a chair conformation. The only short intermolecular contact is a hydrogen bond between O15 and N17 with dimensions O15–N17 = 2.86 Å, O15–H15 = 0.81 Å, and N17–H15 = 2.05 Å. Experimental details and Tables XVII–XIX containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 2 is a computer-generated perspective drawing of **37** from the final X-ray coordinates.

Registry No. **3a**, 126665-91-6; **3b**, 126665-92-7; **5**, 126783-84-4; **8**, 126665-93-8; **11**, 98677-96-4; **12** (isomer 1), 126693-82-1; **12** (isomer 2), 126785-14-6; **13**, 126665-94-9; **14**, 126665-95-0; **15**, 126665-96-1; **16**, 126665-97-2; **17**, 126665-98-3; **18**, 71159-78-9; **19**, 92252-29-4; **21**, 109066-05-9; *cis*-**22**, 126665-99-4; *trans*-**22**, 126666-00-0; *cis*-**23**, 126666-01-1; *trans*-**23**, 126666-02-2; **24**, 126666-03-3; **25**, 126666-04-4; *trans*-**26**, 126666-05-5; *cis*-**26**, 126666-06-6; *trans*-**27**, 126666-07-7; *cis*-**27**, 126666-08-8; **28**, 126666-09-9; **29**, 126666-10-2; **30**, 126693-83-2; **31**, 126666-11-3; **32**, 126666-12-4; **33**, 126666-13-5; **34**, 126666-14-6; **35**, 126666-15-7; **36**, 126666-16-8; **37**, 126666-17-9; hexanal, 66-25-1; benzoquinone, 106-51-4.

Supplementary Material Available: Experimental procedures for preparation of **22**, **24**, **26**, **28**, **29**, and **30** and for the isomerization of **30** to **28**, tables of the MM2/MM2X parameters used in the energy minimization for **10**, **26**, and **27**, and tables of the atomic positional and thermal parameters, bond distances, and bond angles for **3a**, **14**, **16**, and **37** (27 pages). Ordering information is given on any current masthead page.

Chemistry of Dioxenium Cations. Synthetic and Mechanistic Studies on the Stereocontrolled Formation of Tetrahydropyrans from Homoallylic Alcohols and Ortho Esters

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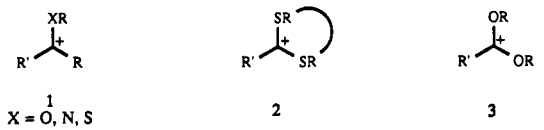
Received January 18, 1991

Despite their long history, dioxenium cations are underutilized reactive synthetic intermediates. It was found that ortho esters and homoallylic alcohols in the presence of Lewis acids provide 4-heterosubstituted pyranosides in a stereoselective manner. The mechanistic course of events was supported by control experiments and synthesis of a putative mixed ortho ester intermediate which exhibited identical reactivity. A transition state for termination of the dioxenium cation–olefin cyclization is proposed, involving intramolecular delivery of chloride by a coordinated tin species. Structure–reactivity relationships indicate that a cation-stabilizing substituent (alkyl or alkoxy) at the internal position of the olefin is required for cyclization. A variety of 3-alkyl-substituted homoallylic alcohols cyclize cleanly to substituted 2-alkoxytetrahydropyrans in good yield. β-silyloxy silyl enol ethers were found to smoothly provide 4-oxotetrahydropyranosides when subjected to the same reaction conditions. For these substrates, the course of the cyclization proceeds in a different manner involving a rapid intermolecular Mukaiyama aldol condensation followed by transacetalization.

Introduction

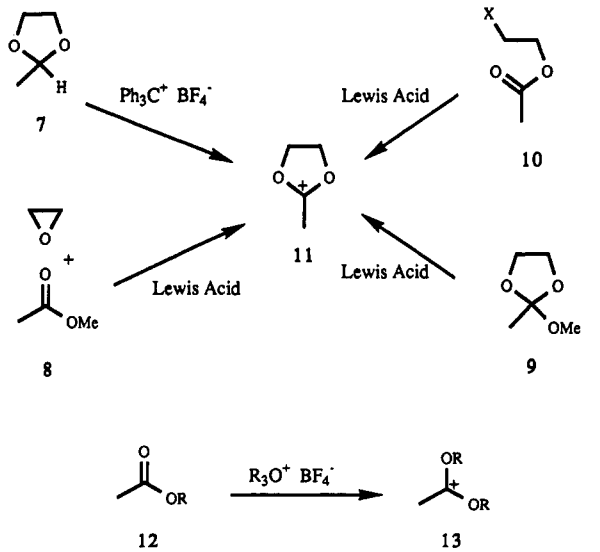
Heteroatom-stabilized carbocations **1** have enjoyed much success as reactive intermediates in organic chemistry. Such species react readily with a wide variety of nucleophilic substances in the formation of new carbon–carbon and carbon–heteroatom bonds. In particular, carbocations stabilized by a single oxygen, nitrogen, or sulfur atom have been utilized extensively as initiators of cation–olefin cyclization processes. Much less well-studied are reactive intermediates in which two heteroatoms stabilize a cationic center. Various aspects of dithienium cation (**2**) chemistry



1 X = O, N, S **2** **3**

including addition to olefins have been studied at various times by a number of groups.[1] The lack of systematic study of the corresponding chemistry of dioxenium cations[2] (**3**) is surprising in view of the greater frequency of occurrence of oxygenated functionality in natural products chemistry. In this paper, we describe in detail our studies[3] which provide some insights on the general reactivity and synthetic utility of dioxenium cations in cation–olefin

Scheme I. Methods of Generating Dioxenium Cations



7 **10** **11** **8** **9** **12** **13**

(1) (a) Andersen, N. H.; Yamamoto, Y.; Denniston, A. D. *Tetrahedron Lett.* **1975**, 4547. (b) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207. Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, *30*, 2653. (c) Rigby, J. H.; Kotnis, A.; Kramer, J. *Tetrahedron Lett.* **1983**, *24*, 2939. (d) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (e) Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 8932.

(2) For a brief review of efforts in this area see: Pindur, U.; Muller, J.; Flow, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, *16*, 75.

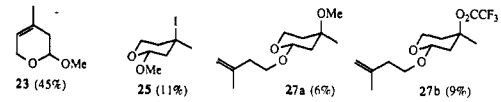
(3) (a) Perron, F.; Albizati, K. *J. Org. Chem.* **1987**, *52*, 4128. (b) Martin, V. A.; Perron, F.; Albizati K. F. *Tetrahedron Lett.* **1990**, *31*, 301.

0022-3263/91/1956-6188$02.50/0

Table I. Results of Dioxenium Cation–Olefin Cyclizations with 3-Methyl-3-buten-1-ol 15

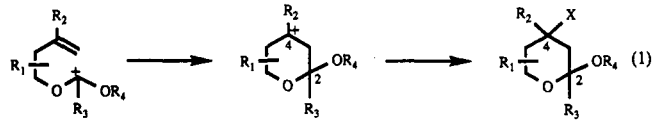
conditions					products					
entry	R	lewis acid	solvent	T (°C)	R′	X	trans	cis	ratio	yield[a] (%)
1	Me	$SnCl_4$	CH_2Cl_2	−78	Me	Cl	**17a**	**17b**	94:6	90
2	Me	$SnCl_4$	CH_2Cl_2	−20	Me	Br	**18a**	**18b**	93:7	75
3	Et	$SnBr_4$	CH_2Cl_2	−20	Et	Cl	**19a**	**19b**	93:7	80
4	Et	$SnBr_4$	CH_2Cl_2	−20	Et	Br	**20a**	**20b**	93:7	75[b]
5	Me	$SnCl_4$	CH_3CN	−78	Me	$NHCOCH_3$	**21**			77
6	Me	$ZnBr_2$	CH_2Cl_2	25	Me	OMe	**22a**	**22b**	8:41[c]	94
7	Me	MgI_2	CH_2Cl_2	−20	$CH_3C(=CH_2)(CH_2)_2$	I	**24a**	**24b**	40:3[d]	87
8	Me	$Mg(OCOCF_3)_2$	CH_2Cl_2	−20	Me	CF_3CO_2	**26a**	**26b**	46:3[e]	78

[a] Yields refer to products isolated by HPLC on silica. [b] Ratio of products determined by ^1H NMR of the crude reaction mixture. [c] Also gave **23**. [d] Also gave **25**. [e] Also gave as minor products **27a** and **27b**.



cyclization processes involving the stereocontrolled construction of functionalized tetrahydropyrans.

The impetus for this study was provided by a desire for a method of construction of 2,4-dihydroxy(or dialkoxy)-tetrahydropyrans **6** (X = OR), key substructures in natural products chemistry.[4] Dioxenium cation–olefin cyclization (eq 1) appears to be well-suited for this purpose because



4 **5** **6**

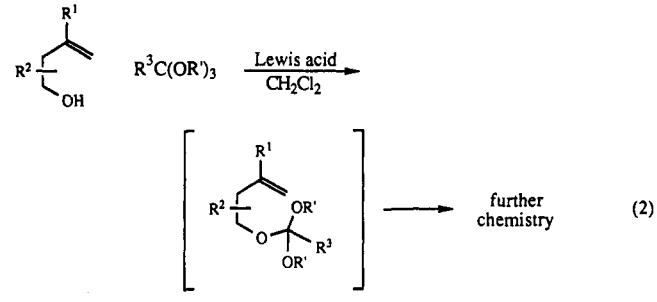
one might expect stereocontrol in kinetic bond-forming processes, perhaps involving six-membered-ring transition states.

Several methods for the formation of dioxenium cations are depicted[5] in Scheme I. Anchimeric assistance by a properly located acyloxy group facilitates the solvolysis of a good leaving group such as –Br, –OTs, –Cl, or –OR under appropriate conditions[6] yielding cyclic dioxenium cations (**10** → **11**). Cyclic and acyclic dioxenium cations can also be produced via hydride abstraction of acetals with trityl cation (**7** → **11**),[7] reaction of an ester carbonyl with an epoxide in the presence of a Lewis acid (**8** → **11**),[8] ionization of orthoesters (**9** → **11**), or treatment of esters with Meerwein salts (**12** → **13**).[9] We have examined four of these five processes for their ability to rapidly produce dioxenium cations at low temperature. After extensive study, the most successful process for the generation and utilization of substances such as **4** has proven to be ionization of ortho esters.

Results and Discussion

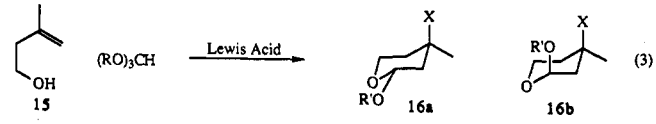
We initially studied the production of dioxenium cations such as **4** by hydride-transfer processes (**7** → **11**) since direct activation of a C–H bond could potentially lead to a larger increase in molecular complexity than generation by any other process. Upon examining a variety of substrates and despite the enormous precedent in this area, very little hydride transfer occurred from any of these substrates. After extensive study, this approach was abandoned. We were also unsuccessful in the silver(I)-promoted intramolecular alkylation approach to dioxenium cations (**10** → **11**; X = Br, I) using halo esters.

We next examined the ortho ester ionization route. Since we did not desire to handle or purify complex ortho esters, our first experiments were designed around the in situ formation of species such as **14** by combination of a simple ortho ester with a homoallylic alcohol under acidic conditions (eq 2). This turned out to be quite expedient.



14

We quickly found that addition of a simple ortho ester to a Lewis acid at −78 °C followed by addition of a homoallylic alcohol led to the formation of the desired tetrahydropyran products (**16a,b**) in good to excellent yield (eq 3). Several functional groups may act as terminators for



15 **16a** **16b**

the cyclization depending on the choice of the Lewis acid and solvent, allowing the formation of a variety of pyranosides functionalized at the 2- and 4-positions. For the initial studies, 3-methyl-3-buten-1-ol (**15**) was used as the model homoallylic alcohol. A variety of reaction protocols

(4) (a) Moore, R. E.; Blackman, A. J.; Cheuk, C. E.; Mynderse, J. S.; Matsumoto, G.; Clardy, J.; Woodard, R. W.; Craig, J. C. *J. Org. Chem.* **1984**, *49*, 2484. (b) Moore, R. E.; Mynderse, J. S. *J. Org. Chem.* **1978**, *43*, 2301. (c) Moore, R. E. In *Marine Natural Products—Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1981; Vol. 4, Chapter 1. (d) Scheuer, P. J.; Kato, Y. *Pure Appl. Chem.* **1975**, *41*, 1. (e) Scheuer, P. J.; Kato, Y. *Pure Appl. Chem.* **1976**, *48*, 29. (f) Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. E.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748. (g) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennell, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319. (h) Phillips, N. J.; Cole, R. J.; Lynn, D. J. *Tetrahedron Lett.* **1987**, *28*, 1619. (i) Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. N.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199. (j) Kihara, T. Kusakabe, H.; Nakamura, J.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1073. (k) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87. (l) Barchi, J. J.; Moore, R. E.; Patterson, G. L. M. *J. Am. Chem. Soc.* **1984**, *106*, 8193. (m) Brufani, M.; Cellai, L.; Musu, C.; Keller-Schierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2329.

(5) De Wolfe, R. H. *Synthesis* **1974**, 153. De Wolfe, R. H. *Carbocyclic Ortho Acid Derivatives*; Academic Press: New York, 1970.

