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Silicon-Based Metalloprotease Inhibitors: Synthesis and Evaluation of Silanol and Silanediol Peptide Analogues as Inhibitors of Angiotensin-Converting Enzyme[1]

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Abstract: Silanols are best known as unstable precursors of siloxane (silicone) polymers, substances generally considered stable and inert, but have the potential to mimic a hydrated carbonyl and inhibit protease enzymes. While previous testing of simple silanediol and silanetriol species as inhibitors of hydrolase enzymes found them ineffective, this study reports polypeptide mimics with a central methylsilanol [SiMeOH] or silanediol [$Si(OH)_2$] group and their assessment as effective transition state analogue inhibitors of the well-studied metalloprotease angiotensin-converting enzyme (ACE). Central to the synthesis strategy, phenylsilanes were employed as acid-hydrolyzable precursors of the silanol group. The *N*-benzoyl Leu-[SiMeOH]-Gly benzyl amides proved to be stable and readily characterized. In contrast, the Leu-[$Si(OH)_2$]-Gly structure was difficult to characterize, possibly because of self-association. Capping the silanediol with chlorotrimethylsilane gave a well-defined trisiloxane, demonstrating that the silanediol was monomeric. The Leu-[Si]-Gly structures were converted to Leu-[Si]-Ala analogues by enolate alkylation. Coupling of the silanol precursors with proline *tert*-butyl ester gave *N*-benzoyl Leu-[Si]-Gly-Pro and *N*-benzoyl Leu-[Si]-Ala-Pro tripeptide analogues. Treatment of these with triflic acid formed the corresponding methylsilanols and silanediols, all of which were monomeric. The silanediol tripeptide mimics inhibited ACE with IC_{50} values as low as 14 nM. Methylsilanols, in contrast, were poor inhibitors, with IC_{50} values above 3000 nM. These data, including comparisons with inhibition data from carbon analogues, are consistent with binding of the silanediols by chelation of the ACE active site zinc, whereas the methylsilanols ligate poorly.

Introduction

Silicon is the second most abundant element and the one most similar to carbon. This close chemical analogy has been the inspiration for many studies of silicon as a replacement for carbon, particularly in biologically active molecules.[2] These investigations were bolstered by the finding that organic derivatives of silicon are devoid of the intrinsic toxicity found with the heavier group 4 elements tin and lead.[3] The strong silicon−carbon bond, and the correspondingly stable organic derivatives, make bioactive organosilanes all the more curious because of their absence from the natural world—silicon carbide has the only naturally occurring silicon−carbon bond.[4] With the discovery of the useful physical and chemical properties of the organosilane polymers,[5,6] particularly the silicones,[7] and the development of the direct process for their synthesis,[8] organosilanes have become cheap and readily available commodities.

Bioactive Organosilanes. Investigations of organosilane properties over the last 40 years have identified an assortment of bioactive substances. Rational searches for bioactive organosilanes have been conducted along two distinct paths, random screening and molecular design. Random screening can discover the biological activity of structures without carbon analogy, but by its very nature it cannot be incorporated into target-directed design programs driven by receptor modeling or substrate-analogy. Alternatively, the systematic replacement of silicon for carbon in bioactive substances is an approach that can be

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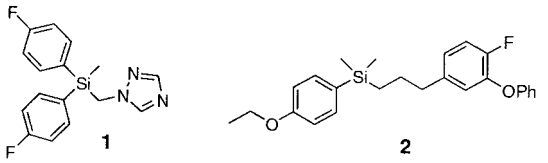

Figure 1. Biologically active organosilanes designed by analogy to carbon compounds.

readily incorporated into design programs, and it has led to the identification of many bioactive organosilanes. Compounds **1** and **2**, Figure 1, are organosilanes designed by analogy. Flusilazole **1**[9] belongs to a class of antifungal sterol biosynthesis inhibitors,[10] most of which do not contain silicon. Silafluofen **2**[11] is a distant relative of the natural pyrethrin insecticides and a direct analogue of the carbon-based MTI-800.[12] Despite decades of effort to discover organosilanes with useful bioactivity, these are the only organosilanes produced commercially because of their biological activity. Nevertheless, ongoing research promises that new examples of bioactive organosilanes will continue to emerge.[13]

Bioactive Organosilane Design. Design of bioactive organosilanes, starting with a molecule of known biological activity and replacing a carbon atom with a silicon atom, has a long history and has taken several forms.[2] The most straightforward version of this approach involves replacement of a quaternary carbon, to give a silicon surrounded by carbons (e.g., **1** and **2**). This takes advantage of the robust silicon−carbon bond and avoids the metabolic instability of the silicon−hydrogen bond[14] and the hydrolytic instability of most silicon−heteroatom bonds. The consequences of this substitution, beyond the generation of a novel and often proprietary structure, are a subtle increase in the molecular volume, a perturbation of the local electronics, and a small increase in the molecular lipophilicity relative to the original carbon structure.[11]

As an alternative to the replacement of a *stable* carbon atom, silicon also has the potential to emulate an *unstable* carbon species. This type of carbon substitution, however, has been an unrealized design strategy. In principle, a silanediol can mimic a hydrated carbonyl group. Tetrahedral, hydrated sp^3 carbonyls are energetically disfavored over their trigonal, unhydrated sp^2 counterparts.[15] Conversely, trigonal silicon species are highly unstable relative to the tetrahedral alternative.[16] In the context of hydrolytic enzyme substrates, replacement of a carbonyl group with a silanol or silanediol would create a transition state analogue and a potential enzyme inhibitor. In terms of binding energetics, a tetrahedral silanediol would not require the energetically disfavored hydration needed by the equivalent ketone inhibitor.

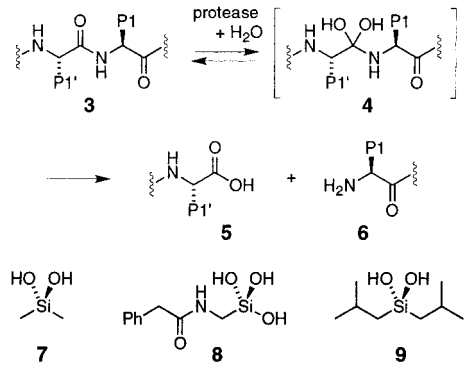

Figure 2. Hydrolysis of peptide bonds by protease enzymes, and silanols that could mimic intermediate **4**.

Protease Inhibitors. Metallo (and aspartic) protease enzymes catalyze the addition of a molecule of water to an amide of **3**, stabilizing the intermediate **4** through chelation of the active site zinc (or hydrogen bonding with aspartic proteases) (Figure 2). Productive collapse of **4** leads to acid **5** and amine **6**. Central to the design of a protease inhibitor is the choice of a nonhydrolyzable isostere (transition state analog) of the tetrahedral hydrated carbonyl intermediate **4**. Transition state analogues are a cornerstone of enzyme inhibitor design[17] and the basis of several successful pharmaceutical agents. Their uses in the treatment of hypertension and for control of the AIDS virus are most notable.[17,18]

The fit of an isostere at an enzyme active site stems from the complementarities of the active site and the isostere, with hydrogen bonding, Coulombic attractions, and hydrophobic surfaces as important components.[19] "Transition state analogues" that have effectively been deployed as protease inhibitors include reduced amides, carbinols, and geminal diols, amino alcohols, ketones, and aldehydes (including hydrated forms). Non-carbon-based structures include boron-, sulfur-, and phosphorus-based groups.

Missing from the hydrolase inhibitor literature are organosilanes, and in particular silanols; several reasons for this absence are easily identified. Silanols, silanediols, and especially silan-

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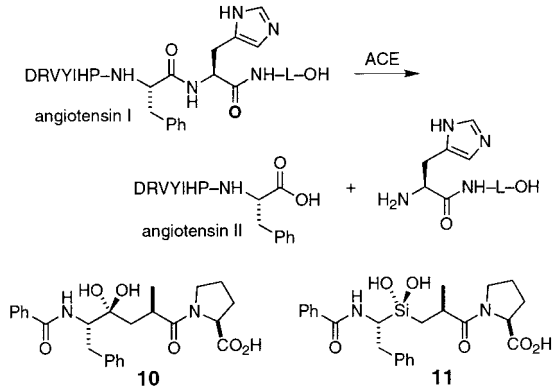

Figure 3. Angiotensin-converting enzyme (ACE) generates angiotensin II, raising blood pressure. Almquist's ketone inhibitor **10** (shown hydrated) and silanediol analogue **11**.

etriols are notoriously unstable toward self-condensation. Indeed, the organosilicon industry was founded largely on the production of silanols, particularly dimethylsilanediol **7**, and their self-condensation to give silicone polymers, prized for their fluid and thermal stability properties.[5] Moreover, in the two instances in which silanols were tested as hydrolase inhibitors, they proved to be completely ineffective. Galardy and Kortylewicz, in a survey of second and third row element-based tetrahedral structures, tested an aqueous solution of dimethylsilanediol **7** as an inhibitor of angiotensin-converting enzyme (ACE)[20] and found no evidence for inhibition. More recently, Curley and Pratt prepared phenylacetamidomethylsilanetriol **8** and evaluated it as an inhibitor of a β-lactamase. Again, no evidence for enzyme inhibition was observed.[21]

While the ability of silanediols to act as enzyme inhibitors was unsubstantiated, examples of stable, difficult to polymerize dialkylsilanediols are plentiful.[22] Sterically hindering alkyl groups inhibit oligomer formation.[23] For example, while dimethylsilanediol **7** is intrinsically unstable toward self-condensation, diethylsilanediol can be isolated and stored in pure form, and diisobutylsilanediol **9** is a liquid crystal.[24] These, and the nearly 100 other characterized silanediols, suggested that silanol-based peptidomimetics could be well-behaved chemical species.

Angiotensin-Converting Enzyme (ACE). Captopril,[25] the first pharmaceutical product designed to inhibit a protease, unequivocally demonstrated that protease inhibition could be an effective approach to therapeutic intervention. Inhibition of ACE by captopril prevents conversion of angiotensin I to angiotensin II (Figure 3), resulting in lower blood pressure. Many other protease targets have been identified, and the invention of protease inhibitors continues to be a prominent avenue for drug design.[18,26]

ACE is a metalloprotease, with a zinc ion at the active site, one of four major classes of protease enzymes categorized by their active site functionality.[18] This zinc ion activates the amide carbonyl toward hydration and stabilizes the resulting tetrahedral intermediate, leading to hydrolysis of the amide bond.[27] Active site-directed metalloprotease inhibitors have a functional group to bind the active site zinc ion. These groups can be zincophilic (thiols), can use a combination of chelation and Coulombic attraction to bind the metal (carboxylate and phosphinate), or it can simply be a metal chelator. Metal chelators can be hydroxamic acids or hydrated ketones (e.g., **10**). The work described here illustrates the first use of a silanediol (**11**) as a transition state analogue, anticipated to emulate the hydrated ketone **10**.

Geminal diols, hydrated aldehydes and ketones, have been known as enzyme inhibitors for some time, and they can be effective metalloprotease inhibitors. Almquist's ketone inhibitor **10**,[28] shown in Figure 3 as the energetically disfavored hydrate, presumably acts by chelating the active site zinc. This compound is an excellent ACE inhibitor, with an IC_{50} value of 1.0 nM.

