Author

Catharine Larsen stopped dancing professionally with the Los Angeles Classical Ballet to do research in organic chemistry at UCI, and she doesn't regret the sacrifice. Instead, she's established the foundation of a blossoming career and picked up honors and recognition along the way, including a National Defense Science and Engineering Graduate Fellowship to further her studies at CalTech and a publication in the *Journal of the American Chemical Society*. Larsen plans "to discover new methodology for the synthesis of pharmaceuticals and other natural products" and aspires to be a professor of organic chemistry.

Key Terms

- Carbon-carbon Bond Formation
- Conformational Analysis
- Inside Attack Model
- Oxocarbenium Ion
- Stereoselectivity
- Substituent Effects
- Tetrahydrofuran

The Inside Attack Model for the Stereoselectivity of Nucleophilic Additions to Five-Membered Ring Oxocarbeniums

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Chemistry

Abstract

For *in vivo* chemical interactions, compounds must fit together in a precise arrangement, like puzzle pieces. Numerous biologically active molecules contain a tetrahydrofuran core structure. The positioning (stereochemistry) of a particular group above or below this oxygen-containing five-membered ring must be precise to allow for biological efficacy. In these systems, controlling the stereochemistry of carbon-carbon bond formation at the C-1 position, adjacent to the oxygen in the ring, often presents the greatest synthetic challenge. Nucleophilic additions to oxocarbenium ions generated from tetrahydrofuran acetals afford the crucial C-1-substituted products; however, no comprehensive, predictive model for the effects of structure and conformation on stereoselectivity of these reactions had been devised. Examination of the allylation products of variously substituted tetrahydrofuran acetals demonstrated that C-3 alkoxy-substituted systems give principally 1,3-*cis* products, whereas C-3 alkyl-substituted systems primarily afford 1,3-*trans* products. Nucleophilic attack occurs on the inside of the envelope conformer of oxocarbenium ion intermediates bearing either an axial alkoxy or an equatorial alkyl substituent at C-3. Computational analysis shows that inside attack on these envelope conformers avoids the energetically unfavorable interactions that would occur during outside attack and leads to a lower-energy staggered product, consistent with observed selectivities.

Faculty Mentor

Catharine Larsen's research focused on understanding the inherent chemical reactivity of a simple organic system found in various biological molecules such as carbohydrates and nucleotides. We have been trying for some time to understand how these systems behaved, since what was known in the literature was at odds with our intuition. When she began her research on this problem, the project was at its early stages. We felt that bridging the divide between the experimental observations and educated predictions of reactivity would teach us a significant amount. At several stages, we thought we knew what was going on, and Catharine would perform the experiment that would prove us wrong. With Catharine's help, we have formulated a hypothesis that, to date, has proven to be accurate.

Keith Woerpel
School of Physical Sciences

Introduction

Organic chemistry is the lifeblood of the pharmaceutical industry. A vast majority of the therapeutic drugs in use today are either synthesized *de novo* or by chemically enhancing the medicinal properties of a pre-existing natural product. The structures of many biologically active compounds include a tetrahydrofuran, a five-membered ring in which a ring carbon is replaced by an oxygen (Postema, 1995; Levy and Tang, 1995). Derivatives of tetrahydrofurans are widely prescribed for a variety of illnesses. Azidothymidine (AZT) is commonly recognized as the first anti-AIDS drug used in antiviral chemotherapy and prophylaxis in the United States (Jawetz, 1992). As a synthetic dideoxynucleoside, AZT inhibits the synthesis of viral DNA, markedly decreasing viral replication. With a few alterations of substituents on the tetrahydrofuran core, one arrives at cytosine deoxyriboside, an antimetabolite used in cancer chemotherapy (Salmon and Sartorelli, 1992). For AZT and cytosine deoxyriboside, it is the β-isomer (Figure 1), with the substituent at C-1 positioned above the ring (a position above the plane of the paper is indicated by a bold wedge), that is used in chemotherapy.

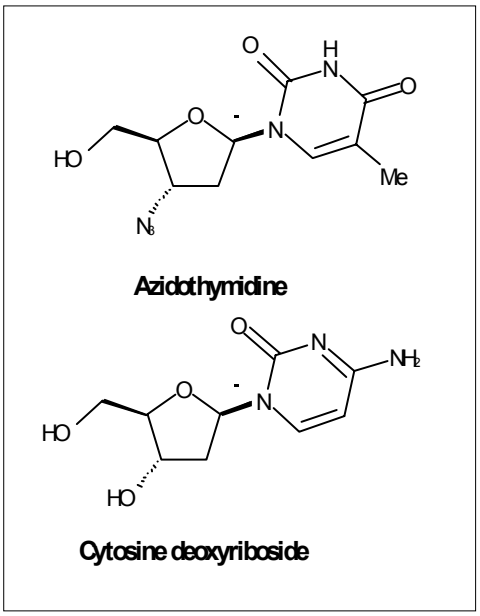
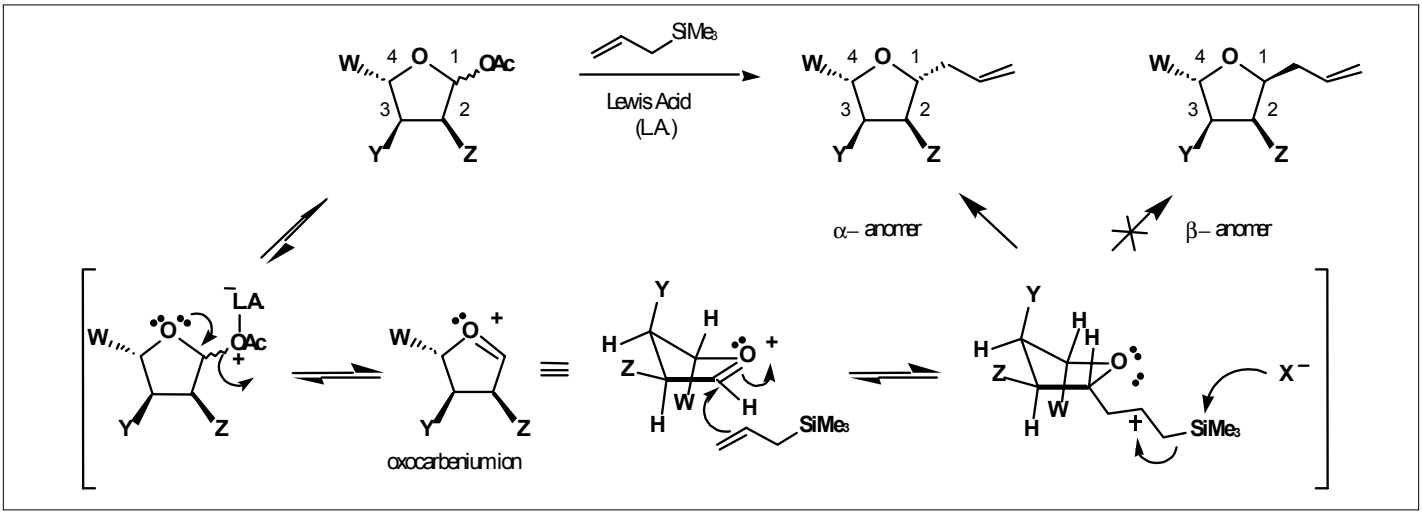


Figure 1
Pharmaceuticals with the tetrahydrofuran core structure

For activity in biological systems, compounds must interact together in a defined arrangement. Not only must the chemical composition of the various groups on the ring be correct, but their stereochemistry (positioning above or below the ring) must also be precise to allow for biological activity and transport. Because the identity and stereochemistry of substituents dictates the biological efficacy of these compounds, the β-isomer of a tetrahydrofuran will commonly exhibit different properties from the α-isomer with the substituent at C-1 positioned below the ring (a position below the plane of the paper is indicated by a dashed wedge). For most tetrahydrofuran compounds, the stereoselective formation of a bond at the C-1 position presents the greatest synthetic challenge. Whereas the stereochemistry of substituents at other positions on the ring can be set readily by known methods, the stereochemistry at the C-1 position for an unprecedented nucleophilic substitution reaction is uncertain. Despite the fundamental need for stereochemical control at C-1, no comprehensive model for the stereoselectivity of nucleophilic substitution to tetrahydrofuran acetals had been published previously.

