# Silicon-Containing Amino Acids and Peptides. Asymmetric Synthesis of (Trialkylsilyl)alanines

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Synthetic amino acids which bear unnatural side chains have proven useful for probing the structural requirements for the activity of numerous peptides and proteins[2,3] and for imparting novel properties, such as metal-complexing abilities, to peptides.[4] Trialkylsilyl groups are known for having nonpolar, hydrophobic properties relevant to biological activity,[5] so we became interested in developing means for imparting such properties into peptides by the use of (trialkysilyl)alanines. Peptides containing such residues in place of naturally occuring residues might exhibit enhanced biological activities, tissue absorbance properties, and proteolytic stabilities due to the hydrophobicity and large volume (relative to the corresponding hydrocarbon groups) of the trialkylsilyl side chains. Moreover, by using the rich substitution chemistry known for organosilanes,[6] one might be able to develop silicon-functionalized trialkylsilyl-containing amino acids for the placement of silicon-bearing functionality into peptides including, conceivably, disiloxane crosslinks and silicone–peptide copolymers, with potential applications to peptide drug design and the development of biocompatible polymeric materials.

(Trimethylsilyl)alanine (**1**) was first synthesized as the racemate in 1968 by Porter and Shive, who found it to lack antimicrobial activity.[7] Fitzi and Seebach,[8] and later Weidmann,[9] reported asymmetric syntheses of **1** (L enantiomer) which utilized the reactions of asymmetric glycine enolate equivalents with (chloromethyl)trimethylsilane ($C_\alpha$–$C_\beta$ bond formation) in the key step. Weidmann also synthesized the *N*-Fmoc and *N*-Boc derivatives of L-(trimethylsilyl)alanine (**1**) and reported that renin inhibitory peptides bearing **1** in place of a phenylalanine residue were synthesizable, more resistant to proteolytic digestion than the Phe-containing peptides, and exhibited biological activity similar to that of the Phe-containing peptides.[9]

In order to increase the variety of silicon-containing amino acids available for incorporation into peptides and to precedent an eventual synthesis of silylalanines bearing functional (nonalkyl) groups on the silicon center, we sought a general synthetic route to (trialkylsilyl)alanines which avoided the acidic hydrolysis steps needed by the previous synthetic routes to **1**. Toward this end, we have developed a synthesis which is based on Evans' asymmetric α-bromination/azide displacement/azide reduction protocol ($C_\alpha$–N bond formation) for synthesizing α-amino acids.[10] In this paper, we report the syntheses of the (trialkylsilyl)alanines L-(trimethylsilyl)alanine (**1**), L-(dimethylphenylsilyl)alanine (**2**), and L-(methyldiphenylsilyl)alanine (**3**) (Scheme 1) using this route, and we also report preliminary experimental details which demonstrate the capability of *N*-Fmoc L-(trimethylsilyl)alanine to undergo some of the typical coupling and deprotection steps associated with peptide synthesis.

As indicated in Scheme 1, the 3-(trialkylsilyl)propionic acids **4**–**6** were obtained either commercially (**4**, as the sodium salt) or prepared[11,12] from the corresponding trialkylsilyl chlorides by allylation,[13,14] hydroboration–oxidation,[15,16] and Jones oxidation.[17] Conversion of the acids **4**–**6** to the chiral *N*-acyloxazolidinones **7**–**9** followed by the asymmetric bromination of the dibutylboron enolates yielded the crude α-bromo derivatives, and subsequent azide displacement gave the α-azido-*N*-acyloxazolidinones **10**–**12** in high overall yields as primarily (>97%) single diastereomers, according to NMR analyses of the crude reaction mixtures. An X-ray crystallographic analysis of the trimethylsilyl-containing product **10** verified the *R* absolute configuration of the α carbon, as anticipated based on precedent.[10] Hydrolytic removal of the oxazolidinone chiral auxiliary produced the α-azido acids **13**–**15**, which were then reduced to the amino acids **1**–**3** in moderate yields. As a prelude to using these amino acids in peptide synthesis, they were converted to the *N*-(9-fluorenylmethoxycarbonyl) (Fmoc) derivatives **16**–**18**. Thus, the three Fmoc-protected (trialkylsilyl)-

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(15) Preparation of 3-(dimethylphenylsilyl)-1-propanol: Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309.

