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Alpha-amino silanes via metalated imines as an approach to the synthesis of silanediol protease inhibitors

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ABSTRACT

Metalation of benzophenone imines for elaboration of the alpha-amino silane component of silanediol-based protease inhibitors allows for rapid diversification of targets. Coupling this chemistry with recently developed asymmetric hydrosilylation chemistry for preparing beta-silyl acids results in a streamlined process for drug design.

1. Introduction

Proteolytic enzymes mediate many biological processes. An improper level of protease activity can cause disease and many disease-causing organisms have proteases that play crucial roles in their life cycle.[1,2] Protease inhibitors are commercial pharmaceuticals, important in the treatments for hypertension, AIDS, cancer, and periodontal disease, to name a few.[3–7]

Design of protease inhibitors based on the protease substrate often begins with a suitable mimic of the tetrahedral intermediate **2** formed during protease-mediated hydrolysis of peptide **1**, Fig. 1.[8] Effective replacements for the hydrated amide **2** include hydroxyethylene **3**, which is found in nearly all HIV protease inhibitors. The choice of functional group to replace this tetrahedral intermediate is often specific to the class of protease (aspartic, metallo-, serine or cysteine) and the functional group carries with it the physical properties of the selected analog, which in turn affects the entire molecule and its pharmacokinetic properties. Our research seeks to add a new analog of **2** to the medicinal chemist's toolbox, the silanediol, exemplified by structure **4**, which has very different structure and properties.[9]

Silicon is the element most similar to carbon, and like carbon has no intrinsic toxicity. Unlike carbon however, silicon only forms double bonds under duress, and therefore silanediols can act as stable tetrahedral *gem*-diol analogs of hydrated carbonyls.[10]

To prepare silanediols like **4** we initially developed the chemistry outlined in Fig. 2.[11,12] At the outset of this endeavor, silanediols with acid or amino functional groups were unknown.

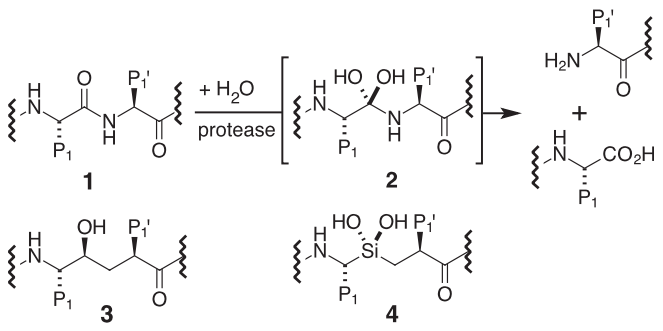

Fig. 1. Protease enzymes stabilize the hydrated amide hydrolysis intermediate. A typical aspartic protease inhibitor structure **3** and silanediol inhibitor **4**.[9]

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Similarly, stereochemistry was not present in known silanediols at that time. Silanediol **5** has two different structural subunits: a beta-silyl amide group and an alpha-amino silane, each carrying a stereogenic center. In this first solution to the structure **5**, the beta-silyl amide was constructed with enantiomerically pure lithium reagent **10**, with absolute stereochemistry derived from the commercially available Roche ester.[12] The alpha-amino silane component was prepared via the silyl ketone **7**. Overall the sequence was effective, but it was lengthy and not particularly general.

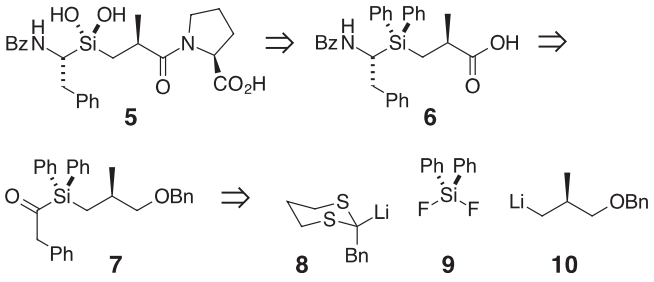

Fig. 2. The first preparation of a silanediol protease inhibitor.[12]

In the approach outlined in Fig. 2, installation of the alpha-amino silane component required five steps, with introduction of the benzyl substituent in the earliest stage (**8**). An intriguing alternative to this approach is the late introduction of the substituent between N and Si by metalation–alkylation of the parent aminomethylsilane, **12**, Fig. 3. This approach has the potential benefit of the well-known stabilization of carbanions alpha to silicon, as well as the potential for asymmetric metalation to control the stereochemistry. This approach has been investigated in the context of Y=Boc, but a suitably efficacious protocol did not emerge.[13] Late introduction of the aminomethylsilane substituent would lend itself to diversification of protease inhibitor structures for study.