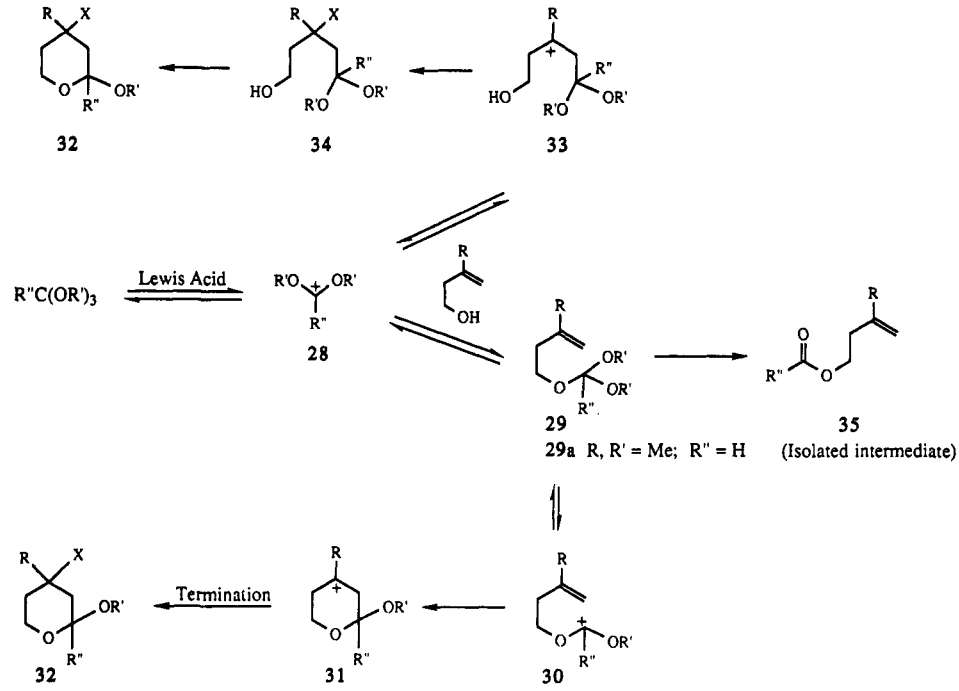
(6) Meerwein, H.; Bodenbenner, K.; Borner, P.; Kunert, F.; Wunderlich, K. *Liebigs Ann. Chem.* **1960**, *632*, 38.

(7) Meerwein, H.; Hederich, V.; Morschel, H.; Wunderlich, K. *Liebigs Ann. Chem.* **1960**, *635*, 1.

(8) Meerwein, H. *Angew. Chem.* **1955**, *67*, 374.

(9) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.

Scheme II



were investigated with the goal of studying both the stereoselectivity and scope of the reaction. The most useful of these results are shown in Table I. It was found that a wide variety of Lewis acids successfully promote the cyclization. The use of certain Lewis acids has to be carefully monitored since electrophilic addition of H–X onto the olefin can be a significant competitive process. For example, the use of an excess (2 equiv) of $TiCl_4$ leads to the formation of unwanted products predominantly arising from competing hydrochlorination of the olefin. From all the reactions examined, tin(IV) halides appear to be the Lewis acids of choice, the stereoselectivity and yield being the highest of those studied. Moreover, the tin(IV)-catalyzed reactions proceed rapidly even at temperatures as low as −78 °C, whereas other catalysts require higher temperatures and longer reaction times. The high degree of incorporation of the Lewis acid counterion advantageously serves our goal, since cationic cyclizations are often terminated by nonregioselective deprotonation, leading to olefinic mixtures. In contrast, zinc(II) salts show little tendency toward incorporation of the counterion, leading to the formation of bismethoxy tetrahydropyrans (**22a**, and **22b**) as well as the unsaturated acetal **23** (Table I, entry 6).[10]

The cyclization was examined with the substituted ortho esters $CH_3C(OCH_3)_3$, $PhC(OCH_3)_3$, ortholactones, and $C(OCH_3)_4$. No cyclization was observed with these substrates. Previous studies have demonstrated that the relative thermodynamic stabilities of the dioxenium cation salts generated from ortho esters follow the trend: $HC^+(OMe)_2 < HC^+(OEt)_2 < MeC^+(OMe)_2 < PhC^+(OMe)_2 < C^+(OMe)_3$.[2,11] The predictable ability of the substituents on the charge-bearing carbon to delocalize the carbocation leads to an increase in thermodynamic stability. The reactivity pattern of these dioxenium cation salts is thus expected to follow the stabilization pattern. Accordingly, the slow reactivity of the trialkoxycarbenium ions generated from ortho carbonates was reported more than 20 years ago in their notable failure to alkylate carboxylic esters whereas dialkoxycarbenium ions smoothly alkylate ethers.[11a]

Mechanistic Considerations

The mechanism around which the methodology was designed is shown in the lower half of Scheme II. The rapidly formed dioxenium cation **28**, when combined with the homoallylic alcohol, leads to the formation of a mixed ortho ester **29**, presumably in equilibrium with a second dioxenium cation **30**. Attack of the olefin on the cation leads to the formation of a cyclic cation **31**, which can be terminated by various nucleophiles (X) leading to the formation of the functionalized pyranoside **32**. Alternatively, another mechanism is possible involving a Prins-like attack of the olefin on the initial dioxenium cation **28**, leading to the formation of an acetal **34**, which in turn would undergo transacetalization.[12] However, species similar to **34** have not been detected, and this latter mechanism does not account for the high stereoselectivity observed in the cyclization process. Indeed, Stapp obtained mixtures of *cis*- and *trans*-4-halo-3-alkyltetrahydropyrans in the Prins-like cyclization of olefins with formaldehyde.[13] On the other hand, we have isolated formate esters (e.g., **35**), which can arise from hydrolysis of the mixed orthoester **29** involved in the dioxenium cation cyclization mechanism. To distinguish between these two possibilities the mixed ortho ester **29a** was independently synthesized via a mild transorthoesterification.[14] When subjected to the standard cyclization conditions ($SnCl_4/CH_2Cl_2$ at −20 °C), **29a** gave rise to same product mixture as in the single-step process,

(10) The stereochemistry of these products was assigned based on coupling constants, ^{13}C NMR shifts, analogy to conformationally locked model compounds (where applicable), and on further 1D ^1H NMR experiments (e.g., NOE measurements). Details of the stereochemical assingments of these compounds and others (vide infra) are given in the supplementary material.

(11) (a) Olah, G. A.; *Aldrichimica Acta* **1973**, *6*, 7. (b) McClelland, R. A.; Steenken, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 5860.

(12) (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (b) Gambaro, A.; Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1983**, *254*, 293.

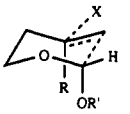
(13) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479.

(14) Perron, F.; Gahman, T.; Albizati, K. F. *Tetrahedron Lett.* **1988**, *29*, 2023.

which is in agreement with the dioxenium cation cyclization mechanism shown in the lower portion of Scheme II.

In order to justify a transition-state argument accounting for the reaction diastereoselectivity, the products must be produced in a kinetically controlled process and not as the result of thermodynamic equilibration. The kinetic nature of the reaction was demonstrated by resubjecting purified isomers **17a** and **17b** separately to the reaction conditions. No interconversion was observed, suggesting a kinetic process. Slower reactions for Zn(II) (and Mg(II)) catalyzed cyclizations as well as formation of the alkoxy-trapped products **22a** and **22b** and elimination product **23** (Table I, entry 6) suggest cationic intermediates which have longer life times. Control experiments were performed in which the dimethoxypyranosides **22a** and **22b** were subjected to the cyclization reaction conditions individually. There was no isomerization or elimination observed, again suggesting a kinetic process induced by this Lewis acid.

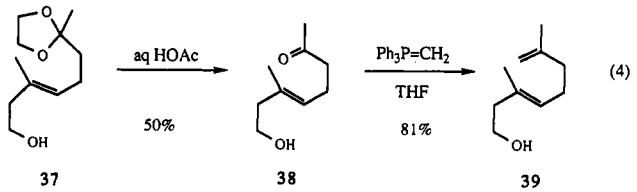
To rationalize the high stereoselectivity of the cyclization, we initially proposed a chairlike transition state **36**



36

which can benefit from a kinetic anomeric effect with the alkoxy group adopting an axial position. In agreement with the Stork Eschenmoser hypothesis and many previous examples, overall addition across the olefin occurs in an antiperiplanar fashion, with equatorial termination by the atom or group X. However, the anomalously high incorporation of the Lewis acid counterion in the reaction products is striking. A review of the literature reveals that $SnCl_4$-promoted cation–olefin cyclizations overwhelmingly favor termination via olefin formation instead of halide incorporation. A similar cyclization of endocyclic oxenium ions has recently been reported by Thompson in which olefins and acetylenes[15] undergo cyclization with high degrees of halide incorporation from $TiCl_4$.[16] These cases differ from the analogous all-carbon cyclizations in that a ring oxygen atom is positioned four atoms away from the site of termination. These data suggest that the *pro*-tetrahydropyran oxygen is involved in the transition state for termination.

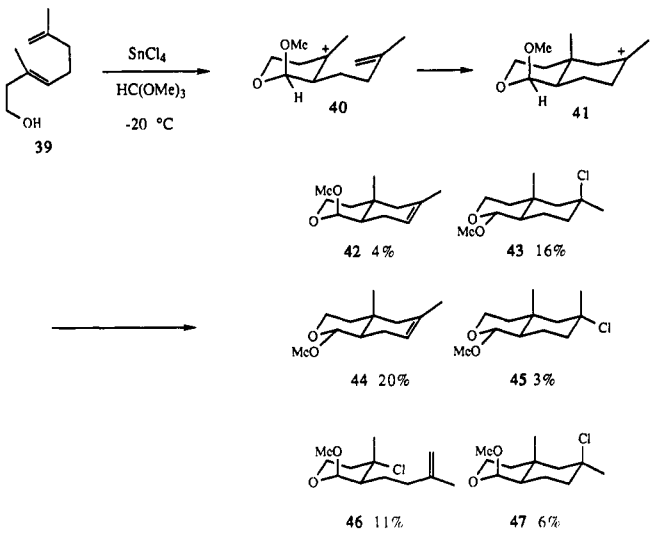
The diene alcohol **39** was designed to probe this question. Initial cyclization to a monocyclic cationic species (perhaps **40**) can be terminated at C4 and should occur with selectivity as before if the tetrahydropyran oxygen is involved. Further cyclization to the bicyclic cation **41** is possible, and if so, should lead to loss of selectivity or termination via another process. The desired diene homoallylic alcohol **39** was synthesized (eq 4) via the known



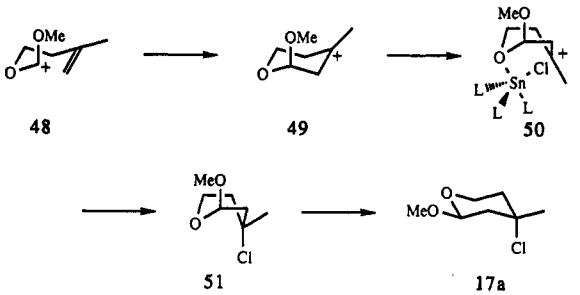
37 38 39 (4)

(15) (a) Bunnelle, W. H.; Seaman, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653. (b) Melany, M. L.; Lock, G. A.; Thompson, D. W.; *J. Org. Chem.* **1985**, *50*, 3925. (c) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelly, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275. (d) Nikolic, N. A.; Gonda, E.; Desmond-Longford, C. P.; Lane, N. T.; Thompson, D. W. *J. Org. Chem.* **1989**, *54*, 2748.

Scheme III



Scheme IV



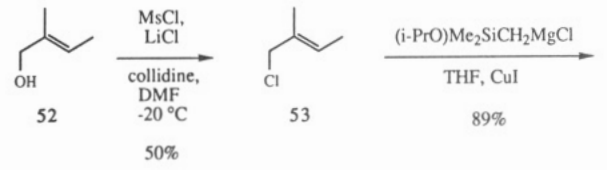
ketal **37** previously described by McMurry.[17] Compound **39** was subjected to the cyclization reaction conditions, resulting in the formation of the six products depicted in Scheme III. The yields represent isolated products and accurately reflect the diastereomeric ratio of the products obtained.[10] For the first time in dioxenium cation cyclizations promoted by $SnCl_4$, loss of a proton was observed in the formation of unsaturated bicyclic products **42** and **44**. Significantly, loss of diastereoselectivity was also observed in the formation of the bicyclic halogenated products **43**, **45**, and **47**. However, the single monocyclic product formed (**46**) exhibited the halogen in a trans position with respect to the alkoxy group, as previously observed with monoolefinic substrates. These data are consistent with the participation in some manner of the tetrahydropyran oxygen and the Lewis acid in the transition state for termination.

A more detailed mechanism, and tentative transition-state proposal, that provides an explanation for both the high degree of stereoselectivity and the lack of elimination observed is illustrated in Scheme IV. Cyclization of dioxenium cation **48** via a chair transition state with an axial methoxy group provides cation **49**. Partial inversion of the six-membered ring to a twist boat **50** followed by delivery of chloride by a coordinated tin species affords the major stereoisomer **17a**. Direct delivery of chloride to the eventual site of termination via the bridging tin species results in rapid termination of the carbocation thus reducing the possibility that elimination will occur. Use of a relatively noncoordinating solvent with low solvating ability such as methylene chloride enhances the ability of

(16) Dioxenium cation–olefin cyclization is also promoted by $TiCl_4$ in a yield and stereoselectivity similar to $SnCl_4$.

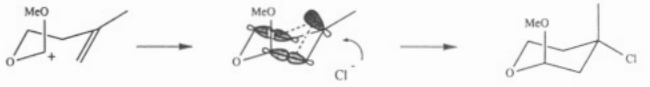
(17) McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885.

Scheme V



52 53 54 55

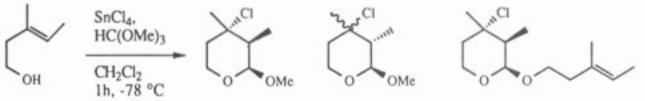
Scheme VI



48 59 17a

tin to bind tightly to the tetrahydropyran oxygen. This also increases the possibility that the newly formed carbocation at C4 will exist as a contact ion pair, thus increasing the amount of substitution product and reducing the amount of elimination.

It is assumed that the methoxy group in **48** occupies an "axial" position; i.e., there is a kinetic anomeric effect operating in the transition state for carbon–carbon bond formation. Although this assumption is reasonable, further evidence was needed in support of this proposition. Toward this end (*E*)-3-methylpent-3-en-1-ol (**55**) was prepared (Scheme V) and subjected to the cyclization conditions. The stereochemistry of the major product **56** was



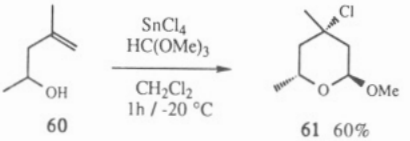
55 56 (77%) 57 (<5%) 58 (12%)

assigned in a similar manner to the previous examples (vide supra) and by NOE measurements.[10] Small amounts of **58** were also isolated. As expected, the major isomer observed (**56**) exhibits a trans relationship between the methoxy and chloro substituents. More importantly, the anomeric methoxy and the C3 methyl have a cis relationship to one another. For this to occur in a six-membered chair transition state the methoxy group must be in an axial orientation.

