Synthesis and Biological Evaluation of Aza-*C*-disaccharides: (1→6), (1→4), and (1→1) Linked Sugar Mimics

Brian A. Johns,[†] Y. T. Pan,[‡] Alan D. Elbein,[‡] and Carl R. Johnson*,[†]

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489, and The Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205-7199

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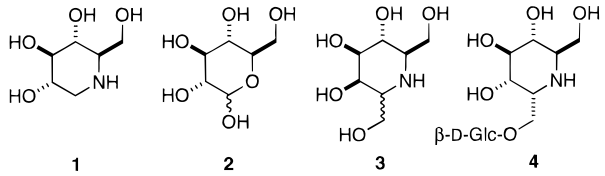
Abstract: The synthesis of (1→6), (1→4), and (1→1) linked aza-*C*-disaccharides, a novel class of glycomimetic compounds, is described. The polyhydroxylated piperidine ring was synthesized using vinyl bromide **11** as a common intermediate which was synthesized *de novo* from bromobenzene utilizing the microbial oxidation metabolite bromodiol **10**. A Suzuki coupling of **11** with an alkylboron reagent derived from olefinated carbohydrate precursors via hydroboration was used to form the *C*-glycosidic bond. Ozonolysis and selective reduction of the resultant carbonyl functions served to produce the azasugar ring. Fully deprotected aza-*C*-disaccharides were obtained upon acidic deprotection. Biological screening of the title compounds against several common glycosidase enzymes as well as *in vitro* anti-HIV assays are reported.

Introduction

Polyhydroxylated piperidines ("azasugars") have received a great deal of attention from the scientific community recently. These alkaloidal sugar mimics contain the same dense stereochemical information as the common hexoses, and many exhibit potent biological activity.[1] The area of biological interest lies in the inhibition of oligosaccharide-processing enzymes called glycosidases and glycosyltransferases. 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.[2] Azasugars are thought to be good inhibitors due to their ability to mimic the transition state oxonium ion as a result of the heterocyclic nitrogen being protonated at physiological pH.[2d] Glycosidases are involved in many biological processes such as digestion and glycopeptide synthesis, as well as the trimming of cell-surface oligosaccharides and hence play a role in the cellular recognition phenomena. Glycosidase inhibitors have potential in the treatment of viral infections,[3] cancer,[4] and diabetes and other metabolic disorders.[5,2b]

Most of the biologically interesting members of this class of compounds are 1-deoxy analogues or diastereomers of deoxynojirimycin (**1**), the stereochemical mimic of D-glucose (**2**). The O/N acetal function of aza-*O*-glycosides is labile under hydrolytic conditions, thus limiting the development of this class of glycomimetics.[6] The presence of an anomeric group, particularly one that resembles a second sugar unit, may provide for greater potency and/or more selectivity in recognition by a targeted enzyme. When carbon groups are used in place of the exo-oxygen of traditional glycosidic links, so-called "*C*-glycosides" are formed; these substances, which are inert to hydrolysis, appear to be conformationally similar to the oxygen-linked natural substances.[7] Several examples of homoazasugars such as homomannojirimycin (**3**) have been isolated from natural sources or prepared synthetically.[8] These materials combine the features of both azasugars and *C*-glycosides. A potent, specific glycosidase inhibitor and an antidiabetic drug candidate has been produced by carrying this concept further with the synthesis of MDL 25,637 (**4**), in which a second sugar is linked by a β-glycosidic bond.[5c] Such β-glycosides are generally more stable toward hydrolysis by pertinent mammalian enzymes.



1 **2** **3** **4**

A first example of an aza-*C*-disaccharide D-azaMan-β-(1→6)-D-Gal (**5**) was reported recently by our laboratories.[9] Since this

[†] Wayne State University.

[‡] University of Arkansas for Medical Sciences.

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(1) (a) Fleet, G. W. J.; Karpus, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F. X.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497.

(2) (a) Jensen, J. L.; Tsuang, S. C.; Uslan, A. H. *J. Org. Chem.* **1986**, *51*, 816. (b) Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717. (c) Cogoli, A.; Semenza, G. *J. Biol. Chem.* **1975**, *250*, 7802. (d) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171.

(3) (a) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206. (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (c) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (d) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229.

(4) (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (b) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Exp. Cell Res.* **1987**, *168*, 116.

(5) (a) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (b) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (c) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539.

(6) (a) Johnson, C. R.; Golebiowski, A.; Sundram, H.; Miller, M. W.; Dwaihy, R. L. *Tetrahedron Lett.* **1995**, *36*, 653. (b) For a recent example of an azasugar thioglycoside, see: Suzuki, K.; Hashimoto, H. *Tetrahedron Lett.* **1994**, *35*, 4119.

(7) For detailed discussions and data on the topic of *C*- vs *O*-glycoside similarities and differences, see: (a) Duda, C. A.; Stevens, E. S. *J. Am. Chem. Soc.* **1993**, *115*, 8487. (b) Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88. (c) Espinosa, J.-F.; Cañada, J.; Asensio, J. L.; Martín-Pastor, M.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1996**, *118*, 10862.

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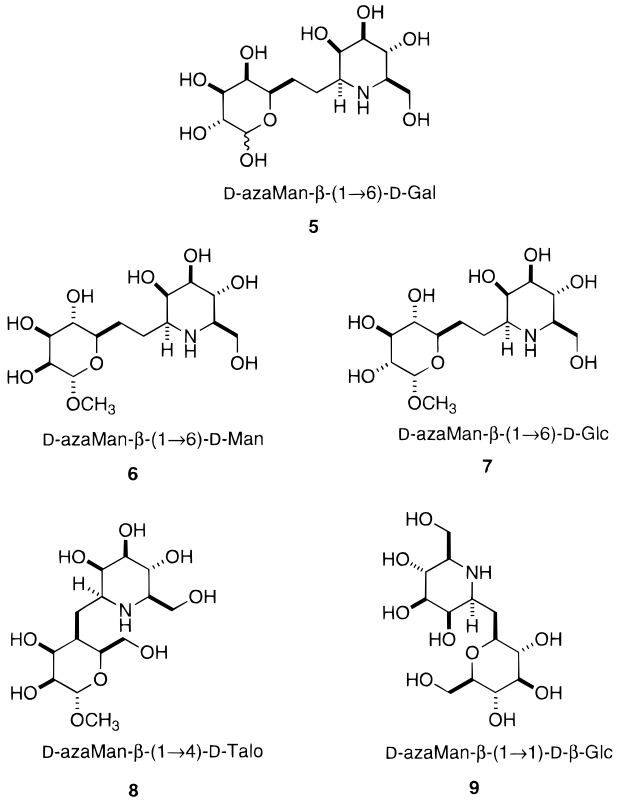
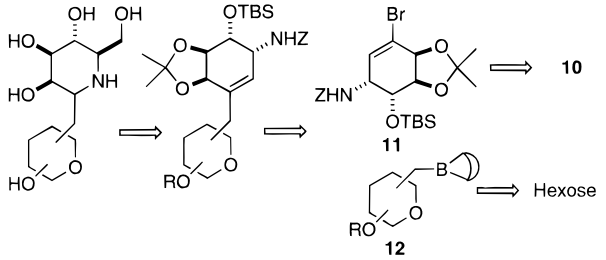
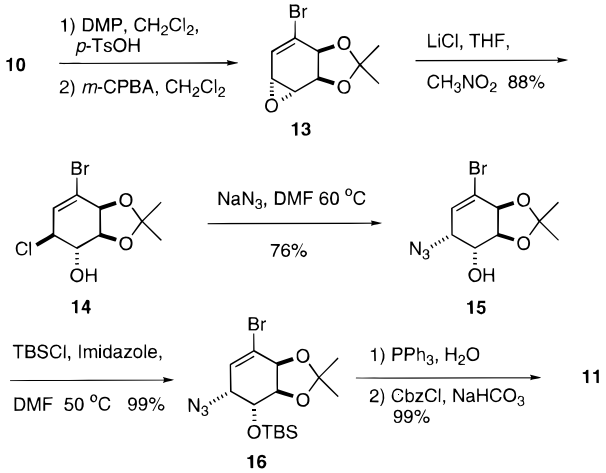
Chart 1. Aza-*C*-disaccharides



Scheme 1



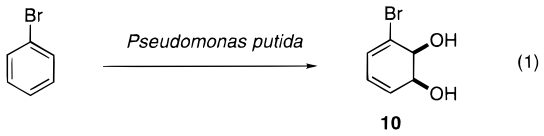
Scheme 2



initial report, the groups of Vogel and Martin have reported syntheses of aza-*C*-disaccharides.[10] We now report the synthesis of D-azaMan-*β*-(1→6)-D-Man (**6**), D-azaMan-*β*-(1→6)-D-Glc (**7**), D-azaMan-*β*-(1→4)-D-Talo (**8**), and D-azaMan-*β*-(1→1)-D-*β*-Glc (**9**) (Chart 1).

Results and Discussion

Recent developments in the microbial oxidation of halobenzenes to produce enantiopure halogen-substituted cyclohexadiene diols has led to the commercial availability of bromodiol **10** (eq 1).[11]



(1)

Our synthetic strategy centers on the palladium-catalyzed Suzuki coupling[12] of vinyl bromide **11** derived from **10** with an alkylboron transmetalation partner **12** generated from the hydroboration of the appropriately olefinated sugar precursor (Scheme 1).

Synthesis of Vinyl Bromide 11. Bromodiol **10** was protected as an acetonide and epoxidized according to the procedure of Hudlicky using *m*-CPBA.[13] The resultant vinyl epoxide was opened regioselectively with LiCl[14] to produce chlorohydrin **14** which was subsequently treated with sodium azide to yield azido alcohol **15**.[15] After protection of the alcohol as its silyl ether (*tert*-butyldimethylsilyl chloride (TBSCl), imidazole, DMF), the azide function was reduced to an amine with triphenylphosphine and protected as a carbamate (CbzCl, $NaHCO_3$) to produce vinyl bromide **11** (Scheme 2).

Synthesis of D-azaMan-*β*-(1→6)-D-Man (6). The 6-hydroxyl group of methyl α-D-mannopyranoside was protected selectively as a silyl ether (*t*-$BuPh_2SiCl$, imidazole, DMF) followed by formation of the 2,3-acetonide ($(CH_3)_2C(OCH_3)_2$, acetone, *p*-toluenesulfonic acid (*p*-TsOH)) to provide alcohol **17**.[16] The 4-hydroxyl group was then transformed into a methoxymethyl ether (MOMCl, $(i\text{-}Pr)_2NEt$), followed by removal of the silyl group (*n*-Bu_4NF, THF) to produce primary alcohol **19**. Oxidation of the resulting alcohol to aldehyde **20** (pyridinium chlorochromate (PCC), molecular sieves 4 Å) followed by Wittig methylenation yielded the desired monosubstituted olefin **21** (Scheme 3).

The desired alkylboron coupling partner was generated *in situ* via the hydroboration of **21** with 9-borabicyclo[3.3.1]nonane

(8) (a) Kite, G. C.; Fellows, L. E.; Fleet, G. W. J.; Liu, P. S.; Schofield, A. M.; Smith, N. G. *Tetrahedron Lett.* **1988**, *32*, 6483. (b) Aoyagi, S.; Fujimaki, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun*. **1990**, 1457. (c) Bruce, I.; Fleet, G. W. J.; di Bello, I. C.; Winchester, B. *Tetrahedron* **1992**, *48*, 10191. (d) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res*. **1993**, *26*, 182. (e) Holt, K. E.; Leeper, F. J.; Handa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 231. (f) Henderson, I.; Laslo, K.; Wong, C.-H. *Tetrahedron Lett*. **1994**, *35*, 359. (g) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett*. **1995**, *36*, 799. (h) Martin, O. R.; Xie, F.; Liu, L. *Tetrahedron Lett*. **1995**, *36*, 4027. (i) Wong, C.-H.; Provencher, L.; Porco, J. A., Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem*. **1995**, *60*, 1492.

(9) (a) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett*. **1994**, *35*, 8991.

