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Further Studies toward the Stereocontrolled Synthesis of Silicon-Containing Peptide Mimics

Dácil Hernández, Karl B. Lindsay, Lone Nielsen, Tina Mittag, Klaus Bjerglund, Stig Friis, Rasmus Mose, and Troels Skrydstrup*

Center for Insoluble Protein Structures, Department of Chemistry and Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

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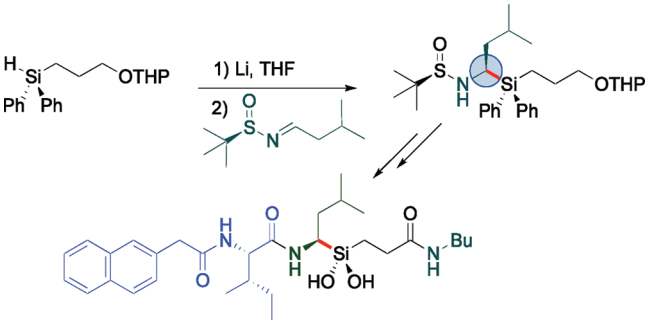

Further studies are reported on the utilization of the versatile reaction between chiral sulfinimines and alkyldiphenylsilyl lithium reagents with the goal of preparing a wide range of silanediol-based protease inhibitors. In particular, focus has been placed to demonstrate how a number of genetically encoded amino acid side chains such as serine, threonine, tyrosine, lysine, proline, arginine, aspartate and asparagine might be incorporated into the overall approach. Efforts to apply this synthetic methodology for accessing biologically relevant silanediol dipeptide mimics are also described. This includes the synthesis of a potential inhibitor of the human neutrophil elastase, as well as a diphenylsilane mimic of a hexapeptide fragment of the human islet amyloid polypeptide.

Introduction

Silicon represents an important option for the isosteric replacement of carbon in the quest for discovery and improvement of bioactive compounds.[1] In particular its size and tetrahedral nature give it all the important features of a carbon atom, but with some differences. For example a Si−C bond is slightly longer than a C−C bond,[1g] and the formation of double bonds at a silicon atom is strongly disfavored as a result of poor p-orbital overlap.[1f,k,m] In stark contrast to the hydrated carbonyl (geminal diol), silicon diols do not form the corresponding silicones via the elimination of water. In fact, this aversion to sp^2 hybridization has been cleverly exploited by the Sieburth group for the preparation of several protease inhibitors containing silicon diols, which exert their effect by behaving as admirable mimics for the tetrahedral intermediate in peptide hydrolysis (Figure 1).[2]

The proof of concept was achieved with a series of silanediol peptide mimics such as **2** prepared as an inhibitor of the metalloprotease ACE (Figure 2).[3] This compound is an analogue of an *N*-acylated Phe-Ala-Pro tripeptide, in which the Phe-Ala peptide bond is replaced by a silanediolmethylene moiety. Silanediol inhibitors of the HIV protease **4**,[4] an aspartyl protease, and thermolysin **6**,[5] a metalloprotease, have also been prepared (Figure 2). All three silanediol inhibitors were designed as analogues of known protease inhibitors containing different TI-mimicking motifs, namely, ketomethylene (**1**), phosphinate (**3**), and hydroxyethylene (**5**). The silanediol analogues demonstrated K_i values comparable to those of their parent compounds. The mode of binding was recently confirmed by a crystal structure of a silanediol inhibitor **3** in the active site of the metalloprotease thermolysin.[6]

The silanediol peptide inhibitor **7**, which targets the human neutrophil elastase (HNE), a serine protease, has also been reported.[7] It is not obvious how the silanediol mimics the TI of serine protease hydrolysis, but some interaction with the active site serine is likely to occur. The oxy-anion hole comprises hydrogen bond donors, for example, amides in the peptide

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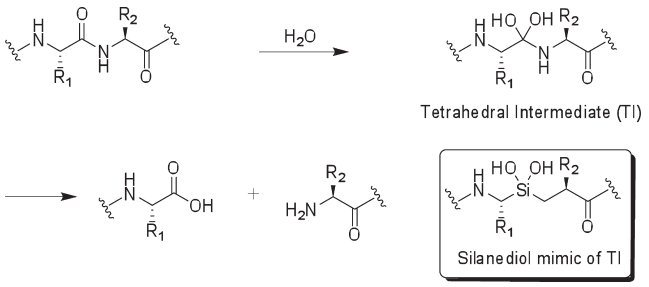

FIGURE 1. Silanediol-based isosteres mimic the tetrahedral intermediate (TI) in peptide hydrolysis.

backbone, which contribute to stabilizing the oxygen anion,[8] and these may similarly engage in hydrogen bonding to the silanediol unit.

All silanediol-based inhibitors are functionalized molecules, which mimic a dipeptide unit. The key step in all syntheses of a silanediol peptide mimic is the introduction of the two functionalized alkyl substituents at silicon, which typically requires two separate steps. Furthermore and depending on the amino acid composition of the dipeptide, in most cases the syntheses would also need to be sufficiently flexible for the installment of two stereogenic carbon centers in the α- and β-position to the silicon center, which increases the complexity of the synthetic route to these compounds.

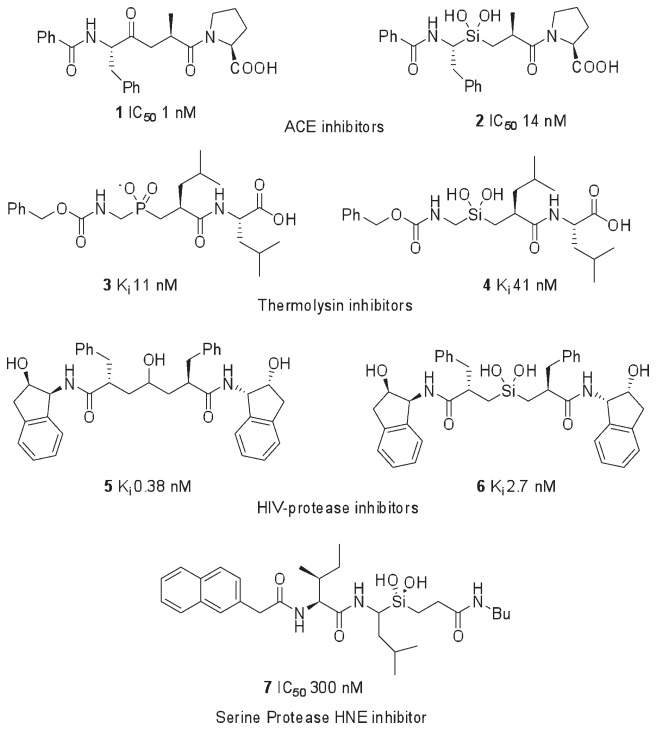

FIGURE 2. Silanediol-based protease inhibitors.

The first syntheses of the silanediol-based protease inhibitors reported by Sieburth and co-workers involved nucleophilic substitution of halosilanes as the means to construct the carbon−silicon bonds.[3f,g] This strategy was successfully applied to the synthesis of nine inhibitors against three different proteases, but the synthetic routes followed were mainly designed for the specific peptide needed. Later, another procedure for the synthesis of silanediol peptide mimics was proposed (Scheme 1).[9] This synthesis utilizes a platinum-catalyzed hydrosilylation of an olefin directly followed by lithiation and

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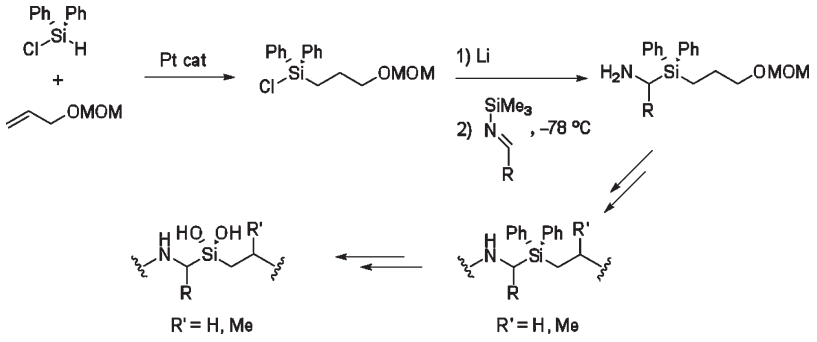
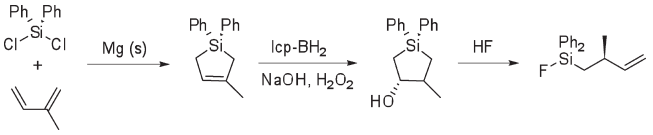
SCHEME 1. An Alternative Synthetic Strategy toward Silanediol Peptide Mimics



