Stereoselectivity and Regioselectivity in the Segment-Coupling Prins Cyclization

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The scope of the segment-coupling Prins cyclization has been investigated. The method is outlined in Scheme 1 and involves esterification of a homoallylic alcohol (**1**), reductive acetylation to give the α-acetoxy ether (**3**), and cyclization on treatment with a Lewis acid to produce a tetrahydropyran (**4**). Alkene geometries dictate the product configurations, with *E*-alkenes leading to equatorial substituents and *Z*-alkenes leading to axial substituents (Table 1). Not unexpectedly, applying the method to allylic alcohols leads to fragmentation rather than a disfavored 5-*endo-trig* cyclization. Dienols in which one alkene is allylic and the other alkene is homoallylic cyclize efficiently and produce the tetrahydropyrans **49**−**54**, Table 3. Dienols with two homoallylic alkenes cyclize with modest to high regioselectively, generating tetrahydropyrans **40**−**45**, Table 2. The relative rates for cyclization decrease in the order of vinyl > *Z*-alkene > *E*-alkene > alkyne. The configurations of the products are consistent with cyclization via a chair conformation, Figure 1. The 2-oxonia Cope rearrangement may be a factor in the regioselectivity of diene cyclizations and in the erosion of stereoselectivity with *Z*-alkenes. This investigation establishes the stereoselectivity and regioselectivity for a number of synthetically useful segment-coupling Prins cyclizations.

The Prins cyclization is a powerful synthetic reaction that can produce a *cis*-2,6-dialkyltetrahydropyran ring from an aldehyde and a homoallylic alcohol in the presence of an acid catalyst.[1] With some substrates, a competing ene reaction leads to unsaturated products.[2] Classic conditions involved the use of mineral acids to promote the reaction, and these harsh conditions limited its utility to unfunctionalized substrates.[3] Using cyclic acetals or mixed acetals as precursors to the intermediate oxocarbenium ions extended the versatility of the reaction.[4] Overman developed cyclizations using mixed acetals and found that medium rings could be prepared efficiently.[5] Although simple alkenes participate in the cyclization, more complex nucleophiles such as allyl trimethylsilanes, vinylsilanes, and vinyl sulfides have been introduced to exert control over the cyclization process.[6] The use of allylsilanes provides a route to the otherwise inaccessible *trans*-2,6-disubstituted tetrahydropyrans.[7] Tandem reactions have been developed to extend the utility of the Prins cyclization.[8,9] Despite the potential of the reaction to build up structural complexity rapidly, the Prins cyclization remains underutilized as a synthetic tool. We have developed a new implementation of the reaction, a segment-coupling Prins cyclization that brings together an acid and a homoallylic alcohol to form a new tetrahydropyran ring. The segment-coupling Prins cyclization overcomes the major limitations of previous methods.[10] Described herein is an investigation of the scope and utility of this reaction.

The segment-coupling Prins cyclization is designed around the reductive acetylation of acyclic esters to give α-acetoxy ethers, Scheme 1.[11] The α-acetoxy ethers are ideal precursors to the oxocarbenium ion intermediates of the Prins cyclization because the acetate is solvolyzed regioselectively upon treatment with a Lewis acid. More importantly, in complex structures, the α-acetoxy ethers are much easier to prepare than the mixed acetals

(1) (a) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053−1061. (b) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479−485.

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(3) For milder versions of the classic Prins cyclization see: (a) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768−5774. (b) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (c) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291−292. (d) Yang, X. F.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 1321−1325. (e) Zhang, W. C.; Li, C. J. *Tetrahedron* **2000**, *56*, 2403−2411.

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(5) (a) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386-4399. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256. (c) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695−5707.

(6) For example, see (a) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303−4. (b) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251−6254. (c) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. (d) Chen, C. F.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252−3254.

(7) (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426−3427. (b) Huang, H. B.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837.

(8) (a) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211−2213. (b) Marko, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595−6598. (c) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973−976.

(9) (a) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940. (b) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093.

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(11) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

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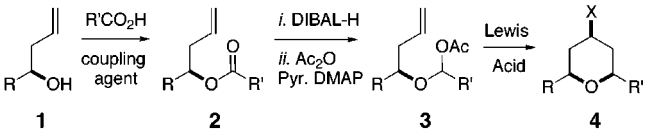
Scheme 1



previously used in the cyclization.[4,5] Lewis acid or protic acid induced cyclizations of unsaturated α-acetoxy ether substrates lead to *cis*-2,6-dialkyltetrahydropyrans with an equatorial halide or acetate at the 4-position, Figure 1. The segment-coupling Prins cyclization has been applied to a short and efficient synthesis of the C22−C26 tetrahydropyran segment of the natural product phoroboxazole B.[12] This method is well suited to the synthesis of complex tetrahydropyrans in a highly convergent manner and should be a powerful tool in natural product synthesis.

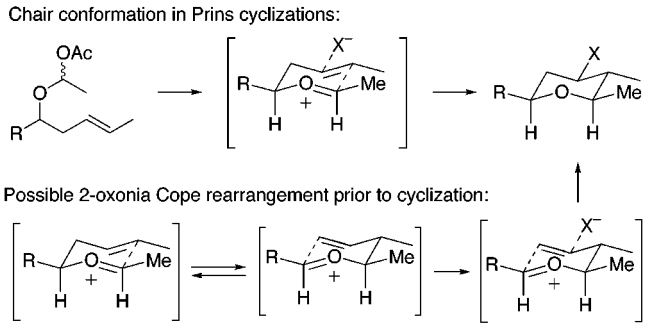


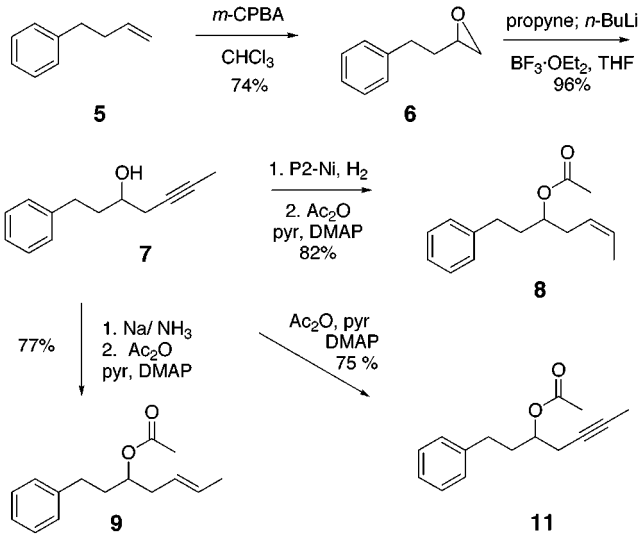
Figure 1. Chair conformation is preferred in Prins cyclizations with α-acetoxy ethers.

Prins cyclizations are often highly stereoselective. In general, the major stereoisomer arises by cyclization of an *E*-oxocarbenium ion[13] in a chairlike conformation. The electrophilic cyclization is concerted with addition of the nucleophile and electrophile to the alkene taking place with an anti-periplanar geometry. A proposed geometry for the transition state is illustrated in Figure 1. The C2 substituent in the incipient THP ring takes the equatorial position and thus influences the stereochemical outcome of the newly generated stereogenic centers. Prins cyclization reactions are not completely stereoselective, however, and some reactions lead to unexpected stereoisomers as minor products.[14] The first topic of investigation is a systematic exploration of the Prins cyclization stereoselectivity using α-acetoxy ether precursors to produce 4-heteroatom-substituted tetrahydropyrans. A second area of interest is the cyclization of substrates with more than one type of internal nucleophile. For instance, with two nonequivalent alkenes in the α-acetoxy ether substrate, will the cyclization take place on one alkene preferentially, or will it be nonselective? Understanding the stereoselectivity and regioselectivity of the segment-couping Prins cyclization will facilitate its application to natural product synthesis.

