

# Synthesis of Silicon Containing Alanines<sup>†</sup>

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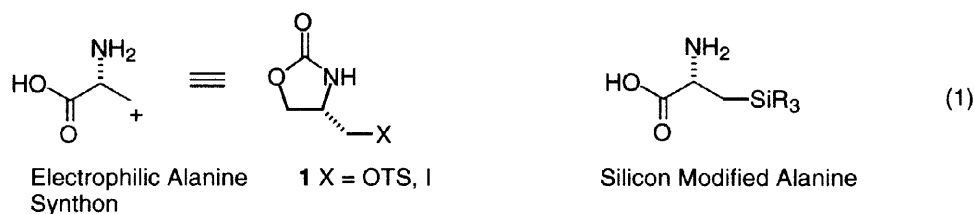
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Received 4 February 1998; revised 26 March 1998; accepted 27 March 1998

**Abstract:** The synthesis of silicon containing alanines in optically pure form from an electrophilic alaninol synthon is described. The overall chemical yields for the synthesis of the novel amino acids range from 19–39%. © 1998 Elsevier Science Ltd. All rights reserved.

**Keywords:** Silicon Amino Acids; Oxazolidinone; Silyl Copper Reagents

New methods for the synthesis of non-proteinogenic amino acids in optically pure form are an area of continued interest since these compounds serve as useful surrogates for their natural counterparts.<sup>1</sup> We have been evaluating new methodologies for the preparation of amino acids which contain large hydrophobic moieties.<sup>2</sup> Peptides derived from these unnatural amino acids may offer such advantages as prevention of hydrophobic pocket collapse, higher lipophilicity, and stability toward proteolytic enzymatic degradation. We surmised that triaryl or alkylaryl silicon containing functional groups at the  $\beta$ -position of alanine could function as such a hydrophobic unit due to their bulk and inertness.<sup>3</sup> In this letter we report the successful application of an electrophilic alanine synthon, readily available from serine, in the synthesis of silicon containing alanines (equation 1).

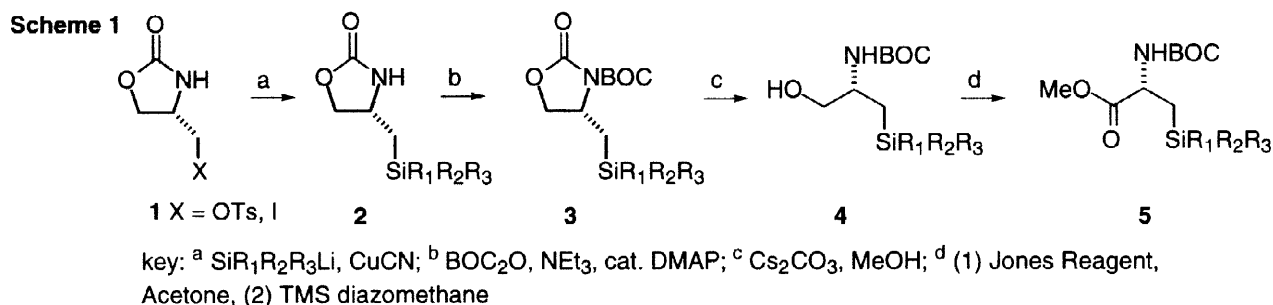


We have been exploring the utility of nucleophilic and electrophilic alaninol (alanine) synthons derived from serine as starting materials for the preparation of unnatural amino alcohols and amino acids.<sup>4</sup> In previous work from this laboratory, the reaction of **1** with copper reagents to furnish substituted oxazolidinones was reported.<sup>5</sup> The present work involves the extension of this methodology to silicon nucleophiles to form

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<sup>†</sup> Dedicated to our colleague and friend Professor Madeleine M. Joullie in celebration of forty years of distinguished teaching and research at the University of Pennsylvania.

