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Stereochemical Studies on the Addition of Allylsilanes to Aldehydes. The S_E' Component

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Dedicated to the memory of Ernest L. Eliel, the doyen of stereochemistry

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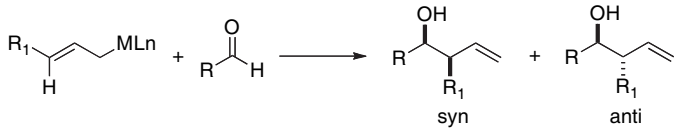
Abstract: Model compounds *ul*-**1** and *lk*-**1** have been studied to determine both the position of the silicon electrofuge and the relative orientation of the double bonds in the transition structure of the allylmetal-aldehyde condensation. The use of the deuterium label allows an unbiased assessment of the *syn* versus *anti* S_E' pathways. The synthesis of configurational proof of model systems *ul*-**1** and *lk*-**1** are discussed as well as the cyclization of the model system. Cyclization of model **1** was found to proceed with high selectivity via an *anti* S_E' pathway regardless of the proximal/distal ratio for all Lewis acids studied. Reactions promoted by fluoride ion favored the proximal product, but both *syn* and *anti* pathways were observed.
Key words: Allyllsilanes, Addition to Aldehides, Condensation Reaction, Cyclization, Stereochemistry.

Resumen: Se estudiaron los compuestos modelo *ul*-**1** y *lk*-**1** para determinar tanto la posición del silicio electrofugo como la orientación relativa de los dobles enlaces en el estado de transición de la condensación alilmetal-aldehído. El uso del marcaje con deuterio permite una evaluación adecuada de los mecanismos *syn* versus *anti* S_E'. Se describe la síntesis de los compuestos modelo *ul*-**1** y *lk*-**1** , así como se discute el proceso de ciclación de dichos compuestos. Se encontró que la ciclación de los compuestos modelo **1** procede con elevada selectividad vía un mecanismo S_E', independientemente de la proporción de los productos proximal/distal que se obtengan y de los ácidos de Lewis estudiados. Las reacciones promovidas por el ion fluoruro favorecen el producto proximal, aunque ambos caminos *syn* y *anti* fueron observados.
Palabras clave: Alilsilanos, adición a aldehídos, reacción de condensación, ciclización, esteroquímica.

Introduction

The controlled construction of stereocenters in open-chain systems is of primary importance in the synthesis of polyketide natural products. Many methods have been developed recently to synthesize the long sequences of stereocenters present in these molecules including the addition of allylmetal reagents to aldehydes [1]. The utility of the allylmetal-aldehyde condensation partly derives from the high yield, excellent regioselectivity, and the mild conditions under which it can be employed.

The reaction of a substituted allylmetal with an aldehyde will result in the formation of a mixture of diastereomeric homoallylic alcohols (Scheme 1) [2]. The allylmetal-aldehyde condensation has proven to be successful with a wide variety of metals including boron [3], tin [4], silicon [5], chromium [6], and titanium [7]. The diastereoselectivity observed in the Lewis acid mediated allylmetal-aldehyde condensations is known to be dependent upon the allylmetal used. This dependence has been classified into the following three groups that relate the stereochemical outcome of the reaction to the geometry of the double bond [1f,8]; Type 1 reactions where the *syn* /*anti* ratio reflects the *Z*/*E* ratio of the starting allylmetal (B, Al, Sn); Type 2 reactions where the reaction is *syn* -selective independent of the geometry of the allylmetal (Sn, Si); and Type 3 reactions where the reaction is *anti*-selective independent of the geometry of the allylmetal (Cr, Ti, Zr).



Scheme 1

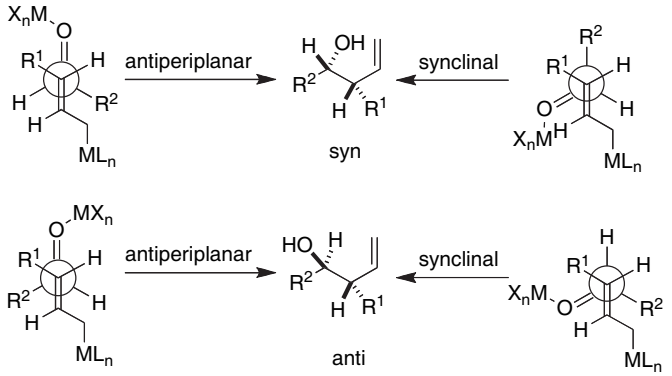
Proposals for transition state geometry have been set forth for all three types of reactions [9]. The stereoselectivities observed in Type 1 reactions have been explained by a chair-like transition structure where the allylmetal is coordinated to the carbonyl oxygen [3a]. The aldehyde is thought to orient in such a manner that the R group is placed in an equatorial position of the chair in order to minimize steric interactions between the ligands on boron and the allyl unit. This proposal accounts for the high degree of stereoselection obtained when isomerically pure *E* or *Z* crotyl boronates or boranes are allowed to react with aldehydes. The addition of an allylborane or allylboronic acid has been studied computationally by Houk [10a] and Gung [10b]. A chair-like arrangement of the two components was predicted for these reactions from ab initio calculations. These results agree with the previous mechanistic proposals for reactions of allylboronates with aldehydes.

Many investigators have extended this method by using enantiomerically enriched auxiliaries to modify the boron unit. High levels of enantioselection have been obtained by using

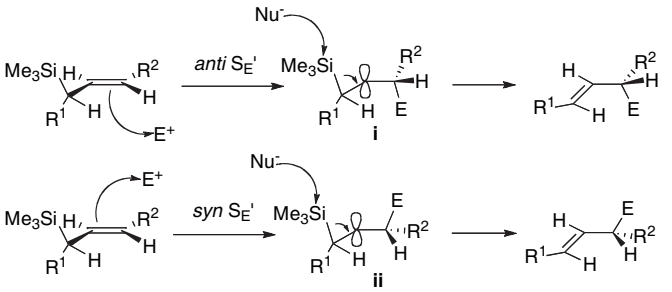
commercially available tartrate esters, (+)- and (-)-pinene and 3-(+)-carene. In all of these reactions the observed diastereoselectivity parallels the isomeric purity of the starting allyl-boron reagent.

The mechanism of Type 3 reactions utilizing Cr, Ti, or Zr as the allylmetal is believed to proceed through a chair-like transition structure [1f]. It is thought that the initially formed allylmetal reagent can equilibrate between the *E* and *Z* forms with the *E* isomer predominating at lower temperatures. This *E*-organometallic reagent can then react through a chair-like transition state to afford *anti* homoallylic alcohols. The selectivities obtained with these organometallic reagents are usually dependent upon the size of the substituents on the aldehyde and the ligands attached to the allylmetal.

Mechanistic proposals have been advanced for Type 2 reactions which involve an open chain arrangement of the reacting species [1f]. The two limiting hypotheses identify the torsional angle between the double bonds (synclinal (60°) and antiperiplanar (180°)) and minimization of nonbonded interactions as key features for internal diastereoselection (Scheme 2). The external induction process is governed primarily by the relative disposition of the metal electrofuge and the aldehyde (*anti* or *syn* S_E') in the transition structure (Scheme 3). Thus, the orientation of the double bonds and the location of the metal in the transition structure uniquely define the stereochemical outcome of the reaction.



Scheme 2



Scheme 3

As will be documented in the following section, the addition of allylsilanes and allylstannanes to aldehydes has been extensively studied. In previous stereochemical studies of the allylation reaction the internal stereoselection process and the external induction process have been addressed independently. Our interest was in elucidating the stereochemical features that control both of these processes simultaneously. This paper describes the synthesis and cyclization of a model system that can *unambiguously* determine the stereochemical course of addition in an allylsilane-aldehyde reaction.

Background

The Lewis acid-mediated addition of electrophiles to allylsilanes has been extensively studied [5]. In most cases the addition of an electrophile to an allylsilane is an *anti* process. In the ground state, simple allylsilanes are known to prefer the conformation where the small substituent H eclipses the double bond [11]. The electrophile can then approach the double bond from the same side as the allylmetal (*syn* S_E') or from the side opposite the allylmetal (*anti* S_E'). The configuration of the newly formed stereogenic center is therefore dependent upon the directionality of attack (Scheme 3). After attack of the electrophile on the double bond only a slight rotation of the C-C bond is necessary for the formation of the intermediate **ii** which is stabilized by hyperconjugation with the silicon atom (Scheme 3) [12]. The silyl group is then released, resulting in the stereoselective formation of a *trans*-olefin.

The site selectivity and stereochemical course of electrophilic additions to allylsilanes have been modeled computationally by Hehre [13]. In this study the conformational profile of 2-silylbut-3-ene was determined and 3 energy minima were observed (Chart I). In the two most stable conformations the C-Si bond is perpendicular to the C-C double bond.

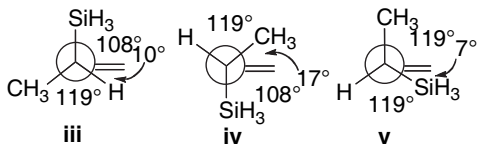
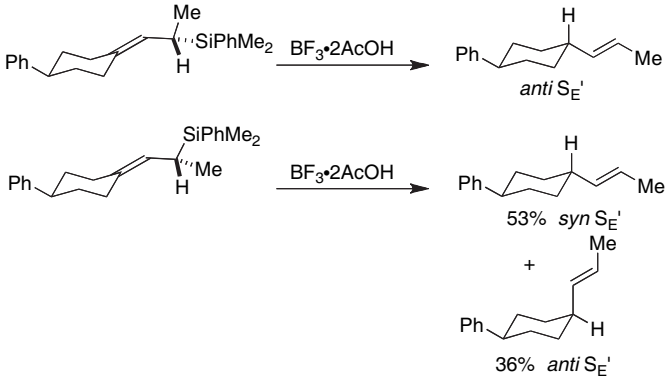


Chart 1

The interaction of a point charge (α proton) and the allylsilane was next studied in the three low energy conformers. By using this "test" electrophile an electrostatic potential map was developed. The electrophilic attack onto the two low energy conformers of 2-silylbut-3-ene, **iii** and **iv**, was shown to occur *anti* to the silyl group. In the high-energy conformer **v**, attack will occur *anti* to the methyl group. These results were interpreted as a tendency of the approaching electrophile to avoid regions of high positive charge (the silyl group) due to electrostatic repulsion.

The stereochemical course of the addition of electrophiles to allylsilanes has been studied to establish the position of the silicon electrofuge in the transition structure of these reactions [14]. In an early study, Fleming examined the additions of electrophiles to stereochemically-defined allylsilanes which were constrained in either a five or six-membered ring [15,16]. The addition of an electrophile to these substrates resulted in the formation of products from both *anti* and *syn* S_E' pathways. Fleming concluded that the stereochemical constraints of the ring systems were likely to be the dominant influence in the observed stereoselectivity of these reactions. Therefore, these models cannot be used to elucidate the intrinsic preference of the S_E' reaction.

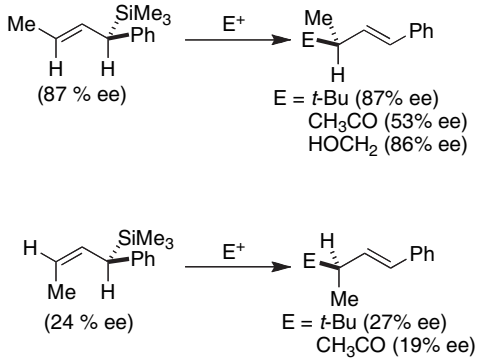
Fleming expanded the study of the S_E' reaction to include the use of acyclic allylsilanes [17]. These allylsilanes were subjected to protiodesilylation, acetylation, and epoxidation. In the protiodesilylation experiments the allylsilane cleanly gives products from an *anti* S_E' reaction whereas the diastereomeric allylsilane affords a mixture of both *syn* and *anti* S_E' products (Scheme 4). Results from a deuteration study indicate that in addition to the *anti* selectivity of the allylsilane, the cyclohexyl ring has a preference for axial protonation. When this axial preference is in opposition to the *anti* selectivity of the allylsilane, the molecule will find an alternative reaction where the stereospecificity is lost.



Scheme 4

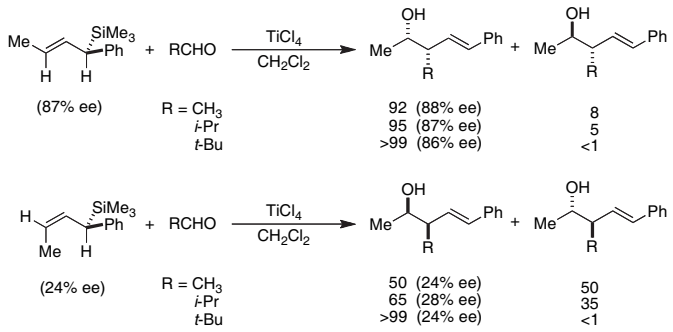
Wetter [18] and Kitching [19] have also examined the stereochemical course of the S_E' reaction. In the studies performed by Wetter the reaction of a disilylalkene proceeds through either the *syn* or *anti* S_E' pathways depending upon the electrophile. Kitching examined the S_E' reaction of some cyclohexenylsilanes, -germanes, and -stannanes. For all three of the allylmetals, the results indicate that attack by proton occurred with *anti* selectivity except when a *trans*-4-*t*-butylcyclohex-2-enyl derivative was used. In these reactions the approach of the electrophile *anti* to the metal is impeded by the presence of the *t*-butyl substituent. Unfortunately, when Kitching extended his study to the use of larger electrophiles such as aldehydes low selectivities were observed for either the *syn* or *anti* S_E' pathways. It is probable that because of the stereochemical constraints imposed by the ring systems these models do not provide an accurate picture of the intrinsic selectivity for the S_E' reaction.

Kumada and Hayashi have extensively studied the stereochemical course of the S_E' reaction using enantiomerically enriched allylic silanes in *tert*-butylation, acylation, and hydroxymethylation reactions (Scheme 5) [20a,20b]. The products obtained from addition of the electrophiles to either the *E* or *Z* allylsilanes were all the *E*-isomers and, except for the acylation reaction, the stereochemical integrity of the starting material was retained in the products. In the acylation reaction the decrease in the enantiomeric purity of the products is thought to result from acid-catalyzed racemization of the product ketone under the reaction conditions. These results indicate that the electrophiles approach the double bond *anti* to the departing silyl group. Deuterodesilylation [20c] and epoxidation [20d] of the same substrates was later performed and these reactions were found to also be completely selective for the *anti* S_E' reaction.



