Supporting Information

Synthesis of Cyclic Proline-Containing Peptide Mimics via Ring Closing Metathesis

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General Methods. All reagents were used as supplied. Grubbs catalyst was obtained from Strem Chemical Company. Solvents were purified by the methods given in *Purification of Laboratory Chemicals* by D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 2nd Edition, Pergamon Press, 1980. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE DRX400 (¹H, 400 MHz; ¹³C, 100 MHz) or a Bruker AVANCE 300 (¹H, 300 MHz; ¹³C, 75 MHz) spectrometer at ambient temperatures. Flash chromatography was performed using Scharlau 60 (40-60 µm mesh) silica gel. Melting points in degrees Celsius (°C) were determined on an Electrothermal® melting point apparatus and are uncorrected. Accurate mass measurements were recorded on a VG-70SE mass spectrometer.

(6*Z*, 9*S*, 12*S*) *N*-Benzyloxycarbonyl-1,4-diaza-12-*tert*-butoxycarbonyl-2-oxobicyclo[7.3.0]dodec-6-ene **20**

To a degassed solution of diene **18** (0.10 g, 0.23 mmol) in dry dichloromethane (56 cm³) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs catalyst) (0.018 g, 0.023 mmol) under an atmosphere of nitrogen and the resultant purple solution heated at reflux for 24 h. Further bis(tricyclohexylphosphine)benzylidineruthenium dichloride (0.018 g, 0.023 mmol) was added and refluxing continued for 24 h. The reaction mixture was cooled to room temperature, dimethyl sulphoxide¹ (0.160 cm³, 2.3 mmol) was added and the orange/brown solution stirred for 24 h. The solvent was removed *in vacuo* and the residue purified by chromatography (SiO₂, 3:1, 2:1, 1:1, hexanes-ethyl acetate,) to give an almost colourless oil which was further purified by chromatography (C₁₈ RP silica, 100:0, 9:1, 9:3, 1:1, 1:9, water-acetonitrile) to give *alkene 20* [0.039 g, 42% (60% based on recovered starting material)] as a colourless oil. Alkene **20** existed exclusively as the *trans* C(O)-NPro conformer. In addition, restricted rotation about the N-CO carbamate bond was also observed resulting in a 1:1 mixture of conformers: [α]_D -118.2 (*c* 0.34 in CH₂Cl₂); δ_H (400 MHz; CDCl₃; Me₄Si) 1.46 [9H, s, C(CH₃)₃], 1.74 (1H, dd, *J* 11.8 and 5.7, 10-*H_AH_B*), 1.93 (1H, dd, *J* 12.5 and 6.5, 11-*H_AH_B*), 2.11-2.45 (4H, m, 8-H₂, 10-*H_AH_B* and 11-*H_AH_B*), 3.53 (1H, dd, *J* 15.7 and 8.0, 5-*H_AH_B*), 4.13-4.37 (4H, m, 3-H₂, 9-H and 12-H), 4.50 (1H, d, *J* 15.4, 5-*H_AH_B*), 5.12-5.29 (2H, m, OCH₂Ph), 5.54-5.82 (2H, m, 6-H and 7-H) and 7.31-7.43 (5H, m, Ph); δ_C (100 MHz; CDCl₃) 26.7 (CH₂, 11-C), 27.8 [CH₃, C(CH₃)₃], 34.0 (CH₂), 34.2 (CH₂), 34.3 (CH₂), 34.4 (CH₂), 43.9 (CH₂, 5-C), 44.5 (CH₂, 5-C), 48.5 (CH₂, 3-C), 49.5 (CH₂, 3-C), 57.2 (CH, 9-C), 57.6 (CH, 9-C), 60.1 (CH, 12-C), 67.6 (CH₂, OCH₂Ph), 81.2

¹ Ahn, Y. M.; Yang, K. L.; Georg, G. I. *Org. Lett.* **2001**, 3, 1411-1413.

