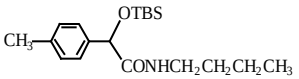
Supporting Informations
A New One-pot Method for the Synthesis of α–Siloxyamides from Aldehydes or Ketones and its Application to the Synthesis of (-)-Bestatin
Hisao Nemoto*, Rujian Ma, Ichiro Suzuki, and Masayuki Shibuya

Experimental Section

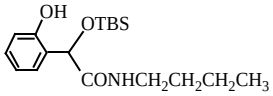
The spectra were measured with the following equipments and conditions unless otherwise noted. IR spectra were measured with PERKIN-ELMER 1720 Infrared Fourier Transfer Spectrometer indicating with cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were measured with JEOL JMN-AL300 Spectrometer at 300MHz and 75MHz, respectively, in chloroform-*d* and indicated as δ value. High Resolution Mass Spectra (HRMS) were measured with JEOL JMS-DX303. All aldehydes and ketones were distilled or recrystallized before use. Acetonitrile was distilled over calcium hydride. Anhydrous tetrahydrofuran (THF) and anhydrous ether were purchased from Kanto Chemicals. All the reactions were carried out under nitrogen atmosphere unless otherwise noted.

A representative procedure for the synthesis of α–silyloxyamides:

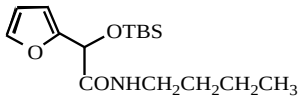
To a solution of *p*-tolaldehyde (120 mg, 1.0 mmol) and **7** (236 mg, 1.2 mmol) in acetonitrile (3 ml) was added *n*-butylamine (80 mg, 1.1 mmol) at 0˚C. After stirring for 5 min, the reaction mixture was concentrated *in vacuo*. The residue was purified with silica gel column chromatography by using hexane-ethyl acetate (10/1) as an eluent to give *N*-butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide: as a colorless oil (322 mg, 0.96 mmol, 96% yield).

***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide:** 

Colorless oil, FT-IR (in $CHCl_3$): 3422, 2958, 2932, 1670, 1526, 1090, 870, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.31 (d, *J*=8.1Hz, 2H), 7.12 (d, *J*=8.1Hz, 2H), 6.79 (br, -N*H*, 1H), 5.03 (s, 1H), 3.39-3.26 (m, 1H). 3.21-3.09 (m, 1H), 2.32 (s, 3H), 1.54-1.42 (m, 2H), 1.41-1.28 (m, 2H), 0.93 (s, 9H), 0.92 (t, *J*=7.5Hz, 3H), 0.08 (s, 3H), -0.04 (s, 3H). ^{13}C-NMR (100MHz): 172.0, 137.5, 137.0, 128.9, 126.0, 75.6, 38.5, 31.6, 25.7, 21.1, 20.0, 18.1, 13.6, -4.8, -5.4; EI-HRMS Calcd for $C_{19}H_{33}NO_2Si$ (M^+): 335.2280, Found 335.2267.

***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(2-hydroxyphenyl)acetamide**: 

Colorless crystals, mp 72-74˚C, FT-IR (in $CHCl_3$): 3415, 3180 (br), 2958, 2932, 1651, 1540, 1484, 1265, 1122, 871, 840 cm^{-1}; ^{1}H-NMR (300MHz): 9.91 (s, Ar-O*H*, 1H), 7.34 (brd, *J*=7.6Hz, 1H), 7.19 (brt, *J*=7.6Hz, 1H), 6.98 (brd, *J*=7.6Hz, 1H), 6.90 (brt, *J*=7.6Hz, 1H), 6.88 (br, -N*H*, 1H), 5.41 (s, 1H), 3.46-3.21 (m, 1H), 3.20-3.05 (m, 1H), 1.57-1.43 (m, 2H), 1.43-1.26 (m, 2H), 0.99 (s, 9H), 0.92 (t, *J*=7.2Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C-NMR (75MHz): 174.5, 154.5, 129.0, 126.2, 124.6, 119.9, 118.3, 70.8, 38.8, 31.3, 25.7, 19.8, 18.2, 13.5, -5.0, -5.7; Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15. Found C, 63.82; H, 9.21; N, 4.06.

***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(2-furyl)acetamide**: 

Colorless oil, FT-IR (in $CHCl_3$): 3421, 2958, 2932, 1676, 1530, 1088, 841 cm^{-1}; ^{1}H-NMR (300MHz): 7.36 (s, 1H), 6.92 (br, -N*H*, 1H), 6.32 (brs, 2H), 5.21 (brs, 1H), 3.47-3.21 (m, 2H), 1.61-1.47 (m, 2H), 1.47-1.31 (m, 2H), 0.94 (t, *J*=7.2Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR (75MHz): 169.6, 152.1, 142.5, 110.4, 108.6, 69.7, 38.8, 31.6, 25.7, 20.0, 18.1, 13.7, -5.1, -5.5; EI-HRMS Calcd for $C_{12}H_{20}NO_3Si$ ($M-{}^{t}Bu)^+$: 254.1212, Found 254.1214.

