, 1H), 4.32 (dd, J = 11.4, 9.5 Hz, 1H), 4.31 (dd, J = 13.6, 4.8 Hz, 1H), 3.78 (dt, J = 2.6, 9.4Hz, 1H), 3.59 (t, J = 9.4 Hz, 1H), 3.26 (ddd, J = 11.4, 9.4, 4.5 Hz, 1H), 3.04 (dd, J = 13.6, 9.3 Hz, 1H) 2.63 (d, J = 2.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.8, 145.2, 137.0, 135.8, 133.2, 129.8, 129.3, 128.7, 128.4, 128.3, 128.1, 126.2, 101.8, 79.9, 78.1, 73.9, 69.2, 67.8, 54.2, 47.1, 21.7; MS (FAB, *m/z*) 546 (M + Li).

Anal. Calcd for $C_{28}H_{29}NO_8S$: C, 62.32; H, 5.42; N, 2.66. Found: C, 62.65; H, 5.40; N, 2.62.

2,3-Anhydro-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol (4). Sodium hydride (2.79 g, 60% dispersion in mineral oil, 69.7 mol) was placed in a flask under argon and washed three times with dry hexane. The residue was suspended in dry THF (300 mL) and to this a solution of **8** (37.6 g, 69.7 mmol) in THF (100 mL) was added slowly. After stirring for 18 h, the reaction was quenched by adding water. The organic layer was extracted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine. After drying (sodium sulfate) and filtration, the organic layer was concentrated and recrystallized using

cyclohexane to give pure **4** (19.2 g, 75%) as white solid: mp 104-105 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 - 7.67 (m, 10H), 5.67 (s, 1H), 5.16 (s, 2H), 4.76 (broad s, 1H), 4.59 (d, J = 15 Hz, 1H), 4.08 (d, J = 10 Hz, 1H), 4.02 (dd, J = 11.4, 4 Hz, 1H), 3.46 (dd, J = 15, 0.9 Hz, 1H), 3.40 (d, J = 3 Hz, 1H), 3.25 (d, J = 3 Hz, 1H), 3.10 (dt, J = 4, 10 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 156.2, 137.8, 136.6, 129.7, 129.1, 128.9, 128.8, 128.5, 126.6, 102.8, 73.0, 70.4, 68.0, 56.0, 54.7, 50.4 and 46.6; MS (*m/z*) 374 (M + Li).

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.64; H, 5.77; N, 3.81. Found: C, 68.21; H, 5.84; N, 3.67.

2,3-Anhydro-4,6-*O*-(*R*-benzylidene)-1,5-dideoxy-1,5-imino-D-mannitol (9). To a solution of **4** (2.08 g, 5.7 mmol) in THF (20 mL) in a Parr hydrogenation flask, 4% Pd on C (400 mg) was added. The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times) and then pressurized to 2 psi hydrogen. After running the reaction on a shaker for 5 h, the system was vented, purged with nitrogen and filtered. The filtrate was concentrated and the crude material was chromatographed (silica gel, ethyl acetate/ 2-propanol 95/5) to give pure **9** (1.13 g, 85%): DSC (mp) 128 °C; IR (KBr) 3400, 2950, 2850, 1445, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.39 (m, 3H), 5.59 (s, 1H), 4.24 (dd, J = 11, 5 Hz, 1H), 3.54 (dd, J = 11, 9 Hz, 1H), 3.52 (d, J = 10 Hz, 1H), 3.41 (d, J = 3 Hz, 1H), 3.39 (d, J = 15 Hz, 1H), 3.18 (d, J = 15 Hz, 1H), 3.17 (d, J = 3 Hz, 1H), 2.53 (ddd, J = 10, 9, 5 Hz, 1H), 0.76 (s, 1H).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.52; N, 5.95.

2,3-Anhydro-4,6-*O*-(*R*-benzylidene)-*N*-(*tert*-butoxycarbonyl)-1,5-dideoxy-1,5-imino-D-mannitol (5). A solution of **9** (1.26 g, 5 mmol) and di-*t*-butyl dicarbonate (1.31 g, 6 mmol) in pyridine (40 mL) was stirred at room temperature. After 20 h, additional di-*t*-butyl dicarbonate (0.65 g, 3 mmol) was added and the mixture stirred at room temperature for 3 days. After evaporation of solvent, the residue was partitioned between EtOAc and 10% aqueous $CuSO_4$ solution. The organic phase was washed with water and with brine. After drying (Na_2SO_4), the filtrate was concentrated and the residue chromatographed over silica gel (EtOAc/hexanes 20/80) to give pure **5** (1.26 g, 76%) as a colorless oil. IR ($CHCl_3$) 3000, 2975, 1697, 1474, 1436, 1392, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 2H), 7.39 (m, 3H), 5.63 (s, 1H), 4.71 (m, 1H), 4.44 (m, 2H), 4.03 (d, J = 10 Hz, 1H), 3.34 (m, 2H), 3.20 (m, 1H), 3.01 (ddd, J = 10, 10, 5 Hz, 1H), 1.47 (s, 9H).

HRMS (*m/z*) Calcd for $C_{18}H_{23}NO_5$: 333.1576. Found: 333.1579.

2,3-Anhydro-4,6-*O*-(*R*-benzylidene)-*N*-butyl-1,5-dideoxy-1,5-imino-D-mannitol (11). To a solution of **9** (1.15 g, 4.9 mmol) in methanol (25 mL), 4Å molecular sieves (3 g) were added. After stirring for 5 min, butyraldehyde (0.89 mL,

9.9 mol), acetic acid (0.5 mL) and sodium cyanoborohydride (95%, 0.41 g, 7.4 mmol) were added. The reaction was stirred at 22 °C for 26 h, filtered and the residue washed with more methanol. The combined organic fractions were concentrated. The residue was redissolved in ethyl acetate and washed with aqueous potassium carbonate, water and brine. After drying ($MgSO_4$) and concentration, the crude product (1.7 g) was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give **11** (1.25 g, 88%) as a clear liquid: ^1H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.39 (m, 3H), 5.57 (s, 1H), 4.38 (dd, J = 11, 5 Hz, 1H), 3.77 (d, J = 10 Hz, 1H), 3.74 (dd, J = 11, 9 Hz, 1H), 3.39 (d, J = 15 Hz, 1H), 3.36 (d, J = 3 Hz, 1H), 3.32 (d, J = 3 Hz, 1H), 2.68 (dd, J = 15, 2 Hz, 1H), 2.54 (m, 1H), 2.32 (m, 2H), 1.44 (m, 2H), 1.27 (m, 2H), 0.9 (t, J = 7 Hz, 3H).

II. Opening of Epoxides 4 and 5 with different nucleophiles

A. With Azide:

2-Azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-D-glucitol (12a) and 3-azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,3,5-trideoxy-1,5-imino-D-altritol (12b). To a solution of epoxide **4** (4 g, 10.9 mmol) in 2-methoxyethanol (80 mL), sodium azide (3.5 g, 54.5 mmol) and ammonium chloride (2.33 g, 43.6 mmol) were added. The reaction mixture was refluxed for 36 h. Part of the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude mixture was chromatographed (silica gel, hexane/ethyl acetate 8/2) to give pure **12a** (1.95 g, 44%) and **12b** (1.81 g, 40%).

12a: DSC (mp) 253 °C; ^1H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.38 (m, 8H), 5.56 (s, 1H), 5.15 (d, J = 12 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 4.80 (dd, J = 12, 5 Hz, 1H), 4.43 (dd, J = 12, 10 Hz, 1H), 4.33 (dd, J = 14, 5 Hz, 1H), 3.70 (td, J = 9, 2 Hz, 1H), 3.62 (dd, J = 10, 9 Hz, 1H), 3.51 (ddd, J = 11, 9, 5 Hz, 1H), 3.23 (td, J = 10, 5 Hz, 1H), 2.81 (d, J = 2 Hz, 1H), 2.70 (dd, J = 14, 11 Hz, 1H).

Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.46; H, 5.40; N, 13.65. Found: C, 61.23; H, 5.46; N, 13.39.

12b: IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.37 (m, 8H), 5.61 (s, 1H), 5.14 (d, J = 12 Hz, 1H), 5.09 (d, J = 12 Hz, 1H), 4.77 (dd, J = 12, 5 Hz, 1H), 4.43 (dd, J = 12, 11 Hz, 1H), 4.29 (dd, J = 10, 3 Hz, 1H), 4.08 (dd, J = 15, 2 Hz, 1H), 4.02 (dd, J = 3, 2 Hz, 1H), 3.87 (m, 1H), 3.70 (ddd, J = 11, 10, 5 Hz, 1H), 3.24 (dd, J = 15, 1 Hz, 1H), 2.16 (d, J = 3 Hz,1H); MS (CI, NH_3, m/z) 411 (MH^+).

Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.46; H, 5.40; N, 13.65. Found: C, 61.31; H, 5.56; N, 13.26.

2-Azido-4,6-*O*-(*R*-benzylidene)-1,2,5-trideoxy-1,5-imino-D-glucitol (21a) and 3-azido-4,6-*O*-(*R*-benzylidene)-1,3,5-trideoxy-1,5-imino-D-altritol (21b). To a solution of epoxide **9** (250 mg, 1.07 mmol) in 2-methoxyethanol (8 mL) and water (1 mL), sodium azide (350 mg, 5.35 mmol) and ammonium chloride (230 mg, 4.3 mmol) were added. The reaction mixture was heated at 110 °C for 24 h. Part of the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate and washed with aqueous potassium carbonate, water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude mixture was chromatographed (silica gel, ethyl acetate/2-propanol 98/2) to give **21a** (26 mg, 9%) and **21b** (143 mg, 48%).

21a: ^1H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.40 (m, 3H), 5.47 (s, 1H), 4.16 (dd, J = 11, 5 Hz, 1H), 3.53 (t, J = 9 Hz, 1H), 3.51 (dd, J = 11, 10 Hz, 1H), 3.30 (ddd, J = 11, 9, 5 Hz, 1H), 3.24 (t, J = 9 Hz,1H), 3.2 (very broad s, 1H), 3.08 (dd, J = 13, 5 Hz, 1H), 2.60 (td, J = 10, 5 Hz, 1H), 2.5 (very broad s, 1H), 2.44 (dd, J = 13, 11 Hz, 1H); MS (CI, CH_4, m/z) 277 (MH^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.56; H, 5.93; N, 20.15.

