bonds as representative examples.

In the intermolecular interstice, two screw chains wind along the crystallographic *b* axis direction. One, W2→W5→W4→W2′, is homodromic, with all water molecules acting as donors and acceptors; see Figures 4 and 5. The other, W1A→O(6)2→W2←W4←O(6)3←W1A′, is antidromic, with W1A donating two hydrogen bonds and W2 acting as double acceptor; see Figure 5.

Two of the circular hydrogen-bond arrangements, a four-membered and a six-membered ring, are shown in Figure 6; see also Figure 5. The four-membered ring is formed by hydroxyl groups of neighboring γ-CD molecules, O(3)1→O(6)7→O(2)5→O(3)6→O(3)1, and is of almost square geometry. The six-membered ring is formed by four water molecules and two hydroxyl groups, W7→O(6)6→W1A→O(6)3→W4→W3→W7. Both are homodromic, indicating the strong influence of the cooperative effect on the directionality of O–D···O hydrogen bonds. A five-membered ring is also observed in this structure, W2→O(3)3→O(2)2→←W3→←W4→W2 (see Figure 5), in which W3 is orientationally disordered with four D positions and acts as both donor and acceptor; because W4 is a double donor, this ring is antidromic. An eight-membered hydrogen-bonding ring is formed by the interconnection of the two screw chains mentioned above, W1A→O(6)3→W4→W2→W5→W4′→W2′←O(6)2←W1A, of which four water molecules, W2, W2′, W4, and W4′, are symmetry related by the screw axis 2_1. It is antidromic: W1A donates two hydrogen bonds and W2′ accepts two hydrogen bonds; see Figure 5.

An example of a finite homodromic chain is O(2)1→O(3)2→O(3)7→O(2)6→W7. In initiates at O(2)1, which acts only as a hydrogen-bond donor, and leads to the cluster of interstitial water molecules.

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Registry No. γ-CD, 17465-86-0.

Supplementary Material Available: Tables II–VIa, listing fractional coordinates and equivalent isotropic temperature factors, anisotropic temperature factors for all atoms, individual bond lengths, bond angles, and selected torsion angles for the γ-CD molecule, and Table X, giving bond lengths and bond angles for the water molecules (20 pages); Table XIII, listing measured and calculated structure factor amplitudes (55 pages). Ordering information is given on any current masthead page.

Studies on the Mechanism and Origin of Stereoselective Opening of Chiral Dioxane Acetals

Scott E. Denmark* and Neil G. Almstead

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801. *Received March 25, 1991*

Abstract: A systematic examination of the mechanism and origin of stereoselection in the reaction of dioxane acetals with allyltrimethylsilane was undertaken. Experimental tests for two limiting mechanisms, synchronous (S_N2-like) and dissociative (S_N1-like) substitution processes, were investigated. The meso 2,4,6-trisubstituted 1,3-dioxane acetals *cis*- and *trans*-**1** provided an interesting opportunity to test the timing of bond breaking and making in the substitution reaction. The modest and C(2)-substituent-dependent selectivity excluded the possibility of a direct S_N2-type attack on a complexed acetal. Further, the enol ethers **3** and **5** and acyclic acetal **7** were studied as precursors of the putative oxocarbenium ion intermediate in the dissociative limit. The weak and inverted selectivity observed with these substrates ruled out the intermediacy of the extended, separated ion in reactions of the cyclic acetals under similar conditions. A unified mechanistic scheme involving three distinct ion pairs is proposed to explain the dependence of allylation selectivity on structural and experimental variables. The three species are analogous to those proposed in the classic Winstein scheme: (1) an intimate ion pair, (2) an external ion pair, and (3) a separated ion. Each of these proposed intermediates has a different stereochemical profile and the ultimate outcome is a composite of those factors that balance the contribution of the different intermediates. The influence of C(2) substituent, acetal configuration, Lewis acid type and stoichiometry, allylsilane stoichiometry, concentration, solvent, and temperature were investigated and integrated in the proposed mechanistic scheme.

Introduction

Due to their stability under basic conditions, acetals are generally employed as the ideal protecting groups for the ketone and aldehyde functions against nucleophiles. Nonetheless, it has been known for some time that acetals can also undergo carbon–carbon bond-forming reactions ostensibly by nucleophilic addition at the carbonyl carbon.[1] Most of the classical examples of these reactions require vigorous conditions and are not generally synthetically useful.[2] However, over the past 15 years the reaction chemistry of acetals has been greatly expanded by the use of Lewis acidic promoters particularly in conjunction with silicon-containing nucleophiles[3] (Scheme I). This reaction evolved in parallel with the related addition of organosilicon nucleophiles to aldehydes in the presence of Lewis acids[4] and has found unique applications

Scheme I

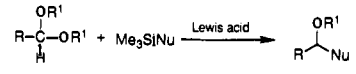

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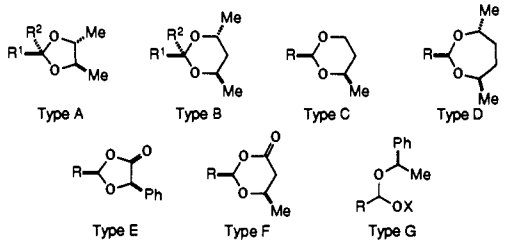
Chart I



in the synthesis of C-glycosides,[5] carbocycles,[6] and heterocycles.[7]

The stereochemical details of the additions to acetals are analogous to those additions to the corresponding aldehydes. The sense of internal diastereoselection[8] with enol silyl ethers[4b] is predominantly syn, independent of the double bond geometry in the nucleophile. However, the situation with allylsilanes is more complex. Aliphatic acetals[9] are likewise syn selective independent of the crotylsilane geometry, but aromatic[9] and allylic[10] acetals (glycals) show a geometry-dependent selectivity.

From a stereochemical perspective, the unique advantage of acetals in addition reactions is the relative asymmetric induction with chiral acetals derived from optically active alcohols.[11] The concept of acetals as chiral templates that temporarily modify the environment and reactivity of carbonyl groups finds its origin in the brilliant work of W. S. Johnson on cationic polyolefin cyclizations.[12] In retrospect, it is remarkable that the first reports, published in 1968[12a] and 1976,[12b] lay dormant until revived in 1983 by Johnson and Bartlett.[13a] Now with organosilicon chemistry and asymmetric induction firmly in the culture of organic synthesis, this paper stimulated the explosive development of chiral acetals as templates for asymmetric synthesis.

As will be documented in the following section, the preparative utility of this technology is considerable. Despite the inherent limitation of destruction of the template, the methods have still been used in the synthesis of complex molecules.[10] The second part of the following section describes the various attempts to explain the high selectivities observed. For the most part these explanations are ad hoc with only a few true mechanistic studies on record. Our interest is in elucidating the origin of stereocontrol in the substitution reactions of acetals and in the relationship between mechanism and stereoselectivity. This paper describes a systematic study of stereoselectivity in a set of substrates designed to address the structural and experimental factors that determine the course of substitution.

Background

Preparative. The diversity of acetal structure and nucleophilic reagent is considerable. The following survey is organized according to acetal structure as indicated in Chart I. The different types of nucleophiles are discussed in each individual class. The chiral acetals derived from optically active 2,3-butanediol (type A, Chart I) were the first employed by Johnson in acetal-initiated alkene cyclizations and then reintroduced by him in conjunction with stereoselective allylsilane additions (76% de).[13a] Independently, Kishi reported the opening of these dioxolane acetals with use of both allylsilane (80% de) and α-silyl ketones (0–88% de).[14] A seminal study by Richter[15] in 1981 set the precedent for asymmetric reduction of ketones via their chiral dioxolane acetals with use of complex aluminum hydrides. Unfortunately, the selectivities were highly variable and modest (3–77% de). Organocopper[16] and -aluminum[17] nucleophiles have also been used to open dioxolane acetals with high selectivity (67–100% de). In both cases, Lewis acids were required to activate the acetal for opening ($BF_3{\cdot}OEt_2$ and $TiCl_4$, respectively). Despite these successes, to a large extent this class has given way to the homologous dioxane acetals (type B), wherein selectivities are comparable and the protocol for final removal of the template is simpler.

The chiral dioxanes (type B) derived from 2,4-pentanediol have been extensively developed by Johnson[13] and H. Yamamoto.[18] Since their original report, the Johnson school has almost exclusively employed this acetal in conjunction with allylsilanes,[13a,f,l] propargylsilanes,[13d,n] silyl acetylenes,[13b,19] enol silyl ethers,[13h,k] ketene silyl acetals,[13i,m] and TMSCN,[13e] as well as organometallic reagents (RLi, RMgX, R_2CuLi) in the presence of Lewis acids.[13f] Selectivities range from 80 to 96% de but are usually between 90 and 95%. For most nucleophiles, $TiCl_4$ is the Lewis acid of choice, but various combinations of $TiCl_4$ and $Ti(O\textit{i}\text{-}Pr)_4$ have proven superior on occasion.[13g]

A powerful and versatile method for the asymmetric reduction of ketones via type B acetals has been developed by H. Yamamoto.[18] Providing that R^1 and R^2 are sufficiently different, highly selective reduction (88–98% de) can be achieved with X_2AlH reagents. The complementary stereoisomers can be obtained with similarly high stereoselectivity by using the $TiCl_4/R_3SiH$ (R_2SiH_2) combination. These methods have also been employed in the selective cleavage of bicyclic acetals.[18c,20] Finally, both organocopper[16] and -titanium[18a] reagents have been found to open type

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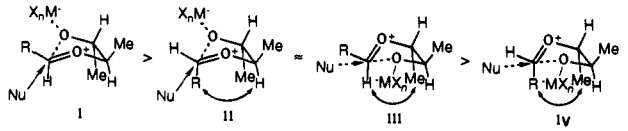
Chart II



B acetals and in the same stereochemical sense as organosilane nucleophiles.

The monosubstituted dioxane acetals (type C) were also introduced by Johnson.[13e] They enjoy the advantage of an inexpensive and readily available diol[21] and yet do not suffer from the formation of isomeric acetals from aldehydes. The highly regioselective and stereoselective opening of these acetals (comparable in magnitude and direction to type B) is also of mechanistic significance (vide infra). It is noteworthy that such high selectivities were only observed for silicon-containing nucleophiles; organocopper reagents[16] reacted less selectively (72% de) than with type B acetals.

The chiral dioxepane acetal (type D) was examined by Normant[16b] in a broad survey of structural types. The selectivity of opening ($R_2CuLi/BF_3{\cdot}OEt_2$) was striking (86% de) but not of preparative significance.

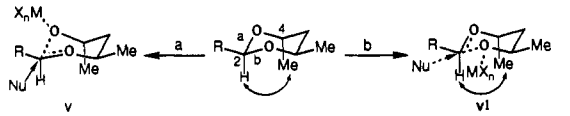
On the basis of both practical considerations and mechanistic reasoning, the more highly oxidized dioxolanones[22] and dioxanones[23,24] (types E and F) were developed. The optically active precursor hydroxy acids are readily available and form the desired heterocycles easily. Furthermore, the expected difference in leaving group ability led to unidirectional opening to form acids. In both cases, the stereoselectivities are nearly independent of the starting isomeric mixture of acetals. The selectivities with silyl nucleophiles were variable but generally higher with type F (26–97% de) than with type E (43–87% de). Moreover, higher order cuprates react very selectively with type F acetals (94–97% de).

Finally, a class of acyclic acetals (type G) has also been employed in asymmetric synthesis. These species are not isolated, but rather generated in situ by the treatment of aldehydes with a titanium complex[25] or a silyl ether[26] of the chiral alcohol, (*S*)-1-phenylethanol. Substitution of the OX group by the allylsilane in situ leads to the homoallyl ether in 78–80% de[25] and 48–99% de.[26] Interestingly, the reactions are most selective with aliphatic aldehydes.

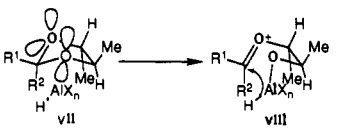
Mechanistic. Given the high selectivities often observed in substitutions of these acetals, it is not surprising to find in most reports an attempt to rationalize the sense and magnitude of the asymmetric induction. The different proposals often cross structural lines and have been applied for several acetal classes. Although one can identify four different rationalizations, each must explain the same basic facts, and thus they all have common features. Most importantly, all of the proposals are in unison that the acetal ring is still basically intact in the transition structure and that the substitution is an invertive type process. They differ, however, in identifying the structure–reactivity features that lead to the selective cleavage of one bond over the other. For the purposes of consistency, we will define all of the acetal stereocenters as *R* to simplify the identification of the cleaving bond and reveal stereochemical similarities.

The first proposal put forward by Johnson[13a] considers the possible ion pairs generated by coordination of a type A acetal with a Lewis acid (Chart II). The origin of the stereoselection is suggested to be reaction via the least sterically congested ion pair (i), leading to cleavage of the *pro-R* oxygen. The implication

Scheme II



Scheme III



Scheme IV

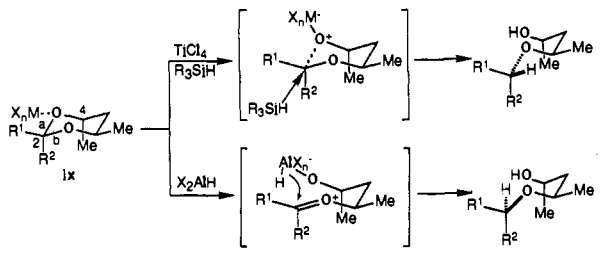
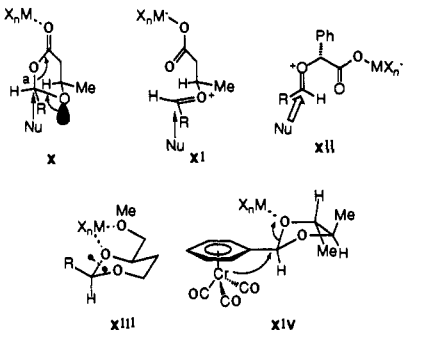


Chart III



is that all of the ion pairs are equally reactive, and the most prevalent leads to the observed products.

The second proposal, also due to Johnson,[13e] was formulated to explain the high selectivities observed in opening type B acetals. This proposal focuses on the selective stabilization of the "S_N2-like" transition state (v), which relieves the 2,4-diaxial interaction in the dioxane ring, leading again to the cleavage of the *pro-R* oxygen (Scheme II).

The essence of this proposal has been incorporated into the third, and most widely accepted rationalization, the preferential complexation of one oxygen and invertive "S_N2-like" substitution or retentive collapse of the oxygen-bound reagent in a separated ion pair. For type A acetals, Richter[15] identified different nonbonding interactions for the diastereomeric complexes and proposed that the oxygen lone pair that is staggered to the acetal methyl groups and eclipses the smaller of the two groups R^1 or R^2 will bear the Lewis acid (vii). From there, internal reduction of the separated ion pair viii leads to the products (Scheme III). While these considerations are reasonable, Richter did not assign the configuration of the products in these reductions, and from the current vantage it is clear that his choice of reactive complex was incorrect.

The two foregoing hypotheses are amalgamated and refined in the proposal put forth by H. Yamamoto[18a] for the preferential complexation/substitution of type B acetals. The preferred complexation of the *pro-R* oxygen in ix (Scheme IV) is based on steric considerations and the complementary lengthening and shortening of bonds a and b, respectively, due to enhancement of the anomeric effect.[27] Lengthening bond a relieves the 2,4-

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Scheme V

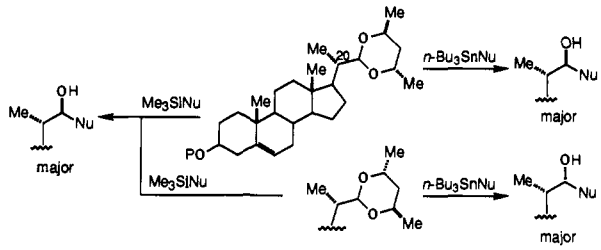
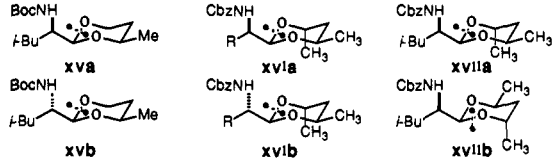


Chart IV



diaxial interaction identified by Johnson. Thus, reaction follows on this complex to cleave the weakened bond either by collapse of the ion pair per Richter (with X_2AlH reagents) or by invertive "S_N2-like" substitution per Johnson (with silane and titanium reagents; Scheme IV). This analysis has also been adopted by Normant[16b] to explain the cleavage of type B acetals with $R_2CuLi/BF_3{\cdot}OEt_2$ reagents.

The final category within this class of mechanisms is the "assisted unidirectional opening" proposal. In the dioxanone class (type F), Seebach[23b] has formulated an S_N2-type substitution of the stereoelectronically polarized bond a in x (Chart III). Since the sense of stereoselection is independent of the starting acetal configuration, the possibility of an open cation xi cannot be excluded. Indeed, the oxocarbenium cation xii was suggested by Kellogg[22] for the type E acetals.

Assisted opening has also been proposed by Corcoran[28] in the highly regioselective cleavage of acetal type H (xiii) bearing a pendant ligating group. Clearly, the simultaneous coordination of the two oxygens by a bicoordinate Lewis acid ($TiCl_4$) gives rise to the observed regioselectivity. The poor relative asymmetric induction is noteworthy.

Finally, the assisted-opening mechanism has been invoked by Davies[17] in the Me_3Al cleavage of type A acetals attached to a chromium arene complex xiv. The overall stereochemical course of substitution is *opposite* to that previously found for this class (and also for type B acetals with Me_3Al[18a]). However, this apparent anomaly can be rectified by invoking a double inversion process, beginning with the activation of the *pro-S* oxygen (based on the proposals described above) and chromium-assisted displacement.[29] Now the usual invertive attack by the nucleophile leads to the observed product.

Restricting discussion to the common types A–C acetals, the preceding rationalizations are based on the synchronous end of the aliphatic substitution spectrum. It is thus remarkable that the few reported mechanistic/stereochemical studies concluded that reactions of type B acetals with silane reagents occurred only after the acetal ring had opened (dissociative). In the first study, Y. Yamamoto[30] examined type B acetals attached to C(20) of a steroid framework (Scheme V) and showed that the stereochemical course of the reaction was dependent on the nucleophilicity of the reagent.[31] With allyl- and alkynyl*silanes*, the configuration at C(20) controlled the course of the addition, regardless of the configuration of the template (Cram's Rule

Scheme VI

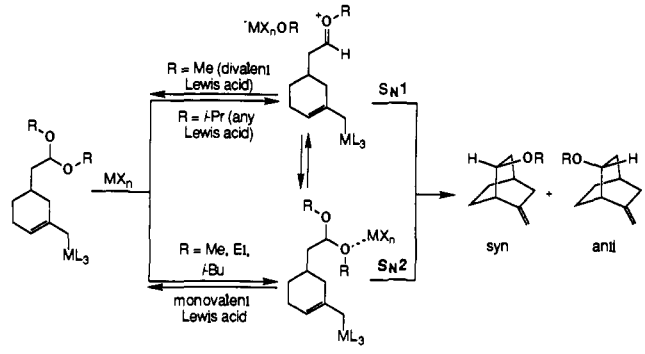


Chart V

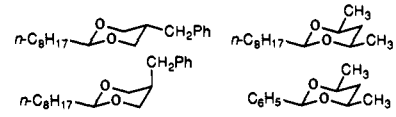
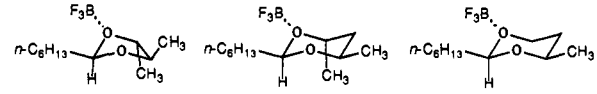


Chart VI



control).[32] In contrast, the more nucleophilic allyltributyl*stannane* reacted in a fashion stereoresponsive to the configuration of the acetal.[33] A similar study with a β-silyloxy acetal led to the conclusion that "chelation control" dominated over template control.[34]

The conclusions from the Y. Yamamoto study are brought into question, however, by the results from the opening of α-substituted chiral acetals. Three different laboratories have independently demonstrated that the amino-bearing stereogenic centers in xva,b, xvia,b, and xviia,b have little influence on the stereochemical course of reaction with either allyltrimethylsilane[13l,35] or cyanotrimethylsilane[36] (Chart IV). In all cases, the product configuration is controlled by the chirality of the template not the α-amino-bearing center. The major products arise from the indicated bond cleavage. This is inconsistent with a dissociative-type mechanism.

In a recently reported study conceptually related to ours described herein, Heathcock, Bartlett, and H. Yamamoto examined the stereochemical course of the opening of meso acetals in the 2,5-disubstituted and 2,4,6-trisubstituted dioxane series (Chart V) to distinguish the limiting S_N1 and S_N2 mechanisms.[37] The stereochemical consequences and analysis of these experiments are discussed below. These investigators reported the completely unselective (1/1) opening of both 2,5-disubstituted acetals and the weakly selective (2.3–4.9/1) opening of the 2,4,6-trisubstituted acetals with the trimethylsilyl enol ether of pinacolone and $TiCl_4$.[38] They concluded that the reactions proceed completely or largely by an S_N1 (oxocarbenium ion) mechanism. However, to rationalize the high selectivity observed with the chiral acetals, the

(28) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101.

(29) (a) Keller, H.; Krieger, S.; Langer, E.; Lehner, H.; Schlögl, K. *Monatsh. Chem.* **1977**, *108*, 113. (b) Davis, R.; Kane-Maguire, L. A. P. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 3, pp 1032–1034.

(30) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

(31) A similar nucleophile-dependent mechanistic divergence has been demonstrated for allylation of thioacetals: Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.

(32) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 5.

(33) This conclusion is supported by the weakly selective reaction of a stannylacetylene with a 1,3-propanediol acetal at C(20) of a steroid: Castedo, L.; Granja, J.; Maestro, M. A.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 4589.

(34) Yamamoto, Y.; Yamada, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1218.

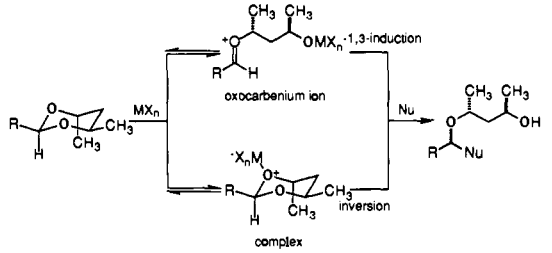
(35) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Lett.* **1987**, 1531.

(36) Herranz, R.; Castro-Pichel, J.; Vinueas, S.; Garcia-Lopez, M. T. *J. Chem. Soc., Chem. Commun.* **1989**, 938.

(37) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. During the course of our studies we became aware of this investigation and we thank Prof. Heathcock for providing a preprint of this paper.

(38) Our own studies with 2,5-disubstituted dioxane acetals using allyltri-*n*-butylstannane and $TiCl_2(Oi\text{-}Pr)_2$ show highly selective (17–19/1) and *complementary* stereochemical outcomes for the cis and the trans series, indicating that rapidly equilibrating ion pairs are not necessarily always involved. Denmark, S. E.; Almstead, N. A. *J. Org. Chem.*, in press.

Scheme VII



proposal was modified to involve oxocarbenium ion pairs that maintain some of the structural features of the intact six-membered rings.

Our own investigations in this area have established a mechanistic divergence between synchronous and dissociative limits in an intramolecular version of the reaction (Scheme VI).[39] By using the syn/anti product ratio as a probe, we have demonstrated that methyl, ethyl, and isobutyl acetals react via a common, synchronous ("S_N2-like") mechanism with monocoordinate Lewis acids (TMSOTf, $BF_3{\cdot}OEt_2$) but via a dissociative ("S_N1-like") mechanism with bicoordinate Lewis acids ($TiCl_4$, $SnCl_4$). Moreover, the bulky diisopropyl acetals react via the dissociative mechanism with all Lewis acids employed. The stereochemical course was independent of the ML_3 group (either trimethylsilyl or tributylstannyl). The recent studies by Heathcock et al.[37] and Otera et al.[31] provide support for the concept of mechanistic divergence and the dependence on acetal structure and the nucleophilicity of the allylating reagent.

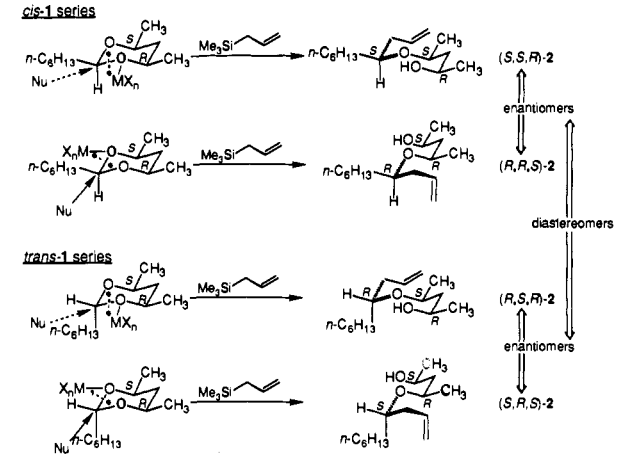
Further, in an extensive study on the structure of Lewis acid–acetal complexes, we have unambiguously established that complexation of types A, B, and C acetals with BF_3(g) is highly biased.[40] The structures of the unique complexes are shown in Chart VI, and indeed correspond to the proposed reactive complexes leading to the observed, ring-cleaved products.