(10) (a) Baudat, A.; Vogel, P. *Tetrahedron Lett*. **1996**, *37*, 483. (b) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett*. **1996**, *37*, 1991. (c) Frérot, E.; Marquis, C.; Vogel, P. *Tetrahedron Lett*. **1996**, *37*, 2023. (d) Saavedra, O. M.; Martin, O. R. *J. Org. Chem*. **1996**, *61*, 6987.

(11) The diol derived from bromobenzene is now prepared in crystalline form on a multikilogram scale by Genecor International, Inc., Rochester, NY.

(12) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc*. **1989**, *111*, 314. (b) Suzuki, A. *Pure Appl. Chem*. **1991**, *63*, 419. (c) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

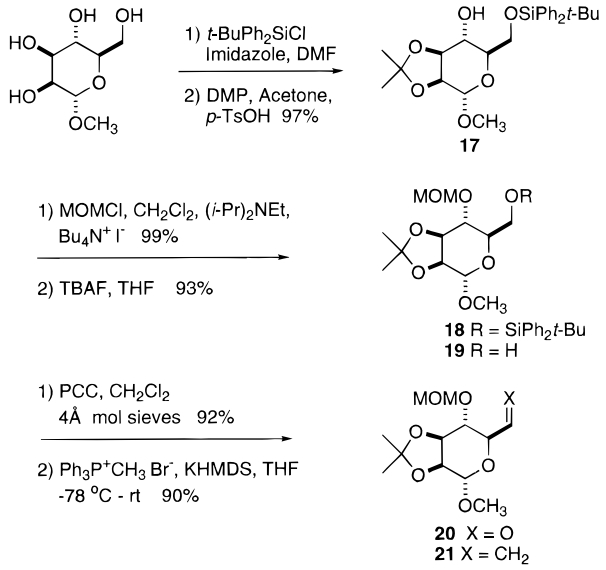
(13) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Anderson, C.; Price, J. D. *Isr. J. Chem*. **1991**, *31*, 229.

(14) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett*. **1991**, *32*, 3021.

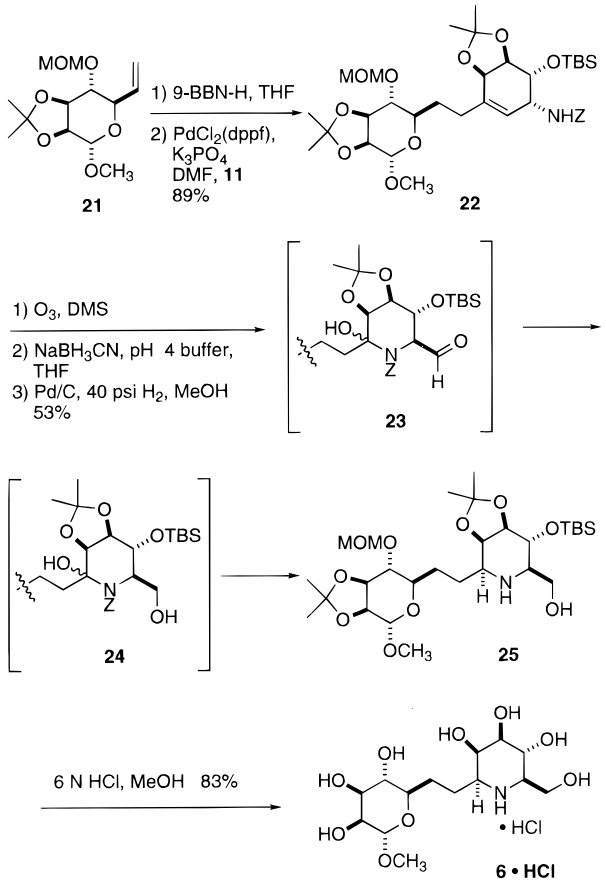
(15) A similar protocol has been demonstrated by Hudlicky using the corresponding vinyl chloride. Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc*. **1994**, *116*, 5099.

(16) Khan, S. H.; Jain, R. K.; Matta, K. L. *Carbohydr. Res*. **1990**, *207*, 57.

Scheme 3



Scheme 4



(9-BBN-H) in THF. The resulting borane and vinyl bromide **11** were coupled smoothly using standard conditions ($PdCl_2$(dppf), 3 M aqueous K_3PO_4, DMF) to produce trisubstituted olefin **22** in excellent yield (Scheme 4). Olefin **22** was transformed into protected disaccharide mimic **25** in three steps requiring only one chromatographic purification. Ozonolysis followed by DMS workup yielded keto aldehyde **23** (which is in equilibrium with its closed form hemiaminal as was observed by ^{1}H NMR). The aldehyde was reduced chemoselectively ($NaBH_3CN$, pH 4 AcOH/NaOAc buffer) producing keto alcohol **24** which was converted to the protected azasugar **25** *via* an intramolecular reductive amination (Pd/C, H_2, CH_3OH). Acidic deprotection (6 N HCl, CH_3OH) produced aza-*C*-disaccharide D-azaMan-β-(1→6)-D-Man (**6**) as its HCl salt. The β stereochemistry was produced exclusively which is consistent with the delivery of H_2 from the α face of the cyclic iminium intermediate (Figure 1a). The stereochemistry was confirmed by a H^1/H^2 coupling constant of 2.5 Hz and NOE enhancements between H^1 and H^5 in both directions (Figure 1b).

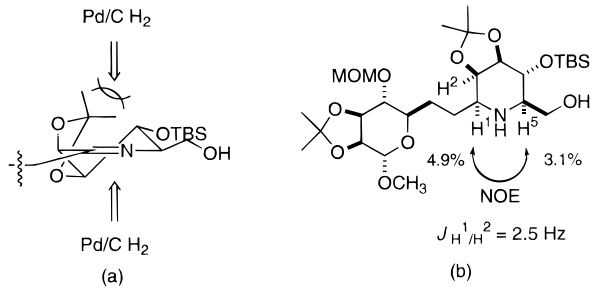
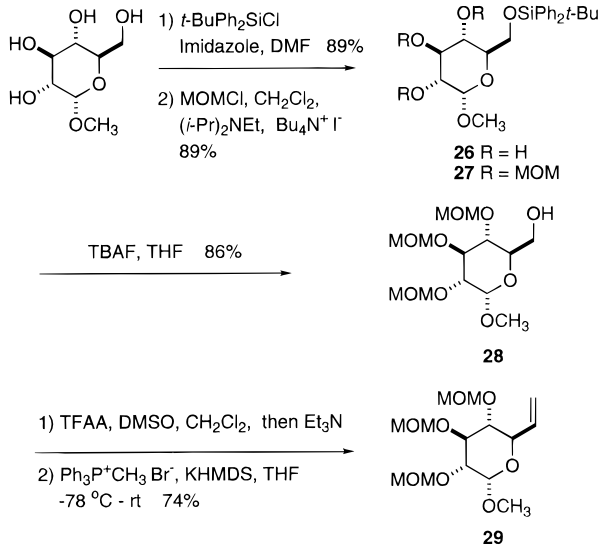


Figure 1. (a) Preferred approach of hydrogenation catalyst. (b) Results of ^{1}H NMR NOE studies of protected aza-*C*-disaccharide **25**.

Scheme 5



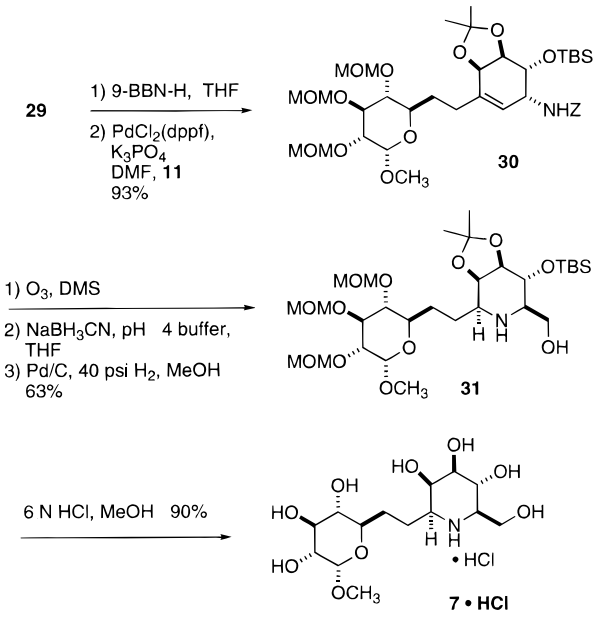
Synthesis of D-**azaMan-β-(1→6)-**D-**Glc (7).** Silylation of the 6-hydroxyl group of methyl α-D-glucopyranoside as described above[17] was followed by protection of the remaining hydroxyl groups as their methoxymethyl ethers (MOMCl, $(i\text{-Pr})_2$NEt) to provide fully protected glucose derivative **27**. Removal of the silyl group with tetrabutylammonium fluoride (TBAF) produced primary alcohol **28** which was oxidized using modified Swern conditions (trifluoroacetic anhydride (TFAA), DMSO, Et_3N),[18] followed by Wittig methylenation, to produce olefin **29** (Scheme 5).

The hydroboration of **29** (9-BBN-H, THF) followed by coupling with **11** ($PdCl_2$(dppf), 3 M aqueous K_3PO_4, DMF) proceeded smoothly to provide trisubstituted olefin **30** (Scheme 6). Ozonolysis followed by reduction of the resultant aldehyde ($NaBH_3CN$, pH 4, THF) and finally intramolecular reductive amination (Pd/C, H_2, CH_3OH) led to protected aza-*C*-disaccharide **31** as a single diastereomer, the expected β isomer as confirmed by NOE and ^{1}H NMR coupling constants. Acid hydrolysis of the remaining hydroxyl protecting groups provided D-azaMan-β-(1→6)-D-Glc (**7**) as its HCl salt.

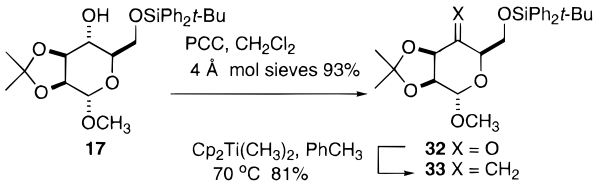
Synthesis of D-**AzaMan-β-(1→4)-**D-**Talo (8).** Alcohol **17** appeared to be well suited for functionalization at the 4-position. Oxidation of the secondary alcohol (PCC, molecular sieves 4 Å) resulted in ketone **32**. A routine Wittig olefination proved to be disasterous, resulting in a poor yield at best of the desired

(17) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(18) Yoshimura, J.; Sato, K.-i.; Hashimoto, H. *Chem. Lett.* **1977**, 1327.