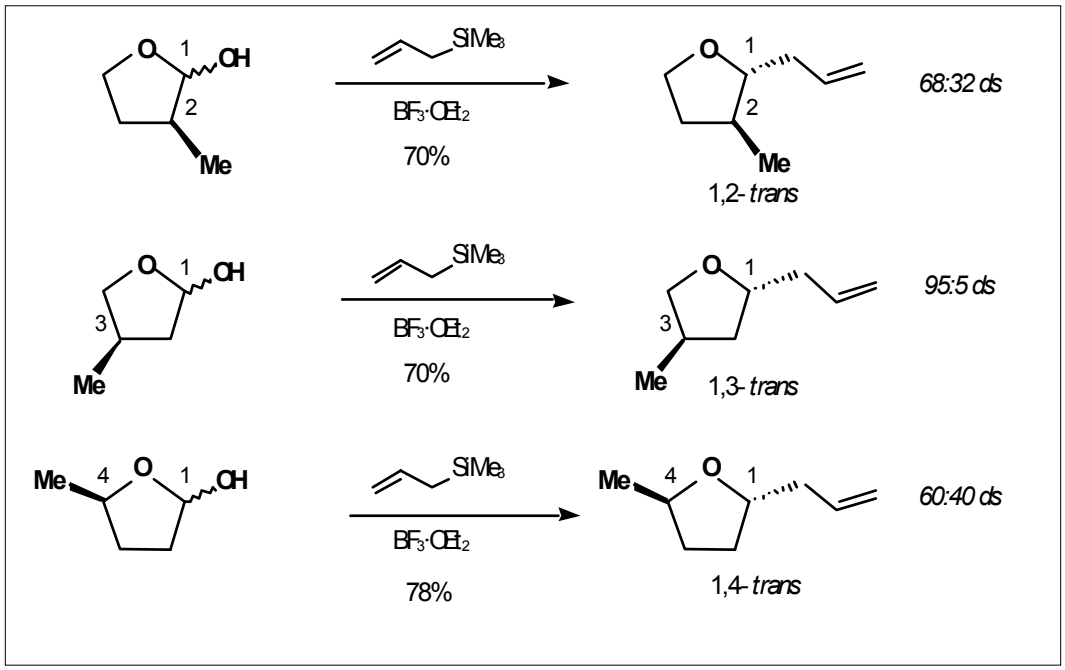
Background

The nucleophilic substitution reaction in which the oxocarbenium ion is a reactive intermediate is an important mode of forming carbon-carbon bonds. Reactions at the oxocarbenium ion allow access to the crucial C-1 position. The mechanism of nucleophilic substitution begins with Lewis



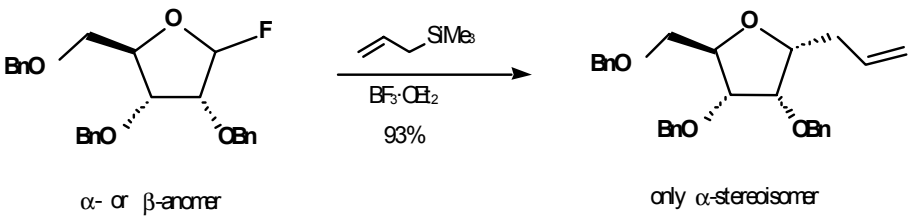
Scheme 1
Mechanism of acid-catalyzed nucleophilic substitution reactions of tetrahydrofuran acetals

acid complexation to the tetrahydrofuran acetal, which activates the acetate leaving group (Scheme 1). The electron lone pairs on oxygen facilitate the formation of the five-membered ring oxocarbenium ion. This cationic intermediate is shown in one of its possible envelope energy minima, a conformation in which four of the five atoms in the ring, including the oxygen, form a plane while the last carbon sits on a flap that deviates from this plane (Paquette et al., 1997). The substituents sit in positions that can be termed "axial" (close to vertical) and "equatorial" (close to horizontal) even though these terms are more correctly reserved for six-membered ring systems (Fuchs, 1978). Nucleophilic addition of allyltrimethylsilane can occur from either the top or bottom face of the envelope. Nucleophilic attack from the bottom face followed by loss of the trimethylsilyl group results in the formation of the α-anomer, indicated by the dashed wedge to the allyl group. Formation of the β-anomer, indicated by the bold wedge to the allyl group, would require attack from the top of the envelope conformer of the generically-substituted five-membered ring oxocarbenium ion. Formation of the α- or β-anomer depends upon the substitution pattern of the ring. In many cases, mixtures of the α- and β-anomers are obtained.



Scheme 2
Substrates from Schmitt and Reissig's study on the effect of methyl substituents on the stereoselectivity of nucleophilic substitution on tetrahydrofuran acetals

Among the numerous examples of nucleophilic substitution reactions on tetrahydrofuran acetals, the "Ribose Result" stands as a classic case of the counterintuitive selectivities observed in these systems (Equation 1) (Araki et al., 1987). Due to the steric bulk of the benzyloxy (OBn) groups which project below the ring of the sugar at C-2 and C-3, a cursory assessment would result in the prediction that the nucleophile attacks from the opposite face of the sugar, positioning itself above the ring to give the β-isomer at C-1. However, starting with either the α- or β-diastereomer of this benzylated ribose derivative, nucleophilic substitution with allyltrimethylsilane as the nucleophile and BF_3-etherate as the Lewis Acid gives only the α-stereoisomer. The substituting group declines to approach by what would seem to be the least congested path on the opposite side of the ring from the bulky C-2 and C-3 benzyloxy groups. Although numerous researchers have observed this contrasteric phenomenon–with different leaving groups such as acetate, a variety of Lewis acids, and even bulky enolsilanes as nucleophiles–and have only ever seen the α-diastereomer, the factors underlying this high diastereoselectivity are neither extensively studied nor adequately explained.



Equation 1
Ribose Result

Schmitt and Reissig's limited study of methyl (Me) substitution on tetrahydrofuran

hemiacetals helps to categorize position-dependent effects in these systems (Schmitt and Reissig, 1990). Allylation of the tetrahydrofuran hemiacetal with a methyl group at the C-2 position resulted in poor selectivity (68:32) for the 1,2-*trans* product, in which the allyl group at C-1 and the methyl group at C-2 are on opposite sides of the ring. Methyl substitution at the C-4 position also gave poor selectivity; however, the *trans* product was still favored. Interestingly, a lone methyl group at the C-3 position afforded high diastereoselectivity (95:5) for the 1,3-*trans* product. Although Reissig presents a rationale that is only applicable to this set of substrates, the results show that only one substituent is required for high diastereoselectivity (Scheme 2).

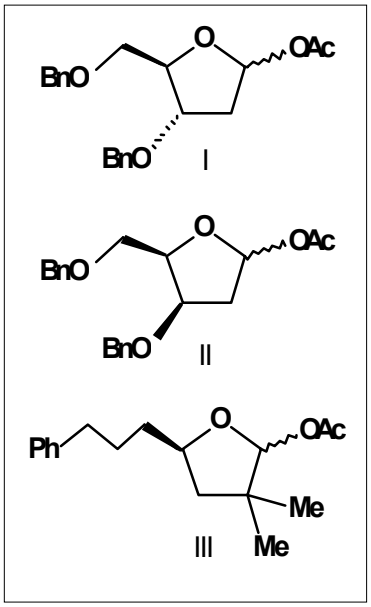


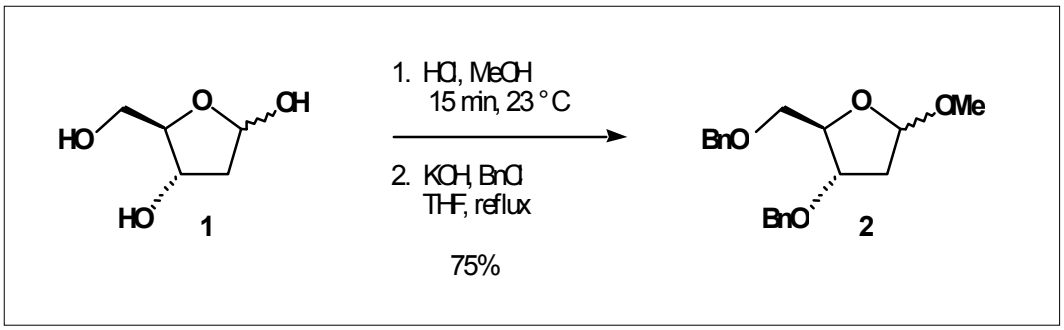
Figure 2
Substrates synthesized to probe substituent effects in nucleophilic addition to five-membered ring oxoarbenium ions.