Results

Cyclizations of Alkenes and Alkynes. Investigation of the stereoselectivity of the Prins cyclization required several simple homoallylic alcohols, and these alcohols were prepared by the route shown in Scheme 2. The *Z*-alkene **8** was prepared as a single geometric isomer by selective hydrogenation[15] of alkyne **7**, followed by esterification. The *E*-alkene **9** was prepared by dissolving metal reduction of the alkyne **7**, followed by esterification. The stereoselectivity of the dissolving metal reduction varied, but the material used in subsequent studies was contaminated with <10% of the *Z*-isomer by GC analysis.[16] The 1-phenyl-3-acetyloxy-5-hexene (**10**) was prepared by addition of allylmagnesium bromide to 3-phenylpropanal, followed by esterification. The alkyne ester **11** was prepared from **7** by esterification. Esters **8**−**11** were used in the Prins cyclization studies.

Scheme 2



The α-acetoxy ethers of **8**−**10** were prepared by DIBAL-H reduction and in situ acetylation using the improved protocol recently reported from our laboratory.[11b] In each case, the yield of the α-acetoxy ether was satisfactory, although minor amounts of the starting ester were present. The α-acetoxy ethers were normally used without further purification, but they could be purified by chromatography on Et_3N-deactivated silica gel. The Prins cyclizations were carried out using either $SnBr_4$ in CH_2Cl_2 at −78 °C or $BF_3{\cdot}OEt_2$ and HOAc in hexanes. With the latter promoter, fluorine was occasionally incorporated into the tetrahydropyran competitively with the acetate. Polar solvents promoted fluorine incorporation: cyclization of the α-acetoxy ether from **10** gave the fluoride **14** in 64% yield when the solvent was trifluoromethylbenzene. Fluorine incorporation was suppressed by running the reaction in a nonpolar solvent such as hexanes and by premixing the acetic acid and $BF_3{\cdot}OEt_2$ in hexanes, cooling to 0 °C, and then transferring this heterogeneous mixture to the cooled solution of the α-acetoxy ether by cannula. The cyclization reactions for each of these three substrates are shown in Table 1, and all of the cyclizations proceeded in good yield. The terminal alkene **10** led to the cyclized products with

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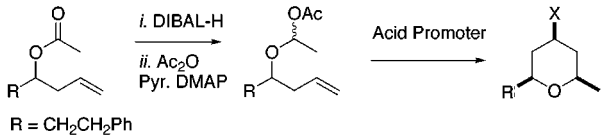
(13) (a) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006−5017. (b) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435−41.

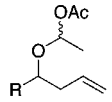
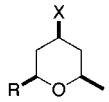
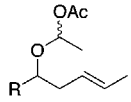
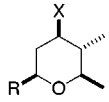
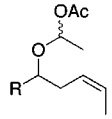
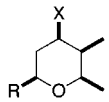
(14) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679−8682.

(15) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553−554. The P-2 Ni hydrogenations produced *Z*-alkenes with >100:1 selectivity in our hands.

(16) The *E*-alkene **9** was contaminated with <10% of the *Z*-alkene **8**. Products **17** and **18** were identified as impurities in the Prins cyclization products in the amounts expected from cyclization of the *Z*-alkene impurity in **9**.

Table 1. Cyclization of α-Acetoxy Ethers with $SnBr_4$ and $BF_3{\cdot}OEt_2$/HOAc Promoters



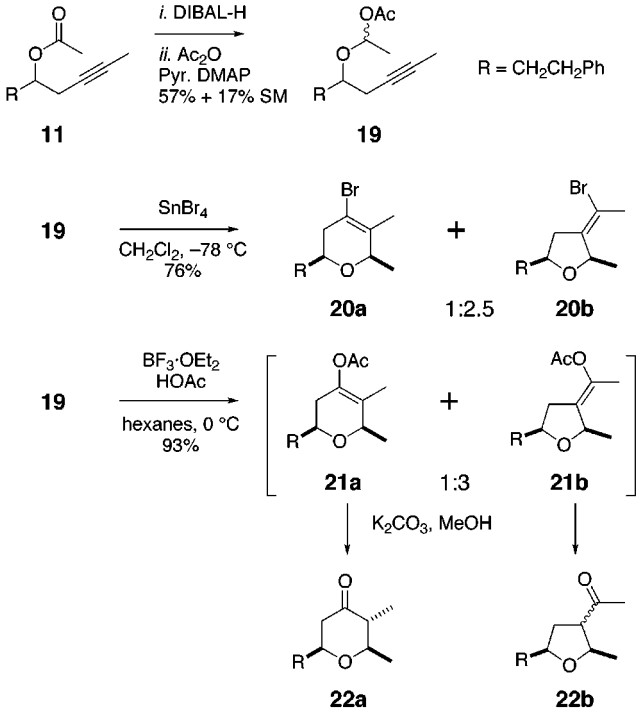
SM	α-Acetoxy Ether (yield)	Conditions[a]	Yield	Isomer ratio[b]	Product
10					
	(75%)[f]	A	73%	1:0	**12**, X = Br
		B	62%	1:0	**13**, X = OAc
		C	64%	1:0	**14**, X = F
9					
	(80%)[f]	A	68%	1:0[c]	**15**, X = Br
		B	67%	1:0[c]	**16**, X = OAc
8					
	(69%)[f]	A	64%	97:3[d]	**17**, X = Br
		B	74%	93:7[e]	**18**, X = OAc

[a] Condition A: $SnBr_4$, CH_2Cl_2, −78 °C. Condition B: $BF_3{\cdot}OEt_2$, HOAc, hexanes, 8 °C. Condition C: $BF_3{\cdot}OEt_2$, HOAc, $C_6H_5CF_3$, 25 °C. [b] The isomer ratios were determined by GC analysis of the reaction mixtures before chromatography. [c] Ratio corrected for the small amount of *Z*-alkene impurity in the SM. [d] The minor diastereomer from this cyclization reaction was **15**. [e] The minor diastereomer from this cyclization reaction was **16**. [f] The remaining mass (at least 90% reisolated) in the reductive acetylation was recovered SM.

excellent selectivity. The *E*-alkene **9** gave tetrahydropyrans **15** and **16** with very high stereoselectivity.[16] The configurations of the products were assigned by analysis of the ^{1}H NMR coupling constants and by NOE measurements. The stereoselectivities of the *Z*-alkene cyclizations were slightly lower, with the equatorial bromide **17** isolated as a 97:3 mixture with **15** and the equatorial acetate **18** isolated as a 93:7 diastereomeric mixture with **16**. Reactions with these simple substrates demonstrate that Prins cyclizations of α-acetoxy ethers generally show high selectivities and that such Prins cyclizations will be useful for creating highly substituted tetrahydropyran rings.

