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Stereoselective *C*-Glycosylation Reactions of Pyranoses: The Conformational Preference and Reactions of the Mannosyl Cation

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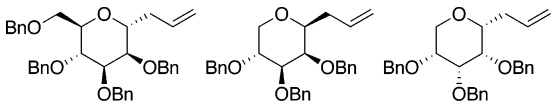
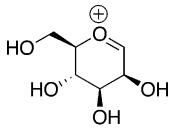


A systematic study of *C*-glycosylations of acetals related to mannose and other pyranoses was conducted. The C-5 alkoxyalkyl group provides only a modest influence on stereoselectivity. On the other hand, studies of pentopyranoses bearing alkoxy groups at C-2, C-3, and C-4 showed that the alkoxy groups exerted powerful influences on selectivity. In the case of mannose, the high α selectivity observed with *C*-mannosylation was reversed to high *β* selectivity if the C-5 alkoxyalkyl group were removed. An analysis of the conformational preferences of the intermediate oxocarbenium ions, including the mannosyl cation, as well as consideration of steric effects that develop in the transition states for nucleophilic attack provide explanations for these phenomena.

Introduction

Mannosylation reactions have attracted significant interest in biological and medicinal chemistry because of their roles in numerous physiological processes. For example, irregularities in the enzymatic mannosylation of proteins are implicated in a number of medical conditions,[1−3] and compounds interacting with mannosidases have emerged as viable therapeutic agents for the treatment of diseases such as cancer.[4,5] Structures resembling the mannosyl cation **1**, a likely intermediate in many mannosylation processes,[6] have been shown to be particularly powerful mannosidase inhibitors.[2,7−15] Designing structural analogues of the mannosyl cation **1**, however, is challenging, because the three-dimensional structure of this cation is not known.[9,16−18]



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In this paper, we analyze the three-dimensional structure of the mannosyl cation **1** on the basis of *C*-glycosylation reactions of several carbohydrate analogues. We demonstrate that the selectivity for the *C*-glycosylation of mannose does not necessarily reflect the ground-state preference of the mannosyl cation **1**. Instead, this reaction involves a Curtin−Hammett scenario[19] in which one conformer of the cation is relatively unreactive,

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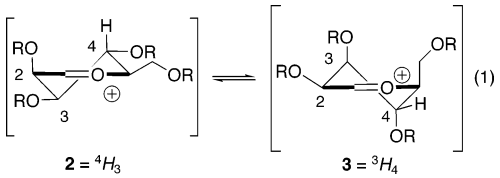
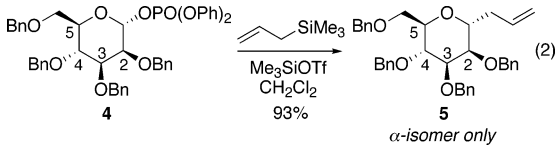
so nucleophilic attack occurs onto the other conformer. In addition, the selectivities observed provide insight into how several alkoxy groups interact within an oxocarbenium ion and control its structure and reactivity, providing an important framework to understand carbohydrate reactivity.[20]

Background

Although the mannosyl cation **1** remains the primary inspiration for many mannosidase inhibitors, a consensus on the three-dimensional structure of this cation has yet to be reached. The mannosyl cation **1** likely exists in one of two half-chair conformations, and it is often represented as the $^4H_3$ conformer **2**, with the maximum number of substituents placed equatorially (eq 1).[9] Computational studies of the conformational preference, however, are conflicting. One calculation indicates that the intuitively expected conformer **2** is slightly preferred (by 0.5 kcal/mol) over the $^3H_4$ conformer **3**;[18] another calculation indicates that the counterintuitive $^3H_4$ conformer **3** is favored by 4.0 kcal/mol.[21] Analysis of biological data also suggests that the $^3H_4$ conformer **3** is favored.[16,17,22] The preference for the $^3H_4$ conformer **3** is consistent with computational studies of monosubstituted oxocarbenium ions, which indicate that alkoxy groups at C-2 favor equatorial positions, and they strongly prefer axial orientations at C-3 and C-4.[23−26] The view that oxocarbenium ions with alkoxy groups at C-3 and C-4 adopt axial conformers is also supported by studies on the rates of glycoside hydrolysis.[20]



Insight into the conformational preference of the mannosyl cation **1** can be gained by considering chemical reactions involving this species. The synthesis of *C*-mannosides has been aggressively pursued,[27−32] because *C*-glycosides are structural analogues of *O*-glycosides[33−36] but are not degraded enzymatically. In general, *C*-mannosylation reactions such as the transformation depicted in eq 2[37] are highly α selective, and this selectivity is observed with various carbon nucleophiles, protecting groups, and solvents.[27−32,38−44] Because these *C*-mannosylation reactions likely involve oxocarbenium ions,[45,46] understanding the origin of selectivity of mannose *C*-glycosylations should lead to a deeper understanding of the structure of the mannosyl cation **1**. This knowledge will be broadly useful not only for the development of potent pharmaceutical agents, but also for understanding biological and chemical processes involving carbohydrate-derived oxocarbenium ions.[47−51]



