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The Effect of Electrostatic Interactions on Conformational Equilibria of Multiply Substituted Tetrahydropyran Oxocarbenium Ions

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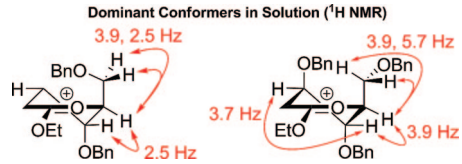

The three-dimensional structures of dioxocarbenium ions related to glycosyl cations were determined by an analysis of spectroscopic, computational, and reactivity data. Hypothetical low-energy structures of the dioxocarbenium ions were correlated with both experimentally determined ^{1}H NMR coupling constants and diastereoselectivity results from nucleophilic substitution reactions. This method confirmed the pseudoaxial preference of C-3 alkoxy-substituted systems and revealed the conformational preference of the C-5 alkoxymethyl group. Although the monosubstituted C-5 alkoxymethyl substituent preferred a pseudoequatorial orientation, the C-5−C-6 bond rotation was controlled by an electrostatic effect. The preferred diaxial conformer of the trans-4,5-disubstituted tetrahydropyranyl system underscored the importance of electrostatic effects in dictating conformational equilibria. In the 2-deoxymannose system, although steric effects influenced the orientation of the C-5 alkoxymethyl substituent, the all-axial conformer was favored because of electrostatic stabilization.

Introduction

Oxocarbenium ions play important roles in both the synthetic and bioorganic chemistry of carbohydrates. The synthesis of oligosaccharides generally involves treatment of glycosyl acetals with Lewis or Brønsted acids to form carbocationic intermediates, which are then trapped by sugar nucleophiles to form the glycosidic linkage.[1] Knowledge of the three-dimensional structures, relative energies, and reactivities of oxocarbenium ions would facilitate the design of selective glycosylation reactions.[2−7] In addition, understanding the conformational preferences of oxocarbenium ions would impact glycobiology and medicinal chemistry. Enzymes that catalyze glycosyl transfer, which can operate by stabilizing transition states with substantial oxocarbenium ion character,[8−14] have emerged as potential targets for the treatment of influenza,[15,16] diabetes,[17,18] and cancer.[19] Although transition state analogues of glycosyl transfer have been identified[20−22] and many inhibitors of glycosidases have been developed,[23−28] the three-dimensional structures of carbohydrate-derived oxocarbenium ions are not well understood, and only recently have computational studies of these structures emerged.[14,29−32] A better understanding of the three-dimensional structures of these cations would clarify the roles of these intermediates and transition states and facilitate the design of therapeutic glycosidase inhibitors.[14,29,30,33,34]

Our studies of the conformational preferences of oxocarbenium ions revealed that electronic effects exert strong influences on the conformational preferences of these cations. For reactions

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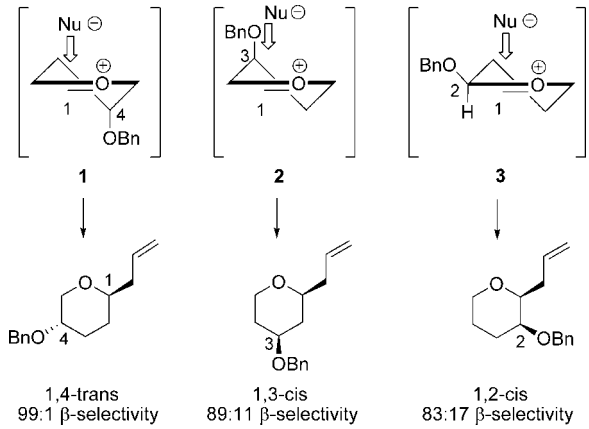
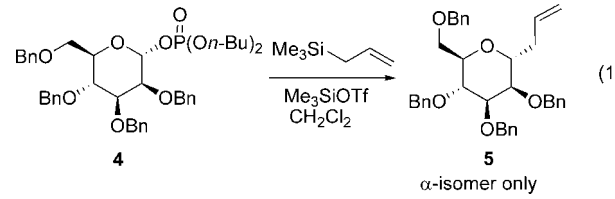


FIGURE 1. Preferred conformations of the oxocarbenium ion intermediates in nucleophilic substitution reactions of monosubstituted tetrahydropyran oxocarbenium ions.

involving C-3 and C-4 alkoxy-substituted tetrahydropyran cations,[35] the pseudoaxial conformations of the oxocarbenium ion intermediates **1** and **2** were consistent with the formation of the 1,4-trans and the 1,3-cis products, respectively (Figure 1).[36−38] The pseudoaxial conformations of the oxocarbenium ions are favored because they are stabilized by electrostatic interactions between the positively charged carbon atoms of the cations and the partially negatively charged substituents.[36,37,39−41] The results with substrates bearing an alkoxy group at C-2 revealed that although electrostatic effects are similar between the pseudoaxial and pseudoequatorial conformers,[42] the pseudoequatorial conformation **3** is stabilized by hyperconjugation from the C-2 carbon−hydrogen bond.[43]

Knowledge of the contributions of individual substituents to the conformational preferences of oxocarbenium ions, however, is not sufficient to predict the reactivities of highly substituted systems such as those formed from carbohydrates.[44] For instance, although the influences of the C-2, C-3, and C-4 substituents on the mannopyranosyl cation should reinforce each other to favor the β-product, α-selectivity was observed upon allylation of the mannosyl phosphate **4** (eq 1).[45−48] This



(1)

observation could be the result of a change in the conformational equilibria of the oxocarbenium ion such that the cationic intermediate now prefers the equatorial conformation **7** (eq 2) to avoid 1,3-diaxial interaction between the C-3 and C-5 substituents. Alternatively, the reversal in facial selectivity could be the result of a Curtin−Hammett scenario,[49,50] where the product distribution was dictated by the relative reactivities of the low-energy conformers. In this case, nucleophilic addition would occur via the higher energy conformer **7**, given that the kinetic barriers to the stereoelectronically disfavored twist transition states were too high in energy and that the lower energy conformer **6** was too sterically congested to react. Although the selectivities exhibited by multiply substituted cations suggested that the observation shown in eq 1 was the result of reaction through intermediate **7**,[51] we required additional evidence to confirm this hypothesis.

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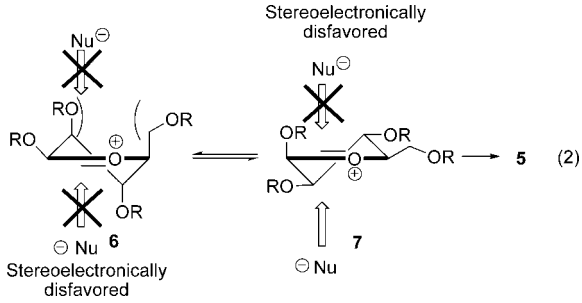
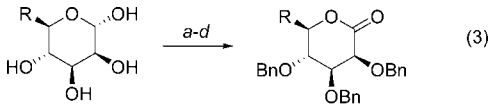


In this paper, we describe spectroscopic studies that illuminate the three-dimensional structures of highly substituted oxocarbenium ions. Although oxocarbenium ions are too reactive[52] to be observed in many cases,[53] the related dioxocarbenium ions[54,55] serve as isolable structural homologues, with conformational preferences that are also sensitive to electronic effects.[56] By comparing the ^{1}H NMR coupling constants of dioxocarbenium ions with those predicted by computational methods, we have established the conformational preferences of both monosubstituted and multiply substituted dioxocarbenium ions with structures related to glycosyl cations. In the absence of severe steric interactions, electrostatic forces dictate the conformational preferences of dioxocarbenium ions. This conclusion underscores the importance of considering electrostatic influences as well as steric effects when predicting conformational preferences in structurally flexible compounds.

