Synthesis of a Val-Pro Diaminodiol Dipeptide Isostere by Epoxyamine Cyclization

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(8*S*)-8-*tert*-Butoxycarbonylamino-9-methyl-7-oxo-dec-5-enoic acid methyl ester (6)
A solution of aldehyde **5c** (1.5 g, 11.8 mmol) in absolute ethanol (50 mL) was added over 2 hours to a stirred suspension of oven dried K_2CO_3 (1.6 g, 11.8 mmol) and phosphonate **4** (3.81g, 11.8 mmol) in absolute ethanol (100 mL). After 6 h the reaction mixture was filtered and the solution was neutralized with glacial acetic acid. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous phase was estracted with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography with diethyl ether and petroleum ether (1:1) as eluant, to give 2.6 g (67%) of colourless oil. $[\alpha]_D^{25}$ = +3.13 (c = 1.95, MeOH). **^{1}H NMR** (δ-$CDCl_3$): 0.75 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.41 (s, 9H), 1.79 (m, 2H), 2.09 (m, 1H), 2.25 (m, 2H), 2.30 (t, 2H, *J* = 7.3 Hz), 3.66 (s, 3H), 4.46 (m, 1H), 5.23 (d, NH, *J* = 8.4 Hz), 6.20 (d, 1H, *J* = 15.6 Hz), 6.92 (dt, 1H, *J* = 6.9, 15.6 Hz). **^{13}C NMR** (δ-$CDCl_3$): 16.75, 19.93, 23.19, 28.38, 30.87, 31.83, 33.26, 51.69, 62.15, 79.57, 128.22, 147.74, 155.98, 173.48, 198.29. **MS** *m/z*: 366 $[MK]^+$, 349 $[MNa]^+$, 345 $[MNH_4]^+$, 328 $[MH]^+$.

(*8S,7R*)-8-*tert*-Butoxycarbonylamino-7-hydroxy-9-methyl-dec-5-enoic acid methyl ester (7)
Sodium borohydride (180 mg, 4.77 mmol) was added in small portions over 10 min, at 0 °C, to a stirred solution of enone **6** (1.56 g, 4.77 mmol) in methanol (50 mL). The mixture was neutralized with glacial acetic acid and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ and the aqueous phase was estracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed undere reduced pressure and the crude 8:1 mixture of diastereoisomers was purified by flash chromatography with diethyl ether and methanol (9:1) as eluant, to give 1.41 g (90%) of colourless oil. $[\alpha]_D^{25}$ = -18.41 (c = 3.2, MeOH). **^{1}H NMR** (δ-$CDCl_3$): 0.92 (d, 3H, *J* = 7.4 Hz), 0.94 (d, 3H, *J* = 7.4 Hz), 1.42 (s, 9H), 1.70 (m, 2H), 1.75 (m, 1H), 2.07 (m, 2H), 2.29 (t, 2H, *J* = 7.3 Hz), 2.66 (broad, OH), 3.47 (m, 1H), 3.65 (s, 3H), 4.16 (m, 1H), 4.45 (d, NH, *J* = 9.5 Hz), 5.46 (dd, 1H, *J* = 6.9, 15.1 Hz), 6.92 (dt, 1H, *J* = 6.3, 15.1 Hz). **^{13}C NMR** (δ-$CDCl_3$): 18.56, 20.23, 24.35, 28.41, 29.15, 31.73, 33.43, 51.58, 60.69, 73.52, 79.65, 129.56, 132.71, 155.89, 174.03. **MS** *m/z*: 368 $[MK]^+$, 352 $[MNa]^+$, 330 $[MH]^+$.

(4S,2S)-6-(4-Isopropyl-2-oxo-oxazolidin-5-yl)-hex-5-enoic acid methyl ester (8)
NaH (60 mg of a 60% suspension in mineral oil, 1.5 mmol) was added in small portions, under an argon atmosphere, to a solution of alcohol **7** (100 mg, 0.3 mmol) in dry THF (3 mL). The mixture

was stirred at room temperature for 12 hours; 10% aqueous NH_4Cl was added (5 mL) and stirring was continued for 10 minutes. The aqueous layer was extracted with ethyl acetate (3 x 5mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and flash chromatography with diethyl ether as eluant, gave 58 mg (72%) of colourless oil. **^{1}H NMR** (δ-$CDCl_3$): 0.85 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 1.77 (m, 3H), 2.14 (m, 2H), 2.32 (t, 2H *J* = 7.32 Hz), 3.55 (m, 1H), 3.67 (s, 3H), 4.96 (t, 1H, *J* = 7.7 Hz), 5.29 (broad, NH), 5.62 (dd, 1H, *J* = 8.4, 15.4 Hz), 5.84 (m, 1H).

