Supplemental Materials

Stereoselective Synthesis of Novel Dipeptide β -Turn Mimetics Targeting Melanocortin Peptide Receptors

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General. ^1H and ^{13}C NMR were performed on 500 or 600 MHz spectrometers using CDCl_3 and TMS as internal standards. High Resolution Mass Spectra (HRMS) were recorded on an instrument in the University of Arizona Mass Spectrum Laboratory. Optical rotations were measured on a polarimeter. Melting points (m.p.) are uncorrected and were obtained in open capillaries. Commercially available starting materials and reagents were of ACS grade or better and used as received. Methylene chloride was distilled from CaH_2 ; THF was distilled from K and benzophenone. HPLC grade methanol was used for hydrogenations. Column chromatography was performed using silica gel (230-400 mesh). Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity, as estimated by ^1H and ^{13}C NMR spectroscopy. All new compounds were characterized by ^1H , ^{13}C NMR and HRMS.

3-(*N*-Phthalimido) propionaldehyde (3). Oxalyl chloride (2M) (55 mL, 110 mmol) was dissolved in dry dichloromethane (140 mL) under Argon atmosphere and cooled at $-78\text{ }^\circ\text{C}$. Dimethyl sulfoxide (8.3 mL, 117 mmol) was added dropwise and the mixture was stirred for 10 min. A solution of *N*-(3-hydroxypropyl) phthalimide (15 g, 73.1 mmol) in dichloromethane (10 mL) was added slowly at $-78\text{ }^\circ\text{C}$ and allowed to react for 1 h. Triethylamine (80 mL, 574 mmol) was added and the cold bath was removed. After stirring at room temperature for 30 min, the reaction mixture was washed with NH_4Cl solution (100 mL), NaCl (100 mL), and dried over Na_2SO_4 . The solvent was concentrated, purified by flash chromatograph (Hexanes:EtOAc = 1:1) to give **3** as white crystals (12.7g, 86%). **3.** ^1H NMR (500 MHz, CDCl_3) δ 9.83 (t, 1H, J = 1.3 Hz), 7.86-7.84 (m, 2H), 7.74-7.72 (m, 2H), 4.04 (t, 2H, J = 7.0), 2.90-2.87 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 199.4, 168.0, 134.1, 131.9, 123.3, 42.3, 31.7.

(*E*)-5-(*N*-Phthalimido)-pent-2-enoic acid *tert*-butyl ester (4). To a solution of **3** (500 mg, 2.46 mmol) in CH₂Cl₂ (20 mL) and H₂O (10 mL) was added (*tert*-butoxycarbonylmethyl)triphenylphosphonium bromide (1.13 g, 2.47 mmol), NaOH (200 mg, 4.92 mmol) and Et₃N (1 mL, 7.38 mmol) at room temperature. After stirring at room temperature for 1 hr, the organic phase was separated and washed with 1 N HCl (30 mL) and saturated aqueous NaHCO₃ (30 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated to give a crude product, which was purified by flash column chromatography (Hexanes:EtOAc = 3:1) to afford pure product **4** as a white solid (704 mg, 95%). **4**. mp 91-93 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.85-7.84 (m, 2H), 7.74-7.71 (m, 2H), 6.81 (dt, 1H, *J* = 15.6, 7.1 Hz), 5.82 (dt, 1H, *J* = 15.6, 1.5 Hz), 3.81 (t, 2H, *J* = 7.3 Hz), 2.60-2.55 (m, 2H), 1.46 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 168.0, 165.3, 142.6, 134.0, 132.0, 125.5, 123.3, 80.3, 36.4, 31.0, 28.1; HRMS (FAB) calcd for C₁₇H₂₀NO₄ (M+H) 302.1392, found 302.1405.