A different method for generating a primary aminomethyl anion is the benzophenone *N*-methylimine **14**.[14] This readily available imine is easily deprotonated to form a nucleophilic aminomethyl anion. Indeed, metalation and alkylation of **14** has been reported repeatedly over the last 43 years and silylation of this anion was first performed 40 years ago.[15,16] The resulting silylmethyl imines have also been hydrolyzed to the free amine.[17]

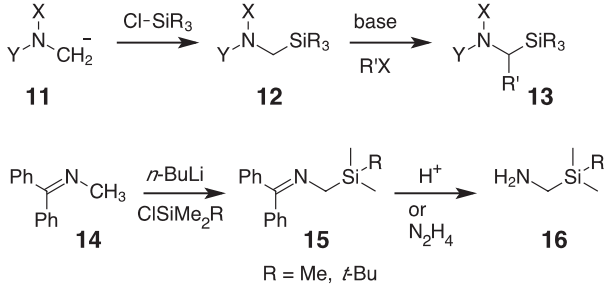

Fig. 3. Alpha-amino silane synthesis by metalation–alkylation.

On the other hand, *N*-silylmethyl imines are also well known precursors of azomethine ylides. Compound **17** has been found to desilylate under a variety of conditions, including simply stirring with water–acetic acid in a polar solvent at ambient temperature, Fig. 4.[18] Nevertheless, the anticipated simplicity of generating structures, such as **15,** and the precedent for hydrolysis to the free amine, stimulated our interest in this approach.

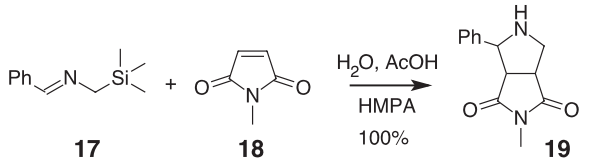

Fig. 4. *N*-Trimethylsilylmethyl imines can desilylate under mild conditions.[18]

2. Results and discussion

Assembly of the protease inhibitor was envisioned to use the sequence outlined retrosynthetically in Fig. 5. The protected inhibitor precursor **20** would come from the imine **22** after hydrolysis of the imine and oxidation of the protected alcohol, or an equivalent. Compound **22** would be prepared by alkylation of **23** after deprotonation between the silicon and imine, and **23** would derive from silylation of lithiated imine **24** and a suitable silane precursor of the beta-silyl acid unit **25**.

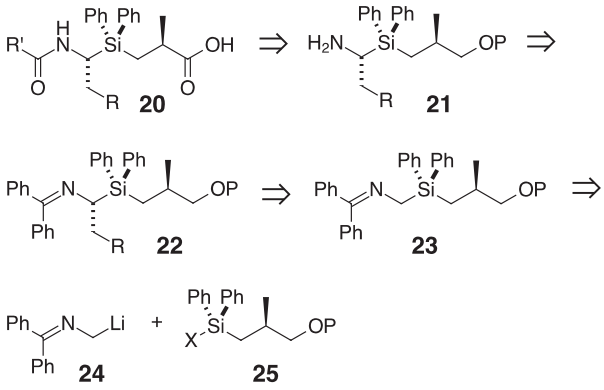

Fig. 5. *N*-Diphenyl(alkyl)silylmethyl imine approach to the protease inhibitors.

Two beta-silyl acid precursors were used in this study, Fig. 6. Fluorosilane **26** is generated by fragmentation of **27**, prepared by asymmetric hydroboration of **28**, the latter a product of magnesium-mediated cyclization of isoprene with dichlorodiphenylsilane.[19] Fluorosilane **29** is readily derived from **30** by asymmetric hydrosilylation of **31**.[20]

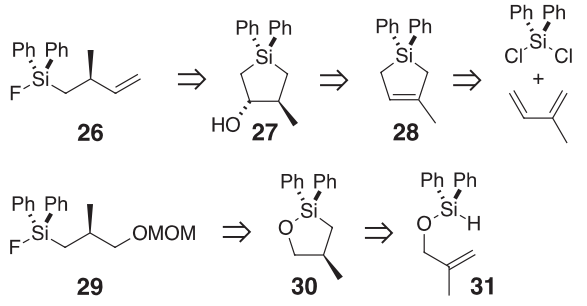

Fig. 6. Electrophilic fluorosilane precursors of beta-silyl acids.[19,20]

In the event, coupling of the lithiated imine derived from **14** with **26** and **29** proceeded in very good yield. In the case of **26**, racemic fluorosilane was used (Fig. 7).

In contrast, hydrolysis of the imine of **33**, using oxalic acid conditions described by Silverman[17] led to cleavage of the just-formed C–Si bond and isolation of silanol **34** in 58% yield

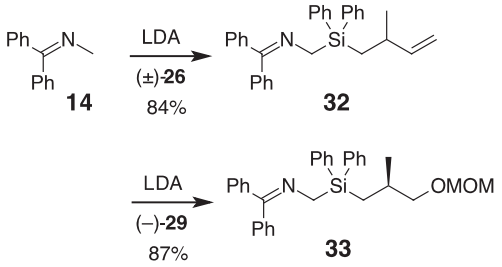

Fig. 7. Silylation of lithiated imine.

(72% based on recovered starting material, Fig. 8). An alternative Silverman procedure using basic conditions, hydrazine hydrate in alcohol, was more successful.[21] Stirring **33** in methanol with excess hydrazine hydrate at reflux led to slow liberation of the amine and after 48 h amine **35** was isolated in 83% yield. Subjecting imine **32** to similar conditions, 1 equiv of hydrazine hydrate in ethanol at ambient temperature, after 4 days produced the amine in 57% yield. This unsaturated amine was accompanied, however, with satd **37** resulting from simultaneous reduction of the alkene.