This ketone was also an ideal starting point for design of a silanol protease inhibitor, because the steric environment of the zinc-chelating group, flanked by substituents on two sides, would inhibit self-condensation. On the other hand, the influence of the nearby amide groups on the silanediol could not be readily predicted because there are only scattered examples of silanols with γ-carbonyl groups. Amide carbonyls capable of intramolecularly coordinating a silicon, to form a five-membered ring and a pentavalent silicon, will do so when the silicon carries a halogen.[29,30] For silanols (one OH), significant coordination of a nearby carbonyl oxygen has only been found when the silanol is protonated.[31,32]

Silanol Properties. The potential for silanols to function as metalloprotease inhibitors hinges, in part, on the ability of the oxygens to ligate or chelate metals. Silanol oxyanions are useful, bulky monodentate ligands for metals,[33] but we are aware of only two crystal structures that show chelation by an O−Si−O group. The permethyl cycloheptasiloxane **12** was serendipitously found to bind potassium,[34] Figure 4. More relevant to the metalloprotease is structure **13** in which *tert*-butyl silicates

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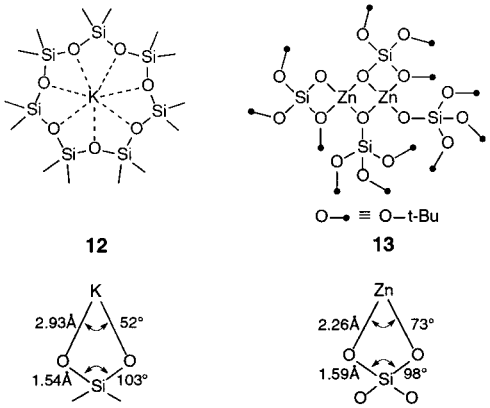


Figure 4. Crystal structures of metals chelated by a siloxane and by silicates.

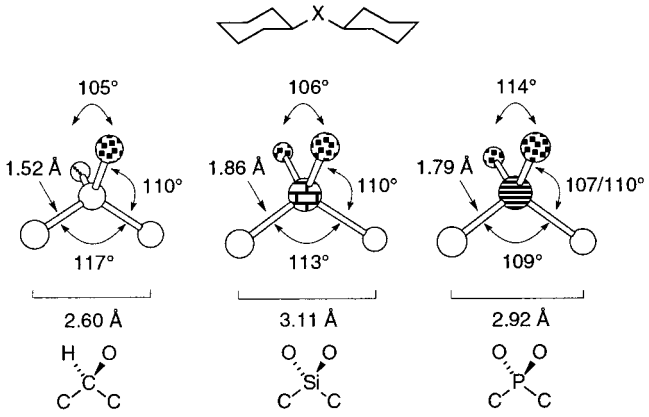
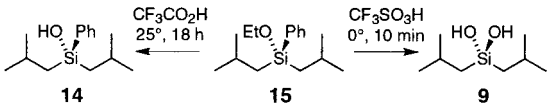


Figure 5. Comparison of dicyclohexylmethanol, dicyclohexylsilanediol, and dicyclohexylphosphinic acid crystal structures.

chelate zinc.[35] The caveat with regard to this latter structure, however, is that the chelating groups are silicate-based oxyanions derived from silanols that are more acidic than the dialkylsilanediols studied here because of the four electronegative groups around silicon. Thus, the ability of a neutral silanediol to act as a metal chelator remained to be tested.

Silicon is not only larger than carbon, but it also adopts slightly different bond angles. The effect of a trialkylsilyl group on the preferred geometry of an attached oxygen has been noted by others.[36] The crystal structures in Figure 5, dicyclohexylcarbinol,[37] dicyclohexylsilanediol,[38] and dicyclohexylphosphinic acid,[39] provide points of comparison for carbon, silicon, and phosphorus structures. Phosphinic and related phosphorus-based acids, notably based on a second row element like the silanols described here, can be potent metalloprotease inhibitors.[40] Comparing these three related structures, the C−X−C bond angle decreases smoothly from X = C (117°) to X = Si (113°) to X = P (109°), while the O−X−C and the O−X−O bond angles are nearly identical for X = C (110°, 105°) and X = Si (110°, 106°), but the O−P−O bond angle is much larger (114°),

Scheme 1. The Phenyl−Silicon Bond Is Stable to TFA but Hydrolyzes Rapidly with TfOH



and the two O−P−C angles are not identical (107° and 110°). The combination of C−X−C bond angles and C−X bond lengths (longest for X = Si) results in a distance between the carbons attached to X that is shortest for X = C and longest for X = Si. The effect of these structural variations on the binding of an inhibitor to an active site will depend, naturally, on the specific enzyme in question.

Results and Discussion

A Silanol Protecting Group. Synthesis of a silanol or silanediol within a peptide backbone required the identification of a suitable silanol protecting group. Among the available options was the use of silyl ethers and readily oxidized silicon substituents such as hydride.[41] The correlation of silyl ether stability and steric hindrance[42] led us to reject this option as too substrate dependent and potentially troublesome. Silicon dihydrides were also rejected as being too air sensitive and potentially reactive with nucleophiles. On the other hand, the lability of unsaturated carbon substituents seemed to make them a more appropriate choice. In the hierarchy of acid-sensitive carbon appendages of silicon,[43] allyl, aryl, and vinyl groups attached to silicon are readily cleaved by acid and other electrophiles, with phenyl less acid sensitive than allyl and more acid sensitive than vinyl groups. Moreover, diarylsilanes can be commercially available, and the sensitivity of the aryl−silicon bond to acid can be modulated by the use of electron-donating and -withdrawing substituents.[44]

In a preliminary study of phenylsilane as a silanol precursor, we prepared ethoxy(diisobutyl)phenylsilane **15** (Scheme 1), with the expectation that this would closely mirror the *second* phenylsilane cleavage of a dialkyldiphenylsilane. The ease of acidic cleavage of unsaturated groups from silicon can be dependent on the electronegativity of the silicon substituents.[45] The ideal reactivity level for the phenyl silane bond would be stability under conditions used for removal of common peptide protecting groups such as the *tert*-butoxycarbonyl (Boc) group, that is, stable to trifluoroacetic acid (TFA) but labile under more strongly acidic conditions used for peptide cleavage from a solid support,[46] so that the protected silanediol could participate in polypeptide synthesis schemes. We were therefore pleased to find that overnight treatment of **15** with neat TFA at ambient temperature led only to exchange of the ethoxy group, to give **14**. In contrast, treatment with trifluoromethanesulfonic acid (triflic acid, TfOH) in TFA at 0 °C for 10 min led to the quantitative isolation of the liquid crystalline diisobutylsilanediol

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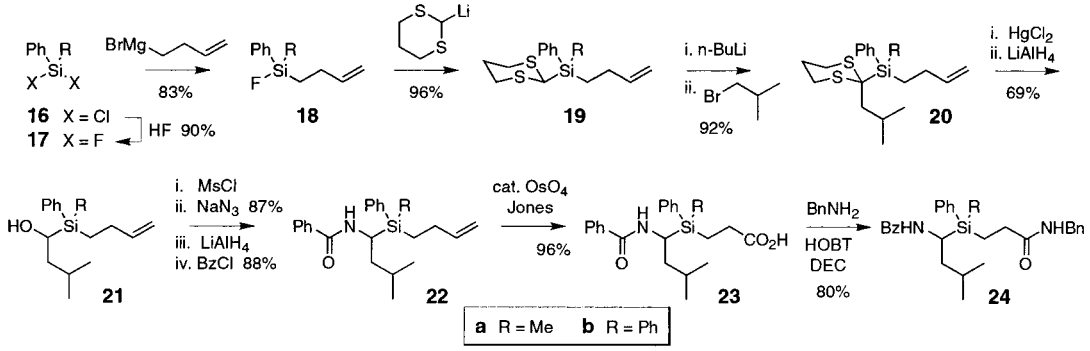
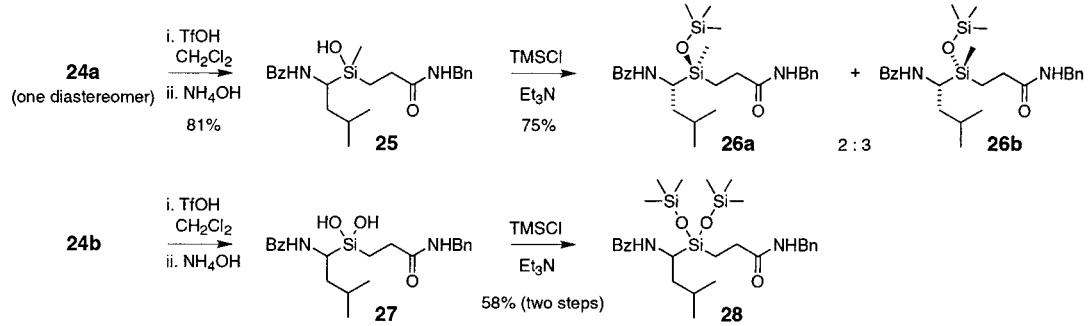
Scheme 2. Synthesis of Silanol and Silanediol Precursors **24a** and **24b** (Yields Shown Are for Diphenylsilane Series **b**)



Scheme 3. Hydrolysis of One Diastereomer of **24a** Gives the Silanol as an Inseparable Mixture of Diastereomers[a]



[a] Capping the silanols **25** and silanediol **27** gave siloxanes **26** and **28** (the diastereomeric identity of **26a** and **26b** is not known).

9.[47] On the basis of these experimental results, dichlorodiphenylsilane **16b** (Scheme 2) was chosen as starting material for the silanediol synthesis.

Silanol Dipeptide Mimics. Before attempting to prepare the silanediol tripeptide mimic **11**, a dipeptide model system was prepared in two forms, containing central methylsilanol and silanediol groups. As a further simplifying step, Phe-[Si]-Gly analogues (**25** and **27**, Scheme 3) were the first goals, instead of Phe-[Si]-Ala systems. Elimination of the alanine methyl group would leave a single stereogenic center in the silanediol precursor **24b** and two diastereomers for the methylsilanol precursor **24a**, Scheme 2. Nevertheless, these would be the most complex silanediols ever prepared. The synthesis of **24a** began with conversion of dichloro(methyl)phenylsilane **16a** to the more reactive and yet more easily handled difluorosilane **17a**, by stirring with aqueous HF following the method of Eaborn.[48] This difluoride was treated with 4-bromomagnesium-1-butene to give **18a**, followed by 2-lithio-1,3-dithiane, and the resulting **19a** was isolated in 50% overall yield from **16a**. Deprotonation of **19a** with *n*-butyllithium and alkylation with isobutylbromide gave **20a** in quantitative yield.[49] Following the acylsilane methodology of Brook[50] and Corey,[51] the dithiane **20a** was hydrolyzed with aqueous, unbuffered mercuric chloride. The resulting ketone was reduced with lithium aluminum hydride to give alcohol **21a** as a mixture of diastereomers. A potential advantage of an acylsilane intermediate was the potential for absolute stereocontrol of the α-aminosilane stereogenic center by asymmetric reduction of the ketone, precedented in the work of Buynak[52] and Soderquist.[53] Mesylation of the alcohol followed by displacement of the mesylate with sodium azide in DMF gave the α-azido silane in 84% overall yield from **20a**. Reduction of the azide with lithium aluminum hydride gave the corresponding amine, which was coupled with benzoyl chloride. Purification of the amide gave **22a** in 74% yield from the azide. Oxidative cleavage of the terminal alkene using Weinreb's mixture of Jones reagent and catalytic osmium tetroxide[54] was followed by coupling with benzylamine using DEC and HOBt. Purification gave diamide **24a** in 69% yield from alkene **22a**. The diastereomers of diamide **24a** were separated chromatographically and characterized individually.

Dichlorodiphenylsilane **16b** was taken through an identical sequence to give **24b**. The yields for each of these steps are shown in Scheme 2.