SCHEME 2. Preparation of β-Silyl Acid Precursor Useful in Silanediol Peptide Mimics Synthesis

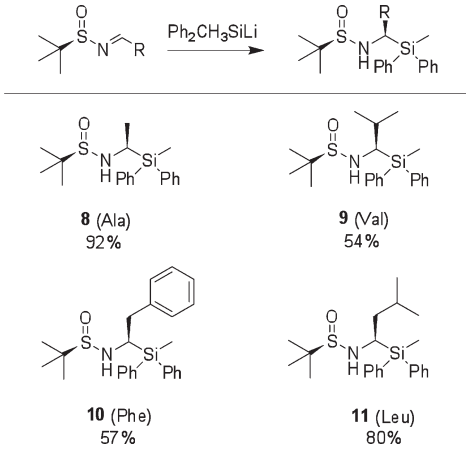


addition to an *N*-silylimine. In two steps, this provides the silane; however, no substituent is present in the position β to the silicon, and no asymmetric control at the α-center is undertaken. Nevertheless, construction of the central silicon carbon framework and simultaneous introduction of the primary amine is achieved in two steps, which make this synthetic approach attractive.

Recently, Sieburth reported a second and elegant synthetic approach toward silanediol peptide mimics focused on the preparation of β-silyl carboxylic acid precursors. This approach applied a magnesium-mediated cyclization of a dichlorodiphenylsilane and a diene to yield a 2,5-dihydrosilole (Scheme 2). Hydroboration followed by hydrofluoric acid promoted ring opening gave the fluorosilane, and further functionalization was accomplished through nucleophilic displacement of the fluoride or by converting the fluorosilane into its corresponding silyl lithium reagent and addition to an electrophile. The alkene was envisaged cleaved under oxidative conditions to give a β-silyl carboxylic acid, and application of the homochiral borane Ipc-BH_2 yielded enantiopure material.[10]

We have previously disclosed the synthesis of simple C-terminal silanediol peptide mimics, via the coupling of a diphenylsilyl lithium reagent with an appropriate Ellman sulfinimine (Scheme 3).[11a] This allowed us to mimic the simple amino acids with aliphatic and aromatic side chains and extend the peptide chain at the N-terminus. However more complex amino acid side chains were not included in that study. In a subsequent report, we developed a method for the two-step assembly of the carbon−silicon backbone of the dipeptide mimic including a hydrosilylation of terminal alkenes with diphenylsilane for the formation of the first C−Si bond, followed by lithiation of the resulting hydridosilane and a highly diastereoselective addition to an optically active *tert*-butanesulfinimine, to generate the second C−Si

SCHEME 3. Previous Additions of Ph_2CH_3SiLi to Chiral Sulfinimines



bond. Although this approach proved to be a potentially viable route to this new class of protease inhibitors, extension of the C-terminus to provide the true silanediol peptide mimics was not undertaken.

Herein, we report our results directed at extending the scope of the synthesis of silanediol peptide mimics. Our recent focus has been placed on facilitating synthetic access to more complex amino acid mimics possessing functionalized/reactive side chains while also allowing for both N- and C-terminus end peptide extensions.

Results and Discussion

Synthesis of New Amino Acid Mimics. To expand upon the library of available diphenyl silane building blocks for incorporation into peptide synthesis, initial focus was placed upon preparation of methyldiphenylsilanes substituted with the 20 side chains of genetically encoded amino acids. From our previous study we had demonstrated that rapid access to simple mimics could be achieved directly for those compounds containing unreactive side chains such as aliphatic and aromatic groups. Thus the mimics of alanine (**8**), valine (**9**), phenylalanine (**10**), and leucine (**11**) were readily available (Scheme 3).[11a] Furthermore, we had also demonstrated that protected alcohols, and doubly protected amines were well tolerated in the coupling reaction.

Using the same protocol as earlier published,[11a] involving lithiation of the silyl chloride with lithium metal in THF at room temperature followed by its addition to a cold ethereal

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solution of the sulfinimine, we have found that the protected versions of serine (**13**), tyrosine (**15**), and threonine (**17**) can also be directly prepared from the diphenylmethylsilyl lithium addition to sulfinimines **12**, **14**, and **16**, respectively, in satisfactory to good yields (Scheme 4).

Because of the strongly basic conditions encountered during the silyl lithium coupling reaction, it was deemed prudent to introduce more reactive amino acid side chains after the addition. While we have previously demonstrated that doubly protected amines can be employed in the coupling reaction with the diphenylmethylsilyl lithium reagent, we have found it more practical to introduce the nitrogen functionality after the coupling reaction, via the corresponding protected alcohol (Scheme 5). This is due in part to the presence of rotamers of doubly protected nitrogen groups complicating the spectra, which makes it problematic to determine the diastereoselectivity of the addition reaction. Furthermore, the additional handling of the protection groups made this approach longer and lower-yielding. Hence, we endeavored to introduce nitrogen functionality after the addition reaction.

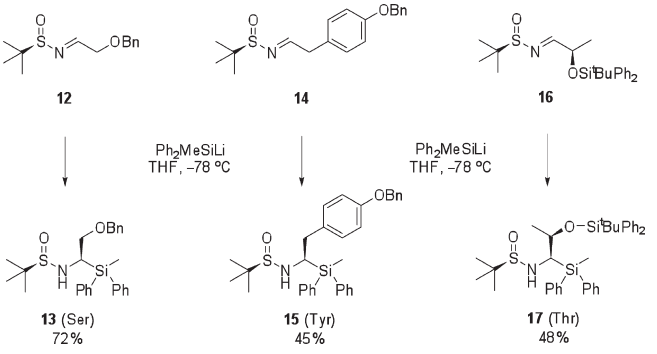
To generate the silicon analogue of the amino acid lysine, we started from the addition product **18** (Scheme 6) obtained in a 79% yield (see Experimental Section). Deprotection of the alcohol and the sulfinamide auxiliary was readily achieved, followed by reprotection of the amine as its corresponding Boc carbamate **19**, which is more practical in terms of peptide synthesis. Further manipulation of **19** by transformation of the alcohol into the corresponding mesylate **20** and then treatment with NaN_3 supplied the azide **21**, which for the purposes of peptide synthesis can also be thought of as a protected amine. Finally, liberation of the free amine from the azide **21** was readily achieved with Pearlman's catalyst under a hydrogen atmosphere.

To access additional amino acid analogues representing proline and arginine as depicted in Scheme 7, we started with the previously reported addition product **23**.[11a] Oxidative removal of the PMB group, hydrolysis of the sulfinamide **23**, and reprotection as the carbamate then afforded the free alcohol **25**, which was converted to the corresponding mesylate **26** using standard methods. When mesylate **26** was treated with NaH, it cyclized rapidly providing the proline mimic **27** in excellent yield. Subjection of the same mesylate **26** to NaN_3 in DMF gave the corresponding azide **28**, which could easily be reduced to afford the free amine **29**. Conversion of amine **29** into the arginine mimic **30** was then obtained by treatment with *N*,*N*′-di-Boc-*N*″-triflylguanidine, which produced the desired side chain in excellent overall yield. This example demonstrates that the *p*-methoxybenzyl group (PMB) may also be used and can be selectively removed without affecting the acid labile sulfinamide, though global deprotection can also be accomplished if necessary.

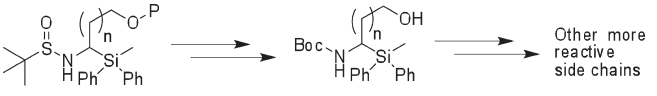
In a similar approach, oxidation of the side chain alcohol in **33** could be accomplished by applying Jones' reagent (Scheme 8). This gave direct access to the mimic of aspartic acid **34**, which could also be converted to the asparagine mimic **35** by treatment with pivaloyl chloride followed by gaseous ammonia. Unfortunately, attempts to promote the same sequence starting from the alcohol **25** to access the corresponding glutamic acid and glutamine analogues was not successful. This was ascribed to the possibility for cyclization of the intermediate aminoaldehyde to the corresponding five-membered ring hemiaminal.