Scheme 6



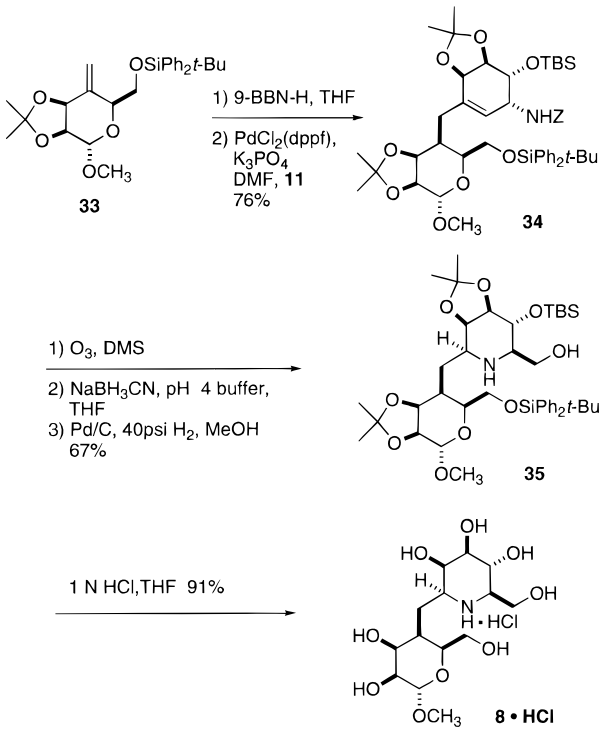
Scheme 7



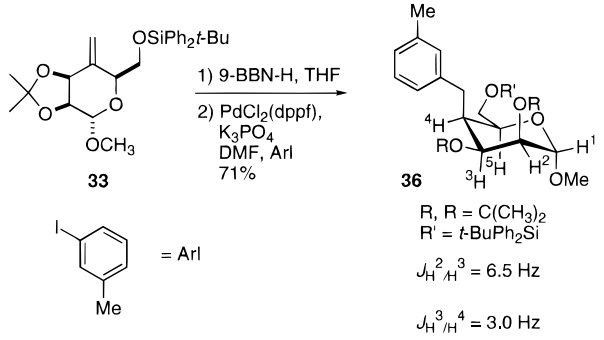
olefin along with epimerization and elimination products resulting from the basic nature of the Wittig conditions. Our efforts were then directed toward the milder metathesis methylenation, namely the Tebbe reaction. In our hands, the traditional Tebbe titanium/aluminum complex gave only modest yields (45−55%) of the desired olefin **33**. The recent development of dimethyltitanocene by Petasis came to our attention.[19] This reagent generates *in situ*, upon warming in toluene, the same titanium alkylidene as the Tebbe reagent. The lower cost along with easier handling of this Tebbe surrogate should also be noted. Methylenation of **32** proceeded nicely with dimethyltitanocene to provide olefin **33** in 81% yield with no evidence of epimerization or elimination products (Scheme 7).

When planning the synthesis of the (1→4) linked sugar, we had concerns about the hydroboration step prior to the Suzuki coupling due to literature precedence for the capricious nature of the hydroboration of disubstituted olefins in the 4-position of carbohydrates.[20] More reactive sources of hydride (BH_3·SMe_2 or combinations of hydroboration reagents such as thexylborane and BH_3) along with extended reaction times were reported as necessary for significant addition to occur. The use of the more reactive and less sterically biased BH_3 led to mixtures of regio- and stereoisomers while only providing moderate yields of products. Another concern was that while the Suzuki coupling works well with 9-BBN-H-derived alkylboron partners, very few other alkylboron reagents facilitate the required transmetalation step to afford the desired coupled product.[12] Much to our delight, our first attempt at the hydroboration of **33** (9-BBN-H, THF, reflux) followed by coupling to **11** ($PdCl_2$(dppf), 3 M aqueous K_3PO_4, DMF) led to olefin **34** as a single diastereomer in good yield (Scheme 8).

Scheme 8



Scheme 9



The stereochemistry of the hydroboration of **33** was determined to be that corresponding to the talo configuration. This result is consistent with an equatorial approach of the sterically demanding borane. This was confirmed using a model system due to the complexity of the ^{1}H NMR spectra of **34** making coupling assignments difficult along with the fact that H^4 of the talo ring resides in an equatorial position which is not set up well for NOE experiments. Olefin **33** was coupled under identical conditions as described above, but vinyl bromide **11** was replaced with 3-iodotoluene, vastly simplifying the ^{1}H NMR spectrum of the product **36** (Scheme 9). The toluene derivative containing a methyl singlet was chosen for determining the diastereomeric ratio resulting from the hydroboration. Only a trace of the minor diastereomer was observed in the ^{1}H NMR spectra of the crude reaction mixture. A coupling constant of 3.0 Hz was observed between H^3 and H^4 of **36** in complete agreement with the expected talo configuration. A *trans* diaxial coupling constant between H^3 and H^4 of 9−10 Hz would be expected for the manno diastereomer.

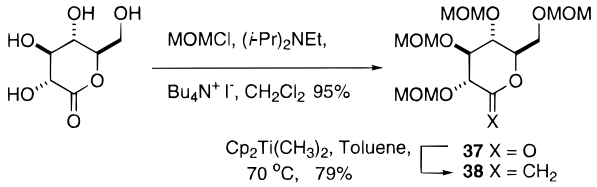
Ozonolysis of **34** followed by the previously described sequence led to protected disaccharide **35** again as a single diastereomer as confirmed by ^{1}H NMR and NOE studies. Acidic deprotection provided D-azaMan-β-(1→4)-D-Talo (**8**) as its HCl salt.

Synthesis of D-azaMan-β-(1→1)-D-β-Glc (9). δ-D-Gluconolactone was protected exhaustively as its tetra(methoxymethyl

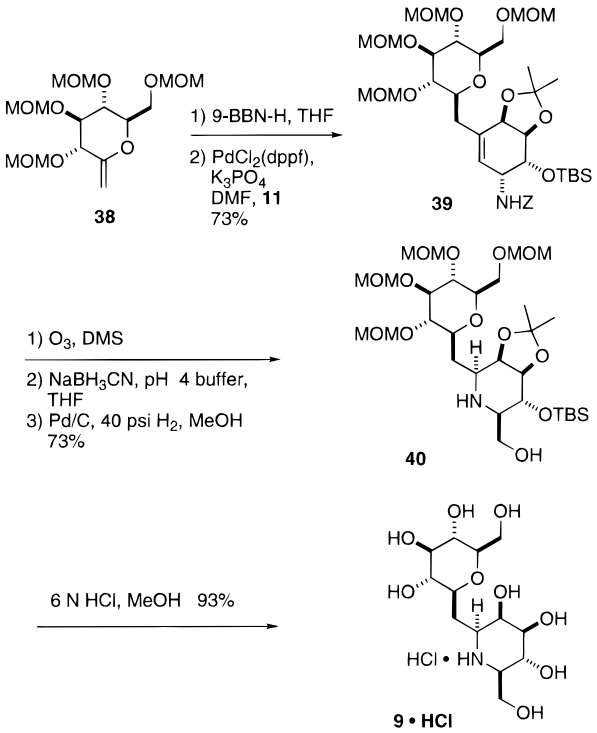
(19) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Csuk, R.; Glänzer, B. I. *Tetrahedron* **1991**, *47*, 1655.

(20) (a) Daly, S. M.; Armstrong, R. W. *Tetrahedron Lett.* **1989**, *30*, 5713. (b) Preuss, R.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 377.

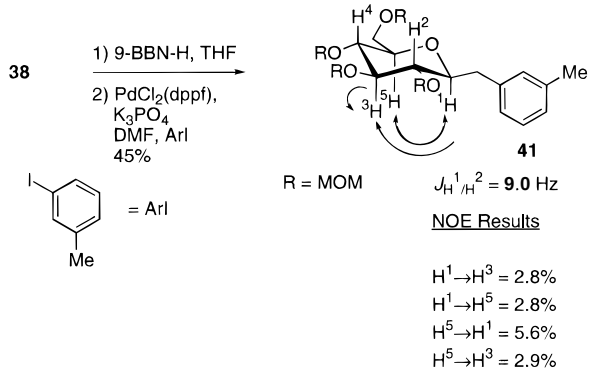
Scheme 10



Scheme 11



Scheme 12



ether) **37** (MOMCl, $(i\text{-Pr})_2$NEt). The lactone function was olefinated with dimethyltitanocene in good yield to provide enol ether **38** (Scheme 10).

Hydroboration of **38** (9-BBN-H, THF, reflux), followed by coupling of the product with vinyl bromide **11** ($PdCl_2$(dppf), 3 M aqueous K_3PO_4, DMF) led smoothly to trisubstituted olefin **39** as a single diastereomer (Scheme 11).

The stereochemical outcome of the hydroboration was determined as previously described by coupling **38** to 3-iodotoluene under the same reaction conditions as were used to form the parent system **39** (Scheme 12). The hydroboration resulted in axial hydride delivery to form **41** having the β-glucose stereochemistry. This was confirmed by a H^1/H^2 coupling constant of 9.0 Hz corresponding to a *trans* diaxial relationship as required by the β-oriented aryl group at C^1 of **41**. The α-oriented aryl group at C^1 would be expected to have an H^1/H^2 coupling of 3−4 Hz and was not observed. NOE experiments were also conducted resulting in positive enhancements between H^1 and H^3 as well as H^1 and H^5, all of which reside in 1,3 axial positions below the ring. This result is consistent with the report that the perbenzylated derivative of **38** undergoes hydroboration with 9-BBN-H followed by oxidation to give only the β-homoglucose.[21]

Table 1. Comparison of Inhibitory Activities

entry	compound	enzyme	IC_{50} (μM)
1	**6**	amyloglucosidase	25
2	**7**	amyloglucosidase	12
3	**8**	amyloglucosidase	150
4	**8**	α-glucosidase	200
5	**8**	α-galactosidase	330[a]
6	**9**	amyloglucosidase	26

[a] Value determined by extrapolation.

Ozonolysis of **39** followed by reduction of the resultant aldehyde ($NaBH_3CN$, pH 4, THF) and finally intramolecular reductive amination (Pd/C, H_2, CH_3OH) led to protected aza-*C*-disaccharide **40** as a single diastereomer corresponding to the expected β isomer which was confirmed by NOE and ^{1}H NMR coupling constants. Acid hydrolysis of the remaining alcohol protecting groups provided D-azaMan-β-(1→1)-D-β-Glc (**9**) as its HCl salt.

Biological Evaluation

Aza-*C*-disaccharides **6**−**9** were screened against seven common glycosidases (amyloglucosidase, α-glucosidase (yeast), β-glucosidase, α-galactosidase, β-galactosidase, α-mannosidase, and β-mannosidase) that accept *p*-nitrophenyl glycosides as substrates.[22] The compounds were tested up to a maximum concentration of 100 μg/mL. All four compounds inhibited amyloglucosidase with **7** exhibiting the best activity (IC_{50} = 12 μM) followed by **6** (IC_{50} = 25 μM) and **9** (IC_{50} = 26 μM), and the weakest inhibitor was **8** (IC_{50} = 150 μM).

Interestingly, derivative **8** exhibited the weakest amyloglucosidase inhibition but was the only compound to inhibit any of the other enzymes which were assayed (Table 1). It should be noted that none of the compounds inhibited the mannosidase enzymes even though the piperidine ring stereochemistry corresponds to the parent mannojirimycin which is a potent mannosidase inhibitor.[1b] This is not a completely unexpected outcome since removal of the anomeric hydroxyl resulting in deoxymannojirimycin (DMJ) vastly decreases the inhibition of mannosidase, and any simple alkyl substitution at the C^1 position renders the DMJ derivatives completely inactive against mannosidase enzymes. The C^1-substituted DMJ derivatives are potent inhibitors of other glycosidases demonstrating that the C^1 position has a crucial role in the activity of azasugars.[23] Our results are consistent with this observation. It is also noteworthy that the differences in biological activity of the title compounds must be attributed to the variations in the linkage and stereochemistry of the pyranose portion of the disaccharides due to the identical nature of the piperidine ring segment.

Aza-*C*-disaccharides **6** and **9** were screened for *in vitro* anti-HIV activity. Unfortunately both compounds were confirmed inactive with an $IC_{50} > 2 \times 10^{-4}$ M.

Conclusion

In summary, an efficient method for the construction of (1→6), (1→4), and, (1→1) linked aza-*C*-disaccharides has been

(21) Rajanbabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458.
(22) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027.
(23) (a) Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 4439. (b) Winchester, B.; Barker, C.; Baines, S.; Jacob, G. S.; Namgoong, S. K.; Fleet, G. *Biochem. J.* **1990**, *265*, 277.

developed. The hydroboration and Suzuki coupling of olefinated sugar derivatives provides a mild method for further functionalization and derivatization of one of the most widely studied and diverse class of organic compounds found in nature. Encouraging biological data has been reported for the title compounds providing impetus for further studies in the area of C^1 substitution of this class of glycomimetics. The differing biological data between the four compounds reported supports our initial hypothesis that further stereochemical information can help in the specificity of polyhydroxylated piperidine-induced glycosidase inhibition. Further studies involving this methodology for the synthesis of other classes of glycomimetics is currently being pursued in our laboratories.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 500, a Varian Gemini 300, or a Nicolet QE 300 spectrometer. Chemical shift values (δ) are reported in ppm. Infrared spectra were recorded on a Nicolet 20DX FTIR spectrometer. High-resolution mass spectra were recorded on a Kratos MS80RFA spectrometer. FAB mass spectra were recorded on a Kratos MS50TC spectrometer. Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. Flash Chromatography was carried out uing Merck Kieselgel (230−400 mesh). Thin-layer chromatography was performed on silica gel. Melting points were taken on a Hoover UniMelt apparatus and are uncorrected. Solvents were purified according to the literature procedures.[24] 9-BBN-H was prepared and stored in its solid dimer form by the known procedure.[25] The 9-BBN-H dimer was typically dissolved in THF as a 0.5 M solution for 3 h before use. 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. Ozonolysis was achieved with an OREC ozonator (Model 03V5-0) and rated to produce ca. 5 g of ozone per hour with a flow rate of 2.8 L/min using an oxygen source.