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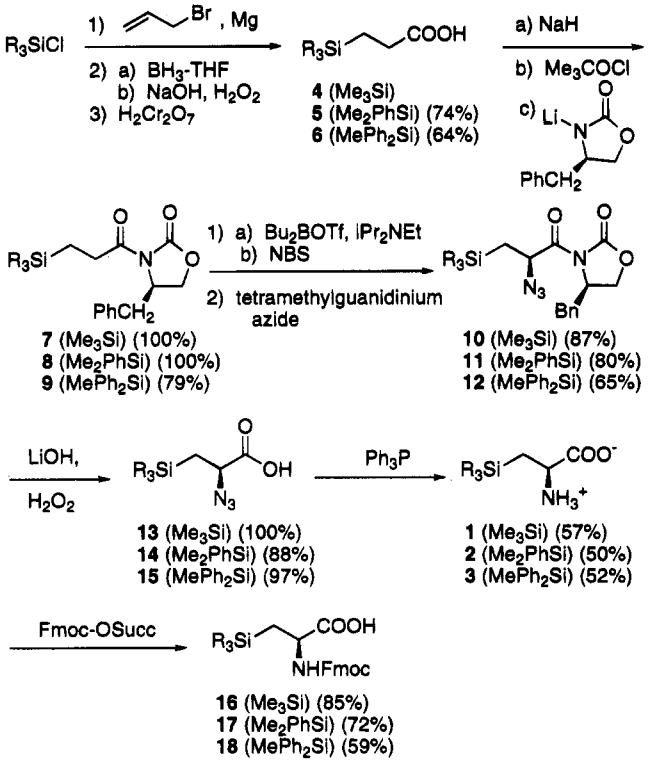
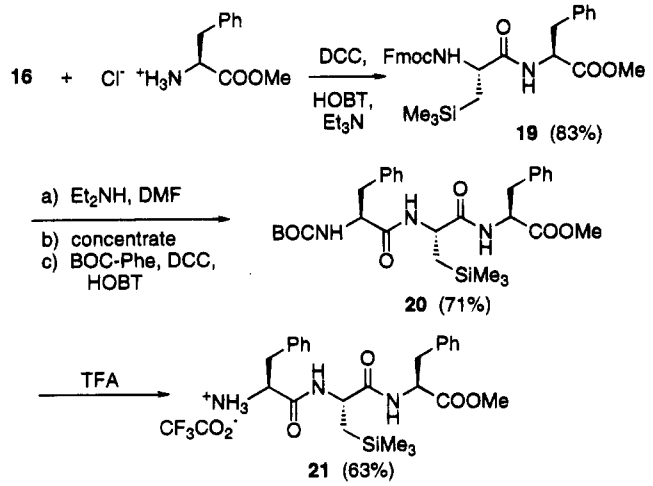
**Scheme 1**




**Scheme 2**




alanines **16**–**18** were produced in 42%, 19%, and 10% overall yields, respectively, in six or nine steps from commercially available starting materials.

To demonstrate that (trialkylsilyl)alanines are capable of undergoing typical reactions associated with peptide synthesis, a tripeptide bearing a (trimethylsilyl)alanine residue was synthesized as shown in Scheme 2. The Fmoc-protected (trimethylsilyl)alanine **16** was coupled with L-phenylalanine methyl ester using the DCC/HOBT coupling conditions to produce the dipeptide **19** in good yield. Removal of the Fmoc group and coupling with *N*-Boc-phenylalanine yielded the tripeptide **20**, which underwent trifluoroacetic acid treatment to yield the peptide **21**, again in good yield. These results, along with those of Weidmann,[9] indicate that at least the simple (trialkylsilyl)alanine **1** is not affected by coupling and deprotection conditions usually associated with peptide synthesis. Moreover, $^1$H and $^{13}$C NMR analysis of the peptides **19**, **20**, and **21** indicated the absence (within limits of detection, ca. 5%) of peaks due to epimerizations at the α carbons of the amino acid residues. In fact, the β effect, which predicts that the trialkylsilyl group in (trialkylsilyl)alanines will destabilize the formation of a carbanionic intermediate by the deprotonation of the α carbon,[18] suggests that (trialkylsilyl)alanines should be particularly resistant to epimerization.

In summary, a general and mild synthetic route to a novel class of silicon-containing amino acids has been developed, and the ability of these amino acids to be incorporated into peptides by solution phase methodology has been demonstrated. Detailed studies of the ability of such amino acids to be used in solid phase peptide synthesis, the chemical and structural properties of (trialkylsilyl)alanine-containing peptides, the effects of (trialkylsilyl)alanine residues upon the biological activity of peptides, and ways to improve the scope and yields of the syntheses of silicon-containing amino acids in general are underway and will be reported in the future.

## Experimental Section

**General.** Unless otherwise indicated, solvents and reagents were reagent grade and used without purification. The solvents used were purified by the usual procedures. Reactions were performed under nitrogen. The progress of reactions and chromatographic separations was followed using thin layer chromatography (TLC). The silica gel used for chromatography was 230–400 mesh. $^1$H- and $^{13}$C-NMR spectra were recorded in solutions in the indicated solvents at 200 and 50 MHz, and chemical shifts are reported relative to either a tetramethylsilane internal standard or the signals due to the solvent (in the cases where $D_2O$ was used as the NMR solvent, dioxane was used as a $^{13}$C-NMR internal standard). Elemental analyses were done by Desert Analytics, Tuscon, AZ. High-resolution mass spectra were measured by the Midwest Center for Mass Spectrometry, University of Nebraska–Lincoln, Lincoln, NB. Optical rotations were measured at the sodium D line (589 nm) using a Rudolph Autopol III polarimeter calibrated using a standard quartz control plate (Rudolph), using a 10-cm cell, and the solvents and concentrations indicated. The reported melting points are uncorrected.