Experimental Approach

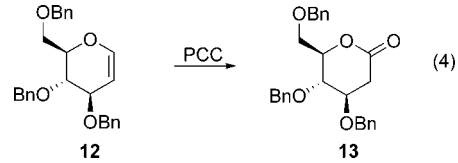
To probe the solution-phase conformational equilibria of the mannosyl oxocarbenium ion, we prepared a series of monosubstituted and multiply substituted tetrahydropyran dioxocarbenium ions and analyzed their conformational preferences. This approach was employed successfully for determining that the C-4 alkoxy-substituted dioxocarbenium ion preferred the pseudoaxial conformation.[56]

Because dioxocarbenium ions can be formed from lactones by alkylation with Meerwein salts,[54,55] a series of lactones were prepared. The lyxo and mannosyl lactones **10** and **11** were prepared by methanolysis of the corresponding sugars, followed by benzylation,[51] hydrolysis,[51] and oxidation (eq 3). The

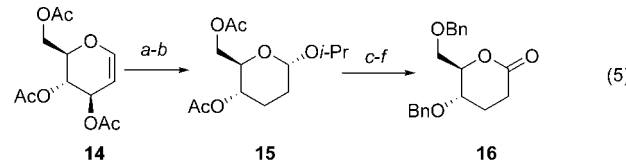


Reagents: *a*) Dowex-50 resin, MeOH; *b*) NaH, BnBr; *c*) cat. H_2SO_4 in 3:1 AcOH:H_2O; *d*) TPAP, NMO.

trisubstituted lactone **13** was prepared in one step by oxidation of the commercially available glycal **12** (eq 4).[57] Lactone **16**



was prepared from the commercially available acetylated glycal **14** through a six-step sequence beginning with a Ferrier reaction[58] and hydrogenation of the resulting olefin to yield the diacetate **15**. Deacetylation followed by benzylation, hydrolysis, and oxidation yielded the requisite lactone (eq 5).[59] Monosubstituted lactones **17** and **18** were prepared according to literature procedures.[36,51]



Reagents: *a*) $BF_3{\cdot}OEt_2$, *i*-PrOH; *b*) PtO_2, H_2 (g); *c*) NaOMe, MeOH; *d*) NaH, BnBr; *e*) AcOH in 1 M HCl; *f*) TPAP, NMO.

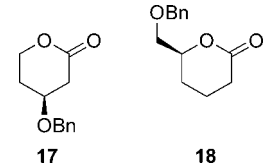
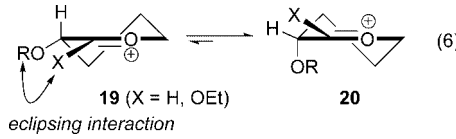


FIGURE 2. Monosubstituted lactones.

The C-2 benzyloxy-substituted dioxocarbenium ions were not examined because it was anticipated that they might give misleading results. The presence of an alkoxy group at C-2 would not only destabilize the cationic center inductively,[60] but it would also magnify a destabilizing eclipsing interaction in the dioxocarbenium ion (X = OEt, eq 6) as compared to the oxocarbenium ion (X = H).



The conformational preferences of the dioxocarbenium ions were established by comparing experimental ^{1}H NMR coupling constants to theoretical coupling constants of the low-energy conformers determined by computational methods.[61] The low-energy conformers of methyl analogues[62] of each cation (to simplify the system) were found by a systematic search of the conformational space using semi-empirical methods (PM3) in Spartan.[63,64] The energies of all minima were determined using low-level ab initio calculations (HF/3-21G). The structures of conformers with energies within 10 kcal/mol of the lowest energy conformer were further optimized with ab initio calculations, using a larger basis set (HF/6-31G*) and also density functional methods (B3LYP/6-31G*). All computed structures

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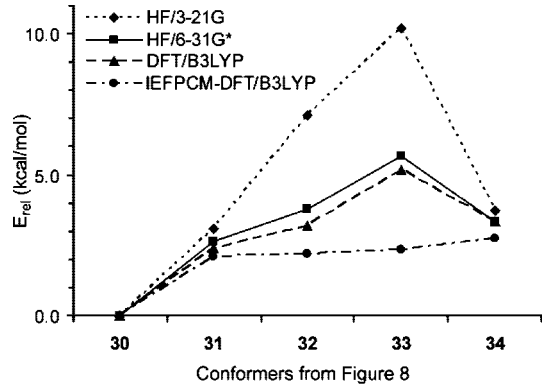


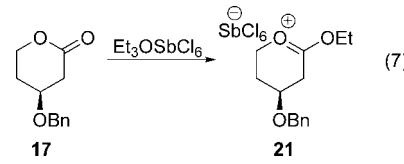
FIGURE 3. Relative energy of conformers at different levels of theory.

were confirmed to be minima using frequency calculations. The relative energies between different conformers do not vary substantially by the method used to calculate them, and the energies converge at higher levels of theory (Figure 3). All energy values are expressed as total energies (ΔE). The theoretical coupling constants were calculated de novo by using the Gaussian03 modeling package,[65] using density functional theory (B3LYP/6-31G*).[66] All calculated structures, relative energies, and coupling constants were evaluated with the Integral-Equation-Formalism Polarizable Continuum Model (IEFPCM)[67] to account for the effect of solvation in dichloromethane.

In all cases, the stereoselective *C*-glycosylation reactions of related oxocarbenium ions were compared with the conformational preferences of the dioxocarbenium ions. Nucleophilic substitution reactions of the oxocarbenium ions were performed with acetate precursors obtained by reductive acetylation[68] of the corresponding lactones prepared earlier (vide supra). Although the acetates were typically obtained as mixtures of anomers, the anomer distributions did not affect the outcome of the substitution reactions.[69] Allyltrimethylsilane was chosen as the nucleophile because addition of this nucleophile to oxocarbenium ions provided kinetic adducts reliably.[70] The stereochemistry of the allylated products was assigned using a combination of ^{1}H NMR coupling constants and NOE measurements.

