

Supporting information for
Synthesis of a Gln-Phe Hydroxyethylene Dipeptide Isostere

Bengt Erik Haug and Daniel H. Rich

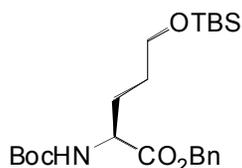
Department of Chemistry and School of Pharmacy, University of Wisconsin-Madison,
Madison, Wisconsin 53706

General

All moisture sensitive reactions were performed in flame dried or oven dried equipment under an atmosphere of argon. Starting materials and reagents were purchased from Aldrich and Bachem and used as delivered. Anhydrous tetrahydrofuran, methylene chloride, diethyl ether, dimethyl formamide and toluene were obtained from the School of Pharmacy anhydrous solvent delivery system. Anhydrous methanol and acetonitrile were purchased from Aldrich in sure seal bottles. Flash column chromatography was performed using Silica gel 60 (230 – 400 mesh) supplied by VWR International and TLC analysis was done using Sigma-Aldrich Silica gel with fluorescent indication on aluminum plates with visualization using ultraviolet light or a solution of 2% ninhydrin in ethanol containing 10 drops of conc. sulfuric acid pr. 100 mL of the solution. ^1H and ^{13}C NMR spectra were taken on a Varian Unity Inova 400 or 500 spectrometer with CDCl_3 as solvent, at ambient temperature unless otherwise noted. Spectra were referenced to TMS or residual undeuterated solvent peak. All coupling constants are given in Hz.

2-*tert*-Butoxycarbonylamino-5-(*tert*-butyl-dimethyl-silyloxy)-pentanoic acid

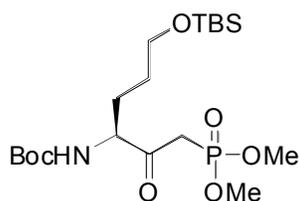
benzyl ester (8)



To a solution of Boc-Glu-OBn (10.05 g, 29.8 mmol) and *N*-hydroxy succinimide (5.12 g, 44.5 mmol) in methylene chloride (500 mL) cooled to -10°C and was added EDCI (8.53 g, 44.5 mmol) in one portion. The mixture was stirred at -10°C for another 30 min and then allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether, and the organic layer was washed three times with a 5%

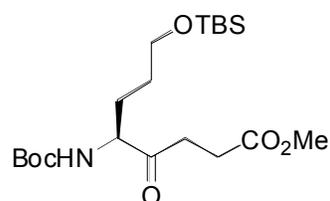
solution of citric acid, twice with a saturated solution of sodium bicarbonate and a saturated solution of sodium chloride before it was evaporated under high vacuum to give a white solid (12.94 g). NaBH₄ (1.693 g, 44.7 mmol) was dissolved in a 0°C stirred mixture of THF/water (4:1, 120 mL) and a 0°C solution of succinimide ester **6** (12.92 g, 29.7 mmol) in THF (200 mL) was added and stirring continued at 0°C for 2 hrs at, which point a solution of saturated ammonium chloride (70 mL) was added. The resulting mixture was extracted three times with ethyl acetate and the combined organics were washed with a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulphate. Filtration of the drying agent, evaporation and drying under high vacuum over phosphorus pentoxide to give a clear oil. To a solution of the crude alcohol **7** in dimethyl formamide (60 mL) was added imidazole (2.55 g, 37.5 mmol) and then *tert*-butyl dimethyl silyl chloride (5.61 g, 37.2 mmol). The mixture was stirred at room temperature over night before it was quenched by pouring into water (250 mL). The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with a 10% solution of citric acid, a saturated solution of sodium chloride and dried over magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum gave the crude product as a yellow oil. Purification by column chromatography (14:86 EtOAc:PE) afforded **8** as a slightly yellow oil (8.48 g, 65%). TLC R_f = 0.34 (14:86 EtOAc:PE); ¹H NMR δ: 7.38-7.30 (5H, m), 5.23-2.0 (2H, m), 5.13 (1H, d, *J* = 12.8), 4.37-4.32 (1H, m), 3.60 (2H, app t, *J* = 6.4, 5.6), 1.95-1.86 (1H, m), 1.77-1.68 (1H, m), 1.60-1.49 (2H, m), 1.44 (9H, s), 0.88 (9H, s), 0.04 (6H, s); ¹³C NMR: 172.9, 155.6, 135.7, 128.7, 128.5, 128.4, 79.9, 67.1, 62.5, 53.6, 29.2, 28.6, 28.5, 26.1, 18.5, -5.2; ESI: Calcd. for C₂₀H₃₉NO₆SiNa [2M + Na]⁺ 897.5093, Found 897.5052.

**[3-*tert*-Butoxycarbonylamino-6-(*tert*-butyl-dimethyl-silyloxy)-2-oxo-hexyl]-
phosphonic acid dimethyl ester (**9**):**



To a stirred solution of methyl dimethylphosphonate (5.30 mL, 48.9 mmol) in THF (180 mL) cooled to -78°C was added a 2.4M solution of *n*-BuLi in hexane (19.8 mL, 475 mmol) in small portions over 20 min and the resulting mixture was stirred at -78°C for 1 hrs at which point a -78°C solution of ester **8** (6.49 g, 14.8 mmol) in THF (55 mL) was added. Stirring was continued at -78°C for 4 hrs before the reaction was quenched by addition of an ice cold saturated solution of ammonium chloride (400 mL). The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with water, a saturated solution of sodium chloride and dried over magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum gave the crude product as a colorless oil. Purification by column chromatography (4:1 EtOAc:PE) afforded **9** as a colorless oil (6.20 g, 92%). Spectroscopic data were found to be in accordance with those previously reported.¹ TLC $R_f = 0.30$ (4:1 EtOAc:PE); $^1\text{H NMR } \delta$: 5.66 (1H, d, $J = 8.0$), 4.27-4.22 (1H, m), 3.74 (3H, d, $J = 11.6$), 3.73 (3H, d, $J = 11.6$), 3.58 (2H, t, $J = 6.0$), 3.27 (1H, dd, $J = 22.0, 14.4$), 3.10 (1H, dd, $J = 22.0, 14.4$), 1.98-1.90 (1H, m), 1.62-1.45 (3H, m), 1.39 (9H, s), 0.84 (9H, s), 0.02 (6H, s).

