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On the stereochemical course of the addition of allylsilanes to aldehydes

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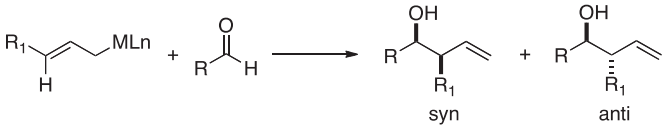
ABSTRACT

Model compounds **3** and **5** have been studied to determine the orientation of the reacting double bonds in the transition state of the allylmetal–aldehyde addition. These models were designed to remove any intrinsic steric bias for the formation of the bicyclic products that would obfuscate a stereoelectronic contribution to the transition states. Model system **3** revealed a modest preference for the synclinal transition state, albeit in very low yields. Model system **5** underwent selective and largely Lewis acid independent cyclization primarily via a synclinal transition state. The high proximal selectivity observed in these cyclizations likely reflects the selectivity of an unhindered allylmetal–aldehyde addition for the synclinal transition state and results from a stereoelectronic preference, not an intrinsic steric bias, for the synclinal arrangement of double bonds.

1. Introduction

The controlled construction of stereocenters in open-chain systems is of primary importance in the synthesis of acyclic natural and non-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 addition is partly derived from the high yield, excellent site selectivity, and the mild conditions under which it can be employed.

The reaction of a substituted allylmetal reagent with an aldehyde can result in the formation of diastereomeric homoallylic alcohols (Scheme 1).[2] The allylmetal–aldehyde addition 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 additions is dependent upon the allylmetal used. This dependence has been classified into three groups that relate the stereochemical outcome of the reaction to the geometry of the double bond.[1f,8] Type 1 reactions wherein the *syn*/*anti* ratio reflects the *Z*/*E* ratio of the starting allylmetal (B, Al, Sn); Type 2 reactions wherein the reaction is *syn*-selective independent of the geometry of the allylmetal (Sn, Si); and Type 3 reactions wherein 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,[1f,9] but those that fall in the Type 2 family are the focus of the studies described herein. Proposals for Type 2 reactions invoke 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 relative diastereoselection (Scheme 2). The internal 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.

Previous investigations from these laboratories have described the synthesis and cyclization of a model system that *unambiguously* determined the stereochemical course of addition in an allylsilane–aldehyde reaction.[10] However, criticisms of this model focused on a potential inherent bias given the diastereomeric relationship of the products. We therefore undertook the investigation of two new model systems that remove this bias.

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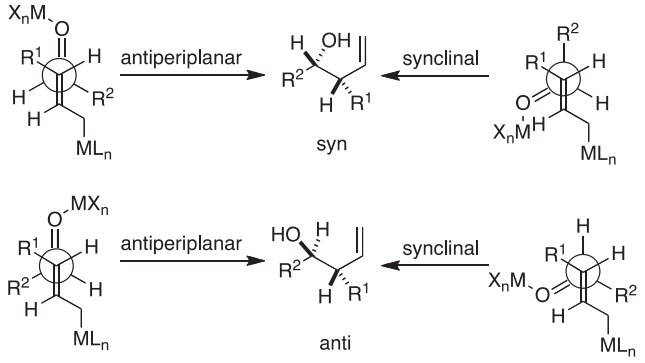
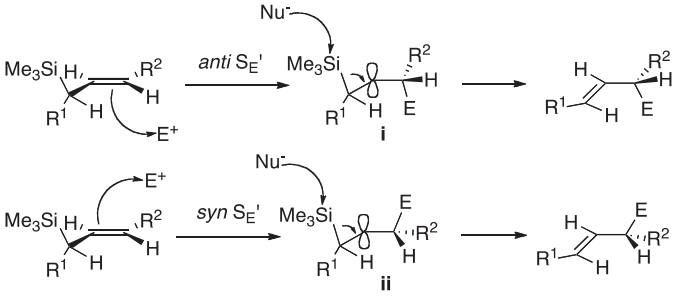


Scheme 2.



Scheme 3.

2. 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* S_E' 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*-double bond.

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 three energy minima were observed (Chart 1). In the two most stable conformers the C–Si bond is perpendicular to the C–C double bond. 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.

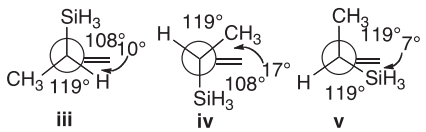
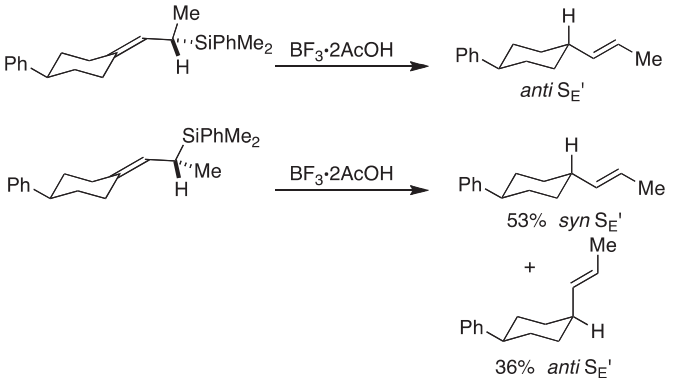


Chart 1.

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 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.

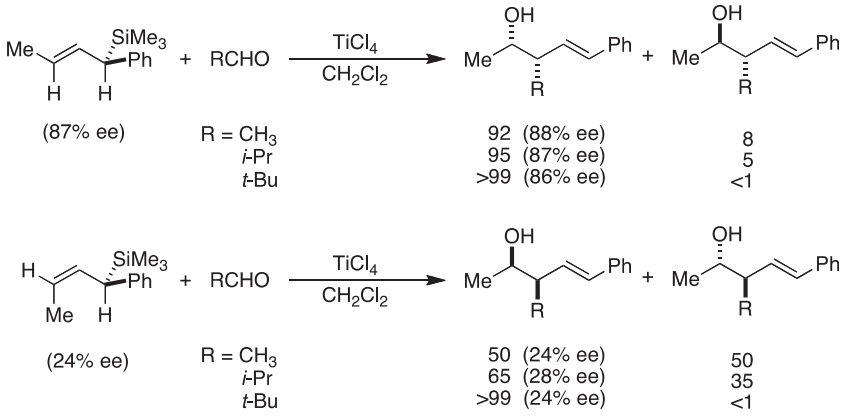
Fleming expanded the study of the S_E' reaction to include the use of acyclic allylsilanes.[17] In protiodesilylation experiments the allylsilane cleanly gives products from an *anti* S_E' reaction whereas the diastereomeric allylsilane affords a mixture of both *syn* and *anti* S_E' products (Scheme 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.



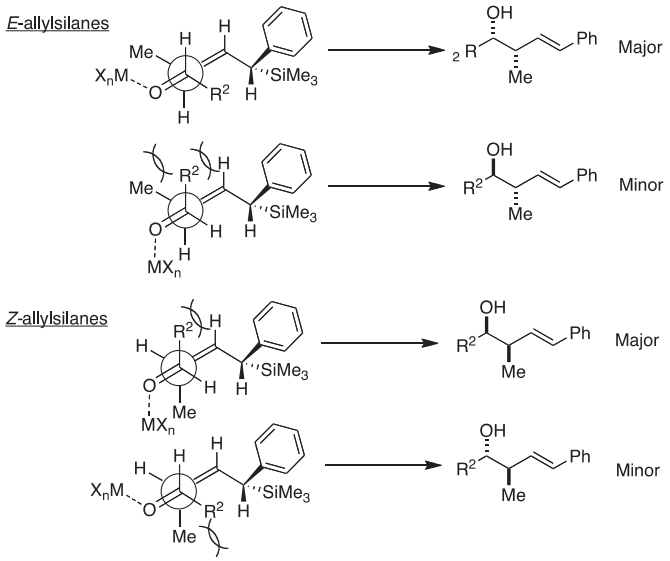
Scheme 4.

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-*tert*-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 *tert*-butyl substituent.

Kumada and Hayashi have carried out extensive studies to define all of the stereochemical features of the addition to aldehydes with titanium tetrachloride (Scheme 5).[20] 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 diastereoselectivity (*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 6).



Scheme 5.

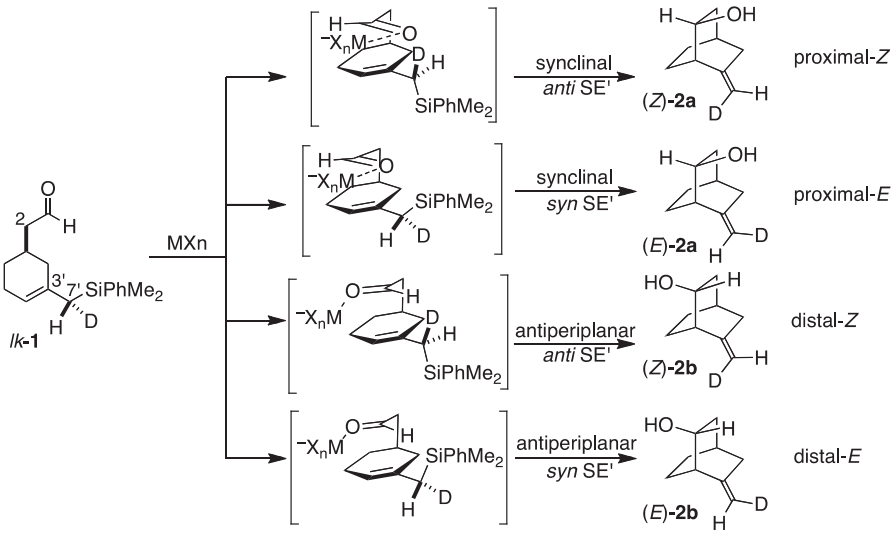


Scheme 6.

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 addition was undertaken in our laboratories to provide an unambiguous correlation between product stereochemistry and transition state geometry.[8,10] To achieve this objective, both the position of the silicon electrofuge and the orientation of the reacting double bonds in the transition structure was unambiguously defined in an *intramolecular* allylmetal–aldehyde reaction. Although intramolecular cyclizations cannot exactly model the corresponding intermolecular reactions, the results from these studies provide useful insights into intrinsic preferences in the transition structure of the allylmetal–aldehyde additions.

The deuterium-labeled model **1** (Scheme 7) was designed to differentiate between the *syn* and *anti* S_E' pathways.[10d,f] 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.

The selectivity observed in the cyclization of the model system **1** 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



Scheme 7.

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[10b,21] then the major steric contribution in the model system would arise from the (phenyldimethylsilyl)methylene group. The formation of any of the proximal product with $SnCl_4$, a Lewis acid known to form 2:1 complexes with aldehydes,[22] was interpreted as a stereoelectronic advantage for the synclinal transition state. The high distal 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.[23] This process is best accommodated by an antiperiplanar transition state in which the developing negative charges experience less repulsion than in a synclinal transition state.

The products from both the synclinal and antiperiplanar transition structures were found to arise from an *anti* S_E' reaction. 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. All of the cyclizations with Lewis acids were greater than 95% selective for the *anti* S_E' reaction. 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.

3. Model design

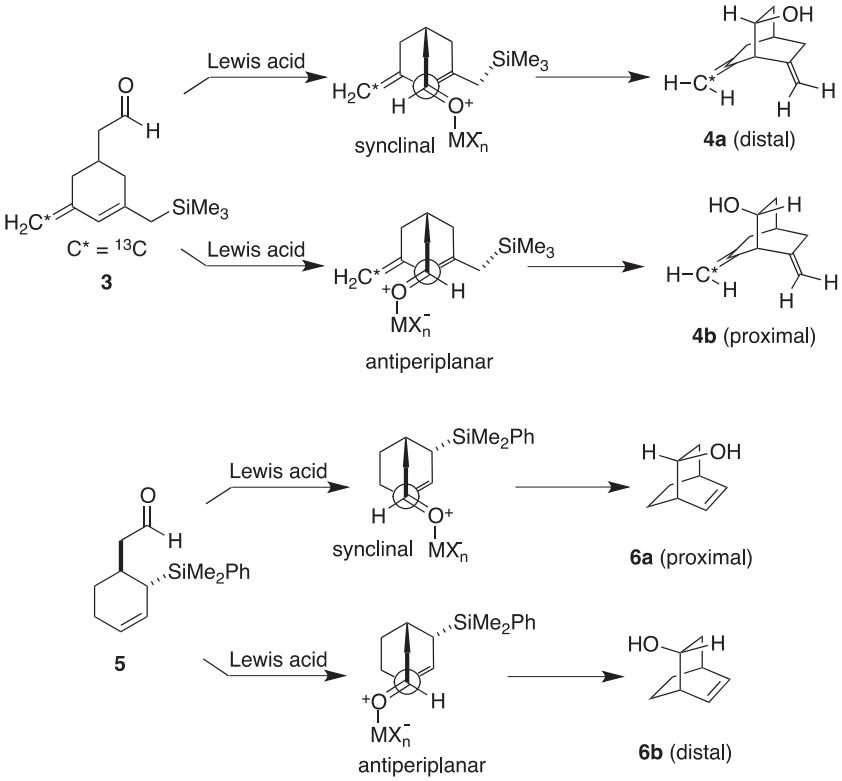
Although model system **1** does not contain any bulky substituents at the methylene group attached to the silicon, an inherent bias might exist because the products are diastereoisomers and thus the ground states are not isoenergetic. A difference in ground state energies could manifest itself in the relative energies of the transition states leading to formation of the products. Two advanced models, **3** and **5** (Scheme 8) were formulated to address the diastereomeric bias inherent in model **1**. Intramolecluar cyclization of **3** will lead to the formation of enantiomeric (ignoring the ^{13}C label) and therefore isoenergetic products **4a** and **4b**.[24] The enantiomeric composition (as established by the ^{13}C label) will provide a direct measure of the energy difference between the antiperiplanar and synclinal transition state geometries. Thus, this model should be ideal for elucidating the existence of stereoelectronic control alone. The ^{13}C label, by synthetic design, will be uniquely located in the methylidene group. The product distribution will be determined by integration of the signals for the pseudoenantiomers in the ^{13}C NMR spectrum.

The second model, **5** seeks to minimize the inherent bias in model **1** by removing the trialkylsilylmethylene group and locating the silicon electrofuge in the ring, but trans to (and therefore away from) the tethered aldehyde moiety. Cyclization of model system **5** leads to the formation of the diastereomeric alcohols **6a** and **6b**. The alcohols **6a** and **6b** do not contain the exocyclic olefin present in the cyclization products of model system **1**. Therefore, the observed selectivity should more accurately reflect the intrinsic preference for the synclinal versus the antiperiplanar transition states.[24]

4. Results and discussion

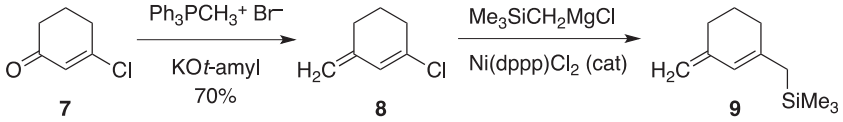
4.1. Synthesis of model system 3

4.1.1. Construction of the pentadienylsilane unit. The construction of the pentadienylsilyl moiety for **6** represented a major synthetic challenge. Any synthetic approach had to take into account the need to place the ^{13}C label exclusively in the methylidene group. A survey of the synthetic methods developed for the preparation of pentadienylsilanes[25] indicated that these methods would not be applicable since they involve the intermediacy of pentadienyl anions, which in model **3** would lead to scrambling of the ^{13}C label. The solution to this problem is outlined in Scheme 9.