21b: ^1H NMR ($CDCl_3$) δ 7.52 (m, 2H), 7.32 - 7.43 (complex band, 3H), 5.62 (s, 1H), 4.22 (dd, J = 11, 5 Hz, 1H), 4.07 (m, 1H), 4.04 (dd, J = 9, 3 Hz, 1H), 3.87 (q, J = 2 Hz, 1H), 3.67 (t, J = 11 Hz, 1H), 3.23 (ddd, J = 11, 9, 5 Hz, 1H), 3.11 (dd, J = 13, 2 Hz, 1H), 2.87 (dd, J = 13, 2 Hz, 1H), 1.56 (broad s, 2H); MS (CI, NH_3, m/z) 277 (MH^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3 \cdot 0.2H_2O$: C, 55.71; H, 5.91; N, 20.02. Found: C, 55.90; H, 6.00; N, 19.68.

B. With Fluoride

4,6-*O*-(*R*-Benzylidene)-*N*-benzyloxycarbonyl-2-fluoro-1,2,5-trideoxy-1,5-imino-D-glucitol (13a) and 4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-3-fluoro-1,3,5-trideoxy-1,5-imino-D-altritol (13b). A mixture of the epoxide **4** (14.67 g, 39.9 mmol) and diisopropylamine trihydrogenfluoride (29.34 g, 196 mmol) in a round-bottom flask was connected to a rotary evaporator under nitrogen and swirled in an oil bath maintained at 125 °C. After swirling for 70 h, the flask was cooled to 20 °C and the mixture was dissolved in ethyl acetate and treated with saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed successively with 0.2N HCl and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to give a brown oil (14.2 g). The crude material was chromatographed (silica gel, methylene chloride and later methylene chloride/ methanol 98/2) to give **13a** (5. 67g, 37%) and **13b** (1.97 g, 13%).

13a was recrystallized from chloroform/hexane to give a white solid: mp 94-95 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 - 7.57 (m, 10H), 5.57 (s, 1H), 5.19 (d, J = 12.1 Hz, 1H), 5.15 (d, J = 12.1 Hz, 1H), 4.87 (dd, J = 11.3, 4.6 Hz, 1H), 4.53 (dddd, J = 48.4, 8.7, 6.6, 4.6 Hz, 1H), 4.26 (t, J = 11.3 Hz, 1H), 4.25 (ddd, J = 14.1, 13.3, 4.6 Hz, 1H), 3.88 (ddd, J = 18.3, 9.6, 6.6 Hz, 1H), 3.65 (t, J = 9.6 Hz, 1H), 3.36 (ddd, J = 10.2, 9.6, 4.6 Hz, 1H), 3.26 (ddd, J = 14.1, 8.7, 6.0 Hz, 1H), 3.06 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 154.9, 137.0, 135.7, 129.3, 128.6, 128.4, 128.3, 128.1, 126.2, 101.7, 89.5 (d, J = 180.5), 79.6 (d, J = 8.6 Hz), 74.4 (d, J = 22 Hz), 69.3, 67.8, 53.4 and 46.1 (d, J = 27.4 Hz); MS (CI, m/z) 388 (MH^+).

Anal. Calcd for $C_{21}H_{22}FNO_5$: C, 65.10; H, 5.74; N, 3.61. Found: C, 65.37; H, 5.82; N, 3.69.

13b was recrystallized from ethanol/hexane to give a white solid: mp 125-127 °C; ^{1}H NMR (CD_3OD) δ 7.28 - 7.49 (m, 10H), 5.57 (s, 1H), 5.12 (d, J = 12 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 4.71 (d of m, J = 49.8 Hz, 1H), 4.42 (t, J = 11.3 Hz, 1H), 4.19 (ddd, J = 29.2, 10.3, 2.1 Hz, 1H), 3.94 - 4.03 (m, 2H), 3.68 (ddd, J = 11.3, 10.3, 4.8 Hz, 1H), 3.44 (ddd, J = 15.4, 3.3, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.9, 137.3, 135.9, 129.2, 128.7, 128.4, 128.3, 128.1, 126.2, 102.1, 87.9 (d, J = 179 Hz), 74.8 (d, J = 16.9 Hz), 69.4, 67.7, 67.2 (d, J = 27.6 Hz), 51.5 and 46.9; MS (CI, m/z) 388 (MH^+).

Anal. Calcd for $C_{21}H_{22}FNO_5$: C, 65.10; H, 5.74; N, 3.61. Found: C, 65.12; H, 5.85; N, 3.63.

C. With Sulfur Nucleophiles:

4,6-*O*-(*R*-Benzylidene)-*N*-(*tert* -butoxycarbonyl)-1,5-imino-2-*S*-methyl-2-thio-D-glucitol (14a) and 4,6-*O*-(*R*-benzylidene)-*N*-(*tert* -butoxycarbonyl)-1,5-imino-3-*S*-methyl-3-thio-D-altritol (14b). A solution of the epoxide **5** (142 mg, 0.426 mmol) and sodium thiomethoxide (149 mg, 2.13 mmol) in 2-methoxyethanol (5 mL) was stirred at reflux for 0.5 h. After cooling, the mixture was partitioned between EtOAc/H_2O and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with water and with brine. The organic layer was dried (Na_2SO_4) and concentrated. Radial chromatography of the residue over silica gel (2 mm layer thickness, hexane/ethyl acetate 75/25) gave **14a** (76mg, 47%) as viscous liquid and **14b** (43 mg, 26%) as a white crystalline solid.

14a: IR ($CHCl_3$) 3588, 2926, 1694, 1458, 1400, 1088 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 7.48 (m, 2H), 7.40 (m, 3H), 5.60 (s, 1H), 4.69 (dd, J = 12, 5 Hz, 1H), 4.41 (t, 1H), 4.29 (dd, J = 12, 5 Hz, 1H), 3.68 (t, J = 8 Hz, 1H), 3.56 (t, J = 11 Hz, 1H), 3.25 (ddd, J = 11, 8, 5 Hz, 1H), 2.82 (m, 2H), 2.65 (ddd, J = 11, 5, 5 Hz, 1H), 2.17 (s, 1H), 1.51 (s, 9H).

HRMS (*m/z*) Calcd for $C_{19}H_{28}NO_5S$: 385.1688. Found: 385.1681.

14b: IR ($CHCl_3$) 3596, 2926, 1694, 1456, 1395, 1088 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.30 (m, 2H), 7.24 (m, 3H), 5.63 (s, 1H), 4.80 (dd, J = 11, 5 Hz, 1H), 4.40 (dd, J = 11, 5 Hz, 1H), 4.34 (t, 1H), 4.11 (m, 1H), 3.93 (dd, J = 13, 4 Hz, 1H), 3.71 (ddd, J = 11, 5, 5 Hz, 1H), 3.40 (dd, J = 13, 4 Hz, 1H), 3.25 (m, 1H), 2.29 (m, 1H), 2.26 (s, 3H), 1.49 (s, 9H).

HRMS (*m/z*) Calcd for $C_{19}H_{28}NO_5S$: 385.1688. Found: 385.1687.

4,6-*O*-(*R*-Benzylidene)-*N*-(*tert*-butoxycarbonyl)-1,5-imino-2-*S*-phenyl-2-thio-D-glucitol (15a) and 4,6-*O*-(*R*-benzylidene)-*N*-(*tert*-butoxycarbonyl)-1,5-imino-3-*S*-phenyl-3-thio-D-altritol (15b). To a solution of sodium thiophenylate, prepared from thiophenol (1.10 g, 10.0 mmol) and sodium (230 mg, 10 mmol), in 2-methoxyethanol (20 mL), the epoxide **5** (666 mg, 2.0 mmol) was added. After refluxing for 1 h, the reaction mixture was cooled and partitioned between EtOAc/H_2O. The aqueous layer was extracted twice with ethyl acetate and the combined extracts were washed with brine and dried (Na_2SO_4). The solution was concentrated and the residue chromatographed over silica gel to give **15a** (490 mg, 55%) and **15b** (360 mg, 41%) as white crystalline solids.

15a: IR ($CHCl_3$) 3586, 2880, 1696, 1586, 1458, 1370, 1086 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.49 (m, 4H), 7.36 (m, 6H), 5.58 (s, 1H), 4.66 (dd, J = 12, 5 Hz, 1H), 4.45 (t, J = 11 Hz, 1H), 4.23 (dd, J = 12, 5 Hz, 1H), 3.69 (t, J = 7 Hz, 1H), 3.57 (t, J = 8 Hz, 1H), 3,15 (m, 2H), 2.89 (m, 1H), 2.78 (dd, J = 13, 11 Hz, 1H), 1.64 (s, 9H).

HRMS (*m/z*) Calcd for $C_{24}H_{29}NO_5S$: 443.1767. Found: 443.1764.

15b: IR ($CHCl_3$) 3382, 2934, 1694, 1584, 1456, 1370, 1061 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.53 - 7.18 (m, 10H), 5.61 (s, 1H), 4.77 (dd, J = 10, 5 Hz, 1H), 4.43 (dd, J = 10, 5 Hz, 1H), 4.34 (t, J = 11 Hz, 1H), 4.03 (m, 1H), 3.95 (dd, J = 13, 3 Hz, 1H), 3.81 (m, 1H), 3.65 (ddd, J = 10, 5, 5 Hz, 1H), 3.51 (dd, J = 14, 3 Hz, 1H), 2.25 (m, 1H), 1.47 (s, 9H).

HRMS (*m/z*) Calcd for $C_{24}H_{29}NO_5S$: 443.1767. Found: 443.1771.

1,5-Dideoxy-1,5-imino-2-*S*-methyl-2-thio-D-glucitol (22a) and 1,5-dideoxy-1,5-imino-3-*S*-methyl-3-thio-D-altritol (22b). A solution of the epoxide **9** (486 mg, 2.09 mmol) and sodium thiomethoxide (732 mg, 10.5 mmol) in 2-methoxyethanol (21 mL) was refluxed for 1 h. After cooling, the mixture was partitioned between EtOAc/H_2O and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4). Chromatography of the residue over silica gel using a gradient of 0 -10% methanol in ethyl acetate as eluent gave **22a** (50 mg, 8.5%) as a white crystalline solid and **22b** (210 mg, 36%) as a pale yellow solid.