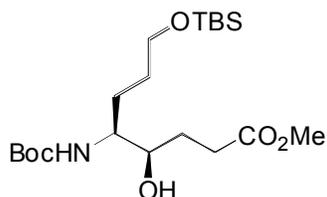
5-*tert*-Butoxycarbonylamino-8-(*tert*-butyl-dimethyl-silyloxy)-4-oxo-octanoic acid methyl ester (5**):**



To a suspension of NaH (0.363 g, 9.08 mmol, 60% emulsion) in 20 mL THF at 0°C was added a 0°C solution of keto phosphonate **9** (1.945 g, 4.24 mmol) in THF (60 mL). The mixture was stirred for 1 h. 25 min at 0°C , then cooled to -78°C and a -78°C solution of freshly prepared dimethyl glyoxalate^{2,3} (13.2 mmol) in THF (22 mL) was added. Stirring was continued at -78°C for 30 min and then at -30°C overnight. The reaction was quenched at -30°C by slow addition of glacial acetic acid (2.75 mL in 5.25 mL of THF) over a period of 1 h. and was then allowed to attain room temperature and evaporated to a small volume. The residue was partitioned between ethyl acetate and water and the water

layer was extracted twice more with ethyl acetate. The combined organic layers were washed with a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate and evaporated to give a clear greenish oil. The oil was dissolved in ethyl acetate (120 mL) and purged with argon before palladium (0.241 g, 10% on activated carbon) was added. The flask was evacuated and filled with hydrogen gas three times and stirred under an atmosphere of hydrogen (balloon) for 4 h. The catalyst was removed by filtration through a 1.5 cm pad of Celite[®]521 and evaporated to give a light yellow oil. Purification by column chromatography (1:4 EtOAc:PE) afforded **5** as a colorless oil (1.44 g, 81%). TLC R_f = 0.24 (1:4 EtOAc:PE); ¹H NMR δ : 5.37 (1H, d, J = 7.2), 4.33-4.22 (1H, m), 3.64 (3H, s), 3.60 (2H, t, J = 6.0), 2.89-2.71 (2H, m), 2.65-2.52 (2H, m), 1.98-1.90 (1H, m), 1.67-1.44 (3H, m), 1.40 (9H, s), 0.86 (9H, s), 0.02 (6H, s); ¹³C NMR δ : 208.1, 173.1, 155.7, 79.8, 62.5, 59.3, 51.9, 34.3, 28.5, 28.3, 27.9, 27.7, 26.1, 18.4, -5.2; ESI: Calcd. for C₂₀H₃₉NO₆SiNa [M + Na]⁺ 440.2444, Found 440.2451.

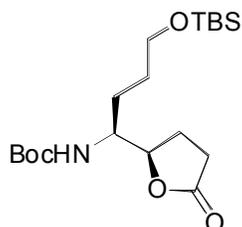
(4*R*, 5*S*)-5-*tert*-Butoxycarbonylamino-8-(*tert*-butyl-dimethyl-silyloxy)-4-hydroxy-octanoic acid methyl ester (10**):**



Absolute ethanol (105 mL) was cooled to -78°C and LiAlH(O-*t*-Bu)₃ (4.414 g, 17.36 mmol) was added in one portion. After stirring the suspension for 45 min a -78°C solution of ketoester **5** (3.613 g, 8.65 mmol) in absolute ethanol (100 mL) was added. Stirring was continued at -78°C for 2 ½ h. The reaction was quenched by addition of a 10% solution of citric acid, the cooling bath was removed and stirring was continued for ½ h.⁴ The resulting mixture was separated between water and ethyl acetate, and the aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were washed with a 10% solution of citric acid, water and a saturated solution of sodium chloride, dried over Anhydrous magnesium sulfate⁴ and evaporated and dried under high vacuum to afford crude **10** as an oil. ¹H NMR: 5.86 (1H, d, J = 7.6), 3.64 (3H, s), 3.62-

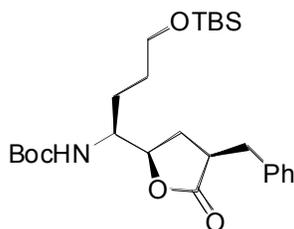
3.56 (4H, m), 3.4 (1H, bs), 2.56-2.39 (3H, m), 1.75-1.53 (5H, m), 1.41 (9H, s), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR: 174.8, 157.1, 79.8, 74.3, 62.8, 55.8, 51.8, 30.9, 29.37, 28.52, 27.9, 26.1, 18.5, -5.2; ESI: Calcd for $\text{C}_{20}\text{H}_{41}\text{NO}_6\text{SiNa}$ 442.2601 $[\text{M} + \text{Na}]^+$, Found 442.2592.

[4-(*tert*-Butyl-dimethyl-silyloxy)-(1*S*)-1-(5-oxo-tetrahydro-furan-(2*R*)-2-yl)-butyl]-carbamic acid *tert*-butyl ester (4):



Alcohol **10** was dissolved in toluene (250 mL), glacial acetic acid (6.1 mL) was added and the mixture heated to reflux for 3 h. After cooling to room temperature the reaction mixture was evaporated under high vacuum to give an oil. Purification by column chromatography (32:68 EtOAc:PE) afforded **4** as a colorless oil (2.909 g, 87%). $R_f = 0.23$ (32:68 EtOAc:PE); ^1H NMR: 4.77 (1H, d, $J = 8.4$), 4.44 (1H, dd, $J = 13.2, 6.8$), 3.73-3.66 (1H, m), 3.63 (1H, t, $J = 6.0$), 2.62-2.46 (2H, m), 2.32-2.23 (1H, m), 2.15-2.04 (1H, m), 1.81-1.72 (1H, m), 1.69-1.53 (2H, m), 1.43 (10H, s and m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR: 177.0, 156.0, 82.5, 79.9, 62.7, 53.4, 28.8, 28.5, 28.4, 26.6, 26.1, 24.6, 18.5, -5.1; ESI: Calcd for $\text{C}_{19}\text{H}_{37}\text{NO}_5\text{Si}$ 410.2339 $[\text{M} + \text{Na}]^+$, Found 410.2338.

