Glycomimetics: A Versatile *de Novo* Synthesis of *β*-1-*C*-Aryl-deoxymannojirimycin Analogues

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The synthesis of 11 *β*-1-*C*-aryl-deoxymannojirimycin analogues using a versatile *de novo* strategy is described. The origins of this report are derived from several recent developments in the area of C_1-substituted glycomimetic polyhydroxylated piperidines. This study is designed as a structure−activity comparison to explore the effects of aryl substitution on the ability of the title compounds to inhibit glycosidase enzymes. The polyhydroxylated piperidine ring was constructed using vinyl bromide **10**, which was synthesized in six steps from the bromobenzene microbial oxidation metabolite bromo diol **9**. A palladium-catalyzed Suzuki cross-coupling of vinyl bromide **10** and the corresponding arylboronic acid served as the key pseudoanomeric carbon−carbon bond-forming step. Ozonolysis and selective reduction of the resultant carbonyl functions followed by reductive amination served to produce the azasugar ring. The complete NMR analysis of the resultant piperidine ring stereochemistry is also discussed. Fully deprotected *β*-1-*C*-aryl-deoxymannojirimycin analogues **8**·HCl were obtained upon acidic deprotection.

Introduction

The inhibition of carbohydrate processing enzymes called glycosidases by polyhydroxylated piperidines and related alkaloids has become an area of vast academic and industrial interest as attested to by literally hundreds of publications and patents over the past several years.[1] These enzymes are responsible for many biological phenomena such as digestion, biosynthesis of glycoproteins, as well as the trimming of cell-surface oligosaccharides and hence play a role in cellular recognition, an area of enormous implications. Glycosidase inhibitors have potential in the treatment of viral infections,[2] cancer,[3] and diabetes and other metabolic disorders.[4] These enzymes act upon the glycosidic linkage of oligosaccharides and glycopeptides by stabilizing an intermediate oxonium ion, thus facilitating the lysis and modification of the anomeric center (Figure 1a).[5] Polyhydroxylated piperidines, commonly referred to as "azasugars", display the same dense stereochemical information as the common hexoses, but contain an NH in place of the pyranose oxygen. The mechanism of inhibition of glycosidase enzymes by azasugars is believed to be a result of the protonation of the nitrogen of the piperidine ring at biological pH, thus providing an electronic mimic of the transition state oxonium ion involved in enzymatic glycoside modification (Figure 1b). The pH dependence of azasugar inhibition is believed to be a result of an ionic interaction with a negatively charged carboxylate ion present in the active site of the enzyme which is responsible for the charge stabilization of the positively charged high energy oxonium ion during normal hydrolysis.[6,1a] When the azasugar is in a protonated form, this interaction is possible, whereas the free base is not capable of anything more than a hydrogen bonding interaction. It is the optimization of the interaction between the positively charged substrate and the enzyme active site that has carried this field of interest.

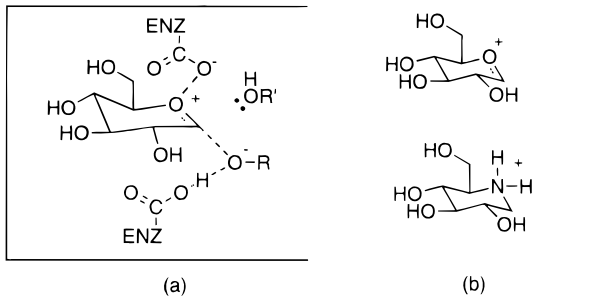

Figure 1. (a) Proposed transition state of enzymatic glycoside lysis. (b) Comparison of charged character of oxonium ion (top) with a protonated azasugar (bottom).

Most of the biologically interesting members of this class of compounds are 1-deoxy analogues or diastereomers of 1-deoxynojirimycin (DNJ) (**1**), the stereochemical equivalent of D-glucose (**2**). The presence of substitution at the C_1 position of azasugars is known to dramatically effect the selectivity and potency of inhibition.[1a] Due to the hydrolytic lability of the N/O aminal function, aza-*O*-glycosides have not emerged as a viable class of glycomimetics for studying glycosidase activity.[7] This is also evident in the relative stabilities of DNJ (**1**) and the