We became interested in mannosylation reactions because our studies with oxocarbenium ions bearing single substituents are inconsistent with the selectivities observed with the mannosyl cation (eq 2[37]). Allylation reactions involving monosubstituted tetrahydropyran cations (Chart 1) indicate that for substrates bearing alkoxy groups at C-2, C-3, and C-4, the major product is the β isomer,[52,53] which is opposite to what was observed in

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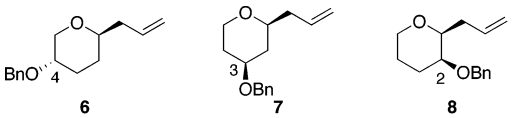
CHART 1. Allylations of Monosubstituted Tetrahydropyran Oxocarbenium Ions



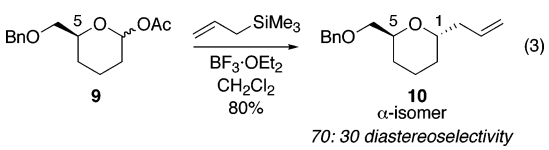
the mannose series (eq 2). These studies established that, for C-3 and C-4, the substituent adopted an axial orientation, consistent with theoretical predictions.[24,54] A preference for axial conformers was also determined for 4-alkoxy-substituted dioxocarbenium ions, using spectroscopic and crystallographic data.[55] Similar conformational preferences were observed with five- and eight-membered ring oxocarbenium ions.[56−58] All of these data for alkoxy-substituted oxocarbenium ions related to the mannosyl cation[26] are difficult to reconcile with the highly α-selective *C*-mannosylation reactions, such as that shown in eq 2.[37]

Experimental Approach

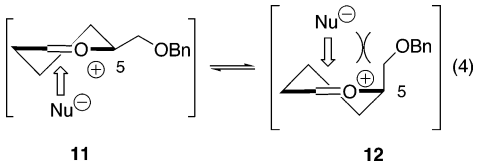
The strategy employed to ascertain the origin of the selectivity of the reactions of the mannosyl cation **1** involved determining the selectivity of *C*-glycosylation of truncated mannose structures. The substrates were all anomeric acetates, and the syntheses of these substrates are provided as Supporting Information. Allylations were chosen because these reactions are high-yielding and irreversible[53,59] and because we have gained evidence that these reactions involve oxocarbenium ion intermediates in related substrates.[45,53,60,61] In addition, developing steric interactions should be minimized upon nucleophilic attack because the nucleophile is relatively small. Consequently, the inherent conformational preference of the cation should be revealed. All diastereoselectivities were determined by combinations of GC and NMR spectroscopy. The relative stereochemical configurations of the products were determined using coupling constants obtained from ^{1}H NMR spectra as well as by NOE measurements; details are provided as Supporting Information.

Results and Discussion

C-5 Alkoxymethyl Substituted Pyran Acetate. Because the most evident difference between our studies shown in Chart 1 and the mannosylations typified by eq 2[37] is the presence of the benzyloxymethyl group at C-5, the reaction of acetate **9** bearing only a C-5 benzyloxymethyl group was examined. Upon allylation, the 1,5-trans product **10** (the α isomer) was formed, which is consistent with the *C*-mannosylation shown in eq 2.[37] The low selectivity, however, indicates that the alkoxymethyl substituent at C-5 is not solely responsible for the behavior of mannose derivatives.



The 1,5-trans selectivity exhibited by the C-5 benzyloxymethyl acetate **9** can be understood by considering the conformational preference of this substituent as well as considering steric interactions that develop upon nucleophilic attack. When the two possible conformers of the oxocarbenium ion (**11** and **12**, eq 4) are considered, low selectivity might be anticipated based upon the modest preference (0.7 kcal/mol) for a methyl group to reside equatorially at this position.[23] Ground state effects, however, are not the only factor to be considered. The stereoelectronically preferred[62] faces of each oxocarbenium ion conformer are sterically dramatically different, and steric effects that emerge in the transition state for nucleophilic attack on oxocarbenium ions can exert powerful influences on selectivities.[53] Nucleophilic attack along an axial trajectory on the axial conformer **12** would require forming a *syn*-pentane interaction[63] in the transition state, thus slowing nucleophilic attack to this cation.