22a: IR (KBr) 3420, 2882, 2850, 1450, 1374, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (m, 2H), 7.36 (m, 3H), 5.55 (s, 1H), 4.31 (dd, J = 10, 5 Hz, 1H), 3.61 (m, 2H), 3.41 (t, J = 10 Hz, 1H), 3.29 (m, 1H), 3.28 (dd, J = 13, 5 Hz, 1H), 2.79 (m, 1H), 2.75 (t, J = 13 Hz, 1H), 2.61 (ddd, J = 9, 4, 4 Hz, 1H), 2.24 (m, 1H), 2.15 (s, 3H), 1.51 (br s, 1H).

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.65; H, 6.85; N, 5.00.

22b: IR (KBr) 3422, 3265, 2920, 2840, 1450, 1382, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.37 (m, 3H), 5.61 (s, 1H), 4.18 (m, 2H), 4.10 (m, 1H), 3.66 (t, J = 11 Hz, 1H), 3.30 (m, 2H), 3.18 (d, J = 12 Hz, 1H), 2.89 (d, J = 12 Hz, 1H), 2.24 (s, 3H), 1.94 (br s, 2H).

Anal. Calcd for $C_{14}H_{19}NO_3S \cdot 1/8\ H_2O$: C, 59.31; H, 6.84; N, 4.94. Found: C, 59.27; H, 6.91; N, 4.94.

D. With Amines:

4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,3,5-trideoxy-3-[{2-(dimethylamino)ethyl}amino]-1,5-imino-D-altritol (16b). A solution of epoxide **4** (734 mg, 2 mmol) in *N,N*-dimethylaminoethylamine (7 mL) was heated at 100 °C for 24 h. The solvent was removed under reduced pressure and the crude residue was chromatographed (silica gel, methylene chloride/methanol/ ammonium hydroxide 90/10/1) to give pure **16b** (700 mg, 76%) as an oil: ^1H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.36 (m, 8H), 5.60 (s, 1H), 5.13 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 4.77 (dd, J = 11, 4.5 Hz, 1H), 4.26 (dd, J = 11, 10 Hz, 1H), 4.20 (dd, J = 10, 4.5 Hz, 1H), 3.89 (ddd, J = 5, 3, 3 Hz, 1H), 3.79 (ddd, J = 10, 10, 4.5 Hz, 1H), 3.77 (dd, J = 15, 5 Hz, 1H), 3.73 (dd, J = 15, 3 Hz, 1H), 3.09 (dd, J = 4.5, 3 Hz, 1H), 2.76 (m, 1H), 2.72 (m, 1H), 2.48 (dd, J = 12.5, 6.3 Hz, 1H), 2.35 (dd, J = 12.5, 5.3 Hz, 1H), 2.20 (s, 6H).

Anal. Calcd for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30; N, 9.22. Found: C, 65.65; H, 7.45; N, 9.02

4,6-*O*-(*R*-Benzylidene)-*N*-benzyloxycarbonyl-3-(butylamino)-1,3,5-trideoxy-1,5-imino-D-altritol (17b). A solution of epoxide **4** (200 mg, 0.55 mmol) in butylamine (4 mL) was refluxed for 24 h. The solvent was removed under reduced pressure and the crude residue was chromatographed (silica gel, hexane/ethyl acetate 70/30) to give the recovered **4** (65 mg, 32%) and pure **17b** (117 mg, 49%): mp 104-106 °C, ^1H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.36 (m, 8H), 5.61 (s, 1H), 5.12 (s, 2H), 4.78 (dd, J = 12, 5 Hz, 1H), 4.44 (dd, J = 12, 10 Hz, 1H), 4.20 (dd, J = 10, 3 Hz, 1H), 4.00 (dd, J = 14, 3 Hz, 1H), 3.95 (ddd, J = 3, 3, 1 Hz, 1H), 3.76 (ddd, J = 10, 10, 5 Hz, 1H), 3.60 (dd, J = 14, 1 Hz, 1H), 3.08 (t, J = 3 Hz, 1H), 2.57 (m, 2H), 1.42 (m, 2H), 1.33 (m, 2H), 0.89 (t, J = 7 Hz, 3H).

Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.04; H, 7.39; N, 6.34

E. With Carbon Nucleophiles:

***N*-Benzyloxycarbonyl-4,4aα,8,8aβ-tetrahydro-8β-hydroxy-2*R*,2α-phenyl-5H-1,3-dioxino[5,4-b]pyridine (19) and *N*-acetyl-4,4aα,5,8,8aβ-tetrahydro-8β-hydroxy-2*R*,2α-phenyl-5H-1,3-dioxino[5,4-b]pyridine (20).** To a cold suspension of cuprous cyanide (195 mg, 2.2 mmol) in THF (2 mL) at -70 °C, methyl lithium (3.1 mL, 1.4 M solution in ether, 4.4 mmol) was injected and the reaction mixture was allowed to warm to 0 °C over 2 h. After stirring at -10 °C to 0 °C for 1h, the reaction mixture was recooled to -78 °C and a solution of **4** (400 mg, 1.09 mmol) in THF (15 mL) was added over 15 min. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature. After 16 h, the reaction was quenched with a solution of concd NH_4OH in saturated ammonium chloride (1/10, 40 mL) and extracted with ethyl acetate. The organic layer was separated and washed with water. After drying over $MgSO_4$, the organic layer was filtered and concentrated. The crude product (380 mg) was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give recovered **4** (180 mg, 45%) and **19** (50 mg, 13%): ^1H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.31 - 7.42 (complex band, 8H), 6.80 (dd, J = 9, 2 Hz, 1H), 5.58 (S, 1H), 5.36 (broad dd, J = 11, 4 Hz, 1H), 5.19 (d, J = 12.5 Hz, 1H), 5.15 (d, J = 12.5 Hz, 1H), 4.88 (dd, J = 9, 2 Hz, 1H), 4.42 (ddt, J = 8, 3, 2 Hz, 1H), 3.83 (dd, J = 11, 10 Hz, 1H), 3.79 (dd, J = 10, 8 Hz, 1H), 3.69 (td, J = 10, 4 Hz, 1H), 2.62 (d, J = 3 Hz, 1H); MS (CI, NH_3, m/z) 368 (MH^+).

Anal. Calcd for $C_{21}H_{21}NO_5 \cdot 0.3\ H_2O$: C, 67.66; H, 5.84; N, 3.76. Found: C, 67.70; H, 5.79; N, 3.68.

Phenylmethyl-4,4aα,8,8aβ-tetrahydro-8β-hydroxy-2*R*,2α-phenyl-5H-1,3-dioxino[5,4-b]pyridine-5-carboxylate (19) and 5-acetyl-4aα,5,8,8aβ-tetrahydro-2*R*,2α-phenyl-4H-1,3-dioxino[5,4-b]pyridine-8β-ol (20). To a cold suspension of cuprous cyanide (600 mg, 6.54 mmol) in THF (7 mL) at -78 °C, methyl lithium (9.3 mL, 1.4 M solution in ether, 13.1 mmol) was injected and the reaction mixture was allowed to warm to -5 °C over 2.5 h. The reaction mixture was recooled to -70 °C and a solution of **4** (400 mg, 1.09 mmol) in THF (10 mL) was added over 15 min. The reaction mixture was stirred at -70 °C for 20 min and then allowed to warm to -5 °C - 0 °C over 1 h. After stirring at this temperature for 5 h, the reaction was quenched with a solution of concd NH_4OH in saturated ammonium chloride (1/10, 120 mL) and extracted with ethyl acetate. The organic layer was separated and washed with water. After drying over $MgSO_4$, the organic layer was filtered and concentrated. The crude product (385 mg) was chromatographed (silica gel, hexane/ethyl acetate 7/3 and later ethyl acetate/2-propanol 98/2) to give recovered **4** (15 mg, 4%), **19** (60 mg, 15%, identical to the product described above) and **20** (59 mg, 19%).

20: ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.47 (m, 3H), 6.45 (dd, J = 9, 2 Hz, 1H), 5.58 (s, 1H), 5.52 (broad dd, J = 11, 4 Hz, 1H), 4.97 (dd, J = 9, 2 Hz, 1H), 4.40 (m, 1H), 3.7 - 3.85 (complex band, 3H), 2.18 (s, 3H)

2,3-Anhydro-4,6-*O*-(*R*-benzylidene)-1,5-dideoxy-1,5-imino-*N*-methyl-D-mannitol (10). To a cold suspension of cuprous cyanide (400 mg, 4.47 mmol) in THF (10 mL) at -78 °C, methyl lithium (6.2 mL, 1.4 M solution in ether, 8.7 mmol) was injected and the reaction mixture was allowed to warm to -5 °C over 2 h. The reaction mixture was recooled to -50 °C and a solution of **9** (200 mg, 0.86 mmol) in THF (5 mL) was added over 15 min. The reaction temperature was allowed to warm to 0 °C over 3 h and then to 20 °C. After stirring for 18 h, the blackish reaction mixture was quenched with a solution of concd NH_4OH in saturated ammonium chloride (1/10, 80 mL) and extracted with ethyl acetate. The organic layer was separated and washed with water and brine. After drying over $MgSO_4$, the organic layer was filtered and concentrated. The crude product (192 mg) was chromatographed (silica gel, ethyl acetate/2-propanol 98/2) to give the recovered **9** (50 mg, 25%) and desired **10** (60 mg, 28%): ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.40 (m, 3H), 5.59 (s, 1H), 4.37 (dd, J = 10.5, 4 Hz, 1H), 3.77 (d, J = 9 Hz, 1H), 3.74 (t, J = 10.5 Hz, 1H), 3.38 (d, J = 3.5 Hz, 1H), 3.36 (broad d, J = 13.5 Hz,1H), 3.32 (m, 1H), 2.54 (dd, J = 13.5, 2 Hz, 1H), 2.21 (s, 3H), 2.13 (ddd, J = 10.5, 9, 4 Hz, 1H); MS (CI, NH_3, m/z) 248 (MH^+).