(4*S*,2*E*)-3-[5-(*N*-Phthalimido)-1-oxo-2-pentenyl]-4-phenyl-2-oxazolidinone (5). A solution of **4** (2 g, 6.64 mmol) in 50% TFA in dichloromethane (15 mL) was stirred at room temperature for 2 hr. The solution was concentrated, neutralized by saturated aqueous NaHCO₃ and extracted with EtOAc (3 30 mL). The organic layers were combined, dried over Na₂SO₄ and evaporated *in vacuo* to give a crude product. To a solution of the crude product in dry THF (20 mL) was added triethylamine (970 L, 6.96 mmol) and trimethylacetyl chloride (900 L, 7.31 mmol) at -78 °C. The reaction mixture was stirred at 0 °C for 1 hr and recooled to -78 °C. Meanwhile, the chiral auxiliary, (*S*)-4-phenyl-2-oxazolidinone (1.08 g, 6.62 mmol), in THF (40 mL) at -78 °C was treated with the dropwise addition of *n*BuLi (1.6 M in hexanes, 4.15 mL, 6.64 mmol). This reaction was stirred at -78 °C for 25 min. The preformed mixed anhydride was cannulated into the lithiated chiral auxiliary solution at -78 °C and stirred in an ice bath

afterward, allowing the reaction mixture to achieve room temperature overnight. Water (100 mL) and diethyl ether (50 mL) were added and the organic phase was separated, washed with water (50 mL) and saturated aqueous NaCl (80 mL), dried over Na₂SO₄ and concentrated to give a crude product, which was purified by flash column chromatography (Hexanes:EtOAc = 1:1) to afford pure product **5** as a white solid (2.31 g, 89%). **5**. mp 139-141 °C; [α]_D²³ +65.4 (*c* 1.14, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.84-7.82 (m, 2H), 7.73-7.70 (m, 2H), 7.39-7.26 (m, 6H), 7.01 (dt, 1H, *J* = 15.4, 7.1 Hz), 5.46 (dd, 1H, *J* = 8.7, 3.9 Hz), 4.68 (t, 1H, *J* = 8.8 Hz), 4.26 (dd, 1H, *J* = 8.9, 3.9 Hz), 3.84-3.82 (m, 2H), 2.68-2.64 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 168.0, 164.0, 153.5, 146.4, 138.9, 134.0, 132.0, 129.2, 128.7, 125.9, 123.3, 122.5, 69.9, 57.7, 36.3, 31.6; HRMS (FAB) calcd for C₂₂H₁₉N₂O₅ (M+H) 391.1294, found 391.1289.

Ni(II)-Complex of the Schiff base of (S)-BPB with (2S and R, 3S)-3-[2-(N-Phthalimido)-ethyl]-5-[(4S)-3-(4-phenyl-2-oxazolidinonyl)] glutamic acid (7a,b). To a suspension of complex (S)-**6** (1.2 g, 2.4 mmol) in DMF (8 mL), complex **5** (1 g, 2.56 mmol) was added with stirring. The mixture was stirred at 0 °C for 10 min to get a homogeneous solution, then DBU (35 L, 0.24 mmol) was added dropwise and cold bath was removed. After 30 min, the reaction was quenched with 5% aqueous acetic acid (10 mL) and the product was extracted with dichloromethane (2 20 mL). The combined organic phase was dried over Na₂SO₄ and concentrated to give a crude product. Diastereomerically pure **7a** was recrystallized from ethyl acetate/hexanes as a red solid (1.82 g, 85%). Diastereomerically pure **7b** was obtained by flash column chromatography (DCM:Acetone = 2:1) as a red oil (200 mg, 8%). **7a**. mp 186-188 °C; [α]_D²³ +1522.1 (*c* 0.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.30 (dd, 1H, *J* = 8.7, 0.8 Hz), 8.02 (d, 2H, *J* = 7.1 Hz), 7.69-7.65 (m, 2H), 7.59-7.55 (m, 2H), 7.46-7.43 (m, 1H), 7.40-7.37 (m, 2H), 7.35-7.22 (m, 6H), 7.16-7.04 (m, 4H), 6.66 (d, 1H, *J* = 7.7 Hz), 6.56-6.47 (m, 2H), 5.19 (dd,