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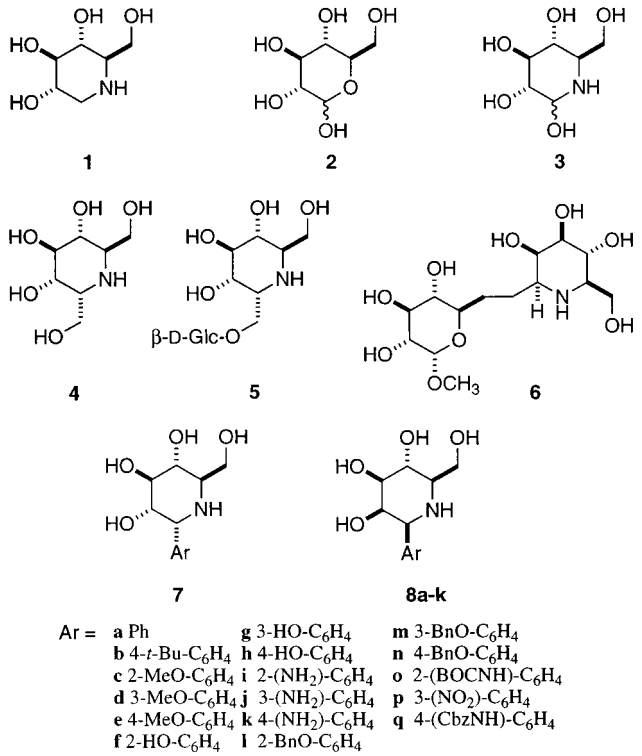
parent nojirimycin (**3**) containing an anomeric hydroxyl. The former does not contain any reactive functionality at the anomeric center and hence cannot undergo any deleterious reactions, yet still retains much of its inhibitory properties. *C*-Glycosides have emerged as one possible answer to the hydrolytic stability problem of many carbohydrates and are well studied for furanose, and pyranose systems.[8] Several studies concerning C_1 carbon substituted azasugars have appeared recently in the literature.[9] Included among these are the homoazasugars such as homonojirimycin (HNJ) (**4**). HNJ was isolated from *Omphaela diandra* and shown to be an inhibitor of several α-glycosidases;[9a] since then several syntheses of homoazasugars have also appeared. A potent and specific glycosidase inhibitor, and an antidiabetic drug candidate has been produced by glycosylation of the C_1 hydroxymethyl substituent of HNJ with the synthesis of MDL 25,637 (**5**).[5b] Several reports of aza-*C*-disaccharides such as **6** from our laboratories and others have recently appeared.[10] Biological results support the suggestion that differing C_1 substituents can dramatically alter the potency and specificity of the azasugar.[10f,9b]



In order to further examine the effects of C_1 substituents on the biological properties of azasugars, we desired to construct C_1-aryl-substituted azasugars. To our knowledge only two such compounds have been reported. Junge reported the synthesis of α-1-*C*-phenyl-deoxynojirimycin (**7a**),[11] and Fleet reported the synthesis of β-1-*C*-phenyl-deoxymannojirimycin (**8a**).[6,9b] Of the two reports, only Fleet presents biological studies. As is common with most C_1-substituted deoxymannojirimycin derivatives, the β-phenyl derivative **8** shows no inhibition of mannosidases, but is a potent inhibitor of α-L-fucosidase. It has been suggested that the 4, 3, and 2 positions of the fuco stereochemistry are mimicked by the 2, 3, and 4 hydroxyl groups in the manno configuration of the inhibitor (Figure 2).[6] The 1-β substituent can also likely occupy the same stereochemical region as the methyl group at the 5 position of fucose. We desired to further explore the effects of aryl substitution on the ability of the β-1-*C*-aryl-deoxymannojirimycin system to inhibit glycosidases. We now report the synthesis of the parent β-1-*C*-phenyl-deoxymannojirimycin (**8a**) and 10 additional analogues (**8b**−**k**) using a versatile route based on a palladium-catalyzed Suzuki cross-coupling[13] as the key carbon−carbon pseudoglycosidic bond forming step.

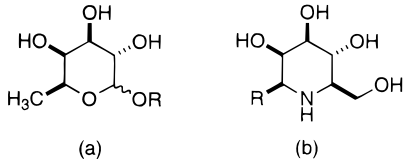
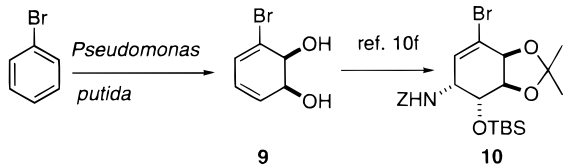


Figure 2. (a) α-L-Fucose. (b) β-1-*C*-Substituted-deoxymannojirimycin.