Prins cyclizations of alkynes have also been reported.[4] The Prins cyclization of alkyne ester **11** was investigated. Reductive acetylation of **11** gave the α-acetoxy ether **19** in good yield (Scheme 3). Cyclization with $SnBr_4$ gave a mixture of two isomers in a 2.5:1 ratio. The major isomer was tetrahydrofuran **20b**, resulting from a 5-*exo*-*dig* cyclization.[17] The minor isomer was the tetrahydropyran **20a**. Both products were isolated as single diastereomers, with 2,5- and 2,6-cis substituents, respectively, as shown by NOE measurements. The geometry of the alkene **20b**

Scheme 3

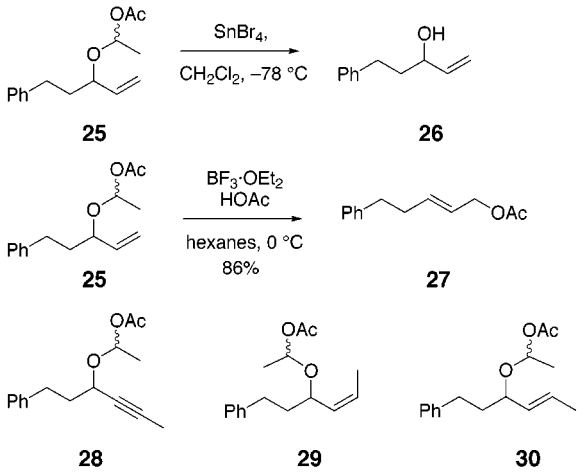


was confirmed by an NOE enhancement between the vinyl methyl group and the allylic CH group in the ring. The cyclization was also carried out with $SnBr_4$ in trifluoromethylbenzene at 23 °C to give **20b** and **20a** in a 1.5:1 ratio. Cyclization with acetic acid and $BF_3{\cdot}OEt_2$ also gave a mixture of five- and six-membered ring products contaminated with impurities. The tetrahydrofuran **21b** was the major product of the 3:1 mixture, and both **21a** and **21b** were present as single diastereomers by NMR analysis. The structure of **21a** was confirmed by hydrolysis with K_2CO_3 in MeOH to give the tetrahydropyran **22a**, the configuration of which was assigned on the basis of ^{1}H coupling constants and NOE measurements. The configuration of **21b** was tentatively assigned by analogy to tetrahydrofuran **20b**. With both cyclization promoters, a modest preference for the five-membered ring product was observed. There was a pronounced preference for the cis dialkyl substitution across the oxygen bridge, which presumably reflects the expected conformational preference of the intermediate oxocarbenium ion.

The Prins cyclization of allylic alcohols was investigated, Scheme 4. In no case was any cyclized material isolated. The substrates were prepared by addition of vinylmagnesium bromide or propargylmagnesium bromide to 3-phenylpropanal. The *E*- and *Z*-alkenes were prepared by selective reduction of the propyne adduct. Esterification and reductive acetylation proceeded uneventfully to produce α-acetoxy ethers **25** and **28**−**30**. The attempted cyclization of the α-acetoxy ether **25** was typical of these allylic substrates. Treatment with $SnBr_4$ gave allylic alcohol **26** in modest yield. The $BF_3{\cdot}OEt_2$ and acetic acid promoted reaction gave the rearranged allylic acetate **27** in good yield. Using the $SnBr_4$ conditions with α-acetoxy ethers **29** and **30** led to *E*,*Z*- or *E*,*E*-1-phenyl-2,4-hexadiene, respectively, in modest yields. We conclude that the allylic and propargylic α-acetoxy ethers do not cyclize and are prone to solvolytic decomposition.

(17) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736−738.

Scheme 4



Regioselectivity of Diene and Enyne Cyclizations. Many of the natural products that are interesting targets for a Prins cyclization strategy have multiple alkenes present in their structure.[18] These additional functional groups complicate the synthetic analysis because they also may react with the oxocarbenium ion intermediate and could give rise to alternate cyclization products. In response to this potential problem, we have investigated the cyclization of a series of simple diene and enyne substrates to determine the intrinsic regioselectivity of the process.

The substrates used to probe the regioselectivity of the Prins cyclization were prepared as illustrated in Scheme 5. Chloroacetaldehyde (50% in water) was coupled with allyl indium generated in situ from allyl bromide and indium metal.[19] The indium metal must be combined with the allyl bromide and allowed to stir for 15 min prior to addition of the chloroacetaldehyde solution. This procedure is particularly convenient, as the commercially available 50% aqueous chloroacetaldehyde may be used directly without any purification or drying. Treatment of **32** with KOH afforded the epoxide, and $BF_3{\cdot}OEt_2$ promoted addition of 1-lithiopropyne gave the enyne alcohol **33**. Esterification followed by reductive acetylation gave the first cyclization substrate **34** in good yield. The *Z*- and *E*-alkenes **35** and **36** were prepared by selective reductions of the alkyne **33**, followed by esterification and reductive acetylation. The final substrate, **39**, was prepared by propyne addition to epichlorohydrin, followed by P-2 Ni hydrogenation to give the expected *Z*-alkene.[15] Epoxide formation, propyne addition, dissolving metal reduction, and acetylation produced *E,Z*-diene **38**. Reductive acetylation gave α-acetoxy ether **39**, the final Prins substrate for the regioselectivity study.

Prins cyclizations of the 4-alkoxy 1,6-diene substrates gave some surprises as shown in Table 2. The enyne substrate **34** led to cyclization of the alkene in the presence of the alkyne, which is not unexpected based on the greater nucleophilicity of alkenes over alkynes. The acetate **40** was isolated as a single diastereomer. Competition between the *Z*-alkene and the terminal alkene in the cyclization of **35** led to preferential cyclization of the terminal alkene and a 5:1 ratio of tetrahydropyrans **41** and **42**. The selectivity for the terminal

Scheme 5

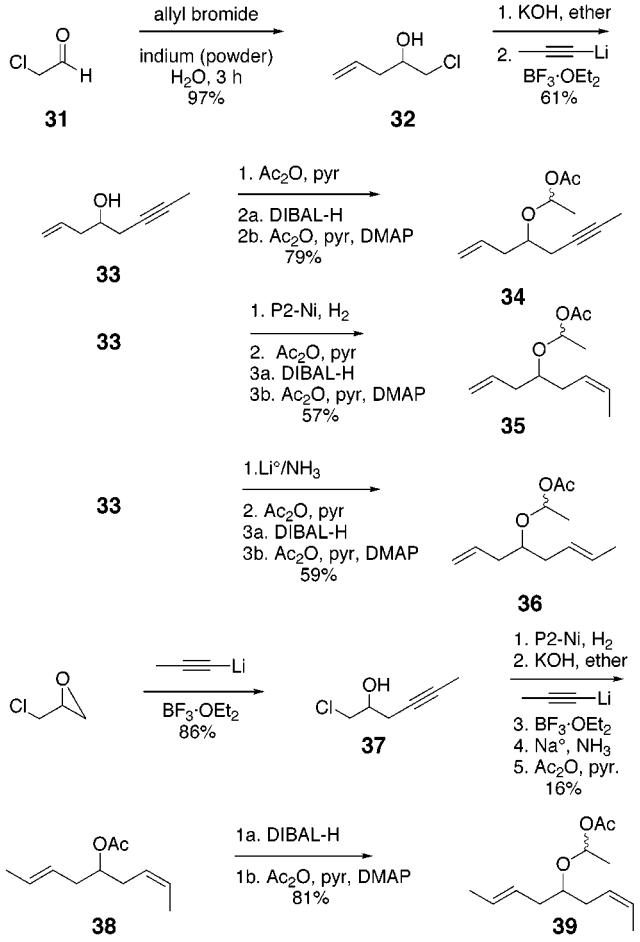
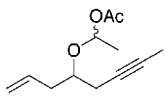
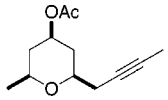
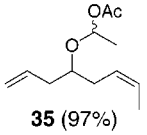
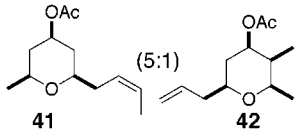
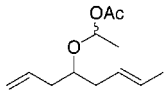
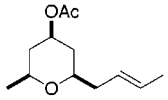
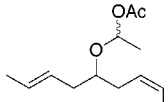
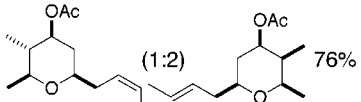


Table 2. Regioselectivity of 1,6-Enyne and 1,6-Diene Cyclizations

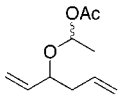
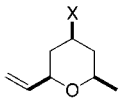
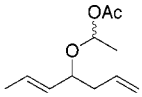
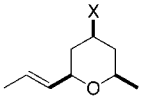
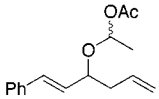
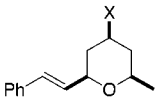
SM (Yield)	Conditions[a]	Product(s)	Yield
 **34** (84%)	A	 **40**	84%
 **35** (97%)	B	 (5:1) **41** **42**	85%
 **36** (82%)	A	 **43**	87%
 **39** (70%)[b]	A	 (1:2) **44** **45**	76%

[a] Condition A: $BF_3{\cdot}OEt_2$, HOAc, hexanes 0 °C. B: $BF_3{\cdot}OEt_2$, HOAc, hexanes, −78 °C. [b] Reductive acetylation product was accompanied by 16% of the recovered SM.