Other studies have examined additions to C-5-substituted tetrahydropyran oxocarbenium ions. In general, additions to oxocarbenium ions bearing substituents such as *n*-alkyl groups at C-5 are highly 1,5-trans selective,[64,65] although examples of low selectivity[66−68] and 1,5-cis selectivity[69,70] have been reported. Nucleophilic additions to C-5 alkoxymethyl-substituted oxocarbenium ions generally result in low selectivity,[66,71] as observed in eq 3, so other strategies such as oxygen-to-carbon rearrangements have been developed.[72] The difference in

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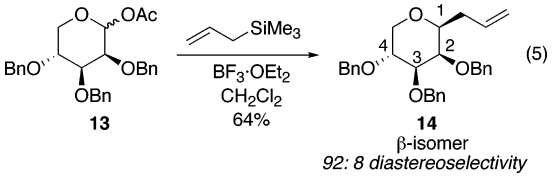
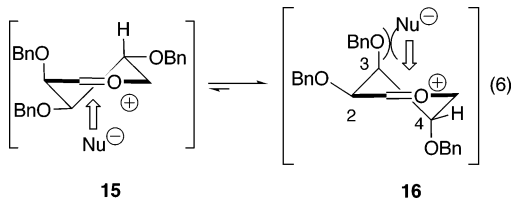
behavior exhibited by alkyl and alkoxyalkyl substituents parallels the powerful influence that the electronic nature of the C-5 substituent (such as the manner in which the oxygen atom of an alkoxyalkyl group was protected) has on selectivities for *O*-glycosylations[73] and *C*-glycosylations.[74] The torsional arrangement of the alkoxy group on a C-5 alkoxyalkyl group also exerts strong influences, such as on the rates of glycoside hydrolysis,[75] the relative energies of different conformers of oxocarbenium ions,[18] and the stereoselectivities of glycosylation reactions.[76]

Allylation of Lyxose Acetate. Because the C-5 alkoxyalkyl substituent alone could not control the selectivity observed for the *C*-glycosylation of mannose (eq 2[37]), it was suspected that some interaction between the different substituents must be responsible for the selectivity. Consequently, a substrate was prepared without a substituent at C-5 to determine the effect of the three benzyloxy groups on the selectivity of *C*-glycosylation.

Allylation of the lyxose acetate **13** occurred with high β selectivity (eq 5). This selectivity was largely independent of solvent (95:5 selectivity was observed using toluene) and Lewis acid (the use of $SnBr_4$ led to a 96:4 selectivity). The β selectivity exhibited in eq 5 matches the selectivities shown in the case of tetrahydropyrans with a single substituent at C-2, C-3, and C-4 (Chart 1), indicating a cooperative (or at least not antagonistic) relationship between the alkoxy groups.[77] The selectivity, however, is precisely opposite to the α selectivity observed with mannose (compare eq 5 with eq 2[37]).

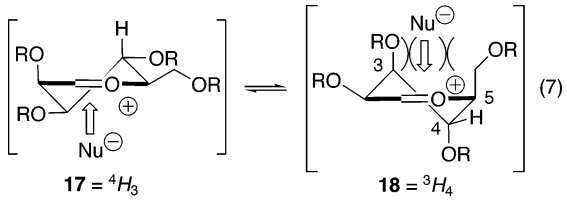


The major product observed in eq 5 must arise from nucleophilic attack to the oxocarbenium ion in which the alkoxy group at C-2 is equatorial and the alkoxy groups at C-3 and C-4 are axial, as in conformer **16** (eq 6). These conformational preferences are consistent with preferences experienced by oxocarbenium ions bearing a single substituent[23,24,78] and are based upon our selectivity data[52,53] and crystallographic evidence.[55] In addition, the methyl ether analogue of conformer **16** has been calculated to be about 3 kcal/mol lower in energy than the cation resembling **15**.[18]



Origin of Selectivity for *C*-Mannosylation. With the results obtained with mannose analogues **9** and **13** (eqs 3 and 5), the selectivity for the *C*-glycosylation reaction of mannose (eq 2[37]) can be analyzed. The array of three alkoxy groups at C-2, C-3, and C-4 should result in the selective formation of the β stereoisomer of the product, whereas the C-5 alkoxyalkyl substituent alone should provide modest α selectivity. Therefore, the high α selectivity must be the result of some interaction between all of these substituents, either in the ground state or in the transition state for nucleophilic attack.

Analysis of the conformational bias of the mannosyl cation **1** provides important insight into understanding the selectivity of *C*-mannosylation reactions. One computational study suggests that the $^4H_3$ conformer **17** should be favored by 0.5 kcal/mol,[18] but another indicates a significant preference (4.0 kcal/mol) for the $^3H_4$ conformer **18**.[21] When the contributions of each individual substituent obtained from theoretical as well as experimental studies are considered,[23,24,26,52,53] the $^3H_4$ conformer **18** should be greatly preferred.[26] The preference for conformer **18** is further supported by the observation that lyxose acetate **13** reacted through the analogous cation **16** (eq 6). Although the diaxial interaction between the C-3 alkoxy group and the C-5 alkyl group destabilizes conformer **18**, this *syn*-butanol interaction only results in 1.8 kcal/mol of steric destabilization.[25]



