

# Enantioselective Organocatalytic Amine Conjugate Addition

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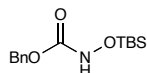
## Supporting Information

**General Information.** Benzyl hydroxycarbamate, *tert*-butyl hydroxycarbamate and fluorenylmethyl hydroxycarbamate were purchased from Aldrich Chemical. All solvents were purified according to the method of Grubbs.<sup>1</sup> All  $\alpha,\beta$ -unsaturated aldehydes were purified by either distillation or silica gel chromatography prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on Silicycle 230-400 mesh silica gel according to the method of Still. Thin-layer chromatography (TLC) was carried out on Silicycle 0.25mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching, iodine, *p*-anisaldehyde or ceric ammonium molybdate staining.

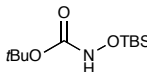
<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury 300 Spectrometer (300 MHz and 75 MHz respectively), and are internally referenced to residual protic solvent signals (CHCl<sub>3</sub> = 7.26 ppm, benzene = 7.16 ppm). Data for <sup>1</sup>H are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for <sup>13</sup>C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm<sup>-1</sup>). Mass spectra were obtained from the California Institute of Technology Mass Spectroscopy Facility. High performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series chromatograph using Daicel Chiracel AD, OD-H, and Regis Whelk-O 2 columns (25 cm) and equivalent guard columns (5 cm). Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments SFC with built-in photometric detector ( $\lambda$  = 214 nm) using Daicel Chiracel OD-H, and AD-H columns (25 cm) as noted. Optical rotations were measured on a Jasco P-1010

polarimeter, and  $[\alpha]_D^{25}$  values are reported in  $10^{-1} \text{ dg cm}^2 \text{ g}^{-1}$ ; concentration (c) is in g/100 mL.

**General Procedure for the Synthesis of Silyloxycarbamate Nucleophiles:** A 100 mL round-bottom flask charged with hydroxycarbamate (10 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (50 mL) and triethylamine (1.1 equiv) was cooled to  $0^\circ\text{C}$  and TBSCl or TBDPSCl (10 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred for 12 hours. Upon completion, the reaction was poured into a 250 mL separatory funnel and washed with  $\text{H}_2\text{O}$ , brine, and then dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by silica gel chromatography of the residue afforded the desired silyloxycarbamate.

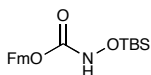


**Benzyl-(*tert*-butyldimethylsilyloxy)carbamate:** Prepared according to general procedure using benzyl-*N*-hydroxycarbamate (1.67 g, 10 mmol), triethylamine (1.56 mL, 11 mmol), and TBSCl (1.50 g, 10.0 mmol). Purification by silica gel chromatography (10%  $\text{Et}_2\text{O}$ /pentane) provided the title compound as a low melting solid (2.53 g, 90% yield). IR (film) 3275, 2930, 1730, 1706, 1498, 1472, 1253  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.08 (s, 6H,  $\text{SiCH}_3$ ), 0.92 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 5.18 (s, 2H,  $\text{PhCH}_2$ ), 6.95 (s, 1H,  $\text{NH}$ ), 7.39 (s, 5H,  $\text{PhH}$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.8, 18.0, 25.8, 67.6, 128.3, 128.4, 128.5, 135.6, 158.6 ppm; HRMS (FAB+) exact mass calculated for ( $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{Si}$ ) requires  $m/z$   $[\text{M}+\text{H}]$  282.1526, found  $m/z$  282.1518.

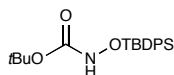


***tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate:** Prepared according to general procedure using *tert*-Butyl-*N*-hydroxycarbamate (1.33 g, 10 mmol), triethylamine (1.56 mL, 11 mmol), and TBSCl (1.50 g, 10.0 mmol). Purification by silica gel chromatography (10%  $\text{Et}_2\text{O}$ /pentane) provided the title compound as a low melting solid (2.27 g, 92% yield). IR (film) 3292, 2931, 1757, 1694, 1473, 1463, 1393, 1368, 1251, 1172  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.17 (s, 6H,  $\text{SiCH}_3$ ), 0.95 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.48 (s, 9H,  $\text{OC}(\text{CH}_3)_3$ ), 6.67 (s, 1H,  $\text{NH}$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.8, 18.0,

25.8, 28.1, 81.5, 157.9 ppm ; HRMS (FAB+) exact mass calculated for (C<sub>11</sub>H<sub>25</sub>NO<sub>3</sub>Si) requires *m/z* [M+H] 248.1682, found *m/z* 248.1679.



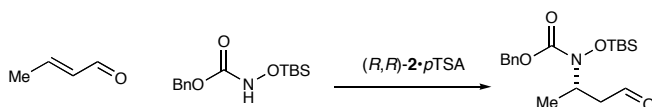
**9-Fluorenylmethyl-(*tert*-butyldimethylsilyloxy)carbamate:** Prepared according to general procedure using 9-fluorenylmethyl-*N*-hydroxycarbamate (2.55g, 10 mmol), triethylamine (1.56 mL, 11 mmol), and TBSCl (1.50 g, 10.0 mmol). Purification by silica gel chromatography (20% Et<sub>2</sub>O/pentane) provided the title compound as a low melting solid (3.14 g, 85% yield). IR (film) 3435, 2930, 2856, 1647, 1475, 1450, 1252 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.16 (s, 6H, SiCH<sub>3</sub>), 0.95 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 4.24 (t, 1H, *J* = 6.9 Hz, CH), 4.50 (d, 2H, *J* = 6.9 Hz, CH<sub>2</sub>), 6.90 (s, 1H, NH), 7.31-7.43 (m, 4H, ArH), 7.61 (d, 2H, *J* = 7.5 Hz, ArH), 7.76 (d, 2H, *J* = 7.5 Hz, ArH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ -5.8, 18.0, 25.9, 47.0, 67.5, 120.0, 125.0, 127.1, 127.8, 141.3, 143.5, 158.7 ppm ; HRMS (FAB+) exact mass calculated for (C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>Si) requires *m/z* [M+H] 370.1838, found *m/z* 370.1841.