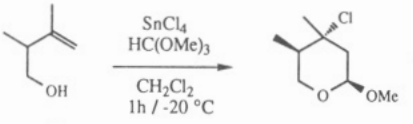
Although an intermediate involving a bridging tin species is particularly attractive, the twist-boat intermediates involved (e.g., **50**) are relatively high energy conformations. With this in mind, an alternative transition state hypothesis that invokes a stereoelectronic argument to explain the high degree of stereoselectivity observed, is proposed in Scheme VI. Cyclization of the initially formed dioxenium cation **48** provides the tertiary carbocation **59**. The stereoselectivity of termination of the carbocation by chloride can be attributed to the stabilizing interaction of C2–C3 and C5–C6 σ overlap with the empty p orbital. This overlap can be enhanced by a slight rehybridization of the carbocation with concomitant pyramidalization. Termination by chloride ion occurs from the more electrophilic face to provide **17a**, which then undergoes ring inversion to the more stable conformation in solution. The lack of elimination can be accounted for by the inductive electron withdrawing effect of the two β-oxygens. It is well-known that electronegative substituents situated β to carbocations (or developing carbocations) exhibit a destabilizing influence. A destabilized carbocation will be more likely to exist as a solvent separated or contact ion pair, thus increasing the probability of termination over elimination.

Synthesis Considerations

Utilizing additional substituted homoallylic alcohols, we have been able to demonstrate stereochemical control over the various positions of the tetrahydropyran ring as depicted in eqs 5 and 6. The stereoselectivities observed are



60 61 60% (5)



62 63 62% (6)

consistent with both the original transition-state proposal and with the tin-bridged transition state. Using the optimal cyclization reaction conditions, we studied the cyclization onto other π-nucleophiles. We found that there must be a substituent at the internal position of the olefin for cyclization to occur to any significant degree. In the case of **64** only trace amounts of cyclized product **65** were observed (eq 7). This, coupled with the results of the

64 65 (<5%) (7)

experiments with higher ortho esters and $C(OMe)_4$ indicates an important prerequisite. For cyclization to occur (**30** → **31**; Scheme II) the cyclic cation (or cationoid) formed must possess greater than secondary cationic character (R ≠ H) and the precursor dioxenium cation **30** must not possess the additional stabilization of an alkyl group (R″ ≠ alkyl). Clearly, the relative stabilities of the dioxenium cation and the cyclic cation play a major role in the position of the transition state in the reaction coordinate and the rate of closure, as might be expected.

With this in mind we have attempted closure onto electron-rich aromatic rings. Cyclization has not been observed in any case so far, including 1-(2-furyl)-2-propanol (**66**) and a variety of 2-phenylethanol derivatives (e.g., **67**).

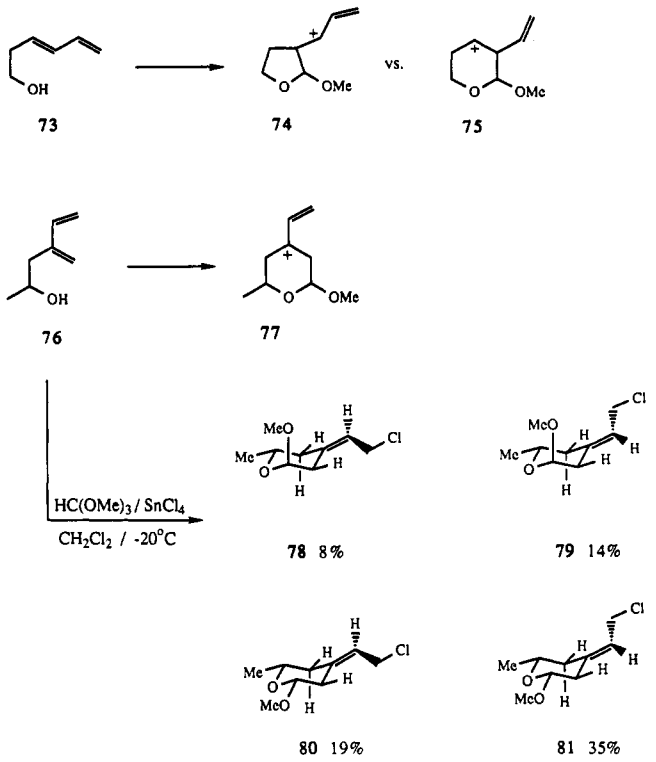
66 67

Vinylsilanes and stannanes are attractive olefinic reaction components due to the ability of a carbon–silicon (or –tin) σ-bond to stabilize a β-carbocation so that the closure will be facilitated and directed regioselectively onto the silicon- or tin-bearing carbon (**70**).[18] We thus synthesized the

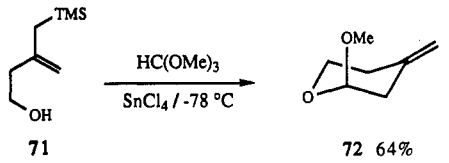
68 M = -SiMe$_3$ *(cis)*
69 = -SnBu$_3$ *(trans)*

70

Scheme VII

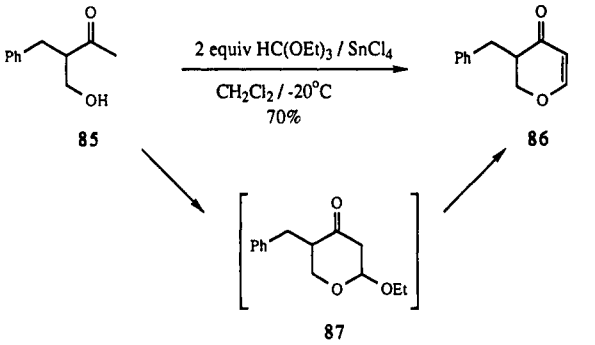


homoallylic alcohol **68** by a known procedure[19] and **69** in 83% yield by photochemically induced *n*-Bu_3SnH addition to 3-butyn-1-ol. When subjected to the standard cyclization conditions no reaction occurred with either substrate. However, a variant was more successful. The known silyl alcohol **71**[20] cyclized under the standard conditions to give the expected *exo*-methylenetetrahydropyran in 64% yield along with minor amounts of an olefin isomer. Not unexpectedly, **72** exists predominantly with the methoxy group in an axial orientation.

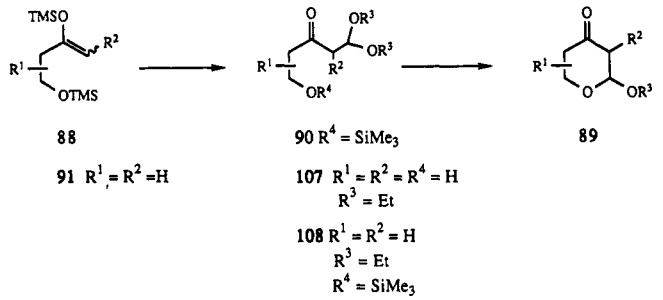


The effect of conjugating substituents was studied. The synthesis of 4-alkylidenepyranosides was envisioned as a possible route toward the formation of 4-oxopyranoside targets. Two substrates (**73**[21] and **76**[22]) were examined, the syntheses of which have been reported (Scheme VII). One would easily predict that formation of the intermediates **74** and **77** would be favored by allylic delocalization of each cation. Reasoning by analogy, the fact that *cationic* 6-*endo-trig* closures are usually favored[23] over 5-*exo-trig* combined with the low stability of the secondary cation **75** (reminiscent of the 3-buten-1-ol case **64**) accounts for the failure of alcohol **73** to cyclize. However, the homoallylic alcohol **76** was quite reactive. Treatment of **76** with 1 equiv of $SnCl_4/CH_2Cl_2$ in the presence of $HC(OMe)_3$ at −20 °C led to the formation of four acetals[10] **78–81** (Scheme VII). Loss of stereocontrol between the 2 and 6 positions compared to the case of **60** is noticeable and puzzling, although in this case a bridged transition state such as **50** is much more strained.

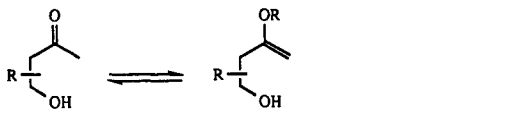
Scheme VIII



Scheme IX



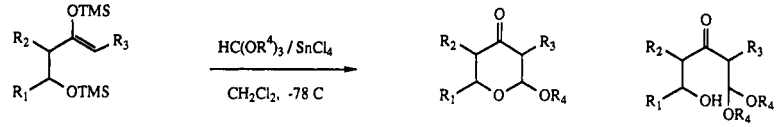
Ideal cyclization terminators toward the synthesis of 4-oxotetrahydropyranosides would be enols **83** or derivatives **84**. Several attempts were made to synthesize a variety of β-hydroxy enol ethers **84** none of which were satisfactory. At this stage, we considered β-hydroxy ketones **82** as potential intermediates for the generation of the desired enol ether.



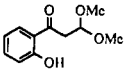
β-hydroxy ketone **85**,[24] when treated with $SnCl_4/CH_2Cl_2$ in the standard manner underwent instant cyclization at −20 °C to produce dihydropyrone **86**, presumably arising via elimination of ethanol from the desired tetrahydropyran **87** (Scheme VIII). Unfortunately, lowering the reaction temperature alleviated the elimination problem only partially. The reaction was somewhat better behaved with the corresponding β-silyloxy silyl enol ethers **88**, affording the desired cyclic acetals **89** in good yield (Scheme IX). The reaction is virtually instantaneous at −78 °C and the results are shown in Table II. The mechanistic course of events may follow a pathway different from that of previous substrates in which transacetalization occurs prior to electrophilic attack on the olefin. An intermolecular Mukaiyama-aldol-like mechanism is reasonable, in which the dioxenium cation reacts first with the enol ether producing an intermediate ketone **90** which closes via trans-

(18) Overman, L. E.; Blumenkopf, T. A. *Chem. Rev.* **1986**, *86*, 857.
(19) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.
(20) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1983**, *31*, 86.
(21) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; LaPalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317.
(22) Nunomoto, S.; Yamashita, Y. *J. Org. Chem.* **1979**, *44*, 4788.
(23) (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734. (b) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, 265.
(24) Hitchcock, S. H.; Perron, F.; Martin, V.; Albizati, K. F. *Synthesis* **1990**, 1059.

Table II. Results of the Reaction between β-Silyloxy TMS Enol Ethers and Dioxenium Cations



entry	no.	R_1	R_2	R_3	R_4	equiv $HC(OR^4)_3$	equiv $SnCl_4$	time (min)	no.	yield (cis:trans)[a] (%)	
1	**91**	H	H	H	Et	1.2	1.3	1	**92,134**	60	5
2	**93**	H	Me	H	Et	1.1	1.1	30	**94a,b**	88 (93:7)	
3	**95**	H	Me	Me	Me	1.2	0.6	15	**96a–d**	62 (4 isomers)	
4	**97**	H	H	Me	Et	1.1	1.1	1	**98a,b**	92 (77:23)	
5	**99**	H	Bn	H	Me	1.0	0.6	5	**100a,b**	75 (95:5)	
6	**101**	$Ph(CH_2)_2$	H	H	Me	1.2	0.6	15	**102**		72[b]
7	**103**	Me_2	H	H	Me	1.2	0.6	15	**104**		69[b]
8	**105**[c]				Me	1.2	0.6	15	**106**[d]		70[b]

[a] Product ratios determined by ^1H NMR. [b] The cyclic product was produced as a mixture with elimination and other byproducts when >1 equiv of $SnCl_4$ was used. [c] 105 =  [d] 106 = 

acetalization to the observed products.[25] Pertinent to this question, we found that when **91** was subjected to 0.25 equiv of $SnCl_4$ (instead of 1 equiv) at −78 °C, no cyclized product was obtained. Instead only the acetal **107** was produced. A number of subsequent β-hydroxy ketones exhibited this phenomenon. Moreover, isolation of a minor product from the cyclization of **91** revealed it to be **108**, the TMS protected compound of **107**. Based on these results an extremely rapid intermolecular Mukaiyama aldol reaction is probably involved. Again, ortho esters higher than orthoformates did not undergo the reaction. This is not surprising because the Mukaiyama aldol reaction itself with higher ortho esters is unknown. The stereochemical assignments were based on the ^1H NMR coupling constant values of chairlike conformations as well as with 1D ^1H NMR decoupling experiments when necessary. From the data described above, the closure appears to proceed via a thermodynamic transacetalization. Thus, minimization of steric interactions and maximization of anomeric effects are expected to dictate the product distribution. Indeed, the equatorial position of the alkyl substituents as well as the axial position of the alkoxy group in the major isomers verifies this assumption.

Summary

In summary, we have developed a method for the formation of 4-heterosubstituted pyranosides. These are produced in good yield and stereoselectivity by treatment of a homoallylic alcohol with an ortho ester in the presence of a Lewis acid at temperatures as low as −78 °C. A variety of heteroatomic groups may be incorporated in the products depending on the Lewis acids used. The reaction, involving the formation of two C–heteroatom and one C–C bond, occurs via kinetic cyclization of an intermediate dioxenium cation generated in situ with predominant formation of one stereoisomer. A tentative transition-state rationalization involving a pentacoordinate Sn(IV) bridging the tetrahydropyran oxygen and the site of termination explains these stereochemical results and those of other workers. Structure–reactivity relationship studies of homoallylic alcohols indicate that a cation-stabilizing group (alkyl, vinyl, or OR) at the internal position of the olefin promotes the cyclization. Additionally, β-silyloxy silyl enol ethers were found to provide 4-oxotetrahydropyranosides when treated with a solution of dioxenium cations derived from orthoformate ionization in CH_2Cl_2. The course of this cyclization proceeds in a different manner as for homoallylic alcohols involving a rapid intermolecular Mukaiyama aldol condensation followed by ring closure via transacetalization resulting in thermodynamic product mixtures.