1H, $J = 8.5, 3.2$ Hz), 4.44 (t, 1H, $J = 8.6$ Hz), 4.37 (d, 1H, $J = 12.7$ Hz), 4.12 (dd, 1H, $J = 8.7, 3.2$ Hz), 4.07 (d, 1H, $J = 6.2$ Hz), 4.00-3.95 (m, 1H), 3.77-3.67 (m, 2H), 3.50-3.42 (m, 4H), 3.17 (dd, 1H, $J = 17.9, 8.3$ Hz), 2.96-2.85 (m, 2H), 2.47-2.38 (m 2H), 2.07-2.03 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 180.3, 177.4, 172.3, 170.2, 167.9, 153.5, 142.8, 139.3, 133.8, 133.7, 133.6, 133.5, 132.3, 131.8, 131.4, 129.5, 129.1, 129.0, 128.9, 128.7, 128.6, 128.3, 128.0, 127.0, 125.9, 125.6, 123.1, 123.0, 120.2, 72.0, 70.5, 70.0, 63.3, 57.5, 57.1, 36.7, 36.0, 35.9, 30.3, 29.7, 23.3; HRMS (FAB) calcd for $\text{C}_{49}\text{H}_{44}\text{N}_5\text{NiO}_8$ ($\text{M}+\text{H}$) 888.2543, found 888.2553. **7b.** [$^{23}\text{D} + 1068.6$ (c 0.07, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.55 (d, 1H, $J = 9.0$ Hz), 7.65-7.62 (m, 2H), 7.55-7.49 (m, 4H), 7.44-7.38 (m, 6H), 7.37-7.30 (m, 2H), 7.27-7.25 (m, 2H), 7.18-7.14 (m, 2H), 7.11 (d, 1H, $J = 7.4$ Hz), 6.75 (d, 1H, $J = 7.4$ Hz), 6.56 (d, 2H, $J = 4.0$ Hz), 5.28-5.25 (m, 2H), 4.61 (t, 1H, $J = 8.7$ Hz), 4.36-4.29 (m, 1H), 4.19 (dd, 1H, $J = 8.7, 3.4$ Hz), 4.15-4.10 (m, 2H), 3.92-3.76 (m, 4H), 3.21 (dd, 1H, $J = 17.4, 8.0$ Hz), 2.94 (dd, 1H, $J = 17.4, 5.9$ Hz), 2.66-2.60 (m, 1H), 2.37-2.29 (m, 2H), 2.06-2.03 (m, 1H), 1.92-1.86 (m, 1H), 1.67-1.57 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 182.5, 177.7, 172.7, 170.2, 168.3, 153.4, 143.1, 139.3, 133.9, 133.8, 133.7, 132.4, 132.3, 131.9, 131.6, 129.5, 129.1, 128.9, 128.8, 128.7, 128.4, 128.2, 126.8, 126.0, 125.5, 123.5, 123.2, 120.4, 72.0, 69.9, 68.4, 60.6, 57.6, 55.8, 37.3, 36.7, 36.6, 31.2, 29.6, 23.6; HRMS (FAB) calcd for $\text{C}_{49}\text{H}_{44}\text{N}_5\text{NiO}_8$ ($\text{M}+\text{H}$) 888.2543, found 888.2543.

Methyl (2S, 3S)-*N*-*tert*-Butoxycarbonyl-3-[2-(*N*-Phthalimido)-ethyl]pyroglutamate

(8). Diastereomerically pure complex **7a** (7 g, 7.88 mmol) was dissolved in methanol (30 mL) and dichloromethane (10 mL) and added to a 1/1 mixture (50 mL) of 3 N HCl and water dropwise at 70 °C. After decomposition of the complex was completed (disappearance of the orange color), the mixture was evaporated *in vacuo*, treated with conc. ammonia and washed with CHCl_3 . The aqueous phase was stirred for 2 hr before the solvent was evaporated *in vacuo*.