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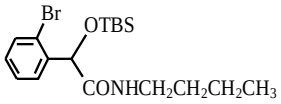
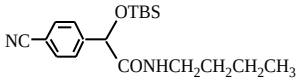
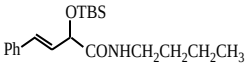
_N_-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(2-bromophenyl)acetamide: 

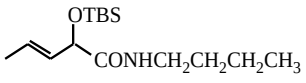
Colorless crystals, mp 38-39˚C, FT-IR (in $CHCl_3$): 3423, 2957, 2932, 1673, 1525, 1092, 870, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.54 (d, *J*=7.9Hz, 1H), 7.19 (brd, *J*=7.9Hz, 1H), 7.28 (t, *J*=7.9Hz, 1H), 7.13 (brt, *J*=7.9Hz, 1H), 6.92 (br, -N*H*, 1H), 5.57 (s, 1H), 3.39-3.16 (m, 2H), 1.59-1.45 (m, 2H), 1.45-1.28 (m, 2H), 0.93 (t, *J*=7.3Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), -0.11 (s, 3H). ^{13}C-NMR (75MHz): 170.8, 139.8, 132.8, 129.4, 128.3, 127.4, 123.4, 74.2, 38.5, 31.5, 25.6, 19.9, 17.9, 13.6, -4.9, -5.4; Anal. Calcd for $C_{18}H_{30}BrNO_2Si$: C, 53.99; H, 7.55; N, 3.50. Found : C, 53.86; H, 7.60; N, 3.48.

_N_-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-cyanophenyl)acetamide: 

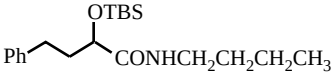
Colorless oil, FT-IR (in $CHCl_3$): 3423, 2957, 2933, 2232, 1673, 1525, 1094, 866, 841 cm^{-1}; ^{1}H-NMR (300MHz): 7.63 (d, *J*=8.8Hz, 2H), 7.59 (d, *J*=8.8Hz, 2H), 6.75 (br, -N*H*, 1H), 5.11 (s, 1H), 3.41-3.23 (m, 1H), 3.23-3.05 (m, 1H), 1.54-1.41 (m, 2H), 1.41-1.24 (m, 2H), 0.95 (s, 9H), 0.91 (t, *J*=7.2Hz, 3H), 0.10 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR (75MHz): 170.5, 145.0, 131.9, 126.6, 118.6, 111.6, 74.8, 38.6, 31.4, 25.5, 19.8, 18.0, 13.5, -5.0, -5.5; EI-HRMS Calcd for $C_{19}H_{31}N_2O_2Si$ $(M+H)^+$: 347.2155, Found 347.2164.

(3E)-_N_-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-but-3-enamide: 

Colorless oil, FT-IR (in $CHCl_3$): 3422, 2958, 2932, 1670, 1526, 1258, 1128, 839 cm^{-1}; ^{1}H-NMR (300MHz): 7.45-7.18 (m, 5H), 6.70 (d, *J*=15.6Hz, 1H), 6.65 (br, -N*H*, 1H), 6.31 (dd, *J*=15.6 and 4.8Hz, 1H), 4.76 (d, *J*=4.8Hz, 1H), 3.45-3.28 (m, 1H), 3.28-3.09 (m, 1H), 1.59-1.43 (m, 2H), 1.43-1.27 (m, 2H), 0.98 (s, 9H), 0.93 (t, J=7.2Hz, 3H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C-NMR (75MHz): 171.5, 136.4, 130.5, 128.5, 127.8, 127.7, 126.6, 74.4, 38.6, 31.6, 25.8, 20.0, 18.2, 13.7, -4.7, -5.4; EI-HRMS Calcd for $C_{20}H_{33}NO_2Si$ (M^+): 347.2281, Found 347.2250.

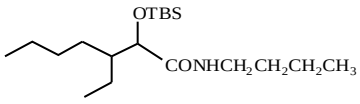
(3E)-_N_-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-pent-3-enamide: 

Colorless oil, FT-IR (in $CHCl_3$): 3421, 2958, 2932, 1665, 1526, 1259, 840cm^{-1}; ^{1}H-NMR (300MHz): 6.64 (br, -N*H*, 1H), 5.78 (dqd, J=15.6, 6.3, 1.3Hz, 1H), 5.53 (ddd, J=15.6, 6.0 and 1.5Hz, 1H), 4.50 (brd, J=6.0Hz, 1H), 3.41-3.25 (m, 1H), 3.25-3.10 (m, 1H), 1.71 (brd, J=6.3Hz, 3H), 1.57-1.43 (m, 2H), 1.43-1.24 (m, 2H), 0.927 (s, 9H), 0.926 (t, *J*=7.2Hz, 3H), 0.09 (s, 6H). ^{13}C-NMR (75MHz): 172.1, 129.3, 127.7, 74.5, 38.5, 31.5, 25.6, 19.9, 18.0, 17.5, 13.6, -4.7, -5.4; EI-HRMS Calcd for $C_{15}H_{31}NO_2Si$ (M^+): 285.2124, Found 285.2105.