**(*R*)-4-Benzyl-3-[3′-(trimethylsilyl)propanoyl]-1,3-oxazolidin-2-one (7), (*R*)-4-Benzyl-3-[3′-(dimethylphenylsilyl)propanoyl]-1,3-oxazolidin-2-one (8), and (*R*)-4-Benzyl-3-[3′-(methyldiphenylsilyl)propanoyl]-1,3-oxazolidin-2-one (9). General Procedure.** To 3-(trimethylsilyl)propanoic acid (**4**) sodium salt (0.66 g, 3.96 mmol) in 20 mL of THF at 0 °C was added trimethylacetyl chloride (0.51 mL, 4.15 mmol), and the mixture was stirred under a dry nitrogen atmosphere for 2 h at 0 °C and then cooled to −78 °C. In a separate flask, 2.6 mL of a 1.6 M solution of n-BuLi in hexanes (4.16 mmol) was added to a stirring solution of (*R*)-(+)-4-benzyl-1,3-oxazolidin-2-one (0.70 g, 3.95 mmol) in 20 mL of THF at −78 °C. After being stirred at −78 °C for 30 min, this solution was transferred via cannula to the flask containing the first solution. The resulting mixture was stirred at −78 °C for 1 h and then at room temperature for 1 h. Workup into ether followed by chromatography (90:10 hexanes/EtOAc) yielded **7** (1.21 g, 100%) as a clear oil: $^1$H NMR ($CDCl_3$) δ 0.05 (s, 9H), 0.89 (dd, $J$ = 13.9, 6.7 Hz, 1 H), 0.89 (dd, $J$ = 7.2, 5.9 Hz, 1 H), 2.75 (dd, $J$ = 13.3, 9.6 Hz, 1 H), 2.91 (dd, $J$ = 13.9, 6.8 Hz, 1 H), 2.91 (dd, $J$ = 8.7, 4.2 Hz, 1 H), 3.30 (dd, $J$ = 13.3, 3.2 Hz, 1 H), 4.12–4.22 (m, 1 H), 7.19–7.38 (m, 5 H); $^{13}$C NMR ($CDCl_3$) δ −1.9, 11.1, 30.4, 37.9, 55.2, 66.1, 127.3, 128.9, 129.4, 135.4, 153.4, 174.8; IR (film) 2953, 1789, 1738, 1694 cm$^{-1}$; $[\alpha]_D$ −15.0° ($c$ = 0.022 g/mL, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_3Si$: C, 62.92; H, 7.59. Found: C, 63.07; H, 7.30.

The acids **5** and **6** were converted to the corresponding *N*-acyloxazolidinones **8** and **9** by following the same procedure, except that the sodium salts were generated initially by adding the acids to a suspension of hexane-washed sodium hydride in the THF solvent. Compound **8** was obtained in quantitative

(18) Jarvie, A. W. P. *Organomet. Chem. Rev. A* **1970**, *6*, 153.

yield as a white solid: mp 62–64 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.34 (s, 6 H), 1.08–1.20 (m, 2 H), 2.74 (dd, $J$ = 13.3, 9.6 Hz, 1 H), 2.97 (dd, $J$ = 10.3, 6.0 Hz, 1 H), 3.28 (dd, $J$ = 13.3, 3.2 Hz, 1 H), 4.11 (d, $J$ = 7.0 Hz, 2 H), 4.50–4.70 (m, 1 H), 7.12–7.40 (m, 8 H), 7.47–7.60 (m, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −3.3, 10.1, 30.2, 37.7, 55.0, 66.0, 127.2, 127.7, 128.8, 129.0, 129.3, 133.6, 135.3, 138.1, 153.2, 174.3; IR (film) 2955, 2359, 1783, 1699 cm$^{-1}$; $[\alpha]_D$ −34.0° ($c$ = 0.020 g/mL, $CHCl_3$); HRMS $m/z$ 352.1369 ($C_{20}H_{22}NO_3Si$ (M − $CH_3$), calcd 352.1369), 290.1220 ($C_{15}H_{20}NO_3Si$ (M − $C_6H_5$), calcd 290.1212). Compound **9** was obtained in 79% yield as a clear oil: $^1$H NMR ($CDCl_3$) $\delta$ 0.62 (s, 3 H), 1.41–1.51 (m, 2 H), 2.68 (dd, $J$ = 13.3, 9.7 Hz, 1 H), 2.94–3.02 (m, 2 H), 3.23 (dd, $J$ = 5.1, 2 H), 4.49–4.61 (m, 1 H), 7.15–7.39 (m, 11 H), 7.53–7.58 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −4.5, 8.7, 30.3, 37.9, 55.2, 66.2, 127.3, 127.9, 128.9, 129.4, 134.6, 135.4, 136.2, 153.3, 174.3; IR (film) 1778, 1697 cm$^{-1}$; $[\alpha]_D$ −34.0° ($c$ = 0.009 g/mL, $CHCl_3$); HRMS $m/z$ 414.1513 ($C_{25}H_{24}NO_3Si$, calcd 414.1525), 352.1376 ($C_{20}H_{22}NO_3Si$ (M − $C_6H_5$), calcd 352.1369).

**(4*R*,2′*R*)-4-Benzyl-3-[2′-azido-3′-(trimethylsilyl)propanoyl]-1,3-oxazolidin-2-one (10), (4*R*,2′*S*)-4-Benzyl-3-[2′-azido-3′-(dimethylphenylsilyl)propanoyl]-1,3-oxazolidin-2-one (11), and (4*R*,2′*S*)-4-Benzyl-3-[2′-azido-3′-(methyldiphenylsilyl)-propanoyl]-1,3-oxazolidin-2-one (12). General Procedure for the Formation of the (4*R*,2′*S*)-4-Benzyl-3-[2′-bromo-3′-(trialkylsilyl)propanoyl]-1,3-oxazolidin-2-ones.** To a stirring solution of **7** (0.840 g, 2.75 mmol) in 10 mL of $CH_2Cl_2$ at −78 °C under nitrogen was added diisopropylethylamine (0.67 mL, 3.85 mmol) and di-*n*-butylboron triflate (3.8 mL of a 1 M solution in $CH_2Cl_2$, 3.80 mmol). The solution was stirred at 0 °C for 4 h and then recooled to −78 °C and transferred via cannula into a stirring solution of 0.61 g (3.43 mmol) of NBS (freshly recrystallized from water) in 20 mL of $CH_2Cl_2$ at −78 °C. After the solution was stirred for 1 h at −78 °C, 10 mL of saturated $NaHCO_3$ was added and the mixture allowed to warm to room temperature. Workup into $CH_2Cl_2$ followed by chromatography (95:5 hexanes/ethyl acetate) yielded **(4*R*,2′*S*)-4-Benzyl-3-[2′-bromo-3′-(trimethylsilyl)propanoyl]-1,3-oxazolidin-2-one** (1.038 g, 98%) as a clear oil. Following cursory characterization, this material was immediately carried on to the next step: $^1$H NMR ($CDCl_3$) $\delta$ 0.07 (s, 9 H), 1.51 (dd, $J$ = 14.2, 5.5 Hz, 1 H), 1.91 (dd, $J$ = 14.1, 10.9 Hz, 1 H), 2.79 (dd, $J$ = 13.8, 9.6 Hz, 1 H), 3.33 (dd, $J$ = 13.4, 3.5 Hz, 1 H), 4.18–4.28 (m, 2 H), 4.66–4.82 (m, 1 H), 5.97 (dd, $J$ = 10.6, 5.5 Hz, 1 H), 7.20–7.42 (m, 5 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.2, 23.7, 36.9, 42.7, 55.3, 66.2, 127.5, 129.0, 134.9, 152.5, 169.7; IR (film) 2954, 1781, 1735, 1687 cm$^{-1}$; $[\alpha]_D$ −33.3° ($c$ = 0.004 g/mL, $CHCl_3$).