The key hydrolysis reactions, taking **24a** to silanol **25** and **24b** to silanediol **27**, were performed using an excess of triflic acid in methylene chloride for 10 min at 0 °C, followed by addition of ammonium hydroxide (Scheme 3). The diastereomers of methylphenyl **24a** were subjected to the hydrolysis individually. The resulting methylsilanol **25**, isolated in 81% yield, was homogeneous by TLC, but was clearly a 3:2 mixture of diastereomers by NMR. Although the diastereomers of silanol **25** could not be separated chromatographically, treatment of **25** with chlorotrimethylsilane and triethylamine[55] gave two chromatographically separable disiloxanes **26a** and **26b** in a ratio

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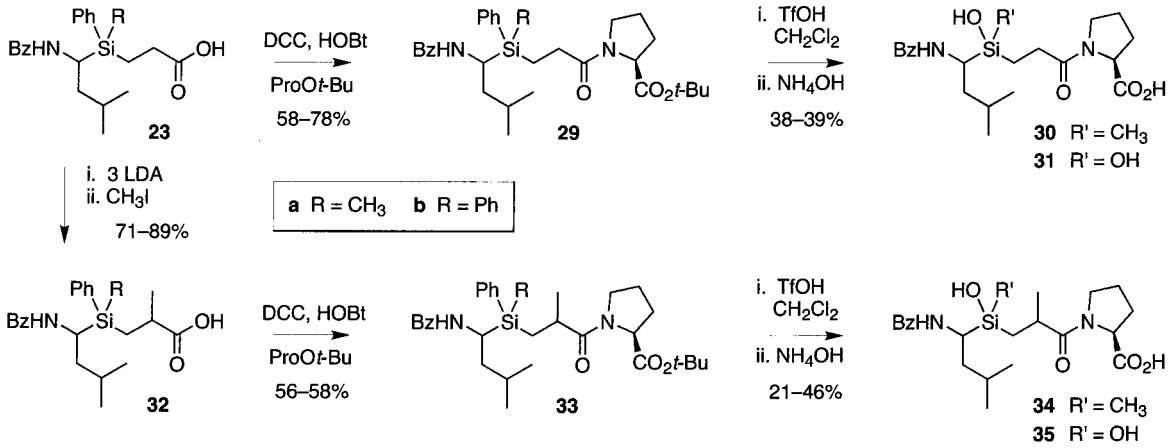
Scheme 4. Introduction of the Methyl Group by Alkylation of the Trianion of **23**, Coupling with Proline, and Hydrolysis



of 3:2 (note that the diastereomeric identity of **24a**, **26a**, and **26b** has not been determined).

Protolytic cleavage of a phenylsilane would be expected to invert stereochemistry at silicon on the basis of Corriu's studies with phenoxide nucleophiles,[56,57] but the effect of a protonated carbon nucleofuge and the acidic reaction conditions were difficult to assess.[58] Electrophilic reactions of Si-chiral allyl silanes have been investigated, but the fate of the silicon chirality appears to have gone undetermined.[59] While inseparable, the diastereomers of **25** were otherwise well defined spectroscopically.

The inseparability of the silanol **25** isomers may be because of a facile epimerization of the silanol stereogenic center. In his seminal studies of silanol chirality, Tacke found that enantiomerically pure silanols were stable in aprotic solvents, but in an aqueous environment racemization occurred within minutes,[60] and diastereomerically pure silanols were found to rapidly epimerize at silicon in an aqueous environment.[61] It is intriguing to consider that the proximal amides in **25** may act as internal nucleophiles and thereby participate in the epimerization of the silanol. Solvents such as DMF are known to racemize stereogenic silicon centers by coordination of the carbonyl oxygen to silicon followed by pseudorotation of the trigonal bipyramid intermediate.[57,58] The rapid epimerization of silanols may provide some advantage in drug design, as control of this stereogenic center could therefore be ignored. In bioassays of silanols, Tacke found that the stereochemistry of the organosilanes had a lesser effect than that of the corresponding carbinols.[60]

Triflic-acid-mediated hydrolysis of diphenylsilane **24b** also proceeded rapidly at 0 °C. After 10 min, ammonium hydroxide was added, and the products were extracted into organic solvents. This gave a product that was, in comparison to **25**, more difficult to characterize. The integration of aromatic and aliphatic absorbances in the proton NMR spectrum indicated that the two phenyl groups attached to silicon had been cleaved, but the resolution was poor, suggesting either intermolecular association of the silanediols or oligomerization to give a complex mixture of diastereomers. The identity of this species was finalized by treatment with chlorotrimethylsilane/triethylamine[55] to give trisiloxane **28**. This trisiloxane was isolated in 58% yield from the diphenylsilane **24b**, nearly identical to the two-step yield of disiloxanes **26** from **24a**.

Silanol Tripeptide Mimics. With the successful synthesis and hydrolysis of the model systems **24**, we turned our attention to tripeptide mimics suitable for enzyme inhibition studies (Scheme 4). Beginning with acids **23a** and **23b**, a DCC/HOBt-mediated coupling with the *tert*-butyl ester of L-proline proceeded without incident to give **29a** (58%) and **29b** (78%). Silane **29a** was a mixture of four diastereomers, and **29b** was a mixture of two diastereomers. Each of these diastereomeric mixtures was subjected to triflic-acid-mediated hydrolysis of the phenylsilane bonds and *tert*-butyl ester cleavage: an excess of triflic acid in methylene chloride at 0 °C for 25 min, followed by dilution with ammonium hydroxide to a pH of 5−6, and then addition of 6 N HCl to give a final pH of 1. The ammonium hydroxide treatment was to ensure that any internal nucleophiles, such as the amides, were hydrolyzed from the silicon center. The silanol **30** and silanediol **31** solutions were then concentrated and purified by HPLC.

To introduce a methyl group adjacent to the carboxylic acid, the trianion of **23** was employed. Three equivalents of LDA was expected to remove the acid proton, the amide proton, and then generate the acid enolate. Addition of iodomethane generated α-methyl **32**. Coupling of **32** with proline *tert*-butyl ester using DIC and HOBt produced esters **33**. Hydrolysis of the phenylsilanes **33a** and **33b** with triflic acid, in a manner identical to that employed for **29a** and **29b**, proceeded smoothly, and the products **34** and **35** were isolated by HPLC. NMR data for all of the proline amides were complicated by the presence of amide rotamers and diastereomeric mixtures.

The diastereomeric silanediols **31** (two isomers) and **35** (four isomers) could not be adequately separated into individual components, and so they were collected and tested as mixtures. Analysis by MALDI-TOF MS gave no indication of oligomer formation, with the exception of **35** in which a trace of dimer

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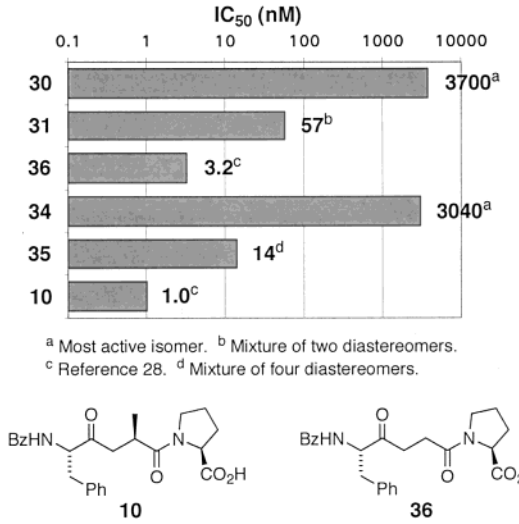

Figure 6. Enzyme inhibition of ACE by ketones **10** and **36** and four silicon analogues, silanols **30** and **34**, and silanediols **31** and **35**.

could be detected. The more complex silanols **30** (four diastereomers) and **34** (eight diastereomers) were separable by HPLC, and were therefore collected and tested individually. MALDI-TOF analysis of the methylsilanols **30** and **34** showed only monomeric species.

Enzyme Assay. The inhibition of ACE was evaluated using Holmquist's modification[62] of the spectrophotometric method of Cushman and Cheung,[63] employing commercially available angiotensin-converting enzyme (Sigma) and *N*-[3-(2-furyl)-acryloyl]-L-phenylalanylglycylglycine (FAPGG, Sigma) as a profluorescent substrate. The assays were conducted in duplicate for those inhibitors with IC_{50} values above 1000 nM, and in triplicate for all others. A summary of the resulting data is shown in Figure 6.

The methylsilanols **30** and **34** proved to be modest inhibitors at best, and data reported in Figure 6 are for the most active diastereomers. With IC_{50} values of 3−4 μM, these silanols are rather far from useful levels of activity. This is not terribly surprising, as carbinols have not been found to be good inhibitors of metalloproteases.[18] The methyl group on silicon may be a steric impediment to binding, and the lone silanol oxygen, as a single point of ligation for the zinc ion, would not be expected to contribute significantly to the binding of the inhibitor.

Silanediols **31** and **35**, capable of chelating a metal ion, were substantially better inhibitors of ACE, with IC_{50} values of 57 and 14 nM, respectively. These two silanediols were mixtures of two and four diastereomers, respectively. Almquist found that high affinity binding of ketone **10** was critically dependent on the configuration of the steregenic centers. The same was found for the diastereomers of **30** and **34**, with IC_{50} values for the least active diastereomers above 10 μM. It is likely, therefore, that most of the enzyme inhibition of the silanediols **31** and **35** is because of a single diastereomer. If one assumes that the observed inhibition can be attributed to a single diastereomer, the concentration required for 50% inhibition of the enyzme could be as low as 29 nM for **31** and 3.5 nM for **35**.

The IC_{50} values for **31** and **35** (different by a factor of 4) roughly parallel the data for **36** and **10** (different by a factor of 3). These pairs of inhibitors, **31**/**35** and **36**/**10**, differ by the absence or presence of a methyl group. The parallel of these inhibitory responses suggests that the binding of the silanediols to ACE is similar to that of the ketones.

Conclusions

These results are consistent with silanediols that chelate the active site zinc ion of ACE, leading to tight binding of these structures, whereas the methylsilanols contribute little to the active site binding and may even sterically inhibit it. Silanediols have been found here to be an effective functional group with which to design metalloprotease inhibitors. Early synthetic difficulties led to the synthesis of silanols with an isobutyl group where Almquist's inhibitors have a benzyl group. The enantioselective synthesis of analogues of **35**, with substitution that will allow a direct comparison with Almquist's inhibitors, will be reported in due course. Ongoing investigations are also anticipated to define the details of the binding mode of silanediols to metalloprotease enzymes.

Silanediols can be potent inhibitors of aspartic proteases (the HIV protease[64]) and metalloproteases (this work), two of the four classes of protease enzymes. Ongoing applications of this new technology to other enzymes and other protease classes are expected to shed additional light on the breadth of its applicability.

Experimental Section

Difluoromethylphenylsilane (17a).[65] To a solution of dichloromethylphenylsilane **16a** (11.8 g, 61.5 mmol) in ethanol (200 mL) at 0 °C was added dropwise over 10 min hydrofluoric acid (48 wt % in water, 10 mL), and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was poured into water (500 mL), and the resulting mixture was extracted twice with 100 mL portions of hexane. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. The colorless oil of crude **17a** was dissolved in toluene and concentrated under reduced pressure to remove any remaining moisture. This product was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, J = 7.5 Hz, 2H), 7.60−7.55 (m, 1H), 7.48−7.44 (m, 2H), 0.62 (t, J_{HF} = 6.0 Hz, 3H).

3-Butenyl(fluoro)methylphenylsilane (18a). A solution of 1-bromomagnesium-3-butene in ether (100 mL, prepared from 9.13 g (67.7 mmol) of 1-bromo-3-butene) was added to **17a** (9.72 g, 61.5 mmol) in toluene (100 mL) at room temperature via cannula over 30 min. After being stirred overnight at room temperature, the reaction mixture was quenched with water (20 mL). The aqueous layer was extracted twice with 30 mL portions of ethyl acetate. The combined organics were washed with saturated NaCl solution and dried over Na_2SO_4. Concentration in vacuo provided crude title compound as a colorless oil in quantitative yield. This product was used in the next reaction without further purification. R_f = 0.75 (hexane). ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 2H), 7.40 (m, 3H), 5.88 (m, 1H), 5.04 (d, J = 17.0 Hz, 1H), 4.95 (d, J = 10.0 Hz, 1H), 2.19 (m, 2H), 1.05 (m, 2H), 0.52 (d, J_{HF} = 6.0 Hz, 3H).