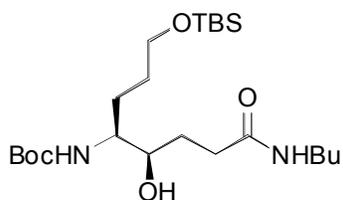
[(1*S*)-1-[(4*R*)-4-Benzyl-5-oxo-tetrahydro-furan-(2*R*)-2-yl]-4-(*tert*-butyl-dimethyl-silyloxy)-butyl]-carbamic acid *tert*-butyl ester (3):



To a stirred solution of LDA, freshly prepared from diisopropyl amine (0.870 mL, 6.21 mmol) in THF (13 mL) and *n*-BuLi (2.68 mL, 6.14 mmol, 2.29 M solution in hexane) at -78°C was added a -78°C solution of **4** (1.080 g, 2.79 mmol) in THF (15 mL). After

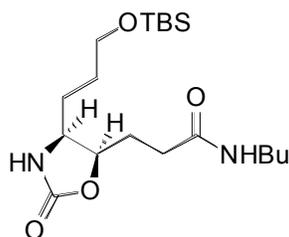
stirring for 1 h., benzaldehyde (0.620 mL, 6.10 mmol) was added and stirring continued at -78°C for 3 $\frac{1}{2}$ h. The reaction was quenched by addition of a saturated solution ammonium chloride and water. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were washed with a 10% solution of citric acid, a saturated solution of sodium bicarbonate and a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation of the solvent and drying under high vacuum gave a colorless oil. The oil was dissolved in acetic anhydride (1.25 mL) and triethyl amine (1.25 mL) and the mixture was heated to reflux for 1 h. 15 min. After cooling to room temperature, ethyl acetate was added and the organic layer washed twice sequentially with a 10% solution of citric acid and a saturated solution of sodium bicarbonate, then with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent and drying under high vacuum gave a yellow oil. The oil was dissolved in ethyl acetate (30 mL) and methanol (7.5 mL), purged with argon and 10% palladium on activated carbon (70 mg) was added. The flask was evacuated and filled with hydrogen gas three times and stirred under an atmosphere of hydrogen (balloon) for 4 h. 15 min. The catalyst was removed by filtration through an Acrodisc[®] 0.2 μm 25 mm filter and the solvent was evaporated to give an oil. Purification by column chromatography (1:4 EtOAc:PE) afforded **3** as a colorless oil (0.790 g, 59%). $R_f = 0.26$ (1:4 EtOAc:PE); $^1\text{H NMR}$: 7.30-7.18 (5H, m), 4.67 (1H, d, $J = 8.0$), 4.30 (1H, bm), 3.64 (1H, bm), 3.59 (2H, app t, $J = 6.0$), 3.27 (1H, dd, $J = 13.8, 4.3$), 2.91-2.85 (1H, m), 2.72 (1H, dd, $J = 13.8, 9.8$), 2.23 (1H, ddd, $J = 13.0, 8.5, 6.0$), 1.83-1.76 (1H, m), 1.67-1.49 (3H, m), 1.41 (9H, s), 1.40-1.34 (1H, m), 0.89 (9H, s), 0.04 (6H, s); $^{13}\text{C NMR}$: 177.9, 155.8, 138.7, 129.0, 128.9, 126.9, 80.7, 79.9, 62.9, 53.4, 42.7, 36.4, 31.3, 28.8, 28.5, 26.4, 26.2, 18.5, -5.1; ESI: Calcd. for $\text{C}_{26}\text{H}_{43}\text{NO}_5\text{SiNa}$ 500.2808 $[\text{M} + \text{Na}]^+$, Found 500.2816.

[4-Butylcarbamoyl-(1*S*)-1-[3-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-(2*R*)-2-hydroxy-butyl]-carbamic acid *tert*-butyl ester (11)



Lactone **4** (0.096 g, 0.246 mmol) was dissolved in butylamine (15 mL, 0.151 mmol), the flask was sealed tight with a stopper and the mixture was heated to 40°C for 4 ½ hrs. The butylamine was evaporated and the residue separated between ethyl acetate and a 10% solution of citric acid. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum afforded **11** as a white solid (0.109 g, 96% crude). The crude product was taken to the next step without further purification. $R_f = 0.24$ (4:1 EtOAc:PE); $^1\text{H NMR}$: 5.74 (1H, bs), 4.84 (1H, , $J = 8.4$), 4.19 (1H, bs), 3.66-3.54 (4H, m), 3.24 (2H, dt, $J = 7.2, 5.6$), 2.39 (2H, t, $J = 6.8$), 1.83-1.53 (5H, m), 1.51-1.45 (2H, m), 1.43 (9H, s), 1.39-1.29 (2H, m), 0.92 (3H, t, $J = 7.2$), 0.89 (9H, s), 0.05 (6H, s); $^{13}\text{C NMR}$: 173.8, 157.0, 79.6, 74.6, 63.0, 55.5, 39.6, 33.6, 31.8, 29.5, 28.65, 28.57, 26.20, 26.16, 20.2, 18.5, 13.9, -5.1; ESI, Calcd. for $\text{C}_{23}\text{H}_{48}\text{N}_2\text{O}_5\text{SiNa}$ 483.3230 $[\text{M} + \text{Na}]^+$, Found 483.3236.

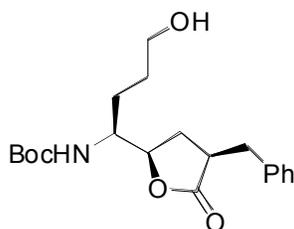
***N*-Butyl-3-[(4*S*)-4-[3-(*tert*-butyl-dimethyl-silyloxy)-propyl]-2-oxo-oxazolidin-(5*R*)-5-yl]-propionamide (**12**)**



To a stirred solution of butylamide **11** (45.5 mg, 0.099 mmol) in DMF (4 mL) was added NaH (12.5 mg, 0.521 mmol, 60% emulsion) and stirring was continued for 2 ½ hrs before a saturated solution of sodium chloride was added to the suspension and the aqueous mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high

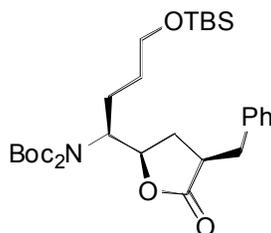
vacuum afforded **12** as a light yellow oil (38.3 mg, calculated crude yield 85%, contains DMF). ^1H NMR: 6.11 (1H, s), 5.78-5.82 (1H, m), 4.59 (1H, ddd, $J = 11.0, 7.7, 2.5$), 3.85-3.80 (1H, m), 3.64 (2H, t, $J = 5.3$), 3.25-3.21 (2H, m), 2.45-2.39 (1H, m), 2.33-2.27 (1H, m), 2.08-2.01 (1H, m), 1.91-1.84 (1H, m), 1.69-1.64 (1H, m), 1.59-1.44 (5H, m), 1.37-1.30 (2H, m), 0.91 (3H, t, $J = 7.3$), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR: 171.8, 159.1, 79.2, 62.9, 55.7, 39.5, 32.5, 31.8, 29.6, 27.5, 26.1, 25.4, 20.2, 18.4, 13.9, -5.2; ESI, Calcd. for $\text{C}_{19}\text{H}_{38}\text{N}_2\text{O}_4\text{SiNa}$ 409.2499 $[\text{M} + \text{Na}]^+$, Found 409.2504.