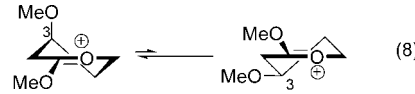
Results and Discussion

Although understanding the conformational preferences of monosubstituted systems alone was not enough to predict the conformational preferences of multiply substituted systems, studies of the simplified dioxocarbenium ions indicated that correlation of spectroscopic data with theoretical calculations could identify low-energy conformers. Spectroscopic studies of the C-3 alkoxy-substituted dioxocarbenium ion **21**[71] confirmed our earlier proposal[37] that the 3-alkoxy oxocarbenium ion adopted a pseudoaxial orientation. Alkylation of lactone **17** provided the dioxocarbenium ion **21** (eq 7), which decomposed



17 **21** (7)

over five hours at room temperature but could be analyzed spectroscopically at 0 °C. The small magnitude of the vicinal (^3J) coupling constants of the hydrogen at C-3 suggested that the alkoxy group was oriented pseudoaxially. This observation is consistent with computational studies (B3LYP/6-31G*) of the corresponding methyl derivative, which showed that the pseudoaxial conformer **22-ax** is favored by 1.4 kcal/mol over the equatorial conformer **22-eq** (eq 8). The coupling constants



22-ax **22-eq** (8)

E_{rel} = 0 kcal/mol E_{rel} = + 1.4 kcal/mol

for the computationally preferred conformer, **22-ax**, are in agreement with experimental *J*-values (Figure 4) and the observed stereoselectivities of additions to the corresponding oxocarbenium ion.[37] We attribute the preference for the pseudoaxial conformer **22-ax** to electrostatic attraction between the positively charged carbon atom of the dioxocarbenium ion[72] and the negatively charged oxygen atom of the alkoxy group, in agreement with our earlier studies with C-4 benzyloxy-substituted dioxocarbenium ions.[36,37,56]

The influence of an alkoxymethyl group at C-5 of a carbohydrate-derived oxocarbenium ion is more complicated than the influence of an alkoxy group at either C-3 or C-4. In addition to the ability to adopt either a pseudoaxial or a pseudoequatorial orientation, the substituent has additional conformational flexibility about the exocyclic C-5−C-6 bond,

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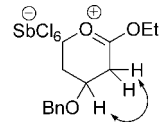
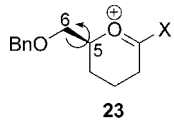
(59) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889–1911.
(60) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270–1277.
(61) Unpurified ^{1}H NMR spectra are provided as Supporting Information.
(62) The C-OMe rotamers found during the conformational search process were either retained or excluded based on the selection criteria described in the Experimental Section (see also "Details of Computation" in the Suppporting Information). If more than one rotamer exists after the HF/3-21G 10 kcal/mol filter, the lowest energy rotamer was used for the final analysis. The relative energy of the rotamers appears to be consistent with steric considerations.
(63) Deppmeier, B. J.; Driessen, A. J.; Hehre, T. S.; Hehre, W. J.; Johnson, J. A.; Klunzinger, P. E.; Leonard, J. M.; Pham, I. N.; Pietro, W. J.; Yu, J. *Spartan'02*, version 115a; Wavefunction, Inc.: Irvine, CA, 2002.
(64) Kong, J. et al. *J. Comput. Chem.* **2000**, *21*, 1532–1548.
(65) Pople, J. A. et al. *Gaussian03*, Revision B.4; Gaussian, Inc.: Pittsburgh, PA, 2003.
(66) (a) The validity of using the DFT/B3LYP method for calculating NMR spin−spin coupling constants have been investigated: Sychrovský, V.; Gräfenstein, J.; Cremer, D. *J. Chem. Phys.* **2000**, *113*, 3530–3547, Recent examples of calculations of NMR coupling constants using the DFT/B3LYP method. (b) Anizelli, P. R.; Vilcachagua, J. D.; Neto, Á. C.; Tormena, C. F. *J. Phys. Chem. A* **2008**, *112*, 8785–8789. (c) Silva, A. M. S.; Sousa, R. M. S.; Jimeno, M. L.; Blanco, F.; Alkorta, I.; Elguero, J. *Magn. Reson. Chem.* **2008**, *46*, 859–864.
(67) Mennucci, B.; Cancès, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506–10517.
(68) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317–8320.
(69) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677.
(70) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961.
(71) Although the C-3 alkoxy-substituted dioxocarbenium ion **21** could be formed at 0 °C, rapid decomposition within hours of product formation hindered our efforts to obtain X-ray quality crystals.
(72) Our calculated Mullikan populations for the C-1 atom of dioxocarbenium ions **22-ax** or **22-eq** are approximately 0.7. The net atomic charges for various simple oxocarbenium ions were also previously calculated and ranged from 0.5 to 0.8: Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 850–858.



4.3, 2.7 Hz (Experimental *J*-values)
3.9, 1.8 Hz (Theoretical *J*-values for **22-ax**)
8.7, 5.5 Hz (Theoretical *J*-values for **22-eq**)

FIGURE 4. Theoretical and experimental *J*-values for C-3 alkoxy dioxocarbenium ion (B3LYP/6-31G*).

as illustrated in cations **23**. This exocyclic dihedral angle can significantly influence the reactivity of carbohydrates.[73]



23
X = H, OEt

Computational studies on monosubstituted dioxocarbenium ion **23** (X = OEt) indicated that the conformational distribution could not be explained by simply invoking steric effects. Although the pseudoequatorial half-chair conformer **26** (which is in the $^4H_3$ orientation)[74] would minimize steric interactions, it was not the lowest energy structure (Figure 5). Despite incurring two gauche interactions, conformers **24** and **25** remained approximately isoenergetic with conformer **26**.[75] The presence of low-energy structures **24** and **25** could not be easily explained by consideration of steric effects. The relative energies of these structures, however, are consistent with the proposal that electrostatic effects stabilize these cations.[37,39−41] The decrease in distance between the electronegative oxygen substituent at C-5 and the carbocationic carbon C-1[76] compensated for the steric penalties associated with additional gauche interactions.

The computational predictions illustrated in Figure 5 are consistent with the NMR coupling constant data obtained for dioxocarbenium ion **23**[77] (X = OEt). The comparison between experimentally determined and calculated coupling constants for conformers **24**−**26** is illustrated in Figure 6. Because deviations between predicted and experimental values are reflected on the *y* axis, a curve which lies close to the *x* axis indicates a good correlation between theoretical and experimental values. The experimental *J*-values of conformer **24**, where the dioxocarbenium ion adopted a half-chair conformation ($^4H_3$) with the electronegative 5-alkoxymethyl group oriented toward the positive charge, agreed most closely with the predicted coupling constants. The substantial deviation between the experimentally determined $J_{H5,H6'}$ value and that calculated for cation **26** indicates that the alkoxymethyl substituent does

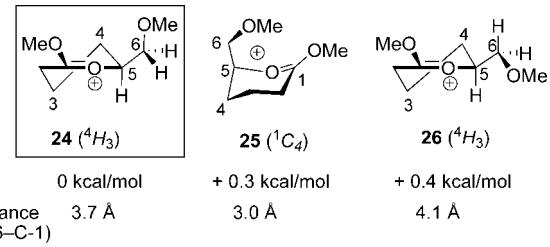


FIGURE 5. Relative low-energy conformers of C-5 alkoxymethyl dioxocarbenium ion (B3LYP/6-31G*).