The analysis of the stereochemical outcome of nucleophilic substitution reactions on tetrahydrofuran acetals with varying substitution patterns of alkyl (carbon backbone) and alkoxy (oxygen-carbon backbone) substituents formed the basis of my research. The most informative of the tetrahydrofuran acetals that were synthesized, allylated, and for which the stereochemistry was determined were Substrates I-III (Figure 2). Substrates I and II were targeted to probe the stereoelectronic effects of alkoxy substituents. The effect of the relative stereochemistry (positioning of substituents relative to each other) could also be analyzed because the C-3 benzyloxy (OBn) groups of Substrates I and II have opposite stereochemistries relative to the C-4 substituent. Identification of the stereoselectivity of the irreversible substitution of an allyl group on these tetrahydrofuran substrates, in addition to data obtained from other substrates, led to the determination of the factors influencing the stereoselectivity of nucleophilic addition to five-membered ring oxocarbenium ions (Larsen et al., 1999). The Inside Attack Model arising from this study relies on simple consideration of the energetics of the interacting molecules. Substrate III was designed to test the model by assessing whether the geminal methyl groups at the C-2 position intensify these steric interactions as the model predicts.

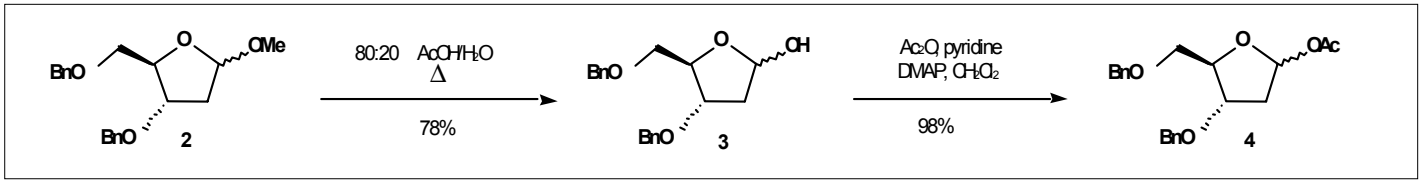
Results and Discussion

Synthesis of Substrate I

The structure of Substrate I was chosen for ease of synthesis from starting material 2-deoxyribose. 2-Deoxyribose is a sugar that possesses the basic functionality and relative stereochemistry desired in which the C-3 and C-4 substituents are positioned on opposite faces of the ring in a trans relationship. Synthesis of 3,5-di-*O*-benzyl-1-acetoxyfuranoside began with the problematic methanolysis of 2-deoxyribose (Equation 2). Prior to allylation of the tetrahydrofuran acetate, the stereochemistry at the C-1 position is not significant, and both C-1 diastereomers (α- and β-anomers) were carried through each step of the synthesis as a mixture. Upon stirring under acidic conditions overnight, the reaction yielded predominantly the more stable pyran product, the undesired six-membered ring analog of the five-membered ring furan (Deriaz et al., 1949). This crude mixture of tetrahydrofurans and tetrahydropyrans was then benzylated. The benzylated pyran and furan isomers are difficult to distinguish because they have the same mass and such similar connectivities that a ^{1}H NMR spectrum of a mixture of benzylated pyran and furan can easily be mistaken as a mixture of C-1 diastereomers of the furan. However, the complexity of the ^{1}H NMR spectrum indicated that conversion to the pyran had occured. The optimal conditions required to obtain furan methyl acetal **2** were found in the literature (Deriaz et al., 1949; Bhat, 1968). 2-Deoxyribose (**1**) was submitted to the methanolysis conditions for the 15 minutes specified before neutralization work-up (Equation 2). The crude methanolysis material was then benzylated to protect the hydroxyl groups while adding mass, giving methyl acetal **2**.



Equation 2
Conversion of 2-deoxyribose to methyl acetal **2**



Equation 3

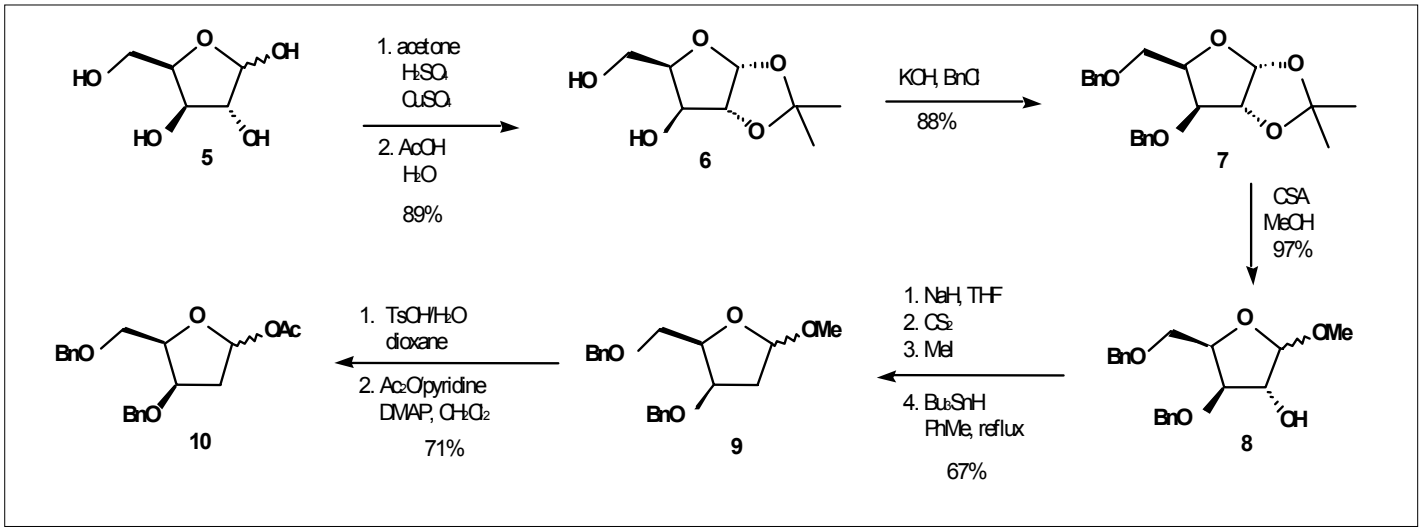
Hydrolysis and acetylation of acetal **2** gives acetate **4** (Substrate I).

The retention factors (Rf's) observed for the methyl acetal diastereomers (**2**) upon thin layer chromatography (TLC) differed enough to raise suspicions that the undesired pyran product was still being formed. This necessitated the separation of the products by flash chromatography for further characterization. Whereas the ^{1}H NMR spectrum for each product showed a very slight difference in the chemical shifts of the anomeric protons–the spectroscopic handle for chemical transformations at the C-1 position–one of the methylene peaks for the lower R_f product caused confusion because of its unusually large coupling constant of 13.9 Hz. Such a large J-value would be expected in a pyran due to the sizeable axial-axial interactions possible for vicinal protons in a six-membered ring system, but not in a five-membered ring system. A lead tetraacetate test, which causes selective cleavage of the six-membered ring and leaves the five-membered ring intact, was considered; however, a negative test might result from problems with reagents and not necessarily be indicative of a five-membered ring product. Instead, both products were seperately hydrolyzed, acetylated, and allylated. The ^{1}H NMR spectra showed miniscule differences, but the ^{13}C NMR spectra were identical in all cases, proving that both products were simply diastereomers of the furan methyl acetal.

Hydrolysis conditions were developed for the conversion of methyl acetal **2** to hemiacetal **3** (Equation 3). The first acid attempted was trifluoroacetic acid (TFA) in concentrations of 90:10, 40:60, and 10:90 TFA to water (by volume). Whereas the 90% acid solution turned brown-red almost immediately, signaling a decomposition of product echoed in the TLC, the 10% solution did not completely convert starting material. The 40% solution seemed to consume all starting material to afford a lower R_f product overnight. Unfortunately, hydrolysis in 40% TFA resulted in only a 10% yield upon purificaton. Hydrochloric acid (HCl) was the next acid utilized. Refluxing in 0.1 M HCl overnight destroyed starting material; however, refluxing in 0.1 M HCl for one hour gave a 67% yield of the desired hemiacetal **3**. Later acid studies showed that an 80:20 solution of acetic acid and water gave a better yield (78%), but the solution had to be heated for two days (Hossain et al., 1998). Acetylation of **3** afforded a nearly quantitative yield of acetate **4**.