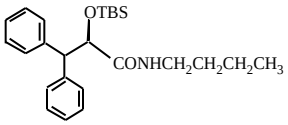
_N_-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanamide: 

Colorless oil, FT-IR (in $CHCl_3$): 3424, 2958, 2931, 1665, 1530, 1104, 839 cm^{-1}; ^{1}H-NMR (300MHz): 7.34-7.21 (m, 2H), 7.24-7.13 (m, 3H), 6.64 (br, -N*H*, 1H), 4.22 (t, *J*=4.8Hz, 1H), 3.40-3.15 (m, 2H), 2.76-2.52 (m, 2H), 2.20-1.89 (m, 2H), 1.56-1.43 (m, 2H), 1.43-1.27 (m, 2H), 0.96 (s, 9H), 0.94 (t, *J*=7.5Hz, 3H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR (75MHz): 173.2, 141.7, 128.41, 128.36, 125.8, 73.1, 38.5, 37.1, 31.7, 30.5,

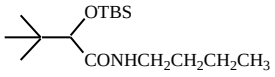
25.7, 20.1, 18.0, 13.7, -4.8, -5.3; EI-HRMS Calcd for $C_{16}H_{26}NO_2Si$ $(M\text{-}^tBu)^+$: 292.1733, Found 292.1745.



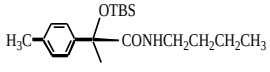
***N*-*n*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-ethylheptanamide**:
Colorless oil, FT-IR (in $CHCl_3$): 3428, 2960, 2932, 1661, 1526, 1465, 1256, 1079, 839 cm^{-1}; ^{1}H-NMR (300MHz): 6.53 (br, -N*H*, 1H), 4.13 (d, *J*=2.4Hz 1H), 3.37-3.19 (m, 2H), 1.71-1.53 (m, 2H), 1.53-1.16 (m, 10H), 0.94 (s, 9H), 1.07-0.80 (m, 6H), 0.90 (t, J=7.5Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR (75MHz): 173.4 and 173.4, 75.1 and 75.0, 44.8 and 44.5, 38.4 and 38.4, 31.6 and 31.6, 29.75 and 29.73, 29.4 and 28.5, 25.7 and 25.7, 23.05 and 23.01, 22.8 and 21.8, 20.0 and 20.0, 17.9 and 17.9, 13.97 and 13.92, 13.6 and 13.6, 12.2 and 12.0, -4.95 and -4.97, -5.2 and -5.2; EI-HRMS Calcd for $C_{15}H_{32}NO_2Si$ $(M\text{-}^tBu)^+$: 286.2202, Found 286.2205.



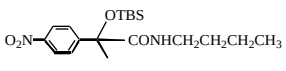
***N*-*n*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,3-diphenylpropanamide**:
Colorless crystals, mp 73-74˚C, FT-IR (KBr): 3280, 2960, 2940, 1654, 1570, 1110, 850 cm^{-1}; ^{1}H-NMR (300MHz): 7.52 (d, *J*=7.5Hz, 2H), 7.35 (d, *J*=7.5Hz, 2H), 7.32-7.14 (m, 6H), 6.19 (br, -N*H*, 1H), 4.64 (d, *J*=3.9Hz, 1H), 4.54(d, *J*=3.9Hz, 1H), 3.12-2.98(m, 1H), 2.98-2.84(m, 1H), 1.16-0.96(m, 4H), 0.88(s, 9H), 0.77(t, *J*=6.4Hz, 3H), -0.14(s, 3H), -0.45(s, 3H). ^{13}C-NMR(75Mz): 171.2, 141.3, 138.8, 130.4, 129.0, 128.2, 128.0, 126.9, 126.5, 78.8, 54.9, 38.4, 31.3, 25.8, 19.8, 18.0, 13.6, -5.6, -6.0; Anal. Calcd for $C_{25}H_{37}NO_2Si$: C, 72.94; H, 9.06; N, 3.40. Found : C, 72.78; H, 9.06; N, 3.43.