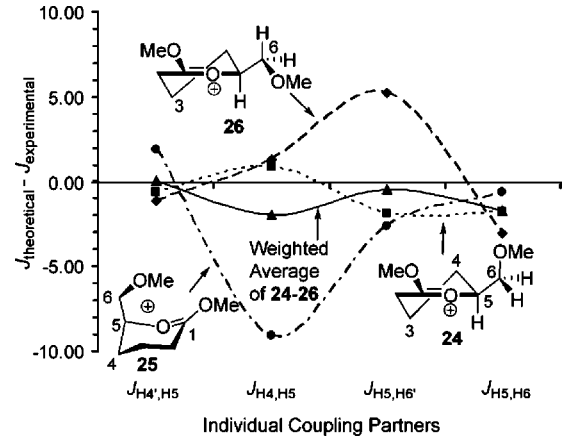
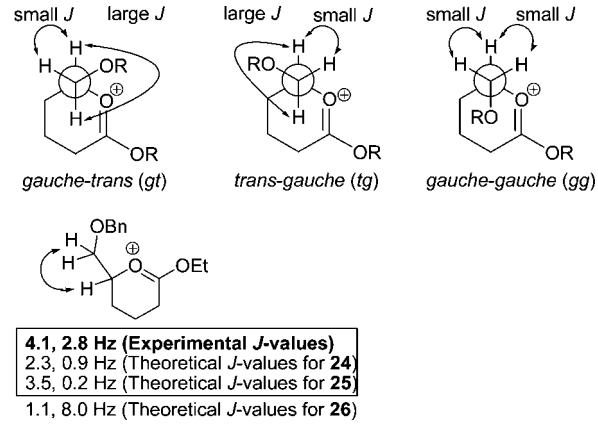


FIGURE 6. Comparison of theoretical and experimental *J*-values of C-5 alkoxymethyl dioxocarbenium ion.



4.1, 2.8 Hz (Experimental *J*-values)
2.3, 0.9 Hz (Theoretical *J*-values for **24**)
3.5, 0.2 Hz (Theoretical *J*-values for **25**)
1.1, 8.0 Hz (Theoretical *J*-values for **26**)

FIGURE 7. Theoretical and experimental *J*-values of C-5 alkoxymethyl rotamers.

not adopt this orientation. This discrepancy can be rationalized by considering the expected magnitude of $^3J_{H5,H6}$ and $^3J_{H5,H6'}$ based on the Karplus equation (Figure 7). Both *gt* and *tg* rotamers would require one large and one small *J*-value, while two small coupling constants would be expected for the *gg* rotamer. The experimental vicinal coupling constants of 4.1 and 2.8 Hz are consistent with a *gg* conformation as found in both **24** ($^4H_3$) and **25** ($^1C_4$) (Figure 5). Because the small energy differences between conformers **24**−**26** suggested a mixture of conformers in solution, a weighted average of their populations (based upon their calculated relative energies) was employed to determine statistically relevant averaged coupling constants. The resulting curve resembles the experimental values, suggesting that all three conformers are present in solution.

The conclusion from spectroscopic evidence that a dioxocarbenium ion with an alkoxymethyl group at C-5 adopts a pseudoequatorial conformation is consistent with reactivity of

(73) Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205–9213.

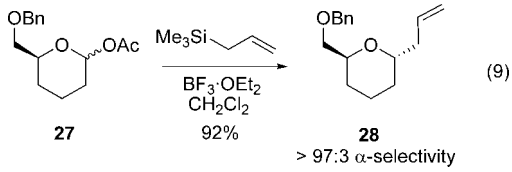
(74) The IUPAC nomenclature ($^OS_2$, $^3H_4$, $B_{O,3}$, etc.) defined for all conformers presented in this paper was assigned based on the method developed by Whitfield et al.: Bérces, A.; Whitfield, D. M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477–491. The endocyclic dihedral angles required for this analysis are supplied as Supplementary Information.

(75) Conformers **24**−**26** are considered to be isoenergetic, because errors associated with the B3LYP method can approach 1 kcal/mol: (a) Weldon, A. J.; Vickrey, T. L.; Tschumper, G. S. *J. Phys. Chem. A* **2005**, *109*, 11073–11079. (b) Woodcock, H. L.; Moran, D.; Pastor, R. W.; MacKerell, A. D., Jr.; Brooks, B. R. *Biophys. J.* **2007**, *93*, 1–10.

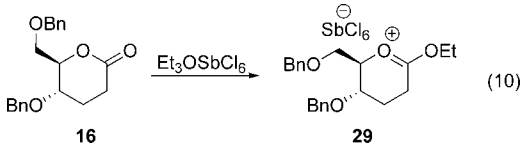
(76) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247–1253.

(77) Repeated attempts, including synthesizing analogues with different protecting groups (such as benzyl, 3-bromobenzyl, and tosyl), did not yield suitable crystals for X-ray crystallography.

the related oxocarbenium ion. Lewis acid-catalyzed nucleophilic substitution of acetate **27** afforded the 1,5-trans product **28** with high diastereoselectivity (eq 9).[78] This result can be explained by stereoelectronically controlled addition to the half-chair conformer analogous to **24** (or even **26**) in which the alkoxymethyl substituent adopts a pseudoequatorial orientation. Nucleophilic addition to the oxocarbenium ion analogous to **25** might give similar selectivity because the alkoxymethyl substituent would hinder approach of the nucleophile to the top face.



The importance of the exocyclic electrostatic effect revealed by the C-5 alkoxymethyl-substituted dioxocarbenium ion **23** (vide supra) was reinforced by results for the trans-4,5-disubstituted dioxocarbenium ion **29**[79] (eq 10). Computational



studies revealed that the dioxocarbenium ion strongly favored the diaxial half-chair conformer **30** (a $^3H_4$ conformer) over other possible conformers (Figure 8). The preference for this diaxial conformation demonstrates that the powerful electrostatic effect of the C-4 alkoxyl group can overwhelm the steric preference of the C-5 substituent to reside pseudoequatorially (vide supra). As with the C-5 alkoxymethyl-substituted dioxocarbenium ion **23**, the exocyclic alkoxymethyl group of **29** assumes a gauche orientation to maximize electrostatic interactions between the C-6 alkoxy group and the cationic carbon atom (as depicted by conformer **30**). Consistent with this argument, conformers **31**, **32**, and **34**, which are stabilized by only one electrostatic interaction, are considerably higher in energy. Although both conformers **30** and **34** have the proper alignment for a σ C-6−H to σ^* C-5−O$^+$ donation,[80] a 2.7 kcal/mol difference in their energy suggests that the stabilization is electrostatic rather than hyperconjugative in nature. Without electrostatic benefits, the diequatorial conformer **33** ($^4H_3$) is predicted to be higher in energy than the diaxial conformer **30** ($^3H_4$).