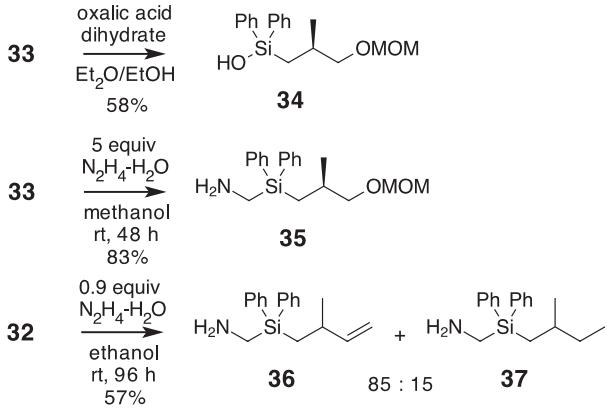

Fig. 8. Hydrolysis and hydrazinolysis of imine **32** and **33**.

We next turned our attention to alkylation of the silylated imines **32** and **33**. For this second deprotonation we found sec-butyllithium to be the most suitable base, Fig. 9. Use of *n*-butyllithium gave none of the anticipated alkylation product and largely recovered starting material, whereas the use of LDA as base led to alkylated product but only in low yield. Addition of a primary bromide (or methyl iodide) gave the anticipated product in good yield as a 1:1 mixture of diastereomers. Notably, these reactions were very clean, with only product and starting material present in the crude mixture, the two readily separated by chromatography.

Hydrazinolysis of the alkylated products focused on **39** as a representative example, and these reactions were found to be more difficult than for the less hindered **32** and **33**. After some experimentation it was found that amine **43** could be isolated in moderate yield after nearly a week in refluxing methanol using a large excess of hydrazine hydrate, Fig. 10. Subsequent deprotection of the alcohol and benzamide formation under Schotten–Baumann conditions gave amide-alcohol **44** in good yield as a mixture of diastereomers. This mixture was identical to this structure previously prepared en route to the ACE inhibitor **5**.[12]

3. Conclusion

This study has demonstrated the use of the benzophenone *N*-methylimine as a viable method for preparation of silanediol

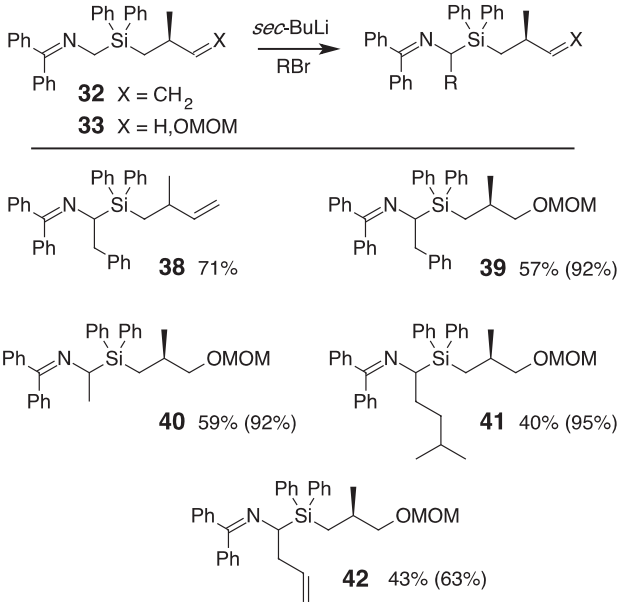

Fig. 9. Alkylation between nitrogen and silicon. Yields in parentheses are based on recovered starting material. In all cases the diastereomeric ratio of products was 1:1.

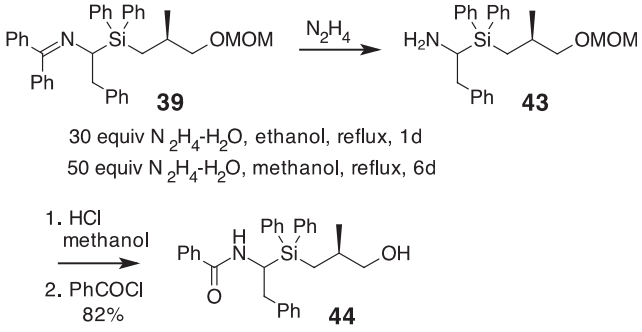

Fig. 10. Hydrazinolysis and conversion to known diastereomers **44**.

protease inhibitors. It intersects nicely with the recently developed beta-silyl ester syntheses. The sequence would profit from a more facile hydrolysis procedure and a diastereoselective alkylation. In principle, the silylation, alkylation, and hydrolysis could be combined into a single operation. Additional results will be reported in due course.

4. Experimental

4.1. General

Reagents and solvents were purchased from Gelest, Aldrich, Fisher Scientific, Alfa Aesar, and Acros. Reaction solvents were purified using a 'Grubbs-style' Solvent Dispensing System purchased from Glass Contour.

Chromatography was conducted over silica gel (170–400 mesh, 60 Å) or basic alumina (activated 50–200 micron).

Analytical thin layer chromatography utilized Analtech Uniplate Silica Gel GF (250 micron) pre-coated glass plates. TLC visualization was conducted with UV light, iodine, and phosphomolybdic acid solution.