C-Terminal End Extension. With an extended armory of amino acid side chains available, we next turned our attention toward extension of the C-terminus. We have previously reported the use of functionalized diphenylhydridosilanes in coupling reactions applying a protocol involving direct lithiation of the silane and addition to the sulfinimine,[11b] and it was felt that this approach would serve well here. One substrate (**38**) in particular drew our attention, as this represented the three-carbon fragment required for the preparation of the glycine mimic at the C-terminus, requiring a mere deprotection and oxidation of the alcohol moiety up to the corresponding acid. Thus silanediol mimics of the Xaa−Gly peptide bond were expected to be prepared (Scheme 9).

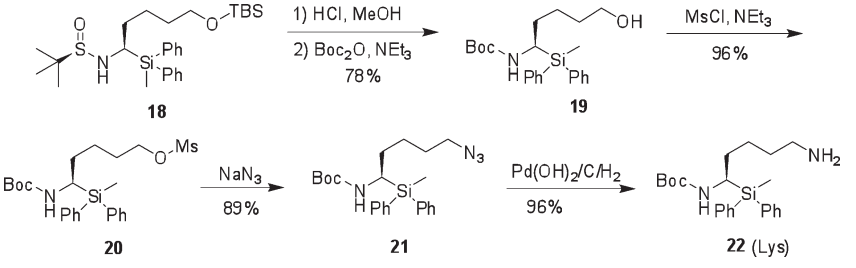
SCHEME 4. Synthesis of Serine, Tyrosine, and Threonine Mimics



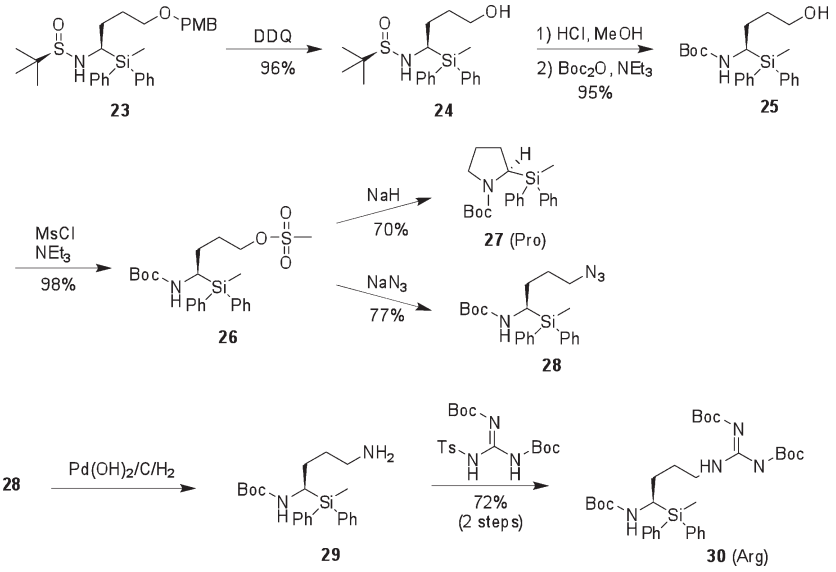
SCHEME 5. Modification of the Amino Acid Side Chains after the Coupling Reaction



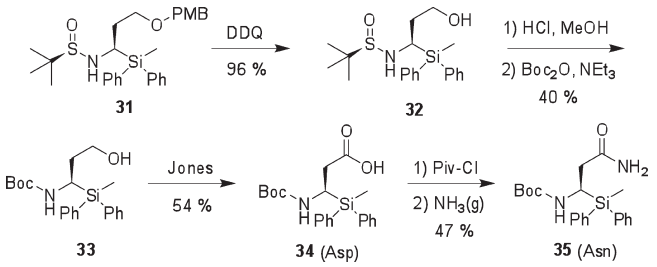
SCHEME 6. Introduction of Nitrogen into the Amino Acid Chain; Synthesis of a Lysine Building Block



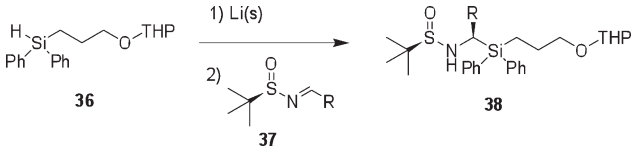
SCHEME 7. Preparation of Proline and Arginine Mimics



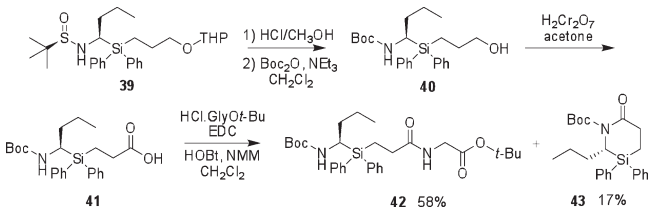
SCHEME 8. Preparation of Aspartate and Asparagine Mimics



SCHEME 9. Lithiation of Hydridosilanes and Subsequent Addition to Sulfinimine



SCHEME 10. Preliminary Oxidation Studies



Silylsulfinamide **39** was used as a model compound for the alcohol oxidation (Scheme 10). Sulfinamide and THP removal had already been accomplished using dry HCl in methanol, and the obtained ammonium salt was reprotected with a Boc protecting group under standard conditions to obtain **40**. Oxidation was first performed using Jones oxidation conditions,[12] which gave the expected carboxylic acid **41** and a byproduct. To circumvent possible issues regarding isolation of the polar carboxylic acid, the crude product was subjected to EDC-promoted peptide coupling with *tert*-butyl glycinate (Scheme 10).

Purification gave the expected dipeptide analogue **42** in 58% yield, and the byproduct was identified as azasilinanone **43**, isolated in a 17% yield. This byproduct may be formed by initial oxidation of the alcohol to an aldehyde and cyclization to give a hemiaminal. Oxidation will then lead to the lactam. It was not clear to us whether the hemiaminal formation occurred because of the strongly acidic conditions or because the hydration and oxidation of the aldehyde was too slow. One way to perform oxidations under mild conditions is by the use of nitroxyl radicals such as TEMPO. The oxidative species in this reaction is the corresponding oxoammonium salt, which can either be prepared in advance or generated in situ by use of a primary oxidant. The latter allows the use of catalytic amounts of TEMPO. The oxidation is sufficiently mild to afford aldehydes from primary alcohols, but specific reaction conditions, particularly use of water as a cosolvent, allows oxidation to carboxylic acids.

Various possibilities for the primary oxidant and reaction conditions are available.[13] Our first choice was to apply sodium chlorite as the primary oxidant and sodium hypochlorite as cocatalyst in a mixture of acetonitrile and a phosphate buffer.[14] These conditions, nevertheless, proved to be too mild, and only the alcohol starting material was observed in the crude reaction mixture (Table 1, entry 1).

The next attempted conditions applied sodium hypochlorite as the primary oxidant and potassium bromide as a cocatalyst. In addition, tetrabutylammonium bromide (TBAB) was used as a phase-transfer catalyst in a biphasic solvent system consisting of dichloromethane and saturated sodium bicarbonate as buffer.[13,15] These reaction conditions did not lead to the

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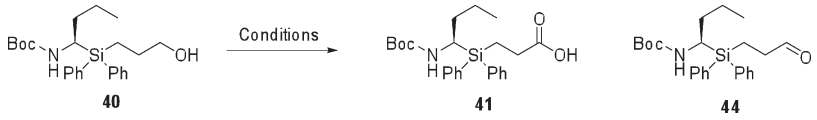
TABLE 1. Different Attempts for the Oxidation of the Primary Alcohol



40 **41** **44**

entry	reactant	conditions	product
1	**40**	TEMPO (cat.), NaOCl (cat.), $NaOCl_2$(aq), CH_3CN, phosphate buffer pH = 6.7, 35 °C	SM
2	**40**	TEMPO (cat.), KBr (cat.), TBAB (aq), $NaClO_2$ (aq), $NaHCO_3$ (satd), CH_2Cl_2, 0 °C	**44**
3	**44**	$NaClO_2$ (aq), Na_2HPO_4 (aq), *t*-BuOH, CH_3CN, 2-methyl-2-butene	**41**
4	**40**	$RuCl_3$ (cat.), $NaIO_4$, CH_3CN, EtOAc, H_2O, rt	**41**

carboxylic acid **41** but instead the corresponding aldehyde **44** (Table 1, entry 2). We attempted to oxidize the aldehyde to **44** applying the mild oxidant sodium chlorite in aqueous sodium dihydrogenphosphate and a solvent mixture of *tert*-butanol, acetonitrile, and 2-methyl-2-butene.[16] The oxidation furnished an impure sample of the carboxylic acid containing both azasilinanone **43**, unconverted alcohol from the first oxidation, and other unidentified side products (entry 3).