Problem Formulation. The basic question that can be distilled from the foregoing analysis concerns the timing of bond breaking and bond making in the reaction of chiral acetals and how this temporal feature impacts the stereoselectivity of the process.[41] That such a relationship may exist has already been shown in our preliminary studies (Scheme VI). Two limiting scenarios can be constructed and may be formulated for type B acetals, shown in Scheme VII: (1) the reaction is synchronous, involving an invertive ("S_N2-like") substitution and (2) the reaction is dissociative, involving the formation of separated ion pairs (oxocarbenium ions) followed by a rapid attack by the nucleophile ("S_N1-like"). The origin of stereoselection in the former case is based on the relative population/reactivity of the diastereomeric Lewis acid complexes (cf. Chart II and Scheme II). The origin of stereoselection in the second case is based on the extent of 1,3-asymmetric induction from the chiral ligand on the oxocarbenium oxygen (cf. structures xi and xii, Chart III). Of course, the possibility that both mechanisms (or a hybrid of both) are operative is a very real one. Nonetheless, it is still essential to know the direction and magnitude of asymmetric induction in these two limiting cases.

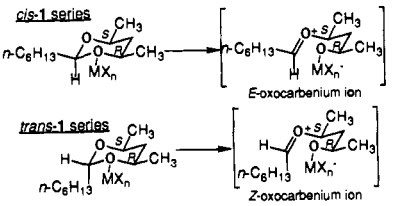
Model Design and Analysis. A. Substitution of a Meso Acetal. To address the issue of stereoselection based on differential complexation of diastereotopic oxygens in a chiral acetal, we recognized the unique opportunities afforded by the opening to an achiral or meso acetal. The concepts outlined here are identical with those reported recently by Heathcock et al.[37] for 2,5-disubstituted and 2,4,6-trisubstituted dioxane acetals. While synthetically uninteresting, this class offers the possibility to test for the importance of differential oxygen activation in the chiral series. The oxygen atoms in the meso acetal *cis*-**1** are enantiotopic, and thus the Lewis acid complexes derived therefrom are enantiomeric

(39) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.
(40) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.
(41) For a discussion of this problem in the context of acetal hydrolysis, see ref 1c.

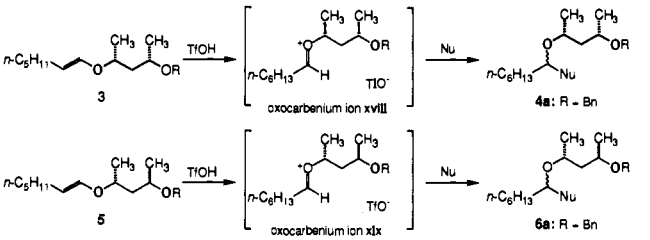
Scheme VIII



Scheme IX



Scheme X

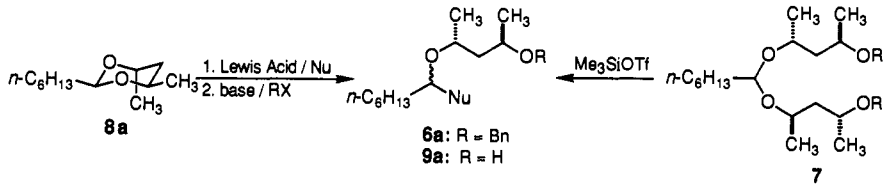


(Scheme VIII). Further, it follows that the products of opening *cis*-**1** with an achiral nucleophile are also enantiomeric. This is clearly illustrated in Scheme VIII. Thus, only a single, racemic diastereomer of the allylated product **2** can result if the reaction occurs by a synchronous pathway (*cis*-**1** → (*S**,*S**,*R**)-**2**)). A similar analysis holds for the diastereomeric acetal *trans*-**1**. As shown in Scheme VIII, this isomer also can lead to only a single racemic diastereomer ((*R**,*S**,*R**)-**2**), which is isomeric with that obtained from *cis*-**1**. *Thus, if the opening of acetals is a synchronous process (with inversion), then the substitution of cis-1 and trans-1 should be stereospecific, giving complementary products.* Any result less than stereospecific implicates an alternative, asynchronous pathway or acetal isomerization.

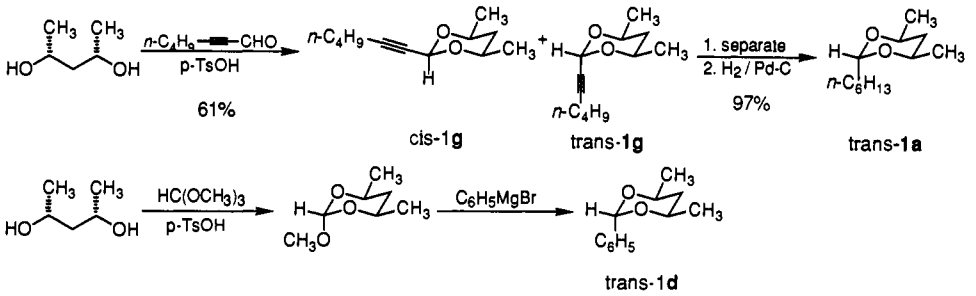
The stereochemical consequences of the reaction of **1** by a dissociative pathway should also be considered. Ideally, this pathway could be established by reaction of the isomeric substrates that, under the dissociative limit, ionize to a common oxocarbenium ion and thus afford a common stereochemical outcome. This is an advantage of the Heathcock model[37] wherein cis and trans 2,5-disubstituted dioxanes prefer the equatorial placement of the C(2) substituent in both diastereomers and form the same oxocarbenium ion in the S_N1 limit. Unfortunately, *cis*-**1** and *trans*-**1** ionize to isomeric oxocarbenium ions, and thus a common stereochemical outcome should not be expected (Scheme IX). Therefore, in principle this model cannot unambiguously distinguish these two pathways.

B. Protonation of a Model Enol Ether. Under the circumstances where the reactions of *cis*-**1** and *trans*-**1** are not stereospecific or lead to similar product mixtures, it is essential to establish the intrinsic 1,3-induction selectivity in the oxocarbenium limit (Scheme VII). We have previously addressed a similar

Scheme XI



Scheme XII



problem in the reaction of simple acyclic acetals, generating the putative oxocarbenium ion by C-protonation of an enol ether.[39] This strategy as it applies to the cyclic acetals is outlined in Scheme X. Clearly it is not possible to precisely model the oxocarbenium ion generated by the opening of the cyclic acetal because of the pendant alcohol. If R = H in the enol ether **3**, this will immediately enter the same manifold accessed by the cyclic precursor, and the stereochemical outcome will be identical. If, however, it cannot close (R ≠ H), then the stereoselectivity observed in the capture may be taken as representative of the intrinsic 1,3-induction in the separated ion. As seen in Scheme X, this cation can be accessed by protonation of a monoprotected enol ether. While this approach worked well for the intramolecular capture with an allylsilane, it was by no means certain that this would succeed in a bimolecular mode. Of conceivable pitfalls, protiodesilylation, enol ether self-condensation, and ether group cleavage were the most worrisome. Two potential problems we did address were the generation of isomeric oxocarbenium ions from different enol ether geometries ((*E*)- and (*Z*)-**3**) and from meso and chiral diol-derived precursors (**3** and **5**). Finally, it was of interest to compare the stereochemical outcome from the acyclic acetal **7** with the chiral cyclic acetal **8a** and the enol ether **5** (Scheme XI). We chose to examine the chiral acetals and their precursors since we ultimately want to make comparisons to that series (i.e. **8** not **1**).

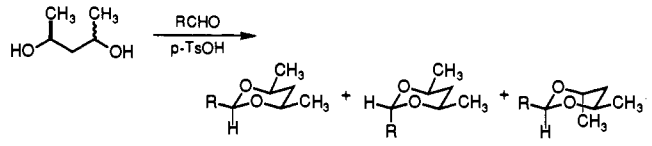
Results

Preparation of Substrates. A. Cyclic Acetals (1 and 8). The meso acetals *cis*-**1a**, *cis*-**1b**, *cis*-**1d**, *cis*-**1e**, *cis*-**1f**, *cis*-**1g**, *trans*-**1g**, and the racemic acetals **8a** and **8d** were obtained by standard acetalization (benzene, *p*-TsOH, Dean–Stark trap) of the corresponding aldehydes with the *meso*-/*d*,*l*-2,4-pentanediol mixture. The diastereomers could be separated easily by column chromatography. In the case of pivalaldehyde (for *cis*-**1c**), the reaction was performed at room temperature with 4-Å molecular sieves as the dehydrating agent and (2*R*,4*S*)-2,4-pentanediol. For the acetals **1a–f**, the cis isomer was formed exclusively. This was expected on the basis of the very large *A* value for substituents at C(2) in 1,3-dioxanes.[42] A scalemic sample of (+)-**8a** was prepared by standard acetalization with (2*R*,4*R*)-2,4-pentanediol.

Isomerically pure samples of the meso and chiral isomers of 2,4-pentanediol were obtained from the commercially available *d*,*l*/meso mixture. Separation of the diols was accomplished by formation of the benzaldehyde acetals *cis*-**1d** and **8d** followed by silica gel chromatography. The two diastereomers were readily identified by the number of resonances in the ^{13}C NMR spectra. The pure samples of the diol were generated by hydrogenolysis of *cis*-**1d** and **8d** with Pd/C.

(42) Eliel, E. L.; Knoeber, M. C., Sr. *J. Am. Chem. Soc.* **1968**, *90*, 3444.

Table I. Preparation of Meso (**1**) and Chiral (**8**) Acetals



entry	R	acetal	yield, %	cis/trans	acetal	yield, %
1	*n*-C_6H_{13}	**1a**	48	cis only	(±)-**8a**	48
2	cyclohexyl	**1b**	51	cis only	(±)-**8b**	46
3[a]	*t*-C_4H_9	**1c**	64	cis only		
4	C_6H_5	**1d**	47	cis only	(±)-**8d**	44
5	4-$CF_3C_6H_4$	**1e**	59	cis only	(±)-**8e**	34
6	4-$NO_2C_6H_4$	**1f**	50	cis only	(±)-**8f**	42
7[a]	*n*-$C_4H_9C{\equiv}C$	**1g**	61	1.7/1		
8[b]	*n*-C_6H_{13}				(+)-**8a**	92

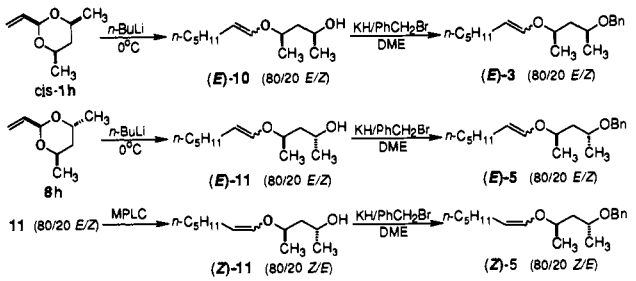
[a] Pure (2*R*,4*S*)-2,4-pentanediol was used. [b] Pure (2*R*,4*R*)-2,4-pentanediol was used.

Table II. Selected Spectroscopic Data for **1** and **8**

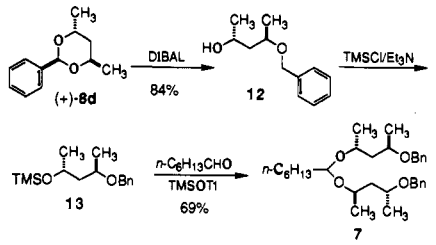
		^1H NMR, ppm		^{13}C NMR, ppm	
entry	acetal	δ HC(2)	δ H_3C(7), H_3C(8)	δ C(2)	δ C(7), C(8)
1	*cis*-**1a**	4.50	1.21	101.51	21.38
2	*trans*-**1a**	5.05	1.18	97.54	21.90
3	*cis*-**1b**	4.21	1.20	104.65	21.60
4	*cis*-**1c**	4.07	1.18	106.80	21.66
5	*cis*-**1d**	5.53	1.31	100.01	21.46
6	*trans*-**1d**	6.19	1.25	96.80	21.65
7	*cis*-**1e**	5.58	1.32	99.52	21.30
8	*cis*-**1f**	5.58	1.31	99.10	21.49
9	*cis*-**1g**	5.24	1.26	90.82	21.07
10	*trans*-**1g**	5.70	1.18	88.29	21.42
11	(±)-**8a**	4.38	1.35, 1.20	94.18	21.77, 17.08

As discussed previously, we also required access to the corresponding trans isomers as well. Two different methods were employed to prepare the *n*-hexyl (*trans*-**1a**) and phenyl (*trans*-**1d**) congeners. The hexyl series was prepared by the ketalization of 2-heptynal to afford a 1.7/1 cis/trans mixture of acetals **1g** (entry 7 Table I). Even in a 1,3-dioxane the acetylene is a sterically insignificant group. The mixture of acetals could be separated by silica gel chromatography, and the trans isomer (*trans*-**1g**) was hydrogenated (Pd/C) to *trans*-**1a** without epimerization (Scheme XI). Following the procedure of Eliel,[42] *trans*-2-methoxy-4,6-dimethyl-1,3-dioxane (prepared from trimethyl orthoformate) was treated with phenylmagnesium bromide to produce *trans*-**1d** as a 92/8 mixture (Scheme XII). Recrystallization afforded an enriched 95/5 mixture. Selected spectroscopic data for all of the

Scheme XIII



Scheme XIV



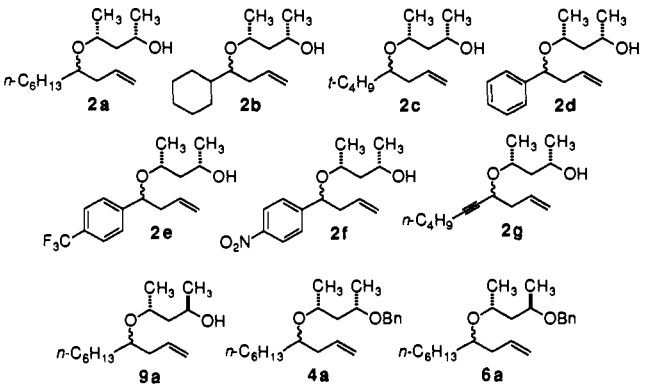
acetals are collected in Table II. The cis and trans isomers are easily distinguished by their chemical shifts in either the ^1H NMR or ^{13}C NMR spectra. In the trans series, HC(2) resonates at a lower field and C(2) at a higher field as compared to the cis series. The chiral acetal **8a** is asymmetric, and thus all carbons are distinct.

B. Enol Ethers (3 and 5). The 2-vinyl-1,3-dioxane *cis*-**1h** was prepared by the method of Hosokawa[43] from acrolein and the *meso*-/*d,l*-2,4-pentanediol mixture. The acetal was treated with *n*-butyllithium to afford a mixture of hydroxy enol ethers **10** in 88% yield by an S_N2' process[44] (Scheme XIII). Capillary GC analysis of the mixture revealed a 4/1 ratio of isomers, the major component of which was assigned to be the *E* isomer on the basis of the larger vicinal J_{HH} of 12.2 Hz compared to 6.3 Hz for the minor component. The benzyl ether **3** was obtained from **10** in 97% yield by treatment with KH and benzyl bromide. The enol ether **3** was also a 4/1 *E*/*Z* mixture of isomers. This mixture was used in the addition reactions described below. The isomeric enol ether **5** was prepared analogously from the acetal **8h** derived from *d,l*-2,4-pentanediol (Scheme XIII). In this case as well, the enol ether product was formed as a 4/1 *E*/*Z* mixture of isomers. A *Z*-enriched mixture of enol ethers (4/1 *Z*/*E*) could be obtained by MPLC separation of the hydroxy enol ethers **11** followed by benzylation.

C. Acyclic Acetal (7). To access the chiral, acyclic acetal **7** we required the monobenzyl ether of (2*R*,4*R*)-2,4-pentanediol **12**. We employed the optically active ether to simplify the preparation of a single diastereomer. Reduction of the optically active acetal (+)-**8d** (derived from (2*R*,4*R*)-2,4-pentanediol) with DIBAL led to the formation of the alcohol **12** in 84% yield.[18a] The alcohol was treated with TMSCl/Et_3N to afford the silyl ether **13** quantitatively. Acetalization of heptanal with **13** according to the method of Noyori[45] using a catalytic amount of TMSOTf gave the desired acetal **3** in 69% yield (Scheme XIV). If the racemic form had been used, the acetalization could give rise to three diastereomers, two meso and one chiral. This acetal was found to have interesting ^1H and ^{13}C NMR spectra. Since **7** is asymmetric, all of the groups are diastereotopic. Several of the carbon resonances close to the oxygens were almost 1 ppm apart; all of the other resonances were twinned.

D. Reference Compounds. Each of the acetals *cis*-**1a–g** and (±)-**8a** was allowed to react with allyltrimethylsilane in the presence of titanium tetrachloride (or $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ for *cis*-**1d**) to give the homoallylic ethers **2a–g** and **9a** (Chart VII) with yields and diastereoselectivities as discussed below. Except for **2a**, all of the diastereomeric mixtures could be resolved, and the pure diastereomers could be characterized. However, the mixture was used for the determination of gas chromatographic response factors (vs cyclododecane). Authentic samples of **4a** and **6a**, the products of allylation of the enol ethers **3** and **5**, were prepared simply by benzylation (KH, BnBr) of the diastereomeric mixture of alcohols **2a** and **9a**.

Chart VII



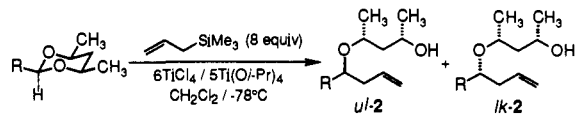
The assignment of configuration for the diastereomers was made by chemical correlation in the *n*-hexyl series as described below. For simplicity, the stereochemical families are defined by the Seebach–Prelog[46] recommendations by consideration of the two stereocenters flanking the ether oxygen. Thus, the major diastereomer from either the meso or chiral acetals is always the *ul* isomer, except in the *n*-hexyl series because of a Cahn–Ingold–Prelog (C–I–P) priority change.

Reactions of Cyclic Acetals. A. C(2) Substituent Dependence. The isomerically pure acetals *cis*-**1a–g** were allowed to react with allyltrimethylsilane under a standard set of optimized conditions. Following the recommendations of Johnson,[13g] the standard protocol involved the use of 8 equiv of allyltrimethylsilane in dichloromethane solution (initially 0.1 M in acetal) at −78 °C. The preferred Lewis acid reagent was a premixed blend ("Ti-blend") of $TiCl_4$ (6 equiv/acetal) and $Ti(O\textit{i}\text{-}Pr)_4$ (5 equiv/acetal). All of the allylations were performed at least in duplicate with conversions, product ratios, and yields determined by capillary GC integration with an internal standard (cyclododecane).

The results of these substitutions are collected in Table III. Most of the reactions proceeded to stereochemically significant conversion and in good yield. Only the *tert*-butyl acetal *cis*-**1c** (entry 3) resisted opening even after a prolonged reaction time. The phenyl acetal *cis*-**1d** (entry 4) gave considerable amounts of a secondary product, 1-chloro-1-phenyl-3-butene,[47] under the standard conditions. This product was not observed at low (but stereochemically significant) conversions. Thus, for this substrate, we employed less "Ti-blend" and short addition and reaction times (10 min). No products other than the expected homoallylic alcohols **2** were detected by GC analysis. *It was immediately apparent that the reactions were not stereospecific and, indeed, exhibited a strong dependence on the nature of the C(2) substituent.* In the aliphatic cases, *cis*-**1a** bearing an *n*-hexyl substituent was the most stereoselective (entry 1), while *cis*-**1b** bearing a cyclohexyl substituent was less selective. The aromatic substrates were less selective still (entries 4–6) but displayed an interesting, albeit weak, dependence on the para substituent. The poor selectivity observed for *cis*-**1d** bearing a phenyl group was improved in *cis*-**1e** and *cis*-**1f** bearing electron-withdrawing groups in the para position although the reactions were also considerably slower. A comparison with aromatic substrates bearing electron-donating groups in the para position (CH_3, OCH_3) was thwarted by hy-

(43) Hosokawa, T.; Yagi, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3380.
(44) Bailey, W. F.; Zartun, D. L. *J. Chem. Soc., Chem. Commun.* **1984**, 34.
(45) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(46) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
(47) This product was identified in reaction mixtures by GC–MS.

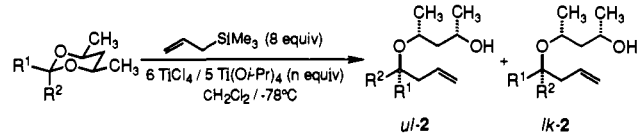
Table III. Allylation of Meso Acetals *cis*-**1a**–*cis*-**1g** (Ti-Blend)[a]



entry	acetal	R	time, h[b]	recovery, %[c]	yield, %[c]	ds, *ul*/*lk*[c]	$\Delta\Delta G^{\ddagger}$[d]
1	*cis*-**1a**	*n*-C_6H_{13}	1	0	100	11.1/1[e]	0.93
2	*cis*-**1b**	cyclohexyl	1	0	98	6.2/1	0.71
3	*cis*-**1c**	*t*-C_4H_9	8	70	0		
4	*cis*-**1d**	C_6H_5	*f*	63	30	2.8/1	0.40
5	*cis*-**1e**	4-$CF_3C_6H_4$	6	50	45	3.8/1	0.52
6	*cis*-**1f**	4-$NO_2C_6H_4$	8	30	70	3.4/1	0.47
7	*cis*-**1g**	*n*-$C_4H_9C{\equiv}C$	0.5	0	100	2.5/1	0.36

[a] All reactions done at 0.1 M. Lewis acid added over 2 h. [b] Reaction time after addition of Lewis acid. [c] Based on response factors versus cyclododecane. [d] At 195 K (kcal/mol). [e] *lk*/*ul* ratio (C–I–P priority change). [f] 5.5 equiv of the "Ti-blend" was used: 10-min addition time and 10-min reaction time.

Table IV. Allylation of Meso Acetals: Isomerization Control Experiments[a]



entry	acetal	R^1	R^2	"Ti", equiv	time, h[b]	yield, %	ds, *ul*/*lk*	recovery	trans/cis
1	*cis*-**1a**	*n*-C_6H_{13}	H	11	3.0	100	11.1/1[c]	0	
2	*trans*-**1a**	H	*n*-C_6H_{13}	11	3.0	76	11.2/1[c]	20	0/1
3	*trans*-**1a**	H	*n*-C_6H_{13}	5.5	0.5	37	11.1/1[c]	51	0/1
4	*cis*-**1d**	C_6H_5	H	5.5	0.25	30	2.8/1	63	
5	*trans*-**1d**	H	C_6H_5	3.6	0.5	17	2.3/1	70	1/2.3
6	*trans*-**1d**	H	C_6H_5	3.6	1.0	16	2.4/1	83	1/13.3
7	*cis*-**1g**	*n*-$C_4H_9C{\equiv}C$	H	11	2.5	100	2.5/1	0	
8	*trans*-**1g**	H	*n*-$C_4H_9C{\equiv}C$	11	2.5	100	1.0/1	0	
9	*trans*-**1g**	H	*n*-$C_4H_9C{\equiv}C$	5.5	0.16	24	1.1/1	64	40/1

[a] All yields and ratios based on response factors versus cyclododecane. [b] Reaction time after addition of Lewis acid. [c] *lk*/*ul* ratio (C–I–P priority change).

perreactivity, affording double allylated products. Since it was on hand, we also examined the alkynyl substrate *cis*-**1g** and found it to be equally unselective as the phenyl substrate *cis*-**1d** and remarkably reactive as well.

B. C(2) Configuration Dependence. The nonstereospecific substitution of the *cis*-**1** acetals does not necessarily exclude the S_N2-type mechanism as outlined in Scheme VI. Conceivably, the substitution may occur with S_N2-like inversion on an equilibrating mixture of cis and trans isomers or isomeric ion pairs. This could be tested by subjecting the isomeric *trans*-**1** acetals to the substitution conditions and evaluating the stereochemical outcome. The three available trans isomers, representing three different C(2) substituent types, *trans*-**1a**, *trans*-**1d**, and *trans*-**1g**, were examined under two sets of conditions (Table IV).

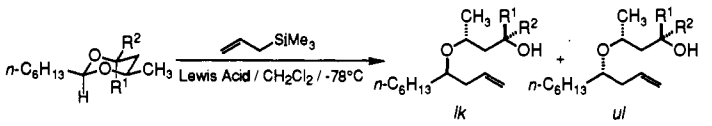
The first series of experiments were done under conditions similar to those employed for the *cis*-**1** acetals (11 equiv "Ti-blend", 3 h). The comparison of the two acetal isomers for all three substrates (juxtaposed in Table IV) shows that the isomeric composition of the product is largely independent of the configuration of the educt for the *n*-butyl and phenyl series (**1a** and **1d** compare entries 1, 2, 4, and 5) but is influential in the hexynyl series (**1g** entries 7 and 8). Interestingly, the reaction of *trans*-**1a** did not go to completion, and the recovered educt had completely isomerized to the cis isomer (entry 2). This was also true in the reaction of *trans*-**1d** wherein the recovered educt was largely isomerized as well (entry 5). No *trans*-**1g** was recovered from the allylation experiment under standard conditions.

A second series of experiments designed to probe the early stages of the reaction employed only 5.5 equiv of the "Ti-blend" and were run for shorter reaction times except in the case of *trans*-**1d**, which produced only a modest conversion with this limited amount of Lewis acid anyway. Under these conditions, the aliphatic substrate *trans*-**1a** (entry 3) was converted to a small amount of product, **2a**, *favoring the same diastereomer* as from *cis*-**1a** (*ul*-**2a**) but with identical selectivity. Again the recovered acetal had completely isomerized to the cis acetal. The other substrate, *trans*-**1d**, also afforded small amounts of the corresponding substitution product, **2d**, with similar isomeric composition as from *cis*-**1d**. In this case as well, the recovered acetal had suffered extensive isomerization. Therefore, the similar stereochemical outcomes for the trans and cis isomers in the **1a** and **1d** series is ambiguous; we cannot rule out prior isomerization of the trans to the cis acetals. Independent control experiments with *trans*-**1a** and *trans*-**1d** (no allyltrimethylsilane) confirmed that they suffered complete isomerization to the corresponding cis isomers with 30 min at −78 °C in the presence of 3.6 equiv of the "Ti-blend".

