J|A|C|S
ARTICLES
Published on Web 07/13/2005

Stereoselective *C*-Glycosylation Reactions of Ribose Derivatives: Electronic Effects of Five-Membered Ring Oxocarbenium Ions

Catharine H. Larsen, Brian H. Ridgway, Jared T. Shaw, Deborah M. Smith, and K. A. Woerpel*

Contribution from the Department of Chemistry, University of California, Irvine, California 92697-2025

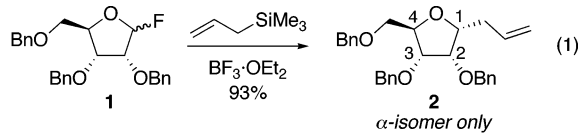
Received April 13, 2005; E-mail: kwoerpel@uci.edu

Abstract: The factors controlling the highly α-selective *C*-glycosylation of ribose derivatives were determined by examining the stereoselective reactions of 18 ribose analogues differing in substitution at C-2, C-3, and C-4. The lowest energy conformers of the intermediate oxocarbenium ions display the C-3 alkoxy group in a pseudoaxial orientation to maximize electrostatic effects. To a lesser extent, the C-2 substituent prefers a pseudoequatorial position, and the alkyl group at C-4 has little influence on conformational preferences. In all cases, the product was formed by stereoelectronically preferred inside attack on the lowest energy conformer.

Introduction

The stereoselective synthesis of substituted tetrahydrofurans remains an important synthetic challenge because this structural motif is prevalent in many target structures. For example, methods have been developed for the construction of the five-membered ring form of carbohydrates, since this framework emerges often in biological systems such as furanoses[1] and nucleosides.[2] Interest in the synthesis of *C*-glycosides[3,4] and *C*-nucleosides[5] has intensified because of the therapeutic potential of these compounds.[6,7] In addition, challenges posed by natural products containing the tetrahydrofuran moiety, such as the Annonaceous acetogenins,[8,9] have heightened interest in the stereocontrolled synthesis of this ring system.[10]

Because of the high level of stereochemical control that can be observed, nucleophilic substitution reactions of five-membered ring acetals are valuable transformations to access highly substituted tetrahydrofurans and furanosides.[10,11] For example, the *C*-glycosylation reaction[3] of the ribose-derived glycosyl fluoride **1** occurred from the α-face to provide the α-glycoside **2** exclusively (eq 1).[12] Because the configuration

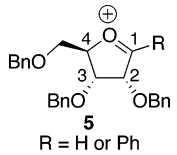


at C-1 of the α-*C*-glycoside **2** is opposite to that for the naturally occurring nucleosides, a complementary strategy has been employed to obtain the biologically relevant *β*-*C*-glycoside. Nucleophilic substitution by hydride onto a hemiacetal bearing a carbon substituent at C-1[13] proceeded from the α-face to provide the desired *β*-*C*-glycoside **4** (eq 2).[14,15]

The proclivity for α-selective substitutions of ribose-derived acetals as exemplified by eqs 1 and 2 has never been adequately explained, limiting the influence of these reactions on synthetic and biological chemistry. Because the anomeric configuration

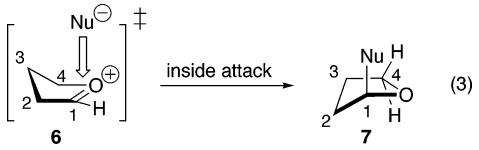
(1) Lowary, T. L. *Curr. Opin. Chem. Biol.* **2003**, *7*, 749−756.
(2) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859−1876.
(3) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959.
(4) For a recent example, see: Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 2611−2614.
(5) Wu, Q.; Simons, C. *Synthesis* **2004**, 1533−1553.
(6) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3818−3822.
(7) el Kouni, M. H. *Curr. Pharm. Des.* **2002**, *8*, 581−593.
(8) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306.
(9) For a recent total synthesis and citations to the recent literature in this field, see: Nattrass, G. L.; Díez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580−584.
(10) For example, the syntheses of members of the amphidinolide T natural products utilize substitution reactions of acetals to introduce a substituent and establish the stereochemistry of the tetrahydrofuran moiety: (a) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374−2375. (b) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512−15520. (c) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297−4307.
(11) For a review that includes nucleophilic substitution on five-membered ring acetals, see: Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754.
(12) Araki, Y.; Kobayashi, N.; Ishido, Y.; Nagasawa, J. *Carbohydr. Res.* **1987**, *171*, 125−139.
(13) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.
(14) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610−612.
(15) For related examples, see: (a) Liu, W.; Walker, J. A., II; Chen, J. J.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1996**, *37*, 5325−5328. (b) Matulic-Adamic, J.; Beigelman, L. *Tetrahedron Lett.* **1997**, *38*, 1669−1672. (c) Dondoni, A.; Formaglio, P.; Marra, A.; Massi, A. *Tetrahedron* **2001**, *57*, 7719−7727.