Proton and carbon NMR spectra were recorded on Bruker Avance 400 spectrometer and Bruker Avance III 500 spectrometers. Chemical shifts were measured relative to the residual solvent resonance. IR spectra were recorded on Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained with an Agilent 6520B

Accurate-Mass Q-TOF LC/MS and from the Mass Spectrometry Facility of University of California at Riverside.

4.2. (2*S*)-3-(Fluorodiphenylsilyl)-2-methyl-1-propyl methoxymethyl ether (29)

To a 0 °C solution of (*S*)-4-methyl-2,2-diphenyl-1-oxa-2-silacyclopentane **30**[20] (1.29 g, 5.07 mmol) in a mixture of dichloromethane/methanol (5:1, 10 mL) was added slowly 48% HF (1.09 mL, 30.1 mmol). The mixture was allowed to warm to rt overnight and then concentrated with a rotary evaporator. The residue was partitioned between ethyl acetate (20 mL) and water (40 mL). The aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organics were washed with water until neutral, washed with satd NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude fluoro(3-hydroxy-2-methylpropan-1-yl)diphenylsilane as a yellow oil (1.38 g), which was used in next step without purification. The yellow oil was taken up in dimethoxymethane (15 mL). Lithium bromide (0.44 g, 5.07 mmol) and *p*-toluenesulfonic acid monohydrate (0.30 g, 1.58 mmol) were added and the mixture was stirred at rt overnight. The solvent was removed with a rotary evaporator, partitioned between ethyl acetate (20 mL) and water (10 mL). The aqueous phase was extracted with ethyl acetate (2×5 mL) and the combined organics were washed with satd NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (9:1 hexanes/ethyl acetate) gave the title compound as a light yellow oil (1.34 g, 4.21 mmol, 83%). R_f=0.68 (4:1 hexanes/ethyl acetate). $[\alpha]_D^{20}$ −0.64 (*c* 1.28, $CHCl_3$). IR: 3071, 2951, 2884, 1591, 1461, 1429, 1386, 1216 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.68 (m, 4H), 7.37–7.50 (m, 6H), 4.55 (d, *J*=6.5 Hz, 1H), 4.54 (d, *J*=6.5 Hz, 1H), 3.32 (s, 3H), 3.29–3.39 (m, 2H), 2.04–2.14 (m, 1H), 1.43–1.52 (m, 1H), 1.09–1.18 (m, 1H), 1.01 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 134.2, 134.1, 133.9, 133.8, 130.6, 128.2, 96.5, 74.9, 55.2, 29.4, 20.0, 19.1 (d, J_{CF}=14.5 Hz). Exact Mass for $C_{18}H_{23}FNaO_2Si$ $[M+Na]^+$; calcd: 341.1344, found: 341.1343.

4.3. *N*-(Diphenylmethylene)-1-[(4-(3-methyl)-1-butenyl)diphenyl silyl]methanamine (32)

Following the procedure for **33** using benzophenone *N*-methylimine (150 mg, 0.77 mmol) and fluorosilane **26**[19] (0.14 g, 0.52 mmol) gave **32** as a light yellow oil (0.19 g, 0.43 mmol, 84%). R_f=0.89 (1:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.49 (m, 6H), 7.31–7.52 (m, 12H), 6.72 (dt, *J*=6.4, 1.6 Hz, 2H), 5.91 (ddd, *J*=17.2, 10.4, 7.2 Hz, 1H), 4.95 (dt, *J*=17.2, 1.6 Hz, 1H), 4.87 (ddd, *J*=10.0, 2.0, 0.8 Hz, 1H), 3.98 (d, *J*=12.0 Hz, 1H), 3.95 (d, *J*=12.0 Hz, 1H), 2.52–2.64 (m, 1H), 1.52 (dd, *J*=15.2, 6.8 Hz, 1H), 1.40 (dd, *J*=14.8, 7.2 Hz, 1H), 1.11 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 146.7, 140.5, 136.5, 135.6, 135.4, 135.3, 129.5, 129.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 111.5, 45.7, 33.9, 24.0, 20.3. Exact Mass for $C_{31}H_{31}NNaSi$ $[M+Na]^+$; calcd: 468.2118, found: 468.2098.

4.4. *N*-(Diphenylmethylene)-1-[(1-((2*S*)-methyl)-3-methoxymethoxypropyl)diphenylsilyl]methanamine (33)

