# Silicon-Tethered Reactions

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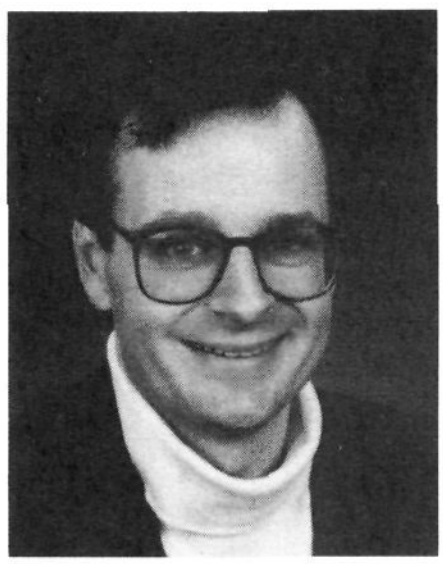
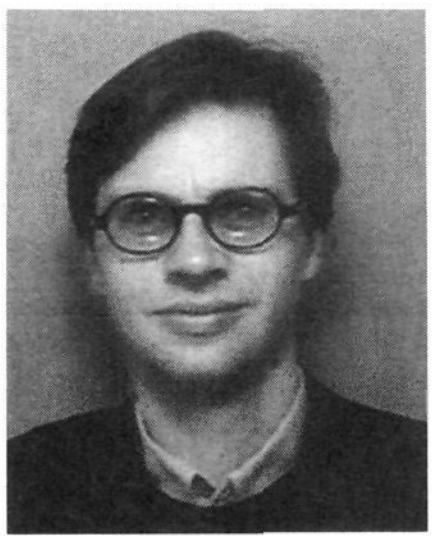
## Contents





Mikael Bols was born in 1961 in Copenhagen, Denmark. He received his M.S. degree in Chemical Engineering in 1985 at the Technical University of Denmark and his Ph.D. degree in 1988 at the same university under the supervision of Dr. Inge Lundt. After being a postdoctoral fellow from 1988 to 1989 in Professor Walter Szareks group at Queen's University, Kingston, Canada, and a research chemist at Leo Pharmaceuticals from 1989–1991, he became an assistant professor at the Technical University of Denmark. His current interests include stereoselective synthesis of oligosaccharides and tethered reactions.

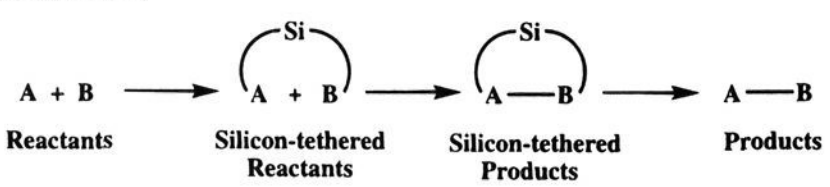


Troels Skrydstrup received his B.S. degree in 1983 from Queen's University, Kingston, Canada, and his Ph.D. degree in 1988 under the direction of Anders Kjaer at the Technical University of Denmark. After several postdoctoral stays at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette, France with Françoise Khuong-Huu (1988–1989) and David S. Grierson (1990–1992) and at the Carlsberg Research Laboratories in Copenhagen with K. Bock (1989–1990), he became *Chargé de Recherche* in the group of J.-M. Beau at the University of Orléans, France (1992) where his current interests include new approaches to *C*-glycoside constructions and natural products syntheses.

## I. Introduction

Intramolecular reactions often display a high degree of both regio- and stereoselectivity, so important in the synthesis of complex molecules. Such selectivities have often been exploited with success in the synthesis of molecules containing ring systems, but cannot be readily extended to the synthesis of acyclic compounds. However, intramolecular reactions can be applied to the synthesis of acyclic molecules by tethering the reactants, carrying out an intramolecular reaction, and finally removing the linker group (Scheme 1).

**Scheme 1**




As to the choice of which linker (or tether) to use, silicon has shown steadily increasing popularity over the last few years. This may be attributed to the fact that silicon derivatives are generally readily made, inert in most reactions, and easily and selectively removed after the reaction. In addition, silicon

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derivatives may not only serve as protecting groups before and after the desired intramolecular reaction has been performed, but may also be transformed into other functionalities, particularly in the case of the carbon–silicon bond. In this review, all intramolecular reactions in which silicon derivatives have served as tethering groups will be covered excluding reactions of silicon derivatives where silicon is not linking the reactants. This subject has not been reviewed prior to now and most of the literature has appeared only in the last decade. We have chosen to divide the material according to reaction types since this approach appears to be useful to most chemists.

## II. Reactions in Which Silicon Bonds Are Neither Broken nor Formed

### A. Cycloadditions

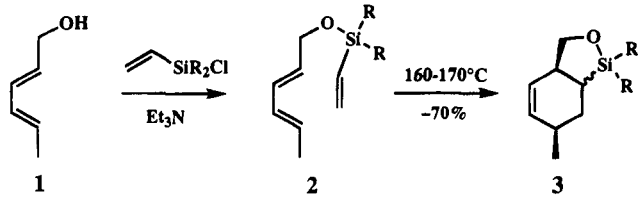
Intramolecular Diels–Alder reactions are often highly stereo- and regioselective,[1] and their usefulness can be enhanced by conversion to their intramolecular counterparts through tethering. In the last couple of years, silicon-tethered Diels–Alder reactions have been investigated. In the following, reactions have been organized according to the length of the tether in atoms between the termini of the diene and the dienophile.

#### 1. 3-Atom Tethers

The shortest silicon tether length used in Diels–Alder reactions is one of three atoms linking the ends of the diene and dienophile so that a 5-membered ring is formed fused to the 6-membered ring of the cyclized product.

Two groups have investigated 3-atom silicon tethers.[2,3] Both studies have dealt primarily with the use of vinylsilanes as dienophiles in an intramolecular Diels–Alder reaction. Reaction of sorbyl alcohol (**1**) with vinyldimethyl-,[2,3] diphenyl- or di-*tert*-butylchlorosilane[2] and triethylamine led to the vinylsilyl ethers **2**. Heating **2** at 160–190 °C for 3.5–20 h then gave the Diels–Alder adducts **3** as a mixture of 1,2-*cis*/*trans* isomers in approximately 70% yields (Scheme 2). It is interesting to note that the bulkier

**Scheme 2**




| | cis / trans |
|---|---|
| R = Me | 2 : 1 |
| R = Ph | 1 : 1 |
| R = t-Bu | 1 : 4 |

the silyl groups were, the greater the preference for the 1,2-*trans* product formed by *exo*-cyclization.[2] The same trend was observed by silylation of 3-vinyl-2-cyclohexenol (**4**) with the same three vinylsilyl chlorides affording the vinylsilyl ethers **5** and cycloaddition in toluene at 190 °C giving the cycloadducts **6** (Scheme 3).[2] However, in all three cases *exo*-addition

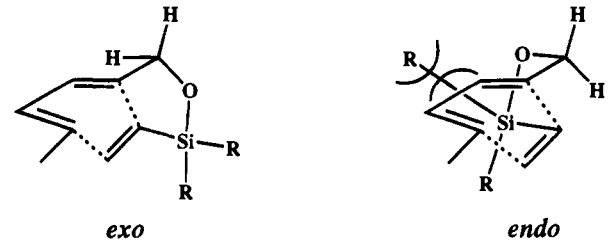
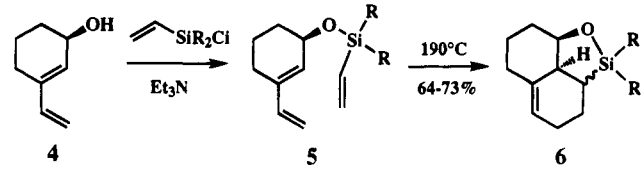



**Figure 1.**

**Scheme 3**

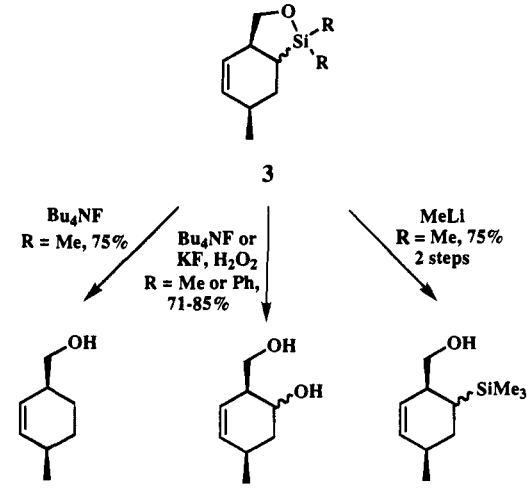



| | cis / trans |
|---|---|
| R = Me | 1 : 4 |
| R = Ph | 1 : 10 |
| R = t-Bu | < 1 : 20 |

was preferred which is not surprising when the structure of the *exo*- and *endo*-transition states are examined (Figure 1). In the latter transition state, unfavorable steric interactions follow between the silicon alkyl groups and the diene, making this pathway less favorable for the bulkier silyl groups used.

The cyclized adducts could also be subjected to further transformations (Scheme 4). Thus **3** (R = Me) would be desilylated by employing tetrabutylammonium fluoride in DMF at 75 °C or subjected to a Tamao oxidation[4] (R = Me, Ph) to substitute the silicon substituent by a hydroxy group with retention of configuration. Oxidative cleavage of the Si–C bond could not be achieved when using the di-*tert*-butylsilyl group. In addition, treatment of **3** (R = Me)

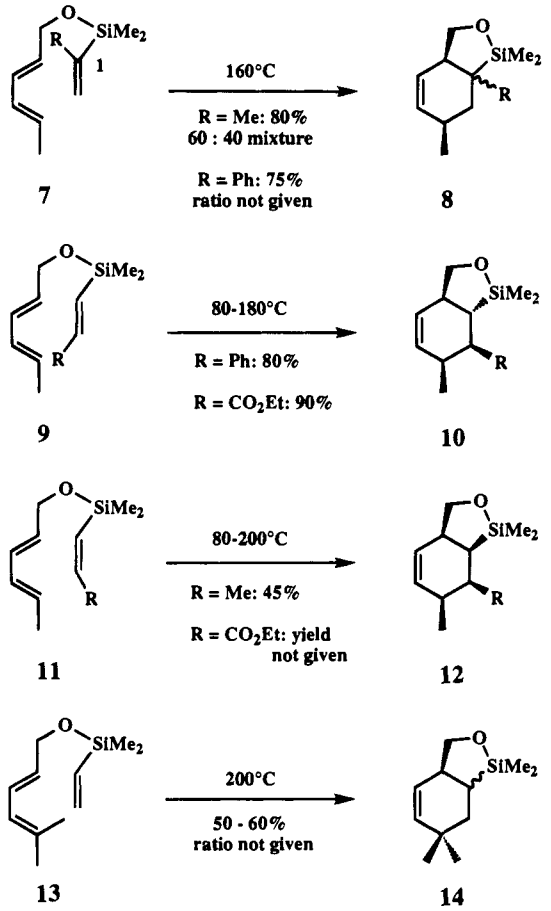
**Scheme 4**



with MeLi afforded the corresponding trimethylalkylsilane in good yields.

Similarly, Stork *et al.* examined the intramolecular Diels–Alder reaction of substituted vinylsilyl ethers of **1** (Scheme 5).[3] The $C_{(1)}$-substituted vinylsilyl

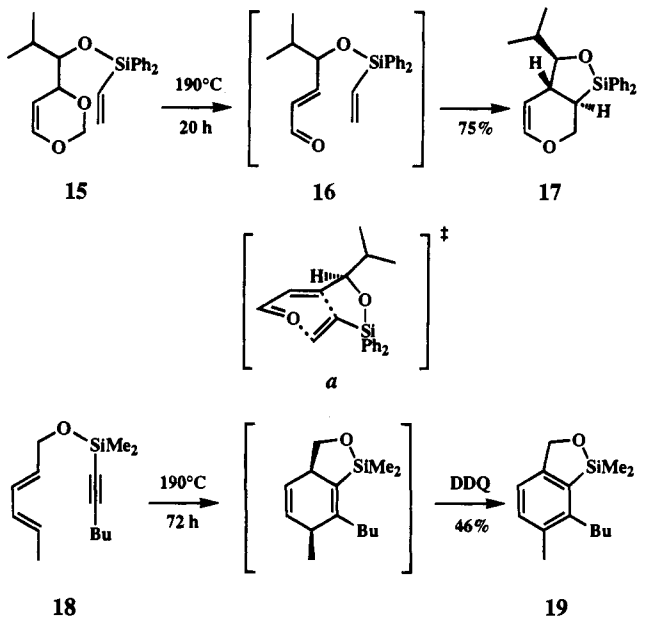
**Scheme 5**




ethers **7** were cyclized at 160 °C in benzene to give the cycloadducts **8** in good yield, as a mixture of stereoisomers at $C_{(1)}$. Higher stereoselectivity was observed when the dienophile was substituted at the $C_{(2)}$ position. For example, only the stereoisomers **10** were formed when the *trans*-compounds **9** were heated in benzene. Not surprising, the reaction was especially facile for **9** (R = $CO_2Et$) at 80 °C. The cycloadducts formed were, again, the result of *exo*-addition with respect to the tether (Figure 1). The *cis*-dienophiles **11**, in contrast, gave cycloadducts **12** resulting from *endo*-addition, although in the case of **11** (R = Me) the yield was low. The stereochemistry of these reactions seemed to be governed by the R group, now giving rise to four contiguous asymmetric centers which were all *cis*. Even the vinyldimethylsilyl ether of 5-methyl-2,4-hexadienyl alcohol (**13**) reacted in benzene at 200 °C to give the cycloadduct **14** in 50–60% yield. This reaction is remarkable since intermolecular Diels–Alder reactions of a 1,1-disubstituted diene are normally not feasible. The configuration at $C_{(1)}$ in the adduct was not given, but **14** could be desilylated with $Bu_4NF$ in DMF to afford a single product.

Intramolecular hetero Diels–Alder reactions were also investigated (Scheme 6).[2] The dioxene derivative

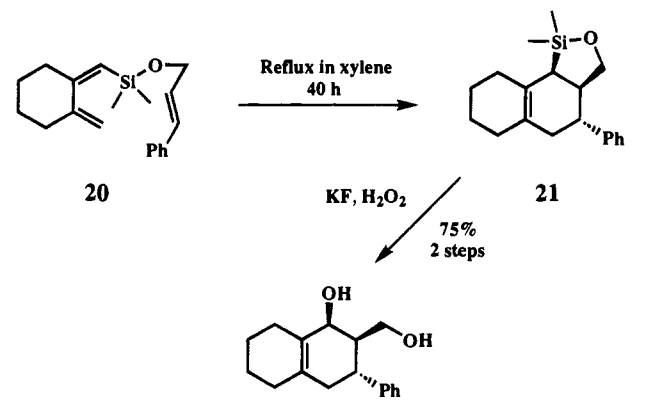
**Scheme 6**




**15** was transformed, upon heating, to the α,β-unsaturated aldehyde **16** which cyclized into a single stereoisomer **17** in 75% yield. The corresponding vinyldimethylsilyl ether gave the analogous product. The configuration obtained in **17** is the result of an *exo*-addition presumably involving the transition state ***a*** (Scheme 6) with minimal nonbonding interactions. An intramolecular Diels–Alder reaction of an alkynyl silyl ether of sorbyl alcohol (**18**) was also possible which, upon heating in toluene at 190 °C for 72 h, led to an adduct that was immediately oxidized with DDQ to the aromatic compound **19** in 46% yield.[2]

Scheme 7 shows an example of a reaction in which

**Scheme 7**

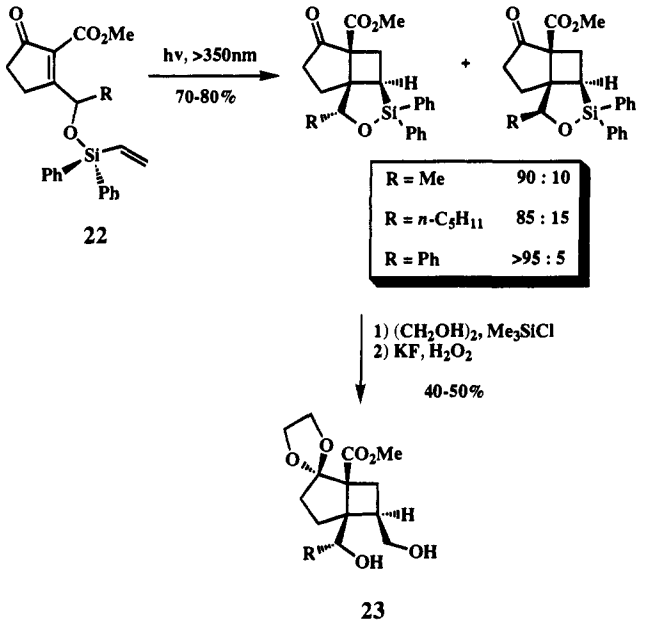



silicon is directly connected to the diene. Silicon-tethered triene **20** was converted, by refluxing for 40 h in xylenes, to a single tricyclic product **21** whose carbon–silicon bond could be oxidized to a hydroxy group with retention of configuration, giving a 75% overall yield for the two steps. Triene **20** was obtained from 1,7-octadiyne by a two-step sequence involving nickel-catalyzed hydrosilation with $HSiMe_2NEt_2$ followed by reaction with (*E*)-3-phenyl-2-propenol.[5]

Recently, Crimmins reported a silicon-tethered [2 + 2] cycloaddition with the cyclopentenone deriva-

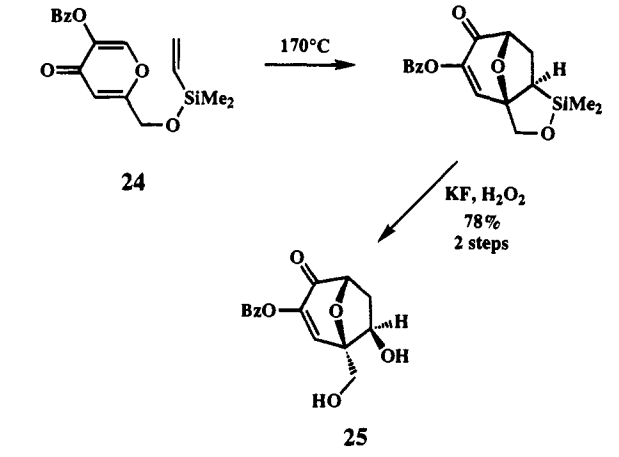
tives **22**.[6] Irradiation led to good yields of the cyclized products in a highly stereoselective manner as shown in Scheme 8. Protection of the carbonyl group of the

**Scheme 8**




major isomer and oxidation afforded the densely functionalized [3.2.0] carbocyclic system **23**. A silicon-tethered [5 + 2] addition was also recently demonstrated (Scheme 9).[7] 3-(Benzoyloxy)-6-(hydroxymeth-

**Scheme 9**

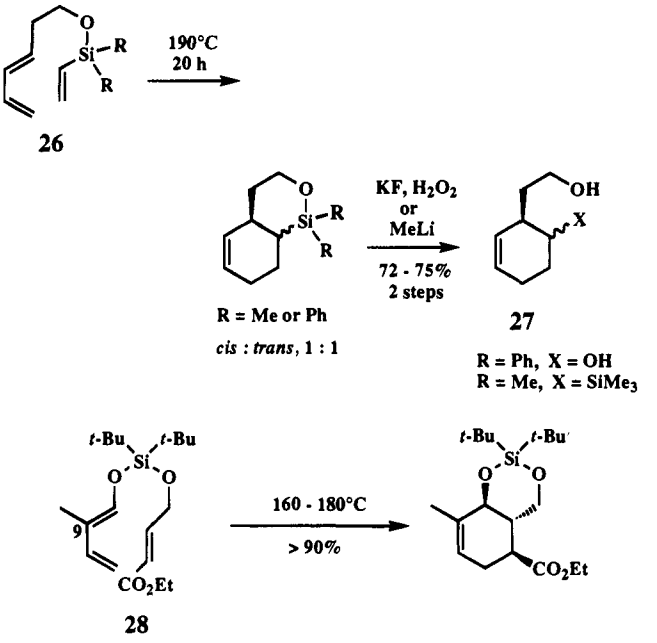



yl)-4-pyrone was silylated with vinyldimethylchlorosilane to give the silyl ether **24** which, upon heating to 170 °C, underwent a formal [5 + 2] addition to the pyrone system. This furnished, after oxidation, the bicyclic product **25** in good yield and with complete control of the regio- and stereoselectivity.