Results and Discussion

The recent development of the microbial oxidation of halobenzenes to produce enantiopure halogen-substituted cyclohexadiene diols into a commercial process has attracted our attention.[12] Specifically, the bromo derivative **9** derived from bromobenzene was envisioned to be a very useful intermediate due to its ability to be functionalized at every position, and eventual use of the vinyl bromide moiety as a partner in a palladium-catalyzed Suzuki cross-coupling,[13] an area of current interest in our group.[14,10f,17] Vinyl bromide **10** was prepared in six steps from bromo diol **9** in an overall yield of 55−60% on a multigram scale as previously reported (eq 1).[10f]



(1)

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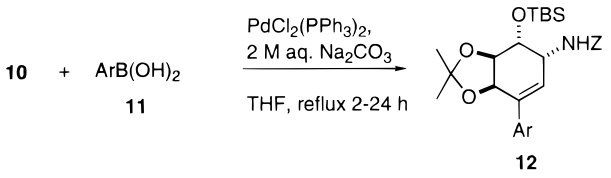
Table 1. Suzuki Cross-Coupling



entry	boronic acid	time, h	product	% yield
1	**11a**	22	**12a**	89
2	**11b**	4.75	**12b**	95
3	**11c**	4.75	**12c**	88
4	**11d**	2	**12d**	75
5	**11e**	23	**12e**	73
6	**11l**	4.5	**12l**	97
7	**11m**	24	**12m**	93
8	**11n**	24	**12n**	84
9	**11o**	5.5	**12o**	79
10	**11p**	5.5	**12p**	92
11	**11q**	14	**12q**	74

Palladium-Catalyzed Suzuki Cross-Coupling. As eluded to above, our synthetic strategy centers on the palladium-catalyzed Suzuki cross-coupling of vinyl bromide **10** with the requisite arylboronic acids to produce trisubstituted olefins **12** (**a-e**, **l-q**) (Table 1). The couplings proceeded smoothly using 10 mol % $PdCl_2(PPh_3)_2$ as the catalyst and 2 M (aq) Na_2CO_3 as the base in refluxing THF (Table 1). Under these conditions complete consumption of the starting vinyl bromide was accomplished without significant aryl−aryl homocoupling or reduction products as is sometimes an issue during such cross-coupling reactions.[13] The choice of catalyst and base were extremely important. The use of tetrakis(triphenylphosphine)palladium(0) as the catalyst and $Ba(OH)_2 \cdot 8H_2O$ as the base resulted in a 65% yield for the coupling of *p*-methoxyphenylboronic acid (**11e**) with vinyl bromide **10**, but an attempt to couple phenylboric acid (**11a**) with **10** under similar conditions resulted in the complete recovery of the vinyl bromide starting material. The use of Na_2CO_3 as the base gave similar results. The more reactive $PdCl_2(PPh_3)_2$ catalyst containing only two triphenylphosphine ligands proved to be the superior choice and worked sufficiently for all cases except for 2-nitrophenylboronic acid.[15] The extremely electron deficient 2-nitrophenylboronic acid resulted in only partial conversion so an alternative coupling partner was sought (entry 9). The boronic acid coupling partners ranged from electron rich (entries 3−8) to slightly electron deficient (entry 10). It should also be noted that the synthesis of boronic acids in entries 6, 9, and 11 resulted in products that contained several boronic species by ^{1}H NMR.[16] This was likely due to dimeric and cyclic trimers of the boronic acid derivatives and was not a problem for the coupling step. The crude boronic acid mixtures underwent coupling smoothly using 1.5 to 2 equiv of the requisite boronic acid to produce only the desired trisubstituted olefinic products. It is known that the Suzuki conditions will easily tolerate unprotected alcohols and amines,[13] but our synthesis required that the phenolic and aniline functionality be protected during the subsequent ozonolysis step discussed below. The coupling of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (**11o**) with vinyl bromide **10** (entry 9) resulted in two products, the desired coupled product in 62% yield along with the *N*-deprotected product in 26% yield presumably derived from the basic hydrolysis of the BOC carbamate under the Suzuki conditions. The *N*-deprotected byproduct was converted to the desired product in 64% yield upon refluxing in THF with BOC_2O.