Short-term reaction of the hexynyl acetal, *trans*-**1g**, using a deficiency of Lewis acid proceeded to only 24% conversion, again affording allylation products unselectively (compare entries 7 and 8). Remarkably, the *unreacted acetal was recovered largely unchanged.* Thus, it is reasonable to assert that the change in selectivity in this case does reflect the stereochemical profile of reactions under kinetic control. An independent control experiment established that *trans*-**1g** underwent only 10% isomerization after 30 min at −78 °C in the presence of 3.6 equiv of the "Ti-blend".

C. Acetal Configuration Dependence. While the allylation of the meso acetal *cis*-**1a** was rather selective (11.1/1), it was considerably less so than the allylation of the chiral acetal (4*R*,6*R*)-2-octyl-4,6-dimethyl-1,3-dioxane (49/1) as reported by Johnson.[13f] We checked this disparity by performing allylations on the analogous *n*-hexyl acetals (±)-**8a** and (+)-**8a**. The results presented in Table V verify the large difference in selectivity between meso and chiral acetals, but also show that the racemic and scalemic substrates behave identically. Moreover, the difference between the two types of acetals nearly disappeared when $TiCl_4$ was used as the Lewis acid. Interestingly, with BF_3(g), both

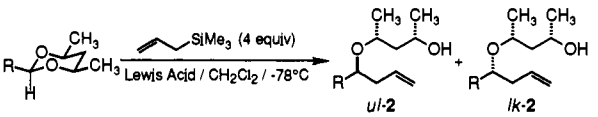
Table V. Comparison of Meso, Racemic, and Scalemic *n*-Hexyl Acetals[a]



acetal	R^1	R^2	Lewis acid	equiv	time, h[c]	yield, %	ds, *lk*/*ul*	$\Delta\Delta G^{\ddagger}$[d]
cis-**1a**	H	CH_3	"Ti-blend"[b]	11	3.0	100	11.1/1	0.93
(±)-**8a**	CH_3	H	"Ti-blend"[b]	11	3.0	100	57.7/1	1.58
(+)-**8a**	CH_3	H	"Ti-blend"[b]	11	3.0	100	59.8/1	1.59
cis-**1a**	H	CH_3	$TiCl_4$	1.0	0.5	92	5.1/1	0.63
(±)-**8a**	CH_3	H	$TiCl_4$	1.0	0.5	100	6.7/1	0.74
(+)-**8a**	CH_3	H	$TiCl_4$	1.0	0.5	99	6.1/1	0.70
cis-**1a**	H	CH_3	BF_3 (g)	1.2	0.5	84	1/1.9	−0.25
(±)-**8a**	CH_3	H	BF_3 (g)	1.2	0.5	78	2.5/1	0.36

[a] All yields and ratios based on response factors versus cyclododecane. [b] 6/5, $TiCl_4$/Ti(O*i*-Pr)$_4$. [c] Total reaction time. [d] At 195 K (kcal/mol).

Table VI. Allylation of Meso Acetals: Lewis Acid Dependence[a]



entry	acetal	R	Lewis acid (equiv)	time, min	yield, %[b]	ds, *ul*/*lk*[b]	$\Delta\Delta G^{\ddagger}$[d]
1	*cis*-**1a**	*n*-C_6H_{13}	$TiCl_4$ (1.0)	30	92	5.1/1[c]	0.63
2	*cis*-**1b**	cyclohexyl	$TiCl_4$ (1.0)	30	96	4.8/1	0.61
3	*cis*-**1c**	*t*-C_4H_9	$TiCl_4$ (1.0)	30	65	4.2/1	0.56
4	*cis*-**1e**	4-$CF_3C_6H_4$	$TiCl_4$ (1.0)	15	96	4.6/1	0.59
5	*cis*-**1f**	4-$NO_2C_6H_4$	$TiCl_4$ (1.0)	60	90	4.5/1	0.58
6	*cis*-**1g**	*n*-$C_4H_9C{\equiv}C$	$TiCl_4$ (1.0)	30	93	1.9/1	0.25
7	*cis*-**1a**	*n*-C_6H_{13}	BF_3 (g) (1.2)	30	84	1/1.9[c]	−0.25
8	*cis*-**1b**	cyclohexyl	BF_3 (g) (1.2)	30	67	1/2.8	−0.40
9	*cis*-**1e**	4-$CF_3C_6H_4$	BF_3 (g) (1.2)	60	72	1/1.7	−0.21

[a] All reactions run at 0.1 M. [b] Based on response factors versus cyclododecane. [c] *lk*/*ul* ratio (C–I–P priority change). [d] At 195 K (kcal/mol).

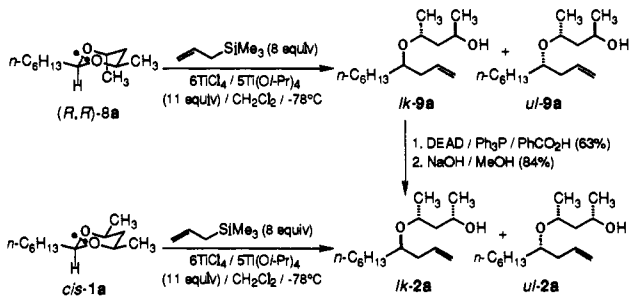
cis-**1a** and (±)-**8a** reacted even less selectively (vide infra).

To enable any comparison of the results from the meso series **1a** and the chiral series **8a** it was necessary to establish the confluence of their reaction pathways. The overall stereochemical course of substitution in the chiral series has been firmly established (cf. Scheme II) to involve cleavage of the *pro-R* oxygen (flanked by an axial methyl group) in the (*R*,*R*)-acetals. Thus, the relationship between the stereogenic centers flanking the ether oxygen in the product **9a** (*R*,*R* or *lk*) should be the same as that in **2a** (*R**,*R** or *lk*) if the stereochemical course of addition is the same (Scheme XV).

Preparative reaction of the chiral acetal (*R*,*R*)-(+)-**8a** with allyltrimethylsilane and the titanium blend proceeded cleanly (98% yield) and with high selectivity for the *lk* diastereomer of **9a**. Treatment of *lk*-**9a** with DEAD/Ph_3P/$PhCO_2H$ (Mitsunobu conditions)[48] produced a benzoate **14** (63% yield), which was saponified (NaOH/CH_3OH) to afford alcohol *lk*-**2a** (84% yield) identical in all respects with the major diastereomer formed from reaction of *cis*-**1a** with allyltrimethylsilane. Thus, the identity of the major reaction pathways for **8a** and *cis*-**1a** was established. The significantly higher selectivity associated with the chiral acetal is intriguing and will be discussed in the following sections.

D. Lewis Acid Dependence. The complete set of *cis*-**1** acetals was subjected to reaction with allyltrimethylsilane (4 equiv) with pure $TiCl_4$ (1.0 equiv) as the Lewis acid (Table VI). The selectivities of the reactions were strikingly similar and did not display the range observed for the weaker Lewis acid. Only the acetylenic acetal *cis*-**1g** reacted with different selectivity that was considerably reduced. Remarkably, the *n*-hexyl acetal reacted less selectively, while the aromatic acetals reacted somewhat more selectively than with the "Ti-blend". Unfortunately, *cis*-**1d** failed to react cleanly, so a clear trend for the para-substituent effect could not be established. A partial set of data was also collected

Scheme XV



for the powerful Lewis acid, BF_3(g) (entries 7–9). Although the selectivities were poor, the results were remarkable in the weak preference for the previously less-favored diastereomer. Again, the reactions were largely insensitive to the C(2) substituent as was the case with $TiCl_4$.

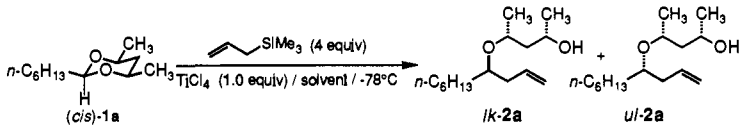
E. Solvent, Temperature Stoichiometry, and Concentration Effects. E.1. Meso Series (*cis*-1a). To further probe the effects of experimental variables on the stereochemical course of the reaction of *n*-hexyl acetals, *cis*-**1a** was treated with allyltrimethylsilane (4 equiv) and $TiCl_4$ (1.0 equiv) in various solvents (0.1 M in acetal) at several different temperatures (Table VII). To aid the comparison, the E_T^N parameters of solvent polarity, defined by Kosower[49] and refined by Reichard,[50] are included. Although dichloromethane is the solvent of choice in the literature for chiral acetals, (vide infra) we found that the less polar solvent chloroform gave higher selectivities (compare entries 1, 2, and 4). Continuing on in the series to carbon tetrachloride gave

(48) Mitsunobu, O. *Synthesis* **1981**, 1.

(49) Kosower, E. M. *An Introduction to Physical Organic Chemistry*; Wiley: New York, 1968; p 293 ff.

(50) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; pp 363–376.

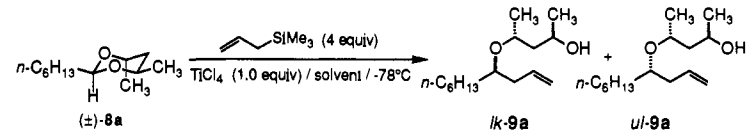
Table VII. Allylation of *cis*-**1a**: Solvent and Temperature Effects[a]



entry	solvent	E_T^N[b]	temp, °C	time, min	yield, %[c]	ds,[c] *ul*/*lk*	$\Delta\Delta G^{\ddagger}$[d]
1	CH_2Cl_2	0.309	−78	30	98	5.1/1	0.63
2	CH_2Cl_2	0.309	−61	30	91	4.5/1	0.63
3	CH_2Cl_2	0.309	−23	5	95	3.7/1	0.65
4	$CHCl_3$	0.259	−61	30	97	6.6/1	0.80
5	$CHCl_3$	0.259	−23	5	95	4.6/1	0.76
6	CCl_4	0.052	−23	5	98	1.7/1	0.26
7	toluene	0.099	−78	30	100	2.1/1	0.29
8	nitroethane	0.398	−78	60	70	1.3/1	0.10
9	hexane	0.009	−78	60	60	2.1/1	0.29

[a] All reactions run at 0.1 M. [b] At 25 °C. [c] Based on response factors versus cyclododecane. [d] At reaction temperature (kcal/mol).

Table VIII. Allylation of (±)-**8a**: Solvent and Temperature Effects[a]



entry	solvent	E_T^N[b]	temp, °C	time, min	yield, %[c]	ds,[c] *lk*/*ul*	$\Delta\Delta G^{\ddagger}$[d]
1	CH_2Cl_2	0.309	−78	30	100	6.7/1	0.74
2	CH_2Cl_2	0.309	−61	30	96	5.5/1	0.72
3	CH_2Cl_2	0.309	−23	5	100	5.7/1	0.87
4	$CHCl_3$	0.259	−61	30	98	4.1/1	0.60
5	$CHCl_3$	0.259	−23	5	85	6.1/1	0.90
6	CCl_4	0.052	−23	5	95	1.7/1	0.26
7	toluene	0.099	−78	30	100	2.1/1	0.29
8	nitroethane	0.398	−78	60	90	1.6/1	0.18
9	hexane	0.009	−78	60	70	1.8/1	0.23

[a] All reactions run at 0.1 M. [b] At 25 °C. [c] Based on response factors versus cyclododecane. [d] At reaction temperature (kcal/mol).

disappointing results. That the low selectivity observed with CCl_4 was not due to the higher reaction temperature was demonstrated by comparison of these solvents at different temperatures. For both dichloromethane and chloroform, the temperature effect was in the expected direction but was small in magnitude as the free energy difference ($\Delta\Delta G^{\ddagger}$) remained constant (entries 1–3 and 4–5). At −23 °C the order of decreasing selectivity was still $CHCl_3 > CH_2Cl_2 > CCl_4$. A wider range of solvent polarity was surveyed within the limits of compatibility with $TiCl_4$ (e.g., no reaction was observed in THF or i-Pr_2O). The results were most surprising (entries 7–9) in two regards: (1) the dramatic drop in selectivity compared to chlorocarbons and (2) the insensitivity of reaction (un)selectivity to solvent polarity ranging from hexane to nitroethane! Possible explanations are discussed in the following sections.

E.2. Chiral Acetal ((±)-8a). The intriguing effects of solvent on the selectivity in reactions of *cis*-**1a** suggested a similar examination of the preparatively more interesting chiral acetal, (±)-**8a**. The results of this study, employing the same set of solvents and temperatures (Table VIII), were again surprising. In contrast to *cis*-**1a**, the reactions of (±)-**8a** were most selective in dichloromethane at −78 °C. However, a comparison of entries 3, 5, and 6 shows the same order or selectivity as for *cis*-**1a**, $CHCl_3 > CH_2Cl_2 > CCl_4$. This outcome is due to an interesting inverse temperature effect on selectivity observed for both dichloromethane and chloroform, with the largest free energy differences attending reactions at −23 °C. In the other solvents, however, (±)-**8a** behaved similarly to *cis*-**1a** in the uniformly lower selectivities and insensitivity to solvent polarity (entries 7–9).

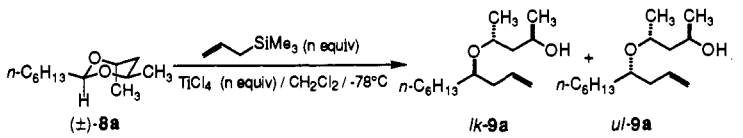
A final series of experiments examined the effects of allylsilane stoichiometry, $TiCl_4$ stoichiometry, and acetal concentration (Table IX). By use of (±)-**8a** in CH_2Cl_2 with $TiCl_4$ (1.0 equiv) as the Lewis acid, the reaction selectivity was found to be insensitive to allylsilane stoichiometry over a 20-fold range (entries 1–4). Further, with 1.0 equiv of allylsilane the reaction was also independent of $TiCl_4$ stoichiometry over a 20-fold range (entries 5–8). However, the initial concentration of the acetal had a significant effect on the allylation selectivity in an inverse relationship (entries 9–13). Over a 100-fold range, the selectivity more than tripled with decreasing concentration.

Reaction of Model Vinyl Ethers (3 and 5). To probe the intrinsic 1,3-asymmetric induction in a model oxocarbenium ion, the enol ethers (*E*)-**3**, (*E*)-**5**, and (*Z*)-**5** were examined. Allylation was performed by treatment of the enol ether with 0.95 equiv of trifluoromethanesulfonic acid in the presence of 2.0 equiv of allyltrimethylsilane (Table X). Although we were initially concerned about competitive protiodesilylation, the allylation products **4a** and **6a** were formed in good yield. Capillary GC analysis of the products from the reaction of (*E*)-**3** established that the allylation was *completely unselective* (entry 1).

The effect of the remote stereogenic center (i.e., the difference between meso and chiral acetals) on the stereochemical outcome was shown to be small. The epimeric enol ether (*E*)-**5** also reacted unselectively, though weakly favoring the *ul* diastereomer, which is the *minor* component in the allylation of (±)-**8a**. Both *E*- and *Z*-enriched samples of **5** were equally unselective (entries 2 and 3), ruling out the potential importance of forming isomeric oxocarbenium ions (vide infra). The methyl ether analogue of **5** was also studied. Allylation proceeded with a similar lack of selectivity but in much lower yield.

Reaction of an Acyclic Acetal (7). The chiral, acyclic acetal **7** represented an independent test for the stereochemical consequences of reaction via an oxocarbenium ion, in this case generated from an acetal. The chiral, nonracemic acetal **7** was chosen to simplify preparation and to remove the ambiguity of a stereogenic acetal carbon. The allylation of **7** was carried out by treating a mixture of **7** and allyltrimethylsilane with either TMSOTf (0.1 equiv/1 h) or the "Ti-blend" (11.0 equiv/3 h) (Scheme XVI). As

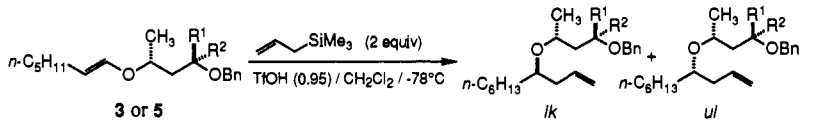
Table IX. Allylation of (±)-**8a**: Stoichiometry and Concentration Effects



entry	silane, equiv	$TiCl_4$, equiv	[acetal], M	time, min	yield, %[a]	ds,[a] *lk/ul*	$\Delta\Delta G^{\ddagger}$[b]
1	20	1.0	0.1	30	95	5.8/1	0.68
2	8	1.0	0.1	30	94	6.2/1	0.71
3	4	1.0	0.1	30	100	6.7/1	0.74
4	1	1.0	0.1	60	98	5.8/1	0.68
5	1	0.5	0.1	180	21	6.8/1	0.74
6	1	2.0	0.1	30	100	6.2/1	0.71
7	1	4.0	0.1	30	100	6.1/1	0.70
8	1	10.0	0.1	30	100	6.3/1	0.71
9	1	1.0	0.5	30	95	3.1/1	0.44
10	4	1.0	0.5	30	100	3.1/1	0.44
11	4	1.0	0.1	30	100	6.7/1	0.74
12	4	1.0	0.01	60	94	9.8/1	0.89
13	4	1.0	0.005	360	99	10.8/1	0.92

[a] Based on response factors versus cyclododecane. [b] At 195 K (kcal/mol).

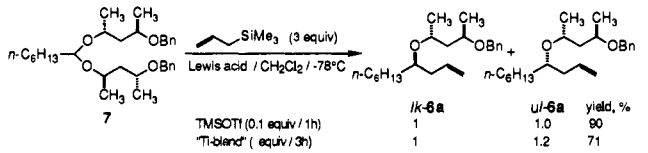
Table X. Allylation of Enol Ethers **3** and **5**[a]



enol ether	*E/Z*	R^1	R^2	product	yield, %[b]	ds,[c] *lk/ul*	$\Delta\Delta G^{\ddagger}$[d]
(*E*)-**3**	80/20	H	CH_3	**4a**	68	1/1.1	−0.04
(*E*)-**5**	80/20	CH_3	H	**6a**	58	1/1.3	−0.1
(*Z*)-**5**	20/80	CH_3	H	**6a**	58	1/1.3	−0.1

[a] Reactions run at 0.05 M. [b] Isolated. [c] Based on response factors versus cyclododecane. [d] At 195 K (kcal/mol).

Scheme XVI



in the case of the enol ether **5**, the reactions were unselective, weakly favoring the *ul* diastereomer with the titanium blend.

The dramatic differences in stereochemical outcome between *cis*-**1a** and (*E*)-**3** and between (±)-**8a** and (*E*)-**5**, (*Z*)-**5**, or **7** provide strong evidence for the existence of multiple and stereochemically distinguishable pathways for the reactions of acetals. The significance of this mechanistic divergence for understanding the stereoselective opening of chiral acetals is discussed below.

Discussion

To facilitate the discussion of the foregoing results and formulate mechanistic conclusions, we reiterate the hypotheses for the origin of stereocontrol illustrated in Scheme VII together with the expectations from our models for each hypothesis.

Limiting mechanistic hypothesis I: direct substitution on acetal Lewis acid complex. Substitution proceeds by inversion (S_N2) of configuration at the acetal center. Selectivity arises from highly biased complexation of the *pro-R* oxygen (flanked by the axial methyl group). The "meso-test" predicts completely diastereoselective substitution.

Limiting mechanistic hypothesis II: substitution occurs by prior ionization to the oxocarbenium ion. Selectivity arises from directed addition to the diastereotopic faces of the ion controlled by the proximal stereogenic center on oxygen (1,3-asymmetric induction). If this mechanism is operative, the *d,l* and *meso* acetals should have nearly the same selectivity in the same sense. Moreover, independent generation of xviii (xix) from enol ethers **3** and **5** should again give similar selectivity (Scheme X).

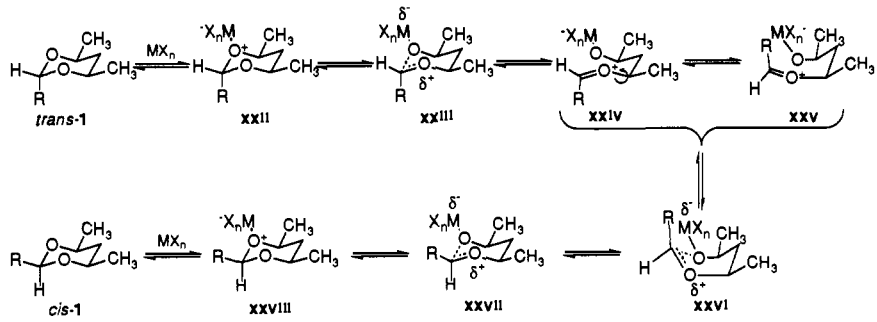
The results of substitution reactions with the meso acetals cis-1 (Table III) immediately ruled out the limiting mechanistic hypothesis I of direct substitution on a complexed acetal. The lack of stereospecificity and dependence of selectivity on the C(2) substituent are incompatible with a pure, invertive S_N2-type substitution. The control experiments with *trans*-**1a** and *trans*-**1b** were inconclusive since isomerization of the acetals was faster than substitution, and the results for both C(2) epimers were the same. For an S_N2 mechanism to be operative here, it is necessary to invoke the unlikely scenario of substitution on an equilibrating mixture of C(2) epimers with an increasing contribution from the less stable trans isomer as the C(2) substituent becomes larger (compare entries 1, 2, and 4, Table III). For the hexynyl acetal, however, the cis and trans isomers gave different selectivities. Significantly, *trans*-**1g** reacted faster than isomerization to *cis*-**1g**. Thus, for this compound direct substitution on a complexed acetal is rigorously excluded.

Apart from the stereochemical evidence, most of the results with meso acetals are qualitatively inconsistent with an S_N2 process. First, the facility of reaction at a secondary center using a weak nucleophile is striking. Further, the similarity of reaction rate between *cis*-**1a** and *cis*-**1b** for the "Ti-blend" (Table III) and among *cis*-**1a**, *cis*-**1b**, and *cis*-**1c** for $TiCl_4$ (Table VI) is uncharacteristic for S_N2 reactions, which are usually very sensitive to α-branching.[51] Allylation of *cis*-**1c** constitutes substitution at a secondary neopentyl center at −78 °C! Finally, the sensitivity of reaction rate to the para substituent on phenyl acetals is greater than would be expected for an S_N2 process.

Does the reaction, therefore, proceed by limiting mechanism II involving prior ionization to an oxocarbenium ion? Several lines of evidence presented previously are also inconsistent with this hypothesis. First, the change in selectivity for the meso acetals

(51) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; pp 547–555.

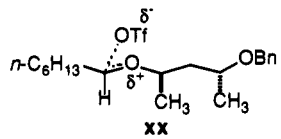
Scheme XVII



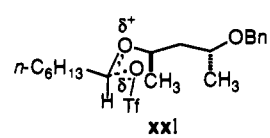
as a function of Lewis acid (Tables V and VI) indicates that an extended or charge-separated zwitterion was not a common intermediate for all of these reactions. Similarly, the striking difference between meso and chiral acetals *cis*-**1a** and (±)-**8a** is also inconsistent with an extended zwitterion intermediate that derives its selectivity solely from 1,3-induction.

The most definitive evidence against an oxocarbenium ion intermediate is the lack of selectivity observed in the allylation of enol ethers (*E*)-**3**, (*E*)-**5**, and (*Z*)-**5**. Irreversible C-protonation of (*E*)-**3** generates the oxocarbenium ion xviii (Scheme X), most likely in the *E* configuration (see below). Attack of the allylating agent on this species gave rise to a equal mixture of both *ul* and *lk* diastereomers of **4a**. Thus the extent of 1,3-asymmetric induction in this species is negligible. Since the substitution of the meso acetal *cis*-**1a** proceeded with significant diastereoselectivity, it is unlikely that an intermediate such as xviii is involved. This argument holds as well for the allylation of (*E*)-**5** and (*Z*)-**5**. We chose to examine both geometrical isomers of **5** to probe the possible intermediacy of geometrically isomeric oxocarbenium ions xix. Studies by Childs and Cremer[52] reveal the possibility that, if formed, such species may maintain configurational identity under our reaction conditions. However, the identical stereochemical outcome from reaction of (*E*)-**5** and (*Z*)-**5** implies a common intermediate, most likely the (*E*)-oxocarbenium xix, and argues against the intervention of isomeric intermediates. Furthermore, the lack of selectivity in the allylation of **5** is taken as strong evidence against the intermediacy of xix in reactions of the *d,l* acetal (±)-**8a**. The highly selective substitution of (±)-**8a**, therefore, does not likely derive from 1,3-asymmetric induction in an extended oxocarbenium ion.

Thus, the foregoing analysis of the stereochemical studies has ruled out both of the limiting hypotheses initially proposed. Before formulating a new hypothesis, however, it is important to critically analyze the limitations of the models used thus far. For the meso acetals, *cis*- and *trans*-**1**, it was not possible to unambiguously rule out an S_N2 process because isomerization of the acetal was faster than reaction, except in the case of *trans*-**1g** where the change in selectivity was too small to be significant. For the enol ethers **3** and **5**, the unselective allylation was taken as evidence against the "S_N1" pathway since both *cis*-**1a** and (±)-**8a** reacted selectively. However, two criticisms must be leveled at this model: (1) the putative oxocarbenium ions xviii and xix may be poor mimics of the oxocarbenium ion formed from opening an acetal with a Lewis acid and (2) it is possible that the enol ethers actually react via an intimate ion pair with triflate, and the two diastereomeric ion pairs (xx and xxi) are equal in energy and reactivity. Indeed, the same set of ion pairs would be formed from either of the isomeric enol ethers (*E*)-**5** or (*Z*)-**5**.



