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Stereoselective Synthesis of Allyl-*C*-mannosyl Compounds: Use of a Temporary Silicon Connection in Intramolecular Allylation Strategies with Allylsilanes

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Methyl mannoside **16** containing an allyldimethylsilyl ether at C(2) was synthesized in nine steps from D-mannose. Reaction with TMSOTf in MeCN at room-temperature effected *C*-glycosylation to provide the α-allyl-*C*-mannosyl product **18** with excellent stereoselectivity. Crossover experiments over a range of reaction concentrations proved that reaction was proceeding via an intermolecular pathway rather than the hoped-for intramolecular delivery route. The exceptionally high stereoselectivity of this allylation in the presence of an acid-scavenger, 2,6-DTBMP, can be attributed to the allylsilyl ether **16** behaving as the allylating agent. Geometrical constraints in the seven-membered ring transition state account for the lack of intramolecular allyl transfer. Attaching a modified allylsilane **29a**−**c** to C(2)OH of methyl mannoside **15** improved matters. Reaction of the tethered mannosides **27a**−**c** with TMSOTf in the presence of 2,6-DTBMP in MeCN at rt provided a range of products, which depended on the size of the alkyl substituents at the silyl ether tether. Diene products were the major compounds irrespective of the size of the alkyl substituents at the silyl ether tether. Their formation can be understood by intramolecular allylation of the allylsilane on to the activated anomeric center, followed by collapse of the intermediate carbocation by preferential attack of an external nucleophile at the silyl ether tether, rather than at the allylic silicon center. A cascade of further reactions rationalizes the formation of the 2-dienyl-substituted tetrahydrofuran **30** and dienes **39** and **40**. The desired *β*-allyl-*C*-mannosyl products **42** and **43** were obtained, albeit in low yield, when bulky ethyl and isopropyl groups were employed at the silyl ether tether. Stereospecific oxidative cleavage of the silyl tether in **42** and **43** provided the corresponding stereodefined diols **44** and **45**, respectively. Attempts to improve the yield and diastereoselectivity of the desired *β*-allyl-*C*-mannosyls by moving to a sulfoxide mannosyl donor, which could be activated at low temperature, proved unsuccessful.

Introduction

C-Glycosyl compounds are an important class of carbohydrate analogue.[1] They occur in a number of important families of natural products,[2] and have also proved to be invaluable intermediates in more general natural product synthesis.[3] Since it has been demonstrated that *C*-glycosyl compounds can adopt similar conformations to their corresponding *O*-glycosides,[4,5] these compounds have also found application in biological and medicinal chemistry programs as hydrolytically stable mimics of *O*-glycosides.[6]

Allyl-*C*-glycosyl compounds (Figure 1) have proved to be particularly important in synthesis owing to the versatility of the terminal olefin functionality which can be employed in a range of further transformations.[7]

A variety of methods has been developed for selectively preparing allyl-*C*-glycosyl compounds. Of the two possible

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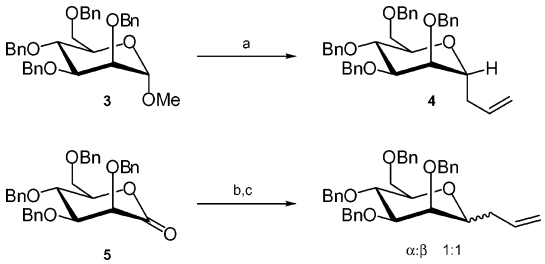
FIGURE 1. Allyl-*C*-glycosyl compounds find widespread use in synthesis.

diastereoisomers, **1** and **2**, the stereoselective synthesis of α-allyl-*C*-glycopyranosyl compounds **1** has proved to be the most straightforward.[8−10] This diastereoisomer is most frequently prepared by reacting a nucleophilic allylmetal with a glycosyl donor.[8] For example, Hosomi and Sakurai demonstrated some time ago that allylsilanes were particularly good allylating agents for this process.[8a] Reaction with a range of methyl glycosides, under Lewis acid activation, provided the corresponding α-allyl-*C*-glycosyl compounds in excellent yield and stereoselectivity. For example, methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside **3** reacted with allyltrimethylsilane, in the presence of TMSOTf, to provide exclusively, the corresponding α-allyl-*C*-mannosyl product **4** in 87% yield (Scheme 1). The corresponding glucosyl analogue was prepared in a similar yield and 91:9 α/*β* diastereoselectivity.[8a] This intermolecular Lewis acid-mediated allylation of methyl mannopyranosides currently provides one of the best and most widely used routes to α-allyl-*C*-mannosyls.

SCHEME 1. Synthesis of α- and *β*-Allyl-*C*-mannosyls[a]



[a] Reagents and conditions: (a) allyltrimethylsilane, TMSOTf (20 mol %), MeCN, rt, 25 h, 87%; (b) (allyl)MgBr, Et_2O, −78 °C; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, MeCN, 0 °C to rt, 67% (two steps).

The stereoselective synthesis of *β*-allyl-*C*-glycosyl compounds **2** has proved to be much more challenging.[11−14] The most commonly employed route to this diastereoisomer was developed by Kishi[11] and exploits the preferential addition of nucleophiles to the α-face of activated glycopyranosides. In a two-step process, addition of an allylmetal into a glyconolactone, provides a tertiary lactol product. Subsequent Lewis acid-mediated reduction with Et_3SiH generates the desired allyl-*C*-glycosyl, usually with the *β*-diastereoisomer predominating (Scheme 1). Another approach to this diastereoisomer involves reacting an allylmetal with a glycal epoxide.[12] However, only by careful choice of allylating agent and/or activating Lewis acid is the *β*-allyl-*C*-glycosyl prepared selectively.[12]

Unfortunately, the presence of an axially oriented alcohol substituent at C(2) in mannopyranosides renders the synthesis of *β*-allyl-*C*-mannosyls particularly difficult. For example, application of Kishi's methodology to the perbenzylated mannonolactone **5** provided a 1:1 mixture of the two diastereoisomeric products (Scheme 1). Kishi proposed that a build-up of unfavorable steric interactions in the transition state (T.S.) leading to the 1,2-syn stereoisomer, i.e., the *β*-product, accounted for the poor stereoselectivity of this reaction. In the corresponding glucose system, where this type of steric interaction is absent, the *β*-allyl-*C*-glucosyl product could be isolated in excellent stereoselectivity (*β*/α, >10:1).[11]

The formation of *β*-*O*-mannosides has, until recently, also been one of the most difficult glycosidic bonds to prepare stereoselectively, and a number of approaches have been developed for addressing this specific prob-

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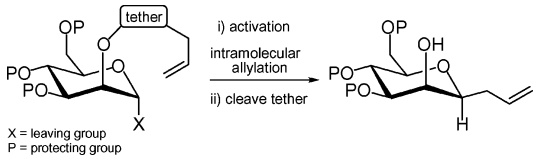


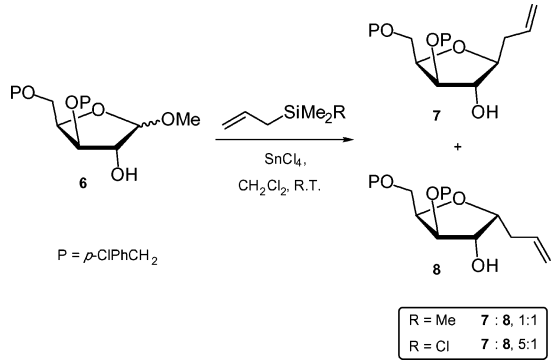
FIGURE 2. Use of an intramolecular delivery strategy to synthesize β-allyl-*C*-mannosyls.

lem.[15] One of the most interesting and creative utilizes the intramolecular aglycon delivery strategy,[16] first introduced by Stork[17] and Hindsgaul.[18] Both groups exploited the axial alcohol at C(2) to *temporarily* attach the acceptor to a suitable glycosyl donor.[19] Activation of the donor then resulted in *intra*molecular transfer of the acceptor to the anomeric center to provide the corresponding β-*O*-mannoside with essentially complete stereocontrol.

Similar tethering strategies have also been used to control the stereoselectivity of a variety of *C*-glycosylation reactions, most of which have involved the generation of a radical at the anomeric center, which has then been trapped by a tethered acceptor.[20] We are interested in investigating the possibility of using a similar strategy to prepare β-allyl-*C*-mannosyls by delivering an allyl nucleophile that has been tethered to the alcohol at C(2) through a silyl ether linkage (Figure 2). This would provide an alternative strategy to the most commonly employed approach to this class of compound, developed by Kishi, which in the case of mannose derivatives is frequently poorly stereoselective (although see Scheme 5).

A number of related studies have shown that the C(2)-OH of a saccharide can be used to deliver a nucleophile to an activated glycosyl donor, usually to provide a 1,2-syn-*C*-glycosyl product.[21] The most significant of these for our purposes comes from Martin et al. who used the C(2)OH in a range of methyl furanosides to tether and subsequently deliver silyl nucleophiles to the activated anomeric center.[21a] In a single example, methyl xylofuranoside **6** was treated with $SnCl_4$ in the presence of allyldimethylsilyl chloride. The two allyl-*C*-furanosyl products **7** and **8** were obtained in good yield with the β-diastereoisomer predominating (Scheme 2).

SCHEME 2. Judicious Choice of Allylating Agent Leads to Improved β-Selectivity



Martin postulated that in situ formation of the 2-*O*-allyldimethylsilyl derivative from **6**, followed by $SnCl_4$-mediated activation of the anomeric center, led to intramolecular delivery of the allyl group to the anomeric center. Molecular models suggested that in this case, reaction through a seven-membered cyclic T.S. would preferentially provide the observed 1,2-trans product, as opposed to the 1,2-cis product that is normally obtained using this type of delivery strategy.[21] This is a consequence of a better alignment of the C−Si bond with the reacting π-system affording improved stabilization of any build-up of positive charge in the T.S. The only evidence to suggest that the reaction was intramolecular came from a comparison of the diastereoselectivity of the reaction when allyltrimethylsilane was employed as the allylating agent. In this case, a 1:1 mixture of α- and β-allyl-*C*-furanosyls **7** and **8** was obtained (Scheme 2).

Results and Discussion

To ensure that allylation proceeded by the desired intramolecular pathway, Martin et al. had to rely on in situ tethering of the allylsilane being faster than any competing intermolecular allylation process (Scheme 2). Since the axial orientation of C(2) in mannose renders derivatization of this alcohol relatively difficult, we took the precautionary measure of separating these two processes, choosing to form the silyl ether connection in a first step and examine the *C*-glycosylation in a second. Methyl mannoside **16** was therefore our first target; its preparation is outlined in Scheme 3.

Synthesis began with peracetylation of commercially available D-mannose, using the conditions reported by Kartha and Field,[22] to provide the corresponding pentaacetate **9** in quantitative yield and as a 3:1 mixture of α/β anomers. These were used without purification in the next step; thus exposure of **9** to HBr in acetic acid provided the corresponding anomeric bromide **10**, in which anchimeric assistance of the acetate at C(2)

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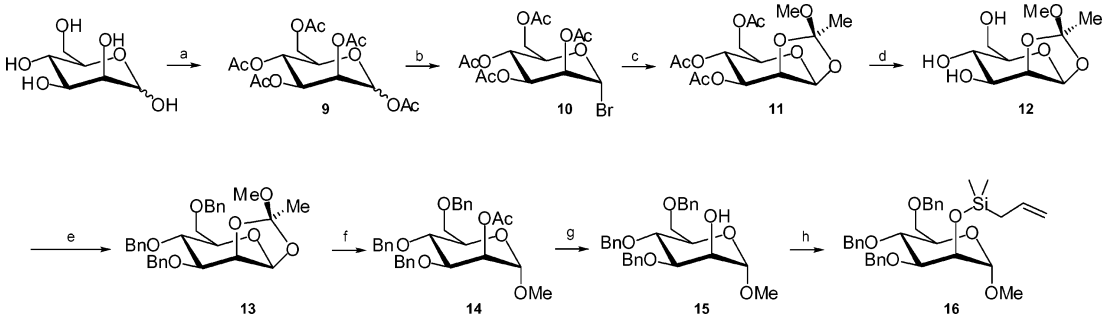
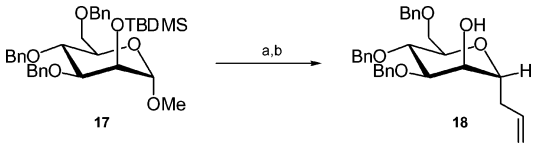
SCHEME 3. Preparation of Allylation Precursor 16 from D-Mannose[a]



[a] Reagents and conditions: (a) Ac_2O, I_2, 0 °C to rt, 1 h; (b) HBr in AcOH (30%), AcOH, 0 °C to rt, 12 h; (c) 2,6-lutidine, MeOH−$CHCl_3$ (1:1), rt, 24 h, 63% (three steps); (d) K_2CO_3, MeOH, rt, 2 h; (e) NaH, BnBr, DMF, 0 °C to rt, 24 h, 90% (two steps); (f) TMSOTf, 4 Å MS, CH_2Cl_2, 0 °C, 1 h, quant; (g) K_2CO_3, MeOH, rt, 1 h, quant; (h) allyldimethylsilyl chloride, imidazole, DMF, rt, 24 h, 80%.

ensured the obtention of exclusively the α-stereoisomer.[23] Examining our target **16**, we next needed to differentiate the alcohol at C(2) from those at C(3), C(4), and C(6). This was readily achieved by temporarily protecting C(2) as an ortho ester. Thus, stirring a solution of bromide **10** and 2,6-lutidine in chloroform/methanol (1:1) provided the desired ortho ester **11** in good yield.[24,25] It was convenient to purify at this stage and recrystallization from ether-methanol provided ortho ester **11** (93:7, exo/endo) in 63% yield over the three steps from D-mannose. Crystals of exo-**11** suitable for analysis by X-ray diffraction were grown from ether-methanol and confirmed the relative stereochemistry of the major diastereoisomer (see the Supporting Information). With the alcohol at C(2) successfully protected as a base-stable ortho ester, removal of the remaining acetate protecting groups at C(3), C(4), and C(6) with K_2CO_3 in MeOH provided the corresponding triol **12**. This was directly benzylated under standard conditions to provide tribenzyl ether **13** in excellent yield (90%) over the two steps. Once again, large-scale purification was readily achieved by recrystallization from EtOAc−hexane (see the Supporting Information for a crystal structure of exo-**13**). TMSOTf-mediated opening of the ortho ester in **13** provided the desired methyl mannoside **14**.[26] Subsequent deacetylation unmasked the alcohol at C(2) in readiness for attaching the allylsilane nucleophile. Silyl ether **16** was prepared by treating alcohol **15** with commercially available allyldimethylsilyl chloride in the presence of imidazole in DMF. The reaction was slow (24 h), as we had expected, although did furnish the desired product **16** in good yield (80%), providing moisture was rigorously excluded from the reaction.[27] With our target in hand, we were now ready to investigate the possibility of intramolecularly transferring the allyl group to the anomeric center to hopefully provide a *β*-allyl-*C*-mannosyl product.

SCHEME 4. Preparation of α-Allyl-*C*-mannosyl 18[a]



[a] Reagents and conditions: (a) allyltrimethylsilane, TMSOTf, MeCN, rt, 2.5 h; (b) TBAF, THF, rt, 20 h, 91% (two steps).