(*8S,7R*)-*8*-*tert*-Butoxycarbonylamino-7-(*tert*-butyl-dimethyl-silanyloxy)-9-methyl-dec-5-enoic acid methyl ester (9)

A suspension of the alcohol **7** (1.24 g, 3.75 mmol), *tert*-butyldimethylsilyl chloride (1.41 g, 9.4 mmol) and imidazole (1.27 g, 18.8 mmol) in dry DMF (15 mL) was stirred at room temperature for 12 hours. Methanol (10 mL) was added and stirring was continued for additional 20 minutes. The reaction mixture was then poured into water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography with petrol and ethyl acetate (6:4) as eluant, afforded 1.33 g (80%) of colourless oil. **^{1}H NMR** (δ-$CDCl_3$): 0.01 (m, 6H), 0.87 (m, 15H), 1.41 (s, 9H), 1.69 (m, 2H) 1.91 (m, 1H), 2.05 (m, 2H), 2.31 (t, 2H, *J* = 7.3 Hz), 3.42 (m, 1H), 3.65 (s, 3H), 4.09 (m, 1H), 4.45 (d, NH, *J* = 10.6 Hz), 5.42 (dd, 1H, *J* = 6.6, 15.4 Hz), 5.58 (dt, 1H, *J* = 6.9, 15.4 Hz). **^{13}C NMR** (δ-$CDCl_3$): -5.00, -4.09, 17.30, 18.16, 20.88, 24.50, 25.88, 27.86, 28.47, 31.63, 33.47, 51.58, 59.37, 74.64, 78.79, 131.35, 131.30, 156.09, 174.03. **MS** *m/z*: 482 $[MK]^+$, 466 $[MNa]^+$, 444 $[MH]^+$.

(7S,6R)-[7-*tert*-Butoxycarbonylamino-6-(*tert*-butyl-dimethyl-silanyloxy)-8-methyl-non-4-enyl]-carbamic acid benzyl ester (10)

25 mL of a 1M aqueous solution of lithium hydroxide was added to the ester **9** (1.2 g, 2.7 mmol) in 25 mL of THF and the resulting mixture was kept at 25 °C for 1 h., then acidified with 10% HCl to pH 4 and extracted with ethyl acetate (3x25 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue (1.03 g, 2.4 mmol) was taken up in dry toluene (50 mL). Diphenyl phosphorazidate (0.61 mL, 2.8 mmol) and triethylamine (0.39 mL, 2.8 mmol) were added to this solution and the mixture was refluxed for 1 hour. Benzyl alcohol (0.5 mL, 4.8 mmol) was added, and reflux continued for 12 hours. The solvent was evaporated under reduced pressure and the resulting residue was partitioned between ethyl acetate and saturated aq. $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (2x20 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with petrol and ethyl acetate as eluant (gradient from 7:3 to 4:6), giving 845 mg (64%) of colourless oil. **$[\alpha]_D^{25}$ =** -26.17 (c = 0.55, MeOH). **^{1}H NMR** (δ-$CDCl_3$): -0.03 (s, 3H), 0.01 (s, 3H), 0.86 (m, 15H), 1.40 (s, 9H), 1.57 (m, 2H), 1.96 (m, 1H), 2.03 (m, 2H), 3.17 (m, 2H), 3.41 (m, 1H), 4.08 (m, 1H), 4.50 (d, NH, *J* = 9.5 Hz), 4.77 (broad, NH), 5.07 (s, 2H), 5.41 (dd, 1H, *J* = 6.2, 15.4 Hz), 5.59 (m, 1H), 7.33 (m, 5H). **^{13}C NMR** (δ-$CDCl_3$): -4.97, -4.02, 17.19, 18.16, 20.84, 25.89, 27.81, 28.49, 29.45, 29.51, 40.64, 59.46, 66.68, 74.61, 78.82, 128.05, 128.17, 128.20, 128.58, 131.30, 136.68, 156.11, 156.41. **MS** *m/z*: 573 $[MK]^+$, 557 $[MNa]^+$, 535 $[MH]^+$.