***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,3-dimethylbutanamide**:
Colorless crystals, mp 41-42˚C, FT-IR (in $CHCl_3$): 3431, 2959, 2932, 1661, 1525, 1087, 868, 840 cm^{-1}; ^{1}H-NMR (300MHz): 6.30 (br, -N*H*, 1H), 3.72 (s, 1H), 3.25 (dt, *J*=6.6, 6.6Hz, 2H), 1.56-1.28 (m, 4H), 0.95 (s, 18H), 0.93 (t, *J*=7.5Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H). ^{13}C-NMR (75MHz): 172.2, 81.2, 38.4, 35.2, 31.8, 26.2, 25.8, 20.2, 18.0, 13.7, -5.16, -5.18; Anal. Calcd for $C_{16}H_{35}NO_2Si$: C, 63.73; H, 11.70; N, 4.64. Found: C, 63.38; H, 11.57; N, 4.74.

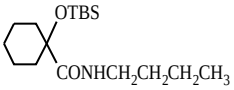


***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)propanamide**:
Colorless oil, FT-IR (in $CHCl_3$): 3425, 2958, 2932, 1666, 1520, 1261, 1139, 985, 839 cm^{-1}; ^{1}H-NMR (300MHz): 7.34 (d, *J*=7.8Hz, 2H), 7.11 (d, *J*=7.8Hz, 2H), 6.98 (br, -N*H*, 1H), 3.30-3.12 (m, 2H). 2.31 (s, 3H), 1.84 (s, 3H), 1.56-1.42 (m, 2H), 1.42-1.23 (m, 2H), 0.97 (s, 9H), 0.91 (t, *J*=7.5Hz, 3H), 0.08 (s, 3H), -0.16 (s, 3H). ^{13}C-NMR (75MHz): 174.9, 141.0, 137.2, 128.8, 125.5, 79.4, 39.0, 31.6, 26.0, 25.9, 21.0, 20.0, 18.3, 13.7, -2.4, -3.0; EI-HRMS Calcd for $C_{16}H_{26}NO_2Si$ $(M\text{-}^tBu)^+$: 292.1733, Found 292.1706.

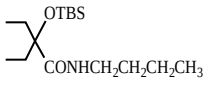


***N*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-nitrophenyl)propanamide**:
Colorless crystals, mp 49-50˚C, FT-IR (in $CHCl_3$): 3429, 2958, 2933, 1673, 1524, 1263, 1145, 985, 862, 838 cm^{-1}; ^{1}H-NMR (300MHz): 8.18 (d, *J*=9.0Hz, 2H), 7.68 (d, *J*=9.0Hz, 2H), 6.91 (br, -N*H*, 1H), 3.32-3.12 (m,

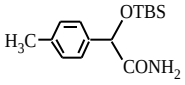
2H), 1.90 (s, 3H), 1.55-1.41 (m, 2H), 1.41-1.25 (m, 2H), 1.01 (s, 9H), 0.91 (t, *J*=7.5Hz, 3H), 0.16 (s, 3H), -0.07 (s, 3H). ^{13}C-NMR (75MHz): 173.4, 151.5, 147.3, 126.5, 123.3, 79.3, 39.1, 31.5, 26.3, 26.0. 20.0, 18.3, 13.7, -2.3, -2.7; Anal. Calcd for $C_{19}H_{32}N_2O_4Si$: C, 59.97; H, 8.48; N, 7.36. Found : C, 59.83; H, 8.51; N, 7.35.

***N*-Butyl-[(*tert*-butyldimethylsilyloxy)cyclohexyl]carboxamide**: 

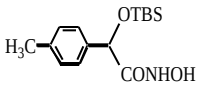
Colorless crystals, mp 47-48˚C, FT-IR (in $CHCl_3$): 3441, 2933, 1662, 1520, 1261, 838cm^{-1}; ^{1}H-NMR (300MHz): 6.37 (br, -N*H*, 1H), 3.21 (dt, *J*=6.2, 6.2Hz, 2H), 2.00-1.83 (m, 2H), 1.78-1.25 (m, 12H), 0.93 (s, 9H), 0.92 (t, *J*=7.5Hz, 3H), 0.13 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR (75MHz): 176.4, 77.9, 38.8, 36.5, 31.6, 25.9, 25.3, 22.2, 20.1, 18.4, 13.7, -2.4; Anal. Calcd for $C_{17}H_{35}NO_2Si$: C, 65.12; H, 11.25; N, 4.47. Found : C, 64.81; H, 11.26; N, 4.50.

***N*-Butyl-2-ethyl-2-[(*tert*-butyldimethylsilyl)oxy]-butanamide**: 

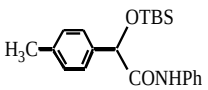
Colorless oil, FT-IR (in $CHCl_3$): 3424, 2957, 2932, 1657, 1525, 1260, 1162, 1020, 838 cm^{-1}; ^{1}H-NMR (300MHz): 6.94 (br, 1H), 3.26 (dt, *J*=6.4, 6.4Hz, 2H), 2.00 (dq, *J*=14.8 and 7.4Hz, 2H), 1.58-1.28 (m, 6H), 1.01 (s, 9H), 0.95 (t, *J*=7.5Hz, 3H), 0.85 (t, *J*=7.4Hz, 6H), 0.21 (s, 6H). ^{13}C-NMR (75MHz): 174.2, 84.1, 38.6, 32.8, 31.7, 26.2, 20.0, 18.6, 13.7, 8.3, -2.4; EI-HRMS Calcd for $C_{12}H_{26}NO_2Si$ (M-^{t}Bu)$^+$: 244.1733. Found 244.1770.

