JOC Article

# Stereocontrolled Synthesis of Methyl Silanediol Peptide Mimics

Lone Nielsen, Karl B. Lindsay,* Jesper Faber, Niels Christian Nielsen, and Troels Skrydstrup*

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

*kbl02@chem.au.dk; ts@chem.au.dk*

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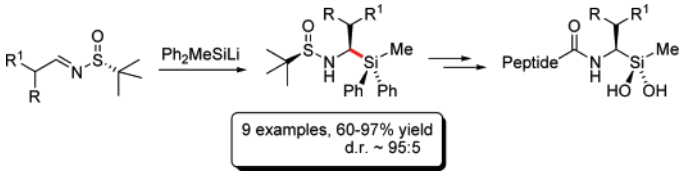


The treatment of chiral sulfinimines with (methyldiphenylsilyl)lithium gives α-(methyldiphenylsilyl)-sulfinamides with excellent diastereoselectivity, and in good yield. The presence of α-protons on the imines is also well tolerated. The sulfinamide auxiliary is easily removed via treatment with methanolic HCl and the resulting amine extended into peptide chains accordingly. The diphenylsilyl moiety is a resilient protecting group for the corresponding silanediol, which can be unmasked via treatment with TfOH, followed by aqueous hydrolysis. The crude silanediol may be isolated and purified as its corresponding bis-TMS siloxane via protection with TMSCl, and converted back to the desired silanediol via hydrolysis with aqueous KOH. Efforts to apply this approach to biologically relevant silanediol peptide mimics, with a view to protease inhibition, are described.

## Introduction

Proteases constitute a large and important class of enzymes, realized by the vast number of physiological processes in which they are involved including digestion, growth, differentiation, cell signaling, immunological defense, and apoptosis among others.[1] Furthermore, they play a crucial role in the disease progression of cancers and infections as well as inflammatory, cardiovascular, and respiratory disorders.[1] Four major types of proteases exist, namely the aspartic, serine, cysteine, and metalloproteases, dubbed according to their active site functionality. Because of their essential physiological roles, proteases have become significant therapeutic targets, and motifs mimicking the tetrahedral intermediate of peptide hydrolysis (e.g., hydroxyethylene, phosphinate, boronic acid, and ketomethylene isosteres) have been successfully applied in the design of potent protease inhibitors.[1,2]

Over the past decade, the Sieburth group has introduced the silanediol moiety as a new tetrahedral intermediate isostere with applications as aspartic and metalloprotease inhibitors.[3] Silanediols represent good mimics of the tetrahedral intermediate formed during peptide bond hydrolysis, because of their reluctance to dehydrate as opposed to their carbon counterparts.[4] Sieburth et al. reported the silanediol analogue **1** of a known hydroxyethylene-containing HIV-protease inhibitor to have a

(1) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305−341.

(2) For some examples of peptide isosteres, see: (a) Garbe, D.; Sieber, S. A.; Bandur, N. G.; Koert, U.; Marahiel, M. A. *ChemBioChem* **2004**, *5*, 1000. (b) Oishi, S.; Kamano, T.; Niida, A.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6162. (c) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (d) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586. (e) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (f) Theberge, C. R.; Zercher, C. K. *Tetrahedron* **2003**, *59*, 1521. (g) Steinmetzer, T.; Zhu, B. Y.; Konishi, Y. *J. Med. Chem.* **1999**, *42*, 3109. (h) Hoffman, R. V.; Tao, J. *Tetrahedron* **1997**, *53*, 7119. (i) Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J.-S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996**, *61*, 2901. (j) Hom, R. K.; Gailunas, A. F.; Mamo, S.; Fang, L. Y.; Tung, J. S.; Walker, D. E.; Davis, D.; Thorsett, E. D.; Jewett, N. E.; Moon, J. B.; John, V. *J. Med. Chem.* **2004**, *47*, 158. (k) Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635. (l) Tao, J.; Hoffman, R. V. *J. Org. Chem.* **1997**, *62*, 6240. (m) Righi, G.; Ronconi, S.; Bonini, C. *Eur. J. Org. Chem.* **2002**, 1573. (n) Benedetti, F.; Magnan, M.; Miertus, S.; Norbedo, S.; Parat, D.; Tossi, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3027. (o) Tamamura, H.; Kato, T.; Otaka, A.; Fujii, N. *Org. Biomol. Chem.* **2003**, *1*, 2468. (p) Akaji, K.; Teruya, K.; Aimoto, S. *J. Org. Chem.* **2003**, *68*, 4755. (q) Datta, A.; Veeresa, G. *J. Org. Chem.* **2000**, *65*, 7609. (r) Leftheris, K.; Kline, T.; Vite, G. D.; Cho, Y. H.; Bhide, R. S.; Patel, D. V.; Patel, M. M.; Schmidt, R. J.; Weller, H. N.; Andahazy, M. L.; Carboni, J. M.; Gullo-Brown, J. L.; Lee, F. Y. F.; Ricca, C.; Rose, W. C.; Yan, N.; Barbacid, M.; Hunt, J. T.; Meyers, C. A.; Seizinger, B. R.; Zahler, R.; Manne, V. *J. Med. Chem.* **1996**, *39*, 224. (s) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.-i.; Fujii, N. *Org. Lett.* **2006**, *8*, 613.

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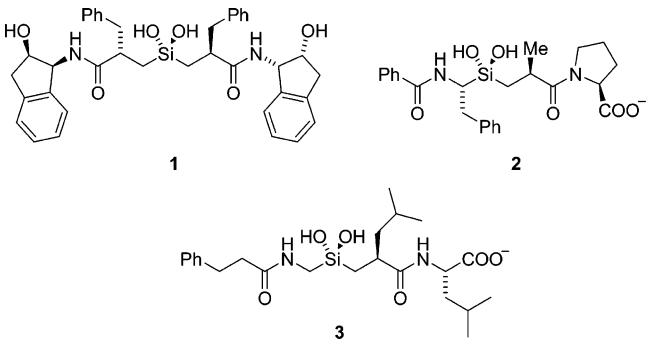


**FIGURE 1.** Silanediol-based protease inhibitors.

$K_i$ value of 2.7 nM against this protease,[3b] and a silanediol analogue **2** of a known ketone-containing inhibitor of angiotensin-converting enzyme with an $IC_{50}$ of 3.8 nM.[3f,g] These inhibitory values are comparable to those of the parent compounds from which they were derived. The mode of binding was recently confirmed by a crystal structure of a silanediol inhibitor **3** in the active site of the metalloprotease thermolysin.[3g]

The impressive results obtained by Sieburth and co-workers demonstrate the applicability of silanediols as tetrahedral intermediate analogues. This pioneer work raises the questions whether the silanediol moiety can be exploited as a general motif for the rational design of protease inhibitors and if silanediol protease inhibitors are qualified drug candidates. To answer these questions, a versatile and stereoselective synthesis of silanediol peptide mimics is highly desirable.

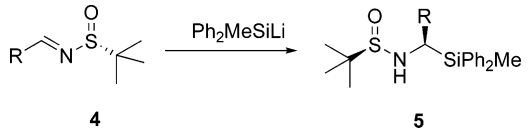
Sieburth's group has successfully synthesized enantiopure silanediol tripeptide analogues,[3e,g] but their synthetic strategy relies on a linear introduction of the required functional groups and therefore may not be ideal in a screening process where many compounds are to be synthesized in a short time. Furthermore, construction of the α-silylamine moiety occurs without stereocontrol.[3g]

Organ et al. have proposed an alternative synthesis applying a platinum-catalyzed hydrosilylation of an olefin followed by conversion to a silyllithium reagent and addition to an imine to yield racemic α-silylamine.[5] This short and convergent strategy affords easy access to the desired diorganodiphenylsilane species, but similarly offers no control of the stereocenter α to the silicon atom.

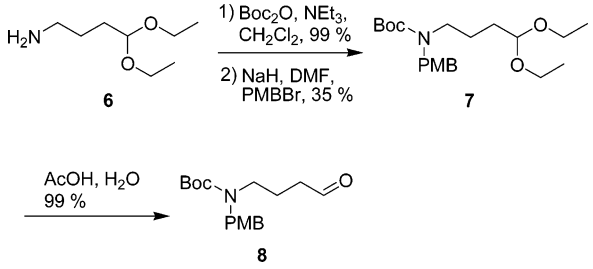
Inspired by these interesting results regarding synthesis and applications of silanediol peptide analogues, we focused our initial studies on the stereoselective synthesis of an α-silylamine structure.

α-Silylamines can be prepared by the addition of silyl anions to chiral *tert*-butanesulfinimines **4** (Scheme 1) as reported by Scheidt et al.[6] The additions usually work in good to high yields

**SCHEME 1**



**SCHEME 2**



and in high diastereoisomeric ratios. $Ph_2MeSiLi$ is easily prepared from $Ph_2MeSiCl$ and lithium metal,[7] and optically pure sulfinimines are easily obtained by the condensation of optically pure (*R*)-*tert*-butanesulfinamide and aldehydes.[8−10] Sulfinimines of this type developed by Davis[9] and Ellman[10] have found prolific use as electrophiles, reacting cleanly and with excellent stereoselectivity with a diverse range of nucleophiles providing rapid access to chiral amines.[8−10] An advantage of the *tert*-butanesulfoxide auxiliary is its ease of subsequent removal by using hydrogen chloride in methanol[10g] and the conversion of the resulting ammonium salt to a carbamate[6] or an amide by using standard procedures.[8] According to Scheidt, sulfinimine substrates with α-protons are not well tolerated in the silyllithium addition reactions,[6] reporting only a single result with the imine derived from acetophenone. As that particular imine is very highly enolizable, we felt encouraged to investigate whether imines derived from less enolizable aldehydes would undergo smooth addition with silyllithiums.