(25) An *intramolecular* example of a Mukaiyama directed aldol condensation that results in the formation of a 4-oxotetrahydropyranoside can be found in: Isaac, K.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1982**, 460.

Experimental Section

General. ^1H NMR data were measured at 300 MHz and ^{13}C data at 75 MHz. All electron impact HRMS data were measured at 70 eV. All nonaqueous reactions were carried out under a dry N_2 atmosphere in flame-dried flasks. THF was freshly distilled from sodium/benzophenone ketyl and was transferred via syringe. CH_2Cl_2 was distilled from CaH_2. HPLC separations were performed on 250 × 20 mm 8-μm silica Magnum semipreparative columns obtained from Rainin. In vacuo removal of solvent refers to the use of a rotary evaporator operating at aspirator pressure. All Lewis acids were used in neat form, unless otherwise noted. Product ratios were determined by ^1H NMR of the reaction mixtures. Yields refer to products isolated by HPLC on silica.

General Procedure for Dioxenium Cation–Olefin Cyclizations with 3-Methyl-3-buten-1-ol (15). (2*R,4*R**)- and (2*S**,4*R**)-4-Chloro-2-methoxy-4-methyltetrahydropyran (17a and 17b) (Table I, Entry 1).** To a solution of 0.274 mL of trimethyl orthoformate (2.5 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added dropwise 2.6 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 2.6 mmol), giving a white precipitate. After 15 min, 0.235 mL of 3-methyl-3-buten-1-ol (200 mg, 2.32 mmol) was added dropwise. After 1 h, the reaction was quenched with a saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue on silica (3:1 hexane/EtOAc) yielded a mixture of diastereomers (94:6) as a yellow liquid (90%). The two isomers were separated by HPLC on silica and eluted with 4:1 hexane/EtOAc.

(17a) (85%): ^1H NMR ($CDCl_3$) δ 4.6 (dd, J = 2.3, 8.1 Hz, 1 H), 3.85 (m, 2 H), 3.5 (s, 3 H), 2.1 (dt, J = 2.0, 13.8 Hz, 1 H), 1.8 (m, 2 H), 1.7 (s, 3 H), 1.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 99.9, 68.9, 61.4, 56.1, 45.8, 40.4, 33.5; IR (neat) 2964, 1466, 1395, 1214, 1180, 1126 cm^{-1}; HRMS calcd for $C_7H_{13}O_2Cl$ 164.0604, found 164.0608.

(17b) (5%): ^1H NMR ($CDCl_3$) δ 4.6 (t, J = 4.1 Hz, 1 H), 4.1 (ddd, J = 3.5, 8.0, 11.9 Hz, 1 H), 3.55 (ddd, J = 3.7, 6.1, 11.9 Hz, 1 H), 3.4 (s, 3 H), 2.15 (ddd, J = 1.2, 4.4, 14.2 Hz, 1 H), 2.0 (m, 2 H), 1.9 (dddd, J = 0.6, 3.9, 7.3, 13.4 Hz, 1 H), 1.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 98.4, 64.7, 58.3, 55.6, 44.9, 40.9, 32.5; IR (neat) 2966, 1447, 1387, 1256, 1197, 1095 cm^{-1}; HRMS calcd for $C_7H_{13}O_2Cl$ 164.0604, found 164.0610.

The following reactions were carried out in the same manner as described above for **17a,b** using the reagents and solvents specified in Table I. The quantities of 3-methyl-3-buten-1-ol (**15**), ortho ester, Lewis acid, and solvent are given in an abbreviated

format followed by the reaction time and temperature.

(2*R,4*R**)- and (2*S**,4*R**)-4-Bromo-2-methoxy-4-methyltetrahydropyran (18a and 18b) (Table I, Entry 2).** 200 mg of **15** (2.23 mmol), 265 mg of $HC(OMe)_3$ (2.5 mmol), 2.5 mL of $SnBr_4$ (1.0 M solution in CH_2Cl_2, 2.5 mmol), 2.5 mL of CH_2Cl_2, 1 h, −20 °C. Purification of the crude reaction product on silica (3:1 hexane/EtOAc) gave a mixture of diastereomers (93:7) (85%) as a light pink liquid. The two isomers were separated by HPLC on silica and eluted with 4:1 hexane/EtOAc.

(18a) (75%): ^1H NMR ($CDCl_3$) δ 4.65 (dd, *J* = 2.3, 8.0 Hz, 1 H), 3.95 (ddd, *J* = 2.7, 4.6, 12.0 Hz, 1 H), 3.85 (ddd, *J* = 2.4, 10.5, 12.0 Hz, 1 H), 3.45 (s, 3 H), 2.25 (dt, *J* = 2.1, 14.1 Hz, 1 H), 1.95 (ddd, *J* = 2.3, 4.6, 14.3 Hz, 1 H), 1.85 (s, 3 H), 1.7 (m, 1 H), 1.55 (dd, *J* = 8.0, 14.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 100.7, 65.9, 62.5, 56.4, 47.1, 41.7, 35.4; IR (neat) 2965, 1464, 1393, 1182, 1086, 1056 cm^{-1}; HRMS calcd for $C_7H_{12}O_2Br$ (M^+ − H) 207.0021, found 207.0019.

(18b) (5%): ^1H NMR ($CDCl_3$): δ 4.65 (dd, *J* = 3.6, 4.7 Hz, 1 H), 4.05 (ddd, *J* = 3.5, 7.4, 11.9 Hz, 1 H), 3.6 (ddd, *J* = 3.5, 6.7, 11.9 Hz, 1 H), 3.4 (s, 3 H), 2.3 (ddd, *J* = 1.0, 4.8, 14.2 Hz, 1 H), 2.25 (dddd, *J* = 0.7, 2.7, 6.7, 14.0 Hz, 1 H), 2.15 (ddd, *J* = 0.6, 3.5, 14.2 Hz, 1 H), 1.95 (m, 1 H), 1.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 98.4, 59.6, 59.2, 55.6, 46.4, 42.4, 33.9; IR 2966, 1448, 1259, 1134, 1078, 1057 cm^{-1}; HRMS calcd for $C_7H_{14}O_2Br$ (M^+ + H) 209.0178, found 209.0180.

(2*R,4*R**)- and (2*S**,4*R**)-4-Chloro-2-ethoxy-4-methyltetrahydropyran (19a and 19b) (Table I, Entry 3).** 800 mg of **15** (9.29 mmol), 1.50 g (10.0 mmol) of $HC(OEt)_3$, 10.4 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 10.4 mmol), 1 h, −20 °C. Purification of the crude reaction product on silica (3:1 hexane/EtOAc) gave a mixture of diastereomers (93:7) (95%) as a light colorless liquid (25:1 mixture of diastereomers by H^1 NMR analysis). The two isomers were separated by HPLC on silica and eluted with 4:1 hexane/EtOAc.

(19a) (75%): ^1H NMR ($CDCl_3$) δ 4.7 (dd, *J* = 1.9, 7.4 Hz, 1 H), 3.9 (m, 3 H), 3.5 (dq, *J* = 7.1, 9.4 Hz, 1 H), 2.15 (dt, *J* = 1.9, 14.0 Hz, 1 H), 1.8 (m, 2 H), 1.65 (s, 3 H), 1.6 (dd, *J* = 7.4, 14.0 Hz, 1 H), 1.2 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 98.6, 69.1, 64.3, 61.5, 46.1, 40.4, 33.6, 15.2; IR (neat) 2974, 1466, 1377, 1082, 1060, 1006 cm^{-1}; HRMS calcd for $C_6H_{10}OCl$ (M^+ − OCH_2CH_3) 133.0420, found 133.0423.

(19b) (5%, contaminated with the major isomer **19a** in a 9:1 ratio): ^1H NMR ($CDCl_3$) δ 4.6 (dd, *J* = 3.7, 5.4 Hz, 1 H), 4.1 (ddd, *J* = 3.8, 6.5, 12.0 Hz, 1 H), 3.85 (dq, *J* = 7.1, 9.7 Hz, 1 H), 3.55 (m, 2 H), 2.1 (m, 3 H), 1.9 (dddd, *J* = 0.9, 3.3, 6.5, 14.0 Hz, 1 H), 1.65 (s, 3 H), 1.2 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 97.4, 64.9, 63.7, 59.3, 45.8, 41.3, 31.6, 15.1; IR (neat) 2974, 1447, 1378, 1256, 1166, 1078 cm^{-1}; HRMS calcd for $C_8H_{15}O_2$ (M^+ − Cl) 143.1072, found 143.1074.

(2*R,4*R**)-4-Bromo-2-ethoxy-4-methyltetrahydropyran (20a) (Table I, Entry 4).** 800 mg of **15** (9.29 mmol), 1.50 g of $HC(OEt)_3$ (10.0 mmol), 10.4 mL of $SnBr_4$ (1 M solution in CH_2Cl_2; 10.4 mmol), 1 h, −20 °C. Purification of the crude reaction product on silica (3:1 hexane/EtOAc) gave a 12:1 mixture of diastereomers (by H^1 NMR analysis) (91%) as a light colorless liquid. The major isomer (**20a**) was isolated by HPLC on silica and eluted with 4:1 hexane/EtOAc (76%): ^1H NMR ($CDCl_3$) δ 4.75 (dd, *J* = 2.2, 8.2 Hz, 1 H), 4.0 (m, 3 H), 3.6 (dq, *J* = 7.1, 9.6 Hz, 1 H), 2.3 (dt, *J* = 2.2, 14.2 Hz, 1 H), 2.1 (ddd, *J* = 2.4, 4.7, 14.5 Hz, 1 H), 1.85 (s, 3 H), 1.7 (ddd, *J* = 4.8, 10.6, 14.5 Hz, 1 H), 1.6 (dd, *J* = 8.2, 14.2 Hz, 1 H), 1.2 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.3, 66.0, 64.3, 62.4, 47.1, 41.4, 35.3, 15.1; IR (neat) 2976, 1378, 1173, 1123, 1080, 1059, 1004 cm^{-1}; HRMS calcd for $C_8H_{15}O_2Br$ 222.0256, found 222.0261.

(2*R,4*R**)-4-Acetamido-2-methoxy-4-methyltetrahydropyran (21) (Table I, Entry 5).** 213 mg of **15** (2.5 mmol), 265 mg of $HC(OMe)_3$ (2.5 mmol), 0.296 mL of $SnCl_4$ (650 mg, 2.5 mmol), 4 mL of CH_3CN, 1 h, −78 °C. One diastereomer predominated and was isolated by HPLC on silica and eluted with 9:1 hexane/EtOAc (77%): ^1H NMR ($CDCl_3$) δ 4.55 (dd, *J* = 2.9, 6.8 Hz, 1 H), 3.95 (ddd, *J* = 4.1, 5.6, 12.0 Hz, 1 H), 3.85 (ddd, *J* = 3.1, 8.8, 12.0 Hz, 1 H), 3.45 (s, 3 H), 2.25 (m, 1 H), 2.15 (m, 1 H), 1.95 (s, 3 H), 1.6 (m, 2 H), 1.4 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.7, 99.3, 59.7, 55.8, 52.4, 41.2, 35.7, 26.8, 24.6; IR (neat) 3442, 1688, 1504, 1131, 1088, 1062 cm^{-1}; HRMS calcd for $C_9H_{17}NO_3$ (M^+ − H) 187.1208, found 187.1211.

Dioxenium Cation–Olefin Cyclization of 15 with $ZnBr_2$ (22a, 22b, 23) (Table I, Entry 6). 800 mg of **15** (9.28 mmol), 2.0 mL of $HC(OMe)_3$ (1.97 g, 18.6 mmol), 4.18 g of $ZnBr_2$ (18.6 mmol), 15 mL of CH_2Cl_2, after 5 min warm from −20 to +25 °C, 6 h at room temperature. Purification on silica gel (1:1 hexane/EtOAc) gave a mixture of diastereomers, along with the unsaturated acetal **34**, as a yellow liquid (97%). The mixture was separated by HPLC on silica and eluted with 1:1 hexane/EtOAc.

(2*R,4*R**)-2,4-Dimethoxy-4-methyltetrahydropyran (22a)** (8%): ^1H NMR ($CDCl_3$) δ 4.5 (dd, *J* = 2.6, 8.1 Hz, 1 H), 3.8 (dt, *J* = 3.8, 11.6 Hz, 1 H), 3.7 (ddd, *J* = 3.0, 10.5, 11.6 Hz, 1 H), 3.4 (s, 3 H), 3.15 (s, 3 H), 1.9 (dt, *J* = 2.2, 13.5 Hz, 1 H), 1.65 (m, 1 H), 1.5 (ddd, *J* = 4.6, 10.5, 13.9 Hz, 1 H), 1.4 (dt, *J* = 8.1, 13.5 Hz, 1 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.7, 72.8, 60.6, 55.9, 48.5, 40.9, 35.0, 24.2; IR (neat) 2966, 1465, 1391, 1074, 1055, 1000 cm^{-1}; HRMS calcd for $C_8H_{15}O_3$ (M^+ − H) 159.1021, found 159.1025.

(2*S,4*R**)-2,4-Dimethoxy-4-methyltetrahydropyran (22b)** (41%): ^1H NMR ($CDCl_3$) δ 4.4 (dd, *J* = 3.5, 5 Hz, 1 H), 3.9 (ddd, *J* = 3.6, 7.4, 11.2 Hz, 1 H), 3.5 (m, 1 H), 3.35 (s, 3 H), 3.2 (s, 3 H), 1.7 (ddd, *J* = 5.0, 14.2 Hz, 1 H), 1.65 (m, 2 H), 1.5 (dddd, *J* = 0.7, 3.8, 7.3, 13.3 Hz, 1 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.5, 71.5, 58.6, 55.6, 48.7, 39.5, 35.9, 23.5; IR (neat) 2963, 1463, 1389, 1144, 1084, 1055 cm^{-1}; HRMS calcd for $C_8H_{15}O_3$ (M^+ − H) 159.1021, found 159.1026.