The resultant crude product was dissolved in methanol (60 mL), and thionyl chloride (4.5 mL, 61.8 mmol) was added dropwise at 0 °C. The mixture was allowed to come to room temperature and be stirred overnight. After evaporation, the residue was dissolved in CH₂Cl₂ (50 mL), washed with saturated aqueous NaHCO₃ solution (50 mL) and brine (50 mL), and dried over Na₂SO₄. After filtration and rotary evaporation, the crude ester was dissolved in CH₃CN (15 mL) and di-*tert*-butyl dicarbonate (1.7 g, 7.79 mmol) and DMAP (50 mg, 0.41 mmol) were added. The reaction mixture was stirred for 5 hr. After removal of the solvent, the residue was purified by column chromatography on silica gel (Hexanes:EtOAc = 3:2) to give the pure product **8** as a colorless oil (1.77 g, 54%). **8**. [α]_D²³ +26.4 (*c* 0.99, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.84 (m, 2H), 7.76-7.74 (m, 2H), 4.32 (d, 1H, *J* = 3.8 Hz), 3.80-3.75 (m, 5H), 2.86 (dd, 1H, *J* = 17.6, 8.8 Hz), 2.36 (dd, 1H, *J* = 17.6, 4.6 Hz), 2.31-2.27 (m, 1H), 2.09-2.05 (m, 1H), 1.88-1.84 (m, 1H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 171.1, 168.1, 149.1, 134.1, 131.9, 123.3, 83.8, 64.2, 52.6, 37.3, 35.4, 33.5, 32.5, 27.8; HRMS (FAB) calcd for C₂₁H₂₅N₂O₇ (M+H) 417.1662, found 417.1675.

Methyl (2S, 3S, 5S)-1-(*tert*-Butyloxycarbonyl)-3-[2-(*N*-Phthalimido)-ethyl]-5-allyl-proline (9). To a solution of **8** (220 mg, 0.53 mmol) in dry THF (5 mL), was added DIBAL-H (1 M solution in hexanes, 2.1 mL) at -78 °C under Ar. After stirring at -78 °C for 15 min, the reaction was quenched with saturated aqueous NH₄Cl (3 mL) and allowed to come to room temperature. The reaction solution was passed through a short column of Celite and dried over Na₂SO₄. After removal of the solvent, the residue was dissolved in methanol (4 mL) and *p*-TsOH•OH (10 mg, 0.05 mmol) was added. After stirring for 3 hr, being quenched with saturated NaHCO₃ (4 mL) and removal of the solvent, the reaction mixture was extracted with diethyl ether (3 × 8 mL). The combined organic extracts were dried over Na₂SO₄, filtered and

concentrated under vacuum. The resultant residue was dissolved in diethyl ether (4 mL) and allyltrimethylsilane (335 μ L, 2.1 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (75 μ L, 0.59 mmol) were added at -40°C under Ar atmosphere. The cold bath was removed after stirring at -40°C for 15 min. The reaction mixture was stirred for additional 40 min, then quenched with NaHCO_3 (2 mL), extracted with diethyl ether (3 $\times$ 5 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated under vacuum to afford the crude product. Purification of the crude product by flash column chromatography (Hexanes:EtOAc = 3:1) afforded pure product **9** as a colorless oil (150 mg, 64%). **9**. $[\alpha]_D^{23} +24.8$ (c 1.84, CHCl_3); ^1H NMR (500 MHz, CDCl_3) (two rotamers) δ 7.86-7.83 (m, 2H), 7.74-7.71 (m, 2H), 5.84-5.76 (m, 1H), 5.10 (dd, 1H, J = 17.1, 1.6 Hz), 5.03 (d, 1H, J = 10.1 Hz), 4.00 (brs, 0.6H), 3.94-3.90 (m, 0.9H), 3.84 (d, 0.5H, J = 8.6 Hz), 3.76-3.65 (m, 5H), 2.68-2.66 (m, 0.6H), 2.57-2.54 (m, 0.4H), 2.34-2.30 (m, 1H), 2.23-2.16 (m, 1H), 2.11-2.05 (m, 2H), 1.74-1.66 (m, 2H), 1.46 (s, 4H), 1.40 (s, 5H); ^{13}C NMR (125 MHz, CDCl_3) (two rotamers) δ 173.3, 173.1, 168.1, 154.0, 153.3, 135.2, 134.0, 132.0, 123.2, 117.1, 80.1, 65.6, 65.1, 57.8, 57.6, 52.2, 52.0, 40.2, 39.3, 39.1, 38.3, 36.2, 35.4, 34.5, 32.2, 32.1, 28.4, 28.2; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) 443.2182, found 443.2177.