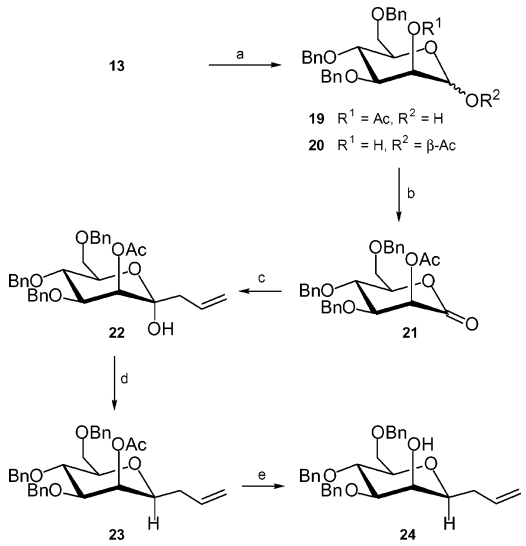
To measure the stereoselectivity of the allylation reaction, we required a sample of the two diastereoisomeric allyl-*C*-mannosyl products that could be produced from the reaction. These were prepared using modifications of approaches already reported in the literature. Synthesis of α-allyl-*C*-mannosyl **18** was achieved using the methodology developed by Hosomi and Sakurai.[8a] Reaction of methyl 3,4,6-tri-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside **17** (readily prepared from alcohol **15**) with allyltrimethylsilane, in the presence of TMSOTf, provided the desired alcohol α-diastereoisomer **18** in good yield (α/*β*, 13:1) after TBAF deprotection of the crude silyl ether products and purification by flash column chromatography (Scheme 4).

Since this route provided only small quantities of the *β*-allyl-*C*-mannosyl compound **24**, we used a modified version of Kishi's methodology[11] to access larger quantities of this diastereoisomer (Scheme 5).

Ortho ester **13** has proved to be a versatile intermediate. For the present purposes, ring-opening in neat AcOH provided two products, **19** (mixture of anomers) and **20**, in quantitative yield.[28,29] In the next step, we needed to oxidize lactol **19** to the corresponding lactone **21**. Since separating **19** and **20** by column chromatography proved difficult, we envisaged this might be unnecessary if we were to use tetra-*n*-propylammonium perruthenate (TPAP)[30] as the oxidant in the next step. This Ru(VII)-based oxidant is particularly useful for lactol oxidation and thus would provide the lactone **21** directly from lactol

(23) Horton, D.; Turner, W. N. *J. Org. Chem.* **1965**, *30*, 3387−3394.
(24) Mazurek, M.; Perlin, A. S. *Can. J. Chem.* **1965**, *43*, 1918−1923.
(25) Ortho ester **11** can also be prepared in good yield by treating bromide **10** with *N*,*N*-dimethylformamide dimethyl acetal and tetrabutylammonium bromide in CH_2Cl_2: Banoub, J.; Boullanger, P.; Potier, M.; Descotes, G. *Tetrahedron Lett.* **1986**, *27*, 4145−4148.
(26) Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6−C9.
(27) In situ conversion of the silyl chloride into the corresponding triflate, by treatment with AgOTf, provided a much more effective silylating agent and afforded the desired silyl ether **16** in 79% yield after only 3 h: (a) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026−7043. (b) Nagashima, H.; Terasaki, H.; Saito, Y.; Jinno, K.; Itoh, K. *J. Org. Chem.* **1995**, *60*, 4966−4967.
(28) Paulsen, H.; Reck, F.; Brokhausen, I. *Carbohydr. Res.* **1992**, *236*, 39−71.
(29) The use of TFA (10% in H_2O) in MeCN, as an alternative approach, provided a similar ratio of products in equally good yield: Franzyk, H.; Meldal, M.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2883−2898.
(30) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

SCHEME 5. Preparation of β-Allyl-*C*-mannosyl 24[a]



[a] Reagents and conditions: (a) 95% AcOH in H_2O, rt, 20 min, quant OR 10% CF_3CO_2H in H_2O, MeCN, 0 °C, 30 min, quant; (b) **19** and **20**, TPAP (5 mol %), NMO, MeCN, 4 Å MS, rt, 10 min, 90%; (c) (allyl)MgBr, THF, −78 °C, 1.5 h, 70%; (d) Et_3SiH, TMSOTf, MeCN, rt, 5 min, 47%; (e) NaOMe, MeOH, rt, 12 h, 85%.

19. However, we were also aware of a report that suggested that the acetate at C(1) in the undesired compound **20** would migrate on to C(2) in the presence of amines to provide lactol **19** in situ.[31a] Since TPAP is employed in sub-stoichiometric quantities, along with a co-oxidant, *N*-methylmorpholine *N*-oxide,[31b] we postulated that we could use the amine byproduct from such an oxidation constructively, to mediate an acetate migration from C(1) to C(2) in **20**. In this way, providing oxidation of the secondary alcohol in **20** was slow, relative to the rate of acetate migration, then it would be possible for both acetates **19** and **20** to converge on the desired lactone product. This indeed proved to be the case and we were delighted to observe that TPAP oxidation of the mixture of alcohols **19** and **20** proceeded rapidly to afford a single lactone product **21** in excellent yield. The appearance of C(2)H in **21** as a doublet with a small (2.9 Hz) equatorial−axial ^3J coupling to C(3)H confirmed that no epimerization of the α-stereogenic center had occurred during the oxidation.

The reaction between allylmagnesium bromide and lactone **21** required some optimization[32] in order to obtain the desired tertiary lactol product **22** in good yield. We found that reaction of **21** with 1.2 equiv of (allyl)MgBr at −78 °C in THF led to the desired tertiary lactol product **22** in 70% yield (Scheme 5).[11] Treatment of lactol **22** with Et_3SiH in the presence of TMSOTf or $BF_3{\cdot}OEt_2$ effected ionic reduction to provide the desired β-allyl-*C*-mannosyl product **23** in 47% yield after careful purification by column chromatography.[32] Once again, we observed some differences to the original Kishi work.[11] The reaction exhibited much higher levels of stereoselectivity with an acetate at C(2) (dr > 20:1) compared with a benzyl ether at the same site (dr 1:1) (Scheme 1). Presumably in our case, interception of the oxocarbenium cation by the neighboring acetate provides an acetoxonium-like intermediate that more effectively blocks the β-face from hydride attack. In the final step, deacetylation under Zemplen conditions provided alcohol **24** in good yield.[33]

TABLE 1. Relative Ratios of Products from the Reaction of 16 with TMSOTf with and without Acid Scavengers

additive[a]	ratio[b] **18**/**24**/**15**
no additive	40:1:17
2,6-lutidine	180:1:20
2,6-DTBMP	320:1:10

[a] 2 equiv. [b] Ratio calculated by HPLC.

The α- and β-allyl-*C*-mannosyls **18** and **24** exhibited quite different ^1H NMR spectra and were also readily separated by analytical HPLC; thus, we were now in a position to investigate the allylation reaction of **16**. The reaction of acyclic acetals with allylsilanes and allylstannanes under Lewis acid activation is frequently carried out in CH_2Cl_2.[34] Martin also employed CH_2Cl_2 in his allylation of methyl furanoside **6** (Scheme 2).[21a] In our case, however, treating methyl mannoside **16** with a range of Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_4$, TMSOTf) in CH_2Cl_2 at either −78 °C or rt only resulted in cleavage of the silyl ether and recovery of the alcohol **15**. Activation of the methyl glycoside was clearly slow relative to the rate of cleavage of the dimethylsilyl ether tether. We were not particularly surprised by this observation since Hosomi and Sakurai reported similar results in their intermolecular allylation study,[8a] and just like this group, we obtained more success employing the much more polar solvent, MeCN ($MeNO_2$ was also suitable but provided lower yields of the desired allylation product). However, even with MeCN as solvent, the only Lewis acid that proved successful in effecting allylation with methyl mannoside **16** was TMSOTf; $SnCl_4$ and $BF_3{\cdot}OEt_2$ both cleaved the silyl ether tether preferentially resulting in the recovery of alcohol **15** and the isolation of no allylation product. In contrast, reaction of methyl mannoside **16** with TMSOTf in MeCN at room temperature led to rapid consumption of starting material (in 1−2 h). Two major products were isolated and identified as the α-allylation product **18**, along with the silyl ether hydrolysis product **15**. Only trace quantities of the β-allyl-*C*-mannosyl product **24** were identified (Table 1). Carrying out the reaction at lower temperatures led to a greatly reduced rate of activation of the anomeric center and cleavage of the silyl ether occurred preferentially. Although this reaction could potentially proceed with sub-

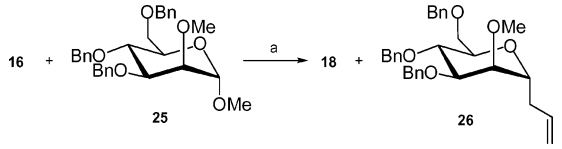
(31) (a) Wood, H. B., Jr.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 2849−2851 and references therein. (b) We acknowledge the probability that the amine oxide is also mediating acetate migration: stirring a solution of **19** and **20** in MeCN in the presence of NMO and activated 4 Å molecular sieves for 1 h at rt did increase the amount of acetate **19** in the reaction mixture.

(32) See the Supporting Information for more details.

(33) Removing the acetate protecting group at C(2) in β-allyl-*C*-mannosyl **23** proved to be much slower than the same reaction involving methyl mannoside **14** (e.g., the use of K_2CO_3 in MeOH proved ineffective). Presumably the equatorially oriented allyl group at C(1) in **23** leads to a build-up of steric compression in the tetrahedral intermediate in the hydrolysis process which serves to reduce the rate of reaction.

(34) (a) Tsunoda, T.; Suzuki, M.; Noyori. R. *Tetrahedron Lett.* **1980**, *21*, 71−74. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910.

SCHEME 6. Cross-Over Experiment Confirmed That Reaction Was Proceeding through an Intermolecular Pathway[a]



[a] Reagents and conditions: (a) TMSOTf, MeCN, rt.

stoichiometric quantities of Lewis acid, this proved not to be the case in our system, and the use of 20 mol % TMSOTf just led to incomplete reaction.

Thus, to our dismay, the α-allyl-*C*-mannosyl product **18** proved to be the major compound using our tethered allylsilane approach! Earlier studies had revealed that our silyl ether temporary connection was acid-labile. We considered that adventitious water in the reaction might be generating triflic acid that would rapidly cleave the tether,[35] generating an allylating agent that could then react intermolecularly. Carrying out the reaction in the presence of an acid scavenger led to significant improvements. Using 2,6-lutidine as the base, appreciably reduced the amount of alcohol **15**, and the α-allylation product **18** was now the major compound isolated (Table 1). The reaction was also significantly slower (reaction required stirring overnight). The situation was further improved when the even more sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) was employed (Table 1).

We initially considered that reaction of **16**, containing our tethered allylsilane nucleophile, was indeed proceeding through an intramolecular pathway, but that the ring size of the T.S., and relatively long bonds to Si, favored delivery of the nucleophile to the α-face, in analogy with Martin's results (Scheme 2). To verify whether this was the case, we carried out a series of crossover experiments. Methyl mannopyranoside **25**, readily obtained by methylation of alcohol **15** (NaH, MeI, DMF), was considered a suitable substrate for these studies. Since silyl ethers and alkyl ethers have similar activating effects on the reactivity of glycosyl donors,[36] both methyl glycosides would be expected to have similar rates of activation in the presence of TMSOTf. This would diminish the likelihood of differential activation of the two donors biasing the results. Reaction of 0.5 equiv of the two methyl glycosides **16** and **25** with 1 equiv of TMSOTf in the presence of 2,6-DTBMP in MeCN at room-temperature provided a 1.2:1.0 mixture of the two possible α-allyl-*C*-mannosyl products **18** and **26** (the corresponding *β*-diastereoisomers were again identified in trace amounts) (Scheme 6). A similar result was also obtained in the absence of the acid scavenger, the only difference being an increase in the rate of reaction.

The isolation of the crossover product **26** therefore provided conclusive evidence that allylation was proceeding through an intermolecular pathway. Furthermore, the approximately 1:1 ratio of products suggested that the allylating agent did not discriminate between the two glycosyl donors, which was suggestive that reaction was *exclusively* an intermolecular process. To further prove this, we carried out the same crossover experiment at different reaction concentrations; an increase in the amount of **18** with dilution, and concomitant reduction in the amount of crossover product **26** would suggest that allylation might also be proceeding through an intramolecular pathway to provide the same product. However, when we carried out the reaction at 0.125 and 0.05 M (at lower reaction concentrations, allylation was sluggish and we only observed slow hydrolysis of the silyl ether), we observed no significant change in the ratio of the two allylation products. This suggested that, at least in this concentration range, our attempted strategy to intramolecularly deliver an allyl nucleophile to the anomeric position of mannose had proved unsuccessful.

Precedent that our proposed intramolecular delivery strategy might have worked comes from the study by Martin and co-workers who reacted methyl furanoside **6**, possessing a free alcohol at C(2), with allyldimethylsilyl chloride in the presence of the Lewis acid $SnCl_4$ (Scheme 2).[21a] While Martin did not conclusively prove that the allylation was proceeding via an intramolecular pathway, the improved stereoselectivity of the reaction compared with a known intermolecular process, was highly suggestive that the reaction was proceeding either by intramolecular delivery of an allyl nucleophile tethered at C(2)OH to the anomeric position or at least by a different mechanism to the 'standard' intermolecular pathway. Intrigued by the differences in reaction pathway between our work and that from Martin and coworkers, we performed a number of control reactions in the hope that these might shed some light on our system.

Since Martin had not conclusively demonstrated that a silane was the active allylating agent, we considered other sources of a nucleophilic allylmetal. We postulated that the $SnCl_4$ Lewis acid might first react with allyldimethylsilyl chloride, in analogy to the reaction with allyltributylstannane,[37] to provide the corresponding allyltrichlorostannane. This would be expected to react much more readily with the Lewis basic alcohol at C(2), than the silyl chloride, to provide a tethered allylstannane ready for delivery on activation of the anomeric center (Scheme 7). Alternatively, the Lewis acidity of this species might also be capable of activating the anomeric center itself and delivering the nucleophile through a push−pull type of mechanism (Scheme 7).[38] Allyltrichlorostannane was prepared by treating allyltributylstannane with $SnCl_4$ at −78 °C in CH_2Cl_2.[39] Unfortunately, addition of the alcohol **15** at −78 °C led to no change in the reaction mixture, nor did adding more $SnCl_4$ and warming to rt overnight; in all cases, the starting material was recovered intact.

(35) Davis, A. P.; Jaspars, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1176−1178.

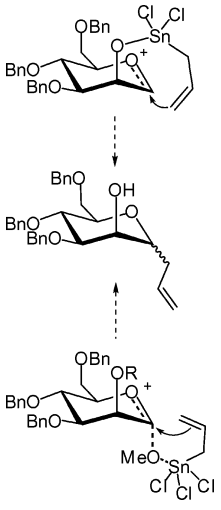
(36) Green, L. G.; Ley S. V. In *Carbohydrates in Chemistry and Biology, Part 1: Chemistry of Saccharides*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, Chapter 17, pp 427−448.

(37) (a) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Tetrahedron* **1989**, *45*, 1067−1078. (b) Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984−986. (c) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136−8141.

(38) Pratt, M. R.; Leigh, C. D.; Bertozzi, C. R. *Org. Lett.* **2003**, *5*, 3185−3188.

(39) (a) Keck, G. E.; Abott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927−3930. (b) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239−6242. (c) Hallett, D. J.; Thomas, E. J. *Synlett* **1994**, 87−88.

