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Influence of Alkoxy Groups on Rates of Acetal Hydrolysis and Tosylate Solvolysis: Electrostatic Stabilization of Developing Oxocarbenium Ion Intermediates and Neighboring-Group Participation To Form Oxonium Ions

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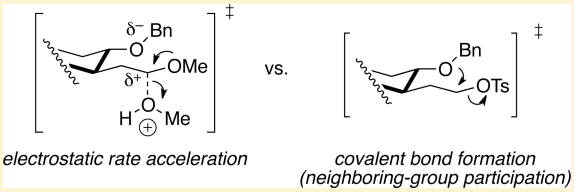
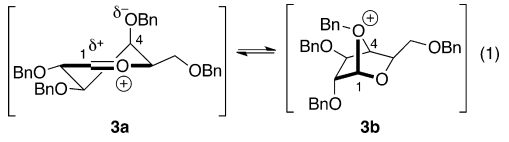
Supporting Information

ABSTRACT: The hydrolysis of 4-alkoxy-substituted acetals was accelerated by about 20-fold compared to that of sterically comparable substrates that do not have an alkoxy group. Rate accelerations are largest when the two functional groups are linked by a flexible cyclic tether. When controlled for the inductive destabilization, an alkoxy group can accelerate acetal hydrolysis by up to 200-fold. The difference in rates of acetal hydrolysis between a substrate where the alkoxy group was tethered to the acetal group by a five-membered ring compared to one where it was tethered by an eight-membered ring was less than 100-fold, suggesting that fused-ring intermediates were not formed. By comparison, the difference in rates of solvolysis of structurally related tosylates were nearly 10^6-fold between the five- and eight-membered ring series. This observation implicates neighboring-group participation in the solvolysis of tosylates but not in the hydrolysis of acetals. The acceleration of acetal hydrolysis by an alkoxy group is better explained by electrostatic stabilization of intermediates that accumulate positive charge at the acetal carbon atom.



INTRODUCTION

The automated synthesis of oligosaccharides depends upon the ability to control both the stereochemical outcome of glycosylation reactions and the relative rates of activation of various components of the reaction.[1,2] The most reliable method for controlling stereochemistry in glycosylation reactions involves using participating groups, most prevalently acyloxy groups, at the adjacent carbon atom to control the stereoselectivity.[3] The relative reactivity issue has been more difficult to address. The relative rates of activation of substrates such as thioglycosides,[1,4] which parallel relative rates of hydrolysis of acetals,[5−7] depend upon the relative stability of the cationic reactive intermediates, leading to differences in rate depending upon the nature of substituents on the ring and the relative stereochemical configurations of those substituents. For example, the activation of glucose-derived thioacetal **1** is slower than the galactose isomer **2**, even though they differ only in the relative stereochemistry at a stereocenter relatively far from the reactive center (Figure 1).[4] Similar rate differences have been observed for hydrolysis.[8] The relative rates of these reactions have been interpreted as deriving from electrostatic stabilization of the positive charge developing at C-1 of the oxocarbenium ion intermediate by the partial negative charge of the alkoxy group at C-4, as illustrated in oxocarbenium ion **3a** (eq 1).[8−10] An alternative explanation, involving reaction of oxonium ion **3b** (which would be in equilibrium with the oxocarbenium ion **3a**), is unlikely because alkoxy groups are generally considered to be nonparticipating groups. Furthermore, such close interaction would be disfavored because it would approximate the formation of a 2,7-dioxabicyclo[2.2.1]heptane structure (**3b**, eq 1), effectively destabilizing this onium ion by up to 15 kcal/mol.[11]



In this Article, we provide evidence that alkoxy groups, which are generally considered to be nonparticipating with respect to stereochemistry,[12−20] can accelerate the ionization of acetals. Preliminary studies suggested that the influence of alkoxy groups on the rates of ionization of acetals (up to 20-fold acceleration compared to that for substrates without alkoxy groups) occurs by electrostatic stabilization of an oxocarbenium ion intermediate, not neighboring-group participation through covalently bonded intermediates.[21] Additional studies with

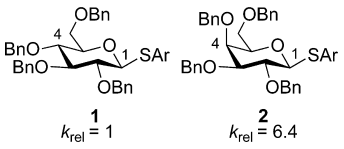


Figure 1. Relative rates of activation of carbohydrate-derived thioacetals (Ar = 4-MeC_6H_4) by *N*-iodosuccinimide/triflic acid.[4]

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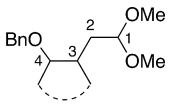
more acetals and also comparisons with the rates of reactions of tosylates, which likely require formation of onium ion intermediates when undergoing ionization, provide further support for this analysis.

RESULTS AND DISCUSSION

To discover whether alkoxy groups can participate in the reactions of acetals such as acid-catalyzed ionization, it was necessary to design substrates that would place the alkoxy group in a position where participation would be possible. In carbohydrate systems, participation by alkoxy groups is highly unlikely because it requires formation of strained rings. In the case of 2-alkoxy systems, the energetic benefit conferred by formation of the oxonium ion (about 15 kcal/mol)[22] would be outweighed by the ring strain of a three-membered ring (27 kcal/mol).[23] Similarly, neighboring-group participation by remote alkoxy groups would create strained bicyclic systems, which are disfavored;[24] such structures are also disfavored for substrates with remote acyloxy groups.[25] Because the strongest evidence for neighboring-group participation of acyloxy groups is found in systems involving fusion of a five-membered ring dioxocarbenium ion to the ring undergoing substitution,[26] we designed substrates **4** that could form five-membered ring oxonium ions. These substrates contain a benzyloxy group that is positioned four carbon atoms away from the acetal carbon (Figure 2). To make the entropic costs of participation in this



4

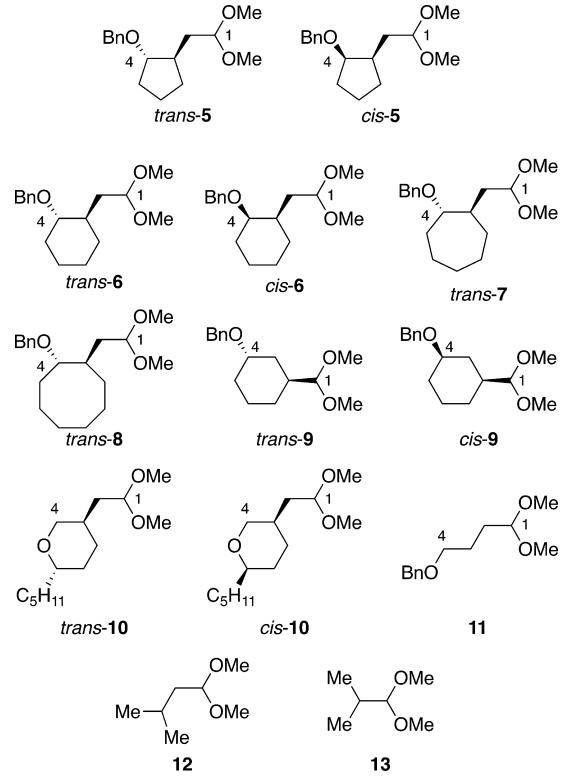
Figure 2. Dimethyl acetal substrate template.

series comparable to those costs for the acyloxy group in glycoside systems,[27] we included a second ring so that any interaction between the alkoxy group at C-4 and the acetal carbon atom C-1 would form a fused bicyclic system, just as for the carbohydrate systems. The benzyloxy group was chosen because it is a commonly used protecting group in carbohydrate chemistry and because loss of this group during ionization would suggest participation through oxonium ions resembling bicyclic ion **3b** (eq 1).[13,28,29]

The rates of ionization of these acetals would be used to provide evidence for or against the involvement of alkoxy groups in ionization. Rates would be compared to constrained model compounds that would exhibit similar through-bond inductive effects[30,31] but, because of their constrained geometry, could not be stabilized efficiently because the alkoxy group could not be brought close to the developing positive charge. Rates of ionization of appropriate compounds without alkoxy groups would also be examined to determine whether an alkoxy group can accelerate hydrolysis, although previous studies with acyclic acetals demonstrated that it cannot.[32]