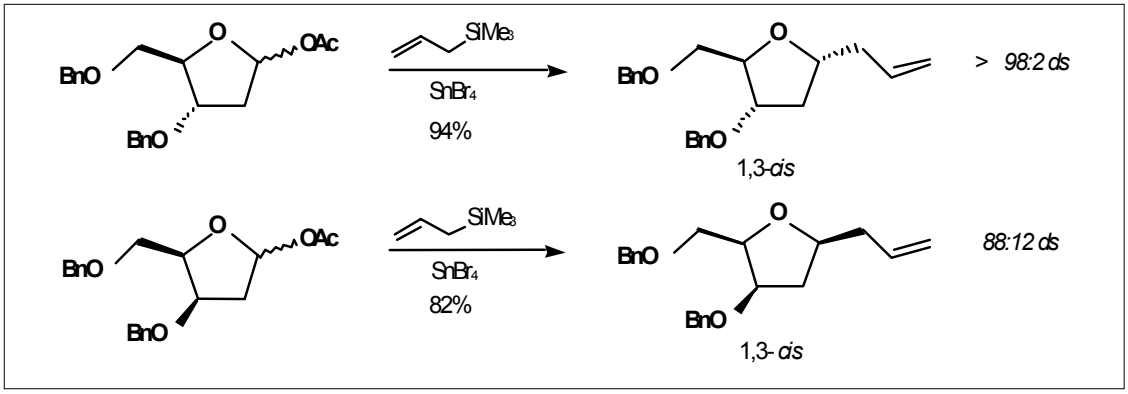
Synthesis of Substrate II

Substrate II was synthesized from xylose, which had the requisite 3,4-*cis* configuration of the ring as opposed to the 3,4-*trans* configuration of 2-deoxyribose. Synthesis of this 2-deoxyxylose derivative required more steps than the 2-deoxyribose derivative because xylose has four hydroxyl groups which must be selectively protected using several rounds of



Scheme 3

Protecting group manipulations and a deoxygenation provide acetate **10** (Substrate II).



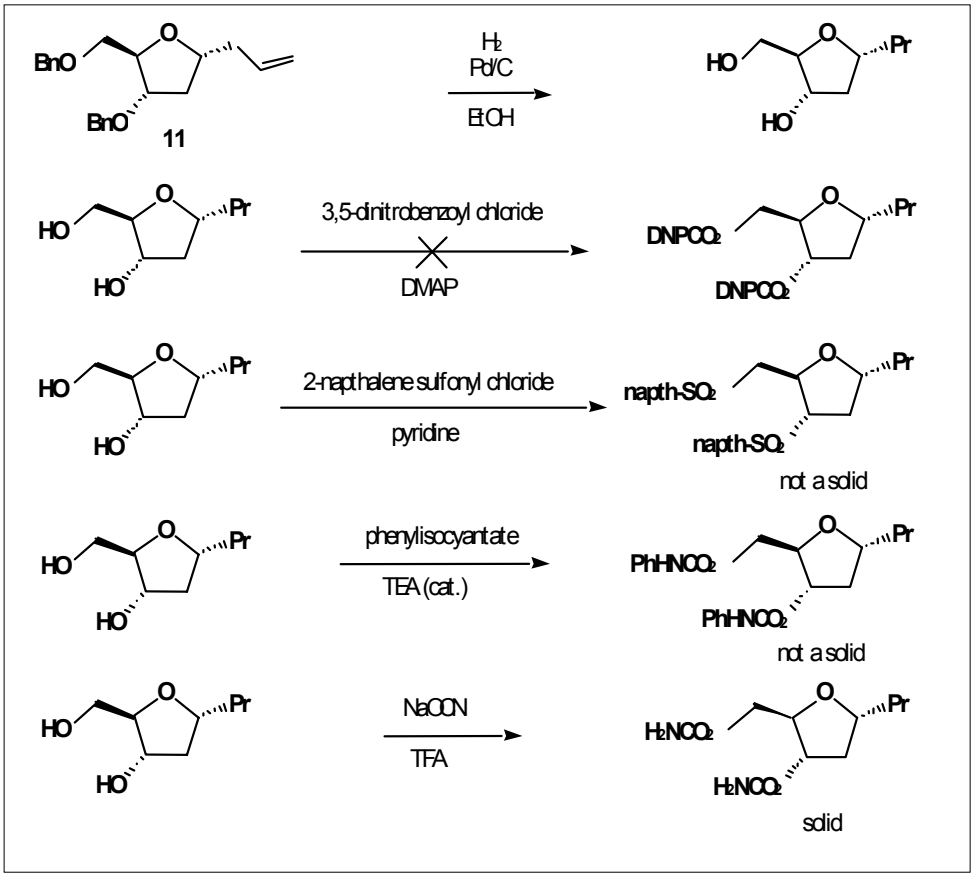
Scheme 4

The allylations of Substrates I and II are selective for the 1,3-*cis* product.

protecting group manipulations with the following goals: 1) robust protection of the C-3 and C-4 hydroxyl substituents, 2) moderate protection of the C-1 position such that it can withstand deoxygenation conditions but remain available for the functionalization necessary to later allylate, and 3) selective deprotection of the C-2 position for deoxygenation. The fine-tuning of reagent quantities was required, but no major stumbling blocks arose. The bisprotection and monodeprotection of xylose (**5**) to afford monoacetonide **6** followed literature procedures (Scheme 3) (Levene and Raymond, 1933; Dyatkina and Azhayev, 1984). Benzylation of monoacetonide **6** afforded fully-protected **7** in high yield. Methanolysis of the acetonide of **7** to give **8**, with the protected methoxy group at C-1 and the free hydroxyl group at C-2, also proceeded in high yield. There was some concern over the vast excess of tributyltin hydride (Bu_3SnH) used for the modified Barton-McCombie deoxygenation of the C-2 position of **8** to give methyl acetal **9** (Dyatkina and Azhayev, 1984). Exposure was limited by additional use of a respirator to avoid inhalation of organotin compounds and by flushing the silica gel column with hexanes before collecting fractions during flash chromatography purification. Because the hydrolysis product was unstable to purification by silica gel chromatography, the crude hydrolysis material was acetylated to give **10**.

Allylation of Substrates I & II

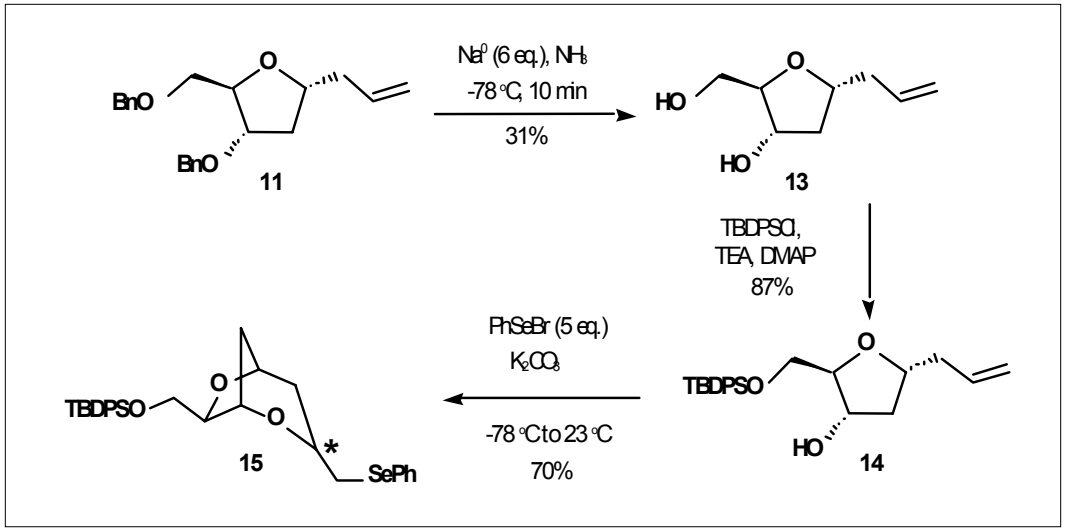
Allyltrimethylsilane was chosen as the nucleophile for this substitution reaction because the stereochemistry of addition is irreversibly set once the trimethylsilyl group is disjoined. The carbon-carbon bond formed and the stereochemistry of that C-1 center will not be altered by the reaction conditions or by further chemical transformations needed to prove stereochemistry. With $SnBr_4$ as the Lewis acid catalyzing the formation of the oxocarbenium ion intermediate from acetates **4** and **10**, addition of allyltrimethylsilane resulted in different stereoselectivities for each substrate as determined by gas chromatography (GC) analysis (Scheme 4) (Larsen et al., 1999). Allylation of 2-deoxyribose derivative **4** provided the



Scheme 5

Derivatizations aimed at stereochemical proof by x-ray crystallography.