SCHEME 7. Possibility that Allyltrichlorostannane Was Acting as the Allylating Agent Was Discounted



In light of the significant reduction in the rate of allylation when acid scavengers are used, we propose that TfOH is responsible for activating the mannosyl donor *and* for cleaving the silyl ether in the absence of base. In the presence of a base, we propose that "TMS^+" (from TMSOTf) activates the anomeric site, albeit less effectively than H^+ (from TfOH), hence the reduced rate in these cases; however, we also believe that TMSOTf does not cleave the silyl ether tether to any appreciable extent (allylsilanes are known to be much more unstable to Brønsted acids than they are to Lewis acids). The question then arises as to the identity of the active nucleophile in these reactions. It is noteworthy that the α/β stereoselectivity in the products from the reaction between TBDMS-protected methyl mannoside **17** and allyltrimethylsilane under TMSOTf activation was 13:1 as determined HPLC, while that from the reaction involving allylsilyl ether **16** under TMSOTf activation in the presence of base was >100:1 (as determined by HPLC). We tentatively propose that in the presence of a bulky base, the active nucleophile is the allylsilyl ether itself. The improved α-stereoselectivity compared with the intermolecular reaction involving allyltrimethylsilane can be accounted for by the greatly increased steric bulk of the ligands on the silicon (even though they are rather remote from the reacting center in the T.S.). In the presence of just TMSOTf there is more than one allyl nucleophile operating, namely the allylsilyl ether **16**, *and* some silyl ether cleavage product (e.g., allyldimethylsilyl triflate or allyldimethylmethoxysilane), which would account for the decreased α/β stereoselectivity in this case.

Allylsilanes are only more nucleophilic than simple olefins because the presence of the C−Si bond can stabilize the accumulation of positive charge on the β-carbon (β-effect),[40] thereby lowering the energy of activation. If the C−Si bond cannot adopt a suitable orientation to allow this charge stabilization, then the reaction may be energetically unfavorable. In the case of allylsilane **16**, we therefore assume that the conformational constraints imposed on the oxocarbenium cation in the pyranose ring may be such as to render an intramolecular delivery pathway, in which the developing charge on the allylsilane can be stabilized by the C−Si bond, conformationally unviable, the net result being that intermolecular allylation pathways are followed instead (Scheme 8). With these considerations in mind, we envisaged that relocating the silyl ether temporary connection to the γ-position of the allylsilane would significantly improve matters. Tethering such a nucleophile to C(2)OH of a methyl mannoside would afford silyl ether **27** (Scheme 8). In this modified system, intramolecular allylation would now proceed through a five-membered T.S., rather than the seven-membered T.S. that would be required using tethered allylsilane **16**. Furthermore, since the allylsilane in **27** would now be exo to the cyclic T.S., rather than endo, as in **16**, we would hopefully encounter no problems with the allylic C_α-Si bond adopting an orientation capable of stabilizing developing positive charge in the T.S. Since reaction through a five-membered T.S. should also be kinetically more favorable and would also much more closely resemble the T.S.s found in other examples of intramolecular aglycon delivery that have successfully delivered a 1,2-syn product,[17,18,41−45] we were more confident of achieving our goal of generating a β-allyl-*C*-mannosyl. This second-generation system possesses a range of other attractive features. Owing to the silyl ether tether remaining intact post allylation, two new stereogenic centers would now be formed in the allylation product **28**; thus, reaction of our second-generation allylsilane **27** would also benefit from increased levels of stereochemical transcription.[46] Bicycle **28** is also synthetically much more versatile than the simple allyl-*C*-mannosyl products (e.g., **18** and **24**) that would be obtained using our first generation system, **16**.

An allylsilane **29**, suitable for tethering to the C(2)OH in a methyl mannoside, was readily prepared using a modified procedure developed by Tamao and Ito (Scheme 9).[47] Although aminosilanes are not commonly used in synthesis,[48−53] they are attractive reagents for forming silyl ethers. Since the only byproduct from the reaction is a volatile secondary amine (Et_2NH in our case), silylation of alcohols can be achieved without having to include acid scavengers, which facilitates workup. The

(40) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. *Acc. Chem. Res.* **1999**, *32*, 183−190 and references therein.

(41) (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767. (b) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680−4681. (c) Dan, A.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1995**, *36*, 7487−7490. (d) Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1997**, *119*, 5562−5566. (e) Dan, A.; Lergenmüller, M.; Amano, M.; Nakahara, Y.; Ogawa, T.; Ito, Y. *Chem. Eur. J.* **1998**, *4*, 2182−2190.

(42) (a) Krog-Jensen, C.; Oscarson, S.; *J. Org. Chem.* **1996**, *61*, 4512−4513. (b) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1998**, *63*, 1780−1784.

(43) Packard, G. K.; Rychnovsky, S. D. *Org. Lett.* **2001**, *3*, 3393−3396.

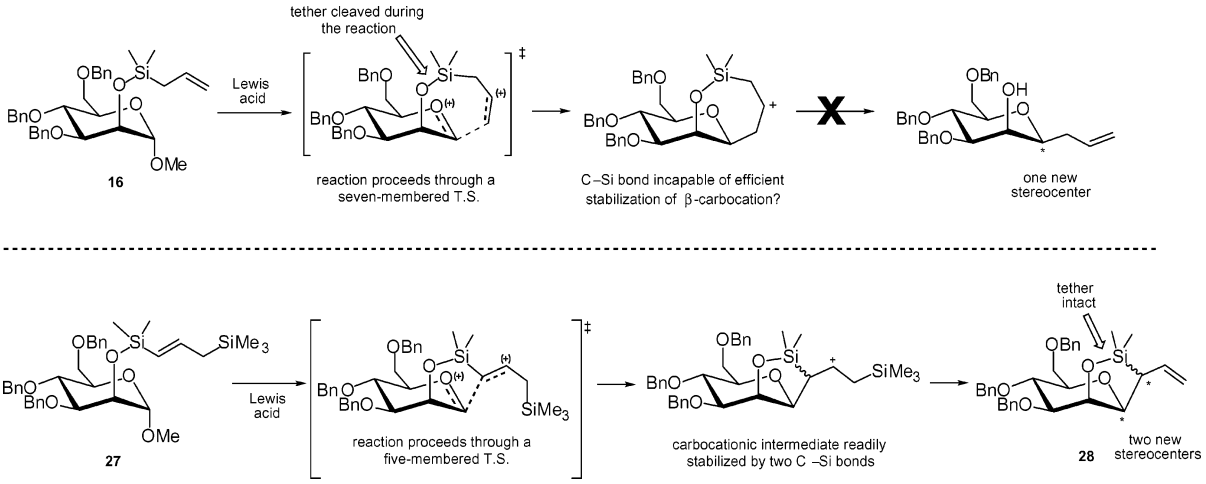
(44) (a) Ennis, S. C.; Fairbanks, A. J.; Tennant-Eyles, R. J.; Yeates, H. S. *Synlett* **1999**, 1378−1390. (b) Seward, C. M. P.; Cumpstey, I.; Aloui, M.; Ennis, S. C.; Redgrave, A. J.; Fairbanks, A. J. *Chem. Commun.* **2000**, 1409−1410.

(45) (a) Bols, M. *J. Chem. Soc., Chem. Commun.* **1992**, 913−914. (b) Bols, M. *Acta Chem. Scand.* **1993**, *47*, 829−834. (c) Bols, M. *Acta Chem. Scand.* **1996**, *50*, 931−937.

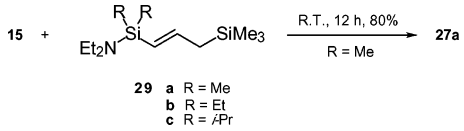
(46) Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671−1678.

(47) A detailed discussion of the synthesis of these allylsilanes will be reported elsewhere. Tamao, K.; Nakajo, E.; Ito, Y. *Tetrahedron* **1988**, *44*, 3997−4007.

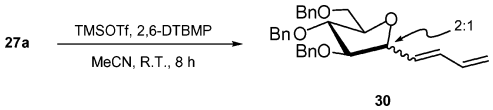
SCHEME 8. Relocating the Silyl Ether Tether to the γ-Position of the Allylsilane Should Favor Intramolecular Allylation and Provide a Synthetically More Versatile Product



SCHEME 9. Use of γ-(Amino)silyl-Substituted Allylsilanes 29 in Tether Formation



SCHEME 10. Reaction of Allylsilane 27a Provided a Tetrahydrofuran Product



reaction between aminosilane **29a** and alcohol **15** was relatively slow (as had been expected). However, with no strong exotherm, silyl ether formation was readily achieved by simply mixing equimolar quantities of the two reagents, in the absence of solvent, and with slight warming to 40 °C to aid mixing of the two reactants. The reaction was conveniently monitored visually (as well as by TLC). At the beginning of the reaction, and without vigorous stirring, two phases were clearly evident in the reaction vessel (the aminosilane **29a** is much less dense than the alcohol **15**). When the reaction had reached completion, the mixture was a single phase containing the product and residual diethylamine, which was readily removed under reduced pressure. At the outset, we were uncertain of the stability of the silyl ether linkage in **27a**. Fortunately, these concerns proved unfounded; the product was air- and moisture-stable and could be purified by silica gel column chromatography without having to take any special precautions.

With our second-generation allylsilane **27a** in hand, we were now ready to investigate its application in *C*-glycosylation (Scheme 10). Using the conditions that had proved most efficient in effecting *C*-glycosylation with our first-generation allylsilane **16** (Table 1), treatment of methyl mannoside **27a** with TMSOTf in the presence of 2,6-DTBMP in MeCN at rt for 8 h, provided what appeared to be a single major product by TLC. Analysis of the crude reaction mixture by NMR, however, suggested the presence of two similar compounds, both containing a terminal (*E*)-1,3-diene; there was no evidence for our desired allylation compounds **28**. Purification of the reaction mixture by silica gel flash column chromatography allowed the isolation of the two diene compounds in modest yield (38%) owing to their apparent instability on silica gel, and extensive NMR experiments confirmed the structure of these products as the ring-contracted tetrahydrofuran **30** (~2:1 mixture of stereoisomers).

In our first approach, we had shown that the simple allylsilane contained within mannoside **16** (Scheme 6) reacted through an intermolecular pathway. We expected the analogous intermolecular reaction involving our second-generation allylsilane **27a** as the reacting species to be severely disfavored owing to the presence of a massive substituent (a protected monosaccharide) at the reacting γ-position of the allylsilane. Indeed, we were unable to find any evidence of possible crossover products when **27a** was treated to our standard activation conditions in the presence of methyl mannoside **25** containing a methyl ether at C(2) (Scheme 11). While the ring-contracted product could also be produced from an initial intermolecular reaction (see below), the fact that mannoside **25** was recovered intact, was highly suggestive that intermolecular pathways were not operating. To verify this further, an attempted intermolecular reaction between γ-(isopropyloxy)dimethylsilyl-substituted allylsilane **31** (prepared from the reaction between **29a** and 2-propanol)[47] and mannoside **25**, failed to provide any products even after 2 days at rt, and both starting materials were recovered intact (Scheme 11).

(48) TMS protection: (a) Ruehlmann, K. *Synthesis* **1971**, 236−253. (b) Yankee, E. W.; Bundy, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 3651−3652. (c) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686−1695. (d) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559−1563. (e) Tanabe, Y.; Murakami, M.; Kitaichi, K.; Yoshida, Y. *Tetrahedron Lett.* **1994**, *35*, 8409−8412.

(49) TES protection: Holton, R. A.; Zhang, Z.; Clarke, P. A.; Nadizadeh, H.; Procter, D. J. *Tetrahedron Lett.* **1998**, *39*, 2883−2886.

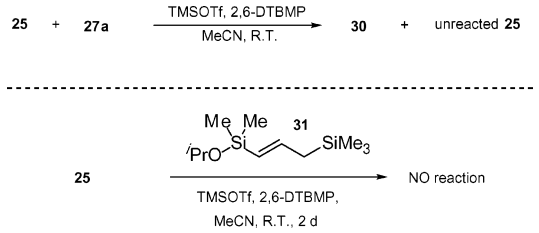
(50) TBDMS protection: see ref 48c.

(51) TIPS protection: Firouzabadi, H.; Iranpoor, N.; Naser, S.; Hamid, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 71−82.

(52) $PhMe_2Si$ protection: Liepin'sh, E. E.; Birgele, I. S.; Zelchan, G. I.; Urtane, I. P.; Lukevits, E. *J. Gen. Chem. USSR (Engl. Transl.)* **1980**, *50*, 2212−2216.

(53) $(Allyl)Me_2Si$ protection: Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889−3898.

SCHEME 11. Intermolecular Allylation Pathways Are Not Important with Allylsilane 27a



We propose that the rather unusual tetrahydrofuran product **30** is formed according to the mechanism outlined in Scheme 12.

Activation of the anomeric center in **27a** provides an oxocarbenium cation that is trapped by the tethered allylsilane as desired. The carbocationic intermediate **32** can benefit from stabilization through the well-known β-effect from both silicon substituents;[54] it can therefore collapse by external nucleophilic attack at either silicon center. To provide the diene product **30** we propose that an external nucleophile preferentially attacks the silyl ether silicon which is more Lewis acidic than the trimethylsilyl silicon owing to it being constrained into a five-membered ring,[55,56] and tethered to an oxygen substituent.[57] Under the Lewis acidic reaction conditions, this allylsilane product **33** reacts further. Lewis acid activation of the pyranose oxygen in **33** effects a vinylogous silicon-mediated olefination[58] providing the ring-opened product **34** containing a (*E*)-1,3-diene. Such olefination processes are known to be effected by Lewis acids, and are also invariably (*E*)-selective.[58] The stereoselectivity of the reaction can be rationalized by assuming a reactive conformation of the intermediate allylsilane in which $A^{1,3}$-interactions are minimized by the allylic hydrogen eclipsing the olefin (Scheme 13).[59]

Under the Lewis acidic reaction conditions, the dienylic alcohol in **34** (C(2) sugar numbering) then ionizes to provide a pentadienyl cation **35** that is rapidly trapped by the TMS ether at C(5) (sugar numbering) to provide the tetrahydrofuran **30** as a mixture of stereoisomers (Scheme 12). The lack of stereoselectvity in this final ring-closure step suggests an S_N1 process is operating, rather than the alternative S_N2 pathway, which would have been expected to provide a single tetrahydrofuran product.

While carrying out this study, we were also investigating the reaction of our allylsilane tethered to a range of β-hydroxy aldehydes **37**.[61] In this system, we also found that diene products were obtained exclusively with a dimethylsilyl ether-tethered allylsilane. However, we were able to efficiently suppress the formation of diene products by increasing the steric bulk of the ligands about the silyl ether linker; thus exchanging the methyl substituents for ethyl groups led to the formation of the desired oxasilacycle products **36** in good to excellent yield (Scheme 14).[61]

Allylsilane **29b** containing a (diethylamino)diethylsilyl substituent in the γ position was readily prepared from Et_2SiCl_2.[47] Tethering to the C(2)OH in methyl mannoside **15**, however, now proved to be unacceptably slow. We found that this step could be improved significantly by first converting the aminosilane **29b** into the corresponding chlorosilane **38b** by treatment with freshly distilled acetyl chloride.[62] Without isolation, addition of mannoside **15** provided the desired silyl ether **27b** in greatly improved yield and reduced reaction time (Scheme 15).