In this paper, we describe the stereoselective synthesis of α-silylamines from *tert*-butanesulfinimines and $Ph_2MeSiLi$. We have found that imines with α-protons are reasonably well tolerated in the addition reactions and also imines bearing fully protected alcohols and amines undergo smooth addition. The resulting sulfinamides were easily deprotected and coupled to *N*-protected amino acids applying standard solution-phase peptide coupling conditions. With use of this approach methyldiphenylsilane di- and tripeptide mimics were prepared; furthermore, one of these was elaborated into a meth-

(3) (a) Sieburth, S. M.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812. (b) Chen, C.-A.; Sieburth, S. M.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. *Chem. Biol.* **2001**, *8*, 1161. (c) Mutahi, M. W.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (d) Kim, J.; Glekas, A.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3625. (e) Kim, J.; Sieburth, S. M. *J. Org. Chem.* **2004**, *69*, 3008. (f) Kim, J.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2853. (g) Kim, J.; Hewitt, G.; Carroll, P.; Sieburth, S. M. *J. Org. Chem.* **2005**, *70*, 5781. (h) Sieburth, S. M.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311.

(4) Apeloig, Y. In *The chemistry of organic silicon compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989; Vol. 1, pp 57−225.

(5) Organ, M. G.; Buon, C.; Decicco, C. P.; Combs, A. P. *Org. Lett.* **2002**, *4*, 2683.

(6) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403.

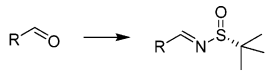
(7) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209.

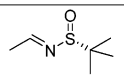
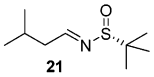
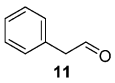
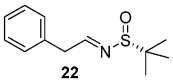
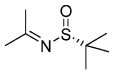
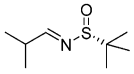
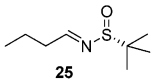
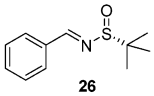
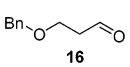
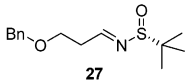
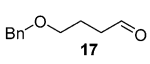
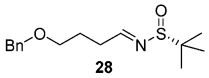
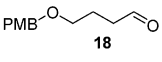
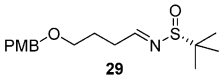
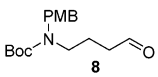
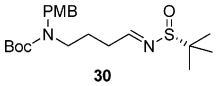
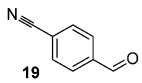
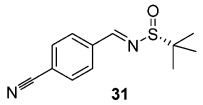
(8) For a comprehensive review see: Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869 and references cited therein.

(9) For a recent perspective on the Davis sulfinimide chemistry, see: Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(10) For selected examples see: (a) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109. (b) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652. (d) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621. (e) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (f) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (g) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (h) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

**TABLE 1. Preparation of Sulfinimines**



| Entry | Aldehyde/Ketone | Method[a] | Imine | Yield |
|---|---|---|---|---|
| 1 |  **9** | A |  **20** | 60 % |
| 2 |  **10** | A |  **21** | 95 % |
| 3 |  **11** | A |  **22** | 87 % |
| 4 |  **12** | B |  **23** | 85 % |
| 5 |  **13** | C |  **24** | 88 % |
| 6 |  **14** | C |  **25** | 63 % |
| 7 |  **15** | C |  **26** | 95 % |
| 8 |  **16** | C |  **27** | 59 % |
| 9 |  **17** | C |  **28** | 44 % |
| 10 |  **18** | C |  **29** | 63 % |
| 11 |  **8** | C |  **30** | 77 % |
| 12 |  **19** | C |  **31** | 68 % |

[a] Method A: $MgSO_4$, PPTS. Method B: $Ti(OEt)_4$. Method C: $Cs_2CO_3$.

ylsilanediol dipeptide mimic via conversion to its TMS-trisiloxane followed by base hydrolysis.

## Results and Discussion

**Synthesis of Precursors.** Aldehyde **8** was prepared from amine **6** in three steps via *N*-Boc protection, *p*-methoxybenzylation, and finally treatment with aqueous acetic acid (Scheme 2). Aldehydes **16**, **17**, and **18** were prepared via monoprotection of the corresponding diols, followed by Swern[11] oxidation as described in the Supporting Information. All other aldehydes are commercially available.

Access to the desired sulfinimines was achieved from the corresponding aldehydes/ketone by condensation with *tert*-butanesulfinamide employing reaction conditions reported by others (Table 1). Sulfinimines **20**−**22** were prepared with use of $MgSO_4$ in the presence of catalytic *p*-toluenesulfonic acid in $CH_2Cl_2$ heated at reflux.[10h] Sulfinimines **24**−**31** were prepared by employing $Cs_2CO_3$ as the dehydrating agent in $CH_2Cl_2$ at reflux.[12] Both approaches are simple and convienient, though the former may be preferable when employing substrates with more acidic α-protons. Nevertheless, the two methods proved unsuccessful for the preparation of sulfinimine **23**, and thus a third method was employed. Treatment of *tert*-butane sulfinamide with $Ti(OEt)_4$, in the presence of excess acetone in THF at reflux, afforded the desired sulfinimine as reported previously by Ellman et al.[10h]

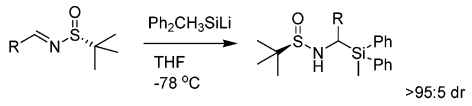
The key step in the synthesis was the addition of a silyllithium nucleophile to an imine in a stereoselective manner as described by Scheidt et al.[6] With the requisite sulfinimines in hand initial studies were undertaken. Treatment of chloro(methyl)diphenylsilane with excess lithium metal in THF affords a solution of (methyldiphenylsilyl)lithium after 4 h at rt. Attempts to react this reagent with sulfinimines at rt or 0 °C only afforded complex mixtures of products. However, dropwise addition of this solution to a precooled (−78 °C) solution of the sulfinimine in THF gave good results affording the desired addition products in good yields. It was pleasantly surprising that even substrates derived from aldehydes/ketones with enolizable protons performed well under the reaction conditions, though in extreme cases (Table 2; entries 3 and 4) the yield was somewhat diminished. The diastereoselectivity for the reaction was generally excellent, and in several cases no minor isomer was detectable by NMR (entries 2, 3, 6, 7, and 10). Where the minor isomer was detected, it could frequently be easily separated by simple flash column chromatography (entries 1, 5, and 9), and in these cases the diastereoselectivity has been assigned based upon the $^1H$ NMR spectra of the crude mixture. The only exception was compound **39** (entry 8), which was isolated as a 92:8 diastereoisomeric mixture. The diastereoisomeric ratio for compound **42** (entry 11) has not been determined due to extensive line broadening attributed to carbamate rotamers. Stereochemical assignment of the major isomer was based upon results previously reported by Scheidt et al.,[6] where an open transition state is assumed with corresponding Felkin−Ahn stereocontrol.

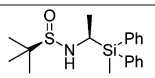
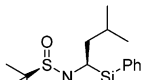
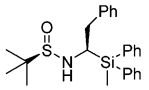
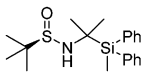
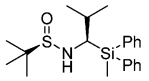
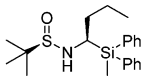
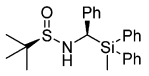
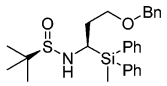
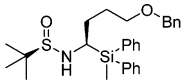
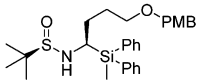
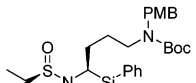
Curiously, when the imine **31** was subjected to the same reaction conditions the desired α-silylsulfinamide was not obtained. Rather, the product **47**, isolated in 56% yield, was that derived from a double aza-Brook rearrangement[13] as depicted in Scheme 3. Formation of this product can be rationalized by the enhanced stabilization in the carbanion **44** afforded by the electron-withdrawing cyano group, and that this anion eliminates a *tert*-butyl sulfoxide anion to afford a second imine **45**. Further reaction with excess $Ph_2MeSiLi$ followed by a second aza-Brook rearrangement would then afford disilazane **47** after workup.

Elaboration of the addition products into silanediol peptide isosteres was achievable in several steps. Initial removal of the sulfinamide auxiliary via treatment with anhydrous methanolic

(11) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Higashibayashi, S.; Tohmiya, H.; Mori, T.; Hashimoto, K.; Nakata, M. *Synlett* **2004**, 457.
(13) Duff, J. M.; Brook, A. G. *Can. J. Chem.* **1977**, *55*, 2589.

