helpful discussions and suggestions. We especially thank Professor A. H. Francis and S. Sibley for luminescence spectroscopy measurements. We also thank Dr. J. Kampf for the X-ray crystallography.

Supplementary Material Available: A listing of the structure-determination summary of [TTF][$(CH_2)_2$Tcbiim] including tables of bond lengths and bond angles, tables of atomic positions and thermal parameters, and additional crystal-packing diagrams and an ORTEP plot of [TTF][$(CH_2)_2$Tcbiim] (14 pages); tables of structure factors for $C_{18}H_8N_8S_4$ (10 pages). Ordering information is given on any current masthead page.

Enzyme-Catalyzed Aldol Condensation for Asymmetric Synthesis of Azasugars: Synthesis, Evaluation, and Modeling of Glycosidase Inhibitors[1]

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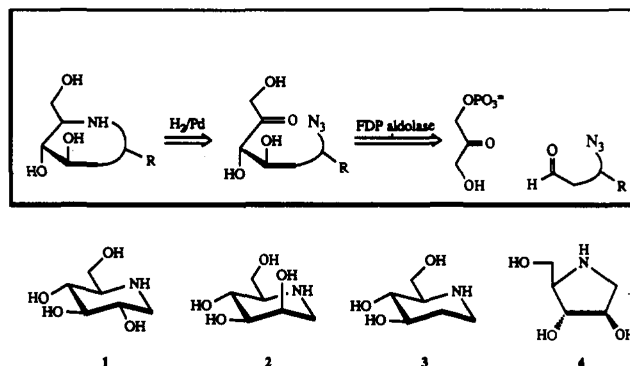
Abstract: A combined fructose 1,6-diphosphate aldolase reaction and catalytic reductive amination has been used in the asymmetric synthesis of azasugars structurally corresponding to *N*-acetylglucosamine, *N*-acetylmannosamine, and deoxyhexoses. The 6-deoxyazasugars were prepared by direct hydrogenolysis of the aldolase product without removal of the 6-phosphate group. Both (*R*)- and (*S*)-3-azido-2-acetamidopropanal used as substrates in the aldolase reactions were prepared from the corresponding lipase-resolved 2-hydroxy species followed by formation of an aziridine intermediate and opening of the aziridine with azide. Evaluation of these azasugars and their diastereomerically pure tertiary amine oxides as well as 5-thioglucose and its sulfoxide derivatives as glycosidase inhibitors was carried out. It was found that all synthetic azasugars and 5-thioglucose were strong inhibitors, but oxidation of the ring heteroatom weakened the inhibition. With the aid of molecular modeling and inhibition analysis, a structure-K_i relation of inhibitors was established which provides useful information for the design of new glycosidase inhibitors.

Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and useful as potent glycosidase inhibitors.[2] This discovery has stimulated interests in the development of effective procedures for the synthesis of various azasugars[3] and analogues[4] for the investigation of glycosidase reactions[5] and the development of specific glycosidase inhibitors for treating metabolic disorders such as diabetes[2,4b,6] or as antiviral,[2,7] antibacterial,[2,8] and anticancer[2,9] agents.

Scheme I



We have recently reported[10] asymmetric syntheses of azasugars **1–4** based on aldolase-catalyzed reaction and Pd-catalyzed re-

(1) Supported by the NIH (GM44154).

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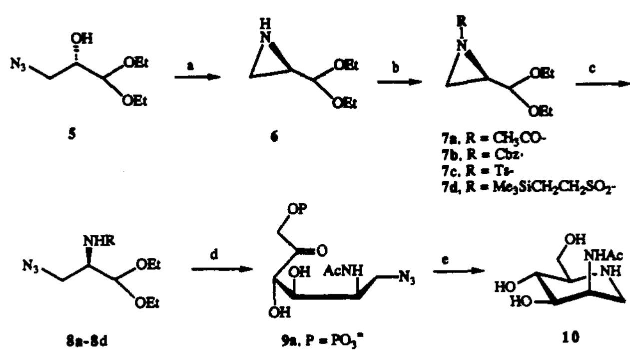
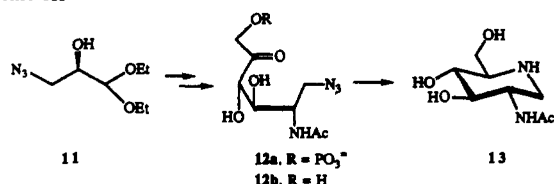
Scheme II[a]



[a](a) 2 equiv of Ph_3P, $PhCH_3$, 40%; (b) for **7a**, Ac_2O (10 equiv), CH_2Cl_2/K_2CO_3 (25 equiv), 25 °C, 62%; (c) NaN_3 (6.0 equiv), **7a** in DMF (0.4 g/18 mL), $ZnCl_2$ in Et_2O (1 M, 18 mL); 75 °C, 3 days, 61%; (d) (1) pH → 1, 45 °C, 8 h; (2) pH → 6.5, FDP aldolase (400 units), DHAP (3 equiv), 4.5 h, 60%; (e) phosphatase (1) (pH 4.5, 1240 units), 37 °C, 1 day; (2) Pd/C (20 mg), H_2 (50 psi), 90%.

Scheme III



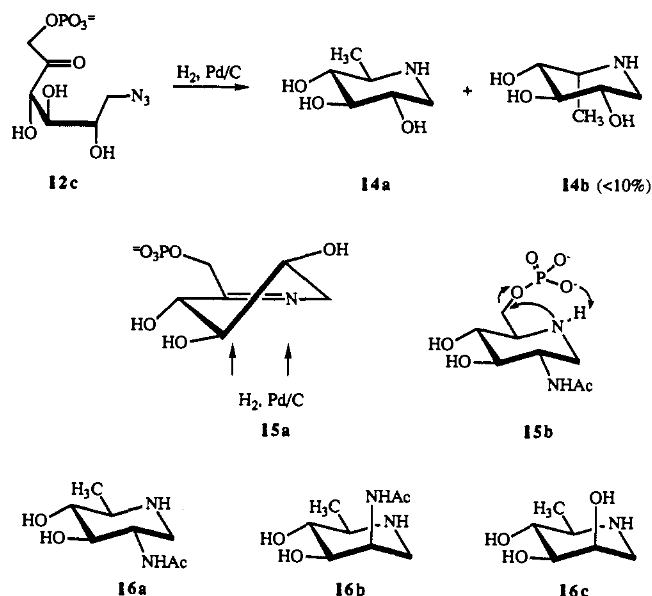
ductive amination (see Scheme I for retrosynthesis). We describe here an extension of this chemical-enzymatic strategy to the synthesis of other azasugars, particularly those corresponding to *N*-acetylmannosamine, *N*-acetylglucosamine, and deoxysugars and evaluation of these compounds and their tertiary amine oxides as glycosidase inhibitors. Molecular modeling and inhibition analysis of several new and known inhibitors were used to establish the structure-K_i relation of inhibitors, which may provide useful information for the design of new glycosidase inhibitors.

Synthesis

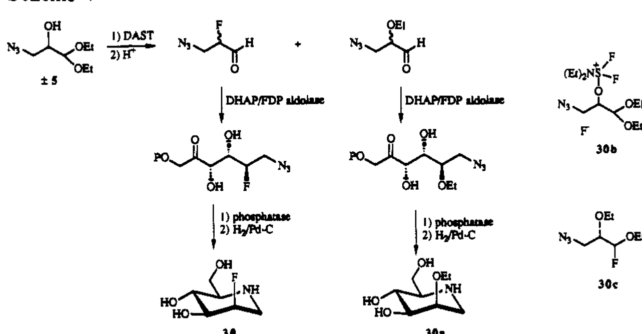
A key element used for the synthesis of the aminoazasugars is the preparation of compound **8a** and its enantiomer (Scheme II). Thus compound **5** (>98% ee) prepared previously[10,11] was converted[11] to **6** followed by N-acetylation to **7a** (95% ee). Nucleophilic opening of aziridine **7a** with sodium azide in the presence of $ZnCl_2$ gave **8a** in 60% yield.[12] After acid hydrolysis to unmask the aldehyde protecting group, the product of compound **8a** (3 equiv) was condensed with 1 equiv of dihydroxyacetone phosphate (DHAP)[13] in the presence of FDP aldolase[14] at pH 6.5 to give **9a** (60%) which, upon removal of the phosphate group catalyzed by phosphatase, was converted via reductive amination to **10** (90%). Compound **13** was prepared similarly from **11** (Scheme III). Starting with racemic **11**, a mixture of **10** and **13** in a 2:1 ratio was obtained, indicating that the (*R*)-aldehyde is a better substrate than the (*S*)-enantiomer.

To synthesize the 6-deoxy analogues of azasugars, the aldolase products **9a**, **12a**, and **12c** were hydrogenated directly to compounds **16a**, **16b**, and **14a**, respectively, in very high yield (~95%) (Scheme IV). This high degree of stereoselectivity in hydrogenolysis is consistent with our previous report[10] that hydrogens are delivered to the bottom face of the imine intermediate as shown in **15a** to give the product with a trans relation between C_4 and

Scheme IV



Scheme V



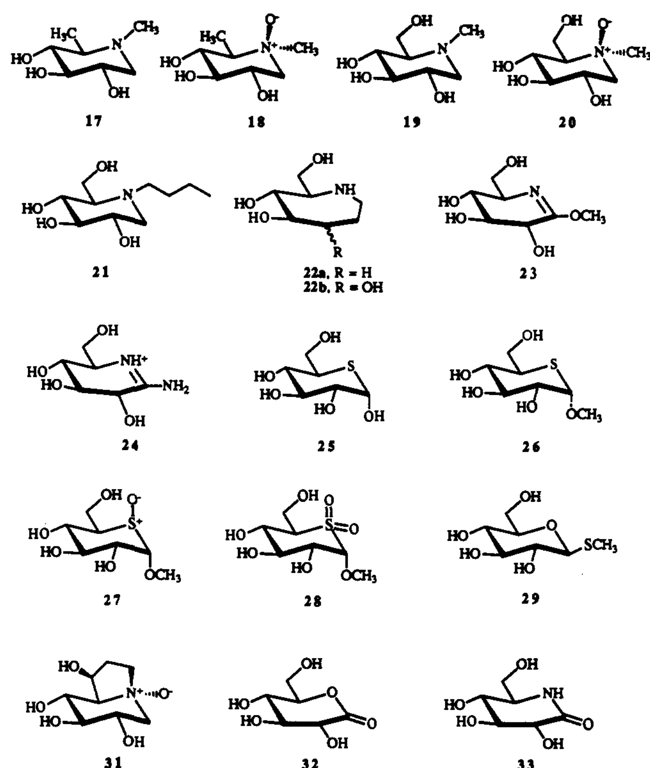
C_5. It is worth noting that treatment of glucose 6-phosphate or DHAP under the same hydrogenolysis conditions showed no reaction; reductive β-elimination or hydrogenolysis at the ketol phosphate stage was therefore ruled out. The ring nitrogen apparently participates in the reaction, with either the phosphate being cleaved at the imine stage (i.e., compound **15a**) or the imine being reduced to deoxynojirimycin 6-phosphate (**15b**) which is subsequently converted intramolecularly to an aziridine derivative.[15] Similarly, **16c** was prepared from **11** or racemic **11**.