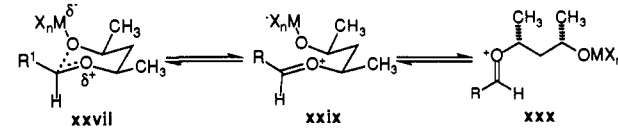
xx



xxi

(52) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.

Scheme XVIII



In the meso 2,4,6-trisubstituted acetal series, the rapid isomerization of trans to cis isomers (due to the large energy difference) foiled the control experiments. Only for **1g**, where the cis/trans energy difference is not large, was reaction faster than isomerization. The low selectivity observed in this case *necessarily excludes* a direct S_N2-like substitution. Therefore, the reaction must proceed through an intermediate or set of intermediates that react with allylsilane faster than they revert to educt. It is instructive to consider the possible mechanisms of isomerization of the acetals to clarify what those reactive intermediates (which must be intercepted for reaction) might be. A simple mechanism of isomerization involves the reversible addition–displacement of a phantom nucleophile such as chloride ion. This pathway is highly plausible since we have isolated α-chloro ethers in our previous studies on the complexation of acetals. Also, incorporation of isopropoxide units was observed, especially with acetals of aromatic aldehydes.

An alternative mechanism that does not require an external nucleophile and may have greater relevance to the allylation is depicted in Scheme XVII. Complexation of the trans acetal by a Lewis acid produces oxonium ion xxii. This species is proposed to isomerize to the complex of the cis acetal through a series of ion pairs. The first ion pair xxiii corresponds to an "internal or intimate ion pair" while the next species xxiv corresponds to an "external or solvent-separated ion pair" by analogy to the classic Winstein scheme.[53] Rotation about the oxocarbenium ion C–O bond in xxiv (to xxv) and return to an intimate ion pair produces a boat conformation xxvi of the more stable ion pair xxvii, the C(2) configurational isomer of xxiii. By microscopic reversibility this is in equilibrium with the oxonium ion xxviii derived from Lewis acid complexation of *cis*-**1**.

Although not explicitly implicated in the isomerization scheme, another set of ion pair species should be considered as candidates for reactive intermediates (Scheme XVIII). The intimate ion pair xxvii (from Lewis acid complex xxviii) can be in equilibrium with the external ion pair xxix and its conformational isomer xxx. This latter species corresponds to the fully dissociated free ion limit in the Winstein scheme but due to the connecting chain cannot become completely separated ions. The stereochemical profile for each of these three species is expected to be different (vide infra).

The results of the control experiment with *trans*-**1g** (entry 9, Table IV) require that, once formed, ion pairs xxiii–xxvii must react with allyltrimethylsilane faster than closure to xxviii.

(53) (a) Winstein, S.; Appel, S.; Baker, R.; Diaz, A. *Organic Reaction Mechanisms*; Special Publication No. 19; The Chemical Society: London, 1965; pp 109–130. (b) Raber, D.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Swartz, M., Ed.; Wiley: New York, 1974; Vol. 2, Chapter 3.

Scheme XIX

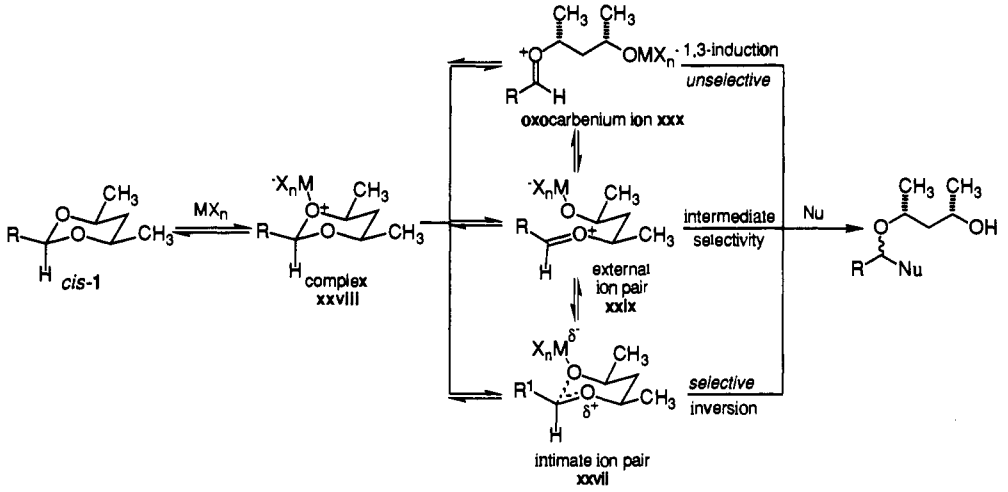
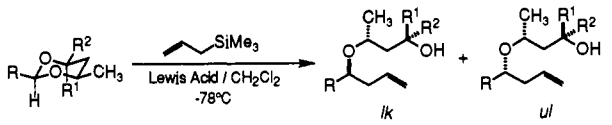


Table XI. Comparison of Lewis Acids



entry	acetal	R	R^1	R^2	Lewis acid	yield, %	ds, *lk/ul*	$\Delta\Delta G^{\ddagger}$ [b]
1	*cis*-**1a**	*n*-C_6H_{13}	H	CH_3	"Ti-blend"	100	11.1/1	0.93
2	*cis*-**1a**	*n*-C_6H_{13}	H	CH_3	$TiCl_4$	98	5.1/1	0.63
3	*cis*-**1a**	*n*-C_6H_{13}	H	CH_3	BF_3 (g)	84	1/1.9	−0.25
4	(±)-**8a**	*n*-C_6H_{13}	CH_3	H	"Ti-blend"	100	57.7/1	1.58
5	(±)-**8a**	*n*-C_6H_{13}	CH_3	H	$TiCl_4$	100	6.7/1	0.74
6	(±)-**8a**	*n*-C_6H_{13}	CH_3	H	BF_3 (g)	78	2.5/1	0.36
7	*cis*-**1b**	cyclohexyl	H	CH_3	"Ti-blend"	98	6.2/1[a]	0.71
8	*cis*-**1b**	cyclohexyl	H	CH_3	$TiCl_4$	96	4.8/1[a]	0.61
9	*cis*-**1b**	cyclohexyl	H	CH_3	BF_3 (g)	67	1/2.8[a]	−0.40
10	*cis*-**1e**	4-$CF_3C_6H_4$	H	CH_3	"Ti-blend"	45	3.8/1[a]	0.52
11	*cis*-**1e**	4-$CF_3C_6H_4$	H	CH_3	$TiCl_4$	96	4.6/1[a]	0.59
12	*cis*-**1e**	4-$CF_3C_6H_4$	H	CH_3	BF_3 (g)	72	1/1.7[a]	−0.21

[a] *ul/lk*, C–I–P priority change. [b] At 195 K (kcal/mol).

Moreover, since the product ratio is different from *cis*-**1g** versus *trans*-**1g**, it is also required that the equilibration of ion pairs xxiii–xxvii is slower than reaction with allyltrimethylsilane. For the substrates **1a** and **1d**, the corresponding oxonium ions and ion pairs equilibrate faster than they react with allyltrimethylsilane since the product distribution are independent of starting C(2) configuration. This difference is easily understood since the small steric size of the alkyne provides little driving force for the isomerization of xxii.

On the basis of this picture for the reactions of cyclic acetals, we propose the unified mechanism in Scheme XIX, which is a modification of the hypothesis in Scheme VII. According to this scheme, the initially formed Lewis acid complex xxviii, though spectroscopically detectable, is not the reactive intermediate. Rather, xxviii is in equilibrium with the true reactive species, the intimate and external ion pairs xxvii and xxix and oxocarbenium ion xxx. The two limiting species, xxvii and xxx, react with completely different stereochemical profiles: (1) stereospecific inversion of configuration at C(2) (for xxvii) and (2) stereorandom (for xxx). The evidence for inversion of configuration with intimate ion pairs comes from the work of Doering[54] and Winstein[55] and extensive studies by Sneen for secondary systems.[56] The evidence for stereorandom reaction with oxocarbenium ion xxx comes from our own studies with the model oxocarbenium ions xviii and xix generated from enol ethers **3** and **5**. The solvent-separated ion pair xxix is suggested to exhibit intermediate selectivity between these two extremes. Thus, the overall stereochemical outcome is determined by the equilibrium composition and relative reactivities of xxvii, xxix, and xxx. In the following discussion we will attempt to rationalize the observed dependence of stereochemistry on structural and experimental variables in terms of the partitioning of reaction via these competing pathways.

C(2) Substituent Dependence. The results in Table III clearly show a dependence on the substituent at C(2) and can be understood in terms of Scheme XIX. Thus, the drop in selectivity from R = *n*-hexyl to R = cyclohexyl represents the change in reactivity expected for ion pair xxvii, requiring a larger fraction of the reaction to proceed via xxix. (The failure of *cis*-**1c** to react may be due to the inaccessibility of the acetal oxygens to the bulky Lewis acid.) Moreover, the drop in selectivity from R = *n*-hexyl to R = *n*-hexynyl or phenyl can be understood in the increased concentration of xxix due to resonance stabilization of charge. The insignificant effect of electron-withdrawing para substituents on stereoselectivity and their dramatic rate-retarding effects are also consistent with our earlier spectroscopic studies on BF_3 and $SnCl_4$ complexation of 2-aryl-1,3-dioxanes.[57] In these experiments, only free acetal and open oxocarbenium ions were detected; no stable Lewis acid complexes were observed. Thus, these acetals most likely can react only via xxix or xxx, and the para substituents will have a large effect on rate and a negligible effect on selectivity.

In contrast to the C(2) dependence with the "Ti-blend" is the striking similarity of all substrates when $TiCl_4$ is used as the Lewis

(54) Doering, W. v. E.; Zeiss, H. H. *J. Am. Chem. Soc.* **1953**, *75*, 4733.
(55) Winstein, S.; Morse, B. K. *J. Am. Chem. Soc.* **1952**, *74*, 1133.
(56) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46. See also ref 51b, pp 322–350.
(57) (a) Denmark, S. E.; Willson, T. M. *NATO ASI Ser., Ser. C* **1989**, *289*, 247. (b) Willson, T. M. Unpublished results from these laboratories.

acid. It is tempting to propose that all of these reactions proceed through a similar intermediate, most likely an external ion pair related to xxix. The modest level of 1,3-asymmetric induction is reasonable and would not be expected to depend on the nature of R. The lower selectivity for R = *n*-hexynyl can be explained by the unhindered nucleophilic approach vector away from the oxocarbenium ion side chain influence.[58]

Lewis Acid Dependence. Although a systematic study of many Lewis acids was not undertaken, some interesting trends and differences within the group examined ("Ti-blend", $TiCl_4$, BF_3 (g)) are noteworthy. The most significant comparisons are collected in Table XI and are grouped to show the similar trends obtained with the different Lewis acids for each substrate. For example, the dramatic drop in selectivity for *cis*-**1a** and (±)-**8a** when $TiCl_4$ was used in place of the "Ti-blend" reflects the greater Lewis acidity of $TiCl_4$ and thus an increased proportion of reaction via the external ion pair xxix. On the other hand, the selectivity with aromatic acetals was negligibly affected, supporting the stated hypothesis that reaction of these acetals proceeds uniformly via external ion pairs xxix or xxx, independent of Lewis acid.

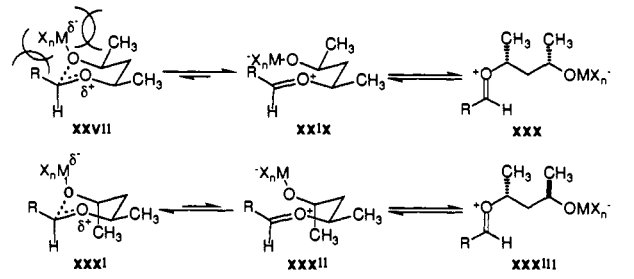
The narrow window of selectivities recorded for reaction with $TiCl_4$ as the Lewis acid is again noted in contrast to the range observed with the "Ti-blend". The modest and C(2)-independent selectivity was rationalized in terms of reaction via external ion pair xxix, wherein Coulombic attraction and conformational factors combined to preserve some stereodirecting influence of the acetal ring.

This hypothesis gains strong support from the stereochemical course of additions using BF_3(g) as the Lewis acid. The striking reversal of selectivity observed with BF_3(g) parallels the results with $TiCl_4$ in the basic lack of dependence on the C(2) substituent (compare entries 3, 9, and 12). Once again, this C(2)-independent behavior suggests a unique structural type for the intermediate in the allylations of all three meso substrates. The weak and "inverted" selectivity observed in these cases is reminiscent of the results from allylation of the *O*-benzyl enol ethers **3** and **5** (Table X). As will be discussed in a following section, we believe the reactive intermediates involved in the allylations of **3** and **5** to be the free oxocarbenium ions xviii and xix. The low selectivity is believed to arise from the weak 1,3-asymmetric induction from the resident stereocenters when the connecting chain is in the extended conformation. Thus, we propose that the intermediate responsible for the analogous results from BF_3-induced allylation of acetals is the analogous separated ion xxx (Scheme XIX). The greater Lewis acidity of BF_3 compared to $TiCl_4$[59] supports this proposal. The highly polarizing fluorine atoms are capable of stabilizing and dispersing the full negative charge on the boron, thus reducing the Coulombic attraction between the terminii.

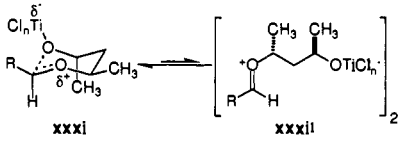
In summary, reactions with the three different Lewis acids employed provide evidence for the three major intermediates proposed. With the titanium blend, acetals react with variable selectivity via the intimate ion pair xxvii or the external ion pair xxix, depending upon the nature of the C(2) substituent. With $TiCl_4$, the acetals apparently react with modest selectivity via the external ion pair while the BF_3(g) they react unselectively primarily via the oxocarbenium ion xxx.

Acetal Configuration Dependence. The emerging picture of multiple reaction pathways via distinct ion/ion pair intermediates gains additional support from the dramatic sensitivity of reaction stereochemistry to acetal configuration. The results in Table V show clearly that when using a Lewis acid capable of inducing reaction via intimate ion pairs (xxvii), the selectivity is significantly higher for the chiral ((±)-**8a**) compared to the meso (*cis*-**1a**) acetal. However, when using $TiCl_4$, a Lewis acid believed to induce reaction solely via external ion pairs xxix, the distinction between acetals nearly vanishes. Thus, if the external ion pair is accessed, there is no difference in reaction selectivity; we therefore conclude that the observed difference is due to the greater propensity of **8a** to react via xxvii.

Scheme XX



Scheme XXI



At first glance this explanation contradicts the "strain release" hypothesis for selective opening of **8a** as depicted in Scheme II. The meso acetal *cis*-**1a** has no axially standing methyl groups and should be less disposed to opening. This is apparently not the case. The behavior of these acetals is better explained by considering the structures of the two intimate ion pairs xxvii and xxxi (Scheme XX). Our study on the solution structure of the precursor BF_3·acetal complexes (Chart VI) identified a critical steric interaction between the ring methyl groups and the BF_3 in the coordinated oxonium ion to explain the preference for the observed complex. In the less favored (not observed) complex of **8a**, the BF_3 eclipses both the C(2) substituent and the equatorial methyl group. In the Lewis acid complex of the meso acetal, xxviii, such eclipsing interactions cannot be avoided, and thus the intimate ion pair xxvii is destabilized toward opening to xxix (or xxx). Indeed the buttressing effect of the equatorial methyl group exacerbates the interaction between MX_n and the C(2) substituent. In the external ion pair xxix, the eclipsing interaction of MX_n with the C(2) substituent is attenuated by distance, and interaction with the vicinal methyl group is avoided by rehybridization (Scheme XX). In the ion pair xxxi, the eclipsing of the Lewis acid with the C(2) substituent can be ameliorated by bending the MX_n group away toward an equatorial hydrogen. Thus, the chiral acetals can react via the intimate ion pair with the expected high selectivity.

Stoichiometry and Concentration Dependence. The selectivity of the reaction of (±)-**8a** using $TiCl_4$ as the Lewis acid was shown to be independent of allylsilane stoichiometry over a 20-fold range. This indicates that equilibration of ion pair intermediates is faster than reaction, i.e., it is not possible to intercept the initially formed complex or intimate ion pair xxxi. Further, the reaction was also independent of Lewis acid stoichiometry over a 20-fold range. This observation is interpreted to imply that all reactive species have the same number of bound $TiCl_4$ units; any effect on selectivity would indicate reaction via a species with a different aggregation state of $TiCl_4$. If different intermediates were characterized by multiples of $TiCl_4$ association, an effect on the stereoselectivity should have been seen. In our previous studies on the mechanism of allylsilane–acyclic acetal addition reactions, we documented a stereochemical dependence on Lewis acid stoichiometry with $SnCl_4$. Parallel spectroscopic studies established that with $SnCl_4$ two different types of acetal complexes could be discerned, $SnCl_4$·L (1:1) and $SnCl_4$·L_2 (1:2). Unfortunately, the studies with $TiCl_4$ were ambiguous due to the complexity of the spectra.

On the other hand, the reaction of (±)-**8a** displayed a remarkable increase in selectivity with decreasing concentration over

(58) For a discussion of this vector analysis, see: (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (b) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966.

(59) (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 809. (c) The enthalpy of complexation of cyclohexanone $\Delta H°$ (kcal/mol): BF_3, -31.3; $TiCl_4$, -27.4. Elegant, L.; Pagliardini, A.; Torri, G.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1972**, 4422. Pagliardini, A.; Torri, G.; Elegant, L.; Azzaro, M. *Bull. Chim. Soc. Fr.* **1971**, 54.

a 100-fold range (Table IX). Although the different hypothetical intermediates xxxi, xxxii, and xxxiii (Scheme XX) represent different degrees of "dissociation", the equilibrium composition is not expected to be concentration dependent. However, if these species existed in different oligomeric states, then the distribution of the ion pairs would be concentration dependent. For example, if the intimate ion pair xxxi is monomeric and the open oxocarbenium ion xxxiii is dimeric (for example by bridging chlorines), then the equilibrium shown in Scheme XXI will be concentration dependent with a predictable influence on the stereochemical course of the reaction. Thus, at higher concentration the equilibrium may shift to favor xxxiii (no selectivity) while at low concentration the monomeric complex xxxi may be favored (higher selectivity).[60]

Solvent Dependence. Of all of the studies in this investigation, the solvent effects are the least understandable. Perhaps most surprising was the lack of a large influence on stereoselectivity, especially considering the range of solvent polarity examined. In the halocarbon group, dichloromethane and chloroform are roughly similar with chloroform being slightly more selective at comparable temperatures. These differences, though reproducible, are too small to warrant serious analysis. Nevertheless, it is tempting to interpret the inverse temperature effect observed for the reaction of (±)-**8a** in these solvents in terms of the equilibrium shown in Scheme XXI. At a given stoichiometry and concentration, it is expected that the composition of monomeric and dimeric species would show a temperature dependence favoring the lower aggregation state (intimate ion pair xxxi) at higher temperature, thus leading to enhanced selectivity.

We expected the less polar solvents, carbon tetrachloride and toluene, to be the most selective on the basis of their diminished ability to support the solvent-separated ion pairs xxix and xxxii or the separated ions xxx and xxxiii. Surprisingly, these solvents, along with hexane and nitromethane (the extreme limits of polarity), gave the least selective reactions with both meso and chiral acetals *cis*-**1a** and **8a**. Rationalization of this curious coincidence is extremely difficult since the structure of the reactive complex is unknown and may vary in the different solvents. Two possible explanations are proposed. To reconcile the low selectivity in these solvents with the intermediacy of separated ions requires that the energetic cost of charge separation be offset by agglomeration of the complexes to distribute the charge. This constitutes another factor that may influence the composition of the equilibrium in Scheme XXI. A second explanation invokes a change in mechanism to involve neutral intermediates such as α-chloro ethers. In this scenario, the ratio of the products will reflect the composition and reactivity of the acyclic intermediates. By analogy to the acyclic acetal **7** (Scheme XVI) the selectivity is expected to be poor.

Vinyl Ethers and Acyclic Acetals. These substrates were examined to serve as independent sources of the putative oxocarbenium ions required by the limiting hypothesis II of a dissociative, S_N1 mechanism. We recognized that the oxocarbenium ions generated from **3**, **5**, and **7** would not accurately mimic the solvent-separated or external ions that still enjoyed some Coulombic attraction between the Lewis acid complexed oxygen and the carbenium ion. Nevertheless, it was expected to provide a reflection of the extent of 1,3-asymmetric induction in a fully extended ion. The weak and inverted selectivity observed for all of these substrates implicates a common intermediate distinct from that involved in the selective reactions of the cyclic acetals under similar conditions. This intermediate is believed to be the extended oxocarbenium ion xviii or xix (Scheme X). Moreover, the strikingly similar behavior of the cyclic acetals in the presence of boron trifluoride is taken as evidence for the intermediacy of separated ions xxx and xxxiii with this reagent. The lack of 1,3-asymmetric induction of this type is not surprising given the similarity of groups around the stereogenic center attached to the oxygen. The highly selective reactions of type G acetals (Chart I) presumably arise from this mode of 1,3-asymmetric induction, but these substrates have sterically more disparate groups on the stereogenic center.[63]

It is instructive at this point, with a mechanistic framework in place, to reconcile the disparate conclusions from the previous mechanistic studies described in the introduction. The apparently inconsistent claims that reactions of chiral acetals with allylsilanes are both substrate-controlled (Scheme V) and template-controlled (Chart IV) can be unified by considering the effects of acetal structure on the nature of the reaction pathway. The steric hindrance at the C(21) position of the steroid in Scheme V makes displacement at the level of the intimate ion pair in an S_N2-like process difficult. The reaction adjusts to this by dissociation to a more accessible and reactive separated ion (oxocarbenium ion), which we have shown should express negligible 1,3-induction from the template. Apparently, the more nucleophilic tin-based reagents can capture the intimate ion pair in a template-controlled reaction.[61] The α-amino acetals in Chart IV are reported to react highly selectively with template control. While the α-center is branched, in all cases it bears an electron-withdrawing group, either a BOC- or Cbz-protected amine. This group is expected to disfavor the more dissociated external ion pair or separated ions that develop positive charge at the acetal center. Accordingly, reactions of these substrates will proceed through the intimate ion pairs and exhibit high, template-controlled selectivity.

Finally, it is appropriate to comment on the conclusions from the Heathcock study.[37] Our results and some of our conclusions agree with those from the previous workers. The possible intermediacy of ion pairs as suggested by Heathcock et al. is central to our analysis as well. By studying a wider range of substrates and reaction conditions we have identified a greater mechanistic continuum than is evident from their work, which used only $TiCl_4$ and silyl enol ethers. The intermediacy of three related ion pairs with different stereochemical profiles that are responsive to changes in structure and reaction conditions can explain the entire spectrum of acetal-opening reactions of which the enol silane/$TiCl_4$ combination is an important subset.

Conclusions

The stereoselectivity of the opening of substituted dioxane acetals has been demonstrated to be influenced by many structural and experimental variables. The primary factors are the structure of the parent aldehyde residue, the nature of the Lewis acid, and the solvent. Secondary factors are the configuration of the acetal, concentration, temperature, and stoichiometry of reagents. The origin of the stereoselectivity can be understood in terms of a unified mechanistic scheme involving three different types of ion pairs, each with a different stereochemical profile. The three species are (1) an intimate ion pair, (2) an external ion pair, and (3) a separated ion pair. The intimate ion pair is capable of highly selective reactions by invertive substitution on the most stable, reactive conformer. Reactions with sterically unhindered, aliphatic acetals with weak Lewis acids involve such intermediates. The external ion pair reacts with modest selectivity due to greater access at the acetal center. The increased dissociation of this species can be caused by sterically demanding or cation-stabilizing substituents or stronger Lewis acids and more highly ionizing medium. The separated ion pair reacts with no selectivity due to the minimal influence of the remote stereogenic center. These species are implicated in reactions with very powerful Lewis acids and may also be involved in reactions in both polar and nonpolar solvents.

The mechanistic insights provided by this study are critical for the design of achiral acetals capable of enantioselective reactions using chiral Lewis acids. The design and synthesis of suitable

(60) This argument is difficult to reconcile with the lack of $TiCl_4$ dependence. If the ion pair can dimerize, we would expect that another $TiCl_4$ molecule could serve the same purpose and shift the equilibrium to the right as well.

(61) This behavior has been reproduced in the case of (±)-**8a**. Reaction with allyltri-*n*-butylstannane (1 equiv) in the presence of the "Ti-blend" (10 equiv) gave a 93% yield of **2a** (*lk*/*ul*, 56/1). Denmark, S. E.; Almstead, N. A. *J. Org. Chem.*, in press.

substrates and Lewis acids is under active investigation.