LDA (5.44 mmol) was prepared by adding 3.39 mL *n*-butyllithium (1.6 M in hexanes) to diisopropylamine (0.76 mL, 5.44 mmol) in THF (6 mL) and stirring for 0.5 h at −78 °C. This was added dropwise to benzophenone *N*-methylimine (0.59 g, 3.02 mmol) in THF (6 mL) at −78 °C. The mixture was stirred for 1.5 h to give a dark red solution that was added to fluorosilane **29** (0.64 g, 2.00 mmol) in THF (4 mL) and this mixture was stirred at −78 °C for 1.5 h. After addition of satd NH_4Cl (2 mL) at −78 °C the solvent was evaporated and the residue was partitioned between ethyl acetate (15 mL) and water (10 mL). The aqueous phase was extracted with ethyl acetate (2×10 mL), the combined organics were washed with satd NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using a gradient elution (10:1–8.5:1 hexanes/ethyl acetate) to give **33** as a light yellow oil (0.86 g, 1.74 mmol, 87%). R_f=0.45 (4:1 hexanes/ethyl acetate). $[\alpha]_D^{20}$ 3.0 (*c* 1.09, $CHCl_3$). IR: 3052, 2949, 2880, 1428, 1110, 1045 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.54 (m, 6H), 7.23–7.40 (m, 12H), 6.55–6.59 (m, 2H), 4.50 (d, *J*=6.5 Hz, 1H), 4.48 (d, *J*=6.5 Hz, 1H), 3.82 (s, 2H), 3.31 (dd, *J*=9.0, 5.5 Hz, 1H), 3.28 (s, 3H), 3.25 (dd, *J*=9.0, 7.0 Hz, 1H), 1.98–2.08 (m, 1H), 1.42 (dd, *J*=15.0, 5.0 Hz, 1H), 1.07 (dd, *J*=15.0, 9.0 Hz, 1H), 0.90 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 140.5, 136.5, 135.6, 135.4, 135.3, 129.6, 129.4, 128.4, 128.3, 128.1, 128.0, 127.9, 96.6, 75.5, 55.3, 45.8, 29.9, 20.5, 16.9. Exact Mass for $C_{32}H_{36}NO_2Si$ $[M+H]^+$; calcd: 494.2510, found: 494.2520.

4.5. 1-[((2*S*)-Methyl)-3-methoxymethoxypropyl]diphenylsilanol (34)

A mixture of **33** (23.6 mg, 47.8 μmol) in ether (2 mL), ethanol (0.3 mL), and oxalic acid dihydrate (3.0 mg, 23.9 μmol) was stirred at rt for 2 d. Satd $NaHCO_3$ was added until the solution was neutral. The aqueous phase was extracted with ethyl acetate (3×2 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography using a gradient elution (30:1–5:1–3:2 hexanes/ethyl acetate) gave silanol **34** as a clear oil (8.7 mg, 27.5 μmol, 58%, 72% based on recovered **33**). R_f=0.34 (4:1 hexanes/ethyl acetate). $[\alpha]_D^{20}$ 1.6 (*c* 0.58 $CHCl_3$). IR: 3413 (br), 3069, 2951, 1428, 1113, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.70 (m, 4H), 7.30–7.44 (m, 6H), 4.46–4.58 (m, 2H), 3.75 (s, 1H, disappearance after adding D_2O), 3.48 (dd, *J*=9.5, 4.5 Hz, 1H), 3.31 (s, 3H), 3.29 (dd, *J*=9.5, 5.5 Hz, 1H), 2.02–2.15 (m, 1H), 1.24 (dd, *J*=15.0, 8.0 Hz, 1H), 1.17 (dd, *J*=15.0, 5.0 Hz, 1H), 0.97 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 137.2, 134.3, 134.2, 129.84, 129.81, 128.1, 128.0, 96.6, 75.5, 55.6, 29.7, 21.8, 21.5. Exact Mass for $C_{18}H_{24}NaO_3Si$ $[M+Na]^+$; calcd: 339.1387, found: 339.1377.

4.6. α-[[(2*S*)-2-Methyl-3-(methoxymethoxy)propyl]diphenylsilyl]methanamine (35)

Following the procedure for **43**, using **33** (230.0 mg, 0.47 mmol) and hydrazine hydrate (0.11 mL, 2.26 mmol) in methanol (1 mL) for 2 d gave **35** as a colorless oil (127.8 mg, 0.39 mmol, 83%). R_f=0.24 (ethyl acetate). $[\alpha]_D^{20}$ 1.1 (*c* 0.58 $CHCl_3$). IR: 3776, 3068, 2950, 2906, 2883, 2822, 1428, 1110, 1045 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.60 (m, 4H), 7.33–7.42 (m, 6H), 4.52 (d, *J*=6.5 Hz, 1H), 4.51 (d, *J*=6.5 Hz, 1H), 3.30 (s, 3H), 3.29 (dd, *J*=8.0, 5.5 Hz, 1H), 3.26 (dd, *J*=9.5, 6.0 Hz, 1H), 2.81 (d, *J*=15.0 Hz, 1H), 2.77 (d, *J*=15.0 Hz, 1H), 1.91–2.01 (m, 1H), 1.38 (dd, *J*=15.0, 4.5 Hz, 1H), 1.26 (br, 2H), 1.01 (dd, *J*=15.0, 8.5 Hz, 1H), 0.89 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.24, 135.23, 135.1, 129.7, 128.2, 96.6, 75.5, 55.3, 29.9, 28.7, 20.5, 16.4. Exact Mass for $C_{19}H_{28}NO_2Si$ $[M+H]^+$; calcd: 330.1884, found: 330.1886.