substituted oxazolidinones which on further modification provide the desired amino acids. An efficient synthesis of the alaninol precursor **1** ( $X = \text{OTS}$  and  $\text{I}$ ) has been achieved starting from L-serine methylester hydrochloride in high overall yields without any chromatographic purification.<sup>6</sup> Nucleophilic displacements using **1** ( $X = \text{OTs}$ ) and several different copper species<sup>7</sup> derived from silyl lithiums were examined (Scheme 1). These reactions indicated the formation of compounds **2** with moderate efficiency. The next set of reactions used **1** ( $X = \text{I}$ ) as the starting material. Treatment of **1** with an excess of silyl copper species ( $2\text{SiR}_3\text{Li}^8 + \text{CuCN}$ ) indicated the formation of **2** cleanly in higher yields than those obtained from the tosylate.<sup>9</sup> The convenient method of Seebach's<sup>10</sup> for *in situ* generation of silyl coppers ( $n\text{-Bu}_2\text{CuCNLi} + \text{SiR}_3\text{Cl}$ ) and further treatment with **1** ( $X = \text{I}$ ) gave none of the desired silyl oxazolidinone **2**. Thus, all the nucleophilic displacement reactions (see Table) were carried out using the higher order copper reagents ( $2\text{SiR}_3\text{Li} + \text{CuCN}$ ) by addition of 2–3 equivalents of the copper species to the iodide (tosylate) at  $-78^\circ\text{C}$  followed by slowly warming to  $0^\circ\text{C}$  (~4–7 hours) and quenching with 10%  $\text{NH}_4\text{OH}$ /saturated ammonium chloride. The purified yields in the displacement reactions were moderate to good (40–78%). Additionally, products from elimination reactions were observed in small amounts when the iodo starting material was used.<sup>11</sup> The silyl oxazolidinones **2** have the potential to function as a new bulky chiral auxiliary similar to the versatile Evans auxiliary, oxazolidinone derived from phenylalaninol.<sup>12</sup>



The next step in the sequence involved the conversion of **2** to **3** using standard conditions. Thus, treatment of **2** with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane at room temperature for 2 hours furnished **3** in high yields (97–99%). With the protected oxazolidinones in hand, selective hydrolysis of the endo carbonyl was carried out using the procedure developed by Kunieda.<sup>13</sup> Treatment of **3a–e** with catalytic  $\text{Cs}_2\text{CO}_3$  in methanol at room temperature for 12–24 h furnished the *N*-BOC alcohols in very good yields (68–87%). There are several methods in the literature for the conversion of *N*-protected amino alcohols to the corresponding amino acids.<sup>14</sup> Jones reagent proved to be ideal for the oxidation of **4**. Treatment of an acetone solution of **4** with an equivalent amount of the freshly prepared Jones reagent furnished the product amino acids which were subsequently converted to their methyl esters **5** using TMS diazomethane.<sup>15</sup> The deprotection of the *N*-BOC protecting group was not observed during the oxidation reaction. Several aspects of the synthetic sequence in the preparation of **5** are noteworthy. The overall yield for the amino esters starting from the iodo oxazolidinone is **5a**, 39%; **5b**, 19%; **5c**, 30%; and **5d**, 20%. The optical purity of **5a–5d** was established to be >98% by chiral HPLC and comparison with racemic materials. The method is amenable to scale up. The nature of the substituents on the silicon is limited only by the ease of the generation of the silyl

lithium reagents. One key point of the methodology is the formation of the (*S*)-enantiomeric series of the final amino acids starting from the natural L-serine methylester.

**Table. Synthesis of Silicon Containing Alanines**

Compound	Silicon Substituent			Yield%, 2a,b,c	Yield%, 3	Yield%, 4	Yield%, 5
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>				
<b>a</b>	Ph	Ph	Ph	78	99	87	58
<b>b</b>	Ph	CH <sub>3</sub>	CH <sub>3</sub>	42 (33)	99	68	68
<b>c</b>	Ph	Ph	CH <sub>3</sub>	63	97	78	63
<b>d</b>	Ph	Ph	t-Bu	40 (43)	98	84	62

<sup>a</sup> Yields are for isolated material after column purification. <sup>b</sup> 2-3 equivalents of the silyl copper was used.