(α or β) of the starting materials **1** and **3** does not determine the stereochemistry of the products, these reactions likely proceed via oxocarbenium ions **5**.[16] Evidently, the nucleophile approaches the electrophilic carbon from the face bearing the two alkoxy groups at C-2 and C-3. To explain the counterintuitive stereochemical outcome shown in eq 1, various arguments have been offered, such as involvement of the counterion and solvent.[12,17,18] These arguments, however, are unsatisfying because the selectivities are only marginally affected by solvent, Lewis acid, anomeric leaving group, and carbon-based nucleophile (eq 1).[19−24] The generality of the α-selective substitution suggests that the selectivity is the result of an inherent stereochemical bias of the substituted oxocarbenium ion **5** and not a result of external variables.



The challenges associated with understanding the perplexing selectivities shown in eqs 1 and 2 prompted us to investigate the origin of stereoselective reactions of highly oxygenated five-membered ring oxocarbenium ions such as **5**. In this article, we demonstrate that electronic [25,26] and stereoelectronic effects dominate the selectivity exhibited by ribose-derived acetal **1** (eq 1). We also show that the conclusions gleaned from the study of ribose-derived acetals allow for predictions of stereochemical courses for new reactions.

Our earlier studies of oxocarbenium ions indicate that five- and six-membered ring oxocarbenium ions display parallel selectivity patterns, suggesting that similar influences control the stereoselectivities of the two related systems. Because five-membered ring systems undergo conformational interconversions more rapidly than six-membered rings,[1,27,28] it is more challenging to develop stereochemical models, and therefore few attempts to codify these reactions have emerged.[29−32] Five-membered rings do exhibit discrete minima, however, as has been demonstrated for ribose systems.[33] Consequently, as established with six-membered ring systems,[34−36] stereoelectronic effects should control the approach of the nucleophile to a five-membered ring oxocarbenium ion.[37−39] Experiments involving conformationally constrained five-membered ring oxocarbenium ions revealed that attack on the prototypical oxocarbenium ion **6** occurred preferentially (up to 96:4 selectivity) from "inside" the envelope to form the staggered product **7** (eq 3).[38] Destabilizing steric effects that emerge in transition



structures also influence selectivities,[26,39] in accordance with the Curtin−Hammett principle.[40] The magnitude of such effects is difficult to estimate a priori, since the precise transition structures for nucleophilic attack on oxocarbenium ions have not been located and are likely to depend on substitution patterns.[41]

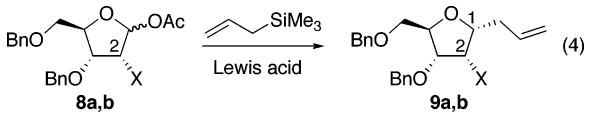
The conformational analysis of heteroatom-substituted six-membered ring oxocarbenium ions allows for an understanding of the behavior of five-membered ring analogues (vide infra). While alkyl groups in six-membered ring oxocarbenium ions prefer equatorially substituted conformers, heteroatom-containing functional groups reside in pseudoaxial orientations at certain positions of the ring.[25,26,42] With the alkoxy group situated in the pseudoaxial position, an attractive electrostatic interaction between the cationic carbon and partially negatively charged substituent is maximized. This paradoxical conformational preference is supported by computational[43,44] and experimental studies with six-membered ring oxocarbenium ions[25,26,42,45−49] and iminium ions[50−52] and operates in the rates of oxocarbenium ion generation.[53,54] As will be demonstrated, the selectivities exhibited by ribose-derived oxocarbenium ions find close analogy to our studies with the six-membered ring systems.[25,26,42]