α-anomer **11** with a diastereoselectivity of greater than 98:2. Allylation of xylose derivative **10** gave β-anomer **12** as the major product with a diastereoselectivity of 88:12. Surprisingly, in both cases, the selectivity is for the 1,3-*cis* product.



Scheme 6
Cyclization proves 1,3-*cis* stereochemistry of allylated product **16**.

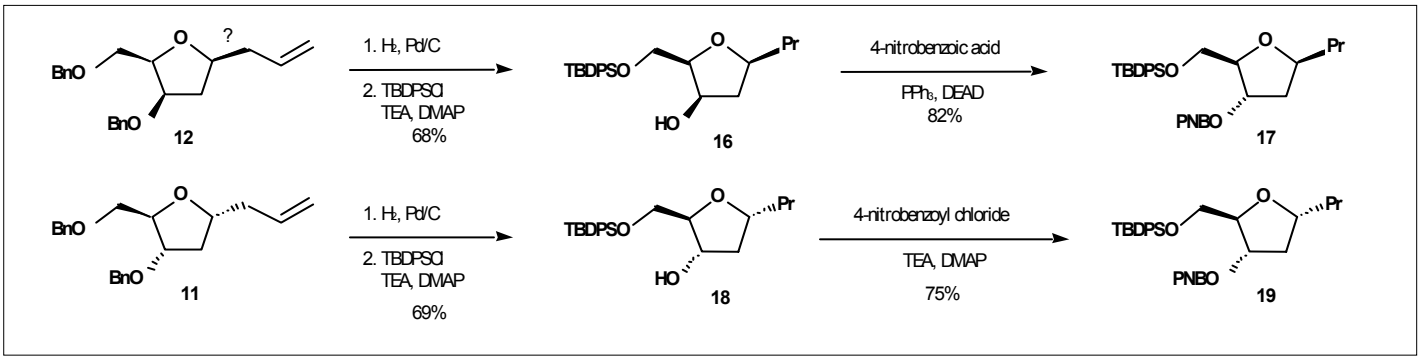
Stereochemical Proof

The most rigorous stereochemical proof of a compound involves forming a crystalline derivative of the compound for a three-dimensional mapping by x-ray crystallography. Allylated product **11** was a single diastereomer and was consequently of primary interest. This product of allylation on 2-deoxyribose derivative **4** was also easily resynthesized in five steps when more material was needed for stereochemical proof. The hydrogenation conditions used to deprotect the hydroxyl (OH) groups by removing the benzyl (Bn) moiety also reduced the C-1 allyl group to a propyl (Pr) group (Scheme 5). The crude diol products were then functionalized with various reagents commonly used in the preparation of crystalline derivatives. Most derivatives formed syrups, and attempts at crystalization rarely yielded a solid, let alone suitable crystals. Even the lone solid derivative, a carbamate, did not provide x-ray quality crystals.

Both nOe (nuclear Overhauser effect) data and chemical derivatives were used to prove the stereochemistry of allylation products **11** and **12**. Analysis of ^{1}H NMR data showed that there was no nOe (through-space interaction) between the C-1 and C-4 hydrogens on either side of the ring oxygen. This result is consistent with but not proof of the C-1 and C-4 hydrogens–and therefore the substituents at those positions–being on the opposite face of the ring. If the major product possesses a 1,4-*trans* configuration, then it also has a 1,3-*cis* stereochemical relationship because the C-3 and C-4 groups are on opposite faces of the ring. To confirm the 1,3-*cis* stereochemistry, 2-deoxyribose allylation product **11** was derivatized and the C-1 and C-3 positions were connected by a cyclization reaction (Scheme 6). A Birch reduction debenzylated **11** to give free hydroxyl (OH) groups without reducing the allyl moiety needed for cyclization. Selective protection of the primary hydroxyl group off the C-4 position of diol **13** provided alcohol **14**. Treatment of **14** with phenylselenium bromide under basic conditions afforded bridged bicyclic **15** in a 3:1 ratio of diastereomers (Uenishi et al., 1996). This stereochemical proof rests on the fact that cyclization of the C-3 hydroxyl and the C-1 allyl group to form the bridge in bicyclic **15** is only possible because the C-1 and C-3 substituents are on the same face of the ring. This cyclization proves that the 2-deoxyribose allylation product exhibits 1,3-*cis* stereoselectivity.

In order to prove the C-1 stereochemistry of 2-deoxyxylose derivative **12**, chemical correlation was employed. Product **12** was correlated to 2-deoxyribose derivative **11** for three reasons: 1) the method that would be found to conclusively prove the stereochemistry of **11** might not work on **12**, 2) the synthetic transformations necessary to correlate **12** to **11** were all known reactions, and 3) the repetition of the much longer synthesis of 2-deoxyxylose acetate **12** should be avoided if possible. This correlation was a viable option due to the fact that the only difference between these two compounds was the stereochemistry at the C-3 position if one ignored the C-1 position. Therefore, once the C-3 stereocenter of **12** was inverted, any difference in structure deduced from the ^{1}H NMR spectra could only be attributed to the C-1 substituent.

Both product **11** and the major isomer of **12** (separated by column chromatography) were hydrogenated to remove the benzyl groups and selectively silylated at the primary hydroxyl group on the C-4 substituent (Scheme 7). The C-3 hydroxyl group of alcohol **16** was then inverted under Mitsunobu conditions to give **17** (Dodge et al., 1994). During the Mitsunobu inversion, the triphenylphosphene (PPh_3) ends up coordinated to the C-3 hydroxyl group, thereby activating it. The conju-



Scheme 7

Chemical correlation of product **17** to product **16** shows that it also possesses 1,3-*cis* stereochemistry.

gate base of the *p*-nitrobenzoic acid displaces this activated hydroxyl group. This S_N2 inversion gives the equivalent of a *p*-nitrobenzoyl-protected (PNB-protected) hydroxyl group at the C-3 stereocenter of 2-deoxyribose derivative **17**. Therefore, the free C-3 hydroxyl of 2-deoxyxylose derivative **18** was simply protected with a PNB group to give **19**. Because the ^{1}H NMR spectra of **18** and **19**, for which the only variance could be from the stereochemistry at the C-1 anomeric center, displayed distinct differences, the major anomer of **12** was assigned as the ß-anomer, which is the opposite of the major α-anomer of **11**. This proves that the favored stereoisomer of both **11** and **12** has a 1,3-*cis* configuration across the ring. In fact, allyated product **12** is the surprising all-*cis* product, which accounts for the lower diastereoselectivity as compared to the high selectivity of **11**.

Stereochemical Model

The key to discovering the origins of the stereoselectivites of the nucleophilic substitution reactions on tetrahydrofurans is the conformation of the oxocarbenium ion intermediate. Relatively electronegative substituents have been shown to stabilize incipient oxocarbenium ions in the more thoroughly studied six-membered ring systems (Romero et al., 2000; Woods et al., 1992; Miljkovic et al., 1997). Most recently, *ab initio* computations from the Woerpel Group indicate that in the axial versus equatorial equilibrium between chair conformers, there exists a strong axial preference for C-3 and C-4 methoxy-substituted pyran oxocarbenium ions (Romero et al., 2000). This axial preference for alkoxy substituents is the opposite of the equatorial conformational preference calculated for alkyl substituents. As shown in Table 1, the C-3 methoxy substituent demonstrates a 2.837 kcal/mol preference for the axial position, and the C-4 methoxy substituent demonstrates a 3.831 kcal/mol preference for the axial position. This translates into approximately a 100:1 and nearly a 1000:1 preference for the axial orientation over the equatorial at the C-3 and C-4 positions, respectively.