[quat., C(CH₃)₃], 126.8 (CH, 6-C), 126.9 (CH, 6-C), 128.0 (CH, Ph), 128.4 (CH, Ph), 128.7 (CH, Ph), 129.9 (CH, 7-C), 136.3 (quat., Ph), 136.4 (quat., Ph), 155.7 (quat., NCO₂), 167.8 (quat., 2-C), 167.9 (quat., 2-C) and 170.7 (quat., 12-CO); *m/z* (EI⁺) 414.2157 (M⁺. C₂₃H₃₀N₂O₅ requires 414.2155).

(8*R*, 3*S*, 11*S*) 1-Aza-3-(*tert*-butyloxycarbonylamino)-11-ethoxycarbonyl-2-oxobicyclo[6.3.0]undec-5-ene 23

To a degassed solution of diene **22** (0.064 g, 0.170 mmol) in dry dichloromethane (43 cm³) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs catalyst) (0.014 g, 0.0170 mmol) under a nitrogen atmosphere and the resultant purple solution heated at reflux for 24 h. The orange/brown solution was cooled to room temperature, dimethyl sulphoxide (0.160 cm³, 2.26 mmol) was added and the solution stirred overnight. The solvent was removed *in vacuo* and the residue purified by chromatography (SiO₂, 2:1, 1:1, hexanes-ethyl acetate,) to give *alkene 23* (0.044 g, 74%) as a colourless oil. *Alkene 23* existed exclusively as the *trans* C(O)-NPro conformer: [α]_D -93.2 (*c* 0.29 in CH₂Cl₂); δ_H (400 MHz; CDCl₃; Me₄Si) 1.25 (3H, t, *J* 7.1, OCH₂CH₃), 1.42 [9H, s, C(CH₃)₃], 1.89-1.98 (2H, m, 10-*H_AH_B* and 9-*H_AH_B*), 2.01-2.09 (1H, m, 9-*H_AH_B*), 2.11-2.16 (1H, m, 10-*H_AH_B*), 2.24-2.33 (1H, m, 4-*H_AH_B*), 2.42 (1H, dq, *J* 15.2 and 3.4, 7-*H_AH_B*), 2.70-2.80 (2H, m, 4-*H_AH_B* and 7-*H_AH_B*), 4.15 (3H, q, *J* 7.1, OCH₂CH₃ and 8-H obscured), 4.47 (1H, dd, *J* 8.4 and 2.8, 11-H), 4.84 (3H, br q, *J* 7.8, 3-H), 5.59 (1H, d, *J* 7.3, N-H), 5.67-5.73 (1H, m, 6-H) and 5.77-5.83 (1H, m, 5-H); δ_C (100 MHz; CDCl₃) 14.0 (CH₃, OCH₂CH₃), 27.1 (CH₂, 10-C), 28.2 [CH₃, C(CH₃)₃], 32.77 (CH₂, 7-C or 9-C), 32.84 (CH₂, 9-C or 7-C), 35.2 (CH₂, 4-C), 51.7 (CH, 3-C), 58.6 (CH, 8-C), 60.2 (CH, 11-C), 60.8 (CH₂, OCH₂CH₃), 79.4 [quat., C(CH₃)₃], 125.7 (CH, 6-C), 129.1 (CH, 5-C), 155.1 (quat., NCO₂), 170.9 (quat., 11-CO) and 171.7 (quat., 2-C); *m/z* (EI⁺) 352.2001 (M⁺. C₁₈H₂₈N₂O₅ requires 352.1998).

(3*S*, 8*R*, 10*S*, 13*S*) 3-Amino-1,11-diaza-8,10-carboxy-2,12-oxobicyclo[13.3.0]hexadecane trifluoroacetate salt 37

