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# Silanediol Protease Inhibitors: From Conception to Validation

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*Dedicated to Iwao Ojima on the occasion of his 60th birthday*

**Keywords:** Drug design / Hydrolases / Inhibitors / Peptidomimetics / Proteases / Silanes / Silicon

Silanediols are isosteric with the unstable hydrated carbonyl group, but are most commonly associated with polymerization to give silicone polymers. Placement of a silanediol in a dipeptide analogue yields a new kind of nonhydrolyzable transition-state-analogue protease inhibitor. Both metallo and aspartic protease inhibitors have been prepared using silanediols, with enzyme inhibition in the low nanomolar range. Structure–activity comparisons with known inhibitors, efficacy in whole cell assays, and a crystal structure of a silanediol inhibitor bound to the thermolysin active site establish these silanediol inhibitors as effective and predictable new protease inhibitor tools. Recent chemistry developments have led to efficient and streamlined preparation of these inhibitors.


## Introduction

Silicon, as the element most similar to carbon, has long stimulated speculation about biologically active derivatives, including silicon-based life forms, a possibility still under discussion today.[1] Beyond the speculation, much effort has been directed at this area of discovery. Indeed, the first review of biologically active organosilanes appeared nearly forty years ago.[2] The fact that all organosilanes are anthropogenic (although there may be exceptions[3]), serves to enhance the intrigue surrounding the development of silanes with biological activity.

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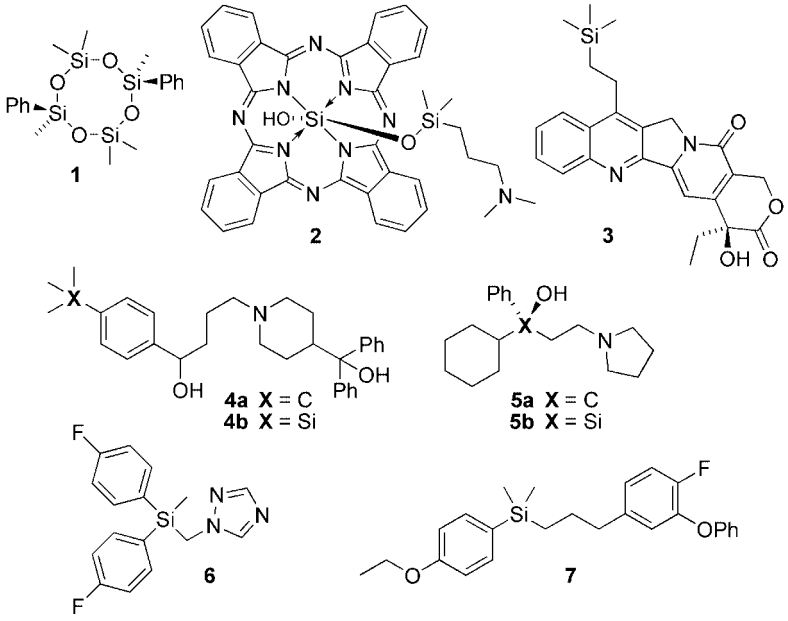
**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

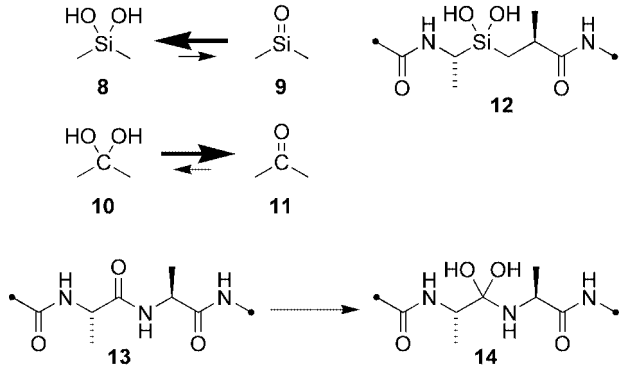
  




Scheme 1. A selection of biologically active organosilanes.

The search for bioactive organosilanes has been pursued in two fundamentally different ways, random screening and molecular design, Scheme 1.[4–8] The former can uncover unprecedented structures such as the siloxane cisobitan (**1**), with its estrogen-like properties,[9] or the photodynamic agent Pc4 (**2**), a cancer treatment currently in clinical trials.[10] Random screening, however, relies completely on chance for lead generation. Alternatively, the design of bioactive organosilanes can be an intellectual exercise in which a silicon atom is strategically introduced to modify an organic compound of known biological activity or one that plays a role in a biological process.[8] Karenitecin[11] (**3**) is a derivative of the natural product camphothecin, carrying a lipophilic trimethylsilylethyl group on the pyridine ring.[12] Promising phase II clinical trials of this silane have recently been completed.[13] A "silicon-for-carbon switch" strategy has also seen many successes. An example of this approach is the conversion of the histamine antagonist terfenadine (**4a**) to sila-terfenadine (**4b**), yielding an effective and novel drug candidate.[14] Similarly, replacing the carbinol of the muscarinic receptor agonist **5a** with a silanol gave **5b** with superior agonist properties.[15] Currently the two organosilanes produced industrially for their biological activity are the antifungal flusilazole (**6**)[16] and the pyrethroid insecticide silafluofen (**7**),[17] both agricultural chemicals and examples of the "silicon-for-carbon switch" approach.

Most commonly, the bioactive organosilane design strategy involves replacement of a quaternary carbon with silicon, e.g., **4**, **6** and **7**, resulting in a subtle modification of the sterics and electronics at that position. A less traveled approach is the replacement of an *unstable* carbon, such as a reactive intermediate or a transition-state structure, with a stable silicon mimic. This strategy takes advantage of inverted chemical stabilities between carbon and silicon structures. One example is the geminal silicon diol **8**, Scheme 2, that only undergoes dehydration under forcing conditions,[18,19] with formation of a silanone **9** (originally called a silicone[20]), whereas the geminal carbon diol **10** is unstable and readily undergoes dehydration to the more stable acetone (**11**). A silanediol **8** therefore has the potential to act as a stable mimic of the unstable hydrated carbonyl **10** (while potentially suffering from another stability issue, see below).




Scheme 2. Comparative stabilities of geminal diols and the first step in peptide hydrolysis.