3-Butenyl(1,3-dithian-2-yl)methylphenylsilane (19a). To a solution of 1,3-dithiane (11.1 g, 91.9 mmol) in THF (150 mL) at −78 °C was added dropwise over 10 min *n*-butyllithium (48 mL of a 1.6 M solution

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in hexane, 76.6 mmol), and the solution was stirred for 2 h. A solution of **18a** (11.9 g, 61.3 mmol) in THF (120 mL) was added dropwise over 30 min, and the mixture was stirred for 3 h at −78 °C and overnight at room temperature. The reaction mixture was diluted with water (100 mL) and extracted with three 100 mL portions of ethyl acetate. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave **19a** mixed with residual 1,3-dithiane. The latter was removed by sublimation (54 °C, 8.0 mmHg) to provide pure **19a** as a yellow oil (9.0 g, 50% for three steps from dichlorosilane **16a**). R_f = 0.55 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.63−7.61 (m, 2H), 7.42−7.38 (m, 3H), 5.97−5.84 (m, 1H), 5.06−4.90 (m, 2H), 3.95 (s, 1H), 2.93−2.83 (m, 2H), 2.72−2.67 (m, 2H), 2.21−1.97 (m, 4H), 1.18−1.09 (m, 2H), 0.49 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 141.0, 134.5, 134.1, 129.9, 127.9, 113.2, 32.9, 31.1, 31.0, 27.2, 25.8, 10.8, −7.0. MS (FAB): *m*/*e* 293 (MH^+, 23), 149 (58), 121 (100), 119 (37), 105 (34). Exact mass (FAB) calcd for $C_{15}H_{23}S_2Si$, 293.0854; found, 293.0861. Anal. Calcd for $C_{15}H_{22}S_2Si$: C, 61.16; H, 7.53. Found: C, 61.31; H, 7.74.

3-Butenyl[2-(2-methylpropyl)-1,3-dithian-2-yl]methylphenylsilane (20a). To a solution of **19a** (6.81 g, 23.1 mmol) in THF (150 mL) at −78 °C was added dropwise over 10 min *n*-butyllithium (14.4 mL of a 1.6 M solution in hexanes, 23.1 mmol). After 3 h, 1-bromo-2-methylpropane (3.52 mL, 32.3 mmol) was added dropwise, and the mixture was stirred for 2 h at −78 °C and then overnight at room temperature. The reaction mixture was quenched with water (10 mL) and extracted with three 100 mL portions of ethyl acetate. The combined organics were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration gave **20a** as a yellow oil in quantitative yield and was used in the next reaction without purification. R_f = 0.75 (1:19 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.69−7.66 (m, 2H), 7.40−7.33 (m, 3H), 5.93−5.82 (m, 1H), 4.99 (dd, J = 17.0, 1.7 Hz, 1H), 4.88 (dd, J = 10.1, 1.7 Hz, 1H), 3.0−2.91 (m, 2H), 2.50−2.40 (m, 2H), 2.13−1.90 (m, 6H), 1.78−1.70 (m, 1H), 1.31−1.24 (m, 2H), 0.94 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.55 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 141.2, 135.1, 134.5, 129.5, 127.5, 112.9, 45.6, 39.5, 27.9, 27.0, 24.7, 24.6, 24.2, 24.1, 11.5, −6.1. IR (neat): 2896, 1430, 1254, 1114, 910, 798, 739, 700 cm^{-1}. MS (CI/CH_4): *m*/*e* 351 (MH^+, 19), 295 (100), 273 (71), 175 (36), 149 (74). Exact mass (FAB) calcd for $C_{19}H_{30}S_2Si$, 350.1558 ($MH^+ - 1$); found, 350.1561.

3-Butenyl-(3-methyl-1-oxobutyl)methylphenylsilane. To a solution of **20a** (6.19 g, 17.7 mmol) in acetonitrile (200 mL) were added water (10 mL) and $HgCl_2$ (24 g, 88 mmol). After being stirred overnight at room temperature, the mixture was concentrated in vacuo and then partitioned between water (100 mL) and hexane (200 mL). The aqueous layer was extracted twice with 50 mL portions of hexane, and the combined organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration in vacuo at room temperature gave the title compound as a yellow oil in quantitative yield. R_f = 0.75 (1:19 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.54−7.51 (m, 2H), 7.41−7.35 (m, 3H), 5.91−5.78 (m, 1H), 4.99 (dd, J = 17.0, 1.7 Hz, 1H), 4.90 (dd, J = 10.0, 1.7 Hz, 1H), 2.44 (d, J = 6.7 Hz, 2H), 2.16−2.06 (m, 3H), 1.16−1.07 (m, 2H), 0.78 (pd, J = 6.7 Hz, 6H), 0.51 (s, 3H).

3-Butenyl-(1-hydroxy-3-methylbutyl)methylphenylsilane (21a). To a solution of 3-butenyl-(3-methyl-1-oxobutyl)methylphenylsilane (4.60 g, 17.7 mmol) in ethyl ether (150 mL) at 0 °C was added dropwise lithium aluminum hydride (88.3 mL of a 1 M solution in ether, 88.3 mmol). After being stirred for 15 min at 0 °C, the reaction mixture was diluted with ethyl ether (200 mL), and saturated Na_2SO_4 solution was added until evolution of hydrogen had ceased. The mixture was dried with anhydrous Na_2SO_4, filtered, the residue was extracted with ether (50 mL), and the organics were combined. Concentration provided **21a** as a yellow oil that was a mixture of diastereomers (3.6 g, 78%). This product was used in the next reaction without further purification. R_f = 0.50 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.58−7.53 (m, 2H), 7.39−7.34 (m, 3H), 5.95−5.82 (m, 1H), 5.03−4.89 (m, 2H), 3.70 (dd, J = 12.0, 2.3 Hz, 1H), 2.15−2.07 (m, 2H), 1.86−1.76 (m, 1H), 1.59−1.49 (m, 2H), 1.23−1.12 (m, 1H), 1.03−0.84 (m, 7H), 0.33 and 0.34 (two singlets due to diastereomers, 3H). ^{13}C NMR ($CDCl_3$): δ 141.5, 135.8, 135.6, 134.7, 134.6, 129.6, 129.5, 128.2, 128.1, 113.2, 62.5, 62.1, 42.3, 42.2, 27.5, 24.2, 24.1, 23.6, 20.7, 20.8, 10.7, 10.5, −7.9, −8.0. IR (neat): 3434, 2954, 2913, 1111, 790, 736 cm^{-1}. MS (CI/CH_4): *m*/*e* 263 ($M^+ + 1$, 2), 175 (69), 137 (100), 115 (41). Anal. Calcd for $C_{16}H_{26}OSi$: C, 73.22; H, 9.98. Found: C, 72.85; H, 10.24.

3-Butenyl(1-azido-3-methylbutyl)methylphenylsilane. To a solution of **21a** (3.4 g, 13 mmol) in CH_2Cl_2 (150 mL) and triethylamine (9 mL, 65 mmol) at 0 °C was added dropwise over 5 min methanesulfonyl chloride (7.4 g, 65 mmol), and the mixture was allowed to warm to room temperature over 1 h. After being stirred overnight, the mixture was cooled to 0 °C and diluted with water (50 mL). The aqueous layer was extracted twice with 50 mL portions of CH_2Cl_2. The combined organics were concentrated in vacuo, and the crude mesylate was dissolved in DMF (150 mL). To this solution was added sodium azide (4.2 g, 64.8 mmol), and, after being stirred overnight at room temperature, the mixture was partitioned between water (200 mL) and ethyl acetate (200 mL). The aqueous layer was extracted twice with 50 mL portions of ethyl acetate. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:19 ethyl acetate/hexane) gave 3-butenyl(1-azido-3-methylbutyl)methylphenylsilane as a colorless oil, as a mixture of diastereomers (3.11 g, 84%). R_f = 0.80 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.53−7.47 (m, 2H), 7.38−7.32 (m, 3H), 5.91−5.78 (m, 1H), 5.0−4.86 (m, 2H), 3.03 and 2.99 (two triplets due to diastereomers, J = 2.7 Hz, 1H), 2.08 (q, J = 7.8 Hz, 2H), 1.82−1.70 (m, 1H), 1.58−1.47 (m, 1H), 1.19−1.10 (m, 1H), 1.06−0.94 (m, 2H), 0.89−0.83 (m, 6H), 0.38 and 0.36 (two singlets due to diastereomers, 3H). ^{13}C NMR ($CDCl_3$): δ 140.8, 134.2, 134.1, 129.6, 128.0, 113.3, 50.4, 50.3, 38.6, 38.5, 27.5, 25.8, 23.3, 20.7, 11.4, 11.0, −6.8, −7.3. IR (neat): 2956, 2099, 1259 cm^{-1}. MS (FAB): *m*/*e* 288 (MH^+, 19), 260 (100), 258 (39), 244 (64), 204 (54). Exact mass (FAB) calcd for $C_{16}H_{26}N_3Si$, 288.1896; found, 288.1895.

***N*-[1-(3-Butenyl(methyl)phenylsilyl)-3-methylbutyl] Benzamide (22a).** A solution of 3-butenyl(1-azido-3-methylbutyl)methylphenylsilane (2.75 g, 9.57 mmol) in ether (100 mL) at 0 °C was added dropwise to lithium aluminum hydride (47.8 mL of a 1 M solution in ether, 47.8 mmol), and the mixture was then allowed to warm to room temperature over 10 min. After being stirred for an additional 30 min, the mixture was cooled to 0 °C and diluted with ether (100 mL). A saturated aqueous Na_2SO_4 solution was added until evolution of hydrogen ceased, the mixture was dried with anhydrous Na_2SO_4, filtered, and the residue was extracted with ether (50 mL). The combined organics were concentrated to give the amine as a colorless oil. This amine was taken up in CH_2Cl_2 (60 mL) and triethylamine (5 mL), and the solution was cooled to 0 °C. To this solution was added dropwise benzoyl chloride (1.34 g, 9.57 mmol), and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted twice with 50 mL portions of CH_2Cl_2, and the combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave **22a**, a mixture of diastereomers, as a sticky colorless solid (2.6 g, 74%). R_f = 0.20 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.69−7.60 (m, 2H), 7.56−7.54 (m, 2H), 7.48−7.37 (m, 6H), 5.95−5.80 (m, 1H), 5.57 (d, J = 9.9 Hz, 1H), 5.0 (d, J = 17.0 Hz, 1H), 4.90 (d, J = 8.6 Hz, 1H), 4.24−4.13 (m, 1H), 2.17−2.07 (m, 2H), 1.68−1.55 (m, 1H), 1.44−1.24 (m, 2H), 1.07−0.99 (m, 2H), 0.93 (d, J = 6.4 Hz, 3H), 0.85 and 0.84 (two doublets due to diastereomers, J = 6.6 Hz, 3H), 0.40 and 0.39 (two singlets due to diastereomers, 3H). ^{13}C NMR ($CDCl_3$): δ 166.7, 140.9, 135.0, 134.7, 134.5, 134.34, 134.31, 131.1, 131.0, 130.5, 129.64, 129.61, 128.8, 128.54, 128.50, 128.0, 126.6, 113.3, 113.2, 40.5, 40.4, 37.2, 36.9, 27.5,

25.1, 23.6, 21.2, 11.3, 10.7, −6.7, −7.4. IR (neat): 3279, 2954, 1628, 1536, 699 cm^{-1}. MS (FAB): *m/e* 366 (MH^+, 11), 310 (34), 288 (100). Exact mass (FAB) calcd for $C_{23}H_{31}NOSi$, 365.2175 ($MH^+ - 1$); found, 365.2172. Anal. Calcd for $C_{23}H_{31}NOSi$: C, 75.56; H, 8.55; N; 3.83. Found: C, 75.18; H, 8.41; N, 3.72.