Using the same procedure, the *N*-acyloxazolidinone **8** was converted to **(4*R*,2′*S*)-4-benzyl-3-[2′-bromo-3′-(dimethylphenylsilyl)propanoyl]-1,3-oxazolidin-2-one**, which was carried on to the next step after cursory characterization: $^1$H NMR ($CDCl_3$) $\delta$ 0.40 (dd, $J$ = 13.7, 3.9 Hz, 1 H), 2.21 (dd, $J$ = 13.7, 12.4 Hz, 1 H), 2.65 (dd, $J$ = 13.7, 9.1 Hz, 1 H), 3.09 (dd, $J$ = 13.7, 3.2 Hz, 1 H), 3.70–4.19 (m, 3 H), 5.87 (dd, $J$ = 12.4, 3.9 Hz, 1 H), 7.11–7.52 (m, 10 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −2.7, −2.5, 23.4, 36.7, 42.0, 54.6, 65.6, 127.2, 127.6, 128.8, 129.2, 129.4, 134.2, 134.7, 136.2, 151.8, 169.0; IR (film) 2359, 2341, 1780, 1700 cm$^{-1}$; $[\alpha]_D$ −48.0° ($c$ = 0.008 g/mL, $CHCl_3$). Likewise, the *N*-acyloxazolidinone **9** was converted to **(4*R*,2′*S*)-4-benzyl-3-[2′-bromo-3′-(methyldiphenylsilyl)propanoyl]-1,3-oxazolidin-2-one**, which was also carried on to the next step after cursory characterization: $^1$H NMR ($CDCl_3$) $\delta$ 0.65 (s, 3 H), 1.93 (dd, $J$ = 14.0, 3.4 Hz, 1 H), 2.57 (t, $J$ = 13.3 Hz, 1 H), 2.61 (dd, $J$ = 13.5, 8.7 Hz, 1 H), 3.00 (dd, $J$ = 13.5, 2.8 Hz, 1 H), 3.69 (t, $J$ = 8.6 Hz, 1 H), 3.93–3.96 (m, 2 H), 5.96 (dd, $J$ = 13.1, 3.3 Hz, 1 H), 7.16–7.59 (m, 15 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 3.4, 21.8, 36.6, 41.7, 54.4, 65.4, 127.2, 127.7, 127.8, 128.8, 129.4, 129.6, 134.5, 134.6, 134.8, 151.6, 168.7; IR (film) 3083–2848, 2660, 2341, 1779, 1699 cm$^{-1}$; $[\alpha]_D$ −59.1° ($c$ = 0.013 g/mL, $CHCl_3$).

**General Procedure for the Formation of the (4*R*,2′*S*)-4-Benzyl-3-[2′-azido-3′-(trialkylsilyl)propanoyl]-1,3-oxazolidin-2-ones.** Tetramethylguanidinium azide[19] (0.105 g, 0.66 mmol) was added to a stirring solution of **7** (0.051 g, 0.133 mmol) in 10 mL of MeCN at 0 °C. Stirring was continued at 0 °C for 2 h, 10 mL of saturated $NaHCO_3$ was added, and then the mixture was worked up into $CH_2Cl_2$ (CAUTION: even though we report the uneventful use of $CH_2Cl_2$ for the workup of these reactions, recent reports of serious explosions due to the shock-sensitive diazidomethane byproduct formed by the reaction between azide anion and $CH_2Cl_2$ (especially when $CH_2Cl_2$ is used as the reaction solvent and thus is exposed to the azide anion for significant periods) prompt us to recommend that $CH_2Cl_2$ *not* be used in this reaction at all. For further information about this hazard and an alternative workup procedure, see ref 20). NMR analysis of the resulting crude solid indicated the absence, within limits of detection (±3%), of peaks due to a second diastereomer. Chromatography (90:10 hexanes/EtOAc) yielded **10** (0.041 g, 89%; 87% overall from **7**) as a white solid: mp 105–106 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.15 (s, 9 H), 1.09–1.32 (m, 2 H), 2.78 (dd, $J$ = 13.4, 9.3 Hz, 1 H), 3.30 (dd, $J$ = 13.4, 3.7 Hz, 1 H), 4.16–4.29 (m, 2 H), 4.64–4.79 (m, 1 H), 4.79 (dd, $J$ = 10.5, 4.8 Hz, 1 H), 7.17–7.42 (m, 5 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.5, 19.2, 37.7, 55.2, 66.8, 127.6, 129.0, 129.5, 134.8, 152.8, 172.9; IR (film) 2938, 2360, 2342, 2099, 1793, 1685 cm$^{-1}$; $[\alpha]_D$ +2.5° ($c$ = 0.005 g/mL, $CHCl_3$); HRMS $m/z$ 331.1238 ($C_{15}H_{19}N_4O_3Si$ (M − $CH_3$), calcd 331.1226). This material was recrystallized from dichloromethane–hexanes to yield colorless plates which were suitable for X-ray crystallographic analysis.