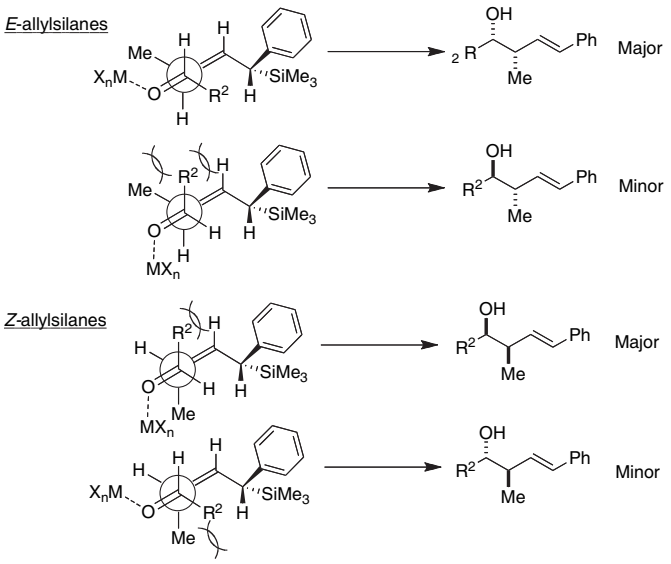
Scheme 5

Kumada and Hayashi extended their study to define all of the stereochemical features of the addition to aldehydes with titanium tetrachloride (Scheme 6) [20b]. The results from this study can be summarized as follows: (1) the enantiomeric excess of the products was essentially the same as the starting materials; (2) the *E*-allylsilanes reacted with high diastere-



Scheme 6

oselectivity (*syn*/*anti*, 92:8 - 99:1); (3) the *Z*-allylsilanes were less selective with the resulting *syn* /*anti* ratio of products dependent upon the structure of the aldehydes (*syn*/*anti*, 50:50 - 99:1). The configuration of the products obtained for all of the reactions studied is interpreted in terms of an *anti* S_E' reaction. To explain the observed selectivities an acyclic transition structure was proposed in which the double-bonds are arranged in an antiperiplanar relationship. The observed diastereoselectivities are proposed to result from a minimization of steric interactions in the transition structures (Scheme 7).

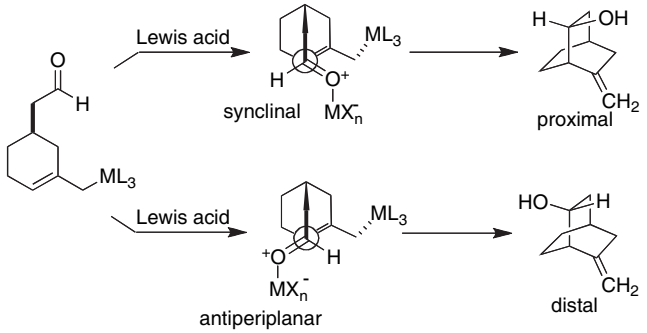


Scheme 7

Panek has recently demonstrated that the addition of a chiral *E*-crotylsilanes to an α- or β-alkoxy aldehyde can be used in the synthesis of substituted furans [21]. An antiperiplanar transition structure was proposed to account for the observed selectivity in an S_E' reaction. This reaction was demonstrated to proceed in high yield with greater than 95% diastereomeric selectivity of the desired tetrahydrofuran. The products of this electrophilic addition correspond to reaction through the *anti* S_E' pathway.

The forgoing stereochemical/mechanistic studies of the allylmetal-aldehyde addition have primarily involved intermolecular reactions. Although the position of the silicon electrofuge with respect to the approaching electrophile has been defined, the exact orientation of the double bonds in the transition state is, in most cases, unknown. The investigation of an *intramolecular* allylmetal-aldehyde condensation was undertaken in our laboratories in order to provide an unambiguous correlation between product stereochemistry and transition state geometry [8,22]. Model system **1** was designed to probe the stereochemical features of Type 2 reactions such only two outcomes are possible: one resulting from a synclinal transition structure, the other from an antiperiplanar transition structure (Scheme 8). Cyclization through a synclinal transition structure will afford the proximal alcohol (hydroxyl group close to the olefin) whereas cyclization through the antiperiplanar transition structure results in the formation of the distal alcohol (hydroxyl group away from the olefin)

The selectivity observed in the cyclization of the model systems is dependent upon the Lewis acid used. The bulky Lewis acid $SnCl_4$ led to a non-selective reaction while cyclization with triflic acid, the sterically least demanding reagent, resulted in a very selective reaction favoring the proximal diastereomer. If *E*-complexation geometry is assumed between the Lewis acid and the aldehyde [23] then the major steric contribution in the model system would arise from the (trimethylsilyl)methylene group. The formation of any of the proximal product with $SnCl_4$, a Lewis acid known to form 2:1 complexes with aldehydes [24], was interpreted as a stereoelectronic advantage for the synclinal transition structure. The selectivity observed with fluoride ion is thought to result from a change in mechanism. The fluoride ion is proposed to initiate a nucleophilic attack on the aldehyde by an allylfluorosiliconate or an allyl anion [25]. This process is best be accommodated by an antiperiplanar transition structure.

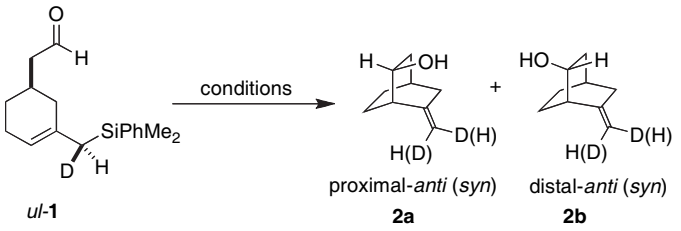


Scheme 8

Model Design. The goal of the study described herein was to unambiguously correlate the product and corresponding transition state stereostructures. To achieve this objective, both the position of the silicon electrofuge and the orientation of the reacting double bonds in the transition structure must be unambiguously defined. This objective can be met only in an *intramolecular* allylmetal-aldehyde reaction. Although intramolecular cyclizations cannot exactly model the corresponding intermolecular reactions, the results from these studies should provide useful insights into intrinsic preferences in the transition structure of the allylmetal-aldehyde additions. The current study would thus expand upon the previous work described above.

The deuterium-labeled model **1** (Scheme 9) was thus designed to differentiate between the *syn* and *anti* S_E' pathways. The position of the deuterium atom in the products can be used to establish if a *syn* or *anti* S_E' pathway has been followed. This model is able to determine *both* the position of the

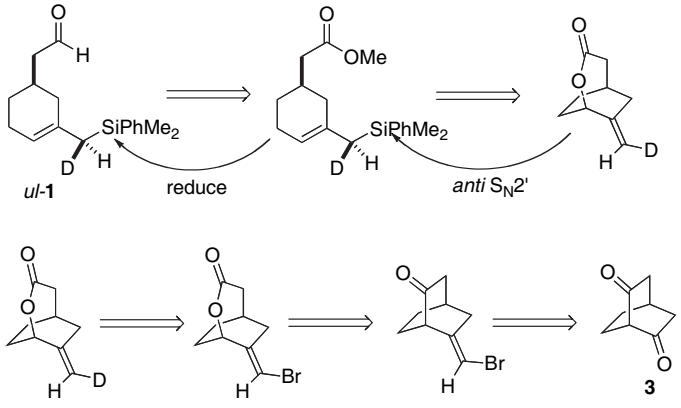
silicon electrofuge and the relative disposition of the double bonds in the transition structure of the allylmetal-aldehyde addition simultaneously. No steric bias for either the *anti* or *syn* reaction pathways should be present in the cyclization of the α-deuterio-substituted allylsilane.



Scheme 9

Results

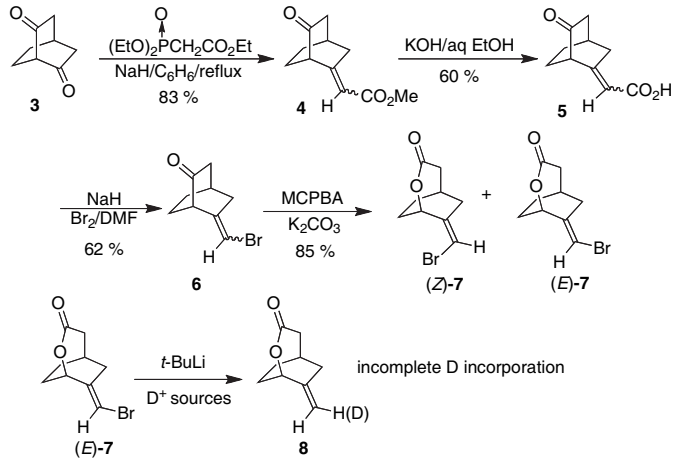
Synthesis of Model System 1. The principle challenge in preparing model **1** is the stereocontrolled introduction of the deuterium label of known relative configuration with respect to the aldehyde electrophile. We envisioned a route that coupled the creation of the deuterium labeled stereogenic center with the formation of the functionalized arm. To implement this synthetic strategy, a method had to be developed to selectively generate a geometrically pure methylidene lactone, Scheme 10. By virtue of the bicyclic structure, the relationship between the latent side chain and the deuterium bearing stereogenic center can be defined through the agency of an S_N2' reaction with a metallosilicon nucleophile (known to proceed with *anti* stereochemical preference) [26]. Indeed, Fleming has shown that silyl cuprates will add to allyl acetates via an *anti* S_N2' process to generate an allylsilane. The bromo lactone would be the product of a Baeyer-Villiger oxidation of the corresponding bromomethylidene ketone, itself obtained by a bromo olefination reaction of the diketone **3.**



Scheme 10

The synthesis of the desired alkylidene bromide began from the known diketone **3** [27], Scheme 11. After initial failures to effect a Wittig type bromomethylidenation [28], the alkylidene bromide could be formed by a decarboxylative bromination of the cycloalkylidene acetic acid. This method was developed initially by Bachman [29] and extended by Wolinsky [30a]. To implement this method diketone **3** was first treated with sodium triethylphosphonoacetate in refluxing benzene to afford the unsaturated ester **4** as a 1:1 mixture of isomers in 83% yield [31]. Saponification of the esters with aqueous potassium hydroxide afforded acids **5** in 60% yield. These acids were converted to their carboxylate salts with sodium hydride and then bromine was added to effect the decarboxylative bromination to form vinyl bromides **10** in 62% yield. Unfortunately, bromo ketone **6** proved to be somewhat unstable and did not survive the reaction conditions necessary to form the deuterio-ketone. Therefore, the lithium-halogen exchange was performed on the next intermediate in the synthetic sequence, the bromo lactone **7**.

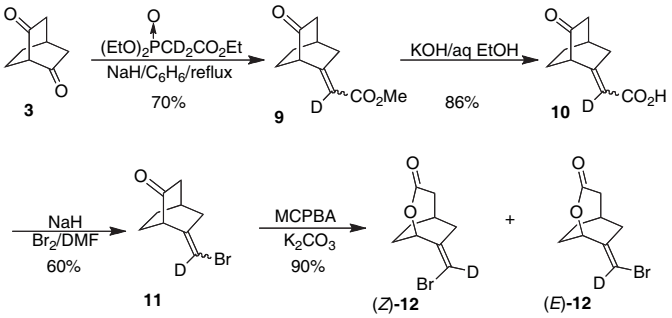
Baeyer-Villager oxidation of bromo ketone **6** by with MCPBA buffered with potassium carbonate afforded bromo lactone **7** in 85% yield. Fortunately, the isomeric *E*- and *Z*-bromo lactones could be readily separated at this stage by silica gel chromatography. Lithium halogen exchange of the bromo lactone **7** was accomplished by first protection of the lactone as its ester enolate with 1.0 equiv of tritylllithium [32] and with 3.0 equiv of *t*-BuLi to effect lithium-halogen exchange. The vinyl anion was quenched with a variety of deuterium sources (CH_3OD, D_2O, CH_3COOD), but at best only a 90% incorporation of deuterium in the lactone **8** was observed. We therefore decided to introduce the deuterium source earlier in the synthetic sequence by the use of a deuterated phosphonoacetate.



Scheme 11

The revised synthesis of the deuterio lactone is shown in Scheme 12. Starting again from bicyclic ketone **3**, the deuterium labeled keto ester **9** was prepared by treatment with d_2-triethylphosphonoacetate. The deuterated phosphonoacetate

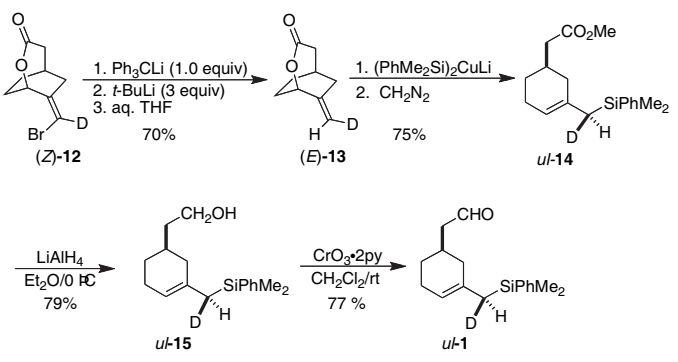
was prepared by treatment of the Horner-Wadsworth-Emmons reagent with a catalytic amount of sodium ethoxide in 20 equiv of ethanol-d_1. The now 90% deuterated ethanol-d_1 was removed and the mixture was treated with another 20 equiv of ethanol-d_1. After several repetitions of this procedure, the deuterium content in the phosphonoacetate was determined to be >99% by ^{1}H-NMR analysis [33]. The resulting ester **9**, obtained in 70% yield, was found to be a mixture of both *Z* and *E* double bond isomers slightly favoring the *Z*-isomer. Hydrolysis of the esters with potassium hydroxide in aqueous ethanol gave the keto acids, **10** in 86% yield.



Scheme 12

Next, vinyl bromide **11** was prepared from the carboxylic acid **10** by formation of the sodium carboxylate salt with NaH followed by treatment of the salt with bromine in DMF. The evolution of carbon dioxide was visible with formation of the vinyl bromides **11** in 60% yield. The mixture of *E* and *Z* vinyl bromides could be separated by chromatography, but we chose to delay that separation to the next stage. Oxidation of the vinyl bromides with sodium carbonate-buffered MCPBA led to the formation of the bicyclic lactones, (*E*)-**12** and (*Z*)-**12** in 90% yield.

In the next sequence of reactions, Scheme 13, the *E* or *Z* lactones were converted to the deuterium labeled allylsilanes as the *lk* or *ul* [34] diastereomers, respectively. Separation of the isomeric lactones was accomplished by silica gel chromatography. The configurationally pure lactone, (*Z*)-**12**, was treated with 1.0 equiv of tritylllithium [32] to form the ester enolate and then 3.0 equiv of *t*-BuLi were added to form the vinyllithium species. The anion was quenched with aqueous THF to afford the lactone, *E*-**8** (70%). The deuterium content in the lactones (*E*)-**13** and (*Z*)-**13** was determined by ^{1}H NMR analysis. At 500 MHz the methylene protons were clearly resolved. Careful integration of the methylidene signals showed that the deuterium content was >95%. In the critical stereochemistry determining step, the lactone was opened by an *anti* S_N2' reaction with phenyldimethylsilyl cuprate [17a] and the resulting carboxylic acid was esterified with diazomethane to afford the methyl ester, *ul*-**14** in 75% yield. The ester was reduced to the primary alcohol *ul*-**15** with $LiAlH_4$ (79%), which was then oxidized to the target aldehyde, *ul*-**1** by a Collins oxidation [35] in 77% yield. Both diastereomers *ul*-**1** and *lk*-**1** could thus be obtained from this procedure simply by starting with either the *E* or *Z* deuterio lactones. The deuterium content in *ul*-**1** and *lk*-**1** was determined by mass spectrometry. The isomer *ul*-**1** contained a 94.9% deuterium incorporation whereas the isomer *lk*-**1** contained a 94.5% deuterium level.