In accordance with the calculated energy differences of the low-energy conformers, experimental coupling constants confirmed that the diaxial conformation **30** (in the box in Figure 8) is the predominant species in solution. The fact that all $^3J_{H,H}$ coupling constants could be obtained for this molecule permitted a thorough analysis of its conformational preferences. As is evident from Figure 9, the experimental coupling constants

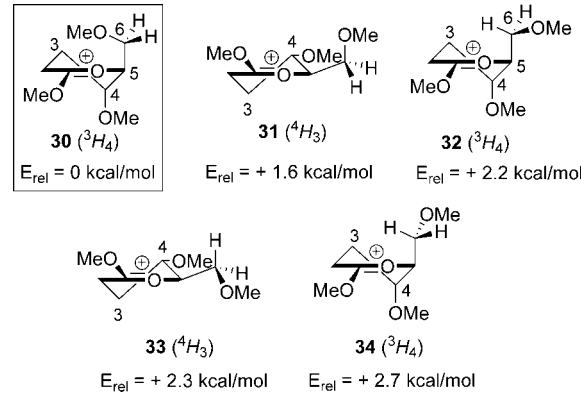
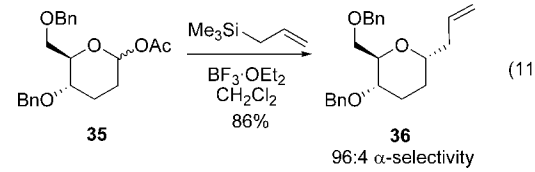


FIGURE 8. Relative low-energy conformers of the 4,5-disubstituted dioxocarbenium ion (B3LYP/6−31G*).

agreed well for most of the values expected for a $^3H_4$ half-chair conformation (**30**, **32**, and **34**[81]), but they corresponded poorly with the $^4H_3$ half-chair conformers (**31** and **33**). The diaxial orientation of the 4,5-disubstituted dioxocarbenium ion was further substantiated by the observed 1.5 Hz W-coupling between the hydrogen atom at C-5 and the equatorial hydrogen atom at C-3. This coupling is only possible when the C-5 substituent is pseudoaxial. The two half-chair conformers **30** and **32** can be distinguished by examination of the $J_{H5,H6'}$ region of the graph. The preference for conformer **30**, with gauche orientations of the hydrogen at C-5 to both hydrogens at C-6, indicates that the alkoxy group at C-6 must be positioned over the ring of the cation, presumably to maximize electrostatic stabilization.

The discrepancy between the conformational preference of the dioxocarbenium ion **29** and the selectivity of the reaction of the analogous oxocarbenium ion derived from **35** illustrates the importance of the Curtin−Hammett principle.[49,50] Although it might be expected that nucleophilic substitution of acetate **35** via its oxocarbenium ion would occur with β-selectivity through a conformer resembling **30**, α-selectivity was observed in this reaction (eq 11). Because interconversion among the different conformers is fast relative to the rate of nucleophilic addition,[40] the major product would arise from the conformer with the lowest transition state.[49,50] Reaction through the diaxial half-chair conformers analogous to **30**, **32**, and **34** would involve higher energy transition states due to developing 1,3-diaxial interactions. Therefore, the product likely resulted from α-attack of the $^4H_3$ diequatorial conformers (**31** or **33**).



Examination of the conformational bias of the dioxocarbenium ion derived from 2-deoxymannolactone **13**[83,84] (eq 12) revealed the limits of the electrostatic stabilization by an exocyclic alkoxy group. The lowest energy conformer identified by density functional methods (B3LYP/6-31G*) was the $^3H_4$ conformer **38** (Figure 10). The $^3H_4$ conformation is similar in structure to the ^3E conformation, a calculated minimum for the mannosyl oxocarbenium ion.[29] The conformer **38** experiences electrostatic stabilization from both C-3 and C-4 alkoxy groups. It does not, however, bring the alkoxy group at C-6 close to

(78) This result is inconsistent with the product ratio (70:30) we previously reported for this reaction (ref 51). In that paper, a minor product was observed in the unpurified reaction mixture, and it was assumed that the minor material was a diastereomer. We have since prepared the cis-isomer of **28** and confirmed that it is not formed in the reaction mixture. The details of these experiments are provided as Supporting Information.

(79) Repeated attempts, including synthesizing analogues with different protecting groups (such as benzyl, 3-bromobenzyl, and naphthyl), did not yield suitable crystals for X-ray crystallography. The benzylated dioxocarbenium ion **29** is stable for at least one month at −25 °C.

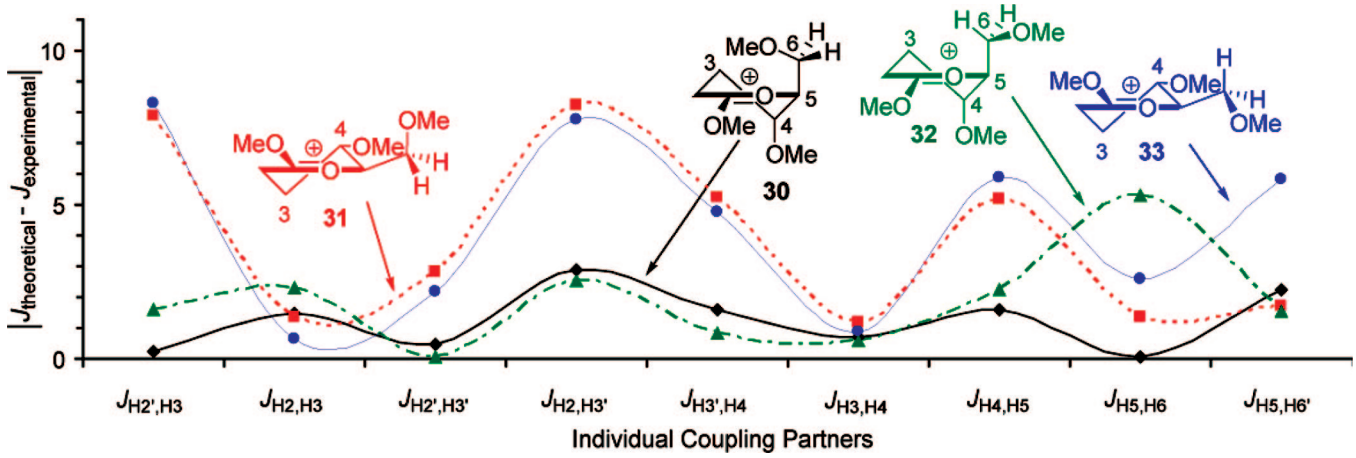
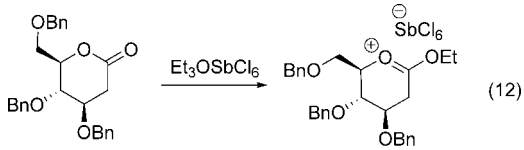


FIGURE 9. Comparison of theoretical and experimental *J*-values for 4,5-disubstituted dioxocarbenium ion.[82]

the cationic center, presumably to avoid interactions with the pseudoaxial C-3 substituent. This conformer would be destabilized not only by *syn*-butanol interactions,[85] but also by bringing two oxygen atoms into proximity.[86] In contrast, although both **40** (the $^{O}S_2$ conformer) and **41** ($^5H_4$) place all three substituents in positions to maximize their electrostatic influences, they remain higher in energy than the half-chair conformer **38**. The conformation predicted based solely on steric grounds, **42** (the half-chair conformer $^4H_3$), was considerably less stable.