Chart 1 shows the alkoxy-substituted acetals used for this study. The two key functional groups were fused to rings of different sizes (five- to eight-membered rings in the trans series) and placed with different relative stereochemical configurations (including cis and trans isomers in some cases) to study how the flexibility of the fused ring and the relative orientation of the benzyloxy group and acetal affected the rate of ionization. The relative positions of the benzyloxy group and the acetal moiety were also investigated with substrates

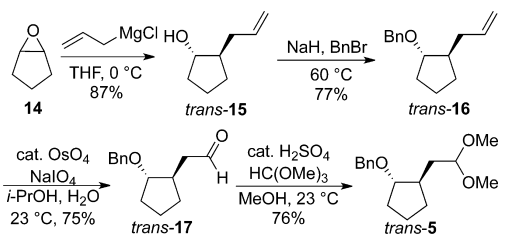
Chart 1. Substrates Evaluated for Rates of Hydrolysis



trans- and *cis*-**9**. Like substrates **5**−**8**, these compounds position a benzyloxy group four carbon atoms away from the acetal carbon atom, but in this case, formation of the oxonium ion by neighboring-group participation would require formation of a bridged bicyclic system, which would develop significant ring strain.[33] Similarly, acetals *trans*- and *cis*-**10** possess an alkoxy group four atoms from the acetal, but they would also engender ring strain if acceleration required the alkoxy group to approach the acetal carbon atom. The hydrolysis of a completely flexible acetal **11**, related to a system that had shown deceleration in acetal hydrolysis experiments under neutral conditions,[32] was also examined. Simple alkyl acetals **12** and **13** with branching similar to that of the cyclic acetals were included as benchmarks to determine whether the presence of an alkoxy group decelerated ionization relative to compounds without an alkoxy group, as has been established for carbohydrates[8] and simple acetals.[32]

Substrate Synthesis. The substrates listed in Chart 1 were prepared by various methods. Scheme 1 shows the route used

Scheme 1



to prepare acetal *trans*-**5**, involving an epoxide ring-opening reaction followed by functionalization.[21] Starting from the appropriate epoxide, acetals *trans*-**6**, *trans*-**7**, and *trans*-**8** with larger rings were prepared by a similar pathway. The synthesis of the five- and six-membered ring acetals *cis*-**5** and *cis*-**6**

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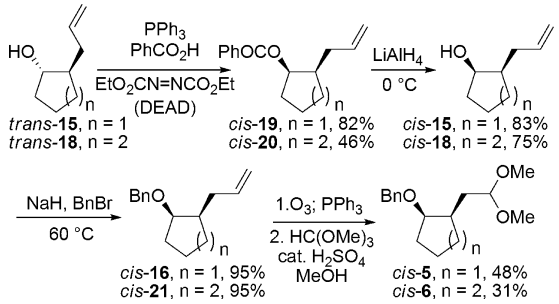
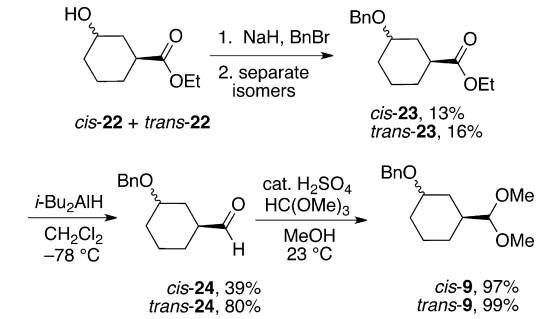
followed the general synthetic route but proceeded through alcohols *cis*-**15** and *cis*-**18**, which were prepared by inversions of the configurations of the hydroxyl groups on alcohols *trans*-**15** and *trans*-**18** (Scheme 2). The disubstituted cyclohexane acetals

Scheme 2



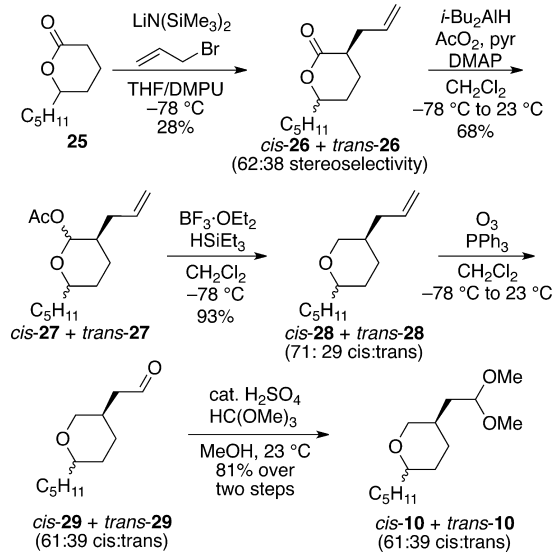
cis-**9** and *trans*-**9** were prepared from a common starting material and separated as esters *cis*-**23** and *trans*-**23**, which were reduced and converted to the acetals separately (Scheme 3).[21]

Scheme 3



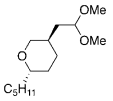
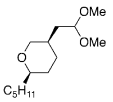
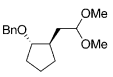
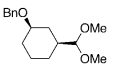
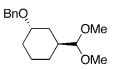
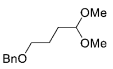
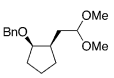
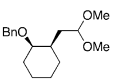
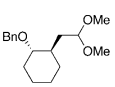
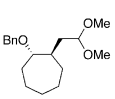
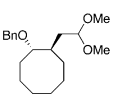
The tetrahydropyran acetals *cis*-**10** and *trans*-**10** were prepared as a mixture of isomers from *δ*-decanolactone (**25**) as shown in Scheme 4.[21] Acetals **11**–**13** have been reported previously.[34−36]

Scheme 4[37]



Rates of Acetal Hydrolysis. The rates of hydrolysis of the acetals shown in Chart 1 were measured by ^{1}H NMR spectroscopy, as illustrated in eq 2. Concentrations were measured over one to six half-lives (depending upon the substrate) by integrations of one-pulse experiments and comparisons of integrations to those of an internal standard (1,4-dimethoxybenzene) of known concentration. Each experiment was repeated at least two additional times. In no case were products other than the aldehyde **31** observed, indicating that no debenzylation occurred (vide infra). The rates were consistent with pseudo-first-order kinetics, with plots of ln[acetal] versus time giving lines with $R^2 \geq 0.96$. Higher concentrations of acid were required to obtain measurable rates of some substrates, so rates are reported as observed rate constants divided by the concentration of acid used. Table 1 reports these normalized rate constants to two significant

Table 1. First-Order Rate Constants at 23 °C and Relative Rates of Hydrolysis of Acetals in Acetone-d_6/D_2O Normalized to the Same Concentration of DCl/D_2O (1 M)

Acetal	Structure	k (s^{-1})	k_{rel}
trans-**10**		6.5×10^{-4}	0.12
cis-**10**		1.3×10^{-3}	0.25
trans-**5**		1.5×10^{-3}	0.28
cis-**9**		2.3×10^{-3}	0.43
trans-**9**		3.1×10^{-3}	0.58
11		4.0×10^{-3}	0.75
12		5.3×10^{-3}	1.0
13		8.2×10^{-3}	1.5
cis-**5**		9.9×10^{-3}	1.9
cis-**6**		1.6×10^{-2}	3.0
trans-**6**		4.3×10^{-2}	8.1
trans-**7**		8.5×10^{-2}	16
trans-**8**		1.1×10^{-1}	21

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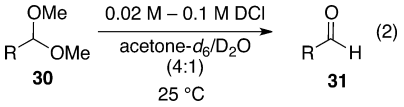
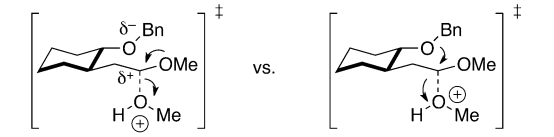
figures for acetal hydrolysis reactions in order from slowest to fastest. Acetal **12**, which contained no alkoxy group, was used as the reference point for establishing the relative rates. It is anticipated that all of the β-branched acetals are sterically similar to acetal **12** because the two-carbon chain of the cyclic acetals would adopt a conformer minimizing double-gauche interactions, as observed for isobutyl-substituted cyclohexanes[38] and 1-butanol,[39] resulting in the acetal group being placed near a methylene group of the ring. It does not appear that steric effects play a considerable role in these reactions,[40] considering that the β-branched and α-branched acetals **12** and **13**, respectively, ionize at similar rates.