2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide: 

Colorless crystals, mp 108-110˚C, FT-IR (in $CHCl_3$): 3523, 3405, 1691, 1561, 1092, 868, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.33 (d, *J*=7.8Hz, 2H), 7.14 (d, *J*=7.8Hz, 2H), 6.73 (br, -N*H*, 1H), 5.62 (br, -N*H*, 1H), 5.03 (s, 1H), 2.33 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), -0.05 (s, 3H). ^{13}C-NMR (75MHz): 176.0, 137.8, 136.7, 129.0, 126.3, 75.6, 25.7, 21.2, 18.1, -4.8, -5.3; Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found : C, 64.36; H, 8.99; N, 4.99.

***N*-Hydroxy-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide**: 

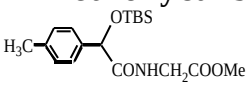
Colorless crystals, mp 109-111˚C (unstable at room temperature), FT-IR (in $CHCl_3$): 3428, 3170 (br), 2956, 2931, 1677, 1257, 1094, 861, 841cm^{-1}; ^{1}H-NMR (300MHz): 9.07 (s, -O*H*, 1H), 7.90 (br, -N*H*, 1H), 7.27 (d, *J*=7.8Hz, 2H), 7.13 (d, *J*=7.8Hz, 2H), 5.12 (s, 1H), 2.33 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H). ^{13}C-NMR (75MHz): 169.9, 138.2, 135.9, 129.1, 126.6, 75.2, 25.7, 21.2, 18.0, -4.9, -5.3; EI-HRMS Calcd for $C_{11}H_{16}NO_3Si$ (M-^{t}Bu)$^+$: 238.0899, Found 238.0917.

***N*-Phenyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide**: 

Colorless oil, FT-IR (in $CHCl_3$): 3386, 3023, 2955, 2931, 1689, 1602, 1526, 1445, 1091, 881, 842 cm^{-1}; ^{1}H-NMR (300MHz): 8.68 (s, -N*H*, 1H), 7.54 (d, *J*=7.9Hz, 2H), 7.37 (d, *J*=7.9Hz, 2H), 7.32 (t, *J*=7.9Hz, 2H), 7.15 (d, *J*=7.9Hz, 2H), 7.09 (t, *J*=7.9Hz, 1H), 5.14 (s, 1H), 2.33 (s, 3H), 0.99 (s, 9H), 0.14 (s, 3H), 0.00 (s,

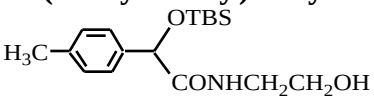
3H). ^{13}C-NMR (75MHz): 170.1, 137.9, 137.4, 136.4, 129.1, 129.0, 126.2, 124.3, 119.3, 75.9, 25.8, 21.1, 18.1, -4.7, -5.3; EI-HRMS Calcd for $C_{17}H_{20}NO_2Si$ (M-^{t}Bu)$^+$: 298.1263, Found 298.1283.

***N*-Methoxycarbonylmethyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide:**



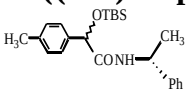
Colorless oil, FT-IR (in $CHCl_3$): 3418, 2956, 2931, 1747, 1678, 1511, 1256, 1235, 1093, 866, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.36 (br, -N*H*, 1H), 7.33 (d, *J*=7.8Hz, 2H), 7.13 (d, *J*=7.8Hz, 2H), 5.08 (s, 1H), 4.16 (dd, *J*=18.9 and 5.7Hz, 1H), 3.93 (dd, *J*=18.9 and 5.7Hz, 1H), 3.76 (s, 3H), 2.32 (s, 3H), 0.95 (s, 9H), 0.11 (s, 3H), -0.04 (s, 3H). ^{13}C-NMR (75MHz): 172.5, 170.1, 137.8, 136.6, 129.0, 126.2, 75.5, 52.3, 40.8, 25.7, 21.2, 18.1, -4.8, -5.3; EI-HRMS Calcd for $C_{18}H_{29}NO_4Si$ (M^+): 351.1866, Found 351.1874.