Scheme 8.

Methylenation[26] of 3-chloro-2-cyclohexenone **7**[27] afforded **8** in 70% yield. The chloro diene was very reactive and had to be quickly subjected to the next set of reaction conditions. The nickel-catalyzed coupling[28] of **8** with trimethylsilylmethylmagnesium chloride[29] afforded diene **9** in 85% yield. Pentadienylsilane **9** was stable to chromatography (alumina), GC, and distillation (bp 90 °C/15 mmHg). A pure sample could be stored at −20 °C without decomposition for extended periods of time.

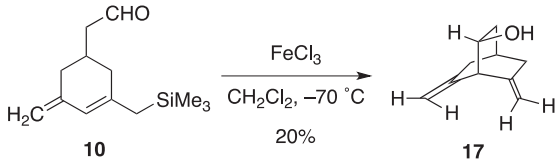


Scheme 9.

Seyferth[25] had previously shown that the Lewis acid catalyzed reactions of (2,4-pentadienyl)trimethylsilane with various electrophiles, such as aldehydes, acetals, and acid chlorides provided adducts in fair to high yields. Accordingly, the Lewis acid catalyzed reactions of **9** with acetaldehyde, benzaldehyde, benzoyl chloride and the dimethyl acetal of benzaldehyde were investigated. Only the Et_2AlCl-catalyzed addition of **9** to benzaldehyde afforded any product (20% yield), which resulted from the attack of the electrophile at a terminus of the pentadienylsilane. This result is consistent with that reported by Seyferth, who observed adducts with only this site selectivity. In all other reactions investigated, complex mixtures with poor mass recovery were obtained.

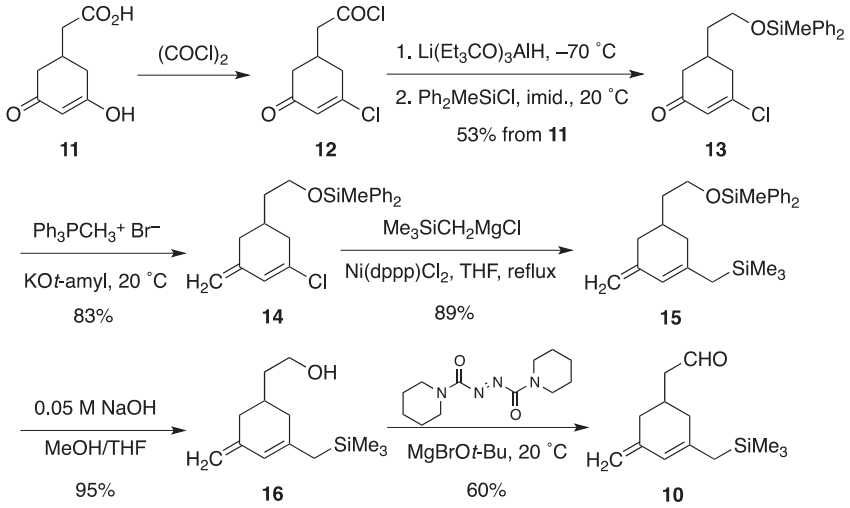
*4.1.2. Preparation of model system **10** (unlabeled).* Considering the sensitivity of the intermediates and potential for self-addition of the target, the initial goal was to synthesize model **3** without the ^{13}C label. The synthesis of the unlabeled model **10** is outlined in Scheme 10. Treatment of the known diketo acid **11**,[30] prepared in four steps in 27% overall yield from diethyl 3-oxoglutarate, with excess oxalyl chloride provided the unstable acid chloride **12**. Reduction of **12** with lithium tris-(3-pentoxy)aluminum hydride[31] and protection of the resulting alcohol as its diphenylmethylsilyl ether[32] afforded chloro enone **13** in 53% overall yield from **11**. The intermediate alcohol was very prone to polymerization upon evaporation of solvent after chromatography, but polymerization could be minimized by keeping the alcohol in solution at all times. Methylenation of **13** as previously described[26] afforded chloro diene **14** in 83% yield. Once again, the chloro diene could not be stored and was immediately subjected to the nickel catalyzed cross-coupling with trimethylsilylmethylmagnesium chloride[29] to provide pentadienylsilane **15** in 89% yield. Treatment of **15** with 0.05 M aqueous sodium hydroxide afforded alcohol **16** in 95% yield. Oxidation of **16** with 1,1′-(azodicarbonyl)dipiperidine and *tert*-butoxymagnesium bromide[33] afforded aldehyde **10** in 60% yield. The basic character of the Mukaiyama oxidation protocol was critical as all other oxidizing agents tested led to decomposition of the pentadienylsilane. The model system was stable to chromatography (Al_2O_3), GC, and could be stored at −20 °C for extended periods without decomposition.

*4.1.3. Cyclization of model system **10**.* Treatment of a 0.05 M solution of **10** in CH_2Cl_2 at −70 °C with 1.1 equiv of $FeCl_3$ for 2.5 h led to the formation of the expected bicyclic alcohol **17** in 20% yield (Scheme 11). Bicyclic alcohol **17** was the only observable product by GC analysis. The ^{13}C NMR spectrum of **17** shows that the methylidene carbon signals are clearly distinguishable at 108.99 and 110.99 ppm, thus direct integration of these signals should be possible.

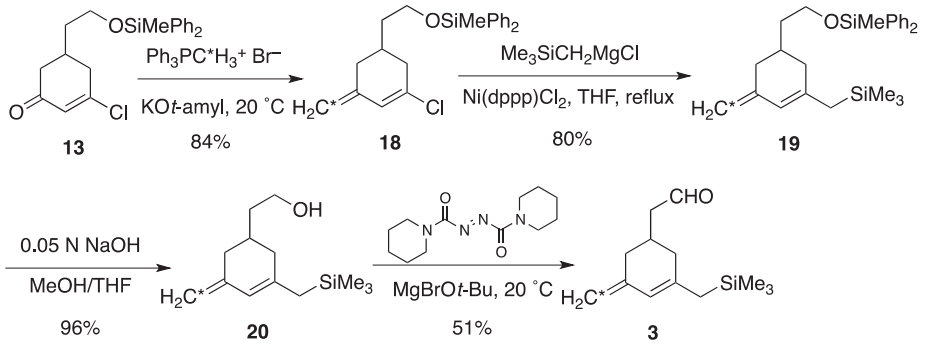


Scheme 11.

*4.1.4. Preparation of ^{13}C labeled model system **3**.* The synthesis of model **3** is outlined in Scheme 12. Treatment of **13** with methylenetriphenylphosphorane enriched with 40% ^{13}C label afforded chloro diene **18** in 84% yield. The ^{13}C-enriched phosphonium salt was prepared by mixing the appropriate amounts of unlabeled



Scheme 10.

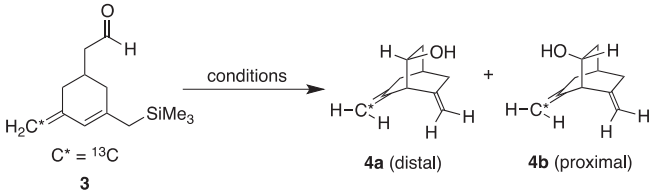


Scheme 12.

methyltriphenylphosphonium bromide with 99% ^{13}C labeled methyltriphenylphosphonium iodide, which in turn was prepared by treating 99% ^{13}C labeled methyl iodide with triphenylphosphine. The high percentage (40%) of ^{13}C label incorporated into **3** facilitated the stereochemical analysis of the reaction products **4a** and **4b**. Coupling of **18** with trimethylsilylmethylmagnesium chloride afforded pentadienylsilane **19** in 80% yield. Deprotection with base proceeded smoothly in 96% yield and oxidation[33] of the resulting alcohol **20** provided model system **3** in 51% yield. The incorporation of the ^{13}C label was clearly evident in the ^{1}H NMR spectrum of **3**. The methylidene protons of the ^{13}C labeled portion of **3** appeared as a doublet of doublets centered at 4.61 ppm with a carbon-hydrogen coupling constant of 156 Hz. The mass spectrum of **3** showed the presence of two molecular ions at 222 and 223 *m*/*z*. The ^{13}C NMR spectrum of **3** showed an enhancement of only the *exo*-methylidene carbon signal at 107.88 ppm, indicating that no scrambling of the ^{13}C label had occurred.

*4.1.5. Cyclization of model system **3**.* The Lewis acid promoted reactions of **3** were performed by treating a 0.05 M solution of **3** in CH_2Cl_2 at −70 °C with 1.1 equiv of Lewis acid (Table 1). The fluoride ion promoted cyclization of **3** was performed by treating a 0.05 M solution of **3** in THF at 20 °C with 1.0 equiv of a 0.32 M solution of tetrabutylammonium fluoride in THF. The proximal/distal ratios were determined by integration of the methylidene carbon signals in the ^{13}C NMR spectrum.[34] Long delay times (>5 s) were used to ensure complete relaxation of the ^{13}C nuclei. Signal to noise ratios of at least 20/1 were obtained for each ^{13}C NMR spectrum to minimize error in the integration of the methylidene carbon signals.

Table 1
Cyclization of model **3**[a]



Entry	Reagent	Time, min	Temp, °C	Yield, %[b]	**4a**/**4b**, %[c]	ΔΔG‡[d]
1	$BF_3{\cdot}OEt_2$[e]	150	−70	6	70/30	0.34
2	$FeCl_3$	150	−70	20	70/30	0.34
3	Et_2AlCl[e]	150	−70	12 (16)	73/27	0.40
4	$SnCl_4$	60	−70	12	67/33	0.29
5	*n*-$Bu_4N^+F^-$[e,f]	60	20	21	53/47	0.05

[a] All cyclizations were performed with 1.05 equiv of Lewis acid in CH_2Cl_2 at −70 °C except where noted.
[b] Yields of isolated material, yield in parentheses based on recovered starting material.
[c] Ratios were determined by ^{13}C NMR analysis.
[d] Calculated at 203 K (in kcal/mol).
[e] Reaction performed in THF at 20 °C.
[f] In addition to the bicyclic alcohols **4a** and **4b**, a 33% yield of aldehyde **21** was obtained.

The results summarized in Table 1 for the cyclization of **3** show a modest preference for the formation of the distal isomer, suggesting a stereoelectronic advantage for synclinal orientation of reactants under electrophilic conditions (Scheme 9).[35] Since the distribution of reaction products **4a** and **4b** is a direct measure of the relative energies of the transition states for synclinal and antiperiplanar geometry, simple energy calculations show that at −70 °C the synclinal geometry is preferred by only 0.40 kcal/mol. The operation of an intrinsic electronic effect that favors synclinal geometry, if present, is very small.

In contrast to model **1**, the range of *syn*-selectivity for the Lewis acid catalyzed cyclization of **3** is very narrow. The insensitivity to the size of the Lewis acid indicates the lack of a steric component. Taking into account the diminished reactivity of **3** compared to **1**,[10f] the lack of a steric component suggests that bond formation occurs in a late transition state. In a late transition state the carbon–carbon bond α to the trimethylsilyl group acquires more double bond character as bond formation takes place, thus minimizing the steric interaction between the Lewis acid–aldehyde complex and the (trimethylsilyl)methylene protons as discussed earlier for the model system **1**. The lack of selectivity observed for the fluoride ion induced cyclization of **3** suggests the formation of a delocalized pentadienyl anion.

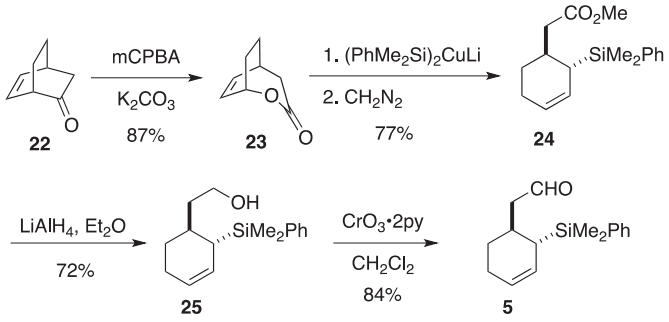
The low yields of reaction products in Table 1 are puzzling. An alternative reaction pathway may be available to **3**, such as the intermolecular addition proceeding through the termini of the pentadienylsilyl moiety. Alternatively, the pentadienylsilane may be undergoing transmetalation with the Lewis acid prior to closure, which would preclude any interpretation of the results.[36]

*4.1.6. ^{13}C NMR study of the transmetalation of **9** with Lewis acids.* The transmetalation of the pentadienylsilane **9** with selected Lewis acids was studied by ^{13}C NMR spectroscopy at low temperature. Pentadienylsilane **9** was very reactive toward $SnC1_4$. The silane was completely consumed with 1.0 equiv of $SnC1_4$ at −70 °C, presumably to form the pentadienyltrichlorostannane derivative. Though these results indicate that transmetalation with $SnCl_4$ may compete with formation of the active Lewis acid–aldehyde complex, this apparently is not the case. Transmetalation would presumably occur through the ^{13}C labeled terminus of the pentadienylsilyl moiety. Cyclization would then take place through a Type I transition state with the result being a decrease in *syn*-selectivity, yet the *syn*-selectivity of the $SnCl_4$ promoted cyclization of **3** is comparable to that of the other Lewis acids. Treatment of **9**

with $BF_3 \cdot OEt_2$ resulted in a complex reaction mixture whose ^{13}C NMR spectrum was not interpretable.

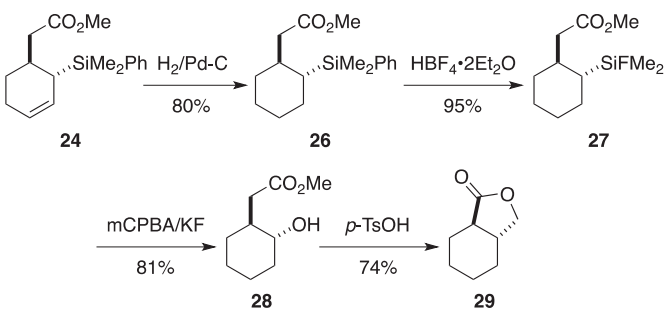
4.2. Synthesis and cyclization of model system 5

*4.2.1. Synthesis of model system **5**.* The synthesis of model system **5** was achieved in four steps starting from the known bicyclic ketone[37] **22** (Scheme 13). Baeyer–Villiger oxidation of **22** with MCPBA buffered with potassium carbonate afforded bicyclic lactone **23** in 87% yield. Treatment of the lactone with $(PhMe_2Si)_2CuLi$[17] followed by addition of diazomethane afforded one isomer of the desired allylsilane **24** in 77% yield. The ester was reduced with lithium aluminum hydride (72% yield) and the resulting alcohol **25** was then oxidized with the Collins reagent[39] to give the target aldehyde **5** in 84% yield.



Scheme 13.