Scheme 1

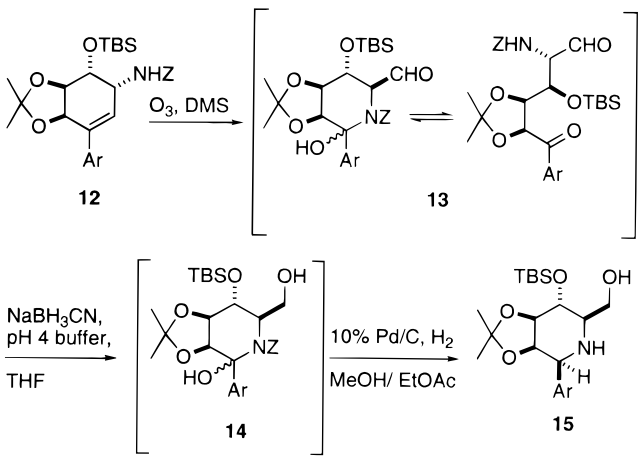


Table 2. Three-Step Azasugar Ring Construction (Scheme 1)

entry	olefin	protected azasugar	% yield
1	**12a**	**15a**	56
2	**12b**	**15b**	67
3	**12c**	**15c**	41
4	**12d**	**15d**	56
5	**12e**	**15e**	74
6	**12l**	**15f**	61
7	**12m**	**15g**	55
8	**12n**	**15h**	66
9	**12o**	**15o**	67
10	**12p**	**15j**	49
11	**12q**	**15k**	66

Azasugar Ring Construction. The trisubstituted olefins **12** underwent smooth ozonolysis to produce the corresponding keto-aldehyde intermediate **13** (Scheme 1). ^{1}H NMR of the crude product mixture suggested that the open chain form of intermediate **13** was the major isomer present of the several possible equilibrium forms. This was confirmed by the presence of an NH signal between 5.5 and 6 ppm, as well as a deshielding in the aromatic protons in conjugation with the ketone carbonyl. The success of the ozonolysis was dependent on having the aromatic nitrogen substituents protected with electron-withdrawing groups (carbamates), and the oxygen substituents protected as their corresponding ethers in order to minimize the possibility for ring oxidation and *N*-oxide formation. Only the 2-methoxy derivative **12c** led to unidentified overoxidation products; this was minimized by short reaction times, and the impurities were removed by chromatography. The aldehyde carbonyl group was selectively reduced in the presence of the equilibrating ketone/aminal function using $NaBH_3CN$ in conjunction with a AcOH/NaOAc (aq) pH 4 buffer in THF. The ^{1}H NMR of the crude corresponding keto-alcohols **14** were not as clean as their precursors due to the presence of several equilibrating species. Finally, the keto-alcohols **14** were subjected to reductive amination conditions (10%

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(16) Complex mixtures of several boronic acid/anhydride species have also been noted by Hoye; see Hoye, T. R; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. These mixtures are difficult to characterize but fortunately present no problems when subjected in crude form to the Suzuki cross-coupling conditions resulting in only the desired coupled products.

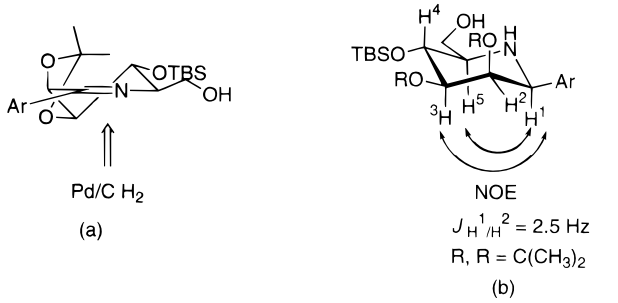


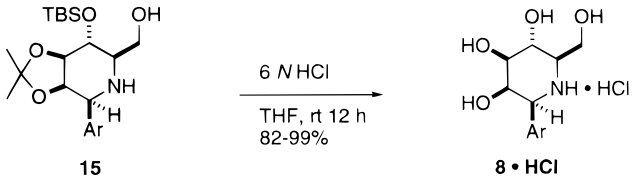
Figure 3. (a) Preferred approach of the hydrogenation catalyst. (b) Results of ^{1}H NMR nuclear Overhauser enhancement (NOE) studies of **15**.