(16) Lowary has shown that *O*-glycosylation of furanosyl triflates occurs with inversion of configuration: Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112−13119.
(17) Jaouen, V.; Jégou, A.; Lemée, L.; Veyrières, A. *Tetrahedron* **1999**, *55*, 9245−9260.
(18) Nishiyama, Y.; Katoh, T.; Deguchi, K.; Morimoto, Y.; Itoh, K. *J. Org. Chem.* **1997**, *62*, 9339−9341.
(19) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289−4296.
(20) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892−897.
(21) Mukaiyama, T.; Kobayashi, S. *Carbohydr. Res.* **1987**, *171*, 81−87.
(22) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145−148.
(23) O'Leary, D. J.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 6629−6636.
(24) Hachiya, I.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 3319−3320.
(25) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.
(26) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528.
(27) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205−8212.
(28) Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1−94.
(29) Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40−42.
(30) Schmitt, A.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 871−876.
(31) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901.
(32) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169−1174.
(33) Brameld, K. A.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1999**, *121*, 985−993.
(34) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032−7035.
(35) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.
(36) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221.
(37) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.
(38) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149−14152.
(39) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063−2066.
(40) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.
(41) Five-membered ring iminium ions are believed to undergo nucleophilic attack by similar transition structures to those for oxocarbenium ions: Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445−3447.
(42) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322−5323.
(43) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864.
(44) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.
(45) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825−8836.
(46) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920.
(47) Isobe, M.; Saeeng, R.; Nishizawa, R.; Konobe, M.; Nishikawa, T. *Chem. Lett.* **1999**, 467−468.
(48) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911−1914.
(49) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523−4526.
(50) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118−4121.
(51) Herdeis, C.; Engel, W. *Tetrahedron: Asymmetry* **1991**, *2*, 945−948.
(52) Vink, M. K. S.; Schortinghuis, C. A.; Luten, J.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2002**, *67*, 7869−7871.
(53) Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419−3421.
(54) McDonnell, C.; López, O.; Murphy, P.; Bolaños, J. G. F.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374−12385.

Results

Experimental Approach. To understand the stereoselective nucleophilic substitution reactions of the ribose-derived acetal **1** (eq 1), we investigated how changing substituents at C-2, C-3, and C-4 of the oxocarbenium ion intermediate **5** would influence selectivity. All substrates were prepared as anomeric mixtures, and control experiments revealed that the anomeric composition did not influence the stereoselectivities, suggesting common intermediates.[55,56] Our studies focused on *C*-glycosylation of anomeric acetates with allyltrimethylsilane in CH_2Cl_2 because the reactions are rapid, high-yielding, and irreversible.[57] The products also cannot be epimerized, and the presence of the pendant alkene in the product permits facile stereochemical proof of the products.[55] We have described in detail other reasons for selecting experiments of this type.[26]

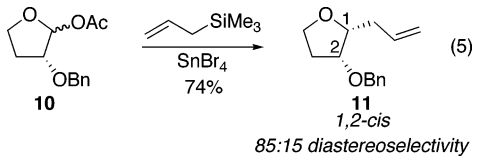
C-2 Alkoxy Group. Stereoselective nucleophilic substitution reactions of 2-deoxyribose derivatives indicate that the electronic nature of the C-2 substituent does not govern the high selectivity of the ribose-derived system (eq 1). Replacing the oxygen at the C-2 position with either hydrogen or fluorine led to the analogous 1,3-cis products with comparable selectivities (eq 4).



compound	X	Lewis acid	selectivity	% yield
a	H	$SnBr_4$	>99 : 1	94
b	F	$TiCl_4$	93 : 7	81

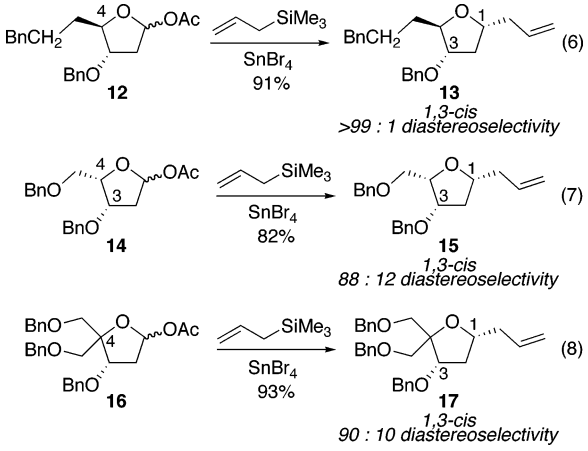
Similar observations for alkylations[23,58−61] and reductions[62] of 2-deoxyribosyl systems resembling **8a** have been reported. In the case of the fluoro compound **8b**, $TiCl_4$ was required to obtain allylation products, presumably since the strongly electron-withdrawing fluorine made formation of the oxocarbenium ion difficult.[63−65] Because these modifications did not equate to a difference in selectivities, substitution at a position other than C-2 must determine the stereochemical course of these reactions.