(12)

Experimental coupling constants for the 2-deoxymannosyl dioxocarbenium ion **37** are more consistent with a weighted average of the low-energy conformers than they are with any particular conformer (Figure 11). On the basis of the energy differences between the low-energy conformers, **38** ($^3H_4$) should dominate the solution-phase equilibrium with some contributions from the twist conformers **39** and **40** (conformers **41** and **42**[87] would, combined, represent less than 3% of the mixture at 298 K). The experimental coupling constants, however, do not match

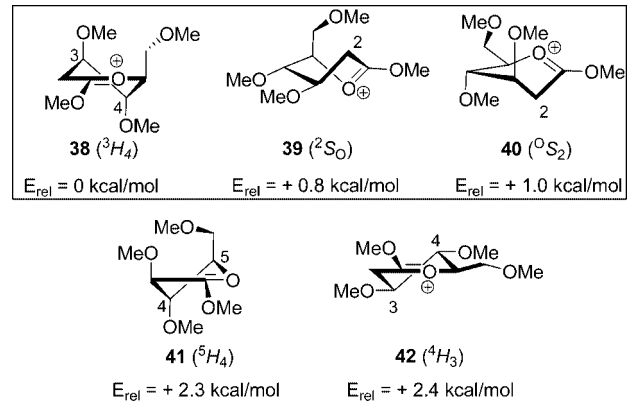


FIGURE 10. Calculated low-energy conformers of the 2-deoxymannosyl oxocarbenium ion (B3LYP/6-31G*).

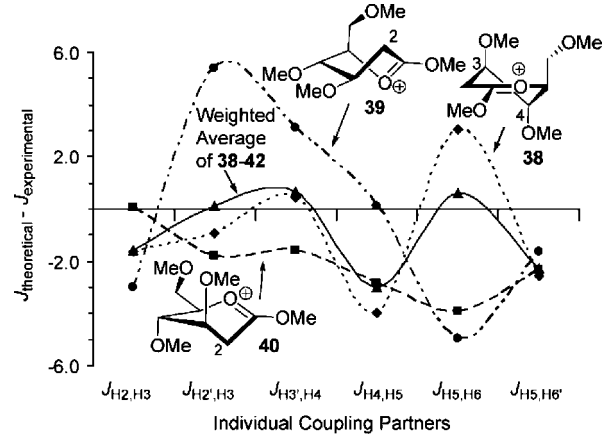


FIGURE 11. Comparison of theoretical and experimental *J*-values of the 2-deoxymannosyl oxocarbenium ion.

well with any individual conformer. A weighted average of their populations was again employed to determine statistically relevant averaged coupling constants. The resulting curve more closely resembles the experimental values, suggesting that multiple conformers (in the box in Figure 10) are present in solution.

If conformations resembling the half-chair conformer **38** ($^3H_4$) and the twist conformers **39** and **40** were also responsible for

(80) We did not consider the σ C-5−H to σ^* C-6−O interaction to be a significant source of stabilization due to prior observations that methoxycyclohexane prefers to adopt an equatorial conformation and 1,2-dimethoxyethane does not adopt a gauche conformation: Lii, J.-H.; Chen, K.-H.; Grindley, T. B.; Allinger, N. L. *J. Comput. Chem.* **2003**, *24*, 1490–1503.

(81) To simplify the graph, the higher energy conformer **34** was omitted from Figure 9. It was plotted along with its C-5−C-6 rotamers (**30** and **33**) in the Supporting Information.

(82) Because one dominant low-energy conformer (**30**) exists for this substrate, we felt that taking the absolute value of the difference between experimental and theoretical *J*-values best illustrates the differences between theoretical values and experimental data. Other means of analyzing the data, such as considering the value of the difference or proportional errors, were considered, and these plots lead to the same conclusion. These plots are provided as Supporting Information.

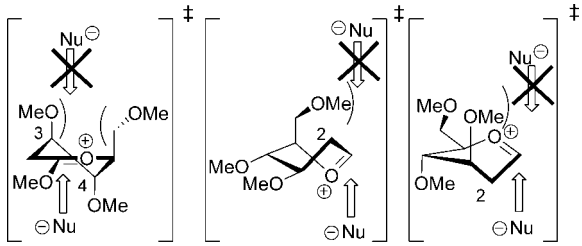
(83) This lactone may be considered to be 2-deoxygluconolactone because mannose and glucose differ only in the configuration at C-2.

(84) Although the trisubstituted dioxocarbenium ion **37** could be formed, rapid decomposition within hours of product formation hindered our efforts to obtain X-ray quality crystals.

(85) Ohno, K.; Yoshida, H.; Watanabe, H.; Fujita, T.; Matsuura, H. *J. Phys. Chem.* **1994**, *98*, 6924–6930.

(86) Law, R. V.; Sasanuma, Y. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 4885–4888.

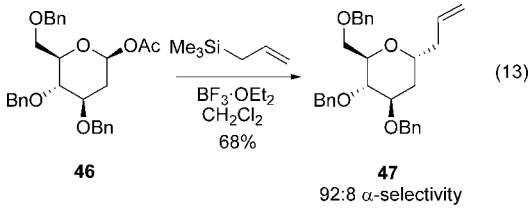
(87) To simplify the graph, higher energy conformers **41** and **42** were omitted from Figure 11. They were plotted along with conformer **38** in the Supporting Information.



43 44 45

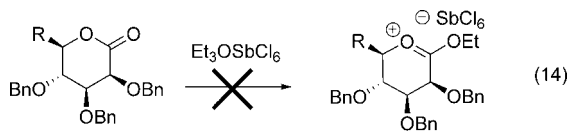
FIGURE 12. Nucleophilic addition to oxocarbenium ions derived from 2-deoxymannolactone.

the reactivity of the related oxocarbenium ion, nucleophilic addition to the oxocarbenium ion should be α-selective. Nucleophilic attacks from the β-faces to conformers analogous to **38**−**40** should be disfavored over the corresponding attacks from the α-faces, because they would lead to transition states with 1,3-diaxial interactions (Figure 12). Alternatively, if any of these modes of nucleophilic attack were slow relative to stereoelectronically controlled addition to the higher energy half-chair conformer **42**, α-selectivity would still be predicted based upon the Curtin−Hammett principle.[49,50] This interpretation was supported by the nucleophilic substitution reaction of acetate **47**, which yielded the α-product (eq 13).



46 **47**
92:8 α-selectivity

The strategy employed to discern the conformational preference of the less substituted oxocarbenium ions described above was not suitable for studying oxocarbenium ions with alkoxy groups at C-2. When the lactone precursors **10** and **11** were subjected to alkylation conditions, the dioxocarbenium ion products **48** and **49** were not observed (eq 14). Instead, the reaction yielded a complex mixture of byproducts.[61] It is possible that the dioxocarbenium ions were formed, but the neighboring electronegative C-2 substituent[60] made these intermediates much more reactive than their deoxy analogues (such as **29** and **37**, vide supra).