[(1*S*)-1-[(4*R*)-4-Benzyl-5-oxo-tetrahydro-furan-(2*R*)-2-yl]-4-hydroxy-butyl]-carbamic acid *tert*-butyl ester (13**)**



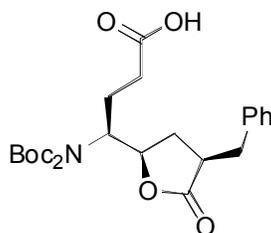
To a solution of TBS silyl ether **3** (0.115 g, 0.241 mmol) in THF (1.0 mL) was added a mixture of acetic acid, water, THF (13:7:3, 2.4 mL) and the resulting mixture was stirred at room temperature for 3 hrs before it was separated between water and ethyl acetate. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed twice with a saturated solution of sodium bicarbonate. The sodium bicarbonate solution was back extracted with ethyl acetate and the combined organic layers were washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtering of the drying agent and evaporation gave the crude product as a colorless oil. Purification by column chromatography (4:1 EtOAc:PE) afforded **13** as a colorless oil (0.067 g, 76%). $R_f = 0.33$ (4:1 EtOAc:PE); ^1H NMR: 7.32-7.18 (5H, m), 4.66 (1H, d, $J = 9.6$), 4.35-4.27 (1H, m), 3.74-3.65 (1H, m), 3.64-3.61 (2H, m), 3.25 (1H, dd, $J = 14.0, 4.4$), 2.95-2.87 (1H, m), 2.76 (1H, dd, $J = 14.0, 9.6$), 2.25 (1H, ddd, $J = 13.0, 8.8, 6.2$), 1.88-1.75 (2H, m), 1.67-1.51 (3H, m), 1.42 (9H, s), 1.42-1.32 (1H, m); ^{13}C NMR: 177.8, 155.9, 138.6, 129.1, 128.9, 126.9, 80.7, 80.1, 62.5, 53.3, 42.6, 36.2, 30.9, 28.7, 28.5, 26.5; ESI: Calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_5\text{Na}$ 386.1943 $[\text{M} + \text{Na}]^+$, Found 386.1928.

[(1*S*)-1-[(4*R*)-4-Benzyl-5-oxo-tetrahydro-furan-(2*R*)-2-yl]-4-(*tert*-butyl-dimethyl-silyloxy)-butyl]-bis carbamic acid *tert*-butyl ester (15**)**



To a solution of N-Boc protected lactone **3** (0.617 g, 1.292 mmol) and DMAP (14.2 mg, 0.116 mmol) in THF (10 mL) was added a solution of Boc₂O (0.424 g, 1.943 mmol) in THF (5 mL) and the mixture was heated to reflux for 16 hrs. Additional Boc₂O (0.280 g, 1.283 mmol) was added and heating was continued for 5 hrs. The deep yellow reaction mixture was cooled down to room temperature and concentrated to a yellowish solid. Purification by column chromatography (13% EtOAc-PE) afforded **15** as a white solid (0.690 g, 92%). R_f = 0.30 (13% EtOAc-PE); ¹H NMR: 7.27-7.12 (5H, m), 4.70-4.64 (1H, m), 4.09 (1H, app dt, *J* = 9.2, 6.4), 3.66-3.55 (2H, m), 3.29 (1H, dd, *J* = 14.0, 4.0), 2.92-2.84 (1H, m), 2.67 (1H, dd, *J* = 14.0, 10.0), 2.26-2.20 (1H, m), 1.89-1.83 (2H, m), 1.68-1.49 (3H, m), 1.46 (18H, s), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ¹³C NMR: 177.8, 153.3 (weak), 138.8, 129.0, 128.8, 126.8, 83.0, 80.2, 62.9, 60.6, 42.7, 36.4, 32.1, 29.5, 28.1, 26.7, 26.2, 18.5, -5.10, -5.12; ESI: Calcd. for C₃₁H₅₁NO₇NaSi 600.3333 [M + Na]⁺, Found 600.3326.

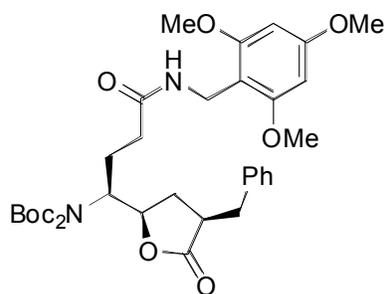
(4*S*)-4-[(4*R*)-4-Benzyl-5-oxo-tetrahydro-furan-(2*R*)-2-yl]-4-bis-*tert*-butoxycarbonylamino-butyric acid (16**)**



A solution of TBS silyl ether **15** (0.469 g, 0.812 mmol) in acetone (9mL) was cooled to -10°C and a solution of Jones reagent (freshly prepared from 0.748 g CrO₃, 0.64 mL conc. H₂SO₄, 2.0 mL water and 8 mL acetone at 0°C) (7 mL, 4.922 mmol) was added drop wise. The resulting solution was stirred at -10°C 1 ½ hrs before isopropanol (3.5 mL) was

added slowly, and stirring continued for 20 min. A solution of saturated sodium bicarbonate (20 mL) was added and the organics were removed on a rotary evaporator. The aqueous solution was acidified by careful addition of 1N HCl at 0°C until the pH reached 4-5 upon which a solution of 10% citric acid (3 mL) was added. Ethyl acetate was added to the turbid greenish aqueous phase and the biphasic mixture was filtered in a Büchner funnel. Layers were separated and the aqueous phase was extracted four times with ethyl acetate. The combined organic layers were washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum gave the crude product as a clear oil. Purification by column chromatography (5% MeOH-CH₂Cl₂) afforded **16** as a white foam (0.302 g, 78%). $R_f = 0.25$ (5% MeOH-CH₂Cl₂); ¹H NMR: 7.31-7.15 (5H, m), 4.71 (1H, ddd, $J = 10.5, 9.5, 5.5$ Hz), 4.09 (1H, ddd, $J = 10.5, 9.5, 4.3$), 3.29 (1H, dd, $J = 14.0, 4.5$), 2.94-2.86 (1H, m), 2.69 (1H, dd, $J = 14.0, 9.5$), 2.44-2.40 (2H, m), 2.27-2.10 (3H, m), 1.60 (1H, app dt, $J = 12.5, 10.5$), 1.46 (18H, s); ¹³C NMR: 178.2, 177.6, 153.1 (weak), 138.7, 129.0, 128.9, 126.9, 83.5, 79.7, 60.2, 42.6, 36.4, 32.1, 30.8, 28.1, 25.4; ESI: Calcd. for C₂₅H₃₄NO₈ [M -H]⁻ 476.2290, Found 476.2279.