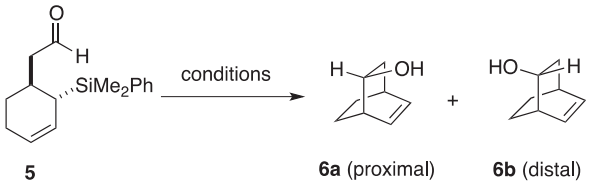
*4.2.2. Proof of relative configuration of model system **5**.* The configuration of **5** was tentatively assigned as trans on the basis of an analogous precedent, namely the addition of a silyl-cuprate reagent to an allyl acetate, which proceeds via an *anti* S_N2' process.[17] Because the configurational assignment is crucial to the interpretation of the results, the relative configuration of **5** was independently established by conversion to a known compound (Scheme 14). Hydrogenation of the allylsilane ester **24** afforded the saturated silane ester **26** in 80% yield. The phenylsilane was treated with fluoroboric acid[39] in ether to afford fluorosilane **27** (95% yield), which was converted to hydroxy ester **28** by treatment with mCPBA[39] in 81% yield. Closure of the hydroxy ester to the known bicyclic lactone[40] **29** was effected by heating in refluxing benzene with a catalytic amount of *p*-toluenesulfonic acid (74% yield). Comparison of the ^1H NMR data with published values indicates that the two compounds are identical. Finally, the configurations of the products of the allylmetal–aldehyde addition of **5** (**6a**/**6b**) were assigned by comparison of their ^{13}C NMR shifts with published values.[41]



Scheme 14.

*4.2.3. Cyclization of model system **5**.* The cyclization of **5** was promoted by various Lewis acids and the results are collected in Table 2. All of the Lewis acids studied were selective for the proximal diastereomer. The results obtained with $BF_3 \cdot OEt_2$ and CF_3SO_3H were almost identical to those obtained with model system **1**.[10f] The cyclization with $TiCl_4$ and $SnCl_4$ were found to be highly selective for the proximal diastereomer. The cyclization with $SnCl_4$ (the sterically most demanding Lewis acid) actually afforded a 90/10 ratio of diastereomers favoring the proximal isomer (entry 1). Foregoing studies revealed that the size of the Lewis acid–aldehyde complex influences the selectivity of the cyclization. For model system **5** only a small change in selectivity was observed between cyclization with either $SnCl_4$ or CF_3SO_3H (compare entries 1 and 4). These results indicate that the steric bulk of the Lewis acid does not play a significant role in determining the stereochemical outcome of the reaction. In model system **5** no external methylene unit exists, which could interact with the Lewis acid–aldehyde complex. In fact, the silane is fixed in an anti orientation with respect to the approaching aldehyde (*anti* S_E'). The cyclization of model system **5** with fluoride afforded primarily the distal product resulting from an antiperiplanar transition state. The results with fluoride indicate that the antiperiplanar transition state is accessible, but is not favored in reactions with the Lewis acids.

Table 2
Cyclization of model **5**[a]

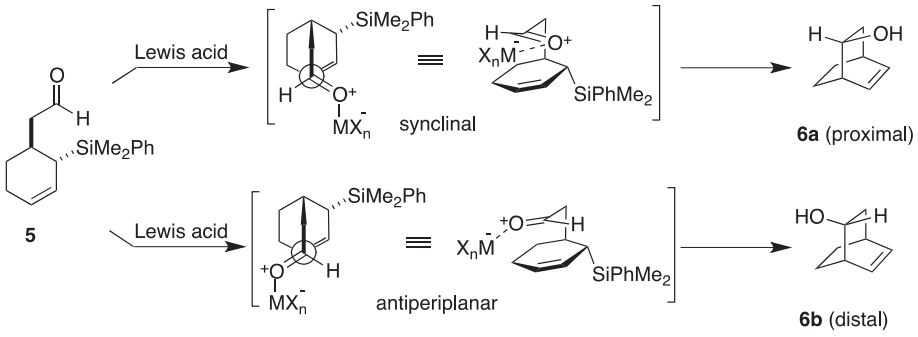


Entry	Reagent	Time, min	Mass recovery, %[c]	**6a**/**6b**, %[b,c]	ΔΔG‡[d]
1	$SnCl_4$	20	80	90/10	0.85
2	$TiCl_4$	3	88	94/6	1.07
3	$BF_3 \cdot OEt_2$	40	80	80/20	0.54
4	CF_3SO_3H[e]	1	80	95/5	1.14
5	$ZrCl_4$	90	89	78/22	0.49
6	n-$Bu_4N^+F^-$[f]	720	71	16/84	−0.64

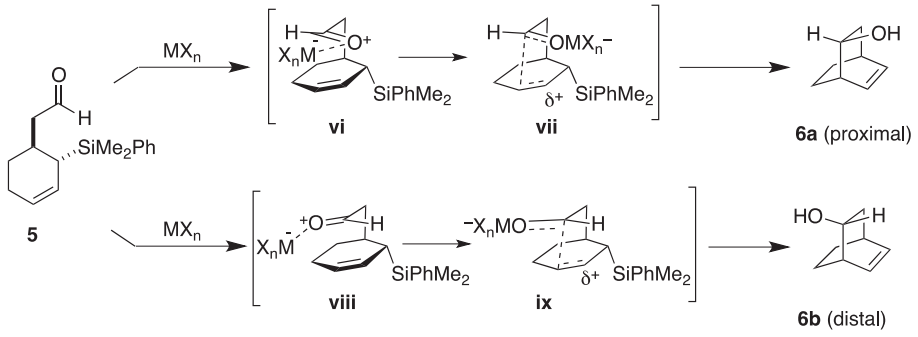
[a] All cyclizations were performed with 1.05 equiv of Lewis acid in CH_2Cl_2 at −78 °C except where noted.
[b] Average of at least three runs within ±3%.
[c] Ratios and yields were calculated based on independently determined response factors versus cyclododecane.
[d] Calculated at 195 K (in kcal/mol).
[e] Only 0.95 equiv of triflic acid used.
[f] Reaction performed in THF at 66 °C.

4.2.4. Stereochemical analysis. The two limiting transition states leading to the formation of the proximal and distal diastereomers are shown in Scheme 15. If the Lewis acid adopts an *E*-complexation geometry with the aldehyde[10b,21] the steric influence from the Lewis acid will be minimal. This is not true with the model system **1** where the (phenyldimethylsilyl)methylene unit can be influenced by the bulky Lewis acid $SnCl_4$. The results from the cyclization of this model demonstrate that the allylmetal–aldehyde addition will proceed through a synclinal transition state when no external steric bias is present.

Although several explanations for the origin of the *syn* selectivity observed in the cyclization of model system **5** can be imagined, the two most plausible will be considered here. The first invokes a Coulombic attraction between the two charged centers in an unsymmetrical transition state, favoring the synclinal over the



Scheme 15.



Scheme 16.

antiperiplanar transition state (Scheme 16). In the activated complexes **vi** and **viii**, the charges are localized on proximal atoms, whereas in the transition state the charges become separated; to a greater extent in the distal transition state **ix** than in the proximal transition state **vii**. In non-polar solvents charge separation is energetically disfavored, leading to the preferential formation of the proximal diastereomer. With more polar solvents, the formation of the distal diastereomer may be more prevalent. Huisgen has used a similar explanation to explain the retention of configuration observed in [2+2] cycloadditions of electronically complementary olefins.[42] In these cycloadditions a large effect was observed between polar and non-polar solvents, influencing both the rate of reaction and the selectivity of the cycloaddition.

To probe this explanation, a solvent study of the cyclization of **5** with $BF_3{\cdot}OEt_2$ was performed. Boron trifluoride etherate was chosen for this study because of the relatively low selectivity observed for the proximal diastereomer with this reagent in CH_2Cl_2. The results obtained from this study are shown in Table 3. Apparently, the effect of solvent polarity in the stereochemical outcome of these cyclizations is marginal. The values shown in the table for E_T^N are from a solvent polarity scale developed by Reichardt.[43] This scale has been normalized so that water and tetramethylsilane are the two possible extremes on the scale, at 1.0 and 0.0, respectively. Changing solvent from nitropropane to hexanes had little effect on the selectivity of the reaction. Unfortunately, solvents more polar than nitromethane could not be used in this study because they generally contain a Lewis basic atom which would compete with the aldehyde for complexation with the Lewis acid. The lack of a solvent effect does not necessarily rule out the possibility of Coulombic attraction in the transition state of the cyclization of model system **5**. In an intramolecular reaction any solvent effect would only arise if the intermediate was highly-polarized or long-lived. If cyclization of model system **5** proceeds via an early transition state (with little charge separation) the solvent effect is expected to be small.

Table 3
Effect of solvent in the $BF_3{\cdot}OEt_2$ mediated cyclization of **5**[a]

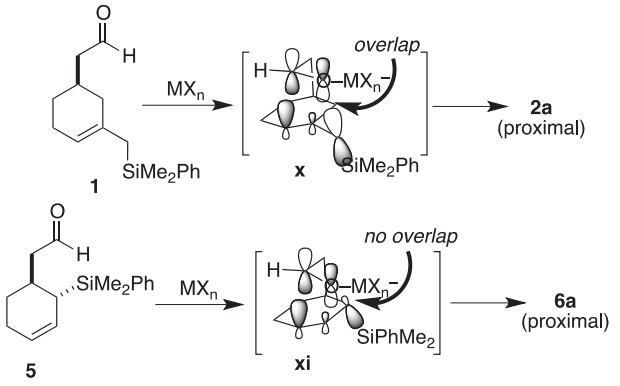
Entry	Solvent	Time, min	**6a**/**6b**, %[b,c]	Mass recovery, %[c]	E_T^N	$\Delta\Delta G^{\dagger}$[d]
1	CH_2Cl_2	40	80/20	80	0.309	0.54
2	Hexane	24 h	82/18	76	0.009	0.59
3	Toluene	180	82/18	80	0.099	0.59
4	Nitropropane	24 h	90/10	72	0.373	0.85

[a] All cyclizations were performed with 1.05 equiv of $BF_3{\cdot}OEt_2$ at −78 °C.
[b] Average of at least three runs within ±3%.
[c] Ratios and yields were calculated based on independently determined response factors versus cyclododecane.
[d] Calculated at 195 K (in kcal/mol).9.

A second explanation for the synclinal transition state preference focused on secondary orbital interactions. Anh and Thanh have suggested that the stereochemical outcome of an aldol reaction may be controlled by the secondary overlap between the frontier molecular orbitals.[44a] In this proposal two energetically favorable interactions are identified: (1) the in-phase overlap between the carbonyl carbon and the internal carbon of allylsilane moiety and (2) the in phase overlap between the carbonyl oxygen and the silane bearing carbon (Scheme 17). Although these interactions may be operative in model system **1** (**x**), the location of the silyl group in model system **5** precludes this type of favorable overlap (**xi**). Given the similar synclinal preferences for these two models, secondary orbital overlap does not provide a convincing explanation. Thus, to provide additional insights into the origin of stereocontrol, computational investigation of the transition states for these addition reactions were undertaken.

4.3. Computational investigations

Model system **5** and a simplified intermolecular system were modeled using density functional theory for purposes of comparison and to judge whether the intramolecular case introduces

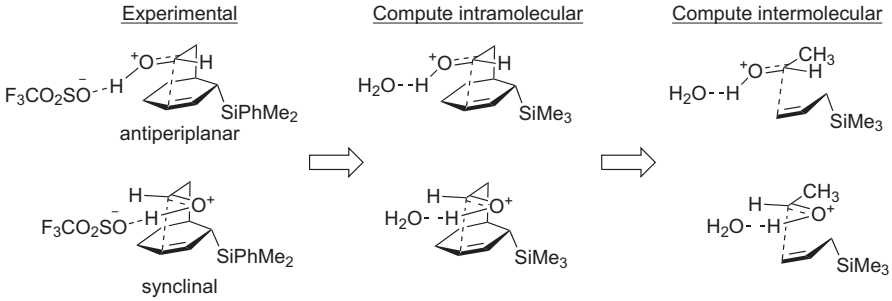


Scheme 17.

unwanted bias for the synclinal conformation (Scheme 18). It was judged that if the calculated energy difference between the synclinal and antiperiplanar transition states for the intramolecular and intermolecular cases were similar to each other as well as to the experimental values, model system **5** would indeed reflect the intrinsic synclinal preference in the transition state.

The transition states were located employing the M06-2X[45] functional, which was chosen because of recent applications that effectively treat reactions of main group elements. Additional functionals were investigated but provided qualitatively similar results and are not discussed further. The transition states were located using the 6-31+G(d,p) basis set and solvation was included using the CPCM[46] model with dichloromethane as the solvent. The electronic energies of the optimized transition state geometries were further refined using the 6-311++G(2d,2p) basis set. The geometries were verified as transition states by analysis of the vibrational frequencies determined from numerically calculated hessians (the method of central differences) applying the same level of theory as that used for locating the geometries. All calculations were performed using the GAMESS[47] program.

Initially the reaction of **5** was modeled wherein CF_3SO_3H was substituted with H_3O^+ (Fig. 1). The preferred transition state takes up a synclinal conformation (**TS-a2**, $\Delta G^{\ddagger}$=2.1 kcal/mol) in qualitative agreement with the experimental results ($\Delta G^{\ddagger}$=1.14 kcal/mol). The electronic energy difference in the intermolecular analogue (**TS-b1** – **TS-b2**, $\Delta E^{\ddagger}$=1.1 kcal/mol) qualitatively compares well to the calculated electronic energy difference in the intramolecular case (**TS-a2** – **TS-a1**, $\Delta E^{\ddagger}$=1.9 kcal/mol). This agreement suggests that the intramolecular case reflects the electronic preference for the synclinal



Scheme 18.

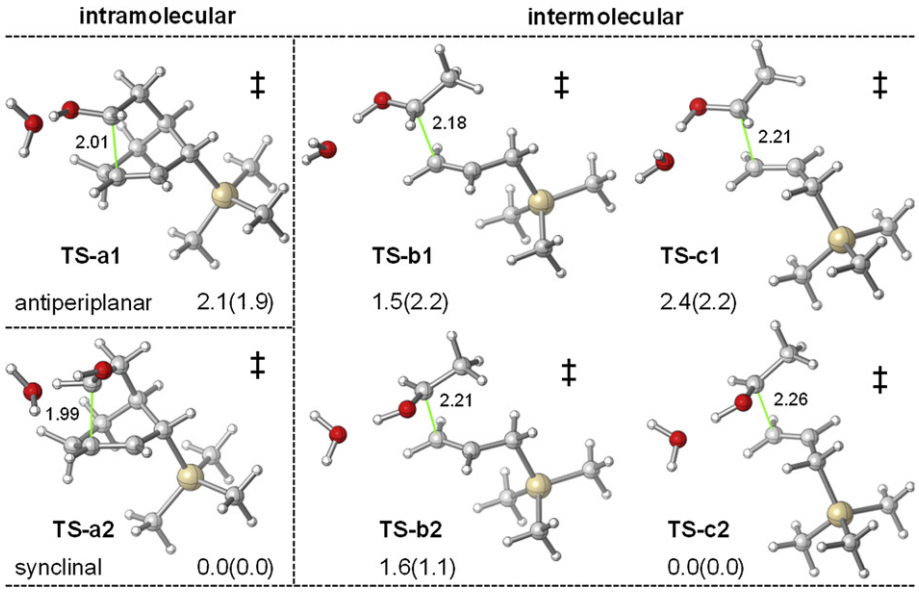
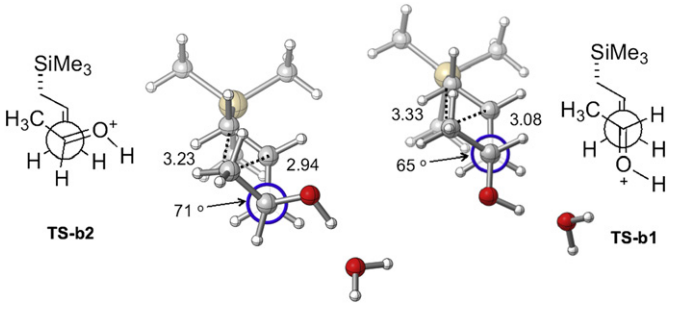


Fig. 1. Relative free energies (kcal/mol) at 195 K and electronic energies in parentheses; energies for **TS-a** are relative to **TS-a2**; energies for **TS-b** and **TS-c** are relative to **TS-c2**; selected distances are labeled in Å; CPCM-M06-2X/6-311++G(2d,2p)//M06-2X/6-31+G(d,p).

orientation in the intermolecular case satisfactorily. The internal nuclear coordinates of the relevant atoms are also similar. The distance of the forming bond is smaller by ~0.2 Å likely reflecting minor intramolecular constraints rather than a later transition state.