***N*-(2-Hydroxy)ethyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide**:



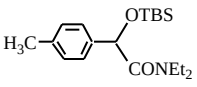
Colorless crystals, mp 69-70˚C, FT-IR (in $CHCl_3$): 3422, 3270 (br), 2931, 1669, 1536, 1256, 1093, 867, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.32 (d, *J*=7.8Hz, 2H), 7.13 (d, *J*=7.8Hz, 2H), 5.06 (s, 1H), 4.72 (s, 1H), 3.71 (dt, *J*=5.0 and 5.0Hz, 2H), 3.55-3.31 (m, 2H), 2.46 (t, J=5.4Hz, -O*H*, 1H), 2.33 (s, 3H), 0.93 (s, 9H), 0.09 (s, 3H), -0.04 (s, 3H). ^{13}C-NMR (75MHz): 173.6, 137.8, 136.8, 129.1, 126.2, 75.7, 62.1, 41.9, 25.8, 21.2, 18.2, -4.7, -5.3; Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found : C, 62.88; H, 8.97; N, 4.33.

***N*-((*1R*)-1-phenylethyl)-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide:**



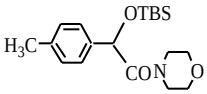
Colorless oil, FT-IR (in $CHCl_3$): 3413, 2955, 2931, 1669, 1510, 1089, 865, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.40-7.01 (m, 9H), 5.15-5.00 (m, 1H), 5.07 and 5.01(s, 1H), 2.33 and 2.31 (s, 3H), 1.52 and 1.44 (d, *J*=6.8Hz, 3H), 0.94 and 0.85 (s, 9H), 0.11, -0.01, -0.03 and -0.08 (s, 6H). ^{13}C-NMR (75MHz): 171.3 and 171.2, 143.1 and 143.0, 137.6 and 137.6, 136.8 and 136.7, 128.99 and 128.96, 128.62 and 128.59, 127.36 and 127.19, 126.10 and 126.07, 126.04 and 125.84, 75.6 and 75.5, 48.3 and 48.0, 25.7 and 25.6, 22.1 and 21.7, 21.15 and 21.12, 18.1 and 18.0, -4.76 and -4.84, -5.37 and -5.46; EI-HRMS Calcd for $C_{19}H_{24}NO_2Si$ (M-^{t}Bu)$^+$: 326.1576, Found 326.1579.

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide**:



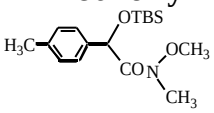
Colorless oil, FT-IR (in $CHCl_3$): 2958, 2932, 1631, 1464, 1256, 1098, 869, 840 cm^{-1}; ^{1}H-NMR (300MHz): 7.31 (d, *J*=8.1Hz, 2H), 7.14 (d, *J*=8.1Hz, 2H), 5.49 (s, 1H), 3.54-3.37 (m, 2H), 3.24-3.05 (m, 2H), 2.33 (s, 3H), 1.08 (t, *J*=6.9Hz, 3H), 0.97 (s, 9H), 0.68 (t, *J*=6.9Hz, 3H), 0.13 (s, 6H). ^{13}C-NMR (75MHz): 171.0, 136.9, 136.7, 129.0, 124.8, 77.7, 40.3, 39.8, 25.9, 21.1, 18.4, 13.2, 12.4, -4.8, -5.2; EI-HRMS Calcd for $C_{15}H_{24}NO_2Si$ (M- ^{t}Bu)$^+$: 278.1576, Found 278.1566.

2-[(*tert*-Butyldimethylsilyl)oxy]-2-(4-methylphenyl)-1-morpholin-4-ylethan-1-one:



Colorless crystals, mp 64-65˚C, FT-IR (in $CHCl_3$): 2958, 2930, 1636, 1463, 1252, 1113, 866, 841cm^{-1}; ^{1}H-NMR (300MHz): 7.31 (d, *J*=8.0Hz, 2H), 7.15 (d, *J*=8.0Hz, 2H), 5.52 (s, 1H), 3.73-3.28 (m, 7H), 3.17-2.97 (m, 1H), 2.34 (s,3H), 0.98 (s, 9H), 0.150 (s, 3H), 0.145 (s, 3H). ^{13}C-NMR (75MHz): 170.5, 137.1, 136.0, 129.2, 124.4, 77.6, 66.7, 66.4, 45.6, 42.7, 25.8, 21.1, 18.3, -4.9, -5.4; Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found : C, 65.03; H, 8.82; N, 4.00.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide**:

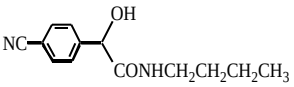


Colorless oil, FT-IR (in $CHCl_3$): 2931, 1670, 1255, 1086, 999, 867, 840cm^{-1}; ^{1}H-NMR (300MHz): 7.32 (d, *J*=8.0Hz, 2H), 7.13 (d, *J*=8.0Hz, 2H), 5.55 (s, 1H), 3.51 (s, 3H), 3.13 (s, 3H), 2.33 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR (75MHz at 55˚C): 172.7, 137.5, 136.7, 129.0, 126.8, 73.6, 60.7, 33.3, 25.9, 21.1, 18.4, -4.8, -5.0. Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found : C, 62.75; H, 8.92; N, 4.28.