The rate acceleration of hydrolysis conferred by a benzyloxy group is significant based upon comparisons of the rates in Table 1. Simply comparing the rate of hydrolysis of acetal *trans*-**6** to that of isovaleraldehyde acetal **12** shows that an alkoxy group can accelerate hydrolysis compared to that of an acyclic acetal by nearly one order of magnitude. Because acetal hydrolysis involves reversible protonation followed by rate-limiting ionization,[8,41] the cationic intermediate formed from acetal *trans*-**6** must be stabilized by the alkoxy group four atoms away. It cannot be differentiated whether this effect results from electrostatic stabilization by the benzyloxy group, as suggested for hydrolysis of galactose (eq 1),[9,10] or whether a new covalent bond is formed during ionization, resulting in formation of an onium ion intermediate (Figure 3).



32 *electrostatic stabilization by OBn* **33** *covalent bond formation to OBn*

Figure 3. Interaction of alkoxy group with ionizing acetal in the transition state for hydrolysis of acetal *trans*-**6**.

The observation that acetal hydrolysis can be accelerated by an alkoxy group would not be anticipated on the basis of previous studies. In carbohydrates, the presence of an alkoxy group at C-4, regardless of its orientation, decelerates hydrolysis. In simple ketone-derived acetals, the presence of an alkoxy group or an alkylthio group decelerated acetal hydrolysis (Figure 4).[32] We observed similar reduced reactivity

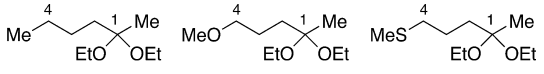
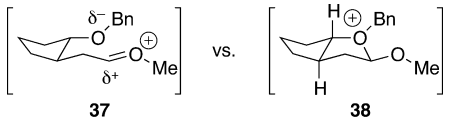


Figure 4. Relative rates of hydrolysis (1:1 dioxane/water) for acetals **34**–**36**.[32]

of the acyclic aldehyde-derived acetal **11**: the presence of the remote alkoxy group decelerated hydrolysis by about 25% compared to the hydrolysis of alkyl acetal **12** (Table 1). In some cases, the presence of a neighboring group can accelerate acetal hydrolysis, but this effect has been observed only with carboxylates as neighboring groups under conditions that favor deprotonation of a nearby carboxylic acid group.[42,43]

The flexibility of the ring connecting the alkoxy group plays a significant role in acetal hydrolysis, with larger rings undergoing ionization more rapidly. While the cyclopentane-derived acetal *trans*-**5** ionized nearly four times slower than the sterically equivalent alkyl acetal **12**, the cyclooctane-derived acetal *trans*-**8** ionized over 20 times faster than the alkyl acetal. The trend of increasing rate as more carbon atoms are introduced to the tethering ring is consistent with the idea that the more flexible ring[44,45] allows the alkoxy group to approach the acetal undergoing substitution more closely, leading to accelerated hydrolysis, as observed for galactosides compared to glucosides (Figure 1). The nearly three-fold slower reaction of the cis-substituted acetal *cis*-**6** with a six-membered ring compared to its trans-substituted analogue *trans*-**6** may reflect minor differences in the energies of transition states resembling fused rings (*trans*-hydrindane being slightly less strained than the cis isomer[46,47]). Too much flexibility did not lead to faster ionization, however, as illustrated by the slower hydrolysis of flexible benzyloxy-substituted acetal **11**. In that case, any enthalpic stabilization to the transition state conferred by the benzyloxy group would be offset by entropic penalties[27] incurred upon restricting conformational mobility.

The slow ionization of cyclopentane-derived acetal *trans*-**5** compared to that of the other trans-substituted acetals and even to the alkyl acetal **12** provides insight into how an alkoxy group accelerates hydrolysis. According to the Hammond postulate,[48] the transition state for hydrolysis should share structural and energetic features with the high-energy cationic intermediate formed upon ionization.[49] The alkoxy group could stabilize the positive charge on the acetal carbon atom[9,10] without forming a new covalent bond (as in oxocarbenium ion **37**, Figure 5). This



37 **38**

Figure 5. Two possible modes of interaction by an alkoxy group upon ionization of acetal *trans*-**5**.

interaction has been proposed to explain the faster hydrolysis of galactose compared to that of glucose.[9,10] A similar electrostatic stabilization has also been invoked to explain the small acceleration observed in the hydrolysis of carbohydrate derivatives bearing acyloxy groups at C-2.[50] Alternatively, a new covalent bond could form between the alkoxy group and the acetal carbon atom during hydrolysis. The resulting intermediate oxonium ion **38**, however, would develop a significant fraction of the ring strain inherent in the *trans*-bicyclo[3.3.0]-octane system (>15 kcal/mol).[46,47] If this pathway were followed, then it would be anticipated that the rate of ionization of the trans-substituted acetal *trans*-**5** would be much slower than that for *cis*-**5**, which would form a *cis*-bicyclo[3.3.0]octane system, which possesses less ring strain than the trans isomer (by about 6 kcal/mol).[46,47] The rate difference between the isomers, however, is only about six-fold (Table 1). Consequently, the small difference in reactivity between the two isomers *cis*-**5** and *trans*-**5** is better accommodated by considering a looser structure resembling oxocarbenium ion **37** rather than an onium ion such as **38**, where the carbon–oxygen bond lengths would need to be shorter.[51]

The above rate accelerations of hydrolysis of up to 21-fold by an alkoxy group do not account for the inherent

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electron-withdrawing nature of the benzyloxy group. This rate difference compares acetals that are not electronically similar. An electronegative group such as an alkoxy group should destabilize positively charged intermediates and transition states, leading to attenuation of reaction rates.[8,50] The more appropriate comparison point would be an acetal that possessed the alkoxy group the same number of atoms away from the acetal carbon atom but with that alkoxy group fixed so that it could not approach the acetal carbon by rotation about the intervening bonds.

To demonstrate whether distal alkoxy groups inductively destabilize reactive intermediates, the rates of hydrolysis for two different types of constrained acetals were examined. It is unlikely that during the hydrolysis of acetals *cis*- and *trans*-**9** and *cis*- and *trans*-**10** that the remote alkoxy groups can approach the acetal carbon atom because they are held in fixed orientations relative to each other. Acetal *trans*-**9** positions both critical substituents on opposite faces of the ring, so they can never be particularly close (*trans*-**39**, Figure 6). Similarly,

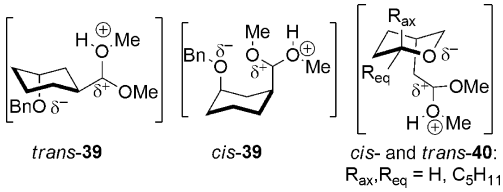


Figure 6. Protonated acetals that would be involved during acetal hydrolysis.

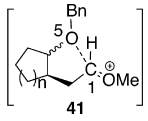
for the acetal and alkoxy groups to approach each other in *cis*-**9**, both would need to be oriented axially (*cis*-**39**, Figure 6), yielding a bicyclic oxonium ion with significant steric and ring strain (approximately 12.1 kcal/mol).[33] Consequently, only through-bond inductive effects were expected to influence the transition state for ionization of these acetals. This prediction was consistent with the observation that hydrolyses of the constrained acetals **9** were slowed by two- to four-fold compared to the ionization of the acetal of isovaleraldehyde (**12**). A similar analysis would pertain to acetals *cis*- and *trans*-**10**: to bring the ring's oxygen atom near to the acetal carbon atom, sterically disfavored axial conformations resembling **40** with a significant number of gauche-butane interactions[52] would need to be formed. As a result, these hydrolyses are four to eight times slower than the reactions of the alkyl acetal **12**.

