Vinylsilane- and Alkynylsilane-Terminated Cyclization Reactions

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Contents

I. Introduction

A. Scope of the Review

The construction of cyclic systems by electrophile additions to alkenes is a well-established, powerful strategy in organic synthesis.[1,2] Although polyolefin cyclizations have been most extensively developed within the context of carbocyclic synthesis,[3,4] a variety of carbon–carbon bond-forming cyclizations have also been employed to prepare heterocyclic systems.[5] One continuing theme in the evolution of these cation-induced reactions has been the development of appropriate functionality to initiate and terminate the ring-forming processes. Recently, vinylsilanes, alkynylsilanes, allylsilanes, and propargylsilanes have emerged as particularly important functional groups for terminating cyclization reactions.[8] While intermolecular electrophilic substitution reactions of vinylsilanes have been studied for more than 30 years,[9] the intramolecular variant had not been demonstrated prior to 1981.[10–12] This review will focus on vinyl- and alkynylsilane terminators whose chemistry is similar as a result of the direct attachment of the silicon atom to the participating π bond.[13–15] The reader is referred elsewhere[8,16] for discussions of cyclization reactions of allylsilanes.

B. Characteristics of Vinylsilanes That Commend Their Use as Cyclization Terminators

Vinylsilane-terminated cyclization reactions have proven to be particularly well-suited for the synthesis of complex natural products. At the outset of this review, we will consider some of the features of vinylsilanes that make them particularly attractive cyclization terminators.

First and foremost, the silicon substituent exerts a powerful influence on the outcome of the cyclization process, since the carbon–silicon bond is strongly polarized due to the high electronegativity of carbon (2.35) relative to silicon (1.64).[17] As a result, a carbonium ion center β to silicon is stabilized by hyperconjugation, i.e., overlap of the σ orbital of a carbon–silicon σ bond with the vacant p orbital of the adjacent carbocation (the so-called β effect, see 1) (Figure 1).[18,19] Since the carbon–silicon bonding σ orbital is higher in energy than carbon–carbon or carbon–hydrogen bonding orbitals and also has a large coefficient on carbon, hyperconjugative stabilization by a β-silyl substituent is more strongly stabilizing than that of an alkyl substituent or hydrogen. The consequences of the β effect were first observed by Ushakov and Itenberg who noted that the elimination of silyl halides to produce olefins was particularly rapid for β-halogeno alkylsilanes ($R_3SiCH_2CH_2X$).[20] Also as a result of silicon's electropositive character, α-silyl carbocations[21] are destabilized relative to cations where the silicon substituent is replaced by an alkyl group.[19]

One result of the ability of a carbon–silicon σ bond to stabilize an adjacent carbocation is that the reactions of an electrophile with a vinylsilane are most often directed regioselectively to the silicon-bearing carbon. Loss of the labile[8d] silicon substituent from intermediate 2 then affords the product of electrophilic substitution. Koenig and Weber[22] were first to clearly demonstrate that electrophilic substitution reactions of this type

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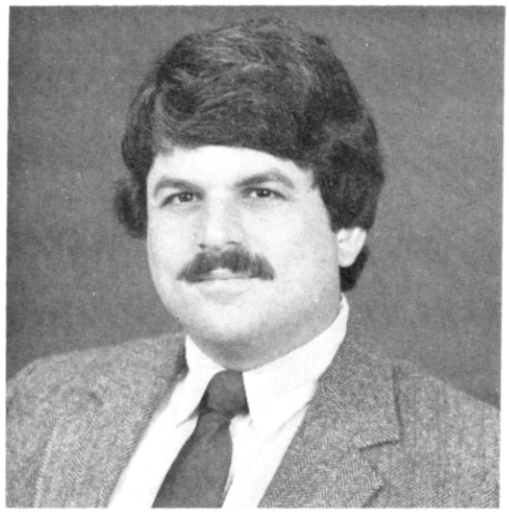

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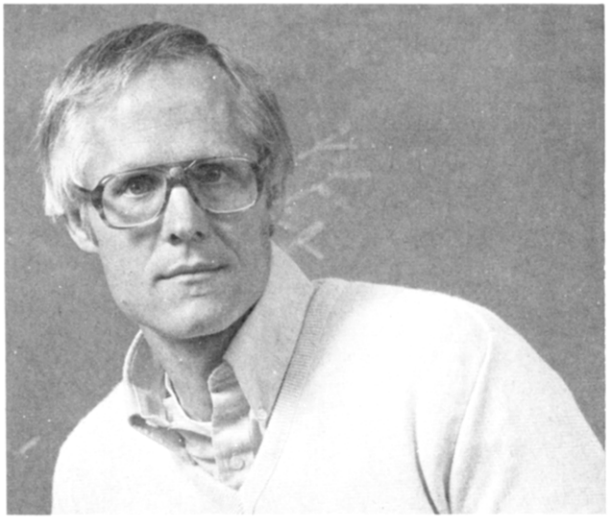


Larry E. Overman was born in Chicago, IL in 1943. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral study in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After an NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971, where he is now Professor of Chemistry. Dr. Overman is the recipient of a Senior Scientist Award of the Alexander von Humboldt Foundation, a Camille and Henry Dreyfus Teacher Scholar Award, a Javits Neuroscience Investigator Award, and has been a Fellow of the A.P. Sloan Foundation. He is currently on the Editorial Boards of *Organic Reactions*, *Organic Syntheses*, and *The Journal of Organic Chemistry*, and is a member of the NIH Medicinal Chemistry Study Section. Dr. Overman's research interests are in the areas of natural product total synthesis, the development of new methods and strategies for organic synthesis, and the catalysis of molecular rearrangements.

occur stereospecifically with retention of configuration;[23,24] they observed that the electrophilic substitution reaction of (*E*)- and (*Z*)-β-(trimethylsilyl)styrene with deuterium chloride occurred with complete retention of stereochemistry (eq 1 and 2). Retention results from the favored 60° rotation of the initially

formed cation **3** to provide the maximally stabilized β-silyl cation **4**, where the carbon–silicon σ bond is coplanar with the adjacent vacant p orbital.[21] Rotation of the initially formed cation **3** in the alternate sense is disfavored; for this isomerization to occur, the carbon–silicon bond would rotate through a conformation in which the carbon–silicon bonding σ orbital and the vacant p orbital would be orthogonal. Subsequent facile cleavage of the carbon–silicon bond is promoted by this $\sigma \rightarrow$ p conjugation, thereby affording the alkene product.[25]

A second important factor in choosing vinylsilanes as the nucleophilic reaction components in cyclization-based synthesis strategies is that the silicon substituent can also be exploited to assist assembly of the cyclization substrate. In particular, silicon is able to stabilize an adjacent negative charge, by either $\sigma \rightarrow \sigma^*$ overlap (see **5**) or overlap of the carbanionic center with the relatively low-energy vacant 3d orbitals of silicon.[8b,26] α-Silylvinyl anions **6** can be generated by a variety of methods, such as hydroalumination[27] of or organocuprate addition[28] to silylacetylenes, and much information is available concerning the reactivity and configurational stability of these anions.[8,29]

A third feature of vinylsilanes, which is particularly important in the context of complex natural products total synthesis, is their stability toward a wide range of reagents. Towards electrophiles the reactivity of vinylsilanes is comparable to that of a corresponding alkene[30] and significantly less than that of an allylsilane.[31] Simple frontier M.O. arguments would suggest that vinylsilanes should be somewhat poorer π donors than alkenes as a result of $\pi \rightarrow \sigma^*$ delocalization (illustrated in **7**); this is seen, perhaps, in the slightly more negative ionization potential of vinyltrimethylsilane than 3-methyl-1-butene (see Figure 2).[32] As a result of the low reactivity of vinylsilanes toward electrophiles, nucleophiles, and oxidizing and reducing agents, many chemical reactions can be carried out in their presence. In our own work, we have found that vinylsilanes are completely stable to a variety of commonly used reagents, some of which are summarized in Figure 2. The chemical stability of the vinylsilane moiety allows it to be carried through several synthetic steps before its desired reactivity is triggered by an intramolecular electrophile.

C. Reaction Modes of Vinylsilane Terminators

Using the terminating alkene as a point of reference, two distinct modes of cyclization are possible: cyclizations can occur in an endocyclic or exocyclic sense[33] with respect to the vinylsilane terminator (see Figure 3). Both modes of vinylsilane cyclizations have been well studied. In each case the silicon substituent controls the regiochemistry of the double bond in the product and in cyclizations occurring in the exocyclic sense, also its stereochemistry. The ability of the silicon substituent to direct the initially formed cation along a single reaction pathway is a key feature in these re-

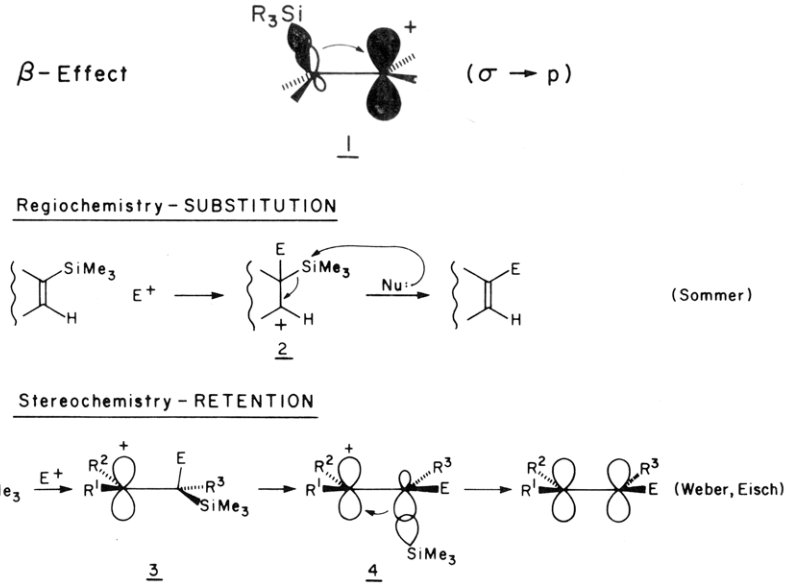


Figure 1.

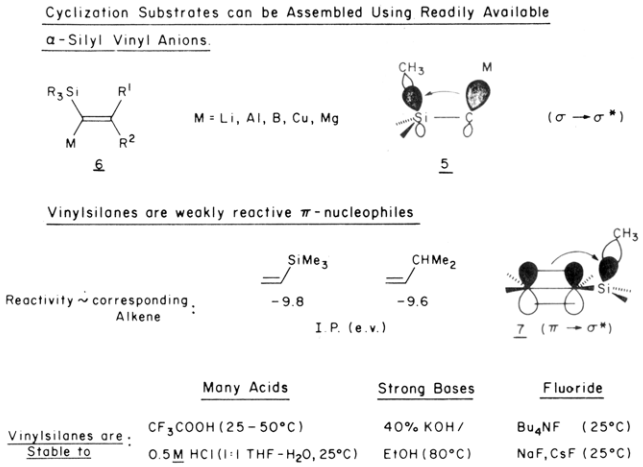


Figure 2.

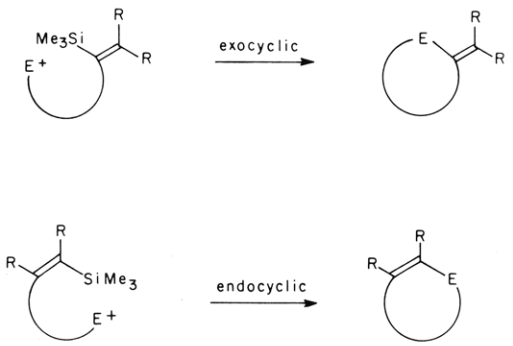
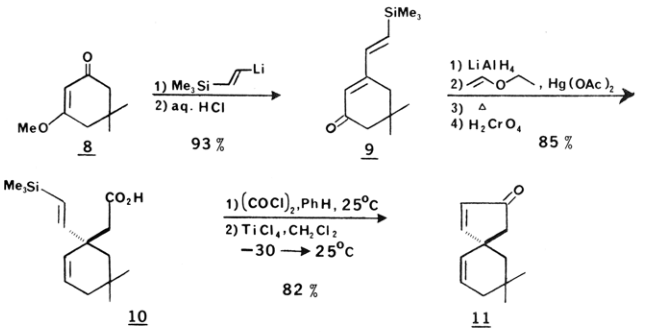


Figure 3.

actions.[34] This control derives from several factors.[25] Besides the stereochemical and regiochemical control discussed earlier, stabilization of the initially formed cyclic cation by the silicon substituent retards hydride or Wagner–Meerwein rearrangements of this intermediate. Moreover, a β-silyl substituent is typically lost from a carbocation more rapidly than a β-hydrogen and also more rapidly than a β-silyl cation is captured by a nucleophile.[8] Thus, a single cyclization product is typically produced and this feature of vinylsilane and alkynylsilane-terminated cyclization reactions will be apparent in the examples that follow.