Using the same procedure, (4*R*,2′*S*)-4-benzyl-3-[2′-bromo-3′-(dimethylphenylsilyl)propanoyl]-1,3-oxazolidin-2-one was converted to **11**, which was obtained as a white solid (80% overall from **8**) which could be recrystallized from $CH_2Cl_2$–hexanes: mp 118–120 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.45 (s, 3 H), 0.46 (s, 3 H), 1.33 (dd, $J$ = 14.6, 11.1 Hz, 1 H), 1.49 (dd, $J$ = 14.6, 4.1 Hz, 1 H), 2.68 (dd, $J$ = 13.4, 9.8 Hz, 1 H), 3.29 (dd, $J$ = 13.4, 3.1 Hz, 1 H), 4.14–4.30 (m, 2 H), 4.67 (octet, $J$ = 3.4 Hz, 1 H), 4.80 (dd, $J$ = 11.0, 4.3 Hz, 1 H), 7.12–7.44 (m, 8 H), 7.52–7.65 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ −2.4, −2.0, 19.7, 38.4, 55.9, 58.3, 67.6, 128.4, 128.8, 129.8, 130.3, 134.6, 135.7, 138.3, 153.6, 173.3; IR (film) 2925, 2108, 1785, 1703 cm$^{-1}$; $[\alpha]_D$ +3.1° ($c$ = 0.050 g/mL, benzene); HRMS $m/z$ 393.1383 ($C_{20}H_{21}N_4O_3Si$ (M − $CH_3$), calcd 393.1383), 331.1223 ($C_{15}H_{19}N_4O_3Si$ (M − $C_6H_5$), calcd 331.1226). Likewise, (4*R*,2′*S*)-4-benzyl-3-[2′-bromo-3′-(methyldiphenylsilyl)-propanoyl]-1,3-oxazolidin-2-one was converted to **12**, a clear oil (65% overall from **9**): $^1$H NMR ($CDCl_3$) $\delta$ 0.76 (s, 3 H), 1.62 (dd, $J$ = 14.5, 10.9 Hz, 1 H), 1.86 (dd, $J$ = 14.5, 4.4 Hz, 1 H), 2.65 (dd, $J$ = 13.4, 9.6 Hz, 1 H), 3.13 (dd, $J$ = 13.4, 3.2 Hz, 1 H), 4.11–4.21 (m, 2 H), 4.56–4.66 (m, 1 H), 4.87 (dd, $J$ = 10.8, 4.4 Hz, 1 H), 7.14–7.39 (m, 11 H), 7.56–7.62 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −4.3, 17.6, 37.5, 55.1, 57.5, 66.7, 127.5, 128.0, 129.0, 129.4, 129.6, 129.6, 134.5, 134.7, 135.1, 135.6, 152.7, 172.1; IR (film) 2360, 2107, 1781, 1701 cm$^{-1}$; $[\alpha]_D$ −15.56° ($c$ = 0.022 g/mL, $CHCl_3$); HRMS $m/z$ 455.1538 ($C_{25}H_{23}N_4O_3Si$ (M − $CH_3$), calcd 455.1539), 393.1397 ($C_{20}H_{21}N_4O_3Si$ (M − $C_6H_5$), calcd 393.1383).

**(*R*)-2-Azido-3-(trimethylsilyl)propanoic Acid (13), (*R*)-2-Azido-3-(dimethylphenylsilyl)propanoic Acid (14), and (*R*)-2-Azido-3-(methyldiphenylsilyl)propanoic Acid (15). General Procedure for the Syntheses of (*R*)-2-Azido-3-(trialkylsilyl)propanoic acids.** To a stirring solution of **10** (0.586 g, 1.69 mmol) in 10 mL of THF and 5 mL of water at 0 °C was added 0.74 mL (approximately 6.8 mmol) of 30% $H_2O_2$ and 0.142 g (3.38 mmol) of LiOH–$H_2O$. The mixture was stirred at 0 °C for 1 h, and then saturated $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (10 mL) were added. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL) to recover the oxazolidinone chiral auxiliary. The aqueous phase was then cooled to 0 °C, 10% HCl was added dropwise until the solution became acidic, and then workup of the solution into EtOAc followed by chromatography (90:10 $CHCl_3$/95% EtOH) yielded **13** (0.320 g, 100%) as a clear oil: $^1$H NMR ($CD_3OD$) $\delta$ 0.05 (s, 9 H), 1.05 (dd, $J$ = 14.6, 9.7 Hz, 1 H), 1.19 (dd, $J$ = 14.6, 6.0 Hz, 1 H), 3.68 (dd, $J$ = 9.6, 6.0 Hz, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ −1.1, 20.6, 62.4, 178.3; IR (film) 2954, 2108, 1712, 1574 cm$^{-1}$; $[\alpha]_D$ + 2.0° ($c$ = 0.013 g/mL, $CHCl_3$). HRMS $m/z$ 172.0548 ($C_5H_{10}N_3O_2Si$ (M − $CH_3$), calcd 172.0542), 145.0688 ($C_6H_{13}O_2Si$ (M − $N_3$), calcd 145.0685).