Compounds **14a** and **1** were N-methylated to give **17** and **19**, respectively. N-Oxidation of **17** and **19** with H_2O_2 resulted in a single stereoisomer with the *N*-CH_3 group at the equatorial position, as indicated in **18** and **20**. Assignment of the stereochemistry (see Figure 1 for **20**) was based on a strong NOE observed between the CH_3 group and the equatorial hydrogen of C-1 and a small NOE between CH_3 and the protons of C-6. Similar NOEs were observed between C_2–H_{ax} and C_4–H_{ax} and C_2–H_{ax} and C_1–H_{eq}. The ^{13}C NMR spectrum of **20** showed that both C_2 and C_4 have the same chemical shift at 76.95 ppm as indicated in the ^1H–^{13}C heterocorrelation 2D spectrum (Figure 1). A complete assignment of chemical shifts for **20** was therefore possible based on the connecting carbon atoms with hydrogens as shown in the 2D spectrum and the ^1H and ^{13}C spectra. Compound **21** was prepared by hydrogenolysis of a mixture of **1** and butyraldehyde over Pd/C as described previously.[10] Attempts to prepare the seven-membered ring azasugars **22a** and **22b** from the corresponding aldolase products by hydrogenolysis gave a mixture of three to four products, and no further isolation was carried out. Compound **23** was prepared from *O*-acetylnojirimycin-δ-lactam by reaction with trimethyloxonium fluoro-

(11) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4898.
(12) Higher yields (75–86%) were obtained with other protecting groups (e.g., **7b–d**). The protecting group of **7d** can be removed by F⁻ (Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, 2099).
(13) For an improved chemical synthesis, see: Pederson, R. L.; Wong, C.-H. *Tetrahedron*, in press.
(14) The enzyme from rabbit muscle or *E. coli* can be used. The rabbit enzyme was used in this paper.

(15) We found that many other aziridine structures are very sensitive to hydrogenolysis.

Chart I



borate followed by deacetylation with sodium methoxide. Compound **30**, 2-deoxy-2-fluoromannojirimycin, was prepared from racemic 3-azido-2-fluoropropanal via the aldol condensation and reductive amination process (Scheme V). A high diastereoselectivity was observed in the aldolase reaction with the D-aldehyde being converted selectively to the product. After phosphatase reaction followed by hydrogenolysis, compound **30** was the only diastereomer produced. During the reaction of racemic **5** with diethylaminosulfurtrifluoride (DAST), a byproduct was obtained in ~20%, which, after hydrolysis and aldol condensation/reductive amination, gave 2-*O*-ethyldeoxymannojirimycin (**30a**). The aldolase substrate 3-azido-2-ethoxypropanal was probably generated during the hydrolysis of **30c**, which might be generated from the initial product (**30b**) of DAST reaction via a 1,2-shift. The aldolase also exhibited a high degree of enantioselectivity for the D-aldehyde to give **30a**. The stereochemistry at C-2 was determined based on the small coupling constants (1.32 and 2.66 Hz) between H_2 and H_{1a}/H_{1e}.

Oxidation of the ring S with H_2O_2 to sulfoxide and sulfone was carried out at room temperature. Protection of anomeric center as methyl thioglucoside is required to prevent the ring opening. The sulfoxide was obtained as a single diastereomer. The stereochemistry of **26** was tentatively assigned as indicated with the oxygen occupying the axial position. This assignment was consistent with the anomeric effect and with the observation of a strong effect on the chemical shift of the methylene group at C-6 after oxidation.

Inhibition Analysis

With these azasugars in hand, experiments were designed to determine the inhibition kinetics, and the results are summarized in Table I. All the inhibition kinetics are competitive at pH 6.5. Since various *N*-alkyl derivatives of azasugars were shown to have different inhibition properties,[7a] compounds **17**, **19**, and **21** were included in the study. Compounds **18** and **20** were thought to be more potent inhibitors than the corresponding precursors **17** and **19** because of their zwitterionic character, which may have a stronger electrostatic interaction with the putative active site carboxylate and carboxylic acid residues of glycosidases.[5] Kinetic analysis indicates, however, that **18** is a less potent inhibitor than **17** for β-glucosidase from sweet almond by an order of magnitude

Table I. Inhibition Constants[a]

compd	enzyme	K_i(M)	ref
1	α-glucosidase (brewers yeast)	8.67×10^{-6}	
	type I (calf liver)	1.0×10^{-6}	*b*
	β-glucosidase (sweet almond)	1.8×10^{-5}	*c*
	α-D-mannosidase (jack bean)	4.0×10^{-4}	
	β-D-galactosidase (jack bean)	no inhibition[d]	
10	α-D-mannosidase (jack bean)	no inhibition	
	β-*N*-acetyl-D-glucosaminidase (bovine kiney)	no inhibition	*e*
13	β-*N*-acetyl-D-glucosaminidase (bovine kiney)	3.8×10^{-7}	
		(6×10^{-7})[c]	
14a	α-glucosidase (brewers yeast)	1.56×10^{-3}	
	β-glucosidase (sweet almond)	7.8×10^{-4}	
17	α-glucosidase (brewers yeast)	1.78×10^{-3}	
	β-glucosidase (sweet almond)	1.4×10^{-4}	
18	α-glucosidase (brewers yeast)	6.95×10^{-3}	
	β-glucosidase (sweet almond)	1.49×10^{-3}	
19	α-glucosidase (brewers yeast)	3.69×10^{-4}	
	type I (calf liver)	7.0×10^{-8}	*b*
	β-glucosidase (sweet almond)	4.3×10^{-5}	
20	α-glucosidase (brewers yeast)	$>1.0 \times 10^{-2}$[f]	
	β-glucosidase (sweet almond)	8.0×10^{-5}	
21	α-glucosidase type I (calf liver)	9×10^{-8}	*b*
23	β-glucosidase (sweet almond)	8.0×10^{-4}	
24	β-glucosidase (sweet almond)	8×10^{-6}	*g*
25	α-glucosidase (brewers yeast)	7.50×10^{-4}[h]	
	β-glucosidase (sweet almond)	$>1.0 \times 10^{-2}$[f]	
26	α-glucosidase (brewers yeast)	$>5.0 \times 10^{-3}$[f]	
	β-glucosidase (sweet almond)	no inhibition	
27	α-glucosidase (brewers yeast)	$>5.5 \times 10^{-3}$[f]	
28	α-glucosidase (brewers yeast)	$>2.0 \sim 10^{-3}$[f]	
29	β-glucosidase (brewers yeast)	$>5.0 \times 10^{-3}$[f]	
30	β-glucosidase (sweet almond)	$>1.0 \times 10^{-3}$	*i*
	α-D-mannosidase (jack bean)	$>1.0 \times 10^{-3}$[f]	
31	β-glucosidase (sweet almond)	2.54×10^{-3}	
		(7.6×10^{-4})[j]	
32	β-glucosidase (sweet almond)	2.0×10^{-4}	*c*
33	β-glucosidase (sweet almond)	3.7×10^{-5}	*c*

[a] All the K_i values shown in this table are competitive inhibition constants determined at pH 6.5. Compound **1** showed pH dependent inhibition (see ref 21). [b] Schweden, J.; Borgmann, C.; Legler, G.; Brause, E. *Arch. Biochem. Biophys.* **1986**, *248*, 335. [c] Dale, M. P.; Ensley, H. E.; Kern, K.; Sastry, K. A. R.; Bayers, L. D. *Biochemistry* **1985**, *24*, 3530. [d] No significant inhibition observed with 10 mM inhibitor in the assay. [e] Fleet, G. W.; Smith, P. W.; Nash, R. J.; Fellows, L. L.; Parekh, R. B.; Rademacher, T. W. *Chem. Lett.* **1986**, 1051. [f] Less than 10% initial velocity decrease observed with the specified inhibitor concentration and 0.25 mM substrate in the assay. [g] Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137. [h] 5-Thiofucose was reported to be a potent inhibitor ($K_i = 4.2 \times 10^{-5}$ M) of fucosidase: Hashimoto, H.; Fujimori, T.; Yuasa, H. *J. Carbohydr. Chem.* **1990**, *9*, 683. [i] Very weak inhibition ($K_i > 10^{-3}$ M) of **30** was also observed for β-glucosidase, α-glucosidase, and α-mannosidase; Evens, S. V.; Hayman, A. R.; Fellows, L. E.; Shing, T. K. M.; Derome, A. E.; Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 1465. [j] Saul, R.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophics* **1984**, *230*, 668.

although it is similar to **17** for the inhibition of α-glucosidase from brewers yeast. Compound **20** is slightly less effective than **19** as a β-glucosidase inhibitor, and no significant inhibition was observed for α-glucosidase. It seems that addition of an oxygen atom to N perturbs the binding to the enzyme, resulting in a weaker complex. The same situation was also observed for castanospermine *N*-oxide, **31**. Compound **21** was used for comparative study because it was shown to be a more potent inhibitor than **19** for HIV-1.[7a] Alkylation of the ring N seems to have different effects on different glycosidases. The relative K_i values of **1**, **19**, **21**, and the *N*-hexyl derivative of **1** for calf liver α-glucosidase (type 1) are 1, 0.7, 0.9, and 1.4, respectively, while those of **1** and **19** for the α-glucosidase from brewers yeast are 1 and 40. For in vivo inhibition, *N*-alkylation, however, may facilitate transport of the inhibitor across the cell membrane, thereby increasing the effectiveness of the inhibition.[7b] Whether the more hydrophobic 6-deoxyazasugars prepared in this study are effective inhibitors