As a stable hydrate, the silanediol could replace an ester or amide carbonyl that is a substrate for a protease or other hydrolyase enzyme. The hydrated amide carbonyl **14** is the key intermediate on the path to amide hydrolysis, promoted and stabilized by protease enzymes. Proteases are categorized by their catalytic machinery. Aspartic proteases catalyze the addition of water to an amide carbonyl group using the hydrogen bonding of two aspartic acid residues, while metalloproteases catalyze this addition with an active site zinc ion, leading to **14**. The remaining three protease classes, serine, threoine or cysteine, employ an amino acid

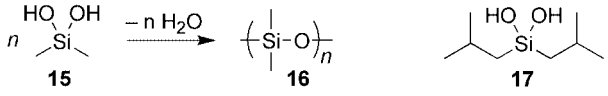
  

side chain alcohol or thiol as the nucleophile, in place of water.

Tight binding of a nonhydrolyzable analogue of **14**, such as **12**, to a protease active site would result in an effective enzyme inhibitor. Protease inhibition is an important drug-design path, applicable to a broad array of diseases.[21–24] We describe here our efforts to demonstrate the silanediol protease inhibitor concept, and then make it a practical method.

## Silanediols and Their Properties

Silanediols were first reported by Dilthey and Eduardoff in 1904[25] and by Kipping in 1909,[26] and nearly 150 structures can now be found in the literature.[27] Massive quantities of the simplest example, dimethylsilanediol (**15**), are produced each year because of their instability toward self-condensation, forming silicone polymers **16** (siloxanes) that have exceeding useful properties, Scheme 3.[28] It is this reaction and the broadly understood stability of the silicones **16** that dominate the concepts surrounding silanediol chemistry, and perceptions of silanol and silanediol instability have stymied the development of their chemistry. The recent report detailing the hydrolytic instability of the first amino acid siloxane by Tacke and Schmid,[29] may help to change these perceptions.

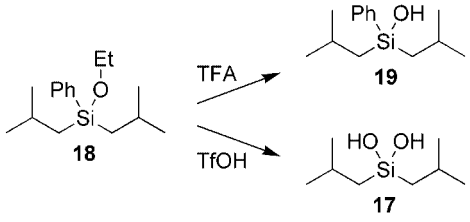



Scheme 3.

Siloxanes have low toxicity, low surface tension, low flammability and a high thermal stability,[30] but are perhaps more prone toward depolymerization than common perceptions would allow.[31,32] Permethylsilicone polymers can readily decompose in the environment to dimethylsilanediol monomers,[32,33] and they also depolymerize and dissolve in aqueous base.[34,35] Moreover, rates of silanediol self-condensation drop as the organic groups increase in size.[36] The liquid-crystal properties of diisobutylsilanediol (**17**), first described by Eaborn in 1955,[37] are an illustration of the steric-based stability of silanediols and their excellent hydrogen-bonding properties.[38]

## A Protecting Group for the Silanediol

At the inception of our investigation, the known silanediols were all simple alkyl and aryl derivatives, without stereochemistry and without functional groups. Preparation of silanediols in the center of a dipeptide analogue (e.g., **12**) would have both, and any synthetic strategy to prepare such a molecule would require a silanol protecting group. Ideally, the silanediol protection would be robust toward a broad range of chemical transformations, yet be readily removed without disturbing peptide functionality. With these criteria in mind, both cyclic and acyclic silyl ethers (acetal analogues) were rejected, based on the documented hydrolytic instability of diphenylsilane as a protecting group for 1,3-diols.[39] Considering the strongly acidic conditions typically used in many peptide deprotection schemes,[40] and the acid lability of unsaturated organic derivatives attached to silicon,[41,42] aryl groups on silicon were anticipated to be a versatile choice. Eaborn had shown that electrophilic substitution of a trialkylsilane on a benzene ring classically responded to electron-donating and withdrawing groups,[43] and therefore the ease of hydrolytic cleavage of aryl–silicon bonds could be adjusted to the desired level of reactivity towards electrophiles. As a first test of a phenyl-to-silanol conversion, ethoxy(diisobutyl)phenylsilane (**18**), Scheme 4, was prepared and treated with trifluoroacetic acid (TFA). At ambient temperature overnight, the silicon–phenyl bond was stable and only the ethoxy group was exchanged to give, after workup, the corresponding silanol **19**. When trifluoromethanesulfonic acid (triflic acid, TfOH) was added to the TFA, however, the phenyl group was hydrolyzed at 0 °C, to give the liquid-crystalline diisobutylsilanediol **17**.[37] This level of reactivity seemed ideal: stable to typical conditions for removal of Boc and *tert*-butyl ester protecting groups,[44] yet labile under standard peptide deprotection conditions.[40]



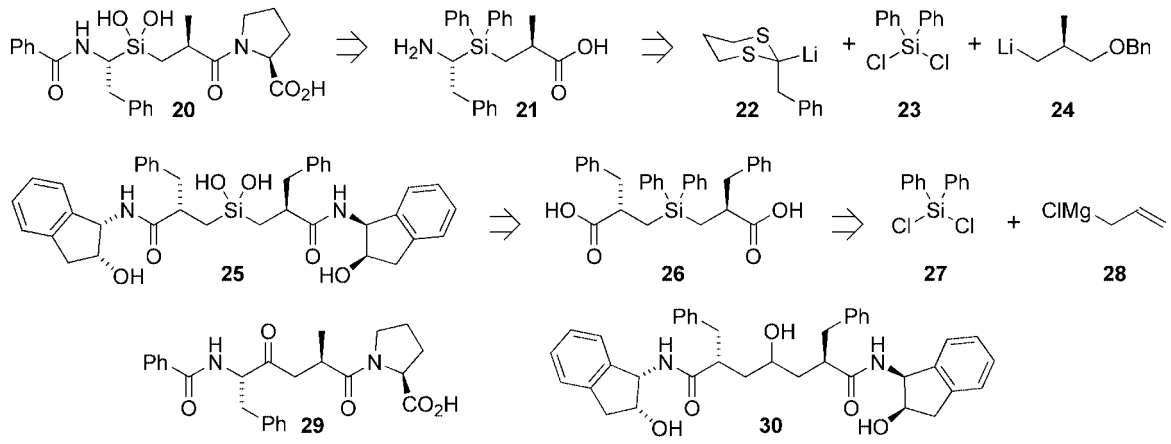

Scheme 4. Acidic cleavage of the silicon–phenyl bond.