To understand the selectivity of the *C*-mannosylation, however, requires more than the determination of the conformational preference of the reactive intermediate. In accordance with the Curtin−Hammett principle,[19] the stereoselectivity of the reaction will depend on the relative energies of the transition states for nucleophilic attack. The approach of a nucleophile onto oxocarbenium ion **18** from the stereoelectronically favored face[62] would result in the development of a *syn*-pentane interaction[63] between the nucleophile and the substituent at C-5 as well as a smaller *syn*-butanol[25] interaction with the substituent at C-3. These interactions should destabilize the transition state for a reaction via **18** as compared to that of the transition state via conformer **17**. Therefore, regardless of the position of the equilibrium of eq 7, the two conformers of the oxocarbenium ion do not react with nucleophiles at the same rate. The α-selective mannosylation thus appears to be a result of an interconverting mixture of conformers, arguably favoring the $^3H_4$ conformer **18**, reacting through the lowest-energy transition state[19] (namely, via conformer **17**), in accord with the Curtin−Hammett kinetic scenario.[19]

Other 2,3,4-Tribenzyloxy-Substituted Pyran Acetates. The high 1,5-trans selectivity observed in *C*-mannosylations (eq 2[37]) is general for other *C*-glycosylation reactions. For example, the syntheses of *C*-glycosides of glucose (**19**),[31,38,39,41,44,79−84] galactose (**20**),[31,80] and fucose (**21**)[85,86] involve 1,5-trans-selective *C*-glycosylation reactions (Chart 2). In each of these cases, the 1,5-trans selectivity might arise for the same reason as for the

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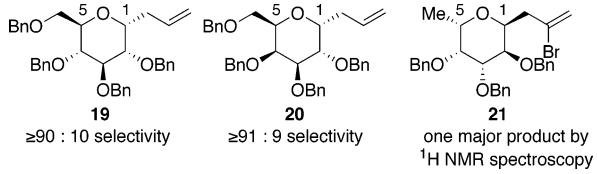
(77) Allylation of a substrate with benzoates as protecting groups, which might participate by anchimeric assistance, also leads to the β product, although with modest selectivity: Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, *24*, 1563−1566.

(78) When the values and analysis presented in ref 26 are applied in this case, conformer **16** should be favored by 9.6 kcal/mol.

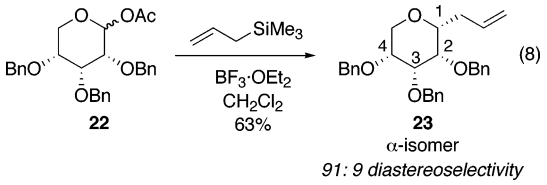
mannose system: nucleophilic addition occurs preferentially to a conformer in which the C-5 substituent is equatorial to avoid powerfully destabilizing interactions in the transition state when this substituent is axial.

CHART 2. Major Products of Pyranose *C*-Glycosylations

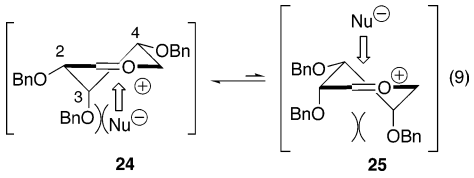


As demonstrated by the substitution reactions of the lyxose acetate **13** (eq 5), the presence of the alkoxy groups alone leads to different stereochemical outcomes. For the lyxose system, all three alkoxy groups were allowed to adopt their preferred orientations (equatorial at C-2 and axial at C-3 and C-4)[23,24,52,53] without engendering destabilizing interactions between the substituents. To determine the cooperative or competitive interactions between the alkoxy substituents, we performed a study on other oxocarbenium ion precursors possessing three alkoxy groups at C-2, C-3, and C-4 with the remaining three possible stereochemical configurations.

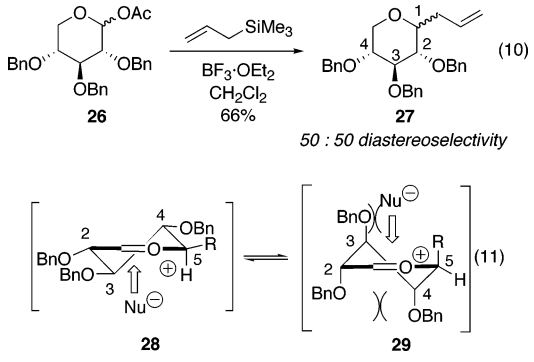
When all three alkoxy groups were cis, as in ribopyranose acetate **22**, *C*-glycosylation was highly stereoselective (eq 8). This system differs in relative stereochemistry from the lyxose series (**13** and **14**, eq 5) only at C-4 (because D-ribose was used as the starting material for the synthesis of acetate **22**, the absolute configurations of products differ at C-2 and C-3). For the allylated ribopyranose **23**, the nucleophile approached cis to the alkoxy groups at C-2 and C-3, just as it had for the C-4 epimer **14** (eq 5); evidently, the alkoxy group at C-4 does not control selectivity. In five-membered ring oxocarbenium ions, substitutions cis to two alkoxy groups at C-2 and C-3 were also observed.[56,58] The contrasteric substitution reaction depicted in eq 8 dramatically illustrates a key feature of addition reactions to oxocarbenium ions that emerged from our studies of five-membered ring oxocarbenium ions:[56,58] a consideration of steric effects alone does not permit the prediction of stereochemical outcomes of substitution reactions.