(18) For example, see phorboxazole A and B: (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423. (b) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(19) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176.

Table 3. Cyclization of 1,5-Dienes with $SnBr_4$ and $BF_3{\cdot}OEt_2$/HOAc Promoters

SM	α-Acetoxy Ether (yield)	Conditions[a]	Yield	Product
46				
	(57%)[b]	A	61%	**49**, X = Br
		B	55%	**50**, X = OAc
47				
	(62%)[b]	A	81%	**51**, X = Br
		B	89%	**52**, X = OAc
48				
	(66%)[b]	A	57%	**53**, X = Br
		B	80%	**54**, X = OAc

[a] Condition A: $BF_3{\cdot}OEt_2$, HOAc, hexanes −78 °C. Condition B: $BF_3{\cdot}OEt_2$, HOAc, hexanes, 0 °C. [b] The reductive acetylation product was accompanied by recovered SM to bring the total mass balance to at least 85%.

alkene was even more pronounced in the cyclization of **36**, where tetrahydropyran **43** was isolated as the sole product in 87% yield. Apparently the *E*-alkene cyclizes onto the oxocarbenium ion more slowly than the *Z*-alkene, and this conclusion is reinforced by the behavior of α-acetoxy ether **39**. Cyclization of **39** led to tetrahydropyran **45**, resulting from cyclization on the *Z*-alkene, with 2:1 selectivity over tetrahydropyran **44.** The relative rates of cyclization observed for these groups are vinyl > *Z*-alkene > *E*-alkene > alkyne. The diene cyclizations were also run under standard $SnBr_4$ conditions (results not shown). The yields were in the range of 68−79%, but the dienes gave lower regioselectivity with the best product ratio of only 2:3. Prins cyclizations of α-acetoxy ethers **34**, **35**, and **36** promoted by $BF_3{\cdot}OEt_2$ and HOAc each led to synthetically useful ratios favoring regioselective closure on the terminal alkene.

Attempted Prins cyclization of the allylic substrates led to solvolytic decomposition as shown in Scheme 4. Would this mode of decomposition preclude cyclization in a 3-alkoxy 1,5-diene substrate? A number of simple substrates were prepared by adding allylmagnesium bromide to α,β-unsaturated aldehydes, followed by acetylation. Reductive acetylation gave the α-acetoxy ether substrates shown in Table 3. These α-acetoxy ethers were submitted to Prins cyclization conditions. In each case, the Prins cyclization product was isolated in good to excellent yield as a single diastereomer. Particularly impressive is the cyclization of **48**, where competing solvolysis through the highly stabilized benzylic cation was not observed. The 3-alkoxy 1,5-diene substrates cyclize efficiently under the optimized conditions.

Discussion

The stereoselectivity of the Prins cyclizations with α-acetoxy ether substrates is consistent with an *E*-oxocarbenium ion intermediate adopting a chair conformation as illustrated in Figure 1. The oxocarbenium ions prefer an *E*-geometry with the hydrogen atom roughly eclipsing the hydrogen atom of the methine across the ether link, and this preference results in the *cis*-2,6-dialkyl tetrahydropyran products observed.[13] Cyclization of an *E*-alkene introduces three new stereogenic centers. The configuration of the products can be explained by invoking a concerted anti addition across the alkene and a chair geometry of the nascent tetrahydropyran. The major products observed in Tables 1−3 are consistent with the chair intermediate. A complicating factor is the possible 2-oxonia Cope rearrangement of the intermediate oxocarbenium ion, Figure 1. The 2-oxonia Cope cyclization has been invoked to explain the outcome of several unusual Prins cyclizations,[20] and the analogous aza-Cope process is well established.[21]

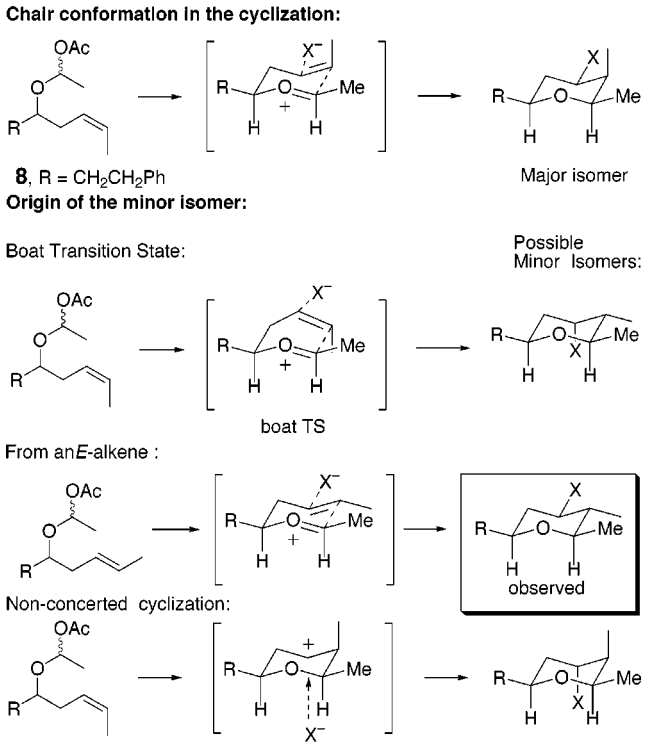


Figure 2. Origin of the minor isomer on the cyclization of the *Z*-alkene derived from ester **8**.

Cyclization of the *Z*-alkene **8** produced a minor stereoisomer that accompanied the expected major isomer, Figure 2. The minor isomer could have arisen from several pathways including the presence of *E*-alkene **9** in samples of **8**, isomerization of the *Z*-alkene to an *E*-alkene in the reaction, or a competing boat transition state in the cyclization. A fourth possibility is a nonconcerted alkene cyclization in which an intermediate secondary cation could react from either face to form the major product or the minor axial bromide product. Three of these pathways will produce different minor isomers. Cyclization of *Z*-alkene **8** (Table 1) with HOAc and $BF_3{\cdot}OEt_2$ gave the major isomer **17** accompanied by the minor isomer **15** in a 93:7 ratio. The minor products arise most

(20) (a) Lolkema, L. D. M.; Hiemstra, H.; Mooiweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365−6368. (b) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115−7128. (c) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129−7140.

(21) Blechert, S. *Synthesis* **1989**, 71−82.

simply from cyclization of the *E*-alkene. Compound **8** contained less than one percent of the *E*-alkene, and the most plausible source of **15** is an in situ isomerization of the *Z*-alkene **8** to the *E*-alkene **9**. An *E*/*Z* isomerization could arise from protonation of the alkene or from a reversible 2-oxonia Cope rearrangement with incomplete chair/boat selectivity. At this time we cannot distinguish between these two possible mechanistic origins of the *E*-alkene. Most Prins cyclizations are highly stereoselective, but when minor isomers are encountered they can provide insight into the mechanism of the reaction.