However, upon the inclusion of thermal corrections, the agreement is lost. In fact, little to no conformational preference is predicted to exist in the analogous intermolecular reaction (**TS-b2** − **TS-b1**, not shown, $\Delta G^{\ddagger}$=0.1 kcal/mol). This disagreement can be understood when considering additional steric interactions in the intermolecular case that are not present in the intramolecular case. Inspection of Newman projections (Scheme 19) reveals a difference in dihedral angle of ~6° (CH_3–C–C–H) and decreased distances between the methyl group of the aldehyde and the allyl moiety of the allylsilane in the synclinal conformation. These geometric differences reflect a degree of rigidity present in **TS-b2** not present in **TS-b1** causing greater unfavorable thermal contributions (mostly entropic) to the total energy because of decreased levels of freedom.



Scheme 19.

A more relevant comparison can be made with **TS-c** in which the position of the trimethylsilylmethyl group attached to the allylsilane is switched (Fig. 1). The presence of differential steric interactions would be small. Much better agreement is seen with the predicted free energy difference in this case (**TS-c1** − **TS-c2**, $\Delta G^{\ddagger}$=2.4 kcal/mol). A counter argument for this being a relevant comparison is that this arrangement now allows for secondary orbital overlap, which may contribute to the synclinal preference (Scheme 17). However, as was pointed out previously, the similarity of the synclinal preference for model systems **1** (secondary orbital interactions possible, $\Delta G^{\ddagger}$=1.1 kcal/mol) and **5** (secondary orbital interactions not possible, $\Delta G^{\ddagger}$=1.1 kcal/mol) clearly suggests that secondary orbital overlap may not be the major contributor to the selectivity.

Although the difference between the predicted and experimental selectivity in **5** may be considered significant (0.96 kcal/mol), the correctly predicted conformation as well as the excellent agreement between the predicted selectivity in **5** and **TS-c** supports a lack of bias in the probing interactions of **5**. Additionally, the fact that **TS-c2** is predicted to be the lowest energy transition state by 1.5 kcal/mol provides further support for the relevance of comparing **TS-c** to **5**. Overall this investigation suggests that the selectivity in **5** reflects an intrinsic synclinal preference in the transition state. The disparity between the experimental and calculated preferences for the synclinal transition structures may be ascribed to the difference in activator (triflic acid vs hydronium ion) and/or the difference in electrofugal group (dimethylphenylsilyl vs trimethylsilyl).

5. Conclusions

The synthesis and cyclization of two new models designed to elucidate the stereoelectronic preferences in allylsilane aldehyde addition reactions were described. Model system **3** required the reaction to take place at C(3) of a pentadienylsilane and consequently yields were very low, but a modest preference for the synclinal transition state persisted. In addition, the highly reactive pentadienylsilane may have undergone transmetalation prior to cyclization. Model system **5** eliminated the steric contribution of the (phenyldimethylsilyl)methylene group and underwent selective cyclization primarily via a synclinal transition state. The selectivities observed in the cyclization of **5** were not highly dependent upon the nature of the Lewis acid studied. The high proximal selectivity observed in these cyclizations probably reflects the selectivity of an unhindered allylmetal–aldehyde addition for the synclinal transition state. Model system **5** removed the possible steric bias of the (phenyldimethylsilyl)methylene unit present in model system **1**. According to computation analysis, the high selectivity observed for the proximal diastereomer in the cyclization of model system **5** most likely results from a stereoelectronic preference, not an intrinsic steric bias, for the synclinal arrangement of double bonds in the transition state.

Taken together, the results from model systems **1**, **3** and **5** allow a number of general conclusions to be drawn: (1) under activation by Lewis and Brønsted acids, the addition of allylic silanes with aldehydes experience a modest preference for the synclinal arrangement of reacting double bonds, (2) the magnitude of this preference is variable and dependent upon the size and coordination geometry of the Lewis acid; smaller Lewis acids lead to greater synclinal preferences, (3) the origin of the synclinal preference is most likely stereoelectronic.

6. Experimental section

6.1. 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 parts per million (δ), coupling constants, J, are reported in hertz. 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/z (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 cross-linked methyl silicone (column A), an HP 50 m HP-5 phenyl-methyl silicone gum (column B), an HP 20 m HP-1 cross-linked methyl silicone megabore (column C), HP 20 m 20 M Carbowax (column D) and an HP 50 m OV-17 (column E) 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), *tert*-butyl methyl ether (TBME): $CaSO_4/FeSO_4$. Solvents for recrystallization were spectral grade. Column chromatography was

performed by the method of Still[48] with 32–63 mm silica gel (Merck). Bulb-to-bulb (Kugelrohr) distillations were performed on a Büchi 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.[49]

*6.1.1. Preparation of 1-(trimethylsilylmethyl)-3-methylidene (**9**). Preparation of 1-chloro-3-methylidenecyclohex-l-ene (**8**).* To a solution of 10.2 g (28.7 mmol) of methyltriphenylphosphonium bromide in 50 mL benzene was added 47.8 mL (28.7 mmol) of 0.06 M potassium *tert*-amylate in benzene. The suspension was heated to reflux for 1 h. The resulting orange suspension was allowed to cool to rt and 2.50 g (19.10 mmol) of 3-chlorocyclohex-2-en-l-one in 10 mL of benzene was added. The resulting dark reaction mixture was stirred at rt for 1 h, then was poured onto 50 mL of satd aq $NaHCO_3$ solution, and then was extracted with ether (3×75 mL). The ether extracts were individually washed in series with one, 25 mL portion of water and 25 mL of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on silica gel with pentane as eluent. Distillation afforded 1.45 g (60% yield) of **8** as a pale-yellow oil, which decomposed readily. Data for **8**: bp 50 °C (7 mmHg); R_f 0.50 (pentane); t_R 5.62 min, column C (75 °C (5 min), 10 °C/min, 150 °C); ^{1}H NMR (390 MHz, CCl_4): δ 1.66–1.93 (m, 2H, $H_2C(5)$), 2.16–2.53 (m, 4H, $H_2C(4)$ and $H_2C(6)$), 4.68 (s, 2H, $H_2C(7)$), 6.15 (s, 1H, HC(2)); IR: 3020 (m), 2970 (m), 2960 (w), 1530 (m), 1480 (w), 1163 (w), 1105 (w), 1060 (w), 1035 (w), 925 (m), 900 (s), 765 (w), 760 (w) cm^{-1}.

*6.1.2. Preparation of 1-(trimethylsilylmethyl)-3-methylenecyclohex-l-ene (**9**).* To a solution of 1.44 g (11.2 mmol) of **8** in 22 mL of ether was added 22.1 mL (16.8 mmol) of a 0.76 M solution of trimethylsilylmethylmagnesium chloride in THF and 0.60 g (0.11 mmol) of Ni(dppp)Cl_2. The resulting pale-orange solution was heated at reflux for 5 h, then was quenched with 35 mL of satd aq $NaHCO_3$ solution and was extracted with pentane (3×50 mL). The pentane extracts were individually washed in series with one, 25 mL portion of water and 25 mL of brine. The pentane layers were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on alumina (neutral, activity I) with pentane as the eluent. Distillation afforded 1.72 g (85%) of **9** as a clear. colorless liquid. Data for **9**: bp 90 °C (15 mmHg); t_R 11.53 min, column C (75 °C (5 min), 10 °C/min, 150 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 9H, $Si(CH_3)_3$), 1.52 (s, 2H, $CH_2Si(CH_3)_3$), 1.66 (q, J=6.0, 2H, $H_2C(5)$), 1.99 (t, J=6.0, 2H, $H_2C(6)$), 2.24 (t of t, J=l.6 and 6.4, 2H, $H_2C(4)$), 4.51 (d, J=4.8, 2H, =CH_2), 5.77 (s, 1H, HC(2)); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.46 ($Si(CH_3)_3$), 24.01, 29.46, 31.15, 32.22. 107.05 (−CH_2), 123.64 (C(2)), 142.17 (C(l)), 145.01 (C(3)); IR: 3080 (w), 3010 (m), 2960 (s), 2830 (w), 1632 (m), 1600 (w), 1655 (w), 1440 (w), 1429 (w), 1417 (w), 1365 (w), 1250 (s), 1215 (m), 1210 (m), 1165 (m), 1133 (w), 1105 (w), 1054 (w), 890 (s), 855 (s) cm^{-1}; MS (70 eV): m/z 180 (M^+, 9), 147 (14), 89 (50), 75 (43), 73 (100), 59 (35), 58 (10), 45 (13), 43 (35). HRMS: Calcd for $C_{11}H_{20}Si$: m/z 180.13342. Found, 180.13365.

6.2. Synthesis and cyclization of 2-[5′-methylidene-3′-(trimethylsilylmethyl)cyclohex-3′enyl]ethanal (model system 10). 2-(3′-keto-5′-chlorocyclohex-4′-enyl)ethanoyl chloride (12)

A mixture of 2.042 g (10.85 mmol) of **11** in 9.51 mL (109 mmol) of oxalyl chloride was heated to a gentle reflux for 0.5 h. The excess oxalyl chloride was removed under reduced pressure. The resulting yellow oil, which decomposed rapidly, was used without further purification. Analytical data were obtained from a distilled sample. Data for **9**: bp 100 °C (0.05 mmHg); ^{1}H NMR (90 MHz, CCl_4): δ 1.90–3.66 (m, 7H), 6.12 (s, 1H, HC(5′)); IR: 1785 (s), 1695 (s), 1601 (s), 1445 (w), 1420 (w) 1385 (w), 1345 (w), 1310 (m), 1250 (w), 1160 (w), 1080 (w), 1060 (w), 1020 (m), 985 (m), 920 (w), 900 (w) cm^{-1}.

*6.2.1. Preparation of 5-[2′-(diphenylmethylsilyloxyethyl)]-3-chloro-2-cyclohexen-1-one (**13**).* To a solution of 2.25 g (10.9 mmol) of **12** in 40 mL of THF at −78 °C was added 32.6 mL (22.8 mmol) of a 0.70 M solution of lithium tris-(3-ethyl-3-pentoxy)aluminum hydride in THF over a period of 30 min. The resulting pale yellow solution was stirred at −78 °C for 4 h and then quenched with 50 mL of satd aq $NaHCO_3$ solution. After warming the mixture to rt, 200 mL of ether was added and the resulting emulsion was filtered through a fritted glass funnel. The residue on the funnel was washed with 50 mL of ether and the aqueous layer of the filtrate was extracted with ether (2×100 mL). The ether layers were individually washed in series with one, 50 mL portion of satd NH_4Cl solution, combined, dried ($MgSO_4$), and evaporated. The residue was immediately purified by chromatography on silica gel with ethyl acetate/hexane, 2:1 as eluent. Prior to evaporation, 8 mL of DMF was added to the eluent. After evaporation of the ethyl acetate/hexane, 1.90 mL (9.21 mmol) of diphenylmethylsilyl chloride and 1.252 g (18.39 mmol) of imidazole were added to the DMF solution. The solution was stirred at rt for 0.5 h, then was poured onto 25 mL of satd aq $NaHCO_3$ solution and extracted with ether (3×50 mL). The ether layers were individually washed in series with one, 25 mL portion of water and 25 mL of brine. The ether layers were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate, 5:1 as eluent to give 2.135 g (53% yield from **11**) of **13** as a clear, colorless oil. Data for **13**: R_f 0.28 (hexane/ethyl acetate, 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (s, 3H, $SiPh_2CH_3$), 1.56–1.63 (m, 3H, HC(5) and 2 HC(1′)), 1.95–2.15 (m, 1H), 2.40–2.43 (m, 3H), 2.55–2.73 (m, 1H), 3.73 (t, J=6.0, 1H, HC(2′)), 6.18 (d, J=1.9, 1H, HC(2)), 7.33–7.58 (m, 10H, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.60 ($Si(CH_3)_3$), 31.20, 37.29, 39.82, 42.44, 60.04, 128.15 (*para*-Cs), 128.35 (C(2)), 130.21 (ortho-C), 134.28 (*meta*-Cs), 135.77 (*ipso*-C), 158.31 (C(3)), 197.31 (C(1)); IR: 3070 (w), 3045 (w), 3005 (w), 2930 (w), 2910 (w), 2885 (w), 1673 (s), 1610 (m), 1428 (m), 1336 (w), 1289 (w), 1255 (s), 1234 (w), 1210 (w), 1119 (s), 1111 (s), 1100 (m), 1081 (m), 995 (w), 951 (w), 883 (w), 806 (w), 706 (m) cm^{-1}; MS (70 eV): m/z 370 (M^+, 1), 357 (16), 356 (11), 355 (42), 295 (45), 294 (25), 293 (100), 277 (10), 219 (12), 217 (34), 200 (16), 199 (90), 198 (12), 197 (60), 195 (10), 181 (20), 171 (44), 157 (14), 155 (18), 137 (25), 121 (17), 115 (35), 105 (20), 91 (27), 77 (32), 67 (16), 65 (14), 45 (18), 39 (14). Anal. Calcd for $C_{21}H_{23}ClO_2Si$: C, 68.00; H, 6.25; Cl. 9.56. Found: C, 67.82; H, 6.38; Cl, 9.64.