**TABLE 2. Additions of $Ph_2CH_3SiLi$ to Sulfinimines**



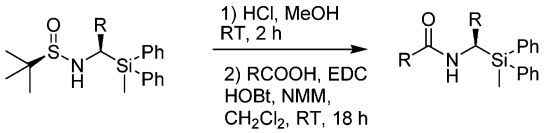

| Entry | Imine | Sulfinamide | Yield | d.r. |
|---|---|---|---|---|
| 1 | **20** |  **32** | 92 % | 95:5 |
| 2 | **21** |  **33** | 80 % | >95:5 |
| 3 | **22** |  **34** | 60 % | >95:5 |
| 4 | **23** |  **35** | 31 % | - |
| 5 | **24** |  **36** | 84 % | 95:5 |
| 6 | **25** |  **37** | 64 % | 95:5 |
| 7 | **26** |  **38** | 96 % | >95:5 |
| 8 | **27** |  **39** | 66 % | 92:8 |
| 9 | **28** |  **40** | 91 % | 95:5 |
| 10 | **29** |  **41** | 97 % | >95:5 |
| 11 | **30** |  **42** | 97 % | n.d.[a] |

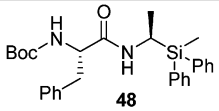
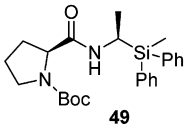
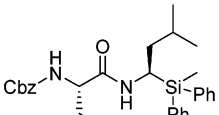
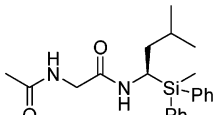
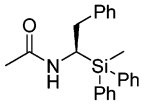
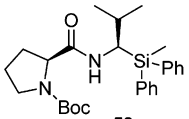
[a] Not determined due to carbamate rotamers.

HCl readily gave the amine salts which were then converted to the desired amides by using standard peptide coupling methods (Table 3).

Further extension of these peptides with additional amino acids is of course also possible by applying standard stepwise extension of the N-terminal via peptide coupling (Scheme 4). The number of amino acid combinations available with this approach is limitless, thus we have limited our own investigations to the peptides depicted in Table 3 and Scheme 4, applying only those sulfinamides that mimic naturally occurring amino acid residues.

**TABLE 3. *N*-Terminal Extension of α-Silylamines**

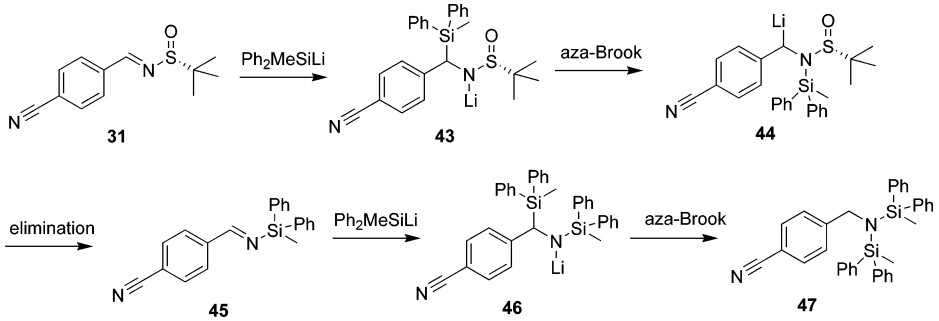



| Entry | Sulfinamide | Peptide | Yield |
|---|---|---|---|
| 1 | **32** |  **48** | 86 % |
| 2 | **32** |  **49** | 76 % |
| 3 | **33** |  **50** | 99 % |
| 4 | **33** |  **51** | 50 %[a] |
| 5 | **34** |  **52** | 69 %[a,b] |
| 6 | **36** |  **53** | 82 % |

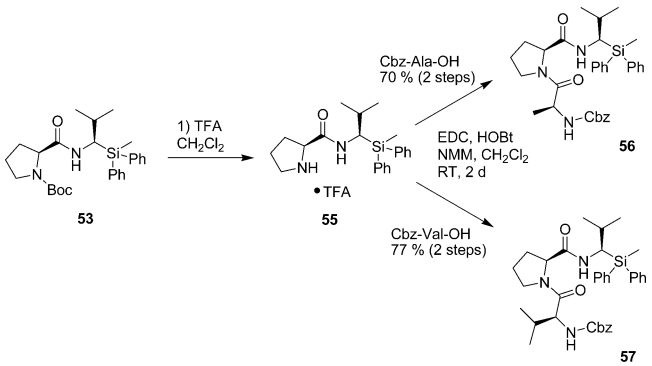
[a] Entry performed with racemic substrate. [b] Second step performed with $Ac_2O$, $NEt_3$.

Conversion of the above peptides into silanediols was envisioned to be achieved via reaction of the diphenylsilane moiety with TfOH, followed by aqueous hydrolysis of the resulting adduct as reported by Sieburth et al.[3] Isolation of the silanediol directly from this approach is, however, not possible due to the propensity for silanediols to form oligomers in concentrated and/or nonpolar conditions.[3h] In previous approaches the crude silanediol is converted to the corresponding silane difloride for example by treatment with concentrated HF.[3] It has also been suggested that the crude silanediol obtained after hydrolysis can be treated with chlorotrimethylsilane and triethylamine to facilitate isolation as its corresponding trisiloxane.[3c] This trisiloxane is also an excellent precursor, and under aqueous basic conditions will hydrolyze to reform the silanediol.

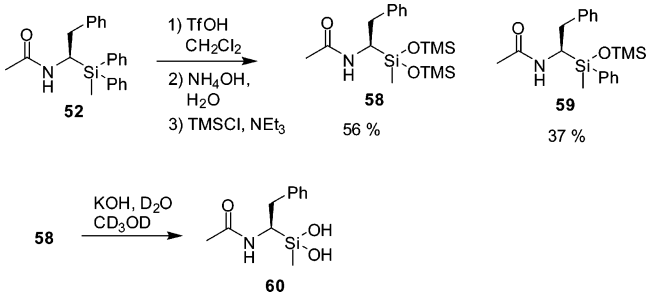
**SCHEME 3**




**SCHEME 4**




**SCHEME 5**

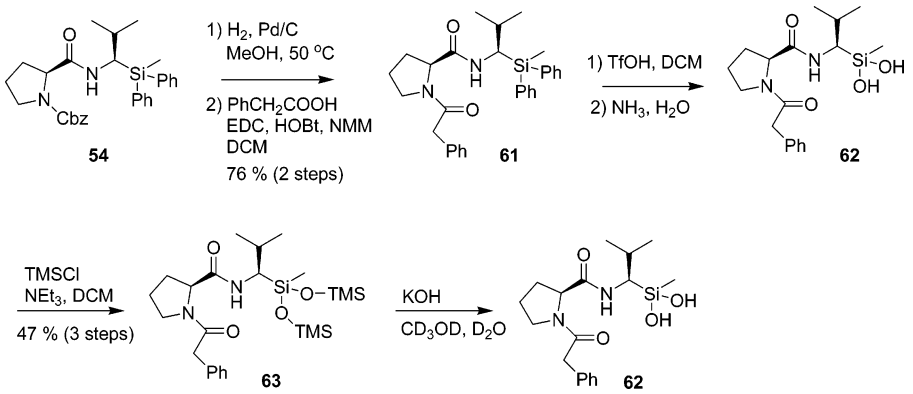



The simple peptide **52** was selected for the initial deprotection study and was treated with TfOH in dichloromethane followed by aqueous ammonia (Scheme 5). Treatment of the crude silanediol with TMSCl and $NEt_3$ afforded the chromatographically stable bis-TMS protected adduct **58** together with the partially deprotected adduct **59** as a mixture of diastereoisomers. Allowing the deprotection to proceed for 25 min afforded a 2:5 mixture of **58** and **59**, respectively. Increasing the reaction time to 4.5 h changed this ratio to 3:2 in favor of trisiloxane **58**. The consumption of starting material is extremely rapid (less than 5 min), as visualized by thin-layer chromatography, indicating that the first phenyl group is cleaved much faster than the second. These findings also support the participation of the amide carbonyl in benzene departure from silicon as proposed by Sieburth et al.[3h] Hydrolysis of the protected adduct **58** via treatment with aqueous KOH in $D_2O$ and $CD_3OD$ then afforded the clean solution of silanediol **60** (and $TMS_2O$) as indicated by $^1H$ NMR analysis of the crude reaction mixture.

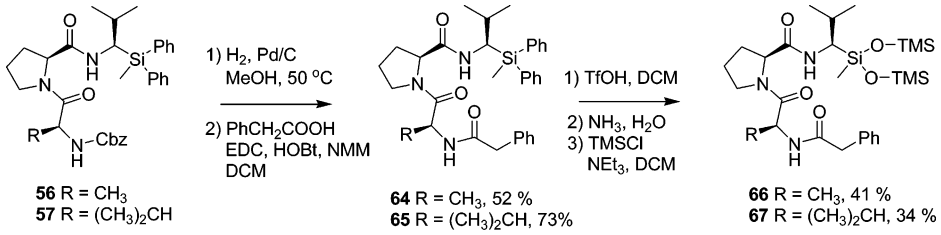
In keeping with a continued interest in the synthesis of peptidomimetic protease inhibitors within the group, we elected to convert compound **54** into a silanediol as depicted in Scheme 6. It was expected that the carbamate protecting group would not survive the harsh conditions required hence it was removed via hydrogenolysis with $PdCl_2$ and then the resulting free amine was converted to a simple amide **61** via an EDC-promoted coupling with phenylacetic acid. Diphenylsilane **61** was treated with triflic acid for 20 h to ensure complete conversion. Subsequent addition of aqueous ammonia followed by TMS protection of the resulting silanediol **62** afforded the trisiloxane **63** in an acceptable 47% yield. Finally, treatment of compound **63** with KOH in a mixture of $D_2O$ and $CD_3OD$ regenerated the silanediol **62**, a mimic of the dipeptide $PhCH_2CO$-Pro-Val-OH.