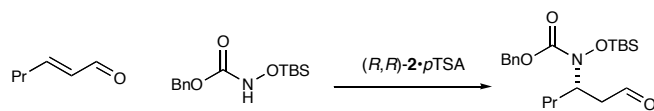
***tert*-Butyl-(*tert*-butyldiphenylsilyloxy)carbamate:** Prepared according to general procedure using *tert*-butyl-*N*-hydroxycarbamate (1.33 g, 10 mmol), triethylamine (1.56 mL, 11 mmol), and TBDPSCl (2.75 g, 10.0 mmol). Purification by silica gel chromatography (20% Et<sub>2</sub>O/pentane) provided the title compound as a solid (3.27 g, 88% yield). IR (film) 3436, 2859, 1757, 1687, 1590, 1473, 1462, 1428, 1247 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.14 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.38 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 6.70 (s, 1H, NH), 7.30-7.45 (m, 6H, PhH), 7.72-7.76 (m, 4H, PhH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 19, 26.9, 28.0, 81.6, 127.7, 130.0, 132.0, 133.0, 135.8, 157.2 ppm ; HRMS (FAB+) exact mass calculated for (C<sub>21</sub>H<sub>29</sub>NO<sub>3</sub>Si) requires *m/z* [M+H] 372.1995, found *m/z* 372.1998.

**General Procedure for the Conjugate Amination of Aldehydes:** A 4-dram vial

equipped with a magnetic stir bar was charged with the *p*TSA or TFA salt of (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (**2**) (0.05 mmol) and the appropriate enal (0.75 mmol) in CHCl<sub>3</sub> (0.75 mL) was cooled to -20 °C. The silyloxycarbamate nucleophile (0.25 mmol) was then added in one portion and the reaction mixture was stirred at -20 °C. Upon completion of the reaction as determined by TLC analysis (12-36 hours), the products were isolated as described below.



***N*-*tert*-butyldimethylsilyloxy[benzyl-(*S*)-1-formylpropan-2-ylcarbamate]: Table 2, entry 1.** Prepared according to the general procedure using catalyst (*R,R*)-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), crotonaldehyde (64  $\mu$ L, 0.75 mmol) in CHCl<sub>3</sub> (0.75 mL) at -20 °C. Benzyl-(*tert*-butyldimethylsilyloxy)carbamate (70 mg, 0.25 mmol) was added in one portion and the reaction was maintained at -20 °C for 24 hours. The reaction mixture was then filtered through a plug of silica, eluted with Et<sub>2</sub>O then concentrated *in vacuo*. Purification by silica gel chromatography (5 to 10% Et<sub>2</sub>O/pentane gradient) provided the title compound as clear oil (81 mg, 92% yield, 92% ee). IR (neat) 3445, 2886, 2856, 1709, 1588, 1498, 1472, 1462 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  0.09 (s, 3H, SiCH<sub>3</sub>), 0.10 (s, 3H, SiCH<sub>3</sub>), 0.91 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.60 (d, 3H, *J* = 6.8 Hz, CHCH<sub>3</sub>), 2.60 (dd, 1H, *J*<sub>1</sub> = 6.5 and *J*<sub>2</sub> = 17.0 Hz, HCHCHO), 2.82 (dd, 1H, *J*<sub>1</sub> = 7.0 and *J*<sub>2</sub> = 17.0 Hz, HCHCHO), 4.51 (m, 1H, NCH), 5.16 (s, 2H, PhCH<sub>2</sub>), 7.36 (m, 5H, PhH), 9.75 (t, *J* = 1.8 Hz, CHO) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  -4.3, -4.2, 18.0, 18.5, 26.2, 47.8, 54.0, 68.3, 128.6, 128.7, 135.9, 159.3, 200.0 ppm; HRMS (FAB+) exact mass calculated for (C<sub>18</sub>H<sub>29</sub>NO<sub>4</sub>Si) requires *m/z* [M+H] 352.1944, found *m/z* 352.1962. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +2.3° (c = 1.1, CHCl<sub>3</sub>). The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with NaBH<sub>4</sub>) using a Regis Technology Whelk-O 2 column (5% *i*PrOH/hexanes, 1.0 mL/min); major enantiomer *t*<sub>r</sub> = 16 min and minor enantiomer *t*<sub>r</sub> = 19 min.



***N*-tert-butyltrimethylsilyloxy[benzyl-(*S*)-1-formylpentan-2-yl]carbamate**: Table 2, entry 2. Prepared according to the general procedure using catalyst (*R,R*)-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), 2-hexenal (87  $\mu$ L, 0.75 mmol) in  $\text{CHCl}_3$  (0.75 mL) at  $-20^\circ\text{C}$ . Benzyl-(*tert*-butyltrimethylsilyloxy)carbamate (70 mg, 0.25 mmol) was added in one portion and the reaction was maintained  $-20^\circ\text{C}$  for 24 hours. The reaction mixture was then filtered through a plug of silica, eluted with  $\text{Et}_2\text{O}$  then concentrated *in vacuo*. Purification by silica gel chromatography (5 to 10%  $\text{Et}_2\text{O}$ /pentane gradient) provided the title compound as clear oil (73 mg, 77% yield, 95% ee). IR (neat) 3439, 2859, 2722, 1727, 1587, 1498, 1471, 1463  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.10 (s, 6H,  $\text{SiCH}_3$ ), 0.90 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.80-1.00 (overlapped t, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.38 (m, 3H,  $\text{HCHCH}_2\text{CH}_3$ ), 1.74 (m, 1H,  $\text{HCHCH}_2\text{CH}_3$ ), 2.52 (ddd, 1H,  $J_1 = 1.9$ ,  $J_2 = 5.6$  and  $J_3 = 16.7$  Hz,  $\text{HCHCHO}$ ), 2.80 (ddd, 1H,  $J_1 = 2.1$ ,  $J_2 = 7.5$  and  $J_3 = 16.7$  Hz,  $\text{HCHCHO}$ ), 4.46 (m, 1H,  $\text{NCH}$ ), 5.17 (s, 2H,  $\text{PhCH}_2$ ), 7.36 (m, 5H,  $\text{PhH}$ ), 9.76 (t, 1H,  $J = 1.8$  Hz,  $\text{CHO}$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$   $-4.5$ , 13.7, 18.3, 19.5, 25.9, 34.4, 46.4, 57.6, 68.0, 128.3, 128.4, 128.5, 135.7, 159.0, 200.0 ppm ; HRMS (EI) exact mass calculated for ( $\text{C}_{20}\text{H}_{33}\text{NO}_4\text{Si}$ ) requires  $m/z$   $[\text{M}+\text{H}]$  380.2248, found  $m/z$  380.2248.  $[\alpha]_D^{25} = -4.4^\circ$  ( $c = 1.2$ ,  $\text{CHCl}_3$ ). The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with  $\text{NaBH}_4$ ) using a Chiralcel OD-H column (2% *i*PrOH/hexanes, 1 mL/min); major enantiomer  $t_r = 20.1$  min and minor enantiomer  $t_r = 23.8$  min.