3-[[1-(Benzoylamino)-3-methylbutyl]methylphenylsilyl] Propionic Acid (23a). To a solution of **22a** (0.7 g, 1.91 mmol) in acetone (22 mL) were added 0.23 mL of a 4 wt % solution of OsO_4 in water (2 mol %) and Jones reagent (2.43 mL, 6.49 mmol).[54] After the mixture was stirred for 24 h at room temperature, 2-propanol (0.5 mL) was added followed by $NaHSO_3$ (0.2 g). The mixture was diluted with water (50 mL) and stirred until a dark-green, homogeneous solution was produced. This solution was diluted further with water (90 mL) and extracted with six 50 mL portions of ethyl acetate. The combined organics were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration gave a colorless solid of crude **23a** as a mixture of diastereomers. This product was used in the next reaction without further purification. $R_f = 0.20$ (1:9 ethyl acetate/hexane). ^1H NMR ($CDCl_3$): δ 7.67−7.62 (m, 2H), 7.54−7.52 (m, 2H), 7.48−7.37 (m, 6H), 5.79 and 5.73 (two doublets due to diastereomers, $J = 10.0$ Hz, 1H), 4.25−4.13 (m, 1H), 2.44−2.34 (m, 2H), 1.64−1.57 (m, 1H), 1.49−1.38 (m, 1H), 1.34−1.21 (m, 3H), 1.03, 0.98, 0.90 and 0.84 (four doublets due to diastereomers, $J = 6.6$ Hz, 6H), 0.40 (s, 3H). MS (FAB): *m/e* 384 (MH^+, 62), 310 (100), 306 (88). Exact mass (FAB) calcd for $C_{22}H_{30}NO_3Si$, 384.1995; found, 384.1995.

***N*-[3-Methyl-1-[[3-oxo-3-[(phenylmethyl)amino]propyl]methylphenylsilyl]butyl] Benzamide (24a).** To a solution of benzylamine (0.25 g, 2.29 mmol) in DMF (25 mL) at 0 °C were added 4-methylmorpholine (0.21 mL, 1.91 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.55 g, 2.87 mmol), 1-hydroxybenzotriazole (0.26 g, 1.91 mmol), and crude carboxylic acid **23a** (1.91 mmol). After being stirred for 30 min at 0 °C under argon, the mixture was allowed to warm to room temperature and was stirred overnight. This mixture was partitioned between water (30 mL) and ethyl acetate (30 mL). The aqueous layer was extracted twice with 30 mL portions of ethyl acetate. The combined organics were washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:1:3 ethyl acetate/hexane/CH_2Cl_2) gave two diastereomers, **24a-1** and **24a-2**, in a ratio of 3:7 (69% from **22a**).

24a-1. 0.18 g, 20%, colorless crystals, $R_f = 0.50$ (1:1 ethyl acetate/hexane). mp 42−44 °C. ^1H NMR ($CDCl_3$): δ 7.60 (d, $J = 7.3$ Hz, 2H), 7.53−7.25 (m, 13H), 6.56 (t, $J = 5.3$ Hz, 1H), 6.13 (d, $J = 10.1$ Hz, 1H), 4.40 (d, $J = 5.7$ Hz, 2H), 4.41 (m, 1H), 2.63−2.52 (m, 1H), 2.37−2.27 (m, 1H), 1.65−1.55 (m, 1H), 1.45 (dt, $J = 14.1$, 3.6 Hz, 1H), 1.35−1.21 (m, 3H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 174.9, 167.1, 138.5, 134.8, 134.6, 134.4, 131.4, 129.9, 128.8, 128.7, 128.3, 128.0, 127.4, 126.8, 43.5, 39.4, 36.6, 30.6, 25.0, 23.3, 20.9, 7.6, −7.1. IR (film): 3284, 1636, 1539, 698 cm^{-1}. MS (FAB): *m/e* 473 (MH^+, 58), 395 (72), 282 (100), 157 (72), 91 (68). Exact mass (FAB) calcd for $C_{29}H_{37}N_2O_2Si$, 473.2624; found, 473.2625. Anal. Calcd for $C_{29}H_{36}N_2O_2Si \cdot H_2O$: C, 70.98; H, 7.81; N, 5.71. Found: C, 71.20; H, 7.49; N, 5.76.

24a-2. 0.44 g, 49%, colorless powder, $R_f = 0.45$ (1:1 ethyl acetate/hexane). mp 190−191 °C. ^1H NMR ($CDCl_3$): δ 7.66 (d, $J = 7.4$ Hz, 2H), 7.54−7.21 (m, 13H), 6.10−6.06 (m, 2H), 4.37 (d, $J = 5.6$ Hz, 2H), 4.32−4.24 (m, 1H), 2.45−2.35 (m, 1H), 2.24−2.13 (m, 1H), 1.68−1.59 (m, 1H), 1.48 (dt, $J = 14.4$, 3.5 Hz, 1H), 1.33−1.15 (m, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.85 (d, $J = 6.5$ Hz, 3H), 0.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 174.5, 167.4, 138.6, 135.0, 134.6, 134.5, 131.5, 130.0, 128.9, 128.8, 128.4, 128.1, 127.6, 126.9, 43.6, 40.0, 36.6, 30.7, 25.1, 23.5, 21.0, 8.7, −7.4. IR (Nujol): 3261, 2949, 2922, 2854, 1652, 1628, 1559, 699 cm^{-1}. MS (FAB): *m/e* 473 (MH^+, 32), 395 (47), 282 (58), 157 (100), 137 (48), 93 (42), 91 (46). Exact mass (FAB) calcd for $C_{29}H_{37}N_2O_2Si$, 473.2624; found, 473.2621. Anal. Calcd for $C_{29}H_{36}N_2O_2Si \cdot 0.2H_2O$: C, 73.13; H, 7.70; N, 5.88. Found: C, 73.09; H, 7.49; N, 5.96.

***N*-[1-[Hydroxy(methyl)[3-oxo-3-[(phenylmethyl)amino]propyl]silyl]-3-methylbutyl Benzamide (25).** To a solution of **24a-1** (88 mg, 0.18 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added trifluoromethanesulfonic acid (3 mL, 34 mmol). After the solution was stirred for 10 min, saturated aqueous NH_4OH (30 mL) was added. The aqueous layer was extracted twice with 5 mL portions of CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated at room temperature. The crude product was passed through a pad of silica gel using ethyl acetate as eluant. Concentration provided **25** as a colorless solid (61 mg, 81%). The diastereomeric ratio was determined by ^1H NMR to be 1:1.6. $R_f = 0.10$ (1:1 ethyl acetate/hexane). mp 35−36 °C. ^1H NMR ($CDCl_3$): δ 7.72−7.67 (m, 2H), 7.45−7.13 (m, 8H), 6.73 and 6.60 (two doublets due to diastereomers, $J = 8.3$ Hz, 1NH), 6.35−6.24 (m, 1NH), 4.39−4.24 (m, 3H), 3.67−3.55 (m, 1H), 2.42−2.30 (m, 2H), 1.73−1.60 (m, 2H), 1.38−1.17 (m, 2H), 0.89 (d, $J = 6.4$ Hz, 6H), 0.14 and 0.05 (two singlets due to diastereomers, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7, 167.8, 167.6, 164.2, 138.1, 138.0, 134.7, 134.6, 131.3, 131.2, 128.7, 128.6, 128.5, 127.8, 127.72, 127.69, 127.50, 127.47, 127.4, 126.9, 43.7, 43.6, 40.0, 39.7, 39.0, 38.9, 30.3, 30.1, 25.4, 25.3, 23.6, 21.3, 10.9, 10.0, 1.0, −3.1, −3.3. IR (film): 3288, 2954, 2926, 1636, 1543, 1262, 888, 879, 804, 704 cm^{-1}. MS (FAB): *m/e* 435 (MNa^+, 100), 101 (92). Exact mass (FAB) calcd for $C_{23}H_{32}N_2O_3Si \cdot Na$, 435.2080; found, 435.2071.

***N*-[1-[Trimethylsilyloxy(methyl)[3-oxo-3-[(phenylmethyl)amino]propyl]silyl]-3-methylbutyl Benzamide (26).** To a solution of **33** (75 mg, 0.18 mmol) in THF (10 mL) at room temperature were added triethylamine (1 mL) and chlorotrimethylsilane (1 mL), and the mixture was stirred for 20 min. This mixture was concentrated in vacuo and then partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted twice with 5 mL portions of CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Purification by preparative thin-layer chromatography (1:3 ethyl acetate/hexane) gave two diastereomers as viscous semisolids, in a ratio of 4:6.

26a. 21 mg, 29%, $R_f = 0.25$ (1:3 ethyl acetate/hexane). ^1H NMR ($CDCl_3$): δ 7.72 (d, $J = 17.2$ Hz, 2H), 7.49−7.22 (m, 8H), 6.58 (d, $J = 9.7$ Hz, 1H), 6.37 (t, $J = 4.8$ Hz, 1H), 4.38 (d, $J = 5.6$ Hz, 2H), 3.86 (m, 1H), 2.45−2.34 (m, 1H), 2.31−2.20 (m, 1H), 1.75−1.66 (m, 1H), 1.55 (dt, $J = 14.1$, 3.8 Hz, 1H), 1.38−1.29 (m, 1H), 1.26−0.86 (m, 8H), 0.14 (s, 3H), 0.10 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.4, 166.8, 138.2, 134.7, 131.1, 128.6, 128.5, 127.7, 127.3, 126.7, 43.6, 39.3, 38.3, 30.1, 25.2, 23.6, 21.3, 11.0, 1.9, −2.9. IR (neat): 3277, 2955, 1635, 1544, 1254, 1066, 848, 703 cm^{-1}. MS (FAB): *m/e* 507 (MNa^+, 100), 395 (55), 294 (50). Exact mass (FAB) calcd for $C_{26}H_{40}N_2O_3Si_2 \cdot Na$, 507.2475; found, 507.2473.

26b. 33 mg, 46%, $R_f = 0.20$ (1:3 ethyl acetate/hexane). ^1H NMR ($CDCl_3$): δ 7.62 (d, $J = 7.1$ Hz, 2H), 7.44−7.18 (m, 8H), 6.38 (t, $J = 5.5$ Hz, 1H), 6.27 (d, $J = 9.2$ Hz, 1H), 4.34 (d, $J = 5.4$ Hz, 2H), 3.88−3.80 (m, 1H), 2.47−2.37 (m, 1H), 2.26−2.15 (m, 1H), 1.73−1.6 (m, 1H), 1.49 (dt, $J = 14.2$, 4.0 Hz, 1H), 1.35−1.26 (m, 1H), 1.02−0.76 (m, 8H), 0.09 (s, 3H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.5, 167.0, 138.3, 134.7, 131.1, 128.6, 128.5, 127.8, 127.3, 126.6, 43.5, 39.4, 38.2, 30.2, 25.3, 23.6, 21.3, 11.2, 1.9, −3.1. IR (film): 3278, 2954, 1633, 1547, 1259, 1074, 846, 704 cm^{-1}. MS (FAB): *m/e* 507 (MNa^+, 31), 395 (100), 294 (35). Exact mass (FAB) calcd for $C_{26}H_{40}N_2O_3Si_2 \cdot Na$, 507.2475; found, 507.2478.

3-Butenyl(fluoro)diphenylsilane (18b). In a two-neck flask equipped with a condenser were placed magnesium (3.46 g, 142 mmol) and a crystal of iodine. The flask was warmed with a heat gun until iodine had sublimed. A solution of 4-bromo-1-butene (9.62 g, 71.3 mmol) in ether (100 mL) was added dropwise in 30 min, and the resulting mixture was refluxed for 2 h. This Grignard solution was cooled to room temperature and added over 30 min via cannula to a second flask

containing **17b** (15.7 g, 71.3 mmol) in ether (100 mL) at room temperature. After being stirred overnight at room temperature under argon, the reaction mixture was quenched with water (20 mL), and the organic layer was isolated. The aqueous layer was extracted twice with 50 mL portions of ether. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Distillation (134 °C, 1.5 mmHg) provided pure **18b** as a colorless oil (15.2 g, 83%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, J = 7.8 Hz, 4H), 7.50−7.39 (m, 6H), 5.97−5.83 (m, 1H), 5.02 (dd, J = 17.1, 1.7 Hz, 1H), 4.94 (dd, J = 10.2, 1.7 Hz, 1H), 2.28−2.20 (m, 2H), 1.38−1.30 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 140.9, 135.9, 134.1, 129.7, 127.8, 113.1, 26.9, 14.0.