The counterintuitive all-cis selectivity depicted in eq 8 can be explained by examining the structure of the oxocarbenium ion intermediate (eq 9). Conformer **24** orients the C-2 and C-3 alkoxy groups in their preferred positions but requires the C-4 alkoxy group to reside equatorially, which is its disfavored orientation.[23,24,52,53] Because the C-4 alkoxy group has the strongest conformational bias of the three alkoxy groups[23] (thus leading to the selectivity trend shown in Chart 1), it might be anticipated that the alternative conformer **25** would be favored. On the other hand, this cation would not only require that both the C-2 and C-3 alkoxy groups take disfavored positions, but this conformer includes a 1,3-diaxial interaction between the alkoxy group at C-2 and the alkoxy group at C-4. This 1,3-diaxial interaction destabilizes 1,3-dimethoxycyclohexane by about 3 kcal/mol,[87] and this arrangement is also strongly disfavored in dimethoxypropane.[88,89] For these reasons, conformer **24** is likely to be favored, and the major product would be formed from this conformer. Although the nucleophile should develop a destabilizing interaction in the transition state with the alkoxy group at C-3, this interaction is not large, as shown by the selectivity of the substrate bearing only an alkoxy group at C-3 (**7**, Chart 1).[52,53]



The disfavored 1,3-diaxial interaction between alkoxy groups is also likely the cause for the unselective allylation of acetate **26** (eq 10), the C-2 epimer of the lyxose system (eq 5). Shuto et al. reported similarly low selectivities for a related transformation.[90] When this allylation was performed using acetonitrile as the solvent, which dramatically improves selectivities of some *O*-glycosylations,[91] no improvement in selectivity was observed. The lack of selectivity can be understood by considering the structures of oxocarbenium ions **28** and **29** (R = H, eq 11). In conformer **28** (R = H), the C-3 and C-4 alkoxy groups are disposed in their disfavored equatorial orientations.[23,24,52,53] In the alternative conformer **29** (R = H), only the C-2 alkoxy



group is placed in a disfavored orientation.[23,52,53] The unfavor-

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(84) Additions of Me_3SiCN are unselective in many *C*-glycosylations. See, for example: (a) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973. (b) Lai, W.; Martin, O. R. *Carbohydr. Res.* **1993**, *250*, 185−193.
(85) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267−5283.
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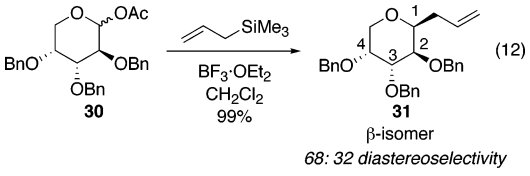
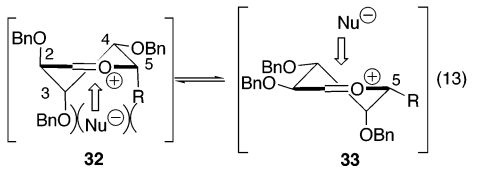
able 1,3-diaxial interaction between the alkoxy groups, however, is present in this conformer, and a destabilizing *syn*-butanol interaction[25] develops in the transition state for nucleophilic attack on this cation. The low selectivity indicates that all of these various influences are balanced.

The highly α-selective *C*-glycosylation of glucose (**19**, Chart 2) can also be understood by considering cations **28** and **29**, which would possess an alkoxyalkyl group at C-5 (eq 11, R = CH_2OBn). The oxocarbenium ion **29** (R = CH_2OBn) would be additionally destabilized by positioning the C-5 alkyl group in an axial orientation, which would engender a *syn*-butanol interaction (disfavored by 1.8 kcal/mol)[25] with the alkoxy group at C-3. In addition, a *syn*-pentane interaction[63] would raise the transition-state energy for attack onto conformer **29**, just at it did with the mannose system (eq 7, vide supra).