The regioselective cyclizations of 1,6-diene-4-ols, Table 2, are surprising because the most electron-rich alkene is not preferred. For substrates such as **35** and **36**, bromination or epoxidation would prefer the more highly substituted double bond.[22] The Prins cyclizations of **35** and **36** show the opposite trend, with the terminal alkene reacting preferentially in each case. One explanation is that the transition state for the Prins cyclization is late, and that the stability of the nascent secondary cation is not materially affected by the presence of an adjacent methyl group. A similar selectivity is observed in the protonation of simple alkenes, where unlike the bromination, no bridged intermediate spreads the charge across the alkene.[23] The rate retardation of the substituted alkene could be ascribed to steric hindrance in the transition state near the forming carbon−carbon bond. However, such rate retardations are not observed in the reaction of diarylmethyl carbenium ions with substituted alkenes, but instead a modest rate accelerations are noted.[24] The explanation for the observed selectivity may be complex, and could involve competition between alternate 2-oxonia Cope rearrangement pathways. More experimental work will be needed to identify the origins of regioselectivity in these systems.

Cyclization of the 1,5-dien-4-ol substrates proceeded without solvolytic decomposition as shown in Table 3. The simple allylic α-acetoxy ethers do not cyclize but rather undergo solvolysis and decomposition, Scheme 4. This outcome is not unexpected, as these reactions are disfavored *5-endo-trig* cyclizations.[17] Given the instability of the simple substrates, cyclization of the 1,5-dien-4-ol substrates in Table 3 is remarkably effective. These Prins reactions can be rationalized either as direct cyclizations or as 2-oxonia Cope rearrangements followed by cyclization. The later pathway would be consistent with the divergent behavior of the simple allylic substrates (e.g., **26**) and the 1,5-diene substrates **46**−**48**. In the future, we plan to investigate the role of 2-oxonia Cope rearrangements in segment-coupling Prins cyclizations.

Conclusion

Segment-coupling Prins cyclizations bring an acid and a homoallylic alcohol together to form a new tetrahydropyran ring. These reactions are made possible by the discovery of a reductive acetylation procedure to produce new α-acetoxy ethers from simple acyclic esters.[11] The present study demonstrates that the cyclizations are highly stereoselective, and that the cyclizations of dienes often take place with useful levels of regioselectivity. The configuration of the products can be rationalized based on a chair conformation of the intermediate oxocarbenium ion. Prins cyclizations form up to three new contiguous stereogenic centers with high levels of selectivity. We will continue to investigate the segment-coupling Prins cyclization as a tool in natural product synthesis.

Experimental Section[25]

General Procedure for the DIBALH Reductive Acetylation Esters. The ester was dissolved in dichloromethane. After the solution was cooled to −78 °C, DIBALH (1 M in toluene, 2 equiv) was added dropwise via syringe. After 45 min, the reaction was treated sequentially with pyridine (3.0 equiv), neat DMAP (3.0 equiv), and acetic anhydride (6.0 equiv) dropwise via syringe. The mixture was stirred at −78 °C for 12−19 h, warmed to 0 °C, and stirred for an additional 30 min, and then the reaction was quenched at 0 °C with saturated aqueous ammonium chloride (10 mL) and saturated aqueous sodium potassium tartrate (7.5 mL). The resultant mixture was warmed to room temperature and stirred vigorously for 30 min to promote clean separation of the layers. After extraction with dichloromethane (×4), the combined dichloromethane extracts were washed with ice-cooled 1 M sodium bisulfate (×2), saturated aqueous sodium bicarbonate (×3), and brine (×1). The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was usually contaminated with a few percent of the starting ester.

4-Bromo-2-methyl-6-phenethyltetrahydropyran (12). To a cooled solution (−78 °C) of α-acetoxy ether **10** (316 mg, 1.21 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added $SnBr_4$ (2.42 mL, 1.0 M in CH_2Cl_2, 2.42 mmol, 2 equiv). The resulting solution was stirred at −78 °C for 1 h, whereupon saturated aqueous $NaHCO_3$ (15 mL) was added. The reaction mixture was warmed to 25 °C, extracted with CH_2Cl_2 (2 × 10 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel (2.5−10% EtOAc/hexanes) to yield 249 mg of **12** as a single diastereomer (73%): IR (neat) 3026, 2972, 2952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5 H), 4.13 (tt, J = 8.8, 4.4 Hz, 1 H), 3.44 (ddt, J = 10.8, 1.6, 4.8 Hz, 1 H), 3.29 (m, 1 H), 2.80−2.73 (m, 2 H), 2.27−2.20 (m, 2 H), 1.93−1.87 (m, 1 H), 1.80−1.72 (m, 3 H), 1.28 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 128.4, 128.3, 125.7, 76.2, 73.5, 46.7, 44.9, 42.9, 37.2, 31.4, 21.4 Hz; HRMS (CI/isobutane) m/z calcd for $C_{14}H_{19}BrO$ $(M + H)^+$ 283.0677, found 283.0653.

2-Methyl-6-phenethyltetrahydropyran-4-yl Acetate (13). A premixed solution of $BF_3{\cdot}OEt_2$ (335 μL, 2.1 mmol, 3 equiv) and AcOH (378 μL, 6.0 mmol, 8.6 equiv) in hexanes (2.0 mL) was added by cannula into a cooled solution (0 °C) of α-acetoxy ether **10** (187 mg, 0.70 mmol, 1 equiv) in hexanes (6.0 mL). The reaction mixture was stirred for 1 h at 0 °C and then warmed to 25 °C, whereupon saturated aqueous $NaHCO_3$ (15 mL) was added. The reaction mixture was diluted with hexanes (5 mL), washed with brine (20 mL), filtered, and concentrated in vacuo. The resulting orange oil was purified by flash chromatography on silica gel (2.5−10% EtOAc/hexanes) to afford 114 mg (62%) of THP **13** as a single diastereomer: IR (neat) 3085−3027, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5 H), 9.93 (tt, J = 11.2, 4.7 Hz, 1 H), 3.54 (ddt, J = 11.1, 1.7, 6.3 Hz, 1 H), 3.42−3.37 (m, 1 H), 2.87−2.72 (m, 2 H), 2.10 (s, 3 H), 2.05−1.93 (m, 3 H), 1.82−1.76 (m, 1 H), 1.38−1.29 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.8, 128.4, 128.2, 125.7, 74.1, 71.3, 70.4, 38.9, 37.5,

(22) (a) Bromination: Anantakrishnan, S. V.; Ingold, C. K. *J. Chem. Soc.* **1935**, 1396−1398. (b) Epoxidation: Swern, D. *Chem. Rev.* **1945**, *49*, 1−68.

(23) For discussions of alkene protonation, see: (a) Riesz, P.; Taft, R. W. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1957**, *79*, 3724−3729. (b) Bartlett, P. D.; Sargent, G. D. *J. Am. Chem. Soc.* **1965**, *87*, 1297−1307. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 739.

(24) Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473−2396.

(25) The general Experimental Section is included in the Supporting Information.

36.9, 31.6, 21.6, 21.2 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{16}H_{22}O_3$ $(M + H)^+$ 263.1569, found 263.1624. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.60; H, 8.28.