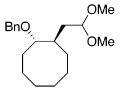
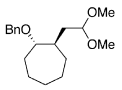
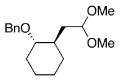
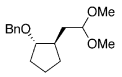
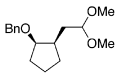
The measurement of the inductive deceleration of acetal hydrolysis by an alkoxy group permits an estimate of how much an alkoxy group can accelerate acetal hydrolysis in unconstrained systems. Comparisons of the rate of hydrolysis of the eight-membered ring acetal *trans*-**8**, the most flexible cyclic system, to the rates of hydrolysis of constrained acetals reveals a 40- to 200-fold acceleration of hydrolysis that can be attributed to bringing the alkoxy group near the acetal carbon atom. The accelerations in the six-membered ring substrate *trans*-**6** are only slightly lower (10- to 70-fold, depending upon the comparison made). Whatever substrate is chosen and whichever comparison is made, it is evident that the influence of an alkoxy group on acetal hydrolysis is larger than the effect determined for acyloxy groups in similar systems, which exert a seven- to thirteen-fold rate acceleration after compensation for inductive destabilization.[50]

The hydrolysis rates reported here indicate that it is not appropriate to make the generalization that an alkoxy group (or likely a hydroxyl group, which is electronically similar) cannot participate in acetal hydrolysis. Instead, in carbohydrate-derived systems, it does not engage in participation because to do so would impart ring strain. The powerful mitigating force of strain is illustrated by the results with the cyclopentane-derived acetal *trans*-**5**, which ionizes about 30 times slower than its cyclohexane-derived analogue *trans*-**6**.

Computational Studies. Computational analyses of the cations formed upon hydrolysis were performed to help understand the observed differences in rates between the acetal substrates. While a more thorough analysis would require investigation of the structures, energies, and conformational distributions of starting materials, products, and transition states for hydrolysis,[53] as well as application of solvent corrections to the calculations,[54] comparisons of the energies of related intermediates were nevertheless informative. Computational analysis involved a search for low-energy conformers of the oxocarbenium ion intermediates for each substrate using semiempirical methods[55] and optimization using density functional methods (B3LYP/6-31G*).[56] Once the lowest energy conformer for each substrate was determined, the proximity of the oxygen atom of the benzyloxy group to the oxocarbenium ion carbon atom was measured. These results are summarized in Table 2.

Table 2. Calculated Distances between C1 and O5 of the Lowest Energy Conformer of Cationic Intermediates 41 Derived from Acetals and Comparison to Relative Rates of Hydrolysis (B3LYP/6-31G*)[57]



Acetal	Structure	k_{rel} for hydrolysis	C1–O5 distance (Å)
trans-**8**		21	1.61
trans-**7**		16	1.64
trans-**6**		8.1	1.99
trans-**5**		0.28	2.44
cis-**5**		1.9	1.64

For related series of compounds, the faster the acetals underwent ionization, the closer the ether oxygen atom (O5) approached the cationic carbon atom (C1) in the calculated structure of the oxocarbenium ion. The correlation between rate of ionization and C1−O5 distance is consistent with the observation that the benzyloxy group stabilizes the oxocarbenium ion intermediate. The longest distance between the atoms was observed for the cyclopentane-derived acetal *trans*-**5**. Because bringing O5 close to the cationic carbon atom C1 would form a ring resembling a trans-fused [3.3.0]-bicyclic system, the benzyloxy group was held further away from the carbocationic carbon atom (2.44 Å), thereby diminishing the stabilization of the transition state for hydrolysis. When the two substituents are positioned cis on the cyclopentane ring, as for acetal *cis*-**5**, the distance between C1 and O5 is closer (1.64 Å), which is reflected in a rate of ionization that is seven times

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faster than *trans*-**5**. Although detailed studies comparing the relative energies of the starting materials and transition states of ionization are required to draw firm conclusions, the data presented here convey a correlation between the proximity of the benzyloxy group and the oxocarbenium ion carbon atom and the rate of ionization.

These computational studies could be interpreted as supporting formation of a new covalent bond to the carbon atom of the oxocarbenium ion (that is, neighboring-group participation[58]) as the mechanism for ionization of acetals (**42**, Figure 7), but that interpretation is not without problems.

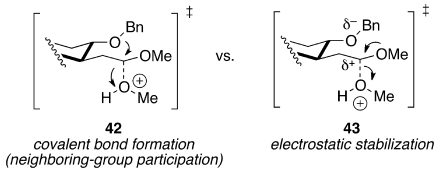


Figure 7. Possible modes of ionization of alkoxy-substituted acetals.

The C−O bond distances of approximately 1.6 Å for the cations related to acetals *cis*-**5**, *trans*-**7**, and *trans*-**8** suggest formation of a covalent bond. Although C−O bonds are typically 1.43 Å,[51,59,60] C−O bonds in oxonium ions can be as long as 1.658 Å,[60] lending support to this argument. This interaction between carbon and oxygen atoms could result from neighboring-group participation, in which the departing MeOH fragment is ejected by the benzyloxy group to form an oxonium ion intermediate (Figure 7).[61] The considerably longer C−O bond length observed in the oxocarbenium ions stemming from the cyclohexane-derived acetal *trans*-**6**, which ionized eight times faster than an acetal without an alkoxy group, however, cannot be readily interpreted as deriving from neighboring-group participation.[60] These distances are, however, consistent with electrostatic stabilization of an oxocarbenium ion, which is even observed in cases where the C−O distance is around 3.3 Å.[24] If the accelerated ionization of trans-substituted acetals *trans*-**7** and *trans*-**8** involved neighboring-group participation and the accelerated ionization of *trans*-**6** did not, then the difference between the efficiency of these mechanisms is small (leading to rate differences less than three-fold), much smaller than normally observed in cases of neighboring-group participation (rate accelerations of several orders of magnitude are more common).[62−64] Furthermore, in an absolute sense, the bond distance in the carbocation is not a good predictor of the rate of ionization. Taken together, the computational studies do not provide strong support for formation of a new covalent bond in the transition state as being responsible for the rate acceleration observed in the ionization of alkoxy-substituted acetals.

Solvolysis Studies. To determine the magnitude that neighboring-group participation could influence ionization rates, we examined the rates of solvolysis of structurally related primary alkyl tosylates (Figure 8). The ionization of primary tosylates likely requires participation of the neighboring alkoxy

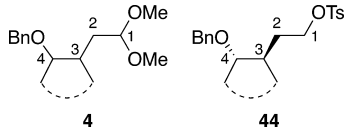
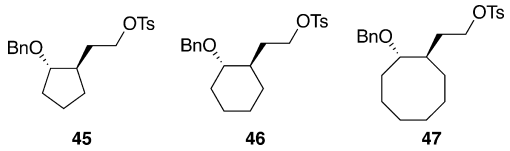
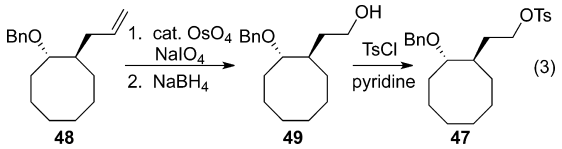


Figure 8. Tosylate substrates **44** designed to be similar to acetals **4**.

Chart 2. Tosylates Evaluated for Rates of Solvolysis

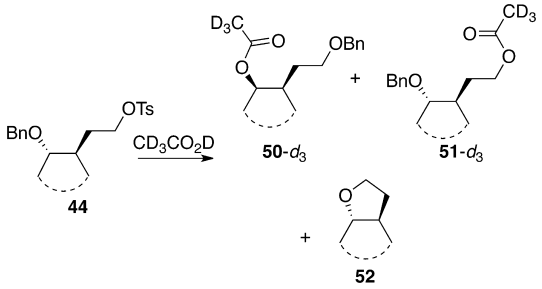


group,[62−67] so the magnitude of the influence of neighboring-group participation could be measured as a function of ring size. Chart 2 displays the tosylates used in the study. Only the trans-fused five-, six-, and eight-membered ring substrates were synthesized (Chart 2) because these substrates span the range of rates of acetal hydrolysis. The synthesis of the tosylates employed intermediates that were used to prepare the acetal substrates; an example of the synthesis is shown in eq 3.