Experimental Section

1. General Methods. ^1H NMR and ^{13}C NMR were recorded on Varian XL-200 (200 MHz ^1H), General Electric QE-300 (300 MHz ^1H, 75.5 MHz ^{13}C), Nicolet NT-360 (360 MHz ^1H), or General Electric GN-500 (500 MHz ^1H, 125 MHz ^{13}C) spectrometers in deuteriochloroform with chloroform as an internal reference (7.26 ppm or 77.0 ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, quart = quartet, m = multiplet), integration, coupling constants (hertz), and assignments where relevant. Infrared spectra were recorded as thin films or KBr disks on an IBM FTIR-32 spectrometer. Peaks are supported in units of cm^{-1} with the following relative intensities: br (broad), s (strong), m (medium), or w (weak). Mass spectra were recorded on a Varian MAT CH-5 spectrometer with ionization voltages of 70 or 10 eV. Data are reported in the form *m/e* (intensity relative to base = 100) and interpretation. GC/MS was performed on an Hewlett-Packard 5970 Mass Selective Detector equipped with an HP 5890 gas chromatograph. A 25-m HP-1 methyl silicone gum column was used in the gas chromatograph. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter in the solvents indicated; five wavelengths were measured but only $[\alpha]_D$ is reported. Analytical gas chromatography was performed on a Hewlett-Packard 5890 equipped with both split and on-column injectors. The columns used were an HP 50-m OV-1 cross-linked methyl silicone and an HP-5 50-m phenyl methyl silicone gum. Retention times (t_R) and integrated ratios were obtained from a Hewlett-Packard 3390A integrator. Analytical thin-layer chromatography was performed on Merck silica gel plates with an F-254 indicator. Visualization was accomplished by UV light, vanillin, iodine, and phosphomolybdic acid. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane, dichloromethane, and ethyl acetate ($CaCl_2$); ether ($FeCl_3$ and $CaCO_3$). Solvents for recrystallization were spectral grade. Column chromatography was performed by the method of Still with 32–63-mm silica gel (Merck). Medium-pressure chromatography was performed on Merck Lobar columns. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were performed on a Buchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures and are uncorrected. *n*-Butyllithium was titrated according to the method of Gilman.[62] Elemental combustion analyses were performed by the University of Illinois Microanalytical Service Laboratory.

2. Starting Materials. Isolation of (2*R*,4*S*)-2,4-Pentanediol. A solution of benzaldehyde (5.10 g, 48.0 mmol), a diastereomeric mixture of 2,4-pentanediols (5.00 g, 48.0 mmol), and *p*-toluenesulfonic acid monohydrate (91.4 mg, 0.48 mmol) in dry benzene (100 mL) was heated at reflux with a Dean–Stark trap for 6 h. The cooled solution was diluted with 40 mL of *tert*-butyl methyl ether and washed with saturated aqueous sodium bicarbonate solution (40 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 40 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The isomers were separated by column chromatography on silica gel (hexane/Et_2O, 96/4) and purified by Kugelrohr distillation to give 4.33 g (47%) of *cis*-**1d** and 4.01 g (44%) of (±)-**8d** as colorless oils. To a solution of *cis*-**1d** (3.57 g, 18.6 mmol) in methanol (35 mL) were added 5% Pd/C (103 mg) and 4 drops of concentrated sulfuric acid. The suspension was stirred for 2 h under 1 atm of hydrogen and then filtered through a plug of Celite and concentrated under vacuum to give a colorless residue. The residue was distilled from K_2CO_3 to give 1.35 g (70.1%) of (2*R*,4*S*)-2,4-pentanediol as a colorless oil.

3. Preparation of Acetals. General Procedure for Acetalization. *rel*-(2*S*,4*R*,6*S*)- and *rel*-(2*S*,4*R*,6*R*)-2-*n*-Hexyl-4,6-dimethyl-1,3-dioxane (*cis*-1a and (±)-8a). To a solution of heptanal (0.90 g, 7.88 mmol) and a diastereomeric mixture of 2,4-pentanediols (0.82 g, 7.88 mmol) in 8.3 mL of dry benzene was added *p*-toluenesulfonic acid monohydrate (15 mg, 0.078 mmol). The resulting solution was heated to reflux with a Dean–Stark trap for 8.5 h. The reaction mixture was cooled to room temperature, washed with saturated aqueous sodium bicarbonate solution, and extracted with diethyl ether (3 × 70 mL). The organic extracts were collected, washed with brine (30 mL), dried (Na_2SO_4), and concentrated under vacuum to give 1.59 g of a pale orange liquid. Purification by column chromatography (hexane/EtOAc, 20/1 then hexane/EtOAc, 10/1) followed by Kugelrohr distillation gave 754 mg (47.7%) of *cis*-**1a** and 758 mg (48%) of (±)-**8a** (overall 96%). Data for *cis*-**1a**: bp 60 °C (0.1 Torr); ^1H NMR (300 MHz) δ 4.50 (t, J = 5.3, 1 H, HC(2)), 3.69 (ddq, J_d = 2.4, J_q = 6.2, J_d = 11.0, 2 H, $H_2C(4,6)$), 1.61 (dt, J_t = 4.5, J_d = 5.9, 2 H, $H_2C(1')$), 1.50 (dt, J_t = 2.4, J_d = 13.1, 1 H, $H_{eq}C(5)$), 1.43–1.16 (m, 9 H), 1.21 (d, J = 6.3, 6 H, $H_3C(7,8)$), 0.86 (t, J = 5.9, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 101.41 (C(2)), 72.02 (C(4), C(6)), 40.30 (C(5)), 34.79 (C(1')), 31.57, 29.00, 24.04, 22.37, 21.38 (C(7), C(8)), 13.85 (C(6')); IR (neat) 2928 (s), 2855 (s), 2724 (w), 1456 (m), 1412 (w), 1375 (s), 1350 (m), 1335 (s), 1227 (w), 1200 (w), 1175 (s), 1127 (s), 1057 (m), 1040 (s), 1024 (s), 992 (m), 974 (m), 941 (w), 904 (w), 843 (w) cm^{-1}; MS (70 eV) *m/e* 199 (M^+ − H, 5), 115 (100), 97 (15), 69 (80), 55 (26), 45 (41), 43 (26), 42 (17), 41 (31); TLC R_f 0.36 (hexane/EtOAc, 10/1); GC t_R 15.42 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{24}O_2$ (200.32): C, 71.95; H, 12.08. Found: C, 72.10; H, 12.11. Data for (±)-**8a**: bp 60 °C (0.1 Torr); ^1H NMR (300 MHz) δ 4.81 (t, J = 5.2, 1 H, HC(2)), 4.28 (quint, J = 6.7, 1 H, HC(6)), 3.92 (ddq, J_d = 2.4, J_q = 6.1, J_d = 11.7, 1 H, HC(4)), 1.82 (ddd, J = 6.2, 12.0, 12.9, 1 H, $H_{ax}C(5)$), 1.50 (m, 2 H, $H_2C(1')$), 1.34–1.03 (m, 9 H), 1.33 (d, J = 6.8, 3 H, $H_3C_{ax}(7)$), 1.18 (d, J = 6.2, 3 H, $H_3C_{eq}(8)$), 0.85 (t, J = 6.4, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 94.18 (C(2)), 67.75 (C(6)), 67.28 (C(4)), 36.71 (C(5)), 35.24 (C(1)), 31.65, 29.05, 24.00, 22.45, 21.77 (C(8)), 17.08 (C(7)), 13.96 (C(6')); IR (neat) 2934 (s), 2859 (s), 2697 (w), 1653 (w), 1458 (s), 1408 (m), 1375 (s), 1339 (m), 1321 (m), 1289 (m), 1240 (m), 1200 (m), 1159 (s), 1103 (s), 999 (s), 970 (m), 939 (m), 903 (m), 847 (w) cm^{-1}; MS (70 eV) *m/e* 199 (M^+ − H, 5), 115 (100), 69 (94), 45 (47), 43 (27), 42 (15), 41 (37); TLC R_f 0.21 (hexane/EtOAc, 10/1); GC t_R 15.52 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{24}O_2$ (200.32): C, 71.95; H, 12.08. Found: C, 72.16; H, 11.99.

***rel*-(2*S*,4*R*,6*S*)-2-Cyclohexyl-4,6-dimethyl-1,3-dioxane (*cis*-1b).** Purification of the residue (4.60 g, 97%) obtained from the general acetalization procedure by column chromatography (hexane/Et_2O, 96/4) followed by Kugelrohr distillation gave 2.40 g (51%) of *cis*-**1b** as a colorless oil: bp 90 °C (0.3 Torr); ^1H NMR (300 MHz) δ 4.21 (d, J = 6.0, 1 H, HC(2)), 3.69–3.63 (ddq, J_d = 2.4, J_q = 6.1, J_d = 11.4, 2 H, HC(4), HC(6)), 1.87–1.82 (m, 2 H, $H_{eq}C(5)$, HC(1')), 1.74–1.56 (m, 3 H), 1.53–1.47 (m, 2 H), 1.26–0.99 (m, 6 H), 1.20 (d, J = 6.4, 6 H, $H_3C(7)$, $H_3C(8)$); ^{13}C NMR (75.5 MHz) δ 104.65 (C(2)), 72.26 (C(4), C(6)), 42.29 (C(1')), 40.68, 27.72, 26.45, 25.80, 21.60 (C(7), C(8)); IR (neat) 2928 (s), 2972 (s), 2853 (s), 1558 (w), 1450 (s), 1404 (w), 1377 (m), 1350 (m), 1334 (m), 1263 (w), 1236 (w), 1176 (s), 1128 (s), 1080 (w), 1055 (s). 1026 (s), 993 (m), 906 (w), 893 (w), 844 (w) cm^{-1}; MS (70 eV) *m/e* 197 (M^+ − H, 18), 116 (42), 115 (100), 113 (29), 111 (17), 95 (79), 83 (100), 81 (13), 79 (11), 73 (21), 71 (13), 70 (32), 69 (100), 68 (23), 67 (26), 57 (14), 56 (11), 55 (100), 54 (11), 53 (19), 45 (100), 43 (93), 42 (38), 41 (100); TLC R_f 0.28 (hexane/EtOAc, 96/4); GC t_R 19.90 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{22}O_2$ (198.30): C, 72.68; H, 11.88. Found: C, 72.72; H, 11.15.

***rel*-(2*S*,4*R*,6*S*)-2-(1',1'-Dimethylethyl)-4,6-dimethyl-1,3-dioxane (*cis*-1c).** To a solution of pivalaldehyde (668 mg, 7.76 mmol), (2*R*,4*S*)-2,4-pentanediol (400 mg, 3.84 mmol), and *p*-toluenesulfonic acid monohydrate (73 mg, 0.384 mmol) in anhydrous ether (10 mL) was added 4-Å molecular sieves (2.0 g). The resulting solution was magnetically stirred for 17 h at room temperature and filtered. After addition of saturated aqueous sodium bicarbonate solution (5 mL), the mixture was extracted with ether, dried ($MgSO_4$), and concentrated under vacuum. Purification of the residue by column chromatography on silica gel (pentane/Et_2O, 40/1) followed by Kugelrohr distillation gave 423 mg (64%) of *cis*-**1c** as a colorless oil: bp 60 °C (200 Torr); ^1H NMR (300 MHz) δ 4.07 (s, 1 H, HC(2)), 3.63 (ddq, J_d = 2.5, J_q = 6.2, J_d = 11.7, 2 H, HC(4), HC(6)), 1.46 (dt, J_t = 2.5, J_d = 12.9, 1 H, $H_{eq}C(5)$), 1.17 (d, J = 6.2, 6 H, $H_3C(7)$, $H_3C(8)$), 1.13 (dt, J_t = 1.9, J_d = 13.0, 1 H, $H_{ax}C(5)$), 0.90 (s, 9 H, $(H_3C)_3C$); ^{13}C NMR (75.5 MHz) δ 106.80 (C(2)), 72.15 (C(4), C(6)), 40.59, 34.69, 24.85 ($(CH_3)_3C$), 21.66 (C(7), C(8)); IR (neat) 2977 (s), 2909 (m), 2855 (m), 1485 (m), 1447 (w), 1406 (w), 1385 (m), 1362 (m), 1350 (w), 1333 (m), 1219 (m), 1175 (s), 1150 (s), 1127 (s), 1082 (s), 1049 (s), 1007 (s), 943 (w), 914 (w), 903 (m) cm^{-1}; MS (70 eV) *m/e* 172 (M^+, 2), 115 (79), 87 (26), 71 (14), 69 (100), 57 (46), 45 (42), 43 (20), 41 (35); TLC R_f 0.35 (pentane/Et_2O, 40/1); GC t_R 15.37 min (HP-5, 50 min, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{10}H_{20}O_2$ (172.27): C, 69.72; H, 11.70. Found: C, 69.75; H, 11.67.

***rel*-(2*S*,4*R*,6*S*)-4,6-Dimethyl-2-[4'-(trifluoromethyl)phenyl]-1,3-dioxane (*cis*-1e).** The isomeric mixture of acetals obtained from the general procedure were separated by column chromatography (hexane/EtOAc, 24/1) and then purified by Kugelrohr distillation to give 1.54 g (59%) of *cis*-**1e** as a white solid (which was recrystallized from hexane) and 0.89 g (34%) of minor diastereomer (±)-**8e** as a colorless oil. Data for *cis*-**1e**: mp 42–44 °C (hexane); ^1H NMR (300 MHz) δ 7.63 (AB q, J = 8.7, 4 H, aryl), 5.57 (s, 1 H, HC(2)), 3.97 (ddq, J_d = 2.4, J_q = 6.2, J_d = 11.2,

(62) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.

(63) For a recent theoretical treatment of the conformational behavior of oxocarbenium ions, see: Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.

2 H, HC(4), HC(6)), 1.64 (dt, J_t = 2.4, J_d = 13.2, 2 H, $H_{eq}C(5)$), 1.40 (dt, J_t = 11.2, J_d = 13.2, 1 H, $H_{ax}C(5)$), 1.31 (d, J = 6.2, 6 H, $H_3C(7)$, $H_3C(8)$)); ^{13}C NMR (75.5 MHz) δ 142.67 (C(1')), 130.44 (q, J = 32.2, C(4')), 126.44 (C(2')), 124.89 (q, J = 3.7, C(3')), 124.09 (q, J = 272.0, CF_3), 99.52 (C(2)), 72.89 (C(4), C(6)), 40.08 (C(5)), 21.30 (C(7), C(8)); IR (CCl_4) 2977 (s), 2939 (s), 2913 (w), 2859 (s), 1931 (w), 1624 (m), 1524 (w), 1447 (m), 1414 (s), 1399 (s), 1383 (s), 1321 (s), 1215 (m), 1127 (s), 1067 (s), 1021 (s), 992 (m), 926 (s), 872 (w), 831 (s), 816 (s) cm^{-1}; MS (70 eV) *m/e* 260 (M^+, 21), 259 ($M^+ - H$, 31), 175 (100), 173 (83), 145 (39), 127 (34), 115 (16), 114 (55), 71 (12), 70 (50), 69 (89), 55 (31), 45 (28), 43 (63), 42 (91), 41 (51), 39 (15); TLC R_f 0.58 (hexane/EtOAc, 90/10); GC t_R 20.22 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{13}H_{15}F_3O_2$ (260.25): C, 60.00; H, 5.81. Found: C, 59.75; H, 5.72.

***rel*-(2*S*,4*R*,6*S*)-4,6-Dimethyl-2-(4'-nitrophenyl)-1,3-dioxane (*cis*-1f).** Purification of the residue (981 mg, 98%) obtained from the standard acetalization procedure was accomplished by three successive MPLC elutions (hexane/CH_2Cl_2/Et_2O, 80/19/1) yielding *cis*-**1f** (498 mg, 50%), a mixture of *cis*-**1f** and (±)-**8f** (32.3 mg, 3%), and (±)-**8f** (422 mg, 42%) as white solids. Total mass, 952 mg; total yield, 95%. Analytical data from *cis*-**1f**: mp 84–85 °C (hexane/EtOAc, 96/4); ^1H NMR (300 MHz) δ 8.21 (d, J = 8.8, 2 H, HC(3'), HC(5')), 7.70 (d, J = 8.8, 2 H, HC(2'), HC(6')), 5.59 (s, 1 H, HC(2)), 3.98 (ddq, J_d = 2.4, J_q = 6.2, J_d = 11.2, 2 H, HC(4), HC(6)), 1.66 (dt, J_t = 2.5, J_d = 13.3, 1 H, $H_{eq}C(5)$), 1.40 (dt, J_t = 11.1, J_d = 13.3, 1 H, $H_{ax}C(5)$), 1.32 (d, J = 6.2, 6 H, $H_3C(7)$, $H_3C(8)$); ^{13}C NMR (75.5 MHz) δ 147.91 (C(4')), 145.33 (C(1')), 127.31 (C(2'), C(6')), 123.33 (C(3'), C(5')), 99.10 (C(2)), 73.20 (C(4), C(6)), 40.11 (C(5)), 21.49 (C(7), C(8)); IR (CCl_4) 2979 (m), 2861 (m), 1611 (w), 1528 (s), 1383 (m), 1348 (s), 1331 (s), 1175 (m), 1121 (s), 1065 (m), 1028 (m), 926 (w), 855 (m) cm^{-1}; MS (70 eV) *m/e* 236 (M^+, 12), 236 (35), 152 (100), 150 (59), 115 (14), 114 (24), 107 (73), 105 (18), 104 (18), 78 (11), 77 (41), 76 (16), 71 (14), 70 (55), 69 (94), 55 (31), 51 (32), 50 (12), 45 (29), 43 (60), 42 (98), 41 (50), 39 (18); TLC R_f 0.29 (hexane/CH_2Cl_2/Et_2O, 60/38/2); GC t_R 23.98 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (10 min)). Anal. Calcd for $C_{12}H_{15}NO_4$ (237.25): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.38; N, 5.87.

***rel*-(2*R*,4*R*,6*S*)-2-(1'-Hexynyl)-4,6-dimethyl-1,3-dioxane (*trans*-1g) and *rel*-(2*S*,4*R*,6*S*)-2-(1'-Hexynyl)-4,6-dimethyl-1,3-dioxane (*cis*-1g).** The dioxanes *trans*-**1g** and *cis*-**1g** were prepared by the general acetalization procedure in 61% yield. The epimers were separated by column chromatography on silica gel (hexane/EtOAc, 94/6), and purified by Kugelrohr distillation to give 402 mg (23%) of *trans*-**1g** and 671 mg (38%) of *cis*-**1g**. Data for *trans*-**1g**: bp 120 °C (0.3 Torr); ^1H NMR (300 MHz) δ 5.70 (s, 1 H, HC(2)), 4.28–4.23 (m, 2 H, HC(4), HC(6)), 2.24 (m, 2 H, $H_2C(3')$), 1.49–1.23 (m, 6 H), 1.18 (d, J = 6.5, 6 H, $H_3C(7)$, $H_3C(8)$)), 0.90 (t, J = 7.2, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 88.29 (C(2)), 87.54 (C(1')), 75.13 (C(2')), 66.18 (C(4), C(6)), 40.73, 30.38, 21.87, 21.42 (C(7), C(8)), 18.17 (C(5')), 13.46 (C(6')); IR (neat) 2967 (s), 2872 (s), 2274 (m), 2251 (m), 2218 (m), 1458 (s), 1446 (s), 1338 (s), 1331 (s), 1226 (s), 1173 (s), 1157 (s), 1134 (s), 1109 (s), 1059 (s), 1018 (s), 989 (s), 939 (m), 897 (s), 824 (m) cm^{-1}; MS (70 eV) *m/e* 195 ($M^+ - 1$, 31), 167 (16), 154 (13), 111 (64), 110 (30), 109 (41), 95 (13), 82 (17), 81 (35), 79 (11), 71 (10), 70 (12), 69 (100), 68 (51), 67 (29), 66 (13), 55 (31), 53 (16), 45 (17), 43 (61), 42 (39), 41 (75), 39 (35); TLC R_f 0.61 (hexane/EtOAc, 90/10); GC t_R 19.88 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{20}O_2$ (196.28): C, 73.43; H, 10.27. Found: C, 73.25; H, 10.18. Data for *cis*-**1g**: bp 120 °C (0.3 Torr); ^1H NMR (300 MHz) δ 5.24 (s, 1 H, HC(2)), 3.81–3.74 (m, 2 H, HC(4), HC(6)), 2.24 (t, J = 7.3, 2 H, $H_2C(3')$), 1.54–1.31 (m, 6 H), 1.26 (d, J = 6.3, 6 H, $H_3C(7)$, $H_3C(8)$), 0.87 (t, J = 7.2, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 90.82 (C(2)), 85.43 (C(1')), 75.39 (C(2')), 72.66 (C(4), C(6)), 39.58, 29.76, 21.56, 21.07 (C(7), C(8)), 17.96, 13.15 (C(6')); IR (neat) 2970 (s), 2934 (s), 2867 (s), 2253 (m), 1447 (s), 1429 (m), 1402 (s), 1375 (s), 1331 (s), 1229 (w), 1172 (s), 1146 (s), 1115 (s), 1053 (s), 1034 (s), 1013 (s), 992 (s), 947 (m), 916 (s), 860 (m) cm^{-1}; MS (70 eV) *m/e* 195 ($M^+ - 1$, 31), 167 (16), 154 (13), 111 (64), 110 (30), 109 (41), 95 (13), 82 (17), 81 (35), 79 (11), 71 (10), 70 (12), 69 (100), 68 (51), 67 (29), 66 (13), 55 (31), 53 (16), 45 (17), 43 (61), 42 (39), 41 (75), 39 (35); TLC R_f 0.42 (hexane/EtOAc, 90/10); GC t_R 18.66 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{20}O_2$ (196.28): C, 73.43; H, 10.27. Found: C, 73.37; H, 10.31.

***rel*-(2*R*,4*R*,6*S*)-2-*n*-Hexyl-4,6-dimethyl-1,3-dioxane (*trans*-1a).** Into a two-necked, 25-mL round-bottom flask was placed Pd/C (5%, 5 mg), and the flask was evacuated and purged with hydrogen three times. A solution of *trans*-**1g** (100 mg, 0.51 mmol) in dry hexane (5 mL) was syringed onto the Pd/C under an atmosphere of hydrogen. The reaction mixture was stirred magnetically for 15 min and filtered through a plug of Celite. Evaporation of the solvent under vacuum followed by Kugelrohr distillation of the residue gave 99 mg (97%) of *trans*-**1a** as a colorless oil: bp 60 °C (0.3 Torr); ^1H NMR (300 MHz) δ 5.05 (t, J = 6.6, 1 H, HC(2)), 4.04–3.98 (m, 2 H, HC(4), HC(6)), 1.82–1.24 (m, 12 H), 1.18 (d, J = 6.1, 6 H, $H_3C(7)$, $H_3C(8)$)), 0.88 (t, J = 6.3, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 97.54 (C(2)), 64.33 (C(4), C(6)), 41.74, 40.34, 31.74, 29.55, 28.99, 24.90, 22.54, 21.90, 14.03 (C(6')); IR (neat) 2928 (s), 2855 (s), 2723 (s), 1456 (s), 1412 (m), 1375 (s), 1350 (m), 1335 (s), 1227 (m), 1200 (m), 1175 (s), 1127 (s), 1057 (m), 1040 (s), 1024 (s), 992 (s), 974 (m), 941 (m), 905 (m), 843 (m); MS (70 eV) *m/e* 199 ($M^+ - 1$, 1.3), 115 (100), 69 (86), 55 (11), 49 (18), 45 (43), 41 (29); TLC R_f 0.37 (hexane/EtOAc, 90/10); GC t_R 18.45 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{12}H_{24}O_2$ (200.32): C, 71.95; H, 12.08. Found: C, 72.01; H, 12.03.

(4*R*,6*R*)-2-*n*-Hexyl-4,6-dimethyl-1,3-dioxane ((+)-8a). The acetal (+)-**8a** was prepared by the general procedure for acetalizations with (2*R*,4*R*)-2,4-pentanediol. Kugelrohr distillation afforded 389 mg (92%) of (+)-**8a** as a colorless oil: bp 60 °C (0.1 Torr); ^1H NMR (300 MHz) δ 4.83 (t, J = 5.2, 1 H, HC(2)), 4.29 (quintet, J = 6.7, 1 H, HC(4)), 3.95–3.93 (m, 1 H, HC(6)), 1.84–1.78 (m, 1 H), 1.60–1.39 (m, 2 H), 1.35 (d, J = 7.0, 3 H, $H_3C(7)$), 1.30–1.27 (m, 10 H), 1.20 (d, J = 6.1, 3 H, $H_3C(8)$), 0.87 (m, 3 H, $H_3C(6')$); ^{13}C NMR (75.5 MHz) δ 94.18 (C(2)), 67.78 (C(6)), 67.28 (C(4)), 36.71 (C(5)), 35.24, 31.65, 29.05, 24.00, 22.45, 21.77 (C(8)), 17.08 (C(7)), 13.97 (C(6')); IR (neat) 3818 (w), 2934 (s), 2858 (s), 2697 (w), 1653 (w), 1321 (m), 1458 (s), 1408 (m), 1375 (s), 1338 (m), 1321 (m), 1289 (m), 1240 (m), 1200 (m), 1159 (s), 1103 (s), 999 (s), 970 (m), 939 (m), 902 (m), 847 (w) cm^{-1}; MS (70 eV) *m/e* 199 ($M^+ - 1$, 4), 115 (100), 69 (94), 55 (21), 45 (47), 43 (27), 42 (15), 41 (37); TLC R_f 0.28 (hexane/EtOAc, 95/5); GC t_R 17.79 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)); $[\alpha]^{26}_D$ +24.6 (1.3, CCl_4). Anal. Calcd for $C_{12}H_{24}O_2$ (200.32): C, 71.95; H, 12.08. Found: C, 72.16; H, 11.99.