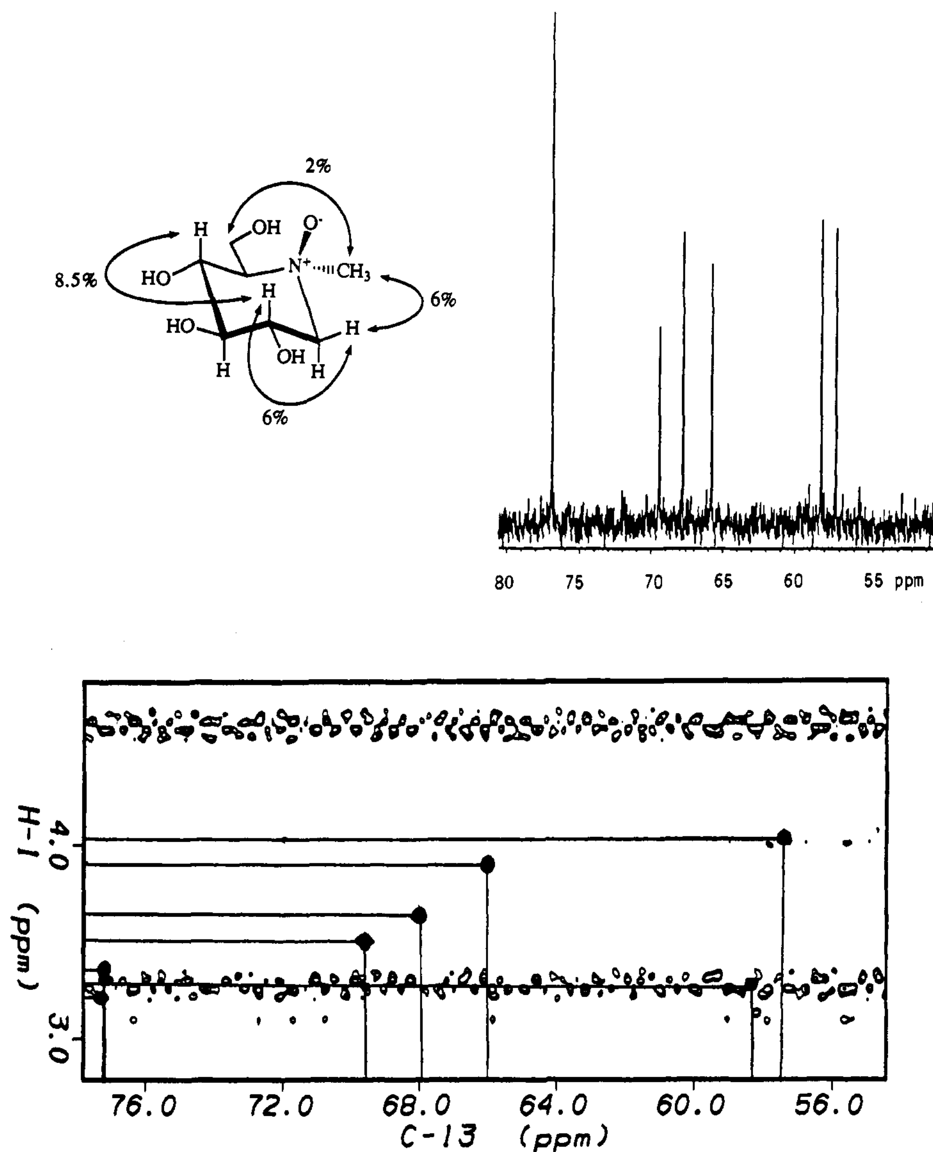


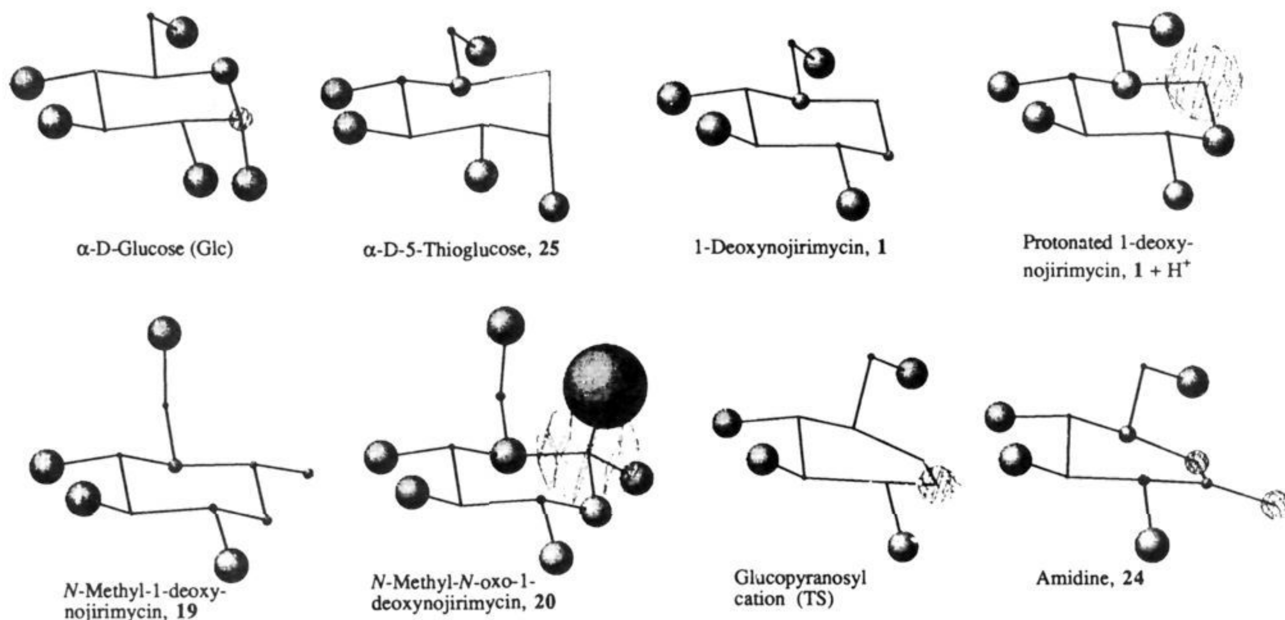
Figure 1. (Bottom) $^1H-^{13}C$ heterocorrelation 2D spectrum of **20**. The horizontal and vertical lines are shown connecting carbon atoms with hydrogen atoms. It is shown that C_2 and C_4 have the same ^{13}C chemical shift at 76.95 ppm. Inserted are the one-dimensional ^{13}C spectrum (top right) and NOE of **20** (top left).

in vivo remain to be investigated.

Although compound **23** possesses a half-chair conformation to mimic the transition state of glycosidic cleavage, it is a neutral molecule and exhibits only moderate inhibition ($K_i = 8.0 \times 10^{-4}$ M) against sweet almond β-glycosidase. It is very unstable in aqueous solution. The neutral half-chair-like inhibitors δ-gluconolactone (**32**, $K_i = 2 \times 10^{-3}$ M) and δ-gluconolactam (**33**, $K_i = 3.7 \times 10^{-5}$ M) also exhibit certain degrees of inhibition but are not as potent as the chair form of azasugar **1**. Amidinium ion **24** possesses a half-chair conformation with a positive charge at neutral pH.[4a] This compound is the most potent synthetic inhibitor of sweet almond δ-glucosidase ($K_i = 8 \times 10^{-6}$ M) reported so far; it is, however, also unstable in aqueous solution. Due to their lability, neither **23** or **24** probably is useful from a practical point of view. Interestingly, 5-thioglucose **25** is a potent inhibitor of α-glucosidase from brewers yeast with a $K_i = 7.5 \times 10^{-4}$ M. The potency is comparable with that of azasugar **19** and the deoxyanalogue **17** and stronger than that of the corresponding N-oxides **18** and **20**. α-D-Glucose, however, showed no detectable inhibition against the α-glucosidase. Compounds **26–28** showed some inhibition against α-glucosidase from brewers yeast but were not as potent as **25** and displayed no inhibition against β-glucosidase from sweet almond. Compound **29** was a weak inhibitor of β-glucosidase. This is similar to the trend observed in the effect of N-oxidation of azasugars. It is worth noting that compound **26** is not a substrate for α-glucosidase, nor is **29** for β-glucosidase. Replacement of the ring oxygen or leaving group oxygen with S cannot be accepted by the enzyme as substrate. Comparison of the K_i values between **17** and **19** and those between **1** and **14a** indicates that the 6-OH group is important for binding, presumably through an interaction with a hydrogen-bond acceptor. A more significant change of inhibition was displayed by the removal of the 2-OH group from **1**. Compound **3** showed no significant inhibition against α- and β-glucosidase and α-mannosidase at the concentration of 1 mM. The 2-deoxy-2-fluoro derivative **30** also showed no significant inhibition at this concentration level. These results indicate that the 2-OH group may interact with a hydrogen-bond acceptor in the active site.

Molecular Modeling

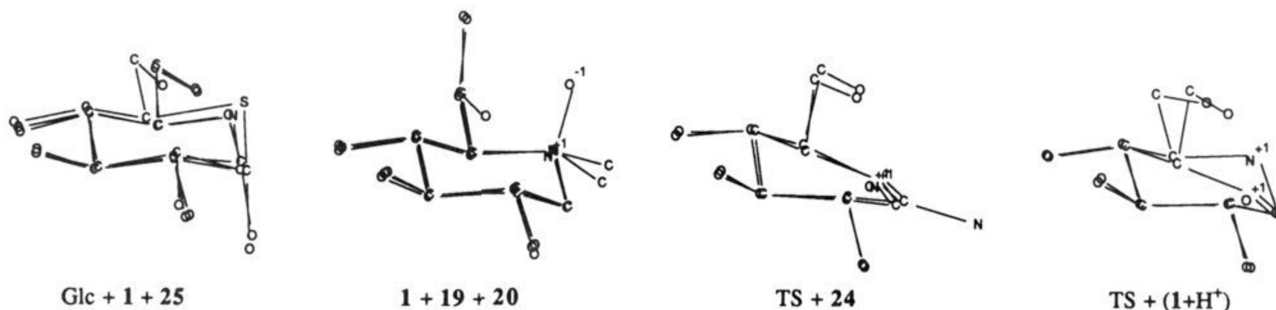
Molecular modeling was next undertaken to understand the structure-inhibition relation of some monosaccharide-based exoglycosidase inhibitors. The structures were optimized first with molecular mechanics (MM2) and then with PM3 in MOPAC (see Experimental Section). The final structures and charge distributions were visualized as high-resolution graphics. As shown in Figure 2, the ring S of **25** has little charge, whereas glucose possesses a high-density negative charge character at the ring oxygen. This difference in charge density may explain why **25** is a good inhibitor. The active-site carboxylate ion located on the



Partial Charge Distribution

Atom	Glc	25	1	1+H$^+$	19	20	TS	24
C_1	0.2226	-0.0029	-0.1046	-0.2989	-0.0920	-0.2936	0.3623	-0.1058
C_2	0.0131	0.0015	0.0521	0.0500	0.0777	0.0864	0.0067	0.1097
C_3	0.0410	0.0329	0.0334	0.0177	0.0322	0.0265	0.0448	0.0340
C_4	0.0164	0.0880	0.0247	0.0813	0.0493	0.0572	0.0106	0.0446
C_5	-0.0128	-0.1991	-0.1646	-0.2745	-0.1319	-0.3390	-0.0066	-0.1656
X	-0.2607	-0.0372	-0.0541	0.7421	-0.0711	0.9840	-0.0086	0.2255

Figure 2. Calculated charge distribution of some glucosidase inhibitors. The positive charges are presented in wired-frame shapes, while the negative charges are in shaded shapes; the sizes are proportional to charge density. X = the ring heteroatom.



Selected Bond Length, Bond Angle and Dihedral Angle

Bond Length (Å)	Glc	25	1	1+H$^+$	19	20	TS	24
C_1-X	1.401	1.845	1.477	1.506	1.491	1.540	1.262	1.356
C_5-X	1.430	1.843	1.488	1.523	1.505	1.562	1.469	1.490
C_1-C_2	1.562	1.554	1.541	1.548	1.535	1.535	1.500	1.530
C_4-C_5	1.552	1.543	1.551	1.554	1.552	1.550	1.552	1.549
Bond Angle (°)								
C_1-X-C_5	115.99	101.25	112.18	111.84	112.55	108.29	123.74	124.89
X-C_1-C_2	113.78	109.09	112.46	111.04	111.17	112.52	125.49	121.46
C_4-C_5-X	111.36	111.37	111.97	110.42	110.04	111.31	115.00	113.09
C_5-C_6-O_6	113.06	113.30	113.40	108.92	114.91	113.65	107.33	111.06
Dihedral Angle (°)								
X-C_5-C_6-O_6	82.35	83.68	76.97	52.80	-70.98	-65.61	61.45	57.18

Figure 3. Superposition of inhibitors and glucopyranosyl cation.