General Procedure A: 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 (1 equiv) in CH_2Cl_2/CH_3OH (1:1) (0.2 M) and cooled to −78 °C. An ozone/oxygen stream from a Model 03V5-0 OREC ozonator 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 room temperature (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 aldehyde unless otherwise stated. The crude material was taken up in THF (0.07−0.1 M) and cooled to 0 °C. $NaBH_3CN$ (1.3 equiv) was added in one portion followed by 1−2 drops of a AcOH/NaOAc pH 4 buffer solution, and the resultant solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was poured into Et_2O or EtOAc and washed with $NaHCO_3$ and brine. The aqueous layers were extracted with Et_2O (3×), 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 CH_3OH (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.

(1*S*,2*S*,5*S*,6*S*)-4-Bromo-2-chloro-5,6-(*O*-isopropylidenedioxy)cyclohex-3-en-1-ol (14). To a solution of epoxide **13**[13] (5.74 g, 23.4 mmol) in THF (100 mL) at rt were added LiCl (9.9 g, 232 mmol) and nitromethane (3.8 mL). The resultant pale brown solution was stirred for 4 d at rt. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel (4:1 to 2:1, hexanes/EtOAc) gave 5.80 g (88%) of chloro alcohol **14** as a viscous clear oil: R_f 0.44 (2:1, hexanes/EtOAc); IR (neat) 3450, 2976, 2912, 1640, 1077 cm^{-1}; $[\alpha]^{20}_D$ −3.90° (*c* 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.56 (s, 3 H), 2.74 (d, 1 H, J = 2.7 Hz), 3.80 (td, 1 H, J = 8.4, 2.7 Hz), 4.16 (dd, 1 H, J = 8.4, 6.3 Hz), 4.32 (ddd, 1 H, J = 8.4, 2.1, 1.5 Hz), 4.70 (dd, 1 H, J = 6.3, 1.2 Hz), 6.26 (d, 1 H, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.87, 28.06, 58.99, 74.12, 77.01, 77.52, 111.27, 120.08, 132.63; HRMS (EI) calcd for $C_9H_{12}BrClO_3$ (M^+) 281.9658 ($M^+ - CH_3$) 266.9424, found 266.9423.

(1*R*,2*R*,5*S*,6*S*)-2-Azido-4-bromo-5,6-(*O*-Isopropylidenedioxy)cyclohex-3-en-1-ol (15). Chloro alcohol **14** (6.31 g, 22.2 mmol) was taken up in 45 mL of DMF, and sodium azide (2.17 g, 33.4 mmol) was added in one portion at rt. The resultant solution was heated to 55 °C for 40 h. The reaction mixture was cooled to rt, poured into EtOAc, and washed with H_2O and brine. The aqueous layers were extracted with EtOAc (4×), and the combined organics were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (4:1, hexanes/EtOAc) gave 4.91 g (76%) of azido alcohol **15** as a white solid: mp 107−108 °C; R_f 0.61 (2:1, hexanes/EtOAc); IR (neat) 3378, 2977, 2871, 2121, 1632, 1073 cm^{-1}; $[\alpha]^{20}_D$ −147.5° (*c* 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.44 (s, 3 H), 2.47 (br m, 1 H), 4.20 (m, 2 H), 4.40 (t, 1 H, J = 5.4 Hz), 4.66 (dd, 1 H, J = 5.4, 0.9 Hz), 6.15 (dd, 1 H, J = 3.9, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.06, 27.64, 59.54, 69.17, 75.99, 76.12, 110.44, 125.38, 126.26; HRMS (EI) calcd for $C_9H_{12}BrN_3O_3$ (M^+) 289.0062 ($M^+ - CH_3$) 273.9827, found 273.9832.

(3*R*,4*R*,5*S*,6*S*)-3-Azido-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-5,6-(*O*-isopropylidenedioxy)cyclohex-1-ene (16). A solution of azido alcohol **15** (4.91 g, 16.9 mmol) in DMF (35 mL) was treated with *tert*-butyldimethylsilyl chloride (3.84 g, 25.5 mmol) and imidazole (2.88 g, 42.3 mmol) at rt. The resultant solution was heated to 60 °C for 18 h. The reaction mixture was then cooled to rt, poured into pentane, and washed with H_2O and brine. The aqueous layers were extracted with pentane (4×), and the combined organics were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (9:1, hexanes/EtOAc) gave 6.80 g (99%) of silyl ether **16** as a clear oil: R_f 0.60 (8:1, hexanes/EtOAc); IR (neat) 2988, 2953, 2931, 2858, 2102, 1645, 1228, 1077 cm^{-1}; $[\alpha]^{20}_D$ −42.5° (*c* 1.22, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ −0.04 (s, 3 H), 0.02 (s, 3 H), 0.86 (s, 9 H), 1.11 (s, 3 H), 1.26 (s, 3 H), 3.48 (m, 1 H), 3.88 (dd, 1 H, J = 6.3, 3.6 Hz), 4.15 (dd, 1 H, J = 6.3, 5.7 Hz), 4.46 (d, 1 H, J = 5.7 Hz), 5.73 (d, 1 H, J = 4.2 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ −4.91, −4.81, 18.13, 25.84, 25.91, 27.66, 60.00, 71.74, 76.89, 77.04, 110.07, 125.57, 127.22; HRMS (EI) calcd for $C_{15}H_{26}BrN_3O_3Si$ (M^+) 403.0927 ($M^+ - CH_3$) 388.0692, found 388.0700.

(3*R*,4*R*,5*S*,6*S*)-3-[(*N*-Benzyloxycarbonyl)amino]-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-5,6-(*O*-isopropylidenedioxy)cyclohex-1-ene (11). Triphenylphosphine (5.50 g, 21 mmol) was added to azide **16** (6.80 g, 16.9 mmol) in THF (60 mL) at rt. The reaction mixture began bubbling within 10 min. The resultant mixture was stirred at rt for 2 h. H_2O (3.0 mL) was then added, and the solution was heated to reflux for 6 h. The mixture was cooled to rt and concentrated at reduced pressure. EtOAc (60 mL) was then added to the reaction flask followed by saturated aqueous $NaHCO_3$ (30 mL). Benzyl chloroformate (3.62 mL, 25.3 mmol) was then added, and the biphasic mixture was stirred vigorously at rt for 16 h. The layers were separated, and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc (3×), and the combined organics were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (9:1, hexanes/Et_2O) gave 8.60 g (99%) of vinyl bromide **11** as a pale brown oil: R_f 0.58 (4:1, hexanes/EtOAc); IR (neat) 3449, 3347, 3033, 2986, 2952, 2931, 2857, 1727, 1500, 1216, 1076 cm^{-1}; $[\alpha]^{20}_D$ −27.7° (*c* 1.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.10 (s, 3 H), 0.87 (s, 9 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 4.24 (t, 1 H, J = 4.5 Hz), 4.28 (t, 1 H, J = 3.3 Hz), 4.50 (dd, 1 H, J = 4.8, 1.8 Hz), 4.55 (br d, 1 H, J = 8.7 Hz), 5.06 (d, 1 H, J = 10.5 Hz), 5.13 (s, 2 H), 5.89 (t, 1 H, J = 1.8 Hz), 7.33−7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.05, −4.76, 17.87, 25.60, 26.59, 27.62, 49.63, 66.91, 69.15, 75.71, 76.60, 110.59, 123.36, 128.15, 128.50, 129.39, 133.57, 136.29, 155.45; HRMS (EI) calcd for $C_{23}H_{34}BrNO_5Si$ (M^+) 511.1390 ($M^+ - C_4H_9$) 454.0685, found 454.0694.

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-*O*-(methoxymethyl)-α-D-mannopyranoside (18). To a cold (0 °C)

(24) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1989.

(25) Soderquist, J. A.; Negron, A. *Org. Synth.* **1991**, *70*, 169.

solution of silyl ether **17**[16] (2.78 g, 5.9 mmol) in CH_2Cl_2 (60 mL) was added diisopropylethylamine (3.07 mL, 17.6 mmol) dropwise, followed by the addition of chloromethyl methyl ether (2.25 mL, 29.5 mmol). Solid tetrabutylammonium iodide (0.65 g, 1.8 mmol) was then added to the reaction mixture, and the solution was allowed to warm to rt. The reaction mixture was stirred in the dark for 14 h. The reaction mixture was poured into CH_2Cl_2 and washed with saturated aqueous NH_4Cl and brine. The aqueous layers were extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (8:1, hexanes/EtOAc) gave 3.01 g (99%) of fully protected sugar **18** as a clear oil: R_f 0.51 (8:1, hexanes/EtOAc); IR (neat) 3071, 3048, 2986, 2932, 2857, 1091, 1032 cm^{-1}; $[\alpha]^{20}_D$ +15.5° (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9 H), 1.36 (s, 3 H), 1.53 (s, 3 H), 3.22 (s, 3 H), 3.38 (s, 3 H), 3.63 (ddd, 1 H, J = 10.2, 5.1, 2.4 Hz), 3.75 (dd, 1 H, J = 10.2, 6.9 Hz), 3.84 (dd, 1 H, J = 11.1, 5.1 Hz), 3.91 (dd, 1 H, J = 11.1, 2.4 Hz), 4.12 (d, 1 H, J = 5.4 Hz), 4.21 (t, 1 H, J = 6.9 Hz), 4.65 (d, 1 H, J = 6.3 Hz), 4.85 (d, 1 H, J = 6.3 Hz), 4.94 (s, 1 H), 7.32−7.46 (m, 6 H), 7.71−7.76 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.27, 26.39, 26.75, 27.80, 54.62, 55.79, 63.27, 69.61, 72.90, 75.85, 78.54, 96.26, 98.02, 109.24, 127.48, 127.58, 129.52, 133.36, 133.73, 135.61, 135.86; HRMS (EI) calcd for $C_{28}H_{40}O_7Si$ (M^+) 516.2543 ($M^+ - CH_3$) 501.2308, found 501.2308.

Methyl 2,3-*O*-Isopropylidene-4-*O*-(methoxymethyl)-α-D-mannopyranoside (19). A cold (0 °C) solution of silyl ether **18** (3.01 g, 5.84 mmol) in THF (50 mL) was treated with 7.59 mL of tetrabutylammonium fluoride (1.0 M in THF, 7.59 mmol). The resultant solution was then warmed to 25 °C, and stirring was continued for 16 h. The reaction mixture was poured into EtOAc and washed with saturated aqueous NH_4Cl and brine. The aqueous layers were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2:1 to 1:1, hexanes/EtOAc) gave 1.52 g (93%) of alcohol **19** as a white solid: mp 41−45 °C; R_f 0.40 (1:1, hexanes/EtOAc); IR (neat) 3486, 2986, 2906, 1090, 1031 cm^{-1}; $[\alpha]^{20}_D$ +77.4° (*c* 1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.53 (s, 3 H), 2.34 (t, 1 H, J = 6.9 Hz), 3.37 (s, 3 H), 3.41 (s, 3 H), 3.57 (dt, 1 H, J = 10.2, 3.6 Hz), 3.72 (dd, 1 H, J = 10.2, 7.2 Hz), 3.82 (m, 2 H), 4.11 (d, 1 H, J = 5.7 Hz), 4.21 (dd, 1 H, J = 7.2, 5.7 Hz), 4.68 (d, 1 H, J = 6.6 Hz), 4.92 (s, 1 H), 4.93 (d, 1 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.30, 27.88, 54.96, 55.99, 62.00, 68.58, 73.59, 75.84, 78.25, 96.79, 98.32, 109.35; HRMS (EI) calcd for $C_{12}H_{22}O_7$ (M^+) 278.1365 ($M^+ - CH_3$) 263.1132, found 263.1134.