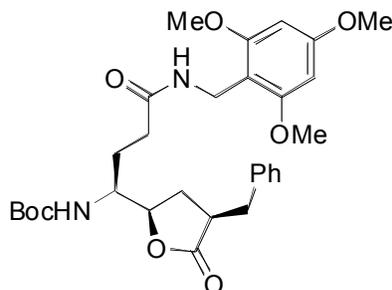
[(1*S*)-1-[(4*R*)-4-Benzyl-5-oxo-tetrahydro-furan-(2*R*)-2-yl]-3-(2,4,6-trimethoxybenzylcarbamoyl)-propyl]-bis carbamic acid *tert*-butyl ester (17**)**



To a solution of carboxylic acid **16** (0.302 g, 0.632 mmol), 2,4,6-trimethoxybenzylamine hydrochloride (0.156 g, 0.668 mmol) and 1-HOBt (0.108 g, 796 μmol) in DMF (5.5 mL) was added diisopropylethylamine (0.360 mL, 2.066 mmol) and the solution was cooled to 0°C before HBTU (0.290 g, 0.765 mmol) was added in one portion. Stirring was continued at 0°C for 30 min before the cooling bath was removed and stirring continued at room temperature for 2 hrs. The reaction mixture was separated between ethyl acetate and a 10% solution of citric acid. The aqueous layer was extracted twice more with ethyl

acetate and the combined organic layers were washed with water, a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum gave the crude product as white foam. Purification by column chromatography (62.5:32.5 EtOAc:PE) afforded **17** as a white foam (0.383 g, 92%). $R_f = 0.35$ (62.5:32.5 EtOAc:PE); $^1\text{H NMR}$: 7.30-7.14 (5H, m), 6.12 (2H, s), 5.78 (1H, t, $J = 5.0$), 4.68 (1H, ddd, $J = 10.0, 9.0, 6.0$), 4.46 (1H, dd, $J = 13.5, 5.0$), 4.41 (1H, dd, $J = 13.5, 5.0$), 4.06-4.02 (1H, m), 3.81 (9H, s), 3.27 (1H, dd, $J = 14.0, 4.0$), 2.91-2.84 (1H, m), 2.66 (1H, dd, $J = 14.0, 10.0$), 2.26-2.13 (5H, m), 1.61-1.54 (1H, m), 1.44 (18H, s); $^{13}\text{C NMR}$: 177.7, 171.2, 161.1, 159.5, 153.3 (weak), 138.7, 129.0, 128.9, 126.9, 107.0, 90.8, 83.4, 80.0, 60.5, 56.0, 55.6, 42.6, 36.4, 33.8, 32.5, 32.1, 28.1, 26.8; ESI: Calcd. for $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_{10}\text{Na}$ 679.3207 $[\text{M} + \text{Na}]^+$, Found 679.3235.

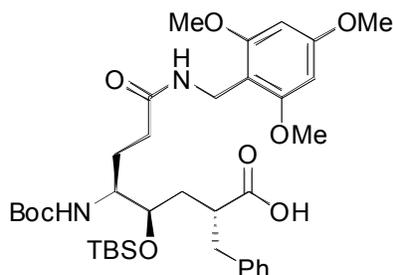
[(1S)-1-[(4R)-4-Benzyl-5-oxo-tetrahydro-furan-(2R)-2-yl]-3-(2,4,6-trimethoxy-benzylcarbamoyl)-propyl]-carbamic acid *tert*-butyl ester (18**)**



To a solution of **17** (0.380 g, 0.579 mmol) in acetonitrile (14 mL) under argon in a 50 mL round bottom flask was added oven dried lithium bromide (0.300 g, 3.454 mmol). The reaction flask was purged with argon and closed tight with a stopper before it was placed in a 65°C oil bath and stirred over night. The resulting mixture was evaporated to give a yellow solid, and purification by flash chromatography (4:1 EtOAc : PE) afforded **18** as a white foam (0.306 g, 95%). $R_f = 0.33$ (4:1 EtOAc : PE); $^1\text{H NMR}$: 7.31-7.27 (2H, m), 7.24-7.18 (3H, m), 6.12 (2H, s), 5.9 (1H, bs), 4.91 (1H, d, $J = 11.5$), 4.49 (1H, dd, $J = 17.0, 7.0$), 4.42 (1H, dd, $J = 17.0, 6.3$), 4.29-4.24 (1H, m), 3.80 (9H, s), 3.70-3.63 (1H, m), 3.27 (1H, dd, $J = 17.5, 5.3$), 2.90-2.82 (1H, m), 2.69 (1H, dd, $J = 17.5, 12.5$), 2.26-2.18 (3H, m), 1.98-1.68 (3H, m), 1.40 (9H, s); $^{13}\text{C NMR}$: 177.8, 171.8, 161.1, 159.5, 156.1, 138.7, 129.0, 128.9, 126.9, 106.7, 90.8, 80.5, 79.9, 56.0, 55.6, 53.4, 42.7, 36.4,

33.0, 32.6, 31.3, 28.4, 26.2; ESI: Calcd. for C₃₀H₄₀N₂O₈Na 579.2682 [M + Na]⁺, Found 579.2693.

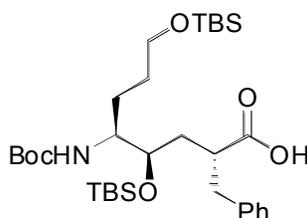
(2*R*, 4*R*, 5*S*)-2-Benzyl-5-*tert*-butoxycarbonylamino-4-(*tert*-butyl-dimethyl-silyloxy)-7-(2,4,6-trimethoxy-benzylcarbamoyl)-heptanoic acid (1**)**