Finally, we went on to explore a transition-metal-catalyzed oxidation (Table 1, entry 4). Ruthenium(III) chloride was applied together with sodium *m*-periodate as the primary oxidant in a solvent mixture of acetonitrile, ethyl acetate, and water. Ethyl acetate was employed as one of the solvents instead of the more commonly used tetrachloromethane.[17] These conditions with an in situ generated perruthenate[18] gave a cleaner conversion of the alcohol to the desired carboxylic acid **41**, which was subsequently coupled to glycine using standard conditions with EDC to give the dipeptide mimic **42** in 63% yield over two steps. This result demonstrated how the prepared silyl sulfinamide **39** could be converted to a Boc-protected dipeptide mimic and further applied in peptide coupling chemistry.

For practical application of this work, an interesting target was suggested. The human elastase inhibitor **7** (Figure 2) has demonstrated excellent inhibitory activity; however, the synthetic approach to this compound provided a 1:1 mixture of stereoisomers at the α-position to the silicon atom. We felt application of the above approach would allow for the synthesis of either diastereoisomer of the target compound and facilitate identification of the more active of the two compounds. Beginning with the commercially available aldehyde **45**, conversion to the imine and addition of the silyl lithium reagent **47** proceeded without incident producing compound **48** (Scheme 11). Global deprotection and reprotection of the amine were followed by oxidation of the free alcohol up to the corresponding acid **50**. The acid was not isolated, rather it was coupled directly to *n*-butylamine using standard conditions affording the butylamide **51** in 47% yield for the 2 steps. Two successive cycles of N-terminal deprotection with TFA followed by peptide coupling afforded the fully protected peptide **53** in excellent overall yield. Treatment with TfOH followed by aqueous basic hydrolysis afforded the silane diol **55** directly.[3g] To facilitate isolation and purification this compound was immediately reacted with HF, which converted the silanediol into difluorosilane **54**. Finally, conversion back to the silanediol **55** can be readily achieved by treatment with aqueous NaOH. Importantly, the approach depicted in Scheme 11 not only is shorter and higher yielding than the previously reported synthesis of **7** but yielded only a single diastereoisomer of the final target.

The same approach was applied to another potential target, the fibrillating hexapeptide Asn-Phe-Gly-Ala-Ile-Leu (NFGAIL), a short fragment of the 37-residue human islet amyloid polypeptide (hIAPP) found in pancreatic deposits in type II diabetes patients, which is closely linked to β cell deterioration.[19]

We have recently been interested in developing analogues of this sequence in order to investigate how the structural alterations in this sequence will influence fibrillation.[20] This sequence displays an internal glycine residue, and a derivative with the phenylalanine-glycine peptide bond replaced by a silanediol methylene moiety may be prepared by the developed method.

As illustrated in Scheme 12, synthesis of the diphenylsilane NFGAIL derivative **64** was initiated by addition of the previously prepared silyllithium **57** to sulfinimine **56**, which gave silylsulfinamide **58** in 47% yield and a dr of 95:5 (Scheme 12). Silyl lithium addition to this sulfinimine has also previously resulted in a relatively low yield, which was attributed to increased α proton acidity.[11a] Deprotection and protection of the amine with a Boc group occurred in 74% yield to furnish alcohol **59**. Ruthenium-catalyzed oxidation and EDC-promoted peptide coupling to the previously prepared tripeptide **61**[20] gave the pentapeptide mimic **62** in a 59% yield. Final peptide coupling with asparagine (**63**) produced the protected hexapeptide **64**.[21]

Conclusions

In summary, we have investigated the possibility of extending the approach for generating silicon-containing dipeptides to more elaborate amino acids with functionalized side chains. The addition of alkyldiphenylsilyl lithium to

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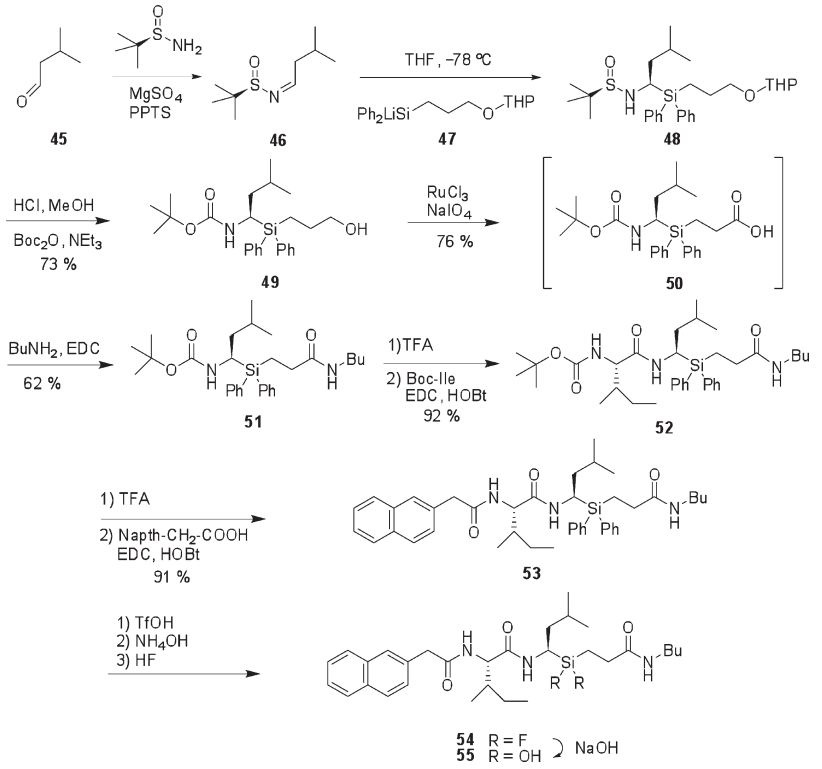
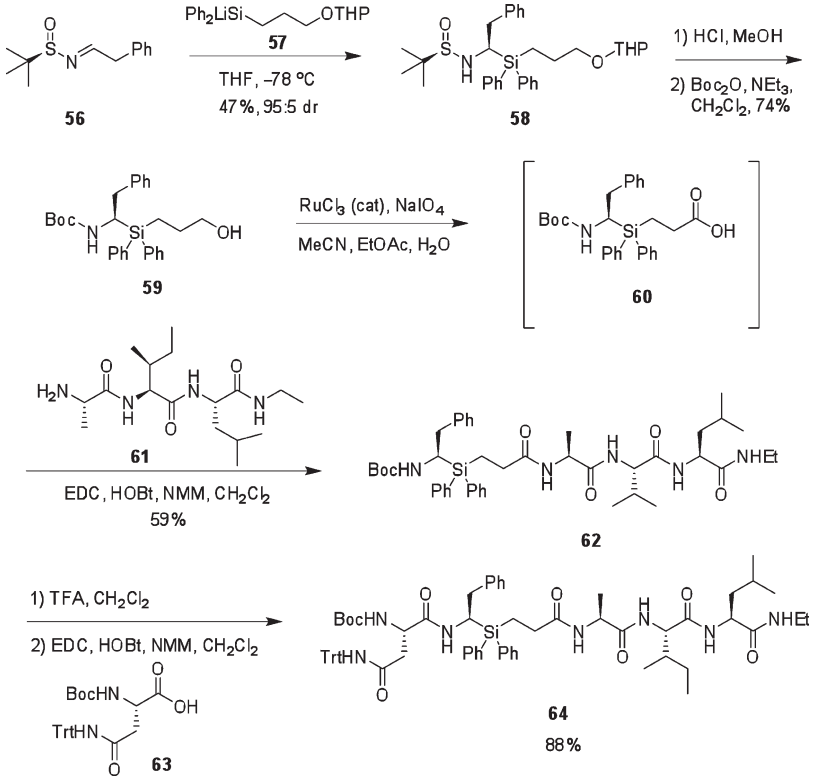
(21) Attempts to cleave the Si−Ph bonds upon treatment with triflic acid as for the diphenylsilane **53**, followed by transformation to the difluoride, were not successful, possibly because of sensitivity of the terminal Boc group to these highly acidic conditions. Nevertheless, we are currently investigating the fibrillating properties of the diphenylsilane analogue of this hexapeptide, as well as its ability to perhaps inhibit the fibrillation process of the parent peptide.