### 2. 4-Atom Tethers

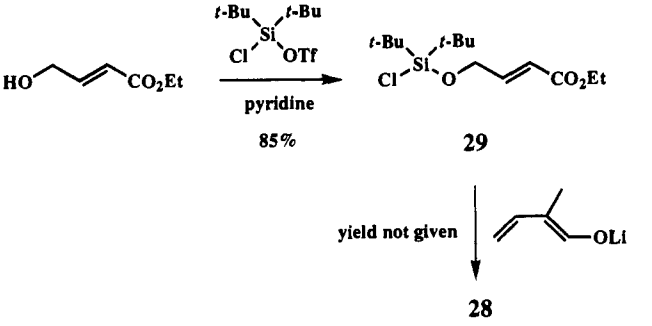
Only a few silicon-tethered Diels–Alder reactions, in which the tether forms a 6-membered ring, have been carried out. However, it is equally feasible to control the regiochemistry of these reactions. Thus, with a simple vinylsilyl ether as dienophile, triene **26** cyclized in 72–75% yield to give, after oxidation or treatment with MeLi (R = Me), the cyclohexene derivative **27** as a 1:1 mixture of stereoisomers (Scheme 10).[2] Compound **26** in turn was readily

**Scheme 10**




prepared by silylation of 3,5-hexadienyl alcohol with vinyldimethyl or diphenylsilyl chloride and $Et_3N$. The general lack of stereoselectivity for these reactions is disappointing but in this case, of little consequence if the resulting siloxanes are subjected to protodesilylation. In contrast, silicon-tethered triene **28** containing a much more electrophilic dienophile reacted to give a single stereoisomer in 90% yield. Its 9-*nor*methyl analog gave nevertheless 10% of the other stereoisomer. In the latter cases, the bulky di-*tert*-butyldisiloxane tether seemed to ensure *exo*-cyclization. Interestingly, the corresponding intermolecular reaction led only to the opposite regioisomer and as a 1:1 mixture of stereoisomers.[8] The di-*tert*-butylsilyl-tethered triene **28** was prepared as illustrated in Scheme 11 from ethyl 4-hydroxycroto-

**Scheme 11**




nate by reaction with di-*tert*-butylchlorosilane monotriflate resulting in the formation of chlorosilane **29**, which was then treated with the lithium enolate of 2-methylcrotonaldehyde. The bulky *tert*-butyl groups even allowed **29** to be purified by column chromatography.

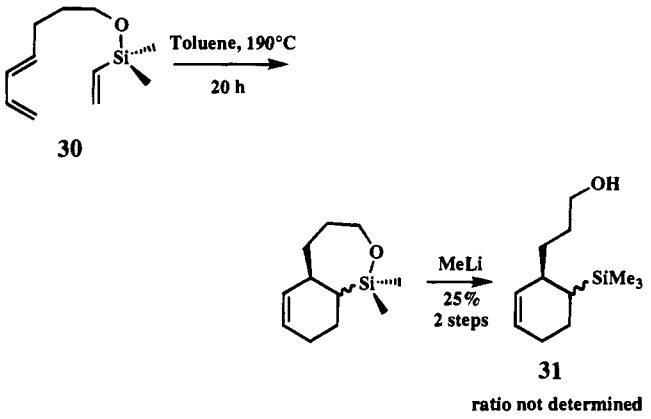
A 4-atom tether was also employed in a [2 + 2] photocycloaddition with a substrate similar to that shown in Scheme 8 (Si–vinyl substituted with Si–

allyl in **22**), again making possible the preparation of products with complete control of the regio- and stereochemistry.[6]

### 3. 5-Atom Tethers

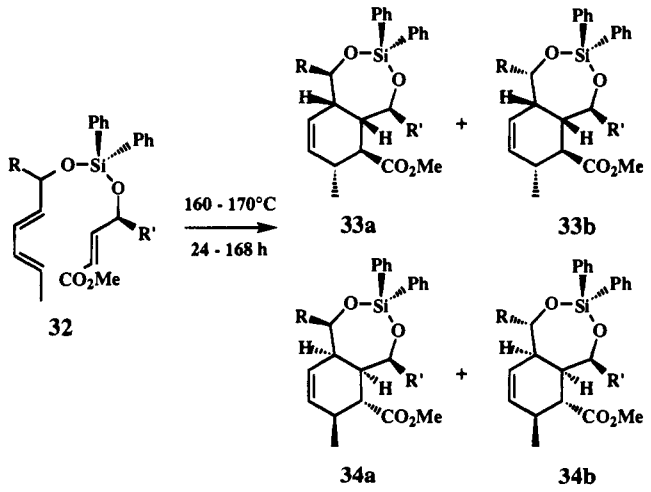
Silicon tethers forming a 7-membered ring after cycloaddtion have been used extensively, particularly silyl acetal tethers. The only case reported using a monosilyl ether was the cycloaddition of the vinylmethylsilyl ether **30** affording alcohol **31** as an undetermined mixture of stereoisomers after treatment of the cyclized product with MeLi (Scheme 12).

**Scheme 12**




The cyclization reaction was slow and the yield only 25%, in contrast to the corresponding reactions with the 5- or 6-membered ring tethers.[2] On the other hand, silyl acetal-tethered reactions in which the tether forms a 7-membered ring are both high yielding and very selective. The silicon-tethered triene **32** (R = R′ = H) underwent a Diels–Alder reaction at 160 °C to give, after 7 days, a single *cis*-fused bicyclic system **33** in 62% yield (Scheme 13).[9] The same high stereoselectivity was observed for the other substituted trienes; only *cis*-fused products were obtained and in high yields.[10,11] Triene **32** (R = R′ = Me) was a 1:1 mixture of diastereomers with each giving rise to one cycloadduct.[11] When the intermolecular counterpart to the cycloaddition of **32** (R = R′ = H) was carried out, four diastereomeric products were formed in a 2:3:3:1 ratio, emphasizing the silicon tether's value.[9] The diphenylsilyl acetal-tethered trienes were prepared from the corresponding alcohols and diphenylsilyl dichloride in 26–47% yield.[9-11]

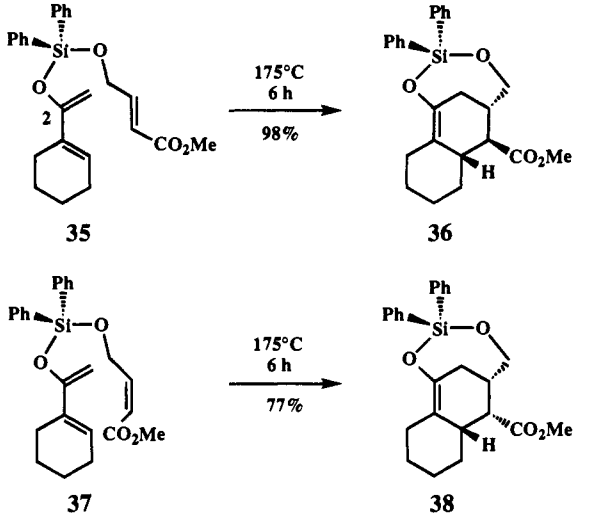
**Scheme 13**




| R | R' | yield | ratio 33a : 33b : 34a : 34b |
|---|---|---|---|
| H | H | 62% | - |
| H | Me | 100% | 1 : 0 |
| Me | H | 100% | 1 : 7 : 7 : 1 |
| Me | Me | 94% | 1 : 1 : 0 : 0 |

Examples of silyl acetal-tethered reactions where the diene is tethered to position 2 of the diene have also been reported (Scheme 14). The silylacetals **35** and **37** were prepared in good yields by lithiation of 1-acetylcyclohexene, and its subsequent treatment with diphenyldichlorosilane and the required alcohol. Triene **35** readily cyclized to the cycloadduct **36** in 98% yield. The *cis*-isomer **37** also gave a single product **35** in 77% yield. In these cycloadditions, the stereocontrol results from the fact that the silicon tethers only allow *exo*-additions.

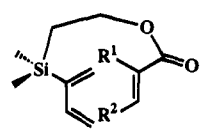
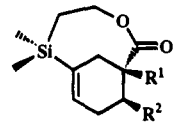
**Scheme 14**




### 4. 6-Atom and Longer Tethers

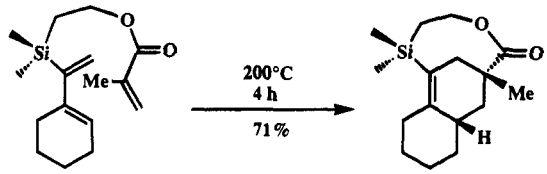
Shea *et al.* found that a silicon tether forming an 8-membered ring fused to the cyclohexene ring precluded any formation of regioisomers in the intramolecular Diels–Alder reaction of dienes linked at $C_{(2)}$.[13] Thus, the trienes shown in Table 1 cyclized in good yields to the bicyclic compounds upon heating in toluene. No isomers were formed. A corresponding intermolecular reaction would be expected to give the other regioisomer preferentially. Indeed when the tether was elongated by one or two oxygen atoms, mixtures of regioisomers were obtained. The cyclized products could be desilylated to afford the monocyclic ketones in 45–63% yields. The silicon-tethered trienes in turn were prepared by coupling the corresponding acyclic acids and 2-[(β-hydroxyethyl)dimethylsilyl]butadiene in the presence of dicyclohexylcarbodiimide. The cycloaddition reaction was also

**Table 1. Cycloadditions with 6-Atom Tethers[13]**

| Entry | Substrate | Product (yield) |
|---|---|---|
| |  |  |
| 1 | $R^1$ = H, $R^2$ = H | 98% |
| 2 | $R^1$ = Me, $R^2$ = H | 88% |
| 3 | $R^1$ = H, $R^2$ = Me | 78% |
| 4 | $R^1$ = H, $R^2$ = Ph | 93% |
| 5 | $R^1$ = Me, $R^2$ = Me | 65% |
| 6 | $R^1$ = CN, $R^2$ = Pr | 53% |

successful with the cyclic triene **39** giving the tricyclic product **40** as a single stereoisomer (Scheme 15).

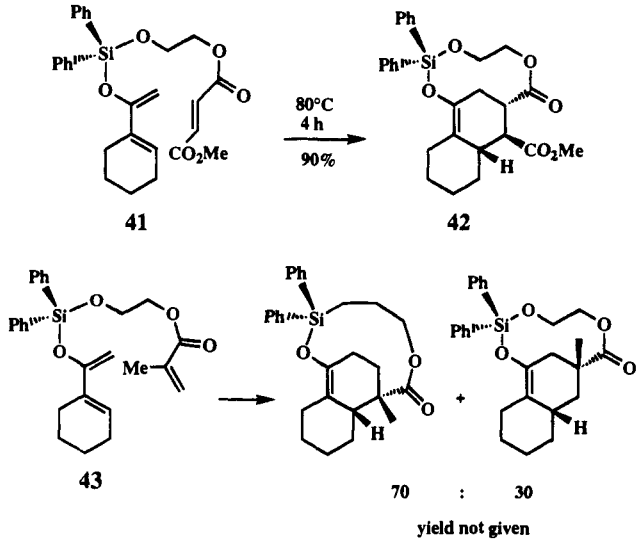
**Scheme 15**




39 40

Even using a silicon tether that forms a 10-membered ring in the cycloadduct can be stereocontrolled. Silyl acetal-tethered triene **41**, readily prepared in good yield from diphenyldichlorosilane, 1-acetylcyclohexene and 2-hydroxyethyl methyl fumarate, underwent cycloaddition at 80 °C to a single cyloadduct **42** in 90% yield (Scheme 16).[13] In this

**Scheme 16**




41 42

43

case as in the reaction of **39**, the silicon tether controls the stereochemistry at the bridgehead so that only one stereoisomer is formed. A limitation was nevertheless observed with triene **43** whereby two regioisomers were obtained on heating with the 1,4-isomer as the major product.

In summary, silicon-tethered cycloadditions, with the majority being Diels–Alder reactions with tether lengths of three or four atoms, proceed with greater ease than if untethered, however with variable stereoselectivity. With longer tethers, the reaction is not greatly facilitated, but stereoselectivity is often excellent. However, the number of cases studied thus far is too limited to make any firm conclusions. Regioselectivity of reactions with tether lengths of 6 or fewer atoms is excellent.

## B. Radical Reactions

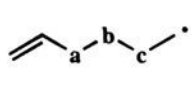
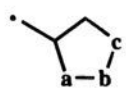
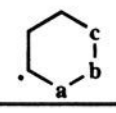
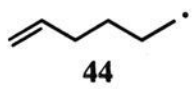
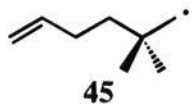
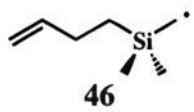
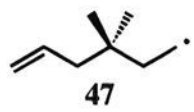
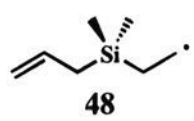
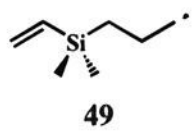
Intramolecular free radical cyclizations employing the temporary silicon connection approach have had by far the greatest success of all the silicon-based tethered reactions, representing to date approximately one-half of the publications in this area. Thus, a silicon tether allows a radical center generated on one of its ligands to react with a proximal radical acceptor on a second ligand, providing high regio- and stereocontrol at the reacting centers, particularly in the case of small-ring formation. This method has been well adapted to a regio- and stereoselective carbon-chain extention of alkenes and alkynes upon liberation of the silicon connector. However, as discussed further, the use of a silicon tether is not without limitations. The longer Si–C and Si–O bonds, compared to those of carbon as well as silicon-induced stereoelectronic effects, may lead to reversed regioselectivities in radical cyclizations.

Radical cyclization reactions will be classified according to the type of ring closure performed. 5-*Exo* and 6-*endo*-cyclization are classified together for the sake of simplicity since these ring formations use the same precursor. As these two ring closures represent a major part of radical cyclizations, all other types will be classified under the same heading. Finally, although limited to only a few examples, a powerful technique for the formation of the otherwise less accessible carbon radicals by radical translocations employing silicon tethers is described under the last heading *"Others"*.