(4*R*,6*R*)-2-Phenyl-4,6-dimethyl-1,3-dioxane ((+)-8d). The acetal (+)-**8d** was prepared by the general procedure for acetalizations with (2*R*,4*R*)-2,4-pentanediol. Kugelrohr distillation afforded 165 mg (89%) of (+)-**8d** as a colorless oil: bp 100 °C (0.3 Torr); ^1H NMR (300 MHz) δ 7.50 (m, 2 H, Ph), 7.35 (m, 3 H, Ph), 5.84 (s, 1 H, HC(2)), 4.48 (quintet, J = 6.7, 1 H, HC(6)), 4.19 (ddq, J_d = 2.4, J_q = 6.1, J_d = 11.8, 1 H, HC(4)), 2.00 (ddd, J = 6.1, 12.5, 12.5, 1 H, $H_{ax}C(5)$), 1.50 (d, J = 7.0, 3 H, $H_3C_{ax}(7)$), 1.44 (m, 1 H, $HC_{eq}(5)$), 1.30 (d, J = 6.2, 3 H, $H_3C_{eq}(8)$); ^{13}C NMR (75.5 MHz) δ 139.03 (Ph), 128.45 (Ph), 128.08 (Ph), 126.05 (Ph), 93.82 (C(2)), 68.47 (C(6)), 67.89 (C(4)), 36.55 (C(5)), 21.80 (C(8)), 17.05 (C(7)); IR (neat) 3034 (w), 2973 (s), 2932 (m), 2870 (m), 1453 (m), 1399 (m), 1375 (s), 1356 (m), 1337 (m), 1310 (m), 1240 (m), 1156 (s), 1134 (s), 1103 (m), 1048 (s), 1028 (s), 999 (s), 907 (m) cm^{-1}; MS (70 eV) *m/e* 192 (31), 191 (65), 123 (11), 115 (14), 107 (62), 106 (19), 105 (100), 79 (24), 78 (12), 77 (36), 70 (12), 69 (51), 55 (15), 51 (14), 45 (11), 43 (21), 42 (18), 41 (21); TLC R_f 0.50 (hexane/EtOAc, 90/10); $[\alpha]^{20}_D$ +20.6 (1.02, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_2$ (192.25): C, 74.97; H, 8.39. Found: C, 75.25; H, 8.33.

4. Preparation of Enol Ethers. *rel*-(1'*R*,3'*S*)-(*E*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-heptene ((*E*)-10). A solution of *cis*-**1h** (420 mg, 2.95 mmol) in ether was cooled to 0 °C, and *n*-BuLi (2.95 mL, 3.54 mmol, 1.2 equiv) was added by syringe. The solution was stirred for 30 min at 0 °C and then poured into a dilute solution of sodium bicarbonate (50 mL). The mixture was extracted with ether (3 × 30 mL), and the combined ethereal extracts were washed with brine (30 mL), dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 7/3) to afford 520 mg (88%) of (*E*)-**10** (*E*/*Z*, 4/1) as a clear colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 150 °C (10 Torr); ^1H NMR (300 MHz) δ 6.01 (d, J = 12.2, 0.8 H, HC(1')), 5.90 (d, J = 6.2, 0.2 H, HC(1')), 4.88 (m, 0.8 H, HC(2)), 4.37 (m, 0.2 H, HC(2)), 3.93 (m, 2 H, HC(1'), HC(3')), 3.09 (s, 0.2 H, OH), 2.95 (s, 0.8 H, OH), 1.99 (m, 0.4 H, $H_2C(2')$), 1.85 (m, 1.6 H, $H_2C(2')$), 1.77–1.45 (m, 2 H, $H_2C(3)$), 1.33–1.13 (m, 12 H), 0.84 (t, J = 7.0, 3 H, $H_3C(7)$); ^{13}C NMR (75.5 MHz) (*E*)-**10** (major isomer) δ 143.74 (C(1)), 107.74 (C(2)), 76.03 (C(1')), 66.73 (C(3')), 45.18 (C(2')), 31.15, 30.01, 27.46, 23.49, 22.39, 20.17, 13.96 (C(7)); (*Z*)-**10** (minor isomer) δ 142.45 (C(1)), 108.40 (C(2)), 77.60 (C(1')), 66.95 (C(3')), 45.18 (C(2')), 31.32, 29.29, 27.46, 23.89, 23.38, 20.72, 13.96 (C(7)); IR (neat) 3426 (br m), 2965 (s), 2924 (s), 2857 (m), 1669 (s), 1653 (m), 1456 (m), 1377 (m), 1229 (m), 1167 (s), 1123 (s), 1041'(m), 1005 (m), 924 (m) cm^{-1}; MS (10 eV) *m/e* 200 (M^+, 10), 199 (6), 182 (5), 141 (17), 116 (6), 115 (83), 114 (40), 113 (12), 103 (17), 97 (29), 96 (43), 87 (19), 86 (13), 81 (20), 71 (13), 70 (20), 69 (100), 68 (42), 57 (30), 45 (39); TLC R_f 0.20 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{12}H_{24}O_2$ (200.31): C, 71.95; H, 12.08. Found: C, 72.04; H, 12.06.

***rel*-(1'*R*,3'*S*)-(*E*)-1-[3'-(Benzyloxy)-1'-methylbutoxy]-1-heptene ((*E*)-3).** Potassium hydride (35% dispersion in mineral oil, 572 mg, 5.00 mmol, 2 equiv) was washed with hexane (2 × 10 mL) and suspended in THF (10 mL). The suspension was cooled to 0 °C, and the enol ether

(*E*)-**10** (*E*/*Z*, 4/1) (500 mg, 2.50 mmol) in THF (10 mL) was added to the solution. After the solution was stirred for 10 min at 0 °C, benzyl bromide (854 mg, 5.00 mmol, 2 equiv) was added. The reaction was quenched with water after stirring for 30 min at room temperature. The solution was poured into water and extracted with ether (3 × 50 mL). The combined ethereal extracts were washed with brine (50 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 97/3) followed by Kugelrohr distillation to afford 645 mg (92%) of (*E*)-**3** (*E*/*Z*, 4/1) as a clear colorless oil: bp 160 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.33 (m, 5 H, Ph), 6.05 (d, J = 12.0, 0.8 H, HC(1)), 5.93 (d, J = 6.2, 0.2 H, HC(1)), 4.87 (m, 0.8 H, HC(2)), 4.59–4.39 (AB q, J = 11.8, 2 H, CH_2Ph), 4.31 (m, 0.2 H, HC(2)), 3.93 (m, 1 H, HC(1')), 3.64 (m, 1 H, HC(3')), 2.04 (m, 1 H, HC(2')), 1.87 (m, 1 H, HC(2')), 1.48 (m, 1 H, HC(3)), 1.33–1.15 (m, 13 H), 0.88 (t, J = 3.0, 3 H, H_3C(7)); ^{13}C NMR (75.5 MHz) (*E*)-**3** (major isomer) δ 144.58 (C(1)), 138.74 (Ph), 128.24 (Ph), 127.57 (Ph), 127.38 (Ph), 106.39 (C(2)), 73.24 (C(1')), 71.84 (CH_2Ph), 70.17 (C(3')), 43.35 (C(2')), 31.20, 30.23, 27.61, 22.46, 19.92, 19.61, 14.05 (C(7)); (*Z*)-**3** (minor isomer) δ 143.38 (C(2), 138.74 (Ph), 128.24 (Ph), 127.57 (Ph), 127.38 (Ph), 107.15 (C(2)), 74.61 (C(1')), 71.81 (CH_2Ph), 70.14 (C(3')), 43.50 (C(2')), 31.41, 29.43, 27.61, 23.87, 20.34, 19.61, 14.05 (C(7)); IR (neat) 3031 (w), 2961 (s), 2924 (s), 2855 (s), 1669 (m), 1651 (m), 1455 (m), 1375 (m), 1200 (m), 1167 (s), 1130 (s), 1067 (s), 1028 (m), 924 (m) cm^{-1}; MS (70 eV) m/e no M$^+$, 177 (1), 176 (5), 135 (3), 92 (10), 91 (100), 70 (11), 43 (9), 41 (12); TLC R_f 0.55 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{19}H_{30}O_2$ (290.43): C, 78.57; H, 10.41. Found: C, 78.57; H, 10.45.

***rel*-(1'*R*,3'*R*)-(*E*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-heptene ((*E*)-11).** A solution of **8h** (420 mg, 2.95 mmol) in ether was cooled to 0 °C, and *n*-BuLi (2.95 mL, 3.54 mmol, 1.2 equiv) was added by syringe. The solution was stirred for 30 min at 0 °C and then poured into a dilute solution of sodium bicarbonate (50 mL). The mixture was extracted with ether (3 × 30 mL), and the combined ethereal extracts were washed with brine (30 mL), dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 7/3) to afford 520 mg (88%) of (*E*)-**11** (*E*/*Z*, 4/1) as a clear colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 100 °C (5 Torr); ^{1}H NMR (300 MHz) δ 6.00 (d, J = 12.2, 0.8 H, HC(1)), 5.91 (d, J = 6.3, 0.2 H, HC(1)), 4.82 (m, 0.8 H, HC(2)), 4.28 (q, J = 6.0, 0.2 H, HC(2)), 3.98 (m, 2 H), 2.63 (s, 0.2 H, OH), 2.55 (d, J = 5.0, 0.8 H, OH), 1.97 (m, 0.4 H, H_2C(2')), 1.83 (m, 1.6 H, H_2C(2')), 1.57 (m, 2 H, H_2C(3)), 1.28–1.11 (m, 12 H), 0.81 (t, J = 7.0, 3 H, H_3C(7)); ^{13}C NMR (75.5 MHz) (*E*)-**11** (major isomer) δ 144.51 (C(2)), 106.85 (C(1)), 73.61 (C(3')), 64.24 (C(1')), 44.96 (C(2')), 31.15, 30.09, 27.47, 23.88, 22.38, 19.96, 13.95 (C(7)); (*Z*)-**11** (minor isomer) δ 143.33 (C(2)), 107.37 (C(1)), 75.04 (C(3')), 64.24 (C(1')), 44.88 (C(2')), 31.32, 29.32, 27.47, 23.87, 22.38, 20.32, 13.95 (C(7)); IR (neat) 3380 (br m), 2963 (s), 2926 (s), 2857 (m), 1669 (s), 1653 (m), 1456 (m), 1375 (m), 1163 (s), 1121 (s), 1043 (m), 924 (m) cm^{-1}; MS (70 eV) m/e 200 (M$^+$, 2.5), 141 (5), 114 (18), 97 (11), 96 (31), 91 (15), 81 (27), 71 (19), 70 (18), 69 (81), 68 (31), 58 (8), 57 (100), 55 (19); TLC R_f 0.20 (hexane/EtOAc, 6/1). Anal. Calcd for $C_{12}H_{24}O_2$ (200.31): C, 71.95; H, 12.08. Found: C, 71.95; H, 11.99.

***rel*-(1'*R*,3'*R*)-(*E*)-1-[3'-(Benzyloxy)-1'-methylbutoxy]-1-heptene ((*E*)-5).** Potassium hydride (35% dispersion in mineral oil, 572 mg, 5.00 mmol, 2 equiv) was washed with hexane (2 × 10 mL) and suspended in THF (10 mL). The suspension was cooled to 0 °C, and a solution of (*E*)-**11** (*E*/*Z*, 4/1) (500 mg, 2.50 mmol) in THF (10 mL) was added. After the solution was stirred for 10 min at 0 °C, benzyl bromide (854 mg, 5.00 mmol, 2 equiv) was added. The reaction was quenched with water after stirring for 30 min at room temperature. The solution was poured into water and extracted with ether (3 × 50 mL). The combined ethereal extracts were washed with brine (50 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 97/3) followed by Kugelrohr distillation to afford 645 mg (92%) of (*E*)-**5** (*E*/*Z*, 4/1) as a clear colorless oil: bp 160 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.33 (m, 5 H, Ph), 6.07 (d, J = 12.4, 0.8 H, HC(2)), 5.98 (d, J = 6.3, 0.2 H, HC(2)), 4.93 (m, 0.8 H, HC(1)), 4.62–4.46 (AB q, J = 11.4, 2 H, CH_2Ph), 4.34 (m, 0.2 H, HC(1)), 4.08 (m, 1 H, HC(1')), 3.81 (m, 1 H, HC(3')), 2.11 (m, 0.4 H, H_2C(2')), 1.92 (m, 1.6 H, H_2C(2')), 1.69 (m, 2 H, H_2C(3)), 1.34–1.16 (m, 12 H), 0.93 (t, J = 7.0, 3 H, H_3C(7)); ^{13}C NMR (75.5 MHz) (*E*)-**5** (major isomer) δ 145.23 (C(2)), 138.77 (Ph), 128.23 (Ph), 127.76 (Ph), 127.37 (Ph), 105.89 (C(1)), 72.87 (C(1')), 71.45 (CH_2Ph), 70.70 (C(3')), 44.89 (C(2')), 31.23, 30.29, 27.61, 22.46, 20.49, 19.81, 14.03 (C(7)); (*Z*)-**5** (minor isomer) δ 144.02 (C(2)), 138.77 (Ph), 128.23 (Ph), 127.76 (Ph), 127.37 (Ph), 106.49 (C(1)), 74.28 (C(1')), 71.59 (CH_2Ph), 70.70 (C(3')), 44.89 (C(2')), 31.42, 29.47, 27.61, 23.89, 20.98, 19.89, 14.03 (C(7)); IR (neat) 3031 (w), 2965 (s), 2924 (s), 2857 (s), 1669 (m), 1653 (m), 1456 (m), 1375 (m), 1167 (s), 1117 (s), 1069 (s), 1028 (m), 924 (m) cm^{-1}; MS (70 eV) m/e no M$^+$, 179 (5), 176 (27), 135 (7), 118 (15), 92 (18), 91 (100), 70 (29); TLC R_f 0.55 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{19}H_{30}O_2$ (290.43): C, 78.57; H, 10.41. Found: C, 78.59; H, 10.28.

***rel*-(1'*R*,3'*R*)-(*Z*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-heptene ((*Z*)-11).** The 4/1 *E*/*Z* mixture of hydroxy enol ethers (2.50 g, 12.5 mmol) was separated by MPLC (aminopropyl column, hexane/EtOAc, 93.5/6.5). The separation was repeated three times to obtain 320 mg of a 20/80 *E*/*Z* mixture of enol ethers ((*Z*)-**11**) as a clear colorless oil: bp 150 °C (10 Torr); ^{1}H NMR (300 MHz) δ 6.03 (d, J = 12.2, 0.2 H, HC(1)), 5.92 (d, J = 6.2, 0.8 H, HC(1)), 4.88 (m, 0.2 H, HC(2)), 4.37 (m, 0.8 H, HC(2)), 3.93 (m, 2 H, HC(1'), HC(3')), 3.09 (s, 0.8 H, OH), 2.95 (s, 0.2 H, OH), 1.99 (m, 1.6 H, H_2C(2')), 1.85 (m, 0.4 H, H_2C(2')), 1.77–1.45 (m, 2 H, H_2C(3)), 1.33–1.13 (m, 12 H), 0.84 (t, J = 7.0, 3 H, H_3C(7)).

***rel*-(1'*R*,3'*R*)-(*Z*)-1-[3'-(Benzyloxy)-1'-methylbutoxy]-1-heptene ((*Z*)-5).** Potassium hydride (35% dispersion in mineral oil, 129 mg, 1.12 mmol, 2 equiv) was washed with hexane (2 × 5 mL) and suspended in THF (10 mL). The suspension was cooled to 0 °C, and the enol ether (*Z*)-**11** (150 mg, 0.75 mmol) in THF (10 mL) was added to the solution. After the solution was stirred for 10 min at 0 °C, benzyl bromide (133 mg, 1.12 mmol, 2 equiv) was added. The reaction was quenched with water after stirring for 30 min at room temperature. The solution was poured into water and extracted with ether (3 × 40 mL). The combined ethereal extracts were washed with brine (40 mL), dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed on silica gel (hexane/EtOAc, 90/10) to afford 162 mg (78%) of (*Z*)-**5** (*Z*/*E*, 4/1) as a clear colorless oil: bp 160 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.33 (m, 5 H, Ph), 6.05 (d, J = 12.0, 0.2 H, HC(1)), 5.93 (d, J = 6.2, 0.8 H, HC(1)), 4.87 (m, 0.2 H, HC(2)), 4.59–4.39 (AB q, J = 11.8, 2 H, CH_2Ph), 4.31 (m, 0.8 H, HC(2)), 3.93 (m, 1 H, HC(1')), 3.64 (m, 1 H, HC(3')), 2.04 (m, 1 H, HC(2')), 1.87 (m, 1 H, HC(2')), 1.48 (m, 1 H, HC(3)), 1.33–1.15 (m, 13 H), 0.88 (t, J = 3.0, 3 H, H_3C(7)).

5. Preparation of Acyclic Acetal. (2*R*,4*R*)-2-(Benzyloxy)-4-pentanol (12). A solution of **8d** (1.70 g, 8.83 mmol) in dichloromethane (50 mL) was cooled to 0 °C, and diisobutylaluminum hydride (44.2 mL, 5 equiv, 1.0 M in toluene) was added. The solution was stirred at room temperature for 4 h and then quenched by the addition of 1 N HCl. The solution was poured into water (50 mL) and extracted with ether (3 × 40 mL). The ethereal extracts were washed with brine (40 mL), dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 6/1) followed by Kugelrohr distillation to afford 1.42 g (84%) of **12** as a clear colorless oil: bp 100 °C (5 Torr); ^{1}H NMR (300 MHz) δ 7.31 (m, 5 H, Ph), 4.58–4.42 (AB q, J = 11.6, 2 H, H_2C(6)), 4.08 (m, 1 H, HC(2)), 3.82 (m, 1 H, HC(4)), 3.09 (s, 1 H, OH), 1.61 (m, 2 H, H_2C(3)), 1.23 (d, J = 6.2, 3 H, H_3C(1)), 1.15 (d, J = 6.2, 3 H, H_3C(5)); ^{13}C NMR (75.5 MHz) δ 138.23 (Ph), 128.20 (Ph), 127.49 (Ph), 127.41 (Ph), 72.47 (C(2)), 70.31 (C(6)), 64.28 (C(4)), 44.44 (C(3)), 23.35 (C(1)), 19.05 (C(5)); IR (neat) 3424 (br m), 3031 (m), 2967 (s), 2928 (m), 1493 (m), 1460 (m), 1453 (m), 1424 (m), 1375 (m), 1345 (m), 1210 (m), 1154 (s), 1119 (s) cm^{-1}; TLC R_f 0.10 (hexane/EtOAc, 6/1).

(2*R*,4*R*)-2-(Trimethylsiloxy)-4-(benzyloxy)pentane (13). To a stirred solution of **12** (0.65 g, 3.35 mmol) and TMSCl (0.85 mL, 6.70 mmol, 2 equiv) in THF (10 mL) was added Et_3N (1.40 mL, 10.05 mmol, 3 equiv). The solution immediately became cloudy white and was stirred at room temperature for 6 h. The solution was poured into water (50 mL) and then extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 9/1) to afford 0.89 g (100%) of **13** as a clear colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 130 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.38 (m, 5 H, Ph), 4.63–4.43 (AB q, J = 11.2, 2 H, H_2C(6)), 4.13 (m, 1 H, HC(4)), 3.75 (m, 1 H, HC(2)), 1.62 (m, 2 H, H_2C(3)), 1.24 (d, J = 6.2, 3 H, H_3C(5)), 1.18 (d, J = 6.2, 3 H, H_3C(1)), 0.15 (s, 3 H, Si(CH_3)$_3$); ^{13}C NMR (75.5 MHz) δ 138.98 (Ph), 128.24 (Ph), 127.47 (Ph), 127.29 (Ph), 72.04 (C(4)), 70.24 (C(6)), 65.26 (C(2)), 47.49 (C(3)), 24.48 (C(5)), 19.91 (C(1)), 0.37 (Si(CH_3)$_3$); IR (neat) 3065 (w), 3031 (w), 2967 (s), 1497 (w), 1455 (m), 1375 (m), 1343 (w), 1250 (s), 1154 (s), 1121 (s), 1057 (s), 976 (m), 947 (m), 893 (m), 841 (s) cm^{-1}; MS (70 eV) m/e no M$^+$, 179 (7), 176 (4), 117 (22), 107 (9), 92 (10), 91 (100), 75 (15), 73 (24), 70 (70), 43 (10); TLC R_f 0.50 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{15}H_{26}O_2Si$ (266.45): C, 67.61; H, 9.84. Found: C, 67.65; H, 9.80.

(1'*R*,3'*R*)-1,1-Bis[3'-(benzyloxy)-1'-methylbutoxy]heptane (7). A solution of **13** (0.69 g, 2.59 mmol) and heptanal (181 μL, 1.29 mmol, 0.5 equiv) in dichloromethane (15 mL) was cooled to −78 °C. Trimethylsilyl triflate (50 μL, 0.259 mmol, 0.1 equiv) was added at −78 °C, and the solution was stirred at −78 °C for 24 h. The reaction was quenched by the addition of pyridine (2 mL) and then warmed to room temperature. The solution was poured into a saturated $NaHCO_3$ solution and extracted

with ether (3 × 40 mL). The combined ethereal extracts were washed with brine (40 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 19/1) followed by Kugelrohr distillation to afford 0.43 g (69%) of **7** as a clear colorless oil: ^{1}H NMR (300 MHz) δ 7.38 (m, 5 H, Ph), 4.67–4.39 (m, 4 H, CH_2Ph), 4.50 (t, J = 5.6, 1 H, HC(1)), 4.03 (m, 1 H, HC(1')), 3.82 (m, 3 H, HC(1'), HC(3')), 1.61 (m, 6 H), 1.22 (m, 20 H), 0.91 (t, J = 6.0, 3 H, H_3C(7)); ^{13}C NMR (75.5 MHz) δ 139.17 (Ph), 138.82 (Ph), 138.21 (Ph), 128.13 (Ph), 127.35 (Ph), 127.32 (Ph), 127.28 (Ph), 127.13 (Ph), 100.26 (C(1)), 72.05 (C(3')), 71.70 (C(3')), 70.46 (CH_2Ph), 70.09 (CH_2Ph), 68.84 (C(1')), 68.13 (C(1')), 45.56 (C(2')), 45.38 (C(2')), 35.27 (C(2)), 31.81 (C(3)), 29.22 (C(4)), 24.58 (C(5)), 22.54 (C(6)), 21.27 (C(1'a)), 20.65 (C(1'a)), 20.08 (C(4')), 19.69 (C(4')), 14.01 (C(7)); IR (neat) 3088 (w), 3065 (w), 3031 (w), 2965 (s), 2926 (s), 2859 (m), 1497 (m), 1453 (m), 1374 (s), 1345 (m), 1154 (s), 1113 (s), 1067 (s), 1038 (m) cm^{-1}; MS (10 eV) m/e no M$^+$, 291 (23), 199 (20), 193 (22), 178 (21), 177 (100), 176 (57), 135 (24), 107 (21), 91 (58), 70 (71); TLC R_f 0.40 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{31}H_{48}O_4$ (484.69): C, 76.81; H, 9.98. Found: C, 76.77; H, 9.93.

6. Preparation of Reference Compounds. Additions to Acetals with $TiCl_4$. General Procedure. A magnetically stirred solution of the acetal (ca. 0.50 mmol) and allyltrimethylsilane (4.0 equiv) in dry dichloromethane (ca. 0.25 M in acetal) was cooled to −78 °C. Titanium tetrachloride (1.0 equiv) was then added. After stirring for the specified reaction time (see below), the reaction was quenched by addition of 1.0 N NaOH in methanol (2 mL), and the solution was allowed to warm to room temperature. The reaction mixture was washed with 1 M HCl (10 mL) and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic extracts were collected, washed with saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to give a light yellow residue. Details of purification are given below for the individual compounds.

Additions to Acetals with the "Titanium Blend" ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5). General Procedure. A Lewis acid solution ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5) was prepared by dissolving titanium tetrachloride (330 μL, 3.0 mmol) in dry dichloromethane (9 mL) followed by the addition of titanium tetraisopropoxide (740 μL, 2.5 mmol). After the addition of titanium tetraisopropoxide, the resulting solution was stirred for 45 min. The freshly prepared Lewis acid solution (1.1 equiv) was added via syringe (addition time 2.0 h) to a cold (−78 °C), magnetically stirred solution of the acetal (ca. 0.50 mmol) and allyltrimethylsilane (8.0 equiv) in dichloromethane (0.1 M in acetal). After complete addition of the Lewis acid solution, the resulting heterogeneous mixture was stirred for an additional period of time at −78 °C (see the tables). The reaction was then quenched by the addition of 1.0 N NaOH in methanol (20 mL) and allowed to warm to room temperature. The reaction mixture was washed with 1 M HCl (20 mL), and the aqueous layer was extracted with dichloromethane (3 × 25 mL). The organic extracts were collected, washed with saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to give a light yellow residue. Details of purification are given below for the individual compounds.