SCHEME 11. Synthesis of Serine Protease HNE Inhibitor



SCHEME 12. Synthesis of Diphenylsilane Derivative 64 of the Fibrillating Hexapeptide NFGAIL



Ellman's sulfinamine as the key step has been elaborated on to include amino acid mimics of Ala, Val, Leu, Phe, Ser, Thr, Tyr, Pro, Arg, Asp, Asn, and Lys. The synthesis is stereoselective and incorporates the opportunity for both N- and C-terminus peptide extension. We have successfully demonstrated the application of this method for the synthesis of two dipeptide mimics of the type Xaa−Gly as fragments of a potential human neutrophil elastase inhibitor and as a

silicon-containing analogue of the fibrillating peptide NFGAIL. Ongoing work in this area is directed at the preparation of the remaining genetically encoded side chains, together with other natural and non-natural amino acid building blocks of medicinal interest. Further to this, we are interested in the development of a more general approach to functionalized hydrido- or chloro- diphenylsilanes, which should allow for the preparation of many more silanediol dipeptide mimics of the type Xaa−Xaa. These results will be reported in due course.

Experimental Procedures

General Procedures for Preparation of Sulfinimines. Method A. (*R*)-*tert*-Butylsulfinamide (200 mg, 1.65 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and the aldehyde (2.0 mmol, 1.2 equiv), PPTS (20 mg, 0.08 mmol, 0.05 equiv) and $MgSO_4$ (993 mg, 8.25 mmol, 5 equiv) were added. The reaction was heated at reflux for 18 h. Then the reaction mixture was filtered, and the solids were washed with CH_2Cl_2 (2 × 10 mL). The combined filtrates were evaporated in vacuo, and the pure product was obtained by column chromatography, using the stated solvent system.

Method B. (*R*)-*tert*-Butylsulfinamide (200 mg, 1.65 mmol) and the aldehyde (2.0 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (10 mL), and Cs_2CO_3 (652 mg, 2.0 mmol, 1.2 equiv) was added. The mixture was heated to reflux for 18 h, then cooled and filtered through a pad of Celite. The solids were washed with CH_2Cl_2, and then the combined filtrates were evaporated in vacuo. The pure product was obtained by column chromatography, using the stated solvent system.

General Procedure for the Addition of (Diphenylmethylsilyl)lithium to Sulfinimines. Lithium (42 mg, 5.0 mmol, 12.0 equiv) was suspended in THF (5 mL) under an argon atmosphere, and then diphenylmethylchlorosilane (0.31 mL, 1.50 mmol, 3.0 equiv) was added, before the mixture was stirred at rt for 4 h. In a separate flask the sulfinimine (0.50 mmol, 1 equiv) was dissolved in THF (5 mL), and the solution was cooled to −78 °C under an argon atmosphere. To this cooled solution was added the solution of lithium diphenylmethylsilane dropwise over 5 min via syringe. The solution was stirred at −78 °C for 18 h, then water (2 mL) was added, and the mixture allowed to warm to rt. The mixture was poured into water (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography.

General Procedure for the Addition of (Diphenylalkylsilyl)lithium to Sulfinimines. Hydridosilane (0.20 mmol, 2 equiv) was dissolved in dry THF (2 mL), and then freshly cut lithium pieces (15 mg, 2.0 mmol, 10 equiv) were added. The mixture was stirred under an argon atmosphere for 4 h, by which time the mixture had turned a rich dark brown color. In a separate flask, the imine (0.10 mmol) was dissolved in dry THF (2 mL), and the solution was cooled to −78 °C. To this cooled solution was added the silyl lithium reagent (2 mL) dropwise via syringe over 3−5 min. The solution was stirred at −78 °C for 18 h, then water (2 mL) was added, and the mixture allowed to warm to rt and treated as in the previous procedure.

(*R*)-*N*-((*R*)-2-(Benzyloxy)-1-(methyldiphenylsilyl)ethyl)-2-methylpropane-2-sulfinamide (13). It was prepared from sulfinimine **12** following the previous general procedure. The pure product was obtained by column chromatography using 1:2:7 Et_2O/EtOAc/pentane as eluant, giving **13** (162 mg, 0.36 mmol, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24−7.60 (m, 15H), 4.56 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.01 (dd, J = 9.6, 3.2 Hz, 1H), 3.71 (dd, J = 9.6, 3.2 Hz, 1H), 3.56 (dt, J = 10.4, 3.2 Hz, 1H), 3.51 (d, J = 10.4 Hz, 1H), 1.08 (s, 9H), 0.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.2. 135.2 (2C), 135.0 (2C), 134.8, 134.7, 129.7, 129.6, 128.3 (2C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.5, 73.4, 73.1, 56.3, 48.3, 22.6 (3C), −4.8. HRMS $C_{26}H_{33}NO_2SSi$ [M + Na^+] calcd 474.1893, found 474.1887.

(*R*)-*N*-((*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-(methyldiphenylsilyl)pentyl)-2-methylpropane-2-sulfinamide (18). It was prepared from sulfinimine **77** following the previous general procedure. The pure product was obtained by column chromatography using 5% to 25% EtOAc in pentane as eluant giving **18** (792 mg, 1.53 mmol, 79%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59−7.49 (m, 4H), 7.43−7.32 (m, 6H), 3.54 (t, J = 6.4 Hz, 2H), 3.36 (ddd, J = 10.0, 7.6, 4.4 Hz, 1H), 2.78 (d, J = 10.0 Hz, 1H), 1.90−1.76 (m, 1H), 1.71−1.32 (m, 5H), 1.01 (s, 9H), 0.88 (s, 9H), 0.63 (s, 3H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 135.1 (2C), 135.0 (2C), 134.7, 134.6, 129.84, 129.82, 128.2 (3C), 127.9, 63.1, 56.4, 47.0, 33.6, 32.9, 26.1 (3C), 23.8, 22.7 (3C), 18.5, −4.9, −5.1 (2C). HRMS $C_{28}H_{47}NO_2SSi_2$ [M + Na^+] calcd 540.2758, found 540.2764.

(*R*)-*tert*-Butyl 5-Hydroxy-1-(methyldiphenylsilyl)pentylcarbamate (19). Sulfinamide **18** (792 mg, 1.53 mmol) was dissolved in anhydrous HCl in MeOH (40 mL, 0.5 M), and the mixture was stirred at rt for 3 h. All volatiles were removed in vacuo giving the crude amino alcohol. The residue was dissolved in dry CH_2Cl_2 (20 mL), and then Boc_2O (323 mg, 1.54 mmol) and NEt_3 (323 mg, 3.23 mmol) were added. The mixture was stirred at rt for 18 h, then 2 M NaOH (aq) (20 mL) was added, and stirring was continued vigorously for a further 2 h. The mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 10% to 50% EtOAc in pentane as eluant), which gave **19** (464 mg, 1.19 mmol, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60−7.52 (m, 4H), 7.43−7.33 (m, 6H), 4.31 (d, J = 10.0 Hz, 1H), 3.82 (td, J = 10.4, 3.2 Hz, 1H), 3.62−3.48 (m, 2H), 2.10 (br s, 1H), 1.66−1.34 (m, 6H), 1.39 (s, 9H), 0.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.6, 135.0 (2C), 134.9 (2C), 134.7, 134.4, 129.74, 129.68, 128.1 (4C), 79.2, 62.6, 38.6, 32.2, 31.8, 28.4 (3C), 23.0, −5.6. HRMS $C_{23}H_{33}NO_3Si$ [M + Na^+] calcd 422.2122, found 422.2134.

(*R*)-5-(*tert*-Butoxycarbonylamino)-5-(methyldiphenylsilyl)pentyl Methanesulfonate (20). The alcohol **19** (464 mg, 1.19 mmol) was dissolved in CH_2Cl_2 (30 mL), and then NEt_3 (237 mg, 2.37 mmol) and MsCl (204 mg, 1.78 mmol) were added. The mixture was stirred at rt for 30 min, then poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 15% to 40% EtOAc in pentane as eluant), which gave **20** (544 mg, 1.14 mmol, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58−7.50 (m, 4H), 7.44−7.33 (m, 6H), 4.23 (d, J = 10.4 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 3.79 (td, J = 10.0, 2.8 Hz, 1H), 2.94 (s, 3H), 1.87−1.74 (1H), 1.70−1.30 (m, 5H), 1.39 (s, 9H), 0.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.4, 135.02 (2C), 134.95 (2C), 134.5, 134.3, 129.9, 129.8, 128.2 (4C), 79.3, 70.2, 38.5, 37.4, 31.5, 28.7, 28.5 (3C), 23.0, −5.6. HRMS $C_{24}H_{35}NO_5SSi$ [M + Na^+] calcd 500.1897, found 500.1897.