4-Fluoro-2-methyl-6-phenethyltetrahydropyran (14). A premixed solution of $BF_3{\cdot}OEt_2$ (335 μL, 2.1 mmol, 3 equiv) and AcOH (378 μL, 6.0 mmol, 8.6 equiv) in trifluorotoluene (2 mL) was added by cannula into a 0 °C solution of α-acetoxy ether **10** (183 mg, 0.70 mmol, 1 equiv) in trifluorotoluene (6 mL). The reaction mixture was stirred for 1 h and then warmed to 25 °C, whereupon saturated aqueous $NaHCO_3$ (15 mL) was added. The reaction mixture was diluted with EtOAc (10 mL), washed with brine (20 mL), filtered, and concentrated in vacuo. The resulting orange oil was purified by flash chromatography on silica gel (2.5−10% EtOAc/hexanes) to afford THP **14** as a single diastereomer (100 mg, 64%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5 H), 4.67 (dtt, J = 49.3, 10.8, 5.1 Hz, 1 H), 3.48−3.43 (m, 1 H), 3.32−3.28 (m, 1 H), 2.86−2.73 (m, 2 H), 2.13−2.08 (m, 3 H), 2.0−1.94 (m, 1 H), 1.83−1.76 (m, 1 H), 1.46−1.32 (m, 1 H and d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 128.5, 128.4, 125.8, 89.4 (d, J = 174.7), 73.7 (d, J = 10.9), 71.0 (d, J = 11.5), 40.1 (d, J = 15.9), 38.1 (d, J = 17.2), 37.4, 31.7, 21.7 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{14}H_{19}FO$ (M^+) 222.1420, found 222.1420.

4-Bromo-2,3-dimethyl-6-phenethyltetrahydropyran (15). Using the procedure described to prepare **12**, α−acetoxy ether **9** (52 mg) was converted into 38 mg (68%) of THP **15**, which was isolated as a single diastereomer: IR (neat) 3040, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (m, 5 H), 3.86 (dt, J = 12.0, 4.8 Hz, 1 H), 3.30−3.28 (m, 1 H), 3.13 (dq, J = 12.0, 6.4 Hz, 1 H), 2.79−2.72 (m, 2 H), 2.32−2.27 (m, 1 H), 2.02−1.89 (m, 2 H), 1.74−1.60 (m, 2 H), 1.31 (d, J = 6.4 Hz, 3 H), 1.09 (d, J = 6.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 128.4, 128.2, 125.7, 78.4, 76.1, 57.1, 46.8, 44.2, 37.0, 31.4, 20.1, 16.2 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{15}H_{21}BrO$ $(M + H)^+$ 297.0851, found 297.0854.

2,3-Dimethyl-6-phenethyltetrahydropyran-4-yl Acetate (16). Using the procedure described to prepare **13**, α-acetoxy ether **9** (52 mg) was converted into 35 mg (67%) of THP **16**, which was isolated as a clear oil: IR (neat) 3027, 1738, 978 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5 H), 4.59 (dt, J = 11.2, 4.8 Hz, 1 H), 3.36−3.31 (m, 1 H), 3.19−3.15 (m, 1 H), 2.79−2.69 (m, 2 H), 2.08 (s, 3 H), 2.03 (ddd, J = 12.0, 6.4, 1.6 Hz, 1 H), 1.92−1.87 (m, 1 H), 1.74−1.71 (m, 1 H), 1.46−1.43 (m, 1 H), 1.31 (q, J = 11.2 Hz, 1 H), 1.29 (d, J = 6.0 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 141.9, 128.4, 128.3, 125.8, 77.20, 75.4, 73.9, 42.5, 37.6, 37.4, 31.7, 21.2, 19.5, 13 Hz; HRMS (CI/isobutane) *m/z* cald for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725, found 276.1720. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.69; H, 8.68.

4-Bromo-2,3-dimethyl-6-phenethyltetrahydropyran (17). Using the procedure described to prepare **12**, the α-acetoxy ether **8** (101 mg,) was converted 70 mg (64%) of THP **17**. GC analysis found a 97:3 mixture of diastereomers (t_R (major) = 15.198 min, t_R (minor) = 15.000 min). **17**: IR (neat) 3040, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.17 (m, 5 H), 4.41 (dt, J = 9.5, 4.6 Hz, 1 H), 3.56 (dq, J = 1.8, 6.4, Hz, 1 H), 3.33−3.27 (m, 1 H), 2.77−2.64 (m, 2 H), 1.95−1.84 (m, 4 H), 1.73−1.66 (m, 1 H), 1.21 (d, J = 6.4 Hz, 3 H), 1.95 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.9, 128.8, 126.3, 77.6, 76.1, 55.5, 41.1, 37.9, 37.6, 32.0, 19.9, 7.8 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{15}H_{21}BrO$ $(M)^+$ 296.0775, found 296.0782.

2,3-Dimethyl-6-phenethyltetrahydropyran-4-yl Acetate (18). Using the procedure described to prepare **13**, the α-acetoxy ether **8** (101 mg) was converted into 75 mg (74%) of THP **18**. GC analysis found a 93:7 mixture of diastereomers (t_R (major) = 15.209 min, t_R (minor) = 15.035 min). **18**: IR (neat) 3033, 1738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.17 (m, 5 H), 4.93 (dt, J = 11.8, 4.8 Hz, 1 H), 3.55 (dq, J = 1.8, 6.5 Hz, 1 H), 3.37−3.32 (m, 1H) 2.79−2.65 (m, 2 H), 2.05 (s, 3 H), 1.95−1.86 (m, 2 H), 1.74−1.64 (m, 2 H), 1.49 (q, J = 12.0 Hz, 1 H), 1.18 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 141.9, 128.4, 128.3, 125.7, 74.8, 73.9, 73.7, 37.4, 36.5, 31.6, 31.4, 21.3, 18.4, 5.4 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725, found 276.1730. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.52; H, 8.67.

Dihydropyran 20a and Tetrahydrofuran 20b. To a −78 °C solution of α−acetoxy ether **19** (80 mg, 0.29 mmol, 1 equiv) in of CH_2Cl_2 (5 mL) was added $SnBr_4$ (560 μL, 1.0 M in CH_2Cl_2, 1.93 equiv). The reaction mixture was stirred for 1 h at −78 °C, whereupon saturated aqueous $NaHCO_3$ (20 mL) was added. Upon warming to 25 °C the reation mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash chromatography on silica gel (gravity flow, 2.5%−7.5% EtOAc/hexanes) to afford 47 mg of **20b** and 18 mg of **20a** (76% overall yield) as yellow oils.

Data for **20a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.17 (m, 5 H), 4.17 (m, 1 H), 3.55 (m, 1 H), 2.82−2.68 (m, 2 H), 2.57−2.51 (m, 1 H), 2.36 (d, J = 16.8 Hz, 1 H), 1.90 (dtd, J = 19.9, 8.6, 5.6 Hz, 1 H) 1.73−1.71 (m, 4 H), 1.31 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 134.8, 128.4, 128.3, 125.8, 116.1, 75.4, 73.5, 42.1, 36.6, 31.5, 19.9, 18.2 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{15}H_{19}BrO$ $(M + H)^+$ 296.0600, found 296.0606.

Data for **20b**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.33−7.20 (m, 5 H) 4.60 (q, J = 6.4 Hz, 1 H), 3.89 (dq, J = 6.4, 5.2 Hz, 1 H), 2.81−2.71 (m, 3 H), 2.35−2.26 (m, 4 H), 2.04−1.88 (m, 2 H), 1.36 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 141.7, 128.2, 128.2, 125.7, 111.5, 77.3, 75.7, 41.9, 37.0, 32.0, 25.0, 21.2 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{15}H_{19}BrO$ $(M + H)^+$ 296.0600, found 296.0604.

Tetrahydropyranone 22a and tetrahydrofuran 22b. A premixed solution of $BF_3{\cdot}OEt_2$ (316 μL, 2.49 mmol, 3.7 equiv) and AcOH (368 μL, 6.43 mmol, 9.6 equiv) in hexanes (2 mL) was added by cannula into a 0 °C solution of α-acetoxy ether **19** (183 mg, 0.67 mmol, 1 equiv) in hexanes (6 mL). The reaction mixture was stirred for 1 h at 0 °C and then warmed to 25 °C, whereupon saturated aqueous $NaHCO_3$ (15 mL) was added. The reaction mixture was diluted with hexanes (10 mL), washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting orange oil was purified by flash chromatography (1% Et_3N, 5% EtOAc/hexanes) to afford a 3:1 mixture of **21a** and **21b** (171 mg, 93%, combined yield of regioisomers): IR (neat) 3028, 1754, 1722 cm^{-1}.