10 R = H
11 R = CH_2OBn

48 R = H
49 R = CH_2OBn

Conclusion

Insight into the conformational preferences of highly substituted tetrahydropyran oxocarbenium ions was obtained by comparing spectroscopic and computational studies of related dioxocarbenium ions with reactivity data of oxocarbenium ions. Experimentally determined coupling constants for dioxocarbenium ions agreed closely with those predicted by computational studies, particularly if relative populations of conformers were considered. These studies revealed strong conformational preferences. As demonstrated by reactions of oxocarbenium ions,[27,28] alkoxy groups at C-3 and C-4[56] exhibited marked preferences to reside in axial orientations. Although the C-5 alkoxymethyl group preferred to reside pseudoequatorially, an electrostatic attraction oriented the C-6 alkoxy group toward the oxocarbenium ion carbon atom. This electrostatic effect was most pronounced in the trans 4,5-disubstituted system, where the powerful electrostatic effect exerted by the C-4 alkoxyl group caused the C-5 alkoxymethyl group to adopt a diaxial conformation with the C-6 alkoxy group pointed over the ring. The trisubstituted system preferred to adopt a half-chair ($^3H_4$) conformation with three axial substituents. These studies provided additional insight that should facilitate understanding reactions that involve carbohydrate-derived oxocarbenium ions.

Experimental Section

General experimental details and the syntheses of lactones and acetates are provided as Supporting Information.

1-Ethoxy-3-benzyloxytetrahydropyrylium Hexachloroantimonate (21). To lactone **17**[36] (0.031 g, 0.15 mmol) in 0.7 mL of CD_2Cl_2 was added triethyloxonium hexachloroantimonate (0.066 g, 0.152 mmol). The reaction mixture was cooled at 0 °C. A ^{1}H NMR spectrum was taken of the reaction mixture after 3 h: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.41−7.29 (m, 5H), 5.38−5.30 (m, 2H), 4.92−4.84 (m, 2H), 4.64 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.30−4.27 (m, 1H), 3.41 (dd, J = 19.9, 4.3 Hz, 1H), 3.28 (ddt, J = 19.8, 2.7, 1.4 Hz, 1H), 2.52−2.39 (m, 2H), 1.55 (t, J = 7.0 Hz, 3H). The 4.3 Hz J-value at δ 3.41 ppm and the 2.7 Hz J-value at δ 3.28 ppm suggest an axial disposition of the C-3 substituent.

1-Ethoxy-5-(benzyloxymethyl)tetrahydropyrylium Hexachloroantimonate (23). To lactone **18**[51] (0.053 g, 0.24 mmol) in 0.7 mL of CD_2Cl_2 was added triethyloxonium hexachloroantimonate (0.111 g, 0.254 mmol). The reaction mixture was protected from light at room temperature in a nitrogen atmosphere dry box. A ^{1}H NMR spectrum was taken of the reaction mixture after 3 h: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.42−7.29 (m, 5H), 5.51 (dtd, J = 9.6, 4.1, 2.8 Hz, 1H), 4.91−4.74 (m, 2H), 4.60 (s, 2H), 4.00 (dd, J = 12.0, 2.8 Hz, 1H), 3.86 (dd, J = 12.0, 4.2 Hz, 1H), 3.26−3.17 (m, 1H), 3.11−3.02 (m, 1H), 2.32−2.03 (m, 4H), 1.54 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 189.9, 137.5, 129.1, 128.7, 128.5, 94.8, 75.0, 74.1, 69.9, 29.1, 23.6, 16.3, 13.9. The 4.1 and 2.8 Hz J-values at δ 5.51 ppm suggest a *gg* orientation of the C-5 substituent.

1-Ethoxy-4,6-di-*O*-benzyl-2,3-dideoxy-D-glucopyrylium Hexachloroantimonate (29). To a solution of lactone **16** (0.068 g, 0.21 mmol) in CD_2Cl_2 (1.0 mL) was added triethyloxonium hexachloroantimonate (0.092 g, 0.21 mmol). The reaction mixture was protected from light in ambient temperature in a nitrogen atmosphere dry box. A ^{1}H NMR spectrum was taken of the reaction mixture after 6 h: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44−7.27 (m, 10H), 5.54 (dtd, J = 3.9, 2.5, 1.5 Hz, 1H), 4.89−4.75 (m, 2H), 4.67 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.15 (dt, J = 5.0, 2.7 Hz, 1H), 4.02 (dd, J = 11.9, 3.9 Hz, 1H), 3.90 (dd, J = 11.8, 2.6 Hz, 1H), 3.18 (ddd, J = 20.5, 9.7, 7.4 Hz, 1H), 3.12 (ddd, J = 20.5, 6.9, 3.4 Hz, 1H), 2.44 (dddd, J = 14.4, 9.8, 7.0, 2.9 Hz, 1H), 2.36−2.27 (m, 1H), 1.53 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 189.9, 137.0, 136.9, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 93.7, 75.5, 74.3, 71.9, 69.8, 67.3, 25.9, 20.9, 13.9. The 3.9, 2.5, and 1.5 Hz J-values at δ 5.54 ppm suggest both axial dispositions of the C-4 and C-5 substituents and the *gg* orientation of the C-5 substituent.

1-Ethoxy-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyrylium Hexachloroantimonate (37). To a solution of lactone **13** (0.042 g, 0.097 mmol) in CD_2Cl_2 (0.7 mL) was added triethyloxonium hexachloroantimonate (0.049 g, 0.112 mmol). The reaction mixture was

protected from light in ambient temperature in a nitrogen atmosphere dry box. A ^{1}H NMR spectrum was taken of the reaction mixture after 2 h: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.41−7.23 (m, 15 H), 5.36 (dt, J = 5.7, 3.9 Hz, 1H), 4.96−4.84 (m, 2H), 4.68−4.46 (m, 6H), 4.23 (q, J = 3.7 Hz, 1H), 4.12 (td, J = 3.9, 0.9 Hz, 1H), 3.92 (dd, J = 11.7, 5.8 Hz, 1H), 3.88 (dd, J = 11.6, 4.0 Hz, 1H), 3.30 (dd, J = 18.3, 4.0 Hz, 1H), 1.54 (t, J = 7.1 Hz, 3H). The 3.7 Hz J-value at δ 4.23 ppm and the 3.9 Hz J-value at δ 5.36 ppm suggest axial dispositions of all three substituents.

General Procedure for the Nucleophilic Substitution of Acetate Substrates. Allyltrimethylsilane (4.0 equiv) was added to a solution of acetate (0.10 M) in CH_2Cl_2, and the mixture was cooled to −78 °C and treated with the Lewis acid (4.0 equiv). After 5 min, the mixture was allowed to warm to −45 °C. After 4 h, the reaction mixture was warmed to room temperature and treated with saturated aqueous $NaHCO_3$ (30 mL per mmol of acetate). The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (10 mL per mmol of acetate), dried over $MgSO_4$, filtered, and concentrated in vacuo.