Scheme 13

Proof of Relative Configuration of Model System 1. Assignment of olefin geometry in the lactone **13** was made by difference NOE. The non-deuterated bromo ketone **6**, the precursor to the lactone, was first assigned by difference NOE. Irradiation of the bridgehead position (labeled HC(1) in Chart 2) resulted in a 12.9% NOE enhancement of the methylidene proton in one isomer (assigned as (*E*)-**6**). When the bridgehead proton was irradiated in the other isomer, no NOE was observed in the methylidene hydrogen (thus assigned as (*Z*)-**6**). After Baeyer-Villager oxidation and lithium-halogen exchange with protic quenching, the resulting non-deuterated lactone **8** was produced. At 500 MHz the methylidene protons were clearly resolved (5.24 ppm and 5.09 ppm). Difference NOE studies of the lactone **8** confirmed the positions of the individual methylidene protons. Irradiation of the bridgehead proton (labeled HC(1) in Chart 2) resulted in a 6.0% NOE enhancement to the lower field methylidene proton (thus, assigned as the Z position).

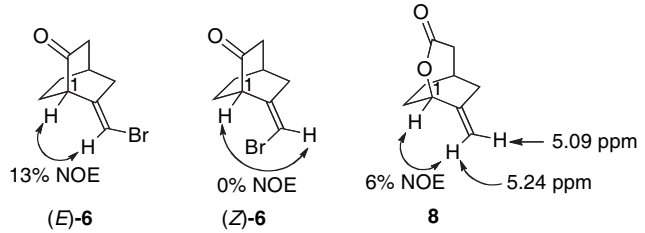


Chart 2

The addition of silylcuprates to lactones and acetates has previously been studied by Fleming and has been shown to be an *anti* S_N2' process [17a]. Because this transformation is so critical to our subsequent stereochemical analyses and that the Fleming system did not involve the opening of a lactone,

we chose to independently vouchsafe the Fleming conclusion. To confirm the assumption of an *anti* S_N2' opening, the product *ul*-**14**, was converted back to the deuterio lactone by a series of simple chemical manipulations the stereochemical course of which have previously been established [17]. Thus, allylsilane ester *ul*-**14** was treated with MCPBA buffered with disodium hydrogen phosphate to form a 1:1 mixture of isomeric epoxides **16** (Scheme 14). Fleming has previously shown that epoxidation of an allylsilane will occur *anti* to the silicon electrofuge [17a]. The formation of a 1:1 mixture indicates that rotation around the carbon-carbon bond adjacent to the silane can occur, placing the silicon electrofuge on either side of the cyclohexene ring. The mixture of epoxides was then opened by treatment with tetrabutylammonium fluoride to afford a 1:1 mixture of allylic alcohols **17a**. The fluoride-promoted desilylation has been demonstrated to proceed via an *anti* pathway [17a]. Lactonization of the allylic alcohol with a catalytic amount of base resulted in the formation of the deuterio lactone **13**. Only the cis isomer of the allylic alcohol could form the desired lactone **13**, the remaining isomer did not close under the reaction conditions. By comparison of spectral data, the lactone formed by these transformations was identical in all respects with the starting lactone and was thus assigned as the *E* isomer. Therefore the S_N2' opening of the deuterio lactone must be an *anti* S_N2' process. For the same isomer to be generated by this sequence, all of the transformations must have the *same* stereochemical outcome. Thus, if epoxidation and epoxide opening are known to be anti, then the lactone opening must be anti as well. This same sequence of reactions was used to prove the relative configuration of the allylsilane ester *lk*-**14** via intermediates **16b**/**16b'** and **17b**/**17b'**. This lactone was transformed into the deuterio lactone (*Z*)-**13**. Thus, the relative configuration of the allylsilane ester **14** has been unambiguously established.

Structure Determination of Cyclization Products 2a and 2b. The cyclization of **1** will lead to four possible diastereomeric alcohols. The assignment of configuration of the proximal and distal alcohols has previously been established by Weber [36] (Apparently, Reference 36 does not have connection with Weber). To determine the stereochemical outcome of the reaction with respect to the position of the silicon electrofuge (*anti* or *syn* S_E') an analytical method had to be devised to differentiate between the four possible diastereomers. In chloroform-d_1, the methylidene protons of **2a** and **2b** appeared as a single resonance, whereas in DMSO-d_6, benzene-d_6, acetone-d_6 and CF_3COOD the methylidene protons were distinct but not baseline resolved. Fortunately, in methanol-d_4 these protons appeared as separate resonances. In fact, the mixture of proximal and distal alcohols did not need to be separated before NMR analysis. All four methylidene protons were clearly resolved in the ^1H NMR (baseline separation) at room temperature in methanol-d_4 at 500 MHz. The assignment of each proton was then made by difference NOE studies of the non-deuterated alcohols **2a** and **2b**.

Irradiation of the bridgehead proton in the proximal diastereomer **2a** resulted in a 4.3% NOE enhancement to the lower field vinyl proton (bridgehead proton labeled HC(1) in Chart 3). No NOE enhancement was observed for the other vinyl proton in this isomer. In the distal diastereomer **2b** each of the vinyl protons were individually irradiated. When the more downfield vinyl proton was irradiated a strong NOE (10.0%) to the bridgehead proton was observed. When the other vinyl proton was irradiated no NOE to the bridgehead proton was observed (Chart 3). After cyclization, the products were isolated and then analyzed by 500 MHz ^1H NMR spectroscopy and gas chromatography. The ratio of the proximal to distal diastereomers was established by gas chromatography using independently determined response factors. The position of deuterium was established by ^1H NMR analysis.

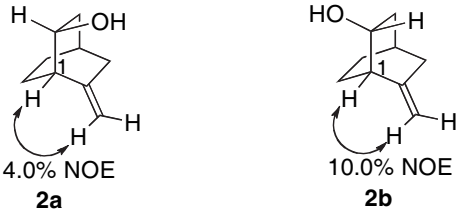
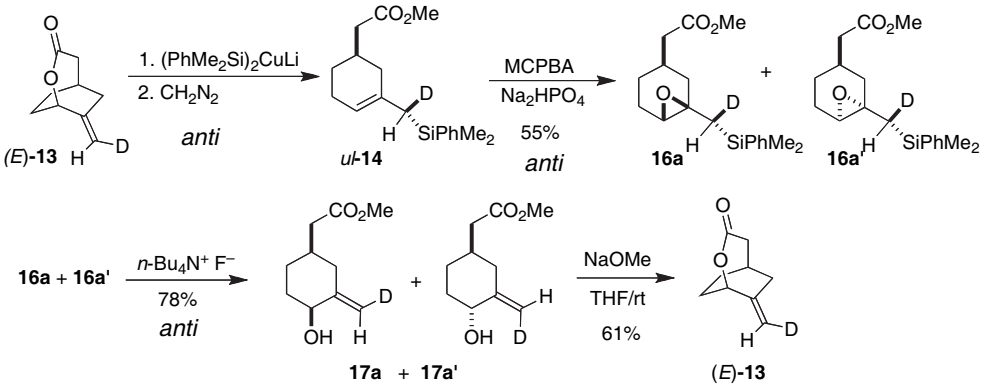


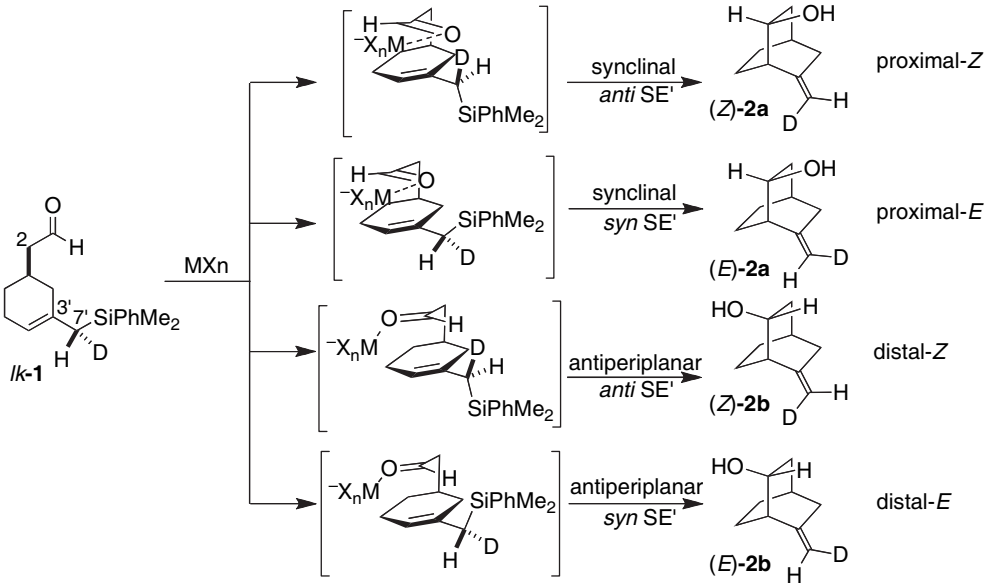
Chart 3



Scheme 14

Cyclization of Model System 1. The cyclization of the model compounds *ul*-**1** and *lk*-**1** with various reagents affords four possible diastereomeric alcohols (*E*)- and (*Z*)-**2a**-**2b** (Scheme 15). The alcohols (*E*)-**2a** and (*Z*)-**2a** will result from reaction through a synclinal arrangement of double bonds in the transition structure. The position of deuterium can then be established to determine whether a *syn* or *anti* S_E' reaction occurred. The alcohols (*E*)-**2b** and (*Z*)-**2b** result from reaction through an antiperiplanar arrangement of double bonds in the transition structure. Again the position of deuterium will determine if the reaction followed an *anti* or *syn* S_E' pathway. In all the limiting transition structures an *E*-complexation geometry is assumed. The cyclizations of *ul*-**1** and *lk*-**1**, were performed on a preparative scale at -78 °C in CH_2Cl_2 so that the product alcohols could be isolated and analyzed by 500 MHz ^{1}H NMR spectroscopy.

The results from cyclizations with various promoters are shown in Table 1. The predominant formation of the *Z* isomer of both the proximal (**2a**) and distal (**2b**) products for a given reagent clearly shows that the cyclizations favor the *anti* S_E' pathway regardless of the Lewis acid employed. The only divergence was seen when fluoride was used to initiate the cyclization wherein a mixture of both *syn* and *anti* S_E' products was formed. The cyclizations with *n*-Bu_4N^+ F^- were found to



Scheme 15

Table 1. Cyclization of Model **1**[a]

entry	model	reagent	proximal/ distal (**2a**/**2b**)[b]	(**2a**) *Z*/*E*[c]	(**2b**) *Z*/*E*[c]	proximal % *anti* S_E'[d]	distal % *anti* S_E'[d]
1	*lk*-**1**	$BF_3{\cdot}OEt_2$	75/25	94/6	94/6	100	100
2	*lk*-**1**	$SnCl_4$	60/40	91/9	94/6	97	100
3	*lk*-**1**	CF_3SO_3H[e]	95/5	93/7	94/6	99	100
4	*lk*-**1**	$SiCl_4$	98/2	95/5	-	100	-
5	*lk*-**1**	*n*-$Bu_4N^+F^-$[f]	20/80	80/20	60/40	85	65
6	*ul*-**1**	$BF_3{\cdot}OEt_2$	73/27	7/93	6/94	97	100
7	*ul*-**1**	$SnCl_4$	62/38	8/92	6/94	96	100
8	*ul*-**1**	CF_3SO_3H[e]	94/6	7/93	-	98	-
9	*ul*-**1**	$SiCl_4$	98/2	5/95	-	100	-
10	*ul*-**1**	*n*-$Bu_4N^+F^-$[f]	16/84	15/85	35/65	90	70

[a]All cyclizations were performed with 1.05 equiv of Lewis acid at -78 °C in CH_2Cl_2 except where noted. [b] Ratios determined by GC using independently determined response factors versus cyclododecane. [c] Ratios were determined by ^{1}H-NMR analysis. [d] Percent *anti* S_E' based on 94.5% *d*-content in **5**. [e] Only 0.95 equiv of triflic acid used. [f] Cyclization with fluoride performed at 70 °C.

proceed quite sluggishly even in refluxing THF. When a more nucleophilic fluoride source was used (TASF) no cyclization products were observed [37].

Discussion

The stereochemical course of the allylmetal-aldehyde addition is determined by the relative asymmetric induction (*anti* or *syn* S_E') and the internal diastereoselection (antiperiplanar or synclinal transition structure) of the reaction. Model system **1** was designed to unambiguously probe these two controlling features. The relative asymmetric induction is controlled by the diastereofacial discrimination of the allylsilane (i.e. the position of the silicon electrofuge in the transition state). The cyclizations initiated with the various Lewis acids all provided products from an *anti* S_E' reaction. In the transition structure of these reactions the silicon electrofuge must be located away from the complexed aldehyde. The *anti* S_E' selectivity observed is independent of the selectivity for either the proximal or distal diastereomers.

The internal stereoselection is controlled by the relative disposition of the double bonds in the transition state. In model system **1** the two limiting transition structures result from reaction through either the synclinal or antiperiplanar arrangement of double bonds. In the cyclizations of model **1** the selectivities observed were dependent upon the nature of the Lewis acid used. The differences in selectivity probably result from steric differences between the various Lewis acid-aldehyde complexes. When a large Lewis acid is used then interaction of this Lewis acid-aldehyde complex with the (phenyldimethylsilyl)-methylene group will result in reaction through an antiperiplanar arrangement of double bonds.

The reaction of fluoride with an allylmetal reagent is thought to proceed through either an allyl anion or an allyl fluorosiliconate intermediate [25]. In 1978 Hosomi proposed that allyl anions were intermediates in the fluoride-catalyzed allylation of carbonyl compounds [38]. In this proposal *n*-$Bu_4N^+F^-$ reacts with the allylsilane to generate Me_3SiF and the allyl anion with an ammonium counterion. Reaction of the allyl anion with the carbonyl compound will then generate the allylated alkoxide that subsequently reacts with the Me_3SiF present in solution to form a silyl ether and regenerating fluoride ion. The generation of this allyl anion was shown to be reversible by Hosomi [38b]. In this study the allylsilanes were found to isomerize to form a thermodynamically more stable allylsilane. DePuy has also observed the formation of allyl anions in the gas phase [39]. Unfortunately, DePuy could not determine if isomerization of *E* and *Z*-crotylsilanes occurred before reaction in this study.