Finally the tripeptides **56** and **57** were also converted into silanediols in the same manner, as depicted in Scheme 7. As before, conversion of the carbamate moiety into an amide was necessary, achieved in 52% and 73% yield for compounds **64** and **65**, respectively, over the two steps. The diphenylsilane **64** was reacted with TfOH, over 1 d, followed by aqueous hydrolysis with $NH_4OH$ affording the TMS-protected silanediol **66** in 41% yield after treatment with TMSCl and $NEt_3$. Treatment of diphenylsilane **65** with TfOH for 1 d, then aqueous

**SCHEME 6**



**SCHEME 7**




$NH_4OH$ and finally TMSCl, afforded the protected adduct **67** in 34% yield for the three steps. It is expected that the protected adducts **66** and **67** will be converted into their corresponding silanediols once an appropriate protease has been selected for testing.

## Conclusions

Herein, we have reported the first studies toward a modular approach to *C*-terminal silanediol peptide mimics. A series of compounds of this type will be synthesized and tested against a range of proteases for any relevant activity. It is intended that these results will be extended to afford peptide mimics where the silanediol is imbedded within the peptide, by replacement of the terminal methyl group by a *C*-terminal peptide chain. Such an extension would give rapid and flexible access to true silanediol peptide isosteres.

## Experimental Procedures

**Methods for Prepartion of Sulfinimines. Method A:** (*R*)-*tert*-Butylsulfinamide (200 mg, 1.65 mmol) and the aldehyde (2.00 mmol, 1.2 equiv) were dissolved in $CH_2Cl_2$ (8 mL) then $MgSO_4$ (993 mg, 8.25 mmol, 5 equiv) and pyridinium tosylate (20 mg, 0.083 mmol, 0.05 equiv) were added. The mixture was heated to reflux for 18 h, cooled, and filtered. 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.

**(*N*(*E*),*S*(*R*))-2-Methyl-*N*-(3-methylbutylidene)-2-propanesulfinamide (21).**[14] The title compound was prepared from (*R*)-*tert*-butylsulfinamide (253 mg, 2.09 mmol) according to Method A. Increasing polarity from 5% to 10% EtOAc in pentane was used as eluant for column chromatography giving 374 mg (1.98 mmol, 95%) as an oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 8.05 (t, $J$ = 5.2 Hz, 1H), 2.40 (ddd, $J$ = 6.8, 5.6, 1.6 Hz, 2H), 2.05 (m, 1H), 1.19 (s, 9H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 169.4, 56.5, 45.0, 26.2, 22.6, 22.5, 22.4 (3C). HRMS $C_9H_{19}NOS$ [M + $Na^+$] calcd 212.1085, found 212.1087.

**Method B: (*S*(*R*))-2-Methyl-*N*-(methylethylidene)-2-propanesulfinamide (23).**[15] (*R*)-*tert*-Butylsulfinamide (200 mg, 1.65 mmol) was dissolved in THF (13 mL) then acetone (0.64 mL, 8.25 mmol) and $Ti(OEt)_4$ (1.90 mL, 8.25 mmol) were added. The mixture was heated to reflux for 44 h, then cooled to rt before it was poured into a rapidly stirred solution of $NaHCO_3$. After the solution was stirred for 5 min, celite was stirred into the slurry and the suspension was filtered through a pad of celite. The solids were washed with EtOAc (3 × 10 mL), and the combined filtrates were transferred to a separatory funnel. The aqueous portion was separated and extracted with EtOAc (2 × 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 5% to 20% EtOAc in pentane as eluant), which gave the title compound (227 mg, 1.408 mmol, 85%) as an oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 2.29 (s, 3H), 2.13 (s, 3H), 1.18 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 182.8, 55.9, 30.3, 23.6, 21.9 (3C). HRMS $C_7H_{15}NOS$ [M + $Na^+$] calcd 184.0772, found 184.0807.

**Method C:** (*R*)-*tert*-Butylsulfinamide (200 mg, 1.65 mmol) and the aldehyde (2.00 mmol, 1.2 equiv) were dissolved in $CH_2Cl_2$ (8 mL), then $Cs_2CO_3$ (652 mg, 2.00 mmol, 1.2 equiv) was added. The mixture was heated to reflux for 18 h, cooled, and filtered through a pad of celite. The solids were washed with $CH_2Cl_2$, and the combined filtrates were evaporated in vacuo. The pure product was obtained by column chromatography with the stated solvent system.

**(*N*(*E*),*S*(*R*))-2-Methyl-*N*-(2-methylpropylidene)-2-propanesulfinamide (24).**[12] The title compound was prepared from (*R*)-*tert*-butylsulfinamide (180 mg, 1.50 mmol) according to Method C. Increasing polarity from 5% to 20% EtOAc in pentane was used as eluant for column chromatography giving 231 mg (1.32 mmol, 88%) as an oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.86 (d, $J$ = 4.8 Hz, 1H), 2.59 (hep d, $J$ = 7.2, 4.0 Hz, 1H), 1.06 (s, 9H), 1.04 (d, $J$ = 7.2 Hz, 3H), 1.04 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 173.2, 56.1, 34.6, 22.0 (3C), 18.6, 18.6. HRMS $C_8H_{17}NOS$ [M + $Na^+$] calcd 198.0929, found 198.0932.

**General Method for the Addition of (Diphenylmethylsilyl)-lithium to Sulfinimines.** Lithium (42 mg, 6.00 mmol, 12 equiv) was suspended in THF (5 mL) under an atmosphere of argon, and then diphenylmethylchlorosilane (0.31 mL, 349 mg, 1.50 mmol, 3 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 cooled to −78 °C under an atmosphere of argon. To this cooled solution was added the solution of (methyldiphenylsilyl)lithium 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 was allowed to warm to rt. The mixture was poured into water (50 mL) and extracted with EtOAc (3 × 20 mL), and the combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography with the stated solvent system.

**(*S*(*R*))-*N*-[(*R*)-1-(Methyldiphenylsilyl)ethyl]-2-methyl-2-propanesulfinamide (32).** The title compound was prepared from imine **20** (80 mg, 0.543 mmol) according to the general method. Increasing polarity from 15% to 60% EtOAc in pentane was used as eluant for column chromatography giving 173 mg (0.500 mmol, 92%) as an oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.60−7.52 (m, 4H), 7.44−7.30 (m, 6H), 3.46 (dq, $J$ = 10.8, 7.6 Hz, 1H), 2.71 (d, $J$ = 10.8 Hz, 1H), 1.45 (d, $J$ = 7.6 Hz, 3H), 1.05 (s, 9H), 0.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 135.0 (2C), 134.9 (2C), 133.9 (2C), 129.7 (2C), 127.9 (2C), 127.9 (2C), 56.1, 42.0, 22.5 (3C), 19.5, −5.8. HRMS $C_{19}H_{27}NOSSi$ [M + $Na^+$] calcd 368.1480, found 368.1480.

**1,1-Dimethylethyl ((*S*)-2-{[(*R*)-1-(Methyldiphenylsilyl)ethyl]-amino}-2-oxo-1-(phenylmethyl)ethyl)carbamate (48).** Sulfinamide **32** (173 mg, 0.501 mmol) was dissolved in MeOH (10 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 4 h, and all volatiles were removed in vacuo, which gave the crude amine (139 mg, 0.50 mmol, 99%) as its corresponding HCl salt.

(14) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276.

(15) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905.

This was dissolved in $CH_2Cl_2$ (20 mL), and NMM (0.50 mL, 4.54 mmol), Boc-L-Phe-OH (265 mg, 1.00 mmol), HOBt (169 mg, 1.10 mmol), and EDC·HCl (213 mg, 1.10 mmol) were added. The mixture was stirred at rt for 2 d, 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 5% to 25% EtOAc in pentane as eluant), which gave the title compound (211 mg, 0.432 mmol, 86%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.53−7.30 (m, 10H), 7.22−7.15 (m, 3H), 7.12−7.05 (m, 2H), 5.79 (d, $J$ = 9.6 Hz, 1H), 5.10 (br s, 1H), 4.22 (app br q, $J$ = 7.2 Hz, 2H), 2.94 (d, $J$ = 6.8 Hz, 2H), 1.37 (br s, 9H), 1.15 (d, $J$ = 7.6 Hz, 3H), 0.50 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.5, 155.5, 136.7, 134.8 (2C), 134.8 (2C), 134.7, 133.7, 129.7 (2C), 129.2 (3C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 126.6, 79.8, 56.0, 38.4, 32.8, 28.1 (3C), 16.9, −5.9. HRMS $C_{29}H_{36}N_2O_3Si$ [M + $Na^+$] calcd 511.2393, found 511.2392.