The selectivity observed for the formation of the galactose and fucose allylation products (**20** and **21**, Chart 2) can be understood by considering allylation of the C-5 unsubstituted analogue **30** (eq 12). Allylation of acetate **30** favored the β isomer, although the magnitude of the stereoselectivity was low. The 1,2-cis selectivity is consistent with the selectivities shown in eqs 5 and 8. An analysis of the two oxocarbenium ions, **32** and **33** (R = H, eq 13), provides an explanation for the 1,2-cis selectivity. In conformer **33**, only the C-3 alkoxy group resides in a disfavored orientation,[23,52,53] so it is the reaction of this cation that leads to the favored product. The approach of a nucleophile to this conformer would not be impeded by substituents, in contrast to an attack on conformer **32**. The magnitude of the selectivity is more difficult to analyze. Our studies of five-membered ring oxocarbenium ions showed that when the C-2 and C-3 alkoxy groups oppose each other, selectivity is lower than would be expected on the basis of a consideration of the influence of individual substituents,[58] similar to the results with acetates **26** and **30**. When this system possesses an alkyl group at C-5, as found in fucose, the β product is formed with high selectivity.[31,80] In this case, conformer **32** (R = Me) is additionally destabilized, and nucleophilic attack on this conformer also becomes more difficult for the same reasons as for the glucose and mannose systems (vide supra). A comparable analysis would explain the selectivity with galactose (**20**, Chart 2).





Conclusion

An examination of *C*-glycosylation reactions of acetals resembling mannose provides insight into the origin of the α stereoselectivity of *C*-mannosylation (eq 2) and the conformational preferences of the mannosyl cation intermediate **1**. When the pentopyranose analogue **13** was examined (eq 5), nucleophilic substitution was highly β selective, demonstrating the powerful influence of the three alkoxy groups at C-2, C-3, and C-4. Analysis of the divergent diastereoselectivities of eqs 2 and 5 leads to two arguments to explain the behavior of the mannosyl cation. The first explanation would require that the mannosyl cation adopts the counterintuitive $^3H_4$ conformer **3** (eq 1), which is supported by considering the influence of each substituent individually.[23,24,26,52,53] Additional support for this conformational bias is provided by biological data[16,17,22] and computational studies,[21] although one computational study shows a small preference for the $^4H_3$ conformer **2** (eq 1).[18] An alternative explanation relies on considering that both conformers are in rapid equilibrium but that nucleophilic attack on the $^3H_4$ conformer **3** develops interactions that destabilize the transition state leading from this intermediate. Consequently, according to the Curtin−Hammett principle,[19] the product ratio would depend on the relative energies of competing transition states, not ground-state energies. The latter explanation is not inconsistent with the notion that the mannosyl cation resides in the $^3H_4$ conformer **3** (eq 1) but instead serves as a reminder that both ground-state and transition-state energies need to be considered in any analysis of reactivity.

Experimental Section

Typical Allylation Procedure: Allyltrimethylsilane (4.0 equiv) was added to a solution of acetate (0.15 M) in CH_2Cl_2, and the mixture was cooled to −78 °C and treated with the Lewis acid (1.2 equiv). The mixture was allowed to warm to 23 °C and quenched with saturated aqueous Na_2HPO_4 (1 mL/mmol of acetate). The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (1 mL/mmol of acetate), dried over Na_2SO_4, and concentrated in vacuo. The unpurified product ratios were determined using GC and confirmed using GCMS. The reported yields are of purified material.

Selectivities were determined by GC analysis and confirmed by ^{1}H NMR spectroscopy. The relative configurations of the products were determined using a combination of ^{1}H NMR coupling constant data and nuclear Overhauser effect (NOE) enhancements. The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, ^{1}H NMR chemical shifts, and ^{1}H NMR coupling constants.

1-Allyl-5-benzyloxymethyltetrahydropyran (10): Under standard allylation conditions using BF_3•OEt_2 as a Lewis acid, acetate **9** (0.113 g, 0.429 mmol) afforded **10** (0.077 g, 73%) as a 70:30 1,5-trans/cis mixture of isomers. The oil was purified by flash chromatography (hexanes to 1:9 Et_2O/hexanes) to afford the 1,5-trans product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 5.85−5.77 (m, 1H), 5.06 (m, 2H), 4.56 (m, 2H), 3.93 (m, 1H), 3.80 (m, 1H), 3.58 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.46 (dd, *J* = 9.9, 5.3 Hz, 1H), 2.48−2.43 (m, 1H), 2.26−2.20 (m, 1H), 1.67−1.55 (m, 4H), 1.46−1.37 (m, 2H); ^{1}H NMR (500 MHz, C_6D_6) δ 7.32−7.08 (m, 5H), 5.89−5.82 (m, 1H), 5.07−5.02 (m, 2H), 4.42−4.37 (m, 2H), 4.00−3.91 (ddd, *J* = 10.3, 5.6, 5.8 Hz, 1H), 3.72−3.67 (qd, *J* = 6.4, 3.8 Hz, 1H), 3.56−3.53 (dd, *J* = 9.7, 5.8 Hz, 1H), 3.41−3.38 (dd, *J* = 9.7, 6.0 Hz, 1H), 2.44−2.39 (m, 1H), 2.09−2.04 (m, 1H), 1.53 (m, 1H), 1.36 (m, 4H), 1.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 135.5, 128.6, 127.9, 127.7, 116.8, 73.5, 71.9, 71.8, 70.3, 37.9, 29.1, 27.3, 18.6; HRMS (EI/GCMS) *m*/*z* calcd for $C_{16}H_{22}NaO_2$ $(M + Na)^+$, 269.1518; found, 269.1525.