SCHEME 1

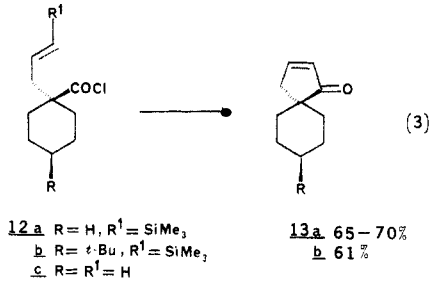


II. Formation of Unsaturated Carbocycles: Scope and Methodology

A. Vinylsilane-Terminated Cyclizations. Acylium Ion-Initiated Cyclizations

Bimolecular Friedel–Crafts acylation of vinylsilanes has been well studied.[8j,35] The first intramolecular variant of this reaction was reported by Burke[11] for the preparation of spiro[4,5]decadienones (see Scheme 1). Dimedone methyl ether **8** was treated with [β-(trimethylsilyl)vinyl]lithium[36] to give dienone **9** with the vinylsilane moiety exclusively in the *E* configuration. Reduction to the allylic alcohol, followed by Claisen rearrangement provided carboxylic acid **10**, after oxidation of the intermediate aldehyde with Jones reagent. Treatment of **10** with oxalyl chloride gave an acid chloride which was not purified, but directly treated with $TiCl_4$. The resulting acylium ion underwent cyclization to give enone **11** in excellent yield, thereby completing the spiroannulation sequence. The entire sequence of reactions is highly efficient, converting dimedone methyl ether **8** into spirocycle **11** in 64% overall yield. Cyclizations of this type on up to 11 g of carboxylic acid **10** were reported, indicating the ease with which these procedures can be scaled-up.

Kuwajima has reported similar cyclizations to give spirocycles **13a** and **13b** (see eq 3).[37] The key role played by the silicon substituent is seen in the fact that intramolecular Friedel–Crafts acylation of acid chloride **12c** was much less clean and gave a mixture of enone



12a R = H, R¹ = SiMe₃
b R = t-Bu, R¹ = SiMe₃
c R = R¹ = H

13a 65–70%
b 61%

(3)

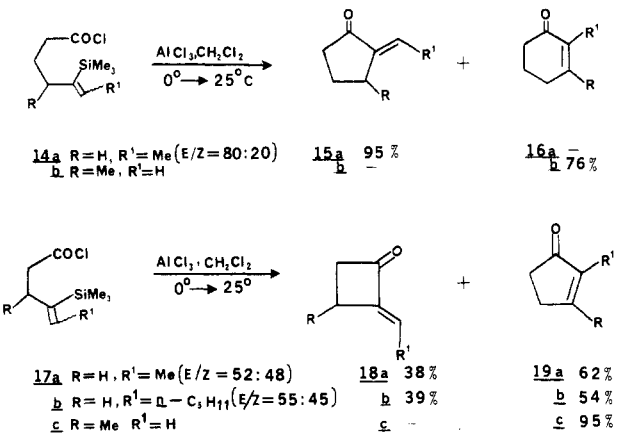
13a and halogenated byproducts.

Nakai later reported examples of the intramolecular acylation of vinylsilanes that occur in an exocyclic mode (see Scheme 2).[38] Cyclization of acid chloride **14a** proceeded, as expected, to give alkylidenecyclopentanone **15a** in excellent yield. Isomerization occurs under these conditions, probably after generation of the enone system, to give almost exclusively the (*E*)-enone. The shorter chain analogues **17a** and **17b** cyclize to give mixtures of alkylidene cyclobutanones **18** and **19**, or in the case of **17c**, exclusively cyclopentenone **19c**. In this case cyclization to the alkylidenecyclobutanones introduces considerably ring strain into the product. A complete reversal of the reaction course one would predict based on the β effect is seen in the conversions of substrates **14b** and **17c**, where electrophilic attack occurs exclusively at the carbon β to silicon leading to the cyclic enones **16b** and **19c**, respectively. The authors postulate a mechanism (illustrated for **14b** in Scheme 3) whereby the initially formed α-silyl cation **20** undergoes a Wagner–Meerwein shift to give β-silyl cation **21** which proceeds to enone **16b** after cleavage of the carbon–silicon bond.

Kuwajima[37] has also reported some competition studies, which along with the results of Nakai,[38] serve to illustrate the limitations of the β effect as a tool for predicting the outcome of vinylsilane-terminated cyclizations (see Scheme 4). Generation of an acylium ion from acid chlorides **23a** and **23b** lead to cyclopentenones **24a** and **24b** by the expected path of electrophilic attack on the vinylsilane substituent. However, compound **23c** led exclusively to cyclopentenone **25**, an outcome that was interpreted to result from chemoselective electrophilic attack on the trisubstituted alkene followed by protodesilylation of the remaining vinylsilane appendage. However, it was not rigorously established that protodesilylation followed cyclization.

Comparison of Kuwajima's and Nakai's results reveals a reactivity pattern that is reasonably interpreted as being governed by the relative stabilities of the initially formed carbonium ion intermediates. Whereas cyclizations of **14a**, **23a**, and **23b** proceed through secondary β-silyl cations, the analogous cyclizations of **14b** and **17c** would proceed through considerably less-favored primary β-silyl cations. As a result, intramolecular electrophilic attack of these latter substrates occurs β to silicon to generate tertiary α-silyl cations which, after rearrangement, proceed via secondary β-silyl cations to their respective products.[39] The internal competition experiments of Kuwajima indicate that while secondary β-silyl cations are generated in preference to secondary carbocations (reactions of **23a** and **23b**), tertiary (trialkyl) carbocations are more stable than secondary β-silyl carbonium ions (reaction of **23c**). A trend is apparent from these results, namely that in

SCHEME 2

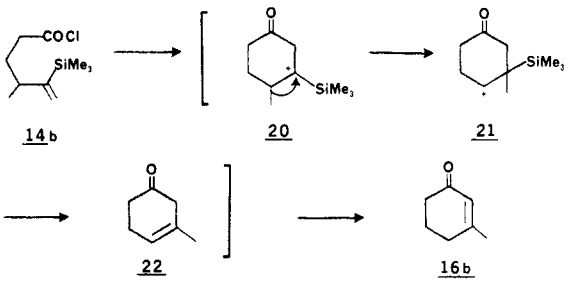


14a R = H, R¹ = Me (E/Z = 80:20) 15a 95%
b R = Me, R¹ = H b –

16a –
b 76%

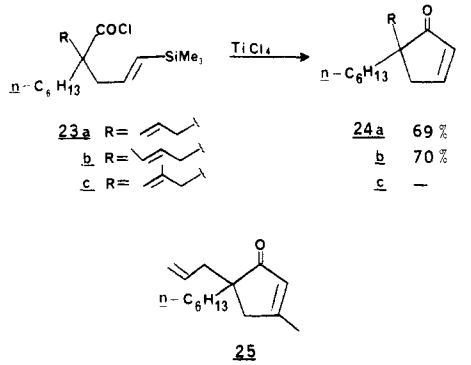
17a R = H, R¹ = Me (E/Z = 52:48) 18a 38% 19a 62%
b R = H, R¹ = n-C₅H₁₁ (E/Z = 55:45) b 39% b 54%
c R = Me R¹ = H c – c 95%

SCHEME 3



14b 20 21 22 16b

SCHEME 4



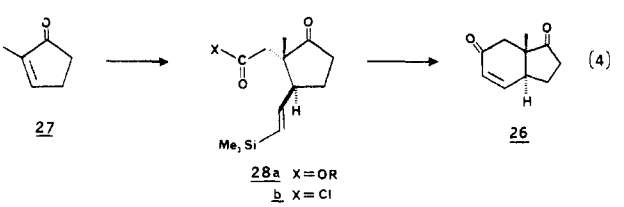
23a R =
b R =
c R =

24a 69%
b 70%
c –

25

the absence of stereoelectronic or other restrictions, vinylsilane-terminated cyclizations will occur preferentially to form carbocations in the following sequence: tertiary trialkyl > secondary β-silyl > tertiary α-silyl, secondary dialkyl > primary β-silyl cations. Much of the published[34] and more recent[40] work in our own laboratories supports this proposition.

Denmark[41] and Kuwajima[42] have reported nearly identical routes to *trans*-hydrindendione **26** via the endocyclic mode of acylium ion-initiated vinylsilane-terminated cyclizations (see eq 4). Copper-catalyzed



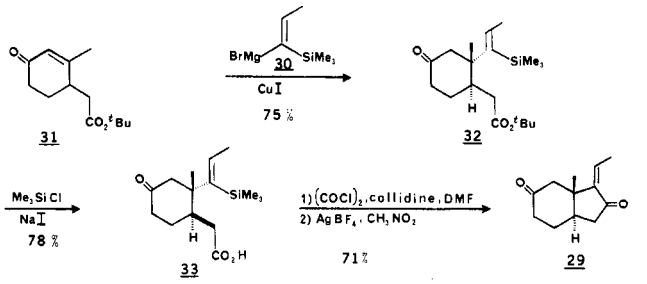
27 28a X = OR
b X = Cl

26

(4)

addition of the Grignard reagent derived from (*E*)-(2-bromovinyl)trimethylsilane[43] to 2-methylcyclopentenone (**27**) yields keto ester **28a** after alkylation with an appropriate α-bromo ester. Conversion to the

SCHEME 5



corresponding acid chloride **28b** and treatment with $AlCl_3$ induces electrophilic attack on the vinylsilane to give compound **26**; the yield for the cyclization reaction was 54%.

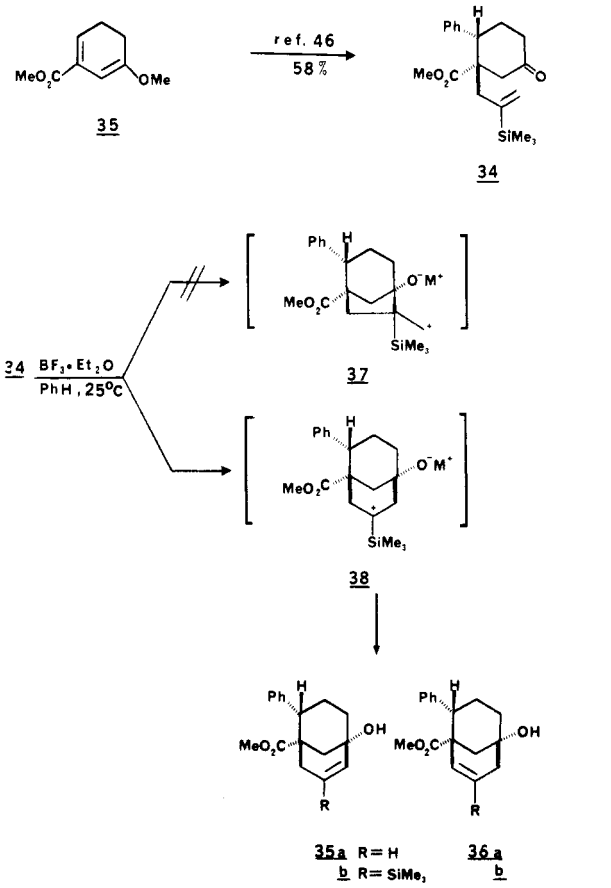
Kuwajima also prepared alkylidene hydrindandione **29** via a sequence in which the key cyclization occurred in the exocyclic sense (see Scheme 5).[42] Copper-catalyzed addition of the Grignard reagent **30** derived from (*E*)-1-bromo-1-(trimethylsilyl)propene to enone **31**[44] afforded ketone **32**. Cleavage of the *tert*-butyl ester with iodotrimethylsilane gave acid **33**. After conversion to the acid chloride, treatment with $AgBF_4$ in nitromethane provided the ethylidene dione **29** in 71% yield as a single double-bond isomer. It is notable that the cyclization could be accomplished with $AgBF_4$ under conditions sufficiently mild that the less stable (*Z*)-ethylidene stereoisomer could be isolated cleanly. The cyclization could be induced also with $TiCl_4$, but equilibration to a 1:1 mixture of (*E*)- and (*Z*)-enones occurs. The preparation of *trans*-hydrindandiones **26** and **29** indicates possible applications of this chemistry to the synthesis of the CD ring system of steroids.