Treatment of allylsilane **27b** under our now-standard activation conditions, provided a range of compounds which were analyzed and separated by reversed-phase HPLC (Scheme 16). Once more, diene compounds accounted for the majority of the mass balance. The ring-contracted tetrahydrofuran product **30** (isolated as a similar ratio of diastereoisomers as was obtained from the reaction with methyl mannoside **27a**) was again identified, although this time in roughly equal proportions with the silyl acetal **39**. Although we initially supposed that diene **39** might be a precursor to tetrahydrofuran **30**, exposure of purified diene **39** to the glycosylation reaction conditions for 24 h led to complete recovery of the starting material. Presumably, the bulkier ethyl groups at the silyl ether tether reduce the propensity for the dienylic alcohol **34** (Scheme 12) to undergo Lewis acid-mediated ionization (leading to formation of the ring-contraction product), allowing this intermediate to proceed along alternative pathways. In this case, intramolecular nucleophilic displacement of the X group in **34** by an alcohol nucleophile at C(5) would account for the formation of silyl acetal **39**.

More significantly in this reaction, we were delighted to identify the desired intramolecular allylation products **42b** and **43b**, in approximately equal amounts. Thus, in analogy to our reaction with aldehyde substrates (Scheme 14), moving to the bulkier diethylsilyl ether tether had once again helped to redirect the course of the reaction along our desired pathway, although admittedly far less efficiently in this case, as diene compounds remained the major products from the reaction. In contrast to the six-membered ring products **36** derived from aldehyde **37** (Scheme 14), which were stable to purification by silica gel column chromatography, the five-membered oxasila-

(54) Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1421−1423.

(55) Leighton and others have recently demonstrated the importance of ring strain in controlling the Lewis acidity of allylsilanes: (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920−7921. (b) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596−9597. (c) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946−948. (d) Robertson, J.; Hall, M. J.; Green, S. P. *Org. Biomol. Chem*, **2003**, *1*, 3635−3638. (e) Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1988**, *110*, 4599−4602.

(56) Silacyclobutane systems are similarly more Lewis acidic: Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152−7155.

(57) We presume that the inductive effect of the electronegative oxygen substituent overrides any pπ−dπ back-bonding effects, which would temper the Lewis acidity of the silicon center.

(58) (a) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179−8188. (b) Bradley, G. W.; Thomas, E. J. *Synlett* **1997**, 629−631. (c) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 534−536.

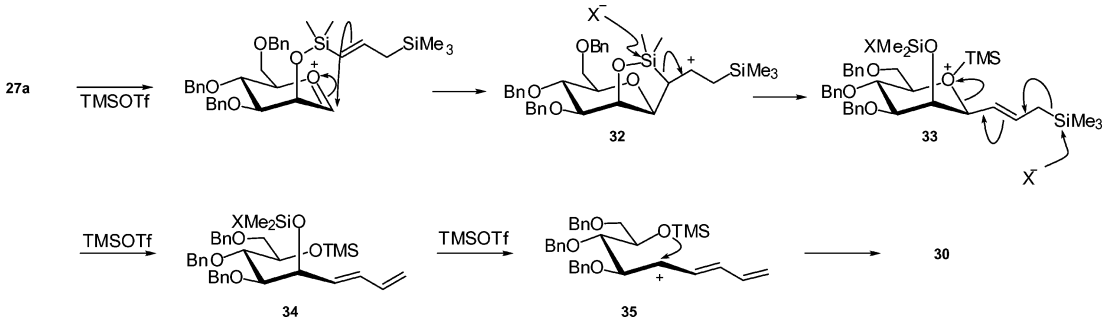
(59) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(60) An anti E′ elimination is shown in Scheme 13; a syn E′ elimination would provide the same product stereoselectivity; similarly the stereochemistry of the olefin in the intermediate allylsilane would also not affect the (*E*)-selectivity; indeed if anything the (*Z*)-stereoisomer might be even more stereoselective. E′ eliminations are not stereospecific processes: Matassa, V. G.; Jenkins, P. R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, *29*, 321−343. See also: Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2749−2763.

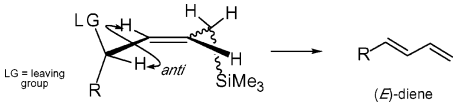
(61) Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, *5*, 4231−4234.

(62) Zechel, D. L.; Foucher, D. A.; Pudelski, J. K.; Yap, G. P. A.; Rheingold, A. L.; Manners, I. *J. Chem. Soc., Dalton Trans.* **1995**, 1893−1899.

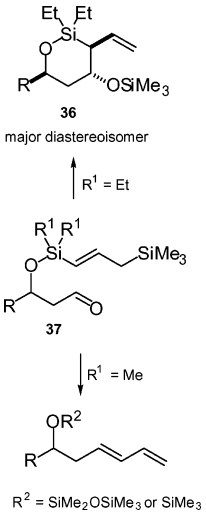
SCHEME 12. Proposed Mechanism for the Formation of Diene 30



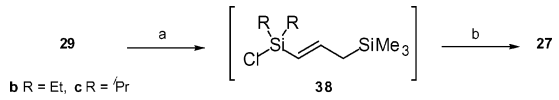
SCHEME 13. Reactive Conformation Leading Selectively to (*E*)-Diene Products[60]



SCHEME 14. Diethylsilyl Ether Tether Suppresses Diene Formation



SCHEME 15. In Situ Formation of Silyl Chloride 38 Allowed a More Efficient Tethering to Mannoside 15[a]



[a] Reagents and conditions: (a) AcCl, CH_2Cl_2, rt, 8 h (R = Et), 24 h (R = ^{i}Pr), then (b) **15**, imidazole, DMAP, rt, 24 h (R = Et), 48 h (R = ^{i}Pr), **27b** 80%, **27c** 72%.

cycles **42b** and **43b** both proved to be rather labile, and on standing gave what were presumed to be ring-opened hydrolysis products (silanols, siloxanes, etc.). The presence of the vinyl substituent on the concave face in **43b** rendered this stereoisomer particularly susceptible to ring-opening, presumably being driven by a greater release in steric compression. The structures of **42b** and **43b** were fully elucidated by extensive 2D-NMR experiments, and NOESY experiments allowed the assignment of relative stereochemistry. Oxidative cleavage of the silicon tether in **42b** and **43b**[63] proceeded uneventfully to provide allylic alcohols **44** and **45**, respectively. The structures were assigned based on the well-precedented assumption that this oxidation proceeds with retention of configuration (Scheme 16).[64,65]

Although moving to a diethylsilyl ether tether had gratifyingly provided the allylation products **42b** and **43b**, dienes were still the major products. Furthermore, owing to the increased reaction time required to consume the starting material, Lewis acid-mediated cleavage of the silyl ether became a competing reaction for the first time, as evidenced by the isolation of TMS ether **41**. Since bulkier ligands at the silyl ether would hopefully suppress this undesirable pathway, we prepared methyl mannoside **27c** containing our allylsilane tethered at C(2) through a diisopropylsilyl ether tether (Scheme 15).

C-Glycosylation of **27c** under our standard conditions once more provided a range of compounds but unfortunately failed to improve significantly the amount of *β*-allyl-*C*-mannosyl products that were isolated. However, in line with our predictions, and despite a further increase in reaction time, using larger ^{i}Pr ligands on the silyl ether tether did efficiently suppress the Lewis acid-mediated cleavage of the silyl ether, and TMS ether **41** was now isolated in only trace quantities. A diene compound, this time acyclic **40**, was the major product. Presumably, moving from ethyl to isopropyl ligands at the silyl ether slows the rate of the later steps in the cascade process required to provide tetrahydrofuran **30** such that once again these intermediates are intercepted and taken along alternative pathways.[66]

Despite the low chemical yields of allyl-*C*-mannosyl product, the stereoselectivity at C(1) demonstrated that our strategy had successfully provided only *β*-*C*-mannosyls. The low diastereoselectivity at the adjacent second stereogenic center, however, implies that there is very little difference in energy between the two transition states in which the allylsilane adopts an exo or endo orientation (Figure 3).

In an effort to increase the amount of *β*-allyl-*C*-mannosyl products, we chose to replace the methyl mannoside with a more reactive donor. Since glycosyl sulfoxides have been used successfully in other examples of intramolecular aglycon delivery,[17,43] we elected to investigate this type of reactive donor, hoping that activation at lower temperature might not only allow the

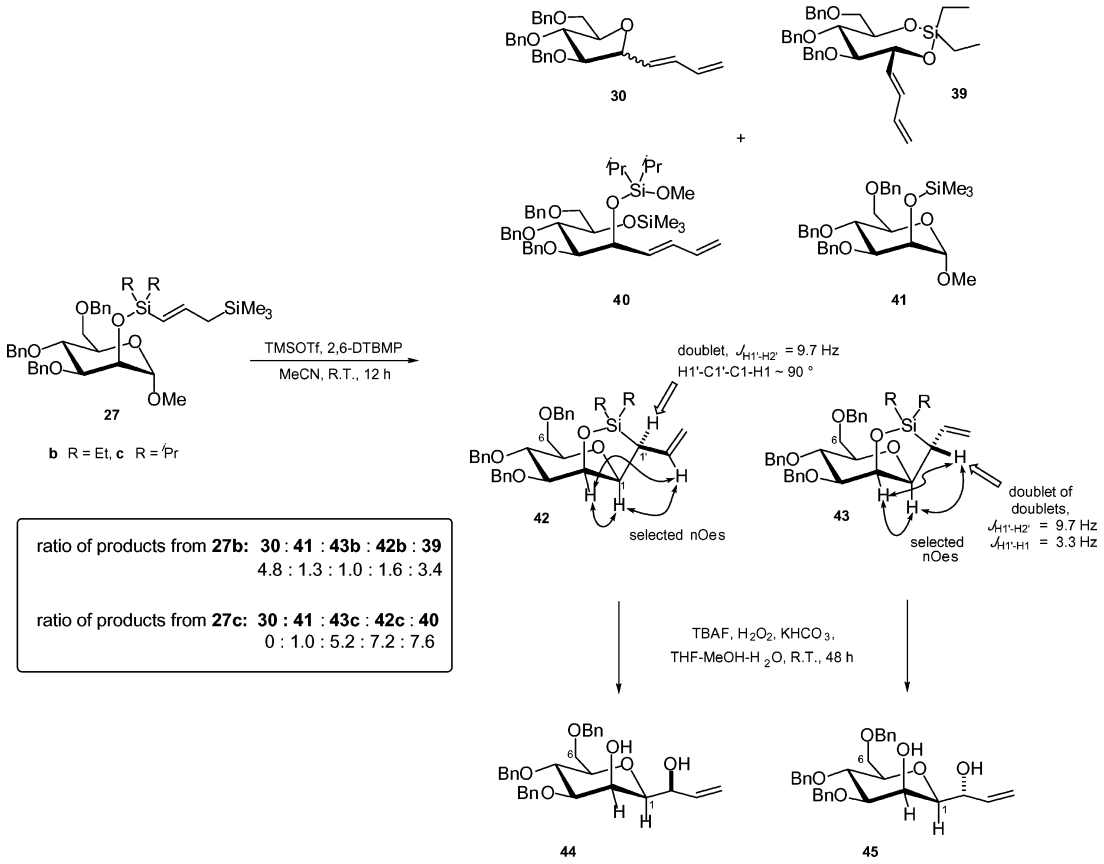
(63) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487−6498.

(64) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983−990.

(65) For a detailed review on this reaction: Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1−64.

(66) This type of diene (**40**) may actually be an intermediate in the formation of tetrahydrofuran **30** when a dimethylsilyl ether tether is employed.

SCHEME 16. Using a Silyl Ether Tether with Bulkier Ligands Provided the Desired *β*-Allyl-*C*-mannosyl Products which Underwent Oxidative Tether Cleavage to Generate the Desired Diols



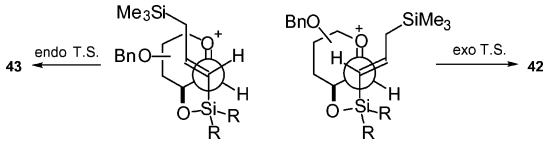
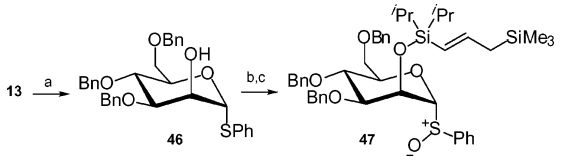


FIGURE 3. There is relatively little discrimination between endo and exo T.S.'s.

SCHEME 17. Preparation of Sulfoxide Donor 47[a]



[a] Reagents and conditions: (a) PhSH, $HgBr_2$, MeCN, 4 and 5 Å MS, rt, 24 h; then NaOMe, MeOH, rt, 6 h, 71%; (b) **38c**, **46**, imidazole, DMAP, CH_2Cl_2, rt, 36 h, 76%; (c) *m*-CPBA, CH_2Cl_2, −78 °C, 88%.

isolation of the desired allylation products in increased yields but potentially also increase the diastereoselectivity of the reaction. The required mannosyl sulfoxide **47** (obtained as one diastereoisomer) containing our allylsilane tethered through a diisopropylsilyl ether tether was prepared uneventfully as outlined in Scheme 17. Of only note was the chemoselective oxidation of the sulfide in the presence of the allylsilane.[67] Activation of sulfoxide **47** using standard conditions (Tf_2O, 2,6-DTBMP)[67] led to rapid consumption of starting material at low temperature. Unfortunately, however, this change in reaction conditions failed to improve the yield of the desired *β*-allyl-*C*-mannosyl products, which were still isolated in low yield. Direct oxidation of the crude reaction mixture provided diols **44** and **45** in low yield (<20% over the two steps). Thus, the change in donor group and *C*-glycosylation conditions had failed to provide preparatively useful yields of the *β*-allyl-*C*-mannosyls.

It is constructive to compare the intramolecular allylation of aldehyde **37 (**Scheme 14) with the same reaction involving the mannoside donors described in this paper. In the former case, we were able to suppress diene products and readily isolate the oxasilacyclic six-membered ring products **36** simply by moving from a dimethyl- to a bulkier diethylsilyl ether tether. Although making the same change in the sugar system gratifyingly allowed the isolation of two *β*-allyl-*C*-mannosyl products, dienes were still the major products. Moving to an even larger diisopropylsilyl ether tether failed to significantly improve matters, as did changing from a methyl mannoside donor to a more reactive sulfoxide. We believe that this difference in reactivity between the two systems is primarily a consequence of the reduced size of the cyclic T.S. In the mannoside system, the result of reducing the cyclic T.S. by one atom is to provide a more strained cationic intermediate product. This serves to greatly increase the Lewis acidity of the silyl ether such that

(67) Kahne, D.; Walker, S.; Cheng, Y.;. van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.

exchanging the ligands from methyl to larger substituents now fails to suppress, to any appreciable extent, reaction pathways that result from collapse of the carbocation by preferential attack on the silyl ether tether.