**1,1-Dimethylethyl (*S*)-2-({[(*R*)-1-(Methyldiphenylsilyl)ethyl]amino}carbonyl)pyrrolidine-1-carboxylate (49).** Sulfinamide **32** (129 mg, 0.385 mmol) was dissolved in MeOH (10 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 4 h, and all volatiles were removed in vacuo, which gave the crude amine as its corresponding HCl salt. This was dissolved in $CH_2Cl_2$ (10 mL), and NMM (0.385 mL, 3.49 mmol), Boc-L-Pro-OH (166 mg, 0.770 mmol), HOBt (130 mg, 0.846 mmol), and EDC·HCl (164 mg, 0.846 mmol) were added. The mixture was stirred at rt for 2 d, 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 5% to 35% EtOAc in pentane as eluant), which gave the title compound (128 mg, 0.292 mmol, 76%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.60−7.45 (m, 4H), 7.44−7.30 (m, 6H), 6.73 (br s, 0.5H), 5.88 (br s, 0.5H), 4.22−4.06 (m, 2H), 3.40−3.10 (m, 2H), 2.22−1.50 (m, 4H), 1.46−1.20 (m, 9H), 1.16 (d, $J$ = 8.0 Hz, 3H), 0.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.9 (br), 155.5/154.6 (br), 134.8 (4C), 134.1 (2C), 129.6 (2C), 128.0 (4C), 80.1, 61.2/60.0 (br), 46.7, 32.8/32.0 (br), 30.9 (br), 28.2 (3C), 24.4/23.4 (br), 17.0, −6.1 (br). HRMS $C_{25}H_{34}N_2O_3Si$ [M + $Na^+$] calcd 461.2236, found 461.2219.

**Phenylmethyl ((*S*)-2-{[(*R*)-3-Methyl-1-(methyldiphenylsilyl)-butyl]amino}-2-oxo-1-(phenylmethyl)ethyl)carbamate (50).** Sulfinamide **33** (89 mg, 0.230 mmol) was dissolved in MeOH (10 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 5 h, and all volatiles were removed in vacuo, which gave the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (12 mL), and NMM (0.10 mL, 0.91 mmol), Cbz-L-Phe-OH (134 mg, 0.45 mmol), HOBt (73 mg, 0.48 mmol), and EDC·HCl (94 mg, 0.49 mmol) were added. The mixture was stirred at rt for 18 h, poured into water (35 mL), and extracted with $CH_2Cl_2$ (3 × 25 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 25% EtOAc in pentane as eluant), which gave the title compound (129 mg, 0.228 mmol, 99%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.52−7.16 (m, 18H), 7.12−7.02 (m, 2H), 5.39 (d, $J$ = 10.4 Hz, 1H), 5.22 (m, 1H), 5.05 (s, 2H), 4.36−4.24 (m, 2H), 3.03 (dd, $J$ = 13.6, 5.6 Hz, 1H), 2.88 (dd, $J$ = 13.6, 7.2 Hz, 1H), 1.47−1.36 (m, 1H), 1.32−1.20 (m, 2H), 0.90 (d, $J$ = 6.4 Hz, 3H), 0.77 (d, $J$ = 6.8 Hz, 3H), 0.46 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.0, 156.0, 136.7, 136.3, 135.3 (2C), 135.1 (2C), 134.5, 134.1, 130.0, 129.9, 129.6 (2C), 128.9 (2C), 128.8 (2C), 128.5 (2C), 128.3, 128.3 (4C), 127.1, 67.2, 56.6, 40.5, 38.3, 36.3, 24.9, 23.7, 21.2, −5.3. HRMS $C_{35}H_{40}N_2O_3Si$ [M + $Na^+$] calcd 587.2706, found 587.2722.

**(±)-2-(Acetylamino)-*N*-[(*R*)-1-(methyldiphenylsilyl)-3-methylbutyl]acetamide (51).** Sulfinamide **33** (275 mg, 0.71 mmol) was dissolved in MeOH (25 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 5 h, and all volatiles were removed in vacuo, which gave the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (25 mL), and NMM (0.35 mL, 3.18 mmol), *N*-acetylglycine (162 mg, 1.38 mmol), and EDC·HCl (223 mg, 1.16 mmol) were added. The mixture was stirred at rt for 18 h, 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 80% to 100% EtOAc in pentane as eluant), which gave the title compound (135 mg, 0.35 mmol, 50%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.58−7.50 (m, 4H), 7.45−7.33 (m, 6H), 6.14 (s, 1H), 5.60 (d, $J$ = 7.8 Hz, 1H), 3.74 ($q_{AB}$d, $J$ = 16.0, 5.2 Hz, 2H), 1.93 (s, 3H), 1.62−1.50 (m, 1H), 1.42−1.24 (m, 2H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.84 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.7, 168.3, 134.8 (2C), 134.7 (2C), 134.5, 134.1, 129.7, 129.5, 128.0 (2C), 127.9 (2C), 43.5, 40.4, 36.3, 25.2, 23.5, 22.7, 21.1, −6.1. HRMS $C_{22}H_{30}N_2O_2Si$ [M + $Na^+$] calcd 405.1974, found 405.1990.

**(±)-*N*-[(*R*)-1-(Methyldiphenylsilyl)-2-phenylethyl]acetamide (52).** Sulfinamide **34** (80 mg, 0.19 mmol) was dissolved in MeOH (10 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 5 h, and all volatiles were removed in vacuo, which gave the crude amine as its HCl salt. This was dissolved in dry $CH_2Cl_2$ (10 mL) under a nitrogen atmosphere. Acetic anhydride (0.14 mL, 1.48 mmol) and triethylamine (0.052 mL, 0.38 mmol) were added and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with water (10 mL) and acidified with 2 M HCl to pH 5. After separation of the phases, the organic extract was washed with brine, dried ($Na_2SO_4$), and filtered and the solvent was removed in vacuo. Toluene (2 mL) was added and removed in vacuo twice. The pure product was obtained by column chromatography (increasing polarity from 5% to 33% EtOAc in pentane as eluant), which gave the title compound (47 mg, 0.13 mmol, 69%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.62−7.56 (m, 4H), 7.45−7.37 (m, 6H), 7.23−7.08 (m, 5H), 5.06 (br d, $J$ = 10.8 Hz, 1H), 4.46 (td, $J$ = 10.8, 4.4 Hz, 1H), 3.00 (dd, $J$ = 14.0, 4.0 Hz, 1H), 2.67 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.74 (s, 3H), 0.59 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 169.4, 139.4, 135.1 (2C), 135.0 (2C), 134.7, 134.5, 129.9, 129.9, 129.0 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 126.4, 39.7, 37.5, 23.3, −5.0. HRMS $C_{23}H_{25}NOSi$ [M + $Na^+$] calcd 382.1603, found 382.1603.

**1,1-Dimethylethyl (*S*)-2-({[(*R*)-2-Methyl-1-(methyldiphenylsilyl)-propyl]amino}carbonyl)pyrrolidine-1-carboxylate (53).** Sulfinamide **36** (300 mg, 0.86 mmol) was dissolved in MeOH (25 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 18 h, and all volatiles were removed in vacuo, which gave the crude amine as its corresponding HCl salt. This was dissolved in $CH_2Cl_2$ (40 mL), and NMM (0.47 mL, 4.30 mmol), Boc-L-Pro-OH (190 mg, 0.86 mmol), HOBt (264 mg, 1.72 mmol), and EDC·HCl (333 mg, 1.72 mmol) were added. The mixture was stirred at rt for 2 d, 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 (25% EtOAc in pentane as eluant), which gave the title compound (330 mg, 0.707 mmol, 82%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$ 55 °C) $\delta$ (ppm) 7.59−7.56 (m, 4H), 7.37−7.31 (m, 6H), 4.23−4.20 (m, 1H), 4.12−4.09 (m, 1H), 3.36−3.28 (m, 2H), 2.22−2.12 (m, 1H), 2.01−1.92 (m, 1H), 1.85−1.77 (m, 3H), 1.40 (s, 9H), 0.86 (d, $J$ = 6.8 Hz, 3H), 0.77 (d, $J$ = 6.8 Hz, 3H), 0.66 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$ 50 °C) $\delta$ (ppm) 171.9, 156.7, 135.7 (2C), 134.9 (4C), 129.4 (2C), 128.0 (4C), 80.3, 60.6 (br), 47.0, 43.9 (br), 30.6, 28.4 (4C), 24.3 (br), 22.2, 19.4, −4.3. HRMS $C_{27}H_{38}N_2O_3Si$ [M + $Na^+$] calcd 489.2539, found 489.2519.

**Phenylmethyl (*S*)-2-({[(*R*)-2-Methyl-1-(methyldiphenylsilyl)-propyl]amino}carbonyl)pyrrolidine-1-carboxylate (54).** Sulfi-

namide **36** (150 mg, 0.40 mmol) was dissolved in MeOH (20 mL) containing 0.4 M anhydrous HCl. The mixture was stirred at rt for 5 h, and all volatiles were removed in vacuo, which gave the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (20 mL), and NMM (0.24 mL, 2.16 mmol), Cbz-L-Pro-OH (112 mg, 0.45 mmol), HOBt (135 mg, 0.86 mmol), and EDC·HCl (166 mg, 0.86 mmol) were added. The mixture was stirred at rt for 42 h, poured into water (20 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 (40% EtOAc in pentane as eluant), which gave the title compound (180 mg, 0.359 mmol, 89%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$ 60 °C) $\delta$ (ppm) 7.58−7.52 (m, 4H), 7.39−7.28 (m, 11H), 5.20 (d, $J$ = 12.4 Hz, 2H), 4.27−4.23 (m, 1H), 4.09 (dd, $J$ = 10.4, 5.2 Hz, 1H), 3.46−3.38 (m, 2H), 2.18−2.08 (m, 1H), 1.95 (oct, $J$ = 6.8 Hz, 1H), 1.90−1.81 (m, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.72 (d, $J$ = 6.8 Hz, 3H), 0.63 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 50 °C) $\delta$ (ppm) 171.5 (br), 156.5 (br), 136.6, 135.6 (2C), 134.9 (4C), 129.5 (2C), 128.6 (2C), 128.0 (7C), 67.3, 61.1 (br), 47.1 (br), 44.1 (br), 30.5, 28.2 (br), 24.4 (br), 22.2, 19.5, −4.4. HRMS $C_{30}H_{36}N_2O_3Si$ [M + $Na^+$] calcd 523.2393, found 523.2405.