B. Vinylsilane-Terminated Cyclizations. Ketone-, Aldehyde-, Acetal-, and Thioacetal-Initiated Cyclizations

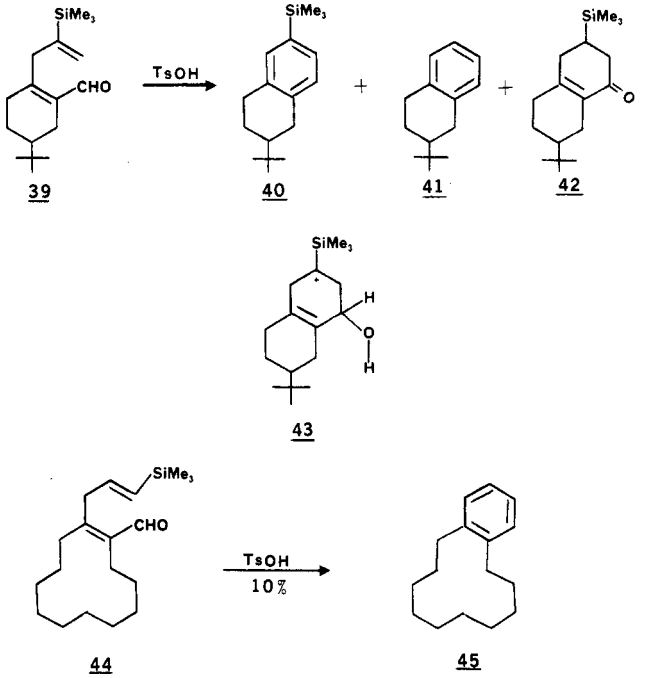
There is only one report of the use[45] of a ketone as a cyclization initiator. De Clercq has reported a one-pot synthesis of keto ester **34**[46] from diene **35** involving trapping of the enolate resulting from conjugate addition of phenylmagnesium bromide with 3-chloro-2-(trimethylsilyl)propene,[47] followed by hydrolysis (see Scheme 6). Treatment of **34** with $BF_3{\cdot}Et_2O$ in benzene gave a mixture of olefins **35a** and **36a** in 50% yield. No products arising from primary β-silyl cation **37** were observed; the formation of this cation is disfavored not only on electronic grounds but also by the ring strain and severe steric congestion of bicyclo[3.2.1]octane intermediate **37**. The formation of bicyclic olefins **35a** and **36a** arises via intermediate tertiary α-silyl cation **38**. The mechanism by which the silicon was lost, presumably either by hydride shift to a secondary β-silyl cation followed by cleavage of the carbon–silicon bond or by protodesilylation of intermediate vinylsilanes **35b** and **36b** was not determined.

There are also very few examples of the intramolecular reaction of vinylsilanes and aldehydes. Tius reported that treatment of vinylsilane aldehyde **39** with *p*-toluenesulfonic acid in refluxing benzene provided a mixture of tetralins **40** and **41** (53% yield) together with ca. 15% of enone **42** (see Scheme 7).[48] He proposes that enone **42** arises from intramolecular 1,3-hydride transfer in intermediate α-silyl cation **43**, although its

SCHEME 6



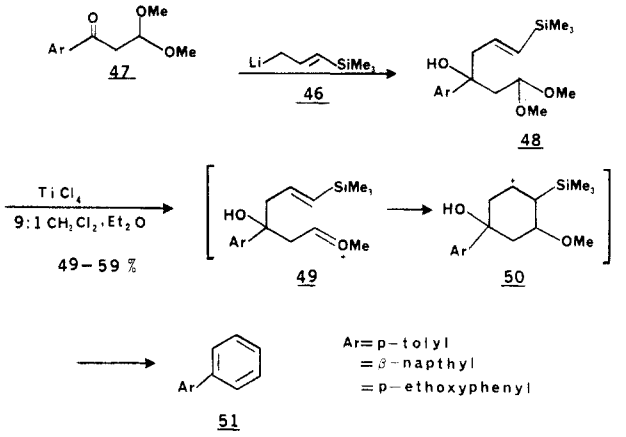
SCHEME 7



formation by two consecutive 1,2-hydride shifts is also possible. Similar treatment of vinylsilane aldehyde **44** produced the benzo compound **45**, but in very poor yield.

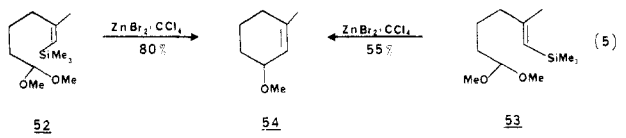
The related cyclization reactions of vinylsilanes and acetals occurs in better yields and is a key step in a synthesis of unsymmetrical biphenyls (see Scheme 8) developed by Tius.[49] Addition of (trimethylsilyl)allyllithium (**46**)[50] to β-keto acetals **47** gave cyclization

SCHEME 8



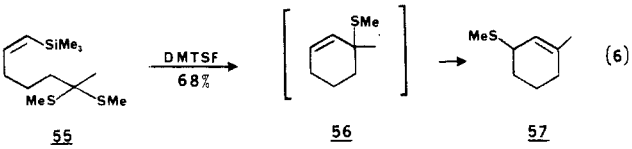
substrates **48** in good to excellent yield. Subsequent treatment with $TiCl_4$ affords biphenyls such as **51**, perhaps via oxonium ion **49** and β-silyl cation **50**, although the timing of the dehydration and methanol loss was not established. The method is limited in that it cannot be applied to the synthesis of benzoannulated aliphatic ketones.[48]

In a related study, Fleming prepared the (*Z*)- and (*E*)-vinylsilane acetals **52** and **53** and showed that both cyclized to give allylic ether **54** (see eq 5).[51] The

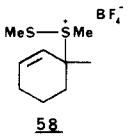


(*Z*)-vinylsilane **52** cyclized twice as fast as the (E)-isomer **53** and, thus, in higher yield, since the yield in this case was compromised primarily by subsequent acid-catalyzed reactions of the labile allylic ether **54**.

As shown by Trost,[12] thioacetals can also be utilized to promote vinylsilane cyclizations. Treatment of **55** with the highly thiophilic reagent dimethyl(methylthio)sulfonium fluoroborate (DMTSF)[52] produces not the expected product **56**, but the rearranged allylic sulfide **57** instead (see eq 6). The transformation of

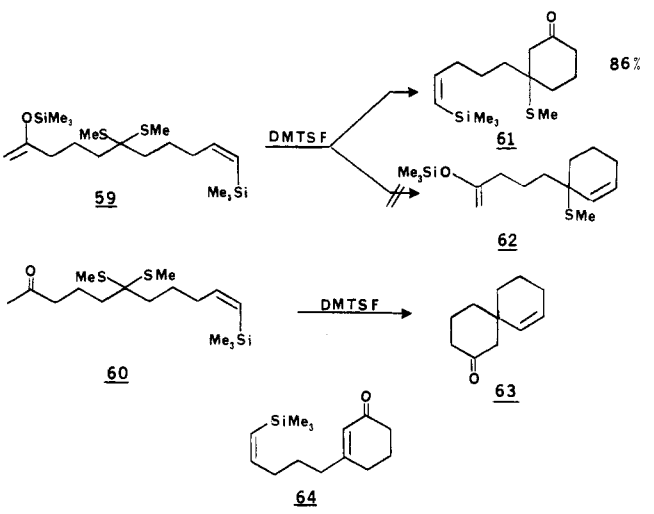


56 into the more stable alkene **57** can be attributed to a 2,3-sigmatropic rearrangement[52] of sulfonium salt **58** arising from reaction of the initially-formed **56** with excess DMTSF.



Trost also reported the interesting experiments summarized in Scheme 9, in which attack on the initiating cation is set as a competition between two π nucleophiles.[12] With substrate **59**, complete chemoselectivity is observed, not surprisingly, for attack by the more nucleophilic enol silane functionality on the intermediate thionium ion. No products arising from the other possible adduct **62** were detected. However, cyclization

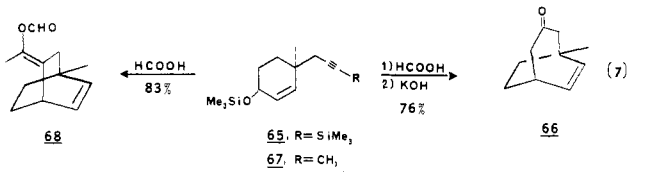
SCHEME 9



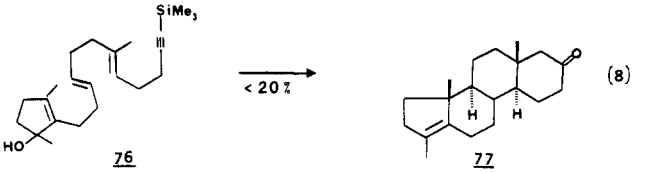
of the corresponding ketone **60** afforded spirocycle **63**. In this latter example cyclization must occur initially on the vinylsilane moiety, as neither ketone **61** nor enone **64** yielded **63** upon treatment with DMTSF. However, no yield for the production of **63** was reported.

C. Alkynylsilane-Terminated Cyclizations. Allylic Alcohols and Ketene Thioacetals as Cyclization Initiators

In 1977, Heathcock reported that treatment of alkynylsilane **65** with formic acid, followed by base cleavage of the enol formate product, gave bicyclo[3.2.2]nonenone **66** in good yield.[53] The decisive role played by this silicon substituent in this cyclization is dramatically illustrated by the fact that cyclization of alkyne **67** occurred completely in the exocyclic sense to afford bicyclo[2.2.2]octene **68**.

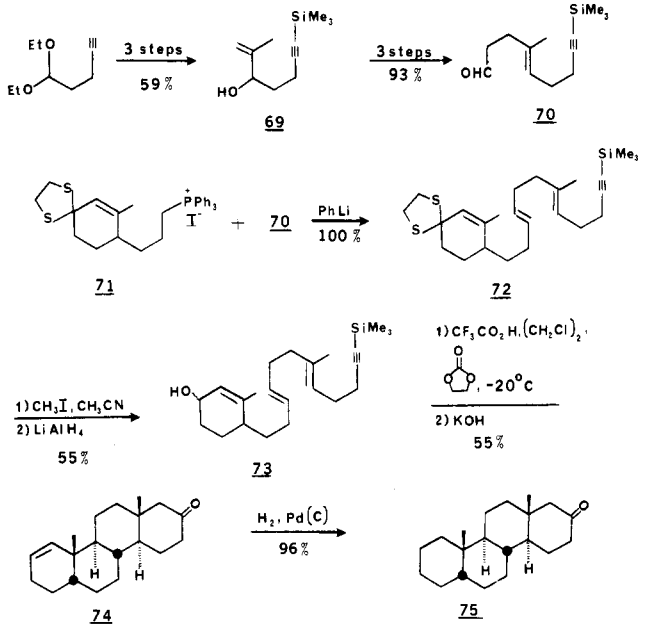


Independently, Johnson investigated silylalkyne terminators for the formation of steroids and triterpenes by biomimetic polyene cyclizations.[4,54] The stereospecific synthesis of tetracycle **75** using such a cyclization as the key step is summarized in Scheme 10. Aldehyde **70**, prepared via ortho ester–Claisen rearrangement of allylic alcohol **69**, was condensed with phosphonium salt **71**[55] using a modification of the Schlosser procedure.[56] Thioacetal hydrolysis and ketone reduction provided cyclization substrate **73**. Treatment of **73** with trifluoroacetic acid under carefully optimized conditions[57] gave, after hydrolysis, tetracycle **74** in good yield. Similar treatment of allylic alcohol **76** provided tetracycle **77**, albeit in poor yield (eq 8).[54,58]

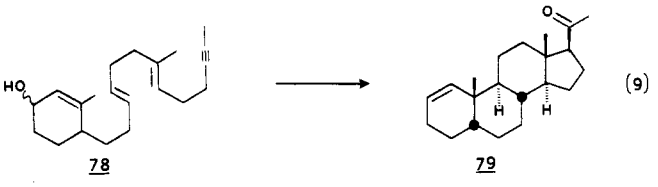


The course of these reactions again depends critically on the silicon substituent. Thus, cyclization of **78** af-

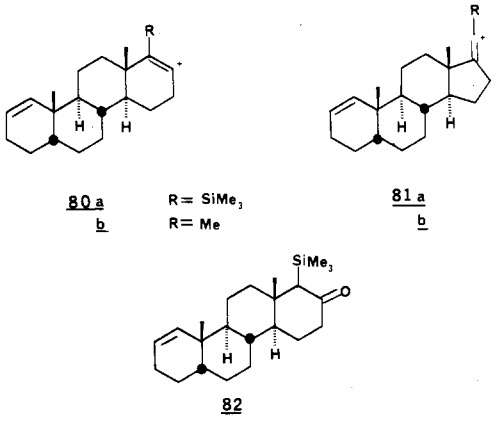
SCHEME 10



fords the steroid-like derivative **79** containing a five-membered D-ring. The formation of **79** was attributed,

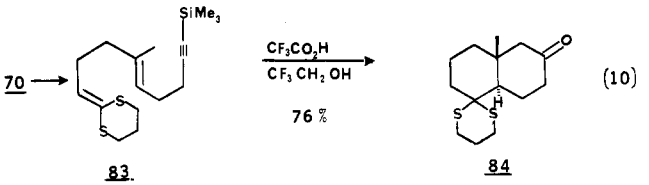


in part, to a transition-state preference for formation of linear vinyl cation **81b** rather than the bent vinyl cation **80b** which would be produced in an endocyclic cyclization.[54] Formation of **74** is governed, therefore, by generation of β-silyl cation **80a**, which presumably leads to α-silyl ketone **82**, a system known to undergo



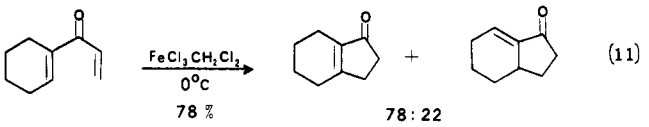
facile desilylation.[59] It is not known whether the predominant formation of **80a** is due to a kinetic preference in the cyclization reaction, or results from subsequent Wagner–Meerwein rearrangement of a kinetically favored linear cation **81a**.[60]

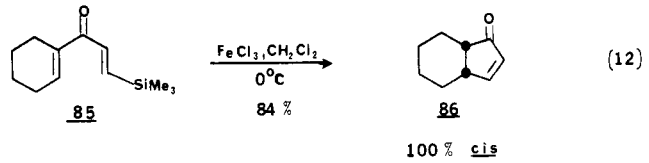
The use of ketene dithioacetals as initiators for silylalkyne terminated cyclizations was briefly investigated by Brinkmeyer (see eq 10).[61] Peterson olefination of aldehyde **70**[54] with the lithium anion of 2-(trimethylsilyl)-1,3-dithiane[62] provided ketene thioacetal **83**, which upon treatment with trifluoroacetic acid gave the monoprotected diketone **84** in good yield. The protonated ketene dithioacetal functions as an acylium ion equivalent in this reaction.