The pioneering work of Stork has demonstrated that using a temporary silicon connection in an intramolecular aglycon delivery strategy can provide an excellent route into 1,2-syn-*O*-glycosides, including such difficult glycosidic linkages as β-mannosides.[17] Although this strategy has been successfully extended to radical chemistry,[20] its application to the intramolecular delivery of *C*-nucleophiles has received far less attention,[19] and currently remains a more challenging problem, at least in the case of *C*-mannosyl synthesis. An efficient solution to the synthesis of β-allyl-*C*-mannosyls through intramolecular aglycon delivery therefore remains elusive. The work described in this paper has highlighted potential problems, identified some solutions, and perhaps hints that a successful application of this methodology to β-allyl-*C*-mannosyl synthesis may well remain elusive. Our findings, however, should prove valuable for future work in this area and do suggest alternative directions. We have demonstrated that simply tethering an allylsilane to the C(2)OH position of a mannosyl is not sufficient to ensure an intramolecular *C*-mannosylation; the location of the silyl connection in the tethered nucleophile is crucial. Indeed, our first generation system resulted in products derived exclusively from intermolecular allylation pathways. While our second-generation system solved this problem and ensured intramolecular allyl transfer, the presence of the silyl connection led to a range of diene products resulting from preferential collapse of the silyl tether. Thus, the tether, while ensuring nucleophile delivery to the β-face, at the same time has become the source of our chemoselectivity problems.

Since changing from a methyl mannoside (**27**) to a sulfoxide donor (**47**) failed to improve the yield of β-allyl-*C*-mannosyl products, even with a diisopropylsilyl ether connection, we suggest that investigating other mannosyl donors will not be productive and instead, propose that changing the *C*-nucleophile will be a more profitable way forward.[68] We have recently had great success in cyclizing propargylsilanes tethered to β-hydroxy aldehydes.[69] The silyl tether in these systems seems far less prone to cleavage, most likely owing to its relative inability to stabilize β-positive charge as efficiently as the propargylic silicon. Future work will therefore be directed to using this type of nucleophile in intramolecular aglycon delivery.

Experimental Section

Methyl 2-*O*-Allyl(dimethyl)silanyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (16). Allyldimethylchlorosilane (37 μL, 0.25 mmol) was added to a solution of alcohol **15** (100 mg, 0.21 mmol) and imidazole (29 mg, 0.42 mmol) in DMF (0.5 mL) and the mixture stirred for 24 h at rt. The reaction mixture was then diluted with Et_2O (2 mL) and quenched with $NaHCO_3$ solution (2 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 2 mL). The combined organic extracts were washed with brine (3 mL) and then dried ($MgSO_4$). Concentration under reduced pressure followed by purification by flash column chromatography (10% EtOAc in hexane) afforded silyl ether **16** as a pale yellow oil (94 mg, 80%): $[\alpha]^{25}_D$ +0.025 (*c* 0.4, $CHCl_3$); R_f = 0.25 (10% Et_2O in hexane); ν_{max} (film)/cm^{-1} 2953s, 2909s, 1630w; δ_H (500 MHz) 0.11 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3), 1.63 (br d, *J* 7.4, 2H, SiCH_2CH=CH$_2$), 3.37 (s, 3H, OCH_3), 3.73−3.78 (stack, 3H, 5-H, 2 × 6-H), 3.80 (dd, *J* 9.2, 2.8, 1H, 3-H), 3.89 (apparent t, *J* 9.0, 1H, 4-H), 4.07 (apparent t, *J* 2.5, 1H, 2-H), 4.52 (A of AB, *J* 11.0, 1H, 4-COCH_AH$_B$Ph), 4.56 (A of AB, *J* 12.5, 1H, 6-COCH_CH$_D$Ph), 4.63 (d, *J* 2.0, 1H, 1-H), 4.67 (A of AB, *J* 11.0, 1H, 3-COCH_EH$_F$Ph), 4.68 (B of AB, *J* 12.5, 1H, 6-COCH$_C$CH_D-Ph), 4.72 (B of AB, *J* 11.0, 1H, 3-COCH$_E$CH_FPh), 4.83−4.89 (stack, 3H, 4-COCH$_A$CH_BPh, SiCH$_2$CH=CCH_2), 5.77−5.86 (m, 1H, SiCH$_2$CH=CH$_2$), 7.16−7.19 (m, 2H, PhH), 7.23−7.28 (stack, 13H, PhH); δ_C(125 MHz) −1.8 (CH$_3$, 1 × SiCH_3), −1.7 (CH$_3$, 1 × SiCH_3), 25.1 (CH$_2$, CH_2CH=CH$_2$), 54.7 (CH$_3$, OCH_3), 69.4 (CH$_2$, 6-C), 70.1 (CH, 2-C), 72.1 (CH, 5-C), 72.7 (CH$_2$, 3-COCH_2Ph), 73.2 (CH$_2$, 6-COCH_2Ph), 74.7 (CH, 4-C), 74.8 (CH$_2$, 4-COCH_2Ph), 80.1 (CH, 3-C), 101.6 (CH, 1-C), 113.5 (CH$_2$, SiCH$_2$CH=CH_2), [127.36 (CH, Ph), 127.44 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 127.7 (CH, Ph), 127.9 (CH, Ph), 128.2 (CH, Ph) some overlap], 134.3 (CH, CH$_2$CH=CH$_2$), [138.5 (quat C, *ipso* Ph), 138.6 (quat C, *ipso* Ph) some overlap]; *m*/*z* (TOF MS ES+) 585.3 [(M + Na)$^+$, 100]; HRMS calcd for $C_{33}H_{42}O_6SiNa$ [M + Na]$^+$ 585.2648, found 585.2654; HPLC t_R = 3.4 min.

1-(3′,4′,6′-Tri-*O*-benzyl-α-D-mannopyranosyl)prop-2-ene (18). Method A (from Silyl Ether 17). TMSOTf (22 μL, 0.12 mmol) was added dropwise over 1 min to a stirred solution of silyl ether **17** (72 mg, 0.12 mmol) and allyltrimethylsilane (47 μL, 0.36 mmol) in MeCN (0.6 mL). The reaction mixture was stirred for 2.5 h at rt, diluted with EtOAc (2 mL), and poured into $NaHCO_3$ solution (3 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The residue was diluted with THF (1 mL), and TBAF (180 μL, 1 M solution in THF, 5% H_2O) was added dropwise at rt. The solution was stirred for 20 h, poured into H_2O (2 mL), and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to afford alcohol **18** as a colorless oil (52 mg, 91%): $[\alpha]^{21}_D$ +24.1 (*c* 1.0, $CHCl_3$); R_f = 0.30 (25% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3441w, 1639w, 1585w, 1088vs; δ_H (400 MHz) 2.27−2.43 (m, 2H, CH_2CH=CH$_2$), 2.45 (d, *J* 4.6, 1H, OH), 3.65−3.83 (stack, 5H, 3′-H, 4′-H, 5′-H, 2 × 6′-H), 3.83−3.85 (m, 1H, 2′-H), 3.92−3.99 (m, 1H, 1′-H), 4.53 (A of AB, *J* 12.2, 1H, OCH_AH$_B$Ph), 4.55 (A of AB, *J* 11.2, 1H, OCH_CH$_D$Ph), 4.59 (B of AB, *J* 12.2, 1H, OCH$_A$CH_BPh), 4.60 (A of AB, *J* 11.5, 1H, OCH_EH$_F$Ph), 4.65 (B of AB, *J* 11.5, 1H, OCH$_E$CH_FPh), 4.75 (B of AB, *J* 11.2, 1H, OCH$_C$CH_DPh), 5.03−5.10 (stack, 2H, CH$_2$CH=CCH_2), 5.75−5.87 (m, 1H, CH$_2$-CH=CH$_2$), 7.21−7.24 (m, 2H, PhH), 7.27−7.34 (stack, 13H, PhH); δ_C (100 MHz) 34.2 (CH$_2$, CH_2CH=CH$_2$), 68.3 (CH, 2′-C), 69.0 (CH$_2$, 6′-C), 72.1 (CH$_2$, CH_2Ph), 72.9 (CH), 73.4 (CH$_2$, CH_2Ph), 74.1 (CH), 74.2 (CH$_2$, CH_2Ph), 74.8 (CH, 1′-C), 79.0 (CH, 5′-C), 117.3 (CH$_2$, CH$_2$CH=CH_2), [127.5 (CH, Ph), 127.8 (CH, Ph), 128.0 (CH, Ph), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 128.6 (CH, Ph) some overlap], 134.1 (CH, CH$_2$-CH=CH$_2$), 137.2 (quat C, *ipso* Ph), 138.1 (quat C, *ipso* Ph), 138.3 (quat C, *ipso* Ph); *m*/*z* (TOF MS ES+) 497.1 ([M + Na]$^+$, 100); HPLC t_R = 8.9 min. Anal. Calcd for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22. Found: C, 75.86; H, 7.31.

Method B (from Silyl Ether 16). TMSOTf (32 μL, 0.18 mmol) was added dropwise over 1 min to a stirred solution of allylsilyl ether **16** (100 mg, 0.18 mmol) and 2,6-DTBMP (45 mg, 0.22 mmol) in MeCN (0.4 mL). The reaction mixture was stirred for 14 h, diluted with EtOAc (10 mL), and poured into

(68) Martin has recently shown that arylsilanes tethered through C(2)OH of 4-pentenyl glucopyranosides can be successfully delivered intramolecularly to provide exclusively the 1,2-cis-α-aryl-*C*-glucosyls: see ref 21e.

(69) Cox, L. R.; Beignet, J.; Ramalho, R. P. S. Unpublished results.

$NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with HCl (1 M, 10 mL), water (10 mL), and brine (10 mL) and then dried ($MgSO_4$). Concentration under reduced pressure provided a yellow oil which was purified by flash column chromatography (10% EtOAc in hexane) to afford alcohol **18** as a colorless oil (78 mg, 92%) that was identical in all respects to the material produced from silyl ether **17**.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (21). A mixture of acetates **19** and **20** (500 mg, 1.0 mmol) and NMO (175 mg, 1.5 mmol) was dissolved in MeCN (2.0 mL) containing activated powdered 4 Å molecular sieves (500 mg). TPAP (17.5 mg, 0.05 mmol) was then added and the mixture stirred at rt. After 5 min, TLC indicated consumption of both starting materials and the formation of one new compound. The solvent was removed under reduced pressure, and the black residue was filtered through a large pad of silica gel, washing with EtOAc (150 mL) to give a pale yellow solid which was submitted to purification by flash column chromatography (20% EtOAc in hexane) to afford lactone **21** as a white powder (441 mg, 90%): $[\alpha]^{24}_D$ +0.23 (*c* 2.3, $CHCl_3$); R_f = 0.42 (30% EtOAc in hexane); ν_{max}(Nujol)/cm^{-1} 2925s, 2854s, 1780s, 1750s, 1496w; δ_H (500 MHz) 2.22 (s, 3H, OC(O)CH_3), 3.64−3.69 (stack, 2H, 2 × 6-H), 3.89 (dd, *J* 6.9, 1.4, 1H, 4-H), 4.05 (dd, *J* 2.9, 1.4, 1H, 3-H), 4.31 (A of AB, *J* 11.4, 1H, 4-COCH_AH$_B$Ph), 4.38−4.41 (stack including [4.40 (B of AB, *J* 11.4, 1H, 4-COCH$_A$$H_B$Ph)], 2H, 4-COCH$_A$$H_B$Ph, 5-H), 4.51 (A of AB, *J* 11.9, 1H, 6-COCH_CH$_D$Ph), 4.55 (B of AB, *J* 11.9, 1H, 6-COCH$_C$$H_D$-Ph), 4.59 (A of AB, *J* 12.6, 1H, 3-COCH_EH$_F$Ph), 4.69 (B of AB, *J* 12.6, 1H, 3-COCH$_E$$H_F$Ph), 5.62 (d, *J* 2.9, 1H, 2-H), 7.13−7.19 (m, 2H, Ph*H*), 7.28−7.36 (stack, 13H, Ph*H*); δ_C (125 MHz) 20.7 (CH_3, OC(O)*C*H$_3$), 68.8 (CH_2, 6-C), 69.7 (CH, 2-C), 71.9 (CH_2, 4-CO*C*H$_2$Ph), 72.6 (CH_2, 3-CO*C*H$_2$Ph), 73.5 (CH_2, 6-CO*C*H$_2$Ph), 75.1 (CH, 4-C), 76.0 (CH, 3-C), 79.0 (CH, 5-C), [127.8 (CH, Ph), 128.0 (CH, Ph), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph) some overlap], 136.7 (quat C, *ipso* Ph), 137.2 (quat C, *ipso* Ph), 137.6 (quat C, *ipso* Ph), 166.4 (quat C, 1-C), 169.6 (quat C, O*C*(O)-CH$_3$); *m*/*z* (TOF MS ES+) 529.2 ([M + K]$^+$, 23), 513.2 (100, [M + Na]$^+$). Anal. Calcd $C_{29}H_{30}O_7$: C, 71.00; H, 6.16. Found: C, 70.94; H, 6.20.

1-(2′-*O*-Acetyl-3′,4′,6′-tri-*O*-benzyl-1′-hydroxy-α-D-mannopyranosyl)prop-2-ene (22). A solution of (allyl)MgBr (0.60 mL, 0.47 mmol, 0.78 M in Et_2O) was added dropwise over 1 h to a stirred solution of lactone **21** (192 mg, 0.39 mmol) in THF (4.0 mL) at −78 °C. The mixture was stirred for a further 30 min at −78 °C, quenched with aqueous NH_4Cl solution (15 mL), and allowed to warm to rt. The resulting mixture was extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure to leave a yellow syrup, which was purified by flash column chromatography (20% EtOAc in hexane) to give lactol **22** as a colorless oil (146 mg, 70%): $[\alpha]^{25}_D$ +0.34 (*c* 1.4, $CHCl_3$); R_f = 0.46 (30% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3414br, 1747s, 1642w, 1606w, 1586w; δ_H (500 MHz) 2.15 (s, 3H, OC(O)CH_3), 2.27 (dd, *J* 16.3, 10.2, 1H, CH_aH$_b$CH=CH$_2$), 2.58 (dd, *J* 16.3, 10.2, 1H, CH$_a$$H_b$CH=CH$_2$), 2.71 (s, 1H, OH), 3.68−3.76 (stack including [3.70 (dd, *J* 11.2, 3.5, 1H, 1 × 6′-H), 3.74 (apparent t, *J* 9.6, 1H, 4′-H)], 3H, 2 × 6′-H, 4′-H), 3.97 (ddd, *J* 9.6, 5.6, 3.5, 1H, 5′-H), 4.10 (dd, *J* 9.6, 3.4, 1H, 3′-H), 4.49 (2 × A of AB, *J* 11.0, 2H, OCH_AH$_B$Ph, OCH_CH$_D$Ph), 4.54 (A of AB, *J* 12.5, 1H, OCH_EH$_F$Ph), 4.64 (B of AB, *J* 12.5, 1H, OCH$_E$$H_F$Ph), 4.72 (B of AB, *J* 11.0, 1H, OCH$_A$$H_B$Ph), 4.85 (B of AB, *J* 11.0, 1H, OCH$_C$$H_D$Ph), 5.19 (br d, *J* 17.4, 1H, CH$_2$CH=CH_{trans}H), 5.28 (br d, *J* 10.6, 1H, CH$_2$CH=CHH_{cis}), 5.41 (d, *J* 3.4, 1H, 2′-H), 5.81−5.91 (m, 1H, CH$_2$CH=CH$_2$), 7.14−7.19 (m, 2H, Ph*H*), 7.22−7.39 (stack, 13H, Ph*H*); δ_C (125 MHz) 21.1 (CH_3, OC-(O)*C*H$_3$), 42.4 (CH_2, *C*H$_2$CH=CH$_2$), 69.4 (CH_2, 6′-C), 70.3 (CH, 2′-C), 71.7 (CH_2, O*C*H$_2$Ph), 72.4 (CH, 5′-C), 73.4 (CH_2, O*C*H$_2$-Ph), 74.3 (CH, 4′-C), 75.0 (CH_2, O*C*H$_2$Ph), 78.9 (CH, 3′-C), 96.6 (quat C, 1′-C), 121.6 (CH_2, CH$_2$*C*H=*C*H$_2$), [127.6 (CH, Ph), 127.70 (CH, Ph), 127.72 (CH, Ph), 127.9 (CH, Ph), 128.2 (CH, Ph), 128.30 (CH, Ph), 128.34 (CH, Ph) some overlap], 131.2 (CH, CH$_2$*C*H=CH$_2$), 138.0 (quat C, *ipso* Ph), 138.5 (2 × quat C, 2 × *ipso* Ph), 170.3 (quat C, O*C*(O)CH$_3$); *m*/*z* (TOF MS ES+) 555.2 ([M + Na]$^+$, 100); HRMS calcd for $C_{32}H_{36}O_7Na$ [M + Na]$^+$ 555.2359, found 555.2358. Anal. Calcd for $C_{32}H_{36}O_7$: C, 72.16; H, 6.81. Found: C, 72.05; H, 6.99.