β-face may experience less repulsive interaction with **25** than with glucose. Methylation and oxidation of the ring N of **1** changes the dihedral angle of N–C_5–C_6–O_6 (Figure 3). The 6-OH group moves toward the *N*-oxygen to form a H-bond. This move may weaken the H-bonding interaction of the 6-OH group with the enzyme. In addition, the *N*-oxide may have a repulsive interaction with the carboxylate ion from the enzyme. These two factors may explain why **20** is less potent than **19** as an inhibitor of the microbial glucosidase. N-Alkylation, however, seems to strengthen the inhibition of liver enzyme. This change may be due to the difference of active-site geometry. Glucopyranosyl cation, the putative transition state or high energy intermediate of glycosidic

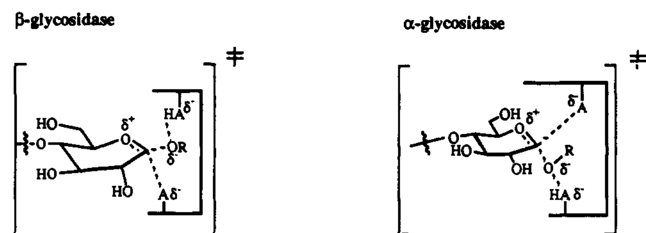


Figure 4.

cleavage (Figure 4), and amidinium ion **24** have similar charge distribution and both superimpose very well. Other chair-form inhibitors show similar bond lengths, bond angles, and dihedral angles (Figure 3), the exception being that **25** is puckered with longer C_1–S and C_5–S bonds and a smaller C_1–S–C_5 angle compared to the corresponding azasugar and glucose and that the dihedral angle X–C_5–C_6–O_6 changes significantly when the ring heteroatom is methylated and/or oxidized.

Knowing the effects of conformation, charge distribution, and substituents of inhibitors on the K_i values, we intend to establish the relation between inhibition constants and inhibitor-binding where contributions from conformation, charge, and topographic orientation of the inhibitor can be addressed. Since all the K_i values described in Table I are competitive inhibition constants at pH 6.5, they are equivalent to dissociation constants which should reflect the energy associated with inhibitor binding. We only considered β-glucosidase at this stage because it has been studied the most and more inhibition constants are available for this enzyme. We assume the 2-OH group, the 6-OH group, a positive charge, and a half-chair conformation are important for a good inhibitor binding to the enzyme. Each of these factors contributes to the overall binding. With these assumptions, we have found taht the pK_i values of β-glucosidase inhibitors correlate well with their binding as indicated by ΔG (eq 1, Figure 5), with a correlation coefficient of 0.929.

$$\Delta G = \Delta G(\text{conformation}) + \Delta G(2\text{-OH}_{eq}) + \Delta G(6\text{-OH}_{eq}) + \Delta G(\text{charge}) \quad (1)$$

The contributions from the 3-OH and 4-OH groups were not included in this study because all inhibitors used in this study contained these two groups. We notice, however, that these two OH groups probably are not important for transition-state binding as δ-valerolactam is an inhibitor ($K_i = 6.5 \times 10^{-2}$ M) of β-glucosidase.[16] The stereochemistry of C_3–C_4, however, is important for chair-form recognition as galactojirimycin (1,5-dideoxy-1,5-imino-D-galactitol) is not effective against β-glucosidase.[17]

The binding-inhibition relation as indicated in Figure 5 is applicable to substrate-like and transition-state-like inhibitors. Inhibitors with transition-state characters (i.e., half-chair conformation with a positive charge), however, bind more strongly to the enzyme, and the stereochemistry of other hydroxyl groups in transition-state recognition is not as important as that in ground-state binding. This is consistent with previous discoveries[4a] that amidinium **24** is nearly as active against α-mannosidase, α- and β-glucosidase, and N-acetylglucosaminidase. It seems clear that the topographic orientation of the hydroxyl groups are important for the recognition and binding of chair-form substrates or inhibitors. Electrostatic interactions between the positive charge of the inhibitor and the enzyme, however, is the most important factor for binding and recognition of half-chair inhibitors. Scheme VI illustrates the difference between the interaction of β-glucosidase with half-chair and chair form inhibitors. The difference led to the prediction that a half-chair amidinium without hydroxyl groups at positions 2, 3, and 4 would be an inhibitor of all glycosidases with K_i in the range of 20–40 μM. Work is in progress to test this prediction.

(16) Dale, M. P.; Ensley, H. E.; Kern, K.; Sastry, K. A. R.; Byers, L. D. *Biochemistry* **1985**, *24*, 3530.
(17) Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305.

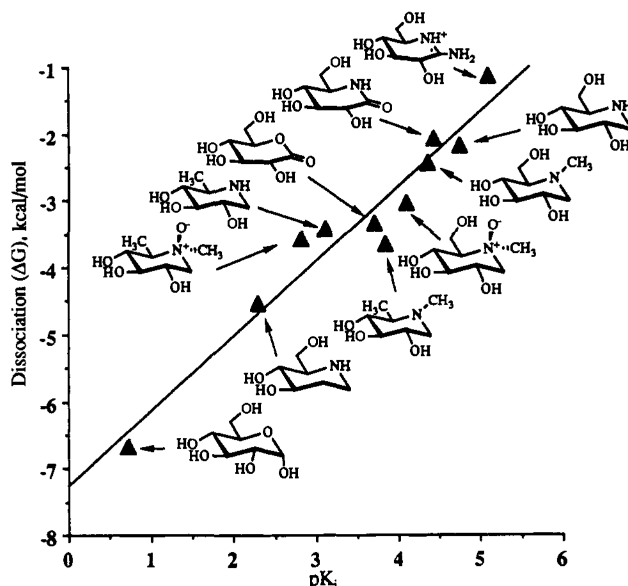
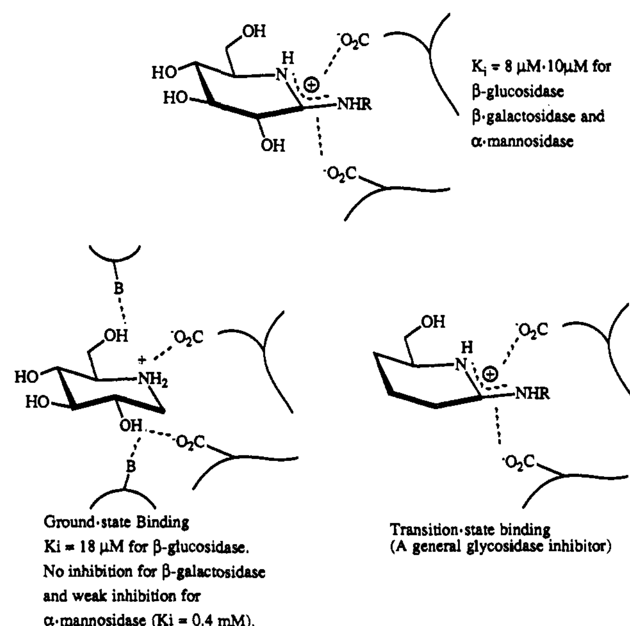


Figure 5. Correlation between binding (indicated as overall dissociation energy ΔG) and pK_i. ΔG is divided into several components shown in the following equation: $\Delta G = \Delta G(\text{conformation}) + \Delta G(2\text{-OH}_{eq}) + \Delta G(6\text{-OH}_{eq}) + \Delta G(\text{charge}) = 2.825F(\text{conformation}) + 2.274F(2\text{-OH}) + 1.167F(6\text{-OH}) + 3.46F(\text{charge}) - 8.181$ where F(conformation) = 1 if the inhibitor is in half-chair conformation and 0 if in chair conformation; F(2-OH) = 1 for the presence of 2-OH_{eq} and 0 for the lack of 2-OH_{eq}; F(6-OH) = 1 if 6-OH is free to be a H-bond donor (i.e., free of intramolecular H-bonding; = 0.5 if 6-OH is in weak intramolecular H-bond (**32**) or there is a strong negative charge to have electrostatic interaction (**18** and **20**) with COOH from the enzyme; = 0 for lack of 6-OH or in strong intramolecular H-bond (Glc); F(charge) = partial charge distribution of the ring heteroatom calculated by PM3. The coefficients were determined based on the ΔG values of individual inhibitors ($\Delta G = -RT \ln K_i$, and all K_i values were normalized to 1 μM standard state with a multivariable least-squares analysis. A linear relation between binding and pK_i was determined to be $\Delta G = 1.12\text{p}K_i - 7.25$ where ΔG contained contributions from conformation, charge on the ring heteroatom, and the equatorial 2-OH and 6-OH groups.

Scheme VI



In summary, this study illustrates a practical and effective chemo-enzymatic procedure for the synthesis of various azasugars and derivatives which are potentially useful glycosidase inhibitors. The strategy based on aldolase reactions is different from most reported procedures where natural sugars were used as starting materials, and multiple protection and deprotection steps are

required (e.g., glucose was used in the synthesis of **1**,[3a,b] **2**,[3a] **10**,[3n] and **13**[3n]). The phosphate group of the aldol products provides two advantages: first, it facilitates product recovery via chromatography or precipitation; second, it serves as an activated group in hydrogenolysis for the synthesis of deoxyazasugars. Given that more than 20 aldolases are known and many of these enzymes accept unnatural aldehyde substrates,[18] aldolases will be useful for the synthesis of a wide range of piperidines and pyrrolidines structurally related to various monosaccharides. These azasugars can be considered as chiral synthons[19] for the synthesis of various heterocycles with interesting biological activities. The monosaccharide-based inhibitors can also be used in the synthesis of sequence-specific endoglycosidase inhibitors.[20]

Molecular modeling in this study indicates that good glycosidase inhibitor should have a half-chair conformation with a positive charge character around the anomeric carbon and ring heteroatom or a chair-form conformation with a positive charge character and the same topographical orientation of the hydroxyl groups as the corresponding monosaccharide. The binding-inhibition relation established in this study provides useful information for the design of new glycosidase inhibitors and the prediction of inhibition constant.

Experimental Section

(*R*)-*N*-Acetyl-2-(diethoxymethyl)aziridine, 7a. To a mixture containing 100 mL of CH_2Cl_2, 5.27 g (36.3 mmol) of (*R*)-2-(diethoxymethyl) aziridine (**6**, 95% ee), and 40.0 g (289.4 mmol) of K_2CO_3 was added 4.0 mL (42.4 mmol) of acetic anhydride. The mixture was stirred at room temperature for 10 h. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to yield 4.27 g of **7a**: 63% yield; $[\alpha]_D^{23}$ + 84.23° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22, 1.25 (each 3 H, t, J = 7.0 Hz, CH_2CH_3), 2.17 (3 H, s, CH_3CO), 2.28 (1 H, d, J = 3.3 Hz, CH_2 of aziridine), 2.35 (1 H, d, J = 6 Hz, CH_2 of aziridine), 2.68 (1 H, m, CH of aziridine), 3.51–3.78 (4 H, m, OCH_2), 4.40 (1 H, d, J = 4.5 Hz, $CH(OEt)_3$); ^{13}C NMR ($CDCl_3$) δ 15.6 (2C), 23.8, 27.7, 38.3, 63.2, 63.3, 101.6, 183.2; HRMS (M + H^+) calcd 188.1286, found 188.1290.