Pd/C Degussa type, H_2, MeOH/EtOAc) to yield exclusively one diastereomer of the corresponding protected azasugars **15** (Table 2). Only one chromatographic purification was necessary for the three-step conversion.

The stereochemical outcome of the reductive amination was determined to be a β-oriented aryl group, corresponding to hydrogen delivery from the α face (Figure 3a). The stereochemistry was confirmed by positive nuclear Overhauser enhancements (NOE) between H_1 and H_5 which reside in a 1,3-diaxial relationship below the piperidine ring, along with a coupling constant of 2.5 Hz between H_1 and H_2 consistent with an axial/equatorial relationship as depicted in Figure 3b. Also worth noting is the removal of the benzyl *O*-protecting groups and Cbz *N*-protecting group in entries 6−8 and 11 respectively. The nitro group in entry 10 was also reduced to an amine under these conditions to yield the *m*-aniline derivative **15j**. The hydrogenation conditions were initially a concern due to the potential for hydrogenolysis of the newly formed benzylic amine functionality at the pseudoanomeric center. This fortunately was not a problem in any of the examples that we encountered.

Deprotection. The remaining protecting groups on **15** were removed under acidic conditions (6 *N* HCl, THF, 12 h, rt) to produce the fully deprotected β-1-*C*-aryl-deoxymannojirimycin azasugars **8** in high yield as their HCl salts (Scheme 2).

Scheme 2



Conclusion

In summary, an efficient and versatile method for the construction of C_1 aryl substituted azasugars containing the manno configuration has been developed. This method takes advantage of the biocatalytic synthesis of enantiopure starting materials, as well as a mild and contemporary method of carbon−carbon bond formation in the use of the versatile Suzuki cross-coupling reaction. Biological studies will be reported in due course. Current work is in progress on methodology to access the corresponding α-1-*C*-aryl-deoxymannojirimycin analogues.[17]

Experimental Section

General. Ozonolysis was performed using a OREC Model 03V5-0 ozonator. The pH 4 buffer used for selective reductions along with $NaBH_3CN$ was prepared as a stock solution by dissolving 1.5 g of sodium acetate along with 5.7 mL of glacial acetic acid in 6 mL of H_2O. Boronic acids **11a** and **11p** were purchased from Aldrich Chemical Co. Boronic acids **11b**, **11l**, and **11q** were prepared *via* lithium−halogen exchange from the corresponding aryl halide. Boronic acids **11l** and **11q** resulted in complex mixtures of monomers along with dimeric and trimeric anhydrides and were used without further purification.[16] The remaining boronic acids were prepared according to the literature methods: **11c**,[15,18] **11d,e**,[19] **11m**,[20] **11n**,[21] **11o**.[22]

General Procedure A: Suzuki Cross-Coupling of Vinyl Bromide 10 with Arylboronic Acids. Vinyl bromide **10** (1 mol equiv) was added to a 25-mL flask. The flask was fitted with a reflux condenser and septum and flushed with argon. THF was added to produce a 0.1 M solution, followed by the arylboronic acid (1.5 to 2.0 mol equiv), and $PdCl_2(PPh_3)_2$ (0.1 mol equiv). To this yellow solution was added 2 M aqueous Na_2CO_3 (4 mol equiv), and the mixture was heated to reflux with vigorous stirring for 2−24 h. The reactions typically turned dark within the first 5 min of heating. When the reaction was deemed complete (absence of starting vinyl bromide by TLC), it was cooled to rt and poured into H_2O and extracted with Et_2O. The organic layers were washed with brine and dried over Na_2SO_4. Filtration, removal of solvent, and flash chromatography on silica gel gave the desired aryl-substituted olefins **12**.