*6.2.2. Preparation of 2-(3′-chloro-5′-methylidenecyclohex-3′-enyl) ethan-1-yl diphenylmethylsilyl ether (**14**).* To a solution of 3.09 g (8.64 mmol) of methyltriphenylphosphonium bromide in 40 mL of benzene was added 4.86 mL (8.21 mmol) of a 1.69 M solution of potassium *tert*-amylate in benzene. The yellow suspension was heated at reflux for 1 h. The resulting yellowish-orange suspension was cooled to rt and 2.14 g (5.76 mmol) of **13** in 5 mL of benzene was added. The dark reaction mixture was stirred at rt for 0.5 h, then was poured onto 25 mL of satd aq $NaHCO_3$ solution and was extracted with ether (3×75 mL). The ether extracts were individually washed with one, 30 mL portion of water and 30 mL of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on silica gel with pentane/ether, 30:1 as eluent to give 1.76 g (83% yield) of **14** as a cloudy, viscous oil, which decomposed readily. Data for **14**: R_f 0.30 (pentane/ether, 30:1); NMR (200 MHz, $CDCl_3$): δ 0.62 (s, 3H, $SiPh_2CH_3$), 1.51–1.66 (q, J=6.5, 2H, 2 HC(2)), 1.90–2.16 (m, 3H), 2.28–2.36 (m, 2H), 3.73 (t, J=6.2, 2H, 2 HC(1)), 4.75 (d, J=9.5, 2H, =CH_2), 6.24 (s, 1H, HC(4′)), 7.33–7.59 (m, 10H, arom. H); IR: 3670 (m), 3610 (m), 3015 (s), 2970 (m), 2930 (m),

2420 (m) (sh), 2390 (m), 1530 (m), 1475 (m), 1425 (m), 1200 (s), 1110 (m), 1040 (m), 925 (m), 910 (s), 750 (s) cm^{-1}; MS (70 eV): *m/z* no M^+, 217 (10), 215 (18), 200 (49), 198 (19), 197 (96), 181 (11), 156 (29), 155 (22), 154 (84), 139 (15), 137 (20), 126 (22), 121 (21), 119 (100), 105 (12), 93 (29), 92 (16), 91 (81), 77 (22).

*6.2.3. Preparation of 2-[5′methylidene-3′-(trimethylsilylmethyl)cyclohex-3′-enyl]ethan-1-yl diphenylmethylsilyl ether (**15**).* To a mixture of 1.75 g (4.74 mmol) of **14** and 25 mg (0.047 mmol) of Ni(dppp)Cl_2 in 10 mL of ether was added 9.48 mL (7.11 mmol) of a 0.75 M solution of trimethylsilylmethylmagnesium chloride in THF. The resulting pale-orange solution was heated to reflux for 12 h. The dark-yellow reaction mixture containing a finely dispersed precipitate was poured onto 25 mL of satd aq $NaHCO_3$ solution followed by extraction with ether (3×25 mL). The ether extracts were individually washed with one, 25 mL portion of water and 25 mL of brine. The ether extracts were combined, dried (K_2CO_3), and evaporated. The residue was chromatographed on Al_2O_3 (neutral, activity I) with pentane/ether, 20:1 as eluent to give 1.767 g (89% yield) of **15** as a clear, colorless oil. Data for **15**: R_f 0.45, silica gel (pentane/ether, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.01 (s, 9H, $Si(CH_3)_3$), 0.63 (s, 3H, $SiPh_2CH_3$), 1.50–1.59 (m, 4H), 1.77–2.05 (m, 4H), 2.28–2.34 (m, 1H), 3.75 (t, *J*=6.6, 2H HC(1)), 4.56 (br d, *J*=13, 2H, =CH_2), 5.75 (s, 1H, HC(4′)), 7.33–7.61 (m, 10H, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.06 ($SiPh_2CH_3$), −1.16 ($Si(CH_3)_3$), 28.62, 31.01 (C(1′)), 36.60, 38.12, 38.46, 61.24 (C(1)), 106.80 (=CH), 122.75 (C(4′)), 127.82 (*para*-Cs), 129.75 (ortho-C), 134.23 (*meta*-Cs), 136.10 (*ipso*-C), 140.49 (C(3′)), 143.90 (C(5′)); IR: 3065 (w), 3000 (m), 2900 (m) (sh), 2930 (m), 2870 (m), 1630 (w), 1589 (w), 1428 (m), 1255 (m), 1116 (s), 1100 (s) (sh), 1130 (s), 1021 (w), 996 (w), 960 (w), 891 (m), 695 (m) cm^{-1}; MS (70 eV): *m/z* 420 (M^+, 1), 410 (17), 397 (20), 396 (54), 395 (100), 333 (17), 332 (29), 331 (23), 319 (27), 318 (73), 317 (100), 257 (24), 256 (14), 255 (46), 209 (15), 206 (25), 199 (13), 198 (11), 197 (46), 196 (13), 195 (73), 193 (13), 190 (12), 181 (30), 180 (11), 165 (25), 163 (13), 152 (20), 151 (62), 120 (17), 119 (19), 105 (35), 91 (41), 89 (24), 79 (19), 77 (44), 75 (20), 74 (41), 73 (100), 59 (17), 45 (23). HRMS: Calcd for $C_{26}H_{36}OSi_2$: *m/z* 420.23046. Found, 420.23010.

*6.2.4. Preparation of 2-[5′-methylidene-3′-(trimethylsilylmethyl)cyclohex-2′-enyl]-l-ethanol (**16**).* A solution of 1.745 g (4.15 mmol) of **15** and 4.15 mL (4.15 mmol) of a 1.0 M solution of sodium hydroxide in MeOH in 84 mL of a THF/MeOH, 1:1 mixture was stirred at rt of 0.5 h. The reaction mixture was poured onto 25 mL of a satd aq $NaHCO_3$ solution and extracted with ether (3×50 mL). The ether extracts were individually washed with one, 25 mL portion of water and 25 mL of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on Al_2O_3 (neutral, activity 1) with hexane/ethyl acetate, 5:1 as eluent to give 0.885 g (95% yield) of **16** as a clear, colorless oil. Data for **16**: R_f 0.28, silica gel (hexane/ethyl acetate, 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.01 (s, 9H, $Si(CH_3)_3$). 1.31–2.07 (m, 8H), 2.32–2.38 (m, 1H), 3.69 (t, *J*=6.5, 2H, 2 HC(1)), 4.58 (d, *J*=92, 2H, =CH_2), 5.76 (s, 1H, HC(4′)); ^{13}C NMR (50 MHz, $CDCl_3$): δ −1.21 ($Si(CH_3)_3$), 28.54, 31.04, 36.56, 38.08, 60.66 (C(1)), 106.95 (=CH_2), 122.75 (C(4′)), 140.29 (C(3′)), 143.67 (C(5′)), 175; IR: 3615 (w), 3070 (w), 3000 (w), 2950 (m), 2920 (m), 2905 (m), 2820 (w), 1632 m, 1425 (w), 1415 (w), 1372 (w), 1250 (s), 1165 (w), 1040 (w), 996 (w), 886 (w), 850 (s) cm^{-1}; MS (10 eV): *m/z* 224 (M^+, 50), 179 (12), 120 (12), 119 (63), 107 (22), 106 (62), 105 (14), 91 (15), 75 (20), 73 (100). HRMS: Calcd for $C_{13}H_{24}OSi$: *m/z* 224.159648. Found, 224.159593.

*6.2.5. Preparation of 2-[5′-methylidene-3′-(trimethylsilylmethyl)cyclohex-3′-enyl]-1-ethanal (**10**).* A solution of *tert*-butoxymagnesium bromide was prepared by adding 0.103 mL (1.093 mmol) of *tert*-butanol to 0.376 mL (1.093 mmol) of a 2.91 M solution of methylmagnesium bromide in ether in 2.5 mL of THF. To this solution was added 203 mg (0.906 mmol) of **16** in 3 mL of THF. After stirring the solution at rt for 5 min, a solution of 275 mg (1.089 mmol) of 1,1′-(azodicarbonyl)dipiperidine in 2 mL of THF was added to the reaction mixture. The resulting dark-red solution was stirred at rt for 12 h. During this time the color faded and a pale-yellow precipitate formed. The reaction mixture was poured onto 10 mL of satd aq $NaHCO_3$ solution, followed by extraction with ether (3×25 mL). The ether extracts were individually washed in series with a one, 10 mL portion of water and 10 mL of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on alumina with pentane/ether, 20:1 as eluent to give 115 mg (60% yield) of **10** as a clear, colorless oil. Data for **10**: R_f 0.35, silica gel (pentane/ether, 20:1). t_R 15.14 min, column E (125 °C (5 min), 10 °C/min, 250 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 9H, $Si(CH_3)_3$), 1.51 (s, 2H, 2 HC(8′)), 1.70–2.20 (m, 3H), 2.33–2.41 (m, 4H), 4.61 (d, *J*=11.7, 2H, 2 HC(=CH_2)), 5.78 (s, 1H, HC(4′)), 9.77 (t, *J*=1.7, 1H, HC(1)). ^{13}C NMR (90 MHz, $CDCl_3$): δ −1.16 ($Si(CH_3)_3$), 28.50, 28.91, 36.24, 27.47, 29.36 (C(2)), 107.88 (C(6′)), 122.80 (C(4′)), 139.40 (C(3′)), 142.40 (C(6′)), 201.95 (C(1)); IR: 1684 (w), 1633 (m), 1600 (w), 1425 (w), 1410 (w), 1373 (w), 1259 (w) (sh), 1249 (s), 1164 (w), 887 (m), 852 (s) cm^{-1}; MS (10 eV): *m/z* 222 (M^+, 17), 207 (14), 132 (13), 117 (20), 106 (15), 91 (20), 75 (14), 73 (100). HRMS: Calcd for $C_{13}H_{22}OSi$: *m/z* 222.14400. Found 222.14405.

*6.2.6. Cyclization of 2-[5′-methylidene-3′-(trimethylsilylmethyl)cyclohex-3′-enyl]-1-ethanal (**10**).* To a suspension of 58 mg (0.358 mmol) of $FeCl_3$ in 5.0 mL of CH_2Cl_2 at −70 °C was added 73 mg (0.328 mmol) of **10** in 1.5 mL of CH_2Cl_2. The resulting reddish-orange solution was stirred at −70 °C for 1.0 h and was quenched with 5.0 mL of 1 M NaOH in MeOH. The orange solution was allowed to warm to rt. The resulting orange suspension was stirred at rt for 12 h, poured onto 20 mL of water, and extracted with ether (3×25 mL). The ether extracts were individually washed in series with one, 10 mL portion of water and one, 10 mL portion of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate, 5:1 as eluent to give 9.5 mg (20% yield) of **17** as a white solid. Data for **17**: mp 61–62 °C; R_f 0.29 (hexane/ethyl acetate, 5/1); t_R 9.55 min, column E (125 °C (5 min), 10 °C/min to 250 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d, *J*=13.7, 1H), 1.70 (d, *J*=8.3, 1H), 1.99–2.10 (m, 3H), 2.23–2.38 (m, 3H), 2.85 (d, *J*=3.5, 1H, −OH), 3.91–3.97 (m, 1H, HC(2)), 4.75 (d, *J*=1.5, 1H, H_{trans}-C(10)), 4.90–4.92 (m, 3H, 2 HC(9) and H_{cis}-C(10)); ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.32, 33.85, 34.81, 37.82, 55.10, 68.80 (C(2)), 108.99 (C(10)), 110.99 (C(9)), 143.88 (C(6)), 145.99 (C(7)); IR: 3070 (w), 3015 (w), 3000 (w), 2975 (w), 2935 (m), 2850 (w), 2815 (w), 1645 (m), 1449 (w), 1431 (w), 1426 (w), 1391 (w), 1328 (w), 1285 (w), 1268 (w), 1250 (w), 1240 (w), 1140 (w), 1064 (s), 1032 (w), 1012 (m), 988 (w), 957 (w), 933 (w), 920 (w), 892 (s), 830 (w) cm^{-1}; MS (70 eV): *m/z* 150 (M^+, 9), 149 (100), 133 (8), 129 (7), 107 (20), 106 (84), 105 (18), 104 (8), 92 (15), 91 (85), 79 (17), 78 (10), 77 (18), 73 (24), 71 (12), 65 (12), 57 (28), 56 (11), 55 (17), 43 (17), 41 (33), 39 (19). HRMS: Calcd for $C_{10}H_{14}O$: *m/z* 150.10446. Found 150.10442.

6.3. Synthesis and cyclization of 2-[5′-[7′-^{13}C]Methylidene-3′-(trimethylsilylmethyl)cyclohex-3′-enyl]-1-ethanal (model system 3). Preparation of 2-(3′-chloro-5′-[7′-^{13}C]methylidenecyclohex-3′-enyl)ethan-1-yl diphenylmethylsilyl ether (18)

To 0.538 g (1.321 mmol) of methyltriphenylphosphonium iodide (99%, ^{13}C) and 1.708 g (1.982 mmol) of methyltriphenylphosphonium bromide in 20 mL of benzene was added 1.95 mL (3.303 mmol) of a 1.69 M solution of potassium *tert*-amylate in benzene. The yellow suspension was heated at reflux for 1 h. The reaction mixture was cooled to rt and a solution of 1.021 g (2.752 mmol) of **13** in 3 mL of benzene was added. The resulting dark-yellow reaction mixture

containing a heavy precipitate was stirred at rt for 0.5 h, then was poured onto 20 mL of satd aq $NaHCO_3$ solution and was extracted with ether (3×50 mL). The ether extracts were individually washed with one, 20 mL portion of water and one, 20 mL portion of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on silica gel with pentane/ether, 3:1 as eluent to give 0.853 g (83% yield) of **18** as a cloudy, viscous oil, which decomposed readily. Data for **18**: R_f 0.30 (pentane/ether, 3/1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.56 (s, 3H, $SiPh_2(CH_3)_3$), 1.48 (q, J=6.3, 2H, 2 HC(2)), 1.83–2.01 (m, 3H), 2.21–2.36 (m, 2H), 3.66 (t, J=6.5, 2H, 2 HC(1)), 4.68 (d of d, J_{13C-H}=158 and J_{H-H}=8.2, 0.8H, HC (^{13}C, 7′)), 4.68 (d, J=8.9, 1.2H, HC(7′)), 6.17 (s, 1H, HC(4′)), 7.28–7.52 (m, 10H, arom. H); IR: 3670 (m), 3615 (m), 3600 (w), 3580 (w), 3020 (s), 2970 (m), 2960 (w), 2930 (m), 2420 (m), 2385 (m), 2370 (w), 2350 (w), 1530 (m), 1480 (m), 1425 (m), 1190 (s), 1160 (w), 1100 (m), 1060 (w), 1040 (m), 925 (m), 900 (s), 750 (s) cm^{-1}; MS (70 eV): m/z no M$^+$, 214 (12), 200 (18), 199 (100), 139 (11), 137 (13), 129 (17), 128 (30), 127 (39), 126 (2), 125 (10), 120 (20), 119 (24), 93 (19), 92 (59), 91 (76), 79 (15), 78 (51), 77 (35), 65 (16), 52 (12), 51 (18), 45 (11), 41 (13).