1-(2′-*O*-Acetyl-3′,4′,6′-tri-*O*-benzyl-β-D-mannopyranosyl)-prop-2-ene (23). TMSOTf (92 μL, 0.51 mmol) was added dropwise over 1 min to a stirred solution of lactol **22** (230 mg, 0.44 mmol) and Et_3SiH (101 μL, 0.64 mmol) in MeCN (4.4 mL) at rt. After 5 min, the reaction mixture was quenched with aqueous $NaHCO_3$ solution (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with water (3 mL) and brine (3 mL) and dried (Na_2SO_4). Removal of the volatiles and purification of the residue by flash column chromatography (10% EtOAc in hexane) afforded acetate **23** as a colorless oil (107 mg, 47%): $[\alpha]^{24}_D$ +0.32 (*c* 2.3, $CHCl_3$); R_f = 0.21 (10% EtOAc in hexane); ν_{max} (film)/cm^{-1} 2925s, 1740s, 1642w, 1605w, 1586w; δ_H (500 MHz) 2.18 (s, 3H, OC(O)CH_3), 2.21−2.29 (m, 1H, CH_aH$_b$CH=CH$_2$), 2.40−2.48 (m, 1H, CH$_a$$H_b$-CH=CH$_2$), 3.44−3.53 (stack, 2H, 1′-H, 5′-H), 3.65 (dd, *J* 9.4, 3.8, 1H, 3′-H), 3.69−3.80 (stack, 3H, 4′-H, 2 × 6′-H), 4.49 (A of AB, *J* 11.3, 1H, 3′-COCH_AH$_B$Ph), 4.51 (A of AB, *J* 10.7, 1H, 4′-COCH_CH$_D$Ph), 4.58 (A of AB, *J* 12.4, 1H, 6′-COCH_EH$_F$Ph), 4.67 (B of AB, *J* 12.4, 1H, 6′-COCH$_E$$H_F$Ph), 4.78 (B of AB, *J* 11.3, 1H, 3′-COCH$_A$$H_B$Ph), 4.87 (B of AB, *J* 10.7, 1H, 4′-COCH$_C$$H_D$Ph), 5.08−5.13 (stack, 2H, CH$_2$CH=CH_2), 5.50 (d, *J* 3.8, 1H, 2′-H), 5.77−5.87 (m, 1H, CH$_2$CH=CH$_2$), 7.13−7.20 (m, 2H, Ph*H*), 7.22−7.40 (stack, 13H, Ph*H*); δ_C(125 MHz) 21.0 (CH_3, OC(O)*C*H$_3$), 35.6 (CH_2, *C*H$_2$CH=CH$_2$), 68.4 (CH, 2′-C), 69.4 (CH_2, 6′-C), 71.6 (CH_2, 3′-CO*C*H$_2$Ph), 73.5 (CH_2, 6′-CO*C*H$_2$-Ph), 74.6 (CH, 4′-C), 75.2 (CH_2, 4′-CO*C*H$_2$Ph), 76.8 (CH, 1′-C), 79.5 (CH, 5′-C), 82.0 (CH, 3′-C), 117.9 (CH_2, CH$_2$CH=*C*H$_2$), [127.56 (CH, Ph), 127.65 (CH, Ph), 127.7 (CH, Ph), 127.88 (CH, Ph), 127.94 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph) some overlap], 133.6 (CH, CH$_2$*C*H=CH$_2$), 137.9 (quat C, 3′-COCH$_2$*ipso* Ph), 138.35 (quat C, 4′-COCH$_2$*ipso* Ph), 138.38 (quat C, 6′-COCH$_2$*ipso* Ph), 170.7 (quat C, O*C*(O)CH$_3$); *m*/*z* (TOF MS ES+) 539.3 ([M + Na]$^+$, 100). See the Supporting Information for more details on this reaction and for characterization of byproducts.

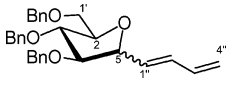
1-(3′,4′,6′-Tri-*O*-benzyl-β-D-mannopyranosyl)prop-2-ene (24). MeONa (7 mg, 0.12 mmol) was added to a solution of acetate **23** (50 mg, 0.10 mmol) in MeOH (1 mL) at rt. The reaction mixture was stirred overnight and then neutralized with Amberlite IR-120(plus) (prewashed with MeOH). The solution was filtered, washing with CH_2Cl_2 (10 mL), washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in hexane) to give alcohol **24** as a colorless oil (41 mg, 85%): $[\alpha]^{24}_D$ −8.0 (*c* 1.0, $CHCl_3$); R_f = 0.26 (20% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3456br, 2923s, 2868s, 1642w; δ_H(400 MHz) 2.36 (s, 1H, O*H*), 2.39−2.50 (m, 1H, CH_aH$_b$CH=CH$_2$), 2.51−2.60 (m, 1H, CH$_a$$H_b$-CH=CH$_2$), 3.35 (apparent t, *J* 7.5, 1H, 1′-H), 3.41 (ddd, *J* 9.8, 4.9, 2.2, 1H, 5′-H), 3.58 (dd, *J* 9.8, 3.4, 1H, 3′-H), 3.67 (dd, *J* 11.3, 4.9, 1H, 1 × 6′-H), 3.74 (dd, *J* 11.3, 2.2, 1H, 1 × 6′-H), 3.76 (apparent t (br), *J* 9.8, 1H, 4′-H), 3.94 (d, *J* 3.4, 1H, 2′-H), 4.52 (A of AB, *J* 10.9, 1H, OCH_AH$_B$Ph), 4.56 (A of AB, *J* 12.3, 1H, OCH_CH$_D$Ph), 4.61 (B of AB, *J* 12.3, 1H, CH$_C$$H_D$Ph), 4.66 (A of AB, *J* 11.4, 1H, OCH_EH$_F$Ph), 4.74 (B of AB, *J* 11.4, 1H, OCH$_E$$H_F$Ph), 4.85 (B of AB, *J* 10.9, 1H, OCH$_A$$H_B$Ph), 5.08 (dd, *J* 10.1, 1.0, 1H, CH$_2$CH=CH_{cis}H), 5.16 (dd, *J* 17.3, 2.1, 1H, CH$_2$CH=CHH_{trans}), 5.85 (ddt, *J* 17.3, 10.1, 7.7, 1H, CH$_2$CH=CH$_2$), 7.11−7.19 (m, 2H, Ph*H*), 7.21−7.41 (stack, 13H, Ph*H*); δ_C (100 MHz) 35.3 (CH_2, *C*H$_2$CH=CH$_2$), 67.5 (CH, 2′-C), 69.3 (CH_2, 6′-C), 71.6 (CH_2, O*C*H$_2$Ph), 73.5 (CH_2, O*C*H$_2$-Ph), 74.7 (CH, 4′-C), 75.2 (CH_2, O*C*H$_2$Ph), 77.6 (CH, 1′-C), 79.3 (CH, 5′-C), 83.5 (CH, 3′-C), 117.5 (CH_2, CH$_2$CH=*C*H$_2$), [127.5 (CH, Ph), 127.7 (CH, Ph), 127.86 (CH, Ph), 127.88 (CH, Ph),

127.9 (CH, Ph), 128.0 (CH, Ph), 128.32 (CH, Ph), 128.34 (CH, Ph), 128.5 (CH, Ph) some overlap], 134.4 (CH, $CH_2CH{=}CH_2$), 137.8 (quat C, *ipso* Ph), 138.2 (quat C, *ipso* Ph), 138.3 (quat C, *ipso* Ph); *m*/*z* (TOF MS ES+) 497.4 ($[M + Na]^+$, 100); HRMS calcd for $C_{30}H_{34}O_5Na$ $[M + Na]^+$ 497.2304, found 497.2312; HPLC t_R = 5.9 min. Anal. Calcd for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22. Found: C, 75.99; H, 7.02.

Cross-Over Experiment: Reaction of Methyl Mannosides 25 and 16 with TMSOTf. TMSOTf (36 μL, 0.20 mmol) was added to a solution of methyl mannoside **25** (50 mg, 0.10 mmol), methyl mannoside **16** (56 mg, 0.10 mmol), and 2,6-DTBMP (45 mg, 0.22 mmol) in MeCN (0.8 mL) at rt. The reaction mixture was stirred for 14 h, diluted with EtOAc (3 mL), and poured into $NaHCO_3$ solution (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with HCl (1 M, 3 mL), water (3 mL), and brine (3 mL) and then dried ($MgSO_4$). Concentration under reduced pressure provided a yellow oil which was analyzed by mass spectrometry and HPLC.

(1′*E*)-Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-[diethyl(3′-trimethylsilanyl)prop-1′-enyl]silanyl-α-D-mannopyranoside (27b). AcCl (130 μL, 1.83 mmol) was added dropwise to a solution of aminosilane **29b** (352 mg, 1.83 mmol) in CH_2Cl_2 (1.8 mL) at 0 °C, and the reaction was stirred for 8 h at rt. This solution was transferred via cannula to a mixture of alcohol **15** (850 mg, 1.83 mmol), imidazole (245 mg, 3.66 mmol), and DMAP (11 mg, 0.09 mmol), and the resulting suspension was stirred for 1 d at rt. The reaction mixture was then poured over $NaHCO_3$ solution (2 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave a yellow residue which was purified by flash column chromatography (6% EtOAc in hexane) to afford silyl ether **27b** as a colorless oil (971 mg, 80%): $[\alpha]^{22}_D$ +38.4 (*c* 2.0, $CHCl_3$); R_f = 0.28 (6% EtOAc in hexane); ν_{max} (film)/cm^{-1} 2953s, 2910s, 1601s; δ_H(300 MHz) −0.03 (s, 9H, Si(CH_3)$_3$), 0.55−0.71 (stack, 4H, OSi(CH_2CH$_3$)$_2$), 0.80−1.00 (stack including [0.94 (t, *J* 7.9, 3H, 1 × OSi(CH$_2$CH_3)$_2$)], 6H, OSi(CH$_2$CH_3)$_2$), 1.55−1.67 (m, 2H, CH=CHCH_2), 3.33 (s, 3H, OCH_3), 3.68−3.80 (stack including [3.77 (dd, *J* 9.1, 2.5, 1H, 3-H)], 4H, 3-H, 5-H, 2 × 6-H), 3.91 (app t, *J* 9.1, 1H, 4-H), 4.10 (app t, *J* 2.5, 1H, 2-H), 4.49 (A of AB, *J* 10.7, 1H, OCH_AH$_B$Ph), 4.55 (A of AB, *J* 12.5, 1H, OCH_CH$_D$Ph), 4.58−4.68 (stack, 3H, OCH_2Ph, 1-H), 4.70 (B of AB, *J* 12.5, 1H, OCH$_C$$H_D$Ph), 4.83 (B of AB, *J* 10.7, 1H, OCH$_A$$H_B$Ph), 5.37 (d, *J* 18.5, 1H, C*H*=CHCH$_2$), 6.18 (dt, *J* 18.5, 8.2, 1H, CH=C*H*CH$_2$), 7.11−7.39 (stack, 15H, Ph*H*); δ_C(75 MHz) −2.0 (CH$_3$, Si(*C*H$_3$)$_3$), 5.64 (CH$_2$, 1 × OSi(*C*H$_2$CH$_3$)$_2$), 5.67 (CH$_2$, 1 × OSi(*C*H$_2$CH$_3$)$_2$), 6.74 (CH$_3$, 1 × OSi(CH$_2$*C*H$_3$)$_2$), 6.78 (CH$_3$, 1 × OSi(CH$_2$*C*H$_3$)$_2$), 28.7 (CH$_2$, CH=CH*C*H$_2$), 54.6 (CH$_3$, O*C*H$_3$), 69.3 (CH), 69.4 (CH$_2$), 71.9 (CH$_2$), 72.0 (CH), 73.1 (CH$_2$), 74.6 (CH), 74.8 (CH$_2$), 80.2 (CH), 101.6 (CH, 1-*C*), 122.9 (CH, =*C*H), [127.4 (CH, Ph), 127.5 (CH, Ph), 127.9 (CH, Ph), 128.10 (CH, Ph), 128.14 (CH, Ph), 128.17 (CH, Ph) some overlap], 138.5 (quat C, *ipso*Ph), 138.6 (quat C, *ipso*Ph), 138.7 (quat C, *ipso*Ph), 147.4 (CH, =*C*H); *m*/*z* (TOF ES+) 685.4 $[(M + Na)^+$, 100]. Anal. Calcd for $C_{38}H_{54}O_6Si_2$: C, 68.84; H, 8.21. Found: C, 68.80; H, 8.31.

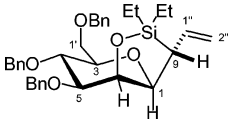
(1″*E*,2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-2-benzyloxymethyl-5-buta-1″,3″-dienyltetrahydrofuran and (1″*E*,2*R*,3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-benzyloxymethyl-5-buta-1″,3″-dienyltetrahydrofuran (30) (Major Stereoisomer Not Determined).