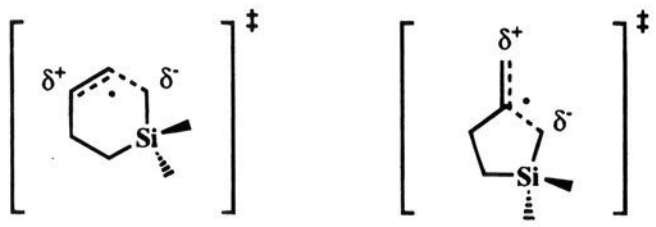
### *1. 5-Exo- and 6-Endo-Ring Formations*

*a. Trig-Cyclizations.* To date, silicon-tethered radical cyclizations using tetraalkylsilanes have not been exploited for synthetic purposes. However, this review would not be complete if the effect of $Me_2Si$ substitution on the cyclization of the 5-hexenyl radical were omitted. In 1981, a surprising observation was reported by Wilt in which replacement of a $CH_2$ at the α- or β-position of the carbon centered 5-hexenyl radical with $SiMe_2$ led to a profound change in regioselectivity in terms of the *exo*/*endo*-cyclization ratios, as well as cyclization rates.[14] While the 5-hexenyl radical **44** including numerous first row heteroatom analogs clearly display preferential 5-*exo*-ring closure,[15–17] 2- and 3-sila-5-hexenyl radicals **46** and **48**, respectively, exhibit an inherent propensity to 6-*endo*-ring formation. Table 2 shows that this dramatic regioselectivity change may not be totally due to an increase in the 6-*endo*-cyclization rate but rather to a substantial decrease in the 5-*exo*-cycliza-

**Table 2. Rate Constants for the Cyclization of 5-Hexenyl and Some Substituted 5-Hexenyl Radicals at 25 °C[20]**

| Radical | $10^{-4}k^5_{exo}$ $s^{-1}$ | $10^{-4}k^6_{endo}$ $s^{-1}$ |
|---|---|---|
|  |  |  |
|  44 | 24 | 0.3 |
|  45 | >200 | ~0.2 |
|  46 | 0.7 | 1.6 |
|  47 | 520 | <10 |
|  48 | - | 0.1 |
|  49 | 6.3 | 0.4 |

tion. On the other hand, the δ-silicon-substituted radical **49** exhibits only a slight deviation from **44**, where the rate of the 5-*exo*-ring closure is modestly reduced. This trend may be explained in part by bond length effects since Si−C bonds are approximately 25% longer than C−C bonds, making radical approach to the closer end of the double bond more difficult.[18] However, the observed preference for *endo*-cyclization of **46** has also been rationalized on the basis of polar effects.[19,20] The transition state ***i*** for *endo*-ring closure bearing a fractional negative charge at the radical center favored by silicon also bears a fractional positive charge on the internal $sp^2$ carbon (Figure 2). On the other hand, this incremental positive charge would be located on the external $sp^2$ carbon for the *exo*-cyclization transition state ***ii***. This results in the *exo*-cyclization mode being disfavored, whereas the *endo*-cyclization is accelerated. These polar factors would not be so important for the γ-substituted radical **49**. It is interesting to note that the rate-accelerating *gem*-dimethyl effect observed for the 2,2-dimethyl-6-hexenyl radical **45** in comparison to **44** in 5-*exo*-



***i*** ***ii***

**Figure 2.**

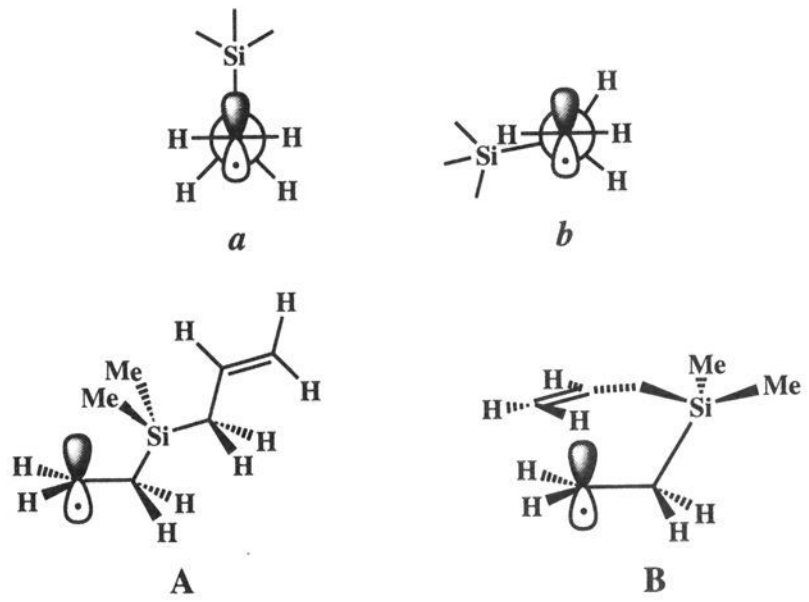


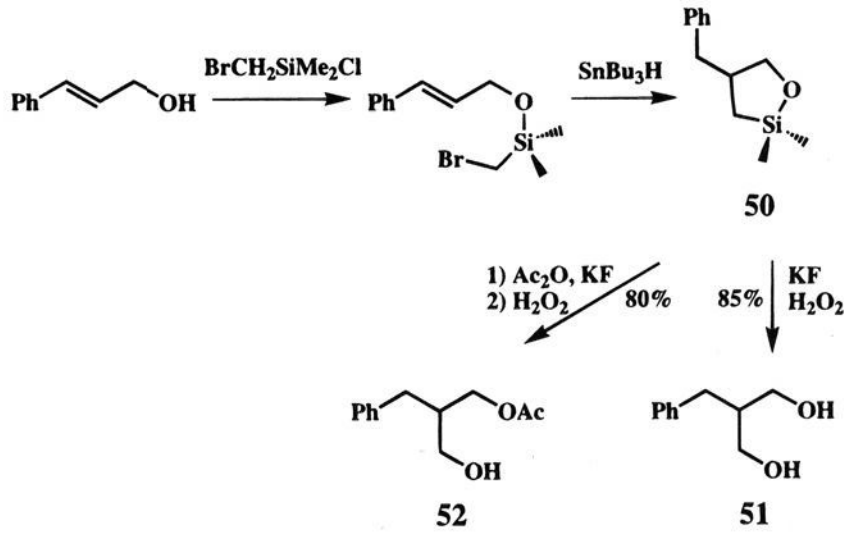
**Figure 3.**

cyclizations does not operate for the dimethyl silicon-substituted versions.[21] Again, the longer Si−C bonds reduce the importance of factors.

It is less clear for the β-Si-substituted hexenyl radical **48**. 5-*Exo* ring products are not detected and the rate of 6-*endo*-ring formation is lower with respect to other dimethylsilyl hexenyl radicals. This is in complete contrast to the all-carbon analog **47** which undergoes preferential *exo*-cyclization approximately 20 times faster than **44**. Wilt and Ingold suggest this may originate from a synperiplanar conformational preference for the β-silicon ethyl radical ***a*** which is 1.3 kcal/mol more favorable than the eclipsed conformer ***b*** (Figure 3).[19,20] In addition, if a considerable barrier to the rotation around the $C_\beta$-Si and the $C_\delta$-Si bonds existed, any distortion from conformation **A** going to conformer **B** which is required for cyclization would be unlikely.

The application of silicon-tethered radical reactions was first rerported in 1984 by Nishiyama as a stereoselective means for the preparation of 1,3-diols via a formal "hydro-hydroxymethylation" of allylic alcohols.[22] In a representative example, silylation of cinnamyl alcohol with (bromomethyl)dimethylchlorosilane and tributyltin hydride reduction afforded the 1-sila-2-oxacyclopentane **50** (Scheme 17). Subjec-

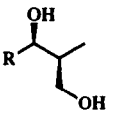
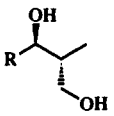
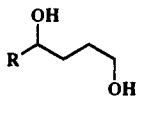
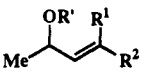
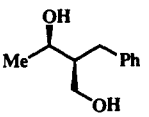
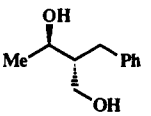
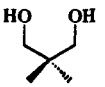
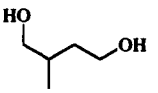
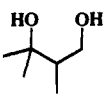
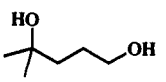
**Scheme 17**



tion to Tamao oxidation[4] gave the 1,3-diol **51** in a high overall yield. Selective protection of one hydroxyl group may also be achieved prior to oxidation giving monoacetate **52**.

Other examples are illustrated in Table 3. It is noteworthy that in cases where terminal alkenes are

**Table 3. Synthesis of Acyclic 1,3-Diols[22]**

| Entry | Substrate (R' = $BrCH_2SiMe_2$) | Product (yields) | | |
|---|---|---|---|---|
| |  |  |  |  |
| 1 | R = Me | 66% | 14% | 15% |
| 2 | R = *i*-Pr | 74% | - | 16% |
| 3 | R = *t*-Bu | 66% | - | 26% |
| 4 | R = vinyl | 52% | 9% | 24% |
| 5 | R = Ph | 48% | 4% | 36% |
| |  |  |  | |
| 6 | $R^1$ = H, $R^2$ = Ph | 71% | 14% | |
| 7 | $R^1$ = Ph, $R^2$ = H | 94% | - | |
| 8 |  |  |  | |
| | | 18% | 34% | |
| 9 |  |  |  | |
| | | 76% | 8% | |

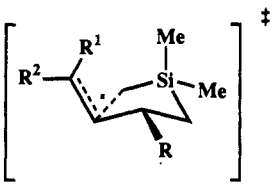


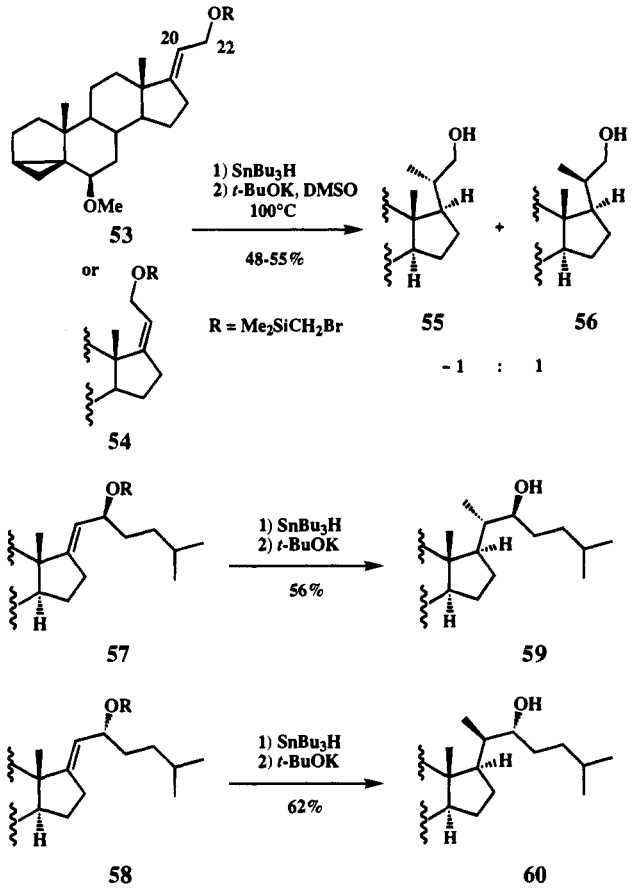
**Figure 4.**

used, 6-*endo*-cyclizations giving rise to 1,4-diols become a major competitive pathway (entries 1–5, 8, and 9) in agreement with the aforementioned observations by Wilt. Examples of allylic alcohols with $C_{(2)}$-substitution show a predominant *syn*-selectivity independent of the substitution pattern at $C_{(3)}$ (entries 1–7). These results agree with a chair-like transition state and the $C_{(1)}$-substituent occupying a pseudo-equatorial position as shown in Figure 4.[21] Formation of the *anti*-isomer may arise through the other possible chair conformation or a supposedly low-energy "boat-like" transition state.[23,24] However, the absence of *anti*-products in entries 2 and 3 as well as 7 is a clear manifestation of the 1,3-allylic strain effect.[25]

As demonstrated by Stork, hydromethylation of allylic alcohols may also be performed by which the same substrate in entry 6 of Table 3 is first subjected to radical cyclization followed by protodesilylation of the intermediate cyclic siloxane with potassium *tert*-butoxide in DMSO.[26] This approach has been used by Wicha for the structural elaboration of sterol side chains as shown in Scheme 18.[27,28] The $C_{(22)}$-unsubstituted allylic silyl ethers **53** and **54**, upon cyclization and desilylation, led to nearly equal amounts of the $C_{(20)}$-epimers **55** and **56**, showing the relatively low steric conjestion of both faces of the double bond. In contrast, with the isopentenyl-substituted derivatives **57** and **58**, only one isomer was formed for each compound, **59** and **60**, respectively. Again, the 1,3-allylic strain is the dominant factor which determines the stereochemical fate of the newly created methyl-bearing carbon center. In all four cases, the carbon-centered radical adds exclusively to the less substituted position of the double bond (5-*exo*-cyclization) and the addition of a hydrogen atom occurs from the least hindered side, opposite to the angular methyl group.

Complete regio- and stereochemical control may be obtained by using cyclic allylic alcohols originally investigated by Nishiyama[22] and Stork[26] (Table 4). A *cis*-vicinal relationship between the hydroxy group and the newly introduced methyl or hydroxymethyl group is observed because upon cyclization the transition state can only proceed to a *cis*-fusion of the 5-membered siloxane ring. The resulting bicyclic system, because of its imposed cup-shape geometry in addition to the absence of any other steric influences, restricts hydrogen abstraction exclusively to the convex side. In certain cases (entries 6 and 7),

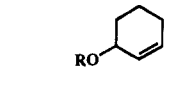
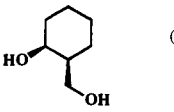
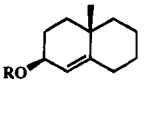
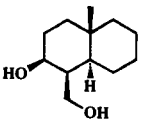
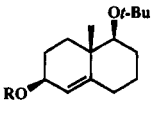
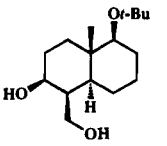
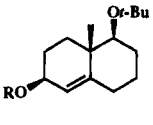
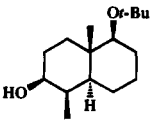
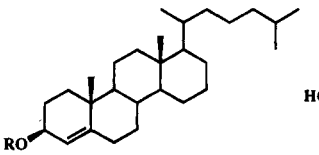
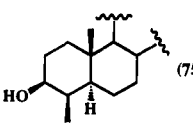
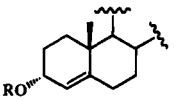
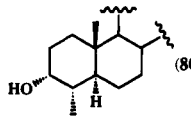
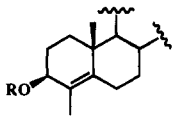
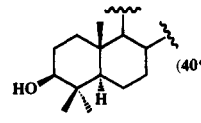
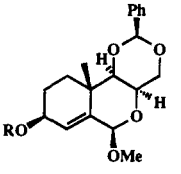
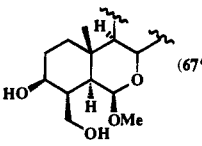
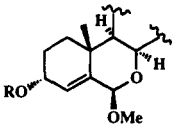
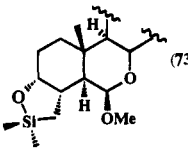
**Scheme 18**




stoichiometric tin hydride conditions lead to substantial amounts of the starting allylic alcohols upon desilylation. In the case of entry 6, this was explained by a less favorable approach of the intermediate α-silyl radical to the double bond with respect to its corresponding epimer (entry 5), hence hydrogen transfer occurs before cyclization.[29] The problem could be remedied by using the catalytic tin hydride process [$Bu_3SnCl$ (0.1 equiv) $NaBH_4CN$, AIBN] or triphenylgermane. Similarly, the rate of cyclization in entry 7 was reduced owing to the sterically congested tetrasubstituted alkene.

The situation becomes somewhat complicated when attempting to introduce angular methyl groups in bicyclic rings. Exclusive 5-*exo*-cyclization was observed for the tricyclic system (Table 5, entry 1) which may also be a manifestation of the cyclization leading to a stable benzylic radical intermediate.[31] On the other hand, problems were encountered by Lallemand *et al.* in similar attempts using the silylated allylic alcohols in entries 2–5.[32] A quantitative yield of the 6-*endo*-cyclization product in entry 2, upon treatment with tributyltin hydride, was obtained combined with a low-yielding oxidation step, whereas the corresponding $C_{(1)}$-epimer (entry 3) proved completely resistant to cyclization. Attempts to bias the regioselectivity by introducing an α,β-unsaturated ketone were successful (entry 4), giving now the desired product from a 5-membered cyclic siloxane. Although, for the corresponding isomer (entry 5) this change led to poor yields and low regioselectivities.

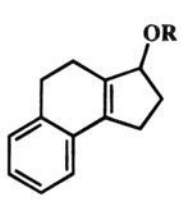
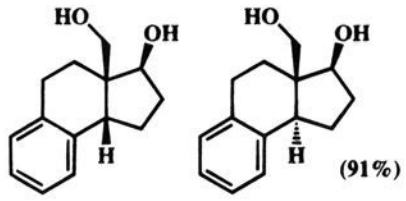
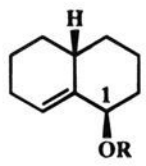
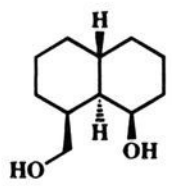
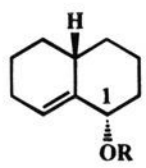
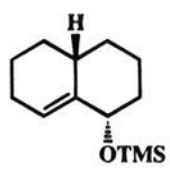
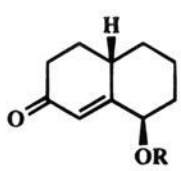
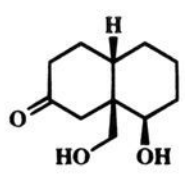
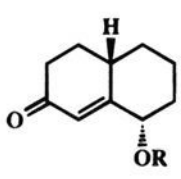
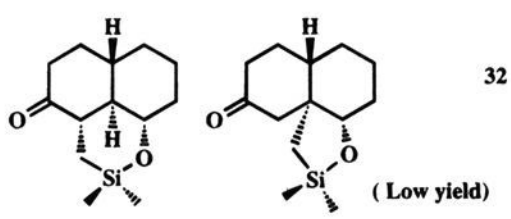
**Table 4. Functionalization of Cyclic Allylic Alcohols**

| Entry | Substrate (R = $BrCH_2SiMe_2$) | Product (yield) | Ref. |
|---|---|---|---|
| 1 |  |  (75%) | 22 |
| 2 |  |  (max. 65%) | 26 |
| 3 |  |  (88%) | 29 |
| 4 |  |  (60%) | 29 |
| 5 |  |  (75%) | 29 |
| 6 |  |  (80%) | 29 |
| 7 |  |  (40%) | 29 |
| 8 |  |  (67%) | 30 |
| 9 |  |  (73%) | 30 |

Steric factors may be the dominating contribution to this regiochemical diversity (Figure 5). The lower degree of substitution at $C_{(8)}$ then $C_{(8a)}$, an unfavorable steric interaction with the vicinal axial hydrogen, combined with the long C–Si bond lengths, may account for the 6-*endo*-selectivity displayed in entry 3 of Table 5 which was reversed upon activation via $C_{(7)}$-oxidation. The low cyclization yields of the $C_{(1)}$-epimer may be explained by the steric congestion of one of the silyl methyl groups with the $C_{(2)}$-axial hydrogen upon the approach of the carbon radical to the olefin. This reduces the cyclization rate leading to competitive reduction.