Using the same procedure, the intermediate **11** was converted to **14**, which was chromatographed (95:5 $CHCl_3$/95% EtOH) to give a clear oil (88%) that was carried on to the next step after cursory characterization: $^1$H NMR ($CDCl_3$) $\delta$ 0.42 (s, 3 H), 0.45 (s, 3 H), 1.31–1.53 (m, 2 H), 3.77 (dd, $J$ = 9.0, 6.4 Hz, 1 H),

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7.26–7.58 (m, 5H), 9.91 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −3.1, −2.7, 18.8, 59.0, 128.0, 129.5, 133.6, 136.9, 177.8; IR (film) 2110, 1717 cm$^{-1}$; $[\alpha]_D$ −9.24 ($c$ = 0.0294 g/mL, $CHCl_3$). Likewise, the intermediate **12** was converted to **15**, which was a clear oil (97%): $^1$H NMR ($CDCl_3$) $\delta$ 0.70 (s, 3 H), 1.62 (dd, $J$ = 14.7, 9.6 Hz, 1 H), 1.77 (dd, $J$ = 9.6, 6.0 Hz, 1 H), 7.20–7.39 (m, 6 H), 7.49–7.58 (m, 4H), 11.06 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −4.1, 17.4, 58.9, 128.0, 128.1, 129.7, 129.8, 134.4, 134.5, 134.7, 135.3, 177.7; IR (film) 3500–2450, 2108, 1715 cm$^{-1}$; $[\alpha]_D$ −15.5° ($c$ = 0.019 g/mL, $CHCl_3$); HRMS $m/z$ 234.0694 ($C_{10}H_{12}N_3O_2Si$ (M − $C_6H_5$), calcd 234.0699), 238.1055 ($C_{15}H_{16}NSi$ (M − $N_2COOH$), calcd 238.1052).

**(*R*)-2-Amino-3-(trimethylsilyl)propanoic Acid (L-(Trimethylsilyl)alanine) (1), (*R*)-2-Amino-3-(dimethylphenylsilyl)propanoic Acid (L-β-(Dimethylphenylsilyl)alanine) (2), and (*R*)-2-Amino-3-(methyldiphenylsilyl)propanoic Acid (L-β-(Methyldiphenylsilyl)alanine) (3). General Procedure for the Synthesis of (Trialkylsilyl)alanines.** To a mixture of the azide **13** (0.253 g, 1.35 mmol) in 10 mL of THF was added 0.389 g (1.5 mmol) of $PPh_3$ and 0.027 mL (1.5 mmol) of $H_2O$. The mixture was stirred for 12 h at room temperature, diluted with 20 mL of 3:1 $CHCl_3$/EtOH, and then poured onto a 2 × 2 cm silica gel pad. The silica gel pad was then washed with 50 mL of 3:1 $CHCl_3$/EtOH to remove the triphenylphosphine oxide byproduct, and then 70:25:5 $CH_2Cl_2$/MeOH/ammonium hydroxide was passed through it to yield a solution of the amino acid product. This solution was concentrated and then chromatographed on a 5 cm (1 cm i.d.) column of Dowex with 50 mL of $H_2O$ followed by 50–100 mL of 10% ammonium hydroxide to give **1** (126 mg, 57%). This amino acid was insoluble in water, so for analytical purposes a sample of it was converted to the hydrochloride salt by dissolving it in 10% HCl followed by concentration under high vacuum: $[\alpha]_D$ + 21.4° ($c$ = 0.032 g/mL, 1 N HCl) [lit.[8] +31° ($c$ = 0.51 in 4 N HCl)]. For spectroscopic and analytical data, see ref 8.

Using the same procedure, the azido acid **14** was converted to **2**, isolated as the hydrochloride salt (50%): $^1$H NMR (HCl salt in $D_2O$) $\delta$ 0.23 (s, 3 H), 0.24 (s, 3 H), 1.20–1.37 (m, 2 H), 3.81 (dd, $J$ = 10.5, 5.9 Hz, 2 H), 7.19–7.31 (m, 3 H), 7.4707.51 (m, 2 H); $^{13}$C NMR (HCl salt in $D_2O$) $\delta$ −2.7, −2.5, 19.3, 52.3, 129.3, 130.8, 134.8, 138.7, 173.7; $[\alpha]_D$ +28.84 ($c$ = 0.005 g/mL, HCl salt in $H_2O$); HRMS $m/z$ 208.0793 ($C_{10}H_{14}NO_2Si$ (M − $CH_3$), calcd 208.0794), 146.0632 ($C_5H_{12}NO_2Si$ (M − $C_6H_5$), calcd 146.0637). Likewise, the azido acid **15** was converted to **3**, also isolated as the hydrochloride salt (52%): $^1$H NMR (HCl salt in $D_2O$) $\delta$ 0.57 (s, 3 H), 1.55–1.78 (m, 2 H), 3.92 (dd, $J$ = 11.0, 5.5 Hz, 1 H), 7.21–7.37 (m, 6 H), 7.41–7.53 (m, 4 H); $^{13}$C NMR (HCl salt in $D_2O$) $\delta$ −4.6, 17.7, 52.1, 129.3, 129.4, 131.0, 131.1, 135.3, 136.6, 136.8, 173.2; $[\alpha]_D$ +20.2° ($c$ = 0.011 g/mL, $H_2O$); HRMS $m/z$ 240.1206 ($C_{15}H_{18}NSi$ (M − COOH), calcd 240.1209), 208.0792 ($C_{10}H_{14}NO_2Si$ (M − $C_6H_5$), calcd 208.0794).