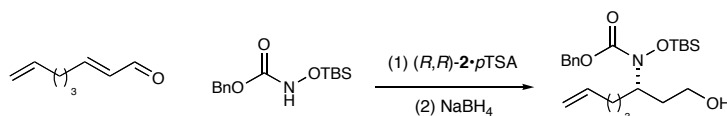
***N*-tert-butyltrimethylsilyloxy[*tert*-butyl-(*S*)-1-formylpentan-2-yl]carbamate**: Table 2, entry 3. Prepared according to the general procedure using catalyst (*R,R*)-2-TFA (18 mg, 0.05 mmol, 0.2 equiv), 2-hexenal (87  $\mu$ L, 0.75 mmol) in  $\text{CHCl}_3$  (0.75 mL) at  $-20^\circ\text{C}$ . *tert*-

Butyl-(*tert*-butyldimethylsilyloxy)carbamate (62 mg, 0.25 mmol) was added in one portion and the reaction was maintained  $-20\text{ }^{\circ}\text{C}$  for 24 hours. The reaction mixture was then filtered through a plug of silica, eluted with  $\text{Et}_2\text{O}$  then concentrated *in vacuo*. Purification by silica gel chromatography (5 to 10%  $\text{Et}_2\text{O}$ /pentane gradient) provided the title compound as clear oil (80.5 mg, 85% yield, 92% ee). IR (neat) 3438, 2898, 2859, 2720, 1728, 1473, 1463  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.15 (s, 6H,  $\text{SiCH}_3$ ), 0.94 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.10-1.60 (m, 6H,  $\text{HCHCH}_2\text{CH}_3$ ), 1.47 (s, 9H,  $\text{OC}(\text{CH}_3)_3$ ), 1.76 (m, 1H,  $\text{HCHCH}_2\text{CH}_3$ ), 2.52 (dd, 1H,  $J_1 = 5.7$  and  $J_2 = 16.5$  Hz,  $\text{HCHCHO}$ ), 2.77 (dd, 1H,  $J_1 = 7.5$  and  $J_2 = 16.7$  Hz,  $\text{HCHCHO}$ ), 4.33 (m, 1H,  $\text{NCH}$ ), 9.77 (s, 1H,  $\text{CHO}$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.42, 13.8, 18.2, 19.6, 26.0, 28.2 34.7, 46.6, 58.1, 81.7, 158.0, 200.9 ppm ; HRMS (EI) exact mass calculated for  $(\text{C}_{17}\text{H}_{35}\text{NO}_4\text{Si})$  requires  $m/z$   $[\text{M}+\text{H}]$  346.2410, found  $m/z$  346.2414.  $[\alpha]_D^{25} = -1.52^{\circ}$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ). The enantiomeric excess was determined by HPLC analysis of the isoxazolidine benzoyl acetal derivative (by treatment with TBAF, then benzoyl chloride and TEA) using Chiralcel OD-H column (2%  $\text{EtOH}$ /hexanes, 1 mL/min); major enantiomer  $t_r = 7.8$  min and minor enantiomer  $t_r = 12.8$  min.



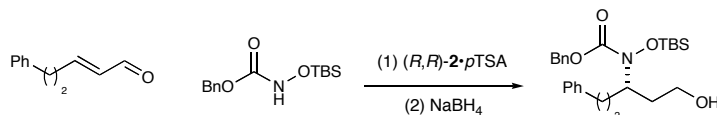
***N*-*tert*-butyldimethylsilyloxy [(fluoren-9-yl)methyl (*S*)-1-formylpentan-2-ylcarbamate]; Table 2, entry 4.** Prepared according to the general procedure using catalyst *(R,R)*-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), 2-hexenal (87  $\mu\text{L}$ , 0.75 mmol) in  $\text{CHCl}_3$  (0.75 mL) at  $-20\text{ }^{\circ}\text{C}$ . 9-Fluorenylmethyl(*tert*-butyldimethylsilyloxy)carbamate (92 mg, 0.25 mmol) was added in one portion and the reaction was maintained  $-20\text{ }^{\circ}\text{C}$  for 36 hours. The reaction mixture was then filtered through a plug of silica, eluted with  $\text{Et}_2\text{O}$  then concentrated *in vacuo*. Purification by silica gel chromatography (5 to 10%  $\text{EtOAc}$ /hexanes gradient) provided the title compound as a clear oil (92 mg, 78% yield, 89% ee). IR (neat) 3433, 2858, 2723, 1727, 1471, 1463, 1450, 1390, 1299, 1252, 1200  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.10(s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.83 (t, 3H,  $J = 13.0$  Hz,  $\text{CH}_3$ ), 0.91 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.26 (m, 3H,  $\text{HCHCH}_2\text{CH}_3$ ), 1.60 (m, 1H,  $\text{HCHCH}_2\text{CH}_3$ ), 2.34 (ddd, 1H,  $J_1 = 1.9$ ,  $J_2 = 6.0$ ,  $J_3 = 17.0$  Hz,  $\text{HCHCHO}$ ), 2.59 (ddd, 1H,  $J_1 = 1.9$ ,  $J_2 =$

7.2,  $J_3 = 17.0$  Hz, **HCHCHO**), 4.18 (m, 1H, **NCH**), 4.25 (t, 1H,  $J = 6.0$  Hz, **CH**), 4.59 (m, 2H, **CH<sub>2</sub>**), 7.28-7.42 (m, 6H, **ArH**), 7.61 (d, 1H,  $J = 8.0$  Hz, **ArH**), 7.77 (d, 1H,  $J = 8.0$  Hz, **ArH**), 9.58 (t, 1H,  $J = 1.7$  Hz, **CHO**) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.6, 13.7, 18.3, 19.5, 26.0, 34.3, 46.3, 47.1, 58.2, 67.3, 120.0, 124.9, 127.1, 127.7, 141.4, 143.6, 159.0, 200.0 ppm ; HRMS (EI) exact mass calculated for ( $\text{C}_{27}\text{H}_{37}\text{NO}_4\text{Si}$ ) requires  $m/z$  [M+H] 468.2586, found  $m/z$  468.2570.  $[\alpha]_D^{25} = -3.17^\circ$  ( $c = 0.66$ ,  $\text{CHCl}_3$ ). The enantiomeric ratio was determined by SFC analysis of the corresponding alcohol (after treatment with  $\text{NaBH}_4$ ) using Chiralcel OD-H column (5 to 50% gradient  $\text{MeOH}/\text{CO}_2$ , 4 mL/min); minor enantiomer  $t_r = 4.22$  min and major enantiomer  $t_r = 4.55$  min.