III. Synthesis of 2-substituted-1-deoxynojirimycins:

A. 2-Azido-deoxynojirimycin derivatives:

2-Azido-4,6-*O*-(*R*-benzylidene)-1,2,5-trideoxy-1,5-imino-D-glucitol (21a). The compound **12a** (3.3 g, 8.05 mol) was added to a previously prepared solution of sodium hydroxide (4 g) in ethanol/water (1/1, 120 mL). After heating the mixture at 70 °C for 20 h, the reaction was cooled and part of the solvent was removed under reduced pressure. The mixture was neutralized with 1N HCl and extracted with methylene chloride. The organic layer was washed with water and brine. After drying ($MgSO_4$) and concentration of the filtrate, the crude product (3.01 g) was chromatographed (silica gel, ethyl acetate/2-propanol 98/2) to give pure **21a** (2.07 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.40 (m, 3H), 5.47 (s, 1H), 4.16 (dd, J = 11, 5 Hz, 1H), 3.53 (t, J = 9 Hz, 1H), 3.51 (dd, J = 11, 10 Hz, 1H), 3.30 (ddd, J = 11, 9, 5 Hz, 1H), 3.24 (t, J = 9 Hz,1H), 3.2 (very broad s, 1H), 3.08 (dd, J = 13, 5 Hz, 1H), 2.60 (td, J = 10, 5 Hz, 1H), 2.5 (very broad s, 1H), 2.44 (dd, J = 13, 11 Hz, 1H); MS (CI, CH_4, m/z) 277 (MH^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.56; H, 5.93; N, 20.15.

2-Azido-4,6-*O*-(*R*-benzylidene)-*N*-butyl-1,2,5-trideoxy-1,5-imino-D-glucitol (24). To a solution of **21a** (3.1 g, 11.23 mmol) in methanol (120 mL), 4Å molecular sieves (3.5 g) were added. After stirring for 5 min, butyraldehyde (1.86 mL, 20.8 mol), acetic acid (1.3 mL) and sodium cyanoborohydride (95%, 1.02 g, 15.4 mmol) were added. The reaction was stirred at 22 °C for 18 h, filtered and the residue washed with more ethyl acetate. The combined organic fractions were concentrated. The residue was redissolved in ethyl acetate and washed with aqueous potassium carbonate, water and brine. After drying ($MgSO_4$) and concentration, the crude product (4.08 g) was chromatographed (silica gel, hexane/ethyl acetate 6/4) to give **24** (3.28 g, 88%) as a white solid: DSC (mp) 115 °C (dec.); ^1H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.38 (m, 3H), 5.50 (s, 1H), 4.39 (dd, J = 10, 4 Hz, 1H), 3.67 (t, J = 10 Hz, 1H), 3.60 (t, J = 9 Hz, 1H), 3.55 (td, J = 9, 5 Hz, 1H), 3.51 (t, J = 9 Hz,1H), 3.03 (dd, J = 12, 5 Hz, 1H), 2.87 (s, 1H), 2.56 (dt, J = 13, 8 Hz, 1H), 2.39 (ddd, J = 10, 9, 4 Hz, 1H), 2.31 (dt, J = 13, 7 HZ, 1H), 2.15 (dd, J = 12, 10 Hz, 1H) 1.42 (m, 2H), 1.17 - 1.38 (complex band, 2H), 0.92 (t, J = 7 Hz, 3H); MS (CI, NH_3, m/z) 333 (MH^+).

Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.40; H, 7.34; N, 16.84.

2-Azido-1,2,5-trideoxy-1,5-imino-D-glucitol (25). A solution of **21a** (1 g, 3.61 mmol) in trifluoroacetic acid/water (4/1, 15 mL) was stirred at 22 °C for 18 h. The solvent was removed under reduced pressure and the thick yellow liquid residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/methanol/ammonium hydroxide 50/50/2.5), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene and **25** (394 mg, 74%) was isolated as a white solid after crystallization from methanol/hexane: mp 142 °C (dec); ^1H NMR (CD_3OD) δ 3.88 (dd, J = 11, 3 Hz, 1H), 3.71 (dd, J = 11, 6 Hz, 1H), 3.30-3.45 (complex band, 2H), 3.29 (distorted t, J = 9 Hz, 1H), 3.20 (distorted dd, J = 13, 4 Hz, 1H), 2.50 (ddd, J = 9, 6, 3 Hz, 1H), 2.47 (distorted dd, J = 13, 10 Hz, 1H); MS (CI, NH_3, m/z) 189 (MH^+).

Anal. Calcd for $C_6H_{12}N_4O_3 \cdot 0.25H_2O$: C, 39.86; H, 6.64; N, 27.75. Found: C, 39.91; H, 6.79; N, 27.59.

2-Azido-*N*-butyl-1,2,5-trideoxy-1,5-imino-D-glucitol (26). A solution of **24** (650 mg, 1.96 mmol) in trifluoroacetic acid/water (4/1, 12 mL) was stirred at 22 °C for 8 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/2-propanol/ water/ammonium hydroxide 70/25/5/2), were pooled and concentrated. The

water in the fractions was azeotropically removed with toluene to give crude **26** (330 mg) which was rechromatographed (silica gel, ethyl acetate/2-propanol/water/ammonium hydroxide 70/25/5/2) to give pure **26** (260 mg, 61%) as a viscous liquid: ^{1}H NMR (CD_3OD) δ 3.84 (d, J = 3 Hz, 2H), 3.38 (t, J = 9 Hz, 1H), 3.35 (td, J = 10, 5 Hz, 1H), 3.19 (dd, J = 10, 9 Hz, 1H), 2.98 (dd, J = 12, 5 Hz, 1H), 2.78 (dt, J = 14, 8 Hz, 1H), 2.58 (dt, J = 14, 7 Hz, 1H), 2.13 (dd, J = 12, 10 Hz, 1H), 2.08 (dt, J = 9, 3 Hz, 1H), 1.45 (m, 2H), 1.22-1.38 (complex band, 2H), 0.93 (t, J = 7 Hz, 3H); MS (CI, NH_3, *m/z*) 245 (MH^+).

Anal. Calcd for $C_{10}H_{20}N_4O_3 \cdot 0.2H_2O$: C, 48.45; H, 8.29; N, 22.60. Found: C, 48.49; H, 8.31; N, 22.40.

B. 2-Amino and 2-amidodeoxynojirimycin derivatives:

2-Amino-4,6-*O*-(*R*-benzylidene)-*N*-butyl-1,2,5-trideoxy-1,5-imino-D-glucitol (30). To a solution of **24** (700 mg, 2.11 mmol) in methanol (70 mL) in a Parr hydrogenation flask, 10% Pd on C (70 mg) was added. The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times) and then pressurized to 5 psi hydrogen. After running the reaction on a shaker for 3.5 h, the system was vented, purged with nitrogen and filtered. The filtrate was concentrated and the crude material (630 mg) was chromatographed (silica gel, methylene chloride/methanol/ammonium hydroxide 90/10/1) to give pure **30** (600 mg, 93%): DSC (mp) 125 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.38 (m, 3H), 5.52 (s, 1H), 4.42 (dd, J = 11, 5 Hz, 1H), 3.69 (dd, J = 11, 10 Hz, 1H), 3.51 (t, J = 9 Hz, 1H), 3.31 (t, J = 9 Hz, 1H), 2.98 (dd, J = 11, 5 Hz, 1H), 2.90 (ddd, J = 10, 9, 5 Hz, 1H), 2.55 (dt, J = 13, 8 Hz, 1H), 2.41 (ddd, J = 10, 9, 5 Hz, 1H), 2.28 (dt, J = 13, 7 Hz, 1H), 2.05 (dd, J = 11, 10 Hz, 1H), 2.03 (broad s, 3H), 1.54 (p, J = 7 Hz, 2H), 1.18 - 1.38 (complex band, 2H), 0.92 (t, J = 7 Hz, 2H); MS (EI, *m/z*) 306 (M^+).

Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.14; H, 8.56; N, 9.08.

2-Amino-*N*-butyl-1,5-imino-1,2,5-trideoxy-D-glucitol (35). A solution of **30** (580 mg, 1.89 mmol) in trifluoroacetic acid/water (4/1, 15 mL) was stirred at 22 °C for 24 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/methanol/ammonium hydroxide 50/50/2.5), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **35** (410 mg) which was rechromatographed (silica gel, ethyl acetate/methanol/ammonium hydroxide 50/50/2.5) to give pure **35** (302 mg, 73%): DSC (mp) 108 °C; ^{1}H NMR (CD_3OD) δ 3.87 (dd, J = 12, 3 Hz, 1H), 3.82 (dd, J = 12, 3 Hz, 1H), 3.33 (dd, J = 9, 8 Hz, 1H), 2.99

(dd, J = 9, 8 Hz, 1H), 2.96 (dd, J = 12, 4 Hz, 1H), 2.80 (dt, J = 13, 8 Hz, 1H), 2.70 (ddd, J = 10, 9, 4 Hz, 1H), 2.54 (dt, J = 13, 8 Hz, 1H), 2.10 (dd, J = 12, 10 Hz, 1H), 2.10 (dt, J = 9, 3 Hz, 1H), 1.48 (p, J = 7 Hz, 2 H), 1.25 - 1.40 (complex band, 2H), 0.93 (t, J = 7 Hz, 3H); MS (CI, CH_4, m/z) 219 (MH^+).

Anal. Calcd for $C_{10}H_{22}N_2O_3 \cdot 0.3H_2O$: C, 53.69; H, 10.18; N, 12.52. Found: C, 53.63; H, 10.02; N, 12.34.

4,6-*O*-(*R*-Benzylidene)-*N*-butyl-1,2,5-trideoxy-2-(dimethylamino)-1,5-imino-D-glucitol (32) and 4,6-*O*-(*R*-Benzylidene)-*N*-butyl-1,2,5-trideoxy-1,5-imino-2-(methylamino)-D-glucitol (31). To a solution of **30** (792 mg, 2.59 mmol) in methanol (75 mL) in a Parr hydrogenation flask, 4% Pd on C (100 mg) and formaldehyde (37 wt % solution in water, 0.23 mL) were added. The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times) and then pressurized to 5 psi hydrogen. After running the reaction on a shaker for 21 h, the system was vented, purged with nitrogen and filtered. The filtrate was concentrated and the crude product (560 mg) was chromatographed (silica gel, methylene chloride/methanol/ammonium hydroxide 90/10/1) to give **32** (310 mg, 36%) and **31** (372 mg, 45%).