TMSOTf (29 μL, 0.16 mmol) was added dropwise to a solution of allylsilane **27a** (100 mg, 0.16 mmol) and 2,6-DTBMP (39 mg, 0.19 mmol) in MeCN (1.6 mL) at rt. The reaction mixture was stirred for 8 h, diluted with CH_2Cl_2 (3 mL), and poured into $NaHCO_3$ solution (2 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide diene **30** as a yellow oil (152 mg, quantitative yield, remaining mass accounting for 2,6-DTBMP and silicon residues). The crude products from two reactions (2 × 100 mg of allylsilane **27a**) were combined and purified by flash column chromatography (5% EtOAc in hexane) to afford diene **30** as a colorless oil (56 mg, 38%, inseparable mixture of anomers (2.2:1): HPLC t_R = 54.87 min; R_f = 0.25 (5% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3087m, 3063m, 3030m, 2864s, 1605m; δ_H (500 MHz) 3.49−3.62 (stack including [3.52 (d, *J* 4.5, 2H, 2 × *H*-1′$_{major}$)], 4H, 2 × 1′-*H*$_{major}$, 2 × 1′-*H*$_{minor}$), 3.83 (d, *J* 3.5, 1H, 4-*H*$_{minor}$), 3.87−3.92 (stack including [3.89 (app t, *J* 4.5, 1H, 4-*H*$_{major}$)], 2H, 4-*H*$_{major}$, 3-*H*$_{minor}$), 4.01−4.07 (stack including [4.04 (app t, *J* 3.8, 1H, 3-*H*$_{major}$)], 2H, 3-*H*$_{major}$, 2-*H*$_{minor}$), 4.16 (app q, *J* 4.5, 1H, 2-*H*$_{major}$), 4.37−4.54 (stack, 14H, 3 × C*H*$_2$Ph$_{major}$, 5-*H*$_{major}$, 3 × C*H*$_2$Ph$_{minor}$, 5-*H*$_{minor}$), 5.07 (d, *J* 9.3, 2H, 4″$_{cis}$-*H*$_{major}$, 4″$_{cis}$-*H*$_{minor}$), 5.17 (d, *J* 16.5, 2H, 4″$_{trans}$-*H*$_{major}$, 4″$_{trans}$-*H*$_{minor}$), 5.72 (dd, *J* 14.4, 7.3, 1H, 1″-*H*$_{major}$), 5.84 (dd, *J* 14.6, 7.9, 1H, 1″-*H*$_{minor}$), 6.18−6.37 (stack, 4H, 2″-*H*$_{major}$, 3″-*H*$_{major}$, 2″-*H*$_{minor}$, 3″-*H*$_{minor}$), 7.18−7.29 (stack, 30H, Ph*H*); δ_C (125 MHz) 70.3 (CH$_2$, 1′-*C*$_{major}$), 70.5 (CH$_2$, 1′-*C*$_{minor}$), 71.6 (CH$_2$, OC*H*$_2$Ph$_{minor}$), 71.8 (CH$_2$, OC*H*$_2$Ph$_{minor}$), 71.9 (CH$_2$, OC*H*$_2$-Ph$_{major}$), 72.1 (CH$_2$, OC*H*$_2$Ph$_{major}$), 73.3 (CH$_2$, OC*H*$_2$Ph$_{minor}$), 73.4 (CH$_2$, OC*H*$_2$Ph$_{major}$), 81.3 (CH, 2-*C*$_{major}$), 81.9 (CH, 5-*C*$_{minor}$), 82.3 (CH, 2-*C*$_{minor}$), 82.8 (CH, 5-*C*$_{major}$), 84.4 (CH, 3-*C*$_{minor}$), 84.5 (CH, 4-*C*$_{minor}$), 84.9 (CH, 3-*C*$_{major}$), 88.3 (CH, 4-*C*$_{major}$), 118.0 (CH$_2$, 4″-*C*$_{minor}$), 118.1 (CH$_2$, 4″-*C*$_{major}$), [127.4 (CH, Ph), 127.6 (CH, Ph), 127.7 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph) some overlap], 128.7 (CH, 1″-*C*$_{minor}$), 131.7 (CH, 1″-*C*$_{major}$), 133.1 (CH, =*C*H$_{major}$), 134.6 (CH, =*C*H$_{minor}$), 136.2 (CH, =*C*H$_{major}$), 136.4 (CH, =*C*H$_{minor}$), 137.77 (quat C, *ipso*Ph), 137.82 (quat C, *ipso*Ph), 137.88 (quat C, *ipso*Ph), 137.93 (quat C, *ipso*Ph), 138.2 (quat C, *ipso*Ph), 138.3 (quat C, *ipso*Ph); *m*/*z* (TOF ES+) 479.3 (100, $[M + Na]^+$); HRMS calcd for $C_{30}H_{32}O_4Na$ $[M + Na]^+$ 479.2198, found 479.2209.

Allylation of Mannoside 27b: Preparation of 30, 39, 42b, 43b, and 41. TMSOTf (89 μL, 0.49 mmol) was added dropwise to a solution of allylsilane **27b** (325 mg, 0.49 mmol) and TTBP (146 mg, 0.59 mmol) in MeCN (4.9 mL) at rt. The reaction mixture was stirred for 12 h, diluted with EtOAc (5 mL), and poured into $NaHCO_3$ solution (5 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil which was analyzed by preparative HPLC to afford a 4.8:1.3:1.0:1.6:3.4 ratio of **30**/**41**/**43b**/**42b**/**39**.

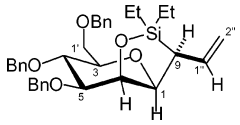
(1*R*,3*R*,4*R*,5*S*,6*S*,9*S*)-4,5-Dibenzyloxy-3-benzyloxymethyl-8,8-diethyl-2,7-dioxa-8-sila-9-vinylbicyclo[4.3.0]-nonane (43b):



HPLC t_R = 59.60 min; R_f = 0.24 (6% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3064m, 3031m, 1628w; δ_H (C_6D_6, 500 MHz) 0.58−0.74 (m, 2H, 1 × OSi(CH_2CH$_3$)$_2$), 0.88−1.11 (stack, 8H, 1 × OSi(CH_2CH$_3$)$_2$, OSi(CH$_2$CH_3)$_2$)), 2.00 (dd, *J* 9.7, 3.3, 1H, 9-H), 3.35 (d (+ unresolved fine coupling), *J* 9.6, 1H, 3-H), 3.45−3.51 (stack including [3.48 (dd, *J* 9.6, 2.6, 1H, 5-H), 2H, 5-H, 1-H), 3.69−3.74 (stack, 2H, 2 × 1′-H), 3.82 (d, *J* 2.6, 1H, 6-H), 4.10 (app t, *J* 9.6, 1H, 4-H), 4.35−4.42 (m, 2H, C(1′)OCH_2Ph), 4.52 (A of AB, *J* 12.1, 1H, C(5)OCH_AH$_B$Ph), 4.58−4.62 (m, 2H, C(4)OCH_2Ph), 4.69 (B of AB, *J* 12.1, 1H, C(5)OCH$_A$$H_B$Ph), 4.97−5.08 (m, 2H, 2 × 2″-H), 6.38 (dt, *J* 17.3, 9.7, 1H, 1″-H), 7.03−7.45 (stack, 15H, Ph*H*); δ_C (C_6D_6, 125 MHz) [5.9, 6.1, 6.9, 7.0 (CH$_2$ and CH$_3$, OSi(*C*H$_2$CH$_3$))], 38.4 (CH, 9-*C*), 70.0 (CH$_2$,

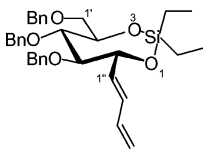
1′-*C*), 70.8 (CH_2, C(5)O*C*H_2Ph), 73.4 (CH_2, C(1′)O*C*H_2Ph), 74.7 (CH, 4-*C*), 75.2 (CH_2, C(4)O*C*H_2Ph), 76.9 (CH, 6-*C*), 79.2 (CH, 3-*C*), 80.5 (CH, 1-*C*), 83.0 (CH, 5-*C*), 112.8 (CH_2, 2″-*C*), [126.5 (CH, Ph), 126.8 (CH, Ph), 127.0 (CH, Ph), 127.5 (CH, Ph), 127.8 (CH, Ph), 128.0 (CH, Ph), 128.2 (CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph), 129.1 (CH, Ph) some overlap], 135.8 (CH, 1″-*C*), [139.5 (quat C, *ipso*Ph), 139.8 (quat C, *ipso*Ph) some overlap]; *m*/*z* (TOF ES+) 581.3 [$(M + Na)^+$, 100]; HRMS calcd for $C_{34}H_{42}NaO_5Si$ [$M + Na]^+$ 581.2699, found 581.2712.

(1*R*,3*R*,4*R*,5*S*,6*S*,9*R*)-4,5-Dibenzyloxy-3-benzyloxymethyl-8,8-diethyl-2,7-dioxa-8-sila-9-vinylbicyclo[4.3.0]nonane (42b):



HPLC $t_R = 60.40$ min; $R_f = 0.26$ (6% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3031w, 2874s, 1629w; δ_H (500 MHz) 0.80−1.04 (stack, 10H, Si(CH_2CH_3)$_2$), 2.25 (d, *J* 9.7, 1H, 9-H), 3.41 (dd, *J* 9.2, 5.3, 1H, 3-H), 3.57−3.61 (m containing d, ^2J 10.5, 1H, 1′$_A$-H), 3.62 (dd, *J* 9.2, 2.6, 1H, 5-H), 3.67−3.72 (m containing d, ^2J 10.5, 1H, 1′$_B$-H), 3.76−3.82 (stack including [3.79 (app t, *J* 9.2, 1H, 4-H)], 2H, 1-H, 4-H), 4.21 (d, *J* 2.6, 1H, 6-H), 4.50−4.58 (stack including [4.52 (A of AB, *J* 10.5, 1H, C(4)OCH_AH$_B$Ph)], 3H, C(4)OCH_AH$_B$Ph, C(1′)OCH_2Ph), 4.75 (A of AB, *J* 12.4, 1H, C(5)OCH_CH$_D$Ph), 4.80 (B of AB, *J* 12.4, 1H, C(5)OCH_CH$_D$Ph), 4.85 (d, *J* 17.0, 1H, 2″$_{trans}$-H), 4.88 (d, *J* 9.7, 1H, 2″$_{cis}$-H), 4.92 (B of AB, *J* 10.5, 1H, C(4)OCH$_A$$H_B$Ph), 5.66 (dt, *J* 17.0, 9.7, 1H, 1″-H), 7.08−7.40 (stack, 15H, Ph*H*); δ_C (125 MHz) 4.6 (CH_2, 1 × OSi(*C*H_2CH$_3$)$_2$), 6.4 (1 × CH_2, 1 × CH_3, 1 × OSi(*C*H_2-CH$_3$)$_2$, 1 × OSi(CH$_2$*C*H$_3$)$_2$), 6.8 (CH_3, 1 × OSi(CH$_2$*C*H$_3$)$_2$), 37.4 (CH, 9-*C*), 69.7 (CH_2, 1′-*C*), 71.5 (CH_2, C(5)O*C*H_2Ph), 73.2 (CH_2, C(1′)O*C*H_2Ph), 74.4 (CH, 4-*C*), 75.3 (CH_2, C(4)O*C*H_2Ph), 75.4 (CH, 6-*C*), 78.5 (CH, 3-*C*), 81.3 (CH, 1-*C*), 81.9 (CH, 5-*C*), 112.4 (CH_2, 2″-*C*), [127.4 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 127.7 (CH, Ph), 127.8 (CH, Ph), 128.0 (CH, Ph), 128.25 (CH, Ph), 128.34 (CH, Ph) some overlap], 135.0 (CH, 1″-*C*), 138.4 (quat C, 2 × *ipso*Ph), 138.5 (quat C, *ipso*Ph); *m*/*z* (TOF ES+) 581.2 [$(M + Na)^+$, 100]; HRMS calcd for $C_{34}H_{42}NaO_5Si$ [$M + Na]^+$ 581.2699, found 581.2689.

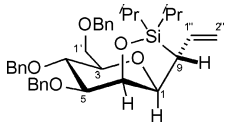
5,6-Dibenzyloxy-4-benzyloxymethyl-7-buta-1″,3″-dienyl-2,2-diethyl-1,3,2-dioxasilepane (39):



HPLC $t_R = 62.63$ min; $R_f = 0.30$ (6% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3088w, 3064m, 3031m, 2958s, 2877s, 1605m; δ_H (400 MHz) 0.67 (q, *J* 8.1, 2H, 1 × Si(CH_2CH$_3$)$_2$), 0.68 (q, *J* 8.1, 2H, 1 × Si(CH_2CH$_3$)$_2$), 0.99 (t, *J* 8.1, 3H, 1 × Si(CH$_2$CH_3)$_2$), 1.01 (t, *J* 8.1, 3H, 1 × Si(CH$_2$CH_3)$_2$), 3.37 (app t, *J* 8.5, 1H, 6-H), 3.64 (app t, *J* 8.5, 1H, 5-H), 3.70−3.75 (m containing d, ^2J 10.0, 1H, 1′$_A$-H), 3.76−3.81 (m containing d, ^2J 10.0, 1H, 1′$_B$-H), 4.07 (ddd, *J* 8.5, 4.8, 2.4, 1H, 4-H), 4.47 (dd, *J* 8.5, 5.8, 1H, 7-H), 4.57 (A of AB, *J* 10.4, 1H, OCH_AH$_B$Ph), 4.59 (A of AB, *J* 11.7, 1H, OCH_CH$_D$Ph), 4.62 (B of AB, *J* 11.7, 1H, OCH$_C$$H_D$Ph), 4.66 (A of AB, *J* 10.4, 1H, OCH_EH$_F$Ph), 4.68 (B of AB, *J* 10.4, 1H, OCH$_A$$H_B$Ph), 4.80 (B of AB, *J* 10.4, 1H, OCH$_E$$H_F$Ph), 5.07−5.12 (m, 1H, 4″$_{cis}$-H), 5.17−5.27 (m, 1H, 4″$_{trans}$-H), 5.88−5.99 (m, 1H, 1″-H), 6.30−6.44 (stack, 2H, 2″-H, 3″-H), 7.16−7.36 (stack, 15H, Ph*H*); δ_C (100 MHz) 3.93 (CH_2, Si(*C*H$_2$CH$_3$)$_2$), 6.36 (CH_3, 1 × Si(CH$_2$*C*H$_3$)$_2$), 6.43 (CH_3, 1 × Si(CH$_2$*C*H$_3$)$_2$), 71.9 (CH_2, 1′-*C*), 72.5 (CH, 7-*C*, 4-*C*), 73.4 (CH_2, O*C*H$_2$Ph), 75.0 (CH_2, O*C*H$_2$Ph), 75.1 (CH_2, O*C*H$_2$Ph), 83.0 (CH, 5-*C*), 87.1 (CH, 6-*C*), 117.1 (CH_2, 4″-*C*), [127.3 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 128.0 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph) some overlap], 131.5 (CH, =*C*H), 133.7 (CH, 1″-*C*), 136.6 (CH, =*C*H), 138.1 (quat C, *ipso*Ph), 138.5 (quat C, *ipso*Ph), 138.6 (quat C, *ipso*Ph); *m*/*z* (TOF ES+) 581.2 (100, $[M + Na]^+$); HRMS calcd for $C_{34}H_{42}NaO_5Si$ $[M + Na]^+$ 581.2699, found 581.2708.

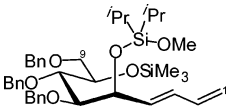
Allylation of Mannoside 27c: Preparation of 42c, 43c, 41, and **40.** TMSOTf (83 μL, 0.46 mmol) was added dropwise to a solution of allylsilane **27c** (315 mg, 0.46 mmol) and 2,6-DTBMP (112 mg, 0.55 mmol) in MeCN (4.6 mL) at rt. The reaction mixture was stirred for 18 h, diluted with EtOAc (5 mL), and poured into $NaHCO_3$ solution (5 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil which was analyzed by preparative HPLC ($t = 0 \rightarrow t = 45$ min, 0 → 100% MeCN in H_2O) to afford a 1.0:7.2:5.2:7.6 ratio of **41**/**42c** (inseparable from two other compounds; data not provided)/**43c**/**40**.