Methyl 2,3-*O*-Isopropylidene-4-*O*-(methoxymethyl)-6-oxo-α-D-mannopyranoside (20). To a suspension of freshly activated powdered 4 Å molecular sieves (4.6 g) in CH_2Cl_2 (50 mL) was added pyridinium chlorochromate (2.25 g, 10.4 mmol). Alcohol **19** (631 mg, 2.27 mmol) in CH_2Cl_2 (5 mL) was added by a cannula at rt resulting in a brown suspension. The reaction mixture was stirred for 35 min upon which time TLC indicated the disappearance of starting material. The reaction mixture was diluted with 125 mL of Et_2O/hexanes (2:1) and filtered through a pad of silica gel. The silica gel was eluted with Et_2O (300 mL). Upon concentration of the eluent, 579 mg (92%) of aldehyde **20** was obtained as a pale brown oil: R_f (streak) 0.19−0.45 (1:1, hexanes/EtOAc); IR (neat) 2985, 2936, 2908, 2828, 1742, 1092, 1033 cm^{-1}; $[\alpha]^{20}_D$ +44.8° (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 1.50 (s, 3 H), 3.33 (s, 3 H), 3.40 (s, 3 H), 3.89 (dd, 1 H, J = 9.3, 6.3 Hz), 4.01 (dd, 1 H, J = 9.3, 1.5 Hz), 4.11 (dd, 1 H, J = 5.7, 1.2 Hz), 4.28 (t, 1 H, J = 5.7 Hz), 4.63 (d, 1 H, J = 6.6 Hz), 4.91 (d, 1 H, J = 6.6 Hz), 4.96 (s, 1 H), 9.71 (d, 1 H, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.10, 27.64, 55.56, 56.03, 72.33, 73.04, 75.07, 77.25, 96.35, 98.52, 109.79, 197.76; HRMS (EI) calcd for $C_{12}H_{20}O_7$ (M^+) 276.1209 ($M^+ - CH_3$) 261.0974, found 261.0968.

Methyl 2,3-*O*-Isopropylidene-4-*O*-(methoxymethyl)-6-methylene-α-D-manno-pyranoside (21). Potassium bis(trimethylsilyl)amide (6.45 mL, 0.5 M toluene, 3.22 mmol) was added dropwise at rt to a suspension of methyltriphenylphosphonium bromide (1.2 g, 3.36 mmol) in THF (39 mL). The resultant bright yellow solution was stirred at rt for 1.5 h. The ylide solution was then cooled to −78 °C, and a solution of aldehyde **20** (613 mg, 2.22 mmol) in THF (5 mL) was added slowly by cannula. After 15 min of stirring at −78 °C, the reaction mixture was allowed to warm to rt and stirred for another 1.5 h. The reaction mixture was quenched at 0 °C with CH_3OH (9 mL), poured into Et_2O, and washed with 30 mL of H_2O/saturated aqueous Rochelle's salt (1:1) and finally with brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (8:1 to 4:1, hexanes/EtOAc) gave 546 mg (90%) of olefin **21** as a clear oil: R_f 0.55 (8:1, hexanes/EtOAc); IR (neat) 2987, 2937, 1093, 1032 cm^{-1}; $[\alpha]^{20}_D$ +31.7° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.53 (s, 3 H), 3.36 (s, 3 H), 3.37 (s, 3 H), 3.53 (dd, 1 H, J = 9.9, 7.2 Hz), 3.94 (dd, 1 H, J = 9.9, 6.3 Hz), 4.11 (dd, 1 H, J = 6.0, 0.6 Hz), 4.18 (dd, 1 H, J = 7.2, 6.0 Hz), 4.63 (d, 1 H, J = 6.9 Hz), 4.85 (d, 1 H, J = 6.9 Hz), 4.92 (s, 1 H), 5.27 (dt, 1 H, J = 10.5, 1.5 Hz), 5.42 (dt, 1 H, J = 17.1, 1.5 Hz), 5.93 (ddd, 1 H, J = 17.1, 10.5, 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.33, 27.80, 54.89, 55.79, 69.42, 75.82, 76.17, 78.23, 96.14, 98.10, 109.30, 118.07, 134.89; HRMS (EI) calcd for $C_{13}H_{22}O_6$ (M^+) 274.1416 ($M^+ - CH_3$) 259.1182, found 259.1185.

Compound 22. A solution of 9-BBN-H (485 mg, 3.98 mmol) in THF (8 mL) was added to olefin **21** (546 mg, 1.99 mmol) at rt. The resultant solution was stirred at rt for 3 h and another one hour at reflux. The reaction mixture was cooled to rt and 3 M aqueous K_3PO_4 (1.6 mL, 4.9 mmol) was added. After 15 min, a solution of vinyl bromide **11** (910 mg, 1.77 mmol) and $PdCl_2$(dppf) (129 mg, 0.17 mmol) in DMF (10 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (8:1 to 4:1, hexanes/EtOAc) gave 1.12 g (89%) of olefin **22** as a clear oil: R_f 0.34 (8:1, hexanes/EtOAc); IR (neat) 3451, 3352, 3031, 2985, 2951, 2898, 2856, 1728, 1500, 1219, 1091, 1028 cm^{-1}; $[\alpha]^{20}_D$ −0.77° (*c* 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.84 (s, 9 H), 1.32 (s, 3 H), 1.33 (s, 3 H), 1.35 (s, 3 H), 1.52 (s, 3 H), 1.61 (m, 1 H), 1.99 (m, 1 H), 2.15 (m, 1 H), 2.46 (m, 1 H), 3.36 (s, 3 H), 3.37 (s, 3 H), 3.47 (m, 2 H), 4.07 (d, 1 H, J = 6.0 Hz), 4.12 (t, 1 H, J = 6.0 Hz), 4.18 (t, 1 H, J = 4.5 Hz), 4.19 (dd, 1 H, J = 7.5, 3.5 Hz), 4.43 (d, 1 H, J = 4.5 Hz), 4.47 (br d, 1 H, J = 8.5 Hz), 4.62 (d, 1 H, J = 6.0 Hz), 4.86 (s, 1 H), 4.96 (br d, 1 H, J = 9.5 Hz), 4.97 (d, 1 H, J = 6.0 Hz), 5.09 (d, 1 H, J = 12.5 Hz), 5.12 (d, 1 H, J = 12.5 Hz), 5.24 (s, 1 H), 7.28−7.36 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.08, −4.74, 17.88, 25.64, 26.35, 26.69, 27.76, 27.86, 28.77, 28.93, 48.06, 55.21, 56.00, 66.65, 67.61, 69.73, 73.10, 75.79, 75.80, 76.39, 78.36, 96.14, 98.03, 109.16, 109.55, 122.20, 128.03, 128.45, 136.56, 137.69, 155.67 (missing 1 quaternary C); HRMS (EI) calcd for $C_{36}H_{57}NO_{11}Si$ (M^+) 707.3701 ($M^+ - C_4H_9$) 650.2997, found 650.3006.

Disaccharide 25. Olefin **22** (117 mg, 0.166 mmol) was subjected to the conditions of general procedure A to provide, after flash chromatography on silica gel (20:1, CH_2Cl_2/CH_3OH), 29.2 mg (53% from **22**) of disaccharide **25** as a pale brown oil: R_f 0.52 (10:1, CH_2Cl_2/CH_3OH); IR (neat) 3490, 3315, 2985, 2932, 1093, 1029 cm^{-1}; $[\alpha]^{20}_D$ +21.74° (*c* 0.69, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.12 (s, 3 H), 0.87 (s, 9 H), 1.32 (s, 3 H), 1.33 (s, 3 H), 1.48 (s, 3 H), 1.52 (s, 3 H), 1.60 (m, 2 H), 1.88 (m, 1 H), 2.02 (m, 1 H), 2.50 (ddd, 1 H, J = 9.5, 8.0, 3.5 Hz), 2.85 (td, 1 H, J = 7.0, 2.5 Hz), 3.35 (m, 1 H), 3.37 (s, 3 H), 3.39 (s, 3 H), 3.47 (m, 3 H), 3.87 (m, 2 H), 4.05 (dd, 1 H, J = 5.5, 2.5 Hz), 4.08 (d, 1 H, J = 6.0 Hz), 4.14 (t, 1 H, J = 6.0 Hz), 4.65 (d, 1 H, J = 6.5 Hz), 4.86 (s, 1 H), 4.95 (d, 1 H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.13, −3.99, 18.05, 25.86, 26.33, 26.47, 27.81, 27.87, 28.19, 28.27, 55.06, 55.76, 55.99, 60.81, 63.40, 68.17, 74.25, 75.79, 75.82, 76.48, 78.42, 81.24, 96.28, 98.06, 108.73, 109.19; HRMS (EI) calcd for $C_{28}H_{53}NO_{10}Si$ (M^+) 591.3439, found 591.3449.

Disaccharide 6. To a solution of protected disaccharide **25** (114.0 mg, 0.193 mmol) in CH_3OH (4 mL) was added aqueous 6 N HCl (2 mL), and the mixture was stirred at rt for 18 h. The solvents were then removed *in vacuo*. The oily residue was taken up in a minimal amount of CH_3OH, and the product was precipitated with Et_2O. The white solid was allowed to settle, and the solution was decanted. The solid was washed with Et_2O followed by decantation (2×), and finally the residual solvents were removed *in vacuo* to provide 59.8 mg (83.4%) of the HCl salt of disaccharide **6** as a white solid: mp > 220 °C (dec); $[\alpha]^{20}_D$ +25.0° (*c* 0.14, CH_3OH); ^{13}C NMR (125 MHz, D_2O with CD_3OD as internal standard) δ 24.77, 27.17, 55.93, 59.13, 59.67, 61.37,

66.62, 68.12, 70.79, 70.96, 71.52, 72.44, 74.25, 102.08; FAB MS for $C_{14}H_{27}NO_9$ (M^+) 353.1686, found ($M^+ + H$) 354 (71.0%).

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-2,3,4-tri-*O*-(methoxymethyl)-α-D-glucopyranoside (27). To a cold solution (0 °C) of triol **26**[17] (3.96 g, 9.17 mmol) in CH_2Cl_2 (40 mL) was added diisopropylethylamine (9.6 mL, 55 mmol) dropwise, followed by the addition of chloromethyl methyl ether (6.9 mL, 91 mmol). Solid tetrabutylammonium iodide (6.7 g, 18.3 mmol) was then added to the reaction mixture, and the solution was allowed to warm to rt. The reaction mixture was stirred in the dark for 20 h. The reaction mixture was cooled to 0 °C, and 20 mL of saturated aqueous NH_4Cl was added. The layers were separated, and the organic layer was washed with brine. The aqueous layer was extracted CH_2Cl_2 (4×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2:1, hexanes/EtOAc) gave 4.62 g (89%) of fully protected sugar **27** as a clear oil: R_f 0.65 (1:1, hexanes/EtOAc); IR (neat) 3071, 3048, 2951, 2931, 2893, 1152, 1111, 1032, 703 cm^{-1}; $[\alpha]^{20}_D$ +43.4° (*c* 1.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 3.16 (s, 3 H), 3.41 (s, 3 H), 3.42 (s, 3 H), 3.43 (s, 3 H), 3.52 (dd, 1 H, J = 10.0, 3.5 Hz), 3.54 (t, 1 H, J = 9.5 Hz), 3.69 (ddd, 1 H, J = 10.0, 5.5, 2.0 Hz), 3.82 (dd, 1 H, J = 11.0, 5.5 Hz), 3.91 (m, 2 H), 4.68 (d, 1 H, J = 6.5 Hz), 4.74 (d, 1 H, J = 7.0 Hz), 4.80 (d, 1 H, J = 6.5 Hz), 4.81 (d, 2 H, J = 7.0 Hz), 4.84 (d, 1 H, J = 6.5 Hz), 4.85 (d, 1 H, J = 3.5 Hz), 7.35−7.44 (m, 6 H), 7.71−7.73 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.28, 26.76, 54.84, 55.50, 56.23, 63.13, 71.17, 76.55, 78.64, 79.14, 97.70, 98.42, 98.67, 127.53, 127.61, 129.57, 133.44, 133.64, 135.65, 135.82.