(7S,6R)-(7-*tert*-Butoxycarbonylamino-6-hydroxy-8-methyl-non-4-enyl)-carbamic acid benzyl ester (11)

Tetrabutylammonium fluoride (1M in THF, 6 mL) was added to a solution of **10** (700 mg, 1.31 mmol) in dry THF (15 mL) and the resulting mixture was stirred at room temperature overnight. The solvent was then removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was

purified by flash chromatography (eluant: petrol and ethyl acetate 7:3 to 5:5) to give 374 mg (68%) of colourless oil which solidified on standing. **m.p.**= 80-81 °C. **$[\alpha]_D^{25}$ =** -19.83 (c=0.57, MeOH). **^{1}H NMR** (δ-$CDCl_3$): 0.93 (m, 6H), 1.41 (s, 9H), 1.58 (m, 2H), 1.74 (m, 1H), 2.09 (m, 2H), 2.84 (broad, OH), 3.18 (m, 2H), 3.48 (m, 1H), 4.13 (m, 1H), 4.80 (broad, 2 NH), 5.08 (s, 2H), 5.44 (dd, 1H, *J* = 6.6, 15.4 Hz), 5.65 (m, 1H), 7.34 (m, 5H). **^{13}C NMR** (δ-$CDCl_3$): 18.56, 20.14, 28.33, 28.84, 29.08, 29.19, 39.97, 60.82, 66.58, 73.44, 79.43, 128.05, 128.46, 129.77, 132.07, 136.54, 156.34, 157.36. **MS** *m/z*: 459 $[MK]^+$, 443 $[MNa]^+$, 421 $[MH]^+$.

(1S,2S)-(1-{[(2R,3R)-3-(3-Benzyloxycarbonylamino-propyl)-oxiran-2-yl]-1-hydroxy-3-methyl}-2-methyl-propyl)-carbamic acid *tert*-butyl ester (12)

To an ice cold solution of **11** (240 mg, 057 mmol) in dichloromethane (5 mL) was added a solution of *m*-chloroperoxybenzoic acid (200 mg, 0.68 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 12 hours, then washed with 10% aqueous sodium metabisulfite (2 x 5 mL), saturated aqueous $NaHCO_3$ (2 x 5 mL) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography eluting with dichloromethane and ethyl acetate (4:6) to give 131 mg (53%) of white solid. **m.p.** = 90-91 °C. **$[\alpha]_D^{25}$ =** +9.6 (c = 0.25 MeOH). **^{1}H NMR** (δ-$CDCl_3$): 0.87 (d, 3H, *J* = 6.7 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 1.41 (s, 11H), 1.63 (m, 2H), 2.05 (m,1H), 2.71 (d, OH, *J* = 6.6 Hz), 2.86 (m, 1H), 2.95 (m, 1H), 3.21 (m, 2H), 3.45 (m, 1H), 3.62 (m, 1H), 4.62 (d, NH, *J* = 9.5 Hz), 5.00 (broad, NH), 5.06 (s, 2H), 7.32 (m, 5H). **^{13}C NMR** (δ-$CDCl_3$): 17.09, 20.09, 26.42, 28.45 (2C), 28.74, 40.59, 56.27, 58.38, 59.55, 66.69, 70.98, 79.59, 128.17, 128.57, 136.64, 156.45, 156.52 (2C). **MS** *m/z*: 475 $[MK]^+$, 459 $[MNa]^+$, 403 $[MNa\text{-}C_4H_8]^+$, 381 $[MH\text{-}C_4H_8]^+$, 337 $[MH\text{-Boc}]^+$.

(1S,2S,3S,2'S)-(2,3-Dihydroxy-1-isopropyl-3-pyrrolidin-2'-yl-propyl)-carbamic acid *tert*-butyl ester (13).

To a solution of **12** (100 mg, 0.23 mmol) in methanol (5 mL) was added 5% Pd/C (5 mg) and the mixture was stirred under a hydrogen-filled balloon for 12 hours. Filtration through Celite to remove the catalyst and evaporation of the solvent under reduced pressure provided 63 mg (91%) of colourless oil which solidified on standing. **M.p.** 129-130 °C (from toluene). **$[\alpha]_D^{25}$** = -12.5 (c = 0.16, MeOH). **^{1}H NMR** (δ-$CDCl_3$): 0.82 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.6 Hz), 1.43 (s, 9H), 1.58 (m, 1H), 1.76 (m, 2H), 1.90 (m, 1H), 2.27 (m, 1H), 2.85 (m, 1H), 2.92 (m, 1H), 3.42 (d, 1H, *J* = 4.0 Hz), 3.58 (m, 3H), 4.24 (broad, 2 OH), 4.57 (d, NH, *J* = 8.4 Hz). **^{13}C NMR** (δ-$CDCl_3$): 15.31, 20.30, 25.11, 26.10, 27.63, 28.39, 45.89, 56.14, 61.67, 70.28, 71.64, 80.09, 157.83.