## The First Silanediol-Based Inhibitors: Inhibitors of ACE and the HIV Protease

At the start it was not clear what protease enzyme would be most likely to yield positive results. Inhibition of angiotensin-converting enzyme (ACE) was the basis of the first successful protease inhibitor drug nearly 30 years ago,[45] and was a mature area with established structure–activity parameters.[46] The design of the silanediol **20**, Scheme 5, was predicated on the ketone inhibitor **29**, described by Almquist et al.[47–49] While the propensity of silanols to chelate metals, and thereby interact with the ACE active site zinc ion was poorly established, the proposed silanediol **20** had sufficient steric shielding to inhibit polymerization. With the diphenylsilane intermediate **21** as the key intermediate, the silanediol **20** became the first structure to be pursued, as a potential inhibitor of ACE.[50]

Shortly after that effort was initiated, the $C_2$-symmetric HIV protease enzyme was identified.[51,52] Development of $C_2$-symmetric inhibitors of this enzyme such as **30** followed quickly and presented what appeared to be substantially less complex compounds for exploration.[53] The silane intermediate **21** contains two different chiral silicon substitu-



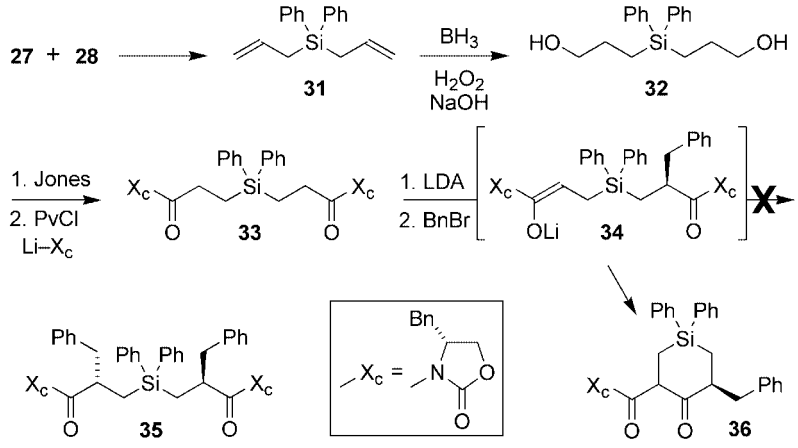
Scheme 5. The first silanediol inhibitor targets **20** and **25**, analogues of **29** and **30**.

ents, whereas intermediate **26** has two identical substituents. Moreover, the similarity of the targets such as **25** to the stable diisobutylsilanediol (**17**) was expected to ensure a level of stability toward oligomer formation. We anticipated that the central silane precursor **26** would be derived from diallyl(diphenyl)silane **31**.

The first approach to the diacid **26** followed the work of Fleming, Scheme 6. The diallylsilane **31** was converted to the diol **32** and then oxidized. Oxidation of **32** with Jones reagent gave the corresponding acid in moderate yield. This was coupled with the Evans chiral auxiliary,[54] setting the stage for a double asymmetric alkylation to give the two identical stereogenic centers of **26**. The relatively slow alkylation of the dienolate of **33**, however, proved to be the undoing of this approach, yielding none of the desired **35**. Instead, after the first alkylation the intermediate **34** rapidly underwent Dieckmann condensation, resulting in the interesting and enantiomerically pure **36**.[55] Unfortunately, **36** was of no use in the preparation of the inhibitor **25**.

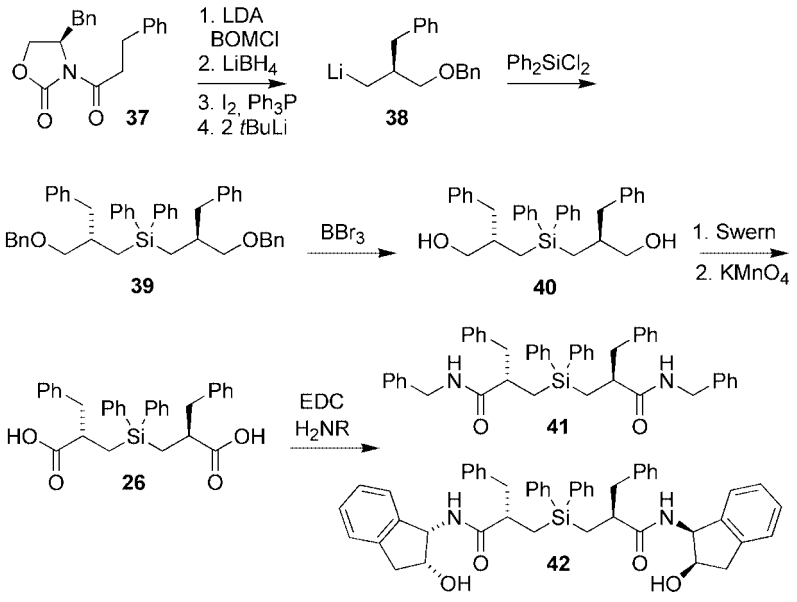
An alternative and ultimately successful approach to the silanediol **25** was to install the stereogenic centers before coupling with the silicon, Scheme 7, and this was readily accomplished. Alkylation of the lithium enolate of the dihydrocinnamic acid derivative **37** with benzyloxymethyl chloromethyl ether (BOMCl) set the desired stereogenic center, and reduction gave the optically active alcohol. Conversion of the alcohol to the iodide and then to the lithium reagent **38** by metal–halogen exchange was followed by reaction with dichloro(diphenyl)silane to give **39**. Removal of the benzyl ether protecting groups from the $C_2$-symmetric **39** was accomplished using boron tribromide. The diol **40** was then oxidized to the dialdehyde using Swern oxidation and then to the diacid **26** with potassium permanganate. Coupling of the diacid with benzylamine and with (5*S*)-amino-(6*R*)-indanol gave the corresponding diamides **41** and **42**, the immediate precursors of the silanediols.

During the final stages of the chemistry shown in Scheme 7, we took advantage of the availability of the intermediate diol **40** and converted it to the dimethyl ether **43**, Scheme 8, to study the triflic acid hydrolysis of the diphenylsilane in the absence of potentially reactive amide functional groups. At this stage of the investigation, the potential nucleophilic interaction of the amides with the silanediol following hydrolysis was a source of concern, because of the impact that this interaction might have on the silanediol reactivity and stability. We reasoned that the dimethyl ether **43** would allow us to study the hydrolytic step and the properties of an advanced silanediol. Therefore, the