D. Silicon-Directed Nazarov Cyclizations

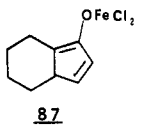
Extensive studies by Denmark have demonstrated the value of vinylsilanes in directing the course of Nazarov-type cyclizations.[63] Classical Nazarov reactions (eq 11) often give the more highly substituted cyclo-



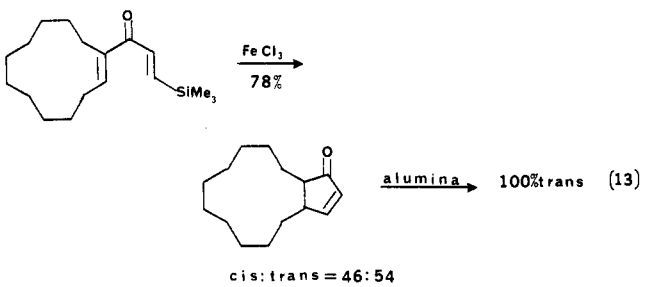


pentenone product and are occasionally complicated by competitive Wagner–Meerwein rearrangements. In contrast, the regiochemical outcome of silicon-directed Nazarov cyclizations is dominated by the β effect (see eq 12).

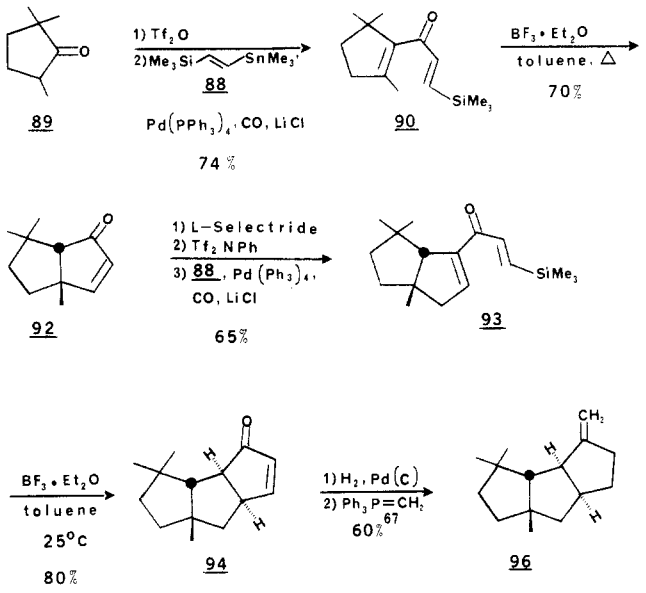
Treatment of **85** with commercial "anhydrous" $FeCl_3$ provides *cis*-hydrindenone **86** in excellent yield as a single double-bond isomer. After surveying a wide range of Lewis acids, Denmark found commercial $FeCl_3$ to be far superior in effecting these transformations. Interestingly, treatment of **85** with rigorously dried $FeCl_3$ gave a complex mixture of products in which **86** was present in, at best, trace amounts. The authors postulate that trace amounts of water are needed to immediately quench the intermediate cross-conjugated enolate **87**, which otherwise decomposes via redox or



nucleophilic pathways.[63c] The failure of other Lewis acids to successfully induce clean cyclization may be due, in part, to the anhydrous nature of these reagents (see, however, section IIIA). This kinetic quench may also account for the tendency of these reactions to yield cis-fused 4,5-dialkyl-2-cyclopentenones to a greater extent than that found at equilibrium (see eq 13).[63b,d] The stereochemical consequences of remote chiral centers in these cyclizations have been studied in detail.[63b]



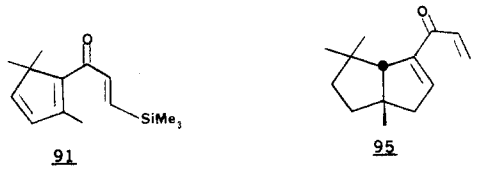
SCHEME 11



III. Formation of Unsaturated Carbocycles: Applications to Total Synthesis

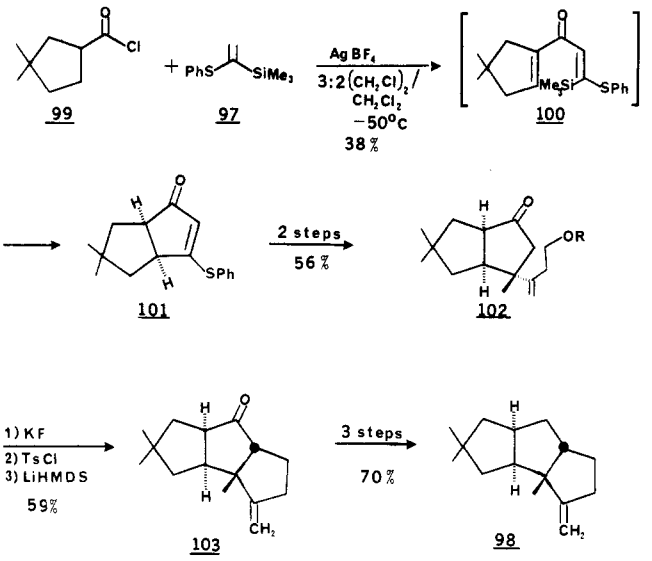
A. Triquinane Sesquiterpenes: Capnellene and Hirsutene

Stille has reported a highly efficient total synthesis of (±)-$\Delta^{9(12)}$-capnellene (**96**),[64] which features the elegant use of palladium-catalyzed carbonylative coupling reactions[65] and *two* silicon-directed Nazarov cyclizations (see Scheme 11). Palladium-catalyzed coupling of trimethyl[2-(trimethylsilyl)vinyl]stannane (**88**) with the vinyl triflate[66] derived from 2,2,5-trimethylcyclopentanone (**89**) provided divinyl ketone **90**. Surprisingly, treatment of **90** with $FeCl_3$ gave predominantly cyclopentadiene **91** and only traces of the desired Nazarov product **92**. In contrast to Denmark's results, substrate **90** was cyclized successfully using BF_3·Et_2O in refluxing toluene. Conjugate reduction of **92**,[66] followed by a repetition of the above reaction sequence provided divinyl ketone **93**, which underwent clean Nazarov cyclization upon treatment with BF_3·Et_2O to give triquinone **94**. By comparison, Paquette had shown earlier that the corresponding divinyl ketone **95** lacking the silicon substituent failed to undergo Nazarov ring closure when exposed to a wide range of Lewis and Bronsted acids.[67] Tricyclic enone **94** was converted to (±)-$\Delta^{9(12)}$-capnellene (**96**) using a reaction sequence previously demonstrated by Paquette.[67] This efficient scheme provided **96** in 9 steps and 16% overall yield from cyclopentanone **89**.

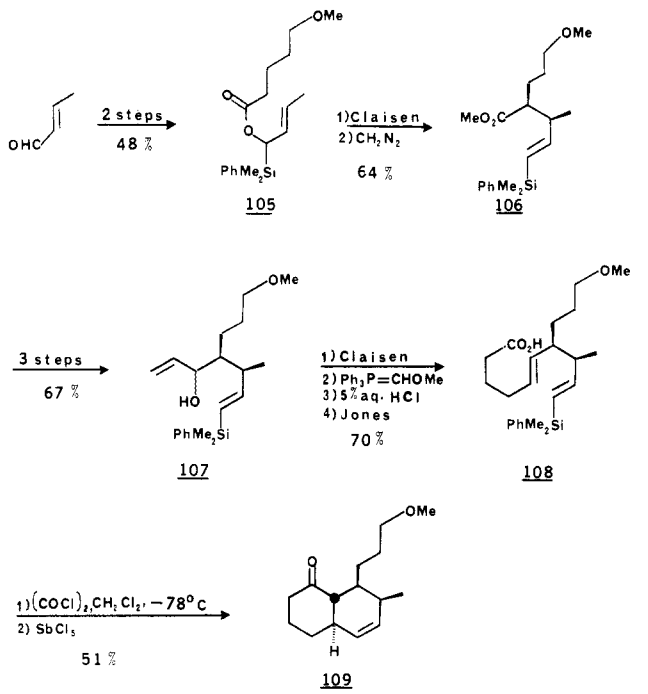


Magnus demonstrated the utility of 1-(trimethylsilyl)-1-(phenylthio)ethylene (**97**)[68] for constructing Nazarov cyclization precursors (see Scheme 12) during his total synthesis of the sesquiterpene (±)-hirsutene (**98**).[69] In terms of stabilization of cationic character, the trimethylsilyl and phenylthio groups in reagent **97** are electronically opposed. Not surprisingly (see section IIA), the initial reaction of reagent **97** with electrophiles is regiochemically directed by the phenylthio group. Thus, treatment of acid chloride **99** with reagent **97** in the presence of $AgBF_4$ generated divinyl ketone **100** which directly underwent silicon-directed Nazarov cyclization[63] to the afford bicyclic β-thiophenyl enone **101** in moderate yield. Conversion to the β-methyl enone followed by treatment with a cuprate reagent derived from 3-bromo-3-buten-1-ol gave compound **102** (R = $SiMe_2$-*t*-Bu) as a single diastereomer. Conversion of silyl ether **102** into its corresponding tosylate and subsequent intramolecular alkylation provided tricyclic ketone **103**. Reduction with $NaBH_4$ followed by removal of the resulting alcohol via the corresponding xanthate ester gave (±)-hirsutene in 9% overall yield from acid chloride **99**.

SCHEME 12

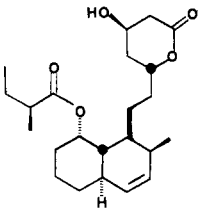


SCHEME 13



B. Hydronapthalene Portion of Dihydrocompactin

Burke has prepared the hydronapthalene portion of dihydrocompactin (**104**) via an interesting acylium



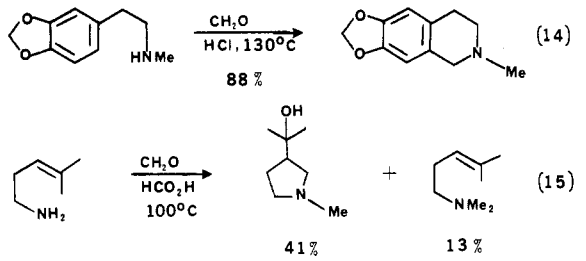
104

ion-initiated vinylsilane-terminated polyene cyclization (see Scheme 13).[70] The sequence begins with the addition of (phenyldimethylsilyl)lithium[71] to crotonaldehyde followed by acylation with 5-methoxypentanoyl chloride to give ester **105**. Ester enolate Claisen rearrangement[72] of **105** provided the (*E*)-vinylsilane **106** with high (42:1) selectivity. Conversion to a mixture of allylic alcohols **107**, Claisen rearrangement to provide a single γ,δ-unsaturated aldehyde, Wittig homologation, and oxidation yielded cyclization substrate **108**.[73] Generation of the requisite acid chloride followed by treatment with $SbCl_5$ induced polyene cyclization to give the desired *trans*-octalone **109** in good yield. This conversion represents the first report of a polyene cyclization terminated with a vinylsilane.