<sup>c</sup> The yields in parenthesis are from reactions when the tosylate was used as the substrate.

In conclusion, we have developed a general methodology for the efficient synthesis of novel silicon containing alanines. The extension of the methodology to other silicon containing amino acids as well as chain extended alanines are underway. Additionally, silicon substituted oxazolidinones **2** hold promise as new bulky chiral auxiliaries.

**Acknowledgment:** We thank NSF (OSR-9108770 and OSR-9452892) and North Dakota State University for providing financial support for this work.

**Experimental Procedures.** Methylene chloride and triethylamine were distilled from calcium hydride. Tetrahydrofuran and benzene were distilled from benzophenone/ketyl prior to use. Methanol was distilled from magnesium. Thin layer chromatographic analyses were performed on silica gel Whatmann-60F glass plates and components were visualized by illumination with UV light or by staining with phosphomolybdic acid. Flash chromatography were performed using E. Merck silica gel 60 (230-400 mesh). Melting points were determined using a Thomas Hoover capillary melting point apparatus or Fisher-Johns melting point apparatus. All glassware was oven/and or flame dried, assembled hot, and cooled under a stream of dry nitrogen or argon before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

<sup>1</sup>H NMR were recorded on a JEOL GSX-400 (400 MHz), JEOL GSX-270 (270 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual CHCl<sub>3</sub> (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, br = broad), integration and coupling constant(s). <sup>13</sup>C NMR were recorded on a JEOL-GSX-400 (100 MHz) and JEOL GSX-270 (65 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of CDCl<sub>3</sub> (77.0 ppm) as an internal standard. HPLC analyses were carried out on either an ISCO system comprising of a 2360 pump, 2350 gradient programmer and a V<sup>4</sup> variable wavelength

UV detector connected to a Hewlett-Packard 3396 II integrator or a Waters M-45 pump connected to an ISCO 228 Absorbance Detector with a type 6 optical unit and a Hewlett-Packard 3396-II integrator. HPLC columns were purchased from Daicel Chemical Ind., Ltd. Rotations were recorded on a JASCO-DIP-370 instrument. Elemental analyses were performed in house on a Perkin Elmer Series II CHNS/O Analyzer 2400.

**Typical procedure for Nucleophilic Displacements:** To a slurry of CuCN (0.45 g, 5 mmol) in 10 mL THF at 0 °C was added dropwise Ph<sub>3</sub>SiLi (prepared from 2.95 g, 10 mmol of Ph<sub>3</sub>SiCl and lithium wire, 0.21 g, 30 mmol). This was stirred for 30 minutes at 0° C and then cooled to -78° C. A solution of **1** (X = I) (0.377g, 1.6 mmol) in 3 mL THF was added dropwise. The green reaction mixture was allowed to warm to ambient temperature over 4 h and quenched with 10% NH<sub>4</sub>OH in sat. NH<sub>4</sub>Cl Solution. Normal workup followed by silica gel column purification gave **2a** as a white solid (0.47g, 78%).

**4-(S)-Triphenylsilylmethyl oxazolidin-2-one (2a):** mp 149-150 °C; Rf 0.29 (1:1 EtOAc:Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55-7.49 (m, 15H), 5.24 (s, 1H), 4.19-4.12 (m, 2H), 3.79 (m, 1H), 1.89-1.84 (m, 1H), 1.77-1.71 (m, 1H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 159.2, 135.6, 133.3, 130.3, 128.5, 72.5, 50.2, 20.9; [α]<sub>D</sub><sup>25</sup> +18.50 ° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>22</sub>H<sub>21</sub>N<sub>1</sub>O<sub>2</sub>Si<sub>1</sub>: C, 73.50, H, 5.89; N, 3.90; found: C, 73.78; H, 6.01; N, 3.86.