32: ^{1}H NMR ($CDCl_3$) d 7.52 (m, 2H), 7.34 (m, 3H), 5.52 (s, 1H), 4.37 (dd, J = 11, 5 Hz, 1H), 3.83 (brs, 1H), 3.65 (dd, J = 11, 10 Hz, 1H), 3.60 (t, J = 9 Hz, 1H), 3.54 (t, J = 9 Hz, 1H), 2.93 (dd, J = 11, 4 Hz, 1H), 2.63 (ddd, J = 11, 9, 4 Hz, 1H), 2.53 (dt, J = 13, 8 Hz, 1H), 2.35 (s, 6H), 2.22-2.37 (complex band, 2H), 2.14 (t, J = 11 Hz, 1H), 1.42 (m, 2H), 1.27 (m, 2H), 0.92 (t, J = 7 Hz, 3H).

31: ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.34 (m, 3H), 5.49 (s, 1H), 4.36 (dd, J = 11, 4 Hz, 1H), 3.65 (dd, J = 11, 10 Hz, 1H), 3.48 (t, J = 9 Hz, 1H), 3.36 (dd, J = 10, 9 Hz, 1H), 3.25 (broad s, 1H), 3.05 (dd, J = 11, 5 Hz, 1H), 2.57 (td, J = 10, 5 Hz, 1H), 2.51 (dt, J = 13, 8 Hz, 1H), 2.39 (ddd, J = 10 , 9, 4 Hz, 1H), 2.37 (s, 3H), 2.30 (ddd, J = 13, 8, 6 Hz, 1H), 2.00 (t, J = 11 Hz, 1H), 1.42 (m, 2H), 1.26 (m, 2H), 0.92 (t, J = 7 Hz, 3H).

4,6-*O*-(*R*-Benzylidene)-*N*-butyl-2-butyramido-3-*O*-butanoyl-1,2,5-trideoxy-1,5-imino-D-glucitol (33). To a solution of **30** (650 mg 2.12 mmol) in pyridine (8 mL), butyric anhydride (2 mL) was added and the reaction mixture was stirred at room temperature. After stirring for 18 h, the reaction mixture was poured over ice and extracted with methylene chloride. The organic layer was washed with water and brine. After drying over $MgSO_4$, the extract was filtered and the solvent removed under reduced pressure. The crude product **33** (1.01 g) was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2H), 7.36 (m, 3H), 5.86 (d, J = 7.5 Hz, 1H), 5.53 (s, 1H), 4.92 (t, J = 10 Hz, 1H), 4.43 (dd, J = 11, 5 Hz, 1H), 4.16 (tdd, J = 10, 7.5, 5 Hz, 1H), 3.74 (t, J = 10 Hz, 1H), 3.73 (dd, J = 11, 10 Hz, 1H), 3.25 (dd, J = 12,

5 Hz, 1H), 2.55 (dt, J = 13, 8 Hz, 1H), 2.46 (td, J = 10, 5 Hz, 1H), 2.35 (dt, J = 15, 7.5 Hz, 1H), 2.29 (dt, J = 15, 7.5 Hz, 1H), 2.27 (dt, J = 13, 7 Hz, 1H), 2.10 (t, J = 7.5 Hz, 2H), 2.06 (dd, J = 12, 10 Hz, 1H), 1.62 (m, 4H), 1.41 (m, 2H), 1.27 (m, 2H), 0.93 (t, J = 7.5 Hz, 1H), 0.90 (t, J = 7.5 Hz, 1H).

***N*-Butyl-1,2,5-trideoxy-1,5-imino-2-(methylamino)-D-glucitol (36).** A solution of **31** (610 mg, 1.91 mmol) in trifluoroacetic acid/water (4/1, 10 mL) was stirred at 22 °C for 24 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/ 2-propanol/ammonium hydroxide 50/50/2.5), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **36** (480 mg), which was rechromatographed (silica gel, ethyl acetate/2-propanol/ammonium hydroxide 50/50/2.5) to give pure **36** (310 mg, 70%): ^{1}H NMR (CD_3OD) δ 3.87 (dd, J = 12, 2.5 Hz, 1H), 3.83 (dd, J = 12, 2.5 Hz, 1H), 3.37 (t, J = 9 Hz, 1H), 3.10 (dd, J = 12, 4 Hz, 1H), 3.08 (dd, J = 10, 9 Hz, 1H), 2.80 (dt, J = 13, 8 Hz, 1H), 2.63 (dt, J = 13, 7.5 Hz, 1H), 2.46 (td, J = 10, 4 Hz, 1H), 2.41 (s, 3H), 2.12 (dt, J = 9, 2.5 Hz, 1H), 2.07 (dd, J = 12, 10 Hz, 1H), 1.48 (p, J = 8 Hz, 2 H), 1.31 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); MS (CI, NH_3, m/z) 233 (MH^+).

Anal. Calcd for $C_{11}H_{24}N_2O_3 \cdot 0.4\ H_2O$: C, 55.16; H, 10.44; N, 11.70. Found: C, 55.24; H, 10.57; N, 11.74.

***N*-Butyl-1,2,5-trideoxy-2-(dimethylamino)-1,5-imino-D-glucitol (37).** A solution of **32** (580 mg, 1.74 mmol) in trifluoroacetic acid/water (4/1, 10 mL) was stirred at 22 °C for 24 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/ 2-propanol/ammonium hydroxide 50/50/2.5), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **37** (300 mg), which was rechromatographed (silica gel, ethyl acetate/2-propanol/ammonium hydroxide 50/50/2.5) to give pure **37** (260 mg, 61%): DSC (mp) 111 °C; ^{1}H NMR (CD_3OD) δ 3.86 (dd, J = 12, 2.5 Hz, 1H), 3.82 (dd, J = 12, 2.5 Hz, 1H), 3.40 (t, J = 9 Hz, 1H), 3.36 (t, J = 9 Hz, 1H), 2.95 (dd, J = 12, 4 Hz, 1H), 2.80 (ddd, J = 13, 10, 6 Hz, 1H), 2.52 - 2.62 (complex band, 2H), 2.40 (s, 6H), 2.23 (dd, J = 12, 11 Hz, 1H), 2.06 (dt, J = 9, 2.5 Hz, 1H), 1.47 (p, J = 7 Hz, 2H), 1.30 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); MS (CI, NH_3, m/z) 247 (MH^+).

Anal. Calcd for $C_{12}H_{26}N_2O_3 \cdot 0.2\ H_2O$: C, 57.66; H, 10.65; N, 11.21. Found: C, 57.88; H, 10.63; N, 11.23.

4,6-*O*-(*R*-Benzylidene)-*N*-butyl-2-butyramido-1,2,5-trideoxy-1,5-imino-D-glucitol (34). To a solution of **33** (900 mg, 2.01 mmol) in methanol (50 mL), saturated aqueous potassium carbonate (30 mL) was added and the mixture was stirred at room temperature for 4 h. After neutralizing with concd HCl to pH 7, methanol was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$) and filtered. Concentration of the extract gave **34** (720 mg, 90%): mp 172 °C (dec); IR (KBr) 1630 cm^{-1}; ^1H NMR (CD_3OD) δ 7.48 (m, 2H), 7.36 (m, 3H), 5.94 (broad s, *w(1/2)* = 19 Hz, 1H), 5.51 (s, 1H), 4.35 (dd, *J* = 10.5, 4.2 Hz, 1H), 4.02 (dddd, *J* = 11.0, 9.8, 7.0, 4.8 Hz, 1H), 3.68 (t, *J* = 10.5 Hz, 1H), 3.56 (dd, *J* = 9.0, 8.4 Hz, 1H), 3.50 (dd, *J* = 9.8, 9.0 Hz, 1H), 3.18 (dd, *J* = 11, 4.8 Hz, 1H), 2.50 (dt, *J* = 13.2, 8.0 Hz, 1H), 2.40 (ddd, *J* = 10.5, 8.4, 4.2 Hz, 1H), 2.25 (dt, *J* = 13.2, 7.2 Hz, 1H), 2.20 (dt, *J* = 14.8, 7.3 Hz, 1H), 2.15 (dt, *J* = 14.8, 7.3 Hz, 1H), 2.05 (t, *J* = 11 Hz, 1H), 1.66 (hextet, *J* = 7.5 Hz, 2H), 1.38 (p, *J* = 7.5 Hz, 2H), 1.19 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 66.99; H, 8.57; N, 7.44. Found: C, 66.82; H, 8.68; N, 7.36.

***N*-Butyl-2-butyramido-1,2,5-trideoxy-1,5-imino-D-glucitol (38).** A solution of **34** (250 mg, 0.66 mmol) in trifluoroacetic acid/water (4/1, 10 mL) was stirred at 22 °C for 24 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/2-propanol/water/ammonium hydroxide 70/25/5/2), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **38** (180 mg) which was rechromatographed (silica gel, ethyl acetate/2-propanol/ water/ammonium hydroxide 70/25/5/2) to give pure **38** (165 mg, 86%): DSC (mp) 203 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR (CD_3OD) δ 3.88 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.84 (ddd, *J* = 11.2, 10.2, 4.6 Hz, 1H), 3.83 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.40 (dd, *J* = 9.5, 8.7 Hz, 1H), 3.22 (dd, *J* = 10.2, 8.7 Hz, 1H), 3.02 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.81 (dt, *J* = 13.8, 8.0 Hz, 1H), 2.57 (dt, *J* = 13.8, 7.0 Hz, 1H), 2.20 (dt, *J* = 14.0, 7.4 Hz, 1H), 2.17 (dt, *J* = 14.0, 7.4 Hz, 1H), 2.16 (m, 1H), 2.13 (t, *J* = 11.2 Hz, 1H), 1.64 (hextet, *J* = 7.4 Hz, 2H), 1.46 (p, *J* = 7.8 Hz, 2H), 1.22 - 1.37 (complex band, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); MS (CI, NH_3, *m/z*) 289 (MH^+).

Anal. Calcd for $C_{14}H_{28}N_2O_4 \cdot 0.5\ H_2O$: C, 56.54; H, 9.83; N, 9.42. Found: C, 56.32; H, 9.50; N, 9.26.