**Phenylmethyl ((*S*)-1-Methyl-2-[((*S*)-{[(*R*)-2-methyl-1-(methyldiphenylsilyl)propyl]amino}carbonyl)pyrrolidin-1-yl]-2-oxoethyl)carbamate (56).** Boc-protected amine **53** (165 mg, 0.35 mmol) was dissolved in dry $CH_2Cl_2$ (2 mL), and TFA (2 mL) was added. The reaction was stirred for 1 h at rt and concentrated in vacuo. This was dissolved in $CH_2Cl_2$ (25 mL), and NMM (0.2 mL, 1.8 mmol), Cbz-L-alanine (82 mg, 0.35 mmol), HOBt (108 mg, 0.71 mmol), and EDC·HCl (136 mg, 0.71 mmol) were added. The mixture was stirred at rt for 50 h, poured into water (20 mL), and extracted with $CH_2Cl_2$ (2 × 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 40% EtOAc in pentane as eluant), which gave the title compound (140 mg, 0.24 mmol, 70%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.58−7.55 (m, 4H), 7.38−7.33 (m, 11H), 6.70 (d, $J$ = 10.4 Hz, 1H), 5.69 (d, $J$ = 7.2 Hz, 1H), 5.11 (d, $J$ = 12.4 Hz, 1H), 5.07 (d, $J$ = 12.4 Hz, 1H), 4.52 (quin, $J$ = 7.2 Hz, 1H), 4.43 (d, $J$ = 6.8 Hz, 1H), 4.12−4.10 (m, 1H), 3.63−3.57 (m, 1H), 3.51−3.47 (m, 1H), 2.22−2.15 (m, 1H), 2.14−2.06 (m, 1H), 1.97−1.87 (m, 2H), 1.74−1.64 (m, 1H), 1.30 (d, $J$ = 7.2 Hz, 3H), 0.81 (d, $J$ = 6.8 Hz, 3H), 0.77 (d, $J$ = 6.8 Hz, 3H), 0.68 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.6, 170.3, 155.7, 136.5, 135.5, 135.5, 134.9 (2C), 134.9 (2C), 129.6, 129.5, 128.6 (2C), 128.2, 128.1 (2C), 128.0 (2C), 128.0 (2C), 66.9, 60.0, 48.3, 47.3, 44.1, 30.4, 26.9, 25.2, 22.0, 19.6, 18.8, −4.7. HRMS $C_{33}H_{41}N_3O_4Si$ [M + $Na^+$] calcd 594.2764, found 594.2756.

**Phenylmethyl (*S*)-2-Methyl-1-[(*S*)-2-({[(*R*)-2-methyl-1-(methyldiphenylsilyl)propyl]amino}carbonyl)pyrrolidin-1-ylcarbonyl]-propylcarbamate (57).** Boc-protected amine **53** (165 mg, 0.35 mmol) was dissolved in dry $CH_2Cl_2$ (2 mL), and TFA (2 mL) was added. The reaction was stirred for 1 h at rt and concentrated in vacuo, redissolved in $CH_2Cl_2$, and evaporated to dryness giving the crude amine as its corresponding TFA salt. This was dissolved in $CH_2Cl_2$ (25 mL), and NMM (0.2 mL, 1.8 mmol), Cbz-L-valine (91 mg, 0.35 mmol), HOBt (108 mg, 0.71 mmol), and EDC·HCl (136 mg, 0.71 mmol) were added. The mixture was stirred at rt for 50 h, then poured into water (20 mL) and extracted with $CH_2Cl_2$ (2 × 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 33% EtOAc in pentane as eluant), which gave the title compound (161 mg, 0.27 mmol, 77%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.58−7.53 (m, 4H), 7.38−7.31 (m, 11H), 6.38 (d, $J$ = 10.4 Hz, 1H), 5.47 (d, $J$ = 9.2 Hz, 1H), 5.10 (d, $J$ = 12.4 Hz, 1H), 5.05 (d, $J$ = 12.4 Hz, 1H), 4.32 (dd, $J$ = 9.2, 6.0 Hz, 1H), 4.27 (dd, $J$ = 8.4, 3.2 Hz, 1H), 4.10 (dd, $J$ = 10.4, 6.0 Hz, 1H), 3.72−3.65 (m, 1H), 3.61−3.53 (m, 1H), 2.03−1.86 (m, 4H), 1.72−1.64 (m, 1H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.81 (d, $J$ = 6.8 Hz, 3H), 0.67 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.9, 170.7, 156.5, 136.5, 135.5, 135.5, 134.9 (2C), 134.8 (2C), 129.6, 129.5, 128.6 (2C), 128.2, 128.1 (2C), 128.0 (2C), 128.0 (2C), 67.0, 60.3, 57.5, 47.7, 44.3, 31.4, 30.7, 27.6, 25.2, 22.0, 19.9, 19.7, 17.5, −4.7. HRMS $C_{35}H_{45}N_3O_4Si$ [M + $Na^+$] calcd 622.3077, found 622.3068.

***N*-((±)-1-{Methylbis[(trimethylsilyl)oxy]silyl}-2-phenylethyl)-acetamide (58) and *N*-[(±)-1-{Methyl(phenyl)[(trimethylsilyl)-oxy]silyl}-2-phenylethyl]acetamide (59).** Diphenylsilane **52** (47 mg, 0.13 mmol) was dissolved in dry $CH_2Cl_2$ (10 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Triflic acid (0.12 mL, 1.3 mmol) was added dropwise and the reaction was stirred for 4.5 h while being allowed to warm to rt. The reaction was cooled to 0 °C, concd $NH_4OH$ (0.30 mL, 1.9 mmol) was added, and the reaction was stirred for another 50 min at 0 °C. The reaction was quenched with water (10 mL) and the pH adjusted to 8−9 by adding 2 M HCl. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (10 mL). The combined organic extracts were washed with brine (15 mL), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residue was dissolved in dry $CH_2Cl_2$ (10 mL) and cooled to 0 °C in an ice bath. Chlorotrimethylsilane (0.33 mL, 2.6 mmol) and triethylamine (0.22 mL, 1.6 mmol) were added and the reaction was stirred at 0 °C for 2.5 h. The reaction was quenched with water (10 mL), the phases were separated, and the organic extract was washed with water (10 mL) and brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. The pure products were obtained by column chromatography (25% EtOAc in pentane as eluant), which gave compound **58** (28 mg, 0.073 mmol, 56%) and compound **59** as a mixture of diastereoisomers (18 mg, 0.048 mmol, 37%). **58**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.28−7.18 (m, 5H), 5.12 (br d, $J$ = 9.2 Hz, 1H), 3.63 (td, $J$ = 9.2, 5.6 Hz, 1H), 2.91 (dd, $J$ = 14.0, 5.6 Hz, 1H), 2.70 (dd, $J$ = 14.0, 9.2 Hz, 1H), 1.87 (s, 3H), 0.12 (s, 9H), 0.09 (s, 9H), 0.03 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 169.4, 139.6, 129.2 (2C), 128.4 (2C), 126.3, 41.6, 36.3, 23.5, 2.0 (6C), −1.2. HRMS $C_{17}H_{33}NO_3Si_3$ [M + $Na^+$] calcd 406.1666, found 406.1663. **59a** (first diastereoisomer): $^1$H NMR (400 MHz, CDCl3) $\delta$ (ppm) 7.57−7.55 (m, 2H), 7.43−7.35 (m, 3H), 7.25−7.10 (m, 5H), 5.13 (br d, $J$ = 9.2 Hz, 1H), 3.83 (ddd, $J$ = 10.8, 9.2, 4.8 Hz, 1H), 2.88 (dd, $J$ = 14.4, 4.8 Hz, 1H), 2.69 (dd, $J$ = 14.4, 10.8 Hz, 1H), 1.81 (s, 3H), 0.39 (s, 3H), 0.14 (s, 9H). **59b** (second diastereoisomer): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.57−7.55 (m, 2H), 7.43−7.35 (m, 3H), 7.25−7.10 (m, 5H), 5.01 (br d, $J$ = 9.6 Hz, 1H), 3.96 (ddd, $J$ = 10.8, 9.6, 4.4 Hz, 1H), 3.01 (dd, $J$ = 14.4, 4.4 Hz, 1H), 2.57 (dd, $J$ = 14.4, 10.8 Hz, 1H), 1.77 (s, 3H), 0.40 (s, 3H), 0.14 (s, 9H). MS $C_{20}H_{29}NO_2Si_2$ calcd 394.2, found 394.2.