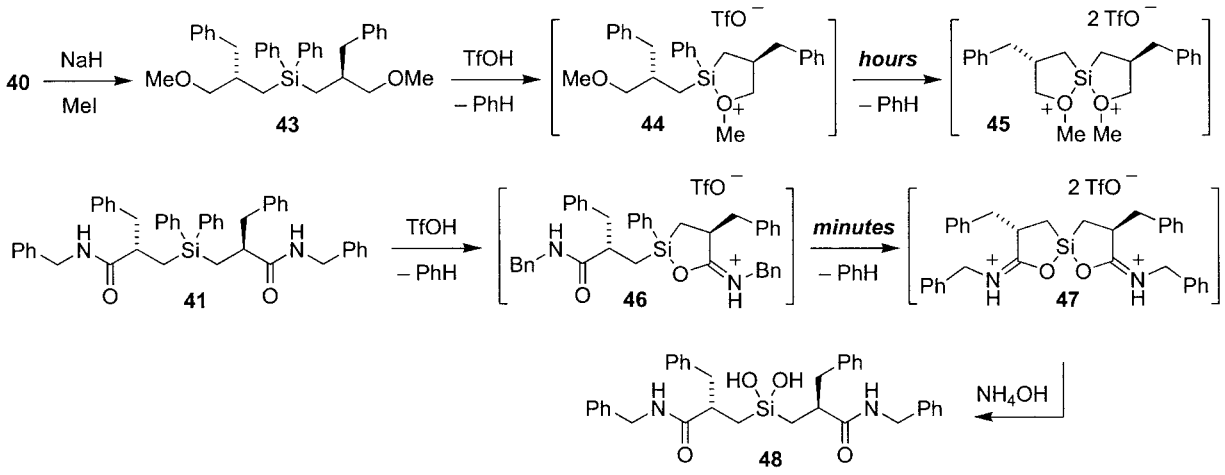


Scheme 6. First attempt to prepare intermediate **26**.



Scheme 7. Successful route to **26** and silanediol precursors **41** and **42**.



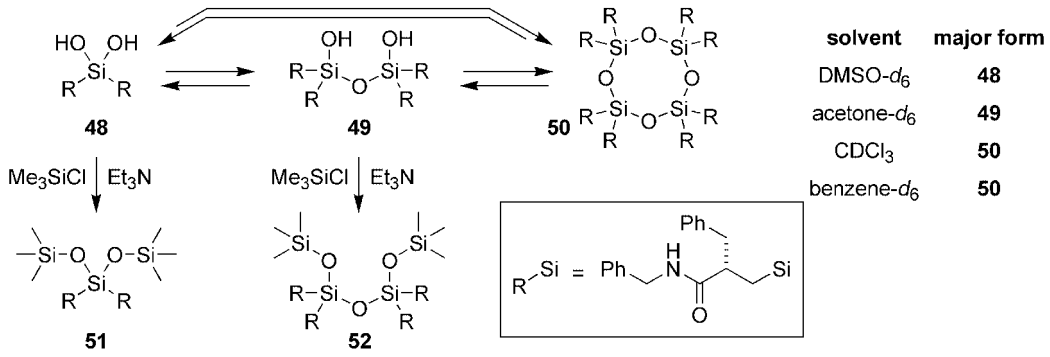
Scheme 8. Amides assist in silicon–phenyl bond cleavage.

dimethyl ether **43** was treated with an excess of triflic acid at ambient temperature in deuteriochloroform and the reaction followed by $^1$H NMR spectroscopy. Under these conditions, the chemical shifts of the identical methyl singlets of the diphenylsilane **43** immediately changed: One remained at 3.1 ppm and one jumped to 3.8 ppm. This change of the chemical shift is consistent with the formation of an intermediate **44**, in which one of the ether oxygen atoms has participated in the displacement of a phenyl group. This intermediate changed slowly over 8–10 hours into a symmetric product, presumably **45**, with both methyl groups found at 3.9 ppm in the proton NMR spectrum. The eventual cleavage of both silicon–carbon bonds of the diphenylsilane was gratifying; however, the sluggishness of the second hydrolytic step under these strongly acidic conditions was troubling. In contrast to the stability of intermediate **44**, under similar conditions the diamide **41** lost *both* phenyl groups within minutes, and an intermediate **46** was not observed by NMR, only the formation of **47** or a related symmetric adduct. Addition of ammonium hydroxide to **47** led to hydrolysis and formation of the silanediol **48**.

With the silanediol **48** in hand, we investigated its propensity toward oligomer formation as a function of solvent. We were fortunate to have a $C_2$-symmetric molecule, as the hydroxy groups of the silanediol are not diastereotopic, so that dimerization (and higher oligomers) would not lead to diastereomers.

The diol **48** was dissolved in a set of NMR solvents and monitored for a week at ambient temperature, Scheme 9. In DMSO-$d_6$, silanediol **48** showed no detectable change. In acetone-$d_6$, however, the silanediol **48** underwent dimerization to give the disiloxanediol **49** and then the tetramer **50**, in a ratio of 2:1. In chloroform-*d*, the same structures **49** and **50** were observed, this time favoring the latter by 1:2.



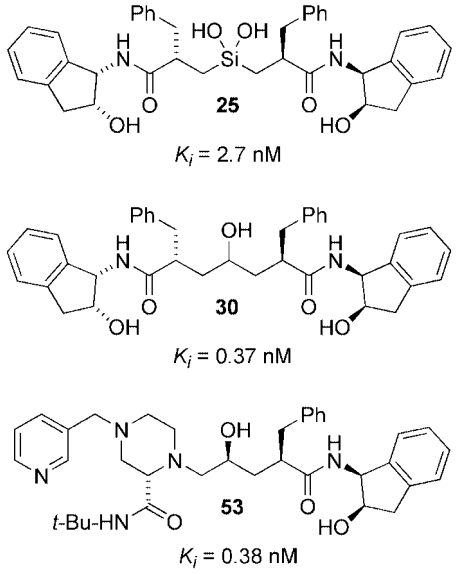

Scheme 9. Oligomer formation is solvent dependent and reversible.

The three substances **48**, **49** and **50** had very similar proton NMR spectra but could be definitively identified and characterized by capping with chlorotrimethylsilane. Each diol **48** and **49** coupled with two equivalents of the chlorosilane, whereas cyclotetrasiloxane did not.

During the analysis of these siloxanes, it was found that purified samples of tetrasiloxane **50** in chloroform-*d*, containing only adventitious water, showed the presence of monomer **48** after several hours. This is surprising in view of the perceived stability of siloxanes – and the fact that cyclotetrasiloxanes are considered to be relatively strain-free.[56,57] Hydrolysis of tetramer **50** to yield the monomer **48** in the presence of only traces of water may be a result of simple steric effects, destabilizing **50** by the presence of the relatively large R groups. It may also be the result of an intramolecular activation of the silicon by the nearby amides (see Scheme 8), transiently forming pentacoordinate species and providing a pathway for both polymerization and depolymerization.