Examining the influence of the C-2 benzyloxy group in the absence of other substituents revealed that this substituent reinforces the stereochemical preference of the ribosyl oxocarbenium ions **5**. Allylation of the 2-benzyloxy acetate **10** was cis-selective (eq 5), matching the selectivity pattern observed



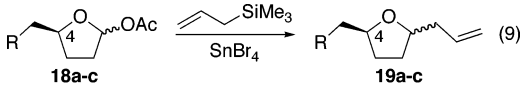
for the ribose system (eq 1). In contrast, additions of allyltrimethylsilane to 2-methyl-substituted five-membered ring acetals are modestly trans-selective.[29−32] These experiments suggest that the C-2 substituent exerts some control but is not responsible for the high α-selectivity observed in eq 1.

C-4 Alkyl Group. The C-4 alkyl group does not control the stereoselectivity of nucleophilic attack for ribose-derived systems (eq 1). Analogues resembling the 2-deoxyribose derivative **8a** with different substituents at the C-4 position were examined to determine if the reaction outcome would deviate from the anticipated 1,3-cis stereoselectivity. Whether the C-4 substituent contained an oxygen atom or not, the nucleophile consistently approached cis to the alkoxy substituent at C-3 (eq 6). In



addition, the relative stereochemistry between the substituent at C-4 and the alkoxy group at C-3 did not strongly influence the 1,3-cis selectivity (eq 7). In contrast to intuition, substitution of acetal **14** provided a product where the nucleophile approached from the same face as the two substituents.[37,66] Geminal substitution at C-4 also had little influence on the high cis selectivity (eq 8).[67,68]

Experiments involving substrates bearing a single alkyl group at C-4 support the notion that this substituent does not control the approach of the nucleophile (eq 9). While 1,4-disubstituted



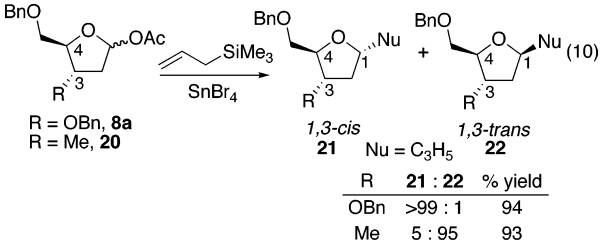
compound	R	selectivity	% yield
a	BnO	57 : 43	91
b	*t*-$BuPh_2SiO$	60 : 40	84
c	$BnCH_2$	67 : 37	77

tetrahydrofurans are found in natural products such as the Annonaceous acetogenins,[8,9] controlling this stereochemical array has been challenging,[11] as demonstrated by other researchers, since this position does not strongly influence selectivities.[29−32,39,69]

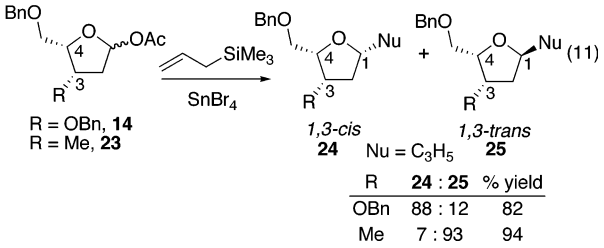
C-3 Alkoxy Group. The electronic nature of the substituent at C-3 exerts a powerful effect upon selectivity. Replacing the

(55) The syntheses of substrates, determination of stereoselectivities, and stereochemical proofs are provided as Supporting Information.
(56) Shenoy, S.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157−1160.
(57) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961.
(58) Uenishi, J.; Sohma, A.; Yonemitsu, O. *Chem. Lett.* **1996**, 595−596.
(59) Shimomura, N.; Saitoh, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 433−436.
(60) For example, see: Ichikawa, Y.-i.; Kubota, H.; Fujita, K.; Okauchi, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 845−852.
(61) Jaouen, V.; Jégou, A.; Veyrières, A. *Synlett* **1996**, 1218−1220.
(62) Wichai, U.; Woski, S. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3465−3468.
(63) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270−1277.
(64) Torsional effects can also influence the rate of ionization of acetals: Dean, K. E. S.; Kirby, A. J.; Komarov, I. V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 337−341.
(65) Partial debenzylation was observed under these conditions: Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346−1353.
(66) For clarity of presentation, this compound was drawn as one enantiomer. Because this substrate was prepared from D-xylose, the material is the enantiomer of the one presented.
(67) Wendeborn, S.; Binot, G.; Nina, M.; Winkler, T. *Synlett* **2002**, 1683−1687.
(68) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L.; Hilmey, D. G.; Galluci, J. *J. Org. Chem.* **2004**, *69*, 7442−7447.