Methyl (2S, 3S, 5R)-1-(tert-Butyloxycarbonyl)-3-[2-(N-Phthalimido)-ethyl]-5-[(3-amino-(N-benzyloxycarbonyl)-3-methoxycarbonyl)-2-propenyl]-prolinate (10). To a solution of **9** (100 mg, 0.23 mmol) in THF (6 mL) and H_2O (3 mL) was added OsO_4 (Cat.) in the dark. After 5 min, NaIO_4 (120 mg, 0.56 mmol) was added. The reaction mixture was stirred at room temperature for 4 hr, then filtered, and washed with MeOH (3 $\times$ 5 mL). After removal of the solvent, the residue was redissolved in dichloromethane (10 mL). The organic solution was washed with brine (3 $\times$ 10 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give a crude product of the aldehyde. Meanwhile, to a solution of

(MeO)₂P(O)CH(NHCbz)CO₂Me (75 mg, 0.23 mmol) in dichloromethane (3 mL) was added DBU (34 L, 0.23 mmol) at room temperature. After 10 min, to the above solution was added a solution of the aldehyde crude product in dichloromethane (2 mL) and the reaction mixture was stirred overnight at room temperature. After removal of the solvent, the residue was redissolved in EtOAc (5 mL), washed with 1N HCl (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to afford a crude product. The crude product was purified by flash column chromatography (Hexanes:EtOAc = 1:1) to give pure product **10** as a colorless oil (117 mg, 79%). **10**. [γ]²³_D +49.7 (*c* 1.84, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (two rotamers) δ 7.83 (brs, 2H), 7.67 (brs, 2H), 7.58-7.29 (m, 5H), 6.65 (brs, 1H), 5.19-5.12 (m, 2H), 4.17-4.10 (m, 1H), 3.91 (d, 0.5H, *J* = 9.5 Hz), 3.80-3.65 (m, 8.5H), 2.70-2.61 (m, 1H), 2.45-2.42 (m, 0.5H), 2.36-2.33 (m, 1.5H), 2.18-2.05 (m, 2H), 1.83-1.65 (m, 2H), 1.39 (s, 4H), 1.35 (s, 5H); ¹³C NMR (125 MHz, CDCl₃) (two rotamers) δ 173.8, 173.6, 168.3, 165.1, 154.9, 154.8, 153.9, 153.4, 136.3, 134.0, 133.9, 133.4, 131.8, 128.3, 128.2, 127.9, 123.3, 80.6, 80.5, 66.9, 65.5, 65.3, 57.2, 57.0, 52.6, 52.3, 52.0, 40.4, 39.5, 37.0, 36.1, 36.0, 35.8, 34.2, 33.5, 32.2, 32.0, 28.1, 28.0; HRMS (FAB) calcd for C₃₄H₄₀N₃O₁₀ (M+H) 650.2714, found 650.2703.

Methyl (2S, 3S, 5R)-1-(tert-Butyloxycarbonyl)-3-[2-(N-Phthalimido)-ethyl]-5-[2-bromo-(3-amino-(N-benzyloxycarbonyl)-3-methoxycarbonyl)-2-propenyl]-prolinate (11).