Similary, stereoselective synthesis of the less accessible branched carbohydrates has been applied to the silicon-mediated hydroxymethylation process (Table 6).[33] In most cases, 5-*exo*-cyclization prevails

**Table 5. Attempts for the Introduction of Angular Functionality**

| Entry | Substrate (R = $BrCH_2SiMe_2$) | Product (yield) | Ref. |
|---|---|---|---|
| 1 |  |  (91%) 3.7 : 1 | 31 |
| 2 |  |  (45%) | 32 |
| 3 |  |  (100%) | 32 |
| 4 |  |  (65%) | 32 |
| 5 |  |  ( Low yield) 3 : 2 | 32 |

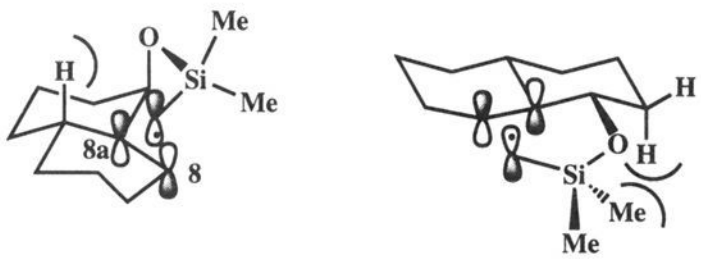
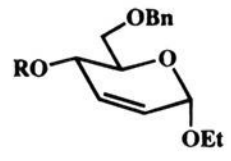
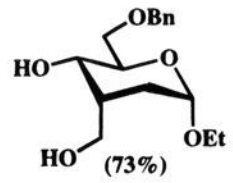
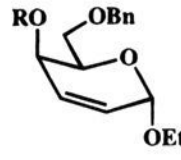
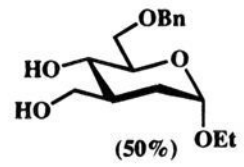
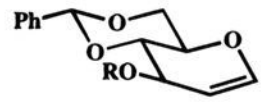
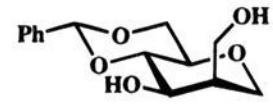
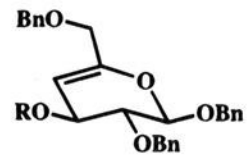
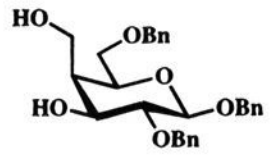
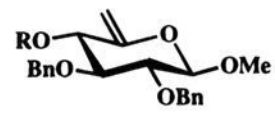
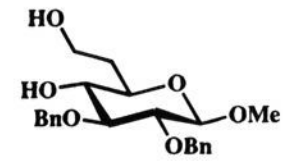


**Figure 5.**

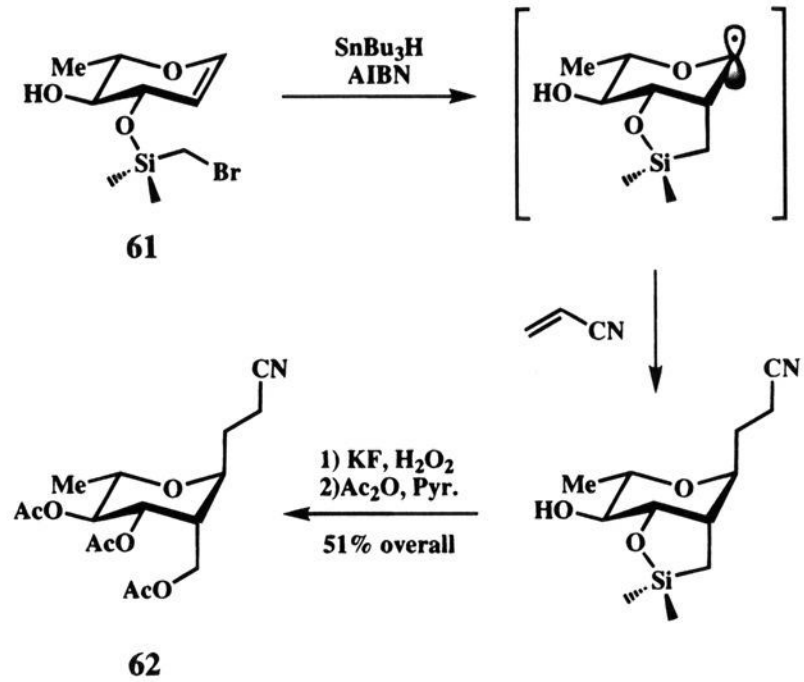
although no reaction was observed for entry 3. This is surprising in light of the similar free radical cyclization of a related bromoacetal derivative.[34] In addition, recent efforts by Fraser-Reid and co-workers have demonstrated an efficient cyclization for the corresponding rhamnal derivative **61** (Scheme 19).[35] A highlight of this reaction is that the intermediate anomeric radical may be trapped with acrylonitrile rather than tin hydride to give after oxidation both a $C_{(2)}$- and $C_{(1)}$-branched sugar **62**, thus allowing an extension of this approach. In entry 5 of Table 5, chain extension was achieved at the $C_{(6)}$- rather than $C_{(5)}$-position, which clearly indicates radical cyclization at the less hindered carbon of the exomethylene group. Also remarkable is the equatorial $C_{(5)}$-configuration in the product which is dictated through the formation of a preferred axial orientation of the radical due to the anomeric effect.[36,37]

A notable application of the preference for 6-*endo*-cyclization was reported by Koreeda in functionalization studies of steroid side chains.[38] Complete stereochemical control was induced for the two newly established stereogenic centers at $C_{(17)}$ and $C_{(20)}$ of **64**

**Table 6. Synthesis of Branched Sugars[33]**

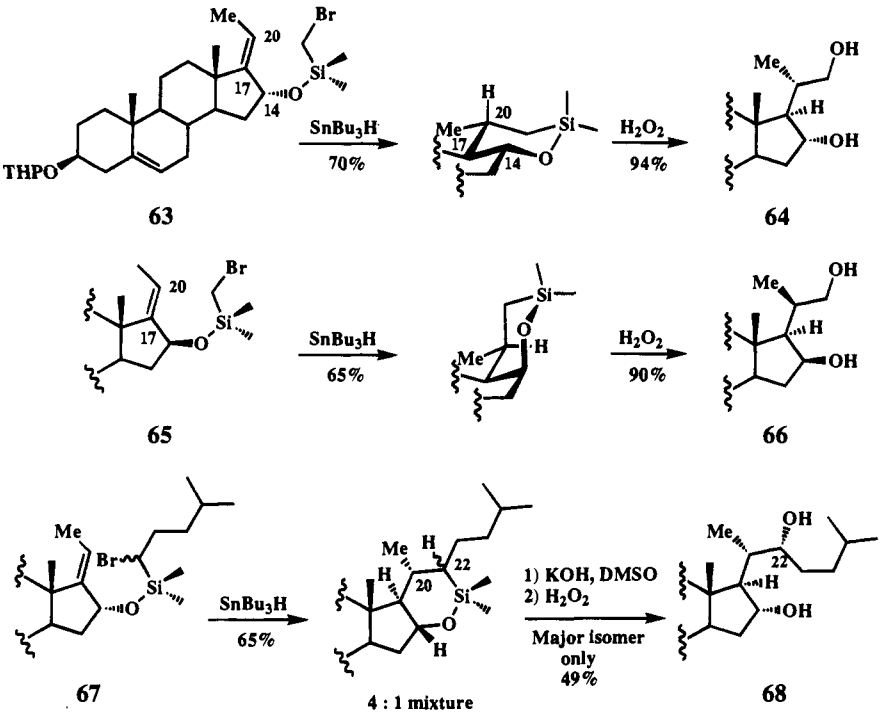
| Entry | Substrate (R = $BrCH_2SiMe_2$) | Product (yield) |
|---|---|---|
| 1 |  |  (73%) |
| 2 |  |  (50%) |
| 3 |  |  (0%) |
| 4 |  |  (71%) |
| 5 |  |  (13%) |

**Scheme 19**



and **66** (Scheme 20), upon cyclization of the silylated *E*-allylic alcohols **63** and **64**. In contrast, the stereoisomeric $C_{(17)}$-ethylidenes of **63** and **65** led to either no cyclization or to low yields, respectively, suggesting that severe steric congestion is created upon approach of the α-dimethylsilyl carbon radical. Elaboration of this procedure for the preparation of $C_{(22)}$-hydroxy cholesterol (**68**) has also been described.[39] In this case, the traditionally used (bromomethyl)-silyl ether was modified by alkyl substitution such that the complete chloresterol side chain could be introduced upon cyclization. In addition, this allowed for the creation of a third stereogenic center. Thus subjecting **67** to tributyltin hydride led to a 4:1 mixture of $C_{(22)}$-diastereomers in 65% yield with the

**Scheme 20**

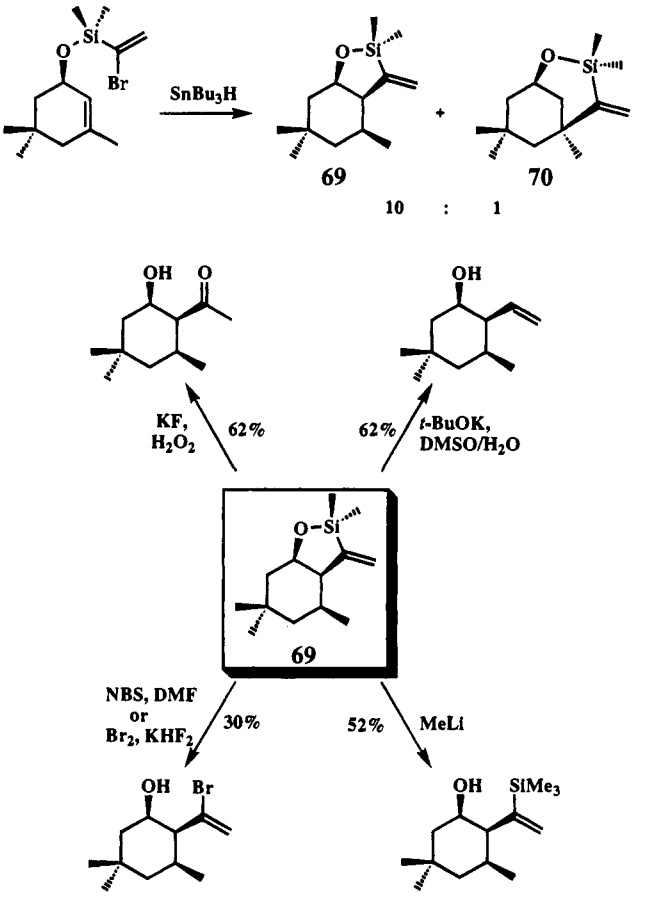



major isomer possessing a *trans*-relationship between the $C_{(20)}$- and $C_{(22)}$-substituents. Surprisingly, under standard oxidative conditions the C–Si bond displayed resistance to cleavage, possibly due to an increased steric encumbrance. However, increasing the electrophilicity of the siloxane via initial methyl displacement with potassium hydroxide allowed for the smooth C–Si oxidation.

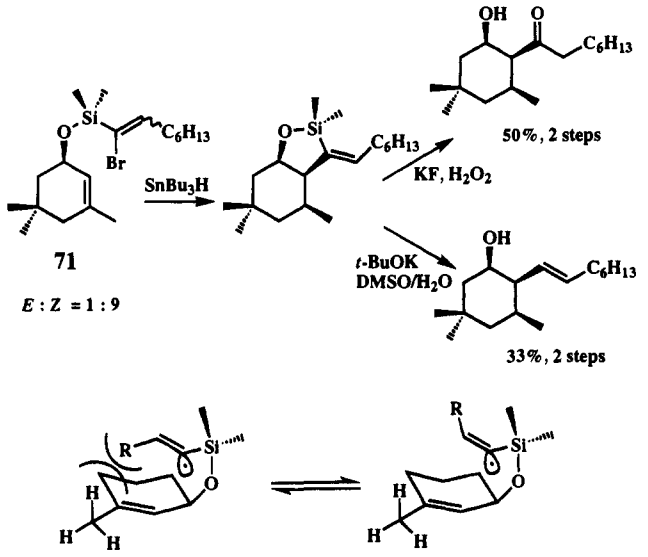
By replacing (bromomethyl)silyl ethers with α-bromovinylsilyl ethers, regio- and stereoselective hydroacylation or -vinylation of allylic alcohols was achieved.[40] The 5-membered siloxane ring **69** was the major cyclization product, in addition to some of the 6-membered ring compound **70** (ratio, 10:1; Scheme 21). The latter, however, may not have originated directly from a 6-*endo*-cyclization pathway of the vinyl radical but rather from a secondary rearrangement involving a cyclopropane intermediate of the initially formed secondary carbon radical after 5-*exo*-ring closure. Similar observations of vinyl radical cyclizations have been noted previously in other systems.[41] Further transformations of siloxane **69** led to the introduction of an acetyl, vinyl, 1-bromovinyls or 1-(trimethylsilyl)vinyl group depending on the cleaving conditions. An example was also provided with a $C_{(2)}$-substituted vinylsilane **71** illustrated in Scheme 22 where only one stereoisomer was obtained upon cyclization of a *cis,trans*-mixture of the (1-bromooctenyl)silyl derivative. This is explained by a rapidly inverting α-silyl alkenyl radical in which unfavorable steric interactions occur in the transtion state upon the addition of the *E*-isomer. The resulting siloxane was then converted into either the β-hydroxy ketone or the homoallylic alcohol upon subjection to Tamao's oxidation conditions or treatment with potassium *tert*-butoxide, respectively.

(1-Chloroethyl)dimethylsilyl enol ethers **72** undergo exclusive 6-*endo*-cyclization when subjected to tributyltin hydride (Scheme 23).[42] After treatment with methyllithium, ring opening gave the δ-trimethylsilyl-substituted alcohols **73**. This procedure lends itself as an alternative to a two-step α-alkylation, reduction sequence of ketones. Several examples are given in Table 7, but in most cases reduction before cyclization was a major competing

**Scheme 21**



**Scheme 22**




**Scheme 23**

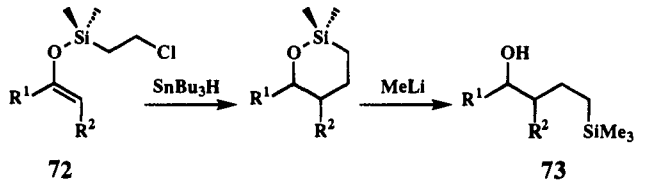
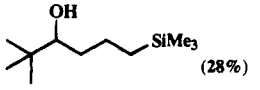
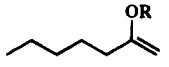
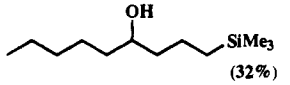
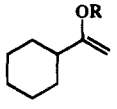
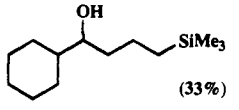
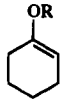
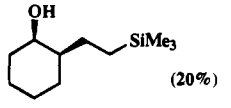
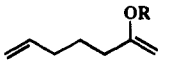
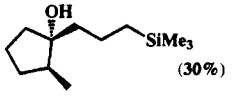


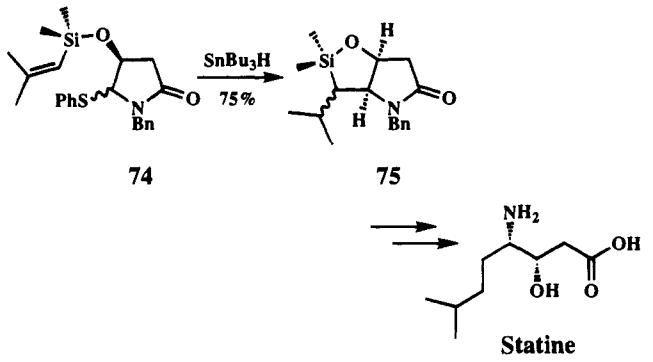

**Table 7. α-Alkylation/Reduction Sequence of Chloroethylenol Silanes[42]**

| Entry | Substrate (R = $ClCH_2CH_2SiMe_2$) | Product (yield) |
|---|---|---|
| 1 |  |  (28%) |
| 2 |  |  (32%) |
| 3 |  |  (33%) |
| 4 |  |  (20%) |
| 5 |  |  (30%) |

pathway. This is in agreement with the earlier results obtained with the β-silyl substituted hexenyl radical **48**.[14] Noteworthy is the predominant *cis*-configuration in entry 4 which reflects a favored axial approach to the enol double bond. A second intramolecular cyclization was noted for a 4-pentenyl enol ether (entry 5) in which a second ring formation was promoted by the intermediary α-oxy-C-radical. The effect of reactivity upon replacement of the methyl substituents of the silicon atom with other ligands was also reported.[43]

The role of the silyl ether derivative may be changed into a radical acceptor rather than donor as shown with **74** in Scheme 24,[44] whose results are in

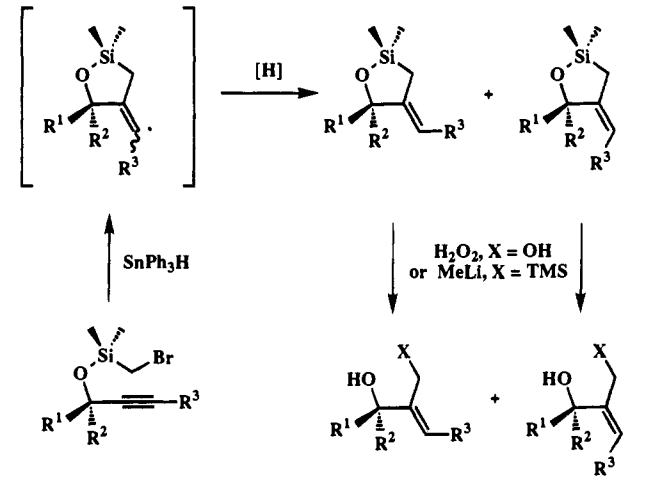
**Scheme 24**




line with others for the construction of *C*-glycosides (see section II.B.1.b). Therefore radical formation and cyclization gave exclusively the formation of the *cis*-fused bicyclic ring system **75** as a 3:2 epimeric mixture, which on protodesilylation and subsequent transformations gave the β-hydroxy-δ-amino acid, statine. Synthesis of **74** was accomplished by silylation of the corresponding alcohol with the (2,2-dimethylvinyl)dimethylaminosilane prepared according to a procedure developed by Stork.[45]

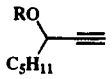
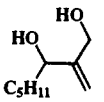
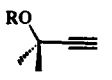
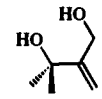
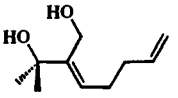
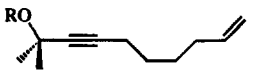
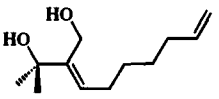
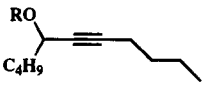
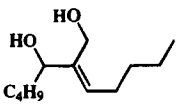
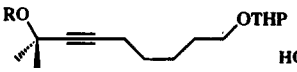
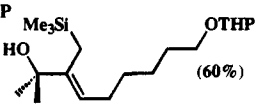
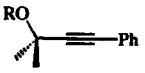
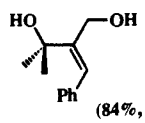
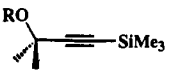
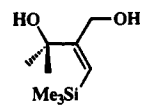
*b. Dig-Cyclizations.* In contrast to cyclizations of (bromomethyl)dimethylsilyl allylic ethers, the corresponding propargylic ethers studied by Malacria and co-workers afforded only cyclized products in the 5-*exo*-mode.[46-48] Even with the long C–Si, O–Si bond lengths, the trajectory approach requirements of the radical center can only be fulfilled for a 5-membered ring formation because of the 180° angle of the C–C≡C bond (Scheme 25). The intermediacy