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-1-decene (2a).** The residue obtained from the reaction of *cis*-**1a** (200 mg, 0.10 mmol), allyltrimethylsilane (634 μL, 3.99 mmol, 4 equiv), and $TiCl_4$ (110 μL, 0.10 mmol, 1.0 equiv) (reaction time 30 min) was purified by column chromatography on silica gel (hexane/EtOAc, 10/1), followed by Kugelrohr distillation to give 184 mg (76%) of a diastereomeric mixture (*lk*/*ul*, 3/1) of **2a** as a colorless oil: bp 140 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 5.78 (ddt, J_d = 7.2, J_d = 10.3, J_t = 10.3, 1 H, HC(2)), 5.05 (m, 2 H, H_2C(1)), 3.97 (s, 1 H, OH (D_2O exchangeable)), 3.93 (m, 1 H, HC(8)), 3.77 (m, 1 H, HC(6)), 3.43 (quint, J = 5.7, 1 H, HC(4)), 2.21 (m, 2 H, H_2C(3)), 2.11–1.09 (m, 18 H), 0.85 (m, 3 H, H_3C(10)); ^{13}C NMR (75.5 MHz) major δ 134.94 (C(2)), 116.82 (C(1)), 75.86 (C(4)), 74.02 (C(1')), 67.85 (C(3')), 45.73 (C(2')), 39.35 (C(3)), 33.39 (C(5)), 31.75, 29.49, 25.09, 23.48, 22.60, 20.44, 14.06 (C(10)); minor δ 134.29 (C(2)), 117.52 (C(1)), 75.33 (C(4)), 73.63 (C(1')), 67.85 (C(3')), 45.78 (C(2')), 38.31 (C(3)), 34.71 (C(5)), 30.91, 29.33, 25.46, 23.42, 22.60, 20.23, 14.06 (C(10)); IR (neat) 3744 (w), 3688 (w), 3468 (s), 1734 (w), 1717 (w), 1700 (w), 1684 (w), 1653 (m), 1636 (m), 1617 (w), 1559 (w), 1539 (w), 1507 (w), 1456 (w) cm^{-1}; MS (70 eV) m/e 115 (24), 97 (39), 87 ($C_5H_{11}O$, 29), 71 (15), 69 (100), 55 (51), 45 (82), 43 (28), 41 (31); TLC R_f 0.21 (hexane/EtOAc, 90/10); GC t_R major (*lk*-**2a**) 22.99 min, minor (*ul*-**2a**), 23.19 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{30}O_2$ (242.40): C, 74.32; H, 12.47. Found: C, 74.20; H, 12.50.

***rel*-(4(*R*,*S*)-1′*R*,3′*S*)-4-Cyclohexyl-4-(3′-hydroxy-1′-methylbutoxy)-1-butene (2b).** The residue (245 mg, diastereomeric mixture (*ul*/*lk*, 3.2/1)) obtained from the reaction of *cis*-**1b** (210 mg, 1.06 mmol), allyltrimethylsilane (674 μL, 4.24 mmol), and $TiCl_4$ (139 μL, 1.27 mmol, 1.2 equiv) (reaction time 30 min) was purified by column chromatography on silica gel (hexane/EtOAc, 97/3), to give 210.5 mg (82%, 42 mg minor (*lk*), 132 mg major (*ul*), 36.5 mg mixed) of **2b** as colorless oils. An analytically pure sample of the major diastereomer (*ul*-**2b**) was obtained by Kugelrohr distillation. Data for *ul*-**2b** (major): bp 110 °C (0.2 Torr); ^{1}H NMR (300 MHz) δ 5.89–5.75 (m, 1 H, HC(2)), 5.05 (br d, J = 9.6, 1 H, HC(1)), 5.00 (br d, J = 8.2, 1 H, HC(1)), 4.00–3.95 (m, 1 H, HC(3')), 3.90 (br s, 1 H, OH), 3.85–3.74 (m, 1 H, HC(1')), 3.28–3.22 (m, 1 H, HC(4)), 2.25–2.10 (m, 2 H, HC(3)), 1.78–1.48 (m, 8 H), 1.27–0.96 (m, 5 H), 1.16 (d, J = 6.3, 3 H, H_3C(4')), 1.12 (d, J = 6, 3 H, H_3C(5')); ^{13}C NMR (75.5 MHz) δ 135.74 (C(2)), 116.27 (C(1)), 80.15 (C(1')), 74.36 (C(4)), 67.39 (C(3')), 46.01 (C(5)), 40.78, 36.29, 28.80, 28.09, 26.54, 26.43, 26.37, 23.45 (C(5')), 20.43 (C(4')); IR (neat) 3431 (m), 3074 (w), 2966 (s), 2926 (s), 2853 (s), 2666 (w), 2359 (w), 1639 (w), 1450 (m), 1373 (m), 1327 (m), 1304 (m), 1232 (m), 1120 (m), 1059 (m), 991 (m), 954 (w), 910 (m), 843 (w) cm^{-1}; CI-MS 241 (M$^+$ + H, 30), 199 (44), 157 (16), 138 (12), 135 (29), 113 (26), 111 (19), 109 (11), 105 (93), 103 (17), 95 (67), 87 (63), 83 (15), 81 (52), 73 (12), 69 (100), 67 (11), 55 (10); TLC R_f 0.09 (hexane/EtOAc, 95/5); GC t_R 26.78 min (HP-5, 50 m, 80 °C (3 min), 6 °C/min, 250 °C (2 min)). Anal. Calcd for $C_{15}H_{28}O_2$ (240.39): C, 74.95; H, 11.74. Found: C, 74.83; H, 11.84. Data for *lk*-**2b** (minor): ^{1}H NMR (300 MHz) δ 5.85–5.71 (m, 1 H, HC(2)), 5.10 (br d, J = 15.6, 1 H, trans HC(1)), 5.05 (br d, J = 9.0, cis HC(1)), 4.12 (br s, 1 H, OH), 3.98–3.92 (m, 1 H, HC(3')), 3.9–3.77 (m, 1 H, HC(1')), 3.24 (q, J = 5.5, 1 H, HC(4)), 2.32 (br t, J = 6.5, 2 H, HC(3)), 1.86–1.52 (m, 8 H), 1.49–1.33 (m, 1 H), 1.23–0.91 (m, 4 H), 1.12 (d, J = 6.0, 3 H, H_3C(4')), 1.08 (d, J = 6.0, 3 H, H_3C(5')); ^{13}C NMR (75.5 MHz) δ 134.68 (C(2)), 117.27 (C(1)), 78.95 (C(1')), 73.48 (C(4)), 67.89 (C(3')), 45.69 (C(5)), 40.61, 35.17, 29.66, 27.36, 26.47, 26.35, 26.22, 23.64 (C(5')), 20.04 (C(4')); CI-MS 241.2 (M$^+$ + H, 22), 199 (47), 181 (6), 157 (13), 153 (12), 137 (79), 135 (29), 113 (24), 111 (20), 105 (97), 103 (15), 95 (67), 87 (59), 83 (12), 81 (53), 73 (13), 69 (100); high-resolution CI-MS calcd for $C_{15}H_{29}O_2$ (M$^+$ + H) 241.2167, found 241.2164; TLC R_f 0.14 (hexane/EtOAc, 95/5); GC t_R 26.91 min (HP-5, 50 m, 80 °C (3 min), 6 °C/min, 250 °C (2 min)).

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-5,5-dimethyl-1-hexene (2c).** The residue obtained from the reaction of *cis*-**1c** (380 mg, 2.20 mmol), allyltrimethylsilane (1.40 mL, 8.82 mmol, 4.0 equiv), and $TiCl_4$ (241 μL, 2.20 mmol, 1.0 equiv) (reaction time 60 min) was purified by column chromatography on silica gel (pentane/Et_2O, 10/1). The diastereomers were separated (*ul*/*lk*, 4.4/1) and Kugelrohr distilled to give 378 mg (80% combined yield) of **2c** as a colorless oil. Data for *ul*-**2c** (major): bp 70 °C (0.4 Torr); ^{1}H NMR (300 MHz) δ 5.90–5.76 (m, 1 H, HC(2)), 4.98 (d, J = 13.8, 1 H, HC(1)), 4.93 (d, J = 5.3, 1 H, HC(1)), 4.05–3.98 (m, 1 H, HC(3')), 3.95 (br s, 1 H, OH), 3.87–3.77 (m, 1 H, HC(1')), 3.07 (dd, J = 3.8, 3.8, 1 H, HC(4)), 2.27–2.23 (m, 1 H, H_2C(2')), 2.12–2.02 (m, 1 H, H_2C(2')), 1.65–1.45 (m, 2 H, H_2C(3)), 1.11 (d, J = 6.2, 3 H, H_3C(4')), 1.08 (d, J = 6.0, 3 H, H_3C(5')), 0.92 (s, 9 H, $(H_3C)_3$C); ^{13}C NMR (75.5 MHz) δ 137.15 (C(2)), 115.74 (C(1)), 84.09 (C(1')), 76.58 (C(4)), 67.17 (C(3')), 46.25, 36.76, 36.42, 26.58, 23.56, 21.25; IR (neat) 3432 (s), 3077 (m), 2969 (s), 1640 (m), 1480 (s), 1462 (s), 1431 (s), 1395 (m), 1364 (s), 1329 (s), 1219 (m), 1165 (m), 1117 (s), 1076 (s), 1048 (s), 1017 (s), 994 (s), 955 (m), 909 (s) cm^{-1}; CI-MS 215 (M$^+$ + H, 64), 173 (23), 115 (12), 111 (44), 105 (100), 87 (32), 69 (20), 59 (18); TLC R_f 0.15 (hexane/EtOAc, 20/1); GC t_R 16.52 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{13}H_{26}O_2$ (214.35): C, 72.85; H, 12.23. Found: C, 72.61; H, 12.33. Data for *lk*-**2c** (minor): ^{1}H NMR (300 MHz) δ 5.94–5.80 (m, 1 H, HC(2)), 5.08 (dd, J = 1.3, 17.0, 1 H, HC(1)), 4.98 (d, J = 10.1, 1 H, HC(1)), 4.30 (s, 1 H, OH), 4.03–3.90 (m, 2 H, HC(1'), HC(3')), 3.14 (dd, J = 6.3, 6.2, 1 H, HC(4)), 2.48–2.39 (m, 1 H, H_2C(2')), 2.25–2.13 (m, 1 H, H_2C(2')), 1.53–1.48 (m, 2 H, H_2C(3)), 1.09 (d, J = 6.3, 3 H, H_3C(4')), 1.05 (d, J = 5.9, 3 H, H_3C(5')), 0.85 (s, 9 H, $(H_3C)_3$C); ^{13}C NMR (75.5 MHz) 137.28 (C(2)), 116.27 (C(1)), 82.08 (C(1')), 73.91 (C(4)), 67.78 (C(3')), 45.71, 36.00, 35.02, 26.35, 23.34, 19.64; CI-MS 215 (M$^+$ + H, 90), 173 (32), 115 (13), 111 (61), 105 (100), 103 (10), 87 (59), 71 (11), 69 (88), 59 (17); high-resolution CI-MS calcd for $C_{13}H_{27}O_2$ (M$^+$ + H) 215.2011, found 215.1998; TLC R_f 0.18 (hexane/EtOAc, 20/1); GC t_R 16.22 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (5 min)).

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-4-phenyl-1-butene (2d).** To a cold (−78 °C) solution of *cis*-**1d** (192 mg, 1.0 mmol) and allyltrimethylsilane (1.27 mL, 8.0 mmol) in 5.0 mL of dichloromethane was added $TiCl_4$/Ti(O*i*-Pr)$_4$ "blend" (1.1 equiv) by syringe over 2.5 h. After addition of the Lewis acid solution, the mixture was allowed to stir for 15 min at −78 °C. The reaction was then quenched by addition of 1 N NaOH/methanol solution (25 mL) and allowed to warm to room temperature. The reaction mixture was washed with 1 M HCl (40 mL), and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with satu-

rated aqueous sodium bicarbonate solution (25 mL), dried over Na_2SO_4, and concentrated to give a light yellow residue. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9/1), followed by Kugelrohr distillation to give 135 mg (57.6%) of a diastereomeric mixture (*ul*/*lk*, 5.75/1) of **2d** as a colorless oil. Data for *ul*-**2d** (major): bp 150 °C (0.2 Torr); ^{1}H NMR (300 MHz) δ 7.29–7.39 (m, 5 H, Ph), 5.72 (ddt, J_d = 7.0, J_d = 10.3, J_t = 17.0, 1 H, HC(2)), 5.04 (ddd, J = 1.6, 9.2, 17.3, 2 H, $H_2C(1)$), 4.49 (t, J = 7.1, 1 H, HC(4)), 4.08 (s, 1 H, OH), 3.78–3.88 (m, 1 H, HC(3′)), 3.50–3.61 (m, 1 H, HC(1′)), 2.37–2.60 (m, 2 H, $H_2C(3)$), 1.40–1.68 (m, 2 H, HC(2′)), 1.12 (d, J = 6.0, 3 H, $H_3C(5')$), 1.08 (d, J = 6.2, 3 H, $H_3C(4')$); ^{13}C NMR (75.5 MHz) δ 141.01 (C(5)), 134.31 (C(2)), 128.56 (Ph), 127.91 (Ph), 127.10 (Ph), 117.33 (C(1)), 77.78 (C(4)), 72.12 (C(1′)), 67.65 (C(3′)), 45.82 (C(3)), 42.68 (C(2′)), 23.28 (C(4′)), 19.07 (C(5′)); IR (CCl_4) 3518 (b), 3078 (m), 3030 (m), 2970 (s), 2932 (s), 1641 (w), 1452 (m), 1377 (m), 1165 (m), 1118 (m), 1080 (s) cm^{-1}; MS (70 eV) *m*/*e* 193 (M$^+$ − 41, 18), 131 (21), 107 (100), 91 (16), 79 (21), 77 (11), 69 (40), 45 (39); TLC R_f 0.24 (hexane/EtOAc, 4/1); GC t_R 20.21 min (HP-5, 50 m, 80 °C (4 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{22}O_2$ (234.34): C, 76.88; H, 9.46. Found: C, 76.69; H, 9.42. Data for *lk*-**2d** (minor): bp 150 °C (0.2 Torr); ^{1}H NMR (300 MHz) δ 7.25–7.33 (m, 5 H, Ph), 5.73 (ddt, J_d = 7.0, J_d = 10.1, J_t = 17.1, 1 H, HC(2)), 5.04–5.12 (m, 2 H, $H_2C(1)$), 4.41 (dd, J = 5.8, 7.1, 1 H, HC(4)), 3.99–4.09 (m, 1 H, HC(3′)), 3.78–3.88 (m, 1 H, HC(1′)), 3.52 (b, 1 H, OH), 2.40–2.61 (m, 2 H, $H_2C(3)$), 1.39–1.76 (m, 2 H, HC(2′)), 1.19 (d, J = 6.2, 3 H, $H_3C(4')$), 1.08 (d, J = 6.2, 3 H, $H_3C(5')$); ^{13}C NMR (75.5 MHz) δ 143.33 (C(5)), 134.19 (C(2)), 128.21 (Ph), 127.35 (C(8)), 126.39 (Ph), 117.83 (C(1)), 80.65 (C(4)), 76.79 (C(1′)), 67.58 (C(3′)), 45.98 (C(3)), 42.88 (C(2′)), 23.65 (C(4′)), 21.50 (C(5′)); TLC R_f 0.17 (hexane/EtOAc, 4/1); GC t_R 20.49 min (HP-5, 50 m, 80 °C (4 min), 8 °C/min, 250 °C (5 min)); CI-MS *m*/*e* 235 (M$^+$ + H, 1), 193 (19), 159 (8), 131 (100), 107 (27), 87 (18), 69 (27); high-resolution CI-MS calcd for $C_{15}H_{22}O_2$ (M$^+$ + H) 235.1698, found 235.1692.

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-[4″-(Trifluoromethyl)phenyl]-4-(3′-hydroxy-1′-methylbutoxy)-1-butene (2e).** The residue obtained from the reaction of *cis*-**1e** (260 mg, 1.0 mmol), allyltrimethylsilane (1.27 mL, 8.0 mmol, 8.0 equiv), $TiCl_4$ (0.66 mL, 6.0 mmol, 6.0 equiv), and $Ti(Oi\text{-}Pr)_4$ (1.49 mL, 5.0 mmol, 5.0 equiv) (reaction time 6 h) was purified by column chromatography on silica gel (hexane/EtOAc, 9/1) followed by Kugelrohr distillation to give 207 mg (68%) of a major diastereomer (*ul*) and 60 mg (20%) of a minor diastereomer (*lk*) (*ul*/*lk*, 3.3/1) of **2e** as colorless oils. Data for *ul*-**2e** (major): bp 115 °C (0.3 Torr); ^{1}H NMR (300 MHz) δ 7.63 (d, J = 8.1, 2 H, HC(3″)), 7.43 (d, J = 8.1, 2 H, HC(2″)), 5.69 (m, 1 H, HC(2)), 5.06 (d, J = 15.1, 1 H, $H_{cis}C(1)$), 5.03 (d, J = 12.0, 1 H, $H_{trans}C(1)$), 4.56 (t, J = 6.4, 1 H, HC(4)), 3.84 (m, 1 H, HC(1′)), 3.82 (br s, 1 H, OH), 3.53 (m, 1 H, HC(3′)), 2.53 (dt, J_t = 7.0, J_d = 14.0, 1 H, $H_aC(3)$), 2.41 (dt, J_t = 6.6, J_d = 14.0, 1 H, $H_bC(3)$), 1.64 (dt, J_t = 9.7, J_d = 14.5, 1 H, $H_aC(2')$), 1.47 (dt, J_t = 2.3, J_d = 14.5, 1 H, $H_bC(2')$), 1.14 (d, J = 6.0, 3 H, $H_3CC(1')$), 1.09 (d, J = 6.2, 3 H, $H_3CC(3')$); ^{13}C NMR (75.5 MHz) δ 145.29 (C(1″)), 133.43 (C(2)), 129.90 (q, J = 32.5, C(4″)), 127.23 (C(2″)), 125.36 (q, J = 3.5 C(3″)), 123.94 (q, J = 272.0, CF_3), 117.24 (C(1)), 77.16 (C(4)), 72.35 (C(1′)), 67.18 (C(3″), 45.73 (C(3)), 42.46 (C(2′)), 23.17 ($CH_3C(1')$), 18.82 ($CH_3C(3')$); IR (neat) 3445 (br m), 3079 (w), 2971 (m), 2934 (m), 2737 (w), 1643 (w), 1620 (w), 1456 (m), 1420 (m), 1377 (m), 1325 (s), 1165 (m), 1124 (s), 1067 (s), 1016 (m), 920 (m), 841 (m) cm^{-1}; CI-MS 303 (M$^+$ + H, 6), 284 (17), 283 (79), 261 (23), 200 (16), 199 (100), 197 (20), 179 (15), 175 (28), 105 (50), 87 (47), 69 (64), 63 (10); TLC R_f 0.43 (hexane/EtOAc, 4/1); GC t_R major (*ul*-**2e**) 23.21 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{16}H_{21}F_3O_2$ (302.34): C, 63.56; H, 7.00; F, 18.85. Found: C, 63.39; H, 7.04; F, 18.79. Data for *lk*-**2e** (minor): bp 115 °C (0.3 Torr); ^{1}H NMR (300 MHz) δ 7.58 (d, J = 8.1, 2 H, HC(3″)), 7.43 (d, J = 8.1, 2 H, HC(2″)), 5.70 (m, 1 H, HC(2)), 5.09 (d, J = 16.2, 1 H, $H_{cis}C(1)$), 5.08 (d, J = 10.8, 1 H, $H_{trans}C(1)$), 4.47 (t, J = 6.3, 1 H, HC(4)), 4.03 (m, 1 H, HC(1′)), 3.83 (m, 1 H, HC(3′)), 3.30 (br s, 1 H, OH), 2.49 (m, 2 H, $H_2C(3)$), 1.73 (dt, J_t = 9.3, J_d = 14.6, 1 H, $H_aC(2')$), 1.53 (ddd, J = 2.4, 3.7, 14.6, 1 H, $H_bC(2')$), 1.20 (d, J = 6.2, 3 H, $H_3CC(1')$), 0.93 (d, J = 6.1, 3 H, $H_3CC(3')$); ^{13}C NMR (75.5 MHz) δ 147.50 (C(1″)), 133.43 (C(2)), 129.47 (q, J = 32.3 (C(4″)), 126.55 (C(2″)), 125.14 (q, J = 3.7 C(3″)), 124.10 (q, J = 272.2, CF_3), 118.29 (C(1)), 79.79 (C(4)), 76.82 (C(1′)), 67.27 (C(3′)), 45.84 (C(3)), 42.78 (C(2′)), 23.62 ($CH_3C(1')$), 21.34 ($CH_3C(3')$); CI-MS 303 (M$^+$ + H, 6), 284 (18), 283 (86), 261 (24), 227 (10), 200 (16), 199 (100), 197 (17), 179 (16), 175 (30), 105 (60), 87 (53), 69 (79), 63 (11); GC t_R 23.62 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)); high-resolution CI-MS calcd for $C_{16}H_{22}F_3O_2$ (M$^+$ + H) 303.1572, found 303.1571.

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-4-(4″-nitrophenyl)-1-butene (2f).** The residue obtained from the reaction of *cis*-**1f** (302 mg, 1.28 mmol), allyltrimethylsilane (810 μL, 5.10 mmol, 4.0 equiv), and $TiCl_4$ (140 μL, 1.28 mmol, 1.0 equiv) (reaction time 60 min) was purified by MPLC (hexane/EtOAc, 90/10) to afford 257 mg of *ul*-**2f** (72%), a 7 mg of mixture of *ul*/*lk*-**2f** (2%), and 80 mg of *lk*-**2f** (23%). Total mass, 345 mg; total yield, 96%. An analytical sample of each diastereomer was obtained by Kugelrohr distillation. Data for *ul*-**2f** (major): bp 165 °C (0.2 Torr); ^{1}H NMR (500 MHz) δ 8.23 (d, J = 8.7, 2 H, HC(3″), HC(5″)), 7.49 (d, J = 8.7, 2 H, HC(2″), HC(6″)), 5.68 (ddt, J_d = 6.9, J_d = 10.0, J_t = 17.3, 1 H, HC(2)), 5.06–5.01 (m, 2 H, $H_2C(1)$), 4.62 (t, J = 6.5, 1 H, HC(4)), 3.88–3.82 (m, 1 H, HC(3′)), 3.57 (b, 1 H, OH), 3.55–3.50 (m, 1 H, HC(1′)), 2.57–2.51 (m, 1 H, $H_aC(3)$), 2.45–2.39 (m, 1 H, $H_bC(3)$), 1.66 (dt, J_t = 9.6, J_d = 14.5, 1 H, $H_aC(2)$), 1.49 (ddd, J = 2.1, J = 3.7, J = 14.5, 1 H, $H_bC(2')$), 1.16 (d, J = 6.0, 3 H, $H_3C(4'$ or $5')$), 1.10 (d, J = 6.2, 3 H, $H_3C(4'$ or $5')$); ^{13}C NMR (75.5 MHz) δ 149.06 (C(4″)), 147.41 (C(1″)), 133.14 (C(2)), 127.78 (C(2″), C(6″)), 126.69 (C(3″), C(5′)), 118.16 (C(1)), 77.02 (C(4)), 72.69 (C(1′)), 66.98 (C(3′)), 45.85 (C(2′)), 42.43 (C(3)), 23.39 (C(4′)), 19.00 (C(5′)); IR (CCl_4) 3625 (w), 3530 (m), 3080 (w), 2972 (m), 2933 (m), 2906 (m), 1642 (w), 1608 (m), 1529 (s), 1493 (w), 1450 (w), 1414 (m), 1378 (m), 1347 (s), 1315 (m), 1289 (m), 1230 (m), 1195 (m), 1165 (m), 1118 (m), 1080 (s), 1014 (m), 994 (m) cm^{-1}; MS (70 eV) *m*/*e* 152 (54), 130 (14), 87 (23), 69 (59), 45 (100), 43 (24), 41 (17); TLC R_f 0.62 (hexane/EtOAc, 50/50); GC t_R 27.79 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (20 min)). Anal. Calcd for $C_{15}H_{21}NO_4$ (279.34): C, 64.49; H, 7.58; N, 5.01. Found: C, 64.41; H, 7.67; N, 5.09. Data for *lk*-**2f** (minor): ^{1}H NMR (500 MHz) δ 8.16 (d, J = 8.8, 2 H, HC(3″), HC(5″)), 7.46 (d, J = 8.7, 2 H, HC(2″), HC(6″)), 5.71–5.63 (m, 1 H, HC(2)), 5.06–5.02 (m, 2 H, $H_2C(1)$), 4.51 (dd, J = 5.9, J = 6.7, 1 H, HC(4)), 4.02–3.96 (m, 1 H, HC(3′)), 3.83–3.77 (m, 1 H, HC(1′)), 3.25 (b, 1 H, OH)), 2.52–2.47 (m, 1 H, $H_a(C(3))$, 2.44–2.39 (m, 1 H, $H_bC(3)$), 1.72 (dt, J_t = 9.1, J_d = 14.5, 1 H, $H_aC(2')$), 1.51 (ddd, J = 2.5, J = 4.3, J = 14.5, 1 H, $H_bC(2')$), 1.17 (d, J = 6.2, 3 H, $H_3C(4'$ or $5')$), 0.92 (d, J = 6.1, 3 H, $H_3C(4'$ or $5')$); ^{13}C NMR (75.5 MHz) δ 151.21 (C(4″)), 147.32 (C(1″)), 133.16 (C(2)), 127.30 (C(2″), C(6″)), 126.67 (C(3″), C(5″)), 118.29 (C(1)), 79.53 (C(4)), 77.65 (C(1′)), 67.28 (C(3′)), 45.97 (C(2′)), 42.82 (C(3)), 23.85 (C(4′)), 21.47 (C(5′)); IR (CCl_4) 3625 (w), 3531 (m), 3080 (w), 2972 (m), 2933 (m), 2906 (m), 1642 (w), 1608 (m), 1529 (s), 1493 (w), 1450 (w), 1414 (w), 1378 (m), 1347 (s), 1315 (w), 1289 (m), 1230 (w), 1195 (w), 1165 (w), 1118 (m), 1080 (s), 1014 (w), 994 (w) cm^{-1}; MS (70 eV) *m*/*e* 152 (56), 130 (18), 88 (11), 87 (27), 69 (58), 45 (100), 43 (24), 41 (18); TLC R_f 0.56 (hexane/EtOAc, 50/50); GC t_R 28.24 min (HP-5, 50 m, 80 °C (4 min), 10 °C/min, 250 °C (20 min)). Anal. Calcd for $C_{15}H_{21}NO_4$ (279.34): C, 64.49; H, 7.58; N, 5.01. Found: C, 60.49; H, 7.58; N, 5.00.