IV. Formation of Unsaturated Heterocycles: Scope and Methodology

A. Iminium Ion-Initiated Cyclizations

Iminium ions are comparatively weak electrophiles, usually requiring rather nucleophilic π bonds as reaction partners, as in, for example, the venerable Pictet–Spengler synthesis of electron-rich tetrahydroisoquinolines (eq 14).[74,75] Analogous cyclizations with



(14)

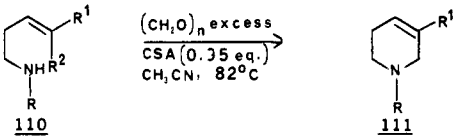
(15)

simple olefins were first reported by Cope[76] (eq 15). However, the use of formic acid as the solvent in these studies led to mixtures of products since Eschweiler–Clarke methylation[77] was often competitive with cyclization. Acetic acid is a better solvent, and Winterfeldt has reported several successful cyclizations of this general type in the indoloquinolizidine alkaloid area.[78]

In contrast to the relatively harsh conditions previously reported for iminium ion cyclizations with alkenes or arenes, we have shown that iminium ion–vinylsilane cyclizations can be accomplished under mild, near-neutral conditions.[34] These cyclizations have been investigated extensively and have significant utility for preparing five-, six-, and seven-membered nitrogen heterocycles containing both endocyclic and exocyclic unsaturation.

Examples of iminium ion–vinylsilane cyclizations that occur in the endocyclic mode to form 1,2,5,6-tetrahydropyridines are shown in Table 1.[79,80] Treatment of compounds **110a–f** with paraformaldehyde and camphorsulfonic acid (CSA) afforded the expected tetrahydropyridines **111** as single double-bond regioisomers. Notable is the synthesis of **111f** which contains an alkene double bond regioselectively functionalized for further elaboration, and the *N*-aryltetrahydropyridines **111a** and **111b**. Typically, *N*-arylpiperidines are difficult to access since they are not generally available from pyridine precursors.

TABLE 1. Tetrahydropyridine Synthesis

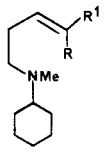


110 **111**

entry	R	R^1	R^2	time, h	yield, %
a	Ph	H	Me_3Si	0.75	61
b	*p*-$MeOC_6H_4$	H	Me_3Si	0.5	85
c	*p*-$MeOC_6H_4CH_2$	H	Me_3Si	1.5	91
d	*n*-C_3H_7	H	Me_3Si	1.5	61
e	*n*-C_3H_7	Me_3Si[b]	H	1.5	71[b]
f	*n*-C_3H_7	Me_3Si	Me_3Si	1.25	82
g	cyclohexyl	H	Me_3Si	2.5	78[a]
h	*i*-C_4H_9	H	Me_3Si	2.5	34[a]

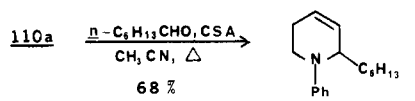
[a] In addition, two byproducts are produced; see text. [b] The product from this cyclization has R^1 = H, R = *n*-C_3H_7.

While *N*-aryl and primary carbinyl *N*-alkyl derivatives undergo cyclization cleanly, secondary carbinyl *N*-alkyl derivatives (e.g. **110g** and **110h**) cyclize at a slower rate allowing Eschweiler–Clarke methylation to compete, once again, with cyclization. When substrate **110g** was subjected to standard cyclization conditions, tetrahydropyridine **111g** was generated in 78% yield accompanied by *N*-methylamines **112a** and **112b**;[80] in



112 a R = $SiMe_3$, R^1 = H
b R = H, R^1 = $SiMe_3$

this case reductive alkylation probably arises due to advantitious formic acid in the paraformaldehyde. Substrate **110h** reacts to give analogous byproducts. This side reaction could be avoided by generation of the intermediate iminium ion, in the absence of reducing agents, from the reaction of the corresponding cyanomethylamine with silver(I)trifluoroacetate.[79–81] 2-Alkyl-1,2,5,6-tetrahydropyridines can also be prepared by the reaction of 4-(trimethylsilyl)-3-butenamines with aldehydes (see eq 16).[79]



(16)

Two mechanisms for these cyclization reactions can be considered (see Scheme 14), the simplest being direct cyclization of iminium salt **113** to β-silyl cation **114** which collapses to the observed product **115**. Alternatively, **113** could undergo a charge-accelerated aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement)[82] to allylsilane **116** which could then cyclize to tetrahydropyridine **115**. Two experiments favor the

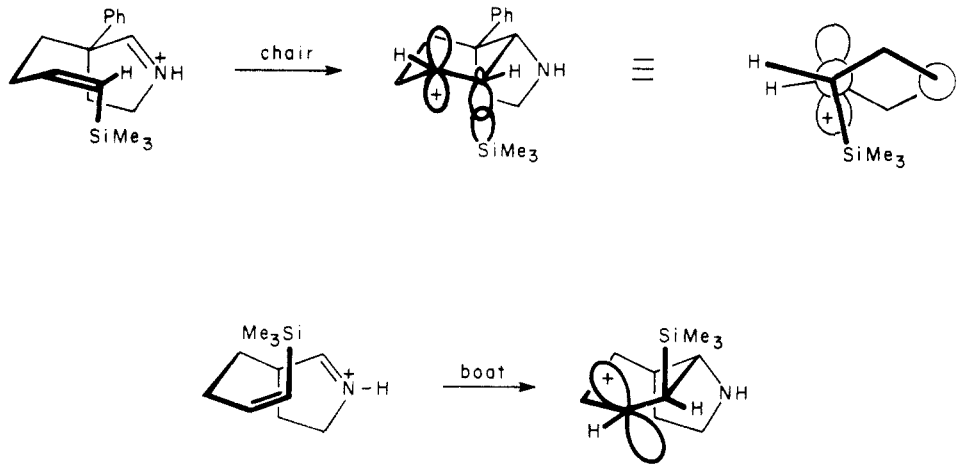
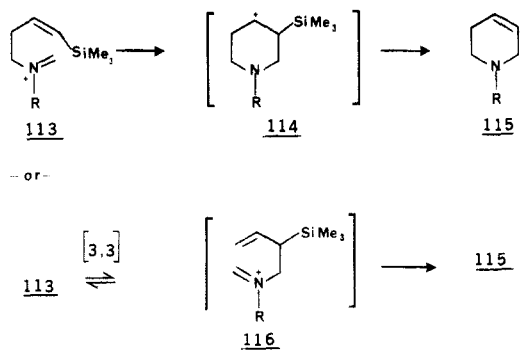


Figure 4.

SCHEME 14



latter interpretation.[79] Under cyclization conditions, substrate **110h** undergoes Eschweiler–Clarke methylation with equilibration of vinylsilane geometry (vide supra); however, this isomerization does not take place in the absence of formaldehyde. In a second experiment, vinylsilane **117** was shown to cyclize to pyrrolidine **120** (see Scheme 15) via intramolecular Mannich cyclization of intermediate **119**. None of the corresponding tetrahydropyridine **121** was isolated. These experiments strongly suggest that cationic aza-Cope equilibration occurs more rapidly than cyclization.

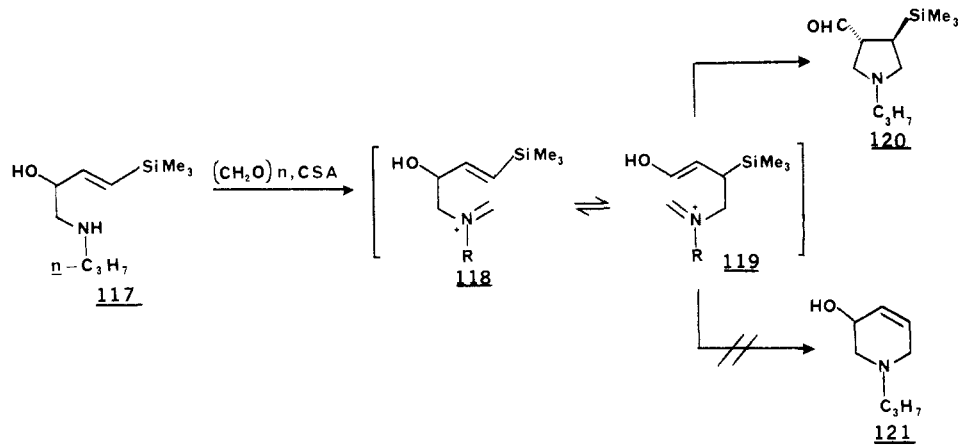
Iminium ion–vinylsilane cyclizations that occur in an endocyclic mode with respect to the vinylsilane and an exocyclic mode with respect to the iminium ion initiator exhibit a dramatic dependence of the reaction rate on the stereochemistry of the vinylsilane terminator (see Scheme 16).[83] While the (*Z*)-vinylsilane imine **122** underwent clean cyclization when treated with acid to give *cis*-hexahydroindole **123**, attempted cyclization of the corresponding (*E*)-isomer **124** under identical conditions afforded no trace of **123**. Reactions of **122** and **124** conducted identically in C_6D_6 at 115 °C showed that the rate of cyclization of the (*Z*)-isomer was *at least 7000 times* that of the (*E*)-isomer. This large rate difference[84] provides a strinking demonstration of the importance of $\sigma \rightarrow$ p hyperconjugation (see section I) in the cyclization transition state. As illustrated in Figure 4, only a (*Z*)-vinylsilane substituent can participate directly in a $\sigma \rightarrow$ p delocalization with the developing carbocation center. These substrates cannot undergo isomerization via a sigmatropic rearrangement analogous to that shown for iminium ion **113**. More reactive cyclization initiators such as acylium ions[11] and oxonium ions[51] (see sections IIA and IIB) are less discriminant of the stereochemistry of the cyclization terminator. This result is not surprising, since with more reactive initiators the transition state should come earlier and involve less charge development at the carbon β to silicon.

Studies in progress in our laboratories show that five- and seven-membered ring unsaturated azacyclics can also be prepared by iminium ion vinylsilane cyclizations.[34,80]

B. Acyliminium Ion-Initiated Cyclizations

Acyliminium ions are powerful cyclization initiators and have been used in a wide range of cationic cycli-

SCHEME 15



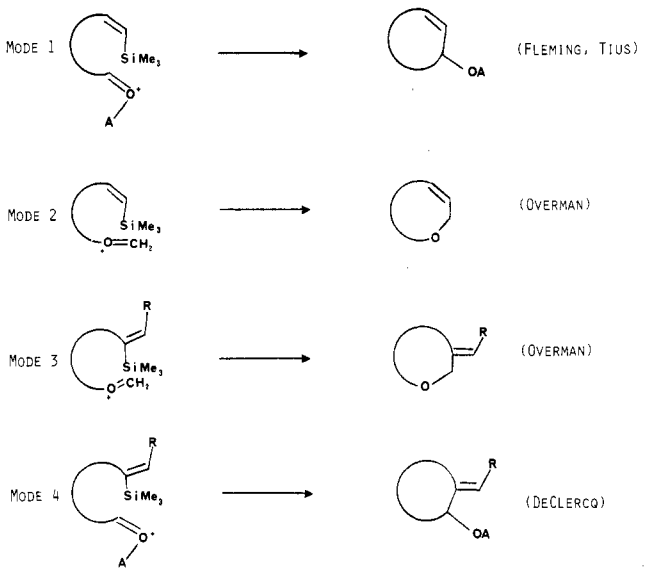
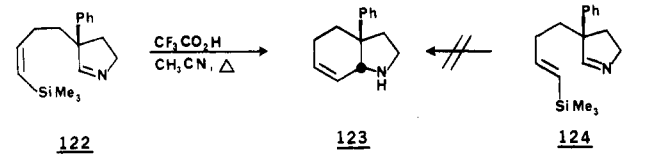
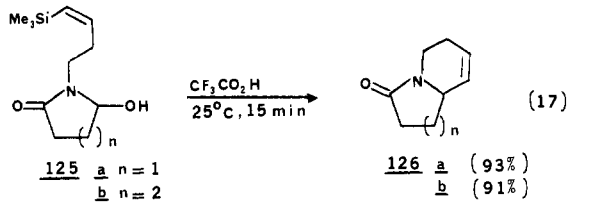


Figure 5. Acetal-initiated cyclizations. A = alkyl group or Lewis acid.

SCHEME 16



zation processes.[7] It is not surprising that this moiety serves well in vinylsilane-terminated cyclizations. Several methods for generation of acyliminium ions from a variety of precursors,[7] most notably from hydroxylactams,[7,85] are now available. Use of trifluoroacetic acid as solvent induced rapid cyclization of hydroxylactams **125a** and **125b** to bicyclic lactams **126** in excellent yields (eq 17).[79a] These reactions provide a nice demonstration of the acid stability (see section I) of vinylsilanes.