**4-(S)-Dimethylphenylsilylmethyl oxazolidin-2-one (2b):** mp 71-72 °C; Rf 0.11 (40% EtOAc:60% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52-7.39 (m, 5H), 4.74 (s, 1H), 4.32 (t, 1H, J=8.1 Hz), 3.97 (m, 1H), 3.83-3.77 (m, 2H), 1.22 (dd, 1H, J=7.0 and 14.7 Hz), 1.12 (dd, 1H, J=7.3 and 14.7 Hz), 0.36 (s, 6H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 159.2, 137.0, 133.3, 129.7, 128.3, 72.3, 50.2, 23.6, -2.7; [α]<sub>D</sub><sup>25</sup> -5.70 ° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>12</sub>H<sub>17</sub>N<sub>1</sub>O<sub>2</sub>Si<sub>1</sub>: C, 61.24 H, 7.28; N, 5.95 found: C, 60.92; H, 7.12; N, 5.93.

**4-(S)-Diphenylmethylsilylmethyl oxazolidin-2-one (2c):** mp 123-124 °C; Rf 0.11 (50% EtOAc:50% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52-7.39 (m, 10H), 4.87 (s, 1H), 4.27 (t, 1H, J=8.1 Hz), 4.04 (m, 1H), 3.81 (dd, 1H, J=7.3 and 8.1), 1.55 (dd, 1H, J=7.3 and 14.7 Hz), 1.44 (dd, 1H, J=7.0 and 14.7 Hz), 0.63 (s, 3H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 159.3, 135.14, 135.08, 134.3, 129.9, 128.3, 128.2, 72.2, 50.1, 22.0, -3.8; [α]<sub>D</sub><sup>25</sup> +4.10 ° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>17</sub>H<sub>19</sub>N<sub>1</sub>O<sub>2</sub>Si<sub>1</sub>: C, 68.65 H, 6.44; N, 4.71 found: C, 68.70; H, 6.32; N, 4.53.

**4-(S)-tert-Butyldiphenylsilylmethyl oxazolidin-2-one (2d):** mp 139-140 °C; Rf 0.17 (40% EtOAc:60% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.63-7.41 (m, 10H), 4.45(s, 1H), 4.11 (t, 1H, J=8.1 Hz), 3.97-3.87 (m, 1H), 3.75 (dd, 1H, J=7.0 and 8.4 Hz), 1.56 (dd, 1H, J=7.7 and 15.0 Hz), 1.48 (dd, 1H, J=6.2 and 15.0 Hz), 1.05 (s, 9H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 158.9, 135.9, 135.8, 133.02, 132.96, 130.0, 129.9, 128.3, 128.2, 72.5, 50.2, 27.6, 18.0, 17.6; [α]<sub>D</sub><sup>25</sup> +26.90 ° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>20</sub>H<sub>25</sub>N<sub>1</sub>O<sub>2</sub>Si<sub>1</sub>: C, 70.76 H, 7.42; N, 4.13 found: C, 70.43; H, 7.31; N, 4.10.

**Typical Procedure for BOC Protection:** To a solution of 0.4228 g (1.18 mmol) of **2a**, 0.30 g (1.4 mmol) BOC<sub>2</sub>O, and 0.18 mL (1.3 mmol) Et<sub>3</sub>N in 12 mL CH<sub>2</sub>Cl<sub>2</sub> was added ~5 mg DMAP and stirred at RT for 2 h.

The reaction was quenched with 10% citric acid solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed H<sub>2</sub>O, and brine, dried over anhydrous MgSO<sub>4</sub> and the solvent was evaporated. The crude product was purified by silica gel chromatography.