**Scheme 25**




of a highly reactive and configurationally labile vinylic radical allows for either a *cis*- or *trans*-substituted alkene whose configuration depends on the substitution pattern of the parent propargylic alcohol. Oxidation of the siloxanes or treatment with methyllithium leads to either the allylic alcohol or allylic trimethysilane, respectively. Several ex-

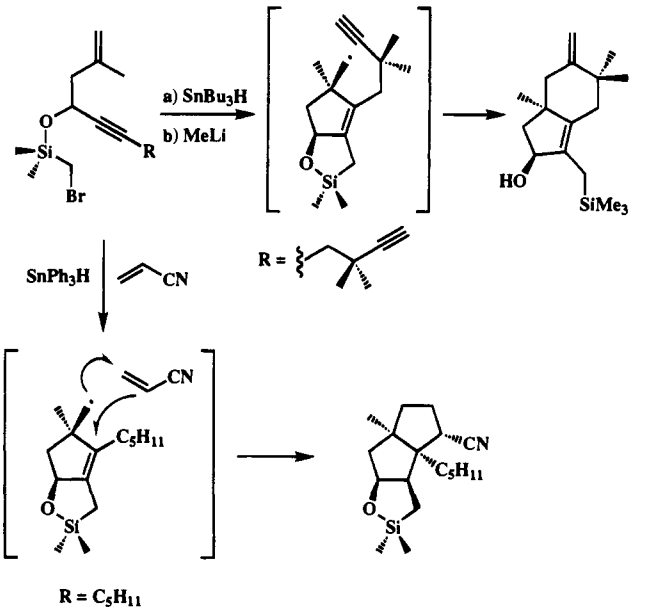
**Table 8. Functionalization of Propargylic Alcohols[46-48]**

| Entry | Substrate (R = $BrCH_2SiMe_2$) | Product (yield) |
|---|---|---|
| 1 |  |  (77%) |
| 2 |  |  (69%) |
| 3 |  |  (75%, E/Z = 75:25) |
| 4 |  |  (70%, E/Z = 95:5) |
| 5 |  |  (65%) |
| 6 |  |  (60%) |
| 7 |  |  (84%, E/Z = 25:75) |
| 8 |  |  (85%, E/Z = 35:65) |

amples are shown in Table 8. With alkyl side chains as shown in entries 3–6, up to 100% of the *Z*-stereoselectivity of trisubstituted alkenes may be obtained. The configuration is reversed with phenyl- and TMS-substituted alkenes (entries 7 and 8). This remarkable stereochemical divergence may be explained for the aliphatic substituents by formation of the thermodynamically more stable product. The bent vinylic radical, where inversion is fast relative to hydrogen abstraction, is insensitive to steric factors of the incoming H-donor. Thus, the product formed is the one in which the 1,3-allylic strain[25] between the *gem*-dimethyl substituents ($R^1$ and $R^2$) and $R^3$ is avoided (Scheme 25). In contrast, kinetic control may be operating for $R^3$ = phenyl and TMS. A stabilized vinylic radical may account for this since unfavorable steric interactions of the incoming $Bu_3SnH$ with the *gem*-dimethyl groups is an important factor.

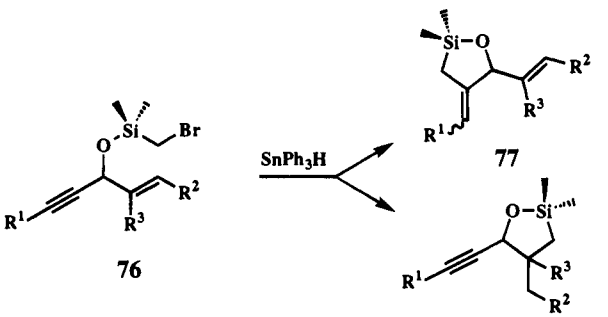
An extension of these silicon-tethered reactions to initiate an array of sequential radical cyclizations was accomplished by the same group.[48-50] Two examples with judiciously chosen side-chain substituents leading to carbocyclic systems are shown in Scheme 26.

**Scheme 26**




Competitive addition of the α-silylmethyl radical to either a double or triple bond as in **76** was found to display a favored 5-*exo*-*dig*- rather than *trig*-cyclization (Scheme 27).[51] This is surprising because

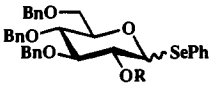
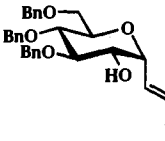
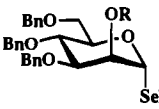
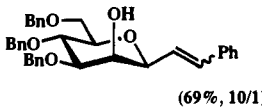
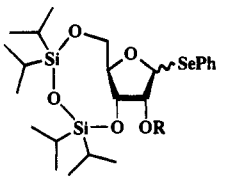
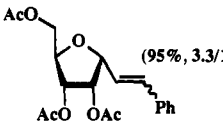
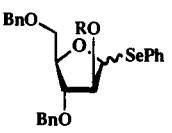
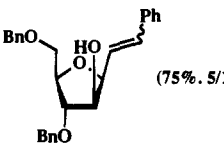
**Scheme 27**




the 5-hexenyl radical normally has a faster cyclization rate than the corresponding 5-hexynyl radical.[21] The reaction appears insensitive to the substitution pattern at $R^1$ and $R^2$ of **76** ($R^3$ = H) leading to the predominant formation of **77**. However, exclusive *dig*-ring closure was noticed with a methyl substituent in the internal double bond position $R^3$.

Reversing the role of the silicon tether as a radical acceptor rather than donor was applied successfully by Stork for the stereocontrolled synthesis of *C*-glycosides.[52] These reactions involved the formation of an α-biased but rapidly equilibrating anomeric radical and its intramolecular cyclization with a silicon-tethered phenylacetylene. Complete stereochemical control at the anomeric center was maintained by the linking hydroxyl group. Examples where the silicon tether was connected to the $C_{(2)}$-hydroxyl group leading to 5-*exo*-cyclizations are shown in Table 9 while others are discussed in the following section (see section II.B.2.). The ring closures work well in either the *gluco*- or *manno*-series leading to the α- or β-styryl *C*-glycoside, respectively (entries 1 and 2) after desilylation with high *E*-selectivities of the newly formed double bonds. In the furanose series, high cyclization yields were

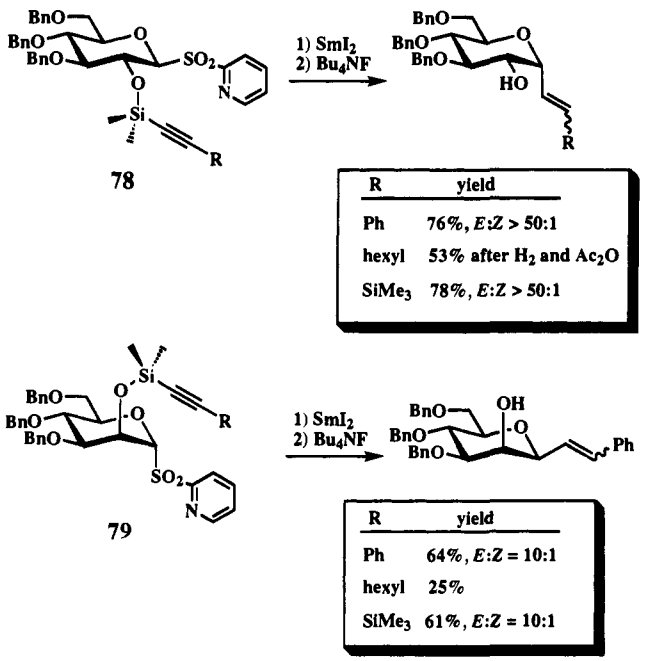
**Table 9. *C*-Glycoside Synthesis From Phenyl Selenoglycosides[52]**

| Entry | Substrate (R = $Me_2SiC{\equiv}CPh$) | Product (yield, *E*/*Z*) |
|---|---|---|
| 1 |  |  (83%, 10/1) |
| 2 |  |  (69%, 10/1) |
| 3 |  |  (95%, 3.3/1) |
| 4 |  |  (75%. 5/1) |

also observed although the *E*/*Z*-stereoselectivity was reduced slightly.

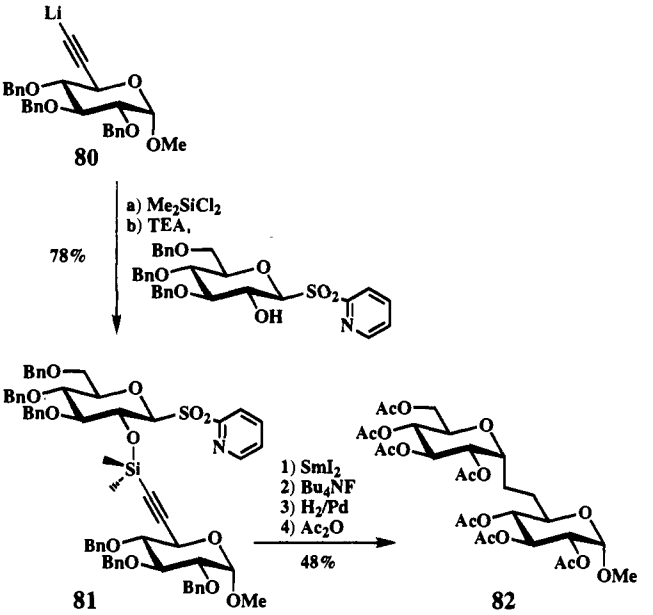
A samarium(II) diiodide promoted version of this *C*-glycosylation process has been presented using glycosyl pyridinyl sulfones (Scheme 28).[53] Reduction

**Scheme 28**




of the sulfone with $SmI_2$ proceeds through the anomeric carbon radical and it is paramount that cyclization be fast with respect to the second electron transfer which would otherwise lead to the anomeric carbanion. This appears to be the case of the glucosyl sulfones **78**, as well as the activated acetylenes in the *manno* series **79** (R = Ph, $SiMe_3$). However, for **79** (R = hexyl), a combination of the unactivated acetylene and the preferred α-configuration of the anomeric radical resulted in a poor cyclization yield where the major product was the corresponding 1-deoxymannose derivative. An application of this procedure for the synthesis of methyl *C*-isomaltoside is also given in Scheme 29. Thus, the readily

**Scheme 29**

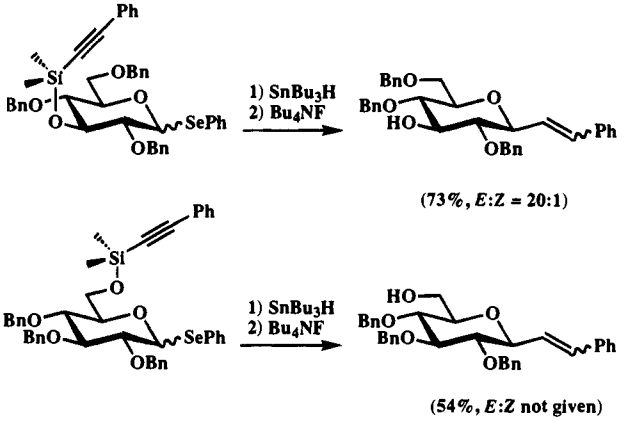



available lithiated alkyne **80** was treated with $Me_2SiCl_2$ followed by evaporation of the excess dichlorsilane, and silylation to give silyl ether **81**. A four-step cylization, desilylation, hydrogenation, and acetylation sequence gave the heptaacetate **82** in good overall yield.

### *2. 6-Exo and Larger Ring Formations*

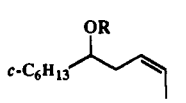
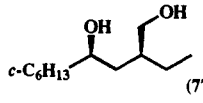
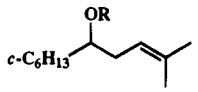
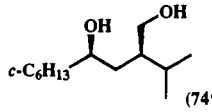
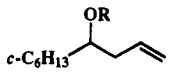
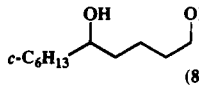
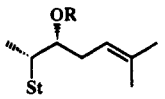
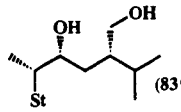
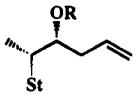
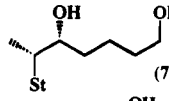
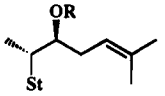
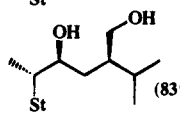
In connection with the *C*-glycoside construction reported by Stork,[52] intramolecular radical cyclizations with a silicon connector on either the 3- or 6-hydroxyl group of the phenylselenoglucosides (Scheme 30) gave good yields of the corresponding

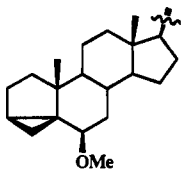
**Scheme 30**




β-*C*-glucosides, exclusively. These reactions are remarkably efficient considering that they are 6-*exo*- and 7-*exo*-*dig*-ring closures. In addition, for cyclization to occur in both cases, a change from the normal $^4C_1$ chair conformation of the pyranose ring must

**Table 10. Synthesis of 1,4- and 1,5-Diols[54]**

| Entry | Substrate (R = $BrCH_2SiMe_2$) | Product (yield) |
|---|---|---|
| 1 |  |  (77%) |
| 2 |  |  (74%) |
| 3 |  |  (80%) |
| 4 |  |  (83%) |
| 5 |  |  (76%) |
| 6 |  |  (83%) |

St = 

occur placing the hydroxyl or hydroxymethyl group in an axial orientation. Good results were also obtained in the furanose series with the silicon tether connected to either the 3- or 5-hydroxyl group.

As with the hydroxymethylation studies of acyclic allylic alcohols (see section II.B.1.a), a similar study with homoallylic alcohols was done by Koreeda,[54] as shown in Table 10. Interestingly and in contrast with allylic alcohols, complete regio- and stereoselective cyclizations were achieved when the corresponding α-bromomethylsilylated alcohols were treated under conditions with a catalytic amount of tributyltin hydride and an excess of $NaB(CN)H_3$. The 6-*exo*-cyclization mode prevails with mono- or disubstituted methyl alkenes producing solely the *cis*-6-membered cyclic siloxanes in 89–98% yields (entries 1, 2, 4, and 6). Subsequent oxidation led to branched-chain 1,4-diols, hence represents an overall *syn*-selective hydroxymethylation of chiral homoallylic alcohols. On the other hand, with terminal olefins, 7-*endo*-ring closure dominates which upon oxidation affords 1,5-diols as the only products (entries 3 and 5). A 6-membered transition state with a pseudoequatorially oriented olefin would explain the *syn*-selectivity observed in the 6-*exo*-cyclizations (Figure 6). However, with the regioselectivity noted for the unsubstituted olefin, this suggests that the corresponding 7-membered transition state is the favored pathway and that steric factors impede this cyclization with a terminally disubstituted olefin.

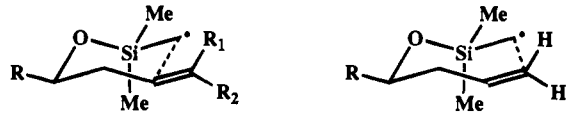
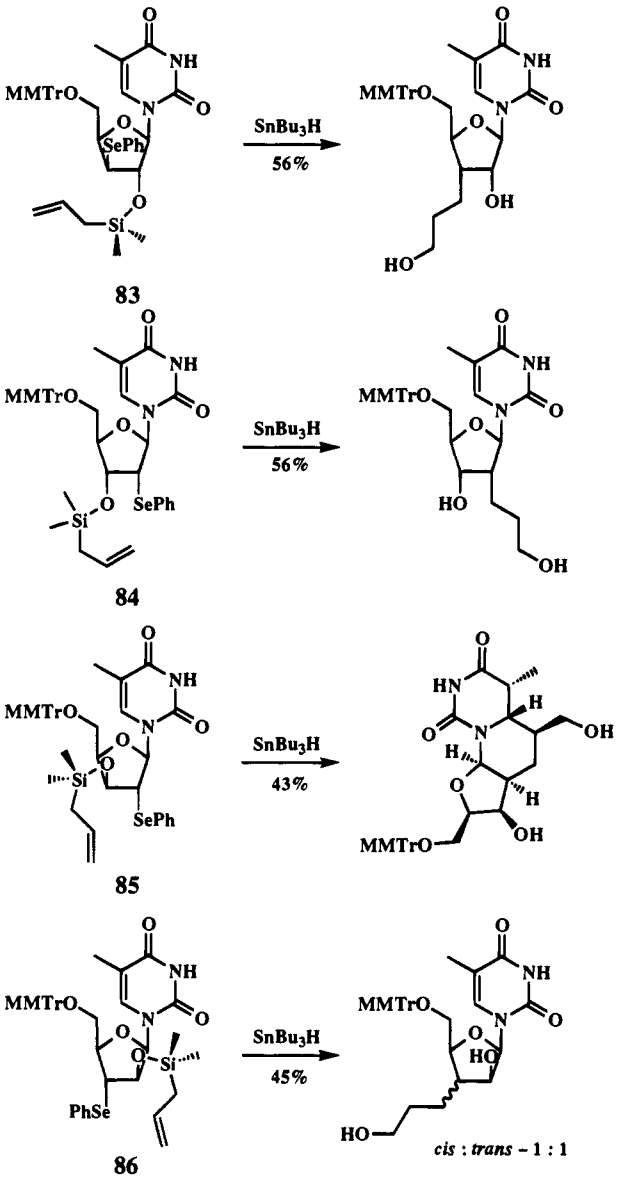


**Figure 6.**

Exclusive 7-*endo*-*trig*-cyclization has been reported as well for the stereocontrolled synthesis of *C*-branched nucleosides (Scheme 31).[55] In the latter

**Scheme 31**

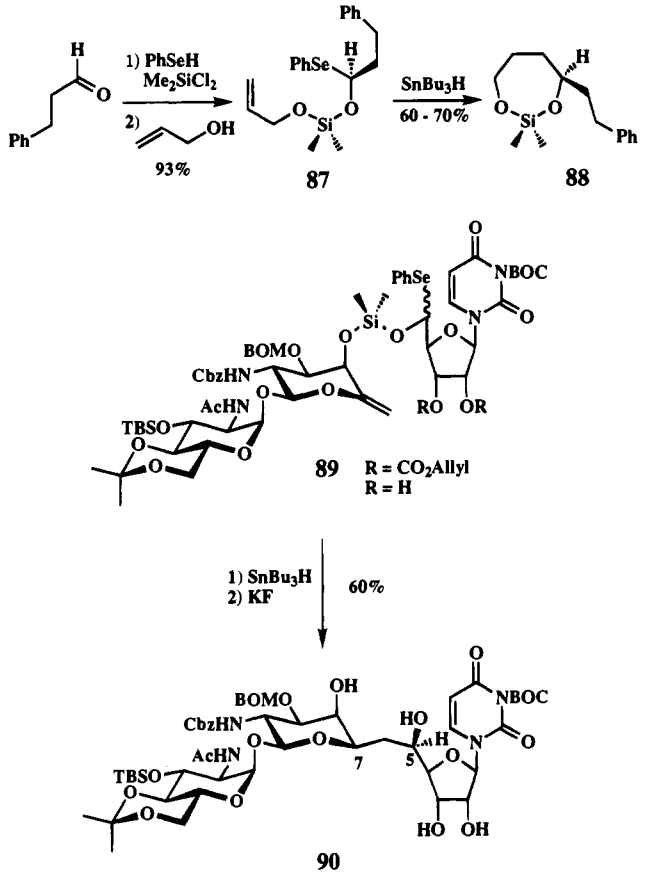



examples, the silicon connector bears an allyl group and represents a radical acceptor rather than donor as in the above examples of *C*-glycoside constructions. Several studies were carried out (compounds **83**–**86**) whereby radical formation and cyclization occurs on the vicinal carbon center to that of the tethered hydroxyl group. With an α-$C_{(2)}$ or α-$C_{(3)}$-hydroxyl group, **83** and **84**, regio- and stereoselective cyclization with formation of the *cis*-fused 7-membered cyclic siloxanes was observed, which, after Tamao oxidation, afforded the corresponding $C_{(2)}$- or $C_{(3)}$-propanol-branched nucleosides. Products from 6-*exo*-ring formation or direct reduction were not detected.