C. 2-Fluorodeoxynojirimycin derivative:

2-Fluoro-1,2,5-trideoxy-1,5-imino-D-glucitol (27). To a solution of **13a** (3.9 g, 10.1 mmol) in methanol (38 mL) and water (10 mL) in a Fisher-Porter bottle, 10%

Pd on carbon catalyst (3.9 g) was added. The bottle was sealed, flushed 3 times with nitrogen (40 psi) and 4 times with hydrogen (50 psi) and then maintained at 50 psi hydrogen pressure. After heating at 50 °C for 21 h, the reaction bottle was cooled, vented and flushed with nitrogen. The contents of the reaction were filtered through a celite bed, and washed with water. The combined filtrates were extracted with ethyl acetate to remove organic impurities and the aqueous layer was concentrated under vacuum at 50 °C to afford an oil. The remaining water was removed by azeotroping with ethanol to provide 1.2 g of a white solid. The solid was dissolved in water and filtered to remove a slight grey color. The solvent was removed again and the solid obtained was recrystallized by dissolving in a minimum amount of water, followed by addition of ethanol and then hexane to afford 0.58 g (35%) of pure **27**: mp 161- 163°C; ^{1}H NMR (D_2O) δ 4.38 (dddd, J = 50.5, 10.8, 9.5, 5.5 Hz, 1H), 3.83 (dd, J = 11.7, 3.0 Hz, 1H), 3.64 (dd, J = 11.7, 6.0 Hz, 1H), 3.62 (dt, J = 14.5, 9.5 Hz, 1H), 3.39 (ddd, J = 12.3, 5.5, 1.5 Hz, 1H), 3.28 (t, J = 9.5 Hz, 1H), 2.65 (ddd, J = 12.3, 10.7, 4.9 Hz, 1H), 2.56 (ddd, J = 9.5, 6,0, 3.0 Hz, 1H); ^{13}C NMR (D_2O) δ 94.6 (d, J = 176.7 Hz), 79.9 (d, J = 16.7 Hz), 74.3 (d, J = 8.6 Hz), 64.3, 63.5, 49.3 (d, J = 24.0 Hz); MS (CI, m/z) 166 (MH^+).

Anal. Calcd for $C_6H_{12}FNO_3$: C, 43.63; H, 7.34; N, 8.48. Found: C, 43.79; H, 7.40; N, 8.37.

D. 2-*S*-Alkyldeoxynojirimycin derivatives:

1,5-Dideoxy-1,5-imino-2-*S*-methyl-2-thio-D-glucitol (28). A solution of **22a** (490 mg,1.74 mmol) and *p*-toluenesulfonic acid (398 mg, 2.09 mmol) in 95% ethanol (35 mL) was refluxed for 20 h. After removal of the solvent, the residue was dissolved in 25% MeOH/H_2O and passed through a basic ion exchange column [Amberlite, IRA-400 (OH)] and eluted with 25% MeOH/H_2O. The fractions containing the product were concentrated. The residual water was removed by repeated azeotropic distillation using toluene to give pure **28** (329 mg, 98%): ^{1}H NMR (D_2O) δ 4.80 (s, 1H), 3.84 (dd, J = 14, 3.7 Hz, 1H), 3.74 (dd, J = 14, 5.7 Hz, 1H), 3.44 - 3.36 (m, 3H), 2.80 (m, 2H), 2.66 (ddd, J = 11, 11, 4.5 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (D_2O) δ 74.82, 71.95, 60.47, 60.34, 47.75, 47.23, 11.98; MS (CI, NH_3, m/z) 194 (MH^+).

Anal. Calcd for $C_7H_{15}NO_3S{\cdot}0.75\ H_2O$: C, 40.66; H, 8.04; N, 6.80. Found: C, 40.46; H, 7.65; N, 6.99.

***N*-Butyl-1,5-dideoxy-1,5-imino-2-*S*-methyl-2-thio-D-glucitol (29).** To a solution of **28** (93 mg, 0.482 mmol) and butyraldehyde (85 mL, 0.94 mmol) in methanol (1.6 mL), 4Å molecular sieves (250 mg), acetic acid (79 mL) and sodium cyanoborohydride (32 mg, 0.51 mmol) were added. After stirring at room temperature for 20 h, the mixture was filtered through celite and concentrated. The residue was chromatographed over silica gel using 50/50 methanol/ethyl acetate as eluent. The fractions

containing the product were concentrated, dissolved in 50/50 trifluoroacetic acid/water and evaporated. The residue was dissolved in 50/50 methanol/water and passed first through a basic ion exchange column [Amberlite, IRA-400 (OH), eluting with 50/50 methanol/water], and then through an acidic ion exchange column [washing successively with water, 50/50 methanol/water and 0.5M ammonium hydroxide]. After concentration, the residue was triturated with ethyl acetate to give the title compound **29** (76 mg, 63%) as a white crystalline solid: DSC (mp) 93.6 °C; ^{1}H NMR (D_2O) δ 4.78 (brs, 1H), 3.93 (m, 2H), 3.44 (t, J = 8 Hz, 1H), 3.29 (t, J = 8 Hz, 1H), 3.16 (dd, J = 12, 5 Hz, 1H), 2.76 (m, 1H), 2.64 (m, 2H), 2.45 (t, J = 12 Hz, 1H), 2.30 (m, 1H), 2.16 (s, 3H), 1.48 (m, 2H), 1.30 (m, 2H), 0.91 (t, J = 7 Hz, 3H).

Anal. Calcd for $C_{11}H_{23}NO_3S$: C, 52.97; H, 9.29; N, 5.62. Found: C, 52.69; H, 9.30; N, 5.57.

IV. Synthesis of 3-substituted-1-deoxynojirimycins:

8ß-Azidohexahydro-*N*-benzyloxycarbonyl-7-oxo-2*R*-2α-phenyl-5H-4,4aα, 8aß-1,3-dioxino[5,4-b]pyridine-5-carboxylate (39). To a cold solution of dimethyl sulfoxide (5.6 mL, 78 mmol) in methylene chloride (50 mL) at -70 °C, trifluoroacetic anhydride (8.32 mL, 59 mmol) in methylene chloride (50 mL) was added over 20 min. After stirring for 15 min, a solution of **12b** (16 g, 39 mmol) in methylene chloride (150 mL) was added over 30 min. at -70 °C. The temperature of the reaction mixture was allowed to rise to -30 °C over 4 h and then the reaction was stirred at -30 °C for 1 h. After recooling to -70 °C, triethylamine (15 mL, 107 mmol) was added and the reaction was warmed to 22 °C in about 1 h and stirred at 22 °C for about 8 h. The reaction was diluted with methylene chloride and washed with water and brine. After drying ($MgSO_4$), filtration and concentration, the crude material (17.8 g) was chromatographed (silica gel, hexane /ethyl acetate 1/1) to give pure **39** (13.9 g, 86%): IR (KBr) 1745, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 - 7.49 (complex band, 10H), 5.71 (s, 1H), 5.13 (s, 2H), 4.85 (d, J = 11 Hz, 1H), 4.61 (dd, J = 11, 4 Hz, 1H), 4.33 (dd, J = 11, 10 Hz, 1H), 4.30 (d, J = 18 Hz, 1H), 4.20 (d, J = 18 Hz, 1H), 4.11 (dd, J = 11, 10, 1H), 3.85 (dt, J = 10, 4Hz, 1H).

3-Azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,3,5-trideoxy-1,5-imino-D-glucitol (40) and 3-azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,3,5-trideoxy-1,5-imino-D-mannitol (41). To a cold solution of **39** (2.5 g, 6.12 mmol) in THF (100 mL) at -78 °C, diisobutylaluminum hydride (9.25 mL, 1 M solution in toluene, 9.25 mmol) was added over 10 min. After stirring at -78 °C for 4 h, methanol (2.5 mL) was added. The reaction was stirred for 10 min, the cold bath was removed and the reaction allowed to rise to 22 °C and stirred for 30 min. After quenching with 0.5 N HCl (10 mL), the reaction was diluted with ethyl acetate

and washed with water and brine. The organic extract was dried ($MgSO_4$), filtered and concentrated to give a crude mixture (2.23 g) as a thick orange liquid. Chromatographic purification (silica gel, hexane/ethyl acetate 1/1) gave **40** (1.57 g, 63%) and **41** (231 mg, 9%).

40: ^1H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.35 (m, 8H), 5.60 (s, 1H), 5.11 (d, J = 12 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 4.83 (dd, J = 12, 5 Hz, 1H), 4.44 (dd, J = 12, 10 Hz, 1H), 4.32 (distorted dd, J = 14, 5 Hz, 1H), 3.67 (distorted t, J = 9 Hz, 1H), 3.50 (m, 1H), 3.47 (m, 1H), 3.27 (td, J = 10, 5 Hz, 1H), 2.79 (s, 1H), 2.74 (distorted dd, J = 14, 10 Hz, 1H); MS (CI, NH_3, m/z) 411 (MH^+); HRMS (m/z) Calcd for $C_{21}H_{23}N_4O_5$ (M + H) 411.1629, Found 411. 1635.

Anal. Calcd for $C_{21}H_{22}N_4O_5 \cdot 0.2H_2O$: C, 60.92; H, 5.45; N, 13.53. Found: C, 61.21; H, 5.78; N, 13.38.

41: ^1H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.33 (m, 8H), 5.62 (s, 1H), 5.08 (s, 2H), 4.77 (dd, J = 12, 5 Hz, 1H), 4.61 (dd, J = 12, 10 Hz, 1H), 4.34 (dd, J = 15, 3 Hz, 1H), 4.19 (t, J = 10 Hz, 1H), 3.85 (m, 1H), 3.53 (dd, J = 10, 3 Hz, 1H), 3.21 (td, J = 10, 5 Hz, 1H), 2.78 (broad d, J = 15 Hz, 1H), 2.66 (broad s, 1H); MS (CI, NH_3, m/z) 411 (MH^+).

Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.46; H, 5.40; N, 13.65. Found: C, 61.37; H, 5.43; N, 13.39.

3-Azido-4,6-*O*-(*R*-benzylidene)-1,3,5-trideoxy-1,5-imino-D-glucitol (42). Compound **40** (1.8 g, 4.39 mol) was added to a previously prepared solution of sodium hydroxide (2 g) in ethanol/water (1/1, 60 mL). After heating the mixture at 75 - 80 °C for 20 h, the reaction was cooled and part of the solvent was removed under reduced pressure. The mixture was neutralized with 1N HCl and extracted with methylene chloride. The organic layer was washed with water and brine. After drying ($MgSO_4$) and concentration of the filtrate, the crude product (3.01 g) was chromatographed (silica gel, methylene chloride/methanol/ammonium hydroxide 90/10/1) to give pure **42** (1.1 g, 91%): DSC (mp) 192 °C; ^1H NMR ($CDCl_3$) δ 7.52 (m, 2H), 7.38 (m, 3H), 5.61 (s, 1H), 4.28 (dd, J = 10.8, 4.8 Hz, 1H), 3.66 (dd, J = 10.8, 10.2 Hz, 1H), 3.50 - 3.58 (complex band, 2H), 3.48 (distorted dd, J = 10, 8.8 Hz, 1H), 3.29 (distorted dd, J = 12.0, 4.8 Hz, 1H), 2.82 (ddd, J = 10.2, 8.8, 4.8 Hz, 1H), 2.67 (distorted dd, J = 12, 10 Hz, 1H); MS (CI, NH_3, m/z) 277 (MH^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.26; H, 5.90; N, 20.08.