3-Butenyl(1,3-dithian-2-yl)diphenylsilane (19b). To a solution of 1,3-dithiane (6.77 g, 56.3 mmol) in THF (120 mL) at −78 °C was added dropwise over 10 min *n*-butyllithium (1.6 M in hexane, 50 mmol), and the solution was stirred for 2 h under argon. A solution of **18b** (11.1 g, 43.3 mmol) in THF (100 mL) was added, and the mixture was stirred for 3 h at −78 °C and overnight at room temperature. The reaction mixture was quenched with water (100 mL), and the organic layer was isolated. The aqueous layer was extracted with two 100 mL portions of ethyl ether. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave **19b** contaminated with 1,3-dithiane. The latter was removed by sublimation (54 °C, 8.0 mmHg). Recrystallization from Et_2O provided pure **19b** as a colorless solid (14.8 g, 96%). R_f = 0.40 (1:49 ethyl acetate/hexane). mp 47−49 °C. ^{1}H NMR ($CDCl_3$): δ 7.66 (d, J = 7.8 Hz, 4H), 7.43 (m, 6H), 5.90 (m, 1H), 5.02 (dd, J = 17.1, 1.7 Hz, 1H), 4.91 (dd, J = 10.2, 1.7 Hz, 1H), 4.26 (s, 1H), 2.92 (t, J = 11.8 Hz, 2H), 2.71 (m, 2H), 2.19 (m, 2H), 2.07 (m, 2H), 1.37 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 141.1, 135.9, 132.4, 130.2, 128.0, 113.2, 32.3, 31.5, 27.5, 25.8, 10.5. IR (film): 3068, 3047, 2897, 1639, 1429, 1112, 911, 744, 703 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 357 (MH^+, 11), 237 (36), 211 (100). Exact mass (FAB) calcd for $C_{20}H_{23}S_2Si$, 355.1010 (MH^+ − 2); found, 355.1020. Anal. Calcd for $C_{20}H_{24}S_2Si$: C, 67.36; H, 6.78. Found: C, 67.08; H, 6.78.

3-Butenyl[2-(2-methylpropyl)-1,3-dithan-2-yl]diphenylsilane (20b). To a solution of **19b** (4.68 g, 13.1 mmol) in THF (100 mL) at −78 °C was added dropwise over 10 min *n*-butyllithium (1.6 M in hexanes, 18.4 mmol). After the mixture was stirred for 3 h under argon, 1-bromo-2-methylpropane (2.14 mL, 19.7 mmol) was added dropwise over 5 min, and the mixture was stirred for 2 h at −78 °C and overnight at room temperature. The reaction mixture was quenched with water (10 mL), and the excess organic solvent was removed under reduced pressure. The crude mixture was extracted with three 100 mL portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave pure **20b** as a colorless solid (5.0 g, 92%). R_f = 0.75 (1:9 ethyl acetate/hexane). mp 67−69 °C. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, J = 6.0 Hz, 4H), 7.41 (m, 6H), 5.88 (m, 1H), 4.97 (dd, J = 17.1, 1.7 Hz, 1H), 4.88 (dd, J = 10.1, 1.7 Hz, 1H), 3.04 (m, 2H), 2.49 (t, J = 4.3 Hz, 1H), 2.44 (t, J = 4.1 Hz, 1H), 2.08 (d, J = 5.1 Hz, 2H), 1.98 (m, 4H), 1.79 (m, 1H), 1.54 (m, 2H), 0.82 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 141.5, 136.7, 132.9, 129.9, 127.7, 113.0, 45.7, 39.9, 28.3, 27.2, 24.6, 24.3, 24.2, 11.0. IR (film): 3068, 3043, 2951, 2912, 1432, 1113, 738, 705 cm^{-1}. MS (EI): *m*/*e* (rel intensity) 289 (M^+ − 123, 3), 183 (72), 175 (100), 159 (32), 105 (35). Exact mass (FAB) calcd for $C_{24}H_{32}S_2Si$, 412.1715 (MH^+ − 1); found, 412.1727. Anal. Calcd for $C_{24}H_{32}S_2Si$: C, 69.84; H, 7.82. Found: C, 70.08; H, 8.07.

3-Butenyl(3-methyl-1-oxobutyl)diphenylsilane. To a solution of **20b** (4.64 g, 11.2 mmol) in CH_3CN (300 mL) were added water (10 mL) and $HgCl_2$ (15.26 g, 56.21 mmol). After being stirred overnight at room temperature, the mixture was concentrated and partitioned between water (100 mL) and hexane (200 mL). The organic layer was isolated, and the aqueous layer was extracted with hexane (50 mL). The combined organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration to dryness in vacuo at room temperature gave the crude title compound as a yellow oil (3.2 g, 88%). R_f = 0.80 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.58 (d, J = 6.4 Hz, 4H), 7.44 (m, 6H), 5.88 (m, 1H), 4.99 (dd, J = 17.1, 1.6 Hz, 1H), 4.91 (dd, J = 10.2, 1.6 Hz, 1H), 2.50 (d, J = 6.6 Hz, 2H), 2.14 (m, 2H), 1.36 (m, 2H), 0.95 (m, 1H), 0.76 (d, J = 6.7 Hz, 6H). IR (neat): 3068, 3046, 2956, 1641, 1431, 1113, 743, 702 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 323 (MH^+, 15), 321 (89), 236 (36), 182 (63), 169 (100). Exact mass (FAB) calcd for $C_{21}H_{25}OSi$, 321.1675 (MH^+ − 2); found, 321.1670.

3-Butenyl(1-hydroxy-3-methylbutyl)diphenylsilane (21b). To a solution of the 3-butenyl(3-methyl-1-oxobutyl)diphenylsilane (3.0 g, 9.3 mmol) in ethyl ether (100 mL) at 0 °C was added lithium aluminum hydride (1.0 M in ethyl ether, 47 mmol). After being stirred for 15 min at 0 °C under argon, the reaction mixture was diluted with ethyl ether (300 mL) and quenched with saturated aqueous Na_2SO_4 until evolution of hydrogen had ceased. The mixture was dried with solid Na_2SO_4 and filtered, and the residue was extracted with ether (50 mL). The organic extracts were combined and concentrated in vacuo. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave pure **21b** as a colorless oil (2.1 g, 69%). R_f = 0.60 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.57 (m, 4H), 7.37 (m, 6H), 5.87 (m, 1H), 4.97 (dd, J = 17.1, 1.7 Hz, 1H), 4.88 (dd, J = 10.2, 1.7 Hz, 1H), 4.08 (d, J = 12.1 Hz, 1H), 2.12 (m, 2H), 1.85 (m, 1H), 1.58 (m, 1H), 1.26 (m, 4H), 0.88 (d, J = 6.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 141.4, 135.7, 133.8, 129.8, 128.2, 113.3, 61.5, 42.4, 27.5, 24.2, 23.7, 20.7, 9.8. IR (neat): 3565, 3452, 2955, 2910, 1642, 1434, 1116, 743, 705 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 323 (MH^+ − 2, 5), 269 (21), 198 (57), 183 (100), 159 (56). Exact mass (FAB) calcd for $C_{21}H_{27}OSi$, 323.1831 (MH^+ − 2); found, 323.1824. Anal. Calcd for $C_{21}H_{28}SiO$: C, 77.72; H, 8.70. Found: C, 77.60; H, 8.67.

3-Butenyl(1-azido-3-methylbutyl)diphenylsilane. To a solution of **21b** (1.68 g, 5.16 mmol) in methylene chloride (100 mL) and triethylamine (3.6 mL) at 0 °C was added dropwise over 5 min methanesulfonyl chloride (2.96 g, 25.8 mmol), and the solution was allowed to warm to room temperature over 1 h. After being stirred overnight under argon, the mixture was cooled to 0 °C and quenched with water (50 mL). The organic layer was isolated, and the aqueous layer was extracted twice with 20 mL portions of methylene chloride. The combined organic extracts were concentrated in vacuo at room temperature. The crude mesylate was dissolved in DMF (100 mL), and to this solution was added sodium azide (1.68 g, 25.8 mmol). After being stirred for 8 h at room temperature, the mixture was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was isolated, and the aqueous layer was extracted twice with 50 mL portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:9 ethyl acetate/hexane) gave the pure title compound as a colorless oil (1.57 g, 87%). R_f = 0.90 (1:9 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.57 (d, J = 6.7 Hz, 4H), 7.41 (m, 6H), 5.88 (m, 1H), 5.00 (dd, J = 17.0, 1.5 Hz, 1H), 4.92 (dd, J = 10.2, 1.5 Hz, 1H), 3.44 (d, J = 12.4 Hz, 1H), 2.12 (m, 2H), 1.84 (m, 1H), 1.60 (t, J = 12.5 Hz, 1H), 1.30 (m, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 140.7, 135.3, 132.6, 129.9, 128.0, 113.3, 49.2, 38.8, 27.5, 25.9, 23.3, 20.7, 10.5. IR (neat): 2957, 2102, 1432, 1116, 743, 701 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 350 (MH^+, 18), 322 (100), 315 (42), 306 (42), 236 (73). Exact mass (FAB) calcd for $C_{21}H_{28}N_3Si$, 350.2053; found, 350.2040. Anal. Calcd for $C_{21}H_{27}N_3Si$: C, 72.16; H, 7.79; N, 12.02. Found: C, 71.99; H, 7.91; N, 11.60.

***N*-[1-(3-Butenyldiphenylsilyl)-3-methylbutyl] Benzamide (22b).** To a solution of 3-butenyl(1-azido-3-methylbutyl)diphenylsilane (1.3 g, 3.72 mmol) in ethyl ether (50 mL) at 0 °C was added dropwise over 5 min lithium aluminum hydride (1 M in ether, 18.6 mmol), and the mixture was allowed to warm to room temperature over 10 min. After

being stirredfor 30 min under argon, the reaction mixture was cooled to 0 °C and quenched successively with water (0.7 mL), 15% NaOH in water (0.7 mL), and water (2.1 mL). The mixture was filtered, and the residue was extracted twice with 20 mL portions of ethyl ether. The combined organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration in vacuo gave quantitatively the crude amine as a colorless oil. This amine was dissolved in methylene chloride (30 mL) and triethylamine (5.0 mL), and the solution was cooled to 0 °C. To this solution was added dropwise over 5 min benzoyl chloride (0.52 g, 3.72 mmol), and the mixture was allowed to warm to room temperature. After being stirred overnight under argon, the reaction mixture was quenched with 10% aqueous K_2CO_3 (20 mL). The organic layer was isolated, and the aqueous layer was extracted twice with 50 mL portions of CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel (1:9 ethyl acetate/hexane) gave pure amide **22b** as a colorless crystalline solid (1.40 g, 88%). $R_f = 0.25$ (1:9 ethyl acetate/hexane). mp 99−101 °C. ^{1}H NMR ($CDCl_3$): δ 7.61 (m, 6H), 7.42 (m, 9H), 5.83 (m, 1H), 5.55 (d, J = 10.3 Hz, 1H), 4.95 (dd, J = 17.1, 1.6 Hz, 1H), 4.87 (dd, J = 10.2, 1.6 Hz, 1H), 4.70 (dt, J = 11.3, 3.1 Hz, 1H), 2.08 (m, 2H), 1.64 (m, 1H), 1.39 (m, 2H), 1.30 (br t, J =7.3 Hz, 2H), 1.03 (d, J = 6.5 Hz, 3H), 0.74 (t, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 167.1, 141.1, 135.8, 135.7, 135.2, 133.3, 132.5, 131.3, 130.1, 128.7, 128.4, 128.4, 126.8, 113.4, 40.9, 34.8, 27.2, 24.9, 23.6, 21.2, 10.6. IR (film): 3302, 2955, 2923, 1640, 1519, 1487, 1429, 1322, 1114, 744, 706 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 428 (MH^+, 8), 372 (22), 351 (34), 350 (100). Exact mass (FAB) calcd for $C_{28}H_{34}NOSi$, 428.2410; found, 428.2411. Anal. Calcd for $C_{28}H_{33}NSiO$: C, 78.64; H, 7.77; N, 3.28. Found: C, 78.28; H, 7.96; N, 3.22.