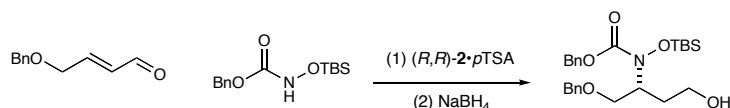
***N*-tert-butyltrimethylsilyloxy[benzyl-(*S*)-hydroxyoct-7-en-3-ylcarbamate]: Table 2, entry 5.** Prepared according to the general procedure using catalyst (*R,R*)-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), 2,7-octadienal (93 mg, 0.75 mmol) in  $\text{CHCl}_3$  (0.75 mL) at  $-20$  °C. Benzyl-(*tert*-butyltrimethylsilyloxy)carbamate nucleophile (70 mg, 0.25 mmol) was added in one portion and the reaction was maintained  $-20$  °C for 36 hours. Upon completion,  $\text{MeOH}$  (100  $\mu\text{L}$ ) was added to the reaction mixture and warmed to  $0$  °C followed by the addition of  $\text{NaBH}_4$  (38 mg, 1 mmol). After 1 hour, the excess  $\text{NaBH}_4$  was quenched by the addition of aqueous 1.0 M  $\text{NaHSO}_4$  then extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL). The combined organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Silica gel chromatography (1%  $\text{MeOH}$  in  $\text{CH}_2\text{Cl}_2$ ) of the resultant residue afforded the title compound as clear oil (88 mg, 87% yield, 96% ee). IR (neat) 3443, 1706, 1641, 1587, 1498, 1472, 1461, 1391  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.10 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.89 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.31-1.48 (m, 3H, **HCHCH<sub>2</sub>CH<sub>2</sub>**), 1.60-1.95 (m, 4H, **CH<sub>2</sub>**), 2.04 (m, 2H, **CH<sub>2</sub>CH=CH<sub>2</sub>**), 3.59 (m, 2H, **CH<sub>2</sub>OH**), 4.08 (m, 1H, **NCH**), 4.91-5.01 (m, 2H, **HC=CH<sub>2</sub>**), 5.15 (s, 2H, **PhCH<sub>2</sub>**), 5.65-5.85 (m, 1H, **CH<sub>2</sub>HC=CH<sub>2</sub>**), 7.31-7.78 (m, 5H, **PhH**) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  0.06, 0.13, 6.2, 22.8, 30.4, 36.7, 37.9, 39.3, 63.9, 72.5, 89.2, 119.2, 132.8, 132.9, 133.0, 133.1, 140.1, 142.9, 164.0 ppm ; HRMS (EI) exact mass calculated for ( $\text{C}_{22}\text{H}_{37}\text{NO}_4\text{Si}$ ) requires  $m/z$  [M+H] 408.2570, found  $m/z$

408.2570.  $[\alpha]_D^{25} = +1.0^\circ$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). The enantiomeric excess was determined by HPLC analysis of the alcohol using Chiralcel OD-H column (2% *i*PrOH/hexanes, 0.75 mL/min); major enantiomer  $t_r = 20.9$  min and minor enantiomer  $t_r = 25$  min.

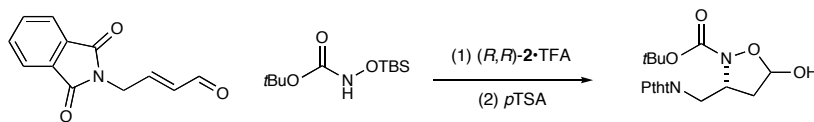


***N*-tert-butyltrimethylsilyloxy[benzyl-(*S*)-5-hydroxyphenylpenta-3-ylcarbamate]:**

**Table 2, entry 6.** Prepared according to the general procedure using catalyst (*R,R*)-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), 5-phenylpent-2-enal (120 mg, 0.75 mmol) in  $\text{CHCl}_3$  (0.75 mL) at  $-20^\circ\text{C}$ . Benzyl-(*tert*-butyltrimethylsilyloxy)carbamate (70 mg, 0.25 mmol) was added in one portion and the reaction was maintained  $-20^\circ\text{C}$  for 36 hours. Upon completion, MeOH (100  $\mu\text{L}$ ) was added to the reaction mixture and warmed to  $0^\circ\text{C}$  followed by addition of  $\text{NaBH}_4$  (38 mg, 1 mmol). After 1 hour, excess  $\text{NaBH}_4$  was quenched by addition of aqueous 1.0 M  $\text{NaHSO}_4$  then extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL). The combined organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc/hexanes) provided the title compound as clear oil (77 mg, 69% yield, 90% ee). IR (film) 3450, 2953, 2930, 1948, 1871, 1805, 1709, 1603, 1587, 1497, 1472, 1455, 1403, 1391, 1362, 1253, 1214  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.13 (s, 3H,  $\text{SiCH}_3$ ), 0.14 (s, 3H,  $\text{SiCH}_3$ ), 0.92 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.17-1.63 (m, 5H,  $(\text{CH}_2)_2$ , OH), 2.76-2.55 (m, 2H,  $\text{CH}_2$ ), 3.67-3.54 (m, 2H,  $\text{CH}_2\text{OH}$ ), 4.19-4.09 (m, 1H, NCH), 5.17 (s, 2H,  $\text{PhCH}_2\text{O}$ ), 7.37-7.13 (m, 10H, PhH) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.2, -4.1, 18.6, 26.2, 33.2, 34.8, 35.2, 59.6, 59.7, 68.3, 126.1, 128.61, 128.63, 128.7, 128.8, 128.9, 135.9, 141.9, 159.8 ppm; HRMS (FAB) exact mass calculated for  $(\text{C}_{25}\text{H}_{37}\text{NO}_4\text{Si})$  requires  $m/z$   $[\text{M}+\text{H}]$  444.2570, found  $m/z$  444.2551.  $[\alpha]_D^{25} = +0.99$  ( $c = 0.58$ ,  $\text{CHCl}_3$ ). The enantiomeric excess was determined by HPLC using a Regis Technology (*R,R*)-Whelk-O 2 column (5% *i*PrOH/hexanes, 0.75 mL/min); major enantiomer  $t_r = 27.7$  min and minor  $t_r = 30.6$  min.