3-Amino-4,6-*O*-(*R*-benzylidene)-1,3,5-trideoxy-1,5-imino-D-glucitol (43). To a solution of **42** (700 mg, 2.54 mmol) in methanol (50 mL) in a Parr hydrogenation flask, 4% Pd on C (150 mg) was added. The system was sealed, purged

with nitrogen (5 times) and hydrogen (5 times) and then pressurized to 5 psi hydrogen. After running the reaction on a shaker for 10 h, the system was vented, purged with nitrogen and filtered. The filtrate was concentrated and the crude material (700 mg) was chromatographed (silica gel, methylene chloride/methanol/ammonium hydroxide 90/10/1) to give pure **43** (590 mg, 93%): ^{1}H NMR (CD_3OD) δ 7.49 (m, 2H), 7.34 (m, 3H), 5.54 (s, 1H), 4.17 (dd, J = 11, 5 Hz, 1H), 3.60 (dd, J = 11, 10 Hz, 1H), 3.40 (ddd, J = 10, 9, 5 Hz, 1H), 3.26 (dd, J = 10, 9 Hz, 1H), 3.08 (dd, J = 12, 5 Hz, 1H), 2.79 (dd, J = 10, 9 Hz, 1H), 2.63 (ddd, J = 10, 9, 5 Hz, 1H), 2.50 (dd, J = 12, 10 Hz, 1H); MS (CI, NH_3, m/z) 251 (MH^+).

Anal. Calcd for $C_{13}H_{18}N_2O_3 \cdot 0.25H_2O$: C, 61.28; H, 7.32; N, 10.99. Found: C, 61.27; H, 7.29; N, 10.72.

3-Amino-1,3,5-trideoxy-1,5-imino-D-glucitol (44). A solution of **43** (480 mg, 1.92 mmol) in trifluoroacetic acid/water (4/1, 8 mL) was stirred at 22 °C for 24 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/methanol/ammonium hydroxide 25/75/3), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **44** which was rechromatographed (silica gel, ethyl acetate/methanol/ammonium hydroxide 25/75/3) to give pure **44** (135 mg, 32%): DSC (mp) 191°C; ^{1}H NMR (CD_3OD) δ 3.81 (dd, J = 11, 3 Hz, 1H), 3.59 (dd, J = 11, 7 Hz, 1H), 3.31 (td, J = 10, 5 Hz, 1H), 3.09 (t, J = 9 Hz, 1H), 3.07 (dd, J = 12, 5 Hz, 1H), 2.53 (dd, J = 10, 9 Hz, 1H), 2.45 (dd, J = 12, 10 Hz, 1H), 2.44 (dd, J = 9, 7, 3 Hz, 1H); MS (CI, NH_3, m/z) 163 (MH^+); HRMS (m/z) calcd for $C_6H_{15}N_2O_3$ (M + H) 163.1088, found 163.1085.

Anal. Calcd for $C_6H_{14}N_2O_3 \cdot 0.25H_2O$: C, 43.23; H, 8.77; N, 16.81. Found: C, 43.66; H, 8.61; N, 16.19.

V. Synthesis of 2,3-disubstituted-1-deoxynojirimycins:

2-Azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-3-*O*-methanesulfonyl-D-glucitol (45). To a solution of **12a** (3.8 g, 9.27 mmol) in pyridine (40 mL), methanesulfonyl chloride (860 μL, 11.11 mmol) was injected over 10 min. After stirring at 22 °C for 20 h, the reaction contents were poured over ice and extracted with ethyl acetate (2 x 700). The combined organic extracts were washed with saturated aqueous potassium carbonate, water and brine. After drying ($MgSO_4$), filtration and concentration, the crude material (6.45 g) was chromatographed (silica gel, hexane/ethyl acetate 6/4) to give pure **45** (4.3 g, 95%) as a white solid: DSC (mp) 222 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.33 (m, 8H), 5.52 (s, 1H), 5.13 (d, J = 12 Hz, 1H), 5.09 (d, J = 12 Hz, 1H), 4.77 (dd, J = 12, 5 Hz, 1H), 4.59 (t, J = 9 Hz,

1H), 4.39 (dd, J = 12, 10 Hz, 1H), 4.33 (dd, J = 14, 5 Hz, 1H), 3.78 (dd, J = 10, 9 Hz, 1H), 3.61 (ddd, J = 11, 9, 5 Hz, 1H), 3.27 (td, J = 10, 5 Hz, 1H), 2.93 (s, 3H), 2.81 (dd, J = 14, 11 Hz, 1H).

Anal. Calcd for $C_{22}H_{24}N_4O_7S \cdot H_2O$: C, 52.17; H, 5.17; N, 11.06. Found: C, 52.29; H, 4.81; N, 10.87.

3-*O*-Acetyl-2-azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-D-allitol (46). A mixture of **45** (2.3 g, 4.7 mmol), cesium acetate (9 g, 47 mmol), 18-crown-6 (1.16 g, 4.7 mmol) in toluene (50 mL) was refluxed for 72 h. The reaction was cooled and filtered and the residue was washed with more toluene. The combined organic fractions were concentrated and the crude product (3.36 g) was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give pure **46** (1.1 g, 52%) as a white solid in addition to the recovered starting material **45** (0.31 g, 14%).

46: ^{1}H NMR ($CDCl_3$) δ 7.31 - 7.45 (complex band, 10H), 5.74 (td, J = 3, 1 Hz, 1H), 5.56 (s, 1H), 5.15 (d, J = 12 Hz, 1H). 5.11 (d, J = 12 Hz, 1H), 4.84 (dd, J = 12, 5 Hz, 1H), 4.48 (dd, J = 12, 10 Hz, 1H), 4.32 (ddd, J = 13, 5, 1 Hz, 1H), 3.79 (dd, J = 10, 3 Hz, 1H), 3.61 (td, J = 10, 5 Hz, 1H), 3.52 (ddd, J = 11, 5, 3 Hz, 1H), 3.16 (dd, J = 13, 11 Hz, 1H), 2.17 (s, 3H); MS (CI, NH_3, m/z) 453 (MH^+).

2-Azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-D-allitol (47) and 2-azido-4,6-*O*-(*R*-benzylidene)-1,2,5-trideoxy-1,5-imino-*N*-methoxycarbonyl-D-allitol (48). A mixture of **46** (970 mg, 2.15 mmol) and sodium methoxide (400 mg, 7.4 mmol) in methanol (50 mL) was refluxed for 18 h. The reaction was cooled and neutralized with 1N HCl and the solvent was removed under reduced pressure. The residue was suspended in ethyl acetate and washed with saturated aqueous potassium carbonate, water and brine. The combined organic extracts were concentrated and the crude product (1.02 g) was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give **47** (550 mg, 57%) and **48** (270 mg, 35%).

47: ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2H), 7.34 (m, 8H), 5.55 (s, 1H), 5.10 (d, J = 12 Hz, 1H). 5.07 (d, J = 12 Hz, 1H), 4.79 (dd, J = 12, 5 Hz, 1H), 4.45 (dd, J = 12, 10 Hz, 1H), 4.22 (broad s, 1H), 4.17 (m, 1H), 3.62 (td, J = 10, 5 Hz, 1H), 3.54 (dt, J = 10, 2 Hz, 1H), 3.24 (m, 1H), 3.21 (m, 1H), 2.87 (s, 1H).

48: ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2H), 7.37 (m, 3H), 5.59 (s, 1H), 4.81 (dd, J = 12, 4 Hz, 1H), 4.48 (dd, J = 12, 9 Hz, 1H), 4.27 (broad s, 1H), 4.12 (dd, J = 12, 2 Hz, 1H), 3.67 (s, 3H), 3.65 (m, 1H), 3.60 (m, 1H), 3.30 (m, 1H), 3.23 (m, 1H), 2.82 (broad s, 1H).

2-Azido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-3-*O*-methanesulfonyl-D-allitol (49). To a solution of **47** (550 mg, 1.34 mmol) in pyridine (10 mL), methanesulfonyl chloride (140 µL, 1.74 mmol)

was injected over 10 min. After stirring at 22 °C for 60 h, the reaction contents were poured over ice and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous potassium carbonate, water and brine. After drying ($MgSO_4$), filtration and concentration, the product obtained, **49** (603 mg, 92%) was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.35 (m, 8H), 5.58 (s, 1H), 5.15 (broad t, J = 2.5 Hz, 1H), 5.11 (s, 2H), 4.87 (dd, J = 12, 5 Hz, 1H), 4.45 (dd, J = 12, 10 Hz, 1H), 4.31 (dd, J = 13, 5 Hz, 1H), 3.80 (dd, J = 10, 2 Hz, 1H), 3.60 (ddd, J = 12, 5, 3 Hz, 1H), 3.56 (td, J = 10, 5 Hz, 1H), 3.10 (dd, J = 13, 12 Hz, 1H), 2.92 (s, 3H).

2-Azido-4,6-*O*-(*R*-benzylidene)-1,2,5-trideoxy-1,5-imino-*N*-methoxycarbonyl-3-*O*-methanesulfonyl-D-allitol (50). To a solution of **48** (217 mg, 0.65 mmol) in pyridine (5 mL), methanesulfonyl chloride (65 µL, 0.84 mmol) was injected over 10 min. After stirring at 22 °C for 30 h, the reaction contents were poured over ice and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous potassium carbonate, water and brine. After drying ($MgSO_4$), filtration and concentration, the product **50** (320 mg, 92%) was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.46 (m, 2H), 7.35 (m, 3H), 5.61 (s, 1H), 5.18 (broad t, J = 2.5 Hz, 1H), 4.88 (dd, J = 12, 5 Hz, 1H), 4.48 (dd, J = 12, 10 Hz, 1H), 4.28 (dd, J = 13, 5 Hz, 1H), 3.83 (dd, J = 10, 2 Hz, 1H), 3.70 (s, 3H), 3.66 (ddd, J = 12, 5, 3 Hz, 1H), 3.58 (td, J = 10, 5 Hz, 1H), 3.12 (dd, J = 13, 12 Hz, 1H), 2.95 (s, 3H).