alkoxy group at C-3 in the 2-deoxyribose system **8a** with a methyl group resulted in formation of the 1,3-trans product (eq 10), which is the opposite selectivity obtained with **8a** (eq



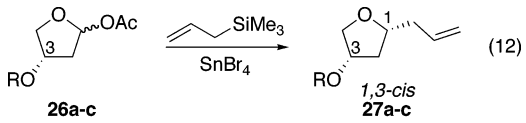
R	21 : 22	% yield
OBn	>99 : 1	94
Me	5 : 95	93



R	24 : 25	% yield
OBn	88 : 12	82
Me	7 : 93	94

4).[38,70,71] This divergence in diastereoselectivity between an alkoxy group and a methyl group[25,26] was independent of the relative stereochemistry between the C-3 and C-4 positions (eq 11).[72] The selectivities observed for acetates **20**[73,74] and **23** have been observed by other workers.[10]

Experiments with monosubstituted acetals **26a**−**c** confirmed the powerful influence of a single alkoxy group at C-3 on selectivity. Substitutions on acetals with an oxygen substituent at C-3, regardless of the protecting group employed, provided the 1,3-cis products with high selectivities (eq 12).[26,75] The 1,3-



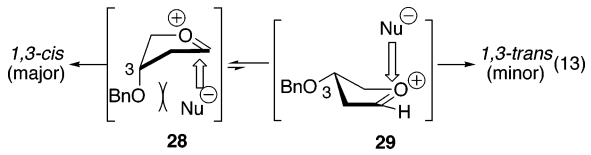
compound	R	selectivity	% yield
a	Bn	94 : 6	97
b	*t*-BuMe$_2$Si	94 : 6	90
c	MeOCH$_2$	94 : 6	93

cis selectivity contrasts with the preferred 1,3-trans selectivity observed for 3-alkyl[29−32] and 3-aryl[31,76] substituted five-membered ring acetals. These 1,3-cis selectivities indicate that steric effects are unlikely to control the stereochemical outcome of the reaction.[37,77]

Discussion

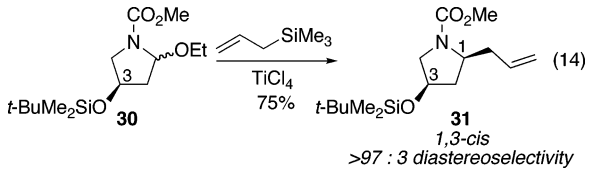
The results obtained from previous investigations[37−39] and this current study of ribose-derived analogues support and shape a general method of analysis applicable to the nucleophilic substitution reactions of alkoxy-substituted five-membered ring oxocarbenium ions. The monosubstituted acetals were examined to understand the independent influence of each substituent on the ground state conformer population of the oxocarbenium ion, which is associated with the selectivity.[78] To understand and predict the selectivity of highly oxygenated systems such as **1**, the influence of each substituent is considered along with the interactions that arise between the groups present.

The C-3 alkoxy group exerts the largest influence on selectivity, leading to the 1,3-cis product. An alkoxy group at C-3 prefers to adopt a pseudoaxial orientation (**28**, eq 13), placing the partially negatively charged substituent in closest proximity to the cationic carbon of the oxocarbenium ion.[25,26,42−44] Nucleophilic attack on the lower energy conformer **28** from the stereoelectronically favored inside face[37−39] affords the observed 1,3-cis product (eq 13). This mode of attack develops a syn-



butanol interaction[79] in the transition state, but this interaction is considerably smaller than a syn-pentane interaction,[80] so it is not destabilizing enough to hinder attack from this trajectory. In contrast, a C-3 alkyl-substituted oxocarbenium would experience a syn-pentane interaction[80] upon attack of the C-3 axial conformer, so attack occurs on the analogous equatorial cation, leading to the 1,3-trans product.

Because five-membered ring iminium ions reside in similar envelope conformations, the observations and analysis of the 3-alkoxy oxocarbenium ion **28** (eq 13) are relevant for the related nitrogen-containing compounds.[41] Seebach reported that reactions of 3-silyloxyiminium ions derived from *N*,*O*-acetal **30** showed preferential 1,3-cis selectivity (eq 14).[81,82] This result



is matched by the selectivity of the 3-silyloxy oxocarbenium system derived from acetal **26b** (eq 12). Similar to the analysis

(69) Improved selectivity for C-4 substituted five-membered ring acetals can be realized with either large substituents at C-4 (Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Reynolds, D. J.; Storer, R. I. *Org. Biomol. Chem.* **2004**, *2*, 1145−1154) or using large nucleophiles (Jalce, G.; Seck, M.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Org. Chem.* **2004**, *69*, 3240−3241).