(*R*)-*tert*-Butyl 5-Azido-1-(methyldiphenylsilyl)pentylcarbamate (21). Mesylate **20** (544 mg, 1.14 mmol) was dissolved in DMF (20 mL), and then NaN_3 (740 mg, 11.39 mmol) was added. The mixture was stirred at rt for 18 h, then poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic portion was dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 5% to 10% EtOAc in pentane as eluant), which gave **21** (432 mg, 1.02 mmol, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58−7.52 (m, 4H), 7.46−7.33 (m, 6H), 4.22 (d, J = 10.8 Hz, 1H), 3.80 (td, J = 10.8, 3.2 Hz, 1H),

3.24−3.14 (m, 2H), 1.70−1.30 (m, 6H), 1.40 (s, 9H), 0.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.4, 135.1 (2C), 135.0 (2C), 134.6, 134.4, 129.84, 129.79, 128.2 (4C), 79.2, 51.5, 38.7, 31.7, 28.6, 28.5 (3C), 24.3, −5.5. HRMS $C_{23}H_{32}N_4O_2Si$ [M + Na^+] calcd 447.2187, found 447.2198.

(*R*)-*tert*-Butyl 5-Amino-1-(methyldiphenylsilyl)pentylcarbamate (22). Azide **21** (432 mg, 1.02 mmol) was dissolved in MeOH (30 mL), and $Pd(OH)_2$/C was added (52 mg, 0.37 mmol). The mixture was stirred under an atmosphere of hydrogen for 18 h. The mixture was filtered through a plug of Celite and silica gel, and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo giving **22** (389 mg, 0.98 mmol, 96%) as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57−7.50 (m, 4H), 7.42−7.32 (m, 6H), 4.31 (d, J = 10.8 Hz, 1H), 3.80 (td, J = 10.0, 2,0 Hz, 1H), 2.64−2.54 (m, 2H), 1.63−1.26 (m, 8H), 1.38 (s, 9H), 0.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.3, 135.0 (2C), 134.9 (2C), 134.8, 134.5, 129.7, 129.6, 128.0 (4C), 79.0, 42.1, 38.8, 33.5, 31.9, 28.4 (3C), 24.3, −5.6. HRMS $C_{23}H_{34}N_2O_2Si$ [M + Na^+] calcd 421.2282, found 421.2287.

(*R*)-*tert*-Butyl 2-(Methyldiphenylsilyl)pyrrolidine-1-carboxylate (27). The mesylate **26** (68 mg, 0.15 mmol) was dissolved in DMF (3 mL), and then NaH (20 mg, 60% dispersion in oil, 0.40 mmol) was added. The mixture was stirred at rt for 1 h, by which time TLC indicated all starting material had been consumed. The mixture was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic portion was washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (5% EtOAc in pentane as eluant) which gave **27** (38 mg, 0.103 mmol, 70%) as a colorless oil. $[\alpha]_D$ −46 (*c* 1.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60−7.52 (m, 4H), 7.42−7.30 (m, 6H), 4.00−3.83 (m, 1H), 3.60−3.32 (m, 1H), 3.16−2.97 (m, 1H), 2.12−1.90 (m, 1H), 1.90−1.76 (m, 1H), 1.74−1.60 (m, 1H), 1.56−1.15 (m, 10H), 0.66 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (br), 135.8 (br), 135.1 (2C), 135.0 (2C), 134.2 (br), 129.4 (2C), 127.9 (4C), 79.5/78.7 (br), 46.8, 34.5 (br), 28.8/28.5 (3C), 25.9 (br), 24.6 (br), −3.4 (br). HRMS $C_{22}H_{29}NO_2Si$ [M + Na^+] calcd 390.1860, found 390.1862.

***N*″-(*R*)-4-(*tert*-Butoxycarbonylamino)-4-(methyldiphenylsilyl)-butyl)-*N*,*N*′-di-*tert*-butyloxycarbonyl-guanidine (30).** Azide **28** (240 mg, 0.58 mmol) was dissolved in MeOH (18 mL), and $Pd(OH)_2$ was added (30 mg, 0.23 mmol). The mixture was stirred under an atmosphere of hydrogen for 18 h, and then the flask was flushed with nitrogen. The mixture was filtered through a plug of Celite and silica gel, and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo giving the crude free amine that was used without further purification. The amine (225 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (24 mL), and then NEt_3 (364 μL, 265 mg, 2.63 mmol) and *N*,*N*′-di-Boc-*N*″-triflylguanidine (259 mg, 0.65 mmol) were added. The mixture was stirred at rt for 30 min, then diluted with CH_2Cl_2 (50 mL), and washed with 2 M $NaHSO_4$ (75 mL) and satd $NaHCO_3$ (75 mL). The organic portion was dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 5% to 20% EtOAc in pentane as eluant), which gave **30** (265 mg, 0.42 mmol, 72%) as a colorless oil. $[\alpha]_D$ −4 (*c* 1.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.42 (br s, 1H), 8.26 (t, J = 4.8 Hz, 1H), 7.57 (m, 4H), 7.42−7.30 (m, 6H), 4.33 (d, J = 10.4 Hz, 1H), 3.78 (td, J = 10.8, 2.0 Hz, 1H), 3.44−3.30 (m, 2H), 1.75−1.34 (m, 4H), 1.48 (s, 9H), 1.47 (s, 9H), 1.37 (s, 9H), 0.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.4, 156.2, 153.3, 151.5, 135.1 (2C), 135.0 (2C), 134.5, 134.3, 129.8, 129.7, 128.2 (4C), 83.1, 79.2, 40.6, 38.8, 29.3, 28.4 (3C), 28.3 (3C), 28.1 (3C), 27.9, 27.0, −5.5. HRMS $C_{33}H_{50}N_4O_6Si$ [M + Na^+] calcd 649.3392, found 649.3397.

(*R*)-3-(*tert*-Butoxycarbonylamino)-3-(methyldiphenylsilyl)-propanoic Acid (34). A round-bottomed flask containing a solution of compound **33** (125 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) and acetone (4 mL) was cooled to 0 °C. Jones reagent (1 mL) was added to the stirred mixture, after which it was allowed to warm to rt. After 1 h 15 min more Jones reagent (0.2 mL) was added, followed by additional 30 min of stirring. After phase separation 3 M HCl (2 mL) was added to the aqueous portion, which was subsequently extracted with CH_2Cl_2 (5 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 0:1:2 to 5:995:0 HCO_2H/EtOAc/pentane as eluant) afforded **34** (70 mg, 0.18 mmol, 54%) as a colorless wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56−7.54 (m, 4H), 7.42−7.36 (m, 6H), 4.76 (d, J = 8.4 Hz, 1H), 4.14 (br s, 1H), 2.65 (dd, J = 16.0, 2.8 Hz, 1H), 2.45 (dd, J = 16.0, 8.0 Hz, 1H), 1.37 (s, 9H), 0.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.7, 156.2, 135.0 (2C), 135.00 (2C), 134.97 (2C), 130.0, 129.9, 128.3 (2C), 128.2 (2C), 79.8, 36.7, 36.1, 28.4 (3C), −5.3. HRMS $C_{21}H_{27}NO_4Si$ [M + Na^+] calcd 408.1607, found 408.1622.