General Procedure B: Ozonolysis, Aldehyde Reduction, and Subsequent Reductive Amination. A 50-mL flask equipped with a side-arm gas bubbling inlet, and a gas outlet was charged with the trisubstituted olefin **12** (1 mol equiv) in CH_2Cl_2/MeOH (1:1) (0.2 M) and cooled to −78 °C. An ozone/oxygen mixture was bubbled through the reaction mixture at a rate of 2 L/min until no starting material remained as judged by TLC (5−15 min). Dimethyl sulfide (1.5 mL) was added at −78 °C, and the reaction mixture was allowed to warm to rt. The resultant solution was stirred for 1.5−2 h and then concentrated *in vacuo*. ^{1}H NMR of the crude product was obtained showing clean conversion to the keto-aldhyde unless otherwise stated. The crude material was taken up in a sufficient amount of THF to form a 0.07 to 0.1 M solution and cooled to 0 °C. $NaBH_3CN$ (1.3 mol equiv) was added in one portion followed by 1−2 drops of a AcOH/NaOAc pH 4 buffer solution; the resultant solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was poured into Et_2O and washed with $NaHCO_3$ and brine. The aqueous layers were extracted three times with Et_2O, and the combined organic layers were dried over Na_2SO_4. Filtration and concentration *in vacuo* provided the corresponding crude keto-alcohol. A high pressure tube was charged with the crude keto-alcohol in MeOH (0.03 M), 10% Pd/C (Degussa type 50 wt % based on substrate), and H_2 (40 psi). The mixture was stirred vigorously for 12 h. Filtration through Celite and concentration *in vacuo*, followed by flash chromatography on silica gel, gave the desired protected azasugar **15**.

General Procedure C: Acid Deprotection of Azasugars. A 25-mL flask was charged with the protected azasugar derivative (10−30 mg) and 2 mL of THF was added followed by the dropwise addition of 1 mL of 6 N HCl. The resultant solution was stirred for 12 h and then concentrated *in vacuo*. The residue was dissolved in a minimal amount of MeOH and the deprotected sugar was precipitated with Et_2O as the corresponding HCl salt. After the solids settled, the excess solvent was removed by pipette and the precipitate was washed twice with Et_2O. The white solids were dried *in vacuo* providing the desired azasugar hydrochlorides (**8**·HCl).

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Typical Procedure for the Preparation of Boronic Acids. 4-*tert*-Butylphenylboronic acid (11b). A 100-mL flask was charged with 1-bromo-4-*tert*-butylbenzene (1.0 g, 4.69 mmol) in 20 mL of THF and cooled to −78 °C. To this solution was added *tert*-butyllithium (1.7 M/hexanes, 5.8 mL, 9.85 mmol) dropwise over 10 min. The resultant solution was stirred at −78 °C for an additional 30 min. Trimethyl borate was added rapidly *via* syringe, and the mixture was stirred for 15 min at −78 °C followed by stirring at rt for 4 h. The reaction mixture was then cooled to 0 °C, 15 mL of 2 N HCl was added, and the mixture was stirred for 16 h. The mixture was poured into Et_2O, the layers were separated, and the aqueous layer was washed three times with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Filtration, removal of solvent, and flash chromatography on silica gel (4:1 to 2:1 to 1:1 hexanes:EtOAc) gave the desired boronic acid **11b** in trimeric anhydride form as a white powder: mp 182−185 °C; R_f 0.17 (4:1, hexanes:EtOAc); IR (neat) 3077, 3032, 2964, 2904, 1608, 1405, 1350, 1312 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 27 H), 7.54 (d, 6 H, J = 8.4 Hz), 8.17 (d, 6 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.20, 35.05, 124.92, 135.57, 155.95; HRMS (EI) calcd for $C_{30}H_{39}O_3B_3$: (M^+) 480.3178, found 480.3172.

(3*R*,4*R*,5*S*,6*R*)-3-[(Benzyloxycarbonyl)amino)]-4-*O*-[(*tert*-butyldimethylsilyl)oxy]-5,6-*O*-(isopropylidenedioxy)-1-(4-*tert*-butylphenyl)cyclohex-1-ene (12b). Vinyl bromide **10** (164 mg, 0.32 mmol) was coupled to 4-*tert*-butylphenylboronic acid (114 mg, 0.64 mmol) following general procedure A to provide, after flash chromatography on silica (8:1, hexanes:EtOAc), 172 mg (95%) of olefin **12b** as a clear oil: R_f 0.54 (4:1, hexanes:EtOAc); IR (neat) 3449, 3333, 3085, 3062, 3027, 2954, 2930, 2857, 1728, 1501, 1215, 1070, 837, 777 cm^{-1}; $[\alpha]^{20}_D$ −38.9 (*c* 0.92, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.12 (s, 3 H), 0.86 (s, 9 H), 1.32 (s, 9 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 4.29 (m, 1 H), 4.33 (t, 1 H, J = 5.0 Hz), 4.69 (d, 1 H, J = 9.0 Hz), 5.01 (dd, 1 H, J = 5.5, 1.0 Hz), 5.07 (d, 1 H, J = 10.0 Hz), 5.14 (s, 2 H), 5.81 (d, 1 H, J = 1.0 Hz), 7.31−7.37 (m, 7 H), 7.42 (d, 2 H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.99, −4.63, 17.94, 25.68, 26.59, 27.76, 31.29, 34.51, 48.73, 66.77, 70.03, 72.62, 76.07, 109.76, 124.37, 125.43, 125.80, 128.08, 128.50, 135.77, 136.56, 136.93, 150.56, 155.74; HRMS (EI) calcd for $C_{33}H_{47}NO_5Si$: (M^+) 565.3223 ($M^+ - C_4H_9$) 508.2519, found 508.2522.