(70) For both of these substrates, the two anomers of the starting material could be separated. When each isomer was subjected separately to the reaction conditions, the same product was obtained with the same diastereoselectivity. These experiments suggest that the reactions of the two anomers proceed via a common intermediate.

(71) This selectivity is independent of Lewis acid ($TiCl_4$, $SnCl_4$, or $BF_3{\cdot}OEt_2$).

(72) Addition of hydride to a structurally related five-membered ring oxocarbenium ion bearing an alkyl group at C-2 occurs with high selectivity with similar stereochemistry: Yoda, H.; Mizutani, M.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 4701−4702.

(73) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417−1419.

(74) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763−766.

(75) Control experiments performed using acetal **26b** indicate that the polarity of the solvent (CH_2Cl_2, hexane, and nitroethane) does not influence selectivity. In addition, the same selectivity can be obtained using protic acids to catalyze the reaction.

(76) Mehta, G.; Sengupta, S. *Tetrahedron Lett.* **1996**, *37*, 8625−8626.

(77) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.

(78) Destabilizing steric effects developing in the transition states do not appear to be large in these ribose-derived systems, probably since the alkoxy substituents are not sterically large.

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

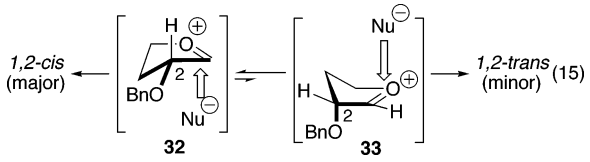
(80) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8029−8038.

(81) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704−1710.

(82) For other examples exhibiting similar selectivities, see: (a) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290−295. (b) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2000**, *41*, 2495−2498. (c) Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643−1646.

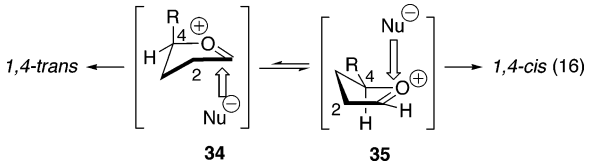
in eq 13, the alkoxy group of the related iminium ion evidently prefers an axial orientation, and nucleophilic attack through the staggered transition state affords the observed cis product.

The contra-steric 1,2-cis product **11** obtained from the reaction of the monosubstituted acetal **10** (eq 5) indicates that the electronic nature of the C-2 alkoxy group contributes to the selectivity. The oxocarbenium ion intermediate prefers to position the C-2 alkoxy group in a pseudoequatorial orientation (**32**, eq 15), consistent with the reactions of related C-2



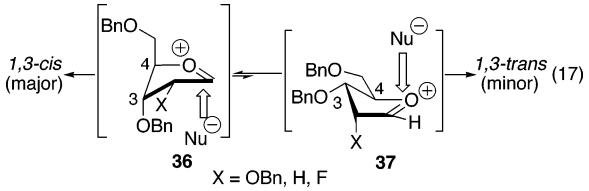
substituted six-membered ring oxocarbenium ions.[43] This conformer maximizes the overlap of the more electron-donating[83,84] σ_{C-H} orbital at C-2 with the adjacent vacant orbital of the oxocarbenium ion.[25,26] Consequently, inside attack on the favored equatorial conformer **32** provides the 1,2-cis product. With an alkyl group at C-2, steric interactions are small,[26] and the hyperconjugative donating abilities of σ_{C-H} and σ_{C-C} orbitals are similar,[84] so both conformers have equivalent energies. Inside attack on the pseudoaxial conformer alleviates destabilizing gauche-butane interactions that develop in the transition state structure involving the pseudoequatorial conformer, providing a moderate selectivity for the 1,2-trans product.