Similarly, with a $\beta$-$C_{(3)}$ hydroxyl group as in **85**, 7-*endo-cis*-ring closure was also the favored pathway, however, in the latter case subsequent cyclization with the $C_{(5')}$–$C_{(6')}$ thymine double bond led to an interesting tricyclic product after oxidation in a good overall yield. In contrast, using **88** with a $\beta$-$C_{(2)}$ hydroxyl group furnished an equal mixture of *cis*- and *trans*-products although both were a result of cyclization to the terminal olefinic carbon. The nondiastereofacially selective reaction of the radical intermediate may be due to the steric encumbrance provided by the $C_{(4)}$-hydroxymethyl group.

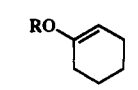
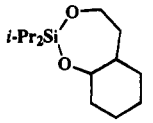
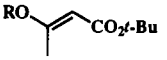
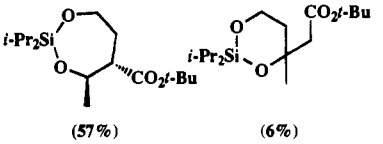
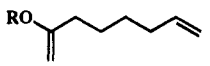
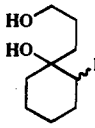
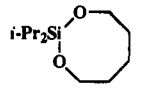
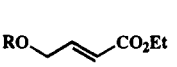
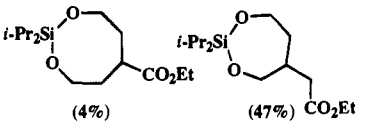
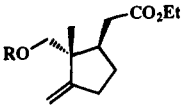
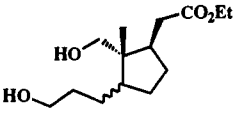
An elegant application of the 7-*endo-trig*-cyclization mode in silicon-tethered reactions was done by Myers and collaborators in their highly convergent synthesis of the glucosyl transferase inhibitor, tunicamycin V.[56-58] The silicon tether plays an essential role allowing efficient coupling of two well-functionalized subunits in the final stage of the synthesis. Initial experiments had shown that the *O*-(allyloxy)silyl hemiselenoacetal **87** cyclizes well on slow addition of tributyltin hydride to form the 7-membered cyclic siloxane **88** in 60–70% yield (Scheme 32). Compound

**Scheme 32**




**87** in turn was prepared in good yields by trapping the hemiacetal of hydrocinnamaldehyde and selenophenol with excess dimethyldichlorosilane followed by removal of the excess dichlorosilane and treatment with allyl alcohol. In a similar manner, the silaketal **89** was obtained as a mixture of $C_{(5)}$-epimers. Free radical cyclization of the corresponding diol gave, after hydrolysis, a 7.5:1 mixture of $C_{(5)}$-diastereomers in a good overall yield (60%), with the major one

**Table 11. Radical Cyclizations with Silaketal Linkers[59]**

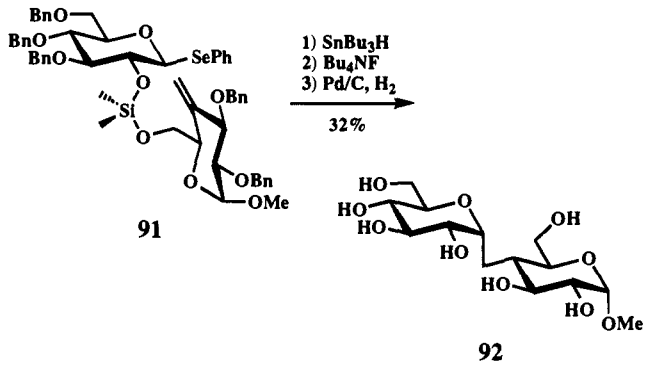
| Entry | Substrate (R = $BrCH_2CH_2OSi$*i*-$Pr_2$) | Products (yield) |
|---|---|---|
| 1 |  |  (50%, *trans*/*cis* 2/1) |
| 2 |  |  (57%) (6%) |
| 3 |  |  (46%, 2:1 mixture) |
| 4 |  |  (59%) |
| 5 |  |  (4%) (47%) |
| 6 |  |  (22%) |

having the desired configuration. The crucial role of the unprotected diol system in achieving this high stereocontrol at $C_{(5)}$ was demonstrated by the radical cyclization of the bis-TBS ethers **89** (R = TBS) which resulted in the predominant formation of the undesired stereoisomer. The selectivity of the cyclization at $C_{(7)}$ of **89** may be attributed to the formation of a $C_{(7)}$-axially oriented carbon radical intermediate which is stabilized by the anomeric effect of the ring oxygen in combination with the $C_{(8)}$-axial silyloxy substituent.[36,37]

The use of silyl acetals has also been demonstrated by Hutchinson *et al.* as a practical method for intramolecular cyclizations.[59] The advantage of this method, which was also shown in the tunicamycin synthesis, is that the protected diol may be easily liberated after cyclization under the mild desilylation conditions normally used. The cyclic precursors were prepared from diisopropyldichlorosilane by treatment with 2-bromoethanol and an unsaturated alcohol or suitable ketone; the diisopropylsilyl linker was chosen in this case because of its greater hydrolytic stability. Examples of cyclizations are shown in Table 11. 7-*Endo* cyclizations predominated with silyl enol ethers (entries 1–3). Cyclization with the additional olefin was noted for entry 3. Even the corresponding 8-*endo*-ring closure proved expedient (entry 4), although with a carbethoxy substituent on the terminal olefin (entry 5), reversed regioselectivity

was observed leading to a majority of the 7-membered ring isomer. Cyclization did not occur and led only to reduced products with terminal alkyl substitution of the silyl allylic ethers. Entry 6 is a good example of 9-*endo*-*trig* radical ring closure albeit in low yield. This type of transformation was exploited by Sinaÿ and co-workers to achieve a simple but elegant synthesis of a *C*-disaccharide (Scheme 33).[60] Sila-

**Scheme 33**



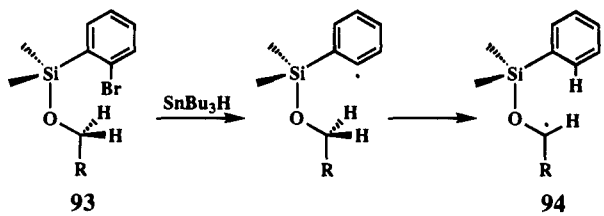

91 92

ketal **91** was prepared from the readily available monosaccharide subunits with dimethyldichlorosilane. Slow addition of tributyltin hydride to **91** and subsequent desilylation led to a surprisingly good yield (40%) of the α-*C*-disaccharide as a single diastereomer. Removal of the protecting groups then furnished the *C*-glycoside analog of α-methyl maltoside **92**. The choice of the silicon linking hydroxyl groups was critical for the stereochemical outcome of the radical cyclization. This was demonstrated by the connection of the radical acceptor to the $C_{(3)}$-hydroxy group which led to a nonselective 8-*endo*-cyclization affording a mixture of 1,4-linked *C*-disaccharides. Recently, a similar approach for the preparation of **92** employing samarium diiodide was presented by the same group.[61]

### 3. Others

Although intramolecular hydrogen transfer reactions have been known for some time, it is only recently that these reactions have been employed intentionally for the generation of carbon-based radicals otherwise difficult to prepare by conventional methods. Particularly noteworthy is the use of a silicon tether to carry out such reactions as demonstrated by Curran and co-workers.[62-64] The principle of this approach is shown in Scheme 34 where

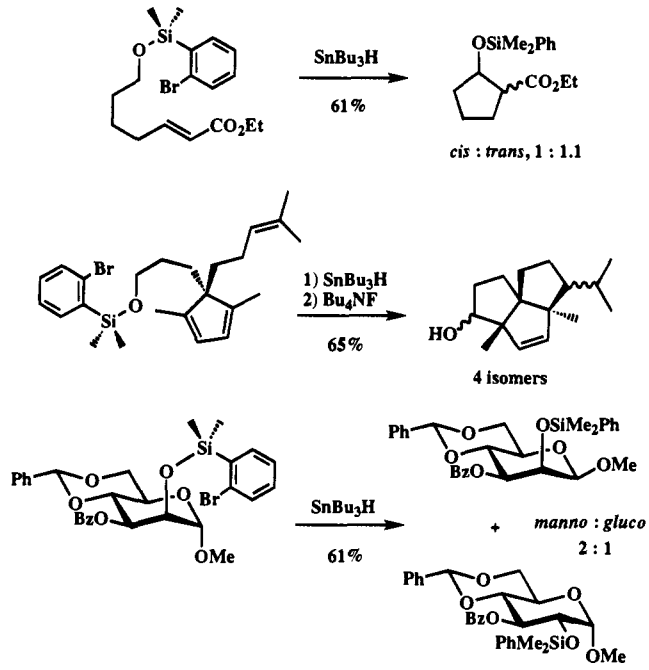
**Scheme 34**




93 94

tributyltin hydride reduction of the aryl bromide **93** affords a reactive phenyl radical which is translocated by an intramolecular 1,5-hydrogen transfer. The newly formed alkoxy radical **94** is now ready to undergo the radical reaction required. The special advantage of this approach is that the silicon connector also represents a hydroxy-protecting group before and after the reactions are performed. Two examples of this method are shown in Scheme 35

**Scheme 35**




where a radical cyclization step is achieved after the hydrogen transfer. An interesting application of the preparation of β-mannosides is shown in the last example of Scheme 35. 1,6-Hydrogen transfer led to the formation of an anomeric radical which is energetically more favorable as its α-anomer. This resulted in a change of the configuration at $C_{(1)}$. 1,5-Hydrogen transfer is a major competing pathway giving, however, a $C_{(2)}$-radical and subsequently affording a methyl glucoside derivative.

## III. Reactions in Which Silicon Bonds Are Broken or Formed

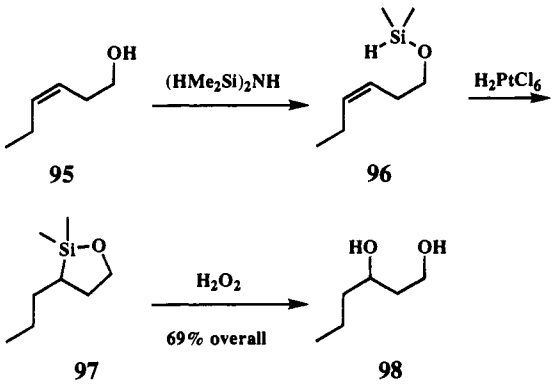
## A. Silicon Addition to Double Bonds

### 1. Addition to C=C Bonds

*a. Hydrosilylation.* Hydrosilylation of carbon–carbon double bonds constitutes the first of a useful two-step procedure for the hydration of olefins, with the second being the oxidation of the resulting carbon–silicon bond.[4,65] The intermolecular version of this reaction is limited, however, due to low reactivity of the initial hydrosilylation step. On the contrary, the intramolecular reaction has been found to be widely applicable because regio- and stereoselective hydration of the double bonds is possible.

The first intramolecular hydrosilylation was carried out by Tamao *et al.*[65] In this pioneering work, alkenol **95** was silylated with 1,3-dihydrotetramethyldisilazane to a hydridosilyl ether **96**, that upon treatment with chloroplatinic acid (Speier's catalyst) cyclized readily to give the siloxane **97** (Scheme 36). Oxidation with hydrogen peroxide subsequently afforded the 1,3-diol **98** in an overall yield of 69% for

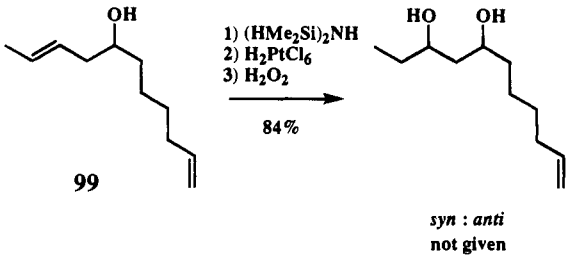
**Scheme 36**




the conversion of **95** to **98**. It should be noted that intermolecular hydrosilylation of the double bond in **95** was not possible.

This reaction, studied with a number of allylic and homoallylic alcohols, showed that silicon addition occurred preferably, resulting in an *exo*-ring closure, especially in the case of homoallylic alcohols. An exception was noted for substituted terminal olefins where an *endo*-ring closure was observed. The power of the intramolecular compared to intermolecular reaction was demonstrated by the regioselective hydroxylation of the more substituted double bond in **99** (84% overall yield) (Scheme 37).[66] The cyclic

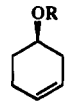
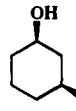
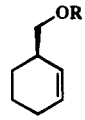
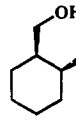
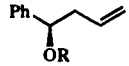
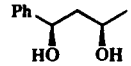
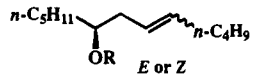
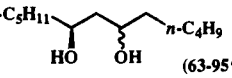
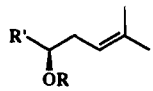
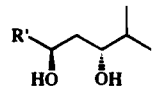
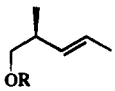
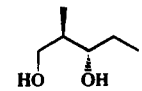
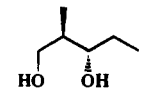
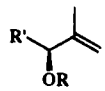
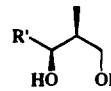
**Scheme 37**




siloxane products of the reactions could be readily converted to unprotected or monoprotected 1,3-diols by oxidation.

In another study, Tamao and Ito reported that intramolecular hydrosilylation of allylic and homoallylic alcohols displayed varying degrees of stereocontrol as indicated in Table 12.[67] The following conclusions were drawn from this investigation: (1) Cyclic homoallylic alcohols led to *cis*-1,3-diols, exclusively (entries 1 and 2). (2) *Syn*-selectivity was achieved with terminal olefins, whereas *anti*-selectivity predominated for trisubstituted olefins (entries 3 and 5–7). On the other hand, as indicated with entry 4, *E*- and *Z*-disubstituted olefins showed no diastereoselection. (3) The *syn*-stereoisomers were the favored products of the homoallylic alcohols in entries 8 and 9 displaying 1,2-stereocontrol. The *Z*-isomer showed much higher stereoselectivity than did the *E*-isomer, probably due to the 1,3-allylic strain effect.[25] (4) 1,2-Stereoselectivity with the *syn*-isomer dominating was achieved with the allylic alcohols in entries 10–13. Selectivity increased with an increasingly large allylic substituent. The protodesilylation of the intermediate 5-membered siloxanes formed in these last examples was studied in relation to the synthesis of rapamycin.[68]

**Table 12. Stereoselective 1,3-Diol Synthesis via Intramolecular Hydrosilylation of Allylic and Homoallylic Alcohols[67]**

| Entry | Substrate (R = $SiMe_2H$) | Products (yield, selectivity) Major isomer shown |
|---|---|---|
| 1 |  |  (73%, >100 : 1) |
| 2 |  |  (52%, >100 : 1) |
| 3 |  |  (71%, 5.7 : 1) |
| 4 |  *E* or *Z* |  (63-95%, ~1 : 1) |
| |  |  |
| 5 | R' = *n*-$C_5H_{11}$ | (72%, 5.3 : 1) |
| 6 | R' = *i*-Pr | (33%, 3.5 : 1) |
| 7 | R' = Ph | (53%, 3.3 : 1) |
| 8 |  |  (40%, 1.6 : 1) |
| 9 |  |  (67%, 6.1 : 1) |
| |  |  |
| 10 | R' = *n*-Bu | (73%, 2.4 : 1) |
| 11 | R' = *i*-Pr | (33%, 24 : 1) |
| 12 | R' = *t*-Bu | (53%, >100 : 1) |
| 13 | R' = Ph | (53%, 6.7 : 1) |

The *syn*-selectivity of entries 10–13 is noteworthy in that the configurations obtained are opposite to those observed with hydroboration of similar systems (*anti*-selectivity).[69] The explanation for this is found in the employment of the staggered transition structure illustrated in Figure 7, where the bulky allylic group R′ is oriented in an *anti* position with respect to the face of attack of the metal hydride complex.