2,3-Diazido-4,6-*O*-(*R*-benzylidene)-1,2,3,5-tetradeoxy-1,5-imino-*N*-methoxycarbonyl-D-glucitol (52). To a solution of **50** (320 mg, 0.77 mmol) in dimethylformamide (10 mL), sodium azide (252 mg, 3.88 mmol) was added. The reaction mixture was heated at 100 - 110 °C for 30 h. Part of the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate and washed with aqueous potassium carbonate, water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude **52** (190 mg, 69%) was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 3H), 5.62 (s, 1H), 4.79 (dd, J = 12, 5 Hz, 1H), 4.45 (dd, J = 12, 10 Hz, 1H), 4.28 (dd, J = 14, 5 Hz, 1H), 3.68 (s, 3H), 3.67 (t, J = 10 Hz, 1H), 3.50 (t, J = 10 Hz, 1H), 3.30 (ddd, J = 11, 10, 5 Hz, 1H), 3.20 (td, J = 10, 5 Hz, 1H), 2.64 (dd, J = 14, 11 Hz, 1H).

2,3-Diazido-4,6-*O*-(*R*-benzylidene)-*N*-benzyloxycarbonyl-1,2,3,5-tetradeoxy-1,5-imino-D-glucitol (51). To a solution of **49** (600 mg, 1.23 mmol) in dimethylformamide (10 mL), sodium azide (400 mg, 6.15 mmol) was added. The reaction mixture was heated at 100 - 110 °C for 72 h. Part of the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate and washed with aqueous potassium carbonate, water and brine. The organic layer was dried ($MgSO_4$),

filtered and concentrated. The crude mixture (760 mg) consisting of **51** and **53** was hydrolyzed to **53** without purification.

2,3-Diazido-4,6-*O*-(*R*-benzylidene)-1,2,3,5-tetradeoxy-1,5-imino-D-glucitol (53). The compound **51** (190 mg) was combined with the mixture of **51** and **53** (650 mg) as obtained in the above step. This combined mixture was added to a previously prepared solution of sodium hydroxide (2 g) in ethanol/water (1/1, 60 mL). After refluxing for 20 h, the reaction was cooled and part of the solvent removed under reduced pressure. The mixture was neutralized with 1N HCl and extracted with ethyl acetate. The organic layer was washed with water and brine. After drying ($MgSO_4$) and concentration of the filtrate, the crude product (280 mg) was chromatographed (silica gel, methylene chloride/ethanol 98/2) to give pure **53** (360 mg, 68% in two steps): ^1H NMR ($CDCl_3$) δ 7.56 (m, 2H), 7.43 (m, 3H), 5.61 (s, 1H), 4.23 (dd, J = 11, 5 Hz, 1H), 3.58 (dd, J = 11, 10 Hz, 1H), 3.53 (dd, J = 10, 9 Hz, 1H), 3.42 (dd, J = 10, 9 Hz, 1H), 3.29 (td, J = 10, 5 Hz, 1H), 3.21 (dd, J = 12, 5 Hz, 1H), 2.71 (td, J = 10, 5 Hz, 1H), 2.54 (dd, J = 12, 10 Hz, 1H), 1.15 (broad s, 1H).

2,3-Diazido-4,6-*O*-(*R*-benzylidene)-*N*-butyl-1,2,3,5-tetradeoxy-1,5-imino-D-glucitol (54). To a solution of **53** (360 mg, 1.19 mmol) in methanol (10 mL), 4Å molecular sieves (0.7 g) were added. After stirring for 5 min, butyraldehyde (0.22 mL, 2.4 mol), acetic acid (0.2 mL) and sodium cyanoborohydride (95%, 111 mg, 1.78 mmol) were added. The reaction was stirred at 22 °C for 18 h, filtered and the residue washed with more methanol. The combined organic fractions were concentrated. The residue was redissolved in ethyl acetate and washed with aqueous potassium carbonate, water and brine. After drying ($MgSO_4$) and concentration, the crude material (0.47 g) was chromatographed (silica gel, hexane/ethyl acetate 8/2) to give pure **54** (410 mg, 94%): ^1H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 3H), 5.58 (s, 1H), 4.43 (dd, J = 11, 5 Hz, 1H), 3.68 (dd, J = 11, 10 Hz, 1H), 3.59 (t, J = 9 Hz, 1H), 3.45 (dd, J = 10, 9 Hz, 1H), 3.38 (td, J = 10, 5 Hz, 1H), 3.07 (dd, J = 12, 5 Hz, 1H), 2.53 (dt, J = 13, 8 Hz, 1H), 2.41 (ddd, J = 10, 9, 5 Hz, 1H), 2.30 (dt, J = 13, 7 Hz, 1H), 2.17 (dd, J = 12, 10 Hz, 1H), 1.39 (m, 2H), 1.28 (m, 2H), 0.92 (t, J = 7 Hz, 3H).

2,3-Diamino-4,6-*O*-(*R*-benzylidene)-*N*-butyl-1,2,3,5-tetradeoxy-1,5-imino-D-glucitol (55). To a solution of **54** (385 mg, 1.08 mmol) in methanol (25 mL) in a Parr hydrogenation flask, 10% Pd on C (60 mg) was added. The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times) and then pressurized to 5 psi hydrogen. After running the reaction on a shaker for 3.5 h, the system was vented, purged with nitrogen and filtered. The filtrate was concentrated and the crude material (320 mg) was chromatographed (silica gel, ethyl acetate/methanol/ammonium hydroxide 50/50/2.5) to give **55** (240 mg, 73%): ^1H NMR (CD_3OD) δ 7.49 (m, 2H), 7.34 (m, 3H), 5.53 (s,

1H), 4.42 (dd, J = 11, 4 Hz, 1H), 3.66 (dd, J = 11, 10 Hz, 1H), 3.36 (dd, J = 10, 9 Hz, 1H), 3.02 (dd, J = 12, 5 Hz, 1H), 2.66 (td, J = 10, 4 Hz, 1H), 2.58 (m, 1H), 2.52 (t, J = 10 Hz, 1H), 2.34 (ddd, J = 10, 9, 5 Hz, 1H), 2.27 (ddd, J = 14, 8, 5 Hz, 1H), 2.04 (dd, J = 12, 10 Hz, 1H), 1.38 -1.53 (complex band, 2H), 1.21 - 1.38 (complex band, 2H), 0.94 (t, J = 7 Hz, 2H); MS (EI, m/z) 305 (M^+).

Anal. Calcd for $C_{17}H_{27}N_3O_2 \cdot 0.25H_2O$: C, 65.88; H, 8.94; N, 13.56. Found: C, 65.53; H, 8.99; N, 13.28.

2,3-Diamino-*N*-butyl-1,2,3,5-tetradeoxy-1,5-imino-D-glucitol (56). A solution of **55** (235 mg, 0.77 mmol) in trifluoroacetic acid/water (4/1, 10 mL) was stirred at 22 °C for 18 h. The solvent was removed under reduced pressure and the residue was passed through an ion-exchange column [Amberlite, IRA-400 (OH)] prewashed with distilled water until neutral. The basic fractions, followed by TLC (silica gel, ethyl acetate/methanol/ammonium hydroxide 25/75/3), were pooled and concentrated. The water in the fractions was azeotropically removed with toluene to give crude **56** (152 mg), which was rechromatographed (silica gel, ethyl acetate/methanol/ammonium hydroxide 25/75/3) to give pure **56** (72 mg, 43%): ^{1}H NMR (CD_3OD) δ 3.88 (dd, J = 12, 2.5 Hz, 1H), 3.84 (dd, J = 12, 2.5 Hz, 1H), 3.26 (dd, J = 10, 9 Hz, 1H), 2.98 (dd, J = 12, 4 Hz, 1H), 2.80 (dt, J = 13, 8 Hz, 1H), 2.61 (td, J = 10, 4 Hz, 1H), 2.57 (dt, J = 13, 7.5 Hz, 1H), 2.29 (t, J = 10 Hz, 1H), 2.12 (dd, J = 12, 10 Hz, 1H), 2.10 (dt, J = 9, 2.5 Hz, 1H), 1.48 (p, J = 7Hz, 2H), 1.32 (hextet, J = 7 Hz, 2H), 0.94 (t, J = 7 Hz, 2H); MS (CI, NH_3, m/z) 218 (MH^+).

Anal. Calcd for $C_{10}H_{23}N_3O_2$: C, 55.27; H, 10.67; N, 19.34. Found: C, 54.86; H, 10.78; N, 19.00.

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17. The C_2-H and C_3-H signals in **12a** and **12b** were differentiated by their coupling to adjacent protons; C_2-H is coupled to both C-1 protons, while C_3-H is coupled to the C-4 proton. In both **12a** and **12b**, coupling to the hydroxyl proton was observed, permitting assignment of the hydroxyl group position. In **12a**, the C-2 and C-3 proton signals each showed two axial-axial couplings ($J_{1,2}$ = 11 Hz, $J_{2,3}$ = 9 Hz and $J_{3,4}$ = 9 Hz), indicating that both protons are axial. The C_3-H signal at δ 3.70, in addition to the axial-axial couplings to C_2-H and C_4-H, showed a 2 Hz coupling to the hydroxyl proton signal at δ 2.81. Acetylation of the hydroxy group shifted the C_3-H signal downfield to δ 5.14 (t, J = 9 Hz), confirming that the hydroxyl was at C-3. In **12b**, the signals due to C_2-H and C_3-H did not show large axial-axial coupling to adjacent protons ($J_{1,2}$ = 2 Hz, $J_{1,2}$ = 1 Hz, $J_{2,3}$ = 2 Hz, $J_{3,4}$ = 3 Hz) suggesting that the substituents at C-2 and C-3 were both axial. In addition, the coupling (t, J = 3 Hz) of C_2-H (δ 3.87) to the hydroxyl proton (δ 2.16) confirmed that the hydroxyl group was at C-2. The phenyl gro^{0}up of the benzylidine in intermediates (e.g, **7** - **17**) has been assigned the equatorial configuration based on NOE experiments done on **12a** and NOESY experiments performed on related compounds to be published later.

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