A C-4 alkyl substituent normally exerts little influence on the selectivities resulting from reactions of oxocarbenium ions.[29−32] It does not strongly bias the conformational equilibrium,[31] nor is it involved in destabilizing interactions in the transition state for nucleophilic attack. As a result, both 1,4-trans and 1,4-cis products are observed (eq 16). A substituent



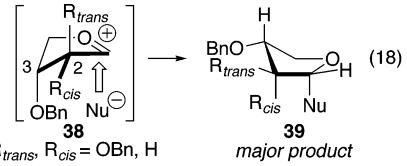
at C-4, however, can exert significant control on selectivity (favoring the 1,4-cis product) if it is constrained to an equatorial position (as in conformer **35**) by geminal substitution at C-2.[18,39] Our observation that the selectivity is independent of the electronic nature of the C-4 substituent (such as in eqs 6 and 9) contrasts with observations of the influence on selectivity exerted by the analogous C-5 substituent for tetrahydropyran cations.[45,85]

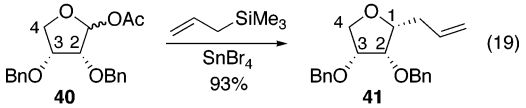
The aggregate influences of the appropriate substituents at C-2, C-3, and C-4 account for the selectivities obtained from nucleophilic substitution reactions of the ribose-derived systems. Because the C-3 alkoxy group has a strong tendency to be pseudoaxial and the C-2 alkoxy group favors pseudoequatorial positions, conformer **36** is strongly favored when X = OBn. The C-4 alkyl group exerts no discernible influence on the conformational preference. Inside attack on the lower energy conformer **36** leads to the observed major product (eq 17). When

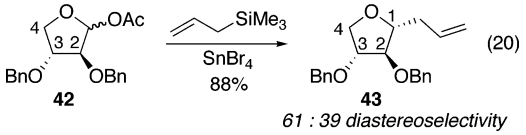


the C-2 alkoxy group is replaced with either H or F as seen for the 2-deoxyribose systems (eq 4), the conformational preference is not dramatically perturbed, demonstrating the powerful influence of the C-3 alkoxy substituent. This argument extends to the selective reduction of the C-1 phenyl-substituted acetal **3** (eq 2), since the presence of a C-1 alkyl or aryl group does not change the selectivities of reactions of five-membered ring acetals.[39]

Extensions to Systems not Derived from Ribose. Our detailed analysis of the stereoselective reactions of ribose-derived electrophiles such as **1** (eq 1) indicates that the C-3 alkoxy substituent dominates the stereoselective reactions of these cations (eq 12). The presence of an alkoxy group at C-2, which favors 1,2-cis selectivity (eq 5), reinforces the selectivity observed in eqs 1 and 2 because it is cis to the C-3 alkoxy group. We anticipated that if a cation had only alkoxy groups at C-2 and C-3 (as in eq 18), 1,3-cis selectivity would be observed. Selectivity would be high if the substituents were cis to each other, because the oxocarbenium ion would adopt the conformer **38**, retaining the preferred pseudoaxial orientation at C-3 and pseudoequatorial orientation at C-2.[25,26,43] On the





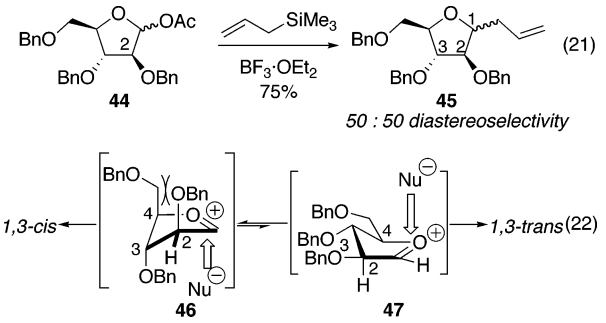


other hand, switching the stereochemistry at C-2 to the 2,3-trans oxocarbenium ion would diminish the preference for conformer **38**, leading to lower selectivity because of the unfavorable axial orientation of the alkoxy substituent at C-2. These hypotheses were verified by experiments: substitutions on the acetals **40** and **42** (eqs 19[86] and 20) occur cis to the C-3 alkoxy group, and lower selectivity is observed when the two substituents are trans.

The modest 1,3-cis selectivity for *C*-glycosylation of arabinose-derived acetal[87] **44** (eq 21)[78,88] illustrates further the "mismatched" selectivities exhibited by trans-substituted acetal

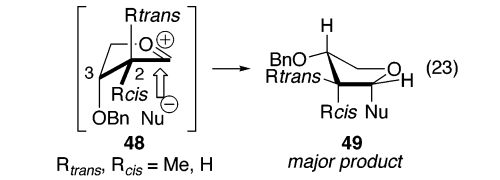
(83) Apeloig, Y.; Schleyer, P. v. R.; Pople, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 5901−5909.
(84) Alabugin, I. V.; Manoharan, M. *J. Org. Chem.* **2004**, *69*, 9011−9024.
(85) Larrosa, I.; Romea, P.; Urpí, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651−4654.
(86) The selectivity can be improved to 98:2 by using toluene as the solvent.
(87) Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605−4609.
(88) Peri, F.; Bassetti, R.; Caneva, E.; de Gioia, L.; La Ferla, B.; Presta, M.; Tanghetti, E.; Nicotra, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 638−644.