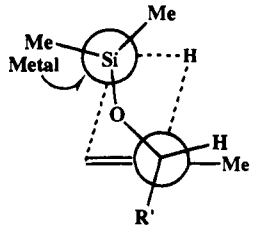
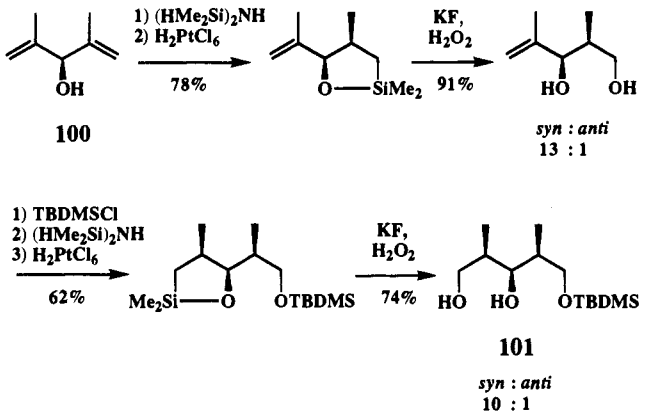



**Figure 7.**

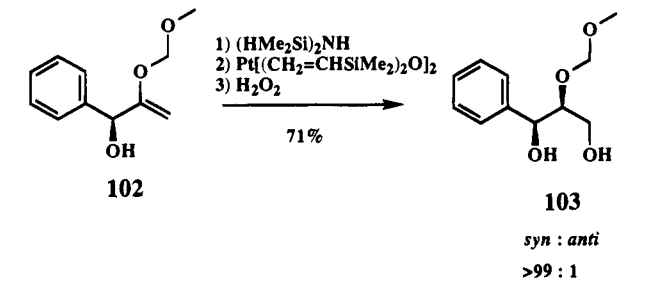
Scheme 38 shows an interesting application of this

**Scheme 38**




reaction to the stereoselective synthesis of the monoprotected triol **101** in a reiterative manner starting from the bis-allylic alcohol **100**.[67] Again, a high *syn*-selectivity was observed in both hydrosilylation reactions. The hydrosilylation and oxidation sequence gave in a similar way impressive results using enol ethers.[70] For instance, an α-hydroxy enol ether **102** was dimethylsilylated with tetramethyldisilazane to give the corresponding silyl ether upon treatment with platinum(0)/divinyltetramethyldisiloxane, and subsequent oxidation gave the diol **103** in an overall yield of 71% for the three steps (Scheme 39). The

**Scheme 39**

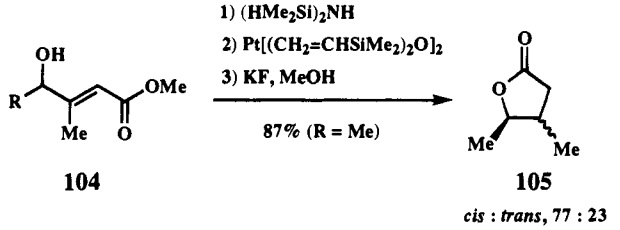



selectivity in this reaction was more than 99:1 in favor of the *syn*-isomer. This reaction was applied successfully to different α-hydroxy enol ethers of the same general type as **102** giving similar high stereoselectivity. Hydrosilylation of α-hydroxy enol ethers has been studied and used in synthetic work of obtusenyne.[71,72]

A study of intramolecular hydrosilylation of δ-hydroxy-α,β-unsaturated ethers has also been carried out.[73] Esters of the **104** type were subjected to silylation with 1,3-dihydrotetramethyldisilazane, hydrosilation catalyzed by platinum(0)/vinyldimethylsiloxane and protodesilylation with KF/MeOH to give the lactone **105** with modest stereoselectivity (Scheme 40). The yield was 87% for R = Me but 15% of unreacted **104** was also recovered. By increasing the size of R, *cis*-selectivity was enhanced, but the yield decreased while the amount of recovered starting material increased. Substituting the silicon methyl groups with other bulkier groups did not lead to any improvements.

Intramolecular hydrosilation of acetylenes is possible as well. Hydrodimethylsilyl ethers of homopro-

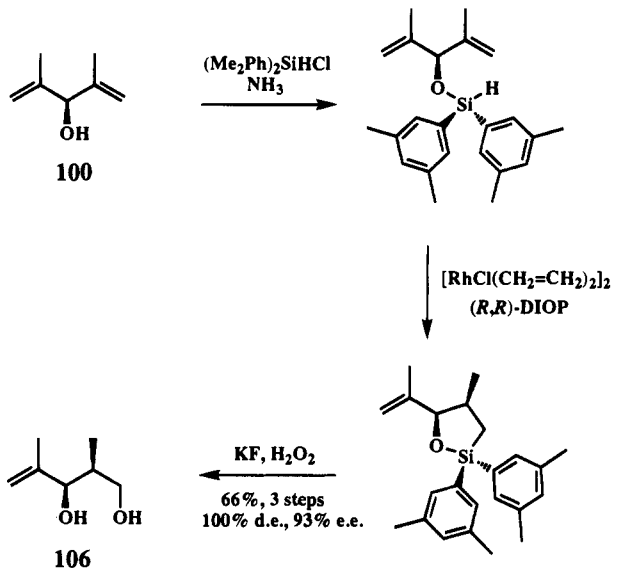
**Scheme 40**




pargylic alcohols gave *exo*-addition generating vinylsilanes.[74] Oxidative cleavage of the silicon-carbon bond with hydrogen peroxide then afforded β-hydroxy ketones.

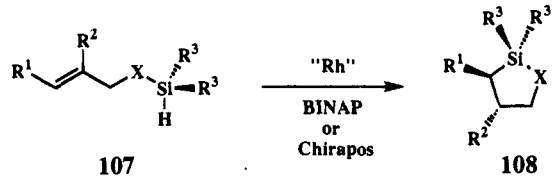
Catalytic asymmetric intramolecular hydrosilylation of di(2-propenyl)methanol (**100**) was studied under a number of different conditions. Silylation of **100** and treatment of the silane with a catalyst in the presence of either (*R,R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(*R,R*)-DIOP] or (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*R,R*)-BINAP] resulted in intramolecular hydrosilation with a very high diastereomeric and enantiomeric excess (Scheme 41). In the best example,

**Scheme 41**




complete diastereoselectivity and an ee of 93% was obtained using (*R,R*)-DIOP and 3,5-dimethylphenyl substituents on the silicon. The siloxane could be oxidized to the 1,3-diol **106** in a 66% overall yield in three steps. With other substituents on silicon, the reaction gave lower stereoselectivity but, in some cases, higher yields. Hydrosilylation could also be carried out on an enol ether equivalent to **100** with slightly lower enantioselectivity (70−78% ee) to afford 1,2,3-triols.[75] A systematic investigation of the factors involved in the intramolecular asymmetric hydrosilylation of **107** type substrates giving silane **108** has been carried out.[76,77] This reaction proceeded with excellent stereoselectivity and high yields when $R^1$ was an aryl group, X was oxygen, the chiral ligand was BINAP, and the silicon substituents $R^3$ were joined in a 5- or 6-membered ring (Scheme 42). On the other hand, the asymmetric induction was much lower when $R^1$ was methyl, or $R^1$ was hydrogen and

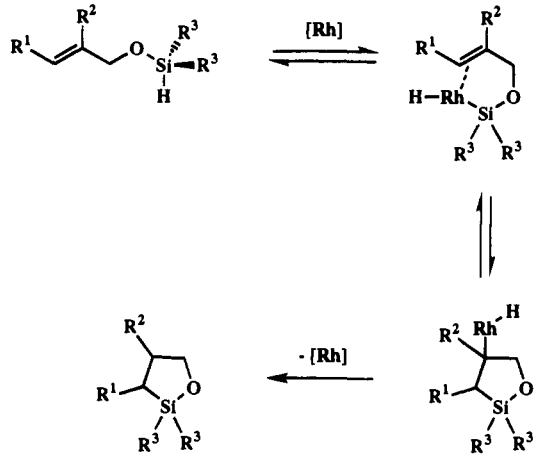
**Scheme 42**




107 108

$R^2$ methyl. The proposed reaction mechanism involves the formation of a rhodium–silicon bond, insertion of the olefin into this bond and reductive elimination of the rhodium, with the inserting of the olefin as probably the rate determining as well as the enantioselective steps (Scheme 43). Nitrogen may

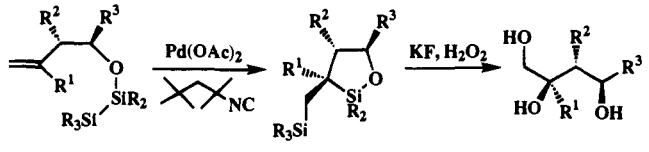
**Scheme 43**




also serve as the linking atom (Scheme 42, X = NH). Interestingly, with terminal olefins ($R^1$ = H) *endo*-silylation was obtained using a rhodium catalyst, whereas with a platinum catalyst, *exo*- or *endo*-silylation was noted.[78-80] So far, no rationale has been provided for this observation.

*b. Bissilylation.* Addition of disilanes to alkenes is normally not possible, but the intramolecular reaction is facile.[81,82] It provides a useful way of dihydroxylating alkenes since the bisilane product can be oxidized to a diol. Disilanyl ethers of type **109** (Scheme 44), readily prepared from the disilanyl

**Scheme 44**




109 110 111

chloride and the alkenyl alcohol, underwent efficient cyclization in the presence of a catalytic amount of palladium acetate and 1,1,3,3-tetramethylbutyl isocyanide to provide 1,2-bis-silane **110**, which on subsequent treatment with potassium fluoride and hydrogen peroxide gave the 1,2,4-triol **111**. The reaction worked well with various substituents on silicon, geminally disubstituted olefins ($R^1$ = Me) as well as with substituents at $R^2$ and $R^3$. In addition, bis-silylation proceeds with high diastereoselection when $R^2$ or $R^3 \neq$ H, affording preferably the siloxane with the *exo*-cyclic chain and $R^2$ in a *trans*-relationship and/or the *exo*-cyclic chain and $R^3$ in a *cis*-relationship (see examples in Table 13). This can be explained by a chairlike transition state where the $R^2$ and $R^3$ substituents prefer to occupy pseudoequatorial positions, hence leading to the observed stereochemistry (Figure 8).[82] Noteworthy are entries 8 and 10 of Table 13 where only one of the substituents could occupy an equatorial position. Neverthe-

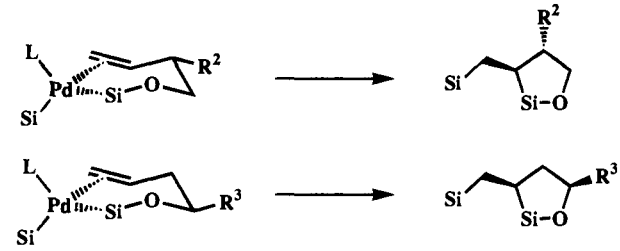
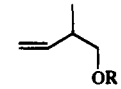
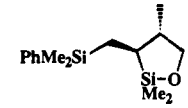
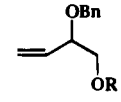
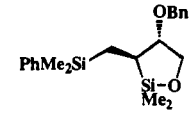
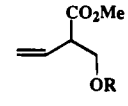
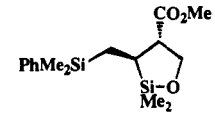
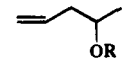
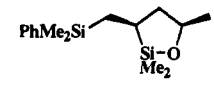
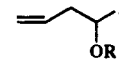
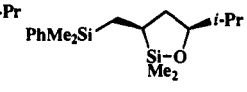
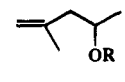
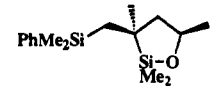
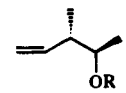
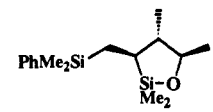
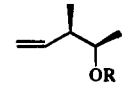
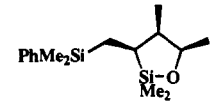
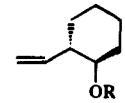
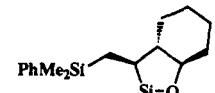
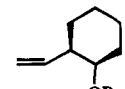
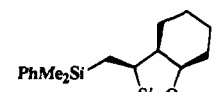


**Figure 8.**

**Table 13. Intramolecular Bis-Silylations of Alkenes[82]**

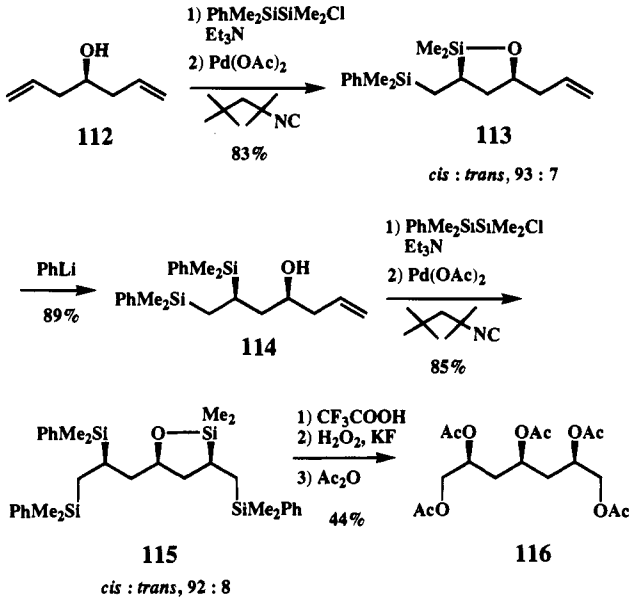
| Entry | Substrate (R = $PhMe_2SiMe_2Si$) | Products (yield, *cis* : *trans*) Major isomer shown | |
|---|---|---|---|
| 1 |  |  | (95%, 7 : 93) |
| 2 |  |  | (92%, 3 : 97) |
| 3 |  |  | (85%, 1 : >99) |
| 4 |  |  | (90%, 93 : 7) |
| 5 |  |  | (98%, 93 : 7) |
| 6 |  |  | (97%, 96 : 4) |
| 7 |  |  | (94%, 96 : 4) |
| 8 |  |  | (96%, 82 : 18) |
| 9 |  |  | (99%, 100 : 0) |
| 10 |  |  | (99%, 82 : 18) |

less, the $\beta$ substitutent to the carbon–carbon double bond governed the stereochemical outcome of the bis-silylation although selectivities were not as high as those of the other entries.

The reaction was also effective when the oxygen in the silyl ether was replaced by a $CH_2$ group or nitrogen.[82] Even good yields were obtained when the oxygen was omitted leaving a two-carbon tether between the disilane and the unsaturation to that a 4-membered ring was formed, although with reduced stereoselectivity.

An application of this approach by Tamao and Ito to the stereocontrolled construction of polyol systems is provided in Scheme 45.[82] Silylation of the prochiral

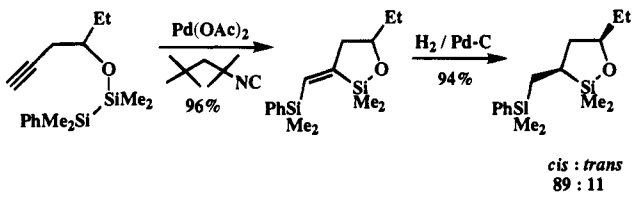
**Scheme 45**




dienol **112** and its subsequent Pd-catalyzed cyclization afforded **113** with *cis/trans*-selectivity of 93:7. Treatment with phenyl lithium then gave the ring-opened product **114** which could be subjected to another bis-silylation sequence giving **115**, again with high *cis/trans*-selectivity. Oxidation and acetylation afforded the pentaacetate **116.**

The reaction could also be applied to the alkynes exemplified in Scheme 46.[83] In these cases, the

**Scheme 46**

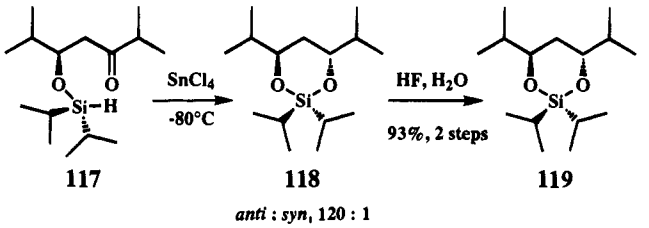



products were 1,2-*cis*-silicon-substituted alkenes, whereby *syn*-hydrogenation of the double bond and oxidative cleavage of the C–Si bonds gave 1,2,4-triols.

### 2. Addition to C=O Bonds

Intramolecular reduction of ketones employing a silicon tether can be performed with remarkable stereoselecitivity. Hydridosilyl ether **117** (Scheme 47), prepared in a 72% yield by silylation of the

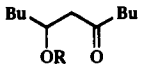
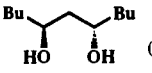
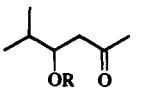
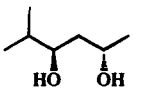
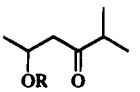
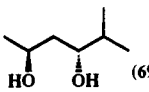
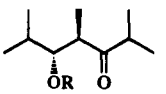
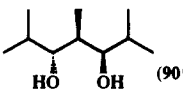
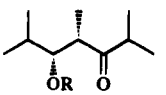
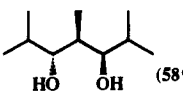
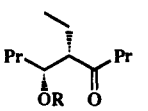
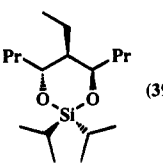
**Scheme 47**




**117** **118** **119**

*anti* : *syn*, 120 : 1

**Table 14. Intramolecular Hydrosilylation of b-Hydroxy Ketones[84–86]**

| Entry | Substrate (R = H(*i*-Pr)$_2$Si) | Products (yield, *anti* : *syn*) Major isomer shown |
|---|---|---|
| 1 |  |  (60%, 40 : 1) |
| 2 |  |  (67%, 50 : 1) |
| 3 |  |  (69%, 40 : 1) |
| 4 |  |  (90%, 250 : 1) |
| 5 |  |  (58%, 300 : 1) |
| 6 |  |  (39%, 97 : 1) |

corresponding $\beta$-hydroxy ketone with diisopropylsilyl chloride and base, could be cyclized in the presence of a catalytic amount of Lewis acids ($SnCl_4$, $MgBr_2$:$OEt_2$, $TiCl_4$, $BF_3$:$OEt_2$, $ZnBr_2$), Brønsted acids ($CF_3CO_2H$), catalytic nucleophiles ($Bu_4NF$), and transition metal complexes [$(Ph_3P)_3RhCl$] to give the silyl acetal **118** with a predominance for the *anti*-configuration. The best results in terms of yield and diastereoselectivity were obtained with $SnCl_4$ (*anti*:*syn*, 120:1). A number of other $\beta$-hydroxy ketones investigated were silylated and cyclized with diastereoselectivities of 40:1 or greater, all in favor of the *anti*-product (see Table 14).[84–86] The stereoselectivity was maintained when the isopropyl groups on silicon were replaced by methyl groups but the yields decreased as a result of the more labile silicon linkage. The stereoselectivity can be explained by a reduction taking place in a chairlike transition state with the terminal isopropyl groups of the $\beta$-hydroxy ketone occupying a pseudo-equatorial position (Figure 9). This orientation is preferable to the other possibility whereby steric interactions with one of the silicon substituents may occur. Further investigations revealed that stereoselectivity was maintained with methyl or ethyl groups $\alpha$ to the carboxyl group (Table 14, entries 4–6). Remarkable *anti*-selectivities were observed

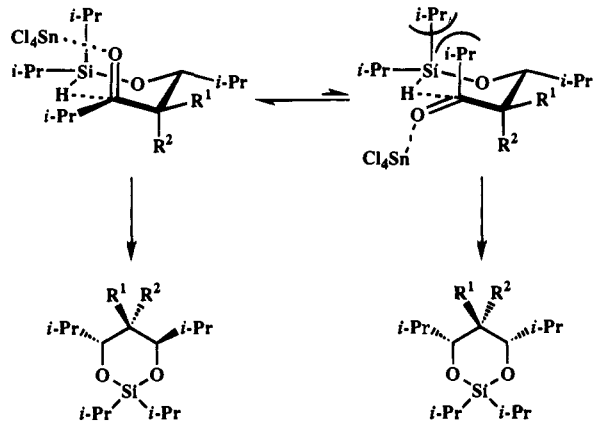


Figure 9.