A small sample of the mixture of compounds **21a** and **21b** was dissolved in MeOH (5 mL) and K_2CO_3 (solid, 2.0 g) was added, and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo and diluted with EtOAc (15 mL), washed with saturated aqueous NH_4Cl (10 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford an orange oil. The crude oil was purified by flash chromatography (2.5% EtOAc/hexanes) to afford samples of **22a** and **22b**.

Data for **22a**: IR (neat) 1736, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.10 (m, 5 H), 3.51−3.46 (m, 1 H), 3.24 (dq, J = 12.0, 6.0 Hz, 1 H), 2.76−2.12 (m, 2 H), 2.33−2.24 (m, 3 H), 1.95−1.88 (m, 1 H), 1.75−1.68 (m, 1 H), 1.31 (d, J = 6.1 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 141.4, 128.4, 128.4, 125.9, 78.9, 76.0, 51.7, 47.9, 37.9, 31.5, 20.5, 9.4 Hz; HRMS (CI/isobutane) *m/z* calcd for $C_{15}H_{20}O_2$ $(M)^+$ 232.1463, found 232.1453.

Data for **22b**: IR (neat) 3027, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.17 (m, 5 H), 4.02−3.96 (m, 1 H), 3.92−3.85 (m, 1 H), 2.78−2.70 (m, 2 H), 2.67−2.60 (m, 1 H), 2.21−2.16 (m, 1 H and s, 3 H), 1.96−1.87 (m, 1 H), 1.83−1.43 (m, 2 H), 1.34 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 208.2, 141.9, 128.4, 128.3, 125.8, 78.3, 77.1, 58.8, 37.4, 35.3, 32.3, 29.9, 20.8 Hz; HRMS (EI/GC−MS) *m/z* calcd for $C_{15}H_{20}O_2$ $(M)^+$ 232.1463, found 232.1465.

Tetrahydropyran 40. A premixed solution of $BF_3{\cdot}OEt_2$ (127 μL, 1.0 mmol, 4 equiv) and AcOH (143 μL, 2.5 mmol, 10 equiv) in hexanes (2 mL) was added by cannula to a 0 °C solution of α-acetoxy ether **34** (55 mg, 0.26 mmol, 1 equiv) in hexanes (5 mL). The mixture was stirred for 1 h at 0 °C and then warmed to 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). The mixture was diluted

with hexanes (20 mL), washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting orange oil was purified by flash chromatography on silica gel (5−10% EtOAc/hexanes) to afford 46 mg (84%) of THP **40** as a clear oil: IR (neat) 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (tt, J = 11.3, 4.7 Hz, 1 H), 3.55−3.44 (m, 2 H), 2.47 (ddq, J = 16.4 5.2, 2.6 Hz, 1 H), 2.27 (ddq, J = 15.5, 7.7, 2.5 Hz, 1 H), 2.18 (ddd, J = 12.2, 4.4, 4.3 Hz, 1 H), 2.04 (s, 3 H), 1.95 (dt, J = 12.3, 4.3 Hz, 1 H), 1.78 (t, J = 2.6 Hz, 3 H), 1.27 (q, J = 11.3 Hz, 2 H), 1.21 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.5, 77.7, 74.8, 74.1, 71.6, 70.3, 38.8, 36.2, 26.1, 21.6, 21.3, 3.5 Hz; Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.80; H, 8.50.

Tetrahydropyrans 41 and 42. The procedure described for the preparation of **40** was followed, using α-acetoxy ether **35** (20 mg) to produce 17 mg (85%) of a clear oil. The product was a 5:1 mixture of the regioisomers of **41** (major) and **42** (minor) by NMR analysis. Data for **41**: IR (neat) 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.3, 10.1, 7.1 Hz, 0.2 H), 5.57−5.50 (m, 1 H), 5.41−5.37 (m, 1 H), 5.08−5.02 (m, 0.4 H), 4.93 (ddd, J = 9.5, 4.7, 4.7 Hz, 0.2 H), 4.85 (tt, J = 16.1, 4.8 Hz, 1 H), 3.58−3.34 (m, 2.4 H), 2.37−2.17 (m, 2.4 H), 2.05 (s, 0.6 H), 2.03 (s, 3 H), 1.98−1.92 (m, 2 H), 1.60 (m, 0.4 H), 1.58 (dd, J = 6.8, 0.8 Hz, 3 H), 1.42 (q J = 12.4 Hz, 2 H), 1.21 (q, J = 12.4 Hz, 2 H, d, J = 6.5 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 0.6 H), 0.87 (d, J = 7.0 Hz, 0.6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major) 170.6, 126.2, 125.6, 75.2, 71.5, 70.6, 39.0, 36.5, 33.5, 21.7, 21.3, 13.0; (minor) 170.6, 134.3, 117.1, 75.3, 74.1, 73.7, 36.5, 31.6, 30.8, 18.4, 14.1, 5.4; LRMS (CI) m/z calcd for $C_{12}H_{20}O_3$ $(M + H)^+$ 213, found 213; HRMS (EI/GC−MS) m/z calcd for $C_{12}H_{20}O_3$ $(M - C_4H_8)^+$ 156.0785, found 156.0790.

Tetrahydropyran 43. The procedure described for the preparation of **40** was followed, using α-acetoxy ether **36** (50 mg) to produce 43 mg (87%) of **43** as a clear oil: IR (neat) 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50−5.26 (m, 2 H), 4.85 (tt, J = 16.1, 4.8 Hz, 1 H), 3.51−3.45 (m, 1 H), 3.36−3.31 (m, 1 H), 2.32−2.27 (m, 1 H), 2.1 (q, J = 7.2 Hz, 1 H), 2.0 (s, 3 H), 1.97−1.91 (m, 2 H), 1.63 (dd, J = 6.0, 1.0 Hz, 3 H), 1.25−1.16 (m, 2 H, d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 127.7, 126.6, 75.3, 71.5, 70.6, 39.3, 38.9, 36.4, 21.7, 21.3, 18.0; LRMS (CI/NH_4) m/z for $C_{12}H_{20}O_3$ $(M + H)^+$ 213, found 213; HRMS (EI/GC−MS) m/z for $C_{12}H_{20}O_3$ $(M - C_4H_8)^+$ 156.0785, found 156.0781.

Tetrahydropyrans 44 and 45. The procedure described for the preparation of **40** was followed, using α-acetoxy ether **39** (16 mg) to produce 12.5 mg (76%) of a clear oil. The product was a 2:1 mixture of regioisomers of **45** (major) and **44** (minor) by NMR analysis: IR (neat) 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.62−5.43 (m, 3 H), 5.0 (dt, J = 12.0, 4.8 Hz, 1 H), 4.63 (td, J = 10.8, 4.7 Hz, 0.5 H), 3.65−3.61 (m, 1 H), 3.49−3.41 (m, 1.5 H), 3.25−3.19 (m, 0.5 H), 2.38−2.10 (m, 1.5 H), 2.06 (s, 4.5 H), 1.98 (m, 1 H), 1.74−1.65 (m, 3 H), 1.61 (d, J = 6.8 Hz, 1.5 H), 1.53−1.40 (m, 1.5 H), 1.35−1.30 (m, 0.5 H) 1.28 (d, J = 6.0 Hz, 1.5 H), 1.20 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 170.1, 127.5, 126.4, 75.8, 74.0, 73.8, 39.3, 36.6, 31.0, 21.5, 18.7, 18.2, 5.6; (minor) 170.1, 125.9, 125.4, 79.2, 75.6, 74.9, 42.6, 37.2, 33.6, 21.4, 18.2, 13.4, 13.2; HRMS (EI/GC−MS) m/z calcd for $C_{13}H_{22}O_3$ $(M)^+$ 226.1569, found 226.1567.