3-[[1-(Benzoylamino)-1-(3-methylbutyl)]diphenylsilyl] Propanoic Acid (23b). To a solution of olefin **22b** (0.63 g, 1.46 mmol) in acetone (23 mL) were added 0.18 mL (2 mol %) of a 4 wt % solution of OsO_4 in water and Jones reagent (1.89 mL, 5.05 mmol). After the mixture was stirred for 24 h at room temperature, 2-propanol (0.73 mL) was added followed by $NaHSO_3$ (0.22 g). The mixture was diluted with water (45 mL) and stirred until a dark-green, homogeneous solution was produced. This solution was diluted with water (90 mL) and extracted with six 50 mL portions of ethyl acetate. The combined organic extracts were dried over $MgSO_4$. Concentration in vacuo gave crude carboxylic acid **23b** as a colorless solid (0.62 g, 96%). R_f = 0.40 (ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.50 (m, 6H), 7.35 (m, 9H), 5.61 (d, J = 10.2 Hz, 1H), 4.63 (dt, J = 10.8, 3.5 Hz, 1H), 2.40 (m, 1H), 2.21 (m, 1H), 1.55 (m, 1H), 1.36 (m, 4H), 0.94 (d, J = 6.4 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H). IR (film): 3320, 2957, 2925, 1713, 1630, 1536, 1430, 1114, 707 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 446 (MH^+, 13), 372 (100), 368 (30), 199 (20). Exact mass (FAB) calcd for $C_{27}H_{32}NO_3Si$, 446.2151; found, 446.2159.

***N*-[3-Methyl-1-[[3-oxo-3[(phenylmethyl)amino]propyl]diphenylsilyl]-butyl] Benzamide (24b).** To a solution of benzylamine (28 mg, 0.26 mmol) in DMF (5 mL) at 0 °C were added 4-methylmorpholine (0.025 mL, 0.22 mmol), DEC (65 mg, 0.34 mmol), HOBT (30 mg, 0.22 mmol), and crude carboxylic acid **23b** (100 mg, 0.22 mmol). After being stirred for 30 min at 0 °C under argon, the mixture was allowed to warm to room temperature and stirred overnight. This mixture was concentrated in vacuo and partitioned between water (8 mL) and ethyl acetate (8 mL). The organic layer was isolated, and the aqueous layer was extracted twice with 8 mL portions of ethyl acetate. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (8 mL) and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (2:3 ethyl acetate/hexane) and recrystallization from ethyl acetate gave pure diamide **24b** as a colorless crystalline solid (96 mg, 80%). R_f = 0.50 (2:3 ethyl acetate/hexane). mp 131−132 °C. ^{1}H NMR ($CDCl_3$): δ 7.41 (m, 20H), 6.42 (t, J = 5.2 Hz, 1H), 5.98 (d, J = 10.1 Hz, 1H), 4.72 (m, 1H), 4.33 (d, J = 5.8 Hz, 2H), 2.54 (m, 1H), 2.10 (m, 1H), 1.65 (m, 1H), 1.45 (m, 4H), 0.98 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.8, 167.3, 138.4, 135.6, 135.4, 134.6, 132.4, 131.4, 130.3, 130.2, 128.7, 128.4, 127.9, 127.4, 126.8, 43.4, 40.0, 34.9, 30.5, 25.0, 23.3, 20.9, 7.6. IR (film): 3280, 2951, 2925, 1636, 1541, 1114, 700 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 535 (MH^+, 30), 457 (87), 344 (100). Exact mass (FAB) calcd for $C_{34}H_{38}N_2O_2Si$, 534.7724 (MH^+ − 1); found, 534.7719. Anal. Calcd for $C_{34}H_{38}N_2SiO_2$: C, 76.36; H, 7.16; N, 5.24. Found: C, 76.21; H, 7.19; N, 5.23.

2-[1-(Benzoylamino)-3-methylbutyl]-1,1,1,5,5,5-hexamethyl-2-[3-oxo-3-[(phenylmethyl)amino]propyl]silyl]trisiloxane (28). To a solution of **24b** (20 mg, 0.037 mmol) in methylene chloride (4.6 mL) at 0 °C was added triflic acid (0.44 mL, 5.0 mmol). After being stirred for 10 min at 0 °C under nitrogen, the reaction mixture was diluted with methylene chloride (20 mL) and transferred via cannula to a second flask containing saturated aqueous NaCl (20 mL) and $NaHCO_3$ (0.82 g, 10.0 mmol) at 0 °C. This mixture was stirred for 15 min at 0 °C, and the organic layer was isolated and dried with Na_2SO_4. The organic solution was cooled to 0 °C under nitrogen, and treated successively with TMSCl (3 mL) and triethylamine (2 mL). After being stirred for 30 min at °C, the mixture was quenched with water (10 mL). The organic layer was isolated and washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Flash chromatography over silica gel (1:2 ethyl acetate/hexane) gave trisiloxane **28** as a thick colorless oil (12 mg, 58%). R_f = 0.50 (1:3 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 7.1 Hz, 2H), 7.45−7.19 (m, 8H), 6.36−6.33 (m, 2H), 4.35 (d, J = 5.7 Hz, 2H), 3.84−3.76 (m, 1H), 2.45−2.33 (m, 1H), 2.25−2.15 (m, 1H), 1.70−1.62 (m, 1H), 1.51−1.41 (m, 1H), 1.37−1.28 (m, 1H), 0.96−0.79 (m, 8H), 0.09 (s, 9H), 0.07 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.4, 166.8, 138.4, 134.8, 131.1, 128.6, 128.5, 127.8, 127.3, 126.7, 43.6, 39.4, 37.7, 30.1, 25.2, 23.7, 21.5, 10.5, 2.0, 1.9. IR (neat): 3272, 2956, 1660, 1638, 1539, 1255, 1080, 845 cm^{-1}. MS (FAB): *m*/*e* (rel intensity) 581 (MNa^+, 48), 469 (99), 368 (100), 207 (51). Exact mass (FAB) calcd for $C_{28}H_{46}N_2O_4Si_3$·Na, 581.2662; found, 581.2662.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]methylphenylsilyl]-1-oxopropyl] L-Proline 1,1-Dimethylethyl Ester (29a). To a solution of **23a** (52 mg, 0.136 mmol) in methylene chloride (1.5 mL) at 0 °C were added DCC (42 mg, 0.204 mmol) and HOBt (28 mg, 0.204 mmol). After 5 min, a solution of L-proline *tert*-butyl ester (L-proline *tert*-butyl ester hydrochloride (42 mg, 0.204 mmol) and triethylamine (28 μL, 0.204 mmol) in 1.5 mL of methylene chloride) was added, and the resulting mixture was stirred at 0 °C for 1 h and then 23 h at room temperature. The mixture was filtered, and the filtrate was washed with 0.2 N NaOH (3 mL). The aqueous phase was extracted with methylene chloride (3 × 2 mL), and the combined organics were washed with water (3 mL), the water wash was extracted with methylene chloride (3 × 2 mL), and the combined extracts were concentrated in vacuo and purified by flash chromatography (1:4 ethyl acetate/methylene chloride) to give 57 mg of **29a** as a clear oil (78%, a mixture of four diastereomers). R_f = 0.40 (1:9 ethyl acetate/methylene chloride). ^{1}H NMR ($CDCl_3$) (complex mixture of four diastereomers): δ 7.91−7.73 (m), 7.55 (m), 7.45−7.34 (m), 7.07 (d, J = 10.4), 6.88 (d, J = 9.7), 6.71 (d, J = 11.0), 6.48 (d, J = 11.0), 6.37 (d, J = 9.8), 4.41−4.02 (m), 3.63−3.24 (m), 2.59−2.46 (m), 2.40−2.35 (m), 2.24−1.81 (m), 1.68−1.55 (m), 1.44 (m), 1.41 (m), 1.39 (s), 1.32−1.23 (m), 0.95−0.79 (m), 0.38 (s), 0.36 (s), 0.33 (s), 0.28 (s), 0.26 (s), 0.25 (s). Exact mass (FAB) calcd for $C_{31}H_{45}N_2O_4Si$ (MH^+), 537.3149; found, 537.3146.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]diphenylsilyl]-1-oxopropyl] L-Proline 1,1-Dimethylethyl Ester (29b). To a 0 °C solution of **23b** (29 mg, 0.065 mmol) in methylene chloride (1 mL) were added DCC (20 mg, 0.098 mmol) and HOBt (13 mg, 0.098 mmol). After 5 min, a solution of L-proline *tert*-butyl ester (L-proline *tert*-butyl ester hydrochloride (20 mg, 0.098 mmol) and triethylamine (14 μL, 0.098 mmol) in 0.5 mL of methylene chloride) was added, and the resulting mixture was stirred at 0 °C for 1 h and then 10 h at room temperature. The mixture was filtered and washed with 0.2 N NaOH. The aqueous

phase was extracted with methylene chloride (3 × 2 mL), and the combined organics were washed with water (3 mL). The water wash was extracted with methylene chloride (3 × 2 mL), and the combined organics were concentrated in vacuo and purified by flash chromatography (1:9 ethyl acetate/methylene chloride) to give 22.5 mg of **29b** as a clear oil (58%, a mixture of two diastereomers). $R_f = 0.40$ (1:9 ethyl acetate/methylene chloride). ^{1}H NMR ($CDCl_3$) (complex mixture of two diastereomers with proline rotamers): δ 7.80 (m), 7.70 (m), 7.64−7.49 (m), 7.45−7.31 (m), 7.05 (d, $J = 9.8$), 6.86 (d, $J = 9.8$), 6.47 (d, $J = 10.4$), 4.68 (m), 4.40−3.83 (m), 3.57−3.15 (m), 2.49−2.39 (m), 2.35−2.23 (m), 2.09−1.79 (m), 1.67−1.50 (m), 1.42 (m), 1.35 (s), 1.26 (m), 1.00−0.93 (m), 0.83−0.79. Exact mass (FAB) calcd for $C_{36}H_{47}N_2O_4Si$ (MH^+), 599.3305; found, 599.3313.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]hydroxymethylsilyl]-1-oxopropyl] L-Proline (30). To a 0 °C solution of **29a** (52 mg, 0.097 mmol) in methylene chloride (12 mL) was added trifluoromethanesulfonic acid (1.63 mL), and the resulting solution was stirred for 25 min. Concentrated NH_4OH was added to give an aqueous phase (pH 5−6), and the pH was adjusted to 1 with 6 N HCl. The aqueous phase was extracted with methylene chloride (3 × 2 mL), and the combined extracts were concentrated in vacuo. Purification by RP-HPLC (250 × 22 mm Vydac Peptide and Protein C18, with a linear gradient of 40−50% aqueous acetonitrile containing 1% trifluoroacetic acid, monitoring at 215 nM) and lyophilyzing the collected fractions gave 15.5 mg of **30** as a colorless solid (38%). ^{1}H NMR (acetone-d_6) (mixture of four diastereomers): δ 10.67 (m), 10.44 (m), 8.08 (m), 7.92 (m), 7.73 (m), 7.58 (m), 7.43 (m), 4.90 (m), 4.77 (m), 4.71 (m), 4.62 (m), 3.83−3.74 (m), 3.52 (m), 3.28−3.18 (m), 2.99 (m), 2.77 (m), 2.60−2.53 (m), 2.42 (m), 2.16 (m), 1.91 (m), 1.77−1.62 (m), 1.28 (m), 0.98−0.88 (m), 0.43 (s), 0.42 (s), 0.38 (s), 0.32 (s), 0.31 (s), 0.28 (s), 0.14 (m). MS (FAB): *m*/*e* (rel intensity) 403 (M − OH, 100), 230 (10), 109 (14). Exact mass (FAB) calcd for $C_{21}H_{31}N_2O_4Si$, 403.2053; found, 403.2048.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]dihydroxysilyl]-1-oxopropyl] L-Proline (31). To a 0 °C solution of **29b** (20 mg, 0.033 mmol) in methylene chloride (2.5 mL) was added trifluoromethanesulfonic acid (0.55 mL), and the resulting solution was stirred for 25 min. Concentrated NH_4OH was added to give an aqueous phase (pH 5−6), and then was adjusted to pH 1 with 6 N HCl. The aqueous phase was extracted with methylene chloride (3 × 2 mL), and the combined extracts were concentrated in vacuo. Purification by RP-HPLC (250 × 4.6 mm Vydac Peptide and Protein C18, with a linear gradient of 20−50% aqueous acetonitrile containing 1% trifluoroacetic acid, monitoring at 215 nM) and lyophilyzing the collected fractions gave 5.5 mg of **31** as a colorless solid (39%). ^{1}H NMR (D_2O): δ 7.93 (s), 7.74 (s), 7.59 (s), 3.74 (s), 3.51 (s), 2.89 (m), 2.39 (m), 2.08 (m), 1.68 (m), 0.93 (m). MS (FAB): 405 ($MH^+ - H_2O$).