*6.3.1. Preparation of 2-(5′-[7′-^{13}C]methylidene-3′-trimethylsilylmethylcyclohex-3′-enyl)ethan-1-yl diphenylmethylsilyl ether (**19**).* To a mixture of 850 g (2.303 mmol) of **18** and 12 mg (0.023 mmol) of Ni(dppp)Cl_2 in 5.0 mL of THF was added 4.73 mL (3.46 mmol) of a 0.73 M solution of trimethylsilylmethylmagnesium chloride in THF. The resulting pale-orange solution was heated at reflux for 12 h. The dark-yellow reaction mixture was poured onto 20 mL of satd aq $NaHCO_3$ solution and was extracted with ether (3×25 mL). The ether extracts were washed with one, 20 mL portion of water and one, 20 mL portion of brine. The ether extracts were combined, dried (K_2CO_3) and evaporated. The residue was chromatographed on alumina (neutral, activity I) with pentane/ether, 20:1 and hexane/ethyl acetate, 5:1 as eluent to give 770 mg (80% yield) of **19** as a clear, colorless oil and 50 mg (10% yield) of **20** as a clear, colorless oil. Data for **19**: R_f 0.45, silica gel (pentane/ether, 20/1); ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.02 (s, 9H, $Si(CH_3)_3$), 0.62 (s, 3H, $SiPh_2CH_3$), 1.49–1.58 (m, 4H), 1.76–2.02 (m, 4H), 2.27–2.32 (m, 1H), 3.74 (t, J=6.5, 2H, 2 HC(1)), 4.56 (br d of d, J_{13C-H}=149 and J_{H-H}=13.8, 0.8H, =^{13}CH_2), 4.56 (br d, J=13.8, 1.2H, =CH_2), 5.74 (s, 1H, HC(4′)), 7.29–7.59 (m, 10H, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.06 ($SiPh_2CH_3$), −1.15 ($Si(CH_3)_3$), 28.62, 31.02 (C(1′)), 36.60, 38.13, 38.46, 61.24 (C(1)), 106.82 (=^{13}CH_2), 122.79 (C(4′)), 127.81 (*para*-Cs), 129.74 (ortho-C), 134.82 (*meta*-Cs), 136.12 (*ipso*-C), 140.44 (C(3′)), 143.88 (C(5′)), 143.88 (d, J_{13C-C}=72, C(5′)); IR: 3070 (w), 3050 (w), 3005 (w), 2955 (m), 2925 (m), 2910 (m), 2870 (m), 2820 (w), 1632 (w), 1590 (w), 1487 (w), 1429 (m), 1372 (w), 1250 (m), 1207 (w), 1165 (w), 1119 (s), 1110 (s), 1091 (m), 1177 (m), 1021 (w), 996 (w), 950 (w), 887 (m), 855 (s), 850 (s) (sh), 800 (w), 701 (m) cm^{-1}; MS (70 eV): m/z no M$^+$, 395 (1), 210 (7), 209 (33), 207 (7), 198 (8), 197 (42), 195 (6), 193 (11), 179 (6), 154 (10), 119 (5), 105 (7), 91 (8), 85 (5), 75 (23), 74 (8), 73 (100), 71 (9), 59 (6), 57 (25), 56 (7), 55 (5), 45 (12), 43 (17), 41 (10). HRMS: Calcd for $C_{26}H_{36}OSi_2$: m/z 420.23047. Found: m/z 420.23053.

*6.3.2. Preparation of 2-[5′-[7-^{13}C]methylidene-3′-(trimethylsilylmethyl)cyclohex-2′-enyl]-1-ethanol (**20**).* This compound was prepared in 96% yield by use of the same procedure as described above for the preparation of **16**. Data for **20**: R_f 0.28, silica gel (hexane/ethyl acetate, 5/1); ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.00 (s, 9H, $Si(CH_3)_3$), 1.37–2.07 (m, 8H), 2.32–2.38 (m, 1H), 3.69 (t, J=6.8, 2H, $H_2C(1)$), 4.58 (d of d, J_{13C-H}=156 and J_{H-H}=9.1 0.8H, HC(=^{13}CH_2)), 4.58 (d, J_{H-H}=9.2, 1.2H, HC(=CH_2)), 5.75 (s, 1H, HC(4′)); ^{13}C NMR (50 MHz, $CDCl_3$): δ −1.12 ($Si(CH_3)_3$), 25.25, 31.10 (C(1′)), 36.60, 38.10, 38.61, 60.79 (C(1)), 106.98 (=^{13}CH_2), 122.79 (C(4′)), 140.32 (C(3′)), 143.69 (d, J_{13C-C}=72, C(5′)), 143.69 (C(5′)); IR: 3610 (w), 3000 (w), 2950 (m), 2920 (m), 2900 (m), 2820 (w), 1630 (m), 1410 (w) (br), 1370 (w), 1257 (w) (sh), 1248 (s), 1164 (m), 1089 (w), 995 (w), 885 (m), 851 (s) cm^{-1}; MS (70 eV): m/z 225 (M$^+$, 4), 224 (M$^+$, 5), 120 (8), 119 (13), 107 (12), 106 (15), 105 (6), 92 (9), 91 (13), 75 (20), 74 (8), 73 (100), 59 (6), 45 (13). HRMS: Calcd for $C_{13}H_{24}OSi$: m/z 224.15963. Found m/z 224.16003.

*6.3.3. Preparation of 2-[5′-[7′-^{13}C]methylidene-3′-(trimethylsilylmethyl)cyclohex-3′-enyl]-1-ethanal (**3**).* This compound was prepared in 51% yield by use of the same procedure as described above in the preparation of **10**. Data for **3**: R_f 0.35 (pentane/ether, 20:1); t_R 15.14 min, column E (125 °C (5 min), 10 °C/min, 250 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.05 (s, 9H, $Si(CH_3)_3$), 1.51 (s, 2H, 2 HC(8′)), 1.73–2.16 (m, 3H), 2.30–2.40 (m, 4H), 4.61 (d of d, J_{13C-H}=156 and J_{H-H}=11.9, 0.8H, =^{13}CH_2), 4.61 (d, J_{H-H}=12.1, 1.2H, =CH_2), 5.77 (s, 1H, HC(4′)), 9.76 (t, J=1.8, 1H, HC(1)); ^{13}C NMR (90 MHz, $CDCl_3$): δ −1.19 ($Si(CH_3)_3$), 28.46, 28.86, 36.20, 37.42, 49.34 (C(2)), 107.85 (C-(^{13}C, 7′)), 122.76 (C(4′)), 139.36 (C(3′)), 142.42 (d, J_{13C-C}=73, C (^{13}C, 5)), 142.42 (C(5′)), 201.90 (C(1)); IR: 3020 (w), 3000 (w), 2950 (m), 2820 (w), 2720 (w), 1722 (s), 1683 (w), 1631 (m), 1600 (w), 1580 (w), 1438 (w), 1425 (w), 1405 (w), 1372 (w), 1259 (w) (sh), 1250 (s), 1230 (w), 1210 (w), 1153 (w), 1133 (w), 1121 (w), 975 (w), 887 (m), 853 (s) cm^{-1}; MS (70 eV): m/z 223 (M$^+$, 6), 22 (M$^+$, 6), 208 (5), 207 (7), 132 (6), 118 (6), 117 (11), 106 (7), 103 (6), 92 (10), 91 (17), 79 (5), 75 (12), 74 (9), 73 (100), 59 (9), 45 (18), 43 (5). HRMS: Calcd for $C_{13}H_{22}OSi$: m/z 222.14398. Found, 222.143831.

*6.3.4. Cyclization of 2-[5′-[7′-^{13}C]methylidene-3′-(trimethylsilylmethyl)cyclohex-3′enyl]-1-ethanal (**3**). General procedures for Et_2AlCl, $BF_3{\cdot}OEt_2$ and $SnCl_4$.* To a solution of **5** (1.1 equiv, 0.05 M) in CH_2Cl_2 at −70 °C was added 1 equiv of Lewis acid. The solution was stirred at −70 °C until complete reaction of **5** was observed and quenched with excess 1 N NaOH in MeOH. For workup and isolation of reaction products see the procedure as described above for the cyclization of **10** with $FeCl_3$.

$FeCl_3$. See the procedure as described for the cyclization of **10** with $FeCl_3$.

n-$Bu_4N^+F^-$. To a mixture of **5** (1.0 equiv, 0.05 M) and $NaHCO_3$ (1.0 equiv) in CH_2Cl_2 at rt was added 1.0 equiv of 0.32 M solution of n-$Bu_4N^+F^-$ in THF. The reaction mixture was stirred at rt for 1.0 h and was quenched with excess 1 N NaOH in MeOH. For workup and isolation of reaction products see the procedure described above for the cyclization of **10** with $FeCl_3$.

*6.3.5. Preparation of rel-(1R,2S,4S)-6,7-[9-^{13}C]-dimethylidenebicyclo[2.2.2]octan-2-ol (**4a**) and rel-(1R,2R,4S)-6,7-[9-^{13}C]-dimethylidenebicyclo[2.2.2]octan-2-ol (**4b**).* Data for mixture isolated from $FeCl_3$ promoted cyclization of **3**. Data for **4a**: white solid, mp 60–61 °C; R_f 0.29 (hexane/ethyl acetate, 5:1); t_R 9.55 min, column E (125 °C (5 min), 10 °C/min to 250 °C); ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.30 (d, J=13.7, 1H), 1.69 (d, J=8.1, 1H), 1.99–2.09 (m, 2H), 2.19 (s, 2H), 2.23–2.38 (m, 2H), 2.85 (d, J=3.1, 1H, −OH), 3.92–3.96 (m, 1H, HC(2)), 4.75 (d of br d, 1H, J_{H-13C}=155 and J_{H-H}=1.4, H_{trans}-C (^{13}C, 9)), and 4.75 (d, J=1.4, 1H, H_{trans}-C(10)), 4.91 (d of m, 1H, J=136, 2 HC (^{13}C, 9)), and H_{cis}-(^{13}C, 9), 4.91 (m, 3H, 2 HC(10) and H_{trans}-C(10)); ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.32, 33.85, 34.81, 37.92, 55.10, 68.79 (C(2)), 109.00 (C (^{13}C, 10)), 110.99 (C (^{13}C, 9)), 143.88 (C(6)), 145.99 (C(7)); IR: 3590 (w), 3540 (w), 3065 (w), 3005 (m), 2985 (w), 2935 (s), 2850 (w), 2840 (w), 1645 (w), 1612 (w), 1480 (w), 1448 (w), 1430 (w), 1425 (w), 1391 (w), 1338 (w), 1317 (w), 1284 (w), 1265 (w), 1235 (w), 1150 (w), 1140 (w), 1064 (s), 1030 (w), 1011 (m), 985 (w), 955 (w), 932 (w), 919 (w), 890 (s), 839 (w), 829 (w) cm^{-1}; MS (70 eV): m/z 150 (M$^+$, 9), 150 (M$^+$, 1), 108 (19), 107 (88), 106 (99), 105 (14), 93 (11), 92 (51), 91(100), 79 (20), 78 (14), 73 (13), 41 (13), 39 (20). HRMS: Calcd for $C_{10}H_{14}O$: m/z 150.10446. Found, 150.10442.

6.3.6. Preparation of 2-[2′-(phenyldimethylsilyl)-3′-cyclohexenyl]-1-ethanal (model system 5). Preparation of 1-oxabicyclo[3.2.2]non-5-

*ene-2-one (**23**).* A flame-dried, 300 mL flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with the ketone **22** (3.57 g, 29.26 mmol), Na_2CO_3 (12.40 g, 117.0 mmol, 4 equiv) and CH_2Cl_2 (180 mL). The mixture was allowed to stir and a solution of m-chloroperbenzoic acid (5.05 g, 29.26 mmol) in CH_2Cl_2 (20 mL) was added by syringe. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was poured into H_2O (150 mL) and was extracted with CH_2Cl_2 (150 mL). The organic extracts were washed with satd aq $NaHCO_3$ solution (2×100 mL) and brine. The organic layers were dried ($MgSO_4$) and concentrated to leave a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/ethyl acetate, 3:2) to afford 3.52 g (87%) of **23** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation. Data for **23**: bp 145 °C (3 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.59 (t, J=8, 1H, HC(6)), 6.36 (t, J=8, 1H, HC(5)), 4.84 (m, 1H, HC(7)), 2.80 (m, 2H, $H_2C(3)$), 2.61 (m, 1H, HC(4)), 1.7–2.4 (m, 4H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 171.85 (C(1)), 139.38 (C(4)), 129.33 (C(5)), 70.30 (C(6)), 40.84 (C(2)), 27.61 (C(3)), 26.56 (C(7)), 23.25 (C(8)); IR: (CCl_4) 3051 (w), 2938 (m), 2880 (w), 1784 (w), 1728 (s), 1387 (m), 1371 (m), 1210 (m), 1181 (s), 1022 (s), 963 (m) cm^{-1}: MS: (70 eV) m/z 139 (M^+, 1.5), 138 (7), 110 (10), 109 (11), 94 (14), 91 (11), 82 (22), 81 (16), 79 (100), 77 (33), 67 (38), 53 (27). Anal. Calcd for $C_8H_{10}O$: C, 69.54; H, 7.30. Found: C, 69.32; H, 7.40.

*6.3.7. 2-[2′-(Phenyldimethylsilyl)-3′-cyclohexenyl]acetic acid methyl ester (**24**).* Lithium (dispersion in mineral oil (30%), 2.66 g, 115.2 mmol, 20 equiv) was washed with hexane (2×20 mL) and suspended in THF (80 mL). A solution of phenyldimethylsilyl chloride (19.68 g, 115.2 mmol, 20 equiv) in THF (20 mL) was added to the reaction mixture via syringe at 0 °C and allowed to stir for 15 min. Gilman titration gave a 0.71 M solution. A flame-dried, 250 mL flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with CuI (3.00 g, 15.93 mmol, 1.1 equiv) and THF (75 mL). The mixture was cooled to 0 °C and a solution of $PhMe_2SiLi$ in THF (45.0 mL, 0.71 M, 28.9 mmol, 2.2 equiv) was added by syringe. A solution of the lactone, **23** (2.00 g, 14.5 mmol) in THF (20 mL) was added by syringe to the red reaction mixture at 0 °C. After 2 h at 0 °C the reaction mixture was quenched by the addition of water (30 mL). The mixture was acidified by addition of 100 mL of a 10% aq oxalic acid solution. The mixture was extracted with ethyl acetate (3×100 mL) and the organic extracts were dried ($MgSO_4$) and concentrated to a yellow oil. Initial purification of the acid was accomplished by silica gel column chromatography (hexane/ethyl acetate, 19:1→1:1). Esterification of the acid with diazomethane (40 mmol) afforded the methyl ester. Purification of the ester by silica gel column chromatography (hexane/ethyl acetate, 93:7) gave 3.19 g (77%) of **24** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation. Data for **24**: bp 150 °C (0.1 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.53 (m, 2H, Ph), 7.36 (m, 3H, Ph), 5.59 (m, 2H, H-C(3′,4′)), 3.62 (s, 3H, (CO_2CH_3)), 2.78 (m, 2H), 1.92 (m, 2H), 1.57 (m, 2H), 1.36 (m, 2H), 0.35 (s, 6H, ($SiPh(CH_3)_2$); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 173.60 (C(1)), 138.02 (Ph), 133.88 (Ph), 128.97 (Ph), 127.67 (Ph), 126.02C(3′)), 123.99 (C(4′)), 51.29 (C(3)), 39.71 (C(2)), 31.59 (C(1′)), 29.60, 25.29, 21.25, −3.96 ($Si(CH_3)_2$); IR: (CCl_4) 3071(w), 3022 (w), 2953 (m), 2842 (w), 1738 (s), 1435 (m), 1428 (m), 1250 (m), 1167 (m), 1113 (m), 831 (m) cm^{-1}; MS: (70 eV) m/z 290 (M^+, 1), 289 (3), 288 (14), 209 (35), 208 (78), 207 (50), 194 (10), 193 (64), 177 (39), 151 (63), 137 (20), 136 (59), 135 (100), 134 (34), 121 (27), 1119 (29), 118 (76), 117 (55), 89 (55). Anal. Calcd for $C_{17}H_{24}O_2Si$: C, 70.78; H, 8.39. Found: C, 70.82; H: 8.40.