(*R*)-*tert*-Butyl 3-Amino-1-(methyldiphenylsilyl)-3-oxopropylcarbamate (35). In a three necked round-bottomed flask, dry NEt_3 (0.15 mL, 1.1 mmol) was added to a solution of compound **34** (66 mg, 0.17 mmol) in CH_2Cl_2 (6 mL), and the mixture was cooled to 0 °C. PivCl (80 mg, 0.65 mmol) was then added, and the reaction mixture was stirred for 40 min. Ammonia was bubbled through the solution, which resulted in the immediate precipitation of white salts. After having stirred for 30 min under an atmosphere of ammonia, the reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 30% to 100% EtOAc in pentane as eluant), which gave **35** (31 mg, 0.08 mmol, 47%) as a colorless oil. $[\alpha]_D$ +6 (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57−7.53 (m, 4H), 7.42−7.36 (m, 6H), 6.82 (br s, 1H), 5.47 (br s, 1H), 4.73 (d, J = 10.4 Hz, 1H), 4.07 (td, J = 10.4, 3.2 Hz, 1H), 2.57 (dd, J = 16.8, 2.8, Hz, 1H), 2.37 (dd, J = 16.8, 10.8 Hz, 1H), 1.37 (s, 9H), 0.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2, 157.1, 135.0 (2C), 134.9 (2C), 133.6 (2C), 130.13, 130.08, 128.4 (2C), 128.3 (2C), 80.2, 38.6, 36.3, 28.4 (3C), −5.6. HRMS $C_{21}H_{28}N_2O_3Si$ [M + Na^+] calcd 407.1767, found 407.1776.

(*R*)-*tert*-Butyl 1-((3-Hydroxypropyl)diphenylsilyl)-3-methylbutylcarbamate (49). Sulfinamide **48** (768 mg, 1.50 mmol) was dissolved in anhydrous 0.5 M HCl in MeOH (15 mL), and the mixture was stirred at rt for 18 h. All volatiles were removed in vacuo to give the crude amine as its hydrochloride salt. This was dissolved in CH_2Cl_2 (15 mL), and then NEt_3 (0.83 mL, 6.00 mmol) and Boc_2O (645 mg, 3.0 mmol) were added. The mixture was stirred at rt for 18 h, and then 2 M NaOH (15 mL) was added. The mixture was stirred vigorously for a further 2 h. The two phases were separated, and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 1% to 3% MeOH in CH_2Cl_2), which gave **49** (470 mg, 1.10 mmol, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 (dd, J = 7.6, 1.2 Hz, 2H), 7.51 (dd, J = 7.6, 1.2 Hz, 2H), 7.46−7.34 (m, 6H), 4.12 (d, J = 10.4 Hz, 1H), 4.03 (td, J = 11.6, 2.4 Hz, 1H), 3.63−3.49 (m, 2H), 2.04 (s, 1H), 1.73−1.50 (m, 2H), 1.50−1.43 (m, 1H), 1.40 (s, 9H), 1.36−1.04 (m, 4H), 0.97 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.3, 135.7 (2C), 135.4 (2C), 133.5, 133.0, 129.8, 129.7, 128.12 (2C), 128.07 (2C), 79.1, 65.2, 41.3, 35.9, 28.5 (3C), 26.8, 25.0, 23.8, 21.3,

7.4. HRMS $C_{25}H_{37}NO_3Si$ [M + Na^+] calcd 450.2435, found 450.2528.

(*R*)-*tert*-Butyl 1-((3-(Butylamino)-3-oxopropyl)diphenylsilyl)-3-methylbutylcarbamate (51). Alcohol **49** (83 mg, 0.20 mmol, 1.0 equiv) was dissolved in a mixture of MeCN (1 mL), ethyl acetate (1 mL), and H_2O (1.5 mL), and NaIO4 (171 mg, 0.80 mmol, 4.1 equiv) and $RuCl_3$ (1 mg) were added. The reaction was stirred at rt for 2 h, and then H_2O (5 mL) was added. The mixture was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude carboxylic acid. The residue was dissolved in CH_2Cl_2 (3 mL), and then NMM (100 mg, 0.95 mmol), *n*-butylamine (150 mg, 2.03 mmol), HOBt (98 mg, 0.63 mmol) and finally EDC (181 mg, 0.95 mmol) were added. The mixture was stirred at rt for 1 d, then poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 5% to 50% EtOAc in pentane as eluant), which gave **51** (148 mg, 0.30 mmol, 62%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 (dd, J = 7.6, 1.6 Hz, 2H), 7.48 (dd, J = 7.6, 1.6 Hz, 2H), 7.45−7.33 (m, 6H), 5.64 (br s, 1H), 4.20 (d, J = 10.4 Hz, 1H), 4.02 (td, J = 11.2, 2.8 Hz, 1H), 3.25−3.06 (m, 2H), 2.28 (ddd, J = 14.4, 12.0, 5.2 Hz, 1H), 2.04 (ddd, J = 14.4, 11.2, 6.0 Hz, 1H), 1.72−1.60 (m, 1H), 1.50−1.20 (m, 8H), 1.40 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.1, 156.3, 135.7 (2C), 135.4 (2C), 132.9, 132.4, 130.0, 129.9, 128.22 (2C), 128.17 (2C), 79.2, 40.9, 39.4, 35.7, 31.8, 30.7, 28.5 (3C), 25.1, 23.8, 21.3, 20.2, 13.8, 7.8. HRMS $C_{29}H_{44}N_2O_3Si$ [M + Na^+] calcd 519.3013, found 519.3043.

***tert*-Butyl (2*S*,3*R*)-1-((*R*)-1-((3-(Butylamino)-3-oxopropyl)-diphenylsilyl)-3-methylbutylamino)-3-methyl-1-oxopentan-2-ylcarbamate (52).** Carbamate **51** (148 mg, 0.30 mmol) was dissolved in CH_2Cl_2 (3 mL), and then TFA (1.5 mL) was added. The mixture was stirred at rt for 1 h, before all volatiles were removed in vacuo, giving the crude amine as its trifluoroacetate ammonium salt. The residue was dissolved in CH_2Cl_2 (3 mL), and then HOBt (201 mg, 1.30 mmol), NMM (127 μL, 1.30 mmol), *N*-Boc-isoleucine (136 mg, 0.59 mmol), and EDC (124 mg, 0.65 mmol) were added. The mixture was stirred at rt for 18 h, then poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 20% to 60% EtOAc in pentane as eluant), which gave the title compound **52** (168 mg, 0.28 mmol, 92%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55−7.30 (m, 10H), 5.99 (br s, 1H), 5.68 (d, J = 9.6 Hz, 1H), 4.91 (d, J = 8.4 Hz, 1H), 4.50−4.40 (m, 1H), 3.78 (t, J = 7.6 Hz, 1H), 3.23−3.08 (m, 2H), 2.32 (ddd, J = 14.4, 12.0, 4.8 Hz, 1H), 1.99 (ddd, J = 14.4, 11.2, 6.0 Hz, 1H), 1.87−1.77 (m, 1H), 1.61−1.49 (m, 1H), 1.49−1.24 (m, 9H), 1.40 (s, 9H), 1.04−0.94 (m, 1H), 0.93−0.76 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.3, 171.2, 155.9, 135.6 (2C), 135.4 (2C), 132.3, 132.1, 130.14, 130.09, 128.31 (2C), 128.25 (2C), 80.1, 60.2, 40.3, 39.4, 36.7, 34.7, 31.8, 30.7, 28.4 (3C), 25.0, 24.8, 23.7, 21.1, 20.2, 15.7, 13.9, 11.4, 8.1. HRMS $C_{35}H_{55}N_3O_4Si$ [M + Na^+] calcd 632.3854, found 632.3865.