A Representative procedure for one-pot synthesis of α–hydroxyamides:

To a solution of *p-tolaldehyde* (131 mg, 1.0 mmol) and **1** (216 mg, 1.2 mmol) in acetonitrile (3 ml) was added *n*-butylamine (80 mg, 1.1 mmol) at 0˚C. After stirring for 5 min, the reaction mixtures was added dropwise THF solution of tetrabutylammonium fluoride (1.0 N, 1.5 ml, 1.5 mmol), and then stirred at 0˚C for 20 min. The resulting reaction solution was concentrated and purified with silica gel column chromatography by using hexane-ethyl acetate (3/1) as an eluent to give *N*-butyl-2-hydroxy-2-(4-methylphenyl)acetamide as a colorless powder (218 mg, 0.94 mmol, 94%).

***N*-Butyl-2-hydroxy-2-(4-methylphenyl)acetamide:**



mp 55-57˚C; FT-IR (in $CHCl_3$): 3426, 3360 (br), 2963, 2232, 1677, 1531cm^{-1}; ^{1}H-NMR (300MHz): 7.62 (d, *J*=8.0Hz, 2H), 7.54 (d, *J*=8.0Hz, 2H), 6.65 (br, 1H), 5.05 (s, 1H), 4.40 (br, -O*H*, 1H), 3.20 (dt, *J*=6.8, 6.8Hz, 2H), 1.52-1.37 (m, 2H), 1.35-1.17 (m, 2H), 0.89 (t, *J*=7.2Hz, 3H). ^{13}C-NMR (75MHz): 171.0, 144.9, 132.3, 127.2, 118.6, 111.9, 73.3, 39.2, 31.4, 19.9, 13.7; Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found : C, 67.14; H, 6.88; N, 11.94.

Benzyl *N*-[(2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)amino-2-*tert*-butyldimethylsiloxy-4-phenylbutanoyl]-*L*-Leucinate (**12**): A mixture of 2-*N*-(bezyloxycabonyl)-D-amino aldehyde (**9**) (28.3 mg, 0.10 mmol), benzyl *L*-Leucinate (**10**) (26.5 mg, 0.12 mmol) and H-MAC-TBS (**7**) (39.2 mg, 0.20 mmol) in diethyl ether (1.5 ml) at 0˚C was added 4-pyrrolidinopyridine (**11**) (14.8 mg, 0.10 mmol) and the mixture was stirred at 0˚C for 5 h. The resultant mixture was concentrated *in vacuo* and purified with short silica gel column chromatography (10:1 hexane/ethyl acetate) to give a mixture of diastereomers **12** and **13** (51.4 mg, 0.080 mmol, 80% yield). The ratio of **12** and **13** was determinated by HPLC (LiChrosorb Si60, 7 mm, 25Å~10 cm, 5:1