Using the same triflic acid-mediated hydrolysis method that had worked well for **41**, the silanediol **25**, Scheme 10, was prepared from **42**. Evaluation of this silanediol as an inhibitor of the HIV protease was conducted at DuPont Pharmaceuticals, side-by-side with the carbinol **30** and indinavir (**53**), Scheme 10.[58] Gratifyingly, the silanediol was found to have a $K_i$ of 2.7 nM, only slightly less effective than the other two. The Merck report describing carbinol **30** noted the precise fit of this structure at the HIV protease active site.[59] The slightly attenuated inhibition of the enzyme by the silanediol **25** may be a consequence of introducing the larger central silicon atom, without subsequent optimization of the overall structure. Nevertheless, the inhibition of the HIV protease demonstrated that the silanediol group could be an effective inhibitor of aspartic proteases.

The silanediol **25** was found to not only inhibit the HIV protease enzyme, but to also protect whole cells against HIV infection, indicating that it can penetrate cell walls with an efficacy similar to **30** and **53**.[58] This protection against HIV infection was also observed when serum proteins were added to the assay, showing that binding of silanediol to serum proteins was of no more consequence than that of compounds **30** and **53**, consistent with the viability of silanediol derivatives as pharmaceuticals.

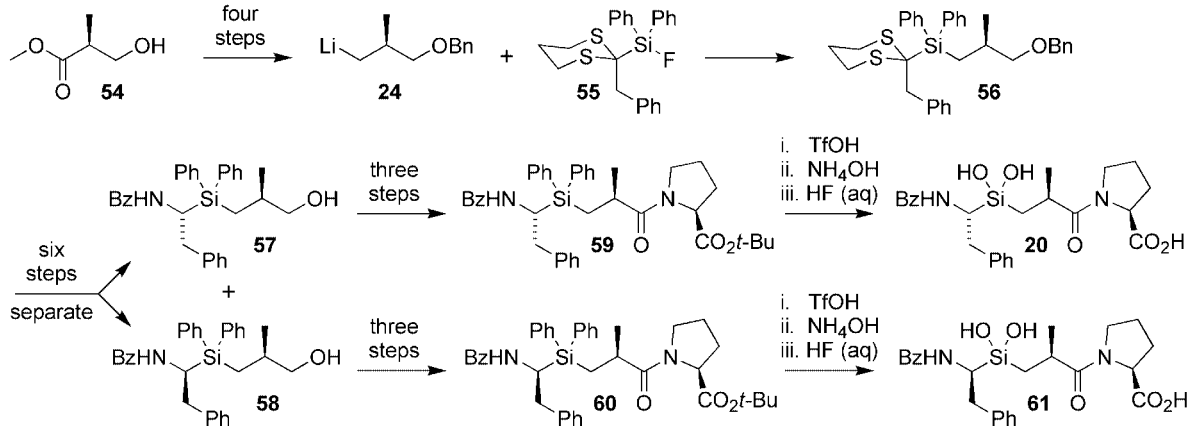



Scheme 10. HIV Protease inhibitors.[58]

## ACE Inhibitors

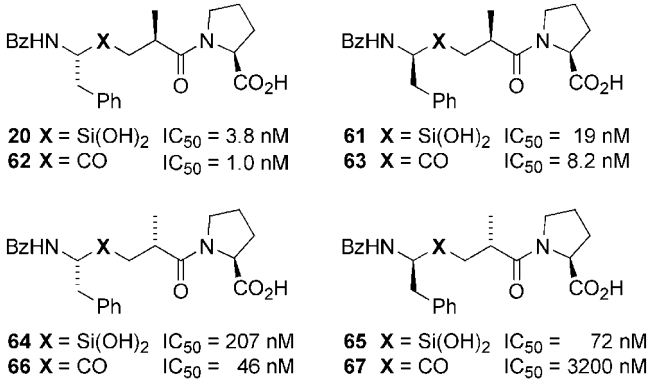
Silanediol inhibitors of the angiotensin-converting enzyme (ACE) were initially prepared as diastereomeric mixtures and demonstrated sufficient inhibition of ACE to warrant further investigation.[60,61] The inhibitor **20** was patterned after Almquist's ketone inhibitor **29**, Scheme 5. Almquist had evaluated four diasteromers of this ketone, and they appeared to be an ideal opportunity to investigate silanediol inhibitor structure-activity relationships. The synthetic approach to the silanediol **20** and diastereomer **61** is outlined in Scheme 11. Commercially available alcohol (*S*)-**54** was converted, using standard methods, to lithium reagent (*R*)-**24**, that coupled with fluorosilane **55** to give **56** containing all the carbon atoms of **20**. Hydrolysis of the dithiane **56** to the corresponding silyl ketone followed by reduction gave the α-hydroxy silane as a mixture of diastereomers. Conversion of this intermediate to a hydroxy benzamide gave a separable mixture of **57** and **58**. Each of the hydroxy groups was oxidized to the corresponding acid, and then coupled with proline *tert*-butyl ester to give **59** and **60**. Hydrolysis of the phenyl groups on silicon using




Scheme 11. Synthesis of silanediol ACE inhibitors.[62]

triflic acid also cleaved the *tert*-butyl ester. The hydrolysis protocol incorporated a final treatment with aqueous HF, followed by hydrolysis of the resulting difluorosilane with sodium hydroxide (described in more detail below). The enantiomer of alcohol **54** was then taken through the same sequence to yield the full set of silanediols **20**, **61** and their diastereomers **64** and **65** (see Schemes 11, 12).




Scheme 12. Inhibition of ACE by silanediols[62,63] and their ketone analogues.[47,49]

The $IC_{50}$ values for inhibition of ACE by the four silanediols compared favorably with the corresponding ketone diastereomers, in three of the four cases, Scheme 12.[63] The three most inhibitory ketones **62**, **63** and **66** were more potent than the silanediols **20**, **61** and **64** by a factor of approximately 2–4, with the methyl group stereochemistry more important for inhibition than the benzyl group stereochemistry. Inversion of both stereogenic centers flanking the X group of the most potent diastereomers **20** and **62**, however, led to the ketone **67** that showed little inhibition of the enzyme and the silanediol **65** that was surprisingly inhibitory. The high $IC_{50}$ value for ketone **67** is understandable as a synergistic effect of the two stereogenic centers. That silanediol **65** has a lower $IC_{50}$ than **64** was unexpected and may indicate an alternative binding mode for this silanediol. The comparable inhibition of ACE by these two sets of inhibitors demonstrates that the silanediols can be reliably incorporated into analogues of known inhibitors of metalloproteases, although not all analogues give completely predictable results. Clearly, more investigation of these inhibitors is warranted.