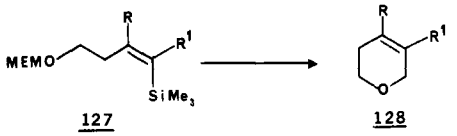


C. Acetal-Initiated Cyclizations

Acetal-initiated cyclizations of vinylsilanes that occur in an exocyclic mode with respect to the initiator to form carbocyclic products have been described, as noted earlier, by Fleming[51] and Tius.[48,49] The related cyclizations that occur in an endocyclic sense with respect to the acetal initiator lead to cyclic ether products. Four modes of oxonium ion initiated cyclizations are thereby possible, depending on the orientation of initiating and terminating functions (see Figure 5). All of these reaction modes have been explored,[46,49,51,86] and examples of successful cyclizations have been reported for all but the last of these cyclization modes.

Cyclizations of nucleophilic alkenes and alkynes with formaldehyde acetals and monothioacetals have been examined recently by Itoh, Kocienski, and Thompson.[87] In our laboratories, we have shown that formaldehyde

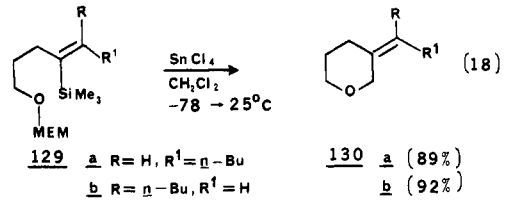
TABLE 2. Preparation of Dihydro-2*H*-pyrans

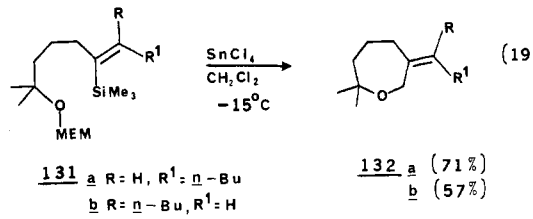


entry	R	R^1	Lewis acid	temp, °C	time, h	yield, %
a	H	H	$SnCl_4$	−20	1	71
b	H	$(CH_2)_3Ph$	$SnCl_4$	−20	1	65
c	Me	H	$TiCl_3(OPr\text{-}i)$	−20	2	83
d	H	Br	$TiCl_4$	−60	2	78

acetals, specifically (methoxyethoxy)methyl (MEM) ethers,[88] are well suited as initiators for cyclizations with vinylsilane terminators.[86] For example, 5,6-dihydro-2*H*-pyrans **128a–d** have been prepared as single double-bond regioisomers from the reaction of vinylsilane acetals **127** with Lewis acids at low temperature (see Table 2).[86,89] It is notable that the cyclization succeeds with **127d**, since 1-bromo-1-(trimethylsilyl)alkenes are weak nucleophiles due to inductive destabilization of the intermediate β-silyl cation by the halogen. This cyclization provides cyclic ether **128d** possessing an alkene regioselectively functionalized for potential further elaboration.

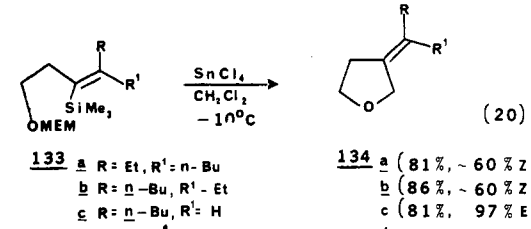
Cyclizations that occur in the exocyclic mode with respect to the terminator have been used to prepare five-, six-, and seven-membered-ring cyclic ethers.[86] Cyclization of acetals **129a** and **129b** proceeded stereoselectively to give alkylidene tetrahydropyrans **130a** and **130b** with greater than 99.5% retention of double-bond geometry[86] (see eq 18). Similarly, seven-membered ring



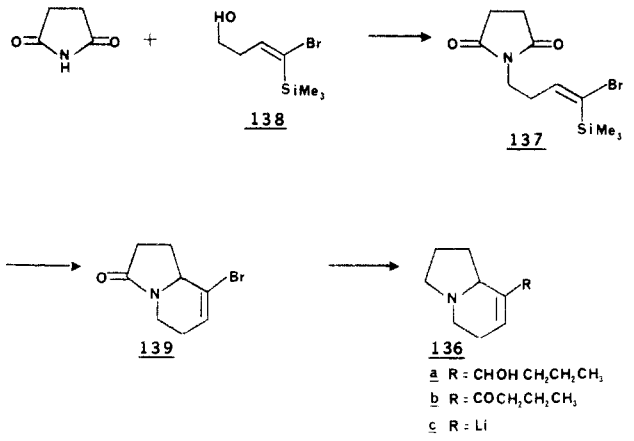


alkylideneoxacycles were prepared from vinylsilane acetals **131a** and **131b**, again with complete stereospecificity (eq 19).[86] These conversions represent the first stereocontrolled method for the preparation of 3-alkylideneoxepanes.

In contrast to the highly stereospecific reactions discussed above, cyclizations to form *tetra*substituted alkylidenetetrahydrofurans **134a** and **134b** provided mixtures of olefin stereoisomers (eq 20).[86] The lack of

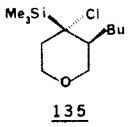


SCHEME 17



stereospecificity in these cyclizations may result from stereomutation of the cyclization precursors (e.g., via 2-oxonia[3,3]sigmatropic rearrangements) or from the possibility that β-silyl participation is less important in stabilizing (and locking the conformation) of a tertiary β-silyl carbocation intermediate.

Although vinylsilane acetal **133c** underwent highly stereospecific cyclization of the (*E*)-alkylidenetetrahydrofuran **134c**, reaction of the corresponding stereoisomeric vinylsilane **133d** afforded none of the anticipated five-membered ring product **134d**. Instead, cyclization to the tetrahydropyran **135** (in 80% yield)

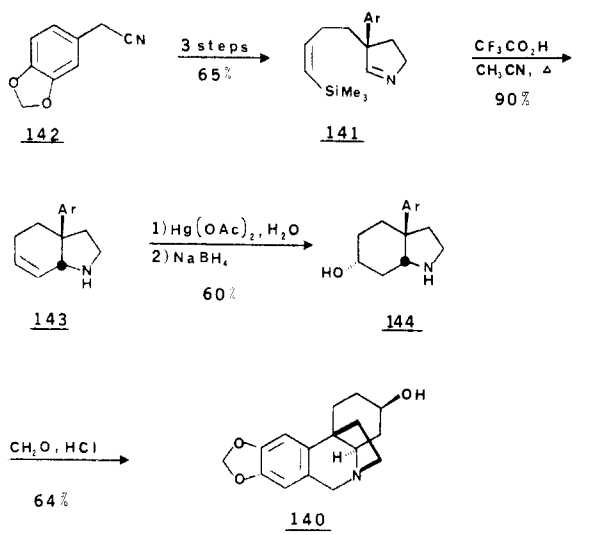


135

occurred rapidly even at −50 °C. This constitutes the first report that the stereochemistry of an alkene can completely control whether a cyclization occurs in an endo- or exocyclic mode with respect to that component. The rate of cyclization at the distal alkene carbon to form a six-membered ring product is suggested to be highly dependent on the orientation of the terminal alkene substituents. Specifically, we have suggested that a terminal substituent cis to the connecting atoms of a nascent ring system should, in general, disfavor cyclization in an endocyclic sense with respect to the terminator as a result of steric interactions between this substituent and the forming ring.[34,86]

Although many experiments remain to be conducted in this area, it seems clear that acetal–vinylsilane cyclizations are a valuable addition to the methods currently available for preparing unsaturated cyclic ethers. In contrast, the related cyclizations to form carbocycles (section IIB) are of limited utility as a result of the acid sensitivity of the carbocyclic allylic ether products (Figure 5, product of cyclization mode 1). The poor overlap that exists between the allylic C–O bond and the alkene π bond in a five-, six-, or seven-membered allylically unsaturated cyclic ether (Figure 5, product of cyclization modes 2 and 3) is undoubtedly responsible for the stability of the unsaturated cyclic ether products described in this section.

SCHEME 18



V. Formation of Unsaturated Heterocycles: Applications to Total Synthesis

A. Elaeocarpus Alkaloids: Elaeocanines A and B

An acyliminium ion-initiated cyclization was the key step in a short synthesis of the indolizinone alkaloids elaeocanines B (**136a**) and A (**136b**) reported from our laboratories.[79] As summarized in Scheme 17, imide **137** was prepared by Mitsunobu coupling[90] of succinimide and vinylsilane alcohol **138**.[91] Imide reduction[85] and cyclization in trifluoroacetic acid at room temperature afforded the regioselectively functionalized bromoindolizidine **139** in 63% yield. Reduction ($LiAlH_4$) to the amine, lithium–halogen exchange (*s*-BuLi), and treatment with butanal gave elaeocanine B (**136a**) as a 1:1 mixture of alcohol diastereomers in 58% yield overall from **139**. It is noteworthy that vinyllithium **136c** was stable to β-elimination. Oxidation[92] of **136a** by Weinreb's procedure[92] provided elaeocanine A (**136b**) in good yield.

B. Amaryllidaceae Alkaloids: Epielwesine

Overman and Burk have reported a short synthesis of the *amaryllidaceae* alkaloid (±)-epielwesine (**140**), which uses an iminium ion–vinylsilane cyclization as a key ring-forming step (see Scheme 18).[83] Cyclization substrate **141** was prepared by a two-pot sequence[93] involving dialkylation and reductive cyclization of 3,4-(methylenedioxy)phenylacetonitrile (**142**). Treatment of Δ^1-pyrroline **141** in refluxing acetonitrile with one equivalent of trifluoroacetic acid gave the *cis*-hexahydroindole **143** in 90% yield. Subsequent oxymercuration was remarkably stereo- and regioselective and gave the requisite alcohol **144** as the sole product. Subsequent Pictet–Spengler cyclization[74] of this intermediate provided (±)-epielwesine **140** in 22% overall yield[83b] from commercially available **142**.

C. Indole Alkaloids: Deplancheine

The preparation of the indoloquinolizidine alkaloid (±)-deplancheine **145a** using an exocyclic variant of an iminium ion-initiated vinylsilane cyclization as the key

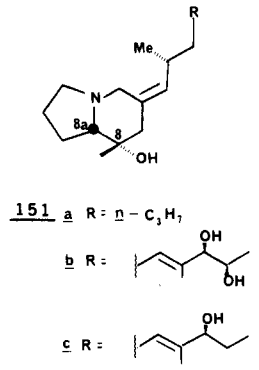


Figure 6.

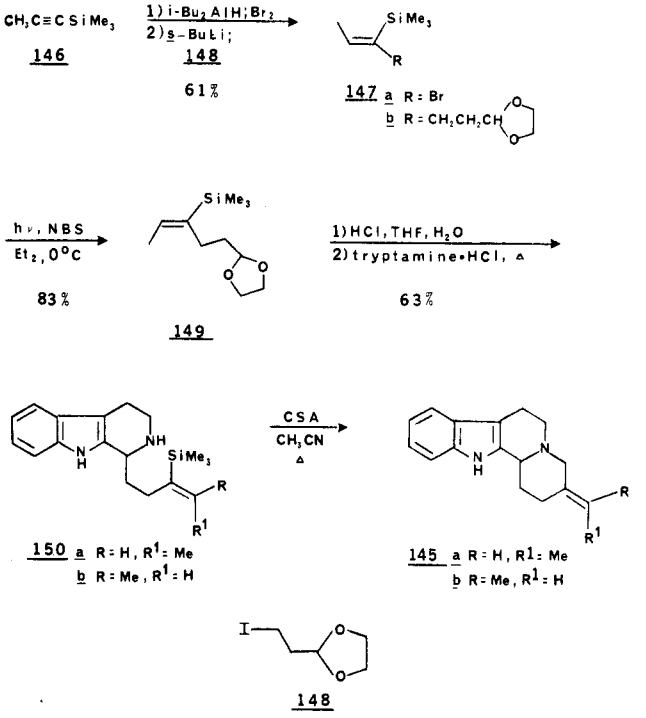
transformation has been reported by Overman and Malone.[94] The synthesis begins with 1-(trimethylsilyl)propyne (**146**), which was hydroaluminated and brominated by the procedure of Zweifel,[27a] to give (*E*)-(1-bromo-1-propenyl)trimethylsilane **147**. Lithium halogen exchange[29] followed by alkylation with iodide **148** provided (*Z*)-vinylsilane acetal **147b**. Bromine atom catalyzed isomerization[95] gave the thermodynamically more stable (*E*)-vinylsilane **149** which underwent Pictet–Spengler cyclization[74] to afford tricycle **150a**. Iminium ion–vinylsilane cyclization was effected by using a mixture of paraformaldehyde and CSA in refluxing acetonitrile to give (±)-deplancheine (**145a**) (95% isomeric purity) in 83% yield, 27% *overall* from silylalkyne **146**.