AcOEt/hexanes, 2.5 ml/min, R_t=17.7 min for **12**, R_t=24.1 min for **13**). Each diastereomer was separated by preparation TLC (10: 1 benzene/ethyl acetate). When **12** was measured by ^{1}H-NMR at 25˚C in $CDCl_3$, most of the peaks are broaded probably because of the slow rotation of C-N bond of amide. Therefore to clarify the purity of **12** and identification of the peaks, ^{1}H-NMR was measured at 100˚C in DMSO-d_6. **12**: Colorless oil; $[\alpha]^{22}_D$ 34.9˚ (*c* 0.81, MeOH); FT-IR ($CHCl_3$): 3419, 2956, 1724 (br), 1670, 1504, 1260, 1108, 841 cm^{-1}; ^{1}H NMR (300MHz, DMSO, 100˚C): 7.45 (d, J=8.1Hz, 1H, -NH), 7.40-7.03 (m, 15H), 6.49 (br, 1H, -NH), 5.14 (d, *J*=12.6Hz, 1H), 5.17 (d, *J*=12.6Hz, 1H), 4.93 (d, *J*=12.7Hz, 1H), 4.82 (d, *J*=12.7Hz, 1H), 4.54-4.37 (m, 1H), 4.17 (d, J=4.9Hz, 1H), 4.03-3.87 (m, 1H), 2.86 (dd, *J*=13.9, 3.7Hz, 1H), 2.60 (dd, *J*=13.9, 10.5Hz, 1H), 1.73-1.55 (m, 3H), 0.90 (s, 9H), 0.87 (d, *J*=6.3 Hz, 3H), 0.85 (d, *J*=6.3Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75MHz): 172.1, 171.7, 155.7, 137.8, 136.6, 135.2, 129.1, 128.6, 128.5, 128.4, 128.4, 128.4, 127.9, 127.8, 126.4, 73.9, 67.1, 66.4, 55.5, 50.3, 41.6, 36.1, 25.7, 24.9, 22.8, 21.9, 17.9, -4.8, -5.4; EI-HRMS Calcd for $C_{37}H_{50}N_2O_6Si$ (M^+): 646.3432, Found 646.3438. **13**: Colorless crystals, mp 100-101 ˚C; $[\alpha]^{22}_D$ 21.1˚ (*c* 2.00, MeOH); FT-IR ($CHCl_3$): 3416, 3344, 2955, 1721 (br), 1678, 1505, 1260, 1106, 839 cm^{-1}; ^{1}H NMR (300MHz): 7.45-7.09 (m, 15H), 6.87 (d, J=7.9Hz, 1H, -NH), 5.44 (d, *J*=8.8Hz, 1H, -NH), 5.23 (d, *J*=12.3Hz, 1H), 5.14 (d, *J*=12.3Hz, 1H), 5.09 (d, *J*=12.3Hz, 1H), 5.03 (d, *J*=12.3Hz, 1H), 4.67-4.54 (m, 1H), 4.28 (brs, 1H), 4.35-4.17 (m, 1H), 2.97 (dd, *J*=14.1, 8.4Hz, 1H), 2.72 (dd, *J*=14.1, 7.3Hz, 1H), 1.80-1.47 (m, 2H), 1.40-1.16 (m, 1H), 0.97-0.88 (m, 6H), 0.87 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (75MHz): 172.8, 171.3, 156.0, 137.9, 136.8, 135.2, 129.4, 128.6, 128.4, 128.4, 128.4, 128.3, 127.8, 127.7, 126.4, 73.3, 67.4, 66.3, 56.9, 50.5, 40.5, 36.4, 25.6, 25.0, 22.9, 21.4, 17.9, -5.1, -5.6; Anal. Calcd for $C_{37}H_{50}N_2O_6Si$: C, 68.70; H, 7.79; N, 4.33. Found : C, 68.77, ; H, 7.93; N, 4.24.

Benzyl *N*-[(2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)amino-2-hydroxy-4-phenylbutanoyl]-L-Leucinate: To the solution of **12** (41 mg, 0.063 mmol) in THF (1.5 ml) was added tetrabutylammonium fluoride (1.0 M solution in THF) (76 µl, 0.076 mmol) at 0˚C and the mixture was stirred for 20 min at 0˚C. The resultant solution was directly purified with silica gel column chromatography by using hexane-ethyl acetate (3/1) as an eluent to give the desired compound as a white solid (32.4 mg, 0.061 mmol, 96%). mp 128-129˚C ; $[\alpha]^{22}_D$ 13.8˚ (*c* 0.9, MeOH); FT-IR ($CHCl_3$): 3431, 3408, 3313 (br), 1728, 1690, 1517, 1271 cm^{-1}; ^{1}H NMR (300MHz): 7.43-7.06 (m, 16H), 5.45 (d, J=8.1 Hz), 5.15 (brs, 1H, -OH), 5.12 (s, 2H), 5.02 (d, *J*=12.3Hz, 1H), 4.96 (d, *J*=12.3Hz, 1H), 4.71-4.59 (m, 1H), 4.15 (brd, *J*=4.5Hz, 1H), 4.20-4.04 (m, 1H), 3.08-2.84 (m, 2H), 1.70-1.46 (m, 3H), 0.86 (d, *J*=5.7 Hz, 3H), 0.85 (d, *J*=5.7 Hz, 3H). ^{13}C NMR (75MHz): 172.3, 172.6, 157.4, 137.7, 136.1, 135.3, 129.3, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 127.9, 126.6, 73.3, 67.1, 67.0, 55.7, 50.5, 41.1, 36.4, 24.8, 22.9, 21.6; Anal. Calcd for $C_{31}H_{36}N_2O_6$: C, 69.91; H, 6.81; N, 5.26. Found : C, 69.88, ; H, 6.91; N, 5.24.

(-)-Bestatin (14): Catalytic hydrogenation of Cbz-Bn-protected (-)-bestatin (28.2 mg, 0.053 mmol) over 10% Pd/C (5.6 mg) was carrried out at atmospheric presure in methanol for 2 h. The mixture was filtered and concentrated *in vacuo* to give **14** (16.4 mg, 0.053 mmol, 100% yield) as the free zwitterion, {mp 231-233˚C dec. [lit.[1] mp 233-236˚C dec]} which was solved in 1N HCl and evopated *in vacuo* to form the HCl salt of **14**. $[\alpha]^{22}_D$ -14.0˚ (*c* 0.5, 1*N* HCl), [lit.[1] $[\alpha]^{22}_D$ -14.3˚ (*c* 0.5, 1*N* HCl)].

Reference

1) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235-4237.