Determination of the ionization rates of tosylates involved dissolving them in acetic acid-d_4 and measuring the disappearance of starting material by ^{1}H NMR spectroscopy. The reactions exhibited first-order kinetics, as determined by plots of $\ln(c_0/c)$ versus time. As with acetal hydrolysis experiments (eq 2), these experiments were repeated in triplicate to ensure that the results were meaningful. The products of the reaction were also analyzed to provide additional insight into the mechanism of solvolysis. Scheme 5

Scheme 5. Products Expected upon Solvolysis of Tosylates in Acetic Acid-d_4



lists the products that were expected to be formed upon hydrolysis if neighboring-group participation by the benzyloxy group occurred.[28,29]

The relative rates of ionization of the tosylates exhibit a profoundly larger dependence upon ring size than did the rates of ionization of the corresponding acetals (Table 3). The differences in solvolysis rates of the tosylates were so large that measuring the relative rates proved to be difficult. Tosylate **47** was so reactive in acetic acid-d_4 that it underwent solvolysis to a significant extent (50%) in the 4 min between preparing the sample and acquiring the first NMR spectrum. By contrast, a sample of tosylate **45** at room temperature in acetic acid-d_4 could be stored at room temperature for several weeks without undergoing any reaction. Heating samples of tosylate **45** to temperatures above 100 °C allowed for a more rapid determination of the rate, and application of the Arrhenius equation allowed for comparison to the solvolysis rate of tosylate **45** at room temperature.[68]

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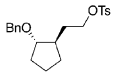
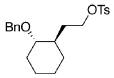
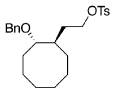
Table 3. Solvolysis Rate Constants, Relative Rates, and Calculated Half-Lives of Solvolysis of Tosylates in Acetic Acid-d_4 at 23 °C

Tosylate	Structure	k (s^{-1})	k_{rel}	$t_{1/2}$ (23 °C)
45		1.8×10^{-9} [a]	1	12 years
46		1.8×10^{-5}	1.0×10^{4}	11 h
47		1.2×10^{-3}	6.7×10^{5}	10 min

[a]Obtained by determining the rate at 100, 110, and 125 °C and applying the Arrhenius equation to estimate the rate at 23 °C, as discussed in the Supporting Information.

Product analysis studies of the solvolysis of tosylates provided evidence that neighboring-group participation had occurred. NMR spectroscopic analysis indicated that cyclic ethers resembling **52** (Scheme 5) were obtained in all cases. The cyclic products likely resulted from formation of cyclic oxonium ion **58** (Figure 9), which then underwent ring

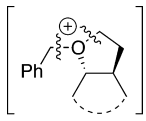
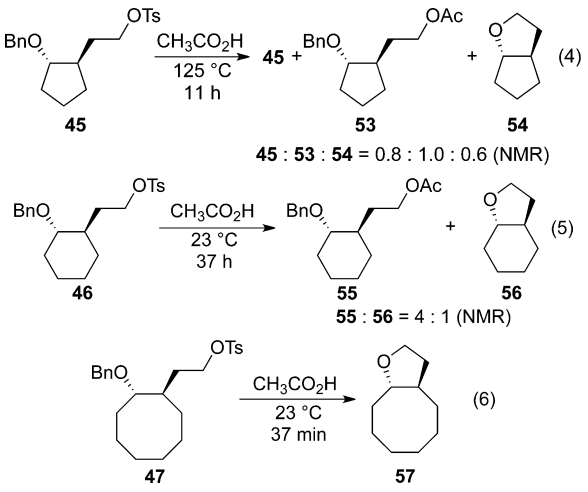


Figure 9. Oxonium ion that would be formed by neighboring-group participation and bonds that were cleaved upon hydrolysis.

opening or debenzylation[28,29] by nucleophiles present in solution. Benzyl acetate-d_3 and benzyl tosylate were also observed. Preparative solvolysis reactions of tosylates **45**–**47** in acetic acid allowed for full characterization of all major products formed (eqs 4–6). It is worth noting that there was no debenzylation in any acetal hydrolysis reactions (eq 2 and Table 1), providing evidence against the formation of oxonium ions in those reactions.



The relative rates of solvolysis of **45**–**47** define a range of reactivity that would be expected for these fused systems should neighboring-group participation occur. The nearly six orders of magnitude difference in rate between the cyclooctane- and the cyclopentane-derived substrates (**47** and **45**, respectively) reflects the difference in ring strain between the bicyclic rings resulting from neighboring-group participation.[69] The larger the second ring, the better it can be accommodated into the fused ring onium ion **58**, so the faster the ionization. The nearly one million-fold difference in rates of solvolysis of tosylates establishes a standard for what differences in rate should be observed during neighboring-group participation by an alkoxy group[62−64,70] compared to ones that do not.

The dramatic differences in rates of reaction versus ring size between the tosylate and acetal substrates suggest a difference in how the alkoxy group facilitates ionization in both series. The cyclooctane-derived tosylate **47** was found to ionize 670,000 times faster than cyclopentane-derived tosylate **45**, an approximately 10,000-fold larger difference in rate than was observed for the hydrolysis of acetals of the same ring size (Figure 10). Whereas the ionizations of the tosylates involve

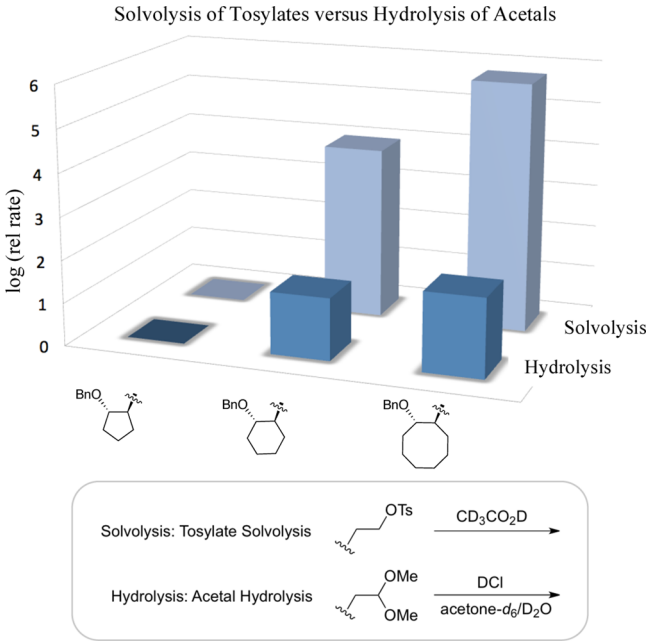


Figure 10. Graphical representation of hydrolysis of acetals versus solvolysis of tosylates, plotting log (relative rates) vs ring size.

significant participation by the alkoxy group, the neighboring benzyloxy group plays only a small role in the case of acetal hydrolysis. This smaller role likely occurs because the cationic intermediate can be stabilized primarily as the oxocarbenium ion, diminishing the need for the cationic carbon atom to gain stabilization by interaction with a neighboring group. Related cases in which other modes of stabilization override neighboring-group participation have been reported for reactions involving cationic intermediates.[71,72]

The relative rate data and product analysis studies suggest that reactions of acetals substituted by alkoxy groups are influenced mostly by electrostatic effects, not by neighboring-group participation. It is not necessary for an alkoxy group to form a covalent bond to the acetal carbon atom upon ionization. Instead, conformational changes can occur that bring the electronegative oxygen atom close to the carbon atom undergoing ionization, stabilizing the developing oxocarbenium ion by electrostatic effects.

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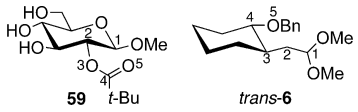
CONCLUSIONS

Our results demonstrate that alkoxy groups can exert strong influences on the formation of oxocarbenium ions, not just in the stereochemistry of their reactions.[73] When an alkoxy group can participate without engendering ring strain, it can exert influences on ionization rates at least as powerfully as acyloxy groups do in carbohydrate systems. The acceleration in the rate of ionization exerted by the acyloxy group of acetal **59** (Figure 11) through neighboring-group participation was



59 *t*-Bu *trans*-**6**

Figure 11. Related acetals.

determined to be 13-fold after correction for inductive effects.[50] In the related acetal *trans*-**6**, which positions an oxygen atom at the same distance (Figure 11), the alkoxy group accelerated the rate of ionization by 33- to 67-fold after correction for inductive effects. These results suggest that appropriate caveats should be taken when it is assumed that an alkoxy group cannot participate in the reactions of acetals.