To a solution of **10** (405 mg, 0.62 mmol) in chloroform (10 mL) was added NBS (122 mg, 0.69 mmol) at room temperature. After 80 min, Dabco (140 mg, 1.25 mmol) was added. The reaction mixture was stirred at room temperature for 24 hr. Then the reaction mixture was washed with saturated NH₄Cl (3 10 mL), and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to flash column chromatography (Hexanes:EtOAc = 4:1) to afford **11**, in 78% yield, as a colorless oil. **11**. [γ]²³_D +10.4 (*c* 1.05 , CHCl₃); ¹H NMR (500 MHz, CDCl₃)

(Rotamer) δ 7.85-7.82 (m, 2H), 7.72-7.69 (m, 2H), 7.36-7.27 (m, 5H), 6.61 (brs, 1H), 5.14-5.11 (m, 2H), 4.38-4.35 (m, 0.6H), 4.34-4.28 (m, 0.4H), 3.95-3.84 (m, 1.5H), 3.83-3.62 (m, 7.5H), 3.12-3.10 (m, 1.5H), 2.91-2.87 (m, 0.5H), 2.44-2.41 (m, 1H), 2.24 (brs, 1H), 2.10-2.03 (m, 1H), 1.72-1.66 (m, 2H), 1.47-1.26 (m, 9H); ^{13}C NMR (125 MHz, CDCl_3) (Rotamer) δ 173.3, 173.1, 168.1, 162.7, 162.5, 153.5, 153.0, 152.9, 152.8, 135.4, 134.1, 134.0, 133.9, 132.1, 132.0, 128.6, 128.5, 128.4, 128.3, 128.2, 123.4, 123.2, 123.1, 80.5, 80.4, 67.9, 67.7, 65.5, 65.0, 57.0, 56.9, 52.7, 52.3, 52.1, 40.3, 39.8, 39.5, 39.2, 36.2, 36.1, 34.4, 33.9, 32.1, 32.0, 28.4, 28.3; HRMS (FAB) calcd for $\text{C}_{34}\text{H}_{39}\text{BrN}_3\text{O}_{10}$ ($\text{M}+\text{H}$) 728.1819, found 728.1804.

Methyl (2S, 3S, 5R)-1-(*tert*-Butyloxycarbonyl)-3-[2-(*N*-Phthalimido)-ethyl]-5-[2-phenyl-(3-amino-(*N*-benzyloxycarbonyl)-3-methoxycarbonyl)-2-propenyl]-prolinate (12).

To a solution of **11** (375 mg, 0.52 mmol) in DME (3 mL) and degassed water (520 μL) was added phenyl boronic acid (185 mg, 1.52 mmol), Na_2CO_3 (165 mg, 1.56 mmol), $\text{Pd}(\text{OAc})_2$ (25 mg, 0.11 mmol) and $\text{P}(o\text{-tolyl})_3$ (30 mg, 0.10 mmol). Then the reaction mixture was stirred at 80 $^\circ\text{C}$ overnight. The reaction mixture was passed through a short column containing a bottom 1'' layer of silica gel and a top 1'' layer of NaHCO_3 using ethyl acetate as eluent. After removal of the solvent, the crude product **12** was subjected to the next step without further purification.