4.7. α-[4-[2-Methyl-1-propenyl]diphenylsilyl]methanamine (36)

Following the procedure for **43**, using **32** (260.0 mg, 0.58 mmol) and hydrazine hydrate (0.02 mL, 0.49 mmol) in ethanol (5.5 mL) at rt for 4 d gave an 85:15 mixture of **36** and **37** as a clear, colorless oil (93 mg, 0.33 mmol, 57%). R_f=0.24 (1:1 hexanes/ethyl acetate). IR: 3436, 3373, 3068, 2958, 2902, 2872, 1428, 1333, 1114, 998, 911 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.66 (m, 4H), 7.30–7.49 (m, 6H), 5.78 (ddd, *J*=17.5, 10.0, 7.5 Hz, 1H), 4.91 (d, *J*=17.0 Hz, 1H), 4.83 (d, *J*=10.0 Hz, 1H), 2.81 (s, 2H), 2.35–2.48 (m, 1H), 1.36 (dd, *J*=15.0, 7.5 Hz, 1H), 1.25 (dd, *J*=15.0, 7.0 Hz, 1H), 1.03 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 135.25, 135.23, 129.6, 129.5, 128.1, 111.7, 34.0, 28.6, 24.1, 19.9.

4.8. *N*-(Diphenylmethylene)-1-[(4-(3-methyl)-1-butenyl)diphenylsilyl]-2-phenylethanamine (38)

Following the procedure for **39**, using **32** (40 mg, 90 μmol) and benzyl bromide (21.2 μL, 180 μmol) gave **38** as a clear, colorless oil, a 1:1 mixture of diastereomers (34 mg, 63.5 μmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (ddd, J=9.3, 5.4, 1.5 Hz, 4H), 7.60 (dd, J=8.0, 1.4 Hz, 4H), 7.54 (dt, J=8.2, 1.2 Hz, 4H), 7.47–7.28 (m, 18H), 7.20–7.11 (m, 8H), 7.02 (td, J=8.2, 2.3 Hz, 4H), 6.93–6.87 (m, 4H), 5.78 (dtd, J=17.1, 10.1, 7.1 Hz, 2H), 5.70 (s, 3H), 4.82 (dt, J=17.1, 1.5 Hz, 1H), 4.77–4.67 (m, 3H), 3.71 (ddd, J=11.4, 9.8, 1.8 Hz, 2H), 3.16 (dd, J=13.2, 11.3 Hz, 2H), 2.95 (ddd, J=13.2, 3.0, 1.8 Hz, 2H), 2.48–2.33 (m, 2H), 1.45 (ddd, J=15.0, 6.2, 4.3 Hz, 2H), 1.37–1.29 (m, 3H), 0.98 (d, J=6.7 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 146.7, 146.6, 141.5, 140.4, 136.5, 136.5, 136.2, 136.1, 134.6, 134.3, 134.2, 134.0, 129.6, 129.3, 129.2, 129.0, 128.1, 127.9, 127.9, 127.8, 127.7, 127.5, 127.3, 125.6, 111.1, 110.9, 58.9, 58.8, 38.58, 38.55, 33.5, 33.3, 23.7, 23.4, 19.1, 19.0. Exact Mass for $C_{38}H_{37}NNaSi$ $[M+Na]^+$; calcd: 558.2587, found: 558.2577.

4.9. *N*-(Diphenylmethylene)-1-[(1-((2*S*)-methyl)-3-methoxymethoxypropyl)diphenylsilyl]-2-phenylethanamine (39)

sec-Butyllithium (0.29 mL of a 1.1 M solution in cyclohexanes, 0.32 mmol) was added to a −78 °C solution of **33** (104 mg, 0.21 mmol) in THF (5 mL). After 1.5 h benzyl bromide (50.1 μL, 0.42 mmol) in THF (1 mL) was added to the dark red solution and then stirred for 5 h. To the resulting light yellow solution was added satd NH_4Cl (0.5 mL) at −78 °C and the mixture was concentrated. The residue was partitioned between ethyl acetate (3 mL) and water (1 mL). The aqueous phase was extracted with ethyl acetate (2×3 mL), the combined organics were washed with satd NaCl (1 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography using gradient elution (12:1–9:1 hexanes/ethyl acetate) gave the **39** as a light yellow oil, a 1:1 mixture of diastereomers (70 mg, 0.12 mmol, 57%). Compound **33** (40 mg, 0.08 mmol) was recovered (92% yield of **39**). R_f=0.12 (30:1 hexanes/ethyl acetate) IR: 3058, 2924, 2882, 1428, 1280 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J=6.4 Hz, 4H), 7.60 (d, J=7.0 Hz, 8H), 7.55 (d, J=7.2 Hz, 4H), 7.27–7.48 (m, 21H), 7.10–7.23 (m, 9H), 7.03 (t, J=7.5 Hz, 4H), 6.92 (d, J=3.6 Hz, 4H), 5.74 (br s, 4H), 4.55 (ABq, J=8.4 Hz, 2H), 4.52 (s, 2H), 3.72 (d, J=11.0 Hz, 2H), 3.32–3.39 (m, 2H), 3.31 (s, 3H), 3.28 (s, 3H), 3.18 (dd, J=25.5, 13.5 Hz, 2H), 2.98 (dd, J=12.8, 8.9 Hz, 2H), 2.01 (dt, J=14.2, 7.7 Hz, 2H), 1.51 (dd, J=15.0, 4.7 Hz, 2H), 1.09–1.18 (m, 2H), 0.90 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 141.73, 141.71, 140.5, 136.6, 136.3, 136.22, 136.18, 134.7, 134.3, 134.0, 129.8, 129.6, 129.55, 129.52, 129.3, 128.25, 128.20, 128.1, 128.01, 127.99, 127.9, 127.8, 127.5, 125.8, 96.61, 96.57, 75.6, 75.5, 59.19, 59.16, 55.3, 55.2, 38.66, 38.62, 29.93, 29.87, 20.64, 20.62, 15.7, 15.5. Exact Mass for $C_{39}H_{42}NO_2Si$ $[M+H]^+$; calcd: 584.2979, found: 584.2992.