***N*-Carbobenzoxy-2-(diethoxymethyl)aziridine, 7b.** To a mixture containing 30 mL of CH_2Cl_2, 1.444 g of racemic **6**, and 10.18 g of $KHCO_3$ was added 1.8 mL (12.6 mmol) of CbzCl. The mixture was stirred at room temperature for 2 h. The product was purified by silica gel column chromatography (hexane/AcOEt = 8:1) to yield 486.1 mg (17%) of **7b**: ^1H NMR ($CDCl_3$) δ 1.16, 1.20 (each 3 H, t, J = 6.8 Hz, CH_2CH_3), 2.30 (1 H, d, J = 6.0 Hz, CH_2 of aziridine), 2.34 (1 H, d, J = 3.6 Hz, CH_2 of aziridine), 2.70 (1 H, m, CH of aziridine), 3.45–3.76 (4 H, m, OCH_2), 4.49 (1 H, d, J = 3.8 Hz, $CH(OEt)_3$), 5.11 (2 H, s, $PhCH_2$), 7.33 (5 H, s, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.3, 27.8, 38.3, 61.5, 62.9, 68.1, 100.0, 128.1, 128.3, 128.5, 135.7, 162.5; HRMS (M + H^+) calcd 280.1549, found 280.1555.

***N*-Tosyl-2-(diethoxymethyl)aziridine, 7c.** To a mixture containing 30 mL of CH_2Cl_2, 1.009 g of racemic **6**, and 9.68 g of K_2CO_3 was added 1.67 g of TsCl. The mixture was stirred at room temperature for 3 h, and after evaporation, the product was purified by silica gel column chromatography (hexane/AcOEt = 10:1) to yield 1.13 g (16%) of **7c**: ^1H NMR ($CDCl_3$) δ 1.06, 1.16 (each 3 H, t, J = 7 Hz, CH_2CH_3), 2.33 (1 H, d, J = 4.5 Hz, CH_2 of aziridine), 2.45 (3 H, s, $ArCH_3$), 2.64 (1 H, d, J = 7.1 Hz, CH_2 of aziridine), 2.95 (1 H, m, CH of aziridine), 3.36–3.68 (4 H, m, OCH_2), 4.22 (1 H, d, J = 4.9 Hz, $CH(OEt)_2$), 7.34, 7.84 (each 2 H, d, J = 8.1 Hz, aromatic); HRMS (M + H^+) calcd 300.1269, found 300.1269.

***N*-[[(Trimethylsilyl)ethyl]sulfonyl]-2-(diethoxymethyl)aziridine, 7d.** To a mixture containing 50 mL of CH_2Cl_2, 0.725 g of racemic **6**, and 1.38 g of K_2CO_3 was added 1.00 g of (trimethylsilyl)ethanesulfonyl chloride. The mixture was stirred at room temperature for 1 day. After evaporation, the product was purified by silica gel column chromatography (hexane/AcOEt = 10:1) to yield 600 mg (39%) of **7d**: ^1H NMR ($CDCl_3$) δ 0.23 (9 H, s, $SiMe_3$), 1.08 (2 H, t, J = 9.3 Hz, CH_2Si), 1.17, 1.18 (each 3 H, t, J = 6.9 Hz, CH_2CH_3), 2.28 (1 H, d, J = 4.4 Hz, CH_2 of aziridine), 2.58 (1 H, d, J = 7.1 Hz, CH_2 of aziridine), 2.85 (1 H, m, CH of aziridine), 3.07 (2 H, t, J = 9.3 Hz, SO_2CH_2), 3.51–3.76 (4 H, m, OCH_2), 4.28 (1 H, d, J = 5.1 Hz, $CH(OEt)_2$); ^{13}C NMR ($CDCl_3$) δ –2.3, 9.0, 15.0 (2C), 28.6, 39.6, 48.4, 62.3, 62.4, 100.6; HRMS (M + H^+) calcd 310.1508, found 310.1509.

(*R*)-3-Azido-2-acetamidopropanal Diethyl Acetal, 8a. To a mixture containing 423.0 mg (2.26 mmol) of **7a** and 1.9 g (29.5 mmol) of sodium azide in 18 mL of DMF was added 18.0 mL of zinc chloride (1.0 M solution in Et_2O), and the reaction mixture was stirred at 75 °C for 3 days. The mixture was extracted with AcOEt, and the organic layer was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (hexane/AcOEt = 3:2) to yield 318.6 mg of **8a** (61% yield, $[\alpha]_D^{23}$ –23.8° (*c* 0.15, $CHCl_3$)): ^1H NMR ($CDCl_3$) δ 1.23 (6 H, t, J = 7.1 Hz, CH_2CH_3), 2.03 (3 H, s, CH_3CO), 3.45–3.61 and 3.66–3.76 (6 H, m), 4.24 (1 H, m, –CHNH), 4.53 (1 H, d, J = 3.9 Hz, –$CH(OEt)_2$), 5.83 (1 H, d, J = 7.8 Hz, –NH); ^{13}C NMR ($CDCl_3$) δ 15.5, 15.6, 23.7, 50.8, 51.0, 63.7, 64.4, 101.3, 170.5; HRMS (M + Cs^+) calcd 363.0433, found 363.0450.

3-Azido-2-[(*N*-carbobenzoxy)amino]propanal Diethyl Acetal, 8b. To a mixture containing 112.7 mg of **7b** and 355.5 mg of sodium azide in 4.5 mL of DMF was added 1.1 mL of zinc chloride diethyl ether complex (2.2 M solution in CH_2Cl_2). The mixture was heated at 75 °C for 4 days, followed by the same workup. The residue was purified by silica gel chromatography (hexane/AcOEt = 10:1) to yield 111.3 mg (86%) of **8b**: ^1H NMR ($CDCl_3$) δ 1.20, 1.21 (each 3 H, t, J = 7.0 Hz, CH_2CH_3), 3.47–3.56, 3.66–3.76 (6 H, m), 3.97 (1 H, m, CHNH), 4.50 (1 H, d, J = 3.8 Hz, $CH(OEt)_3$), 5.12 (2 H, s, $PhCH_2$), 7.36 (5 H, s, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 15.2, 50.8, 52.8, 63.5, 64.2, 67.0, 101.3, 128.1 (2C), 128.2, 128.5 (2C), 136.3, 156.1; HRMS (M + H^+) calcd 323.1719, found 323.1720.

3-Azido-2-[(*N*-tosyl)amino]propanal Diethyl Acetal, 8c. In a similar manner as **8b**, the mixture containing **7c** was stirred at room temperature for 1 day, followed by the same workup and silica gel chromatography (hexane/AcOEt = 15:1) to yield 120.0 mg (86%) of **8c**: ^1H NMR ($CDCl_3$) δ 1.08, 1.13 (each 3 H, t, J = 7 Hz, CH_2CH_3), 2.42 (3 H, s, $ArCH_3$), 3.31–3.63 (6 H, m), 4.42 (1 H, d, J = 3.5 Hz, $CH(OEt)_2$), 5.22 (1 H, d, J = 7.2 Hz, NH), 7.30, 7.80 (each 2 H, d, J = 8.2 Hz, aromatic); HRMS (M + H^+) calcd 343.1440, found 343.1460.

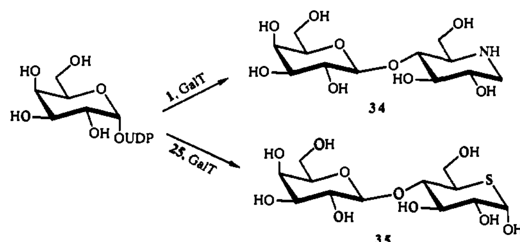
3-Azido-2-[[[(*N*-trimethylsilyl)ethyl]sulfonyl]amino]propanal Diethyl Acetal, 8d. The product **8d** was prepared similarly from **7d** and purified by silica gel chromatography (hexane/AcOEt = 10:1) to yield 80.0 mg (75%): ^1H NMR ($CDCl_3$) δ 0.0 (9 H, s, $SiMe_3$), 1.04 (2 H, m, CH_2Si), 1.17 (6 H, t, J = 7 Hz, CH_2CH_3), 2.99 (2 H, m, SO_2CH_2), 3.43–3.58, 3.67–3.72 (6 H, m), 4.49 (1 H, d, J = 2.2 Hz, $CH(OEt)_2$), 4.72 (1 H, d, J = 7.8 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 2.1, 10.3, 15.2 (2C), 49.9, 51.4, 55.9, 64.6, 64.8, 102.1; HRMS (M + Cs^+) calcd 485.0655, found 485.0666.

Compound 9b. A mixture containing 1.006 g (4.37 mmol) of **8a** and 30 mL of a HCl buffer (pH 1) was heated to 45 °C for 8 h. A solution of DHAP (17 mL, 80.7 mM) was then added, and the pH was adjusted to 6.5 with 1 N NaOH. To this solution, rabbit muscle FDP aldolase (400 units) was added, and the mixture was stirred slowly for 4.5 h. After DHAP was consumed completely based on enzymatic assay,[21] the mixture was passed through Dowex 1 (HCO_2^-) (2.4 × 19 cm) and eluted with water (400 mL), 0.1 M NaCl (250 mL), 0.4 M NaCl (700 mL), and 0.5 M NaCl solution, successively. After adding 200 mL of water to the fraction eluted by the 0.4 M NaCl solution (700 mL), the pH was adjusted to 4.7 with 1 N HCl and acid phosphatase (from sweet potato, type X, 1240 units) was added, and the mixture was stirred slowly at 37 °C for 1 day. The pH was adjusted to 7.0, and water was removed by evaporation. The residue was treated with a mixed solvent of $CHCl_3$/$MeOH$/H_2O = 8:2:0.1 (100 mL). The soluble portion was collected and purified by silica gel chromatography ($CHCl_3$/$MeOH$/H_2O = 8:2:0.1)

(18) Whitesides, G. M.; Wong, C.-H. *Angew. Chem.* **1985**, *24*, 617. Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365. Wong, C.-H. *Chemtracts—Organic Chemistry* **1990**, *3*, 91. Wong, C.-H. *Science* **1989**, *244*, 1145.

(19) For example, compound **1** was used for the synthesis of castanospermine and its 6-epimer (Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5494), an aziridine derivative,[4d] compound **13** (Boshagen, H.; Heiker, F.-R.; Schuller, A. M. *Carbohydr. Res.* **1987**, *164*, 141), D-*galacto*-1-deoxynojirimycinin (Heiker, F.-R.; Schueller, A. M.; *Carbohydr. Res.* **1990**, *203*, 314), and 2-acetamido-1,2-dideoxy-D-*galacto*-nojirimycin (Schueller, A. M.; Heiker, F.-R. *Carbohydr. Res.* **1990**, *203*, 308) in addition to the various *N*-alkyl derivatives described here and elsewhere.

(20) For example, we have used β-1,4-galactosyltransferase (GalT) in the synthesis of galactosyl deoxynojirimycin **34** and galactosyl thioglucose **35** (Gautheron, C. M.; Wong, C.-H., unpublished). Details of GalT-catalyzed synthesis of novel oligosaccharides will be published separately.



to yield 74.2 mg (60%) of **9b**: ^{13}C NMR (CD_3OD) δ 22.6, 51.8, 52.7, 68.1, 72.5, 76.8, 173.8, 213.8.