(6R, 8S, 9S)-1-Aza-3-*N*-benzoxycarbonylamino-9-methoxycarbonyl-4-phenyl 8-[2-(*N*-Phthalimido)-ethyl]-2-oxobicyclo[4.3.0]non-3-ene (13). To a solution of above crude product **12** in dichloromethane (2.4 mL) was added TFA (0.6 mL) at room temperature. The mixture was stirred for 30 min, then saturated NaHCO_3 (10 mL) was added. After stirring for 20 min, the organic solution was dried over Na_2SO_4 and concentrated under vacuum. The reaction residue was redissolved in chloroform (5 mL) and stirred at room temperature for 48 hr. After removal of the solvent, the crude product was chromatographed (Hexanes:EtOAc = 1:1) to afford

13 as a colorless oil in 61% overall yield from **11**. **13**. [^{23}D] -5.7 (c 1.04, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.85 (m, 2H), 7.75-7.72 (m, 2H), 7.37-7.33 (m, 4H), 7.31-7.23 (m, 4H), 7.20-7.19 (m, 2H), 6.51 (brs, 1H), 4.97 (d, 1H, $J = 12.3$ Hz), 4.89 (d, 1H, $J = 12.3$ Hz), 4.36 (s, 1H), 4.22-4.15 (m, 1H), 3.84-3.72 (m, 5H), 2.90-2.80 (m, 2H), 2.40 (q, 1H, $J = 7.0$ Hz), 2.19 (dd, 1H, $J = 12.8, 5.7$ Hz), 2.07-2.02 (m, 1H), 2.01-1.92 (m, 1H), 1.83-1.76 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 168.2, 161.8, 153.4, 138.2, 137.9, 136.2, 134.1, 132.0, 128.5, 128.4, 128.3, 127.9, 127.2, 124.2, 123.4, 67.0, 63.4, 54.0, 52.6, 39.7, 36.4, 36.0, 35.8, 32.7; HRMS (FAB) calcd for $\text{C}_{34}\text{H}_{32}\text{N}_3\text{O}_7$ ($\text{M}+\text{H}$) 594.2240, found 594.2222.

(6R, 8S, 9S)-1-Aza-3-N-benzoxycarbonylamino-9-methoxycarbonyl-4-phenyl 8-[2-(N, N'-di-Boc-guanidino)-ethyl]-2-oxobicyclo[4.3.0]non-3-ene (15). To a solution of **13** (31 mg, 0.052 mmol) in absolute ethanol (2 mL) and chloroform (400 μL) was added anhydrous hydrazine (11 μL , 0.35 mmol) at room temperature. After stirring at room temperature for 24 hr, the reaction solution was filtered to remove the white precipitate and the filtrate was concentrated in vacuum to afford crude product of **14**. The crude product **14** was then dissolved in dichloromethane (2 mL) to give the solution which was added TEA (45 μL , 0.33 mmol) and *N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-triflylguanidine (31 mg, 0.079 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 hr before the solvent was removed *in vacuo*. The crude product was chromatographed (Hexanes:EtOAc = 1:1) to afford **15** as a colorless oil (30.5 mg, 83%). **15**. [^{23}D] -7.8 (c 2.07, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 11.48 (brs, 1H), 8.43 (brs, 1H), 7.37-7.25 (m, 8H), 7.21-7.19 (m, 2H), 6.48 (brs, 1H), 4.99 (d, 1H, $J = 12.3$ Hz), 4.91 (d, 1H, $J = 12.3$ Hz), 4.36 (s, 1H), 4.20-4.13 (m, 1H), 3.78 (s, 3H), 3.66-3.59 (m, 1H), 3.52-3.47 (m, 1H), 2.84 (d, 2H, $J = 8.9$ Hz), 2.43 (q, 1H, $J = 14.7, 7.4$ Hz), 2.11-2.07 (m, 1H), 2.05-1.99 (m, 1H), 1.80-1.75 (m, 2H), 1.50 (s, 18H); ^{13}C NMR (125 MHz, CDCl_3)

δ 171.7, 163.5, 161.8, 156.2, 153.5, 153.3, 138.3, 138.2, 136.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.2, 124.3, 83.3, 79.4, 67.0, 62.8, 54.0, 52.6, 39.5, 38.6, 36.4, 36.3, 33.3, 28.3, 28.1, 27.8;
HRMS (FAB) calcd for $C_{37}H_{48}N_5O_9$ (M+H) 706.3452, found 706.3445.