4.10. *N*-(Diphenylmethylene)-1-[(1-((2*S*)-methyl)-3-methoxymethoxypropyl)diphenylsilyl]-1-ethanamine (40)

Following the procedure for **39**, compound **33** (38.2 mg, 77.4 μmol) and methyl iodide (9.6 μL, 155 μmol) gave **40** as a clear oil, a 1:1 mixture of diastereomers (23 mg, 45.3 μmol, 59%, 92% based on recovered starting material). R_f=0.71 (4:1 hexanes/ethyl acetate). IR: 3067, 2949, 2924, 2884, 1428 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J=6.5, 5.5 Hz, 4H), 7.57 (dd, J=6.5, 5.0 Hz, 4H), 7.54 (dd, J=5.5, 4.5 Hz, 4H), 7.27–7.44 (m, 24H), 6.85 (br s, 4H), 4.49 (dd, J=10.2, 6.3 Hz, 2H), 4.46 (dd, J=8.6, 6.2 Hz, 2H), 3.74 (q, J=7.1 Hz, 2H), 3.27 (s, 3H), 3.24 (s, 3H), 3.15–3.29 (ddd, J=14.5, 9.2, 6.9 Hz, 4H), 1.85–2.00 (m, 2H), 1.38 (d, J=5.0 Hz, 3H), 1.38 (d, J=5.0 Hz, 3H), 1.33–1.42 (m, 2H), 1.02 (dt, J=15.1, 8.6 Hz, 2H), 0.83 (d, J=6.6 Hz, 3H), 0.79 (d, J=6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 140.7, 137.0, 136.2, 134.9, 134.7, 134.5, 134.4, 129.53, 129.46, 128.5, 128.4, 128.3, 128.2, 127.9, 127.84, 127.82, 127.78, 96.59, 96.55, 75.6, 75.5, 55.24, 55.20, 51.21, 51.18, 29.9, 29.8, 20.6, 20.5, 18.2, 15.65, 15.59. Exact Mass for $C_{33}H_{38}NO_2Si$ $[M+H]^+$; calcd: 508.2666, found: 508.2669.

4.11. *N*-(Diphenylmethylene)-1-[(1-((2*S*)-methyl)-3-methoxymethoxypropyl)diphenylsilyl]-4-methyl-1-pentanamine (41)

Following the procedure for **39**, using **33** (38.0 mg, 77.0 μmol) and 1-bromo-3-methylbutane (18.5 μL, 154 μmol) gave **41** as a clear oil, a 1:1 mixture of diastereomers (17 mg, 30.9 μmol, 40%, 95% based on recovered starting material). R_f=0.83 (4:1 hexanes/ethyl acetate). IR: 3068, 2952, 2927, 1428 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J=7.4 Hz, 8H), 7.52 (dd, J=7.0, 0.9 Hz, 4H), 7.25–7.38 (m, 24H), 6.59 (d, J=3.6 Hz, 4H), 4.51 (q, J=6.4 Hz, 2H), 4.48 (d, J=0.8 Hz, 2H), 3.59 (dd, J=4.5, 2.2 Hz, 1H), 3.57 (dd, J=4.5, 2.2 Hz, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 3.16–3.33 (m, 4H), 1.85–2.02 (m, 4H), 1.65 (ddd, J=13.2, 6.7, 4.0 Hz, 2H), 1.42 (ddd, J=14.9, 10.0, 4.9 Hz, 2H), 1.31 (ddd, J=13.2, 8.3, 5.0 Hz, 2H), 1.13–1.24 (m, 2H), 1.05 (ddd, J=14.8, 8.8, 1.0 Hz, 2H), 0.86–0.91 (m, 2H), 0.85 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.6 Hz, 3H), 0.75 (d, J=2.6 Hz, 3H), 0.74 (d, J=2.6 Hz, 3H), 0.72 (d, J=2.8 Hz, 3H), 0.71 (d, J=2.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 140.7, 137.2, 136.3, 136.2, 136.1, 135.1, 134.7, 134.6, 134.4, 129.45, 129.39, 129.36, 129.3, 128.5, 128.31, 128.26, 128.1, 127.89, 127.85, 127.74, 127.71, 96.61, 96.56, 75.6, 75.5, 56.75, 56.69, 55.3, 55.2, 38.52, 38.48, 30.06, 30.00, 29.89, 29.85, 28.0, 22.9, 22.6, 20.6, 15.6, 15.4. Exact Mass for $C_{37}H_{46}NO_2Si$ $[M+H]^+$; calcd: 564.3292, found: 564.3368.