Methyl 2,3,4-Tri-*O*-(methoxymethyl)-α-D-glucopyranoside (28). A cold (0 °C) solution of silyl ether **27** (4.62 g, 8.2 mmol) in THF (41 mL) was treated with 10.6 mL of tetrabutylammonium fluoride (1.0 M in THF, 10.6 mmol). The resultant solution was then warmed to 25 °C, and stirring was continued for 18 h. The reaction mixture was poured into EtOAc and washed with saturated aqueous NH_4Cl and brine. The aqueous layers were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (1:2, hexanes/EtOAc) gave 2.29 g (86%) of alcohol **28** as a clear oil: R_f 0.44 (1:4, hexanes/EtOAc); IR (neat) 3489, 2932, 2896, 1152, 1108, 1037 cm^{-1}; $[\alpha]^{20}_D$ +105.9° (*c* 1.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.60 (br s, 1 H) (OH), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.43 (s, 3 H), 3.51 (dd, 1 H, J = 10.0, 3.5 Hz), 3.56 (t, 1 H, J = 9.5 Hz), 3.62 (ddd, 1 H, J = 10.0, 3.5, 2.0 Hz), 3.77 (dd, 1 H, J = 12.5, 2.0 Hz), 3.88 (dd, 1 H, J = 12.5, 3.5 Hz), 3.92 (t, 1 H, J = 9.5 Hz), 4.69 (d, 1 H, J = 6.0 Hz), 4.70 (d, 1 H, J = 6.5 Hz), 4.76 (d, 1 H, J = 6.5 Hz), 4.77 (d, 1 H, J = 6.5 Hz), 4.81 (d, 1 H, J = 3.5 Hz), 4.82 (d, 1 H, J = 6.0 Hz), 4.91 (d, 1 H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.15, 55.46, 56.10, 56.36, 61.59, 70.35, 76.57, 78.19, 79.04, 97.64, 98.19, 98.97, 99.11; HRMS (EI) calcd for $C_{13}H_{26}O_9$ (M^+) 326.1576 ($M^+ - CH_3O$) 295.1393, found 295.1397.

Methyl 2,3,4-Tri-*O*-(methoxymethyl)-6-methylene-α-D-glucopyranoside (29). To a cold (−78 °C) solution of DMSO (0.52 mL, 7.4 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic anhydride (0.78 mL, 5.54 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 10 min. Alcohol **28** (1.20 g, 3.7 mmol) in CH_2Cl_2 (4 mL) was added to the cold reaction mixture slowly *via* cannula, and the resultant solution was stirred for 30 min. Triethylamine (1.44 mL, 10.3 mmol) was added dropwise at −78 °C. The mixture was allowed to warm to rt after 10 min, and stirring was continued for another 20 min. The mixture was then partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with brine. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent, the resultant oil was taken up in Et_2O and filtered through Celite to remove the remaining triethylamine hydrochloride. Upon concentration, the corresponding aldehyde was obtained as determined by ^1H NMR. This material was used without further purification.

Potassium bis(trimethylsilyl)amide (16.25 mL, 0.5 M toluene, 8.12 mmol) was added dropwise at rt to a suspension of methyltriphenylphosphonium bromide (3.04 g, 8.5 mmol) in THF (40 mL). The resultant bright yellow solution was stirred at rt for 1 h. The ylide solution was then cooled to −78 °C, and a solution of the crude aldehyde (3.69 mmol) in THF (15 mL) was added slowly by cannula. After 30 min of stirring at −78 °C, the reaction mixture was allowed to warm to rt, and stirring was continued for another 18 h. The reaction was quenched at rt with CH_3OH (5 mL), poured into Et_2O, and washed with 10 mL of H_2O/saturated aqueous Rochelle's salt (1:1) and finally with brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (4:1 to 2:1 to 1:1, hexanes/EtOAc) gave 877 mg (74% from **28**) of olefin **29** as a clear oil: R_f 0.77 (1:1, hexanes/EtOAc); IR (neat) 2988, 2932, 2895, 1032 cm^{-1}; $[\alpha]^{20}_D$ +80.0° (*c* 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.36 (m, 1 H), 3.37 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.42 (s, 3 H), 3.53 (dd, 1 H, J = 10.0, 3.5 Hz), 3.92 (t, 1 H, J = 9.0 Hz), 4.01 (dd, 1 H, J = 10.0, 7.0 Hz), 4.66 (d, 1 H, J = 7.0 Hz), 4.71 (d, 1 H, J = 6.5 Hz), 4.78 (d, 1 H, J = 6.5 Hz), 4.79−4.84 (m, 4 H), 5.29 (ddd, 1 H, J = 10.0, 1.5, 1.0 Hz), 5.41 (ddd, 1 H, J = 17.0, 1.5, 1.0 Hz), 5.92 (ddd, 1 H, J = 17.0, 10.0, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.16, 55.47, 56.20, 56.37, 71.49, 78.07, 78.98, 79.62, 97.69, 98.09, 98.35, 98.98, 118.97, 135.35; FAB MS $C_{14}H_{26}O_8$ (M^+) 322.1627, found (M^++H) 323 (3.8%).

Compound 30. A solution of 9-BBN-H (303 mg, 2.48 mmol) in THF (5 mL) was added to olefin **29** (402 mg, 1.25 mmol) at rt. The resultant solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, and 3 M aqueous K_3PO_4 (1.04 mL, 3.11 mmol) was added. After 15 min, a solution of vinyl bromide **11** (556 mg, 1.09 mmol) and $PdCl_2$(dppf) (45 mg, 0.06 mmol) in DMF (8 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2:1 to 1:1, hexanes/EtOAc) gave 768 mg (93%) of olefin **30** as a clear oil: R_f 0.60 (1:1, hexanes/EtOAc); IR (neat) 3444, 3347, 2949, 2930, 2894, 1727, 1500, 1051, 1030 cm^{-1}; $[\alpha]^{20}_D$ +19.50° (*c* 1.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.85 (s, 9 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 1.59 (m, 1 H), 2.03 (m, 1 H), 2.15 (m, 1 H), 2.42 (m, 1 H), 3.25 (t, 1 H, J = 9.5 Hz), 3.37 (s, 3 H), 3.38 (s, 6 H), 3.39 (s, 3 H), 3.47 (dd, 1 H, J = 10.0, 3.5 Hz), 3.54 (td, 1 H, J = 9.5, 2.0 Hz), 3.85 (t, 1 H, J = 9.5 Hz), 4.19 (m, 2 H), 4.43 (d, 1 H, J = 5.5 Hz), 4.47 (d, 1 H, J = 8.5 Hz), 4.66 (d, 1 H, J = 6.5 Hz), 4.70 (d, 1 H, J = 7.0 Hz), 4.75 (d, 1 H, J = 3.5 Hz), 4.76 (d, 1 H, J = 6.0 Hz), 4.77 (d, 1 H, J = 6.0 Hz), 4.81 (d, 1 H, J = 6.0 Hz), 4.92 (d, 1 H, J = 6.5 Hz), 4.95 (d, 1 H, J = 9.5 Hz), 5.09 (d, 1 H, J = 12.0 Hz), 5.12 (d, 1 H, J = 12.0 Hz), 5.25 (s, 1 H), 7.29−7.76 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.03, −4.71, 17.92, 25.68, 26.72, 27.79, 28.62, 28.80, 48.10, 55.27, 55.44, 56.24, 56.47, 66.67, 69.14, 69.76, 73.20, 75.83, 78.63, 79.07, 80.08, 97.62, 98.36, 98.48, 98.77, 109.56, 122.14, 128.04, 128.47, 136.57, 137.74, 155.70; MS (EI) calcd for $C_{37}H_{61}NO_{13}Si$ (M^+) 755.3912, found ($M^+ - C_4H_9$) 698 (5.4%), (CI) ($M^+ - CH_3$) 740 (0.2%), ($M^+ - CH_3O$) 724 (5.0%), ($M^+ - C_4H_9$) 698 (3.5%).

Disaccharide 31. Olefin **30** (52.3 mg, 0.069 mmol) was subjected to the conditions of general procedure A to provide, after flash chromatography on silica gel (20:1, CH_2Cl_2/CH_3OH), 28.0 mg (63%) of disaccharide **31** as a clear oil: R_f 0.50 (10:1, CH_2Cl_2:CH_3OH); IR (neat) 3493, 3310, 2929, 1034 cm^{-1}; $[\alpha]^{20}_D$ +46.1° (*c* 0.94, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.13 (s, 3 H), 0.87 (s, 9 H), 1.34 (s, 3 H), 1.49 (s, 3 H), 1.54 (m, 1 H), 1.64 (m, 1 H), 1.86 (m, 1 H), 2.07 (m, 1 H), 2.19 (br m, 2 H), 2.54 (ddd, 1 H, J = 10.0, 7.5, 3.5 Hz), 2.88 (td, 1 H, J = 7.5, 2.5 Hz), 3.27 (t, 1 H, J = 9.5 Hz), 3.38 (m, 1 H), 3.38 (s, 3H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.41 (m, 1 H), 3.41 (s, 3 H), 3.49 (dd, 1 H, J = 9.5, 3.5 Hz), 3.58 (td, 1 H, J = 9.5, 2.5 Hz), 3.87 (t, 1 H, J = 9.5 Hz), 3.89 (m, 2 H), 4.07 (dd, 1 H, J = 5.0, 2.5 Hz), 4.69 (d, 1 H, J = 6.5 Hz), 4.70 (d, 1 H, J = 6.5 Hz), 4.75 (d, 1 H, J = 3.5 Hz), 4.76 (d, 1 H, J = 7.0 Hz), 4.77 (d, 1 H, J = 6.5 Hz), 4.82 (d, 1 H, J = 6.5 Hz), 4.93 (d, 1 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.11, −3.99, 18.07, 25.86, 26.43, 27.59, 28.16, 28.23, 55.17, 55.45, 55.77, 56.24, 56.43, 60.87, 63.23, 69.71, 73.97, 75.89, 78.70, 79.09, 80.02, 81.09, 97.62, 98.38, 98.54, 98.75, 108.84; HRMS (EI) calcd for $C_{29}H_{57}NO_{12}Si$ (M^+) 639.3650 ($M^+ - CH_3O$) 608.3466, found 608.3457.

Disaccharide 7. To a solution of protected disaccharide **31** (27.4 mg, 0.043 mmol) in CH_3OH (1 mL) was added aqueous 6 N HCl (0.75 mL), and the mixture was stirred at rt for 18 h. The solvents were then removed in vacuo. The oily residue was taken up in a minimal amount of CH_3OH, and the product was precipitated with Et_2O. The

white solid was washed with Et_2O followed by decantation (2×), and the residual solvents were removed in vacuo to provide 15.1 mg (90.5%) of the HCl salt of disaccharide **7** as a white solid: mp 131−135 °C; $[\alpha]^{20}_D$ +67.9° (*c* 0.61, CH_3OH); ^{13}C NMR (125 MHz, CD_3OD) δ 25.46, 28.21, 55.95, 59.96, 60.44, 62.55, 67.58, 69.00, 72.02, 73.70, 74.95, 75.14, 75.46, 101.54; FAB MS for $C_{14}H_{27}NO_9$ (M^+) 353.1686, found ($M^+ + H$) 354 (28.9%).