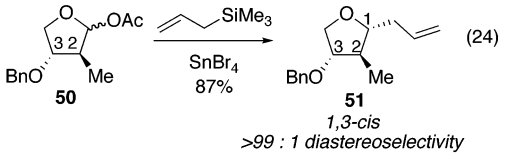
42. For the C-3 alkoxy group to occupy the preferred pseudo-

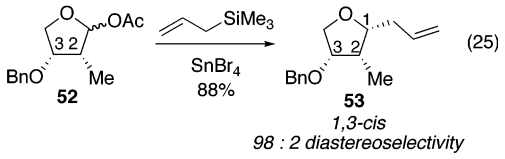


axial orientation, all substituents must be pseudoaxial (**46**, eq 22). This arrangement not only would place the C-2 alkoxy group in the electronically disfavored pseudoaxial orientation but also would create an unfavorable syn-butanol interaction[79] between the benzyloxy substituent at C-2 and the alkoxymethyl group at C-4. Although the magnitude of the syn-butanol interaction is not high (approximately 1.8 kcal/mol),[79] the transition state leading to the observed product would involve two such interactions. Considering these destabilizing interactions, the reaction via the all-equatorial conformer **47** should also be possible, leading to a poorly selective reaction.[88−90]

Because a single alkoxy group at C-3 is generally sufficient to control the conformational equilibrium and provide high selectivity, it was anticipated that the influence of a C-3 alkoxy group would overwhelm the modest influence on selectivity conferred by an alkyl group at C-2.[29−32] A C-3 alkoxy oxocarbenium ion substituted at C-2 with a methyl group either cis or trans to it should adopt the electrostatically stabilized conformer **48**, and inside attack would lead to the 1,3-cis product **49** (eq 23). This prediction was also validated by experiments (eqs 24 and 25). As with two other disubstituted substrates examined (eqs 7 and 19), the major product obtained in eq 25







would not be anticipated based upon consideration of steric effects alone, since the nucleophile approaches the electrophile from the same face as the substituents.

Conclusion

By systematically varying the substitution of the ribose-derived acetal **1** (eq 1), we determined that the alkoxy group at C-3 principally governs the selectivity. As with six-membered rings,[25,26,42] the electronic nature of substituents exerted an enormous influence on the selectivity of these reactions. The lowest energy conformers bear the C-3 alkoxy group in a pseudoaxial orientation. To a lesser extent, the C-2 substituent prefers to occupy a pseudoequatorial position, a preference that is accommodated by the ribose stereochemistry but not the arabinose stereochemistry. The alkyl group at C-4 exerts no influence on the stereoselective reactions of ribose-derived acetals. In all cases, the product was formed by stereoelectronically preferred inside attack on the lowest energy conformer. The studies reported in this paper indicate that a knowledge of the unusual conformational preferences of alkoxy groups in oxocarbenium ions[25,26,42−44] and a stereoelectronic model to explain reactions of five-membered ring oxocarbenium ions[37−39] can be combined to predict selectivities in highly substituted oxocarbenium ions and also iminium ions.

Acknowledgment. We dedicate this paper to the memory of our friend and colleague Dr. Jacqueline Smitrovich, whose insight and inspiration profoundly influenced us. This research was supported by the National Institutes of Health, National Institute of General Medical Sciences (GM-61066) and by Johnson & Johnson. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. C.H.L. thanks Pfizer for a Summer Undergraduate Research Fellowship. J.T.S. thanks the American Chemical Society Division of Organic Chemistry, sponsored by Merck, for a graduate fellowship. D.M.S. thanks Johnson & Johnson for a graduate research fellowship. K.A.W. thanks Merck Research Laboratories and Johnson & Johnson for awards to support research. We thank Michelle Tran-Dubé for her contributions to this project, Dr. John Greaves and Dr. John Mudd for mass spectrometric data, and Dr. Phil Dennison for assistance with NMR studies.

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.

JA0524043

(89) Addition of allyltrimethylsilane to a tetrabenzyl fructose-derived acetal, which is stereochemically similar to the arabinose system except that it bears an alkoxymethyl group at C-2, gives similar selectivity: Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1987**, *52*, 5627−5630.
(90) Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett.* **1997**, *38*, 9051−9054.