Other studies also confirm the energetic stabilization of oxocarbenium ions with alkoxy substituents at the C-3 and C-4 positions. In a prior study, Bowen reports molecular modeling (MM2 and MM3) calculations correlated to experi-

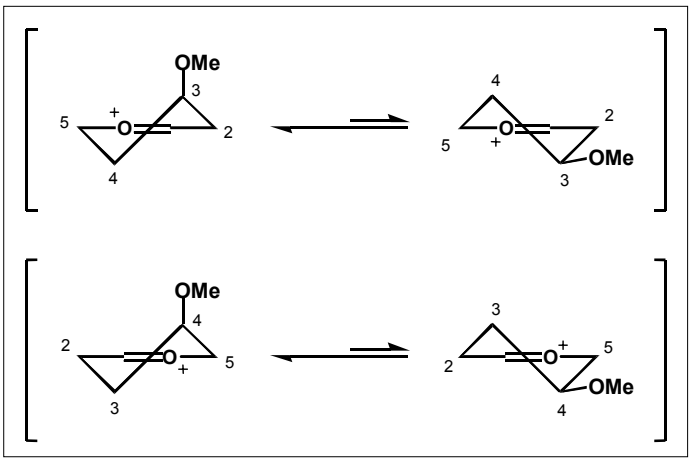


Figure 3

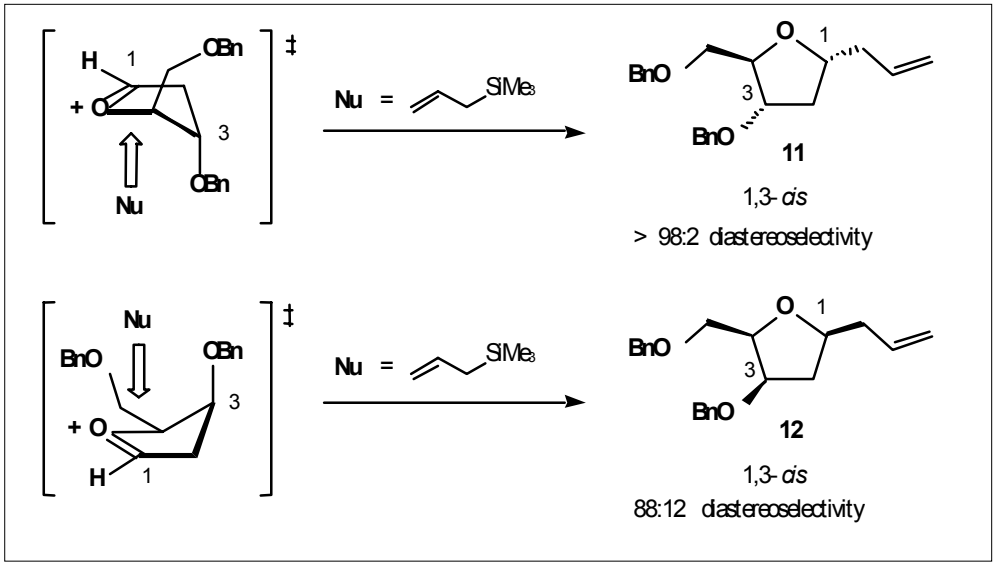
Conformational equilibria for methoxy-substituted oxocarbenium ions

Table 1

A-Values of Methoxy Substituted Oxonium Ion (B3LYP/6-31G* //HF/6-31G*)

$A = -\Delta G = RT \ln([eq]/[ax])$

Position	No Solvent (kcal/mol)	Preference
C3	-2.827	axial
C4	-3.831	axial



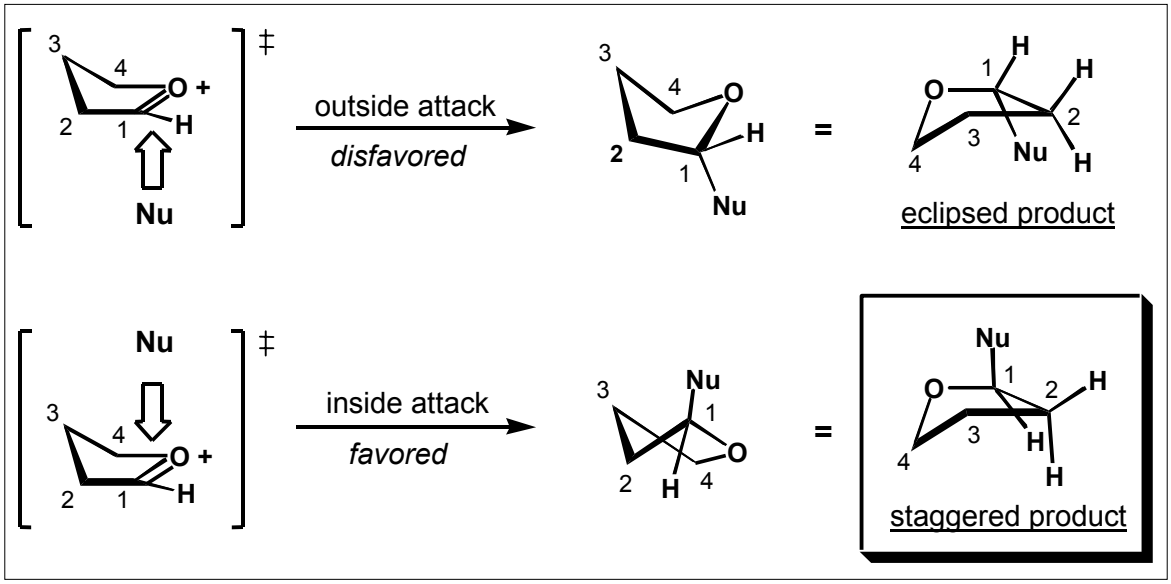
Scheme 8

The major product of allylation arises from nucleophilic attack on the inside of the more stable envelope conformation of the five-membered ring oxocarbenium ion.

mental hydrolysis data supporting enhanced electrostatic interactions of axial hydroxyl groups at the C-3 and C-4 positions which stabilize the forming oxocarbenium ions (Woods et al., 1992). With more rigorous *ab initio* calculations, Miljkovic supports an electron donation process from the axially oriented electronegative substitutent at the C-3 and C-4 positions of galactopyranoside rings to the oxocarbenium ion (Miljkovic et al., 1997). In fact, when the five-membered ring oxocarbenium ion with an alkoxy group at the C-3 position is modeled, the only energy minimum found is that with the C-3 alkoxy group in an axial position.

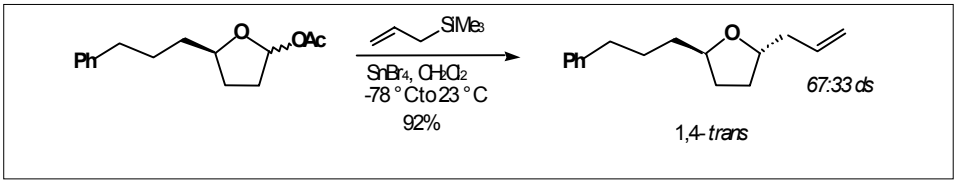
With this information in hand, the conformations of the alkoxy-substituted oxocarbenium ion intermediates can be accurately visualized to better assess what occurs during nucleophilic addition to the oxocarbenium ion. Given the high 1,3-*cis* selectivity demonstrated by chemical correlation, the nucleophile must attack the oxocarbenium ion from the same side of the ring as the C-3 benzyloxy substituent (Scheme 8). In both cases, this attack occurs on the inside of the envelope conformation of the oxocarbenium ion. This designation of inside attack as the preferred direction of attack stems directly from the observed selectivities.

To understand why the major products observed seem to arise from attack on the inside of the envelope conformer of the five-membered ring oxocarbenium ion, first principles must be revisited. The interactions between the nucleophile and the electrophilic carbon center to which it adds must be carefully considered. The interaction as the nucleophile bonds to C-1 will affect the conformation, and therefore the energy, of the products which can be formed. If the nucleophile were to attack from the outside of the envelope, as it interacted with the vacant p-orbital at the C-1 position of the oxocarbenium ion, it would pull that carbon down towards it. This mode of attack would result in high-energy eclipsing interactions between adjacent substituents in the product (Scheme 9). As the nucleophile attacks from the inside of the envelope, the same attraction during bond formation between the entering nucleophile and the C-1 carbon would result in a staggered product without unfavorable steric interactions. Therefore,



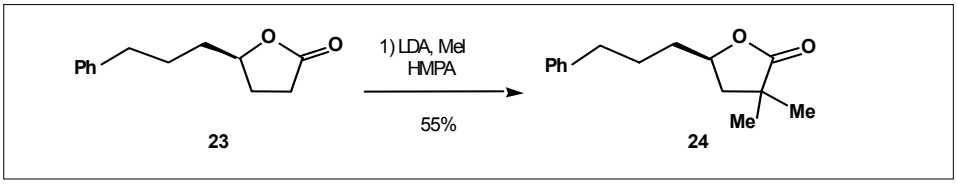
Scheme 9

The staggered product of inside attack is energetically favored.