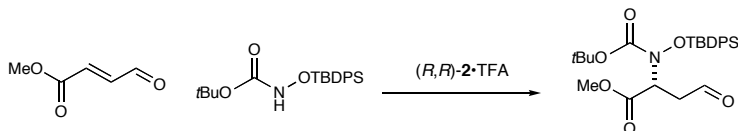


***N*-*tert*-butyldimethylsilyloxy[benzyl-(*S*)-(benzyloxy)-4-hydroxybutan-2-ylcarbamate]: Table 2, entry 7.** Prepared according to the general procedure using catalyst (*R,R*)-2-*p*TSA (21 mg, 0.05 mmol, 0.2 equiv), 4-(benzyloxy)but-2-enal (132 mg, 0.75 mmol) in CHCl<sub>3</sub> (0.75 mL) at –20 °C. Benzyl-(*tert*-butyldimethylsilyloxy)carbamate (70 mg, 0.25 mmol) was added in one portion and the reaction was maintained –20 °C for 36 hours. Upon completion, MeOH (100 μL) was added to the reaction mixture and warmed to 0 °C followed by the addition of NaBH<sub>4</sub> (38 mg, 1 mmol). After 1 hour, excess NaBH<sub>4</sub> was quenched by the addition of aqueous 1.0 M NaHSO<sub>4</sub> then extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc/hexanes) provided the title compound as clear oil (80 mg, 70% yield, 96% ee). IR (film) 3450, 3065, 3032, 2953, 2929, 2884, 2858, 2741, 2712, 1950, 1874, 1808, 1713, 1606, 1587, 1497, 1472, 1455, 1390, 1362, 1305, 1252, 1214 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.11 (s, 3H, SiCH<sub>3</sub>) 0.12 (s, 3H, SiCH<sub>3</sub>), 0.90 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.94-1.65 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>OH), 2.44 (br s, 1H, OH), 3.78-3.45 (m, 4H, BnOCH<sub>2</sub>, CH<sub>2</sub>OH), 4.36-4.27 (m, 1H, CHN), 4.51 (s, 2H, PhCH<sub>2</sub>O), 5.13 (s, 2H, PhCH<sub>2</sub>O), 7.35-7.31 (m, 10H, PhH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ –4.6, –4.2, 18.5, 26.2, 31.9, 59.8, 60.1, 68.3, 70.4, 73.2, 127.8, 127.9, 128.6, 128.7, 128.8, 135.9, 138.3, 160.0 ppm; HRMS (FAB) exact mass calculated for (C<sub>25</sub>H<sub>37</sub>NO<sub>5</sub>Si) requires *m/z* [M+H] 460.2519, found *m/z* 460.2536. [α]<sub>D</sub><sup>25</sup> = +7.51° (c = 0.50, CHCl<sub>3</sub>). The enantiomeric excess was determined by HPLC using a Regis Technology (*R,R*) Whelk-O 2 (25 cm x 4.6 mm) column (5% *i*PrOH/hexanes, 1.0 mL/min); major isomer *t*<sub>r</sub> = 26.6 min and minor isomer *t*<sub>r</sub> = 31.8 min.



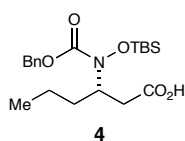
**(3*S*,5*S*)-*tert*-Butyl-3-(*N*-methylphthalimido)-5-hydroxyisoxazolidine-2-carboxylate: Table 2, entry 8.** Prepared according to the general procedure using catalyst (*R,R*)-2-TFA (18 mg, 0.05 mmol, 0.2 equiv), 4-(*N*-methylphthalimido)but-2-enal (161mg, 0.75 mmol) in CHCl<sub>3</sub> (0.75 mL) at –20 °C. *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (62 mg, 0.25 mmol) was added in one portion and the reaction was maintained –20 °C for 36

hours. The reaction was warmed to ambient temperature followed the addition of acetone-H<sub>2</sub>O (1 mL, 4:1) and *p*TSA·H<sub>2</sub>O (47.5 mg, 0.25 mmol). After 12 hours the reaction was passed through a plug of silica gel, eluted with Et<sub>2</sub>O and concentrated *in vacuo*. Purification by silica gel chromatography (20 to 30% EtOAc/hexanes gradient) provided the title compound as amorphous solid (74 mg, 85% yield, 87% ee). IR (film) 3470, 3362, 1774, 1716, 1614, 1468, 1430, 1396, 1370, 1354 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.24 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.05 (m, 1H, HCH), 2.40 (dd, 1H, *J*<sub>1</sub> = 8.4 and *J*<sub>2</sub> = 12.2 Hz, HCH), 3.67 (dd, 1H, *J*<sub>1</sub> = 5.1 and *J*<sub>2</sub> = 13.5 Hz, phthNCH<sub>2</sub>), 3.87 (dd, 1H, *J*<sub>1</sub> = 8.4 and *J*<sub>2</sub> = 13.5 Hz, phthNCH<sub>2</sub>), 4.67 (m, 1H, NCH), 5.29 (br s, 1H, OH), 5.78 (d, 1H, *J* = 4.8 Hz, OCHOH), 7.69-7.75 (m, 2H, ArH), 7.82-7.89 (m, 2H, ArH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 27.9, 39.5, 41.6, 56.5, 82.5, 98.7, 123.4, 132.0, 134.0, 158.4, 168.0 ppm; HRMS (EI) exact mass calculated for (C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>) requires *m/z* [M+H] 349.1400, found *m/z* 349.1398. [α]<sub>D</sub><sup>25</sup> = -60.0° (c = 0.6, CHCl<sub>3</sub>). The enantiomeric ratio was determined by SFC analysis using a Chiralcel OD-H column (5 to 50% MeOH/CO<sub>2</sub> gradient, 4 mL/min); major enantiomer *t*<sub>r</sub> = 3.1 min and minor enantiomer *t*<sub>r</sub> = 3.45 min.