To a solution of lactone **18** (0.260 g, 0.544 mmol) in dioxane (13 mL) was added drop wise a 1M solution of lithium hydroxide (3.25 mL) and the resulting mixture was stirred at room temperature for 1 hrs. Workup of the reaction mixture was performed in a cold room at 3-5°C according to a previously reported procedure.⁵ The reaction mixture was separated between a 1:1 mixture of saturated sodium bicarbonate and saturated sodium chloride and a 8:2 mixture of ethyl acetate and ethanol. The aqueous layer was extracted three more times with the organic mixture, and the combined organic layers were washed twice with a saturated solution of sodium chloride before drying over a 1:1 mixture of anhydrous magnesium sulfate and anhydrous potassium carbonate. The drying agents were removed by filtration, the solution was concentrated at 20°C under high vacuum before thorough drying in a vacuum desiccator over phosphorus pentoxide to give 0.301 g of a white solid. The solid was dissolved in DMF (4.5 mL) and to this mixture was added imidazole (0.761 g, 11.18 mmol) and TBSCl (0.766 g, 5.08 mmol) and the reaction mixture was stirred at room temperature for 44 hrs before methanol (20 mL) was added and stirring continued for 3 ½ hrs. The mixture was evaporated to a small volume and separated between ethyl acetate and a 10% solution of citric acid. The aqueous layer was extracted once with ethyl acetate and the combined organic layers were washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation gave yellow oil. Purification by flash chromatography (7% MeOH-CH₂Cl₂) gave **1** as a white foam (0.284 g, 82%). Contains 2.5% residual DMF. R_f = 0.26 (7% MeOH-CH₂Cl₂); ¹H NMR: 7.23-7.12 (5H, m), 6.13

(2H, s), 6.13-6.07 (1H, m), 6.03 (1H, bm), 4.80 (1H, d, $J = 9.0$), 4.46 (2H, d, $J = 5.0$), 3.82 (9H, s), 3.56-3.49 (1H, m), 3.04-2.98 (1H, m), 2.78-2.71 (2H, m), 2.16-2.10 (1H, m), 2.05-1.99 (1H, m), 1.87-1.80 (1H, m), 1.64-1.53 (3H, m), 1.40 (9H, s), 0.87 (9H, s), 0.04 (6H, s); ^{13}C NMR: 178.3, 172.5, 161.1, 159.5, 156.2, 139.0, 129.3, 128.7, 126.6, 107.0, 90.8, 79.6, 72.6, 56.0, 55.6, 53.7, 43.4, 38.5, 35.6, 33.6, 32.5, 28.6, 26.1, 24.6, 18.2, -4.3, -4.5; ESI: Calcd. for $\text{C}_{36}\text{H}_{55}\text{N}_2\text{O}_9\text{Si}$ 687.3677 $[\text{M} - \text{H}]^-$, Found 687.3666.

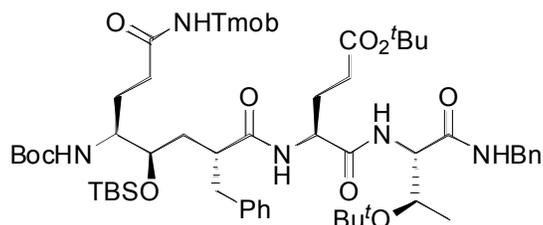
(2*R*, 4*R*, 5*S*)-2-Benzyl-5-*tert*-butoxycarbonylamino-4,8-bis-(*tert*-butyl-dimethyl-silyloxy)-octanoic acid (2)



To a solution of lactone **3** (0.260 g, 0.544 mmol) in dioxane (13 mL) was added drop wise a 1M solution of lithium hydroxide (3.25 mL) and the resulting mixture was stirred at room temperature for 1 hrs. Workup of the reaction mixture was performed in a cold room at 3-5°C according to a previously reported procedure.⁵ The reaction mixture was separated between a 1:1 mixture of saturated sodium bicarbonate and saturated sodium chloride and a 8:2 mixture of ethyl acetate and ethanol. The aqueous layer was extracted three more times with the organic mixture, and the combined organic layers were washed with a saturated solution of sodium chloride, and then once more with a saturated solution of sodium chloride at room temperature before drying over a 1:1 mixture of anhydrous magnesium sulfate and anhydrous potassium carbonate. The drying agents were removed by filtration, the solution was concentrated at 20°C under high vacuum before thorough drying in a vacuum desiccator over phosphorus pentoxide to give 0.268 g of a white solid. The solid was dissolved in DMF (4.5 mL) and to this mixture was added imidazole (0.387 g, 5.69 mmol) and TBSCl (0.790 g, 5.181 mmol) and the reaction mixture was stirred at room temperature for 50 hrs before methanol (20 mL) was added and stirring continued for 3 ½ hrs. The mixture was evaporated to a small volume and separated between ethyl acetate and a 10% solution of citric acid. The aqueous layer was extracted once with ethyl acetate and the combined organic layers were washed with a

saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation gave a yellow oil. Purification by flash chromatography (4% MeOH-CH₂Cl₂) gave **2** as a white solid (0.266 g, 84%). Contains 3% residual DMF. *R*_f = 0.20 (3% MeOH-CH₂Cl₂); ¹H NMR: 7.29-7.18 (5H, m), 4.63 (1H, *J* = 8.8), 3.86-3.78 (1H, bm), 3.58-3.45 (3H, m), 3.07-3.00 (2H, m), 2.78-2.70 (2H, m), 1.87-1.78 (1H, m), 1.62-1.48 (2H, m), 1.42 (9H, s), 1.28-1.22 (2H, m), 0.89 (9H, s), 0.87 (9H, s), 0.05 (3H, s), 0.04 (9H, s); ¹³C NMR (DMSO): 176.2, 155.3, 139.4, 128.7, 128.1, 126.1, 77.3, 72.0, 62.3, 54.0, 42.9, 37.4, 35.6, 29.2, 28.2, 25.8, 25.2, 17.9, 17.7, -4.6, -5.30, -5.33; ESI: Calcd. for C₃₂H₅₈NO₆Si₂ 608.3808 [M - H]⁻, Found 608.3802.

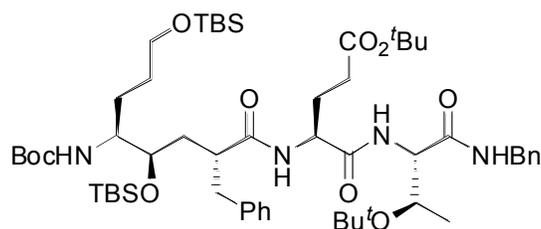
Boc-Gln(Tmob)ψ[CH(OH)CH₂]Phe-Glu(OtBu)-Thr(tBu)-NHBn (19)