4-Bromo-2-methyl-6-vinyltetrahydropyran (49). The procedure described for the preparation of **12** was followed, using α-acetoxy ether **46** (108 mg) to produce 73 mg (61%) of **49** as a light yellow oil: IR (neat) 3027, 3058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.2, 10.6, 5.7 Hz, 1 H), 5.26 (dd, J = 17.2, 1.4 Hz, 1 H), 5.11 (dd, J = 10.6, 1.3 Hz, 1 H), 4.17 (tt, J = 12.0, 4.3 Hz, 1 H), 3.85−3.82 (m, 1 H), 3.51 (dq, J = 1.9, 6.2 Hz, 1 H), 2.29−2.06 (m, 2 H), 1.78 (q, J = 12.3 Hz, 1 H), 1.72 (q, J = 12.3 Hz, 1 H), 1.23 (d, J = 6.2 Hz, 3 H); ^{13}C (125 MHz, $CDCl_3$) δ 137.5, 115.9, 78.0, 73.5, 46.3, 44.6, 42.6, 21.5 Hz; HRMS (CI/isobutane) m/z calcd for C_8H_{13}-BrO $(M - Br)^+$ 125.0966, found 125.0969.

2-Methyl-6-vinyltetrahydropyran-4-yl Acetate (50). The procedure described for the preparation of **13** was followed, using α-acetoxy ether **46** (108 mg) to produce 59 mg (55%) of **50** as a single diastereomer: IR (neat) 3010, 1740, 1380, 962 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.2, 10.6, 5.7 Hz, 1 H), 5.25 (dd, J = 17.2, 1.4 Hz, 1 H), 5.11 (dd, J = 10.6, 1.3 Hz, 1 H), 4.91 (tt, J = 11.3, 4.9 Hz, 1 H), 3.89 (dddd, J = 7.5, 5.7, 3.4, 1.8 Hz, 1 H), 3.56 (dq, J = 1.9, 6.2 Hz, 1 H), 2.03 (s, 3 H), 2.02−1.94 (m, 2 H), 1.33 (q, J = 11.5 Hz, 1 H), 1.30−1.25 (m, 1 H), 1.24 (d, J = 6.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 137.9, 115.6, 75.9, 71.5, 70.2, 38.7, 36.7, 21.6, 21.2 Hz; HRMS (EI/GC−MS) m/z calcd for $C_{10}H_{16}O_3$ $(M - C_2H_3O_2)^+$ 125.0922, found 125.0924. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.24; H, 8.94.

4-Bromo-2-methyl-6-propenyltetrahydropyran (51). The procedure described for the preparation of **12** was followed, using α-acetoxy ether **47** (73 mg) to produce 65 mg (81%) of THP **51** as a clear oil: IR (near) 2972, 1446, 965 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (dq, J = 15.4, 6.4 Hz, 1 H), 5.44 (dd, J = 15.4, 6.6 Hz, 1 H), 4.12 (tt, J = 12.0, 4.3 Hz, 1 H), 3.76−3.73 (m, 1 H), 3.45 (dq, J = 12.2, 6.2 Hz, 1 H), 2.19 (dt, J = 4.0, 2.0 Hz, 2 H), 1.75 (q, J = 11.6 Hz, 1 H), 1.69−1.62 (m, 4 H), 1.98 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.6, 128.2, 78.0, 73.7, 46.3, 44.5, 42.9, 21.5, 17.7 Hz; HRMS (EI/GC−MS) m/z calcd for $C_9H_{15}BrO$ $(M)^+$ 218.0306, found 218.0304. Anal. Calcd for $C_9H_{20}BrO$; C, 49.33; H, 6.90. Found: C, 49.50; H, 6.87.

2-Methyl-6-propenyltetrahydropyran-4-yl Acetate (52). The procedure described for the preparation of **13** was followed, using α-acetoxy ether **47** (308 mg) to produce 274 mg (89%) of **52** as an oil: IR (neat) 2973, 1742, 967 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddq, J = 15.4, 1.0, 6.5 Hz, 1 H), 5.48 (ddd, J = 15.4, 3.3, 1.6 Hz, 1 H), 4.88 (tt, J = 9.5, 4.7 Hz, 1 H), 3.82 (ddd, J = 10.5, 6.7, 1.0 Hz, 1 H), 3.52 (ddt, J = 11.3, 2.0, 6.2 Hz, 1 H), 2.02 (s, 3 H), 2.06−1.91 (m, 2 H), 1.66 (ddd, J = 6.5, 1.6, 0.74 Hz, 3 H), 1.34 (q, J = 11.4 Hz, 1 H), 1.26−1.16 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 131.0, 128.0, 76.0, 71.2, 70.3, 38.7, 37.0, 21.7, 21.3, 122.8 Hz; HRMS (CI/isobutane) m/z calcd for $C_{11}H_{18}O_3$ $(M + H)^+$ 199.1334, found 199.1340. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.47; H, 9.41.

Tetrahydropyran 53. The procedure described for the preparation of **12** was followed, using α-acetoxy ether **48** (213 mg) to produce 131 mg (57%) of **53** as a colorless oil: IR (neat) 3081, 3026, 747, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5 H), 6.63 (d, J = 16.0 Hz, 1 H), 6.20 (ddd, J = 16.0, 6.2, 1.5 Hz, 1 H), 4.24 (tt, J = 12.0, 4.5 Hz, 1 H), 4.04 (ddd, J = 9.2, 6.2, 1.2 Hz, 1 H), 3.59 (ddq, J = 11.0, 1.8, 6.2 Hz, 1 H), 2.38 (ddd, J = 11.0, 4.3, 2.0 Hz, 1 H), 2.29 (ddd, J = 11.0, 4.3, 2.0 Hz, 1 H), 1.93 (q, J = 12.7 Hz, 1 H), 1.78 (q, J = 12.5 Hz, 1 H), 1.30 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 131.2, 128.6, 128.5, 127.8, 126.5, 76.7, 73.6, 46.1, 44.6, 43.0, 21.5 Hz; HRMS (CI/isobutane) m/z calcd for $C_{14}H_{17}BrO$ $(M)^+$ 280.0462, found 280.0463.

Tetrahydropyran 54. The procedure described for the preparation of **13** was followed, using α-acetoxy ether **48** (107 mg) to produce 86 mg (80%) of THP **54** as a colorless oil: IR (neat) 3059, 3027, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.20 (m, 5 H), 6.60 (d, J = 16.0 Hz, 1 H), 6.21 (dd, J = 16.0, 6.1 Hz, 1 H), 4.96 (tt, J = 11.3, 4.7 Hz, 1 H), 4.12−4.06 (m, 1 H), 3.63 (ddq, J = 12.4, 1.9, 6.2 Hz, 1 H), 2.13−2.06 (m, 1 H), 2.05 (s, 3 H), 2.04−1.98 (m, 1 H) 1.45 (t, J = 11.5 Hz, 1 H), 1.33 (t, J = 11.3 Hz, 1 H), 1.28 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 136.5, 130.8, 129.1, 128.4, 127.6, 126.5, 75.8, 71.6, 70.2, 38.2, 37.1, 21.7, 21.3 Hz. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.70; H, 7.62.

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Supporting Information Available: Experimental procedures for cyclization precursors **8**, **9**, **11**, **32**, **33**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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