3-[[1-(Benzoylamino)-3-methylbutyl]methylphenylsilyl]-2-methylpropionic Acid (32a). To a solution of **23a** (128 mg, 0.334 mmol) in THF (1 mL) was added a solution of LDA, prepared from diisopropylamine (164 μL, 1.17 mmol), THF (1 mL), and *n*-butyllithium (0.5 mL, 2.3 M in hexanes, 1.16 mmol). The resulting solution was stirred at 0 °C for 1 h and then cooled to −78 °C. Iodomethane (73 μL, 1.17 mmol) was added, and stirring continued for 2.5 h. After the solution was warmed to room temperature, water (2 mL) was added, and the aqueous phase was washed with 1:3 ethyl acetate/hexane, acidified to pH 1 with 6 N HCl, and extracted with methylene chloride (3 × 2 mL). The combined organics were concentrated and purified by flash chromatography (1:9 methanol/methylene chloride) to give 94.4 mg of **32a** as a tan oil (71%). $R_f = 0.54$ (1:9 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 7.69−7.65 (m), 7.60−7.51 (m), 7.47−7.33 (m), 7.28−7.22 (m), 6.98−6.94 (m), 5.92 (d, $J = 9.2$), 5.76 (d, $J = 11$), 4.43 (m), 4.19 (m), 1.63−0.83 (m), 0.53−0.40 (m). Exact mass (FAB) calcd for $C_{23}H_{31}NO_3Si$ (MH^+), 398.2151; found, 398.2156.

3-[[1-(Benzoylamino)-3-methylbutyl]diphenylsilyl]-2-methylpropionic Acid (32b). To a solution of **23b** (36 mg, 0.081 mmol) in THF (0.5 mL) was added a solution of LDA, prepared from diisopropylamine (40 mL, 0.28 mmol), THF (1 mL), and *n*-butyllithium (0.12 mL, 2.3 M in hexanes, 0.28 mmol). The resulting solution was stirred at 0 °C for 1 h and then cooled to −78 °C. Iodomethane (18 μL, 0.28 mmol) was added, and stirring continued for 2 h. After the solution was warmed to room temperature, water (2 mL) was added, and the aqueous phase was acidified to pH 1 with 6 N HCl, and extracted with 1:1 ethyl acetate: hexanes (3 × 2 mL). The combined organics were concentrated and purified by flash chromatography (1:9 methanol/methylene chloride) to give 36 mg of **32b** as a tan oil (89%). $R_f = 0.47$ (1:9 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 7.61−7.54 (m), 7.47−7.32 (m), 7.23 (m), 5.66 (d, $J = 10.3$), 4.70 (m), 2.54−2.47 (m), 2.31−2.23 (m), 1.65−1.55 (m), 1.48−1.36 (m), 1.26 (m), 1.05 (d, $J = 6.4$), 1.02 (s, $J = 6.8$), 0.93 (m), 0.83 (m). Exact mass (FAB) calcd for $C_{28}H_{34}NO_3Si$ (MH^+), 460.2308; found, 460.2303.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]methylphenylsilyl]-2-methyl-1-oxopropyl] L-Proline 1,1-Dimethylethyl Ester (33a). To a 0 °C solution of **32a** (94.4 mg, 0.238 mmol) in methylene chloride (1 mL) were added DIC (56 μL, 0.357 mmol) and HOBt (48 mg, 0.357 mmol). After 5 min, a solution of L-proline *tert*-butyl ester (L-proline *tert*-butyl ester hydrochloride (74 mg, 0.357 mmol) and triethylamine (49 μL, 0.357 mmol) in 1.5 mL of methylene chloride) was added, and the resulting mixture was stirred at 0 °C for 1 h and then 11 h at room temperature. The mixture was filtered and washed with 0.2 N NaOH (3 mL). The aqueous phase was extracted with methylene chloride (3 × 2 mL), and the combined organics were washed with water (10 mL). The water wash was extracted with methylene chloride (3 × 2 mL), and the combined organics were concentrated in vacuo and purified by flash chromatography (1:4 ethyl acetate/methylene chloride) to give 131.1 mg of **33a** as a clear oil (58%). $R_f = 0.36$ (1:4 ethyl acetate/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 7.78 (m), 7.57 (m), 7.37 (m), 6.91 (m), 6.60−6.49 (m), 6.09−5.95 (m), 4.36−4.26 (m), 4.20−4.08 (m), 3.56−3.26 (m), 2.70 (m), 2.59 (m), 2.56 (m), 1.82 (m), 1.60 (m), 1.47−1.35 (m), 1.25 (m), 1.13 (m), 1.06−0.81 (m), 0.47−0.36 (m), 0.22 (s). Exact mass (FAB) calcd for $C_{32}H_{47}N_2O_4Si$ (MH^+), 551.3305; found, 551.3329.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]diphenylsilyl]-2-methyl-1-oxopropyl] L-Proline 1,1-Dimethylethyl Ester (33b). To a 0 °C solution of **32b** (33 mg, 0.072 mmol) in methylene chloride (0.5 mL) were added DIC (17 μL, 0.108 mmol) and HOBt (15 mg, 0.108 mmol). After 5 min, a solution of L-proline *tert*-butyl ester (L-proline *tert*-butyl ester hydrochloride (22 mg, 0.108 mmol) and triethylamine (15 μL, 0.108 mmol) in 0.5 mL of methylene chloride) was added, and the resulting mixture was stirred at 0 °C for 1 h and then 13 h at room temperature. The mixture was washed with 0.2 N NaOH (3 mL). The aqueous phase was extracted with methylene chloride (4 × 2 mL), and the combined organics were washed with water (10 mL). The water wash was extracted with methylene chloride (2 × 2 mL), and the combined organics were concentrated in vacuo and purified by flash chromatography (1:4 ethyl acetate/methylene chloride) to give 24 mg of **33b** as a tan oil (56%). $R_f = 0.49$ (1:4 ethyl acetate/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 7.81−7.76 (m), 7.72−7.70 (m), 7.63−7.57 (m), 7.55−7.50 (m), 7.45−7.29 (m), 7.06 (d, $J = 9.8$), 6.86 (d, $J = 10.7$), 6.73 (d, $J = 10.7$), 6.47 (d, $J = 9.8$), 4.68 (m), 4.55 (m), 4.31 (m), 4.20 (m), 4.05 (m), 3.95 (m), 3.60 (m), 3.52 (m), 3.44 (m), 3.30 (m), 3.20 (m), 2.43 (m), 2.07−1.80 (m), 1.65−1.45 (m), 1.42 (m), 1.35 (m), 1.26 (m), 0.96 (m), 0.81 (m). Exact mass (FAB) calcd for $C_{37}H_{49}N_2O_4Si$ (MH^+), 613.3462; found, 613.3470.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]hydroxymethylsilyl]-2-methyl-1-oxopropyl] l-Proline (34). To a 0 °C solution of **33a** (58 mg, 0.105 mmol) in methylene chloride (9 mL) was added trifluoromethanesulfonic acid (1.77 mL), and the resulting solution was stirred for 25 min. Concentrated NH_4OH was added to give an aqueous phase (pH 5−6), and then was adjusted to pH 1 with 6 N HCl. The aqueous phase was extracted with methylene chloride (3 × 4 mL), and the combined extracts were concentrated in vacuo. Purification by RP-

HPLC (250 × 22 mm Vydac Peptide and Protein C18, with a linear gradient of 35−50% aqueous acetonitrile containing 1% trifluoroacetic acid, monitoring at 215 nM) and lyophilyzing the collected fractions gave 21.1 mg of **34** as a colorless solid (46%). ^{1}H NMR (CD_3CN): δ 9.14 (m), 7.92 (d, J = 6.9), 7.71 (t, J = 6.9), 7.57 (t, J = 7.8), 4.74 (m), 4.56 (m), 4.47 (m), 3.79 (m), 3.72 (m), 3.57 (m), 3.11 (m), 2.93 (m), 2.36−1.81 (m), 1.46 (m), 1.32−1.24 (m), 0.96 (m), 0.40−0.30 (m). MS (FAB): *m*/*e* (rel intensity) 417 (M − OH, 100), 403 (20). Exact mass (FAB) calcd for $C_{22}H_{33}N_2O_4Si$, 417.2210; found, 417.2221.

1-[3-[[1-(Benzoylamino)-3-methylbutyl]dihydroxysilyl]-1-oxopropyl] L-Proline (35). To a 0 °C solution of **33b** (24 mg, 0.039 mmol) in methylene chloride (3.7 mL) was added trifluoromethanesulfonic acid (0.66 mL), and the resulting solution was stirred for 25 min. Concentrated NH_4OH was added to give an aqueous phase (pH 5−6), and then was adjusted to pH 1 with 6 N HCl. Saturated NaCl (2 mL) was added, the aqueous phase was extracted with methylene chloride (3 × 2 mL), and the combined extracts were concentrated in vacuo. Purification by RP-HPLC (250 × 22 mm Vydac Peptide and Protein C18, with a linear gradient of 25−40% aqueous acetonitrile containing 1% trifluoroacetic acid, monitoring at 215 nM) and lyophilyzing the collected fractions gave 3.6 mg of **35** as a colorless solid (21%). ^{1}H NMR (D_2O): δ 7.97 (m), 7.78−7.69 (m), 7.63 (m), 4.56 (m), 3.77 (m), 3.57−3.19 (m), 2.91 (m), 2.42 (m), 2.11 (m), 1.75 (m), 2.10 (m), 1.75 (m), 1.44−1.18 (m), 0.99 (m). MS (MALDI-TOF): 420 (M − 16).

General Assay Procedure. Following the procedure of Cushman and Cheung,[63] as modified by Holmquist,[62] test compounds were dissolved in deionized water buffered with 0.3 M NaCl and 0.05 M Trizma (Sigma), to give a pH of 8.3 at 37 °C. A solution of porcine ACE (Sigma) in a buffered human serum base (0.10 mL) was added to 1.0 mL of a 0.5 mM solution of *N*-[3-(2-furyl)acryloyl]-L-phenylalanylglycylglycine (FAPGG, Sigma) in a 1 cm disposable cuvette. The test compound solution was added, and the mixture was incubated for 5 min. Enzymatic activity was followed by monitoring at 340 nm over a period of 5 min, relative to an identical solution not containing the inhibitor. The silanediols **31** and **35**, the most active species, were assayed in triplicate, and the less active methylsilanols **30** and **34** were assayed in duplicate.

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Supporting Information Available: Proton NMR spectra for **19**−**28** and plotted inhibition data for silane inhibitors (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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