EXPERIMENTAL SECTION

The synthesis and characterization of compounds *trans*-**5**, *trans*-**6**, *trans*-**7**, *trans*-**8**, **9**, **10**, *trans*-**15**−**18**, **45**, **46**, **48**, **55**, and **56** have been reported previously.[21]

4-Benzyloxybutyraldehyde Dimethyl Acetal (11). To a solution of 4-benzyloxy-1-butane (0.507 g, 2.81 mmol) in CH_2Cl_2 (14 mL) were added 3 Å molecular sieves (1.41 g), silica (1.33 g), and pyridinium chlorochromate (1.22 g, 5.66 mmol). After stirring overnight at room temperature, the reaction mixture was filtered through diatomaceous earth and silica gel with Et_2O (300 mL). Concentration in vacuo yielded a clear oil (0.390 g). To this oil were added anhydrous methanol (5 mL), 3 Å molecular sieves (1.09 g), and concentrated H_2SO_4 (3 drops). After stirring overnight at room temperature, the solids were removed by filtration. The resulting filtrate was diluted with CH_2Cl_2 (125 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel thin-layer chromatography (10:90 EtOAc/hexanes) afforded dimethyl acetal **11** as a clear oil (0.262 g, 40% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.53 (s, 2H), 4.40 (t, J = 5.4, 1H), 3.51 (t, J = 6.1, 2H), 3.33 (s, 6H), 1.74−1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 104.5 (CH), 73.0 (CH_2), 70.1 (CH_2), 52.9 (CH_3), 29.4 (CH_2), 25.0 (CH_2); IR (ATR) 2940, 2856, 1102 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{13}H_{20}NaO_3$ (M + Na)$^+$, 247.1310; found, 247.1311.

(1*R,2*R**)-2-Allylcyclopentyl Benzoate (*cis*-19).** To a cooled (−40 °C) solution of PPh_3 (0.736 g, 2.81 mmol) and $PhCO_2H$ (0.343 g, 2.81 mmol) in PhMe (8.5 mL) was added alcohol *trans*-**15** (0.295 g, 2.34 mmol) in PhMe (1.7 mL). Diethyl azodicarboxylate (DEAD, 0.44 mL, 2.81 mmol) in PhMe (3 mL) was added dropwise over 5 min. After stirring for 1.5 h at −40 °C, the reaction mixture was brought to room temperature. After 4 h, saturated aqueous $NaHCO_3$ (15 mL) was added, the layers were separated, and the organic layer was concentrated in vacuo. Purification by flash chromatography (2:98 EtOAc/hexanes) afforded ester *cis*-**19** as a colorless oil (0.441 g, 82%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04−8.02 (m, 2H), 7.56−7.54 (m, 1H), 7.46−7.42 (m, 2H), 5.81 (ddt, J = 17.0, 10.1, 7.0, 1H), 5.41 (td, J = 4.9, 1.4, 1H), 4.99 (ddt, J = 17.0, 2.0, 1.5, 1H), 4.94 (ddt, J = 10.1, 2.1, 1.1, 1H), 2.34 (quint of t, J = 7.0, 1.3, 1H), 2.19−2.14 (m, 1H), 2.07−2.00 (m, 2H), 1.94−1.82 (m, 3H), 1.69−1.62 (m, 1H), 1.61−1.54 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2 (C), 137.6 (CH), 132.9 (CH), 131.0 (C), 129.6 (CH), 128.5 (CH), 115.5 (CH_2), 78.3 (CH), 44.5 (CH), 34.1 (CH_2), 32.7 (CH_2), 29.8 (CH_2), 22.2 (CH_2); IR (ATR) 3073, 1713, 1641, 1270, 1069 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{18}NaO_2$ (M + Na)$^+$, 253.1199; found, 253.1198. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.96; H, 8.07.

(1*R,2*R**)-2-Allylcyclopentanol (*cis*-15).** Ester *cis*-**19** (2.58 g, 11.2 mmol) in Et_2O (112 mL) was added by cannula to a cooled (0 °C) solution of $LiAlH_4$ (0.890 g, 22.4 mmol) in Et_2O (112 mL). After 30 min, H_2O (11.5 mL) was added, followed by NaOH (23 mL, 1.0 M in H_2O) and H_2O (35 mL) again. The layers were separated, and the organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10:90 EtOAc/hexanes) afforded alcohol *cis*-**15** as a yellow oil (1.18 g, 83%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91−5.84 (m, 1H), 5.08 (dq, J = 17.1, 1.7, 1H), 4.99 (ddt, J = 10.1, 2.1, 1.2, 1H), 4.18−4.16 (m, 1H), 2.30−2.25 (m, 1H), 2.20−2.14 (m, 1H), 1.88−1.72 (m, 4H), 1.69−1.63 (m, 1H), 1.60−1.53 (m, 2H), 1.45−1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (CH), 115.2 (CH_2), 74.7 (CH), 45.4 (CH), 34.8 (CH_2), 33.9 (CH_2), 28.9 (CH_2), 22.0 (CH_2); IR (ATR) 3372, 1640, 989 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_8H_{18}NO$ (M + NH_4)$^+$, 144.1383; found, 144.1392.

((((1*R,2*R**)-2-Allylcyclopentyl)oxy)methyl)benzene (*cis*-16).** NaH (1.12 g, 60% dispersion in mineral oil, 28.0 mmol) and BnBr (1.3 mL, 11.0 mmol) were added to a solution of alcohol *cis*-**15** (1.18 g, 9.34 mmol) in THF (19 mL), and the reaction mixture was heated at 60 °C. After 14 h, saturated aqueous NH_4Cl (20 mL) and Et_2O (40 mL) were added, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined Et_2O layers were washed with brine (120 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (1:99 EtOAc/hexanes) afforded benzyl ether *cis*-**16** as a colorless oil (2.05 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.30 (m, 4H), 7.29−7.25 (m, 1H), 5.83 (ddt, J = 17.2, 10.1, 7.2 1H), 5.03 (ddt, J = 17.1, 2.3, 1.5, 1H), 4.93 (ddt, J = 10.1, 2.2, 1.1, 1H), 4.55 (d, J = 12.1, 1H), 4.39 (d, J = 12.1, 1H), 3.84 (td, J = 4.8, 2.6, 1H), 2.43−2.36 (m, 1H), 2.17−2.09 (m, 1H), 1.90−1.81 (m, 2H), 1.79−1.65 (m, 3H), 1.60−1.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5 (C), 138.9 (CH), 128.4 (CH), 127.5 (CH), 127.4 (CH), 114.8 (CH_2), 81.7 (CH), 70.8 (CH_2), 44.8 (CH), 33.7 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 21.8 (CH_2); IR (ATR) 1640, 1205, 1065 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{21}O$ (M + H)$^+$, 217.1587; found, 217.1592. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.04; H, 9.35.

((((1*R,2*R**)-2-(2,2-Dimethoxyethyl)cyclopentyl)oxy)-methyl)benzene (*cis*-5).** Ozone was bubbled into a cooled (−78 °C) solution of benzyl ether *cis*-**16** (0.509 g, 2.35 mmol) in CH_2Cl_2 (12 mL) for 15 min. After stirring for 1 h at −78 °C, PPh_3 (1.85 g, 7.06 mmol) was added, and the reaction mixture was brought to room temperature. After 14 h, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc/hexanes) afforded an aldehyde as a colorless oil (0.309 g, 60%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (t, J = 1.7, 1H), 7.34−7.32 (m, 2H), 7.30−7.25 (m, 3H), 4.53 (d, J = 11.9, 1H), 4.32 (d, J = 11.9, 1H), 3.95−3.93 (m, 1H), 2.81 (ddd, J = 17.3, 7.5, 1.6, 1H), 2.49 (ddd, J = 17.3, 6.7, 1.7, 1H), 2.37−2.31 (m, 1H), 1.89−1.71 (m, 4H), 1.62−1.53 (m, 1H), 1.51−1.40 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0 (CH), 139.0 (C), 128.4 (CH), 127.60 (CH), 127.56 (CH), 81.2 (CH), 70.8 (CH_2), 44.1 (CH_2), 38.8 (CH), 30.6 (CH_2), 29.7 (CH_2), 22.1 (CH_2); IR (ATR) 2953, 2869, 1720, 1205, 1064 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{14}H_{18}NaO_2$ (M + Na)$^+$, 241.1199; found, 241.1194.