Majetich has also studied the intramolecular allylmetal-aldehyde condensation with fluoride activation [40]. In these reactions the intermediacy of a pentacoordinated organosilicon species is proposed. Majetich discounted the possible formation of an allyl anion in solution because of the high pKa of propene, the conjugate acid of an allylic carbanion. The pentacoordinated siliconate can be readily formed by attack of fluoride ion onto the electropositive silicon atom. The pentacoordinated siliconate will then react with the carbonyl compounds by nucleophilic addition. Corriu and others have studied the mechanism of nucleophilic catalysis by pentacoordinated siliconates [41]. The experiments performed by Corriu indicate that nucleophilic activation of the silicon atom occurs in preference to heterolytic bond cleavage of the Si-C bond.

Evidence against the intermediacy of allyl anions can be found by examination of the selectivities observed from reaction of model system **1** with fluoride ion (Table 1, entries 5 and 10). As seen in entry 5, the products obtained with fluoride ion favor the distal diastereomer (20/80 proximal/distal). In this reaction a 60/40 *Z*/*E* ratio of deuterium-labeled products was obtained for the distal product (indicating approximately 60/40 *anti* /*syn* S_E'). Reaction of the diastereomer *ul*-**1** led to the formation of a 16/84 mixture of proximal/distal products. The opposite ratio of *E*/*Z* deuterium-labeled products was obtained in this cyclization for the distal product (35/65 *E*/*Z*). These results unambiguously rule out the intermediacy of a free allyl anion because the *Z*/*E* ratios obtained for cyclization with both diastereomers was very different. If an allyl anion were an intermediate in these reactions the same ratio of products would be expected from reaction of either the *ul* or *lk* model systems [42].

The configurational stability of the allylsilane in the presence of fluoride was of interest to correctly interpret the results of the cyclizations with this activator. If equilibration of the allylsilane occurs prior to cyclization then the results cannot be interpreted as arising from kinetic control. To probe the configurational stability, several experiments with *n*-$Bu_4N^+F^-$ were performed in which the cyclizations were stopped at approximately 50% completion. The products obtained from the cyclization were analyzed to determine the stereochemical course of reaction. The unreacted starting material was then subjected to cyclization with CF_3SO_3H, a reagent know to proceed through an *anti* S_E' pathway. The results obtained from these experiments are shown in Table 2. The ratios of the product bicyclic alcohols obtained from the cyclizations of recovered **1** with CF_3SO_3H are identical to those obtained from pure samples of **1** (compare Table 2, entries 2 and 4 with Table 1 entries 3 and 8). These results demonstrate that equilibration of the starting material *does not occur* during reaction with fluoride ion. If an allyl anion were an intermediate in these reactions some amount of isomerization would be expected unless, once formed, the allyl anion immediately reacts with the aldehyde. The results from these control experiments provide additional evidence that an allyl anion is not an intermediate in the fluoride-induced cyclizations.

The reactions initiated with fluoride ion can be further analyzed by determining the percentage of distal and proximal products reacting through either the *anti* or *syn* S_E' pathways for model systems *ul*-**1** or *lk*-**1**. These results are shown in equations 1-4. First, the results obtained from the cyclization of model *lk*-**1** were analyzed. This cyclization (entry 5, Table I) afforded a 20/80 mixture of proximal to distal products.

Table 2. Control Experiments on the Cyclization of **1** with *n*-$Bu_4N^+F^-$ and CF_3SO_3H.

entry	model	reagent	proximal/ distal (**2a**/**2b**)	(**2a**) *Z*/*E*	(**2b**) *Z*/*E*	recovery[a]
1	*lk*-**1**	*n*-$Bu_4N^+F^-$[b]	18/82	-	20/80	54
2	*from entry 1*	CF_3SO_3H[c]	93/7	5/95	-	-
3	*ul*-**1**	*n*-$Bu_4N^+F^-$ [b]	22/78	78/22	65/35	44
4	*from entry 3*	CF_3SO_3H[c]	94/6	94/6	-	-

[a]Recovery is recovered starting material after reaction proceeded approximately halfway. [b]Cyclizations with *n*-$Bu_4N^+F^-$ performed at 70 °C in THF. [c]Cyclization performed with 0.95 equiv CF_3SO_3H at -78 °C.

The percentage of reaction which proceeded through the *anti* or *syn* S_E' pathways was then calculated in equations 1 and 2. For example, the ratio of proximal to distal products obtained from the *anti* S_E' pathway can be calculated as follows: 20% of the products were obtained via a synclinal transition structure (proximal) and 80% of these products proceeded through the *anti* S_E' pathway; 80% of the products were obtained by an antiperiplanar transition structure (distal) and 60% of these products proceeded through the *anti* S_E' pathway. Thus, a 25/75 ratio of proximal/distal products were obtained through the *anti* S_E' pathway.

Model system *lk*-1

1) Ratio of proximal to distal (**2a**/**2b**) products reacting through *anti* S_E' pathway

$$\frac{\%\ proximal\ \times\ fraction\ anti\ S_E'}{\%\ distal\ \times\ fraction\ anti\ S_E'} = \frac{20\ \times\ 0.8}{80\ \times\ 0.6} = \frac{16}{48} = \frac{25}{75}$$

2) Ratio of proximal to distal (**2a**/**2b**) products reacting through *syn* S_E' pathway

$$\frac{\%\ proximal\ \times\ fraction\ syn\ S_E'}{\%\ distal\ \times\ fraction\ syn\ S_E'} = \frac{20\ \times\ 0.2}{80\ \times\ 0.4} = \frac{4}{32} = \frac{11}{89}$$

The percentage of the cyclizations proceeding through either the *anti* or *syn* pathways was also calculated for the diastereomer, *ul*-**1**

Model system *ul*-1

3) Ratio of proximal to distal (**2a**/**2b**) products reacting through *anti* S_E' pathway

$$\frac{\%\ proximal\ \times\ fraction\ anti\ S_E'}{\%\ distal\ \times\ fraction\ anti\ S_E'} = \frac{16\ \times\ 0.85}{84\ \times\ 0.65} = \frac{13.6}{54.6} = \frac{20}{80}$$

4) Ratio of proximal to distal (**2a**/**2b**) products reacting through *syn* S_E' pathway

$$\frac{\%\ proximal\ \times\ fraction\ syn\ S_E'}{\%\ distal\ \times\ fraction\ syn\ S_E'} = \frac{16\ \times\ 0.15}{84\ \times\ 0.35} = \frac{2.4}{29.4} = \frac{7.5}{92.5}$$

Remarkably, the ratio of proximal to distal products was dependent upon the mode of cyclization (*syn* versus *anti* S_E'). Cyclization through the *syn* S_E' pathway led to the predominant formation of the distal products, whereas cyclization through the *anti* S_E' pathway was less selective for the distal products. This preference for the distal products with the *syn* S_E' pathway suggests that a steric contribution exists for internal stereoselection in the reactions with fluoride ion. Little preference for cyclization through either the *syn* or *anti* pathways was observed. Possibly, the difference could be due to a weak Coulombic repulsion which favors formation of the distal products and reaction through an *anti* S_E' pathway. That such a steric component exists also rules out the intermediacy of closed transition structures. These transition structures were previously proposed by both Corriu [41] and Sakurai [43] to explain the selectivities observed with fluoro and alkoxysiliconates.

The Lewis acid promoted cyclization of the deuterium labeled model was found to give products corresponding to an *anti* S_E' reaction. All of the cyclizations with Lewis acids were greater than 95% selective for the *anti* S_E' reaction. Model system **1** does not contain any bulky substituents at the methylene group attached to the silicon. The high selectivity observed demonstrates that *in a sterically unbiased* S_E' *reaction an anti orientation of the electrophile with respect to silicon is preferred.* The products from both the synclinal and antiperiplanar transition structures were found to be *anti* selective. The arrangement of double bonds in the transition structure does not affect the relative disposition of the silicon electrofuge that must be disposed away from the approaching electrophile.

The results obtained for the cyclization of **1** with *n*-$Bu_4N^+F^-$ indicate that reaction proceeds through a pentacoordinated fluorosiliconate. Attack of this species onto the aldehyde was found to occur primarily through an antiperiplanar arrangement of double bonds. The selectivities observed for the S_E' reaction were poor, although the *anti* S_E' pathway was favored.

Conclusions

The synthesis and cyclization of the deuterium-labeled model system **1** was accomplished. This model system was designed to differentiate between the *syn* and *anti* S_E' pathways. The results from the cyclization of model **1** with various Lewis acids indicate that the *anti* S_E' pathway is preferred with Lewis-acid mediated reactions. This transition structure requires that the silicon electrofuge is located away from the approaching aldehyde when the aldehyde is complexed to a Lewis acid. When fluoride ion was used to initiate the cyclizations a mixture of both the *syn* and *anti* S_E' products was observed. Evidence was presented that rules out the intermediacy of an allyl anion in the fluoride-mediated reactions. Instead, the intermediacy of an allylfluorosiliconate species is proposed for these reactions.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200, 300, 400, or 500 MHz in $CDCl_3$ with $CHCl_3$ as an internal reference (7.26 ppm). ^{13}C NMR spectra were recorded at 75.5, 100.6, or 125.8 MHz in $CDCl_3$ solutions with $CHCl_3$ (77.0 ppm) as internal reference. Chemical shifts are reported in ppm (d), coupling constants, *J*, are reported in Hz. Infrared spectra were recorded either as thin films, solutions (CCl_4) or as KBr pellets, on an IBM FTIR-32 spectrometer. Peaks are reported in units of cm^{-1} with the following relative intensities: br (broad), s (strong 67-100%), m (medium 33-67%), or w (weak 0-33%). 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%). 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 crosslinked methyl silicone (column A), an HP-5 50 m phenyl-methyl silicone gum (column B), and an HP 10 m HP-1 crosslinked methyl silicone megabore (column C). Retention times (t_R) and integrated ratios were obtained from either a Hewlett-Packard 3393A recorder or a Hewlett-Packard 3396II recorder. Analytical high pressure liquid chromatography (HPLC) was performed on a Hewlett-Packard HP 1090 liquid chromatograph with a Perkin-Elmer LC-75 Spectrophotometric Detector. A Supelco LC-Si 5-m column was used. The detector wavelength was set to 254 nm. Retention times (t_R) and integrated ratios were obtained from an HP 3390A recorder. Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator, visualization was accomplished by UV light, vanillin, and iodine. Solvents used in reactions were reagent grade and were distilled from the indicated drying agents: hexane, dichloromethane (CaH_2); ether, THF (Na/ benzophenone). Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: dichloromethane (CH_2Cl_2), pentane, hexane, ethyl acetate: $CaCl_2$; diethyl ether (Et_2O), *t*-butyl methyl ether (TBME): $CaSO_4$/$FeSO_4$. Solvents for recrystallization were spectral grade. Column chromatography was performed by the method of Still [44] with 32-63 mm silica gel (Merck). Bulb-to-bulb (Kugelrohr) distillations were performed on a Buchi GKR-50 Kugelrohr; boiling points (bp) refer to air bath temperatures and are uncorrected. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Organolithium reagents were titrated according to the method of Gilman [45]. The preparation of d_2-triethylphosphonoacetate was accomplished by washing triethylphosphonoacetate with d_1-EtOD and a catalytic amount of sodium. The ethanol had to be recycled several times in order to achieve 99% deuterium incorporation in the phosphonoacetate. The following compounds were prepared by literature methods: bicyclo-[2.2.2]-octan-2,6-dione (**3**), [27] phenyldimethylsilyllithium [26a].

Bicyclo-[2.2.2]-octan-2-one-6-methylideneacetic Acid Methyl Ester (4). Sodium hydride (60% dispersion in mineral oil, 3.53 g, 88.3 mmol) was washed with hexane (3 × 20 mL) and then suspended in benzene (100 mL). Trimethylphosphon oacetate (16.9 g, 92.7 mmol, 1.05 equiv) was added slowly by syringe to the suspension of sodium hydride at room temperature. Vigorous gas evolution resulted from this addition, and continued for one hour after the addition was complete. The diketone, **3**, (12.20 g, 88.3 mmol) was added in one portion to the reaction mixture, which became slightly gray. The reaction mixture was heated to reflux for 2 h, and the mixture became clear. The solution was cooled to room temperature and poured into water (200 mL). The mixture was extracted with ether (3 × 150 mL) and the combined ethereal extracts were dried ($MgSO_4$) and concentrated to a yellow oil on the rotavap. The *E* and *Z* isomers were separated by silica gel column chromatography (hexane/EtOAc 8:1) to give 7.34 g (43%) of the *E*-isomer (*E*-**4**) and 6.80 g (40%) of the *Z*-isomer (*Z*-**4**). Analytical data for (*E*)-**4**: bp 150 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (t, *J* = 2.2, 1 H, HC(9)), 3.66 (s, 3 H, CO_2CH_3), 2.96 (t, *J* = 2.4, 1 H, C(1)), 2.87 (m, 2 H, $H_2C(3)$), 2.39 (m, 1 H, HC(4)), 2.30 (m, 2 H, $H_2C(5)$), 1.92 (m, 2 H, $H_2C(7)$), 1.71 (m, 2 H, $H_2C(8)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.97 (C(2)), 166.37 (C(10)), 158.40 (C(6)), 115.32 (C(9)), 55.65 (C(1)), 51.02 C(11)), 43.91 (C(3)), 35.15 (C(5)), 27.71 (C(4)), 24.11 (C(8)), 23.86 (C(7)); IR (neat) 2950 (s), 1723 (s), 1649 (s), 1435 (m), 1400 (m), 1373 (m), 1219 (s), 1161 (s), 1089 (m), 1028 (m) cm^{-1}; MS (70 eV) *m/e* 195 (3.2, M^+1), 194 (24), 166 (32), 163 (28), 162 (74), 151 (23), 150 (70), 138 (64), 119 (39), 118 (69), 92 (25), 91 (100), 79 (48), 77 (42), 74 (44); TLC R_f 0.75 (Et_2O) Anal. Calcd for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.27. Found: C, 67.77; H, 7.47. Analytical data for (*Z*)-**4:** bp 150 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (t, 1 H, *J*=2.0, H-C(9)), 4.55 (t, 1 H, *J*=2.8, HC(1)), 3.63 (s, 3 H, CO_2CH_3), 2.37 (m, 5 H), 1.92 (m, 2 H, $H_2C(7)$), 1.70 (m, 2 H, $H_2C(8)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.90 (C(2)), 165.97 (C(10)),

156.44 (C(6)), 116.48 (C(9)), 51.11 (C(11)), 48.74 (C(1)), 43.97 (C(3)), 36.25 (C(5)), 27.64 (C(4)), 24.02 (C(8)), 23.51 (C(7)) IR (neat) 2590 (m), 1719 (s), 1649 (m), 1433 (m), 1370 (m), 1208 (m), 1157 (m), 1026 (w) cm^{-1}; MS (70eV) *m/e* 195 (2.5, M^+1), 194 (23), 166 (34), 163 (32), 162 (78), 151 (23), 150 (74), 138 (62), 120 (27), 119 (42), 118 (73), 92 (26), 91 (100), 79 (51), 77 (40), 74 (46), 39 (66); TLC R_f 0.70 (Et_2O); Anal. Calcd for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.27. Found: C, 67.88; H, 7.40.