***rel*-(4(*R*,*S*),1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-1-decen-5-yne (2g).** The residue obtained from the reaction of *cis*-**1g** (329 mg, 1.68 mmol), allyltrimethylsilane (1.068 mL, 6.72 mmol), and $TiCl_4$ (234 μL, 2.12 mmol, 1.25 equiv) (reaction time 60 min) was purified by column chromatography on silica gel (hexane/EtOAc, 90/10). The diastereomers were separated (*ul*/*lk*, 2.0/1) and Kugelrohr distilled (86% combined yield). Data for *ul*-**2g** (major): bp 140 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 5.88 (m, 1 H, HC(2)), 5.15–5.09 (m, 2 H, $H_2C(1)$), 4.23 (m, 1 H, HC(4)), 4.10 (m, 1 H, HC(1′)), 4.00 (m, 1 H, HC(3′)), 3.74 (s, 1 H, OH), 2.42 (m, 2 H, $H_2C(7)$), 2.19 (t, J = 5.2, 2 H, $H_2C(3)$), 1.61–1.37 (m, 6 H), 1.14 (d, J = 6.2, 3 H, $CH_3C(3')$), 1.11 (d, J = 6.0, 3 H, $CH_3C(1')$), 0.91 (t, J = 7.0, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 133.38 (C(2)), 117.66 (C(1)), 86.67 (C(5)), 77.89 (C(6)), 73.09 (C(1′)), 67.57 (C(4)), 65.37 (C(3′)), 45.37 (C(2′)), 40.52 (C(3)), 30.52 (C(8)), 23.03 (C(4′)), 21.64 (C(7)), 19.02 (C(5′)), 18.05 (C(9)), 13.32 (C(10)); IR (neat) 3744 (w), 3484 (m), 3079 (m), 2965 (s), 2934 (s), 2874 (s), 1644 (m), 1456 (m), 1431 (m), 1377 (s), 1321 (s), 1293 (m), 1121 (s), 1078 (s), 994 (s), 957 (m), 918 (s) cm^{-1}; MS (70 eV) *m*/*e* 197 (15), 111 (88), 93 (16), 91 (18), 87 (23), 79 (17), 77 (17), 69 (100), 67 (13), 55 (24), 45 (83), 43 (24), 41 (48), 39 (16); TLC R_f 0.20 (hexane/EtOAc, 90/10); GC t_R 21.47 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 10.99. Found: C, 75.56; H, 10.98. Data for *lk*-**2g** (minor): bp 140 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 5.88 (m, 1 H, HC(2)), 5.13 (m, 2 H, $H_2C(1)$), 4.12 (m, 1 H, HC(4)), 3.95 (m, 1 H, HC(1′)), 3.81 (m, 1 H, HC(3′)), 3.20 (s, 1 H, OH), 2.44 (t, J = 6.6, 2 H, $H_2C(7)$), 2.19 (dt, J_d = 1.5, J_t = 6.6, 2 H, $H_2C(3)$), 1.72–1.60 (dt, J_d = 9.3, J_t = 14.6, 2 H, $H_2C(2')$), 1.52–1.35 (m, 4 H), 1.30 (d, J = 6.0, 3 H, $H_3C(3')$), 1.15 (d, J = 6.3, 1 H, $H_3C(1')$), 0.90 (t, J = 7.0, 3 H, H_3C-(10)); ^{13}C NMR (75.5 MHz) δ 133.65 (C(2)), 118.19 (C(1)), 86.34 (C(5)), 79.85 (C(6)), 77.00 (C(1′)), 68.78 (C(4)), 67.43 (C(3′)), 46.01 (C(2′)), 41.37 (C(3)), 30.71 (C(8)), 23.71 (C(4′)), 21.97 (C(7)), 21.46 (C(5′)), 18.47 (C(9)), 13.65 (C(10)); IR (neat) 3445 (m), 3078 (w), 2965 (s), 2934 (s), 2874 (s), 2230 (w), 1836 (w), 1644 (m), 1458 (m), 1431 (m), 1377 (s), 1323 (s), 1230 (w), 1124 (s), 1068 (s), 993 (m), 956 (m), 916 (s) cm^{-1}; MS (70 eV) *m*/*e* 197 (16), 111 (87), 93 (17), 91 (19), 87 (24), 81 (11), 79 (19), 77 (19), 69 (100), 67 (15), 55 (27), 45 (95),

43 (28), 41 (57), 39 (19); TLC R_f 0.14 (hexane/EtOAc, 90/10); GC t_R 21.93 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 10.99. Found: C, 75.53; H, 11.01.

***rel*-(1′*R*,3′*S*)-4-[3′-(Benzyloxy)-1′-methylbutoxy]-1-decene (4a).** Potassium hydride (35% dispersion in mineral oil, 330 mg, 2.88 mmol, 2 equiv) was washed with hexane (2 × 5 mL) and suspended in DME (5 mL). The suspension was cooled to 0 °C, and **2a** (350 mg, 1.44 mmol) in DME (7 mL) was added to the suspension. After the solution was stirred for 10 min at 0 °C, benzyl bromide (493 mg, 2.88 mmol, 2 equiv) was added. The reaction was quenched with water after stirring for 1 h at room temperature. The solution was poured into water and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with brine (25 mL), dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 19/1) followed by Kugelrohr distillation to afford 430 mg (90%) of **4a** as a clear colorless oil: bp 200 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.34 (m, 5 H, Ph), 5.79 (m, 1 H, HC(2)), 5.05 (m, 2 H, $H_2C(1)$), 4.61–4.41 (AB q, J = 10.0, 2 H, CH_2Ph), 3.63 (m, 2 H, HC(1′), HC(3′)), 3.36 (m, 1 H, HC(4)), 2.22 (m, 2 H, $H_2C(2')$), 1.98 (m, 1 H, HC(3)), 1.47–1.10 (m, 17 H), 0.90 (m, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 138.91 (Ph), 135.40 (C(2)), 135.25 (C(2)), 128.23 (Ph), 127.58 (Ph), 127.34 (Ph), 116.62 (C(1)), 116.45 (C(1)), 76.66 (C(4)), 76.38 (C(4)), 72.06 (CH_2Ph), 70.58 (C(1′)), 70.35 (C(1′)), 70.16 (C(3′)), 70.10 (C(3′)), 44.64 (C(2′)), 44.41 (C(2′)), 39.31 (C(3)), 38.95 (C(3)), 34.56 (C(5)), 34.28 (C(5)), 31.85 (C(8)), 31.82 (C(8)), 29.47 (C(7)), 29.44 (C(7)), 25.48 (C(6)), 25.35 (C(6)), 22.62 (C(9)), 20.73 (C(1′a)), 20.35 (C(1′a)), 19.89 (C(4′)), 19.83 (C(4′)), 14.08 (C(10)); IR (neat) 3069 (w), 3031 (w), 2965 (s), 2928 (s), 2857 (s), 1497 (m), 1455 (m), 1374 (s), 1337 (m), 1115 (s), 1067 (s), 1028 (s), 997 (m), 912 (m) cm^{-1}; MS (70 eV) *m/e* no M + 1, 199 (9), 177 (17), 159 (6), 147 (5), 117 (5), 107 (9), 105 (5), 91 (100), 85 (5), 70 (18), 69 (10); TLC R_f 0.70 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{22}H_{36}O_2$ (332.42): C, 79.46; H, 10.91. Found: C, 79.46; H, 10.95.

(4*R*,1′*R*,3′*R*)-4-(3′-Hydroxy-1′-methylbutoxy)-1-decene (9a). The residue obtained from the reaction of **8a** (102 mg, 0.50 mmol), allyltrimethylsilane (630 μL, 4.0 mmol), and the "titanium blend" (10.07 mL, 11.0 equiv) was purified by column chromatography on silica gel (hexane/EtOAc, 90/10) followed by Kugelrohr distillation to give 18 mg (98%) of **9a** as a colorless oil: bp 150 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 5.79–5.73 (m, 1 H, HC(2)), 5.05–4.99 (m, 2 H, $H_2C(1)$), 4.11–4.06 (m, 1 H, HC(3′)), 3.85–3.80 (m, 1 H, HC(1′)), 3.38–3.36 (m, 1 H, HC(4)), 3.34 (d, J = 2.5, 1 H, OH), 2.33–2.15 (m, 2 H, $H_2C(2')$), 1.63–1.29 (m, 12 H), 1.16–1.13 (m, 6 H, $H_3C(4')$, $H_3C(5')$), 0.85 (m, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 135.01 (C(2)), 116.75 (C(1)), 76.78 (C(3′)), 71.47 (C(4)), 64.24 (C(1′)), 44.33, 39.05, 33.58, 31.73, 29.44, 24.97, 23.54 (C(5)), 22.54, 19.52 (C(4)), 14.01 (C(10)); IR (neat) 3852 (w), 3677 (w), 3438 (m), 3076 (w), 2963 (s), 2930 (s), 2858 (s), 2365 (w), 1826 (w), 1641 (w), 1458 (m), 1373 (m), 1337 (m), 1154 (m), 1119 (s), 1057 (s), 995 (m), 961 (w), 912 (m) cm^{-1}; MS (70 eV) (no M$^+$) 201 (66), 143 (37), 115 (36), 97 (17), 87 (45), 69 (100), 45 (12); TLC R_f 0.17 (hexane/EtOAc, 90/10); GC t_R 21.68 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{30}O_2$ (242.40): C, 74.32; H, 12.47. Found: C, 74.40; H, 12.53.

***rel*-(1′*R*,3′*R*)-4-[3′-(Benzyloxy)-1′-methylbutoxy]-1-decene (6a).** Potassium hydride (35% dispersion in mineral oil, 330 mg, 2.88 mmol, 2 equiv) was washed with hexane (2 × 5 mL) and suspended in DME (5 mL). The suspension was cooled to 0 °C, and **9a** (350 mg, 1.44 mmol) in DME (7 mL) was added to the suspension. After the solution was stirred for 10 min at 0 °C, benzyl bromide (493 mg, 2.88 mmol, 2 equiv) was added. The reaction was quenched with water after stirring for 1 h at room temperature. The solution was poured into water and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with brine (25 mL), dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography (hexane/EtOAc, 19/1) followed by Kugelrohr distillation to afford 430 mg (90%) of the ether as a clear colorless oil. For **6a**: bp 200 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 7.33 (m, 5 H, Ph), 5.86 (m, 1 H, CH(2)), 5.07 (m, 2 H, $H_2C(1)$), 4.67–4.39 (AB q, J = 11.2, 2 H, CH_2Ph), 3.79 (m, 2 H, HC(1′), HC(3′)), 3.35 (m, 1 H, HC(4)), 2.25 (m, 2 H, $H_2C(2')$), 1.67–1.13 (m, 14 H), 0.89 (t, J = 8, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 139.01 (Ph), 138.99 (Ph), 135.23 (C(2)), 135.25 (C(2)), 128.38 (Ph), 128.30 (Ph), 127.66 (Ph), 127.66 (Ph), 127.48 (Ph), 127.38 (Ph), 127.36 (Ph), 116.71 (C(1)), 116.39 (C(1)), 77.16 (C(4)), 76.53 (C(4)), 72.05 (C(3′)), 71.91 (C(3′)), 70.24 (CH_2Ph), 70.08 (C(1′)), 69.62 (C(1′)), 45.78 (C(2′)), 39.27 (C(3)), 38.71 (C(3)), 34.50 (C(5)), 34.15 (C(5)), 31.90 (C(8)), 31.88 (C(8)), 29.58 (C(7)), 29.48 (C(7)), 25.60 (C(6)), 25.45 (C(6)), 22.65 (C(9)), 21.48 (C(1′a)), 20.97 (C(1′a)), 19.87 (C(4′)), 19.83 (C(4′)), 14.12 (C(10)), 14.09 (C(10)); IR (neat) 3067 (w), 3031 (w), 2965 (s), 2928 (s), 2859 (s), 1640 (w), 1497 (m), 1455 (m), 1374 (s), 1345 (m), 1154 (s), 1115 (s), 1092 (s), 1065 (s), 1028 (s), 997 (m), 911 (m) cm^{-1}; MS (70 eV) *m/e* (no M$^+$) 199 (9), 177 (17), 159 (6), 147 (5), 117 (5), 107 (9), 105 (5), 91 (100), 85 (5), 70 (18), 69 (10); TLC R_f 0.70 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{22}H_{36}O_2$ (332.42): C, 79.46; H, 10.91. Found: C, 79.58; H, 10.86.

7. Correlation of Configuration. (4*R*,1′*R*,3′*S*)-4-[3′-(Benzoyloxy)-1′-methylbutoxy]-1-decene (14). To a solution of **9a** (98 mg, 0.41 mmol), benzoic acid (50 mg, 0.41 mmol), and triphenylphosphine (108 mg, 0.41 mmol) in THF (410 μL) was added a solution of diethyl azodicarboxylate (71 mg, 0.41 mmol) in THF (410 μL). After the solution was stirred at room temperature for 3 h, the solvent was removed under vacuum and the residue purified by column chromatography on silica gel (hexane/EtOAc, 94/6) followed by Kugelrohr distillation to give 89 mg (63%) of **14** as a colorless oil: bp 180 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 8.03 (d, J = 7.0, 2 H, HC(2″), HC(6″)), 7.55 (t, J = 7.5, 1 H, HC(4″)), 7.43 (t, J = 7.8, 2 H, HC(3″), HC(5″)), 5.83–5.77 (m, 1 H, HC(2)), 5.24–5.19 (m, 1 H, HC(3′)), 5.04–4.98 (m, 2 H, $H_2C(1)$), 3.62–3.58 (m, 1 H, HC(1′)), 3.35–3.32 (m, 1 H, HC(4)), 2.08–2.06 (t, J = 6.4, 2 H, $H_2C(2')$), 2.08 (m, 2 H, $H_2C(3)$), 1.68–1.63 (m, 2 H), 1.37 (d, J = 6.1, 3 H, $H_3C(4')$), 1.27–1.22 (m, 8 H), 1.17 (d, J = 6.2, 3 H, $H_3C(5')$), 0.88 (t, J = 6.8, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 165.95 (C(O)), 135.34 (Ph), 132.73 (Ph), 130.71 (Ph), 129.45 (Ph), 128.26 (C(2)), 116.48 (C(1)), 76.84 (C(4)), 70.32, 69.24, 43.62, 39.33, 34.29, 31.82, 29.50, 25.38, 22.62, 20.70 (C(4′)), 20.54 (C(5′)), 14.06 (C(10)); IR (neat) 3070 (w), 2932 (s), 2859 (m), 1719 (s), 1642 (w), 1603 (w), 1586 (w), 1453 (m), 1377 (m), 1335 (m), 1314 (m), 1273 (s), 1175 (m), 1103 (s), 1069 (s), 1026 (m), 997 (m), 912 (m) cm^{-1}; TLC R_f 0.32 (hexane/EtOAc, 94/6); GC t_R 33.20 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (15 min)). Anal. Calcd for $C_{22}H_{34}O_3$ (346.51): C, 76.26; H, 9.89. Found: C, 76.22; H, 9.86.

(4*R*,1′*R*,3′*S*)-4-(3′-Hydroxy-1′-methylbutoxy)-1-decene (2a). A solution of ester **14** (89 mg, 0.26 mmol) in 0.18 M methanolic NaOH (1.79 mmol in 10.1 mL) was magnetically stirred at room temperature for 10 h. The solvent was removed under vacuum, and the residue was partitioned between diethyl ether (10 mL) and water (10 mL). The organic phase was removed and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried (K_2CO_3) and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 90/10) followed by Kugelrohr distillation to give 53 mg (84%) of **2a** as a colorless oil: bp 140 °C (0.1 Torr); ^{1}H NMR (300 MHz) δ 5.86–5.81 (m, 1 H, HC(2)), 5.07–5.01 (m, 2 H, HC(1)), 3.99–3.94 (m, 1 H, HC(3′)), 3.89 (s, 1 H, OH), 3.83–3.76 (m, 1 H, HC(1′)), 3.46–3.42 (m, 1 H, HC(4)), 2.28–2.19 (m, 2 H, $H_2C(2')$), 1.16–1.01 (m, 6 H, $H_3C(4')$, $H_3C(5')$), 0.89 (m, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) δ 134.95 (C(2)), 116.79 (C(1)), 75.91 (C(1′)), 74.00 (C(4)), 67.85 (C(3′)), 45.81, 39.37, 33.43, 31.75, 29.49, 25.10, 23.49 (C(5′)), 22.58, 20.45 (C(4′)), 14.03 (C(10)); IR (neat) 3443 (m), 3076 (w), 2965 (s), 2932 (s), 2858 (s), 2363 (w), 1830 (w), 1642 (w), 1456 (m), 1374 (m), 1335 (m), 1300 (w), 1121 (m), 1080 (m), 1053 (m), 997 (m), 995 (w), 912 (m), 843 (w) cm^{-1}; MS (70 eV) (no M$^+$) 115 (24), 97 (39), 87 (29), 71 (16), 69 (100), 55 (50), 45 (79), 43 (25), 41 (31); TLC R_f 0.21 (hexane/EtOAc, 9/1); GC t_R 22.99 min (HP-5, 50 m, 80 °C (5 min), 8 °C/min, 250 °C (5 min)). Anal. Calcd for $C_{15}H_{30}O_2$ (242.40): C, 74.32; H, 12.47. Found: C, 74.19; H, 12.53.

8. General Procedure for Allylation of Acetals, "Titanium Blend" ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5). A Lewis acid solution ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5) was prepared by dissolving titanium tetrachloride (330 μL, 3.0 mmol) in dry dichloromethane (9 mL) under an atmosphere of nitrogen and then adding titanium tetraisopropoxide (740 μL, 2.5 mmol) with magnetic stirring. After complete addition of titanium tetraisopropoxide, the resulting solution was stirred for 45 min. For every acetal the reactions were run in triplicate under the following conditions: The acetal (0.50 mmol) and allyltrimethylsilane (636 μL, 4.0 mmol) were dissolved in dry dichloromethane (5.0 mL, 0.1 M in acetal) and cooled to −78 °C under an atmosphere of nitrogen. The freshly prepared Lewis acid solution (10.07 mL, 11 equiv) was added via syringe (addition time 2.0 h) to the magnetically stirred acetal and allyltrimethylsilane solution. After complete addition of the Lewis acid solution, the resulting heterogeneous solution was stirred for an additional period of time (see table), followed by quenching with 1.0 N NaOH in methanol (10 mL) and warming to room temperature. The quenched solution was diluted with diethyl ether (15 mL), filtered through a plug of Florisil, and analyzed by gas chromatography.

Control Additions with "Titanium Blend" ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5). A Lewis acid solution ($TiCl_4$/Ti(O*i*-Pr)$_4$, 6/5) was prepared by dissolving titanium tetrachloride (330 μL, 3.0 mmol) in dry dichloromethane (9 mL) under an atmosphere of nitrogen and then adding titanium tetraisopropoxide (740 μL, 2.5 mmol) with magnetic stirring. After complete addition of titanium tetraisopropoxide, the resulting solution was stirred for 45 min. For every acetal the reactions were run in triplicate under

the following conditions: The acetal (0.10 mmol) and allyltrimethylsilane (125 μL, 0.8 mmol) were dissolved in dry dichloromethane (1.0 mL, 0.1 M in acetal) was cooled to −78 °C under an atmosphere of nitrogen. The freshly prepared Lewis acid solution (659 μL, 3.6 equiv) was added via syringe (addition time 9 min) to the magnetically stirred acetal and allyltrimethylsilane solution. After complete addition of the Lewis acid solution, the resulting heterogeneous solution was stirred for an additional 36 min, quenched with 1.0 N NaOH in methanol (500 μL), and warmed to room temperature. The quenched solution was diluted with diethyl ether (2 mL), filtered through a plug of Florisil, and analyzed by gas chromatography.

Solvent Study. For each solvent the reactions were run in triplicate under the following conditions: A solution of **1** (20 mg, 0.10 mmol) and allyltrimethylsilane (64 μL, 0.40 mmol) in an appropriately dried solvent (see Tables VII and VIII) (1.0 mL, 0.1 M) was cooled to −78 °C under an atmosphere of nitrogen. Then titanium tetrachloride (13 μL, 0.12 mmol) was added to the above solution with magnetic stirring. After stirring for 1 h, the reaction mixture was quenched with 1.0 N NaOH in methanol (2 mL), and the solution was warmed to room temperature. The reaction mixture was diluted with diethyl ether (5 mL) and filtered through a plug of Florisil. The resulting solution was analyzed by gas chromatography.

Concentration Study. A magnetically stirred solution of acetal *cis*-**1a** (0.50 mmol, 0.005–0.5 M) and allyltrimethylsilane (1–20 equiv) in dry dichloromethane was cooled to −78 °C. Then titanium tetrachloride (0.5–10 equiv) was added to the above solution. After stirring (see specific substrate for reaction time), the reaction mixture was quenched with 1.0 N NaOH in methanol, and the solution was warmed to room temperature. The quenched solution was diluted with diethyl ether, filtered through a plug of Florisil, and analyzed by gas chromatography.

General Procedure for the Allylation of 3 and 5. A solution of enol ether **3** or **5** (30 mg, 0.103 mmol) and allyltrimethylsilane (32.8 μL, 0.207 mmol, 2.0 equiv) in dichloromethane (2 mL) was cooled to −78 °C. Trifluoromethanesulfonic acid (8.7 mL, 0.098 mmol, 0.95 equiv) was added neat at −78 °C, and the solution was stirred for 5 min. The reaction was quenched by the addition of 1 mL of 1 N NaOH/MeOH solution and was allowed to warm to room temperature. A 1-mL aliquot was removed, washed with water, and extracted with EtOAc. This aliquot was passed through a short plug of Florisil (3 cm) and then analyzed by capillary gas chromatography to obtain diastereomeric ratios.

General Procedure for the Allylation of 7 (TMSOTf). A solution of the acyclic acetal, **7** (50 mg, 0.103 mmol), and allyltrimethylsilane (50 μL, 0.309 mmol, 3 equiv) in dichloromethane (2 mL) was cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (2 μL, 0.01 mmol, 0.1 equiv) was next added at −78 °C, and the solution was stirred for 2 h. The reaction was quenched by the addition of 1 mL of 1 N NaOH/MeOH solution and was allowed to warm to room temperature. A 1-mL aliquot was removed, washed with water, and extracted with EtOAc. This was passed through a short plug of Florisil (3 cm) and then analyzed by capillary gas chromatography to obtain diastereomeric ratios.

General Procedure for the Allylation of 7 ("Titanium Blend" $TiCl_4$/$Ti(Oi\text{-}Pr)_4$, 6/5). A Lewis acid solution ($TiCl_4$/$Ti(Oi\text{-}Pr)_4$, 6/5) was prepared by dissolving titanium tetrachloride (102 μL, 0.93 mmol) in dry dichloromethane (3 mL) under an atmosphere of nitrogen and then adding titanium tetraisopropoxide (231 μL, 0.78 mmol) with magnetic stirring. After complete addition of titanium tetraisopropoxide, the resulting solution was stirred for 45 min. The reactions were run in triplicate under the following conditions: The acetal **7** (0.155 mmol) and allyltrimethylsilane (197 μL, 1.24 mmol) were dissolved in dry dichloromethane (1.6 mL, 0.1 M in acetal) and cooled to −78 °C under an atmosphere of nitrogen. The freshly prepared Lewis acid solution (3.3 mL, 11 equiv) was added via syringe (addition time 2.0 h) to the magnetically stirred acetal and allyltrimethylsilane solution. After complete addition of the Lewis acid solution, the resulting heterogeneous solution was stirred for an additional 2 h followed by quenching with 1.0 N NaOH in methanol (2 mL) and warming to room temperature. The quenched solution was diluted with diethyl ether (5 mL), filtered through a plug of Florisil, and analyzed by gas chromatography.

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Photochemical and Photophysical Studies of Tetracycline[1]

Harry Morrison,* Gerard Olack, and Changhe Xiao

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907. *Received May 6, 1991. Revised Manuscript Received June 24, 1991*

Abstract: The photochemistry and photophysics of tetracycline (Tc) have been studied in aqueous and organic media. The primary photochemical reaction upon excitation into S_1 is conversion to lumitetracycline (LTc) and dimethylamine at pH's <7.5. Higher pH's and especially the presence of 2-mercaptoethanol favor the formation of anhydrotetracycline. Oxygen quenches LTc formation but has a minimal effect on Tc fluorescence; benzophenone sensitizes LTc formation. Triplet sensitization also produces de(dimethylamino)tetracycline (DTc), as does photolysis into S_2. It is proposed that DTc and LTc are derived from upper and lower triplets, respectively. Tc fluorescence shows a profound abnormal Stokes shift relative to absorption and a significant blue shift in this emission in basic media. The former phenomenon is attributed to an adiabatic excited-state intramolecular proton transfer (ESIPT) from the phenol functionality to the oxygen at C11. Subsequent intersystem crossing and/or an analogous ESIPT within T_1 provides a triplet species the decay of which is accompanied by intramolecular displacement of dimethylamine by C11a to give LTc. The blue-shifted emission in base is associated with a red shift in absorption; both spectral manifestations are attributed to deprotonation of the Tc ground state at C12 to form Tc^-, a species apparently unable to undergo ESIPT and photochemical conversion to LTc.

The tetracyclines represent a class of well-known phototoxic antibiotics.[2,3] The primary photochemical events and the cellular targets involved in the phototoxic response are as yet unknown, and it is also unclear as to whether the parent molecules, and/or photoproducts thereof, are responsible for the phenomenon. In fact, several major photoproducts of tetracycline (Tc) have been isolated and identified. These are shown in Scheme I and include

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