**(*R*)-*N*-(9-Fluorenylmethoxycarbonyl)-3-(trimethylsilyl)propanoic Acid (Fmoc-L-β-(trimethylsilyl)alanine) (16), (*R*)-*N*-(9-Fluorenylmethoxycarbonyl)-3-(dimethylphenylsilyl)propanoic Acid (Fmoc-L-β-(dimethylphenylsilyl)alanine) (17), and (*R*)-*N*-(9-Fluorenylmethoxycarbonyl)-3-(methyldiphenylsilyl)propanoic Acid (Fmoc-L-β-(methyldiphenylsilyl)alanine) (18). General Procedure for the Syntheses of the Fmoc-(trialkylsilyl)alanines.** To a mixture of the hydrochloride salt of **1** (0.037 g, 0.187 mmol) in 3 mL of water was added 0.0397 g (0.374 mmol) of sodium carbonate, 5 mL of DMF, and 0.060 g (0.178 mmol) of *N*-[(9-fluorenylmethoxycarbonyl)oxy]succinimide. If the mixture became cloudy upon the addition of the succinimide reagent, more water was added dropwise until a clear solution was obtained. This solution was stirred at room temperature for 12 h, then 20 mL of $H_2O$ was added and it was extracted with ether (3 × 10 mL). The combined organic extracts were then extracted with saturated $NaHCO_3$ (2 × 5 mL), and these aqueous extracts were combined with the original aqueous phase, acidified with 10% HCl, and extracted with EtOAc (3 × 10 mL). The ethyl acetate extracts were dried over $MgSO_4$ and concentrated to give the crude product, which upon chromatography (95:5 $CHCl_3$/EtOH) yielded **16** (0.0582 g, 85%) as a clear oil: $[\alpha]_D$ −8.7° ($c$ = 0.035 g/mL, $CHCl_3$) [lit.[9] −9.1° ($c$ = 1.0, $CH_2Cl_2$)]. For spectroscopic and analytical data, see ref 9.

Using the same procedure, the amino acid **2** was converted to **17**, obtained as a clear oil (72%): $^1$H NMR ($CDCl_3$) $\delta$ 0.36 (s, 3 H), 1.24 (dd, $J$ = 14.9, 10.3 Hz, 1 H), 1.45 (dd, $J$ = 14.9, 5.0 Hz, 1 H), 4.15 (t, $J$ = 7.0, 1 H), 4.28–4.44 (m, 3 H), 5.09 (d, $J$ = 8.4 Hz, 1 H), 7.24–7.65 (m, 11 H), 7.74–7.76 (m, 2 H), 8.44 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −3.1, −2.7, 20.0, 47.0, 66.9, 119.9, 135.1, 127.0, 127.7, 128.0, 129.3, 133.4, 137.8, 141.2, 143.6, 143.8, 155.7, 178.3; IR (film) 3700–2800, 1714, 1649 cm$^{-1}$; $[\alpha]_D$ −9.2° ($c$ = 0.029 g/mL, $CHCl_3$). HRMS $m/z$ 400.1718 ($C_{25}H_{26}NO_2Si$ [M − COOH], calcd 400.1733), 172.0428 ($C_6H_{10}NO_3Si$ [M − $C_{14}H_{11}$ − $C_6H_5$ − OH], calcd 172.0430). Likewise, **3** was converted to **18**, a clear oil (59%): $^1$H NMR ($CDCl_3$) $\delta$ 0.64 (s, 3 H), 1.57 (dd, $J$ = 15.0, 10.4 Hz, 1 H), 1.79 (dd, $J$ = 15.0, 4.9 Hz, 1 H), 4.06–4.11 (m, 1 H), 4.22–4.24 (m, 2 H), 4.37–7.46 (m, 1 H), 5.01 (d, $J$ = 8.2 Hz, 1 H), 7.24–7.52 (m, 16 H), 7.73–7.75 (m, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −4.4, 18.5, 47.1, 51.0, 67.2, 120.1, 125.2, 127.2, 127.8, 128.2, 128.2, 129.8, 134.5, 135.8, 141.4, 143.8, 143.9, 155.7, 178.0; IR (film) 3789–2778, 2084, 1701, 1666 cm$^{-1}$; $[\alpha]_D$ +11.2° ($c$ = 0.010 g/mL, $CHCl_3$); HRMS $m/z$ 234.0589 ($C_{11}H_{12}NO_3Si$ [M − $C_{14}H_{11}$ − $C_6H_5$ − OH], calcd 234.0586).