3,6-Dihydro-2-methoxy-4-methyl-2*H*-pyran (23) (45%): ^1H NMR ($CDCl_3$) δ 5.4 (bs, 1 H), 4.7 (t, *J* = 2.9, 4.3 Hz, 1 H), 4.2 (m, 2 H), 3.4 (s, 3 H), 2.3 (bd, 1 H), 1.9 (bd, 1 H), 1.7 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 128.9, 118.7, 97.8, 60.2, 55.2, 34.7, 22.7; IR (neat) 3076, 1652, 1446, 1373, 1260, 1124 cm^{-1}; HRMS calcd for $C_7H_{12}O_2$ 128.0837, found 128.0830.

Dioxenium Cation–Olefin Cyclization of 15 with MgI_2 (24a, 24b, 25) (Table I, Entry 7). 1.88 mL of **15** (11.6 mmol), 1.42 mL of $HC(OMe)_3$ (13.0 mmol), 6.45 g of MgI_2 (23.2 mmol), 15 mL of CH_2Cl_2, after 5 min, warm from −20 to +25 °C, then 25 °C for 6 h. The crude reaction product was purified on silica (3:1 hexane/EtOAc) to give a mixture of diastereomers (**24a, 24b**), along with **25** (87%). The mixture was separated by HPLC on silica and eluted with 3:1 hexane/EtOAc.

(2*R,4*R**)-4-Iodo-4-methyl-2-(3-methyl-3-butenyloxy)-tetrahydropyran (24a)** (40%): ^1H NMR ($CDCl_3$) δ 4.8 (ol m, 3 H), 4.05 (ddd, *J* = 2.69, 4.4, 12.1 Hz, 1 H), 3.95 (dt, *J* = 7.1, 9.6, Hz, 1 H), 3.75 (ddd, *J* = 2.3, 10.4, 12.1 Hz, 1 H), 3.6 (dt, *J* = 7.1, 9.6 Hz, 1 H), 2.3 (ol m, 3 H), 2.15 (s, 3 H), 2.05 (dddd, 1 H), 1.7 (s, 3 H), 1.3 (ol m, 2 H); ^{13}C NMR ($CDCl_3$) δ 142.5, 111.6, 100.7, 67.4, 63.9, 50.0, 49.4, 44.1, 38.9, 37.7, 22.7; IR (neat) 2963, 1650, 1443, 1377, 1235, 1089, 1075 cm^{-1}; HRMS calcd for $C_6H_{10}IO$ (M^+ − C_5H_9O) 224.9778, found 224.9782.

(2*S,4*R**)-4-Iodo-4-methyl-2-(3-methyl-3-butenyloxy)-tetrahydropyran (24b)** (3%): ^1H NMR ($CDCl_3$) δ 4.8 (bd, 2 H), 4.65 (dd, *J* = 3.3, 5.5 Hz, 1 H), 3.85 (ol m, 2 H), 3.65 (ddd, *J* = 3.2, 7.6, 11.9 Hz, 1 H), 3.5 (dt, *J* = 7.1, 9.6 Hz, 1 H), 2.45 (ol m, 2 H), 2.3 (t, *J* = 7 Hz, 2 H), 2.15 (ol s, 3 H and m, 1 H), 1.8 (dddd, *J* = 0.65, 3.1, 6.2, 13.9 Hz, 1 H), 1.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.5, 111.6, 96.4, 66.9, 60.5, 50.0, 49.5, 45.8, 37.7, 37.1, 22.8; IR (neat) 2964, 1648, 14444, 1376, 1196, 1157 cm^{-1}; HRMS calcd for $C_6H_{10}IO$ (M^+ − C_5H_9O) 224.9778, found 224.9783.

(2*R,4*R**)-4-Iodo-2-methoxy-4-methyltetrahydropyran (25)** (11%): ^1H NMR ($CDCl_3$) δ 4.65 (dd, *J* = 2.2, 8.0 Hz, 1 H), 4.1 (ddd, *J* = 2.7, 4.5, 12.2 Hz, 1 H), 3.8 (ddd, *J* = 2.3, 10.6, 12.2 Hz, 1 H), 3.5 (s, 3 H), 2.35 (dt, *J* = 2.0, 14.3 Hz, 1 H), 2.15 (s, 3 H), 2.1 (ddd, *J* = 2.3, 4.6, 14.8 Hz, 1 H), 1.35 (ddd, *J* = 4.4, 10.5, 14.8 Hz, 1 H), 1.25 (dd, *J* = 8.0, 14.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 101.9, 63.9, 56.2, 50.0, 49.3, 44.1, 39.0; IR (neat) 2958, 1464, 1445, 1182, 1145, 1114 cm^{-1}; HRMS calcd for $C_7H_{14}IO_2$ (M^+ + H) 257.0040, found 257.0044.

Dioxenium Cation–Olefin Cyclization of 15 with $Mg(OCOCF_3)_2$ (26a, 26b and 27a, 27b) (Table I, Entry 8). 0.24 mL of **15** (2.32 mmol), 0.39 mL of $HC(OMe)_3$ (3.64 mmol), 2.32 mL of $Mg(OCOCF_3)_2$ (1 M solution in CH_2Cl_2; 2.32 mmol), 5 mL CH_2Cl_2, −20 °C, warm to 25 °C after 5 min. Purification by chromatography on silica (3:1 hexane/EtOAc) gave a yellow liquid as a mixture of pyranosides (78%). The mixture was separated by HPLC on silica and eluted with 3:1 hexane/EtOAc.

(2*S,4*R**)-2-Methoxy-4-methyl-4-(trifluoroacetoxy)-tetrahydropyran (26a)** (3%): ^1H NMR ($CDCl_3$) δ 4.7 (bs, 1 H), 4.1 (td, *J* = 2.5, 11.9 Hz, 1 H), 3.6 (ddd, *J* = 2.3, 4.8, 11.7 Hz, 1

H), 3.3 (s, 3 H), 2.9 (dt, J = 1.8, 15 Hz, 1 H), 1.9 (m, 1 H), 1.8 (m, 1 H), 1.7 (dd, J = 3.7, 15 Hz, 1 H), 1.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 97.4, 82.4, 55.5, 54.7, 37.4, 35.9, 26.0; IR (neat) 2944, 1783, 1215, 1172, 1122, 1061 cm^{-1}; HRMS calcd for $C_7H_{13}O_2$ (M^+ - OTf) 129.0916, found 129.0920.

(2*R,4*R**)-2-Methoxy-4-methyl-4-(trifluoroacetoxy)-tetrahydropyran (26b)** (46%): ^{1}H NMR ($CDCl_3$) δ 4.5 (dd, J = 2.9, 6.9 Hz, 1 H), 3.85 (dt, J = 4.8, 12.1 Hz, 1 H), 3.6 (ddd, J = 3.3, 9.1, 12.1 Hz, 1 H), 3.4 (s, 3 H), 2.3 (bddd, J = 1.8, 2.7, 14 Hz, 1 H), 2.15 (dddd, J = 1.7, 3.2, 5.0, 14 Hz, 1 H), 1.8 (dddd, J = 0.7, 4.3, 9.1, 14 Hz, 1 H), 1.7 (ddd, J = 0.8, 6.9, 14 Hz, 1 H), 1.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.6, 156.0, 155.5, 154.9, 98.8, 86.6, 59.4, 55.8, 40.9, 35.4, 24.9; IR (neat) 2971, 1776, 1468, 1451, 1220, 1168, 1080 cm^{-1}; HRMS calcd for $C_9H_{12}O_4F_3$ 241.0688, found 241.0682.

(2*R,4*R**)-4-Methoxy-4-methyl-2-[(3-methyl-3-butenyl)-oxy]tetrahydropyran (27a)** (6%): ^{1}H NMR ($CDCl_3$) δ 4.75 (bd, 2 H), 4.65 (dd, J = 2.5, 8.2 Hz, 1 H), 3.9 (dt, J = 7.0, 9.6 Hz, 1 H), 3.8 (dt, J = 3.8, 11.5 Hz, 1 H), 3.65 (ddd, J = 2.9, 11.5, 13.5 Hz, 1 H), 3.5 (dt, J = 7.0, 9.6 Hz, 1 H), 3.15 (s, 3 H), 2.3 (t, J = 7.0 Hz, 2 H), 1.9 (dt, J = 2.2, 13.5 Hz, 1 H), 1.75 (s, 3 H), 1.65 (bdq, J = 3.05, 5.2, 13.7 Hz, 1 H), 1.5 (bdd J = 4.8, 11.0, 13.7 Hz, 1 H), 1.4 (dd, J = 8.0, 13.3 Hz, 1 H), 1.2 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.7, 111.4, 98.5, 72.8, 67.1, 60.7, 48.4, 41.1, 37.8, 35.1, 24.1, 22.6; IR (neat) 2968, 1648, 1462, 1169, 1074 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_2$ (M^+ - CH_3) 183.1385, found 183.1381.

(2*R,4*R**)-4-Methyl-2-[(3-methyl-3-butenyl)oxy]-4-(trifluoroacetoxy)tetrahydropyran (27b)** (8%): ^{1}H NMR ($CDCl_3$) δ 4.8 (bd, 2 H), 4.7 (dd, J = 2.8, 6.8 Hz, 1 H), 3.85 (m, 2 H), 3.61 (ddd, J = 3.1, 9, 12.1 Hz, 1 H), 3.5 (dt, J = 6.9, 9.6 Hz, 1 H), 2.35 (ol m, 3 H), 2.15 (dddd, J = 1.7, 3.2, 5.1, 14.1 Hz, 1 H), 1.8 (m, 2 H), 1.7 (s, 3 H), 1.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 181.7, 156.6, 156.1, 155.6, 155.0, 142.5, 111.6, 97.6, 86.7, 66.9, 59.4, 41.1, 37.7, 35.5, 24.8, 22.6; IR (neat) 3078, 1781, 1648, 1454, 1223, 1167, 1130 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_2$ (M^+ - OTf) 183.1385, found 183.1389.

(*E*)-8-Hydroxy-6-methyl-5-octen-2-one (38). The ethylene acetal 37[18] (9.0 g, 44.9 mmol) was stirred in a 66% aqueous solution of HOAc (150 mL) at 65 °C for 1.5 h. The reaction mixture was quenched by addition to a cold saturated $NaHCO_3$ solution (1.5 L) and extracted with Et_2O. The combined extracts were washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated in vacuo to afford 38 as a yellow liquid (50%; >90% pure). The crude reaction product was purified by chromatography on silica and eluted with 2:1 hexane/EtOAc followed by Et_2O: ^{1}H NMR ($CDCl_3$) δ 5.2 (bt, 1 H), 3.6 (t, 2 H), 2.5–2.2 (ol m, 6 H), 2.1 (s, 3 H), 1.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.0, 132.7, 125.6, 60.1, 43.4, 42.5, 29.9, 22.3, 15.7; IR (neat) 3428, 2934, 1706, 1409, 1367, 1043 cm^{-1}; HRMS calcd for $C_9H_{14}O$ (M^+ - H_2O) 138.1045, found 138.1040.

(*E*)-3,7-Dimethyl-3,7-octadien-1-ol (39). To a suspension of 10.7 g of $Ph_3PCH_3^+Br^-$ (30 mmol) in dry THF (50 mL) at 0 °C was added dropwise 12.0 mL of *n*-BuLi (30 mmol, 2.5 M in hexanes). After addition was completed, the reaction was warmed to 25 °C. After 50 min, the reaction mixture was cooled to −10 °C and a solution of 1.56 g of the keto alcohol 38 (10 mmol) in THF was added dropwise with the immediate formation of a white precipitate. The reaction was warmed to 25 °C. After 2 h, the reaction was quenched with a saturated $NaHCO_3$ solution and extracted with pentane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude reaction product was purified by chromatography on silica and eluted with 10:1 hexane/Et_2O followed by 2:1 hexane/Et_2O to give 39 as a yellow liquid (81%): ^{1}H NMR ($CDCl_3$) δ 5.2 (bt, J = 1.0, 6.8 Hz, 1 H), 4.7 (d, 2 H), 3.6 (t, J = 6.2 Hz, 2 H), 2.4–2.0 (ol m, 6 H), 1.9 (bs, 1 H), 1.75 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.6, 131.4, 127.4, 110.1, 59.9, 42.6, 37.6, 26.1, 22.2, 15.7; IR (neat) 3347 (bd), 3074, 1649, 1447, 1382, 1043 cm^{-1}; HRMS calcd for $C_{10}H_{16}$ (M^+ - H_2O) 136.1252, found 136.1256.

Dioxenium Cation–Olefin Cyclization of 39. 0.280 mL of 39 (1.62 mmol), 0.186 mL of $HC(OMe)_3$ (1.70 mmol), 0.200 mL of $SnCl_4$ (1.70 mmol), 10 mL of CH_2Cl_2, after 2 h at −78 °C, warm to −20 °C. The crude reaction product was separated by HPLC on silica and eluted with 90:10 hexane/EtOAc to give six products 42–47 in 58% combined yield.

(2*S,3*R**,8*S**)-(*E*)-6,8-Dimethyl-2-methoxy-1-oxabicyclo[4.4.0]dec-5-ene (42)** (4%): ^{1}H NMR ($CDCl_3$) δ 5.4 (bs, 1 H), 4.5 (d, J = 3.6 Hz, 1 H), 3.9 (td, J = 2.2, 11.8 Hz, 1 H), 3.55 (ddd, J = 1.7, 4.8, 11.5 Hz, 1 H), 3.35 (s, 3 H), 2.1 (bt, 1 H), 2.0–1.4 (m, 6 H), 1.6 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 131.4, 119.9, 101.1, 56.7, 55.1, 48.1, 42.5, 40.2, 30.1, 24.4, 23.8, 19.0; IR (neat) 2969, 1441, 1400, 1274, 1182, 1151 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 197.1466.

(2*R,3*R**,6*S**,8*R**)-6-Chloro-6,8-dimethyl-2-methoxy-1-oxabicyclo[4.4.0]decane (43)** (16%): ^{1}H NMR ($CDCl_3$) δ 4.15 (d, J = 8, 5 Hz, 1 H), 3.9 (m, 2 H), 3.4 (s, 3 H), 2.4–1.1 (overlapping resonances, 15 H); ^{13}C NMR ($CDCl_3$) δ 101.7, 69.6, 61.1, 56.2, 55.0, 49.4, 42.9, 40.9, 36.3, 33.6, 25.9, 18.4; IR (melt) 2961, 1451, 1170, 1161, 1136, 1078 cm^{-1}; HRMS calcd for $C_{11}H_{18}OCl$ (M^+ - OCH_3) 201.1046, found 201.1045.