**3-*N*-(*tert*-Butoxycarbonyl)-4-(*S*)-dimethylphenylsilylmethyl oxazolidin-2-one (3a):** mp 126–127 °C; Rf 0.24 (20% EtOAc:80% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59–7.40 (m, 15H), 4.56–4.47 (m, 1H), 3.76 (t, 1H, *J*=8.4 Hz), 3.47 (dd, 1H, *J*=3.5 and 9.0 Hz), 2.36 (dd, 1H, *J*=1.1 and 14.3 Hz), 1.75 (dd, 1H, *J*=12.5 and 14.3 Hz), 1.53 (s, 9H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 152.0, 149.5, 135.5, 133.3, 130.1, 128.3, 83.8, 67.4, 53.4, 28.0, 18.9; [α]<sub>D</sub><sup>25</sup> -31.70° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>27</sub>H<sub>29</sub>N<sub>1</sub>O<sub>4</sub>Si<sub>1</sub>: C, 70.56 H, 6.36; N, 3.05; found: C, 70.52; H, 6.23; N, 2.96.

**3-*N*-(*tert*-Butoxycarbonyl)-4-(*S*)-dimethylphenylsilylmethyl oxazolidin-2-one (3b):** mp 61–62 °C; Rf 0.47 (40% EtOAc:60% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.51–7.38 (m, 5H), 4.37–4.28 (m, 1H), 4.03 (t, 1H, *J*=8.4 Hz), 3.59 (dd, 1H, *J*=3.7 and 8.8 Hz), 1.53 (m, 10H), 1.22 (dd, 1H, *J*=11.9 and 14.1 Hz), 0.38 (s, 3H), 0.37 (s, 3H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 152.2, 149.4, 137.0, 133.5, 129.8, 128.4, 83.7, 67.8, 53.4, 28.1, 22.2, -2.4, -2.8; [α]<sub>D</sub><sup>25</sup> -45.30° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>17</sub>H<sub>25</sub>N<sub>1</sub>O<sub>4</sub>Si<sub>1</sub>: C, 60.87 H, 7.51; N, 4.18; found: C, 60.49; H, 7.17; N, 4.15.

**3-*N*-(*tert*-Butoxycarbonyl)-4-(*S*)-diphenylmethylsilylmethyl oxazolidin-2-one (3c):** mp 96–97 °C; Rf 0.59 (50% EtOAc:50% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55–7.39 (m, 10H), 4.46–4.37 (m, 1H), 3.90 (t, 1H, *J*=8.6 Hz), 3.53 (dd, 1H, *J*=3.7 and 8.8 Hz), 1.96 (dd, 1H, *J*=2.0 and 14.2 Hz), 1.53 (m, 10H), 0.65 (s, 3H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 152.1, 149.4 135.2, 135.0, 134.5, 134.4, 130.1, 130.0, 128.40, 128.36, 83.9, 67.6, 53.4, 28.2, 20.4, -3.5; [α]<sub>D</sub><sup>25</sup> -36.00° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>22</sub>H<sub>27</sub>N<sub>1</sub>O<sub>4</sub>Si<sub>1</sub>: C, 66.47; H, 6.85; N, 3.52; found: C, 66.52; H, 6.63; N, 3.52.

**3-*N*-(*tert*-Butoxycarbonyl)-4-(*S*)-*tert*-butyldiphenylsilylmethyl oxazolidin-2-one (3d):** mp 123–124 °C; Rf 0.60 (40% EtOAc:60% Hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.71–7.59 (m, 4H), 7.44–7.39 (m, 6H), 4.41–4.28 (m, 1H), 3.54 (t, 1H, *J*=8.3 Hz), 3.28 (dd, 1H, *J*=3.5 and 9.0 Hz), 2.10 (dd, 1H, *J*=1.5 and 14.3 Hz), 1.59–1.41 (m, 10H), 1.06 (s, 9H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) δ 152.1, 149.5, 136.0, 135.8, 133.6, 132.5, 129.9, 128.2, 128.1, 83.8, 67.1, 53.7, 28.2, 27.6, 18.2, 15.7; [α]<sub>D</sub><sup>25</sup> -16.80° (c=1.00, CH<sub>2</sub>Cl<sub>2</sub>); Analysis Calc'd for C<sub>25</sub>H<sub>33</sub>N<sub>1</sub>O<sub>4</sub>Si<sub>1</sub>: C, 68.30; H, 7.57; N, 3.19; found: C, 68.17; H, 7.40 N, 3.08.