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-oxo-α-D-*lyxo*-hexopyranoside (32). To a suspension of freshly activated powdered 4 Å molecular sieves (8.5 g) in CH_2Cl_2 (80 mL) was added pyridinium chlorochromate (4.10 g, 19.0 mmol). Alcohol **17** (2.0 g, 4.23 mmol) in CH_2Cl_2 (10 mL) was added by cannula at rt resulting in a brown suspension. The mixture was stirred for 1.5 h upon which time TLC indicated the disappearance of starting material. The reaction mixture was diluted with 140 mL of Et_2O/hexanes (2:1) and filtered through a pad of silica gel. The silica was eluted with 500 mL of Et_2O. Upon concentration of the eluent, 1.85 g (93%) of ketone **32** was obtained as a clear oil: R_f 0.68 (4:1, hexanes/EtOAc); IR (neat) 2931, 2857, 1743, 1114, 1092 cm^{-1}; $[\alpha]^{20}_D$ +56.4° (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.35 (s, 3 H), 1.39 (s, 3 H), 3.49 (s, 3 H), 3.99 (dd, 1 H, J = 11.1, 6.9 Hz), 4.05 (dd, 1 H, J = 11.1, 3.9 Hz), 4.30 (dd, 1 H, J = 6.9, 4.5 Hz), 4.39 (d, 1 H, J = 6.9 Hz), 4.45 (dd, 1 H, J = 6.6, 1.2 Hz), 4.94 (s, 1 H), 7.35−7.44 (m, 6 H), 7.67−7.73 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.22, 25.43, 26.69, 26.75, 55.71, 63.37, 75.18, 75.89, 78.73, 98.42, 111.51, 127.69, 129.70, 133.11, 133.29, 135.60, 135.70, 202.28; HRMS (EI) calcd for $C_{26}H_{34}O_6Si$ (M^+) 470.2125 ($M^+ - CH_3$) 455.1890, found 455.1876.

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-deoxy-4-methylene-α-D-*lyxo*-hexopyranoside (33). A solution of ketone **32** (1.85 g, 3.92 mmol) in toluene (20 mL) was treated with dimethyltitanocene (0.401 M in toluene, 20.5 mL, 8.23 mmol) and heated to 70 °C in the dark for 40 h. The resultant solution was cooled to rt, and pentane was added producing a yellow precipitate. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography on silica gel (10:1, hexanes/EtOAc) gave 1.48 g (81%) of olefin **33** as a yellow oil: R_f 0.55 (8:1, hexanes/EtOAc); IR (neat) 3071, 3049, 2932, 2857, 1582, 1089 cm^{-1}; $[\alpha]^{20}_D$ +45.7° (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 3.42 (s, 3 H), 3.81 (dd, 1 H, J = 10.2, 5.7 Hz), 4.02 (dd, 1 H, J = 8.7, 7.2 Hz), 4.10 (d, 1 H, J = 6.9 Hz), 4.36 (t, 1 H, J = 6.3 Hz), 4.66 (s, 1 H), 4.69 (d, 1 H, J = 7.2 Hz), 5.11 (s, 1 H), 5.32 (s, 1 H), 7.36−7.46 (m, 6 H), 7.71−7.76 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.27, 25.19, 26.69, 26.86, 55.67, 67.74, 72.72, 75.11, 76.10, 99.52, 110.02, 116.67, 127.62, 129.59, 133.67, 133.71, 135.73, 138.75; HRMS (EI) calcd for $C_{27}H_{36}O_5Si$ (M^+) 468.2332 ($M^+ - CH_3$) 453.2097, found 453.2087.

Compound 34. A solution of 9-BBN-H (552 mg, 4.52 mmol) in THF (10 mL) was added to olefin **33** (847 mg, 1.81 mmol) at rt. The resultant solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, and 3 M aqueous K_3PO_4 (1.7 mL, 5.1 mmol) was added. After 15 min, a solution of vinyl bromide **11** (756 mg, 1.47 mmol) and $PdCl_2$(dppf) (66 mg, 0.09 mmol) in DMF (18 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (8:1 to 4:1, hexanes/EtOAc) gave 1.10 g of of olefin **34** contaminated with borane byproducts. The impure product was dissolved in THF (40 mL) and cooled to 0 °C. To this solution was added 10% aqueous NaOH (3 mL) followed by 30% aqueous H_2O_2 (3 mL), and the resultant solution was stirred at 0 °C for 30 min and another 1 h at rt. The reaction mixture was again cooled to 0 °C, and saturated aqueous $NaHSO_3$ was added dropwise (*caution: can bubble vigorously)* until bubbling stopped. The resultant solution was poured into Et_2O, and the layers were separated. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (4:1, hexanes/EtOAc) gave 1.00 g (76%) of olefin **34** as a foam: R_f 0.56 (4:1, hexanes/EtOAc); IR (neat) 3553, 3447, 2930, 1728, 1500, 1212, 1081 cm^{-1}; $[\alpha]^{20}_D$ +15.8° (*c* 1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.08 (s, 3 H), 0.85 (s, 9 H), 1.03 (s, 9 H), 1.15 (s, 3 H), 1.21 (s, 3 H), 1.28 (s, 3 H), 1.35 (s, 3 H), 2.04 (dd, 1 H, J = 14.0, 8.0 Hz), 2.29 (dd, 1 H, J = 14.0, 8.5 Hz), 2.58 (m, 1 H), 3.43 (s, 3 H), 3.82 (d, 1 H, J = 8.0 Hz), 3.83 (dd, 1 H, J = 6.5, 4.0 Hz), 4.02 (m, 2 H), 4.20 (m, 3 H), 4.43 (br d, 1 H, J = 5.0 Hz), 4.46 (d, 1 H, J = 4.0 Hz), 4.50 (br d, 1 H, J = 9.0 Hz), 4.92 (t, 1 H, J = 10.0 Hz), 5.11 (d, 1 H, J = 13.0 Hz), 5.14 (d, 1 H, J = 13.0 Hz), 5.21 (s, 1 H), 7.30−7.39 (m, 11 H), 7.64−7.71 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.99, −4.73, 17.90, 19.24, 25.09, 25.75, 26.63, 26.91, 27.01, 27.73, 31.41, 34.46, 48.02, 56.20, 62.42, 66.78, 69.71, 73.28, 73.44, 74.42, 75.21, 75.79, 98.22, 109.34, 109.64, 124.46, 127.59, 127.66, 128.07, 128.16, 128.47, 129.57, 129.63, 133.57, 133.64, 135.45, 135.64, 135.72, 136.47, 155.63; MS (EI) calcd for $C_{50}H_{71}NO_{10}Si_2$ (M^+) 901.4617 ($M^+ - C_4H_9$) 844 (4.5%), (CI) ($M^+ - CH_3O$) 870 (0.8%), ($M^+ - C_4H_9$) 844 (1.9%).

Disaccharide 35. Olefin **34** (145.6 mg, 0.16 mmol) was subjected to the conditions of general procedure A to provide, after flash chromatography on silica gel (4:1 to 2:1, hexanes/EtOAc), 84.9 mg (67%) of **35** as a clear oil: R_f 0.57 (2:1, hexanes/EtOAc); IR (neat) 3487, 3067, 3043, 2954, 2930, 1112 cm^{-1}; $[\alpha]^{20}_D$ +18.3° (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.13 (s, 3 H), 0.88 (s, 9 H), 1.06 (s, 9 H), 1.26 (s, 3 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 1.47 (s, 3 H), 1.66 (m, 2 H), 2.44 (ddd, 1 H, J = 9.5, 8.0, 3.5 Hz), 2.61 (m, 1 H), 2.84 (m, 1 H), 3.31 (m, 2 H), 3.43 (s, 3 H), 3.84−3.92 (m, 5 H), 3.97−4.01 (m, 3 H), 4.31 (dd, 1 H, J = 7.0, 3.5 Hz), 4.51 (d, 1 H, J = 4.0 Hz), 7.35−7.42 (m, 6 H), 7.68−7.71 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.14, −3.97, 18.05, 19.17, 24.95, 25.87, 26.52, 26.84, 27.02, 28.26, 29.38, 32.36, 52.59, 56.13, 60.71, 63.42, 72.83, 74.24, 74.70, 74.95, 76.65, 81.20, 98.48, 108.79, 109.24, 127.67, 129.65, 133.64, 135.65, 135.68; HRMS (EI) calcd for $C_{42}H_{67}NO_9Si_2$ (M^+) 785.4354 ($M^+ - CH_3$) 770.4120, found 770.4106.

Disaccharide 8. To a solution of protected disaccharide **35** (52.8 mg, 0.067 mmol) in THF (2 mL) was added aqueous 1 N HCl (2 mL), and the mixture was stirred at rt for 48 h. (Some hydrolysis of the methyl glycoside was observed when reaction times were extended. Too short of a reaction time resulted in incomplete hydrolysis of the *tert*-butyldiphenylsilyl ether.) The solvents were then removed *in vacuo*. The oily residue was taken up in a minimal amount of CH_3OH, and the product was precipitated with Et_2O. The white solid was allowed to settle, and the solution was decanted. The solid was washed with Et_2O followed by decantation (2×), and finally the residual solvents were removed *in vacuo* to provide 24 mg (91%) of the HCl salt of disaccharide **8** as a white solid: mp > 220 °C (dec); $[\alpha]^{20}_D$ +10.1° (*c* 0.68, CH_3OH); ^{13}C NMR (125 MHz, CD_3OD) δ 26.00, 37.50, 55.30, 59.63, 60.48, 62.41, 63.11, 67.84, 70.32, 70.60, 71.98, 72.80, 75.66, 103.97; FAB MS calcd for $C_{14}H_{27}NO_9$ (M^+) 353.1686, found ($M^+ + H$) 354 (51%).

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-deoxy-4-[(3-methylphenyl)methyl]-α-D-talopyranoside (36). A solution of 9-BBN-H (101 mg, 0.83 mmol) in THF (1.7 mL) was added to olefin **33** (155.4 mg, 0.33 mmol) at rt. The resultant solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, and 3 M aqueous K_3PO_4 (0.31 mL, 0.93 mmol) was added. After 15 min, a solution of 3-iodotoluene (0.038 mL, 0.30 mmol) and $PdCl_2$(dppf) (12 mg, 0.016 mmol) in DMF (3 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10:1, hexanes/EtOAc) gave 118.1 mg (71%) of 4-arylmethyl sugar **36** as a clear oil: R_f 0.85 (4:1, hexanes/EtOAc); IR (neat) 3072, 3046, 2931, 2857, 1104, 1088, 702 cm^{-1}; $[\alpha]^{20}_D$ +43.2° (*c* 1.14, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 2.30 (s, 3 H), 2.45 (m, 1 H), 2.54 (dd, 1 H, J = 13.0, 5.5 Hz), 2.60 (dd, 1 H, J = 13.0, 10.5 Hz), 3.47 (s, 3 H), 3.77 (dd, 1 H, J = 6.5, 4.0 Hz), 3.87 (m, 1 H), 4.05 (dd, 1 H, J = 6.5, 3.0 Hz), 4.10 (m, 2 H), 4.53 (d, 1 H, J = 4.0 Hz), 6.93 (d, 1 H, J = 7.5 Hz), 6.98 (s, 1 H), 7.01 (d, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.36−7.43 (m, 6 H), 7.67−7.72 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.22, 21.37, 25.05, 26.88, 27.25, 33.32, 38.41, 56.32, 62.79, 72.17, 74.88, 75.09, 98.44; 109.22, 126.02, 126.92, 127.68, 128.24, 129.62, 129.80, 133.63, 133.69, 135.63, 135.65, 137.92, 139.39; HRMS (EI) calcd for $C_{34}H_{44}O_5Si$ (M^+) 560.2958 ($M^+ - C_4H_9$) 503.2254, found 503.2265.