The (*Z*)-vinylsilane **147b** was also converted to the *Z* isomer **145b** of deplancheine. Significantly, **150b** underwent iminium ion–vinylsilane cyclization to give **145b** of greater than 98% isomeric purity. This series of experiments provides an additional illustration of the nearly total stereospecificity of vinylsilane cyclization reactions that occur in the exocyclic mode with respect to the vinylsilane nucleophile.

D. Pumiliotoxin A Alkaloids: Pumiliotoxins A, B, and 251D

A more demanding arena for exploring the iminium ion–vinylsilane cyclization approach to alkylidene azacycles is provided by the pumiliotoxin A alkaloids (see Figure 6),[96] a large class of frog toxins that have the (*Z*)-6-alkylideneindolizidine ring system in common. These compounds are of interest since they exhibit significant cardiotonic activity and are not readily

SCHEME 19



available from natural sources.[97,98]

The enantioselective approach outlined in Figure 7 has been successfully applied to the synthesis of three members of this alkaloid group: pumiliotoxin 251D (**151a**), pumiliotoxin B (**151b**), and pumiliotoxin A (**151c**). The basic strategy is to start with L-proline whose *S* stereocenter will become C-8a of the toxin target and utilize an iminium ion–vinylsilane cyclization to both elaborate the piperidine ring and establish the *Z* stereochemistry of the alkylidene side chain.

The first reported intramolecular electrophilic substitution reaction of a vinylsilane was the key cyclization step in the total synthesis of (±)-pumiliotoxin 251D (**151a**). This enantioselective synthesis is summarized in Scheme 20.[10,99] The last step in this synthesis involved treatment of cyclopentaoxazolidine **152** with 1 equiv of camphorsulfonic acid in refluxing ethanol to cleanly yield the natural pumiliotoxin (+)-251D (**151a**). Cyclopentaoxazolidine **152**, in turn, was generated under neutral conditions from the reaction of amino alcohol **153** with paraformaldehyde. When the cyclization was attempted directly on this amino alcohol, compe-

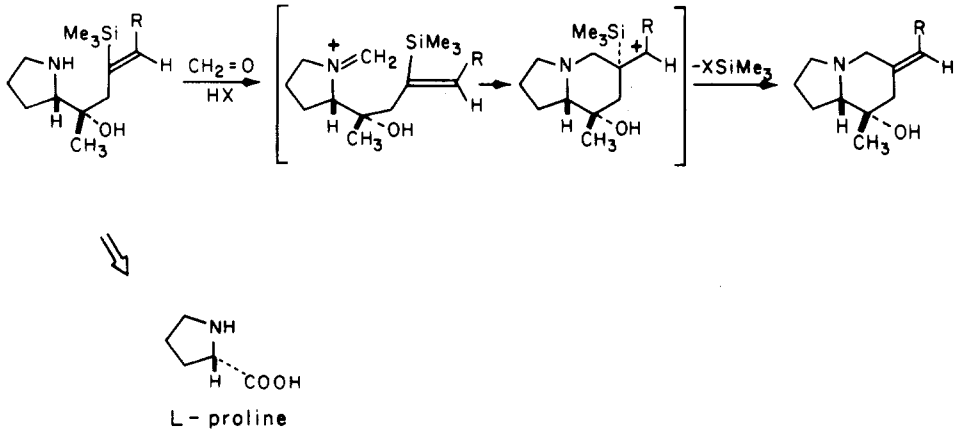
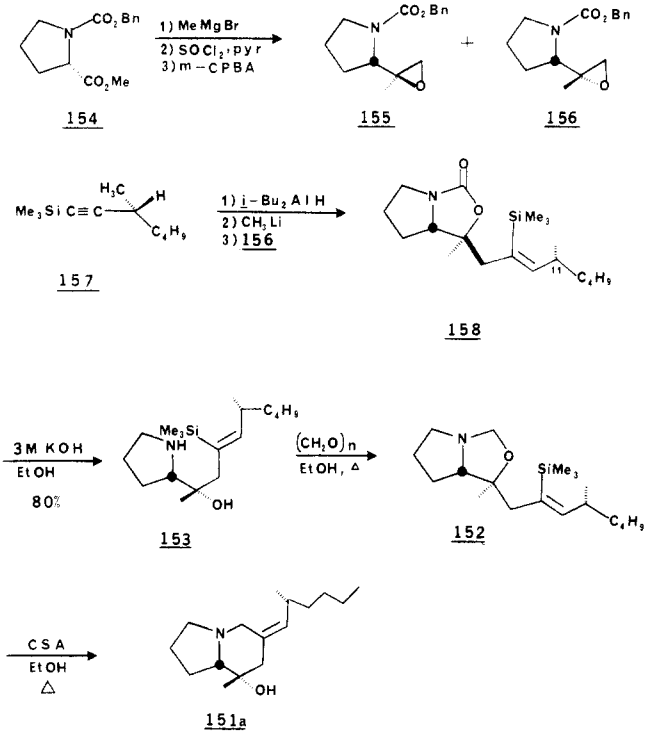
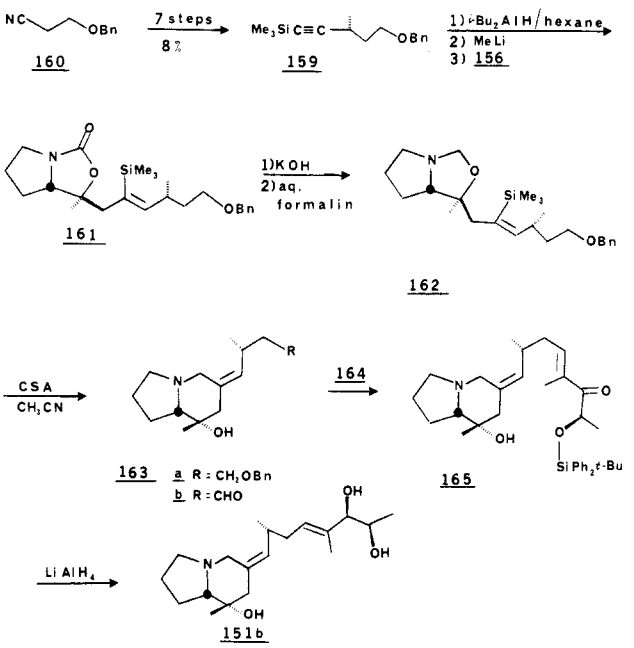


Figure 7.

SCHEME 20



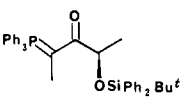
SCHEME 21



titive protodesilylation of the vinylsilane moiety was observed. Since simple trisubstituted vinylsilanes are stable to protodesilylation in the presence of amine salts,[100] the observed side reaction must result from intramolecular participation of the protonated nitrogen.[99]

Amino alcohol **153** was prepared in optically active form from methyl *N*-[(benzyloxy)carbonyl]-L-prolinate (**154**). Sequential treatment of **154** with methylmagnesium iodide, $SOCl_2$, and *m*-chloroperbenzoic acid afforded a 1:1 mixture of epoxides **155** and **156**.[101] Separation by chromatography on silica gel provided **156** in 17% overall yield from **154**. Silyl alkyne **157**, prepared in 3 steps and 92% enantiomeric purity from 1-heptyn-3-one, was treated sequentially with *i*-Bu_2AlH, methyllithium, and epoxide **156** to give carbamate **158** and its C-11 epimer as a 13:1 mixture in 41% yield. This one-pot reaction both establishes the critical *Z* stereochemistry of the vinylsilane terminator and joins the side chain and nuclear fragments. Basic hydrolysis of **158** furnished amino alcohol **153**. The synthesis of (+)-pumiliotoxin 251D is convergent and furnished the natural product in 6.3% overall yield from L-proline derivative **154**.

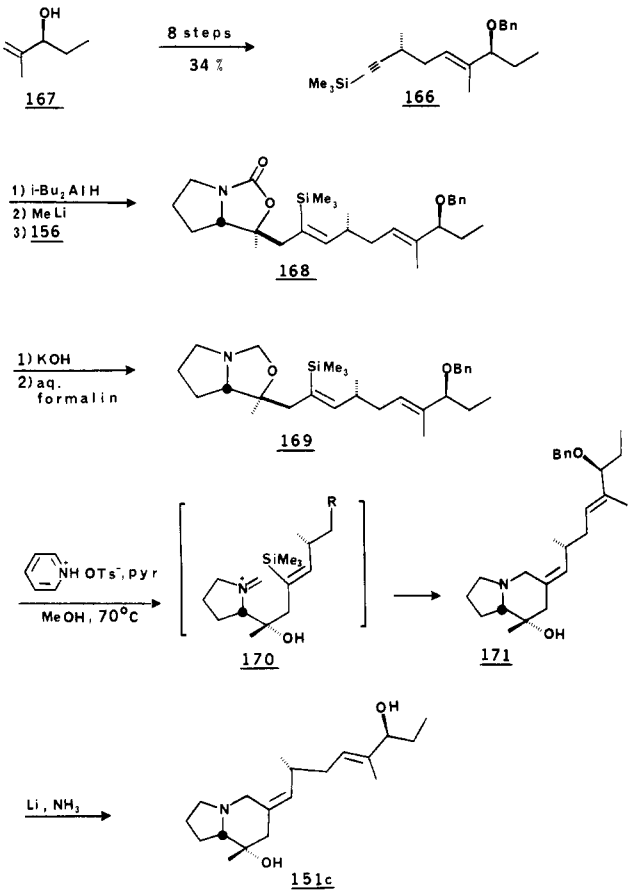
A similar approach was employed by Overman and Ito[99] to prepare (+)-pumiliotoxin B (see Scheme 21). This synthesis unambiguously established the complete stereostructure of this potentially important cardiac agent;[98] the stereorelationship of the side-chain diol and the indolizidine fragment had not been previously rigorously established. The required silyl alkyne **159**, was prepared in 93% enantiomeric purity from readily available nitrile **160** via a seven-step sequence (8% overall yield). Hydroalumination of **156**, followed by conversion to the alanate and reaction with epoxide **156** afforded bicyclic carbamate **161** in 70–77% yield from epoxide **156**. Basic hydrolysis followed by reaction of the crude amino alcohol with aqueous formalin provided cyclopentaoxazolidine **162** which was cyclized directly with CSA in refluxing acetonitrile to give (*Z*)-alkylideneindolizidine **163a** as a single double-bond stereoisomer in 50–65% yield. Debenzylation and Swern oxidation[102] provided aldehyde **163b** which was allowed to react with the optically pure phosphorane **164**, to give the (*E*)-enone **165** exclusively in 38% yield



overall from **163a**. Stabilized phosphorane **164** was prepared[103] in five steps from ethyl L-lactate. Threoselective reduction[103] of the α'-alkoxy enone **165** with $LiAlH_4$ was accompanied by silyl ether cleavage to give (+)-pumiliotoxin B (**151b**) as a separable 15:1 mixture of syn and anti diastereomers, the former being the natural configuration to the target compound. This synthesis required 13 steps to convert **160** into pumiliotoxin-B (0.8% overall yield), or 9 steps (1.8% overall yield) from proline derivative **156**. Several active analogues of PTX-B were prepared also by using this synthesis approach.[98]

The best illustration of the compatability of iminium ion–vinylsilane cyclizations with complex functionality is found in the enantioselective synthesis of (+)-pumiliotoxin A (**151c**) reported by Overman and Lin in 1985.[104] The key cyclization step in this synthesis was carried out on a substrate with a fully functionalized side chain (see Scheme 22). Silyl alkyne **166**, a key intermediate in this synthesis, was prepared in 8 steps and 34% overall yield from the (S)-allylic alcohol **167**, which was obtained in 95–98% enantiomeric purity by Sharpless kinetic resolution.[105] In a one-pot sequence, **166** was hydroaluminated, converted to the corresponding alanate with methyllithium, and alkylated with epoxide **156** to provide the (*Z*)-vinylsilane carbamate **168**. Hydrolysis followed by addition of excess formalin afforded the cyclization substrate cyclopentaoxazolidine **169**.

SCHEME 22



Mild conditions were required to form iminium ion **170**, or else competitive solvolysis of the sensitive allyl benzyl ether group on the side chain complicated the desired cyclization reaction. This was best accomplished by heating **169** in a methanolic pyridine–pyridinium tosylate buffer solution which gave (*Z*)-alkylideneindolizidine **171** in 71% overall yield from carbamate **168**. As should now be expected, the cyclization occurred with complete stereospecificity. Reductive debenzylation provided the natural product (+)-pumiliotoxin A (**151c**), thereby rigorously establishing the previously unknown side-chain stereochemistry of this material. This convergent synthesis is, by far, the most efficient entry yet developed to the pumiliotoxin A alkaloids. The 13-step route from allylic alcohol **167** proceeded in 5% overall yield and serves to highlight the utility of vinylsilane-terminated cyclizations in target-directed organic synthesis.