To a solution of diene **36** (0.041 g, 0.0589 mmol) in dry dichloromethane (7.5 cm³) was added bis(tricyclohexylphosphine)-benzylidineruthenium dichloride (0.015 g, 0.0126 mmol) under an atmosphere of nitrogen. The purple solution was heated at reflux for 48 h, cooled to room temperature and dimethyl sulphoxide (0.045 cm³, 0.63 mmol) added. The orange-brown solution was stirred for 24 h, filtered through a short plug of silica gel (eluting with hexanes:ethyl acetate, 1:3), and purified by chromatography (C₁₈ RP silica, water:acetonitrile, 20%-70%) to give the metathesis product^φ (48 mg) and other unidentified product(s) as a yellow oil, [*m/z* (FAB⁺) 668.2977 (MH⁺. C₃₈H₄₂N₃O₈ requires 668.2972)]. Metathesis product was divided into 2 samples (~25 mg each); the first sample was dissolved in tetrahydrofuran/water (4:1, 5 cm³) and 10 wt. % palladium on activated carbon (0.008 g, 0.00749 mmol) was added under an atmosphere of nitrogen. To the reaction flask was fitted a balloon

^φ performing the metathesis reaction at a concentration of 4M (50 mg in 18 cm³ of CH₂Cl₂) for 24 h resulted in incomplete reaction; starting diene and metathesis product are inseparable.

of hydrogen and stirred for 21 h at room temperature. The reaction mixture was filtered through a pad of Celite™, washed with methanol/water (4:1) and concentrated *in vacuo* to yield a film. The second sample was dissolved in tetrahydrofuran (3 cm³) and platinum (IV) oxide^ψ (0.00078 g, 0.0034 mmol) added under an atmosphere of nitrogen. To the reaction flask was fitted a balloon of hydrogen and stirred for 16 h at room temperature. The reaction mixture was filtered through a pad of Celite™, washed with methanol: and concentrated *in vacuo* to yield a film that was dissolved in methanol:water (4:1, 5 cm³) and 10 wt. % palladium on activated carbon (0.008 g 0.00749 mmol) was added under an atmosphere of nitrogen. To the reaction flask was fitted a balloon of hydrogen and stirred for 5 h at room temperature. The reaction mixture was filtered through a pad of Celite™, washed with methanol/water (4:1) and concentrated *in vacuo* to yield a film. Both samples were combined, purified by RP HPLC [10% acetonitrile:90% water (containing 0.05% trifluoroacetic acid) then 80:20, 70:30] and dried on a freeze drier to give **37** (0.016 g, 58% from **35**) as a white solid. **37** existed exclusively as the *trans* conformer: mp 150-240 °C^ξ; [α]_D -39.4 (*c* 0.0864 in water); δ_{H} (400 MHz; D₂O), 1.20-1.62 (6H, m, 5-H₂, 14-H₂, 7-H₂), 1.81-1.90 (1H, m, 4-H_AH_B), 2.04-2.36 (7H, m, 4-H_AH_B, 9-H₂, 6-H₂, 15-H₂), 2.43 (1H, br t, *J* 6.2, 8-H), 3.68-3.79 (2H, m, 16-H₂), 4.48-4.49 (1H, m, H-3) and 4.51-4.55 (1H, m, 10-H) [13-H obscured by HOD]; δ_{C} (100 MHz; D₂O) 18.2 (CH₂, 5-C), 23.9 (CH₂, 14-C), 24.2 (CH₂, 15-C), 26.0 (CH₂, 6-C), 26.8 (CH₂, 4-C), 28.0 (CH₂, 7-C), 30.3 (CH₂, 9-C), 38.2 (CH, 8-C), 47.1 (CH₂, 16-C), 50.6 (CH, 10-C), 50.9 (CH, 3-C), 59.5 (CH, 13-C), 116.25 (q, *J* 291.7, CF₃), 162.8 (q, *J* 35.2, CF₃CO₂H), 169.2 (quat., 2-C), 174.0 (quat., 10-CO), and 179.8 (quat., 8-CO); *m/z* (FAB+) 356.1811 [MH(free base)]⁺. C₁₆H₂₆N₃O₆ requires 356.1821].

^ψ PtO₂ cleanly reduces the double bond; the subsequent debenzylation with 10 % Pd/C is much cleaner than just hydrogenation/debenzylation in the one pot with 10% Pd/C.

^ξ from 150-220 °C sample fused together and browned; 220-240 °C emulsified to an oil.