1-Allyl-2,3,4-tri-*O*-benzyllyxopyranose (14): Under standard allylation conditions using BF_3•OEt_2 as a Lewis acid, acetate **13** (0.263 g, 0.569 mmol) afforded **14** (0.377 g, 64%) as a 92:8 1,4-trans/cis mixture of isomers. The oil was purified by flash

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chromatography (hexanes to 1:9 Et_2O/hexanes) to afford the 1,4-trans product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.20 (m, 15H), 5.69−5.65 (m, 1H), 5.03−4.99 (m, 3H), 4.84−4.77 (m, 3H), 4.65 (d, J = 11.5 Hz, 1H and d, J = 11.6 Hz, 1H), 4.08−4.03 (m, 2H), 3.77−3.75 (d, J = 2.6 Hz, 1H), 3.57−3.51 (dd, J = 8.8, 2.8 Hz, 1H), 3.26−3.24 (t, J = 7.0 Hz, 1H), 3.17−3.12 (t, J = 12.6 Hz, 1H), 2.44−2.40 (m, 1H), 2.22−2.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 139.05, 139.03, 135.1, 128.92, 128.89, 128.8, 128.3, 128.2, 128.13, 128.09, 128.0, 117.8, 84.7, 79.5, 75.9, 75.7, 75.1, 74.0, 73.3, 69.2, 36.3; IR (thin film) 3030, 2860, 1496, 1454, 1362, 1129, 1093 cm^{-1}; HRMS (EI/GCMS) *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M + Na)^+$, 467.2198; found, 467.2191. Anal. Calcd for $C_{29}H_{32}O_4$: C, 78.35; H, 7.26. Found: C, 78.29; H, 7.05.

1-Allyl-2,3,4-tri-*O*-benzylribopyranose (23): Under standard allylation conditions using $BF_3{\cdot}OEt_2$ as a Lewis acid, acetate **22** (0.371 g, 0.802 mmol) afforded **51** (0.237 g, 63%) as a 91:9 1,4-cis/trans mixture of isomers. The oil was purified by flash chromatography (hexanes to 1:9 Et_2O/hexanes) to afford the 1,4-cis product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.47−7.31 (m, 15H), 5.88−5.82 (m, 1H), 5.16−5.09 (m, 2H), 5.00 (d, J = 11.8 Hz, 1H), 4.86 (d, J = 12.5 Hz, 1H), 4.80−4.67 (m, 4H), 4.19−4.15 (dd, J = 12.1, 4.5 Hz, 1H), 3.79−3.74 (m, 3H), 3.55 (m, 1H), 3.52−3.49 (dd, J = 12.1, 2.6 Hz, 1H), 2.85−2.79 (m, 1H), 2.51−2.45 (m, 1H); ^1H NMR (500 MHz, C_6D_6) δ 7.40−7.08 (m, 15H), 6.00−5.92 (m, 1H), 5.16−5.06 (m, 2H), 4.74 (m, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.44−4.35 (m, 3H), 4.07−4.03 (dd, J = 11.6, 6.2 Hz, 1H), 3.60 (m, 2H), 3.43 (t, J = 3.3 Hz, 1H), 3.34−3.32 (dt, J = 6.1, 3.1 Hz, 1H), 3.30 (m, 1H), 3.00 (m, 1H), 2.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 139.2, 139.9, 136.0, 128.8, 128.7, 128.6, 128.5, 128.3, 127.92, 127.87, 127.81, 127.78, 117.3, 79.1, 78.6, 75.6, 73.6, 73.5, 72.2, 72.0, 34.9; IR (thin film) 3029, 2866, 1453, 1358, 1108, 1066 cm^{-1}; HRMS (EI/GCMS) *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M + Na)^+$, 467.2198; found, 467.2187.