VI. Concluding Remarks

In a short 5 years vinylsilanes have emerged as unusually useful reaction components for cyclization-based synthesis strategies. Vinylsilane-terminated cyclizations have been demonstrated to be of value for the synthesis of carbocycles as well as oxygen and nitrogen heterocycles. The utility of vinylsilanes for the synthesis of complex target structures, alkaloids in particular, has already been amply demonstrated. It is a reasonable expectation that future years will see a continued evolution of the useful cyclization chemistry of vinyl and alkynylsilanes. The combination of these π nucleophiles with other initiating electrophiles as well as the use of these organosilanes to terminate polyene cyclizations that form two or more rings are obvious areas for future development.

VII. Acknowledgments

Our investigations of vinylsilane-terminated cyclization reactions have been supported by PHS Grants HL-25854 and GM-30859. Postdoctoral Fellowship support for T.A.B. (NRSA Grant GM-09444) is gratefully acknowledged. We also wish to acknowledge the invaluable assistance of Doris McCurdie in the preparation of this manuscript.

VIII. References

(1) For excellent reviews, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapters 5–6.
(2) For the papers that provided the major impetus for this field of research, see: Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(3) For a recent review of this methodology within the context of sesquiterpene synthesis, see: Vanderwalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767.
(4) For a review of W. S. Johnson's pioneering work in this area, see: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.
(5) Many of the classical reactions for preparing unsaturated heterocycles are of this type.[6] The use of cyclizations initiated by acyliminium ions provides a recent illustration of the use of this strategy to prepare azacyclics.[7]
(6) Katritsky, A.; Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 1–6.
(7) For a recent review, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(8) For general reviews of organosilicon chemistry, see: (a) Sakurai, H., Ed. *Organosilicon and Bioorganosilicon Chemistry: Structure, Bonding, Reactivity, and Synthetic Application*; Halsted: New York, 1985. (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. (c) Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1983. (d) Fleming, I. In Comprehensive Organic Chemistry; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, p 539. (e) Magnus, P. D.; Sarkar, T.; Djuric, S. In *Comprehensive Organometallic Chemistry*; Wilkinson, G. W.; Stone, F. G. A.; Abel, F. W., Eds.; Pergamon: Oxford, 1982; Vol. 7, p 515. (f) Paquette, L. A. *Science* **1982**, *217*, 793. (g) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. (h) Magnus, P. *Aldrichimica Acta* **1980**, *13*, 43. (i) Calas, R. *J. Organometal. Chem.* **1980**, *200*, 11. (j) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. (k) Colvin, E. W. *Chem. Soc. Rev.* **1978** *7*, 15. (l) Hudrlik, P. F. In *Journal Organometallic Chemistry Library*; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976; Vol. 1, p 127.
(9) Sommer, L. H.; Bailey, D. L.; Goldberg, G. M.; Buck, C. E.; Bye, T. S.; Evans, F. J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1954**, *76*, 1613.
(10) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.
(11) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith Strickland, S. M.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400.
(12) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.
(13) Vinylsilanes have also been utilized in a number of ring-forming reactions that cannot be considered electrophilic additions, e.g., Diels–Alder reactions,[14a] Claisen cyclizations,[14b] photochemically-induced cycloadditions,[14c] and various intramolecular reactions of organometallics.[14d] These interesting reactions are outside the context of this review.
(14) (a) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1976**, 681. Jung, M. E.; Gaede, B. *Tetrahedron* **1979**, *35*, 621. (b) Kuwajima, I.; Tanaka, T.; Atsumi, K. *Chem. Lett.* **1979**, 779. (c) Wilson, P.; Wolff, S.; Agosta, W. C. *Tetrahedron Lett.* **1985**, *26*, 5883. Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462. (d) See, inter alia: Boardman, L. D.; Bagheri, V.; Sawada, H.; Negishi, E. *J. Am. Chem. Soc.* **1984**, *106*, 6105. Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1999.
(15) (Trimethylsilyl)allenes, useful for (trimethylsilyl)cyclopentene annulation, undergo electrophilic attack regiospecifically at C-3 (i.e., they react initially as allylsilanes) and will not be discussed within the context of this review. See: Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935.

(16) Majetich, G.; Behnke, M.; Hull, K. *J. Org. Chem.* **1985**, *50*, 3615. Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308. Majetich, G.; Desmond, R.; Casares, A. M. *Tetrahedron Lett.* **1983**, *24*, 1913. Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251.

(17) These nonempirical values are derived from ab initio FSGO wave functions: Simons, G.; Zandler, M. E.; Talaty, E. R. *J. Am. Chem. Soc.* **1976**, *98*, 7869.

(18) For early studies on this phenomenon, see: Jarvie, A. W. P. *Organometal. Chem. Rev., Sect. A.* **1970**, *6*, 153. Hanstein, W.; Berwin, H. J.; Traylor, T. G. *J. Am. Chem. Soc.* **1970**, *92*, 829, 7476.

(19) For a recent theoretical study of the β effect and many leading references, see: Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.

(20) Ushakov, S. N.; Itenberg, A. M. *Zh. Obshch. Khim.* **1937**, *7*, 2495.

(21) Mechanisms involving α-silyl cations have been postulated, the first such report appearing 40 years ago: Whitmore, F. C.; Sommer, L. H.; Gold, J. *J. Am. Chem. Soc.* **1947**, *69*, 1976. For a recent experimental study, see Apeloig, Y.; Stanger, A. *J. Am. Chem. Soc.* **1985**, *107*, 2806.

(22) Koenig, K. E.; Weber, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 3416. See also: Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520. Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P. v. R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221, and ref 9.

(23) We use the term stereospecific for a reaction whose stereochemical outcome depends on the stereochemistry of the reactant. See: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 307–308 and ref 40a, b therein.

(24) Reaction of 2-alkylvinylsilanes with halogens (e.g., Br_2, Cl_2, ICl) generally proceed via addition across the double bond to give an intermediate *vic*-dihalide, followed by anti-elimination of R_3SiX to give the vinyl halide with overall inversion of alkene geometry. See ref 8b, c.

(25) It should be noted that earlier work with allylsilanes, most notably by Fleming and co-workers, highlighted the ability of a silicon substituent to control the outcome of cationic cyclization reactions. See: Fleming, I.; Roessler, F. *J. Chem. Soc., Chem. Commun.* **1980**, 276, and other papers in this series.

(26) The importance of 3d orbitals in this stabilization has been debated. See: Baechler, R. D.; Casey, J. P.; Cook, R. J.; Senkler, G. H., Jr.; Mislow, K. *J. Am. Chem. Soc.* **1972**, *94*, 2859. Baechler, R. D.; Andose, J. D.; Stackhouse, J.; Mislow, K. *Ibid.*, **1972**, *94*, 8060.

(27) (a) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739. (b) Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, *25*, 131.

(28) Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1977**, 1823.

(29) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1974**, *44*, 4623.

(30) Daniels, R. G.; Paquette, L. A. *J. Org. Chem.* **1981**, *46*, 2901, and ref 2–8 therein.

(31) See, inter alia, ref 8f and 15.

(32) Bock, H.; Seidl, H. *J. Organometal. Chem.* **1968**, *13*, 87.

(33) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(34) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59.

(35) Cf. Fleming, I.; Pearce, A. *J. Chem. Soc., Chem. Commun.* **1975**, 633.

(36) Cunico, R. F.; Clayton, F. J. *J. Org. Chem.* **1976**, *41*, 1480.

(37) Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499.

(38) Mikami, K.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795.

(39) Over 30 years ago Sommer and co-workers demonstrated that HCl addition to isopropenyltrimethylsilane occurred via an α-silyl tertiary cation to give (2-chloropropyl)trimethylsilane: Sommer, L. H.; Bailey, D. L.; Goldberg, G. M.; Buck, C. E.; Bye, T. S.; Evans, F. J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1954**, *76*, 1613.

(40) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; McCann, S. F.; Thompson, A., unpublished results.

(41) Denmark, S. E.; Germanas, J. P. *Tetrahedron Lett.* **1984**, *25*, 1231.

(42) Fukuzaki, K.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 3591.

(43) Boeckman, R. K., Jr.; Bruza, K. J. *J. Org. Chem.* **1979**, *44*, 4781.

(44) Prepared from 1,3-cyclohexanedione by the method of Stork and Danheiser: Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(45) Hoflack, J.; De Clercq, P. J. *Bull. Soc. Chim. Belg.* **1983**, *92*, 407.

(46) Grootaert, W. M.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1982**, *23*, 3287.

(47) Mironov, V. F. *Dokl. Akad. Nauk SSSR* **1963**, *153*, 848.

(48) Tius, M. A.; Sadaquat, A. *J. Org. Chem.* **1982**, *47*, 3163.

(49) Tius, M. A. *Tetrahedron Lett.* **1981**, *22*, 3335.

(50) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004, and references cited therein.

(51) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815.

(52) Kim, J. K.; Kline, M. L.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 6243.

(53) Kozar, L. G.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1977**, *42*, 1386.

(54) Johnson, W. S.; Yarnell, T. M.; Myers, R. F.; Morton, D. R. *Tetrahedron Lett.* **1978**, 2549. Johnson, W. S.; Yarnell, T. M.; Myers, R. F.; Morton, D. R.; Boots, S. G. *J. Org. Chem.* **1980**, *45*, 1254.

(55) Markezich, R. L.; Willy, W. E.; McCarry, B. E.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4414. McCarry, B. E.; Markezich, R. L.; Johnson, W. S. *Ibid.* **1973**, *95*, 4416.

(56) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126.

(57) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274.

(58) For a detailed discussion of the stereochemical course of these biomimetic polyene cyclizations, see ref 1 and 4.

(59) Baukov, Y. I.; Lutsenko, I. F. *Organometal. Chem. Rev. Sect. A* **1970**, *6*, 355. Brook, A. G. *J. Am. Chem. Soc.* **1957**, *79*, 4373. Brook, A. G.; Schwartz, N. V. *J. Org. Chem.* **1962**, *27*, 2311.

(60) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Okorie, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 8604.

(61) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207.

(62) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926.

(63) (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377. (c) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2397. (d) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

(64) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

(65) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.

(66) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979, and references therein.

(67) Stevens, K. E.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 4393.

(68) Cooke, F.; Moerck, R.; Schwinderman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046. Ager, D. J. *Tetrahedron Lett.* **1982**, *23*, 1945.

(69) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621.

(70) Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. *Tetrahedron Lett.* **1985**, *26*, 1131.

(71) Gilman, H.; Lichtenwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 607. Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520.

(72) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479, and references cited therein.

(73) A shorter, but less stereoselective, synthesis of **108** is also illustrated in the original publication.

(74) Whaley, W. M.; Govindachar, T. R. *Org. React.* **1951**, *6*, 151. Stuart, K.; Woo-Ming, R. *Heterocycles* **1975**, *3*, 223. For a recent study with leading references, see: Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164.

(75) Decker, H.; Becker, P. *Justus Liebigs Ann. Chem.* **1913**, *395*, 342.

(76) Baltzly, R. *J. Am. Chem. Soc.* **1953**, *75*, 6038. Cope, A. C.; Burrows, W. D. *J. Org. Chem.* **1965**, *30*, 2163. Cope, A. C.; Burrows, W. D. *Ibid.* **1966**, *31*, 3099.

(77) Moore, M. L. *Org. React.* **1949**, *51*, 301.

(78) Ahmad, V. U.; Feuerherd, K.-H.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 3624, and references therein.

(79) (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.

(80) Malone, T. C. Ph.D. Thesis, University of California, Irvine, 1986.

(81) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741.

(82) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021, and earlier papers in this series.

(83) (a) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739. (b) Burk, R. M. Ph.D. Thesis, University of California, Irvine, 1986.

(84) Compare with eq 5.[51]

(85) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682, and references cited therein. See also: Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(86) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.

(87) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. Nichiyama, H.; Narimatsu, S.; Sakuta, K.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1982**, 459. Cockerill, G. S.; Kocienski,

P. *Ibid.* **1983**, 705. Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653. Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925. Cockrill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093.
(88) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(89) The success of these cyclizations was highly dependent on the reaction temperature.
(90) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(91) See: ref 79a, footnote 5, and ref 80.
(92) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.
(93) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5737.
(94) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297.
(95) Zweifel, G.; On, H. P. *Synthesis* **1980**, 803.
(96) For recent reviews, see: Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205. Witkop, B.; Gossinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, Chapter 5.
(97) Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kaufman, F. C.; Tamburini, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1980**, *19*, 411. Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189.
(98) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, *28*, 482, and references cited therein.
(99) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.
(100) Overman, L. E.; Ellison, D. H.; Woo, R., unpublished results.
(101) A 1:2 mixture of **155** and **156** could be obtained if the epoxidation was conducted in hexane rather than CH_2Cl_2. However, due to solubility problems, the oxidation in hexane was not readily adaptable to large-scale preparation of **156**.
(102) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(103) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.
(104) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669.
(105) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.