2,6-Anhydro-3,4,5,7-tetra-*O*-(methoxymethyl)-1-deoxy-D-*gluco*-hept-1-enitol (38). To a cold solution (0 °C) of δ-gluconolactone (1.00

g, 5.61 mmol) in CH_2Cl_2 (56 mL) was added diisopropylethylamine (7.8 mL, 44.7 mmol) dropwise, followed by the addition of chloromethyl methyl ether (6.4 mL, 84.1 mmol). Solid tetrabutylammonium iodide (10.4 g, 28.0 mmol) was then added to the reaction mixture, and the solution was allowed to warm to rt. The reaction mixture was stirred in the dark for 48 h. The reaction mixture was cooled to 0 °C, and 10 mL of saturated aqueous NH_4Cl was added. The layers were separated, and the organic layer was washed with brine. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (1:1, hexanes/EtOAc) gave 1.88 g (95%) of lactone **37** as a clear oil. A solution of lactone **37** (1.88 g, 5.32 mmol) in toluene (27 mL) was treated with dimethyltitanocene (0.331 M in toluene, 33.7 mL, 11.2 mmol) and heated to 70 °C in the dark for 24 h. The resultant solution was cooled to rt, and hexane was added producing a yellow precipitate. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography on silica gel (4:1 to 2:1, hexanes/EtOAc) gave 1.48 g (79%) of olefin **38** as a clear oil. A small amount of an unidentified inseparable impurity was present but did not present any problems with further chemistry. For **38**: R_f 0.50 (1:1, hexanes/EtOAc); IR (neat) 2988, 2938, 2892, 1660, 1151, 1030 cm^{-1}; $[\alpha]^{20}_D$ +97.6° (*c* 1.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.38 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.42 (s, 3 H), 3.71 (dd, 1 H, J = 11.5, 5.5 Hz), 3.74 (dd, 1 H, J = 9.5, 5.5 Hz), 3.82 (t, 1 H, J = 5.5 Hz), 3.85 (dd, 1 H, J = 11.5, 2.0 Hz), 3.94 (ddd, 1 H, J = 9.5, 5.5, 2.0 Hz), 4.15 (d, 1 H, J = 5.5 Hz), 4.42 (s, 1 H), 4.66 (d, 1 H, J = 6.5 Hz), 4.68−4.70 (m, 3 H), 4.71 (d, 1 H, J = 6.5 Hz), 4.79−4.81 (m, 2 H), 4.82 (d, 1 H, J = 6.5 Hz), 4.86 (d, 1 H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.32, 55.88, 56.06, 56.22, 66.75, 74.13, 75.74, 76.47, 79.84, 94.48, 94.62, 96.77, 96.99, 97.26, 154.50; HRMS (EI) calcd for $C_{15}H_{28}O_9$ (M^+) 352.1733 ($M^+ - C_3H_8O_2$) 276.1209, found 276.1203.

Compound 39. A solution of 9-BBN-H (351 mg, 2.88 mmol) in THF (6 mL) was added to olefin **38** (405 mg, 1.15 mmol) at rt. The resultant solution was heated to reflux for 5 h. The reaction mixture was cooled to rt, and 3 M aqueous K_3PO_4 (1 mL, 3 mmol) was added. After 15 min, a solution of vinyl bromide **11** (412 mg, 0.81 mmol) and $PdCl_2$(dppf) (84 mg, 0.11 mmol) in DMF (10 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted three times with Et_2O, and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2:1 to 1:1, hexanes/EtOAc) gave 458 mg (73%) of olefin **39** as a clear oil: R_f 0.51 (1:1, hexanes/EtOAc); IR (neat) 3453, 3447, 3032, 2984, 2951, 2894, 1727, 1501, 1152, 1103, 1078, 1025 cm^{-1}; $[\alpha]^{20}_D$ −40.1° (*c* 1.45 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.08 (s, 3 H), 0.84 (s, 9 H), 1.31 (s, 3 H), 1.32 (s, 3 H), 2.26 (dd, 1 H, J = 15.0, 10.0 Hz), 2.60 (d, 1 H, J = 15.0 Hz), 3.23 (t, 1 H, J = 9.0 Hz), 3.28 (m, 1 H), 3.31 (s, 3 H), 3.35 (m, 1 H), 3.40 (s, 3 H), 3.42 (s, 3 H), 3.43 (s, 3 H), 3.45 (t, 1 H, J = 9.5 Hz), 3.57 (t, 1 H, J = 9.5 Hz), 3.59 (dd, 1 H, J = 11.0, 5.0 Hz), 3.76 (dd, 1 H, J = 11.0, 2.0 Hz), 4.14 (t, 1 H, J = 5.0 Hz), 4.19 (br m, 1 H), 4.48 (br d, 1 H, J = 8.5 Hz), 4.61 (s, 2 H), 4.65 (d, 1 H, J = 5.5 Hz), 4.69 (d, 1 H, J = 6.5 Hz), 4.70 (d, 1 H, J = 6.5 Hz), 4.81 (d, 1 H, J = 6.0 Hz), 4.82 (d, 1 H, J = 6.5 Hz), 4.84 (d, 1 H, J = 6.5 Hz), 4.87 (d, 1 H, J = 6.5 Hz), 5.02 (d, 1 H, J = 9.5 Hz), 5.10 (s, 2 H), 5.34 (s, 1 H), 7.30−7.36 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.08, −4.71, 17.90, 25.65, 26.67, 27.72, 35.13, 48.16, 55.08, 56.48, 66.49, 66.59, 69.81, 74.49, 75.80, 77.08, 78.12, 79.39, 80.77, 84.37, 96.57, 98.46, 98.69, 98.73, 109.33, 124.02, 127.98, 128.41, 136.06, 136.59, 155.64; HRMS (EI) calcd for $C_{38}H_{63}NO_{14}Si$ (M^+) 785.4018, ($M^+ - C_4H_9$) 728.3314, found 728.3333.

Disaccharide 40. Olefin **39** (317 mg, 0.404 mmol) was subjected to the conditions of general procedure A to provide, after flash chromatography on silica gel (20:1, CH_2Cl_2/CH_3OH), 197.3 mg (73%) of disaccharide **40** as a clear oil: R_f 0.26 (20:1, CH_2Cl_2/CH_3OH); IR (neat) 3489, 3315, 2930, 2893, 1105, 1026 cm^{-1}; $[\alpha]^{20}_D$ −25.0° (*c* 1.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.12 (s, 3 H), 0.87 (s, 9 H), 1.31 (s, 3 H), 1.46 (s, 3 H), 1.73 (ddd, 1 H, J = 14.5, 9.5, 2.5 Hz), 2.06 (ddd, 1 H, J = 14.5, 10.0, 2.5 Hz), 2.49 (ddd, 1 H, J = 9.5, 8.0, 3.5 Hz), 3.16 (td, 1 H, J = 10.0, 2.5 Hz), 3.27 (t, 1 H, J = 9.5 Hz), 3.30 (m, 1 H), 3.35 (m, 2 H), 3.36 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.45 (t, 1 H, J = 9.5 Hz), 3.55 (td, 1 H, J = 9.5, 2.5 Hz), 3.59 (t, 1 H, J = 9.0 Hz), 3.64 (dd, 1 H, J = 11.5, 5.5 Hz), 3.83 (dd, 1 H, J = 11.5, 2.0 Hz), 3.87 (m, 2 H), 4.02 (dd, 1 H, J = 5.5, 2.5 Hz), 4.64 (d, 1 H, J = 6.5 Hz), 4.66 (d, 1 H, J = 6.5 Hz), 4.67 (d, 1 H, J = 6.5 Hz), 4.72 (d, 1 H, J = 6.5 Hz), 4.83 (m, 3 H), 4.89 (d, 1 H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.13, −3.99, 18.06, 25.86, 26.48, 28.24, 33.97, 51.98, 55.36, 56.42, 56.44, 56.52, 60.82, 63.44, 66.76, 74.27, 75.97, 77.27, 77.50, 78.32; 80.30, 81.37, 84.51, 96.73, 98.47, 98.61, 98.74, 108.66; HRMS (EI) calcd for $C_{30}H_{59}NO_{13}Si$ (M^+) 669.3756 ($M^+ - CH_3O$) 638.3571, found 638.3558.

Disaccharide 9. To a solution of protected disaccharide **40** (197.3 mg, 0.294 mmol) in CH_3OH (5 mL) was added aqueous 6 N HCl (3 mL), and the mixture was stirred at rt for 18 h. The solvents were then removed *in vacuo*. The oily residue was taken up in a minimal amount of CH_3OH, and the product was precipitated with Et_2O. The white solid was allowed to settle, and the solution was decanted. The solid was washed with Et_2O followed by decantation (2×), and finally the residual solvents were removed *in vacuo* to provide 102.5 mg (92.5%) of the HCl salt of disaccharide **9** as a white solid: mp > 150 °C (dec); $[\alpha]^{20}_D$ −9.64° (*c* 0.17, CH_3OH); ^{13}C NMR (125 MHz, CD_3OD) δ 32.49, 58.09, 59.93, 62.28, 62.90, 67.61, 71.54, 71.67, 74.65, 75.35, 78.58, 79.62, 81.99; FAB MS for $C_{13}H_{25}NO_9$ (M^+) 339.1529, found ($M^+ + H$) 340 (48.2%).

2,6-Anhydro-3,4,5,7-tetra-*O*-(methoxymethyl)-1-deoxy-1-(3-methylphenyl)-*β*-D-*gluco*-heptanol (41). A solution of 9-BBN-H (53 mg, 0.43 mmol) in THF (1 mL) was added to olefin **38** (61.3 mg, 0.17 mmol) at rt. The resultant solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, and 3 M aqueous K_3PO_4 (0.17 mL, 0.52 mmol) was added. After 15 min, a solution of 3-iodotoluene (0.023 mL, 0.18 mmol) and $PdCl_2$(dppf) (11 mg, 0.015 mmol) in DMF (2 mL) was added *via* cannula. The dark mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (3×), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2:1 to 1:1, hexanes/EtOAc) gave 34.5 mg (45%) of *C*-arylmethyl glycoside **41** as a clear oil: R_f 0.46 (1:1, hexanes/EtOAc); IR (neat) 2980, 2938, 2893, 2823, 1153, 1107, 1026, 920 cm^{-1}; $[\alpha]^{20}_D$ −26.1° (*c* 1.33, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 2.17 (s, 3 H), 2.71 (dd, 1 H, J = 14.0, 9.0 Hz), 3.10 (ddd, 1 H, J = 10.0, 5.0, 2.0 Hz), 3.13 (s, 3 H), 3.17 (s, 3 H), 3.18 (s, 3 H), 3.22 (s, 3 H), 3.28 (dd, 1 H, J = 14.0, 2.0 Hz), 3.31 (t, 1 H, J = 9.0 Hz), 3.38 (td, 1 H, J = 9.0, 2.0 Hz), 3.53 (t, 1 H, J = 9.0 Hz), 3.62 (dd, 1 H, J = 11.5, 5.0 Hz), 3.63 (t, 1 H, J = 9.0 Hz), 3.78 (dd, 1 H, J = 11.5, 2.0 Hz), 4.53 (d, 1 H, J = 6.5 Hz), 4.55 (d, 1 H, J = 6.5 Hz), 4.57 (d, 1 H, J = 6.0 Hz), 4.59 (d, 1 H, J = 6.5 Hz), 4.74 (d, 1 H, J = 6.5 Hz), 4.76 (d, 1 H, J = 6.0 Hz), 4.80 (d, 1 H, J = 6.0 Hz), 4.88 (d, 1 H, J = 6.5 Hz), 6.91 (d, 1 H, J = 7.5 Hz), 7.13 (m, 1 H), 7.20 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 21.84, 38.83, 55.27, 56.49, 56.62, 67.18, 77.81, 79.25, 80.54, 81.35, 84.95, 97.31, 98.91, 99.15, 99.22, 127.47, 127.55, 131.25, 137.95, 139.99.

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Supporting Information Available: ^{13}C NMR spectra for **6**−**9**, ^1H and ^{13}C NMR spectra for **11**, **14**−**16**, **18**−**22**, **25**, **27**−**36**, and **38**−**41** (52 pages). See any current masthead page for ordering and Internet access instructions.

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