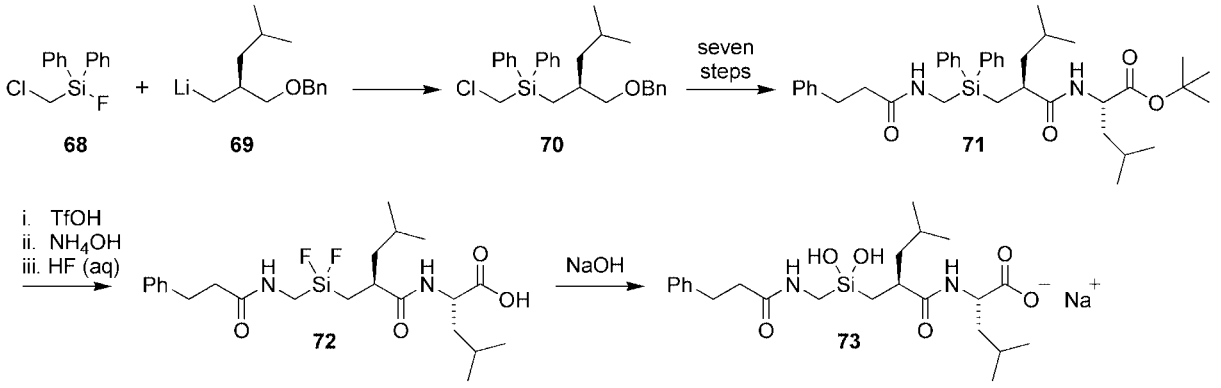
### Thermolysin Inhibitors

Thermolysin is a benchmark metalloprotease.[64] As such, it was a natural substrate with which to study inhibition by silanediols. Using phosphorus-based inhibitors of thermolysin as a starting point, the silanediol **73** became our focus, Scheme 13.

Assembly of the 2-alkyl-3-silyl carboxylic acid using an optically active 2-alkyl-3-lithiopropyl ether reagent was again used, Scheme 13. The enantiomerically pure lithium reagent **69** was coupled with the chloromethylsilane **68** to give the intermediate **70**. Standard chemistry was used to convert the chloromethyl group of **70** to the derivatized aminomethyl group, and the benzyl ether to the carboxylic acid, yielding the silanediol precursor **71**.

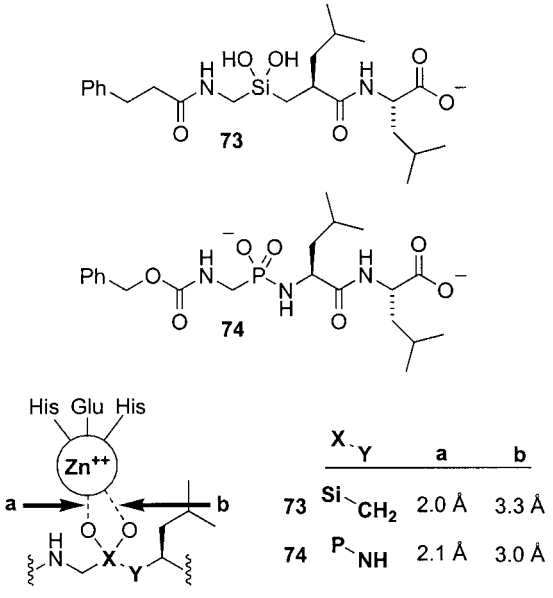
The diphenylsilane **71** was then subjected to triflic acid-mediated hydrolysis to give silanediol **73**. Relative to HIV protease inhibitor **25** and ACE inhibitor **20**, the substitution of **73** provides much less steric shielding of the silicon. The use of triflic acid for hydrolysis, followed by treatment with ammonium hydroxide to hydrolyze the expected intermediate (see Scheme 8), led to the silanediol **73** that appeared to be mixed with siloxane oligomers. While the silanediol could be purified from this mixture, we sought to refine the hydrolysis procedure. After some experimentation, a third step was introduced in the hydrolysis scheme, the addition of aqueous hydrofluoric acid. Aqueous HF converts silicon–heteroatom bonds, including those of siloxanes, to silicon–fluorine bonds,[65] resulting in crystalline, monomeric and easily isolated difluorosilane **72**. The Si–F bond is one of the strongest covalent bonds,[66,67] yet it is easily hydrolyzed under mildly basic conditions. Treatment of the difluorosilane **72** with aqueous sodium hydroxide led, within minutes, to silanediol **73**, with no trace of oligomer formation.




Scheme 13. Synthesis of thermolysin inhibitor **73**.

Silanediol **73** was prepared as an analogue of the phosphorus-based thermolysin inhibitor **74**, Scheme 14. As second-row elements, silicon and phosphorus have similar atomic radii (1.10 and 1.05 Å, respectively) and therefore would present structures of similar size at the enzyme active site. Electronically, however, these structures are very different. Silanediol **73** would be a neutral ligand for the zinc dication at the active site of this metalloprotease. In contrast, phosphonamide **74** carries a negative charge at a pH above 4, providing a Coulombic attraction to the positively charged active site zinc. It was perhaps surprising therefore, that while phosphonamide **74** has a $K_i$ = 10 nM, silanediol **73** was similarly inhibitory, with a $K_i$ = 40 nM. Moreover, the crystal structure of silanediol **73** bound to thermolysin was found to have a conformation and enzyme interactions nearly identical to that of **74**, with the exception of the dihydrocinnamoyl and Cbz groups.[68] Most intriguingly, the oxygen atoms on the silicon and phosphorus were found to have very similar distances to the zinc ion, Scheme 14. Whereas some phosphorus-based inhibitors of thermolysin related to **74** bind at the active site with two similar oxygen–zinc bonding distances (e.g., 2.2 and 2.6 Å),[69] inhibitor phosphonamide **74** has one oxygen substantially closer to the zinc (2.1 and 3.0 Å). Despite their electronic differences, the oxygen–zinc distances for silanediol **73** (2.0 and 3.3 Å) are very similar to those of **74**.



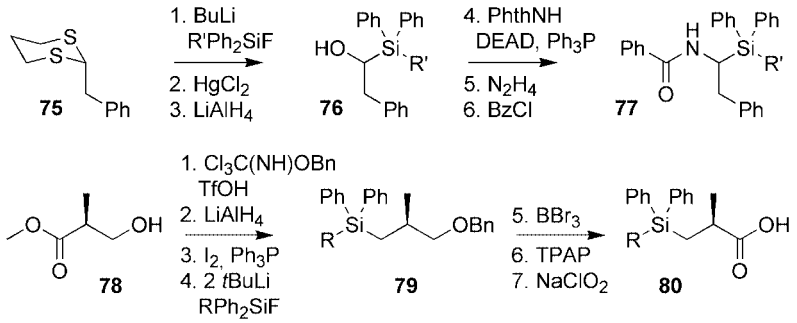

Scheme 14. Two second-row element-based thermolysin inhibitors, and comparison of their oxygen distances to the active site zinc.