(*E*)-Bicyclo-[2.2.2]-octan-2-one-6-methylideneacetic Acid ((*E*)-5). The ester (*E*)-**4** (0.85g, 4.38 mmol) was added to a 2 M solution of potassium hydroxide (20 mL) at 0 °C. The solution was acidified by the addition of 2N HCL until a pH of ~ 3 was achieved. The aqueous mixture was saturated with NaCl and then was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated on the rotavap to a brown oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 3:2) to afford 400 mg (60%) of the acid (*E*)-**5** as a white solid. Analytical data for (*E*)-**5**: mp 159-160 °C (methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (t, 1 H, *J* = 2.4, HC(9)), 3.04 (t, 1 H, *J* = 2.8, HC(1)), 2.92 (m, 2 H, $H_2C(3)$), 2.43 (m, 1 H, HC(4)), 2.30 (m, 2 H, $H_2C(5)$), 1.97 (m, 2 H, $H_2C(7)$), 1.74 (m, 2 H, $H_2C(8)$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.75 (C(2)), 171.30 (C(10)), 161.36 (C(6)), 115.28 (C(9)), 55.93 (C(1)), 43.88 (C(3)), 35.44 (C(5)), 27.69 (C(4)), 24.04 (C(8)), 23.83 (C(7)); IR (KBr pellet) 3090 (m br), 2963 (m), 1711 (s), 1646 (s), 1397 (w), 1202 (s), 11657 (s), 1098 (s), 866 (m) cm^{-1}; MS (70 eV) *m/e* 181 (2.6, M+1), 180 (23), 162 (23), 152 (14), 137 (20), 136 (100), 124 (25), 118 (37), 93 (42), 92 (25), 91 (85), 76 (32), 41 (35), 39 (51); TLC R_f 0.52 (Et_2O); Anal. Calcd for $C_{10}H_{12}O_3$ (180.19): C, 66.65; H, 6.71. Found: C, 66.72; H, 6.68.

(*Z*)-Bicyclo[2.2.2]-octan-2-one-methylideneacetic Acid ((*Z*)-5). The ester (*Z*)-**4** (0.85g, 4.38 mmol) was added to a 2 M solution of potassium hydroxide (20 mL) at 0 °C. The solution was acidified by the addition of 2N HCl until a pH of ~ 3 was achieved. The aqueous mixture was saturated with NaCl and then was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated on the rotavap to a brown oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 3:2) to afford 480 mg (62%) of the acid (*Z*)-**5** as a white solid. Analytical data for (*Z*)-**5**: mp 155 °C (methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (t, 1 H, *J* = 2.4, HC(9)), 3.04, 1 H, *J* = 2.8, HC(1)), 2.92 (m, 2 H, $H_2C(3)$), 2.43 (m, 1 H, HC(4)), 2.30 m, 2 H, $H_2C(5)$), 1.97 (m, 2 H, $H_2C(7)$), 1.74 (m, 2 H, $H_2C(8)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.84 (C(2)), 170.82 (C(10)), 159.39 (C(6)), 116.28 (C(9)), 49.00 (C(1)), 43.97 (C(3)), 36.57 (C(5)), 27.66 (C(4)), 24.00 (C(8)), 23.59 (C(7)); IR (KBr pellet) 3090 (m, br), 2963 (m), 1711 (s), 1646 (s), 1397 (w), 1202 (s), 1167 (s), 1098 (s), 866 (m) cm^{-1}; MS (70 eV) *m/e* 181 (2.3, $M^+ + 1$), 180 (22), 162 (21), 137 (20), 136 (100), 124 (27), 118 (40), 93 (42), 92 (27), 91 (91), 79 (47), 41 (42), 39 (65); TLC R_f 0.50 (Et_2O); Anal. Calcd for $C_{10}H_{12}O_3$ (180.19): C, 66.65; H, 6.71. Found: C, 66.65; H, 6.70.

6-Bromomethylidenebicyclo-[2.2.2]-octane-2-one (6). Sodium hydride (60% dispersion in mineral oil, 1.33 g, 33.3 mmol) was washed with hexane (3 × 15 mL) and suspended in dry DMF (25 mL). The keto acid, **5**, (6.0 g, 33.3 mmol), was slowly added to the suspension at 0 °C and immediately hydrogen gas was evolved from the reaction mixture. The solution was stirred for 30 minutes at room temperature at which time the evolution of hydrogen gas had ceased. A solution of bromine in DMF (33.3 mL, 33.3 mmol, 1.0 M) was slowly added. The bromine was discolored immediately upon addition, and evolution of CO_2 gas was observed. After stirring at room temperature for 1 h the reaction was quenched by the addition of water (25 mL). The mixture was poured into water (100 mL), and extracted with ether (3 × 100 mL). The ethereal extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated on the rotavap to a colorless oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 9:1) to afford 4.40 g (62%) of the vinyl bromides as colorless oils. Analytical data for (*E*)-**6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (t, *J* = 2, 1 H, HC(9)), 3.01 (t, *J* = 2.4, 1 H, HC(1)), 2.30 (m, 5 H), 1.89 (m, 2 H, $H_2C(7)$), 1.72 (m, 2 H, $H_2(C(8))$; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.70 (C(2)), 140.31 (C(9)), 102.43 (C(6)), 53.67 (C(1)), 43.93 (C(3)), 34.81 (C(5)), 27.85(C(4)), 24.30 (C(7)), 22.98 (C(8)). TLC R_f 0.31 (hexane/EtOAc, 7:1); Analytical data for (*Z*)-**6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (t, *J* = 1.8, 1 H, HC(9)), 3.58 (t, *J* = 2.4, 1 H, HC(1)), 2.35 (m, 5H), 1.91 (m, 2 H, $H_2C(7)$), 1.68 (m, 2 H, $H_2C(8)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.75 (C(2)), 138.80 (C(9)), 101.07 (C(6)), 50.15 (C(1)), 44.22 (C(3)), 34.81 (C(5)), 28.38 (C(4)), 24.20 (C(7)), 22.98 (C(8)); TLC R_f 0.30 (hexane/EtOAc, 7:1).

7-Bromomethylidene-2-oxabicyclo-[3.2.2]-nonan-3-one (7). To a suspension of sodium carbonate (2.27 g, 21.4 mmol, 4 equiv) in dichloromethane (50 mL) was added the keto bromide **6** (1.15 g, 5.35 mmol). The suspension was cooled to 0 °C and *m*-chloroperbenzoic acid (0.92 g, 5.35 mmol) was added. The solution was stirred for 90 minutes at 0°C and then poured into water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (75 mL), dried ($MgSO_4$), and concentrated on the rotary evaporator to a yellow oil. Purification by silica gel column chromatography (hexane/EtOAc, 6:1) afforded 0.55 g (45%) of the *E* bromo lactone ((*E*)-**7**) and 0.50 g (40%) of the *Z* bromo lactone ((*Z*)-**7**). The purification by silica gel column chromatography had to be performed twice to separate the *E* and *Z* isomers. Analytical data for (*E*)-**7**: bp 150 °C (1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (t, 1H, *J* = 2.4, HC(10)), 4.75 (t, 1H, *J* = 2.2, HC(1)), 2.88 (m, 2H, $H_2C(4)$), 2.48 (m, 2H, $H_2C(6)$), 2.33 (m, 1H, HC(8)), 2.26 (m, 1H, HC(5)), 1.98 (m, 1H, HC(8)), 1.82 (m, 2H, $H_2C(9)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.35 (C(3)), 139.27 (C(7)), 110.69 (C(10)), 76.34 (C(1)), 42.26 (C(4)), 33.24 (C(6)), 26.28 (C(8)), 25.28

(C(5)), 23.74 (C(9)); IR (neat) 3070 (w), 2942 (m), 1719 (s), 1629 (w), 1371 (s), 1165 (s), 1019 (s), 969 (m) cm^{-1}; MS (70 eV) *m/e* 232 (M^+ + 1, 13), 231 (M^+, 2), 230 (14), 159 (18), 157 (18), 151 (35), 123 (11), 107 (65), 105 (23), 91 (57), 83 (37), 80 (53), 79 (100), 77 (34), 55 (40), 39 (80); TLC R_f 0.25 (hexane/EtOAc, 4:1); Anal. Calcd for $C_9H_{11}BrO_2$ (231.09): C, 46.77; H, 4.80; Br, 34.58. Found: C, 46.75; H, 4.82; Br, 34.75. Analytical data for (*Z*)-**7**: bp 150 °C (1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1 H, HC(10)), 5.23 (t, 1 H, *J* = 2.8, HC(1)), 2.79 (m, 2 H, H_2C(4)), 2.50-2.20 (m, 4 H), 1.92-1.70 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.69 (C(3)), 138.45 (C(7)), 107.63 (C(10)), 73.44 (C(1)), 42.39 (C(4)), 34.74 (C(6)), 25.49 (C(8)), 25.14 (C(5)), 23.35 (C(9)); IR (neat) 3069 (w), 2942 (m), 1719 (s), 1628 (w), 1370 (s), 1165 (s), 1019 (s), 968 (m), 831 (w) cm^{-1}; MS (70 eV) *m/e* 232 (M^+ + 1, 12), 231 (M^+, 2), 230 (12), 159 (15), 157 (13), 151 (61), 123 (13), 107 (73), 105 (28), 91 (51), 83 (29), 80 (41), 79 (100), 77 (38), 55 (43), 41 (43), 39 (77); TLC R_f 0.22 (hexane/EtOAc, 4:1); Anal. Calcd for $C_9H_{11}BrO_2$ (231.09): C, 46.77; H, 4.80; Br, 34.58. Found: C, 46.58; H, 4.84; Br, 34.91.

Bicyclo-[2.2.2]-octan-2-one-6-methylidene-9-*d* Acetic Acid Ethyl Ester (9). Sodium hydride (60% dispersion in mineral oil, 2.39 g, 60.0 mmol) was washed with hexane (3 × 20 mL) and then suspended in benzene (100 mL). Triethylphosphonoacetate-d_2 (13.50 g, 60.0 mmol) was added slowly by syringe to the suspension of sodium hydride at room temperature. Vigorous hydrogen gas evolution resulted from this addition, and continued for 2 h after the addition was complete. The diketone, **3** (8.24 g, 60.0 mmol) was added in one portion to the reaction mixture, which became slightly gray. The reaction mixture was heated to reflux for 2 h, and the mixture became clear. The solution was cooled to room temperature and poured into water (100 mL). The mixture was extracted with ether (4 × 100 mL) and the combined ethereal extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to a yellow oil on the rotavap. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 3:1) to give 8.01 g (70%) of the keto ester as a clear colorless oil. Analytical data for **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 0.05 H, HC(9)), 4.60 (t, *J* = 2.9, 0.37 H, HC(1)), 4.13 (q, *J* = 7.2, 2 H, H_2C(11)), 2.98 (t, *J* = 2.8, 0.63 H HC(1)), 2.91 (m, 0.74 H, H_2C(3)), 2.60-2.20 (m, 4.26 H), 1.94 (m, 2 H, H_2C(7)), 1.71 (m, 2 H, H_2C(8)), 1.24 (m, 3 H, H_3C(12)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.87 (C(2)), 210.77 (C(2)), 165.82 (C10)), 165.38 (C(10)), 157.79 (C(6)), 155.84 (C(6)), 116.82 (C(9)), 115.64 (C(9)), 59.70 59.60, 55.49, 48.52, 43.88, 43.78, 36.05, 34.96, 27.57, 23.99, 23.93, 23.73, 23.37, 14.16; IR (neat) 2596 (s), 2874 (m), 1728 (s) 1707 (s), 1634 (s), 1468 (w), 1447 (w), 1401 (w), 1366 (w), 1339 (w), 1321 (m), 1298 (s), 1240 (m), 1206 (s), 1157 (w), 1138 (w), 1094 (s), 1071 (m), 1046 (s), 972 (w) cm^{-1}; TLC R_f 0.3 (hexane/EtOAc, 5:1).

Bicyclo-[2.2.2]-octan-2-one-6-methylidene-9-*d* Acetic Acid (10). The keto ester, **9**, (16.50 g, 78.9 mmol) was added to EtOH (100 mL) and water (150 mL). An aqueous solution (50 mL) of potassium hydroxide (28 g, 7 equiv) was added to the solution at 0 °C and the mixture was stirred for 8 h. The solution was acidified by the addition of 2N HCl until a pH of ~4 was achieved. The solution was saturated with NaCl and extracted with methylene chloride (4 × 150 mL). The organic extracts were dried ($MgSO_4$) and concentrated on the rotavap to a yellow-white solid. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 1:1) to afford 12.20 g (86%) of the keto acid as a white solid. Analytical data for **10** (*E* and *Z* mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 0.05 H, HC(9)), 4.61 (t, *J* = 2.8, 0.38 H, HC(1)), 3.03 (t, *J* = 2.7, 0.62 H, HC(1)), 2.99 (m, 0.76 H, HC(3)), 2.62-2.21 (m, 4.24 H), 1.95 (m, 2 H, H_2C(7)), 1.73 (m, 2 H, H_2C(8)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.76 (C(2)), 210.68 (C(2)), 171.16 (C10)), 170.84 (C(10)), 161.18 (C(6)), 159.25 (C(6)), 55.89 (C(1)), 48.94 (C(1)), 43.94 (C(3)), 43.88 (C(3)), 36.48 (C(5)), 35.38 (C(5)), 27.69 (C(4)), 27.64 (C(4)), 24.05 (C(7)), 23.98 (C(7)), 23.84 (C(8)), 23.57 (C(8)); IR (KBr pellet) 3095 (m, br), 2963 (m), 1711 (s), 1640 (s), 1396 (w), 1204 (s), 1165 (s), 1098 (s) cm^{-1}; TLC R_f 0.4 (hexane/EtOAc, 2:1).