**(±)-*N*-{1-[Dihydroxy(methyl)silyl]-2-phenylethyl}acetamide (60).** Trisiloxane **58** (17 mg, 0.044 mmol) was dissolved in $CD_3OD$ (0.3 mL) and transferred via syringe to a solution of KOH (3 mg, 0.055 mmol) in $D_2O$ (0.5 mL). The reaction was stirred under nitrogen at rt for 18 h and directly subjected to NMR analysis. Yield not determined. $^1$H NMR (400 MHz, $D_2O/CD_3OD$) $\delta$ (ppm) 7.27−7.14 (m, 5H), 3.44 (dd, $J$ = 12.8, 3.6 Hz, 1H), 3.00 (dd, $J$ = 14.4, 3.6 Hz, 1H), 2.60 (dd, $J$ = 14.4, 12.8 Hz, 1H), 1.76 (s, 3H), −0.05 (s, 3H). $^{13}$C NMR (100 MHz, $D_2O/CD_3OD$) $\delta$ (ppm) 173.0, 142.2, 129.8 (2C), 129.1 (2C), 126.8, 45.5, 36.6, 22.8, −1.9. MS $C_{11}H_{17}NO_3Si$ [M + $K^+$] calcd 278.1, found 278.1.

**(*S*)-*N*-[(*R*)-2-Methyl-1-(methyldiphenylsilyl)propyl]-1-(phenylacetyl)pyrrolidine-2-carboxamide (61).** Cbz-protected amine **54** (65 mg, 0.13 mmol) was dissolved in absolute EtOH (7 mL) before concd HCl (2 drops) and Pd/C 10% (15 mg) were added. The system was flushed with nitrogen before being subjected to a positive atmosphere of hydrogen and heated to 50 °C. After 1, 3, and 6.5 h another portion of Pd/C 10% was added, and after 19 h, $PdCl_2$ (11 mg, 0.065 mmol) was added to furnish the complete conversion of starting material after a further 3 h. The reaction mixture was cooled to rt, filtered through celite, and washed with $CH_2Cl_2$. The combined filtrates were evaporated in vacuo, and then

toluene (2 mL) was added and removed in vacuo to give the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (10 mL), and DIPEA (0.11 mL, 0.65 mmol), phenylacetic acid (22 mg, 0.16 mmol), HOBt (39 mg, 0.26 mmol), and EDC·HCl (49 mg, 0.26 mmol) were added. The mixture was stirred at rt for 47 h, then poured into water (40 mL) and extracted with $CH_2Cl_2$ (2 × 40 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 the title compound (48 mg, 0.099 mmol, 76%) as a colorless solid. Major rotamer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.61−7.56 (m, 4H), 7.43−7.23 (m, 11H), 6.95 (d, $J$ = 10.0 Hz, 1H), 4.46 (d, $J$ = 6.8 Hz, 1H), 4.05 (dd, $J$ = 10.0, 5.6 Hz, 1H), 3.53−3.40 (m, 2H), 2.27−2.21 (m, 1H), 2.07−1.98 (m, 1H), 1.95−1.85 (m, 2H), 1.71−1.61 (m, 1H), 0.79 (d, $J$ = 6.8 Hz, 3H), 0.71 (d, $J$ = 6.8 Hz, 3H), 0.70 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.3, 170.7, 135.8 (2C), 134.9 (2C), 134.9 (2C), 134.4, 129.5, 129.4, 129.1 (2C), 128.8 (2C), 128.0 (2C), 127.9 (2C), 127.0, 60.0, 47.8, 44.4, 42.1, 30.4, 27.2, 25.1, 22.1, 19.7, −4.7. Minor rotamer (inter alia): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 5.92 (br d, $J$ = 10.6 Hz, 1H), 4.33 (dd, $J$ = 10.6, 5.2 Hz, 1H), 4.20 (dd, $J$ = 8.4, 2.4 Hz 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 134.9, 134.4, 128.7, 128.6, 128.3, 61.8, 46.9, 43.2, 41.4, 31.9, 30.5, 22.7, 22.5, 19.5. HRMS $C_{30}H_{36}N_2O_2Si$ [M + $Na^+$] calcd 507.2444, found 507.2441.

**(*S*)-*N*-{(*R*)-2-Methyl-1-[dihydroxy(methyl)silyl]propyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide (62).** Trisiloxane **63** (30 mg, 0.058 mmol) was dissolved in $CD_3OD$ (0.3 mL) under nitrogen. $D_2O$ (0.3 mL) and KOH dissolved in $D_2O$ (0.077 M, 0.1 mL, 0.0077 mmol) were added and the reaction was placed in a sonicator for 5 h. The reaction mixture was used directly for NMR. $^1$H NMR (400 MHz, $D_2O/CD_3OD$) major rotamer $\delta$ (ppm) 7.37−7.20 (m, 5H), 4.40 (dd, $J$ = 8.8, 4.0 Hz, 1H), 3.77−3.48 (m, 4H), 3.03 (d, $J$ = 6.4 Hz, 1H), 2.36−2.27 (m, 1H), 2.20−2.07 (m, 1H), 2.04−1.87 (m, 3H), 0.91 (d, $J$ = 6.8 Hz, 3H), 0.87 (d, $J$ = 6.4 Hz, 3H), −0.07 (s, 3H); minor rotamer (inter alia) $\delta$ (ppm) 4.57 (dd, $J$ = 8.4, 2.4 Hz, 1H), 3.14 (d, $J$ = 6.0 Hz, 1H), −0.05 (s, 3H).

**(*S*)-*N*-((*R*)-2-Methyl-1-{methylbis[(trimethylsilyl)oxy]silyl}-propyl)-1-(phenylacetyl)pyrrolidine-2-carboxamide (63).** Diphenylsilane **54** (24 mg, 0.049 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Triflic acid (0.04 mL, 0.49 mmol) was added dropwise and the reaction was stirred at 0 °C for 20 h while being allowed to warm to rt. The reaction was cooled to 0 °C, concd $NH_4OH$ (0.11 mL, 0.74 mmol) was added, and the reaction was stirred for another 2 h at 0 °C. The reaction was quenched with water (2 mL) and the pH adjusted to 9 by dropwise addition of 2 M HCl. The two phases were concentrated and trace water removed by consecutive addition of toluene (2 mL) and removal in vacuo. The residue was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Chlorotrimethylsilane (0.090 mL, 0.74 mmol) and triethylamine (0.070 mL, 0.49 mmol) were added and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (5 mL), the phases were separated, and the organic extract was washed with water (5 mL) and brine (5 mL), dried ($Na_2SO_4$), filtered, and concentrated. The product was purified by column chromatography (25% EtOAc in pentane as eluant) to give the title compound (12 mg, 0.0265 mmol, 47%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.32−7.21 (m, 5H), 6.84 (d, $J$ = 10.4, 1H), 4.61 (dd, $J$ = 8.0, 1.6 Hz, 1H), 3.70 (s, 2H), 3.66−3.40 (m, 2H), 3.26 (dd, $J$ = 10.4, 5.2 Hz, 1H), 2.46−2.39 (m, 1H), 2.21−2.08 (m, 1H), 1.99−1.90 (m, 1H), 1.87−1.71 (m, 2H), 0.82 (d, $J$ = 6.8 Hz, 3H), 0.78 (d, $J$ = 6.8 Hz, 3H), 0.11 (s, 9H), 0.10 (s, 9H), 0.05 (s, 3H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$ (ppm) 171.2, 170.8, 134.5, 129.2 (2C), 128.8 (2C), 127.0, 60.1, 47.8, 46.5, 42.2, 29.8, 27.2, 25.3, 21.3, 19.6, 1.9 (6C), −0.7. HRMS $C_{24}H_{44}N_2O_4Si_3$ [M + $Na^+$] calcd 531.2507, found 531.2501.

**(*S*)-*N*-[(*R*)-2-Methyl-1-(methyldiphenylsilyl)propyl]-1-[(*S*)-2-(phenylacetamido)propanoyl]pyrrolidine-2-carboxamide (64).** Cbz-protected amine **56** (69 mg, 0.12 mmol) was dissolved in absolute EtOH (5 mL) before concd HCl (2 drops) and Pd/C 10% (15 mg) were added. The system was flushed with nitrogen before being subjected to a positive atmosphere of hydrogen and heated to 50 °C. After 1.5 h another portion of Pd/C 10% was added, and after 6 h, $PdCl_2$ (11 mg, 0.065 mmol) was added to furnish the complete conversion of starting material after a further 1 h. The reaction mixture was cooled to rt, filtered through celite, and washed with $CH_2Cl_2$. The combined filtrates were evaporated in vacuo, and then toluene (2 mL) was added and removed in vacuo to give the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (10 mL), and NMM (0.07 mL, 0.61 mmol), phenylacetic acid (19 mg, 0.13 mmol), HOBt (38 mg, 0.24 mmol), and EDC·HCl (47 mg, 0.24 mmol) were added. The mixture was stirred at rt for 42 h, then poured into water (10 mL) and extracted with $CH_2Cl_2$ (2 × 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 50% to 100% EtOAc in pentane as eluant), which gave the title compound (35 mg, 0.063 mmol, 52%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.56−7.53, (m, 4H), 7.38−7.27 (m, 11H), 6.52 (br d, $J$ = 10.8 Hz, 1H), 6.38 (br d, $J$ = 6.8 Hz, 1H), 4.70 (quint, $J$ = 6.8 Hz, 1H), 4.40 (dd, $J$ = 8.0, 2.4 Hz, 1H), 4.10 (dd, $J$ = 10.8, 5.6 Hz, 1H), 3.67−3.57 (m, 1H), 3.55 (s, 2 H), 3.49−3.44 (m, 1H), 2.18−2.11 (m, 1H), 1.96−1.86 (m, 2H), 1.73−1.64 (m, 2H), 1.22 (d, $J$ = 6.8 Hz, 3H), 0.80 (d, $J$ = 6.8 Hz, 3H), 0.74 (d, $J$ = 6.8 Hz, 3H), 0.65 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.4, 170.3, 170.3, 135.5, 135.4, 134.9 (4C), 134.8, 129.6, 129.5, 129.4 (2C), 129.0 (2C), 128.1 (2C), 128.0 (2C), 127.4, 60.0, 47.3, 46.8, 44.1, 43.7, 30.5, 27.1, 25.1, 22.1, 19.6, 18.4, −4.6. HRMS $C_{33}H_{41}N_3O_3Si$ [M + $Na^+$] calcd 578.2815, found 578.2836.