(2*R,3*R**,8*S**)-(*E*)-6,8-Dimethyl-2-methoxy-1-oxabicyclo[4.4.0]dec-5-ene (44)** (20%): ^{1}H NMR ($CDCl_3$) δ 5.4 (bs, 1 H), 4.2 (d, J = 4.2 Hz, 1 H), 3.9 (ddd, 1 H), 3.7 (td, 1 H), 3.4 (s, 3 H), 2.2–1.2 (overlapping resonances, 10 H), 0.9 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 131.8, 119.4, 103.4, 62.0, 56.3, 46.5, 43.8, 40.0, 31.7, 23.8, 23.3, 17.1; IR (neat) 2964, 1443, 1396, 1126, 1098, 1079 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 197.1465.

(2*R,3*R**,6*R**,8*R**)-6-Chloro-6,8-dimethyl-2-methoxy-1-oxabicyclo[4.4.0]decane (45)** (3%): ^{1}H NMR ($CDCl_3$) δ 4.15 (d, J = 8, 5 Hz, 1 H), 3.9 (m, 2 H), 3.4 (s, 3 H), 2.4–1.1 (overlapping resonances, 15 H); ^{13}C NMR ($CDCl_3$) δ 101.6, 70.9, 61.2, 57.7, 56.0, 49.0, 43.5, 40.7, 35.0, 32.1, 20.6, 18.4; IR (neat) 2955, 1448, 1377, 1124, 1117 cm^{-1}; HRMS calcd for $C_{11}H_{18}OCl$ (M^+ - OCH_3) 201.1046, found 201.1051.

(2*S,3*S**,4*S**)-4-Chloro-2-methoxy-4-methyl-3-(3-methyl-3-butenyl)tetrahydropyran (46)** (11%): ^{1}H NMR ($CDCl_3$) δ 4.8 (bd, 2 H), 4.7 (d, J = 3.7 Hz, 1 H), 3.75 (td, J = 2.2, 11.8 Hz, 1 H), 3.6 (ddd, J = 2.4, 5, 11.8 Hz, 1 H), 3.35 (s, 3 H), 2.35–1.4 (ol m, 7 H), 1.8 (s, 3 H), 1.7 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.2, 110.7, 99.9, 77.1, 57.8, 55.3, 50.6, 44.1, 35.2, 26.5, 23.0, 22.0; IR (neat) 3069, 2961, 1647, 1447, 1384, 1360, 1154, 1127 cm^{-1}; HRMS calcd for $C_{12}H_{21}O_2$ (M^+ - Cl) 197.1541 found 197.1546.

(2*S,3*R**,6*S**,8*R**)-6-Chloro-6,8-dimethyl-2-methoxy-1-oxabicyclo[4.4.0]decane (47)** (6%): ^{1}H NMR ($CDCl_3$) δ 4.5 (d, J = 3.2 Hz, 1 H), 4.0 (d, J = 3.1, 11.8, 1 H), 3.55 (m, 1 H), 3.35 (s, 3 H), 2.4–1.2 (overlapping resonances, 15 H); ^{13}C NMR ($CDCl_3$) δ 101.8, 76.4, 56.5, 56.3, 55.3, 47.8, 43.7, 41.2, 36.5, 32.0, 20.8, 20.4; IR (neat) 2962, 1446, 1391, 1132, 1109 cm^{-1}; HRMS calcd for $C_{11}H_{18}OCl$ (M^+ - OCH_3) 201.1046, found 201.1044.

(*E*)-2-Methyl-2-buten-1-ol (52) was prepared according to the procedure of Bury.[26]

(*E*)-1-Chloro-2-methyl-2-butene (53). Following the method of McMurry,[17] methanesulfonyl chloride (15.2 mL, 196 mmol) was added to a solution of (*E*)-2-methyl-2-buten-1-ol 52 (12.2 g, 142 mmol), LiCl (14.7 g, 349 mmol), and collidine (24.8 mL, 188 mmol) in DMF (268 mL) at 0 °C. The resulting mixture was stored at −20 °C overnight, diluted with 750 mL of cold water, and extracted into pentane. The organic layer was washed successively with water, saturated $Cu(NO_3)_2$, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo at 0 °C provided 53 as a light yellow volatile liquid (7.35 g, 50%): ^{1}H NMR ($CDCl_3$) δ 5.60 (q, J = 5.7, 1.1 Hz, 1 H), 4.01 (s, 3 H), 1.72 (s, 3 H), 1.64 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 132.4, 125.1, 52.4, 13.9, 13.5; IR (neat) 2911, 1727, 1670, 1441, 1264, 683 cm^{-1}; HRMS calcd C_5H_9Cl 104.0393, found 104.0394.

Dimethylisopropoxy((*E*)-3-methyl-3-butenyl)silane (54). Following the procedure of McMurry[17] a solution of (*i*-PrO)-Me_2SiCH_2Cl (15.5 mL, 86.0 mmol) in THF (90 mL) was added dropwise to Mg turnings (2.3 g, 94.7 mmol) at 25 °C. After 3 mL of the silane solution had been added the reaction was initiated by addition of an iodine crystal and 33 μL of dibromoethane. After disappearance of the iodine color, the remaining silane solution was added over a 2-h period. The reaction rate was moderated through the use of a water bath. After addition was complete the reaction mixture was heated to 45 °C. After 1 h, the solution was cooled to 0 °C and CuI (1.47 g, 7.74 mmol) was added. The resulting solution was cooled to −78 °C, and chloride 53 (6.0 g, 57 mmol) was added dropwise over 15 min. The mixture was

(26) Bury, A.; Corker, S. T.; Johnson, M. D. *J. Chem. Soc., Perkin Trans 1* 1982, 645.

allowed to warm slowly to 25 °C. After 12 h the reaction was quenched by addition of 3.3 mL of water and concentrated in vacuo. The residue was diluted with 125 mL saturated NH_4Cl and 12.5 mL concentrated NH_4OH and extracted into pentane. The organic extract was washed sequentially with water, dilute HCl (3 M), saturated $NaHCO_3$, and brine. After drying over Na_2SO_4 the filtrate was concentrated in vacuo to yield silane **54** as a light yellow liquid of sufficient purity for further use (10.3 g, 89%): ^1H NMR ($CDCl_3$) δ 5.20 (m, 1 H), 3.96 (septet, J = 6.1 Hz, 1 H), 1.98 (t, J = 8.5 Hz, 2 H), 1.58 (s, 3 H), 1.54 (d, J = 6.6 Hz, 3 H), 1.13 (d, J = 5.9 Hz, 6 H), 0.67 (m, 2 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 116.8, 64.6, 33.0, 25.8, 15.2, 13.3; IR (neat) 2973, 1381, 1251, 1174, 1131, 1030, 842 cm^{-1}; HRMS calcd $C_{11}H_{24}OSi$ 200.1593, found 200.1596.

(*E*)-3-Methyl-3-penten-1-ol (55). The procedure of McMurry[18] was modified. Silane **54** (9.5 g, 47 mmol) was added to a solution of methanol (107 mL), THF (107 mL), and $NaHCO_3$ (13.5 g). After bringing the mixture to reflux, H_2O_2 (30%, 172 mL) was added in 15-mL increments every 15 min. After cooling the white suspension to 25 °C, it was extracted three times with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude alcohol **55** (2.6 g, 55%). The crude reaction product was purified by HPLC on silica and eluted with 93:7 hexane/EtOAc to give pure alcohol **55** as a colorless oil (1.63 g, 34%): ^1H NMR ($CDCl_3$) δ 5.31 (m, 1 H), 3.62 (t, J = 6.3 Hz, 2 H), 2.22 (t, J = 6.3 Hz, 2 H), 1.78 (br s, 1 H), 1.59 (br s, 3 H), 1.57 (d, J = 0.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 131.9, 121.7, 60.1, 42.6, 15.3, 13.4; IR (neat) 3355, 2920, 1445, 1382, 1004 cm^{-1}; HRMS calcd for $C_6H_{12}O$ 100.0888, found 100.0895.

Dioxenium Cation–Olefin Cyclization of 55. 0.3 g of **55** (3 mmol), 1.31 mL of $HC(OMe)_3$ (12 mmol), 1.40 mL of $SnCl_4$ (12 mmol), 15 mL CH_2Cl_2, 2 h, −78 °C. The reaction produced 0.303 g of a mixture of products. Purification by HPLC on silica and elution with 93:7 hexane/EtOAc provided **56** and **58** in a ratio of 6.4:1.

(2*S,3*R**,4*S**)-4-Chloro-2-methoxy-3,4-dimethyltetrahydropyran (56)** (77%): ^1H NMR (C_6D_6) δ 4.35 (d, J = 3.3 Hz, 1 H), 3.41 (ddd, J = 12.4, 10.2, 2.9 Hz, 1 H), 3.29 (ol ddd, J = 16.1, 8.8, 4.4 Hz, 1 H), 2.99 (s, 3 H), 2.09 (ddd, J = 14.1, 7.1, 3.4 Hz, 1 H), 1.97 (ddd, J = 14.0, 10.1, 4.2 Hz, 1 H), 1.63 (ddd, 13.5, 4.0, 3.0 Hz, 1 H), 1.49 (s, 3 H), 0.98 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 101.9, 72.4, 59.1, 55.7, 46.4, 41.5, 27.4, 10.3; IR (neat) 2940, 1453, 1386, 1096, 1063, 1040 cm^{-1}; HRMS calcd $C_8H_{15}ClO_2$ ($M^+ - OCH_3$) 147.0577, found 147.0580.

(2*S,3*R**,4*S**)-4-Chloro-3,4-dimethyl-2-[((*E*)-3-methyl-3-pentenyl)oxy]tetrahydropyran (58)** (12%): ^1H NMR ($CDCl_3$) δ 5.29–5.21 (m, 1 H), 4.67 (d, J = 3.3 Hz, 1 H), 3.83–3.71 (m, 2 H), 3.63 (ol ddd, J = 11.8, 4.5 Hz, 1 H), 3.38 (ol ddd, J = 9.6, 6.6 Hz, 1 H) 2.26–2.11 (ol m, 3 H) 2.02 (ddd, J = 13.5, 4.2, 3.2 Hz, 1 H) 1.65 (s, 3 H), 1.62 (s, 3 H), 1.56 (d, J = 6.7, 1.0 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 133.0, 120.4, 100.6, 72.0, 66.8, 58.9, 46.5, 42.1, 39.6, 26.9, 15.7, 13.3, 10.5; IR (neat) 2972, 1454, 1383, 1143, 1040 cm^{-1}; HRMS calcd $C_{13}H_{23}ClO_2$ ($M^+ - C_6H_{11}O$) 147.0577, found 147.0570.

(2*S,4*S**,6*R**)-4-Chloro-2-methoxy-4,6-dimethyltetrahydropyran (61).** 0.206 mL of **60** (1.99 mmol), 0.218 mL of $HC(OMe)_3$ (1.99 mL), 0.995 mL of $SnCl_4$ (1.0 M in CH_2Cl_2, 0.995 mmol), −20 °C, 1 h. The crude reaction product was purified by chromatography on silica (3:1 hexane/EtOAc) to give one major isomer (along with 3–5% of a minor product by ^1H NMR analysis) as a colorless liquid (77%). The major isomer **61** was isolated by HPLC on silica and eluted with 9:1 hexane/EtOAc in 60% yield: ^1H NMR ($CDCl_3$) δ 4.75 (t, J = 2.7 Hz, 1 H), 3.9 (m, 1 H), 3.3 (s, 3 H), 2.2 (bd, 1 H), 2.0 (ol m, 3 H), 1.85 (s, 3 H), 1.2 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.1, 66.9, 63.1, 54.9, 49.7, 44.9, 31.3, 21.1; IR (neat) 2978, 2935, 2896, 1447, 1383, 1324, 1197, 1127, 1115, 1049, 978, 867, 773 cm^{-1}; HRMS calcd for $C_7H_{12}OCl$ ($M^+ - OCH_3$) 147.0577, found 147.0574.

(2*S,4*R**,5*R**)-4-Chloro-2-methoxy-4,5-dimethyltetrahydropyran (63).** 0.500 mL of **62** (4.28 mmol), 0.500 mL of $HC(OMe)_3$ (4.6 mmol), 0.540 mL of $SnCl_4$ (4.6 mmol), 1 h, −20 °C. The crude reaction product (90%) consisted of essentially one acetal isomer by ^1H NMR analysis. Purification of the product by HPLC on silica and elution with 95:5 hexane/EtOAc affords **63** (62%): ^1H NMR ($CDCl_3$) δ 4.7 (t, J = 3.6 Hz, 1 H), 3.7 (dd, J = 4.0, 11.8 Hz, 1 H), 3.5 (m, 1 H), 3.35 (s, 3 H), 2.1 (ol m, 3 H), 1.6 (s, 3 H), 1.0 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.5, 71.9, 64.5, 55.1, 45.3, 42.6, 26.9, 12.2; IR (neat) 2964, 1450, 1362, 1197, 1130, 1088 cm^{-1}; HRMS calcd for $C_7H_{12}OCl$ ($M^+ - OCH_3$) 147.0577, found 147.0579.

3-[(Trimethylsilyl)methyl]-3-buten-1-ol (71) was prepared according to the procedure of Ochiai[20] in 33% yield.

4-Methylidene-2-methoxytetrahydropyran (72). 0.47 g of **71** (3.0 mmol), 0.36 mL of $HC(OMe)_3$ (3.3 mmol), 0.176 mL of $SnCl_4$ (1.5 mmol), 5 mL of CH_2Cl_2, −78 °C, 2 h. The reaction gave pure **72** as a colorless oil (0.2474 g, 64%): ^1H NMR ($CDCl_3$) δ 4.76 (s, 1 H), 4.73 (s, 1 H), 4.56 (t, J = 3.6 Hz, 1 H), 3.80 (ddd, J = 10.8, 9.0, 4.0 Hz, 1 H), 3.57 (m, 1 H), 3.35 (s, 3 H), 2.39 (m, J = 10.2, 1.7 Hz, 1 H), 2.31–2.12 (bm, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.9, 110.3, 100.0, 61.6, 55.0, 39.7, 34.2; IR (neat) 2956, 1718, 1654, 1380, 1124, 1053 cm^{-1}; HRMS calcd $C_7H_{12}O_2$ ($M^+ - OCH_3$) 97.0653, found 97.0654.