1,2-Dideoxy-2-acetaminomannojirimycin, 10. To a solution of 70.0 mg of **9b** in 15.0 mL of EtOH was added 13.0 mg of Pd–C, and the mixture was hydrogenated under the pressure of 50 psi. After 1 day, the catalyst was filtered off, and the filtrate was concentrated and purified by silica gel chromatography ($CHCl_3/MeOH/H_2O$ = 6:4:0.7) to yield **10** (52.5 mg): $[\alpha]_D^{23}$ + 36.5° (*c* 104, MeOH); ^{1}H NMR (D_2O) δ 1.96 (3 H, s, CH_3CO), 2.50 (1 H, m, H-5), 2.75, 2.96 (each 1 H, dd, *J* = 2.4 and 13.7 Hz, H_2-1), 3.41 (1 H, t, *J* = 9.7 Hz, H-4), 3.61–3.68 (2 H, m, H-6 and H-3), 3.73 (1 H, dd, *J* = 3.1 and 11.8, H-6), 4.15 (1 H, m, H-2); ^{13}C NMR (D_2O) δ 22.5, 46.7, 50.8, 61.1 (2C), 68.9, 73.2, 175.1; HRMS (M + H$^+$) calcd 205.1188, found 205.1190.

Compound 12b. The procedure was essentially the same as that used for the preparation of **9b**. (*S*)-3-Azido-2-acetaminopropanal diethyl acetal (1.008 g, 4.38 mmol) was converted to 102.0 mg (30%) of **12b**: ^{13}C NMR (CD_3OD) δ 22.7, 52.6, 52.7, 67.8, 72.1, 77.0, 173.9, 212.8.

Compound 12c. A solution of **11** (480 mg, 2.54 mmol) in 10 mL of the pH 1 buffer solution was stirred at 70 °C for 4 h. GC analysis (J&W Scientific DB-5 column (15 m × 0.522 mm), 40 °C for 1 min to 250 °C at 20 °C/min) showed complete hydrolysis of the acetal (room temperature of starting material 6.33 min, corresponding aldehyde 2.65 min). The solution was adjusted to pH 7, then DHAP (2 mmol) was added, and the solution was readjusted to pH 7. Rabbit muscle FDP aldolase (400 units) was then added, and the solution was stirred slowly for 36 h. Enzymatic assay showed no DHAP remaining. $BaCl_2 \cdot 2H_2O$ (1.22 g, 4.80 mmol) and 2 equiv volume of acetone were added to the solution. The solution was maintained at –20 °C overnight. The precipitate was recovered and treated with Dowex X 50(H$^+$) in 20 mL of water to remove barium cation. After filtration, the solution was adjusted to pH 7 and then lyophilized to obtain **12c** (550 mg, 1.79 mmol, 90% based on DHAP) as a white hygroscopic solid: R_f 0.46 (2-propanol/NH_4OH/H_2O = 6:3:2); ^{1}H NMR (D_2O) δ 3.36 (1 H, dd, *J* = 13.25, 5.88 Hz), 3.48 (1 H, dd, *J* = 13.25, 3.28 Hz), 3.68–3.89 (1 H, m), 4.03–4.07 (1 H, m), 4.25–4.33 (1 H, m) ppm; ^{13}C NMR (D_2O) δ 50.65, 66.35, 74.82, 76.32, 79.96, 101.25 (d, *J* = 8.5 Hz); HRMS (M + H$^+$) calcd 307.1319, found 307.1321.

1,2-Dideoxy-2-acetamidonojirimycin, 13. In a procedure analogous to that used for the preparation of **10**, compound **13** (30 mg) was prepared from 40.0 mg of compound **12b**: ^{1}H NMR (D_2O) δ 1.92 (3 H, s, CH_3CO), 2.35 (1 H, t, *J* = 12.3 Hz, H-1a), 2.47 (1 H, m, H-5), 2.98 (1 H, dd, *J* = 4.6 and 12.3 Hz, H-1e), 3.22 (1 H, t, *J* = 9.0 Hz, H-4), 3.31 (1 H, t, *J* = 9.0 Hz, H-3), 3.58 (1 H, dd, *J* = 10.5 and 6.0 Hz, H-6), 3.64 (1 H, m, H-2), 3.74 (1 H, br d, H-6); ^{13}C NMR (D_2O) δ 22.5, 47.3, 52.5, 60.9, 61.6, 72.3, 76.2, 174.8; $[\alpha]_D^{23}$ +20.9° (*c* 0.67, MeOH) (lit.[19] + 16.4 (*c* 1.0, H_2O)). The ^{1}H NMR values are consistent with the reported value.[22]

1,6-Dideoxynojirimycin, 14a. A solution of compound **12c** (550 mg, 1.79 mmol) in 10 mL water was hydrogenated with 50 mg of 10% Pd/C under 45 psi of hydrogen for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated and chromatographed on a short silica gel column ($CHCl_3/MeOH/H_2O$ = 5:5:2) to yield **14a** (250 mg, 95%) as a white fluffy compound: R_f 0.60 (2-propanol/NH_4OH/H_2O = 6:3:2); $[\alpha]_D^{23}$ + 12.0° (*c* 2.5, H_2O); ^{1}H NMR (D_2O) δ 1.10 (3 H, d, *J* = 6.4 Hz, CH_3), 1.27 (3 H, d, *J* = 6.8 Hz, 5-epimer-CH_3), 2.48 (1 H, t, $J_{1a,1e} = J_{1a,2}$ = 12 Hz, H-1a), 2.63 (1 H, dd, $J_{5,6}$ = 6.4, $J_{5,4}$ = 3.6 Hz, H-5), 3.03 (1 H, t, $J_{3,4} = J_{4,5}$ = 9 Hz, H-4), 3.47–3.52 (1 H, m, H-2); ^{13}C NMR (D_2O) δ 16.82, 48.22, 55.76, 69.98, 75.37, 77.83; HRMS (M + H$^+$) calcd 148.1001, found 148.0979.

Preparation of 16a, 16b, and 16c. The aldehyde liberated from racemic **8a** (1g) was mixed with 18 mL of DHAP (71.3 mmol), and the pH was adjusted to 6.5 with 1 N NaOH. To this solution, rabbit muscle FDP aldolase (400 units) was added, and the mixture was stirred slowly for 4.5 h. The mixture was passed through Dowex 1 (HCO_2^-) and eluted with water and NaCl as described previously. To the solution eluted with 0.4 M NaCl was added Pd–C (103.0 mg), and the mixture was hydrogenated under the pressure of 50 psi. After 1 day, the catalyst was filtered off, and the filtrate was lyophilized. The residue was treated with a mixed solvent ($CHCl_3/MeOH/H_2O$ = 6:4:1). The soluble portion was collected and purified by silica gel chromatography ($CHCl_3/MeOH/H_2O$ = 6:4:0.7) to yield **16a** and **16b** in a 12:1 ratio. Starting with enantiomerically pure aldehyde substrates, compounds **16a** and **16b** were separately obtained. **16a**: ^{1}H NMR (D_2O) δ 1.33 (3 H, d, *J* = 6.3 Hz, H-6), 1.94 (3 H, s, CH_3CO), 2.85 (1 H, t, *J* = 12.5 Hz, H-1a), 3.10 (1 H, m, H-5), 3.36 (1 H, dd, *J* = 12.5 and 4.9 Hz, H-1e), 3.39, 3.51 (each 1 H, t, *J* = 9.8 Hz, H-3,4), 3.99 (1 H, ddd, *J* = 12.5, 9.8, and 4.9 Hz, H-2); ^{13}C NMR (D_2O) δ 14.8, 22.3, 44.0, 48.2, 54.9, 72.9, 73.1, 174.2; HRMS (M + Na$^+$) calcd 211.1059, found 211.1053. **16b**: ^{1}H NMR (D_2O) δ 1.34 (3 H, d, *J* = 6.6 Hz, H-6), 1.97 (3 H, s, CH_3CO), 3.10 (1 H, m, H-5), 3.15, 3.43 (each 1 H, dd, *J* = 13.7 and 3.0 Hz, H-1), 3.62 (1 H, t, *J* = 9.4 Hz, H-4), 3.80 (1 H, dd, *J* = 9.4 and 4.6 Hz, H-3), 4.32 (1 H, dt, *J* = 4.6 and 3.0 Hz, H-2); ^{13}C NMR (D_2O) δ 14.5, 22.4, 44.4, 47.6, 55.0, 69.9, 70.0, 174.7; HRMS (M + Na$^+$) calcd 211.1059, found 211.1050. **16c**: R_f 0.12 ($CHCl_3/MeOH/H_2O$ = 5:5:1.5); $[\alpha]_D^{23}$ –4° (*c* 2.5, H_2O); ^{1}H NMR (D_2O) δ 1.213 (3 H, d, *J* = 6.5 Hz, CH_3), 2.893 (1 H, dd, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 3.00 (1 H, d, $J_{1a,1e}$ = 13.5 Hz, H-1a), 3.16 (1 H, dd, $J_{1e,1a}$ = 13.5 Hz, $J_{1e,2}$ = 3 Hz, H-1e), 3.45 (1 H, t, $J_{1e,2} = J_{2,3}$ = 3 Hz, H-2), 3.46 (1 H, t, *J* = 9.5 Hz, H-4), 3.675 (1 H, dd, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 3 Hz, H-3); ^{13}C NMR (D_2O) δ 15.24 (CH_3), 48.31(C-1), 56.17(C-5), 66.74, 70.88, 72.92; HRMS (M + H$^+$) calcd 148.0974, found 148.0900.

***N*-Methyl-1,6-dideoxynojirimycin, 17.** To a solution containing **14a** (47 mg, 0.32 mmol), formaldehyde (300 mL, 37% wt solution), and 10 mg of 10% Pd/C was hydrogenated under 45 psi of hydrogen in 10 mL of $MeOH/H_2O$ (1:1) solution for 1 day. The solvent was removed under reduced pressure to yield compound **17** (52 mg, quantitative yield) as hygroscopic material: R_f 0.65 (2-propanol/NH_4OH/H_2O = 6:3:2); $[\alpha]_D^{23}$ +4.58° (*c* 1.75, H_2O); ^{1}H NMR (D_2O) δ 1.12 (3 H, d, *J* = 6.5 Hz), 2.36 (1 H, dd, *J* = 11.5, 6.5 Hz), 2.63 (1 H, d, *J* = 5 Hz), 3.02–3.06 (2 H, m), 3.18 (1 H, t, *J* = 9.5 Hz), 3.48–3.53 (1 H, m); ^{13}C NMR (D_2O) δ 16.96, 43.87, 61.17, 65.96, 70.68, 76.64, 79.95; HRMS (M + H$^+$) calcd 161.1052, found 162.1129.

***N*-Methyl-1,6-dideoxynojirimycin Oxide, 18.** Hydrogen peroxide (42 mg, 50% wt solution) was added to a 1-mL H_2O solution containing **17** (10 mg, 0.062 mmol), and the mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure to obtain pure **18** (10 mg, 91%) as a single stereoisomer of white hygroscopic compound: R_f 0.53 (2-propanol/NH_4OH/H_2O = 6:3:2); $[\alpha]_D^{23}$ +5.40° (*c* 3.00, H_2O); ^{1}H NMR (D_2O) δ 1.12 (3 H, d, *J* = 6.5 Hz, CH_3), 3.14 (1 H, dd, $J_{5,4}$ = 10, J_{5,CH_3} = 6.5 Hz, H-5), 3.20 (1 H, t, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 3.28 (1 H, t, $J_{1a,1e} = J_{1a,2}$ = 10 Hz, H-1a), 3.39 (1 H, dd, $J_{1e,1a}$ = 10, $J_{1e,2}$ = 5 Hz, H-1e), 3.41 (1 H, t, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 3.88 (1 H, td, $J_{1a,2} = J_{2,3}$ = 10, $J_{2,1e}$ = 5 Hz, H-2); ^{13}C NMR (D_2O) δ 8.65, 55.89, 67.85, 64.52, 70.21, 70.60, 75.44; HRMS (M + H$^+$) calcd 177.2009, found 177.2014.