To a 0°C solution of hydroxyethylene isostere **1** (129.1 mg, 0.187 mmol), amine **24** (97.6 mg, 0.217 mmol) and HOBT (38.5 mg, 0.285 mmol) in DMF (3.0 mL) was added EDCI (45.5 mg, 0.238 mmol) in one portion. The resulting mixture was stirred at 0°C for 30 min upon which the cooling bath was removed and stirring was continued at room temperature for 5 hrs. The reaction mixture was partitioned between ethyl acetate and a 10% solution of citric acid. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with water, a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying gave the crude product as white solid (202 mg). Purification by flash chromatography (2:1 EtOAc : PE) afforded **19** as a white solid (158 mg, 75%). *R*_f = 0.26 (2:1 EtOAc : PE); ¹H NMR: 7.53 (1H, t, *J* = 5.8), 7.36-7.30 (3H, m), 7.26-7.20 (3H, m) 7.15 (2H, d, *J* = 7.0), 7.11-7.07 (2H, m), 6.97 (1H, d, *J* = 6.5), 6.15 (2H, s), 5.72 (1H, t, *J* = 5.0), 4.82, (1H, d, *J* = 8.5), 4.55-4.47 (2H, m), 4.44-4.38 (2H, m), 4.34-4.28 (2H, m), 3.83 (6H, s), 3.82 (3H, s), 3.73-3.69 (1H, m), 3.41 (1H, t, *J* = 9.5), 2.89 (1H, dd, *J* = 13.0, 5.0), 2.62-2.57 (1H, m), 2.51 (1H, dd, *J* = 13.0, 9.3), 2.40-2.29 (2H, m), 2.16-2.09 (1H, m), 2.06-1.89 (3H, m), 1.80-

1.74 (1H, m), 1.43 (9H, s), 1.40 (9H, s), 1.12 (9H, s), 1.07 (3H, d, $J = 6.0$), 0.85 (9H, s), 0.03 (3H, s), 0.01 (3H, s); ^{13}C NMR: 175.9, 172.9, 172.2, 171.2, 169.7, 161.2, 159.6, 156.0, 139.3, 138.5, 129.3, 128.65, 128.57, 128.2, 127.4, 126.4, 107.0, 90.8, 80.9, 79.3, 75.0, 72.3, 66.4, 58.5, 56.0, 55.6, 54.2, 53.3, 44.8, 43.7, 39.2, 35.6, 33.5, 32.5, 32.2, 29.9, 28.6, 28.5, 28.3, 27.4, 26.1, 23.1, 19.3, 18.2, -4.3, -4.7; ESI: Calcd. for $\text{C}_{60}\text{H}_{93}\text{N}_5\text{O}_{13}\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 1142.6437, Found 1142.6415.

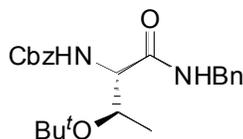
Boc-TBS-HE ψ [CH(OH)CH₂]Phe-Glu(OtBu)-Thr(tBu)-NHBn (20)



To a 0°C solution of hydroxyethylene isostere **2** (103 mg, 0.169 mmol), amine **24** (82.2 mg, 0.183 mmol) and HOBt (35.4 mg, 0.262 mmol) in DMF (3.0 mL) was added EDCI (40.6 mg, 0.212 mmol) in one portion. The resulting mixture was stirred at 0°C for 30 min upon which the cooling bath was removed and stirring was continued at room temperature for 5 hrs. The reaction mixture was partitioned between ethyl acetate and a 10% solution of citric acid containing a small volume of saturated sodium chloride solution. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with water, a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying gave the crude product as a white solid (159 mg). Purification by flash chromatography (1:2 EtOAc : PE) afforded **20** as a white solid (127 mg, 72%). $R_f = 0.24$ (1:2 EtOAc : PE); ^1H NMR: 7.54 (1H, t, $J = 5.5$), 7.35-7.29 (4H, m), 7.26-7.23 (3H, m), 7.18-7.12 (3H, m), 6.98 (1H, d, $J = 7.0$), 4.64 (1H, d, $J = 7.5$), 4.53 (1H dd, $J = 14.8, 6.3$), 4.40 (1H, dd, $J = 14.8, 4.8$), 4.33 (1H, app q, $J = 13.5, 6.0$), 4.29 (2H, d, $J = 6.5$), 3.74-3.71 (1H, m), 3.51-3.47 (1H, m), 3.42-3.37 (1H, m), 3.33-3.29 (1H, m), 2.92-2.87 (1H, m), 2.53-2.46 (3H, m), 2.37 (2H, t, $J = 7.3$), 2.18-2.11 (1H, m), 2.00-1.93 (1H, m), 1.77-1.71 (1H, m), 1.44 (9H, s), 1.40 (9H, s), 1.31-1.22 (2H, m), 1.21-1.14 (2H, m), 1.11 (9H, s), 1.07 (3H, d, $J = 6.0$), 0.88 (9H, s), 0.85 (9H, s), 0.033 (3H, s), 0.028 (3H, s), 0.02 (3H, s), -0.01 (3H, s); ^{13}C

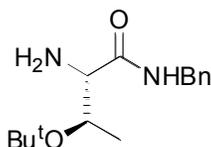
NMR: 175.9, 173.1, 171.1, 169.7, 155.8, 139.2, 138.5, 129.2, 128.61, 128.55, 128.2, 127.4, 126.5, 81.0, 79.3, 75.0, 72.3, 66.3, 63.0, 58.5, 54.4, 53.5, 45.2, 43.7, 39.1, 35.5, 32.2, 29.7, 28.7, 28.5, 28.2, 27.4, 26.1, 26.0, 23.0, 19.3, 18.5, 18.2, -4.3, -4.8, -5.1 ESI: Calcd. for $C_{59}H_{96}N_4O_{10}Si_2Na$ $[M + Na]^+$ 1063.6563, Found 1063.6514.

Cbz-Thr(tBu)-NHBn (21)



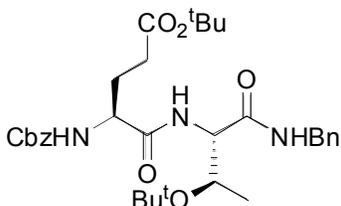
To a solution of Cbz-Thr(tBu)-OH (0.272 g, 0.88 mmol) in DMF cooled to 0°C was added 1-HOBt (0.181 g, 1.34 mmol) and EDCI (0.220 g, 1.15 mmol) and stirring was continued for 30 min. Benzylamine (0.130 mL, 1.19 mmol) was added drop wise and the mixture was stirred for another 30 min at 0°C upon which it was allowed to warm to room temperature over 2 hrs. The reaction mixture was diluted with ethyl acetate and washed with a 10% solution of citric acid. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with water, a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum afforded **21** as a white solid (0.329 g, 94% crude). The crude product was taken to the next step without further purification. $R_f = 0.47$ (2:3 EtOAc:PE); 1H NMR: 7.37-7.26 (10H, m), 6.00 (1H, d, $J = 4.0$), 5.15 (1H, dd, $J = 12.0$), 5.09 (1H, dd, $J = 12.0$), 4.53-4.42 (2H, m), 4.25-4.15 (2H, m), 1.22 (9H, s), 1.05 (3H, d, $J = 6.8$); ^{13}C NMR: 169.5, 156.4, 138.1, 136.4, 128.9, 128.8, 128.4, 128.2, 127.8, 127.7, 75.6, 67.1, 67.0, 59.1, 43.8, 28.4, 17.5; MALDI: Calcd. for $C_{23}H_{30}N_2O_4Na$ $[M + Na]^+$ 421.2103, Found 421.2094.