6-Bromomethylidene-9-*d*-bicyclo-[2.2.2]-octan-2-one (11). Sodium hydride (60% dispersion in mineral oil, 1.94 g, 48.5 mmol) was washed with hexane (3 × 15 mL) and suspended in dry DMF (50 mL). The keto acid, **10**, (8.79 g, 48.5 mmol), was slowly added to the suspension at 0 °C and immediately hydrogen gas was evolved from the reaction mixture. The solution was stirred for 30 minutes at room temperature at which time the evolution of hydrogen gas had ceased. A solution of bromine in DMF (24.3 mL, 48.5 mmol, 2.0 M) was slowly added. The bromine was discolored immediately upon addition, and evolution of CO_2 gas was observed. After stirring at room temperature for 30 minutes the reaction was quenched by the addition of water (25 mL). The mixture was poured into water (100 mL), and extracted with ether (3 × 75 mL). The ethereal extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated on the rotavap to a colorless oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 9:1) to afford 5.40 g (60%) of the vinyl bromides as colorless oils. Analytical data for **11** (*E* and *Z* mixture): bp 100 °C (1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (t, *J* = 2.9, 0.6 H, HC(1)), 2.98 (t, *J* = 2.8, 0.4 H, HC(1)), 2.46-2.20 (m, 5 H), 1.88 (m, 2 H, H_2C(7)), 1.69 (m, 2 H, H_2C(8)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.57 (C(2)), 210.52 (C(2)), 140.18 (C(6)), 138.69 (C(6)), 101.72 (t, *J* = 40, C(9)), 100.76 (t, *J* = 40, C(9)), 53.61 (C1)), 50.09 (C(1)), 44.21 (C(3)), 43.91 (C(3)), 34.75 (C(5)), 28.39 (C(4)), 27.85 (C(4)), 24.30 (C(7)), 24.20 (C(7)), 23.65 (C8)), 22.97 (C(8)); IR (neat) 2944 (br m), 2870 (w), 1727 (s), 1613 (w), 1466 (w), 1447 (w), 1433 (w), 1401 (m), 1337 (w), 1316 (w), 1227 (w), 1208 (w), 1094 (m), 1069 (w), 978 (m), 934 (w), 916 (w), 876 (w), 862 (w) cm^{-1}; TLC R_f 0.30 (hexane/EtOAc, 7:1);

(*E*)-7-Bromomethylidene-10-*d*-2-oxa-bicyclo[3.2.2]-nonan-3-one ((*E*)-12 and (*Z*)-12). To a suspension of sodium car-

bonate (10.59 g, 100 mmol, 4 equiv) in dichloromethane (50 mL) was added the keto bromide **11** (5.40 g, 25.0 mmol). The suspension was cooled to 0 °C and *m*-chloroperbenzoic acid (4.95 g, 28.75 mmol) was added. The solution was stirred for 90 minutes at 0°C and then poured into water (100 mL). The aqueous layer was extracted with EtOAc (3 × 75 mL), washed with brine (75 mL), dried ($MgSO_4$), and concentrated on the rotary evaporator to a yellow oil. Purification by silica gel column chromatography (hexane/EtOAc, 6:1) afforded 2.76 g (48%) of the *E*-bromo lactone ((*E*)-**12**) and 2.45 g (42%) of the *Z*-bromo lactone ((*Z*)-**12**). The purification by silica gel column chromatography had to be performed twice to separate the *E* and *Z* isomers. Analytical data for (*E*)-**12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (m, 0.05 H, HC(10)), 4.74 (m, 1 H, HC(1)), 2.88 (m, 2 H, H_2C(4)), 2.51 (m, 2 H, H_2C(6)), 2.33 (m, 1 H, HC(8)), 2.26 (m, 1 H, HC(5)), 1.98 (m, 1 H, HC(8)), 1.82 (m, 2 H, H_2C(9)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.27 (C(3)), 139.27 (C(7)), 110.45 (t, *J* = 30, C(10)), 76.41 (C(1)), 42.33 (C(4)), 33.28 (C(6)), 26.38 (C(8)), 25.39 (C(5)), 23.84 (C(9)); IR (neat) 2942 (m), 1720 (s), 1611 (w), 1462 (w), 1437 (m), 1371 (s), 1237 (m), 1168 (s), 1100 (m), 1049 (m), 1019 (s), 978 (s), 911 (m), 872 (w) cm^{-1}; TLC R_f 0.24 (hexane/EtOAc, 6:1); Analytical data for (*Z*)-**12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (m, 0.05 H, HC(10)), 5.21 (m, 1 H, HC(1)), 2.79 (m, 2 H, H_2C(4)), 2.50-2.20 (m, 4 H), 1.92-1.70 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.48 (C(3)), 138.31 (C(7)), 107.17 (t, *J* = 31, C(10)), 73.33 (C(1)), 42.30 (C(4)), 34.71 (C(6)), 25.42 (C(8)), 25.08 (C(5)), 23.28 (C(9)); IR (neat) 2942 (m), 1721 (s), 1611 (w), 1464 (w), 1437 (m), 1372 (s), 1237 (m), 1169 (s), 1100 (m), 1049 (m), 1019 (s), 978 (s), 911 (m), 872 (w), 828 (w) cm^{-1}; TLC R_f 0.22 (hexane/EtOAc, 6:1).

(*Z*)-7-Methylidene-10-*d*-2-oxabicyclo-[3.2.2]-nonan-3-one (*Z*-13). Triphenylmethane (2.30 g, 9.39 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. To this solution was added *n*-BuLi (6.71 mL, 9.39 mmol, 1.40 M) and the resulting dark red solution was stirred at room temperature for 30 minutes. The solution was cooled to -78 °C and the bromo lactone ((*E*)-**12**) (2.18 g, 9.39 mmol) in THF (20 mL) was added. The solution was stirred for 5 minutes at -78 °C and then *t*-BuLi (17.8 mL, 28.2 mmol, 1.60 M, 3 equiv) was added. The solution was stirred for an additional 5 minutes at -78 °C and then quenched by the addition of 25% aqueous THF (3 mL). The solution immediately became faint yellow in color and was warmed to room temperature. The reaction mixture was poured into water (50 mL) and extracted with ether (4 × 50 mL). The combined ethereal extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated on the rotavap to a yellow oil. The mixture was purified by silica gel column chromatography (hexane/EtOAc, 9:1 → 4:1) to afford 1.00 g (70%) of the lactone (*Z*)-**13**. An analytical sample was obtained by Kugelrohr distillation. Analytical data for (*Z*)-**13**: bp 120 °C (1 Mm Hg) (air bath); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 0.05 H, HC(9)), 5.09 (s, 1 H, HC(9)), 4.70 (t, 1 H, *J* = 3.2 HC(6)), 2.79 (m, 2 H, H_2C(2)), 2.45 (m, 2 H, H_2C(4)), 2.27 (m, 1 H, HC(7)), 2.13 (s, 1 H, HC(3)), 1.90 (m, 1 H, HC(7)), 1.78 (m, 2 H, H_2C(8)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.41 (C(3)), 142.30 (C(7)), 117.03 (t, *J* = 24, C(10)), 78.34 (C(1)), 42.69 (C(4)), 33.97 (C(6)), 26.45 (C(8)), 25.77 (C(5)), 23.67 (C(9)); IR (neat) 2943 (s), 1719 (s), 1539 (w), 1465 (w), 1435 (m), 1374 (m), 1326 (w), 1221 (m), 1169 (s), 1093 (w), 1045 (m), 1021 (s), 973 (m), 907 (m), 888 (w) cm^{-1}; MS (70 eV) *m/e* 154 (M^+ + 1, 1.2), 153 (M^+, 4.3), 125 (64), 124 (16), 110 (14), 109 (14), 97 (20), 96 (85), 95 (16), 94 (58), 93 (32), 92 (32), 83 (89), 82 (25), 81 (42), 80 (100), 79 (43), 78 (29), 68 (47), 67 (42), 66 (87), 55 (62); TLC R_f 0.25 (hexane/EtOAc, 4:1); Anal. Calcd for $C_9H_{11}D_1$ (153.19): C, 70.56; H, 7.90. Found: C, 70.30; H, 8.02.

(*E*)-7-Methylidene-10-*d*-2-oxabicyclo-[3.2.2]-nonan-3-one ((*E*)-13). Triphenylmethane (2.40 g, 9.81 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. To this solution was added *n*-BuLi (7.0 mL, 9.81 mmol, 1.40 M) and the resulting dark red solution was stirred at room temperature for 30 minutes. The solution was cooled to -78 °C and the bromo-lactone ((*Z*)-**12**) (2.27 g, 9.81 mmol) in THF (20 mL) was added. The solution was stirred for 5 minutes at -78 °C and then *t*-BuLi (18.6 mL, 29.4 mmol, 1.58 M, 3 equiv) was added. The solution was stirred for an additional 5 minutes at -78 °C and then quenched by the addition of 25% aqueous THF (3 mL). The solution immediately became faint yellow in color and was warmed to room temperature. The reaction mixture was poured into water (50 mL) and extracted with ether (4 × 75 mL). The combined ethereal extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated on the rotavap to a yellow oil. The mixture was purified by silica gel column chromatography (hexane/EtOAc, 9:1 → 4:1) to afford 1.04 g (70%) of the lactone (*E*)-**13**. An analytical sample was obtained by Kugelrohr distillation. Analytical data for (*E*)-**13**: bp 120 °C (1 Mm Hg) (air bath); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1 H, HC(9)), 5.07 (s, 0.05 H, HC(9)), 4.66 (t, 1 H, *J* = 3.3 HC(6)), 2.79 (m, 2 H, H_2C(2)), 2.45 (m, 2 H, H_2C(4)), 2.27 (m, 1 H, HC(7)), 2.13 (s, 1 H, HC(3)), 1.90 (m, 1 H, HC(7)), 1.78 (m, 2 H, H_2C(8)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.23 (C(1)), 142.18 (C(5)), 116.82 (t, *J* = 24, C(9)), 78.23 (C(6)), 42.54 (C(2)), 33.80 (C(3)), 26.31 (C(7)), 25.61 (C(3)), 23.51 (C(8)); IR (neat) 2942 (s), 1719 (s), 1653 (w), 1559 (w), 1539 (w), 1464 (w), 1435 (m), 1373 (m), 1325 (w), 1221 (m), 1169 (s), 1092 (w), 1044 (m), 1021 (s), 972 (m), 907 (m), 887 (w) cm^{-1}; MS (70 eV) *m/e* 154 (M^+ + 1, 1.1), 153 (M^+, 7.2), 125 (64), 124 (60), 110 (13), 97 (19), 96 (78), 95 (17), 94 (56), 93 (31), 92 (30), 83 (81), 82 (24), 81 (43), 80 (100), 79 (44), 66 (86), 55 (63), 41 (69), 40 (48), 39 (78); TLC R_f 0.25 (hexane/EtOAc, 4:1); Anal. Calcd for $C_9H_{11}D_1O$ (153.19): C, 70.56; H, 7.90. Found: C, 70.53; H, 9.00.

***rel*-(1'*R*,7'*R*)-2-3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)cyclohex-3'-enylacetic Acid Methyl Ester (*lk*-14).** To a suspension of CuI (1.43 g, 7.50 mmol, 1.1 equiv)) in THF (20 mL) at 0 °C was added phenyldimethylsilyllithium (18.76 mL, 15.0 mmol, 0.80 M, 2.2 equiv). The solution was allowed to stir at 0 °C for 15 minutes. The lactone (*E*)-**13** (1.05 g, 6.82

mmol) in THF (10 mL) was added at 0 °C and the solution was stirred at 0 °C for 2 h. The reaction was quenched by the addition of water (175 mL) and then acidified with dilute oxalic acid (10 mL). The solution was poured into water (50 mL) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to a yellow oil. The oil was purified by silica gel column chromatography (hexane/EtOAc, 9:1 → 1:1) to give the acid. Addition of diazomethane to the acid led to the formation of the methyl ester. The methyl ester was purified by chromatography (hexane/EtOAc, 19:1) afforded 1.54 g (75%) of the ester *lk*-**14** as a clear colorless oil. Analytical data for *lk*-**14**: bp 200 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ph), 7.33 (m, 3 H, Ph), 5.18 (s, 1 H, HC(4')), 3.63 (s, 3 H, OCH_3), 2.17 (m, 2 H, H_2C(2)), 2.01 (m, 3 H, H_2C(6'), HC(1')), 1.81 (m, 1 H, HC(2')), 1.61 (m, 3H), 1.15 (m, 1 H, HC(5')), 0.27 (d, 6 H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.36 (C(1)), 139.23 (C(3')), 133.52 (Ph), 133.36 (Ph), 128.81 (Ph), 127.60 (Ph), 119.14 (C(4')), 51.34 (OCH_3), 40.69 (C(2)), 37.08 (C(2')), 31.17 (C(1')), 28.18 (C(5')), 26.27 (t, *J* = 18, C(7')), 24.79 (C(8)), -2.81 (SiPhCH_3), -2.84 (SiPhCH_3); IR (neat) 3069 (w), 2952 (m), 2915 (m), 2840 (m), 1738 (s), 1585 (m), 1428 (m), 1356 (m), 1281 (m), 1248 (s), 1202 (m), 1156 (s), 1113 (s), 1067 (m), 999 (m), 833 (s) cm^{-1}; MS (70 eV) *m/e* 304 (M^+ + 1, 1.9), 303 (M^+, 7.4), 247 (9), 136 (14), 135 (100), 93 (36), 81 (16), 43 (9); TLC R_f 0.30 (hexane/EtOAc, 19:1); Anal. Calcd for $C_{18}H_{25}D_1O_2Si$ (303.47): C, 71.24; H, 8.64. Found: C, 71.37; H, 8.58.

rel-(1'*R*,7'*S*)-2-3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)cyclohex-3'-enylacetic Acid Methyl Ester (*ul*-14). To a suspension of CuI (1.61 g, 8.44 mmol, 1.1 equiv) in THF (20 mL) at 0 °C was added phenyldimethylsilyl lithium (14.30 mL, 16.88 mmol, 1.18 M, 2.2 equiv). The solution was allowed to stir at 0 °C for 15 minutes. The lactone (*Z*)-**13** (1.17 g, 7.67 mmol) in THF (10 mL) was added at 0 °C and the solution was stirred at 0 °C for 2 h. The reaction was quenched by the addition of water (175 mL) and then acidified with dilute oxalic acid (10 mL). The solution was poured into water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to a yellow oil. The oil was purified by silica gel column chromatography (hexane/EtOAc, 9:1 → 1:1) to give the acid. Addition of diazomethane to the acid led to the formation of the methyl ester. The methyl ester was purified by chromatography (hexane/EtOAc, 12:1) afforded 1.50 g (64%) of the ester *ul*-**14** as a clear colorless oil. Analytical data for *ul*-**14**: bp 200 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ph), 7.33 (m, 3 H, Ph), 5.18 (s, 1 H, HC(4')), 3.63 (s, 3 H, OCH_3), 2.17 (m, 2 H, H_2C(2)), 2.01 (m, 3 H, H_2C(6'), HC(1')), 1.81 (m, 1 H, HC(2')), 1.61 (m, 3 H), 1.15 (m, 1 H, HC(5')), 0.27 (d, 6 H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.36 (C(1)), 139.23 (C(3')), 133.52 (Ph), 133.36 (Ph), 128.81 (Ph), 127.60 (Ph), 119.14 (C(4')), 51.34 (OCH_3), 40.69 (C(2)), 37.08 (C(2')), 31.17 (C(1')), 28.18 (C(5')), 26.27 (t, *J* = 18, C(7')), 24.79 (C(8)), -2.81 (SiPhCH_3), -2.84 (SiPhCH_3); IR (neat) 3069 (w), 2952 (m), 2913 (m), 2842 (m), 1738 (s), 1435 (m), 1428 (m), 1358 (m), 1298 (m), 1279 (m), 1246 (s), 1200 (m), 1156 (s), 1113 (s), 1065 (m), 1013 (w), 997 (m), 872 (w), 833 (s) cm^{-1}; MS (70 eV) *m/e* 304 (M^+ + 1, 1.9), 303 (M^+, 6.7), 247 (8), 136 (14), 135 (100), 94 (8), 93 (38), 81 (17), 43 (12); TLC R_f 0.30 (hexane/EtOAc, 19:1); Anal. Calcd for $C_{18}H_{25}D_1O_2Si$ (303.47): C, 71.24; H, 8.64. Found: C, 71.27; H, 8.56.