***N*-Methyldeoxynojirimycin, 19.** A solution containing deoxynojirimycin (10 mg, 0.061 mmol), formaldehyde (300 mL, 37% wt solution), and 10 mg of 10% Pd/C was hydrogenated under 50 psi of hydrogen in 5 mL of methanol/water (1:1) solution for 36 h. The solvent was removed under reduced pressure to yield **18** (10 mg, 93%). All the physical data were consistent with the reported value.[23]

***N*-Methyldeoxynojirimycin Oxide, 20.** Compound **20** was prepared similarly by reaction with H_2O_2, except a longer reaction time (4 days) was needed. After removing the solvent by evaporation, compound **20** was obtained as a single stereoisomer (95%): R_f 0.63 (2-propanol/NH_4OH/H_2O = 6:4:2); $[\alpha]_D^{23}$ +27.83° (*c* 1.15, H_2O); ^{1}H NMR (D_2O) δ 3.20 (1 H, d, $J_{5,4}$ = 10 Hz, H-5), 3.30 (1 H, t, $J_{1a,1e} = J_{1a,2}$ = 10 Hz, H-1a), 3.34 (1 H, td, $J_{3,4} = J_{2,3}$ = 10 Hz, J_{gauche} = 2 Hz, H-3), 3.47 (1 H, dd, $J_{1e,1a}$ = 10 Hz, $J_{1e,2}$ = 4.5 Hz, H-1e), 3.62 (1 H, td, $J_{3,4} = J_{4,5}$ = 10, J_{gauche} = 2 Hz, H-4), 3.89 (1 H, m, H-2), 4.02 (2 H, m, H-6); ^{13}C NMR (D_2O) δ 57.24, 58.17, 65.85, 67.83, 69.23, 76.95; HRMS (M + H$^+$) calcd 326.0000, found 194.1030.

Improved Hypoiodite Oxidation of Nojirimycin to Nojirimycin-δ-lactam. Nojirimycin was obtained from the nojirimycin bisulfite adduct by the known procedure[2d] and oxidized to lactam by a modified procedure of that reported previously.[2d] A stirring solution of nojirimycin (1 g, 4.1 mmol) in water (50 mL) was treated with 0.1 N of I_2 solution dropwise (total vol. 100 mL), and the pH was maintained at 8.5 by adding 0.1 N NaOH with a peristaltic pump. The addition required about 1 h. The solution was allowed to stand at 23 °C for an additional hour. The brown solution was decolorized by adding Dowex MR-3 resin until the solution turned clear. The resin was filtered off and washed with water (100 mL). The solution was lyophilized to afford nojirimycin-δ-lactam which was crystallized from water and ethanol to yield 188 mg (26%). All the physical data were identical with the reported values.[4a]

Acylation of Nojirimycin-δ-lactam. Nojirimycin-δ-lactam (177 mg, 1 mmol) in 0.76 mL of acetic anhydride and 15 mL of dry pyridine was stirred at room temperature for 1 day, then water was added to quench the reaction. Extraction of the solution with CH_2Cl_2, washing with 2 N HCl, $NaHCO_3$(saturated), drying with Na_2SO_4, and evaporation of the solvent yielded the corresponding tetraacetate, 258 mg (75% yield); R_f 0.50 (EtOAc/hexane = 2:3); $[\alpha]_D^{23}$ +104° (*c* 1.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.15–2.05 (12 H, ssss), 3.81–3.77 (1 H, m), 3.96 (1 H, dd,

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J = 7, 12 Hz), 4.28 (1 H, dd, J = 2.7, 12 Hz), 5.07 (1 H, d, J = 9.4 Hz), 5.23 (1 H, t, J = 10 Hz), 5.58 (1 H, t, J = 9.4 Hz), 6.05 (1 H, br).

Nojirimycin-δ-lactim Methyl Ether Tetraacetate. A mixture of 213 mg (0.62 mmol) of nojirimycin-δ-lactam tetraacetate and 150 mg (1.02 mmol) of trimethyloxonium fluoroborate in 20 mL of dry CH_2Cl_2 was stirred and refluxed under nitrogen for 24 h. The reaction was quenched by the addition of 250 mg of potassium carbonate in 20 mL of cold water. Immediately, the solution was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated in vacuo. The crude lactim methyl ether was purified by column chromatography on silica gel (EtOAc/hexane = 2:3 v/v) to yield the lactim methyl ether, 134 mg (0.37 mmol, 60%): R_f 0.63 (EtOAc/hexane = 2:3); $[\alpha]_D^{23}$ +167.6° (c 4.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.10–2.04 (12 H, 4 × s), 3.68 (3 H, s), 4.23–4.21 (12 H, m), 5.20 (1 H, t, J = 9.8 Hz), 5.50–5.37 (2 H, m).

Nojirimycin-δ-lactim Methyl Ether, 23. To a solution containing nojirimycin-δ-lactim methyl ether tetracetate (60 mg, 0.17 mmol) was added sodium methoxide (10 mg) in 10 mL of dry methanol. The mixture was stirred at room temperature for 30 min. Dowex 50 (H^+) was added to the solution to reach pH 7. The solvent was removed under reduced pressure to yield **23** as a light yellow liquid (29 mg, 94%): $[\alpha]_D^{23}$ +70.23° (c 7.54, CH_3OH); ^{1}H NMR (CD_3OD) δ 3.09 (1 H, m), 3.32 (1 H, t, J = 10 Hz), 3.45 (1 H, m), 3.54 (3 H, s), 3.57 (1 H, dd, J = 10, 3.5 Hz), 3.68 (1 H, dd, J = 10, 3.5 Hz), 3.77 (1 H, dd, J = 10, 2.5 Hz); ^{13}C NMR (CD_3OD) δ 53.6, 62.7, 63.8, 70.4, 72.4, 76.9, 163.9; HRMS (M + H^+) calcd 191.0794, found 191.0825.

Preparation of 26, 27, and 28. Compound **26** was prepared according to the literature procedure:[24-26] $[\alpha]_D$ +297° (c 0.34, H_2O) [lit.[24] $[\alpha]_D^{23}$ +208° (c 0.90, MeOH)]; ^{1}H NMR (D_2O) δ 2.96–3.06 (1 H, m, H-5), 3.41 (3 H, s, OMe), 3.52–3.63 (2 H, m, H-3,4), 3.76–3.89 (3 H, m, H-2, 6a, 6b), 4.90 (1 H, d, J = 2.97, H-1). The ^{13}C spectral data were in good accord with those reported.[22] To prepare **27** and **28**, a solution of 64 mg of **26** (0.30 mmol) and 0.2 mL of 30% H_2O_2 in 2.5 mL of AcOH was stirred for 12 h at room temperature and diluted with methanol and concentrated in vacuo. The residual syrup was chromatographed on silica gel [$CHCl_3$/EtOAc/MeOH (5:2:1.5)] to give two products, which were separately dissolved in water and freeze-dried to afford **28** (18 mg, 25% yield) and **27** (16 mg, 24% yield) [R_f 0.39, charred dark brown, and 0.21, charred black, respectively, EtOAc/AcOH/H_2O (8:2:1)].

For **27**: $[\alpha]_D^{23}$ +210° (c 0.20, H_2O); ^{1}H NMR (D_2O) δ 2.98 (1 H, dt, J = 4.35, 10.24, H-5), 3.60 (3 H, s, OMe), 3.70 (1 H, t, J = 9.60, H-3), 3.78 (1 H, dd, J = 9.60, 10.24, H-4), 3.93 (1 H, dd, J = 10.29, 11.98, H-6a), 4.10 (1 H, dd, J = 2.73, 9.60, H-2), 4.24 (1 H, dd, J = 4.25, 11.97, H-6b), 4.96 (1 H, d, J = 2.73, H-1); ^{13}C NMR (D_2O) δ 57.05, 57.45, 61.58, 67.58, 68.55, 73.23, and 90.43; HRMS (M + Cs^+) calcd for $C_7H_{14}O_6S$ 358.9656, found 358.9599.

For **28**: $[\alpha]_D^{23}$ +105.7° (c 0.35, H_2O); ^{1}H NMR (D_2O) δ 3.47 (1 H, ddd, J = 2.48, 5.09, 10.72, H-5), 3.66–3.75 (2 H, m, H-3,4), 3.71 (3 H, s, OMe), 3.96 (1 H, dd, J = 3.29, 9.46 Hz, H-2), 4.16 (1 H, dd, J = 4.99, 12.98, H-6a), 4.24 (1 H, dd, J = 2.42, 12.97, H-6b), 4.62 (1 H, d, J = 3.18, H-1); ^{13}C NMR (D_2O) δ 54.23 (C-5), 59.60 (C-6), 62.41 (OMe), 67.91 (C-4), 69.61 (C-2), 73.41 (C-3), and 94.42 (C-1); HRMS (M + Cs^+) calcd for $C_7H_{14}O_7S$ 374.9515, found 374.9539.

Castanospermine *N*-Oxide, 31. The compound was described,[27] but no characterization was reported. The oxidation with H_2O_2 was carried out according to the previous procedure.[27] The reaction took 3 days to complete. After the removel of the solvent under reduced pressure, castanospermine *N*-oxide (**31**) was obtained quantitatively as a white solid: R_f 0.35 (isopropyl alcohol/MeOH/H_2O = 6:3:2); $[\alpha]_D^{23}$ +37.86° (c 1.4, H_2O); ^{1}H NMR (D_2O) δ 2.163 (1 H, dddd, J = 14.5, 9.5, 9.5, 1.5 Hz, H-2b), 2.500 (1 H, dddd, J = 14.5, 8, 7, 2, Hz, H-2a), 3.030 (1 H, t, J = 11.5 Hz, H-5a), 3.092 (1 H, dd, J = 10.5, 4.5, Hz, H-9), 3.301 (1 H, q, J = 10 Hz, H-3a), 3.372 (1 H, t, J = 9.5 Hz, H-7), 3.555 (1 H, dd, J = 9.5, 5.5 Hz, H-5b), 3.573 (1 H, ddd, J = 9, 8.5, 2 Hz, H-3b), 4.010 (1 H, dd, J = 10.5, 9.5 Hz, H-8), 4.068–4.030 (1 H, m, H-6), 4.378 (1 H, ddd, J = 6.5, 4.6, 1.5 Hz, H-1); ^{13}C NMR (D_2O) δ 33.06, 65.14, 66.37, 67.99, 68.27, 69.61, 77.01, 78.14; HRMS (M + H^+) calcd 206.1028, found 206.1032.

3-Azido-2-fluoropropanal Diethyl Acetal. To a stirring solution of 3-azido-2-hydroxypropanal diethyl acetal (7.32 g, 38.73 mmol) in dry benzene (50 mL) was added (diethylamino)sulfur trifluoride (20.6 mL) at −78 °C. After the addition, the solution was stirred room temperature for an hour and then heated to 70 °C for 12 h. The reaction was quenched by the addition of methanol at 0 °C and dilution with water. After dichloromethane extraction, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified with silica gel column chromatography (hexane/ether = 9:1, v/v) to yield 3-azido-2-fluoropropanal diethyl acetal as an oil (65%): R_f 0.84 EtOAc/hexane = 2:3); ^{1}H NMR (CD_3Cl) δ 1.215–1.219 (6 H, m) 3.526 (2 H, dm, J = 15.3 Hz), 3.642–3.670 (2 H, m), 3.680–3.808 (2 H, m), 4.514 (1 H, dm, J = 45.9 Hz). Compound **30c** was obtained as a byproduct which showed a characteristic chemical shift at 5.254 ppm (ddd, J_{H-F} = 65.5 Hz) for C*H*FOEt.