To the aldehyde (0.282 g, 1.29 mmol) in MeOH (6 mL) were added $HC(OMe)_3$ (1.4 mL, 13 mmol) and H_2SO_4 (1 drop). After 4 h, saturated aqueous $NaHCO_3$ (6 mL) and CH_2Cl_2 (15 mL) were added, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (1:5:94 Et_3N/EtOAc/hexanes) afforded dimethyl acetal *cis*-**5** as a yellow oil (0.271 g, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.31 (m, 4H), 7.28−7.24 (m, 1H), 4.57 (d, J = 12.1, 1H), 4.36 (t, J = 6.0, 1H and d, J = 12.2, 1H), 3.82 (td, J = 4.7, 2.1, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 1.95 (ddd, J = 13.7, 6.9, 6.0, 1H),

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1.89−1.83 (m, 2H), 1.82−1.63 (m, 4H), 1.60−1.53 (m, 1H), 1.50−1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 128.4 (CH), 127.6 (CH), 127.4 (CH), 104.2 (CH), 81.6 (CH), 70.5 (CH_2), 52.9 (CH_3), 52.7 (CH_3), 40.8 (CH), 31.9 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 22.0 (CH_2); IR (ATR) 2828, 1193, 1123, 1059 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{24}NaO_3$ (M + Na)$^+$, 287.1618; found, 287.1625. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.93; H, 9.06.

(1*R,2*R**)-2-Allylcyclohexyl Benzoate (*cis*-20).** Following a procedure by Hon and co-workers,[74] a solution of alcohol *trans*-**18** (2.74 g, 19.6 mmol) in PhMe (14 mL) was added to a cooled (−40 °C) solution of PPh_3 (6.15 g, 23.5 mmol) and $PhCO_2H$ (2.87 g, 23.5 mmol) in PhMe (80 mL). DEAD (3.70 mL, 23.5 mmol) in PhMe (25 mL) was then added dropwise over 20 min. After stirring for 1.5 h at −40 °C, the reaction mixture was brought to room temperature. After 13.5 h, saturated aqueous $NaHCO_3$ (100 mL) was added, and the layers were separated. The organic layer was washed with $NaHCO_3$ (100 mL) and H_2O (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The unpurified compound was passed through a plug of silica gel (3:97 EtOAc/hexanes) and used without further purification to afford compound *cis*-**20** as a colorless oil (2.20 g, 46% unpurified yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (m, 2H), 7.59−7.54 (m, 1H), 7.49−7.44 (m, 2H), 5.78 (ddt, J = 17.3, 10.2, 7.1, 1H), 5.29−5.25 (m, 1H), 4.99−4.92 (m, 2H), 2.16 (quint of t, J = 6.9, 1.0, 1H), 2.09−1.98 (m, 2H), 1.81−1.75 (m, 1H), 1.72−1.63 (m, 2H), 1.61−1.52 (m, 4H), 1.41−1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C), 136.8 (CH), 132.9 (CH), 131.1 (C), 129.7 (CH), 128.5 (CH), 116.3 (CH_2), 72.7 (CH), 40.6 (CH), 37.1 (CH_2), 30.4 (CH_2), 27.6 (CH_2), 25.3 (CH_2), 21.2 (CH_2); HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{20}NaO_2$ (M + Na)$^+$, 267.1361; found, 267.1356.

(1*R,2*R**)-2-Allylcyclohexanol (*cis*-18).** To a cooled (0 °C) solution of $LiAlH_4$ (0.700 g, 17.4 mmol) in Et_2O (87 mL) was added ester *cis*-**20** (2.13 g, 8.72 mmol) in Et_2O (87 mL) by cannula. After 40 min, H_2O (10 mL) was added, followed by NaOH (20 mL, 1.0 M in H_2O) and then H_2O (30 mL). The layers were separated, and the organic layer was washed with brine (180 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10:90 EtOAc/hexanes) afforded alcohol *cis*-**18** as a colorless oil (0.910 g, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.2, 10.1, 7.1, 1H), 5.05 (ddt, J = 17.0, 2.2, 1.5, 1H), 5.00 (ddt, J = 10.1, 2.2, 1.0, 1H), 3.91−3.87 (m, 1H), 2.16 (quint of t, J = 7.1, 1.2, 1H), 2.02 (quint of t, J = 7.3, 1.2, 1H), 1.80−1.76 (m, 1H), 1.68−1.63 (m, 1H), 1.59−1.54 (m, 1H), 1.53−1.47 (m, 1H), 1.46−1.41 (m, 2H), 1.40−1.34 (m, 1H), 1.33−1.30 (m, 1H), 1.28−1.21 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6 (CH), 115.9 (CH_2), 69.2 (CH), 41.4 (CH), 36.8 (CH_2), 33.2 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 20.6 (CH_2); HRMS (TOF MS ES+) m/z calcd for $C_9H_{17}O$ (M + H)$^+$, 141.1279; found, 141.1274.

((((1*R,2*R**)-2-Allylcyclohexyl)oxy)methyl)benzene (*cis*-21).** NaH (0.780 g, 60% dispersion in mineral oil, 19.5 mmol) and BnBr (0.930 mL, 7.89 mmol) were added to a solution of alcohol *cis*-**18** (0.910 g, 6.49 mmol) in THF (13 mL). The reaction mixture was heated at 60 °C for 14 h. Saturated aqueous NH_4Cl (15 mL) and Et_2O (30 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine (90 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (1:99 EtOAc/hexanes) afforded benzyl ether *cis*-**21** as a colorless oil (1.41 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 4H), 7.29−7.24 (m, 1H), 5.78 (ddt, J = 17.1, 10.1, 7.1, 1H), 5.04−5.01 (m, 1H), 4.99−4.95 (m, 1H), 4.59 (d, J = 11.9, 1H), 4.39 (d, J = 11.9, 1H), 3.58−3.54 (m, 1H), 2.30−2.23 (m, 1H), 2.09−2.02 (m, 1H), 2.00−1.94 (m, 1H), 1.68−1.47 (m, 4H), 1.44−1.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7 (C), 138.2 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 115.5 (CH_2), 76.4 (CH), 70.3 (CH_2), 41.3 (CH), 36.2 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 25.1 (CH_2), 21.2 (CH_2); HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{22}NaO$ (M + Na)$^+$, 253.1568; found, 253.1563. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.52; H, 9.57.

((((1*R,2*R**)-2-(2,2-Dimethoxyethyl)cyclohexyl)oxy)methyl)benzene (*cis*-6).** Ozone was bubbled into a cooled (−78 °C) solution of benzyl ether *cis*-**21** (0.561 g, 2.43 mmol) in CH_2Cl_2 (12 mL) for 15 min. After stirring for 1 h at −78 °C, PPh_3 (1.90 g, 7.29 mmol) was added, and the reaction mixture was brought to room temperature. After 14 h, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc/hexanes) afforded an aldehyde as a colorless oil (0.217 g, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, J = 1.9, 1H), 7.36−7.31 (m, 4H), 7.29−7.26 (m, 1H), 4.58 (d, J = 11.9, 1H), 4.35 (d, J = 11.9, 1H), 3.56−3.52 (m, 1H), 2.63 (ddd, J = 16.9, 6.4, 1.7, 1H), 2.37 (ddd, J = 16.8, 6.8, 2.2, 1H), 2.28−2.20 (m, 1H), 1.94−1.86 (m, 1H), 1.66−1.54 (m, 3H), 1.49−1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (CH), 139.1 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 76.4 (CH), 70.3 (CH_2), 46.1 (CH_2), 35.7 (CH), 28.3 (CH_2), 27.8 (CH_2), 24.5 (CH_2), 21.2 (CH_2); IR (ATR) 2928, 2856, 1720, 1206, 1059 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{20}NaO_2$ (M + Na)$^+$, 255.1361; found, 255.1356.

To the aldehyde (0.157 g, 0.677 mmol) in MeOH (7 mL) were added $HC(OMe)_3$ (0.74 mL, 6.80 mmol) and H_2SO_4 (1 drop), and the reaction mixture was stirred for 4 h. Saturated aqueous $NaHCO_3$ (7 mL) and CH_2Cl_2 (15 mL) were added, and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (1:10:89 Et_3N/EtOAc/hexanes) afforded dimethyl acetal *cis*-**6** as a yellow oil (0.154 g, 82%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37−7.31 (m, 4H), 7.27−7.24 (m, 1H), 4.59 (d, J = 11.9, 1H), 4.38 (d, J = 12.0, 1H and t, J = 6.0, 1H), 3.51 (dt, J = 5.1, 2.6, 1H), 3.279 (s, 3H), 3.275 (s, 3H), 1.97−1.94 (m, 1H), 1.80 (dt, J = 14.0, 6.2, 1H), 1.71−1.66 (m, 1H), 1.64−1.50 (m, 4H), 1.44−1.26 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.5 (C), 128.4 (CH), 127.7 (CH), 127.4 (CH), 103.3 (CH), 76.6 (CH), 70.1 (CH_2), 52.8 (CH_3), 52.5 (CH_3), 36.9 (CH), 34.2 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 25.0 (CH_2), 21.2 (CH_2); IR (ATR) 2855, 1193, 1027 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{17}H_{26}NaO_3$ (M + Na)$^+$, 301.1775; found, 301.1780. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.28; H, 9.51.