(1*R*,3*R*,4*R*,5*S*,6*S*,9*S*)-4,5-Dibenzyloxy-3-benzyloxymethyl-8,8-diisopropyl-2,7-dioxa-8-sila-9-vinylbicyclo[4.3.0]nonane (43c):HPLC t_R 64.59 min; $R_f = 0.22$ (3% EtOAc in



hexane); ν_{max} (film)/cm^{-1} 3064w, 3031w, 2941s, 2865s, 1629w; δ_H (500 MHz) 1.02−1.10 (stack, 14H, OSi(C*H*(CH$_3$)$_2$)$_2$), 2.24 (dd, *J* 10.2, 3.5, 1H, 9-H), 3.37−4.43 (m, 1H, 3-H), 3.59 (dd, *J* 9.4, 2.8, 1H, 5-H), 3.61−3.66 (m containing d, ^2J 9.9, 1H, 1′$_A$-H), 3.71−3.76 (m containing d, ^2J 9.9, 1H, 1′$_B$-H), 3.78 (d, *J* 3.5, 1H, 1-H), 3.84 (app t, *J* 9.4, 1H, 4-H), 3.91 (d, *J* 2.8, 1H, 6-H), 4.50−4.56 (m, 2H, C(1′)OCH_2Ph), 4.58 (A of AB, *J* 10.8, 1H, C(4)OCH_AH$_B$Ph), 4.74−4.78 (br s, 2H, C(5)OCH_2Ph), 4.89 (d, *J* 10.2, 1H, 2″$_{cis}$-H), 4.94 (B of AB, *J* 10.8, 1H, C(4)OCH$_A$$H_B$-Ph), 4.98 (d, *J* 17.4, 1H, 2″$_{trans}$-H), 6.16 (dt, *J* 17.4, 10.2, 1H, 1″-H), 7.12−7.42 (stack, 15H, Ph*H*); δ_C(125 MHz) 12.9 (CH, 1 × OSi(*C*H(CH$_3$)$_2$)$_2$), 13.3 (CH, 1 × OSi(*C*H(CH$_3$)$_2$)$_2$), [17.46, 17.53, 17.9 (CH_3, OSi(CH(*C*H$_3$)$_2$)$_2$)], 36.5 (CH, 9-*C*), 69.8 (CH_2, 2-*C*), 71.5 (CH_2, C(5)O*C*H$_2$Ph), 73.2 (CH_2, C(1′)O*C*H$_2$Ph), 74.7 (CH, 4-*C*), 75.3 (CH_2, C(4)O*C*H$_2$Ph), 77.3 (CH, 6-*C*), 78.7 (CH, 3-*C*), 79.9 (CH, 1-*C*), 82.1 (CH, 5-*C*), 112.9 (CH_2, 2″-*C*), 127.4 (CH, Ph), 127.5 (CH, Ph), 127.61 (CH, Ph), 127.64 (CH, Ph), 127.8 (CH, Ph), 128.0 (CH, Ph), 128.1 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 135.6 (CH, 1″-*C*), [138.56 (quat C, *ipso*Ph), 138.60 (quat C, *ipso*Ph) some overlap]; *m*/*z* (TOF ES+) 609.4 $[(M + Na)^+$, 100]; HRMS calcd for $C_{36}H_{46}NaO_5Si$ $[M + Na]^+$ 609.3012, found 609.3013.

(3*E*,5*R*,6*S*,7*S*,8*R*)-6,7,9-Tribenzyloxy-5-diisopropyl(methoxy)silanyloxy-8-trimethylsilanyloxynona-1,3-diene (40):



HPLC $t_R = 79.36$ min; $R_f = 0.33$ (3% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3032w, 2946s, 2867s, 1604, 1095s; δ_H (300 MHz) −0.09 (s, 9H, Si(CH_3)$_3$), 1.00−1.05 (br s, 14H, Si(C*H*(CH$_3$)$_2$)$_2$), 3.49 (s, 3H, OCH_3), 3.57 (dd, *J* 10.0, 6.2, 1H), 3.65 (app t, *J* 5.3, 1H), 3.71 (dd, *J* 10.1, 3.5, 1H), 3.79 (dd, *J* 5.9, 3.6, 1H), 4.05 (dd, *J* 8.0, 5.8, 1H), 4.49 (br s, 2H, OCH_2Ph), 4.53 (dd, *J* 7.8, 3.5, 1H), 4.64 (A of AB, *J* 10.8, 1H, OCH_AH$_B$Ph), 4.68 (br s, 2H, OCH_2Ph), 4.81 (B of AB, *J* 10.8, 1H, OCH$_A$$H_B$Ph), 5.09 (d, *J* 9.9, 1H, 1$_{cis}$-H), 5.18 (d, *J* 16.6, 1H, 1$_{trans}$-H), 5.96 (dd, *J* 14.8, 7.8, 1H, 4-H), 6.21−6.43 (stack, 2H, 2-H, 3-H), 7.12−7.46 (stack, 15H, Ph*H*); δ_C (75 MHz) −0.6 (CH_3, Si(CH_3)$_3$), 12.28 (CH, 1 × Si(*C*H(CH$_3$)$_2$)), 12.35 (CH, 1 × Si(*C*H(CH$_3$)$_2$)),

17.4 (CH_3, 1 × Si(CH(CH_3)$_2$)), 17.52 (CH_3, 1 × Si(CH(CH_3)$_2$)), 17.54 (CH_3, 1 × Si(CH(CH_3)$_2$)), 17.6 (CH_3, 1 × Si(CH(CH_3)$_2$)), 51.2 (CH_3, OCH_3), 71.9 (CH_2), 72.7 (CH), 73.3 (CH_2), 74.6 (CH), 74.9 (CH_2), 75.0 (CH_2), 82.0 (CH), 84.0 (CH), 117.5 (CH_2, 1-*C*), [127.27, 127.30, 127.4, 127.7, 127.9, 128.0, 128.12, 128.13, 128.3 (CH, Ph, =CH) some overlap], 133.1 (CH, =CH), 136.5 (CH, =CH), 138.4 (quat C, *ipso*Ph), 139.13 (quat C, *ipso*Ph), 139.16 (quat C, *ipso*Ph); *m*/*z* (TOF ES+) 713.5 [(M + Na)$^+$, 100]; HRMS calcd for $C_{40}H_{58}NaO_6Si_2$ [M + Na]$^+$ 713.3670, found 713.3665.

(1*S*)-1-(3′,4′,6′-Tri-*O*-benzyl-β-D-mannopyranosyl)prop-2-en-1-ol (44). Method A. H_2O_2 (26 mg, 0.46 mmol, 60% in H_2O), $KHCO_3$ (11 mg, 0.11 mmol), and TBAF (110 μL, 1 M solution in THF) were added to a solution of silyl ether **42b** (13 mg, 23 μmol) in MeOH/THF (1:1) (0.3 mL), and the resulting mixture was stirred at rt for 2 d. The mixture was then poured into $Na_2S_2O_3$ solution (2 mL) and stirred for 30 min. The solution was extracted with EtOAc (4 × 2 mL), and the combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to afford diol **44** as a colorless oil which solidified as an amorphous white solid upon storage at 4 °C (8 mg, 69%): $[\alpha]^{21}_D$ −12.7 (*c* 1.8, $CHCl_3$); R_f = 0.25 (50% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3462br s, 1645w; δ_H (400 MHz) 2.50−2.75 (br s, 2H, 2 × O*H*), 3.22 (d, *J* 5.8, 1H, 1′-H), 3.44 (ddd, *J* 9.6, 4.9, 2.0, 1H, 5′-H), 3.56 (dd, *J* 9.6, 3.0, 1H, 3′-H), 3.67−3.73 (m containing d, ^2J 10.9, 1H, 6′$_A$-H), 3.73−3.78 (m containing d, ^2J 10.9, 1H, 6′$_B$-H), 3.83 (app t, *J* 9.6, 1H, 4′-H), 4.32 (d, *J* 3.0, 1H, 2′-H), 4.49−4.53 (stack including [4.52 (A of AB, *J* 10.8, 1H, OC*H*$_A$H$_B$Ph)], 2H, OC*H*$_A$H$_B$Ph, 1-H), 4.55 (A of AB, *J* 12.2, 1H, OC*H*$_C$H$_D$Ph), 4.61 (B of AB, *J* 12.2, 1H, OCH$_C$*H*$_D$Ph), 4.65 (A of AB, *J* 11.5, 1H, OC*H*$_E$H$_F$Ph), 4.76 (B of AB, *J* 11.5, 1H, OCH$_E$*H*$_F$Ph), 4.86 (B of AB, *J* 10.8, 1H, OCH$_A$*H*$_B$Ph), 5.25 (dt, *J* 10.6, 1.4, 1H, 3$_{cis}$-H), 5.44 (dt, *J* 17.3, 1.4, 1H, 3$_{trans}$-H), 5.99 (ddd, *J* 17.3, 10.6, 5.2, 1H, 2-H), 7.12−7.38 (stack, 15H, Ph*H*); δ_C (100 MHz) 66.3 (CH, 2′-*C*), 69.3 (CH_2, 6′-*C*), 71.5 (CH_2, *C*H_2Ph), 72.2 (CH, 1-*C*), 73.4 (CH_2, *C*H_2-Ph), 74.5 (CH, 4′-*C*), 75.2 (CH_2, *C*H_2Ph), 79.2 (CH, 1′-*C*), 79.5 (CH, 5′-*C*), 83.0 (CH, 3′-*C*), 116.1 (CH_2, 3-*C*), [127.7 (CH, Ph), 127.8 (CH, Ph), 127.9 (CH, Ph), 128.0 (CH, Ph), 128.3 (CH, Ph), 128.5 (CH, Ph) some overlap], 137.3 (CH, 2-*C*), 137.8 (quat C, *ipso*Ph), 138.2 (quat C, *ipso*Ph), 138.3 (quat C, *ipso*Ph); *m*/*z* (TOF ES+) 513.2 [(M + Na)$^+$, 100]; HRMS calcd for $C_{30}H_{34}NaO_6$ [M + Na]$^+$ 513.2253, found 513.2259.

Method B. TMSOTf (58 μL, 0.32 mmol) was added dropwise to a solution of allylsilane **27c** (220 mg, 0.32 mmol) and 2,6-DTBMP (79 mg, 0.38 mmol) in MeCN (3.2 mL) at rt. The reaction mixture was stirred for 18 h, diluted with EtOAc (3 mL), and poured into $NaHCO_3$ solution (3 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil which was subjected to oxidation (method A): H_2O_2 (363 mg, 6.40 mmol, 60% in H_2O), $KHCO_3$ (160 mg, 1.60 mmol), and TBAF (1.60 mL, 1 M solution in THF) were added to a solution of the crude products in MeOH/THF (1:1) (3.2 mL), and the resulting mixture was stirred at rt for 2 d. The mixture was then poured into $Na_2S_2O_3$ solution (2 mL) and stirred for 30 min. The solution was extracted with EtOAc (4 × 3 mL) and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to afford diol **44** as a colorless oil (13 mg, 8% over two steps).

Method C. Tf_2O (78 μL, 0.48 mmol) was added dropwise to a solution of allylsilane **47** (318 mg, 0.40 mmol) and 2,6-DTBMP (164 mg, 0.80 mmol) in CH_2Cl_2 (4 mL) at −78 °C. The reaction mixture was stirred for 10 min, and then $NaHCO_3$ solution (4 mL) was added dropwise at this temperature. The slurry was allowed to warm to rt, and the layers were then separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil which was subjected to oxidation (method A): H_2O_2 (453 mg, 8.00 mmol, 60% in H_2O), $KHCO_3$ (200 mg, 2.00 mmol), and TBAF (2.00 mL, 2.00 mmol, 1 M solution in THF) were added to a solution of the crude products in MeOH/THF (1:1) (4 mL). The resulting mixture was stirred at rt for 3 d. The mixture was then poured into $Na_2S_2O_3$ solution (4 mL) and stirred for 30 min. The solution was extracted with EtOAc (4 × 4 mL), and the combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAC in hexane) to afford diol **44** as a colorless oil (19 mg, 10%).

(1*R*)-1-(3′,4′,6′-Tri-*O*-benzyl-β-D-mannopyranosyl)prop-2-en-1-ol (45). H_2O_2 (16 mg, 0.28 mmol, 60% in H_2O), $KHCO_3$ (7 mg, 70 μmol), and TBAF (70 μL, 70 μmol, 1 M solution in THF) were added to a solution of silyl ether **43b** (8 mg, 14 μmol) in MeOH/THF (1:1) (0.3 mL). The resulting mixture was stirred at rt for 2 d. The mixture was then poured into $Na_2S_2O_3$ solution (1 mL) and stirred for 30 min. The solution was extracted with EtOAc (4 × 1 mL), and the combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (60% EtOAc in hexane) to afford diol **45** as a colorless oil, which provided a white amorphous solid upon storage at 4 °C (5 mg, 71%): R_f = 0.25 (60% EtOAc in hexane); ν_{max} (film)/cm^{-1} 3435br s, 1646w; δ_H (500 MHz) 3.15 (d, *J* 7.0, 1H, 1′-H), 3.42 (ddd, *J* 9.5, 4.2, 2.5, 1H, 5′-H), 3.57 (dd, *J* 9.5, 3.1, 1H, 3′-H), 3.68−3.78 (stack, 2H, 2 × 6′-H), 3.83 (app t, *J* 9.5, 1H, 4′-H), 4.04 (d, *J* 3.1, 1H, 2′-H), 4.48 (app t, *J* 7.0, 1H, 1-H), 4.53 (A of AB, *J* 12.2, 1H, OC*H*$_A$H$_B$Ph), 4.54 (A of AB, *J* 10.8, 1H, OC*H*$_C$H$_D$-Ph), 4.61 (B of AB, *J* 12.2, 1H, OCH$_A$*H*$_B$Ph), 4.66 (A of AB, *J* 11.5, 1H, OC*H*$_E$H$_F$Ph), 4.71 (B of AB, *J* 11.5, 1H, OCH$_E$*H*$_F$-Ph), 4.84 (B of AB, *J* 10.8, 1H, OCH$_C$*H*$_D$Ph), 5.27 (d, *J* 10.5, 1H, 3$_{cis}$-H), 5.48 (d, *J* 17.2, 1H, 3$_{trans}$-H), 5.86 (ddd, *J* 17.2, 10.5, 7.0, 1H, 2-H), 7.17−7.20 (stack, 2H, Ph*H*), 7.24−7.36 (stack, 13H, Ph*H*); δ_C (125 MHz) 66.7 (CH, 2′-*C*), 69.1 (CH_2, 6′-*C*), 71.8 (CH_2, O*C*H_2Ph), 72.3 (CH, 1-*C*), 73.4 (CH_2, O*C*H_2Ph), 74.5 (CH, 4′-*C*), 75.2 (CH_2, O*C*H_2Ph), 79.2 (CH, 5′-*C*), 80.8 (CH, 1′-*C*), 83.2 (CH, 3′-*C*), 118.2 (CH_2, 3-*C*), [127.6 (CH, Ph), 127.75 (CH, Ph), 127.85 (CH, Ph), 127.98 (CH, Ph), 128.02 (CH, Ph), 128.4 (CH, Ph), 128.6 (CH, Ph) some overlap], 135.4 (CH, 2-*C*), 137.7 (quat C, *ipso*Ph), 138.2 (quat C, 2 × *ipso*Ph); *m*/*z* (TOF ES+) 513.2 [(M + Na)$^+$, 100]; HRMS calcd for $C_{30}H_{34}NaO_6$ [M + Na]$^+$ 513.2253, found 513.2252.

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Supporting Information Available: General experimental details, experimental procedures and full characterization data for intermediates **9**−**15**, **17**, **19**, **20**, **25**−**27a**,**c**, **41**, **46**, **47**, and **50**−**53**, crossover experiment between **25** and **27a**, preparation of (allyl)MgBr and titration details, and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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