4-(2-Chloroethylidene)-2-methoxy-6-methyltetrahydropyran (78–81). 0.250 mL of **76**[22] (2.15 mmol), 0.254 mL of $HC(OMe)_3$ (2.32 mmol), 2.4 mL of $SnCl_4$, 1 h, −20 °C. The crude reaction product was purified by chromatography on silica (3:1 hexane/EtOAc) to give a mixture of diastereomeric 4-(2-chloroethylidene)-2-methoxy-6-methyltetrahydropyrans (83%). The four diastereomers were separated by HPLC on silica and eluted with 95:5 hexane/EtOAc.

(*Z*)-(2*R,6*R**)-4-(2-Chloroethylidene)-2-methoxy-6-methyltetrahydropyran (78)** (8%): ^1H NMR ($CDCl_3$) δ 5.5 (bt, J = 8.0 Hz, 1 H), 4.2 (dd, J = 2.4, 9.3 Hz, 2 H), 4.05 (m, 2 H), 3.5 (s, 3 H), 3.45 (m, 1 H), 2.7 (bd, J = 1.9, 13.5 Hz, 1 H), 2.15 (bd, 1 H), 1.95 (bq, 2 H), 1.25 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.3, 120.9, 102.0, 71.0, 56.2, 42.6, 39.5, 34.4, 21.2; IR (neat) 2975, 1667, 1444, 1376, 1158, 1075 cm^{-1}; HRMS calcd $C_8H_{12}OCl$ ($M^+ - OCH_3$) 159.0577, found 159.0580.

(*E*)-(2*R,6*R**)-4-(2-Chloroethylidene)-2-methoxy-6-methyltetrahydropyran (79)** (14%): ^1H NMR ($CDCl_3$) δ 5.5 (bt, J = 7.7 Hz, 1 H), 4.3 (ddd, J = 1.23, 2.3, 9.25 Hz, 1 H), 4.1 (m, 2 H), 3.5 (s, 3 H), 3.49 (m, 1 H), 2.55 (dt, 1 H), 2.35 (dt, 1 H), 2.2 (bt, 1 H), 1.8 (bt, 1 H), 1.25 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.7, 121.1, 102.7, 70.7, 56.2, 41.4, 39.5, 35.7, 21.6; IR (neat) 2973, 1668, 1445, 1373, 1111, 1070 cm^{-1}; HRMS calcd $C_9H_{15}O_2Cl$ 190.0761, found 190.0765.

(*Z*)-(2*S,6*R**)-4-(2-Chloroethylidene)-2-methoxy-6-methyltetrahydropyran (80)** (19%): ^1H NMR ($CDCl_3$) δ 5.5 (bt, 1 H), 4.8 (bd, J = 3.8 Hz, 1 H), 4.1 (m, 2 H), 3.85 (m, 1 H), 3.3 (s, 3 H), 2.6 (bd, 1 H), 2.2 (m, 2 H), 2.1 (bt, 1 H), 1.2 (d, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 120.9, 98.5, 65.6, 54.6, 42.7, 39.8, 33.0, 21.3; IR (neat) 2975, 1670, 1445, 1384, 1121 cm^{-1}; HRMS calcd $C_9H_{15}O_2Cl$ 190.0761, found 190.0766.

(*E*)-(2*S,6*R**)-4-(2-Chloroethylidene)-2-methoxy-6-methyltetrahydropyran (81)** (35%): ^1H NMR ($CDCl_3$) δ 5.5 (bt, 1 H), 4.8 (bd, J = 3.89 Hz, 1 H), 4.1 (m, 2 H), 3.85 (m, 1 H), 3.3 (s, 3 H), 2.6 (bd, 1 H), 2.2 (ol m, 2 H), 2.1 (bt, 1 H), 1.2 (d, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 120.6, 98.9, 64.8, 54.6, 39.6, 39.4, 35.6, 21.5; IR (neat) 2974, 1669, 1446, 1381, 1178, 1122, 1047 cm^{-1}; HRMS calcd $C_9H_{15}O_2Cl$ 190.0761, found 190.0763.

3-Benzyl-2,3-dihydro-4-pyranone (86). 0.376 mL of **85**[25] (2.26 mmol), 0.755 mL of $HC(OEt)_3$ (4.5 mmol), 4.5 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 4.5 mmol), 1 h, −78 °C. The crude reaction product (84%) was purified by chromatography on silica (3:1 EtOAc/hexane) followed by HPLC on silica (3:1 EtOAc/hexane) to give dihydropyrone **86** (70%): ^1H NMR ($CDCl_3$) δ 7.36–7.15 (ol m, 6 H), 5.4 (d, J = 6 Hz, 1 H), 4.3 (dd, J = 4.5, 11.4 Hz, 1 H), 4.1 (dd, J = 8.4, 11.5 hz, 1 H), 3.22 (dd, J = 3.7, 13.4 Hz, 1 H), 2.7 (m, 1 H), 2.6 (dd, J = 10.7, 13.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 193.7, 162.9, 138.1, 128.9, 128.5, 126.5, 106.4, 70.3, 46.4, 32.6; IR (neat) 3072, 1681, 1601, 1501, 1452, 1031 cm^{-1}; HRMS calcd $C_{12}H_{12}O_2$ 188.0837, found 188.0840.

β-Silyloxy TMS Enol Ethers (91–105) were prepared from the corresponding β-hydroxy ketones via their distal aldolate dianions.[27]

The following reactions were carried out in the same manner as described above for **17a**, and **17b** using the reagents and solvents

(27) (a) Martin, V. A.; Murray, D. H.; Pratt, N. P.; Zhao, Y.-B.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965. (b) Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1988**, *53*, 5986.

specified in Table II. The quantities of the various β-silyloxy TMS enol ethers, ortho esters, Lewis acid, and solvent are given in an abbreviated format followed by the reaction time and temperature.

2-Ethoxytetrahydropyran-4-one (92). 2 mL of **91** (7.65 mmol), 1.55 mL of $HC(OEt)_3$ (9.3 mmol), 9.6 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 9.6 mmol), 1 h, −78 °C. The crude reaction product was purified by chromatography on silica (1:3 EtOAc/hexane) followed by HPLC on silica (3:1 hexane/EtOAc) to give pyranone **92** in 70% yield along with 5% of uncyclized acetal **108**.

(92): ^1H NMR ($CDCl_3$) δ 5.0 (bt, J = 2.6 Hz, 1 H), 4.0 (td, J = 3.9, 11.0 Hz, 1 H), 3.8 (m, 1 H), 3.65 (m, 1 H), 3.4 (m, 1 H), 2.6–2.2 (ol m, 4 H), 1.1 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 204.4, 98.6, 62.8, 58.7, 47.2, 41.3, 14.6; IR (neat) 2981, 1724, 1448, 1381, 1077, 1055 cm^{-1}; HRMS calcd $C_7H_{12}O_3$ 144.0786, found 144.0786.

1,1-Diethoxy-5-[(trimethylsilyl)oxy]-3-pentanone (108): ^1H NMR ($CDCl_3$) δ 4.9 (t, J = 5.6 Hz, $CH(OCH_2CH_3)_2$), 3.9 (t, J = 6.3 Hz, CH_2OTMS), 3.7 (m, OCH_2CH_3), 3.5 (m, OCH_2CH_3), 2.8 (d, J = 5.6 Hz, $CH_2CH(OCH_2CH_3)_2$), 2.7 (t, J = 6.4 Hz, CH_2CH_2OTMS), 1.2 (t, J = 7.1 Hz, OCH_2CH_3), 0.1 (s, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 206, 99.8, 62.3, 57.6, 48.2, 46.7, 15.2, −0.7; IR (neat) 3464, 2981, 1705, 1381, 1063 cm^{-1}; HRMS calcd $C_{12}H_{26}O_4Si$ 262.1600, found 262.1603.

2-Ethoxy-5-methyltetrahydropyran-4-one (94a,94b). 2.49 mL of **93** (8.6 mmol), 1.55 mL of $HC(OEt)_3$ (9.3 mmol), 9.6 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 9.6 mmol), 30 min, −78 °C. Purification of the crude reaction product (88%) was achieved by chromatography on silica (1:3 hexane/EtOAc), yielding a mixture of diastereomers. The pair of diasteromers was separated by HPLC on silica and eluted with 1:3 hexane/EtOAc.

(2*R*,5*R)-2-Ethoxy-5-methyltetrahydropyran-4-one (94a)** (55%): mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 5.2 (dd, J = 1.3, 4.3 Hz, 1 H), 3.85 (dd, J = 7.1, 11.0 Hz, 1 H), 3.6 (ol m, 2 H), 3.4 (dq, 1 H), 2.65 (ol m, 2 H), 2.45 (dd, J = 1.3, 14.3 Hz, 1 H), 1.15 (t, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.4, 99.4, 65.0, 62.8, 46.9, 45.1, 14.9, 9.3; IR (KBr) 2981, 1715, 1472, 1385, 1162, 1097 cm^{-1}; HRMS calcd $C_8H_{14}O_3$ 158.0943, found 158.0944.

(2*R,5*R**)-2-Ethoxy-5-methyltetrahydropyran-4-one (94b)** (4%): ^1H NMR ($CDCl_3$) δ 4.7 (dd, J = 3.3, 6.7 Hz, 1 H), 4.1 (dd, J = 5.8, 11.5 Hz, 1 H), 3.85 (dq, 1 H), 3.5 (dq, 1 H), 3.3 (dd, J = 8.2, 11.5 Hz, 1 H), 2.7 (dd, J = 3.3, 14.6 Hz, 1 H), 2.53 (m, 1 H), 2.4 (ddd, J = 1.1, 6.7, 14.6 Hz, 1 H), 1.2 (t, J = 7.1 Hz, 3 H), 1.05 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.4, 100.3, 66.2, 64.1, 46.9, 44.6, 15.0, 11.2; IR (neat) 2979, 1722, 1462, 1378, 1104, 1063 cm^{-1}; HRMS calcd $C_8H_{14}O_3$ 158.0943, found 158.0945.

2-Methoxy-3,5-dimethyltetrahydropyran-4-one (96a–d). 730 mg of **95** (2.8 mmol), 0.360 mL of $HC(OMe)_3$ (3.3 mmol), 0.2 mL of $SnCl_4$ (1.7 mmol), 10 mL of CH_2Cl_2, 15 min, 25 °C. This reaction provides a mixture of four diastereomers **96a–d** (9:40:25:26 by ^1H NMR analysis) in 62% combined yield. The four diastereomers were separated by repetitive HPLC on silica and eluted with 5:1 hexane/EtOAc.

(2*R,3*S**,5*R**)-2-Methoxy-3,5-dimethyltetrahydropyran-4-one (96a):** ^1H NMR ($CDCl_3$) δ 4.18 (dd, J = 6.8, 11.5 Hz, 1 H), 4.09 (d, J = 8.3 Hz, 1 H), 3.5 (s, 3 H), 3.2 (t, J = 11.2 Hz, 1 H), 2.65 (m, 1 H), 2.5 (m, 1 H), 1.09 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.3, 107.4, 67.4, 56.7, 51.2, 44.3, 9.4, 8.8; IR ($CDCl_3$) 2976, 1719, 1357, 1260, 1152, 1068 cm^{-1}.

(2*S,3*S**,5*R**)-2-Methoxy-3,5-dimethyltetrahydropyran-4-one (96b):** ^1H NMR ($CDCl_3$) δ 4.87 (d, J = 3.8 Hz, 1 H), 3.87 (dd, J = 7.2, 10.8 Hz, 1 H), 3.5 (t, J = 11.0 Hz, 1 H), 3.3 (s, 3 H), 2.8–2.6 (ol m, 2 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.6, 104.8, 65.7, 54.9, 49.3, 44.6, 8.9; IR (neat): 2976, 1723, 1456, 1357, 1169, 1051 cm^{-1}.

(2*S,3*S**,5*S**)-2-Methoxy-3,5-dimethyltetrahydropyran-4-one (96c):** ^1H NMR ($CDCl_3$) δ 4.8 (d, J = 3.8 Hz, 1 H), 4.1 (dd, J = 4.2, 11.3 Hz, 1 H), 3.5 (dd, J = 3.2, 11.3 Hz, 1 H), 3.4 (s, 3 H), 2.88 (m, 1 H), 2.5 (m, 1 H), 1.26 (d, J = 7.2 Hz, 3 H), 1.03 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 103.9, 65.2, 55.3, 46.2, 44.4, 15.6, 9.2; IR (neat) 2978, 1717, 1458, 1369, 1192, 1076, 1045 cm^{-1}.

(2*S,3*R**,5*R**)-2-Methoxy-3,5-dimethyltetrahydropyran-4-one (96d):** ^1H NMR ($CDCl_3$) δ 4.63 (bd, J = 2.1 Hz, 1 H), 3.84 (dd, J = 7.0, 11.0 Hz, 1 H), 3.65 (t, J = 10.8 Hz, 1 H), 3.4 (s, 3 H), 2.75 (m, 1 H), 2.5 (m, 1 H), 1.22 (d, J = 7.2 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.6, 105.6, 65.1, 54.9, 49.7, 41.1, 14.5, 10.0; IR (neat) 2976, 1717, 1362, 1207, 1085, 1011 cm^{-1}.