Equation 4

A C-4 alkyl-substituted tetrahydrofuran acetal is somewhat selective for the 1,4-*trans* product.



Equation 5

Bismethylation to arrive at lactone **37.**

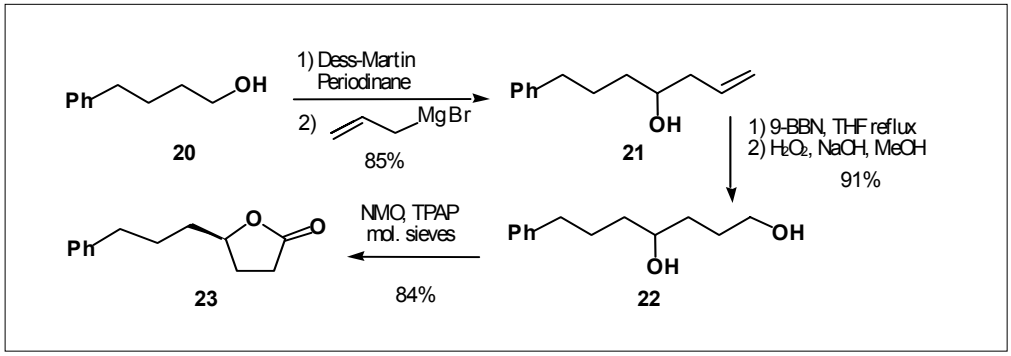
the high stereoselectivities observed are the result of the preference for the lower-energy, staggered conformation that inside attack provides.

Test of the Inside Attack Model

To support this explanation, replacing the hydrogens at C-2 with bulkier methyl groups should augment the eclipsing interactions that occur during outside attack on the oxocarbenium ion, thereby improving upon and possibly even reversing poor diastereoselectivities. In addition to further disfavoring outside attack for a system such as Substrate III (Figure 2), the attachment of geminal methyl substituents at the C-2 position will increase the steric preference of the oxocarbenium ion to adopt a conformation in which the C-4 propylphenyl substituent is equatorial. An equatorial substituent at C-4 sits on the same face as the inside of the envelope whereas an axial substituent would be on the outside of the envelope. Therefore, inside attack to afford the 1,4-*cis* product should be favored for a tetrahydrofuran with two methyl groups at C-2 even if the only other substituent is a long-chain alkyl group at C-4. It has been previously shown that allylation of a tetrahydrofuran acetate with solely a propylphenyl group at C-4 results in a 67:33 ratio of diastereomers (Equation 4) (Ridgway and Woerpel, unpublished results). As the propylphenyl group is just a long-chain alkyl group, a majority of the 1,4-*trans* product is consistent with Schmitt and Reissig's results (Schmitt and Reissig, 1990). Therefore, the Inside Attack Model is further supported if allylation of Substrate III affords a majority of the 1,4-*cis* product–instead of the 1,4-*trans* product seen in a C-4 alkyl tetrahydrofuran without geminal methyl substitution at C-2.

The synthesis of Substrate III was not without its share of obstacles. The problematic oxidation of starting material **20**, 4-phenyl-1-butanol, was followed by extremely clean addition of allyl Grignard to the aldehyde formed upon oxidation to afford alcohol **21** (Scheme 10). The TEMPO/KBr/NaOCl oxidation conditions used by Ridgway did not give decent conversion. Pyridinium chlorochromate (PCC) oxidation proceeded with high conversion, but the large amounts of chromium waste generated on this gram-scale reaction needed to be avoided if possible. When more material was needed, Dess-Martin periodinane was utilized due to the fact that it consistently provides clean oxidation of primary alcohols to the corresponding aldehyde (Ireland and Liu, 1993). Hydroboration and oxidation of the double bond of allyl alcohol **21** easily installed a second alcohol to afford diol **22**. N-methylmorphaline N-oxide/tetrapropyl ammonium perruthenate (NMO/TPAP) cyclization of the diol gave lactone **23**.

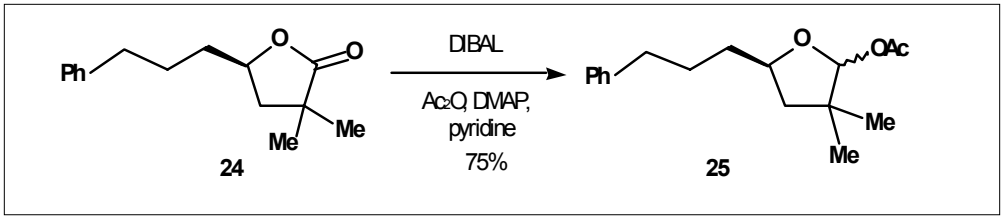
Numerous conditions were examined for the bismethylation of lactone **23**. A one-step bismethylation of lactone **23** was first attempted using NaH as the base and MeI as the alkylating electrophile, but the reaction conditions decomposed the starting material (Equation 5). Using lithium diisopropylamide (LDA) as the base gave incomplete conversion to the monomethylated product. Resubmission of this lactone mixture to the LDA/MeI conditions resulted in a mixture of



Scheme 10

A simple alcohol is elaborated to lactone **36**.

bismethylated, monomethylated, and unmethylated lactone. Increasing the equivalents of reagents did not enhance the conversion. Considering the possibility that the LDA was too hindered to deprotonate at the tertiary center formed after the first methylation, lithium diethylamide was used, but the results were no better. If the problem was not one of steric interactions reducing reactivity, then it could be that the deprotonation by the nitrogen anion could also be impeded in a different way. Coordination of the lithium cation to the nitrogen anion of diisopropylamine is known to decrease anion reactivity by increasing its stability. Hexamethylphosphoramide (HMPA) is generally employed as a dipolar aprotic solvent with the ability to form cation-ligand complexes. HPMA solvates the lithium, thereby enhancing the ability of the nitrogen anion to deprotonate (Paquette, 1995). Complete, but still low-yielding, bismethylation of lactone **23** was finally achieved by employing the LDA/HMPA conditions along with a new source of MeI. Although filtering the MeI through basic alumina to remove any HI formed is normally sufficient for alkylation, the MeI that had been used most likely contained too much HI and MeOH (formed upon exposure to moisture) for this simple purification protocol.



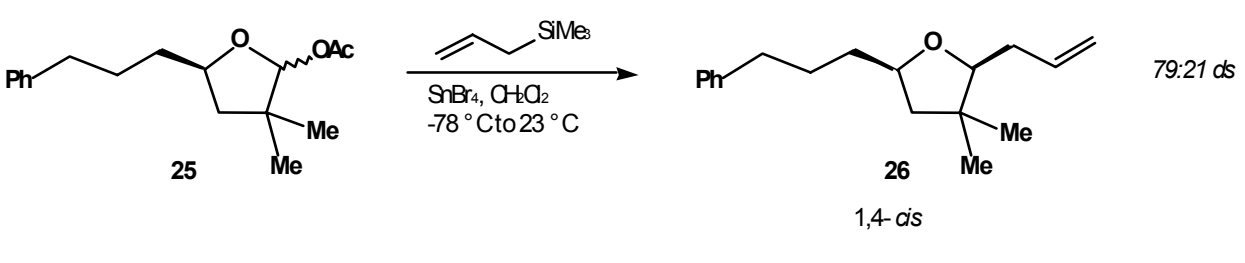
Equation 6

A one-pot reduction-acetylation provides acetate **25** (Substrate III).

Bismethylated lactone **24** was converted to acetate **25** using a one-pot reduction-acetylation procedure (Equation 6) (Dahanukar and Rychnovsky, 1996). Unfortunately, some hydrolysis of acetate **25** occurred during purification by column chromatography due to the acidic nature of the silica gel. This hydrolysis problem was not observed previously in the sugar derivatives because the relatively electronegative oxygens on the ring sequester some of the electron density that would stabilize the incipient positive charge of the oxocarbenium ion, destabilizing formation of the oxocarbenium ion through their electron-withdrawing effect. Bismethylated acetate **25** was more sensitive to hydrolysis due to the presence of electron-donating alkyl groups with the ability to stabilize formation of an oxocarbenium ion. Resubmission to acetylation conditions and addition of triethylamine to the chromatography eluent circumvented the hydrolysis of acetate **25**. Allylation of acetate **25** proceeded cleanly to afford **26** (Equation 7). The diastereoselectivity of this reaction could not be determined by GC analysis because the product peaks did not separate under any conditions examined. However, the C-1 and C-4 protons were well separated in the ^{1}H NMR spectrum of the allylated substrate, and the diastereoselectivity was determined by integration. The diastereoselectivity was not as high as expected, but it was higher than would be expected without the Inside Attack Model. ^{1}H NMR data also proved the stereochemistry. The major diastereomer of **26** showed nOe peaks between the C-1 and C-4 hydrogens, indicating that these hydrogens are on the same face of the ring. This implies that the C-1 allyl group and the C-4 alkyl group are also both on the same face; therefore, the selectivity of allylation of bimethylated acetate **25** was designated 1,4-*cis*. This reversal of diastereoselectivity from 1,4-*trans* for Ridgway's substrate (Equation 4) to substrate **25** supports the predictive capabilities of the Inside Attack Model.