*6.3.8. 2-[2′-(Phenyldimethylsilyl)-3′-cyclohexenyl]-1-ethanol (**25**).* A flame-dried, 100-mL flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with the ester **24** (0.50 g, 1.75 mmol) and diethyl ether (45 mL). The mixture was cooled to 0 °C and lithium aluminum hydride (66 mg, 1.75 mmol) was added in one portion. The reaction was quenched after 2 h by the addition of 1 mL of water followed by 1 mL of 15% aq NaOH and 3 mL of water. A gray precipitate formed, which was filtered off through Celite with the aid of diethyl ether. The ethereal filtrate was evaporated to leave a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/ethyl acetate, 92:8) to afford 0.32 g (72%) of **25** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation. Data for **25**: bp 200 °C (0.2 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.55 (m, 2H, Ph), 7.37 (m, 3H, Ph), 5.62 (m, 2H, HC(3′), HC(4′)), 3.58 (t, J=7, 2H, $H_2C(2)$), 1.20–2.00 (m, 9H), 0.35 (s, 6H, ($SiPh(CH_3)_2$)); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 138.40 (Ph), 133.77 (Ph), 128.91 (Ph), 127.66 (Ph), 126.42 (C(3′)), 124.27 (C(4′)), 60.86 (C(1)), 38.05 (C(2)), 31.64 (C(1′)), 28.75 (C(2′)), 25.77 (C(5′)), 21.46 (C(6′)), −3.85 ($SiPhCH_3$), −4.14 ($SiPhCH_3$); IR: (CCl_4) 3638 (m), 3071 (w), 3021 (m), 2930 (s), 2841 (m), 1428 (m), 1250 (s), 1111 (s), 1061 (m) cm^{-1}; MS: (70 eV) m/z 260 (M^+, 1), 246 (1), 245 (3), 182 (5), 137 (22), 136 (14), 135 (100), 108 (19), 107 (11), 80 (65), 79 (24), 43 (12), 28 (15). Anal. Calcd for $C_{16}H_{24}OSi$: C, 73.78; H, 9.29. Found: C, 73.74; H: 9.21.

*6.3.9. 2-[2′-(Phenyldimethylsilyl)-3′-cyclohexenyl]-1-ethanal (**5**).* A flame-dried, 100-mL flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with pyridine (2.99 mL, 36.9 mmol, 12 equiv) and methylene chloride (20 mL). The mixture was cooled to 0 °C and chromium (III) oxide (1.84 g, 18.43 mmol, 6 equiv) was added in portions to give a reddish-brown solution. After 15 min a solution of alcohol **25** (0.80 g, 3.07 mmol) in CH_2Cl_2 (15 mL) was added by syringe and the black mixture was stirred for 2 h. The reaction mixture was filtered through Celite with the aid of ether. The ethereal extracts were washed with 5% aq NaOH (150 mL) and brine. The organic layers were dried ($MgSO_4$) and the solvent evaporated to leave a yellow oil. Purification was accomplished by silica gel column chromatography (hexane/ethyl acetate, 93:7) to afford 664 mg (84%) of **5** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation. Data for **5**: bp 180 °C (0.1 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.64 (t, J=1.8, 1H, CHO), 7.53 (m, 2H, Ph), 7.36 (m, 3H, Ph), 5.61 (m, 2H, CH=CH), 2.37 (m, 3H), 1.94 (m, 2H), 1.58 (m, 2H), 1.36 (m, 1H), 0.36 (s, 6H, ($SiPh(CH_3)_2$)); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 202.87 (C(1)), 137.83 (Ph), 133.80 (Ph), 129.08 (Ph), 127.75 (Ph), 125.97 (C(3′)), 124.21 (C(4′)), 49.37 (C(2)), 31.78 (C(1′)), 27.24 (C(2′)), 25.83 (C(5′)), 21.44 (C(6′)), −3.84 ($SiPhCH_3$), −4.19 ($SiPhCH_3$); IR: (CCl_4) 3023 (m), 2926 (m), 2840 (m), 1727 (s), 1428 (m), 1250 (m), 1113 (m), 833 (m) cm^{-1}; MS: (70 eV) m/z 181 (M^+, 0.46), 180 (1.4), 179 (7), 163 (7), 137 (6), 136 (9), 135 (64), 81 (7), 80 (100), 79 (13), 75 (11), 43 (13). Anal. Calcd for $C_{16}H_{22}OSi$: C, 74.36; H, 8.58. Found: C, 74.29; H, 8.63.

*6.3.10. Preparation of authentic samples of 5-hydroxybicyclo[2.2.2]oct-2-ene (**6a** and **6b**).* A flame-dried, 25-mL flask equipped with a magnetic stir bar and nitrogen inlet was charged with a solution of ketone **22** (0.5 g, 4.09 mmol) in EtOH (10 mL). The mixture was cooled to 0 °C, whereupon $NaBH_4$ (155 mg, 4.09 mmol, 4 equiv) was added and the mixture was stirred for 2 h at 0 °C. The mixture was poured into 1 M HCl (50 mL) and was extracted with diethyl ether (3×50 mL). The combined ethereal extracts were washed with satd aq $NaHCO_3$ and brine was dried ($MgSO_4$). The solvent was evaporated to leave a white solid. Separation of the diastereomers was accomplished by radial chromatography (4 mm, ethyl acetate/hexane as eluent) to afford 80 mg of the minor diastereomer **6b** and 170 mg of the major diastereomer **6a**. Data for **6a** (proximal): bp 160 °C (100 mmHg, air bath): ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.43 (t, J=7.3, 1H, HC(2)), 6.10 (t, J=7.3, 1H, HC(3)), 3.91 (s, 1H, OH), 2.71 (m, 1H), 2.55 (m, 1H), 1.95 (dd, 1H), 1.06–1.49 (m, 6H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 136.70C(3), 129.62C(2), 70.41C(6), 39.11C(5), 37.65C(1), 30.00C(4), 23.92C(8), 21.75C(7). Data for **6b** (distal): bp 160 °C (100 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.24 (t,

J=6.8, 1H, HC(2)), 6.16 (t, J=6.9, 1H, HC(3)), 3.81 (s, 1H, OH), 2.50 (t, J=3, 2H), 1.07–2.03 (m, 7H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 135.33C(3), 131.91C(2), 69.27C(6), 37.65C(1), 35.56C(5), 29.93C(4), 25.91C(8), 17.16C(7). These data matched the literature values.[42]

*6.3.11. Proof of configuration of 2-[2′-(phenyldimethylsilyl)-3′-cyclohexenyl]-1-ethanal (**5**). Preparation of 2-[2′-(phenyldimethylsilyl)cyclohexyl]acetic acid methyl ester (**26**).* An oven-dried, 100 mL, 3-necked flask equipped with a magnetic stir bar was charged with **24** (1.25 g, 4.33 mmol), EtOH (50 mL), and 5% Pd/C (50 mg). The mixture was stirred under 1 atm of hydrogen for 12 h. The solvent was removed by evaporation. Purification was accomplished by silica gel column chromatography (hexane/ethyl acetate, 92:8) to afford 0.90 g (80%) of **26** as a colorless oil. Data for **26**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.49 (m, 2H, Ph), 7.30 (m, 3H, Ph), 3.58 (s, 3H, (CO_2CH_3)), 2.4–1.0 (m, 12H), 0.34 (s, 3H, ($SiPhCH_3$)), 0.26 (s, 3H, ($SiPhCH_3$)); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 173.51 (C(1)), 139.67 (Ph), 133.62 (Ph), 128.76 (Ph), 127.78 (Ph), 51.28 (C(2)), 41.64, 36.10, 29.85, 27.92, 27.30, 25.86, −2.65 ($SiPhCH_3$), −3.94 ($SiPhCH_3$).

*6.3.12. 2-[2′-(Fluorodimethylsilyl)cyclohexyl]acetic acid methyl ester (**27**).* A flame-dried, 50-mL, three-necked flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with a solution of the silane **26** (850 mg, 2.96 mmol) and CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and $HBF_4\cdot 2Et_2O$ (312 mg, 3.55 mmol, 1.2 equiv) was added by syringe. The mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was diluted with diethyl ether (50 mL) and was poured into satd aq $NaHCO_3$ solution. The ethereal extract was washed with brine, dried ($MgSO_4$) and evaporated to leave 650 mg (95%) of **27** as a light yellow oil. Data for **27**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.65 (s, 3H, (CO_2CH_3)), 2.57 (dd, J=4, 15, 1H), 2.10 (m, 1H), 1.9–0.9 (m, 10H), 0.22 (2d, J=6, 6H, $SiPh(CH_3)_2$); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 173.27 (C(1)), 51.37 (C(2)), 41.12, 34.77, 33.59, 31.42, 26.75, 26.08, 25.77, −2.03 (J_{C-F}=15), −2.87 (J_{C-F}=15).

*6.3.13. 2-(2′-Hydroxycyclohexyl)acetic acid methyl ester (**28**).* An oven-dried, 50-mL, three-necked flask equipped with a magnetic stir bar and nitrogen inlet tube was charged with the fluorosilane **27** (464 mg, 2.00 mmol), DMF (25 mL), KF (232 mg, 4.0 mmol, 2 equiv) and m-chloroperbenzoic acid (1.035 g, 6.0 mmol, 3 equiv). After stirring the mixture for 10 min at room temperature the mixture became warm and was left to stir for 4 h at room temperature. The reaction mixture was poured into water (50 mL) and extracted with ether (3×25 mL). The ethereal extracts were washed with satd aq $NaHSO_4$ (50 mL) and satd aq $NaHCO_3$ (3×50 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated to leave a light yellow oil. Purification was accomplished by silica gel column chromatography using successively 4:1 and then 1:1 hexane/ethyl acetate as the eluent to give 280 mg (81%) of **28** as a colorless oil. Data for **28**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.62 (s, 3H (CO_2CH_3)), 3.15 (m, 1H, HC(2′)), 2.66 (dd, J=5.15, 1H, HC(2)), 2.35 (s, 1H, OH), 2.13 (dd, J=7, 14, 1H, HC(2)), 1.94 (m, 1H, HC(1′)), 1.64 (m, 4H), 1.19 (m, 4H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 174.53 (C(1)), 74.56 (C(2′)), 57.58 (C(2)), 42.46, 38.32, 35.78, 31.37, 25.38, 24.89.

*6.3.14. trans-Hexahydro-2(3H)-benzofuranone (**29**).* A flame-dried, 25-mL flask equipped with a magnetic stir bar and reflux condenser was charged with hydroxy ester, **28** (150 mg, 0.87 mmol), benzene (10 mL), and p-toluenesulfonic acid (25 mg). The mixture was heated at reflux for 3 h, during, which time methanol was removed by azeotropic distillation. The reaction mixture was washed with satd aq $NaHCO_3$ and the solvent was removed by evaporation. Purification of the resulting oil was accomplished by silica gel column chromatography on silica gel (hexane/ethyl acetate, 4:1) to afford 90 mg (74%) of **29** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation. Data from **29**: bp 110 °C (5 mmHg, air bath); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.73 (td, J=4, 11, 1H, HC(8)), 2.44 (dd, J=6, 16, 1H, HC(4)), 2.18 (m, 2H, H_2C(3)), 1.2–1.9 (m, 8H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 176.41 (C(2)), 84.91 (C(8)), 44.54 (C(3)), 35.63 (C(4)), 29.97, 28.07, 25.08, 23.83; IR: (CCl_4) 2944 (s), 2863 (m), 1788 (s), 1447 (m), 1210 (s), 1186 (s), 1075 (s), 1036 (s), 930 (m), 818 (m) cm^{-1}; MS: (70 eV) m/z 140 (M^+, 2), 139 (2), 121 (2), 97 (s), 96 (18), 81 (20), 79 (12), 69 (6), 68 (39), 67 (100), 66 (15). These data matched the literature values.[41]

6.4. General procedures for the cyclization of model system 5

6.4.1. $SnCl_4$, $BF_3\cdot OEt_2$, $SiCl_4$, Et_2AlCl, CF_3CO_2H, CF_3SO_3H. A magnetically stirred solution of **5** (0.05 M), cyclododecane (1.0 equiv, internal standard), and dichloromethane were cooled to −78 °C. At −78 °C, 1.05 equiv of the Lewis acid was added by syringe. The reaction was stirred at −78 °C until the complete reaction was observed. The reaction mixture was then quenched at −78 °C by the addition of 5 equiv of a 1 N NaOH/MeOH solution and subsequent stirring at room temperature for 2 h. The mixture was extracted with ethyl acetate and washed with water (5 mL). The aqueous layer was back extracted with ethyl acetate (2×2 mL) and the combined organic extracts were passed through a short Florisil column (5×75 mm). The organic layer was analyzed by 'on-column' capillary GC (column B). Program: 60 °C (2 min), 10 °C/min, 90 °C (5 min), 20 °C/min, 250 °C (5 min). Final ratios and yields were calculated based on independently determined response factors relative to the cyclododecane as internal standard. GC: **5** t_R=15.44 min, response factor=1.18; **6a** t_R=8.18 min, response factor=0.616; **6b** t_R=8.62 min, response factor=0.641.

6.4.2. $ZrCl_4$. In a flame-dried, 5-mL flask, equipped with a magnetic stir bar and a nitrogen inlet tube, was placed the Lewis acid (1.05 equiv) and cyclododecane (1.0 equiv, internal standard) in dichloromethane. The suspension was cooled to −78 °C and a solution of **5** was added. The reaction mixture was stirred at −78 °C until complete, quenched at −78 °C by the addition of 5 equiv of 1 M NaOH/MeOH and subsequent stirring at room temperature for 2 h. The mixture was extracted with ethyl acetate (3 mL) and washed with water (5 mL). The aqueous layer was back-extracted with ethyl acetate (2×2 mL) and the combined organic extracts were passed through a short Florisil column (5×75 mm). The organic layer was analyzed by 'on-column' capillary GC.

6.4.3. n-$Bu_4N^+F^-$. A 0.05 M solution of **6** in THF was added to 3.0 equiv of n-$Bu_4N^+F^-$ buffered with 3.0 equiv of $NaHCO_3$. The mixture was heated to reflux for 6 h. After cooling to room temperature a 0.5 mL aliquot was removed and washed with 1 mL of satd aq $NaHCO_3$ solution and water (1 mL). The organic layer was extracted with ethyl acetate (3×2 mL). The combined organic extracts were passed through a short Florisil column (5×75 mm) and analyzed by 'on-column' capillary GC.

6.4.4. Procedure for calculation of relative response factors. Stock solutions of known molarity of cyclododecane, proximal diastereomer (**6a**) and distal diastereomer (**6b**) were prepared by dissolving known amounts of each in separate volumetric flasks and diluting to the mark with CH_2Cl_2. A portion of each of the solutions containing the epimeric alcohols were then separately mixed with an equimolar amount of the cyclododecane stock solution. The resulting solutions were then injected onto GC column B and the area of the alcohol peak was divided by the area of the cyclododecane peak. The injections were repeated in triplicate and averaged to give a response factor relative to cyclododecane. The

entire procedure was repeated twice more and the numbers obtained averaged to give the final relative response factors.