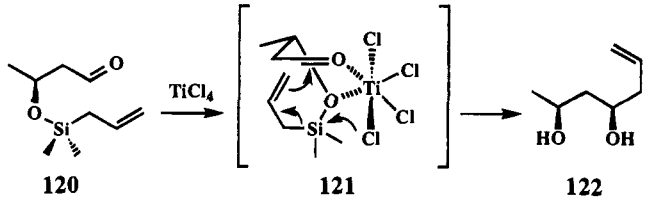
when $R^1$ or $R^2$ = Me (250:1 and 300:1, respectively), even higher than those obtained for the unsubstituted compounds ($R^1 = R^2 = H$). With $R^1$ = Et, the *anti:syn* ratio was 97:1, while it dropped to 5:1 when $R^2$ = Et. The lowering of the ratio is to be expected as the ethyl group, in the latter case, must occupy a pseudo-axial position in the transition state. All in all, the two-step silylation, reduction sequence represents an alternative to Evans' protocol for the preparation of *anti*-1,3-diols from β-hydroxy ketones, with the interesting exception that in the former method, both hydroxy groups are in their protected form after the reduction step. Recently, this approach was employed for the reduction of β-hydroxy esters.[88]

## B. Nucleophile Delivery

The inert and electropositive nature of silicon makes it an attractive atom for tethering nucleophiles with the aim of obtaining stereoselective reactions. This has been used particularly in the carbohydrate field.

An early example of a silicon-tethered nucleophilic addition with an allyl group was reported by Reetz.[89] The (β-allyldimethylsiloxy)butyraldehyde (**120**) reacted in the presence of $TiCl_4$ to give *syn*-diol **122** with greater than 20:1 diastereoselectivity (Scheme 48). It is notable that the corresponding intermolecular reaction between a β-benzyloxy aldehyde and an allylsilane does not proceed at all selectively. The remarkable diastereoselectivity is possibly a result of the chelation between the two oxygens and titanium in the transition state **121**. However only two examples of the reaction have been reported.

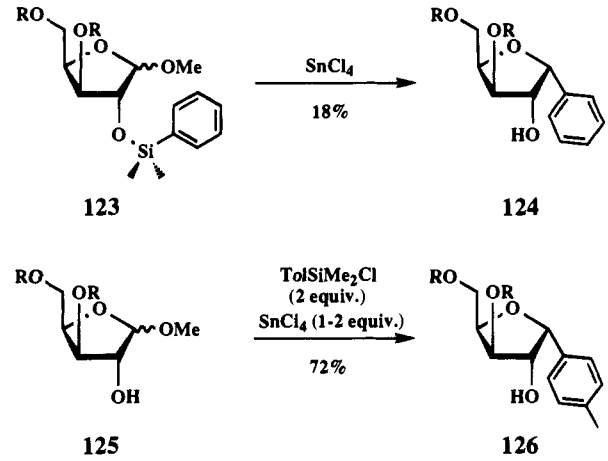
**Scheme 48**



*syn* : *anti*, >20 : 1
yield not given

The main use of silicon for nucleophile delivery has been the intramolecular reactions of 2-*O*-organosilyl glycosides. In initial studies, it was found that certain *C*-nucleophiles, for example aryl and vinyl groups, could be transferred stereoselectively to an electrophilic $C_{(1)}$ carbon of a furanose from a silicon tether at $C_{(2)}$.[90] Thus the 2-(phenyldimethylsilyl)-xylofuranoside **123** upon reaction with $SnCl_4$ gave the α-*C*-aryl glycoside **124** in 18% yield with 65% of the α-anomer **123** resulting from cleavage of the Si–O bond by $SnCl_4$ (Scheme 49). This bond breakage was

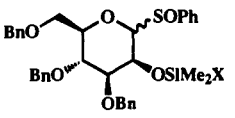
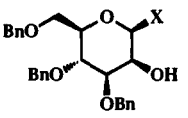
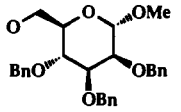
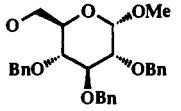
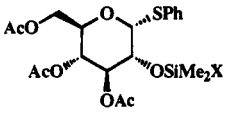
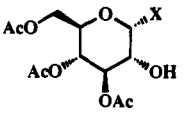
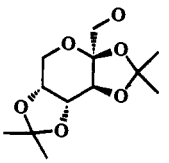
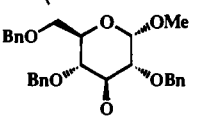
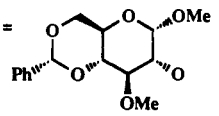
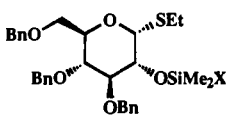
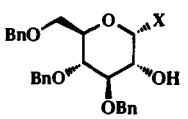
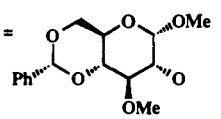
**Scheme 49**



expected to result in the formation of phenyldimethylsilyl chloride and be reversible. Therefore, a direct reaction between the untethered alcohol **125**, and a large excess of tolyldimethylsilyl chloride and $SnCl_4$ was attempted with the aim of running the silylation and aromatic substitution in one pot. This increased the yield to 72% of *C*-glycoside **126**. That the reaction was indeed intramolecular was demonstrated by the fact that the 2-*O*-methyl ether of **125** did not give any *C*-glycoside when reacted under identical conditions. No *C*-glycoside appeared in the reaction between **125** and (trimethylsilyl)benzene as well. This method was extended to *ribo*- and *arabino*-isomers and even allowed the transfer of a vinyl instead of the aryl group. The yields were, however, in all cases lower (30–50%), but the stereoselectivity at the anomeric center was maintained. On the other hand, an allyl group could not be transferred with control to the anomeric center.

The possibility of using a silicon tether for the stereocontrolled synthesis of 1,2-*cis*-*O*-glycosides has also been investigated by two groups. The nucleophile was the oxygen of an alcohol tethered to the $C_{(2)}$-hydroxy group of a saccharide by means of a silyl acetal. Stork and co-workers applied this approach to an elegant synthesis of β-mannosides which are normally difficult to obtain from an intermolecular glycosidation (Scheme 50).[91] Thiomannoside **127** was allowed to react with 3 equiv of the alkoxydimethylsilyl chloride of the alcohol to be glycosylated which gave dimethylsilyl acetals **128** in good yield. When this alcohol was another monosaccharide, the alkoxydimethylsilyl chloride was prepared by treatment with butyl lithium followed by excess dimethylsilyl dichloride. The silyl acetals **128** on treatment with *m*-chloroperoxybenzoic acid (MCPBA) followed by triflic anhydride and 2,6-di-*tert*-butylpyridine then gave stereoselectively the β-mannosides **129** in 61–

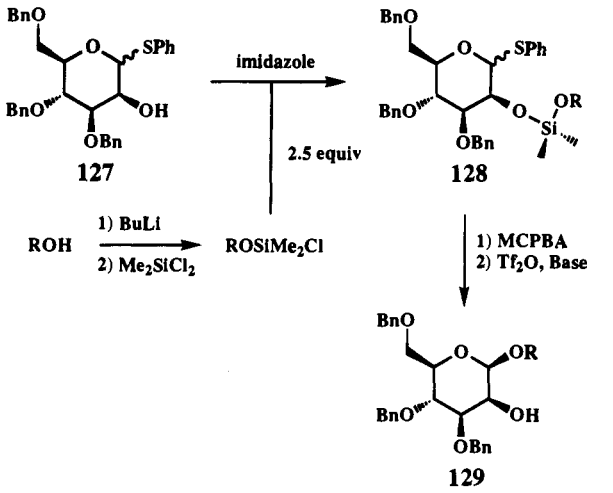
**Table 15. Stereoselective O-Glycoside Formation**

| Entry | Substrate | Product (yield) | Ref. |
|---|---|---|---|
| |  |  | |
| 1 | X = OMe | not given | 91 |
| 2 | = $OCHMe_2$ | not given | 91 |
| 3 | =  | 68% | 91 |
| 4 | =  | 61/73% | 91 |
| |  |  | |
| 5 | X = $O(CH_2)_7Me$ | 59% | 93 |
| 6 | = $OC_6H_{11}$ | 62% | 93 |
| 7 | = $OCMe_3$ | 61% | 93 |
| 8 | = OPh | 72% | 93 |
| 9 | =  | 85% | 95 |
| 10 | =  | 74% | 95 |
| 11 | =  | 39% | 95 |
| |  |  | |
| 12 | X =  | 67% | 95 |

73% yield. None of the α-mannosides were detected. Several examples are shown in Table 15 (entries 1–4).

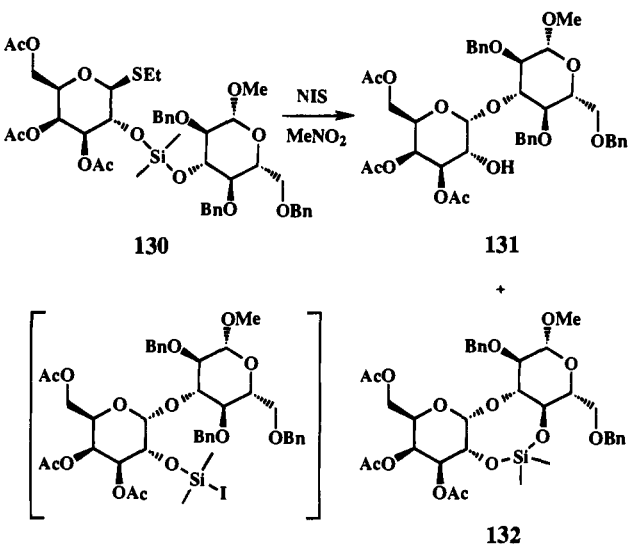
In a similar approach, a stereocontrolled synthesis of α-glucosides and α-galactosides was carried out by Bols.[92-95] Phenylthio 3,4,6-tri-*O*-acetylglucopyranoside was allowed to react with chlorodimethylsilyl ethers of primary, secondary, and tertiary aliphatic alcohols and phenol in the presence of pyridine to

**Scheme 50**




form the silyl acetal thioglycosides in good yield. The reaction of these with *N*-iodosuccinimide (NIS) and catalytic triflic acid gave exclusively α-glucosides in 59–72% yield (Table 15, entries 5–8). The reaction was shown to be intramolecular because the corresponding intermolecular version afforded a mixture of stereoisomers. Furthermore, a silicon-tethered tertiary alcohol was glycosylated preferentially over a nontethered primary alcohol.[93] This method was also extended to a disaccharide synthesis exemplified in entries 9–12 of Table 15. These glycosylations were performed with NIS in refluxing nitromethane, as the use of NIS/triflic acid only led to low yields of the desired disaccharide.[95] A modest yield was noted for entry 11, which could be increased substantially using the more reactive ethyl thioglucoside (entry 12). In the case of an α-galactosylation, an interesting side reaction was observed as shown in Scheme 51. When silyl acetal **130** was allowed to react with NIS in nitromethane, only 31% of the expected disaccharide **131** was formed. The major product (46%) was found to be silyl acetal **132**, in which the benzyl ether group at $C_{(4)}$ had been selectively cleaved. This can be explained by taking into consideration a silyl iodide intermediate (Scheme 51) in which the orientation around the newly formed glycosidic linkage is such

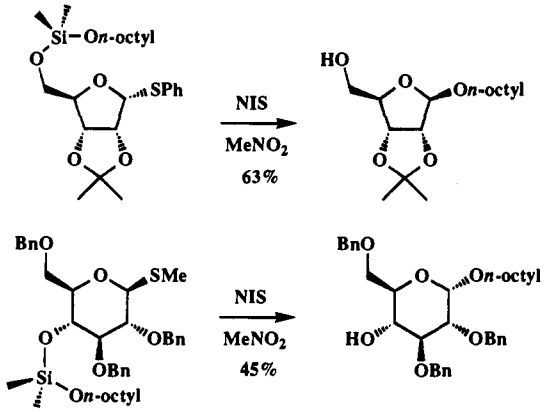
**Scheme 51**



that an interaction between the $C_{(4)}$-benzyl ether and the silyl iodide groups can occur. It is nevertheless surprising that a similar side product was not observed with the *gluco*-derivative of entry 10 in Table 15.

In an attempt to broaden the scope of this approach, Bols and Hansen investigated intramolecular glycosylation reactions involving bridged ring intermediates.[96] They found that such reactions are generally less favorable than the nonbridged ones, with nevertheless surprisingly high selectivities in some cases (Scheme 52).

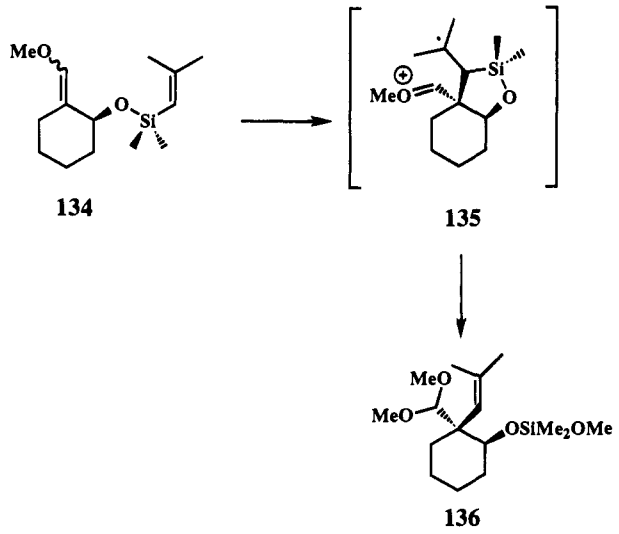
**Scheme 52**




## C. Miscellaneous

A silicon-tethered electrochemical reaction was employed to form quaternary carbon centers stereoselectively. Vinylsilyl ether **134** was oxidized at the vitreous carbon anode in 0.4 N $LiClO_4$ in MeOH/THF giving 72% of **136** as the sole product, with **135** being the proposed intermediate (Scheme 53).[97]

**Scheme 53**




## IV. Summary and Outlook

In this review we have seen the application of a great variety of silicon-tethered reactions beginning with their first appearance in the early 1980s. Quite characteristic of such reactions is the increased reactivity of the tethered partners in comparison to their untethered counterparts, mainly due to reduced entropic factors. In addition, high regioselectivity, often with complete control, is generally imposed by the silicon linker. In fact one group has even made the comparison of a silicon-tethered reaction with an enzymatic reaction.[60] The silicon tether brings together the two reagents (active site binding), a chemical reaction occurs, aided perhaps by an external factor (coenzyme), and finally the products are released upon removal of the transient tether.

So far four main types of silicon-tethered reactions have been examined. Cycloadditions, of which the majority are Diels–Alder, have been studied extensively, usually displaying high regioselectivity although stereoselection appears to vary with the silicon tether length. An important aspect of this approach is that certain reactions may be carried out which are either difficult or impossible to perform in the intermolecular version, e.g. ethylene as a dienophile. Silicon-tethered cycloadditions need not be confined to only Diels–Alder reactions but could be applied to all types, although only a few examples exist to date. Certainly a more indepth study of this approach should be explored even in the area of asymmetric synthesis using, for example, chiral ligands on silicon to induce asymmetry in the cycloaddition products.

In radical reactions, the use of (α-bromomethyl)-dimethylsilyl ethers for the hydroxy methylation of allylic alcohols is now accepted as a standard transformation in organic synthesis. This is primarily due to the ease in which these reactions can be carried out as well as the high yields obtained. Interesting applications in the synthesis of natural products or corresponding mimics have only recently been made using other radical cyclizations.

So far hydrosilylation or bis-silylation studies have been mainly done by one research group but with impressive results, particularly in the stereoselection achieved. The newly created carbon–silicon bonds upon hydrosilylation represent masked but inert carbinol functionalities which may be transformed to the latter during the final stages of a synthesis. This becomes an interesting alternative to polyol systems compared to certain previous syntheses employing hydroxy-protecting group strategies.

The use of silicon-tethered reactions in nucleophile delivery is a relatively new synthetic approach which has already demonstrated some important applications to previously existing synthetic problems, particularly the stereospecific 1,2-*cis*-*O*-glycoside formation. This method complements the 1,2-*trans*-glycosylation methodology.

Although we feel that most silicon-tethered reactions are still in their infancy, we hope this review will stimulate others to apply this strategy to concrete problems in organic synthesis. Until now the reactions in which this method was used represent only a fraction of the ensemble of organic synthetic transformations available today, making this approach to other applications a vast open field to explore.

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