2-Ethoxy-3-methyl-tetrahydropyran-4-one (98a,98b). 2.5 mL of **97** (as a mixture of cis and trans isomers) (8.6 mmol), 1.55 mL of $HC(OEt)_3$ (9.3 mmol), 9.6 mL of $SnCl_4$ (1 M solution in CH_2Cl_2; 9.6 mmol), 1 h, −78 °C. An inseparable mixture of diastereomers **98a** ((2*S**,3*S**)isomer) and **98b** ((2*S**,3*R**)isomer), in a ratio of 77:33, was obtained in 92% yield: ^1H NMR (C_6D_6) δ 4.6 (d, J = 3.9 Hz, H_{2a}), 4.08 (d, J = 5.4 Hz, H_{2b}), 3.9 (td, J = 3.7, 11.3 Hz, H_{6eax}), 3.6 (overlapping multiplets, $(OCH_2CH_3)_b$, H_{6bax}), 3.4 (overlapping multiplets, H_{6eeq}, $(OCH_2CH_3)_a$), 3.12 (overlapping multiplets, H_{6beq}, $(OCH_2CH_3)_b$), 3.0 (m, 1 H, $(OCH_2CH_3)_a$), 2.33 (m, H_{3b}), 2.17 (m, H_{3a}), 2.1 (m, H_{5bax}), 2.02 (m, H_{5eax}), 1.93 (m, H_{5eeq}), 1.84 (m, H_{5beq}), 0.97 (2d, CH_3CH_{5a}, CH_3CH_{5b}), 0.85 (t, $(OCH_2CH_3)_a$, $(OCH_2CH_3)_b$); ^{13}C NMR (C_6D_6) (the underlined ^{13}C NMR resonances correspond to the major isomer **98a**), δ 206.2, 204.6, 104.8, 102.8, 63.7, 63.0, 59.8, 59.3, 51.2, 49.8, 41.6, 39.9, 15.1, 14.8, 11.6, 9.4; IR (neat) 2985, 1717, 1423, 1363, 1100, 1054 cm^{-1}; HRMS calcd $C_8H_{14}O_3$ 158.0943, found 158.0946.

5-Benzyl-2-methoxytetrahydropyran-4-one (100a,b). 180 mg of **99** (0.56 mmol), 0.062 mL of $HC(OMe)_3$ (0.56 mmol), 0.040 mL of $SnCl_4$ (0.34 mmol), 4 mL of CH_2Cl_2, 5 min, 25 °C. This reaction affords a mixture of two diastereomers **100a**, and **100b** (75%; 95:5 by ^1H NMR analysis). The two diastereomers were separated by HPLC on silica and eluted with 65:35 hexane/EtOAc.

(2*S,5*R**)-5-Benzyl-2-methoxytetrahydropyran-4-one (100a):** ^1H NMR ($CDCl_3$) δ 7.32–7.15 (m, 5 H), 5.07 (dd, J = 1.5, 4.4 Hz, 1 H), 3.83–3.67 (ol m, 2 H), 3.3 (s, 3 H), 3.27 (dd, J = 4.8, 14.3 Hz, 1 H), 2.85 (m, 1 H), 2.72 (ddd, J = 0.9, 4.5, 14.3 Hz, 1 H), 2.57 (dd, J = 1.4, 14.2 Hz, 1 H), 2.4 (dd, J = 9, 14.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.1, 138.9, 128.7, 128.4, 126.2, 100.7, 63.2, 54.6, 51.5, 46.9, 31.0; IR (neat) 2933, 1722, 1497, 1454, 1140, 1118, 1040 cm^{-1}; HRMS calcd $C_{13}H_{16}O_3$ 220.1099, found 220.1101.

(2*S,5*S**)-5-Benzyl-2-methoxytetrahydropyran-4-one (100b):** ^1H NMR ($CDCl_3$) δ 7.32–7.17 (m, 5 H), 4.85 (t, J = 4.3 Hz, 1 H), 4.05 (dd, J = 4.5, 11.8 Hz, 1 H), 3.5 (dd, J = 5.2, 11.8 Hz, 1 H), 3.4 (s, 3 H), 3.1 (dd, J = 4.5, 13.1 Hz, 1 H), 2.85–2.6 (ol m, 3 H), 2.5 (ddd, J = 0.9, 4.5, 14.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 206.3, 138.2, 128.9, 128.5, 126.5, 100.8, 62.2, 55.3, 51.8, 45.9, 33.6; IR (neat) 2934, 1720, 1603, 1497, 1120, 1055 cm^{-1}; HRMS calcd $C_{13}H_{16}O_3$ 220.1099, found 220.1101.

5-Hydroxy-1,1-dimethoxy-7-phenyl-3-heptanone (102). 188 mg of **101** (0.56 mmol), 0.072 mL of $HC(OMe)_3$ (0.66 mmol), 0.040 mL of $SnCl_4$ (0.34 mmol), 4 mL of CH_2Cl_2, 15 min, −78 °C. Purification of the crude reaction product by HPLC on silica (1:1 hexane/EtOAc) gave **102** in 82% yield: ^1H NMR ($CDCl_3$) δ 7.3–7.16 (m, 5 H), 4.78 (t, J = 5.6 Hz, 1 H), 4.11–4.03 (m, 1 H), 3.35 (s, 6 H), 3.13 (bs, 1 H), 2.85–2.65 (ol m, 2 H), 2.73 (d, J = 5.6 Hz, 2 H), 2.61 (t, J = 3.8 Hz, 2 H), 1.89–1.78 (m, 1 H), 1.76–1.64 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 208.5, 141.7, 128.4, 128.3, 125.8, 101.3, 66.7, 53.8, 53.7, 51.4, 47.0, 37.9, 31.6; IR (neat) 3468 (br), 2938, 1712, 1496, 1454, 1071 cm^{-1}.

5-Hydroxy-1,1-dimethoxy-5-methyl-3-hexanone (104). 145 mg of **103** (0.56 mmol), 0.072 mL of $HC(OMe)_3$ (0.66 mmol), 0.040 mL of $SnCl_4$ (0.34 mmol), 4 mL of CH_2Cl_2, 15 min, −78 °C. Purification by HPLC on silica (1:3 hexane/EtOAc) gave **104** in 69% yield: ^1H NMR ($CDCl_3$) δ 4.75 (t, J = 5.9 Hz, 1 H), 3.68 (s, 1 H), 3.3 (s, 6 H), 2.7 (d, J = 2 Hz, 2 H), 2.6 (s, 2 H), 1.2 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 209.5, 101.4, 69.6, 54.4, 53.8, 47.8, 29.2; IR (neat) 3475 (br), 2974, 1705, 1466, 1124, 1057 cm^{-1}; HRMS calcd $C_9H_{18}O_4$ 190.1205, found 190.1198.

1-(2-Hydroxyphenyl)-3,3-dimethoxy-1-propanone (106). 157 mg of **105** (0.56 mmol), 0.072 mL of $HC(OMe)_3$ (0.66 mmol), 0.040 mL of $SnCl_4$ (0.34 mmol), 4 mL of CH_2Cl_2, 15 min, −78 °C. Purification by HPLC on silica (1:1 hexane/EtOAc) afforded **106** in 70% yield: ^1H NMR ($CDCl_3$) δ 7.73 (dd, J = 1.6, 8.1 Hz, 1 H), 7.46 (ddd, J = 1.6, 7.2, 8.6 Hz, 1 H), 6.96 (dd, J = 1.1, 8.4 Hz, 1 H), 6.89 (ddd, J = 1.0, 7.3, 8.1 Hz, 1 H), 4.98 (t, J = 5.5 Hz, 1 H), 3.4 (s, 6 H), 3.29 (d, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.8, 162.6, 136.5, 130.2, 119.5, 118.9, 118.4, 101.7, 54.0, 42.1; IR (neat) 2992, 1641, 1489, 1447, 1121, 1079 cm^{-1}; HRMS calcd $C_{11}H_{14}O_4$ 210.0892, found 210.0896.

1,1-Diethoxy-5-hydroxy-3-pentanone (107). 2 mL of **91** (7.65 mmol), 1.55 mL of $HC(OEt)_3$ (9.3 mmol), 2.4 mL of $SnCl_4$ (1 M

solution in CH_2Cl_2; 2.4 mmol), 1 h, −78 °C. The crude reaction product was purified by HPLC on silica and eluted with 1:3 hexane/EtOAc to yield acetal **107** in 63% yield: ^1H NMR ($CDCl_3$) δ 4.9 (t, J = 5.6 Hz, 1 H), 3.8 (bs, 2 H), 3.7 (m, 2 H), 3.5 (m, 2 H), 2.5 (ol m, 5 H), 1.15 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.2, 99.6, 62.2, 57.5, 47.7, 46.0, 15.0; IR (neat) 3464, 1705, 1295, 1222, 1123 cm^{-1}; HRMS calcd $C_9H_{18}O_4$ 190.1205, found 190.1202.

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Registry No. **15**, 763-32-6; **17a**, 109553-12-0; **17b**, 109553-16-4; **18a**, 135695-69-1; **18b**, 135695-70-4; **19a**, 135695-71-5; **19b**, 135695-72-6; **20a**, 109553-13-1; **20b**, 109553-17-5; **21**, 109553-14-2; **22a**, 109553-15-3; **22b**, 109553-18-6; **23**, 31080-83-8; **24a**, 135695-73-7; **24b**, 135720-62-6; **25**, 135695-76-0; **26a**, 135695-74-8; **26b**, 135695-75-9; **27a**, 135695-77-1; **27b**, 135695-78-2; **37**, 110589-84-9; **38**, 135695-79-3; **39**, 19788-92-2; **42**, 135695-80-6; **43**, 135695-81-7; **44**, 135695-82-8; **45**, 135695-83-9; **46**, 135695-84-0; **47**, 135695-85-1; **52**, 497-02-9; **53**, 23009-73-6; **54**, 135695-86-2; **55**, 1594-24-7; **56**, 135720-63-7; **58**, 135695-87-3; **60**, 2004-67-3; **61**, 135695-88-4; **62**, 1708-93-6; **63**, 135695-89-5; **64**, 627-27-0; **65**, 6559-36-0; **71**, 86341-37-9; **72**, 135695-90-8; **76**, 71885-98-8; **78**, 135695-91-9; **79**, 135759-64-7; **80**, 135759-65-8; **81**, 135759-66-9; **85**, 127841-27-4; **86**, 135695-92-0; **91**, 117201-93-1; **92**, 113195-06-5; **93**, 117201-94-2; **94a**, 127841-28-5; **94b**, 127841-29-6; **95**, 127841-24-1; **96a**, 127841-32-1; **96b**, 127841-30-9; **96c**, 127841-33-2; **96d**, 127841-31-0; **97**, 117202-11-6; **98a**, 127841-34-3; **98b**, 127841-35-4; **99**, 127841-26-3; **100a**, 127841-36-5; **100b**, 127841-37-6; **101**, 127841-25-2; **102**, 127841-38-7; **103**, 117201-96-4; **104**, 127841-39-8; **105**, 60068-17-9; **106**, 127841-40-1; **107**, 135695-93-1; **108**, 135695-94-2; $(MeO)_3CH$, 149-73-5; $(EtO)_3CH$, 122-51-0; (*i*-ArO)Me_2SiCH_2MgCl, 122588-50-5; $Ph_3PCH_3^+Br^-$, 1779-49-3.

Supplementary Material Available: Details on the stereochemical assignments of compounds **18a**, **22a**, **22b**, **56**, **42–47**, and **78–81** and ^1H and ^{13}C NMR spectra of all new compounds (56 pages). Ordering information is given on any current masthead page.

Regioselective Conversion of Cycloalkanones to Vinyl Bromides with 1,2-Functionality Transposition. A General Stratagem

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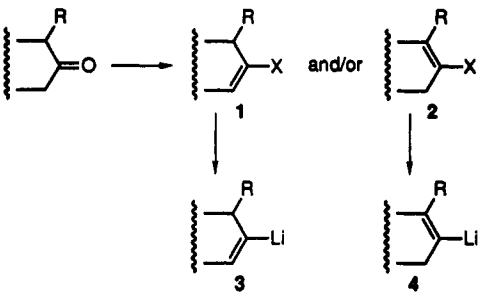
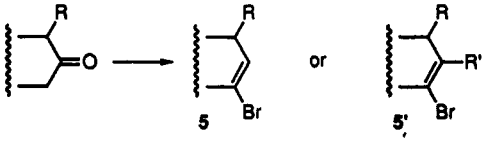
Cyclic β-keto esters, available by regioselective acylation of cycloalkanone enolates, are rapidly transformed to α,β-unsaturated acids. This functionality transposition allows the derived 3-hydroxy-4-methylthiazole-2-(3*H*)-thione derivatives to serve as precursors to synthetically useful vinyl bromides. The process involves heating the hydroxamate ester with AIBN in bromotrichloromethane solution. Alkylative and ring contractive variants of the methodology are highlighted. The short sequence makes available precursors to vinyl anions that are not otherwise conveniently accessible.

In recent years, cycloalkenyllithiums have been used with increasing frequency as nucleophiles to achieve carbon–carbon bond construction. The requirement that this class of reactive intermediates be routinely available has been met with the development of increasingly sophisticated methods of preparation. In those specific cases where electronic and strain effects are appropriate, direct deprotonation of a cyclic olefin precursor can be utilized satisfactorily. Cyclic enol ethers[2-4] and cyclopropenes[5] fall into this category. More commonly, reliance is placed upon umpolung of a cycloalkanone carbonyl group as shown in Scheme I. The classical method involving the reaction of a ketone with PCl_5 to produce vinyl chlorides[6] is ineffective.

Scheme I



Scheme II



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(2) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, *18*, 4187. (b) Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959. (c) Kocienski, P.; Yeates, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1879. (d) Nicolson, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925. (e) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926. (f) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinaÿ, P. *Tetrahedron Lett.* **1986**, *27*, 6201. (g) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (h) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (i) Cox, P.; Mahon, M. F.; Molloy, K. C.; Lister, S.; Gallagher, T. *Tetrahedron Lett.* **1988**, *29*, 1993. (j) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.

(3) (a) Fetizon, M.; Goulaouic, P.; Hanna, I. *Tetrahedron Lett.* **1985**, *26*, 4925. (b) Guillaumet, G.; Trumtel, M. *Synthesis* **1986**, 337. (c) Lee, T. V.; Leigh, A. J.; Chapleo, C. B. *Synthesis* **1989**, 208. (d) Blanchot, V.; Fetizon, M.; Hanna, I. *Synthesis* **1990**, 755. (e) Lee, T. V.; Leigh, A. J.; Chapleo, C. B. *Tetrahedron* **1990**, *45*, 921.

(4) Giles, M.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1990**, 831.

(5) (a) Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1963**, *85*, 99. (b) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyashi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4728. (c) Binger, P.; Müller, P.; Wenz, R.; Mynott, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1037.

0022-3263/91/1956-6199$02.50/0