6.4.5. Electronic energies, Gibbs free energies, and Cartesian coordinates for calculated transition structures

TS-a1

E=−872.714264
G(195 K)=−872.409913
C 6.0 0.4368091839 −0.6264807398 −0.6893720498
C 6.0 −0.5724557795 −2.6587123862 0.4040993718
C 6.0 1.0241093939 −0.1749654226 0.6565121235
C 6.0 0.3144514037 −2.1534382257 −0.7551977615
H 1.0 1.3062016937 −2.6111993687 −0.7146126083
H 1.0 −0.1164008265 −3.5237439681 0.8971881195
H 1.0 1.1832506358 0.9110119238 0.6948495705
H 1.0 −0.1203295873 −2.4414827061 −1.7161052227
C 6.0 −0.9819665849 −0.0182761670 −0.8031516183
H 1.0 −1.4977590189 −0.4335846664 −1.6733167094
H 1.0 −0.9058097909 1.0648785635 −0.9331133896
SI 14.0 2.8229847500 −0.8458955211 1.0713560702
C 6.0 3.5082836161 0.2993732670 2.3887379086
H 1.0 3.5747930016 1.3308215529 2.0303703994
H 1.0 4.5142758137 −0.0276504041 2.6706937215
H 1.0 2.8875273225 0.2851622105 3.2903619174
C 6.0 2.7636976762 −2.6025500540 1.7398498976
H 1.0 2.4607713658 −3.3386818350 0.9908677021
H 1.0 2.0866299515 −2.6818963821 2.5968663014
H 1.0 3.7670624124 −2.8748048725 2.0844721366
C 6.0 3.7876665937 −0.7367557278 −0.5319277511
H 1.0 3.3939422717 −1.4235313279 −1.2875801499
H 1.0 4.8324838374 −1.0044151880 −0.3441717129
H 1.0 3.7643656677 0.2788281119 −0.9386406622
H 1.0 −1.5518410655 −2.9884937470 0.0452718805
C 6.0 −1.8605503205 −0.2833517426 0.4042123882
C 6.0 −0.7934070923 −1.6055858363 1.4681164037
H 1.0 −1.4719462680 −1.8738528790 2.2753772907
H 1.0 1.0501817520 −0.2576747378 −1.5154281730
H 1.0 −2.0095114852 0.5336607258 1.1101341971
O 8.0 −2.9556965213 −0.9924650626 0.1576565253
C 6.0 0.1143132096 −0.5925105119 1.7068738499
H 1.0 0.0545500683 −0.0309002520 2.6392084600
H 1.0 −3.6328940523 −0.8576505736 0.8792792424
H 1.0 −5.5497327733 −0.2388048931 1.8069629335
O 8.0 −4.6310365337 −0.4022444878 2.0579524887
H 1.0 −4.6612572367 −0.8690160754 2.9028181250

TS-a2

E=−872.717268
G(195 K)=−872.413289
H 1.0 0.3162195211 −0.7892937744 0.0768247203
C 6.0 0.0512508130 −0.6144496108 1.1225350136
C 6.0 −0.0112707011 1.0930280477 2.9910626805
C 6.0 −1.6830483595 −0.7968925071 2.7838653887
C 6.0 −0.8649576603 −0.0146550657 3.5746324426
C 6.0 −1.4383952233 −0.9148933005 1.3569635978
C 6.0 0.3971945383 0.8222368969 1.5235619534
H 1.0 −1.0846288031 0.0484687717 4.6384919806
H 1.0 −0.1093518103 1.5213088513 0.8524367619
H 1.0 −0.5860789556 2.0216645289 3.0708592976
H 1.0 −2.4314618118 −1.4269915283 3.2618031166
H 1.0 −1.7046234820 −1.9241102437 1.0145080105
H 1.0 1.4696448201 0.9896802681 1.3906822150
C 6.0 0.8211685427 −1.6146060473 2.0162534340
H 1.0 1.8989132386 −1.4374021431 1.9325291232
H 1.0 0.6133493036 −2.6381924524 1.6926815531
SI 14.0 −2.6977765853 0.1950709508 0.3502729144
C 6.0 −4.3121446765 −0.7600409074 0.3173418192
H 1.0 −4.1829122004 −1.7467826564 −0.1374283299
H 1.0 −5.0514757129 −0.2088679943 −0.2726719473
H 1.0 −4.7202673407 −0.8924293225 1.3244917997
C 6.0 −2.9753285714 1.8562633087 1.1850423305
H 1.0 −2.1178725323 2.5302872901 1.1084569633
H 1.0 −3.2268944375 1.7293741987 2.2434082164
H 1.0 −3.8252825810 2.3473478734 0.6988770319
C 6.0 −1.9747547897 0.3770154501 −1.3699585853
H 1.0 −1.0361002447 0.9391401034 −1.3661434390
H 1.0 −2.6870117503 0.9168085437 −2.0026619691
H 1.0 −1.7924535748 −0.6017593169 −1.8246387640
C 6.0 0.4448012967 −1.5126420254 3.4752696344
H 1.0 1.0818164073 −0.8891793510 4.1073870754
O 8.0 0.0538906898 −2.6466923119 4.0429014854
H 1.0 0.8705218510 1.2332028304 3.6246450903
H 1.0 0.0949944414 −2.5551282076 5.0340731482
H 1.0 −0.5529237896 −2.1584880328 7.1464569604
O 8.0 0.2153714893 −2.0354998448 6.5733816904
H 1.0 0.9807052562 −2.3294926073 7.0847851933

TS-b1

E=−757.189334
G(195 K)=−756.935374
C 6.0 −2.9427756569 −2.0622451355 −0.5188670145
H 1.0 −3.2101322331 −2.5064662551 0.4425594369
H 1.0 −3.7833355550 −2.2118355145 −1.2078439704
C 6.0 −2.7653340415 −0.5938918279 −0.3974987901
H 1.0 −2.2278209804 −0.0498053576 −1.1740511636
O 8.0 −3.6937931788 0.0471660140 0.2339185418
H 1.0 −3.6118021957 1.0509679598 0.0736209432
H 1.0 −2.0607372877 −2.5453443223 −0.9352650431
H 1.0 −3.4390684994 3.1635810236 0.3667648544
O 8.0 −3.2194034792 2.4742657991 −0.2760376538
H 1.0 −3.4727992987 2.8280220729 −1.1400769737
C 6.0 −0.1737354416 −1.0700919756 0.4024754169
C 6.0 0.1435239897 −2.4677016912 0.6753177744
H 1.0 0.4108090189 −3.0222905167 −0.2306249941
H 1.0 −0.6536129074 −2.9846514075 1.2211816940
SI 14.0 1.7123811382 −2.5570324547 1.8197890625
C 6.0 3.1114186816 −1.6282733520 0.9793241547
H 1.0 2.8874602567 −0.5599193280 0.8984305213
H 1.0 3.3006595974 −2.0192548577 −0.0254260399
H 1.0 4.0325910921 −1.7345791799 1.5610229049
C 6.0 2.1149234259 −4.3793451255 2.0140818998
H 1.0 1.2808771254 −4.9216483486 2.4695410271
H 1.0 2.9918681307 −4.5000429140 2.6581936356
H 1.0 2.3387611638 −4.8376844262 1.0459421079
C 6.0 1.2612519834 −1.7628619286 3.4592787289
H 1.0 0.4348576030 −2.2942296959 3.9417899619
H 1.0 0.9654789644 −0.7180964154 3.3206346198
H 1.0 2.1201940503 −1.7835395668 4.1373275922
C 6.0 −1.1369441151 −0.3369575705 1.0331151504
H 1.0 −1.1549689351 0.7431263516 0.9209533925
H 1.0 −1.6932182253 −0.7617570083 1.8662222134
H 1.0 0.4196732606 −0.5738924354 −0.3672183402

TS-b2

E=−757.191168
G(195 K)=−756.935409
C 6.0 3.2978863346 1.0867330920 0.9782481766
H 1.0 4.1656082702 1.7359011044 0.8071661550
H 1.0 2.5224514448 1.6683666383 1.4790084403
C 6.0 2.8478241645 0.6265449785 −0.3604268155
H 1.0 3.4961601925 −0.0523886867 −0.9171070661
O 8.0 2.1005374069 1.4291320084 −1.0434007719
H 1.0 2.0205580522 1.1195110184 −2.0101485968
H 1.0 3.6172003668 0.2538994806 1.6040028867
H 1.0 1.1645266625 0.4697540809 −3.8642997234

O 8.0 1.9809481309 0.3951694911 −3.3509564162
H 1.0 2.7080267275 0.5343984385 −3.9734140384
C 6.0 0.9392291627 −0.6558446804 0.8511103409
C 6.0 1.0978985936 −0.8759789685 2.2876860063
H 1.0 0.9630363567 0.0422481937 2.8707139659
H 1.0 2.0535863570 −1.3504395250 2.5361426854
SI 14.0 −0.2749272859 −2.1016205653 2.9002488008
C 6.0 −1.9549670655 −1.3370335586 2.5535380665
H 1.0 −2.1409379004 −1.2617627277 1.4773591351
H 1.0 −2.0357522067 −0.3362226988 2.9892478515
H 1.0 −2.7454662099 −1.9585216166 2.9862031431
C 6.0 0.0139760765 −2.3340572687 4.7392737769
H 1.0 1.0073301678 −2.7505986415 4.9318107620
H 1.0 −0.7304644984 −3.0213747235 5.1537052374
H 1.0 −0.0692319062 −1.3803562514 5.2691052388
C 6.0 −0.0674552391 −3.7064424503 1.9477335694
H 1.0 0.9454527429 −4.1069445613 2.0583896467
H 1.0 −0.2628102206 −3.5553036526 0.8812369959
H 1.0 −0.7705032828 −4.4599938047 2.3165497087
C 6.0 1.6877610758 −1.2423323503 −0.1237172670
H 1.0 1.3827623757 −1.2107674376 −1.1652041664
H 1.0 2.4672169160 −1.9553450536 0.1391471791
H 1.0 0.1444365725 0.0250914288 0.5407853064

TS-c1

E=−757.189449
G(195 K)=−756.934111
C 6.0 −0.1676418667 −0.8325579049 0.3755505841
C 6.0 −2.8281001452 −2.1201898483 −0.3766226030
H 1.0 −3.0555647520 −2.5132124337 0.6161899471
H 1.0 −3.6704564115 −2.3564751407 −1.0381976960
C 6.0 0.6277535167 −0.2288455296 −0.6926807789
H 1.0 0.2179782565 0.7315128339 −1.0266913740
H 1.0 0.7541046144 −0.9045537211 −1.5464779635
SI 14.0 2.4246650507 0.1390327908 −0.0578828840
C 6.0 2.2808902710 1.2672993660 1.4351087455
H 1.0 1.7373382071 0.7781723758 2.2494468034
H 1.0 1.7563985301 2.1928464209 1.1770145374
H 1.0 3.2763603969 1.5345567937 1.8033767622
C 6.0 3.3119014653 0.9769993316 −1.4833492519
H 1.0 3.3084067837 0.3419720974 −2.3744064057
H 1.0 4.3529654857 1.1816320895 −1.2144012385
H 1.0 2.8319983612 1.9279600581 −1.7339182045
C 6.0 3.2271468823 −1.4976414111 0.3944322903
H 1.0 3.2190048028 −2.1875346985 −0.4552734765
H 1.0 2.7126241114 −1.9758826482 1.2338730895
H 1.0 4.2690941487 −1.3364572245 0.6887805736
C 6.0 −1.1197700228 −0.1871542919 1.1041567644
H 1.0 −1.2527527380 0.8876245853 0.9951237036
C 6.0 −2.7195937249 −0.6382853661 −0.3488861841
H 1.0 −2.1708795200 −0.1172126634 −1.1363810150
O 8.0 −3.6924609120 −0.0034860326 0.2102360637
H 1.0 −3.6333529338 0.9967473938 0.0081435614
H 1.0 0.0078034081 −1.8881598757 0.5883744161
H 1.0 −1.9262756530 −2.5836014357 −0.7741776848
H 1.0 −1.5826709055 −0.6643241426 1.9621198469
H 1.0 −3.4487951845 3.1029633554 0.2811171091
O 8.0 −3.2303215846 2.4074103598 -0.3552617183
H 1.0 −3.4728329231 2.7584139222 −1.2236882093

TS-c2

E=−757.192915
G(195 K)=−756.937875
C 6.0 0.6730404514 −0.4293965984 0.7725663210
C 6.0 3.1848839704 1.0431993882 1.0508041278
H 1.0 4.0785687317 1.6656749175 0.9179593344
H 1.0 2.3966181408 1.6659044561 1.4762069578
C 6.0 −0.3551281882 0.5507306448 0.4217065961
H 1.0 −0.2575058709 0.8989186921 −0.6134671012
H 1.0 −0.3550054211 1.4066741342 1.1061489986
SI 14.0 −2.1105468936 −0.2522562115 0.5444938620
C 6.0 −2.1991299251 −1.6338967137 −0.7241220704
H 1.0 −1.4559177905 −2.4102632751 −0.5172897134
H 1.0 −2.0285119601 −1.2544018827 −1.7367138190
H 1.0 −3.1895745108 −2.0994588437 −0.7002650791
C 6.0 −3.3453910242 1.1090560219 0.1604390122
H 1.0 −3.2685278757 1.9227442352 0.8881404746
H 1.0 −4.3653933358 0.7135251299 0.1989765061
H 1.0 −3.1779602666 1.5224212692 −0.8388731905
C 6.0 −2.3540874043 −0.9116773349 2.2860190857
H 1.0 −2.2389747933 −0.1145724566 3.0272785667
H 1.0 −1.6368293413 −1.7053619101 2.5181486110
H 1.0 −3.3609837861 −1.3281573903 2.3908245741
C 6.0 1.3862099517 −1.1794369696 −0.1091461625
H 1.0 1.1639294419 −1.1597085872 −1.1743258381
C 6.0 2.8124605304 0.5566338435 −0.3033823934
H 1.0 3.4043246537 −0.2334886299 −0.7667509131
O 8.0 2.2081484660 1.3835802262 −1.0816138730
H 1.0 2.1836403237 1.0304706064 −2.0409331535
H 1.0 2.0492330823 −1.9646915640 0.2417505784
H 1.0 0.8820182954 −0.5683928283 1.8338948232
H 1.0 3.4382273132 0.2178986978 1.7150710786
H 1.0 1.4346109795 0.3280412024 −3.9122658776
O 8.0 2.2047498291 0.2484516445 −3.3328812474
H 1.0 2.9833671990 0.3185557351 −3.9028410343

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35. Treatment of **3** with trifluoroacetic acid or SiCl4 gave only the desilylated product **21**.
36. To establish that the reaction conditions for cyclization of **3** were not catalyzing the migration of silicon before cyclization, the ^{13}C NMR spectrum of unreacted **3** recovered from the reaction with Et_2AlCl was obtained. The distance between the termini in the pentadienylsilane system is about 5 Å ruling out a [1,5] silicon migration. However, two successive [1,3] migrations could not be ruled out but could be easily detected by the ^{13}C label. The ^{13}C NMR spectrum of the recovered aldehyde **3** indicated no scrambling of the ^{13}C label.
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