## Enhanced Chemistry

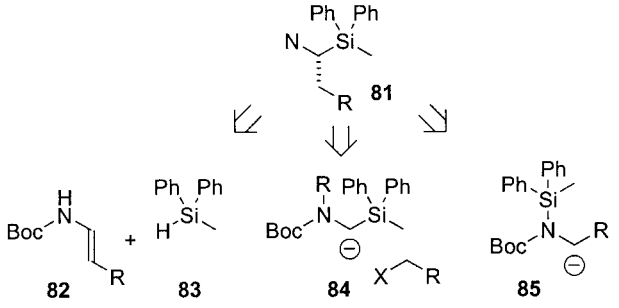
With effective silanediol inhibitors for three enzymes in hand,[58,63,70] development of a more efficient method with which to assemble the silanediols became paramount. The chemistry initially used for synthesis of angiotensin-converting enzyme inhibitors was effective but lengthy, as outlined in Scheme 15.[62] In this instance, all of the carbon atoms of the α-amino portion of molecule **77** were introduced using the dithiane **75**, but conversion of the dithiane to a benzamide required an additional five stages. The stereogenic center adjacent to the acid in **80** was derived from commercially available **78**. Converting this fragment to a suitable nucleophile, attachment of the silane and functional-group manipulation was accomplished in seven steps. Overall, more than a dozen reactions were required for assembly of the silanediol inhibitors. While this and related routes were effective and led to the first silanediol inhibitors, more streamlined and general methods were clearly in order.

The two very different substituents of the silanediol suggested that different approaches would be required. For preparation of the α-amino silane component, several synthetic methods were investigated, three of which were summarized in Scheme 16. Hydrosilylation is one of the most important methods for silicon–carbon bond formation,[71–73] and hydrosilylation of *N*-alkenyl amides such as **82**, Scheme 16, had been been the subject of several reports.[74,75] Alternatively, alkylation of an anion between silicon and nitrogen in **84** was studied, an anion that would profit from stabilization by the silicon[76] and could be prepared using the metalation-directing capacity of the Boc group.[77] A related anion **85**, where the silicon migrates from nitrogen to carbanion has turned out to be the most effective of these methods. Each of these investigations are briefly described below.

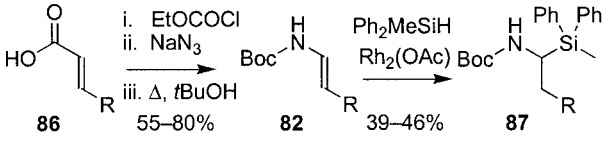



Scheme 15. An effective but lengthy chemistry for silanediol protease inhibitor synthesis.[62]



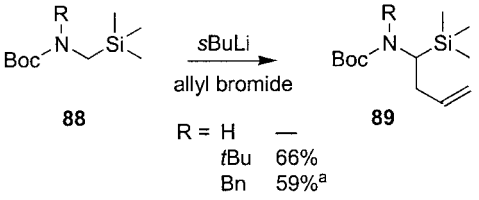

Scheme 16. Three approaches to α-alkyl-amino silanes.

Curtius rearrangement of acyl azides derived from acrylic acids **86**, Scheme 17, provides a general route to Boc-derivatized vinylamines **82**.[78] Rhodium-catalyzed hydrosilylation has been found to provide the desired regioselectivity.[74,75] In these studies, triethylsilane gave the highest yields for this reaction, but a diphenylsilyl group was required as a precursor to the silanediols. This substrate did form the desired products **87**, however, the yields proved to be modest, at best.[79]




Scheme 17. Hydrosilylation of *N*-alkenyl carbamates.[79]

An alternative approach, alkylation of an anion between nitrogen and silicon, was expected to be a general synthetic method, one that would enjoy stabilization of the anion by silicon and be accessible using the metalation-directing capabilities of a Boc-protected nitrogen, Scheme 18. Several chloromethylsilanes are commercially available, including chloromethyl(trichloro)silane from which almost any α-aminotrialkyl(arlyl)silane can be prepared (for an example see **68**, Scheme 13). Once again, the results were mixed: the procedure worked well when the nitrogen of **88** was substituted with a *tert*-butyl group, but not at all when R = H, which involved dianion generation. An *N*-alkyl group avoided the need for a dianion intermediate, but the *tert*-butyl group could not be easily removed. Using an *N*-benzyl group that could subsequently be removed gave the alkylation in reasonable yield, but as a mixture of α-silyl and α-phenyl alkylation.[80] Thermodynamically, the benzyl anion was more stable than the silicon-stabilized anion, making this approach also unsatisfactory.[81]

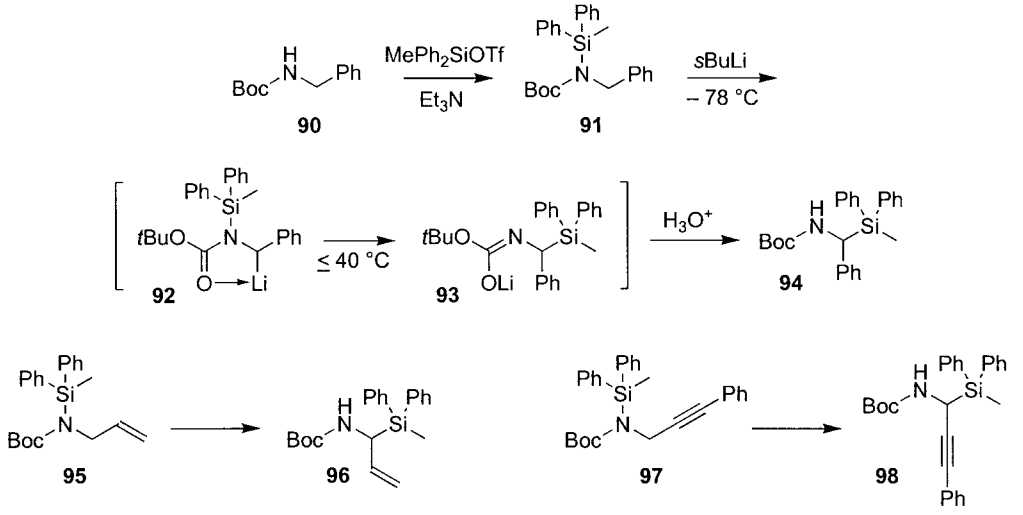



Scheme 18. Alkylation of metalated α-amino silanes ([a] mixture of α-silyl and benzyl alkylation).[80]