For allylation of 5-substituted acetate **27**, the unpurified product ratios were determined by using GCMS and confirmed with ^{1}H NMR spectroscopy. For allylation of the disubstituted acetate **35**, the product ratios were based on isolated yield of the minor isomer and confirmed by GCMS and ^{1}H NMR spectroscopy of the unpurified material. For allylation of trisubstituted acetate **46**, the product ratios were based on ^{1}H NMR spectroscopy of the unpurified material. The reported yields are of purified materials. For allylated products **28** and **36**, the relative configurations were determined by nuclear Overhauser effect (NOE) enhancements. For compound **47**, the relative configurations were determined by correlation to previously published spectral data.[88]

1-Allyl-5-benzyloxymethyltetrahydropyran (28). Under standard allylation conditions with $BF_3\cdot OEt_2$ as the Lewis acid, acetate **27**[51] (0.144 g, 0.546 mmol) afforded **28** (0.123 g, 92%) as a >97:3 1,5-trans:cis mixture of isomers. The absence of the minor cis isomer was confirmed by the synthesis of authentic minor material (which is described in the Supporting Information). The oil was purified by flash chromatography (1:4 Et_2O:pentane) to afford the 1,5-trans product **28** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 5.81 (ddt, J = 17.0, 10.3, 7.0 Hz, 1H), 5.09 (dq, J = 17.2, 1.6 Hz, 1H), 5.04 (dt, J = 2.0, 1.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 3.98−3.92 (m, 1H), 3.84−3.78 (m, 1H), 3.58 (dd, J = 9.9, 6.4 Hz, 1H), 3.44 (dd, J = 10.0, 5.3 Hz, 1H), 2.46 (qnt, J = 7.0, 1.3 Hz, 1H), 2.23 (qnt, J = 7.1, 1.1 Hz, 1H), 1.70−1.55 (m, 1H), 1.50−1.34 (m, 2H), 1.73−1.54 (m, 4H), 1.50−1.34 (m, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 138.5, 135.4, 128.4, 127.7, 127.6, 116.7, 73.2, 71.64, 71.59, 70.0, 37.7, 28.9, 27.1, 18.4; IR (neat) 3066, 3030, 2935, 2864, 1641, 1454 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{22}O_2Na$ $(M + Na)^+$ 269.1518, found 269.1520. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.75; H, 8.92.

1-Allyl-5-benzyloxymethyl-4-benzyloxytetrahydropyran (36). Under standard allylation conditions with $BF_3\cdot OEt_2$ as the Lewis acid, acetate **35** (0.205 g, 0.553 mmol) afforded **36** as a 96:4 1,5-trans:cis mixture of isomers. The product distribution was determined based on isolated yield of the minor isomer and confirmed with GCMS and ^{1}H NMR spectroscopy of the unpurified material. Purification by flash column chromatography on silica gel (1:9 Et_2O:hexanes) afforded 1,5-trans isomer **36** (0.142 g, 86%) and 1,5-cis isomer (0.007 g, 4%) as colorless oils. **Major Isomer (36):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 10H), 5.80 (ddt, J = 17.1, 10.3, 7.1 Hz, 1H), 5.08 (dt, J = 1.8, 1.5 Hz, 1H), 5.04 (dt, J = 2.2, 1.1 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.52, (d, J = 12.2 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 3.88−3.82 (m, 1H), 3.80 (ddd, J = 6.7, 4.6, 4.2 Hz, 1H), 3.69 (dd, J = 10.3, 5.0 Hz, 1H), 3.62 (dd, J = 10.3, 3.8 Hz, 1H), 3.50−3.45 (m, 1H), 2.54−2.46 (m, 1H), 2.28−2.21 (m, 1H), 1.97−1.89 (m, 1H), 1.77−1.63 (m, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 138.7, 138.5, 135.2, 128.44, 128.41, 127.9, 127.8, 127.64, 127.63, 116.8, 73.4, 73.2, 72.9, 71.8, 70.8, 69.6, 36.7, 26.2, 24.3; IR (neat) 3064, 3030, 2938, 2862, 1951, 1871, 1812, 1641, 1496, 1454, 1364, 1101, 913, 736, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{28}O_3Na$ $(M + Na)^+$ 375.1936, found 375.1947. Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.25; H, 8.13. $[\alpha]^{24}_D$ +57.5 (c 1.17, CH_2Cl_2). **Minor Isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.22 (m, 10H), 5.84 (dddd, J = 17.0, 10.2, 7.4, 6.9 Hz, 1H), 5.11−5.01 (m, 2H), 4.64 (d, J = 12.3 Hz, 1H), 4.61−4.55 (m, 2H), 4.40 (d, J = 11.5 Hz, 1H), 3.77 (dd, J = 10.5, 1.6 Hz, 1H), 3.67 (dd, J = 10.8, 4.8 Hz, 1H), 3.42−3.36 (m, 3H), 2.43−2.35 (m, 1H), 2.30−2.15 (m, 2H), 1.72−1.97 (m, 1H), 1.50−1.27 (m, 2H).

1-Allyl-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (47). Under standard allylation conditions with $BF_3\cdot OEt_2$ as the Lewis acid, acetate **46** (0.202 g, 0.425 mmol) afforded a 92:8 α:β mixture of anomers.[89] Purification by flash column chromatography on silica gel (1:4 Et_2O:hexanes) provided the α-isomer **47** as a colorless oil (0.133 g, 68%). The spectral data correlate with the previously reported data for **47**:[88] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.19 (m, 15H), 5.07−5.03 (m, 1H), 5.03−5.01 (m, 2H), 4.78 (d, J = 11.3 Hz, 1H), 4.62−4.48 (m, 5H), 4.03 (tt, J = 7.5, 4.4 Hz, 1H), 3.82−3.73 (m, 3H), 3.69−3.63 (m, 1H), 3.54 (t, J = 7.1 Hz, 1H), 2.44 (dddt, J = 14.3, 7.8, 6.7, 1.3 Hz, 1H), 2.21 (dtt, J = 14.2, 7.2, 0.9 Hz, 1H), 1.98 (dt, J = 13.4, 4.3 Hz, 1H), 1.76 (ddd, J = 13.6, 9.4, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.5, 138.4, 134.8, 128.52, 128.48, 128.4, 128.1, 128.0, 127.77, 127.75, 127.74, 127.67, 117.1, 77.0, 76.5, 74.2, 73.5, 72.9, 71.4, 70.6, 69.1, 36.8, 32.5; HRMS (ESI) m/z calcd for $C_{30}H_{34}O_4Na$ $(M + Na)^+$ 481.2355, found 481.2358. $[\alpha]^{24}_D$ +32.2 (c 1.29, CH_2Cl_2).

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Supporting Information Available: Complete refs 16, 64 and 65, experimental procedures, product characterization, stereochemical proofs, details of computations, 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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(88) Characterization data for the β-isomer: Crich, D.; Lim, L. B. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2205–2208. Characterization data for the α-isomer: Wang, Z.; Shao, H.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105.

(89) The minor isomer was identified in the unpurified spectrum by comparison to previously reported ^{1}H NMR spectrum for the β-isomer.