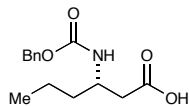
***N*-tert-butyl dimethylsilyloxy[*tert*-butyl-(*R*)-1-methoxycarbonyl-2-formylethyl]carbamate]: Table 2, entry 9.** Prepared by the modification of the general procedure using catalyst (*R,R*)-2-TFA (18 mg, 0.05 mmol, 0.2 equiv), methyl-3-formoylacrylate (86 mg, 0.75 mmol) in CHCl<sub>3</sub> (0.25 mL) at 4 °C. *tert*-Butyl-(*tert*-butyldiphenylsilyloxy)carbamate (93 mg, 0.25 mmol) was added in one portion and the reaction was maintained 4 °C for 12 hours. The reaction mixture was then filtered through a plug of silica, eluted with Et<sub>2</sub>O then concentrated *in vacuo*. Purification by silica gel chromatography (10 to 20% of Et<sub>2</sub>O/pentane gradient) provided the title compound as clear oil (95 mg, 78% yield, 97% ee). IR (neat) 3421, 2895, 2859, 2727, 1731, 1590, 1568, 1488, 1463, 1474, 1429 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.14 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.22 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.60 (dd, 1H, *J*<sub>1</sub> = 5.0 and *J*<sub>2</sub> = 17.8 Hz, HCHCHO), 3.12 (ddd, 1H, *J*<sub>1</sub> = 1.3, *J*<sub>2</sub> = 8.3 and *J*<sub>3</sub> = 17.8 Hz, HCHCHO), 3.56 (s, 3H,

OCH<sub>3</sub>), 4.84 (dd, 1H,  $J_1 = 6.0$  and  $J_2 = 8.2$  Hz, NCH), 7.33-7.45 (m, 6H, PhH), 7.66-7.76 (m, 4H, PhH), 9.55 (s, 1H, CHO) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 19.4, 27.0, 27.8, 43.1, 52.3, 60.8, 82.7, 127.5, 127.6, 127.8, 129.6, 130.0, 132.0, 132.4, 136.0, 136.3, 136.4, 158.8, 169.8, 198.3 ppm ; HRMS (EI) exact mass calculated for (C<sub>26</sub>H<sub>35</sub>NO<sub>6</sub>Si) requires  $m/z$  [M+H] 486.2312, found  $m/z$  486.2308.  $[\alpha]_D^{25} = +22.7^\circ$  (c = 0.80, CHCl<sub>3</sub>). The enantiomeric excess was determined by SFC analysis of the aldehyde Chiralcel OD-H column (10% AcCN/CO<sub>2</sub>, 4 mL/min); minor enantiomer  $t_r = 1.91$  min and major enantiomer  $t_r = 2.14$  min.

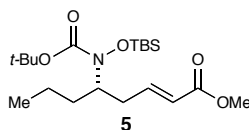


***N*-tert-butyl dimethylsilyloxy[benzyl (*S*)-3-carbamate-hexanoic acid] (4):** Prepared according to the general procedure using catalyst (*R,R*)-**2**-pTSA (84 mg, 0.20 mmol, 0.2 equiv) in CHCl<sub>3</sub> (3 mL), 2-hexenal (348 μL, 3 mmol) in CHCl<sub>3</sub> (0.75 mL) at -20 °C. Benzyl-(*tert*-butyl dimethylsilyloxy)carbamate (281 mg, 1.0 mmol) was added in one portion and the reaction was maintained at -20 °C for 24 hours. Upon completion (a small aliquot was removed for ee determination in accord to table 2, entry 2) the reaction was warmed to 4 °C, isobutene (1 mL), *tert*-butanol (4 mL), H<sub>2</sub>O (2 mL), KH<sub>2</sub>PO<sub>4</sub>, (544 mg, 4 mmol), and NaClO<sub>2</sub> (360 mg, 4 mmol) were added sequentially. The reaction was allowed to stir at this temperature for 12 hours. The mixture was diluted with H<sub>2</sub>O (10 mL) and the organic layer separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL) and the combined organic layer washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (5 to 10% Et<sub>2</sub>O/pentane gradient) provided the title compound as clear oil (285 mg, 72% yield, 92%ee). IR (neat) 3200, 2859, 1713, 1432, 1391, 1293, 1257, 1089 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.11 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.87 (t, 3H,  $J = 6$  Hz, CH<sub>3</sub>), 0.90 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.26-1.45 (m, 3H, HCHCH<sub>2</sub>CH<sub>3</sub>), 1.73 (m, 1H, HCHCH<sub>2</sub>CH<sub>3</sub>), 2.50 (dd, 1H,  $J_1 = 6.3$  and  $J_2 = 16.0$  Hz, HCHCO<sub>2</sub>H), 2.76 (dd, 1H,  $J_1 = 7.2$  and  $J_2 = 16.0$  Hz, HCHCO<sub>2</sub>H), 4.37 (m, 1H, NCH), 5.15 (s, 2H, PhCH<sub>2</sub>), 7.35 (m, 5H, PhH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ -4.7, -4.5, 13.7, 18.3, 19.5, 25.9, 34.4, 37.1, 53.4, 59.0, 67.9, 128.2, 128.3, 128.4, 135.8,

159.1, 176.9 ppm; HRMS (EI) exact mass calculated for (C<sub>20</sub>H<sub>33</sub>NO<sub>5</sub>Si) requires  $m/z$  [M+H] 396.2206, found  $m/z$  396.2201.  $[\alpha]_D^{25} = -2.23^\circ$  (c = 0.64, CHCl<sub>3</sub>).