2-((1*R,2*S**)-2-(Benzyloxy)cyclooctyl)ethanol (49).** An aldehyde was prepared from alkene **48** using methods previously reported.[21] $NaBH_4$ (0.144 g, 3.81 mmol) was added in portions to the aldehyde (0.331 g, 1.27 mmol) in anhydrous MeOH (12.7 mL) at 0 °C. The reaction mixture stirred for 24 h at room temperature (23 °C). H_2O (13 mL) and Et_2O (26 mL) were added, and the layers were separated. The organic layer was washed with H_2O (2 × 26 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (10:90 EtOAc/hexanes) to afford the alcohol as a yellow oil (0.208 g, 63%, over two steps from alkene **48**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.34 (m, 4H), 7.33−7.27 (m, 1H), 4.61 (d, J = 11.2, 1H), 4.35 (d, J = 11.2, 1H), 3.71−3.57 (m, 2H), 3.32−3.28 (m, 1H), 2.22 (br s, 1H), 1.93−1.74 (m, 5H), 1.73−1.62 (m, 4H), 1.60−1.51 (m, 1H), 1.47−1.34 (m, 4H), 1.31−1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 84.4 (CH), 70.8 (CH_2), 61.6 (CH_2), 39.8 (CH), 37.8 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 25.9 (CH_2); IR (ATR) 3382, 1357, 1089, 1062 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{17}H_{26}NaO_2$ (M + Na)$^+$, 285.1830; found, 285.1825. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.66; H, 10.18.

2-((1*R,2*S**)-2-(Benzyloxy)cyclooctyl)ethyl 4-methylbenzenesulfonate (47).** *p*-TsCl (0.729 g, 3.83 mmol) was added to alcohol **49** (0.502 g, 1.91 mmol) in pyridine (3.3 mL) at 0 °C, and the reaction mixture was stirred until the solids dissolved. The reaction mixture was then stored in the freezer (−22 °C) for 2 days. The resulting needles were filtered off. The filtrate solution was poured into ice water, and Et_2O (6 mL) was added to the solution. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 6 mL). The combined organic layers were washed with H_2O (18 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The unpurified mixture of tosylate **47** contained cyclic ether **57**, benzyl tosylate, and unreacted *p*-TsCl. The tosylate was not stable to chromatography and was used unpurified for future experiments (0.498 g, 62%

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unpurified yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3, 2H), 7.35−7.31 (m, 2H), 7.29−7.26 (m, 5H), 4.54 (d, J = 11.4, 1H), 4.25 (d, J = 11.4, 1H), 4.10−4.06 (m, 2H), 3.19−3.16 (m, 1H), 2.42 (s, 3H), 2.06−2.00 (m, 1H), 1.84−1.80 (m, 2H), 1.79−1.74 (m, 1H), 1.66−1.50 (m, 7H), 1.42−1.35 (m, 2H), 1.34−1.22 (m, 4H). Experimental integration values below δ 2.0 ppm for tosylate **47** are slightly higher than expected due to overlapping peaks from cyclic ether **57**, which was present in an 88:12 ratio with tosylate **47**, as the minor product: ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6 (C), 138.7 (C), 133.4 (C), 129.9 (CH), 128.5 (CH), 127.99 (CH), 127.97 (CH), 127.6 (CH), 83.6 (CH), 70.8 (CH_2), 70.2 (CH_2), 39.5 (CH), 33.2 (CH_2), 28.6 (CH_2), 27.6 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.2 (CH_2), 22.0 (CH_3); IR (ATR) 1595, 1358, 1172 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{24}H_{32}NaO_4S$ (M + Na)$^+$, 439.1919; found, 439.1914.

Characterization of Solvolysis Products. General procedures for the isolation of solvolysis products and characterization of the products from solvolysis of tosylate **46** (eq 5) have previously been reported (see the Supporting Information).[21]

Products from Equation 4. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture showed a 1:0.80:0.61 ratio of **53** to tosylate starting material **45** to cyclic ether **54**. The listed spectroscopic data for the cyclic ether **54** was obtained using the unpurified reaction mixture, which also contained benzyl acetate and benzyl tosylate. Experimental integration values for **54** are higher than expected due to overlapping peaks of acetate **53**, tosylate starting material (**45**), and possible impurities from the reaction mixture. The following was obtained by referencing the integration of acetate **53** to 1: (3a*R**,6a*S**)-Hexahydro-2*H*-cyclopenta[*b*]furan (**54**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15−4.02 (m, 5.4H), 1.98−1.78 (m, 10.9H), 1.75−1.48 (m, 12.7H), 1.26−1.06 (m, 3.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.2 (CH), 66.0 (CH_2), 42.4 (CH), 32.7 (CH_2), 32.4 (CH_2), 31.8 (CH_2), 31.7 (CH_2); HRMS (TOF MS ES+) m/z calcd for $C_7H_{13}O$ (M + H)$^+$, 113.0966; found, 113.0961. 2-((1*R**,2*S**)-2-(Benzyloxy)cyclopentyl)ethyl acetate (**53**): The spectral data (^{1}H NMR and ^{13}C NMR) are consistent with the data reported for the authentic acetate **53** shown below. The spectral data for benzyl acetate and benzyl tosylate are consistent with the reported data (^{1}H NMR and ^{13}C NMR).[75,76]

Products from Equation 6. The product was purified by flash chromatography (1:99 EtOAc/hexanes) to afford cyclic ether **57** as a mixture with benzyl acetate. (3a*R**,9a*S**)-Decahydrocycloocta[*b*]furan (**57**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74−3.70 (m, 1H), 3.69−3.63 (m, 2H), 2.13−2.08 (m, 1H), 2.03−1.95 (m, 2H), 1.91−1.86 (m, 1H), 1.77−1.62 (m, 4H), 1.56−1.37 (m, 5H), 1.35−1.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 84.5 (CH), 65.9 (CH_2), 43.5 (CH), 36.6 (CH_2), 35.2 (CH_2), 34.3 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 25.3 (CH_2), 23.1 (CH_2); HRMS (TOF MS ES+) m/z calcd for $C_{10}H_{18}O$, 154.1358; found, 154.1356. The spectral data for benzyl acetate is consistent with the data reported (^{1}H NMR and ^{13}C NMR).[76]

2-((1*R,2*S**)-2-(Benzyloxy)cyclopentyl)ethyl Acetate (53).** An authentic sample of acetate **53** was prepared from an alcohol whose synthesis has previously been reported.[21] 4-(Dimethylamino)pyridine (0.042 g, 0.343 mmol), triethylamine (0.383 mL, 2.75 mmol), and acetic anhydride (0.078 mL, 0.824 mmol) were added to a solution of the alcohol (0.151 g, 0.686 mmol) in CH_2Cl_2 (3.4 mL), and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (5:95 EtOAc/hexanes) to afford acetate **53** as a colorless oil (0.104 g, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.32 (m, 4H), 7.30−7.25 (m, 1H), 4.54 (d, J = 11.8, 1H), 4.44 (d, J = 11.8, 1H), 4.13−4.08 (m, 2H), 3.60−3.57 (m, 1H), 2.04 (s, 3H), 2.00−1.90 (m, 2H), 1.88−1.82 (m, 2H), 1.77−1.58 (m, 3H), 1.57−1.50 (m, 1H), 1.18 (dq, J = 11.8, 7.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C), 138.9 (C), 128.5 (CH), 127.8 (CH), 127.6 (CH), 86.0 (CH), 71.4 (CH_2), 63.8 (CH_2), 42.7 (CH), 33.0 (CH_2), 31.1 (CH_2), 30.1 (CH_2), 22.5 (CH_2), 21.2 (CH_3); IR (ATR) 1735, 1387, 1236, 1097, 1065 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{22}NaO_3$ (M + Na)$^+$, 285.1467; found, 285.1461. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.52.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, NMR spectroscopic data for all new compounds, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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