H₂N-Thr(tBu)-NHBn (22)



Cbz-Thr(tBu)-NHBn (0.303g, 0.760 mmol) was dissolved in methanol (20 mL) and the mixture was flushed with argon before 10% palladium on activated carbon (32 mg) was added. The reaction flask was sequentially evacuated and filled with hydrogen gas three times and stirred under an atmosphere of hydrogen (ballon) for 5 hrs. The catalyst was removed by filtration through an Acrodisc[®] 0.2 μm 25 mm filter and the solvent was evaporated and dried under high vacuum to afford **22** as a light yellow oil (0.200 g, 99% crude). The crude product was taken to the next step without further purification. ¹H NMR: 7.77 (1H, bs), 7.34-7.25 (5H, m), 4.48 (1H, dd, $J = 15.0, 6.0$), 4.43 (1H, dd, $J = 15.0, 6.0$), 4.16 (1H, dq, $J = 6.5, 2.5$), 3.18 (1H, d, $J = 2.5$), 1.62 (2H, bs), 1.16 (3H, d, $J = 6.0$), 1.14 (9H, s); ¹³C NMR: 173.7, 138.7, 128.8, 127.9, 127.5, 74.2, 68.0, 60.1, 43.5, 28.8, 20.2; MALDI: Calcd. for C₁₁H₁₅N₂ONa 287.1736 [M + Na]⁺, Found 287.1733.

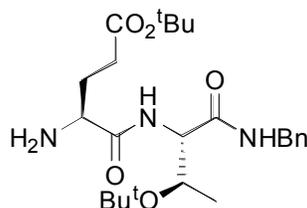
Cbz-Glu(OtBu)-Thr(tBu)-NHBn (23)



To a stirred solution of Cbz-Glu(OtBu)-OH (0.246 g, 0.729 mmol), **22** (0.183 g, 0.690 mmol) and 1-HOBt (0.141 g, 1.043 mmol) in DMF (4 mL) cooled to 0°C was added EDCI (0.172 g, 0.898 mmol) and stirring was continued for 20 min and then at room temperature for 2 hrs. The reaction mixture was diluted with ethyl acetate and washed with a 10% solution of citric acid. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with water, a saturated solution of sodium bicarbonate, a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation and drying under high vacuum afforded **23** as a white solid (0.388 g, 96% crude). The crude product was taken to the next step without further purification. ¹H NMR: 7.82-7.75 (1H, m), 7.36-7.24 (10H, m), 7.16 (1H, d, $J = 6.5$), 5.85 (1H, d, $J = 6.5$), 5.06 (1H, d, $J = 12.0$), 5.00 (1H, d, $J = 12.0$), 4.30 (1H, dd, $J = 6.5, 3.0$), 4.28-4.23 (1H, m), 4.22-4.18 (1H, m), 2.43-2.30 (2H, m), 2.15-2.08 (1H, m), 2.05-1.94 (1H, m), 1.43 (9H, s), 1.16 (9H, s), 1.04 (3H, d, $J = 6.5$); ¹³C NMR: 173.0, 171.3, 169.5, 138.2, 136.3, 128.8, 128.7, 128.4, 128.3, 128.0,

127.5, 81.4, 75.3, 67.3, 66.3, 58.2, 55.5, 43.8, 32.1, 28.4, 28.2, 27.1, 18.7; MALDI: Calcd. for $C_{32}H_{45}N_3O_7Na$ $[M + Na]^+$ 606.3155, Found 606.3148, ESI: Found 606.3173.

H-Glu(OtBu)-Thr(tBu)-NHBn (**24**)



Cbz-Glu(OtBu)-Thr(tBu)-NHBn (0.200g, 0.343 mmol) in methanol (9 mL) was hydrogenated as described for **22** using 10% palladium on activated carbon (20 mg) to afford **24** as a colorless oil (0.153 g, 99% crude). The crude product was taken to the next step without further purification. 1H NMR: 8.00 (1H, d, $J = 5.6$), 7.38-7.24 (6H, m), 4.52 (1H, dd, $J = 15.2, 5.6$), 4.44 (1H, dd, $J = 15.2, 5.6$), 4.18, (1H, dq, $J = 6.8, 4.0$), 3.41 (1H, dd, $J = 7.6, 4.8$), 2.36-2.32 (2H, m), 2.15-2.06 (1H, m), 1.87-1.78 (3H, m and bs), 1.43 (9H, s), 1.23 (9H, s), 1.04 (3H, d, $J = 6.5$); ^{13}C NMR: 174.9, 172.8, 169.7, 138.3, 128.9, 127.8, 127.6, 80.8, 75.7, 66.5, 57.6, 55.1, 43.8, 32.3, 30.7, 28.4, 28.3, 17.4; ESI: Calcd. for $C_{24}H_{40}N_3O_5$ $[M + H]^+$ 450.2968, Found 450.2975.

References and notes:

- (1) Shikata, K.; Azuma, H.; Tachibana, T.; Ogino, K. *Tetrahedron* **2002**, *58*, 5803-5809.
- (2) Schuda, P. F.; Ebner, C. B.; Potlock, S. J. *Synthesis* **1987**, 1055-1057.
- (3) To a stirred suspension of dimethyl tartrate (1.178 g, 6.613 mmol) in diethyl ether (12 mL) was added periodic acid (1.501 g, 6.585 mmol) in small portions over a period of 30 min. During the addition a white solid separates out, and the reaction mixture was stirred for an additional 20 minutes until the solution turned clear. The white solid was allowed to settle and the reaction mixture poured through a folded filter. The solid was washed with 10 mL of diethyl ether and poured through the filter before the filter was rinsed with two small portions of diethyl ether and the combined ethereal solution was stirred with anhydrous magnesium sulfate for 30 min. Filtering of the drying agent and evaporation of the ether on the rotary evaporator gave a yellow oil which was further dried under high vacuum for 5-10 min. The crude aldehyde was kept under argon wrapped in aluminum foil until it was used as is.

- (4) Prolonged stirring after addition of citric acid resulted in some cleavage of the TBS silyl ether.
- (5) Brewer, M.; Rich, D. H. *Preceding manuscript in this journal*.