Application of the Inside Attack Model

With the development of the Inside Attack Model, instead of having to consider both outside and inside attack, one now only needs to consider nucleophilic attack on the inside of the envelope conformers in equilibrium. An assessment of the energetics of nucleophilic attack starting with the energies of the variously-substituted oxocarbenium ions and



Equation 7

As predicted by the Inside Attack Model, the allylation of Substrate III favors the formation of the 1,4-*cis* product.

following with the energies of the first-formed products to probe the trajectory of the nucleophile explains the selectivities observed in the systems heretofore presented, including Schmitt and Reissig's results. For example, this Inside Attack Model explains the sole selective substrate in Schmitt and Reissig's survey, the C-3 methyl-substituted tetrahydrofuran hemiacetal. Again, anaylsis begins with the conformation of the oxocarbenium ion intermediate formed upon Lewis acid treatment. As expected in this C-3 alkyl-substituted system, conformer A_1 with the equatorial methyl group is lower in energy than conformer A_2 with the methyl group axial (Figure 4). In addition, nucleophilic attack on the inside of the envelope with the methyl group axial leads to destabilizing 1,3-diaxial interactions between the methyl group at C-3 and the incoming nucleophile. Therefore, high diastereoselectivity (95:5) for the 1,3-*trans* product from the A_1 mode of attack is observed rather than the 1,3-*cis* product arising from the A_2 mode of attack.

The Inside Attack Model also explains unselective cases such as the C-2 methyl-substituted tetrahydrofuran hemiacetal. Conformer B_1 with the methyl group equatorial is favored over conformer B_2 with the methyl group axial because it avoids a 1,3-diaxial interaction between the methyl at C-2 and a C-4 hydrogen (Figure 5). However, nucleophilic approach on this equatorial conformer leads to unfavorable gauche-butane interactions between the methyl group at C-2 and the approaching nucleophile. Therefore, low selectivities are observed for systems with C-2 substitution because there is a higher energy nucleophilic approach on the lower-energy envelope conformer and a lower energy nucleophilic approach on the higher-energy envelope conformer.

Similar effects also account for the low selectivities observed in tetrahydrofuran systems with C-4 substitution. Conformer C_1 with the methyl group equatorial is lower in energy than conformer C_2 which experiences an unfavorable 1,3-diaxial interaction between the methyl group at C-4 and a C-2 hydrogen (Figure 6). Nucleophilic approach on the lower-energy equatorial conformer leads to a pseudo-1,3-diaxial interaction between the methyl group at C-4 and the approaching nucleophile. Therefore, low diastereoselectivities are observed again.

Knowing that neither C-2 nor C-4 substituents direct selectivity, the 3,4-disubstituted sugar systems can be simplfied as a C-3 benzyloxy-substituted system. Conformer D_1 with the alkoxy group axial is extremely favored over equatorial conformer D_2 due to stabilizing electrostatic interactions (Figure 7). In examining the nucleophilic approach on this axial con-

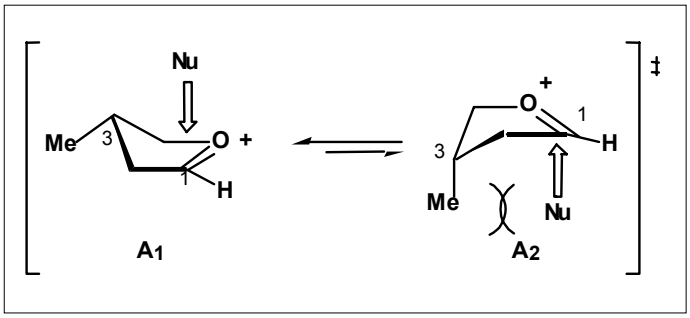


Figure 4

Nucleophilic attack on the inside of the lower-energy envelope conformer in which the C-3 alkyl substituent is equatorial leads to the observed 1,3-*trans* product.

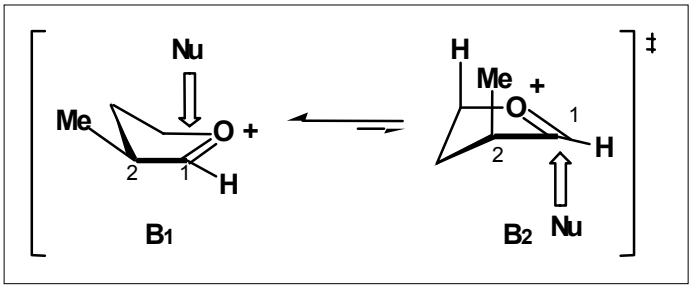


Figure 5

The lack of an energetic preference for attack on either conformer explains the poor diastereoselectivity of C-2 alkyl-substituted systems.

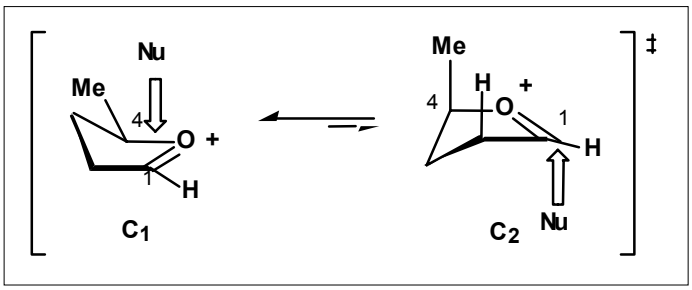


Figure 6

As in the C-2 systems, the lack of an energetic preference for attack on either conformer explains the poor selectivity of C-4 alkyl substituted systems.

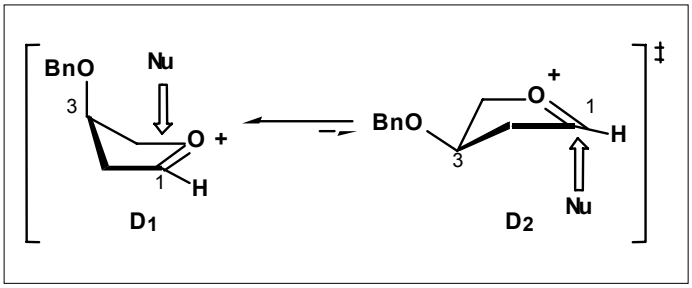


Figure 7

Nucleophilic attack on the inside of the lower-energy envelope conformer in which the C-3 alkoxy substituent is equatorial leads to the observed 1,3-*cis* product.

former, potential 1,3-diaxial interactions between the nucleophile and the C-3 substituent are not going to be as significant as in the methyl-substituted case because an alkoxy group possesses less steric bulk than a methyl group. These energetic considerations explain the high diastereoselectivity for the 1,3-*cis* product in C-3 alkoxy-substituted tetrahydrofuran acetates, including the "Ribose Result."

Conclusions

The stereochemical results of allylation described have contributed to the understanding of these stereoselectivities and to the development of the Inside Attack Model for nucleophilic substitution on tetrahydrofuran acetals. Using corroborating data on the through-space stabilization of incipient oxocarbenium ions by electronegative substituents, the favored conformers of these intermediates during nucleophilic attack can be correctly considered. Analysis of the stereoselectivity of nucleophilic addition to the C-1 position of five-membered ring oxocarbenium ions shows that the major product results from attack from the inside of the envelope conformation of the oxocarbenium ion intermediate. Inside attack on the more stable conformer leads to a lower-energy staggered product as opposed to the higher energy eclipsed product of outside attack. This model explains the selectivities observed in the Woerpel Group as well as those in literature, including the aforementioned ribose result. The Inside Attack Model for the stereoselectivity of nucleophilic addition to five-membered ring oxocarbenium ions will help organic chemists plan syntheses with the knowledge that certain substituents at specified positions on the ring will give the desired stereochemistry, saving time and money that would otherwise be lost pursuing less selective synthetic pathways.

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