Aldolase-Catalyzed Synthesis of 2-Fluoro-1,2-dideoxynojirimycin, 30. A mixture of racemic 3-azido-2-fluoropropanal diethyl acetal (750 mg, 3.93 mmol) and 1 N HCl (20 mL) was heated at 65 °C for 30 h. The mixture was cooled to room temperature and DHAP (1 mmol) was added, and the pH was adjusted to 7 with 10 N NaOH. To the solution, rabbit muscle FDP aldolase (500 units) was added, and the solution was stirred slowly for 36 h. Enzymatic determination indicated that all of the DHAP had been consumed. The pH of the solution was adjusted to 4.5 with 2 N HCl. Acid phosphatase (400 units) was added, and the mixture was incubated at 37 °C with stirring for 48 h. The solution was readjusted to pH 7, filtered, and lyophilized. The yellow syrup was treated with methanol and filtered to remove the insoluble material. The methanol was removed under reduced pressure. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 9:1) to yield 5,6-dideoxy-5-fluoro-6-azido-L-sorbose: 20 mg, 9.6%; R_f 0.23 ($CHCl_3$/MeOH = 6:1); ^{13}C NMR (CD_3OD) δ 52.99 (d, J = 18.75 Hz), 68.21, 71.44 (d, J = 26.25 Hz), 76.30, 91.91 (d, J = 175 Hz), 213.02.

A solution containing this product (20 mg) and 10% Pd-C (5 mg) in 10 mL methanol was hydrogenated at 50 psi for 1 day. The catalyst was filtered off, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 3:1) to yield 2-fluoro-1,2-dideoxynojirimycin (**30**) (8 mg, 50%): R_f 0.22 ($CHCl_3$/MeOH = 1:1); $[\alpha]_D^{23}$ −125° (c 0.8, H_2O); ^{1}H NMR (CD_3OD) δ 2.275–2.309 (1 H, m, H-5), 2.659 (1 H, dd, $J_{1a,F}$ = 38 Hz, $J_{1e,1a}$ = 14.5 Hz, H-1a), 3.073 (1 H, ddd, $J_{1e,1a}$ = 14.5, $J_{1e,F}$ = 11.5, $J_{1e,2}$ = 3 Hz, H-1e), 3.319 (1 H, ddd, $J_{3,F}$ = 29.5, $J_{3,4}$ = 9.5 Hz, H-3), 3.609–3.643 (2 H, br d, H-6), 4.574 (1 H, br d, J_{HF} = 50.5 Hz, H-2); ^{13}C NMR (CD_3OD) δ 47.51 (d, J = 47.5 Hz), 60.776, 62.468, 68.784, 74.368 (d, J = 13.75 Hz), 90.867 (d, J = 173 Hz); HRMS (M + H^+) calcd 166.0879, found 166.0863.

In an analogous manner, **30c** was converted to **30a**: ^{1}H NMR (D_2O) δ 1.02 (3 H, t, J = 7.04 Hz, OCH_2CH_3), 2.28–2.34 (1 H, m, H-5), 2.42 (1 H, dd, $J_{1a,2}$ = 1.32 Hz, $J_{1a,1e}$ = 14.0 Hz, H-1a), 3.04 (1 H, dd, $J_{1e,2}$ = 2.66 Hz, H-1e), 3.32 (1 H, dq, J = 7.04 and 10.1 Hz, OC*H*HCH$_3$), 3.38–3.42 (2 H, m, H-3,4), 3.33 (1 H, dq, J = 7.04 and 10.1 Hz, OCH*H*CH$_3$), 3.34–3.36 (1 H, m, H-2), 3.37 (1 H, dd, $J_{6a,5}$ = 5.32 Hz, $J_{6a,6b}$ = 11.1 Hz, H-6a), 3.62 (1 H, dd, $J_{6b,5}$ = 3.19 Hz, H-6b); ^{13}C NMR (D_2O) δ 16.0, 46.2, 62.0, 62.3, 66.56, 70.3, 75.8, 78.4.

Inhibition Study. Materials. All of the buffers, enzymes, and substrates were purchased from Sigma and used as received. The include piperazine-*N*,*N'*-bis (2-ethanesulfonic acid) (PIPES), sodium acetate (NaOAc), ethylenediamine tetraacetic acid (EDTA), β-D-glucosidase (from sweet almond), *p*-nitrophenyl β-D-glucoside, α-D-glucosidase, *p*-nitrophenyl α-D-glucoside, β-*N*-acetyl-D-glucosaminedase, *p*-nitrophenyl β-*N*-acetyl-D-glucosaminide, α-D-mannosidase, and *p*-nitrophenyl α-D-mannoside.

Preparation of Solutions. (a) PIPES buffer (0.05 M with 0.01 mM EDTA, pH 6.5): To 1 L of deionized H_2O was added 15.1 g of PIPES and 35.7 mg of EDTA. The pH was adjusted to 6.5 with NaOH (10 M). (b) PIPES–NaOAc buffer (0.01 M PIPES, 0.2 M NaOAc, and 0.01 mM EDTA, pH 6.5): This buffer was prepared according to the literature procedure.[16] (c) β-D-Glucosidase: The stock enzyme solution was prepared by dissolving 15 mg of solid protein (4 units mg) in 1 mL of PIPES–NaOAc buffer solution. This enzyme solution was diluted 5-fold for the enzymatic assay. (d) α-D-Glucosidase: 1.5 mg of solid protein (70 units/mg) was dissolved in 1 mL of PIPES–NaOAc buffer solution and used for assays without further dilution. (e) β-*N*-Acetyl-D-glucosaminedase: 25 units of the protein was suspended in 0.55 mL of 3.2 M $(NH_4)_2SO_4$ solution as distributed by Sigma. (f) α-D-Mannosidase: 5 mg of the solid protein was suspended in 1 mL of 3.0 M $(NH_4)_2SO_4$ and 0.1 ZnOAc, as distributed by Sigma. (g) Substrate solutions: all substrates were dissolved in the corresponding buffer solution for enzymatic assay.

General Procedure for Enzyme Assay. For each inhibitor, five inhibitor concentrations, ranging 0 to 3 times K_i, were generally used to determine the K_i value. At each inhibitor concentration, six substrate concentrations, spanning from $0.4K_m$ to $4K_m$, were used to obtain a single Lineweaver–Burk plot. The amount of enzyme added in each assay was adjusted so that less than 10% of the substrate, with its lowest substrate concentration, would be consumed within 45 s. Since all of the substrates have *p*-nitrophenol as leaving group, the assays were monitored at 400

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nm, where the molecular extinction coefficient, ε, was calibrated to be 3204.5 M^{-1} cm^{-1} at pH 6.5. The following example illustrates the detailed procedure.

To a 1-mL disposable cuvette was added 950 μL of the NaOAc–PIPES buffer solution, 20 μL of the inhibitor solution, and 20 μL of the *p*-nitrophenyl β-D-glucoside solution (100 mM in PIPES–NaOAc buffer, pH 6.5). The solution was well mixed, and 20 μL of the β-D-glucosidase solution was injected into the cuvette to start the reaction. The reaction was monitored at 400 nm on a Beckman DU-70 photospectrometer for 45 s, and the initial hydrolysis rate was calculated. The same procedure was repeated with five other substrate concentrations. After all the initial rates were accumulated, the corresponding Lineweaver–Burk plot at that inhibitor concentration was constructed.

PIPES–NaOAc buffer was used for all the enzymes except β-D-acetyl-D-glucosaminedase, for which PIPES buffer was used.

Structure Optimization, Calculation and Modeling. The structures of inhibitors were optimized with molecular mechanics (MM2) and then with PM3 in MOPAC,[28] all equipped in a Tetronix CAChe system operated on a Macintosh IIX with an 88K acceleration board. The same parameter settings, which include keywords BFGS, RHF, and PRECISE, were employed throughout the calculation. The final structures were visualized as high-resolution graphics, and partial charge distributions were presented in both graphics and numeric formats.

Supplementary Material Available: Inhibition analysis of compounds **1**, **10**, **13**, **14a**, **17–20**, **23**, and **25–31** (7 pages). Ordering information is given on any current masthead page.

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Novel Synthesis of (η^3-Allyl)platinum(II) Complexes from Enol Triflates and Simple Olefins and Their Regiospecific Deprotonation†

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Abstract: Reaction of bis(triphenylphosphine)(ethylene)platinum(0) (**1**) with alkylvinyl triflates **2a–c** in ethylene-saturated solutions, exclusively yields the stable cationic (η^3-allyl)platinum(II) complexes **5a–c**. Solution chemistry establishes that the reaction proceeds through the intermediacy of σ-vinyl complexes **3a–c** followed by rate-limiting ethylene migratory insertion. The interaction of **3a** with propylene regiospecifically produces η^3-allyl complex **6**. The σ-vinyl adducts **3b,c** were not isolable, but were characterized in situ by NMR spectroscopy. A single-crystal molecular structure determination is reported for **5b**. Heating **6** and **5b** in the presence of triethylamine at as low as 50 °C in THF cleanly affords 2,3-dimethylbutadiene (**16**) and 2-methyl-1,3-pentadiene (**17**), respectively.

Introduction

The palladium-catalyzed olefination of vinyl electrophiles such as halides[1-3] with alkenes is an excellent method of carbon–carbon bond formation between two unsaturated carbon units. Recently, enol triflates have been utilized and prove to be superb substrates for this important transformation.[4-7] Their high selectivity and tolerance toward various functional groups have allowed for the efficient synthesis of a wide variety of functionalized conjugated dienes. However, such a 1,3-diene synthesis has been limited to "activated" alkenes having ester, amide, carbonyl, nitrile, aryl, or other electron-withdrawing substituents. The olefination with "nonactivated" simple alkenes generally results in mixtures of dienes.[3a,8]

η^3-Allyl intermediates have been proposed for the olefination as well as other transition-metal-mediated reactions.[3c,9-11] Therefore, a considerable number of η^3-allyl complexes have been synthesized in an effort to elucidate the mechanism of the catalytic reactions and develop stoichiometric processes.[12-16] Typical preparations of the group 10 metal complexes include allylic hydrogen abstraction of monoolefins, oxidative addition of allylic electrophiles, and nucleophilic addition to dienes. Direct synthesis via C–C bond formation between two unsaturated carbon units has rarely been reported. The only examples are the preparations of (η^3-allyl)palladium(II) chloride dimers from Li_2PdCl_4, alkenes, and vinylmercurials.[17] Such a synthesis for monomeric (η^3-allyl)platinum(II) complexes is hitherto unknown.

Of the three group 10 metals, only (η^3-allyl)palladium(II) compounds have been extensively studied.[13a,16] Trost and coworkers examined the formation of the palladium complexes from olefins and their nucleophilic addition reactions.[16] The chemistry of (η^3-allyl)platinum(II) complexes is not well-documented.[12] The

† Dedicated to Professor Michael Hanack on the occasion of his 60th birthday.

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