rel-(1'*R*,7'*R*)-2,3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)-cyclohex-3'-enylethan-1-ol (*lk*-15). The ester, *lk*-**14**, (2.04 g, 6.72 mmol) in Et_2O (40 mL) was cooled to 0 °C. Lithium aluminum hydride (188 mg, 6.72 mmol) was added in one portion and the solution was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of EtOAc (3 mL), water (0.3 mL), 15% NaOH (0.3 mL) and then water (0.9 mL) to form a white precipitate. The reaction mixture was filtered through Celite with the aid of ether and the solvent was then removed. Purification by silica gel column chromatography (hexane/EtOAc, 9:1) afforded 1.55 g (79%) of the alcohol *lk*-**15** as a clear colorless oil. An analytical sample was obtained by Kugelrohr distillation. Analytical data for *lk*-**15**: bp 200 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2 H, Ph), 7.31 (m, 3 H, Ph), 5.16 (s, 1 H, HC(4')), 3.54 (m, 2 H, H_2C(1)), 1.96 (m, 2 H, H_2C(2)), 1.49 (m, 7 H), 1.10 (m, 2 H, H_2C(6')), 0.27 (d, 6 H, Si(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.38 (C(3')), 133.82 (Ph), 133.61 (Ph), 128.82 (Ph), 127.59 (Ph), 119.34 (C(4')), 60.81 (C(1)), 39.30(C(2)), 37.56 (C(2')), 30.58 (C(1')), 28.68 (C(5')), 26.41 (t, *J* = 18, C(7')), -2.74 (SiPhCH_3), -2.89 (SiPhCH_3); IR (neat) 3337 (br m), 3069 (w), 3046 (w), 3013 (w), 2909 (s), 2834 (m), 1426 (m), 1356 (w), 1337 (w), 1246 (s), 1148 (w), 1111 (s), 1055 (m), 999 (w), 899 (w), 831 (s) cm^{-1}; MS (70 eV) *m/e* 276 (M^+ + 1, 1.0), 275 (M^+, 3.4), 137 (14), 136 (14), 135 (100), 123 (12), 95 (17), 94 (30), 43 (11); TLC R_f 0.50 (Et_2O); Anal. Calcd for $C_{17}H_{25}D_1OSi$ (275.46): C, 74.12; H, 9.51: Found: C, 74.09; H, 9.49.

rel-(1'*R*,7'*S*)-2,3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)cyclohex-3'-enylethan-1-ol (*ul*-15). The ester, *ul*-**14**, (189 mg, 0.63 mmol) in Et_2O (20 mL) was cooled to 0 °C. Lithium aluminum hydride (17.5 mg, 0.63 mmol) was added in one portion and the solution was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of EtOAc (3 mL), water (0.2 mL), 15% NaOH (0.2 mL) and then water (0.6 mL) to form a white precipitate. The reaction mixture was filtered through Celite with the aid of ether and the solvent was then removed. Purification by silica gel column chromatography (hexane/EtOAc, 9:1) afforded 150 mg (89%) of the alcohol *ul*-**15** as a clear colorless oil. An analytical sample was obtained by Kugelrohr distillation. Analytical data for *ul*-**15**: bp 200 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2 H, Ph), 7.36 (m, 3 H, Ph), 5.22 (s, 1 H, HC(4')), 3.59 (m, 2 H, H_2C(1)), 2.01 (m, 2 H, H_2C(2)), 1.51 (m, 7 H), 1.15 (m, 2 H, H_2C(6')), 0.29 (d, 6 H, Si(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.38 (C(3')), 133.82 (Ph), 133.61 (Ph), 128.82 (Ph), 127.59 (Ph), 119.34 (C(4')), 60.81 (C(1)),

39.30(C(2)), 37.56 (C(2')), 30.58 (C(1')), 28.68 (C(5')), 26.41 (t, J = 18, C(7')), -2.74 (SiPh*C*H$_3$), -2.89 (SiPh*C*H$_3$); IR (neat) 3335 (br m), 3069 (w), 3044 (w), 3017 (w), 2909 (s), 2834 (m), 1426 (m), 1356 (w), 1337 (w), 1246 (s), 1148 (w), 1111 (s), 1053 (m), 997 (w), 899 (w), 876 (w), 831 (s) cm^{-1}; MS (70 eV) *m/e* 276 (M^+ + 1, 0.9), 275 (M^+, 3.6), 137 (13), 136 (14), 135 (100), 123 (12), 95 (16), 94 (31), 43 (12); TLC R_f 0.50 (Et_2O); Anal. Calcd for $C_{17}H_{25}D_1OSi$ (275.46): C, 74.12; H, 9.51. Found: C, 74.19; H, 9.57.

rel-(1'*R*,7'*R*)-2,3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)-3'-cyclohexenylethanal (*lk*-1). Pyridine (5.18 mL, 64.0 mmol, 12 equiv) in dichloromethane (30 mL) was cooled to 0 °C and CrO_3 (3.20 g, 32.0 mmol, 6 equiv) was added in one portion to form a reddish-brown solution. The alcohol, *lk*-**15**, (1.47 g, 5.34 mmol) in dichloromethane (10 mL) was added and the solution immediately became black. The solution was allowed to stir for 2 h at room temperature and the reaction mixture was filtered through Celite with the aid of ether. The ethereal layer was washed with 5% NaOH (2 × 30 mL), brine and dried (Na_2SO_4). The solvent was removed to leave a yellow oil. Purification by silica gel column chromatography (hexane/EtOAc, 19:1) afforded 1.10 g (75%) of the aldehyde *lk*-**1** as a clear, colorless oil. An analytical sample was obtained by Kugelrohr distillation. Analytical data for *lk*-**1**: bp 160 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (t, J = 2, 1 H, CH(1)), 7.51 (m, 2 H, Ph), 7.36 (m, 3 H, Ph), 5.23 (m, 1 H, HC(4')), 2.25 (m, 2 H, H_2C(2)), 2.07 (m, 3 H), 1.80 (m, 1 H), 1.60 (m, 3 H), 1.19 (m, 1 H), 0.30 (d, J = 1, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.65 (C(1)), 139.09 (C(3')), 133.55 (Ph), 133.34 (Ph), 128.88 (Ph), 127.62 (Ph), 119.16 (C(4')), 50.04 (C(2)), 37.17 (C(2')), 28.82 (C(5')), 28.22 (C(1')), 26.31 (t, J = 18, C(7')), 24.65 (C(6')), -2.80 (SiPh*C*H$_3$), -2.87 (SiPh*C*H$_3$); IR (neat) 3069 (w), 3048 (w), 3023 (w), 2913 (s), 2836 (m), 2716 (w), 1725 (s), 1659 (w), 1428 (s), 1248 (s), 1113 (s) cm^{-1}; MS (70 eV) *m/e* 274 (M^+ + 1, 1.5), 273 (M^+, 4.6), 217 (9), 137 (28), 136 (25), 135 (100), 121 (29), 107 (14), 106 (16), 105 (15), 93 (51), 92 (14), 43 (25); TLC R_f 0.60 (hexane/EtOAc, 7/3); Anal. Calcd for $C_{17}H_{23}D_1OSi$ (273.44): C, 74.67; H, 8.85. Found: C, 74.62; H, 8.93.

rel-(1'*R*,7'*S*)-2-3'-(Phenyldimethylsilyl-(7'-*d*)-methyl)-3'-cyclohexenylethanal (*ul*-1). Pyridine (0.41 mL, 5.18 mmol, 12 equiv) in dichloromethane (15 mL) was cooled to 0 °C and CrO_3 (0.26 g, 2.59 mmol, 6 equiv) was added in one portion to form a reddish-brown solution. The alcohol, *ul*-**15**, (119 mg, 0.43 mmol) in dichloromethane (5 mL) was added and the solution immediately became black. The solution was allowed to stir for 1 h at room temperature and the reaction mixture was filtered through Celite with the aid of ether. The ethereal layer was washed with 5% NaOH (2 × 25 mL), brine and dried (Na_2SO_4). The solvent was removed to leave a yellow oil. Purification by silica gel column chromatography (hexane/EtOAc, 19:1) afforded 95 mg (83%) of the aldehyde *ul*-**1** as a clear, colorless oil. An analytical sample was obtained by Kugelrohr distillation. Analytical data for *ul*-**1**: bp 160 °C (0.1 Mm Hg) (air bath); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, J = 2, 1 H, CH(1)), 7.49 (m, 2 H, Ph), 7.35 (m, 3 H, Ph), 5.22 (m, 1 H, HC(4')), 2.26 (m, 2 H, H_2C(2)), 2.03 (m, 3 H), 1.83 (m, 1 H), 1.60 (m, 3 H), 1.22 (m, 1 H), 0.28 (d, J = 1, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.65 (C(1)), 139.08 (C(3')), 133.54 (Ph), 133.34 (Ph), 128.87 (Ph), 127.62 (Ph), 119.15 (C(4')), 50.04 (C(2)), 37.17 (C(2')), 28.82 (C(5')), 28.21 (C(1')), 26.31 (t, J = 18, C(7')), 24.64 (C(6')), -2.80 (SiPh*C*H$_3$), -2.88 (SiPh*C*H$_3$); IR (neat) 3069 (w), 3048 (w), 3023 (w), 2913 (s), 2838 (m), 2716 (w), 1725 (s), 1659 (w), 1426 (m), 1246 (s), 1113 (s), 831 (s) cm^{-1}; MS (70 eV) *m/e* 274 (M^+ + 1, 0.8), 273 (M^+, 2.8), 258 (4), 137 (15), 136 (14), 135 (100), 121 (15), 93 (26), 43 (13); TLC R_f 0.60 (hexane/EtOAc, 7/3); Anal. Calcd for $C_{17}H_{23}D_1OSi$ (273.44): C, 74.67; H, 8.85. Found: C, 74.63; H, 8.92.

General Procedure for the Cyclization of *ul*-1 and *lk*-1

1. *$SnCl_4$, BF_3OEt_2, $SiCl_4$, CF_3SO_3H.* In a flame-dried, 25-mL flask, equipped with a magnetic stir bar and nitrogen inlet tube, was placed *ul*-**1** or *lk*-**1** (1.0 equiv, 0.05M) in dichloromethane. At -70 °C 1.05 equiv of the Lewis acid was added by syringe. The reaction was stirred at -70 °C until the complete reaction of *ul*-**1** or *lk*-**1** was observed. The reaction mixture was quenched at -70 °C by the addition of 5 equiv of a 1N NaOH/MeOH solution and subsequent stirring at room temperature for 2 h. The solution was extracted with EtOAc and washed with water (5 mL). The aqueous layer was back extracted with EtOAc (2 × 2 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to an oil. Purification was accomplished by chromatography (hexane/EtOAc, 6:1) to give the *syn* and *anti* alcohols. The organic layer was analyzed by on column capillary GC to determine the *syn* /*anti* ratio (column B) Program: 60 °C (2 min), 10 °C/min, 90 °C (5 min), 20 °C/min, 250 °C (5 min). GC : **1**, t_R = 15.95 min.; **2a**, t_R = 5.54 min.; **2b**, t_R = 6.19 min. The product alcohols were also analyzed by NMR on the GN-500 spectrometer.

2. *$(n\text{-}Bu)_4N^+F^-$.* A 0.05 M solution of *ul*-**1** or *lk*-**1** in THF was added to 3.0 equiv of (n-Bu)$_4$NF$^-$ buffered with 3.0 equiv of $NaHCO_3$. The mixture was heated to reflux for 24 h. After cooling to room temperature a 0.05 mL aliquot was removed and washed with saturated $NaHCO_3$ (1 mL) and water (1 mL). The organic layer was extracted with EtOAc (3 × 2 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to an oil. Purification was accomplished by chromatography (hexane/EtOAc, 6:1) to give the *syn* and *anti* alcohols. The organic layer was analyzed by on column capillary GC to determine the *syn* /*anti* ratio. The product alcohols were also analyzed by NMR on the GN-500 spectrometer.

NMR Analysis Conditions: The product alcohol **2a** and **2b** were analyzed on the General Electric GN-500 spectrometer (500 MHz ^{1}H). The solvent used was CD_3OD which was found to give the best dispersion of the methylene protons on the bicyclic system. The ^{1}H-NMR spectra for each sample was acquired (at least 5 T_1's between acquisition) and integrated at least 3 times to give reproducible results.

rel-(1'*R*,7'*S*)-2,3'-(3'-Epoxyphenyldimethylsilyl-(7'-*d*)-methyl)cyclohex-3'-enylacetic Acid Methyl Ester (16a). To a cold (0 °C) solution of the ester *ul*-**14** (255 mg, 0.84 mmol) in dichloromethane (10 mL) was added sodium hydrogen phosphate (119 mg, 0.84 mmol) and MCPBA (144 mg, 0.83 mmol). The resulting solution was stirred at 0 °C for 2 h. The solution was poured into saturated sodium bicarbonate solution (30 mL) and then extracted with ether (3 × 30 mL). The ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 9:1) to afford 147 mg (55%) of the epoxides **16a**/**16a'** as a colorless oil. Analytical data for **16a**/**16a'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 5 Ph), 4.80 (m, 1 H, HC(4')), 4.02 (m, 1 H, HC(1')), 3.66 (s, 3 H, OCH_3), 2.20-1.20 (m, 9 H), 0.39 (s, 3 H, SiCH_3), 0.36 (s, 3 H, SiCH_3); IR (neat) 2952 (m), 2915 (m), 2840 (m), 1739 (s), 1428 (m), 1356 (m), 1293 (m), 1242 (s), 1200 (m), 1156 (s), 1112 (s), 1065 (m), 995 (m), 872 (w), 833 (s) cm^{-1}; TLC R_f 0.35 (hexane/EtOAc, 19:1);

rel-(1'*R*,7'*S*)-2,3'-(3'-Epoxyphenyldimethylsilyl-(7'-*d*)-methyl)cyclohex-3'-enylacetic Acid Methyl Ester (16b). To a cold (0 °C) solution of the ester *lk*-**14** (450 mg, 1.48 mmol) in dichloromethane (25 mL) was added sodium hydrogen phosphate (210 mg, 1.48 mmol) and MCPBA (255 mg, 1.48 mmol). The resulting solution was stirred at 0 °C for 2 h. The solution was poured into saturated sodium bicarbonate solution (30 mL) and then extracted with ether (3 × 30 mL). The ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 9:1) to afford 180 mg (45%) of a 1:1 mixture of the epoxides *lk*-**16a**/*lk*-**16a'** as a colorless oil. Analytical data for **16b/16b'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 5 Ph), 4.80 (m, 1 H, HC(4')), 4.02 (m, 1 H, HC(1')), 3.66 (s, 3 H, OCH_3), 2.20-1.20 (m, 9 H), 0.38 (s, 3 H, SiCH_3), 0.36 (s, 3 H, SiCH_3); IR (neat) 2956 (m), 2913 (m), 2837 (m), 1738 (s), 1428 (m), 1358 (m), 1293 (m), 1242 (s), 1200 (m), 1156 (s), 1112 (s), 1068 (m), 995 (m), 872 (w), 832 (s) cm^{-1}; TLC R_f 0.35 (hexane/EtOAc, 19:1).