**Typical Procedure for Oxazolidinone Cleavage:** To a solution of 0.5448 g (1.18 mmol) of **3a** in 12 mL MeOH was added 0.155 g (0.48 mmol) of Cs<sub>2</sub>CO<sub>3</sub> and stirred at RT while monitoring the reaction by TLC. When the reaction was judged complete, 0.18 g (0.94 mmol) of citric acid was added. The solvent was removed, H<sub>2</sub>O was added and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine and dried over anhydrous MgSO<sub>4</sub>. Purification was accomplished by silica gel chromatography or recrystallization.

**2-(S)-N-(tert-Butoxycarbamoyl)-3-triphenylsilyl-1-propanol (4a):** mp 127–128 °C; Rf 0.30 (40% EtOAc:60% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56–7.35 (m, 15H), 4.45 (m, 1H), 3.95 (m, 1H), 3.59 (m, 1H), 3.46 (m, 1H), 2.46 (m, 1H), 1.73–1.54 (m, 2H), 1.33 (s, 9H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 135.5, 134.2, 129.7, 128.1, 79.4, 68.5, 50.1, 28.2, 16.5;  $[\alpha]_{\text{D}}^{25}$  -3.60° (c=1.00,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{26}\text{H}_{31}\text{N}_1\text{O}_3\text{Si}_1$ : C, 72.02; H, 7.21; N, 3.23; found: C, 72.01; H, 7.14; N, 3.20.

**2-(S)-N-(tert-Butoxycarbamoyl)-3-dimethylphenylsilyl-1-propanol (4b):** mp 96–97 °C; Rf 0.22 (30% EtOAc:70% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51–7.49 (m, 2H), 7.36–7.34 (m, 3H), 4.50 (d, 1H,  $J=8.0$  Hz), 3.78 (s, 1H), 3.53 (m, 1H), 3.39 (m, 1H), 2.64 (s, 1H), 1.40 (s, 9H), 1.04–0.93 (m, 2H), 0.33 (s, 6H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 138.6, 133.4, 129.1, 127.9, 79.5, 68.5, 50.1, 28.3, 19.0, -2.7;  $[\alpha]_{\text{D}}^{25}$  -3.90° (c=1.00,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{16}\text{H}_{27}\text{N}_1\text{O}_3\text{Si}_1$ : C, 62.10; H, 8.79; N, 4.53; found: C, 61.71; H, 8.46; N, 4.56.

**2-(S)-N-(tert-Butoxycarbamoyl)-3-diphenylmethylsilyl-1-propanol (4c):** mp 68–70 °C; Rf 0.48 (50% EtOAc:50% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52–7.50 (m, 4H), 7.40–7.33 (m, 6H), 4.41 (m, 1H), 3.86 (bs, 1H), 3.57 (bs, 1H), 3.41 (m, 1H), 2.28 (bs, 1H), 1.55–1.29 (m, 11H), 0.63 (s, 3H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 136.5, 134.3, 129.5, 128.0, 79.5, 68.4, 50.1, 28.3, 17.4, -4.3;  $[\alpha]_{\text{D}}^{25}$  -12.92° (c=1.05,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{21}\text{H}_{29}\text{N}_1\text{O}_3\text{Si}_1$ : C, 67.89; H, 7.87; N, 3.77; found: C, 67.70; H, 7.79; N, 3.79.