4-*O*-(*tert*-Butyldimethylsilyl)-β-1-*C*-(4-*tert*-butylphenyl)-2,3-*O*-isopropylidene-deoxymannojirimycin (15b). Olefin **12b** (80.0 mg, 0.14 mmol) was subjected to the conditions of general procedure B to provide, after recrystallization from $CHCl_3$:hexane, 43.2 mg (67%) of azasugar derivative **15b** as a white solid: mp 272−275 °C dec; R_f 0.53 (2:1, hexanes:EtOAc); IR (neat) 3397, 2956, 2930, 2857, 1568, 1245, 1221, 1135, 1115, 1071, 1051, 835, 778 cm^{-1}; $[\alpha]^{20}_D$ +27.8 (*c* 1.08, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 0.20 (s, 3 H), 0.24 (s, 3 H), 0.94 (s, 9 H), 1.30 (s, 3 H), 1.33 (s, 9 H), 1.61 (s, 3 H), 3.34 (ddd, 1 H, J = 10.0, 6.5, 3.5 Hz), 3.82 (dd, 1 H, J = 11.5, 6.5 Hz), 4.02 (dd, 1 H, J = 11.5, 3.5 Hz), 4.06 (dd, 1 H, J = 10.0, 6.5 Hz), 4.22 (dd, 1 H, J = 6.5, 5.5 Hz), 4.56 (dd, 1 H, J = 5.5, 2.5 Hz), 4.85 (d, 1 H, J = 2.5 Hz), 7.50 (s, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ −4.75, −3.64, 19.17, 26.36, 26.50, 28.54, 31.78, 35.70, 59.65, 60.59, 63.08, 71.28, 76.62, 81.06, 111.78, 126.97, 129.40, 131.52, 153.95; HRMS (EI) calcd for $C_{25}H_{43}NO_4Si$: (M^+) 449.2961, found 449.2951.

β-1-*C*-(4-*tert*-Butylphenyl)-deoxymannojirimycin Hydrochloride (8b). Protected azasugar derivative **15b** (36.5 mg, 0.081 mmol) was treated with HCl according to general procedure C to provide 26.9 mg (99%) of azasugar **8b** as its HCl salt: mp 199−201 °C; $[\alpha]^{20}_D$ +32.3 (*c* 1.15, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 1.32 (s, 9 H), 3.23 (ddd, 1 H, J = 10.5, 7.5, 3.0 Hz), 3.73 (dd, 1 H, J = 9.5, 2.5 Hz), 3.87 (dd, 1 H, J = 12.0, 7.5 Hz), 3.89 (dd, 1 H, J = 10.5, 9.5 Hz), 4.01 (d, 1 H, J = 2.5 Hz), 4.08 (dd, 1 H, J = 12.0, 3.0 Hz), 4.49 (s, 1 H), 7.49 (s, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 31.80, 35.63, 60.22, 63.34, 63.59, 68.01, 72.74, 75.65, 126.85, 128.80, 133.17, 153.40; HRMS (EI) calcd for (−HCl) $C_{16}H_{25}NO_4$: (M^+) 295.1784, ($M^+ - CH_3O$) 264.1599, found 264.1595.

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Supporting Information Available: Experimental details and characterization data for **12**, **15**, and **8**, and ^1H NMR and ^{13}C NMR for **11b**, **12**, **15**, and **8** (84 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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