4'-Hydroxy-3'-methylidene-(7'-*d*)-cyclohexaneacetic Acid Methyl Ester (17a). To a cold (0 °C) solution of the ester **16a/16a'** (143 mg, 0.44 mmol) in THF (10 mL) was added tetrabutylammonium fluoride solution (0.53 mL, 1.0 M in THF, 1.2 equiv) and the resulting solution was stirred at 0 °C for 1 h. The solution was poured into saturated sodium bicarbonate solution (30 mL) and then extracted with ether (3 × 30 mL). The ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 4:1) to afford 50 mg (60%) of the alcohols **17a**/**17a'** as a colorless oil. Analytical data for **17a**/**17a'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (m, 0.5 H, HC(7')), 4.88 (m, 0.5 H, HC(7')), 4.21 (m, 0.5 H, HC(4')), 4.00 (m, 0.5 H, HC(4')), 3.69 (s, 3 H, OCH_3), 2.46-1.20 (M, 11 H); TLC R_f 0.20 (hexane/EtOAc, 3:1).

4'-Hydroxy-3'-methylidene-(7'-*d*)-cyclohexaneacetic Acid Methyl Ester (17b). To a cold (0 °C) solution of the ester **16b**/**16b'** (55 mg, 0.22 mmol) in THF (10 mL) was added tetrabutylammonium fluoride solution (0.26 mL, 1.0 M in THF, 1.2 equiv) and the resulting solution was stirred at 0 °C for 1 h. The solution was poured into saturated sodium bicarbonate solution (30 mL) and then extracted with ether (3 × 30 mL). The ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 5:1) to afford 25 mg (78%) of the alcohols **17b** as a colorless oil. Approximately a 1:1 mixture of diastereomers was determined by NMR analysis. Analytical data for **17b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (m, 0.5 H, HC(7'), 4.89 (m, 0.5 H, HC(7')), 4.20 (m, 0.5 H, HC(4')), 4.02 (m, 0.5 H, HC(4')), 3.62 (s, 3 H, OCH_3), 2.20-1.20 (m, 11 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.71 (C(3')), 148.46 (C(3')), 109.50 (t, J = 22, C(7')), 105.00 (t, J = 22, C(7')), 72.17 (C(4')), 71.72 (C(4')), 51.52, 51.48, 39.96, 36.74, 35.73, 35.64, 34.62, 34.56, 32.85, 30.62, 26.74; TLC R_f 0.20 (hexane/EtOAc, 3:1).

(*E*)-7-Methylene-10-*d*-2-oxabicyclo-[3.2.2]-nonan-3-one ((*E*)-13). A solution of the ester **17a** (20 mg, 0.107 mmol) and sodium methoxide (2 mg) in THF (5 mL) was stirred at room temperature for 24 h. The solution was poured into water (30 mL) and then extracted with ether (3 × 10 mL). The ethereal extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 4:1) to afford 10.2 mg (61%) of the lactone (*E*)-**13** as a colorless oil. This product was identical by ^{1}H NMR to a sample obtained previously. Analytical data for (*E*)-**13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 1 H, HC(9)), 5.07 (s, 0.10 H, HC(9)), 4.66 (t, 1 H, J = 3.3 HC(6)), 2.79 (m, 2 H, H_2C(2)), 2.45 (m, 2 H, H_2C(4)), 2.27 (m, 1 H, HC(7)), 2.13 (s, 1 H, HC(3)), 1.90 (m, 1 H, HC(7)), 1.78 (m, 2 H, H_2C(8)); TLC R_f 0.25 (hexane/EtOAc, 4:1).

(*Z*)-7-Methylene-10-*d*-2-oxabicyclo-[3.2.2]-nonan-3-one ((*Z*)-13). A solution of the ester **17b** (45 mg, 0.24 mmol) and sodium methoxide (2 mg) in THF (5 mL) were stirred at room temperature for 24 h. The solution was poured into water (10 mL) and then extracted with ether (3 × 10 mL). The ethereal extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/EtOAc, 4:1) to afford 22.2 mg (60%) of the lactone (*Z*)-**13** as a colorless oil. This product was identical by ^{1}H NMR to a sample obtained previously. Analytical data for (*Z*)-**13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 0.05 H, HC(9)), 5.09 (s, 1 H, HC(9)), 4.70 (t, 1 H, J = 3.2 HC(6)), 2.79 (m, 2 H, H_2C(2)), 2.45 (m, 2 H, H_2C(4)), 2.27 (m, 1 H, HC(7)), 2.13 (s, 1 H, HC(3)), 1.90 (m,

1 H, HC(7)), 1.78 (m, 2 H, $H_2C(8)$); TLC R_f 0.25 (hexane/EtOAc, 4:1).

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References

1. For pertinent reviews of allylmetal additions see: (a) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 489-503. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207-2293. (c) Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E. Eds.; *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; E21; Thieme; Stuttgart, 1996; Vol. 3; pp 1357-1602. (d) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (e) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 27. (f) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*, Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (g) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763-2793.
2. To effectively describe the products observed in these reactions the stereochemical descriptors suggested by Masamune will be employed: Masamune, S.; Kaiko, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521-5523.
3. Reviews: (a) Hoffmann, R. W. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Cambridge; 1994; pp 259-274. (b) Roush, W. R. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; E21; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme Stuttgart: New York, 1996; Vol. 3; pp 1410-1486. (c) Hall, D. G.; Lachance, H. *Org. React.* **2008**, *73*, 1-573.
4. Reviews: (a) Gung, B. W. *Org. React.* **2004**, *64*, 1-413. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243-249.
5. Reviews: (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1-22. (b) Majetich, G. In *Organic Synthesis: Theory and Application*s; Hudlicky, T., Ed.; JAI Press: Greenwich, 1989; Vol. 1, p. 173-240. (c) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200-206. (d) Fleming, I.; Dunogués, J.; Smithers, R. *Org. React.* **1989**, *37*, 57-575. (e) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192. (f) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375-1408. (g) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293-1316. (h) The intramolecular reactions of allylsilanes have also been reviewed: Schinzer, D. *Synthesis* **1988**, 263-273.
6. Reviews: Furstner, A. *Chem. Rev.* **1999,** 99, ~~(4),~~ 991-1045. (b) Cintas, P. *Synthesis* **1992**, 248-257. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C., *Chem. Soc. Rev.* **1999,** *28*, 169-177. (d) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007,** 349, 2407-2424.
7. Reviews: (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807-832. (b) Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Rothe-Streit, P.; Rihs, G. *Pure Appl. Chem.* **1992**, *64*, 1897-1910. (c) Hoppe, D. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme, Stuttgart: New York, 1995; Vol. E 21b, pp 1551-1583.
8. Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655-1660.
9. For an early, general discussion of the topological features of reactions of double bonds see: Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413-1423.
10. (a) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236-1240. (b) Gung, B. W.; Xue, X. *Tetrahedron: Asymmetry* **2001**, *12*, 2955-2959.
11. (a) Imachi, M.; Nakagawa, J.; Hayashi, M. *J. Mol. Struct.* **1983**, *102*, 403-412. (b) Hayashi, M.; Imachi, M.; Saito, M. *Chem. Lett.* **1977**, 221-222. (c) Beagley, B.; Foord, A.; Moutran, R.; Roszondai, B. *J. Mol. Struc.* **1977**, 117-120. (d) Ohno, K.; Toga, K.; Murata, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2870-2876.
12. White, J. M.; Clark, C. I. In *Topics in Stereochemistry*; Denmark, S. E., Ed.; Wiley: New York, 1999; pp 137-200.
13. Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650-663.
14. For a thorough disquisition on the state of the art in S_E' reactions see: Matassa, V. G.; Jenkins, P. R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, *29*, 321-343.
15. (a) Fleming, I.; Terrett, N. K. *Pure Appl. Chem*. **1983**, *55*, 1707-1713. (b) Fleming, I. *Pure Appl. Chem.*, **1988**, *60*, 71-78.
16. (a) Carter, M. J.; Fleming, I. *J. Chem. Soc. Chem. Commun*, **1976**, 679-680. (b) Au-Yeung, B.-W.; Fleming, I. *J. Chem. Soc. Chem. Commun.* **1977**, 79-80. (c) Au-Yeung, B.-W.; Fleming, I. *J. Chem. Soc. Chem. Commun.* **1977**, 81. (d) Fleming, I.; Williams, R. V. *J. Chem. Soc. Perkin I*, **1981**, 684-688. (e) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc. Perkin I*, **1981**, 2415-2434. (f) Chan, T. H.; Fleming, I. *Synthesis*, **1979**, 761-786. (g) Fleming, I.; Au-Yeung, B. -W. *Tetrahedron Suppl. 1* **1981**, *37*, 13-24. (h) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1984**, *25*, 5103-5104.
17. (a) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99-118. (b) Fleming, I. Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153-4156. (c) Chow, H.-F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397-400. (d) Fleming, I.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc. Chem. Commun.* **1987**, 157-159.
18. (a) Wetter, H.; Scherer, P.; Schweizer, W. B. *Helv. Chim. Acta* **1979**, *62*, 1985-1989. (b) Wetter, H.; Scherer, P. *Helv. Chim. Acta* **1983**, *66*, 118-122.
19. (a) Young, D.; Kitching, W. *Tetrahedron Lett.* **1983**, *24*, 5793-5796. (b) Wickham, G.; Kitching, W.*J. Org. Chem.* **1983**, *48*, 612-614. (c) Wickham, G.; Kitching, W. *Organometallics* **1983**, *2*, 541-547. (d) Young, D.; Kitching, W.; Wickham, G. *Tetrahedron Lett.* **1983**, *24*, 5789-5792. (e) Young, D.; Kitching, W. *Aust. J. Chem.* **1985**, *38*, 1767-1777. (f) Young, D.; Jones, M.; Kitching, W. *Aust. J. Chem.* **1986**, *39*, 563-573. (g) Wickham, G.; Young, D.; Kitching, W. *Organometallics* **1988**, *7*, 1187-1195.
20. (a) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963-4965. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281-282. (c) Hayashi, T.; Ito, H.; Kumada, N. *Tetrahedron Lett.* **1982**, *23*, 4605-4606. (d) Hayashi, T.; Okamoto, Y.; Kabeta, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1984**, *49*, 4224-4226.
21. Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868-9870.
22. (a) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970-7971. (b) Denmark, S. E.; Henke, B. R.; Weber, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 2512-2514. (c) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053-1065.
23. (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **1990**, *29*, 256-272. (b) Ooi, T.; Maruoka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 1. (c) Saito, S.; Yamamoto, H. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 2. (c) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405-2408. (d) Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am.*

Chem. Soc. **1987**, *109*, 2512-2514. (e) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133-3139.
24. (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847-3849. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478-5480. (c) Filippini, F.; Susz, B. -P. *Helv. Chim. Acta* **1971**, *54*, 835-845. (d) Beattie, I. R. *Quart. Rev.* **1963**, *17*, 382-405.
25. Biddle, M. M.; Reich, H. J. *J. Org. Chem.* **2006**, *71*, 4031-4039.
26. (a) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99-118. (b) Fleming, I. Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153-4156. (c) Chow, H.-F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397-400. (d) Fleming, I.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc. Chem. Commun.* **1987**, 157-159.
27. Gerlach, H.; Mueller, W. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1030-1031.
28. (a) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833-2838. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021-4024.
29. (a) Bachman, G. B. *J. Am. Chem. Soc.* **1933**, *55*, 4279-4284. (b) Farrell, J. K.; Bachman, G. B. *J. Am. Chem. Soc.* **1935**, *57*, 1281-1283.
30. (a) Wolinsky, J.; Erickson, K. L. *J. Org. Chem.* **1965**, *30*, 2208-2211. (b) Dawson, T. M.; Dixon, J.; Littlewood, R. S.; Lythgoe, B. *J. Org. Chem.* **1971**, 2352-2355.
31. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73-253.
32. (a) Tomboulian, P.; Stehower, K. *J. Org. Chem.* **1968**, *33*, 1509-1512. (b) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341-1348.
33. Reider, P. J.; Eichen Conn, R.; S.; Davis, P.; Grenda, V. J.; Zambito, A. J.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 3326-3334.
34. The stereochemical families are defined by the Seebach-Prelog recommendations by consideration of the two stereocenters of the allylsilane: Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654-660.
35. Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002.
36. The configuration of the hydroxyl group was assigned on the basis of the slope of the LIS of the methylidene group with $Eu(fod)_3$: *syn*-**2**, 6.61 ppm/equiv.; *anti*-**2**, 2.81 ppm/equiv. See reference 8.
37. (a) Middleton, W. J. *Org. Syn*. **1985**, *64*, 221-225. (b) Szarek, W. A.; Hay, G. W.; Dozoszewski, B. *J. Chem. Soc., Chem. Commun*. **1985**, 663-664.
38. (a) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett*. **1978**, 3043-3046. (b) Hosomi, A.; Shirahata, A.; Sakurai, H. *Chem. Lett.* **1978**, 901-904.
39. DePuy, C. H.; Bierbaum, V. M.; Flippin, L. A.; Grabowski, J. J.; King, G. K.; Schmitt, R. J.; Sullivan, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5012-5015.
40. (a) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* **1986**, *51*, 1745-1753. (b) Majetich, G.; Desmond, R. W. Jr.; Soria, J. J. *J. Org. Chem.* **1986**, *51*, 1753-1769.
41. (a) Corriu, R. *Pure Appl. Chem.* **1988**, *60*, 99-106. (b) Corriu, R. J. P.; Guerin, C.; Moreau, J. J. E. *Top. Stereochem.* **1984,** *15*, 158-178. (c) Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron*, **1988**, *44*, 2675-2749.
42. This conclusion assumes that the rotation of the terminal methylene group of the allyl anion is faster than addition to the aldehyde.
43. Sakurai, H. *Synlett.* **1989**, *1*, 1-8.
44. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923-2925.
45. Gilman, H.; Schulze, F. *J. Am. Chem. Soc.* **1925**, *47*, 2002-2005.