**(*S*)-*N*-[(*R*)-2-Methyl-1-(methyldiphenylsilyl)propyl]-1-[(*S*)-3-methyl-2-(phenylacetamido)butanoyl]pyrrolidine-2-carboxamide (65).** Cbz-protected amine **57** (68 mg, 0.11 mmol) was dissolved in absolute EtOH (5 mL), before concd HCl (2 drops) and Pd/C 10% (15 mg) were added. The system was flushed with nitrogen before being subjected to a positive atmosphere of hydrogen and heated to 50 °C for 5.5 h. The reaction mixture was cooled to rt, filtered through celite, and washed with $CH_2Cl_2$. The combined filtrates were evaporated in vacuo, and then toluene (2 mL) was added and removed in vacuo to give the crude amine as its HCl salt. This was dissolved in $CH_2Cl_2$ (10 mL), and then NMM (0.062 mL, 0.57 mmol), phenylacetic acid (18 mg, 0.12 mmol), HOBt (35 mg, 0.23 mmol), and EDC·HCl (43 mg, 0.23 mmol) were added. The mixture was stirred at rt for 43 h, then poured into water (10 mL) and extracted with $CH_2Cl_2$ (2 × 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 40% to 50% EtOAc in pentane as eluant), which gave the title compound (48 mg, 0.082 mmol, 73%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.57−7.52 (m, 4H), 7.37−7.25 (m, 11H), 6.27 (br d, $J$ = 10.8 Hz, 1H), 6.09 (br s, 1H), 4.57 (dd, $J$ = 8.8, 6.8 Hz, 1H), 4.24 (dd, $J$ = 8.0, 2.8 Hz, 1H), 4.09 (dd, $J$ = 10.8, 6.0 Hz, 1H), 3.78−3.70 (m, 1H), 3.64−3.51 (m, 3H), 2.06−2.00 (m, 1H), 1.95−1.82 (m, 4H), 1.72−1.64 (m, 1H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.83 (d, $J$ = 6.4 Hz, 3H), 0.78 (d, $J$ = 6.8 Hz, 3H), 0.76 (d, $J$ = 6.4 Hz, 3H), 0.66 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.6, 170.9, 170.8, 135.5, 135.4, 134.9 (2C), 134.8 (3C), 129.6, 129.6, 129.4 (2C), 129.0 (2C), 128.0 (2C), 128.0 (2C), 127.4, 60.3, 55.5, 47.8, 44.3, 43.8, 31.4, 30.7, 27.7, 25.1, 22.0, 19.9, 19.6, 17.6, −4.6. HRMS $C_{35}H_{45}N_3O_3Si$ [M + $Na^+$] calcd 606.3128, found 606.3098.

**(*S*)-*N*-((*R*)-2-Methyl-1-{methylbis[(trimethylsilyl)oxy]silyl}-propyl)-1-[(*S*)-2-(phenylacetamido)propanoyl]pyrrolidine-2-carboxamide (66).** Diphenylsilane **64** (17.6 mg, 0.032 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Triflic acid (0.028 mL, 0.32 mmol) was added dropwise and the reaction was stirred at 0 °C for 25 h while being allowed to warm to rt. The reaction was cooled to

0 °C, concd $NH_4OH$ (0.075 mL, 0.48 mmol) was added, and the reaction was stirred for another 2.5 h at 0 °C. The reaction was quenched with water (2 mL) and the pH adjusted to 9 by dropwise addition of 2 M HCl. The two phases were concentrated and trace water removed by consecutive addition of toluene (2 mL) and removal in vacuo. The residue was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Chlorotrimethylsilane (0.061 mL, 0.48 mmol) and triethylamine (0.044 mL, 0.32 mmol) were added and the reaction was stirred at 0 °C for 20 h. The reaction was quenched with water (5 mL), the phases were separated, and the organic extract was washed with water (5 mL) and brine (5 mL), dried ($Na_2SO_4$), filtered, and concentrated. The product was purified by column chromatography (increasing polarity from 40% to 50% EtOAc in pentane as eluant) to give the title compound (7.6 mg, 0.013 mmol, 41%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.36−7.28 (m, 5H), 6.61 (br d, $J$ = 10.4, 1H), 6.41 (br d, $J$ = 6.8 Hz, 1H), 4.73 (quin, $J$ = 6.8 Hz, 1H), 4.57 (dd, $J$ = 8.0, 2.0 Hz, 1H), 3.65−3.58 (m, 1H), 3.57 (s, 2H), 3.53−3.48 (m, 1H), 3.27 (dd, $J$ = 10.4, 5.2 Hz, 1H), 2.46−2.39 (m, 1H), 2.22−2.10 (m, 1H), 2.03−1.94 (m, 1H), 1.88−1.75 (m, 2H), 1.29 (d, $J$ = 6.8 Hz, 3H), 0.83 (d, $J$ = 6.8 Hz, 3H), 0.82 (d, $J$ = 6.8 Hz, 3H), 0.11 (s, 18H), 0.04 (s, 3H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$ (ppm) 172.4, 170.3 (2C), 134.8, 129.5 (2C), 129.1 (2C), 127.4, 60.0, 47.2, 46.9, 46.3, 43.8, 29.8, 26.8, 25.3, 21.3, 19.5, 18.7, 1.9 (6C), −0.7. HRMS $C_{27}H_{49}N_3O_5Si_3$ [M + $Na^+$] calcd 602.2878, found 602.2874.

**(*S*)-*N*-((*R*)-2-Methyl-1-{methylbis[(trimethylsilyl)oxy]silyl}-propyl)-1-[(*S*)-3-methyl-2-(phenylacetamido)butanoyl]pyrrolidine-2-carboxamide (67).** Diphenylsilane **65** (24 mg, 0.041 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Triflic acid (0.040 mL, 0.41 mmol) was added dropwise and the reaction was stirred at 0 °C for 22 h while being allowed to warm to rt. The reaction was cooled to 0 °C, concd $NH_4OH$ (0.10 mL, 0.61 mmol) was added, and the reaction was stirred for another 2 h at 0 °C. The reaction was quenched with water (2 mL) and the pH adjusted to 9 by dropwise addition of 2 M HCl. The two phases were concentrated and trace water removed by consecutive addition of toluene (2 mL) and removal in vacuo. The residue was dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. Chlorotrimethylsilane (0.078 mL, 0.61 mmol) and triethylamine (0.057 mL, 0.41 mmol) were added and the reaction was stirred at 0 °C for 2 h. The reaction was quenched with water (5 mL), the phases were separated, and the organic extract was washed with water (5 mL) and brine (5 mL), dried ($Na_2SO_4$), filtered, and concentrated. The product was purified by column chromatography (increasing polarity from 20% to 50% EtOAc in pentane as eluant) to give the title compound (8.4 mg, 0.014 mmol, 34%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.36−7.28 (m, 5H), 6.42 (br d, $J$ = 10.4 Hz, 1H), 6.07 (br d, $J$ = 9.2 Hz, 1H), 4.61 (dd, $J$ = 9.2, 6.4 Hz, 1H), 4.47 (dd, $J$ = 8.0, 2.8 Hz, 1H), 3.79−3.73 (m, 1H), 3.63−3.53 (m, 3H), 3.26 (dd, $J$ = 10.4, 5.2 Hz, 1H), 2.36−2.29 (m, 1H), 2.21−2.10 (m, 1H), 2.00−1.90 (m, 2H), 1.88−1.78 (m, 2H), 0.93 (d, $J$ = 6.4 Hz, 3H), 0.87 (d, $J$ = 6.8 Hz, 3H), 0.85 (d, $J$ = 6.8 Hz, 3H), 0.79 (d, $J$ = 6.8 Hz, 3H), 0.10 (s, 18H), 0.05 (s, 3H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$ (ppm) 171.8, 170.9, 170.7, 134.9, 129.5 (2C), 129.1 (2C), 127.4, 60.3, 55.5, 47.8, 46.5, 43.9, 31.6, 30.0, 27.6, 25.3, 21.2, 19.8, 19.7, 17.7, 1.97 (3C), 1.95 (3C), −0.6. HRMS $C_{29}H_{53}N_3O_5Si_3$ [M + $Na^+$] calcd 630.3191, found 630.3195.

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**Supporting Information Available:** Experimental methods for the preparation of compounds **7**, **8**, **16**−**18**, **20**, **22**, **25**−**31**, **33**−**42**, and **47** and copies of $^1$H NMR and $^{13}$C NMR spectra for compounds **7**, **8**, **16**−**18**, **20**−**42**, **47**−**54**, and **56**−**71**. This material is available free of charge via the Internet at http://pubs.acs.org.

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