1-Allyl-2,3,4-tri-*O*-benzylxylopyranose (27): Under standard allylation conditions using $BF_3{\cdot}OEt_2$ as a Lewis acid, acetate **26** (0.158 g, 0.342 mmol) afforded **27** (0.100 g, 66%) as a 1:1 1,4-trans/cis mixture of isomers.[90] Careful flash chromatography (hexanes to 1:9 Et_2O/hexanes) provided a clean sample of the 1,4-trans product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 15H), 5.80 (m, 1H), 5.10 (m, 2H), 4.97 (d, J = 11.0 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.63−4.61 (d, J = 11.7 Hz, 1H and d, J = 10.8 Hz, 1H), 3.99 (dd, J = 11.0, 5.0 Hz, 1H), 3.65−3.57 (m, 2H), 3.30−3.23 (m, 2H), 3.16 (t, J = 10.8 Hz, 1H), 2.61 (m, 1H), 2.20 (m, 1H); ^1H NMR (500 MHz, C_6D_6) δ 7.36−7.01 (m, 15H), 6.08−6.00 (m, 1H), 5.12 (m, 2H), 5.00 (d, J = 11.4 Hz, 1H), 4.93 (d, J = 11.3 Hz, 1H), 4.82 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.34 (d, J = 11.9 Hz, 1H), 3.94−3.90 (dd, J = 11.0, 5.0 Hz, 1H), 3.62−3.59 (t, J = 9.0 Hz, 1H), 3.57−3.51 (ddd, J = 10.3, 9.1, 5.2 Hz, 1H), 3.25 (m, 2H), 3.08−3.03 (t, J = 11.0 Hz, 1H), 2.65−2.61 (m, 1H), 2.33−2.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 138.73, 138.69, 135.1, 129.0, 128.93, 128.90, 128.40, 128.37, 128.32, 128.26, 128.1, 117.7, 86.9, 81.7, 79.7, 79.3, 76.0, 75.7, 73.7, 68.5, 36.7; IR (thin film) 3064, 3030, 2909, 2863, 1496, 1454, 1102 cm^{-1}; HRMS (EI/GCMS) *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M + Na)^+$, 467.2198; found, 467.2186.

1-Allyl-2,3,4-tri-*O*-benzylarabinopyranose (31): Under standard allylation conditions using $BF_3{\cdot}OEt_2$ as a Lewis acid, acetate **30** (0.479 g, 1.04 mmol) afforded **31** (0.454 g, 99%) as a 68:32 1,4-trans/cis mixture of isomers. The isomers were resolved by careful flash chromatography (hexanes to 1:9 Et_2O/hexanes) to allow for individual characterization.

1,4-trans Isomer (β Isomer): ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.18 (m, 15H), 5.73−5.65 (m, 1H), 5.01 (m, 2H), 4.74 (m, 1H), 4.52 (m, 3H), 4.40 (m, 2H), 3.86 (m, 3H), 3.71 (m, 2H), 3.33 (m, 1H), 2.41−2.36 (m, 1H), 2.20−2.14 (m, 1H); ^1H NMR (500 MHz, C_6D_6) δ 7.34−7.07 (m, 15H), 5.84 (m, 1H), 5.06 (m, 2H), 4.80 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.30−4.18 (m, 4H), 4.01−3.93 (m, 5H), 3.40−3.39 (dd, J = 3.9, 1.6 Hz, 1H), 2.69−2.64 (m, 1H), 2.41−2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.7, 138.2, 135.2, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.93, 127.90, 117.2, 76.5, 74.3, 73.3, 73.2, 73.0, 72.7, 71.7, 64.8, 35.4; IR (thin film) 3030, 2868, 1454, 1096 cm^{-1}; HRMS (EI/GCMS) *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M + Na)^+$, 467.2198; found, 467.2213.

1,4-cis Isomer (α Isomer): ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.18 (m, 15H), 5.94−5.89 (m, 1H), 5.09 (m, 2H), 4.89 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 12.7 Hz, 1H), 4.73−4.62 (m, 3H), 4.55 (d, J = 12.0 Hz, 1H), 4.09 (dd, J = 12.8, 2.1 Hz, 1H), 3.75 (m, 1H), 3.72 (t, J = 9.2 Hz, 1H), 3.56−3.54 (dd, J = 9.2, 3.2 Hz, 1H), 3.26−3.23 (m, 2H), 2.63 (m, 1H), 2.35 (m, 1H); ^1H NMR (500 MHz, C_6D_6) δ 7.37−7.07 (m, 15H), 6.15 (m, 1H), 5.14 (m, 2H), 5.02 (d, J = 11.3 Hz, 1H), 4.55 (m, 2H), 4.40−4.20 (m, 3H), 3.90 (m, 2H), 3.34 (m, 2H), 3.27−3.23 (ddd, J = 9.1, 7.8, 3.1 Hz, 1H), 2.83 (d, J = 12.3 Hz, 1H), 2.71−2.69 (m, 1H), 2.47−2.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 135.4, 128.63, 128.61, 128.6, 128.4, 128.2, 128.04, 127.92, 127.89, 127.86, 117.1, 83.2, 79.9, 78.6, 75.6, 72.7, 71.7, 71.3, 67.1, 36.5; ^{13}C NMR (125 MHz, C_6D_6) δ 139.3, 139.1, 138.7, 135.7, 128.5, 128.44, 128.39, 127.7, 127.62, 127.60, 127.5, 116.6, 77.6, 74.6, 74.2, 73.4, 73.3, 72.7, 71.3, 64.4, 35.6; IR (thin film) 2907, 2862, 1453, 1093 cm^{-1}; HRMS (EI/GCMS) *m/z* calcd for $C_{29}H_{32}O_4$ $(M + Na)^+$, 467.2198; found, 467.2199.

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Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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