***N*-(9-Fluorenylmethoxycarbonyl)-L-[β-(trimethylsilyl)alanyl]-L-phenylalanine Methyl Ester (19).** The Fmoc-protected L-β-(trimethylsilyl)alanine **16** (0.024 g, 0.063 mmol), L-phenylalanine methyl ester hydrochloride (0.0135 g, 0.063 mmol), 1-hydroxybenzotriazole hydrate (0.0085 g, 0.063 mmol), and $Et_3N$ (0.009 mL, 0.063 mmol) were dissolved in 10 mL of THF and stirred at 0 °C while *N*,*N*-dicyclohexylcarbodiimide (0.0142 g, 0.069 mmol) was added. The mixture was stirred at room temperature for 20 h and then diluted with 20 mL of ethyl acetate, washed with 5% citric acid solution (10 mL) and then with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, concentrated, and chromatographed (gradient from 95:5 to 80:20 hexanes/ethyl acetate) to yield **19** (0.0284 g, 83%): $^1$H NMR ($CDCl_3$) $\delta$ 0.38 (s, 9 H), 0.86–1.04 (m, 1 H), 1.09 (dd, $J$ = 12.1, 5.4, 1 H), 3.00–3.20 (m, 2 H), 3.71 (s, 3 H), 4.11–4.47 (m, 4 H), 4.85 (dt, $J$ = 7.7, 6.0 Hz, 1 H), 5.18 (d, $J$ = 8.4 Hz, 1 H), 6.54 (d, $J$ = 7.9 Hz, 1 H), 7.06–7.44 (m, 9 H), 7.59 (d, $J$ = 7.2 Hz, 2 H), 7.77 (d, $J$ = 7.5 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.2, 20.4, 37.8, 47.1, 52.2, 52.3, 53.2, 67.1, 120.0, 125.0, 127.0, 127.7, 128.5, 129.2, 141.3, 143.7, 155.7, 171.7, 172.5; IR (film) 3400–3125, 2850, 2359, 1745, 1698, 1660 cm$^{-1}$. HRMS $m/z$ 544.2387 ($C_{31}H_{36}N_2O_5Si$, calcd 544.2393), 529.2133 ($C_{30}H_{33}N_2O_5Si$ (M − $CH_3$), calcd 529.2159).

***N*-(*tert*-Butoxycarbonyl)-L-(phenylalanyl)-L-[β-(trimethylsilyl)alanyl]-L-phenylalanine Methyl Ester (20).** A solution of the dipeptide **19** (0.015 g, 0.027 mmol) dissolved in a solution of 10% diethylamine in DMF (1 mL) was stirred at room temperature for 1 h and then concentrated to dryness. The residue was then dissolved in 10 mL of THF and cooled to 0 °C, 1-hydroxybenzotriazole hydrate (0.004 g, 0.029 mmol), *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (0.008 g, 0.03 mmol), and *N*,*N*-dicyclohexylcarbodiimide (0.0063 g, 0.03 mmol) were added, and the mixture was stirred at room temperature for 12 h. It was then diluted with EtOAc (10 mL), washed with $H_2O$ (5 mL), dried ($MgSO_4$), concentrated, and chromatographed (gradient from 80:20 to 50:50 hexanes/EtOAc) to yield 0.0109 g (71%) of the tripeptide **20**: $^1$H NMR ($CD_2Cl_2$) $\delta$ 0.36 (s, 9 H), 0.78 (dd, $J$ = 14.7, 8.7 Hz, 1 H), 1.11 (dd, $J$ = 14.7, 8.74, 1 H), 1.37 (S, 9 H), 2.93–3.10 (m, 4 H), 3.68 (s, 3 H), 4.30–4.37 (m, 2 H), 4.72 (dt, $J$ = 7.67, 6.2 Hz, 1 H), 4.95 (d, $J$ = 8.3 Hz, 1 H), 6.33 (d, $J$ = 7.2 Hz, 1 H), 6.65 (d, $J$ = 6.5 HZ, 1 H), 7.11–7.32 (m, 10 H); $^{13}$C NMR ($CD_2Cl_2$) $\delta$ −1.1, 21.4, 28.6, 38.5, 39.2, 49.7, 51.4, 55.2, 57.0, 80.6, 127.6, 127.9, 129.4, 129.6, 130.3, 130.4, 138.0, 138.7, 157.5, 173.2, 173.6, 175.1; HRMS $m/z$ 554.2695 ($C_{29}H_{40}N_3O_6Si$ (M − $CH_3$), calcd 554.2686).

**L-(Phenylalanyl)-L-[β-(trimethylsilyl)alanyl]-L-phenylalanine Methyl Ester (21).** A solution of the tripeptide **20** (0.0042 g, 0.0084 mmol) in 1 mL of dichloromethane at 0 °C was stirred while 1 mL of trifluoroacetic acid was added, stirring was continued for 30 min, and then the solution was concentrated to dryness and treated under high vacuum to yield **21** (0.0031 g, 63% assuming isolation as the TFA salt) in pure form according to NMR analysis: $^1$H NMR ($CD_2Cl_2$) $\delta$ −0.09 (s, 9 H), 0.45–0.98 (m, 2 H), 3.05–3.18 (m, 4 H), 3.62 (s, 3 H), 4.19–4.33 (m, 2 H), 4.60–4.71 (m, 1 H), 7.09–7.33 (m, 10 H); $^{13}$C NMR ($CD_2Cl_2$) $\delta$ 0.2, 21.9, 39.0, 52.3, 54.4, 57.0, 129.0, 130.0, 130.6, 131.2, 131.3, 131.5, 136.0, 138.2, 173.9, 174.6 (signals due to the trifluoroacetate counterion were not detected due to the small sample size); IR (film) 3695–2825, 1741, 1672, 1552 cm$^{-1}$; HRMS

*m/z* 469.2399 ($C_{25}H_{35}N_3O_4Si$, calcd 469.2397), 454.2162 ($C_{24}H_{32}N_3O_4Si$ (M − $CH_3$), calcd 454.2162).

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**Supplementary Material Available:** Experimental procedures for the syntheses of the acids **5** and **6** and $^1H$ and $^{13}C$ NMR spectra for compounds **1**−**3**, **7**−**21**, and the three α-bromo derivatives of **7**−**9** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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