**2-(S)-N-(tert-Butoxycarbamoyl)-3-tert-butylidiphenylsilyl-1-propanol (4d):** mp 93–95 °C; Rf 0.50 (40% EtOAc:60% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65–7.37 (m, 10H), 4.37 (d, 1H,  $J=7.0$  Hz), 3.74 (bs, 1H), 3.47 (bs, 1H), 3.35 (bs, 1H), 2.49 (bs, 1H), 1.50–1.36 (m, 11H), 1.04 (s, 9H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 135.8, 134.2, 133.9, 129.4, 129.3, 127.8, 79.2, 68.3, 50.3, 28.2, 27.7, 18.1, 13.3;  $[\alpha]_{\text{D}}^{25}$  -1.05° (c=1.24,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{24}\text{H}_{35}\text{N}_1\text{O}_3\text{Si}_1$ : C, 69.69; H, 8.53; N, 3.39; found: C, 69.32; H, 8.40; N, 3.39.

**Typical Procedure for Oxidation Followed by Esterification:** To a solution of 88.1 mg (0.20 mmol) of **4a** in 1 mL of acetone cooled to 0 °C was added freshly prepared Jones reagent dropwise every 20–30 minutes. The reaction was monitored by TLC and judged complete after 3 h. The solvent was removed, quenched with  $\text{H}_2\text{O}$ , extracted with EtOAc. The combined organic extracts were washed with sat.  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , and brine, and dried over  $\text{MgSO}_4$ . The resultant acid was used in the next step without purification.

To a solution of acid (0.20 mmol) in 1.5 mL benzene and 0.5 mL MeOH was added 0.13 mL (0.26 mmol) of a 2 M solution of  $\text{TMSCHN}_2$  in hexanes. Evolution of gas was observed and the reaction was complete almost immediately. The reaction was quenched with  $\text{H}_2\text{O}$  and solvent was evaporated. The aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were washed with brine and dried over anhydrous  $\text{MgSO}_4$ . Purification was accomplished by silica gel chromatography or recrystallization.

**2-(S)-N-(tert-Butoxycarbamoyl)-3-triphenylsilyl methylpropionate (5a):** mp 142–144 °C; Rf 0.18 (20% EtOAc:80% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54–7.31 (m, 15H), 4.77 (d, 1H,  $J=7.5$  Hz), 4.45 (appt q,

1H), 3.36 (s, 3H), 1.97 (dd, 1H,  $J=6.7$  and  $14.8$  Hz), 1.81 (dd, 1H,  $J=8.8$  and  $14.8$  Hz), 1.34 (s, 9H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  174.1, 154.8, 137.7, 133.8, 129.9, 128.2, 79.7, 51.9, 50.6, 28.3, 18.1;  $[\alpha]_{\text{D}}^{25}$   $-30.00^\circ$  ( $c=0.66$ ,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{27}\text{H}_{31}\text{N}_1\text{O}_4\text{Si}_1$ : C, 70.25 H, 6.77; N, 3.03; found: C, 70.04; H, 6.80; N, 2.85. The enantiomeric purity was checked with chiral HPLC [Column: Chiralcel OD (0.46 cm x 25 cm);  $\lambda$ : 254 nm; Solvent: hexane: i-PrOH=99:1, flow rate=1.0 mL/min.  $R_t$  17 min (*S*-isomer);  $R_t$  24 min. (*R*-isomer)]