4.12. *N*-(Diphenylmethylene)-4-[(1-((2*S*)-methyl)-3-methoxymethoxypropyl)diphenylsilyl]-1-buten-4-amine (42)

Following the procedure for **39**, using **33** (32 mg, 64.8 μmol) and allyl bromide (11.2 μL, 130 μmol) gave **42** as a clear oil, a 1:1 mixture of diastereomers (15 mg, 28.1 μmol, 43%, 63% based on recovered starting material). R_f=0.71 (4:1 hexanes/ethyl acetate). IR: 3069, 2949, 2925, 2883, 1428, 1109, 911 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.66 (m, 12H), 7.20–7.37 (m, 24H), 6.61–6.74 (m, 4H), 5.61 (ddt, J=13.3, 7.4, 6.8 Hz, 2H), 4.88 (d, J=12.2 Hz, 4H), 4.48 (dd, J=4.6, 2.1 Hz, 4H), 3.71 (dt, J=10.9, 2.1 Hz, 2H), 3.28 (s, 3H), 3.24 (s, 3H), 3.16–3.33 (m, 4H), 2.64–2.75 (m, 2H), 2.35–2.45 (m, 2H), 1.85–1.96 (m, 2H), 1.41 (ddd, J=15.0, 4.4, 3.7 Hz, 2H), 1.06 (dd, J=9.0, 5.0 Hz, 1H), 1.03 (dd, J=9.0, 5.0 Hz, 1H), 0.83 (d, J=7.0 Hz, 3H), 0.81 (d, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 140.7, 138.4, 136.9, 136.3, 136.21, 136.17, 134.7, 134.3, 134.2, 134.0, 129.6, 129.52, 129.50, 129.4, 128.6, 128.4, 128.2, 128.1, 127.99, 127.94, 127.91, 127.84, 127.79, 115.7, 96.60, 96.56, 75.50, 75.49, 56.51, 56.46, 55.3, 55.2, 36.85, 36.81, 29.88, 29.83, 20.59, 20.57, 15.7, 15.5. Exact Mass for $C_{35}H_{40}NO_2Si$ $[M+H]^+$; calcd: 534.2823, found: 534.2829.

4.13. 1-[(1-((2*S*)-Methyl)-3-methoxymethoxypropyl)diphenylsilyl]-2-phenyl-1-ethanamine (43)

Hydrazine monohydrate (0.26 mL, 5.35 mmol) was added to a solution of **39** (63.5 mg, 0.11 mmol) in methanol (2 mL) and the solution was heated to reflux for 6 d. The mixture was concentrated and then partitioned between ethyl acetate (5 mL) and water (1 mL). The aqueous phase was extracted with ethyl acetate (2×5 mL) and the combined organics were washed with satd NaCl (1 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using a gradient elution (12:1–2:1 hexanes/ethyl acetate) to give **43** as a clear oil (18.4 mg, 0.044 mmol, 40%). Compound **39** (22 mg, 0.038 mmol) was recovered (62% yield based on recovered starting material).

The same reaction (67 mg of **39**, 0.08 M in ethanol) with hydrazine hydrate (30 equiv) under reflux for 1 d gave 15% yield (24% based on recovered starting material).

R_f=0.75 (1:1 hexanes/ethyl acetate). IR: 3364, 3297, 3069, 3024, 2925, 1428, 1109 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.62–7.71 (m, 7H), 7.34–7.47 (m, 12H), 7.24–7.32 (m, 5H), 7.17–7.22 (m, 2H), 7.12–7.17 (m, 4H), 4.48–4.54 (m, 4H), 3.292 (s, 3H), 3.288 (s, 3H), 3.21–3.28 (m, 4H), 3.04–3.13 (m, 4H), 2.28–2.36 (m, 2H), 1.87–1.97 (m, 2H), 1.39 (br, 4H), 1.34–1.49 (m, 2H), 1.06 (dd, J=15.0, 8.5 Hz, 2H), 0.87 (d, J=6.5 Hz, 3H), 0.83 (dd, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.74, 140.72, 135.9, 134.3, 134.2, 134.14, 134.09, 129.8, 129.3, 128.7, 128.2, 126.4, 96.6, 75.5, 75.4, 55.3, 41.6, 40.6, 29.95, 29.93, 20.5, 20.4, 16.0. Exact Mass for $C_{26}H_{34}NO_2Si$ $[M+H]^+$; calcd: 420.2353, found: 420.2357.

4.14. *N*-[1-[[(2*S*)-3-Hydroxy-2-methylpropyl]diphenylsilyl]-2-phenylethyl]-benzamide (44)[12]

A methanolic solution of HCl (17.5 μL, 4 M) was added to **43** (4.9 mg, 11.7 μmol) at 0 °C and stirred at rt overnight. The solvent was removed with a rotary evaporator, the residue was dissolved in ethyl acetate (1 mL) and mixed with satd $NaHCO_3$ (0.5 mL). To the stirred two phase mixture at rt was added benzoyl chloride (1.36 μL, 11.7 μmol). After stirring at rt overnight, the aqueous phase was extracted with ethyl acetate (2×1 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (2:1 hexanes/ethyl acetate) to give **44** as a colorless foam (4.6 mg, 9.6 μmol, 82%).

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Supplementary data

^1H and ^{13}C NMR spectra of new compounds is available as Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.022.

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