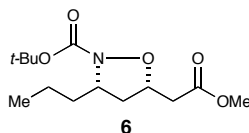


**Benzyl (S)-3-carbamate-hexanoic acid:** A 4-dram vial charged with **3** (39 mg, 0.1 mmol) in AcOH-H<sub>2</sub>O (250  $\mu$ L, 4:1) was heated to 65 °C, after 15 min Zn dust (4 X 16.4 mg, 1.0 mmol, 10 micron) was added in 4 portions at 30 minute intervals. The reaction was maintained at 65 °C for 6 hours. Upon cooling to ambient temperature, the reaction was diluted with H<sub>2</sub>O (2 mL), 1M HCl (3 mL), and aqueous solution was extracted with EtOAc (3 X 10 mL). The combined organic layers was washed successively with H<sub>2</sub>O, brine, then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (20 to 30% EtOAc/hexanes gradient) provided the title compound as a solid (24.4 mg, 92% yield). All spectroscopic data matched literature reported values.<sup>2</sup> IR (film) 3329, 2957, 1693, 1539, 1455, 1303, 1266 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  0.92t,  $J = 7.0$  Hz, CH<sub>3</sub>, 1.35 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.54 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.60 (m, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 3.99 (m, 1H, NCH), 5.09 (s, 2H, PhCH<sub>2</sub>), 5.18 (br, 1H, NH), 7.35 (m, 5H, PhH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  13.7, 19.4, 36.4, 38.7, 47.7, 66.8, 128.1, 128.2, 128.5, 136.4, 155.9, 176.7 ppm; HRMS (EI) exact mass calculated for (C<sub>14</sub>H<sub>19</sub>NO<sub>4</sub>) requires  $m/z$  265.1314 [M+], found  $m/z$  265.1311.  $[\alpha]_D^{25} = -11.45^\circ$  (c = 0.50, MeOH). The observed optical rotation was consistent with the (S)-configuration for benzyl (S)-3-carbamate-hexanoic acid, based on the previously reported (R)-configuration<sup>3</sup> having the opposite sign of rotation ( $[\alpha]_D^{25} = +12.9^\circ$  (c = 0.55, MeOH)).



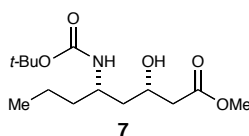
**N-tert-butyltrimethylsilyloxy[tert-butyl-(S)-1-(methoxycarbonyl)hept-1-en-4-yl]carbamate (5):** Prepared according to the general procedure using catalyst (R,R)-

2·TFA (72 mg, 0.20 mmol, 0.2 equiv), 2-hexenal (348  $\mu$ L, 3 mmol) in  $\text{CHCl}_3$  (3 mL) at  $-20$   $^\circ\text{C}$ . *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (247 mg, 1.0 mmol) was added in one portion and the reaction was maintained at  $-20$   $^\circ\text{C}$  for 24 hours. Upon completion (determined by TLC), methyl (triphenylphosphorylidine) acetate (1.03g, 3.0 mmol) was added and allowed to warm to ambient temperature. After 2 hours, the reaction mixture was concentrated to a viscous oil, and the triphenylphosphine oxide byproduct was precipitated by the addition of  $\text{Et}_2\text{O}$ . The solid was removed by filtration and the organic layer concentrated *in vacuo*. Purification by silica gel chromatography (2.5 to 10%  $\text{Et}_2\text{O}$ /pentane gradient) provided the title compound as clear oil (285 mg, 71% yield). IR (neat) 2933, 2859, 1729, 1704, 1660, 1472, 1466, 1392, 1362, 1319  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.15 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.91 (t, 3H,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 0.95 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.3-1.40 (m, 3H,  $\text{HCHCH}_2\text{CH}_3$ ), 1.45 (s, 9H,  $\text{O}(\text{CCH}_3)_3$ ), 1.70 (m, 1H,  $\text{HCHCH}_2\text{CH}_3$ ), 2.28 (ddd, 1H,  $J_1 = 5.7$ ,  $J_2 = 12.9$  and  $J_3 = 20.4$  Hz,  $\text{HCHCCH=}$ ), 2.63 (ddd, 1H,  $J_1 = 7.2$ ,  $J_2 = 14.4$  and  $J_3 = 20.4$  Hz,  $\text{HCHCH=}$ ), 3.71 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.95 (m, 1H,  $\text{NCH}$ ), 5.88 (d, 1H,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH=CHCO}_2\text{CH}_3$ ), 6.94 (dt, 1H,  $J_1 = 7.2$  and  $J_2 = 14.4$  Hz,  $\text{CH}_2\text{CH=CH}$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.3, -4.4, 13.8, 18.2, 19.7, 26.0, 28.2, 34.5, 35.3, 51.3, 61.6 81.3, 122.9, 146.3, 158.6, 166.8 ppm; HRMS (FAB+) exact mass calculated for  $(\text{C}_{20}\text{H}_{39}\text{NO}_5\text{Si})$  requires  $[\text{M}-\text{H}] m/z$  400.2519, found  $m/z$  400.2514.  $[\alpha]_D^{25} = -8.3^\circ$  ( $c = 0.765$ ,  $\text{CHCl}_3$ ). The enantiomeric excess was determined by HPLC using a Regis Technology (*R,R*)-Whelk-O 2 column (0.5% *i*PrOH/hexanes, 0.75 mL/min, 215 nm); Major enantiomer  $t_r = 21.0$  min and minor  $t_r = 22.8$  min.

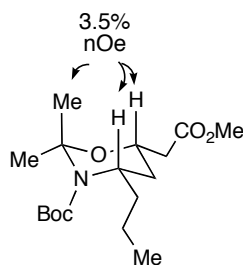


**(3*S*,5*S*)-*tert*-Butyl-5-((methoxycarbonyl)methyl)-3-propylisoxazolidine-2-carboxylate (6):** A 4 dram screw-cap vial charged with **5** (150 mg, 0.37 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added acetic acid (29  $\mu$ L, 0.50 mmol). The mixture was cooled to  $0$   $^\circ\text{C}$  and TBAF (0.5 mL, 0.5 mmol, 1M in THF) was added. The reaction was allowed to stir at this temperature for 48 hours. Upon completion, the reaction mixture was filtered through a plug of silica, eluted with  $\text{Et}_2\text{O}$  and concentrated *in vacuo*. Purification by silica gel