**2-(*S*)-*N*-(*tert*-Butoxycarbamoyl)-3-triphenylsilyl methylpropionate (5b):** oil;  $R_f$  0.38 (30% EtOAc:70% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (m, 2H), 7.35 (m, 3H), 4.82 (d, 1H,  $J=7.8$  Hz), 4.32 (dd, 1H,  $J=8.5$  and  $14.9$  Hz), 3.54 (s, 1H), 1.40–1.33 (m, 10H), 1.18 (dd, 1H,  $J=9.3$  and  $14.7$  Hz), 0.35 (s, 3H), 0.32 (s, 3H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  174.4, 155.0, 138.2, 133.5, 129.3, 128.0, 79.8, 52.1, 50.6, 28.4, 20.6, -2.7, -2.9;  $[\alpha]_{\text{D}}^{25}$   $-22.56$  ( $c=1.25$ ,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{17}\text{H}_{27}\text{N}_1\text{O}_4\text{Si}_1$ : C, 60.50 H, 8.06; N, 4.15; found: C, 60.29; H, 7.67; N, 4.12. The enantiomeric purity was checked with chiral HPLC [Column: Chiralcel AD (0.46 cm x 25 cm);  $\lambda$ : 254 nm; Solvent: hexane: i-PrOH=93:7, flow rate=0.7 mL/min.  $R_t$  11 min (*S*-isomer);  $R_t$  13.7 min. (*R*-isomer)]

**2-(*S*)-*N*-(*tert*-Butoxycarbamoyl)-3-diphenylmethylsilyl methylpropionate (5c):** mp 44–46  $^\circ\text{C}$ ;  $R_f$  0.70 (40% EtOAc:60% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53–7.48 (m, 4H), 7.38–7.25 (m, 6H), 4.84 (d, 1H,  $J=7.8$  Hz), 4.41 (appt. q, 1H), 3.42 (s, 3H), 1.73–1.67 (m, 1H), 1.56–1.50 (m, 1H), 1.38 (s, 9H), 0.67 (s, 3H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  174.1, 154.9, 136.4, 135.9, 134.4, 129.7, 129.6, 128.1, 79.8, 52.0, 50.6, 28.4, 19.1, -4.4;  $[\alpha]_{\text{D}}^{25}$   $-35.76$  ( $c=1.18$ ,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{22}\text{H}_{29}\text{N}_1\text{O}_4\text{Si}_1$ : C, 66.13 H, 7.32; N, 3.51; found: C, 66.49; H, 6.36; N, 3.44. The enantiomeric purity was checked with chiral HPLC [Column: Chiralcel AD (0.46 cm x 25 cm);  $\lambda$ : 254 nm; Solvent: hexane: i-PrOH=93:7, flow rate=0.7 mL/min.  $R_t$  13 min (*S*-isomer);  $R_t$  21 min. (*R*-isomer)]

**2-(*S*)-*N*-(*tert*-Butoxycarbamoyl)-3-*tert*-butyldiphenylsilyl methylpropionate (5d):** oil;  $R_f$  0.61 (40% EtOAc:60% Hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65–7.59 (m, 4H), 7.42–7.35 (m, 6H), 4.61 (d, 1H,  $J=7.2$  Hz), 4.25 (appt. q, 1H), 3.36 (s, 3H), 1.75 (dd, 1H,  $J=6.2$  and  $15.0$  Hz), 1.57 (dd, 1H,  $J=8.9$  and  $15.0$  Hz), 1.30 (s, 9H), 1.02 (s, 9H).  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  174.2, 154.7, 136.0, 135.9, 133.8, 133.2, 129.5, 127.92, 127.87, 79.5, 51.9, 50.7, 28.3, 27.8, 18.3, 14.7;  $[\alpha]_{\text{D}}^{25}$   $-29.01$  ( $c=1.72$ ,  $\text{CH}_2\text{Cl}_2$ ); Analysis Calc'd for  $\text{C}_{25}\text{H}_{35}\text{N}_1\text{O}_4\text{Si}_1$ : C, 67.99 H, 7.99; N, 3.17; found: C, 68.05; H, 7.12; N, 2.86. The enantiomeric purity was checked with chiral HPLC [Column: Chiralcel AD (0.46 cm x 25 cm);  $\lambda$ : 254 nm; Solvent: hexane: i-PrOH=98:2, flow rate=1.0 mL/min.  $R_t$  11 min (*S*-isomer);  $R_t$  17.5 min. (*R*-isomer)]

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