The difficulty with metalation and alkylation of **88** was the need for a suitable protecting group for the nitrogen, however it was found that this protection and introduction of the silicon could be combined. Starting with Boc-protected benzylamine **90**, Scheme 19, *N*-silylation removes the acidic proton. Metalation of **91** is directed by the Boc group, leading to benzyllithium **92**. This anion is unstable and rearranges to **93**, a reverse-aza-Brook rearrangement. The aza-Brook rearrangement has been well studied,[82–84] but has generally not been useful because of the high p$K_a$ of both carbon and nitrogen anions, leading to equilibrium mixtures and competing reactions under the strongly basic conditions. In the case of **92/93**, the stabilization of the nitrogen anion by the Boc group is a driving force for the reaction and lowers the ultimate basicity of the reaction conditions. This reverse-aza-Brook rearrangement can be extended to other substrates with anion-stabilizing groups, such as allyl and propargyl substrates **95** and **97**. Unfortunately, we have not been able to extend this reaction to more stabilized anions, such as ester enolates.[85] The ambident allyl anion intermediate formed during conversion of **95** to **96** has the potential to yield either 1,2- or 1,4-migraton of silicon, yet only the 1,2-migration product **96** is observed.

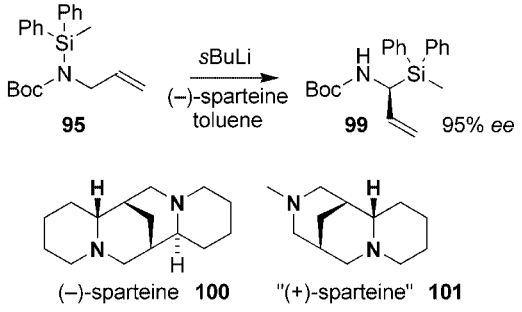
The rearrangements shown in Scheme 19 all create a new stereogenic center. To evaluate the potential for creating this center enantioselectively, the metalation was performed using the *sec*-butyllithium–sparteine complex.[87] Delightfully, performing this reaction in toluene led to the rearrangement product **99** with good enantiomeric excess, Scheme 20. Moreover, rearrangement of benzyl and propar-



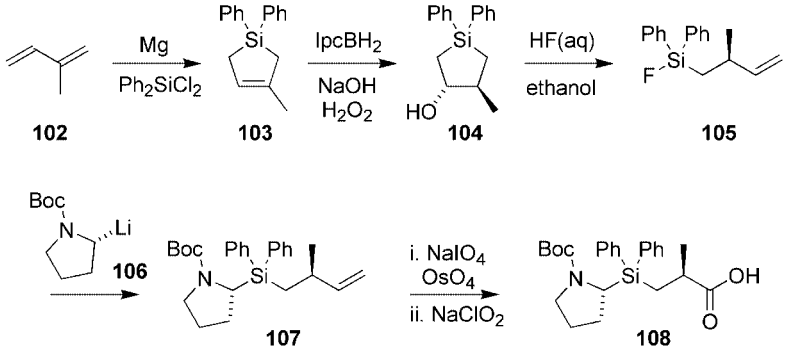
Scheme 19. Reverse-aza-Brook rearrangement.[86]

gylamine substrates **91** and **97** also gave high levels of enantioselectivity when treated with the same chiral complex. X-ray crystallography of a derivative of **99** found the new steregenic center to have the (*S*) configuration, as shown (Scheme 20).[86] This absolute stereochemistry derived from (–)-sparteine-mediated rearrangement is the opposite of that required for the α-aminoalkyl portion of the silanediol protease inhibitors (see, **12**, Scheme 2 and **20** Scheme 5). However, the readily prepared (+)-sparteine equivalent **101** is an excellent ligand for introducing the opposite stereochemistry.[88] The optically active silanes such as **99** have been oxidized to optically active α-silyl amino acids, but that is another story.[89]



Scheme 20. Asymmetric reverse-aza-Brook rearrangement.[86]

The reverse-aza-Brook rearrangement is a convergent and efficient method for building the α-alkyl-α-amino silane substituent of the silanediols. As a new approach to the other substituent, α-alkyl-β-silyl propionate, the magnesium-mediated reaction of 1,3-dienes with dichlorosilanes and reactions of its cycloadduct has been investigated, Scheme 21. Following the procedures of Mignani et al. for cycloaddition of dichloro(diphenyl)silane with 1,3-butadiene,[90] coupling with isoprene **102** gave the 2,5-dihydro-3-methyl-1,1-diphenylsilole (**103**). This reaction is easily run on a large scale, and **103** can be isolated by distillation. Asymmetric hydroboration with (monoisopinocampyl)-borane[91] yields the alcohol **104** in 70–75% *ee*. A single recrystallization increases the *ee* to >95%. Treatment of the alcohol **104** with an excess of aqueous HF in refluxing ethanol leads to dehydration and ring cleavage, forming the fluorosilane **105** with no evidence for other products or additional silicon–carbon bond cleavage. Fluorosilane **105** is stable to moisture and yet very reactive toward nucleophiles.



Scheme 21. A 2,5-dihydrosilole method for chiral α-alkyl-β-silyl propionate synthesis.

Treatment of **105** with the 2-lithiopyrrolidine **106** yields the silane **107**, which can then be oxidized to protected amino acid building block **108**, an Ala–Pro dipeptide mimic prepared for an investigation of inhibitors of anthrax lethal factor.[92] Overall, this sequence yields a central silicon protease inhibitor structure, with full stereogenic control, in only six steps. While this is five steps beyond the ideal synthesis,[93] it provides the key intermediates efficiently using easily scalable chemistries.

### Future Directions

New areas for this research include the testing of inhibitors against the remaining protease classes: serine, threonine and cysteine proteases.[94] These protease differ from metallo and aspartic proteases in that they attack an amide carbonyl with an alcohol or thiol nucleophile that is part of the enzyme, rather than use water as the nucleophile. Effective inhibition would therefore require more than structural recognition of the inhibitor, it might also require replacement of a silanol hydroxy by the enzyme nucleophile.

The new chemistries developed for the silanediol synthesis streamline their construction, although there is always room for improvement. Catalytic asymmetric hydrosilylation[95] has the potential for constructing both silicon–carbon bonds, perhaps even with the silicon at the silanediol oxidation level, which would obviate the need for a strongly acidic deprotection step.

In the three examples described here, silanediols have proven to be effective inhibitors of metallo and aspartic proteases, with inhibition in the range of 3–40 nM. The comparative stereochemical study of ACE inhibition and the crystallographic evidence of active site binding in thermolysin, make a strong case for the silanediol as a protease inhibitor design structure that can be implemented as part of a protease inhibitor or drug design program with a high degree of confidence.

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