(2*S*,3*R*)-*N*-((*R*)-1-((3-(Butylamino)-3-oxopropyl)diphenylsilyl)-3-methylbutyl)-3-methyl-2-(2-(naphthalen-2-yl)acetamido)-pentanamide (53). Carbamate **52** (168 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (3 mL), and then TFA (1.5 mL) was added. The mixture was stirred at rt for 90 min, before all volatiles were removed in vacuo, giving the crude amine as its trifluoroacetate ammonium salt. The glassy residue was dissolved in CH_2Cl_2 (3 mL), and then 2-napthylacetic acid (120 mg, 0.63 mmol), HOBt (214 mg, 1.40 mmol), NMM (136 μL, 1.40 mmol), and finally EDC (133 mg, 0.70 mmol) were added. The mixture was stirred at rt for 18 h, then poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 1% to 5% MeOH in CH_2Cl_2 as eluant), which gave the title compound **53** (170 mg, 0.25 mmol, 91%) as a colorless solid. $[\alpha]_D$ −16 (*c* 1.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82−7.72 (m, 3H), 7.59 (s, 1H), 7.56−7.52 (m, 2H), 7.50−7.33 (m, 10H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 5.92 (d, J = 8.8 Hz, 1H), 5.79 (t, J = 5.6 Hz, 1H), 5.65 (d, J = 10.4 Hz, 1H), 4.37 (ddd, J = 12.0, 10.4, 2.8 Hz, 1H), 4.14 (dd, J = 8.8, 6.8 Hz, 1H), 3.67 (AB system, J = 15.6 Hz, 2H), 3.14 (td, J = 7.2, 6.0 Hz, 2H), 2.30 (ddd, J = 14.4, 11.6, 4.4 Hz, 1H), 2.01 (ddd, J = 14.4, 11.2, 6.4 Hz, 1H), 1.81−1.70 (m, 1H), 1.48−1.16 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.82−0.75 (m, 1H), 0.75−0.68 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.1, 170.9, 170.4, 135.7 (2C), 135.4 (2C), 133.7, 132.6, 132.3, 132.2, 132.1, 130.2, 130.1, 129.0, 128.34 (2C), 128.30 (2C), 128.2, 127.8, 127.7, 127.0, 126.6, 126.2, 58.4, 44.0, 40.2, 39.4, 36.5, 34.8, 31.7, 30.7, 25.1, 24.6, 23.6, 21.1, 20.2, 15.6, 13.9, 11.3, 7.8. HRMS $C_{42}H_{55}N_3O_3Si$ [M + Na^+] calcd 700.3905, found 700.3910.

(2*S*,3*R*)-*N*-((*R*)-1-((3-(Butylamino)-3-oxopropyl)difluorosilyl)-3-methylbutyl)-3-methyl-2-(2-(naphthalen-2-yl)acetamido)pentanamide (54). Diphenylsilane **53** (50.8 mg, 0.076 mmol) was dissolved in dry CH_2Cl_2 (5 mL) under an argon atmosphere and cooled to 0 °C in an ice bath. Triflic acid (0.1 mL, 15 equiv, 1.14 mmol) was added dropwise, and the reaction was stirred at 0 °C for 24 h while being allowed to warm to rt. The reaction was cooled to 0 °C, diluted with CH_2Cl_2 (5 mL), concd NH_4OH (0.3 mL) was added, and the reaction was stirred for another 1 h at 0 °C. Then 48% HF solution (0.2 mL) was added, to give a pH of 2−3. Stirring was continued for 30 min and after addition of CH_2Cl_2 (10 mL), the solution was washed with water (10 mL) and saturated NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated to give **54** (37.5 mg, 0.068 mmol, 89%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (br s, 1H), 7.82−7.77 (m, 3H), 7.73 (s, 1H), 7.49−7.48 (m, 2H), 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 6.74 (br s, 1H), 5.77 (br s, 1H), 4.50 (t, J = 8.4 Hz, 1H), 3.71−3.80 (m, 2H), 3.20 (dt, J = 7.2, 6.0 Hz, 1H), 2.77−2.74 (m, 1H), 2.26 (ddd, J = 15.6, 12.8, 8.0 Hz, 1H), 1.80−1.73 (m, 1H), 1.63−1.56 (m, 1H), 1.49−1.25 (m, 8H), 1.04−0.96 (m, 2H), 0.91−0.76 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.0, 173.9, 171.9, 133.7, 132.7, 132.0, 128.9, 128.2, 127.83, 127.79, 127.1, 126.6, 126.2, 55.8, 43.7, 39.7, 38.8, 38.4 (dd, J = 26.5, 21.2 Hz), 37.0, 31.7, 30.7, 25.9, 25.0, 23.7, 21.0, 20.2, 15.3, 13.9, 11.9 (t, J = 20.4 Hz), 11.1.

(2*S*,3*R*)-*N*-((*R*)-1-((3-(Butylamino)-3-oxopropyl)dihydroxysilyl)-3-methylbutyl)-3-methyl-2-(2-(naphthalen-2-yl)acetamido)-pentanamide (55). Difluorsilane **54** (5 mg, 0.009 mmol) was dissolved in a mixture of CD_3CN (0.1 mL) and D_2O (0.4 mL), and 0.2 M NaOH solution in D_2O (0.1 mL) was added. The reaction was stirred for 30 min, and the mixture was used directly for NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96−7.92 (m, 3H), 7.84 (br s, 1H), 7.61−7.55 (m, 2H), 7.48 (br d, J = 7.6 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 3.67 (AB system, J = 14.4 Hz, 2H), 3.20 (dd, J = 12.0, 2.4 Hz, 1H), 3.10 (t, J = 6.8 Hz, 2H), 2.25−2.14 (m, 2H), 1.91−1.81 (m, 1H), 1.48−1.39 (m, 4H), 1.34−1.24 (m, 4H), 1.15−1.08 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.6 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H), 0.73 (d, J = 6.0 Hz, 3H), 0.72 (d, J = 6.0 Hz, 3H), 0.70−0.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.8, 174.3, 172.5, 133.3, 133.0, 132.2, 128.0, 127.6, 127.5 (2C), 127.3, 126.2, 125.8, 55.6, 42.2, 39.0, 38.9, 38.6, 36.3, 30.9, 29.6, 25.2, 24.6, 22.9, 19.9, 19.6, 14.6, 13.1 (2C), 10.2.

***tert*-Butyl (5*S*,8*R*,14*S*,17*S*,20*S*)-8-Benzyl-17-*sec*-butyl-20-isobutyl-14-methyl-3,6,12,15,18,21-hexa-oxo-1,1,1,9,9-pentaphenyl-2,7,13,16,19,22-hexaaza-9-silatetracosan-5-ylcarbamate (64).** Trifluoroacetic acid (3 mL) was added to a solution of pentapeptide analogue **62** (59 mg, 0.07 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at rt for 1 h, and then the solvents were evaporated in vacuo giving the crude trifluoroacetate ammonium salt as a colorless gum. The crude material was redissolved in CH_2Cl_2 (3 mL) and *N*-methyl morpholine (41 μL, 0.37 mmol), Boc-L-Asn(Trt)−OH (**63**) (39 mg, 0.08 mmol), EDC (28 mg, 0.15 mmol), and HOBt (23 mg, 0.15 mmol) were added. The mixture was stirred at rt for 2 days and then poured into water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 50% to 90% EtOAc in CH_2Cl_2 as eluant), which gave **64** (76 mg, 0.07 mmol, 88%) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 7.57−7.60 (m, 4H), 7.38−7.48 (m, 6H), 7.09−7.27 (m, 20H), 4.17−4.43 (m, 3H), 4.25 (q, J = 7.2 Hz, 1H), 4.18 (d, J = 6.8 Hz, 1H), 3.17 (q, J = 7.2 Hz, 1H), 3.17 (q, J = 7.2 Hz, 1H), 2.93 (d, J = 12.4 Hz, 1H), 2.64 (dd, J = 14.0, 11.6 Hz, 1H), 2.16−2.38 (m, 4H), 1.80−1.87 (m, 1H), 1.43−1.64 (m, 6H), 1.40 (s, 9H), 1.16−1.29 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H), 1.09 (t, J = 7.6 Hz, 3H), 0.86−0.91 (m, 12H). ^{13}C NMR (400 MHz, CD_3OD) δ (ppm) 176.9, 175.6, 174.1, 173.3 (2C), 171.4, 157.2, 145.8 (3C), 140.9, 136.6 (2C), 136.5 (2C), 133.8, 133.5, 131.12, 131.09, 130.0 (6C), 129.9 (2C), 129.32 (4C), 129.27 (2C), 128.7 (6C), 127.8 (3C), 127.2, 80.8, 71.7, 59.4, 53.4, 53.1, 51.0, 41.7, 41.0, 40.3, 38.1, 38.0, 35.3, 30.8, 28.8 (3C), 26.0, 25.8, 23.5, 22.0, 17.5, 16.0, 14.8, 11.6, 8.3. HRMS $C_{68}H_{85}N_7O_8Si$ [M + Na^+] calcd 1178.6121, found 1178.6127.

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Supporting Information Available: Experimental methods for the preparation of compounds **12**, **14**−**17**, **23**−**26**, **28**, **29**, **31**−**33**, **39**−**44**, **46**, **48**, **56**, **58**, **59**, and **62** and their characterization. Copies of ^{1}H NMR and ^{13}C NMR spectra of the new compounds (**12**−**22**, **24**−**28**, **30**−**35**, **40**, **42**, **43**, **48**−**55**, **58**−**60**, 62, and **64**). This material is available free of charge via the Internet at http://pubs.acs.org.