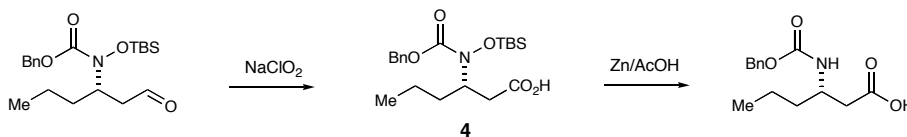
chromatography provided (10 to 20% Et<sub>2</sub>O/pentane gradient) the title compound as clear oil (106 mg, 99% yield, 10:1 *syn/anti*). *Syn-disatereomer*: IR (film) 2959, 2875, 1740, 1707, 1457, 1438, 1393, 1368, 1319, 1171 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 0.83 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 1.12 (m, 2H, CH<sub>2</sub>), 1.30 (m, 2H, CH<sub>2</sub>), 1.38 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.06-2.17 (m, 1H, HCH), 2.18 (dd, 1H, *J*<sub>1</sub> = 6.8 and *J*<sub>2</sub> = 16 Hz, HCHCO<sub>2</sub>CH<sub>3</sub>), 2.51 (dd, 1H, *J*<sub>1</sub> = 5.9 and *J*<sub>2</sub> = 15.8 Hz, HCHCO<sub>2</sub>CH<sub>3</sub>), 3.21 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.15 (m, 2H, NCH and OCH) ppm; <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ 13.9, 20.0, 28.2, 37.6, 38.8, 40.6, 51.2, 60.4, 77.2, 80.8, 158.8, 169.0 ppm ; HRMS (EI) exact mass calculated for (C<sub>14</sub>H<sub>25</sub>NO<sub>5</sub>) requires *m/z* [M+] 287.1733, found *m/z* 287.1725. [α]<sub>D</sub><sup>25</sup> = +39.3° (c = 0.23, CHCl<sub>3</sub>).



**(2*S*,4*S*)-tert-Butyl-1-(methoxycarbonyl)-2-hydroxyheptan-4-ylcarbamate (7):** An oven-dried 10 mL round-bottom flask charged with **6** (58 mg, 0.20 mmol) in degassed MeOH (1 mL) was added SmI<sub>2</sub> (6 mL, 0.1 M in THF) under an argon atmosphere. The deep-blue solution was allowed to stir at ambient temperature until the reaction turned pale-yellow (1 hour) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively with aqueous 1M NaHSO<sub>4</sub>, H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. Purification by silica gel chromatography provided (10 to 30% EtOAc/hexanes gradient) the title compound as clear oil (58 mg, 99% yield). IR (film) 3363, 2959, 2875, 1689, 1525, 1439, 1252, 1172 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 0.75 (t, 3H, *J* = 6.3 Hz, CH<sub>3</sub>), 0.99-1.13 (m, 4H, CH<sub>2</sub>), 1.32 (m, 2H, CH<sub>2</sub>), 1.38 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.25-2.35 (m, 1H, HCHCO<sub>2</sub>CH<sub>3</sub>), 2.40-2.45 (m, 1H, HCHCO<sub>2</sub>CH<sub>3</sub>), 3.23 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.40 (br s, 1H, OH), 3.69 (br s, 1H, NH), 4.00-4.14 (br s, 2H, NCH and OCH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.7, 18.9, 28.1, 37.8, 41.1, 42.5, 47.9, 50.7, 66.1, 78.3, 155.7, 172.6 ppm ; HRMS (EI) exact mass calculated for (C<sub>14</sub>H<sub>27</sub>NO<sub>5</sub>) requires *m/z* [M+H] 290.1967, found *m/z* 290.1977. [α]<sub>D</sub><sup>25</sup> = +3.81° (c = 1.38, CHCl<sub>3</sub>).



**(4*S*,6*S*)-tert-Butyl 6-((methoxycarbonyl)methyl)-2,2-dimethyl-4-propyl-1,3-oxazinane-3-carboxylate:** A half-dram vial charged with **7** (10 mg, 0.034 mmol) in DMF (100  $\mu$ L) was added a crystal of *p*TSA followed by dropwise addition of methoxypropene (14.3  $\mu$ L, 0.15mmol). The reaction was stirred at ambient temperature for 1 hour. Upon completion, the reaction was diluted with Et<sub>2</sub>O (10 mL) and sequentially washed with H<sub>2</sub>O (3 X 5 mL), brine, then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (5% EtOAc/hexanes) provided the title compound as clear oil (9.3 mg, 85% yield). IR (film) 2959, 1734, 1700, 1689, 1560, 1367 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  0.85 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>), 1.16-1.21 (m, 1H, HCH), 1.27-1.45 (m, 3H, HCHCH<sub>2</sub>), 1.38 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 1.71 (s, 3H, CH<sub>3</sub>), 1.79 (s, 3H, CH<sub>3</sub>), 1.80-1.90 (m, 2H, CH<sub>2</sub>), 2.10 (dd, 1H, *J*<sub>1</sub> = 5.4 and *J*<sub>2</sub> = 15.8 Hz, HCHCO<sub>2</sub>CH<sub>3</sub>), 2.47 (dd, 1H, *J*<sub>1</sub> = 8.4 and *J*<sub>2</sub> = 15.8 Hz, HCHCO<sub>2</sub>CH<sub>3</sub>), 3.27 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.27 (m, 2H, NCH and OCH) ppm; <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  13.9, 20.0, 24.9, 28.1, 28.6, 32.3, 40.2, 42.2, 49.6, 50.7, 63.0, 78.7, 88.1, 153.5, 170.3 ppm; HRMS (EI) exact mass calculated for (C<sub>17</sub>H<sub>31</sub>NO<sub>5</sub>) requires *m/z* [M+H] 330.2280, found *m/z* 330.2289.  $[\alpha]_D^{25} = -29.2^\circ$  (*c* = 0.40, CHCl<sub>3</sub>). The relative *syn*-configuration of the H–CN and H–CO protons was determined by irradiation of the 4.27 ppm peak which resulted in a nOe (3.5%) on the 1.71 ppm singlet.



**Determination of Absolute Configuration by Chemical Correlation:** *N*-tert-butyl dimethylsilyloxy[benzyl-(*S*)-1-formylpentan-2-ylcarbamate] (Table 2, entry 2) was derivatized to the  $\beta$ -amino acid by Pinnick oxidation according to procedure described for compound **4**. Removal of the silyl-protecting group and reduction of N–O bond was

accomplished in a single step with acetic acid and Zn dust to afford benzyl (*S*)-3-carbamate-hexanoic acid. All spectroscopic data matched literature reported values.<sup>2</sup> The observed optical rotation ( $[\alpha]_D^{25} = -11.45^\circ$  ( $c = 0.50$ , MeOH)) was consistent with the (*S*)-configuration for benzyl (*S*)-3-carbamate-hexanoic acid, based on the previously reported (*R*)-configuration<sup>3</sup> having the opposite sign of rotation ( $[\alpha]_D^{25} = +12.9^\circ$  ( $c = 0.55$ , MeOH)).

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